PATHOPHYSIOLOGICAL BASIS OF CEREBRAL ARTERIAL AIR EMBOLISM

Stephen C. Helps

Thesis submitted for the degree of

Doctor of Philosophy

in

THE UNIVERSITY OF ADELAIDE

FACULTY OF MEDICINE
DEPARTMENT OF ANÆSTHESIA AND INTENSIVE CARE

22 April, 1994

ABBREVIATIONS USED

±	plus or minus Standard error of the mean
µg	micrograms (mass)
µl	microlitres (volume)
µm	micrometres (distance)
ANOVA	Analysis of Variance
ATP	Adenosine triphosphate
CAGE	Cerebral Arterial Gas Embolism
CBF	Cerebral Blood Flow
CD	Cluster of Differentiation antigen
CGRP	Calcitonin Gene Related Peptide
CMR-glucose	Cerebral Metabolic Rate for glucose
CSER	Cortical Somatosensory Evoked Response
CSER AP_2	Cortical Somatosensory Evoked Response Amplitude of Peak 2
CVR	Cerebrovascular Resistance
DCI	Decompression Illness (new terminology)
DCS	Decompression Sickness (old terminology)
DIC	Disseminated intravascular coagulation
EDRF	Endothelium-Dependent Relaxing Factor (usually nitric oxide)
H^+	Hydrogen ions
H_2O_2	Hydrogen peroxide
He	Helium
HOCl	Hypochlorous acid
m.w.	molecular weight (Daltons)
MABP	mean arterial blood pressure
MAC	Membrane Attack Complex
mls	millilitres (volume)
mM	milliMolar (concentration)
mmHg	millimetres mercury (pressure)
MPO	Myeloperoxidase
NO	Nitric oxide; probably Endothelium-Dependent Relaxing Factor
O_2	Oxygen
O_2^-	Superoxide
OH^-	hydroxyl radical
P_aCO_2	Partial pressure of arterial carbon dioxide
PAF	Platelet Activating Factor
P_aO_2	Partial pressure of arterial oxygen
SD	Standard deviation of the mean
SEM	Standard error of the mean
SOD	Superoxide dismutase
$t_{½}$	Half life
T^oC	Temperature in degrees Celsius

Trademark names are shown in the text in SMALL CAPITALS.

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SUMMARY

The natural history of air embolism of the brain was studied by observing bubbles in the pial vessels of rabbits and the effect of different doses of air on brain function and blood flow. Air was injected through a cannula placed near the left internal carotid artery, which remained patent throughout the experiment. The smallest amount of intracarotid air that could be seen in the pial vessels was 25 µl. This dose of air passed through the pial vessels rapidly producing a transient pial arteriolar vasodilation which was followed by a progressive reduction of cerebral blood flow and brain electrical activity. There was no effect on right cerebral blood flow demonstrating this insult is limited to the side of injection. This model is thought to correlate well with the natural history of divers with air embolism of the brain.

Various doses of intracarotid air up to 400 µl were also given. A 400 µl dose of intracarotid air produced air embolism in which there was temporary bubble trapping. This was accompanied by a transient pial arterial vasodilation, a progressive reduction in brain blood flow and a sustained deterioration in brain function. All doses of intracarotid air caused;

1. a transient dilation of the pial arteries to as much as 140% of baseline which recovered within 30 to 45 minutes;
2. a progressive reduction of cerebral blood flow to approximately 50% of baseline for the 3 hours of the experiment, and;
3. suppression of the amplitude of the second peak of the somatosensory evoked responses to approximately 40% of baseline. This suppression of evoked responses was progressive for the 3 hours of the experiment in doses of intracarotid air less than 300 µl. A 400 µl dose of air produced a sudden suppression of the second peak of the somatosensory evoked responses to 28%

of baseline which gradually recovered to approximately 40% of baseline.

Treatment of rabbits with mechlorethamine 3 days prior to experiment reduced the white cell count to 10% of baseline, affecting mainly the granulocyte numbers. When compared to baseline or to untreated controls, leukocytopenia did not change the pial arteriolar response to air embolism. Similarly, cerebral blood flow and somatosensory evoked responses were not significantly affected in the leukocytopenic group given cerebral arterial air embolism.

Further studies in which rabbits were treated with dextran sulphate (m.w. 500,000) to reduce granulocyte adhesion to vascular endothelium showed this treatment also provided significant protection against the effects of cerebral arterial air embolism. Cerebral arterial air embolism induced a sustained pial arterial dilation to approximately 120% of baseline in the dextran sulphate treated rabbits. Cerebral blood flow increased to 145% of baseline by 15 minutes post embolus but by 30 minutes had recovered to approximately 75% of baseline. Somatosensory evoked responses showed a transient suppression to 50% of baseline before recovering to approximately 75% of baseline for the duration of the study.

A new model for the pathophysiological basis of CAGE is proposed in which the formed elements of the circulation, most likely the granulocytes, adhere to vascular endothelium damaged by passage of air bubbles and further damage adjacent brain. It appears this damage can be largely prevented if granulocytes are inhibited from adhering to the vascular endothelium.

PUBLICATIONS ARISING FROM THESE STUDIES

JOURNAL PUBLICATIONS

Helps SC, Parsons DW, Reilly PL, Gorman DF (1990) Gas emboli invoke changes in cerebral blood flow, pial arteriole diameter and neural function in rabbits. *Stroke* 21:94-99

Helps SC, Myer-Witting MW, Reilly PL, Gorman DF (1990) Increasing doses of intracarotid air and cerebral blood flow in rabbits. *Stroke* 21:1340-1345

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CONFERENCE PROCEEDINGS

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ABSTRACTS

Helps SC, Gorman DF (1990) The effect of air emboli on brain blood flow and function in leukocytopenic rabbits. *Undersea Biomedical Research* 17:s71

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DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

When deposited in the University Library, I give consent to this copy of my thesis being available for loan and photocopying.

Stephen C. Helps
April 1994

ACKNOWLEDGMENTS

I am indebted to a number of people who variously assisted and resisted the work undertaken in the preparation of this thesis.

I am pleased to be able to thank my supervisors, Dr. W.J. (John) Russell and Prof. W.B. (Bill) Runciman for their support and encouragement. Much of my thinking was influenced by how well it would stand the scrutiny of John Russell and I am particularly grateful he stepped into the breach during a difficult time. Bill Runciman (tried to) teach me the value of that great question in medical research; *"so what"* and endured my shortcomings as a research manager at least long enough for me to finish this thesis. I am also pleased to have known and worked with Dr. Martina Myer-Witting who contributed substantially to CHAPTER 4. Dr. Paul Drew and Eric Smith conducted the studies described in APPENDIX A.5 and during our heated exchanges provided many opportunities for *"thought experiments"* which greatly assisted in focusing my thinking. I am also obliged to Dr. Des Gorman who first stimulated my interest in cerebral arterial gas embolism and with whom some of the earlier experimental work was conducted.

During my candidature I was awarded the *Elizabeth Penfold Simpson Prize* (for Neuroscience). My outlook was considerably enhanced by this award which has encouraged me to finish this thesis and continue my studies of cerebral arterial air embolism.

I am especially grateful to the Royal Adelaide Hospital Jepson Library staff, Julie, Pam and Tina for procuring a large number (and some of the more obscure) references cited in this thesis (Annelise Weibkin also helped with this).

There are a number of others to whom I am grateful for support and encouragement in various forms; Peter Reilly who first instilled my interest in

the study of blood flow in the brain and who proofread this thesis; Charlene Adcock (nee Carr) who was my technical assistant for the larger part of the project; Allison Chapman who took over from Charlene; David Kerr who reminded me that one page a day was all it would take and in a year I would have my thesis finished; David Parsons who gave me a great start in how to do the somatosensory evoked responses; Chris Penhall who fixed a lot of the broken equipment and helped me with the analog/digital hardware; David Doolette who proffered many ancient manuscripts supporting the general view that nothing is new and Sharyn Townsend who translated a 200 year old manuscript from French which described why cerebral air embolism is fatal.

I have also had the privilege of working at other times and in other laboratories with people such as Dr David H. Overstreet, Professor Roger W. Russell and Dr. John Oliver. Their positive influence(s) have been fundamental to the way I learned to approach research with its many practical and theoretical problems..

Without the support of others such as Jesus H. Christ, Geoff Hurst, Jack Dempsey, Barry Severn, Helen Wainwright, Colin Carate and numerous others I would spent more time SCUBA diving and fishing and may not have ever finished writing up.

I am thankful to my parents who were supportive during some difficult times and to my offspring, Briony, Erin and Simon who endured what to them seemed a lot of nonsense. I hope they will understand one day the advantages of opportunity and the rewards of patience.

And to My-Helen, to whom I owe the most of all.

CHAPTER 1.

BACKGROUND AND REVIEW OF THE LITERATURE

"the little bubbles generated ... in the blood, juices, and soft parts of the body, may by their vast number, and their conspiring distension, variously strengthen in some places, and stretch in others, the vessels, especially the smaller ones, that convey the blood and nourishment; and so by choking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the blood; not to mention the pains that such distensions may cause in some nerves and membranous parts, which, by irritating some of them into convulsions, may hasten the death of animals and destroy them sooner, by occasion of that irritation..." [Boyle 1670].

1.1. OVERVIEW

Gas embolism occurs when bubbles enter or form in the blood vessels where it is generally believed they can obstruct the flow of blood by blocking smaller arteries and capillaries. The symptoms of patients affected by arterial gas embolism generally resolve rapidly and completely after treatment with hyperbaric therapy, the rationale being that the trapped bubbles are compressed to a size at which they no longer occlude the end capillaries. However, hyperbaric therapy for *cerebral arterial gas embolism* (CAGE) is not always completely effective [Gorman *et al* 1988; Sutherland *et al* 1993; Weinmann *et al* 1991]. Furthermore, a number of studies examining the ætiology of gas embolism have found that bubbles occlude the end capillaries for longer than a few minutes only under exceptional conditions [Dutka *et al* 1988; Furlow 1982]. There is also increasing evidence that bubbles in the circulation activate a number of processes which persist after the bubbles have gone [Dutka *et al* 1992b;

Hallenbeck *et al* 1982b; Kochanek & Hallenbeck 1992; Kochanek *et al* 1988; Ward *et al* 1990]. These processes may be more important in the ætiology of CAGE than is widely recognised. The conventional wisdom may be an over-simplification.

1.1.1. Scope of this review

The following review of the gas embolism literature briefly covers the gaseous phase gases in the circulation, a classification of gas embolism, the behaviour of gas in the circulation and some causes of gas embolism. Basic cerebrovascular physiology and anatomy are discussed as is treatment of CAGE. In particular the role of leukocyte and complement system activation after CAGE are considered.

There are a large number of other reviews of the gas embolism literature [Catron *et al* 1984; Gorman *et al* 1987a; Gorman 1987b; Gorman 1989], each emphasising different aspects of ætiology, risk or treatment of CAGE [Dutka 1985; Leitch & Green 1986].

1.1.2. Terminology

The formation of tissue gas after decompression has in the past been referred to as *decompression sickness*. Decompression sickness has been further classified into minor, major and central nervous system (types I, II and III [Neuman & Bove 1987]). Gas may also enter the body due to over inflation of the lungs or other gas containing spaces and intra-vascular gas (often intra-arterial) may then enter the brain or spinal cord circulation. However, because both decompression sickness and arterial air embolism may exist in the same patient producing symptoms for which the contemporary treatment is hyperbaric O_2 therapy, an alternative classification system has been proposed [Francis & Smith 1991]. The term *decompression illness* (DCI) is used to describe all

manifestations of decompression barotrauma and decompression sickness. This new classification system does not require an interpretative step between observation and diagnosis. A brief description of this classification system can be found in APPENDIX D.

Blood is a mobile tissue and bubbles can form in the blood just as they form in the non-mobile tissues. Bubble formation after decompression has been observed in veins [Brubakk *et al* 1986; Dixon *et al* 1986; Lehtosalo *et al* 1983; Hills & Butler 1981; Webb *et al* 1988] as well as arteries [Brubakk *et al* 1986; Lynch *et al* 1985] further confusing the distinction between DCI and arterial gas embolism. The term "*autochthonous bubbles*" is used to describe bubbles which form in the non-mobile tissues. This phenomenon is most prevalent in the spinal cord after decompression, and is discussed below as a special type of dysbaric injury.

Embolism is a term which is usually applied when an embolus (particle or body) causes arterial obstruction. Unfortunately the "*gas embolism*" literature is not in agreement as to whether gas is embolic in this sense or not. Arterial gas has been used to induce transient or permanent ischæmia depending on the amount of gas used, the particular model being studied and the disposition of the authors. As shall be discussed below, arterial gas embolism probably does cause an obstruction to the blood flow but is itself obstructive only transiently or under certain conditions. The terms gas embolism and air embolism are often used interchangeably. Air embolism refers specifically to instances in which the composition of the embolus is known to be air. Gas embolism refers to emboli which involve bubbles of unknown composition or of gases other than air.

Neither gas embolism nor DCI are to be confused with "*nitrogen narcosis*" which is an effect of high partial pressures of dissolved inert gas (not bubbles) on cognitive function.

1.2. HISTORICAL ASPECTS OF GAS EMBOLISM

Robert Boyle conducted experiments in 1657 in which bubbles were produced *in vivo* by hypobaric decompression. Boyle used his newly invented air pump to evacuate a chamber occupied by a variety of objects, including living animals. On many occasions he observed intravascular (and in one case intraocular) gas bubbles and speculated they may cause ischæmia or even irritate blood vessels in some lethal way [Boyle 1670].

In his extensive review of medical and experimental studies published in 1769 Morgagni described two cases which exhibited gas in the blood vessels at autopsy. He surmised that death in these cases was due to gas bubbles entering the brain circulation [Morgagni 1769].

The first recognised case of gas embolism due to surgery may have been as early as 1821 when Magendie was removing a tumour from the shoulder of a patient who interrupted the surgical procedure with a cry (in French) "*my blood is falling into my body, I'm dead...*" before collapsing and dying [Magendie 1821]. In 1822 Barlow reported hearing a hissing sound from the blood vessels of the neck during surgery to remove a neck tumour, presumably the sound of room air draining into the veins of the neck. He concluded death in this case was due to gas embolism of the circulation [Barlow 1830].

Bichat believed that gas bubbles in the brain circulation could be lethal whilst gas bubbles in the chambers of the heart could be tolerated. In 1829 he described a surgical case in which the jugular vein was accidentally opened during surgery for removal of a tumour from the shoulder. The patient died

and at autopsy exhibited gas bubbles in both the heart and in the cerebral vessels. Bichat went on to conduct experiments in dogs to reproduce the conditions of this surgical accident. He was able to show that venous entrainment of air could be lethal but that the fatal dose was dependent on the dose of air as well as on the site of injection. He further demonstrated that even small amounts of air injected into the cerebral arterial circulation of horses (*via* the carotid arteries) were fatal [Bichat 1829].

In 1912 Brandes identified a possible route for air entry into the arterial circulation. He wanted to outline the boundaries of an empyema cavity (caused by a pleural infection) in a patient. After injecting bismuth paste into the empyema cavity the patient died. At autopsy the bismuth paste was found to be disseminated throughout the arteries of both cerebral hemispheres, having apparently passed into the arterial circulation through the open pulmonary veins [Brandes 1912]. Brauer later suggested that the symptoms and signs of "*pleural shock*" could be explained by gas embolism from the pulmonary circulation and he was probably the first to use the term arterial gas embolism [Brauer 1913].

Rukstinat and LeCount advised that post-mortem examinations should be done under water when gas embolism is suspected [Rukstinat & LeCount 1928]. Wever only ever found gas bubbles in the blood vessels when the patient had suddenly collapsed and died [Wever 1914] (presumably death in these cases was due to CAGE of the brainstem). If the heart was beating for a few minutes after the collapse, in general, no bubbles could be found post-mortem [Wever 1914] suggesting that bubbles were able to pass from the arterial to the venous side of the circulation provided there was a driving pressure. Van Allen, Hrdina and Clark conducted experiments in 1929 in which they injected air into pulmonary veins and proposed that the presence of gas bubbles in the coronary and carotid arteries was itself harmful [Van Allen *et al* 1929].

Gas embolism has been extensively studied by the diving and hyperbaric community. Human exposure to compressed air was recorded as early as 332 BC. From the time of Alexander the Great (316-349 BC) there have been periodic reports of the use of open bottom bells from which divers could emerge for work on the shallow ocean floor. Decompression sickness was recognised as an occupational hazard for sponge divers in 1872 [Calder 1986]. However, a lack of understanding of the hyperbaric environment and the strong financial incentives for salvage of treasure and other artefacts from sunken ships encouraged divers to go deeper for longer probably resulting in many decompression accidents [Bond 1977]. The development of a satisfactory regulator for supply of breathing air under water by Rouquayrol in France in 1866, and the subsequent refinement and adaptation of this regulator to the 130 BAR air cylinders available by 1943 allowed Cousteau and Gagnan to popularise the *Self Contained Underwater Breathing Apparatus* (SCUBA). SCUBA diving techniques were improved by the demands of military combat during World War II and since 1947 SCUBA diving has become very popular as a recreational past time.

With the development in the 1840's of pressurised caissons for construction of bridge foundations and underwater tunnels, large numbers of workmen were exposed to hyperbaric environments. Decompression illness (then called caisson sickness) was common and many fatal accidents have been documented [Bond 1977].

With the steady increase in the scope and complexity of intrathoracic and vascular surgical procedures accidental entry of air into major tributaries of the circulation is not uncommon [Clayton *et al* 1985; Reyer & Kohl 1926; Spencer *et al* 1990]. Veins under negative pressure may entrain air or intra-arterial air may be introduced accidentally [Spencer *et al* 1990]. Even though ultrasonic

Doppler devices are used to detect intravascular gas during surgery they are often removed after surgery is complete but before the patient has recovered from anæsthesia. A patient who then suffers CAGE may remain in a coma or exhibit other symptoms which may then be treated inappropriately [Dutka 1985].

CAGE is associated with a significant morbidity and mortality [Gillen 1968]. Whereas the accepted immediate treatment is to increase ambient pressure and so reduce bubble volume, even compression to 6 BAR is frequently ineffectual. Experimental studies have suggested 2.8 BAR of O_2 is as effective as 6 BAR of air [Ah-See 1977a; McDermott *et al* 1992a]. Indeed a recent study has found no additional benefit in initiating treatment at 6 BAR even though O_2 partial pressures are higher than O_2 partial pressures at 2.8 BAR [McDermott *et al* 1992a] (suggesting that 2.8 BAR of pure O_2 is in some way an optimal dose of O_2). Even when treatment with 6 BAR air is started within 5 minutes of CAGE being diagnosed, 5% of patients may be expected to die and up to 30% do not respond to treatment [Ah-See 1977a; Brooks *et al* 1986]. These observations as well as a large number of clinical and experimental studies have suggested the ætiology of CAGE depends on more complex processes than the simple obstructive effects of intravascular bubbles.

1.3. THE CEREBRAL CIRCULATION - BASIC PHYSIOLOGY

The brain requires a constant supply of O_2 and glucose and also needs metabolic wastes such as CO_2 to be removed continuously [Losasso *et al* 1992; Roland 1985]. As regional neuronal activity waxes and wanes local *cerebral blood flow* (CBF) varies according to the minute-by-minute regional metabolic requirements [Ingvar & Schwartz 1974; Risberg & Ingvar 1973]. Peripheral tissues, such as muscle, have large effective reserves of O_2 in myoglobin, as well as the capacity for anærobic metabolism. Cerebral metabolism is, however,

almost completely ærobic, the cerebral tissues having little tolerance for metabolic wastes and almost no capacity for storing O_2 and other metabolic substrates. The strong coupling between regional brain metabolism and regional CBF is characteristic of the cerebral circulation whether brain activity is expressed as regional glucose utilisation [Ginsberg *et al* 1987; Kuschinsky *et al* 1981; McCulloch *et al* 1982a; McCulloch *et al* 1982b; Roland 1985] or electrical activity [Goadsby *et al* 1992]. Regional CBF is kept at adequate levels during variations in arterial blood pressure, blood gas concentrations, intracranial pressure and other influences by a complex series of mechanisms including those regulated locally and those controlled by the perivascular nerves [Armstead & Leffler 1992; Ganong 1989].

1.3.1. Cerebrovascular anatomy

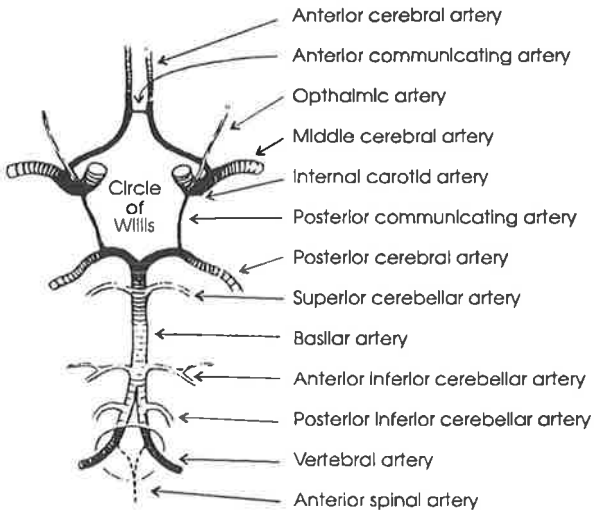
The principle arterial inflow to the brain in humans (and most mammals that have been studied) is *via* the internal carotid and the vertebral arteries. The vertebral arteries combine to form the basilar artery and the basilar and carotid arteries join at the Circle of Willis, the origin of the 6 arteries which supply the cerebral cortex. Arterial pressure on both sides of the Circle is usually the same and the anastomotic channels are small. Whereas it is generally believed there normally is little or no communication of blood from one side of the Circle to the other the anatomy of this arterial structure is very variable and it is possible it may in fact be an important anastomotic channel (see figure 1.1.).

The archicortex and paleocortex have a simple angioarchitecture while the vascularisation of the isocortex is more complex, each cell layer having its own blood supply (see figure 1.2). There are no (documented) arterial-arterial anastomoses within the parenchyma, although arterio-venous channels have been described [de Reuck 1972; Hasegawa *et al*

1967]. Short and medium length arteries supply cortical layers 1 to 4 with arterioles leaving the trunks at right angles. These vessels often form complex spirals which extend horizontally and vertically [Saunders & Bell 1971]. The arterioles have ring shaped compressions (possible sphincters) at the point where they branch to become capillaries [Nakai *et al* 1981]. Layers 5 and 6 of the cerebral cortex are supplied by long penetrating arterioles which terminate in a fan of vessels which turn upwards and form a characteristic *candelabra* [Rowbotham & Little 1963]. The white matter end zones are located just under the cortex at the level of the arcuate fibres and the periventricular white matter [de Reuck 1972].

The venous drainage of the cerebral hemispheres can be divided into an outer (superficial) segment and an inner (cerebral) segment. The cerebral segment, comprising the cerebral veins proper, carries blood away from the brain and empties it into the dural sinuses of the superficial segment. The cerebral segment can be further divided into superficial veins and deep cerebral veins. The superficial veins coalesce across the cerebral surface from where they carry blood away from the cortex and the subjacent white matter before emptying into the dural sinuses. The deep cerebral veins drain blood in a centripetal direction from the deep white matter, the basal ganglia and the diencephalon toward the lateral ventricles. The larger subependymal veins empty into the internal cerebral veins and the basal veins before joining to form the great cerebral vein of Galæn. The large veins which empty into the great vein are collectively referred to as the Galænic venous system and portions of this system are sometimes called the cisternal veins. Both the cerebral veins and the dural sinuses lack valves.

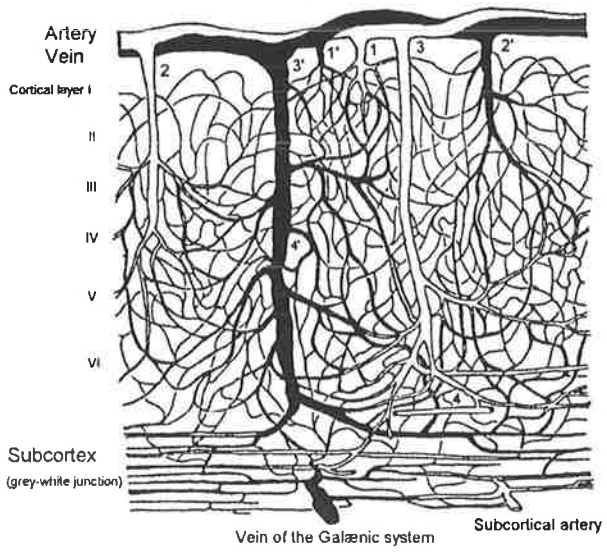
FIGURE 1.1. SCHEMATIC REPRESENTATION OF THE CIRCLE OF WILLIS



After Anderson [1978]

FIGURE 1.2. REPRESENTATION OF THE CEREBRAL CORTICAL MICROCIRCULATION

The microcirculatory system of the cerebral cortex showing short [1], middle [2] and long [3] penetrating arteries and short [1'], middle [2'] and long [3'] ascending veins. Arterial [4] and venular [4'] anastomosis have been identified. The subcortex drains into the *"Galænic"* venular system. (A more detailed description of the cortical microcirculation can be found in Capra & Kapp [1987] or Hasegawa *et al* [1967] from which this illustration was adapted.)



The walls of the cerebral veins are thin and lack the typical three layered tunic normally associated with vascular structures [Capra & Kapp 1987].

Tumour metastases and bacterial abscesses are commonly found at the grey-white junction suggesting that various kinds of emboli will preferentially trap where the vessels are of a similar diameter and branch often [Dutka *et al* 1988].

1.3.2. Cerebrovascular carbon dioxide reactivity

Arterial CO_2 (P_aCO_2) is a powerful vasodilator. Global CBF varies with P_aCO_2 in an approximately linear way when P_aCO_2 is between 20 and 60 mmHg. This effect is seen when the CBF change is expressed as a percent of baseline [Harper & Glass 1965; Griffiths 1973; Shapiro *et al* 1965] or as an absolute flow [Grubb *et al* 1974; Reivich *et al* 1969; Waltz 1970]. Below a P_aCO_2 of about 20 mmHg the cerebral vessels would be maximally constricted except that brain hypoxia then stimulates vasodilation, counteracting any further reduction in blood flow [Quint *et al* 1980; Weiss *et al* 1983]. At these low P_aCO_2 levels human subjects become drowsy, EEG slows and there is an accumulation of lactate in the cerebrospinal fluid, most likely due to tissue hypoxia [Granholm *et al* 1968]. At P_aCO_2 levels greater than 65 mmHg the cerebral vessels are maximally dilated. If the P_aCO_2 is held very high or very low for some hours (*viz;* at high altitude [Goldberg *et al* 1992], or during anæsthesia with controlled ventilation [Clivati *et al* 1992]) CBF returns to normal [Muizelaar *et al* 1988]. Reactivity to P_aCO_2 is also lower in states of depressed neuronal function such as during anæsthesia [Dubbink 1992]. Isolated cerebral vessels have also been shown to be sensitive to changes in CO_2 [Shalit *et al* 1967].

1.3.3. Cerebrovascular oxygen response

When P_aO_2 drops below 60 mmHg (viz; the O_2 saturation is less than 85%) the cerebral vessels dilate and CBF can increase by as much as 3 times normoxic levels [Aritake *et al* 1986; McDowall 1966; Shockley & LaManna 1988]. A high P_aO_2, achieved by breathing 100% O_2 at 1 BAR, induces mild cerebral vasoconstriction [Kety & Schmidt 1948; Kohshi *et al* 1991; Miller 1973; Torbati *et al* 1978]. At O_2 partial pressures of 1000 mmHg (achieved by breathing pure O_2 at 2 BAR) vasoconstriction produces a 25% drop in CBF [Jacobson *et al* 1963a]. At these higher O_2 partial pressures the O_2 concentration in plasma alone is approximately 3 mls of O_2/100 mls of blood and so the supply of O_2 to the brain is unchanged even though the cerebral vessels are constricted [Miller *et al* 1970]. At concentrations of O_2 above 2000 mmHg CO_2 accumulation may over-ride the ability of the cerebral vessels to constrict further [Bean 1961; Dise *et al* 1987; Kohshi *et al* 1991].

1.3.4. Cerebral perfusion pressure

Local cerebral perfusion pressure can be defined as arterial blood pressure minus venous blood pressure. The pressure difference is a function of the local cerebrovascular resistance which itself is a function of arteriolar and cerebral venous pressure [Baumbach & Heistad 1983; Jacobson *et al* 1963b; Kety *et al* 1948; Langfitt *et al* 1965a; Langfitt *et al* 1965b]. For practical purposes, perfusion pressure can be calculated as arterial pressure minus the measured intracranial pressure [North & Reilly 1990].

Since the cerebral veins hold the greater amount of blood in the calvarium [Capra & Kapp 1987] even small changes in cerebral venous tone may produce dramatic changes in cerebral volume and thus affect

cerebrovascular resistance and perfusion pressure [Ekstrom-Jodal 1970; Jacobson et al 1963b].

1.3.5. Capillary cycling or capillary recruitment?

In brain, the density of perfused capillaries correlates well with CBF (r = 0.93) and with local cerebral glucose utilisation (r = 0.97) [Klein *et al* 1986]. The lowest density of perfused capillaries is found in the white matter and the highest in the inferior colliculus [Klein *et al* 1986], suggesting the density of capillaries depends on local functional demands.

1.3.5.1. Capillary cycling

The observation that capillaries in peripheral tissues can open and close with changes in metabolism [Sweeney & Sarelius 1989] has led to speculation that the cerebral circulation behaves in a similar way. Some workers have suggested that less than 100% of the cerebral capillaries are actively perfused tissue at any one time [Shockley & LaManna 1988] and that the total number of these perfused capillaries can be shown to vary when either CBF or cerebral blood volume changes [Shockley & LaManna 1988].

1.3.5.2. Capillary recruitment

On the other hand, all cerebral capillaries may be actively perfused (see figure 1.3). Flow rate would then be heterogenous with respect to erythrocyte flow [Gobel *et al* 1989]. The capillary diffusion capacity depends on, among other things, the available capillary surface area which would increase with recruitment of capillaries. In the case of capillary perfusion heterogeneity, the capillary diffusion capacity could only be increased by

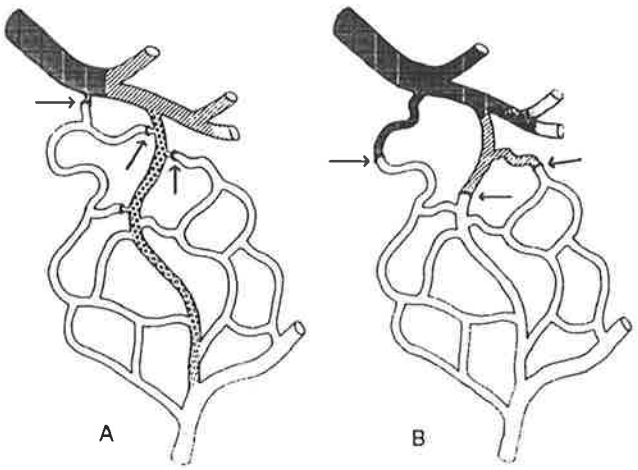
"homogenisation of the perfusion rate", slowly perfused capillaries becoming faster perfused [Kuschinsky 1992].

FIGURE 1.3. REPRESENTATION OF CAPILLARY PERFUSION

A. Capillary recruitment. The mainstream of capillary blood flow take place through a thoroughfare channel.

B. Capillary cycling. Pre-capillary sphincters separate terminal arterioles from capillaries. Different parts of the capillary net are subject to varying rates of perfusion, but all capillaries are perfused at any one time.

Pre-capillary sphincters are indicated by black arrows. The shaded portion represents arteriolar inflow with venous outflow to the bottom of the picture.
Figure after Hammersen & Hammersen [1984].



1.3.5.3. Embolism and capillary cycling or recruitment

Swelling of endothelial microvilli [Dietrich *et al* 1984], and leukocyte [Yamakawa *et al* 1987] or platelet-induced plugging of capillaries [Turcani *et al* 1988] can impair capillary perfusion. Air emboli might be expected to enter only part of a regional vascular bed (in the case of capillary recruitment) or nearly all of a regional vascular bed in the case of capillary cycling. If capillaries were

being recruited, some parts of the capillary bed would be spared (until they were recruited) whereas if capillaries were being cycled, all capillaries at the end of an embolised arteriole might be embolised. If regulation of flow through the cerebral micro-circulation is different from the extracerebral circulation then care must be taken comparing data from intravital preparations such as the hamster cheek pouch used to study arterial gas embolism [Lynch *et al* 1985] and cerebral (or indeed spinal) arterial gas embolism.

1.3.6. Neural mechanisms of CBF regulation

The role of neuronal mechanisms in the regulation of CBF is still controversial even though it is known that the cerebral circulation is supplied with at least two vasodilator systems. The parasympathetic system stores and releases vasoactive intestinal polypeptide, histidine isoleucine, acetylcholine and in a subpopulation of nerves, neuro-peptide Y [Edvinsson 1991]. The sensory system, mainly originating in the trigeminal ganglion, stores and releases substance P, neurokinin A and calcitonin gene related peptide (CGRP). Recent knowledge of the innervation and effects of the dilator neuropeptides in the cerebral circulation has been reviewed by Edvinsson [1991].

1.3.7. The blood-brain barrier

The existence of a *"barrier"* for molecules between blood and brain has been known since early works by Ehrlich [1885]. The blood-brain barrier is comprised of the vascular endothelial cells [Lefauconnier & Hauw 1984; Janzer 1993] and possibly their surfactant coating [Hills 1989a; Hills 1989b; Hills & James 1991]. The cerebrovascular endothelial cells are characterised by tight cell-cell junctions and transport enzymes,

carrier systems, and other enzymes which obstruct the passage of various substances from the circulation to the brain [Evans & Schulemann 1914; Janzer 1993]. The properties of the blood-brain barrier are not intrinsic to the endothelial cells but appear to be induced by factors secreted by the adjacent astrocytic end-feet [Janzer 1993]. Indeed, for many years it was believed the astrocytic end feet were the blood-brain barrier (see figure 1.4).

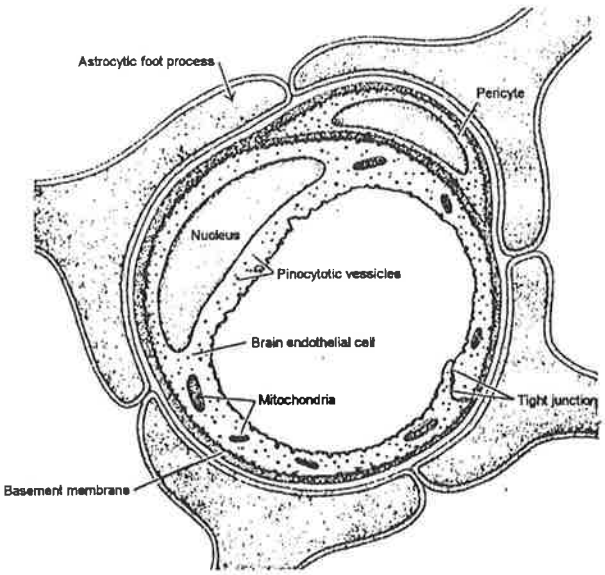
Enzymes contained in the endothelial cells appear to be differentially distributed [Hardebo & Owman 1984]. Cytochemical and biochemical studies have shown that alkaline phosphatase and γ-glutamyl transpeptidase are located in both the luminal and antiluminal cytoplasmic membranes of the brain capillary endothelial cells. On the other hand, K^+-dependent phosphatase activity (associated with Na^+, K^+-ATPase) and 5'-nucleotidase are located only on the antiluminal surface. Thus the luminal and anti-luminal membranes of brain capillaries are biochemically and functionally different [Betz *et al* 1980].

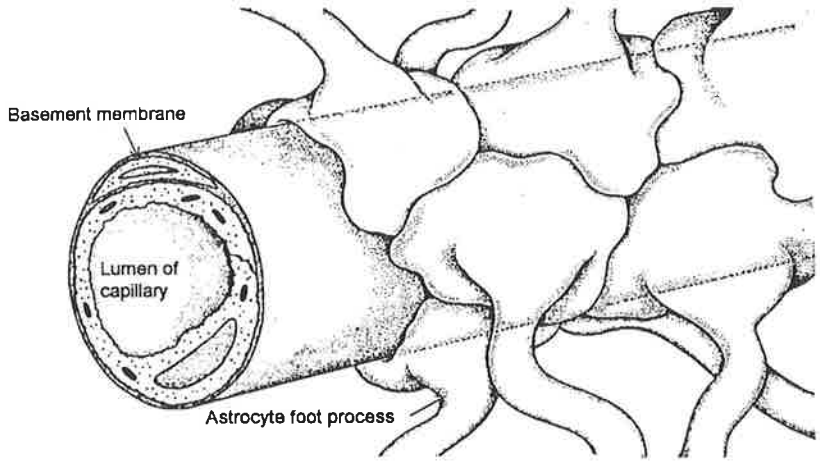
1.3.8. Role of the vascular endothelium in the regulation of CBF

Vascular endothelial cells line blood vessels. The endothelium is closely associated with apposed astrocyte end-feet, is metabolically active and comprises the functional site of the blood-brain barrier (see figure 1.4). Pressure autoregulation is thought to be mediated by the vascular endothelium of arterioles [Hishikawa *et al* 1992; Harrison *et al* 1992; Willette & Sauermelch 1990] and it also likely the cerebrovascular response to CO_2 is ultimately due to release of endothelium-derived relaxing factor (EDRF) [which is probably nitric oxide (NO)] from the vascular endothelial cells [Iadecola 1992; Goadsby *et al* 1992].

FIGURE 1.4. ASTROCYTES AND END-FEET

Astrocyte end-feet almost completely surround the brain capillary and it was previously believed the blood-brain barrier was formed by their close apposition. It is now accepted that the endothelial cells comprise the blood-brain barrier and various substances which mediate its function originate form the astrocytes. The basement membrane holds the endothelial cells together and helps maintain the tubular form. After Goldstein & Betz [1986].





The principle site of EDRF production is most likely the endothelial cells [Rosenblum 1986; Rosenblum *et al* 1987] but astrocytic end feet [Murphy *et al* 1990] and possibly neurones [Garthwaite *et al* 1988; Toda & Okamura 1991] may also contribute. An inhibitor of EDRF synthesis N^{ω}-nitro-L-arginine (L-NA) almost abolishes the CBF response to hypercarbia [Iadecola 1992] and to spreading depression [Goadsby *et al* 1992]. This observation was not expected since it has previously been argued that the CBF response to hypercarbia results from a direct vascular effect of H^+ ions causing smooth muscle hyperpolarisation [Busija & Heistad 1984; Heistad & Marcus 1980; Jiffry 1979].

Endothelial cells also mediate vasoconstriction by releasing endothelin, a 23 amino acid peptide [Haynes & Webb 1992]. Perivascular application of endothelin in doses of 10^{-5} M can produce reductions in CBF lasting up to 60 minutes which are severe enough to produce ischæmic neuronal damage in anaesthetised rats [MacRae *et al* 1993].

Thus, damage to the vascular endothelium might be expected to disturb both the normal regulation of CBF and the function of the blood-brain barrier.

1.3.9. Cortical-somatosensory evoked responses

Evoked responses have been used to assess central nervous system function in a variety of clinical and experimental situations [Desmedt *et al* 1990; Grundy 1990]. Activation of the sensory pathways by an electrical stimulus results in a complex pattern of inputs to central structures, the signal being transmitted by peripheral nerves, plexuses, nerve roots, dorsal columns of the spinal cord, the lemniscal pathways to the thalamus and ultimately to the primary sensory area of the contra-lateral cerebral cortex [Cohen *et al* 1981; Dimitrijevic *et al* 1978]. In the

experimental laboratory this is usually effected by electrical stimulation of pure sensory or mixed nerves and the signal recorded from the scalp or brain surface Such a signal is called a *cortical-somatosensory evoked response* (CSER) [Chiappa & Ropper 1982a; Chiappa & Roper 1982b; Grundy 1990].

Evoked potentials can be classed as *"near-field"* or *"far-field"*. Far field potentials arise in structures more than a few centimetres from the recording electrode. Stimulation voltage amplitudes are generally less than 1 mVolt with the rate of stimulation typically being 4 to 30 Hz (*viz;* 250 to 33 msec between stimuli). A negative wave seen over the specific sensory cortex contralateral to the side of the stimulation occurs approximately 20 msec after median nerve stimulation [Allison *et al* 1980]. This wave is though to originate in the thalamus or from the thalamocortical radiations [Chiappa *et al* 1980]. A preceding positive wave 13 to 17 msec after the stimulation is thought to originate in sub-cortical structures [Desmedt & Brunko 1980; Mauguiere & Courjon 1981]. (Figure 2.4 shows a CSER from a rabbit after forepaw stimulation.)

Abnormal body temperature, hypoxia or abnormal P_aCO_2 levels can affect CSER [Browning *et al* 1992; Nakagawa *et al* 1984]. Pathological changes at any point along the conducting pathway from the site of stimulation to the specific somatosensory cortex can affect either the latency or the amplitude of the evoked response [Cusick *et al* 1979; Desmedt & Noel 1973; Dorfman *et al* 1980; Hattori *et al* 1979]. Localisation of a lesion is often possible if early peaks are present and stable and late peaks are absent or visibly abnormal [Glover *et al* 1981; Jones 1979; Noel & Desmedt 1980; Williamson *et al* 1970].

Several studies have demonstrated a close relationship between regional CBF and CSER stimulation [Foit *et al* 1980; Leniger-Follert & Hossmann 1979]. Measurement of CSER is particularly useful as an index of brain function in which there are subtle, sublethal or potentially lethal effects on the brain circulation such as may occur during transient [Branston *et al* 1974; Mizoi *et al* 1987], partial [Graf *et al* 1986; Iwayama *et al* 1986; Kaplan *et al* 1987; Loftus *et al* 1987a] or total ischæmia [Bo *et al* 1987; Coyer *et al* 1987a; Coyer *et al* 1987b; Koga *et al* 1988]

Although CSER is only measuring functional integrity of the somatosensory system, it is often used as a monitor of general central nervous system integrity during surgical procedures which involve the cerebral circulation [Amantini *et al* 1992; Colon *et al* 1985; Loftus *et al* 1987b] as well as during studies of cerebral hypoxia [Coyer *et al* 1988; Iwayama *et al* 1986; McPherson *et al* 1986] and of CAGE [Dutka *et al* 1992a; Evans *et al* 1989; Francis *et al* 1988; Francis *et al* 1990; Leitch & Hallenbeck 1984; McDermott *et al* 1992b; Yiannikas & Beran 1988].

1.4. CAUSES OF GAS EMBOLISM

Because gas emboli are not normally found in the circulation, they must originate from somewhere. Once in the circulation, it is widely held that gas bubbles exert their effects by blocking arterioles and so there is considerable interest in whether gas embolism is arterial or venous in origin and to what extent venous gas may become arterial gas (so called "*paradoxical embolism*"). The amount of gas in the circulation as well as factors which change right to left atrial pressures can affect the progress of gas embolism. According to this mechanistic view, the three main causes of gas embolism can be classified as dysbaric, iatrogenic or traumatic.

1.4.1. Dysbaric causes of arterial gas embolism

Dysbaric gas embolism can be caused by over inflation and tearing of gas filled body spaces (particularly the lungs), allowing gas to directly enter the circulation or else by formation of bubbles from dissolved gas during decompression such as may occur after SCUBA diving, æroplane or space flight. Early classifications of gas embolism or decompression sickness were based on symptoms rather than ætiology. More recently it has been recognised that many of the symptoms produced by a dysbaric episode can be due to venous as well as arterial gas embolism [Francis 1990]. Even in the absence of a substantial inert gas load intravascular bubbles can form during sudden decompression. During submarine escape training intravenous or intra-arterial air bubbles have been detected using ultrasonic pre-cordial Doppler monitoring [Ornhagen *et al* 1988]. The various classifications of decompression sickness have been reviewed and a reclassification based on a descriptive terminology has been proposed [Francis & Smith 1991] (see APPENDIX D for more details of this classification). Previously, gas embolism and decompression sickness were treated as separate disorders. Decompression sickness itself was classified as type I (moderate) or type II (severe) and a further category of combined decompression sickness and CAGE called type III has also been suggested [Neuman & Bove 1987]. The classification of decompression sickness as type I or type II is arbitrary and symptoms may overlap. Furthermore, because the treatment for decompression sickness type II and III and for CAGE is the same, the value of this classification is questionable.

1.4.1.1. Decompression illness

Gases dissolve in body fluids and tissues in direct proportion to their pressure. For example, at a depth of 40 metres of seawater,

the blood stream can absorb up to five times the volume of nitrogen that it can at the surface. Body tissues will equilibrate with breathing gas according to a time dependent formula [Bayne & Wurzbacher 1982] but if a diver or aviator ascends too rapidly to lower ambient pressure, gas bubbles form. These bubbles may form in tissue directly (autochthonous bubbles), may form in the venous circulation and subsequently arterialise, or under rapid decompression may even form in the arterial circulation [Ornhagen *et al* 1988]. Divers typically exhibit clinical symptoms fifteen minutes to one hour after the returning to the surface although in some instances symptoms may not be conspicuous for up to 6 hours [Spencer *et al* 1969; Vann *et al* 1982]. The most common manifestations are pain in the limbs, dizziness and paresis. Dyspnoea, collapse and unconsciousness are less common but more serious. Both intravascular bubbles and autochthonous bubble formation in tissues are probably involved in the manifestations of DCI [Francis 1990]. The conventional view is that the severity of the symptoms depends on the volume of gas liberated and the site of its liberation. However there is not universal agreement. The spinal cord, which has a low blood flow, is often severely affected by DCI while more highly perfused tissues may not be [Francis 1990]. It has been suggested that autochthonous bubble formation is possibly more important in the spinal cord than in other parts of the body [Francis 1990].

1.4.1.2. Decompression schedules

In order to avoid DCI, divers normally surface at a rate which minimises bubble formation. The ascent may be interrupted with "*decompression stops*" in order to allow additional time for

dissolved inert gas to escape from the body and to minimise the rate of growth of any bubbles which may have already formed. Divers often refer to one of the many "*decompression tables*" to determine the decompression required for any particular dive. This will depend on the duration of the dive, the depths attained, the time elapsed since the last dive and several other factors. More recently, "*decompression computers*", which are worn on the diver's wrist, are being used. These log the actual duration at each depth and are considered by many to be a more accurate way of determining the decompression required [Volm 1989]. Both the decompression tables and decompression computers calculate the decompression needed according to mathematical models, most of which are based on the original work by Boycott, Damant and Haldane [1908]. Further empirical modification of the calculated tables is often incorporated into the schedule in order to provide a safety factor and to account for variations in diver fitness and physique [Imbert & Fructus 1989].

In accordance with the view that bubbles mediate DCI the ideal decompression rate for divers and aviators must be the one that creates the maximum gradient for inert gas elimination without causing physiologically significant bubbling [Hills 1977]. However, the conditions under which bubbles form during decompression of divers is not known. That bubbles form in blood vessels during decompression even after very short exposures to pressure, has been established in animal models [Evans & Walder 1969; Gillis *et al* 1968b; Powell 1974; Spencer & Campbell 1968; Spencer *et al* 1969] and in human studies [Bayne *et al* 1985; Eatock & Nishi 1987; Evans *et al* 1972; Gardette 1979;

Neuman *et al* 1976; Nashimoto & Gotoh 1976; Ornhagen *et al* 1988; Powell & Johanson 1978; Spencer 1976] where bubbles were detected using ultrasound.

Decompression illness is frequently seen after multiple dives [Gorman *et al* 1988]. This may be due to a build up of pre-existing gas bubbles in the circulation interfering with gas elimination gradients [Hills 1977; Hills 1978; Kindwall *et al* 1975]. Alternatively, bubbles formed in the veins may be trapped in the pulmonary vascular bed whereupon subsequent recompression (during the next dive) makes the bubbles small enough to escape from the pulmonary circulation. This cycle of compression-decompression increases the amount of circulating gas to symptomatic levels. Some professional diving operations conduct decompression in a dry chamber above the surface. The diver must surface before being transferred to a chamber for immediate recompression followed by decompression back to the surface. Such "*surface decompression*" procedures increase the likelihood and severity of DCI [Gorman *et al* 1988] and probably constitute treatment of DCI which has not had time to exhibit symptoms.

There are considerable disparities between thermodynamic predictions and the observed occurrence of bubbles during decompression [Weathersby *et al* 1982]. Attempts to resolve these discrepancies have centred on looking for ways in which the energy required for a bubble to form may be reduced (*viz;* bubble nuclei and surface defect theories) [Evans & Walder 1969; Hills 1977; Vann *et al* 1980]. The uptake and elimination of an inert gas during and after hyperbaric exposure is influenced by tissue perfusion and the solubilities and diffusion coefficients of the

gases present [Hills 1977]. Gas elimination is much slower than uptake for unknown reasons [Hempleman 1969; Reid *et al* 1991] and is even slower still if bubbles continue to form [Hills 1978; Kindwall *et al* 1975].

1.4.1.3. Gas gradients

Bubbles will grow or shrink in the presence of gas concentration gradients. For example, it has been shown bubbles can form in the absence of decompression when the inert gas being used to dilute O_2 is changed [Lambertsen & Idicula 1975]. However, because gas flux in and out of tissues (and bubbles) depends on the diffusion and solubility coefficients of the gas in the bubble, the effect on bubble volume *in vivo* can be controlled to some extent by which inert gas is used.

Munson and Merrick have shown that an anæsthetic mixture containing 50:50 N_2O:O_2 can double intravascular bubble volume and a 70:30 N_2O:O_2 mixture can produce an approximately three fold increase in bubble size [Munson & Merrick 1966]. Intravascular bubbles of inert gas can also undergo a transient increase in size during hyperbaric O_2 therapy. Bubbles produced in rat adipose tissue by decompression grow continuously larger if untreated [Hyldegaard & Madsen 1989]. During breathing of pure O_2 these bubbles may grow slightly before shrinking or may not shrink at all initially. They will shrink and eventually disappear from view during 80:20 He:O_2 (HELIOX) breathing although if the breathing gas is changed from 80:20 He:O_2 back to air or to 80:20 N_2O:O_2 the bubbles grow again [Hyldegaard & Madsen 1989].

1.4.1.4. Limb bends

Symptoms ranging from severe aching pain to "*niggles*" can occur in the joints, immediately or several hours after a dysbaric exposure. There is considerable variation as to the susceptibility of people and experimental animals to limb bends and the sources of this variability have been variously ascribed to age [Edmonds *et al* 1992; Hills 1977], temperature [Mano 1987; Mekjavic & Kakitsuba 1989], exercise [Krutz & Dixon 1987; Jauchem 1988], acclimatisation to repeat hyperbaric exposure [Hills 1969], sex [Zwingelberg *et al* 1987] and obesity [Gray 1951; Lam & Yau 1989]. Although no lesion has yet been identified in either animals or man it is possible that autochthonous bubbles cause limb pain after decompression by direct compression of sensory nerve roots.

1.4.1.5. Decompression "*folklore*"

The probability of decompression disease increases with increasing diver age, tissue inert gas tensions, adiposity (for fat soluble inert gases such as nitrogen), dehydration, hæmoconcentration and exercise [Gray 1951]. Although some authors have reported that being female is a risk factor for DCI [Robertson 1992] there is no compelling evidence to suggest women are at a higher risk than men [Zwingelberg *et al* 1987]. Similarly alcohol is though by some clinicians to predispose an individual to DCI because it is a diuretic and causes hæmoconcentration [Lampl *et al* 1989; Levin *et al* 1981; Webb *et al* 1988]. However, treatment of DCI with alcohol has been advocated by some because it will lower blood viscosity at the level of the microcirculation by

inhibiting platelet aggregation as well as increasing dissolved blood nitrogen content [Zhang *et al* 1989].

There is anecdotal evidence that repeated compressed air diving can lead to an increased tolerance to DCI [Walder 1968]. Whereas it has been postulated that exhaustion of bubble nuclei may account for this apparent acclimatisation or adaptation it seems more probable there is an altered sensitivity to the pathological effects initiated by intravascular bubbles. For example, the unexpected occurrence of DCI in a diver after a previously innocent dive and acclimatisation may simply be due to normal variations in complement activity [Ward *et al* 1986; Ward *et al* 1990] or other vessel related phenomena which may be activated by presentation with a hydrophobic surface such as a bubble.

1.4.1.6. Decompression illness and *"silent bubbles"*

Some of the more non-specific symptoms of DCI (fatigue, malaise and headache) are often reported by divers (or hyperbaric chamber personnel) who have performed a dive profile within accepted no-decompression limits. The incidence of this sub-clinical disease is unknown but has given rise to the concept of *"silent bubbles"*. Eckenhoff *et al* dived subjects to 8 metres for 48 hours (a comparatively shallow depth, but extended period) and produced no decompression disease, but was able to detect venous gas bubbles with an ultrasonic Doppler device [Eckenhoff *et al* 1986] suggesting that asymptomatic bubbles may occur more often than is commonly believed. The conventional view is that these *"silent bubbles"* trap in the pulmonary capillaries [Butler & Hills 1979; Butler & Hills 1985] where they cause moderate increases in pulmonary artery and right heart pressure which may

then increase the number of bubbles passing through the pulmonary capillaries to the pulmonary veins. Bubbles may also proceed to the arterial circulation from the right heart to the left heart when the right to left pressure gradient is high enough to open a patent foramen ovale or other septal defect [Butler & Hills 1985; Butler & Katz 1988; Moon *et al* 1989]. On the other hand resistant subjects may simply be insensitive to the small number of bubbles produced during these mildly provocative dives.

1.4.1.7. Spinal cord decompression sickness

Spinal cord decompression sickness (not illness) is different from cerebral DCI and CAGE. The unique pathophysiology of spinal decompression sickness has prompted some investigators to devote special energy to understanding its mechanisms and these will only be considered briefly here.

For many years it has been widely held that spinal cord decompression sickness was part of a general category of so called type II (neurological) decompression sickness and was caused by bubbles blocking the spinal cord circulation. However, spinal symptoms exceed cerebral symptoms by a factor of approximately 3 [Hallenbeck *et al* 1975]. This is in spite of the much higher flow of blood to the brain [Kety 1991] which might be expected to carry more bubbles to the brain than to the spinal cord. Furthermore in well established blood-borne embolic diseases (such as fat embolism) the brain is the major target [Blackwood 1958]. Various explanations for this paradox have been offered but Hills has recently proposed that an embolic mechanism is not important in spinal decompression sickness because it is repeatedly pressure reversible, symptoms recurring with decompression [Hills 1993]

implying the bubbles causing spinal cord DCI are stationary in the cord tissue. Furthermore Hills has demonstrated that the spinal cord may be more susceptible to extravascular autochthonous bubble formation [Hills 1993] possibly due to a larger proportion of lamellar bodies which act as nuclei for bubble formation in the cord parenchyma. Interestingly, lamellar bodies found in brain tend to be intravascular rather than intraparenchymal [Hills 1993]. The presence of these putative bubble nuclei in the brain blood vessels may promote formation of intravascular bubbles in the brain blood vessels during decompression.

1.4.1.8. Barotrauma

Polak and Tibbals described what they called *"barotraumatic CAGE"* in 1930 [Polak & Tibbals 1930]. By 1932 Polak and Adams had detailed the clinical consequences of pulmonary over-inflation leading to arterial gas embolism in 10 cases [Polak & Adams 1932]. Moderate over-inflation of the lungs, produced by failing to (or being unable to) exhale during reductions in ambient pressure can result in arterialisation of air. This can occur during ascent from depth after compressed air diving [Dick & Massey 1985; Wachholz 1985; Williamson *et al* 1990] or during submarine escape training [Gillen 1968; Liebow *et al* 1959]. Even ascent from shallow depths (3 to 4 metres) may provide sufficient changes in pressure to produce arterialisation of air. Similar pressure changes can occur when flying unpressurised high performance aircraft to high altitude or during sudden decompression of a pressurised commercial passenger aircraft [Neubauer *et al* 1988].

When the transpulmonary pressure gradient exceeds 50 mmHg normal alveoli can rupture and air can escape into the pulmonary

interstitium, the pleural space or the pulmonary veins [Calverley *et al* 1971]. Air liberated into the pulmonary interstitium can track along the perivascular sheaths and cause mediastinal emphysema while air in the pleural space produces a pneumothorax. Areas of partial bronchial obstruction can act like one way valves and so produce areas of segmental pulmonary hyperinflation which may continue to force air into the circulation with each breath [Liebow *et al* 1959].

1.4.1.9. Submarine escape training

Submarine escape training is a military training exercise in which participants are rapidly compressed to approximately 4 BAR before passing through an air lock and entering the bottom of a water column 30 meters deep. The subject then surfaces rapidly, exhaling continuously to prevent pulmonary barotrauma. Among Navy submarine escape trainees, CAGE occurs in approximately 1:10,000 submarine escape training ascents with 5 to 15% of those accidents being fatal [Ah-See 1977b; Gillen 1968; Kinsey 1954; Liebow *et al* 1959]. Because the subjects are compressed for only a few minutes before being rapidly decompressed it is commonly believed that there is no risk of DCI. Whereas air is thought to enter the circulation due to pulmonary hyperinflation in those divers who suffer fatal CAGE after submarine escape training [Liebow *et al* 1959] the incidence of pulmonary hyperinflation in those submariners suffering non-fatal CAGE is not known [Ingvar *et al* 1973]. Ornhagen *et al* have challenged this view, and have shown significant amounts of nitrogen can dissolve in the circulation during the brief compression cycle required to enter the air lock and can form arterial bubbles during the rapid ascent,

the rates of which far exceed those considered acceptable for SCUBA divers [Ornhagen *et al* 1988]. Thus it is possible that those submariners who suffer symptoms of CAGE may do so because of intravascular formation of bubbles.

1.4.2. Iatrogenic causes of gas embolism

Almost any surgical procedure (or trauma) in which the wound is above the level of the heart can lead to air entrainment into open veins [Clayton *et al* 1985].

The sitting position is preferred for some neurosurgical procedures because of good surgical access and improved venous drainage. [Clayton *et al* 1985; Zentner *et al* 1991]. Unfortunately the dura and cranial vault can hold negatively pressurised veins open and so allow air to be aspirated into the diploic venous plexus, suboccipital venous plexus, occipital emissary veins or dural sinuses. Venous gas embolism during neurosurgical procedures (detected by Doppler ultrasound and air aspiration from a right atrial catheter) was observed in 25% (100 of 400) patients in the sitting position, 8% [5 of 60] patients in the lateral position 14% [7 of 48] patients in the supine position, and only 10% [1 of 10] individuals monitored in the prone position [Albin *et al* 1978]. To reduce the chance of air entering the venous circulation in this way, venous pressure can be raised, either by use of an *"anti-gravity"* suit [Tinker & Vandam 1972], compression of the neck [Tausk & Miller 1983], leg banding [Albin *et al* 1976; Geevarghese 1977] or intravenous fluid loading [Colohan *et al* 1985]. Moderate hypoventilation for the period of time the veins are actually open, followed by normoventilation has been recommended by some authors [Zentner *et al* 1991].

Muraoka *et al* showed by pre- and post-operative computed tomography of the brain that even after uneventful cardiac operations, subclinical changes in brain morphology are apparent [Muraoka *et al* 1981]. They suggested that the membrane oxygenator used caused microembolisation of fat or silicon particles, or caused cerebral hypoxia due to inadequate perfusion [Heller *et al* 1970].

1.4.3. Traumatic causes of gas embolism

Gas embolism due to trauma can be arterial or venous and a patient may be subject to paradoxical gas embolism if a patent foramen ovale is present or if the lungs are injured. Systemic arterial gas embolism is frequently unrecognised as a cause of death among patients with isolated penetrating lung injury caused by gunshot or stabbing [Estrera *et al* 1990; Halpern *et al* 1983]. Barotrauma can be produced by mechanical ventilation if pressures exceed the tensile strength of the alveolar membrane, causing air to be pushed through the membrane into the pulmonary veins [Kane *et al* 1988].

If recognised early, traumatic gas embolism responds well to conventional hyperbaric and pharmacological treatment [Halpern *et al* 1983].

1.5. CLASSIFICATION OF GAS EMBOLISM

Bubbles can enter the arteries or veins directly (iatrogenic gas embolism or pulmonary barotrauma) or form in arteries or veins as gas comes out of solution during a reduction in ambient pressure (DCI). Systemic venous gas may shunt into the arterial circulation *via* a patent foramen ovale or pass through the pulmonary capillary bed into the arterial circulation (see below). The term

"*paradoxical embolism*" is used when there is evidence of venous gas embolism but symptoms of arterial gas embolism.

1.5.1. Arterial gas embolism

Air can enter the arterial system directly because of accidents with indwelling arterial catheters or during vascular, cardiac or neurosurgery Alternatively, venous air can be shunted from the right heart through a patent foramen ovale (see below) or ductus arteriosus or may pass through the pulmonary circulation.

It has generally been thought that bubbles do not form *de novo* in arterial blood, because blood leaving the lungs is essentially in equilibrium with alveolar gas [Lynch *et al* 1985]. However, bubbling in arteries has been detected after rapid decompression, such as may occur during submarine escape training [Ornhagen *et al* 1988]. A number of submarine escape trainees have developed disordered brain function in the absence of pulmonary barotrauma [Gorman 1984; Gorman 1987a] further validating Ornhagen's data.

Arterial bubbles in SCUBA divers probably arise secondarily from the arterialisation of venous bubbles if an appropriate decompression schedule is not observed. During a normal ascent the rate of change of pressure is slow enough for blood leaving the lungs to be in equilibrium with alveolar gas and so bubbles do not form [Lynch *et al* 1985].

1.5.2. Venous gas embolism

Air can enter the venous circulation directly (*via* indwelling venous catheters or during vascular, cardiac or neurosurgery) or form during decompression after diving.

During decompression, inert gas supersaturation will occur first in tissues and then in veins, so any bubbles which form will be detected in the veins before the arteries [Buckles 1968; Hills 1977]. Venous air proceeds to the right heart and then to the lungs where a certain amount will trap producing acute pulmonary hypertension. If air is in sufficient quantity the right heart may become air filled, although this tends to occur only if there is coronary artery gas embolism [Clayton *et al* 1985; Geoghegan & Lom 1953].

The venous circulation can tolerate relatively large doses of air if the air is injected or produced slowly [Butler & Hills 1985; Durant *et al* 1947; Hare 1902; Van Allen *et al* 1929]. The pulmonary circulation has a capacity to filter venous air bubbles which is dependent on both the rate and total amount of gas delivered to it [Butler & Hills 1985]. Trans-pulmonary passage of bubbles is increased by O_2 toxicity, the use of bronchodilators or by compression of bubbles during recompression treatment or multiple dysbaric exposures [Butler & Hills 1981; Butler & Hills 1985; Butler & Katz 1988]. Venous bubbles returning to the right heart can be detected using an ultrasonic Doppler device [Bayne & Wurzbacher 1982; Spencer *et al* 1969; Vann *et al* 1982].

Bubbles which have crossed the pulmonary circulation may become stabilised by being coated with pulmonary surfactants such as di-palmitoyl lecithin [Hills 1985], phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, and lysophosphatidylcholine [Hills *et al* 1985]. Such bubbles may provide a comparatively stable reservoir of circulating gas bubbles in the body [Hills & Barrow 1982; Butler & Hills 1979].

1.5.3. Paradoxical gas embolism

Paradoxical gas embolism is said to occur when there is evidence of gas in the arterial circulation which must have orginiated from the venous circulation. The amount of air which can arterialise is affected by a variety of factors.

1.5.3.1. The patent foramen ovale

As early as 1930 Thompson and Evans suggested that gas emboli could pass into the arterial circulation *via* a patent foramen ovale [Thompson & Evans 1930] which is one of several types of atrial septal defect. These defects can be classified as either valvular competent (patent foramen ovale), an atrial septal defect or as a large communication between the coronary sinus and the left atrium (not a true atrial septal defect) [Edwards 1960]. In 20 to 25% of normal human hearts it is possible to pass a probe from the right to the left atrium [Patten 1938; Scammon & Norris 1918; Wright *et al* 1948] even though no functional inter-atrial communication can be demonstrated under normal conditions. A foramen ovale that is functionally closed by a competent valve which prevents blood flowing from the left to the right atrium has been called a *"probe patent foramen ovale"* [Patten 1931] or a *"valvular-competent, patent foramen ovale"* [Kirklin *et al* 1955; Weidman *et al* 1957]. This condition should be considered a variant of the normal because of its frequency and because the vestigial channel remains closed except when there is a left to right atrial pressure gradient [Edwards 1960].

Right to left shunting may occur during pulmonary hypertension (secondary, for example, to venous gas embolism [Butler & Hills

1985]). Transient reversal of the left to right atrial pressure gradient during a portion of each cardiac cycle can be demonstrated in pigs [Black *et al* 1989]. Furthermore, studies which have examined the effects of ventilation on paradoxical gas embolism showed no difference during intermittent positive pressure ventilation, intermittent positive pressure ventilation with positive end-expiratory pressure or spontaneous ventilation [Black *et al* 1989].

1.5.3.2. The Valsalva manœuvre

The Valsalva manœuvre (achieved by expiration against a closed glottis) increases venous pressure and may be used as a provocative procedure to facilitate demonstration of right-to-left shunting [Black *et al* 1990]. Paradoxical gas embolism has been reported in a patient given repeated Valsalva manœuvres during the course of neurosurgery in the sitting position [Albin 1984].

1.5.3.3. Foramen ovale and diving

The presence of a right-to-left inter-atrial shunt has been considered a possible risk factor for the development of DCI in SCUBA divers. This idea is based on the view that venous bubbles are not harmful, since they are removed in the lungs before they arterialise. Divers with a patent foramen ovale may shunt venous air into the arterial circulation which could cause CAGE.

Moon *et al* reported that 37% [11 of 30] divers with a history of decompression sickness exhibited right-to-left shunting through a patent foramen ovale. Of those with serious symptoms and signs 61 % [11 of 18] exhibited shunting whereas only 5% [9 of 176] of the healthy volunteer control group showed any sign of shunting

during normal breathing. Whether or not these data are statistically significant is not clear since the expected count in one or more cells is less than 5 for this data set. However, these authors report a $p < 0.01$, $Chi^2 = 49.5$ Chi^2. Ten subjects exhibited right-to-left shunting during a Valsalva manœuvre (during which the right-left pressure gradient favours shunting of gas through the foramen ovale) [Moon *et al* 1989]. Another study later in the same year by Wilmshurst *et al* [1989] repeated the work of Moon *et al* [1989] but used unaffected divers as a control group (rather than volunteers) reporting that only 17% [4 of 24] of divers who developed symptoms more than 30 minutes after surfacing had inter-atrial shunts [Wilmshurst *et al* 1989]. Cross *et al* [1992] recently published a study in which SCUBA divers who had never exhibited symptoms of decompression sickness were examined by contrast echocardiography. They found that 30% [24 of 78] of these divers had patent foramen ovale.

Only about 300 episodes of neurological DCI are reported in Australia annually from an active diving population of more than 400,000 and yet between 15 and 30% (60,000 to 120,000) of this population would be expected to have a patent foramen ovale [Hagen *et al* 1984]. The microbubbles injected into the circulation to help to identify any left-right shunting [Moon *et al* 1989; Wilmshurst *et al* 1989] may themselves produce mild symptoms of CAGE [Wilmshurst *et al* 1989].

Although the presence of patent foramen ovale may be a risk factor for the development of DCI in some divers, the need to survey potential divers for a patent foramen-ovale has not been

established [Adkisson *et al* 1989; Moon *et al* 1989; Wilmshurst *et al* 1989].

1.5.3.4. Failure of the pulmonary filter

Butler and Hills [1979] used an ultrasonic Doppler device for non-invasive monitoring of the femoral artery of anæsthetised dogs whilst microbubbles were infused into the right ventricle through a Swan-Ganz catheter. Under normal conditions, bubbles smaller than 22 µm are retained by the pulmonary circulation. Bubbles escaped entrapment after more than 20 mls of gas (0.35 mls/kg) had been infused, at which point the lungs are overloaded. Changes in respiration profile were observed as the pulmonary gas load increased. Pre-treatment with a pulmonary vasodilator (aminophylline) reduced the capacity of the lungs to filter air [Butler & Hills 1979]. Pulmonary vascular filtration of the venous air infusions was complete for the lower air doses (up to 0.3 mls/kg). When the filtration threshold (0.35 mls/kg) was exceeded, arterial spill-over of bubbles occurred in 50% of the animals. Significant elevations in pulmonary arterial pressure and pulmonary vascular resistance were also observed while systemic blood pressure and cardiac output decreased. Left ventricular end-diastolic pressure remained unchanged [Butler & Hills 1985; Butler & Hills 1979].

1.5.3.5. Effects of posture

Neck vein compression (to increase cerebral venous pressure) was studied in dogs moved from a prone to a position in which the head was elevated 300 mm above the heart. This manœuvre by itself markedly decreased intracranial and dorsal sagittal sinus pressure. With the head elevated, compression of neck veins

doubled intracranial and sagittal sinus pressure (3.6 ± 2.2 to 6.8 ± 4.8 and -2.5 ± 2.7 to 2.3 ± 2.3 mmHg [mean ± SEM; n = 9; $p < 0.05$]) while total or regional CBF and $CMRO_2$ remained unchanged. Thus, this manœuvre may be useful for identifying potential sources of air entry in the head neck region during surgery [Toung *et al* 1988].

1.5.3.6. Effects of ventilation

Positive end-expiratory pressure ventilation (equivalent to 15 cm water [peak]) will change right atrial pressure (-4.7 ± 1.7 to -0.1 ± 3.4 mmHg, $p < 0.05$), but will not normally affect intracranial pressure, CBF or $CMRO_2$ [Toung *et al* 1988]. In a venous embolism model in sheep however, active lung inflation increases the likelihood of paradoxical embolism [Pfitzner & McLean 1987]. However, this increase in central vein pressure seems to occur with active lung inflation only if central venous pressure is elevated before the injection of air [Pfitzner & McLean 1987].

1.5.3.7. Effects of immersion

Arborelius reported that humans immersed in water (but with their heads above water) exhibit increases in right atrial and pulmonary arterial transmural pressures of up to 13 mmHg with a concomitant decrease in peripheral vascular resistance [Arborelius *et al* 1972]. Similar data have been reported by Echt *et al* [1974] who took the additional trouble of using a thermoneutral bath to eliminate any effects due to temperature.

These pressure increases may be enough to shunt air through a patent foramen ovale when a diver enters the water. There are many anecdotal reports in the literature of fatal cerebral arterial

gas embolism after very shallow dives. Pulmonary barotrauma was suspected in these cases but no lung damage could be demonstrated. The increase in right atrial pressure with immersion may be why some patients undergo CAGE during immersion to only very shallow depths [Bayne & Wurzbacher 1982].

1.6. BEHAVIOUR OF GASEOUS PHASE GASES IN THE CIRCULATION

Butler *et al* [1988] injected bubbles into a tube arranged at various angles to the vertical and through which blood was pumped downwards. They found that the velocity of larger bubbles (3.86 mm) tended to increase as the tube was raised from the horizontal to an angle of 30° whereas the velocity of the smaller bubbles (2.37 mm) did not change. When the tube was positioned vertically, the larger bubbles moved to the top of the apparatus against the direction of flow whereas the smaller bubbles travelled in the direction of blood flow [Butler *et al* 1988]. In general, a bubble in a small vessel (where the bubble occupies the entire width of the vessel) will distribute with flow whereas a bubble in a larger vessel will distribute according to buoyancy [Butler *et al* 1987; Gorman & Browning 1986; Gorman *et al* 1987b; Van Allen *et al* 1929].

Small doses of air injected into the aorta of an sitting or standing subject will enter the carotid arteries before dispersing into the branches of the middle cerebral artery and distributing mainly across the ipsilateral hemisphere. These gas emboli pass slowly through arterioles forming long columns of gas that arrest when surface tension at the air-endothelial interface exceeds the local arterial (or driving) pressure [Furlow 1982; Gorman & Browning 1986; Gorman *et al* 1987b; Lee 1974].

Bubbles arising during decompression are about 20 µm in diameter at normal atmospheric pressure [Hills & Butler 1981]. They are likely to be universally distributed in the blood and whereas it has been suggested that they may arrest briefly at the capillary level [Hills & James 1991] it may just be that they simply pass more slowly than larger air emboli. Very large bubbles (longer than 5000 µm) in the cerebral circulation have been observed to arrest in vessels of between 50 and 200 µm diameter [Gorman *et al* 1987b]. The grey-white subcortical junction offers all the conditions necessary for prolonged bubble trapping and may be especially vulnerable to air embolism [Dutka *et al* 1988]. (Cortical angiomorphology is discussed below.) Although direct observation of the grey-white subcortical junction is presently impossible, confocal microscopic techniques may one day allow direct observation of these microvessels during air embolism [Dirnagl *et al* 1992; Villringer *et al* 1991].

1.6.1. Bubble passage through cerebral vessels

Peak arterial pressure is an important determinant of embolus passage [Gorman 1987a]. The trailing (or proximal) blood-gas interface of gas emboli in the pial circulation of anæsthetised rabbits pulsates with each systole. These pulsations are damped by the gas embolus, the larger emboli damping the pressure pulses more than smaller emboli. Pressure at the leading (or distal) interface of a large bubble will be less than peak systolic pressure and cannot be greater than mean arterial pressure. Therefore, larger (and so longer) gas emboli would be expected to trap more readily than smaller gas emboli and this is in fact what is observed [Gorman 1987a].

Passage of gas emboli is facilitated by an increase in cerebral perfusion pressure as well as the profound (but transient) cerebral vasodilatation that sometimes accompanies gas embolism of the brain. Most bubbles

will pass through the cerebral arterioles and capillaries to the veins at once or after a temporary period of trapping [Gorman 1987a; Gorman & Browning 1986; Van Allen *et al* 1929]. It has been shown that for gas emboli to arrest in the cortical arteries of the mammalian brain they must be more than 200 µm in diameter [Gorman & Browning 1986]. At this size, arterial pressure drives the bubble into the vasculature until the surface tension produced by elongation of the bolus is sufficient to arrest flow. Smaller bubbles coalescence into bigger bubbles and form long columns of gas which then occupy several generations of branching, small arterioles (20 to 50 µm diameter) [Gorman 1987a; Gorman & Browning 1986]. In the brain, multiple generations of branching, small arterioles are found in the cerebral cortex and at the grey-white matter boundary (between the cerebral cortex and the underlying corona radiata) [Dutka *et al* 1988]. Vascular occlusion tends to occur at vessel bifurcations (where the vessel diameters are 30 to 60 µm) but is usually transient unless blood pressure is falling (*viz;* during gas embolism of the brain stem) [Gorman 1987a]. The reason for this is that if nett surface tension pressure opposing embolus transit is to exceed cerebral perfusion pressure the advancing (distal) bubble-blood interface must be in a smaller vessel than the trailing (proximal) interface. If cerebral perfusion pressure is less than 100 mmHg, the distal interface of the bubble is in a vessel of 100 µm diameter and the proximal interface must be in a vessel of less than 13 µm diameter, the intra-arterial bubble will arrest [Gorman 1987a]. If the proximal blood-bubble interface reaches the capillary (5 µm diameter) passage to the veins will be promoted by the larger venous end of the capillary (9 µm). Thus, a significant proportion of gas entering the cerebral circulation typically passes to the venous circulation and does not cause vessel occlusion [De la Torre *et al*

1962b; Fries *et al* 1957; Fritz & Hossmann 1979; Grulke & Hills 1978; Hossmann & Fritz 1978; Pate 1957; Van Allen *et al* 1929].

If there is no driving pressure (*viz;* after death) microbubbles in the circulation become static in the cerebral arteries and tend to coalesce into cylindrical plugs rather than remain as spherical bubbles [Grulke & Hills 1978; Waite *et al* 1967]. This finding alone has contributed significantly to the widely held belief that air emboli arrest on the arterial side of the circulation causing tissue death by ischæmia.

1.6.2. Coalescence

Circulating gas emboli are more likely to exist in juxtaposition if the surface tension is reduced by a surfactant, of which there are many present in the body [Pattle 1966]. Although Harvey *et al* suggested as early as 1944 that intravascular coalescence could not occur [Harvey *et al* 1944a; Harvey *et al* 1944b], coalescence of gas in blood vessels has been observed after bolus injection of air into the cerebral circulation [De la Torre *et al* 1962a; Waite *et al* 1967]. When a large number of bubbles enter a branch of the arterial tree they generally coalesce within 5 to 30 seconds of forming intimate accumulations [Grulke & Hills 1978].

More recently, studies have been undertaken using uniformly sized bubbles (the type expected in DCI) with measured diameters [Grulke & Hills 1978]. These studies have shown that a single bubble 40 to 250 μm in diameter will travel at the velocity of the blood until it deforms into a smaller vessel, the vessel dilating so the path ahead is wider than the vessel behind. The bubble may stop at a vessel bifurcation and if it does a second bubble entering the same vessel will tend to stop at an earlier bifurcation, catching up with the first as the blood between the bubbles escapes through radiating arterioles. Coalescence of these bubbles can

form long and continuous columns of intravascular air such as are found in the brains of humans and experimental animals following fatal CAGE [Chase 1934; Fries *et al* 1957].

FIGURE 1.5. REPRESENTATION OF SOME OF THE PHYSICAL PRINCIPLES OF THE PASSAGE OF BUBBLES THROUGH MICROVESSELS

In a blood vessel with a hydrophilic lumen the bubble deforms as it moves through vessels of lesser diameter [Grulke & Hills 1978] maintaining a fluid film between the bubble and the vessel wall.

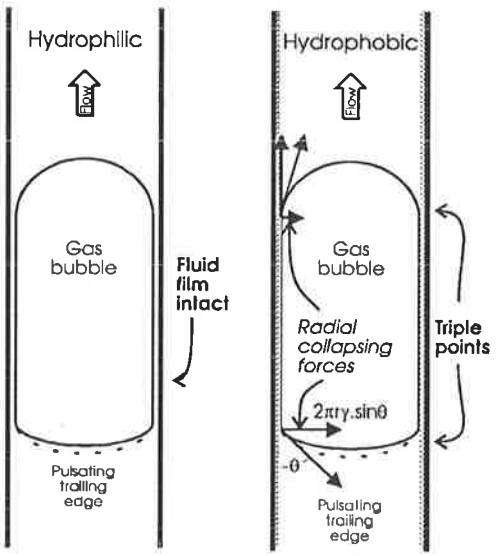
If the hydrophilic film was disrupted by the *"disjoining pressure"* (induced by any hydrophobic lining; see section 1.8.1) it could then induce axial forces which would tend to arrest bubble movement while the radial forces would tend to induce vascular collapse.

If the lumen is hydrophobic there is a further collapsing pressure even in the absence of a bubble [Israelachvili 1985]. The liquid-air interface in the vessel with a hydrophilic lumen would compete with the wall for any adsorbed surfactant [Hills 1992b] (as postulated by Hills [1992a]).

θ contact angle between trailing edge of bubble and vessel lumen

r radius of vessel lumen

γ surface tension of plasma ($\approx$ 45 dynes/cm)



(Figure after Hills 1992a)

Microbubble accumulations are less likely to coalesce and will dissolve faster if they contain O_2 or if the subject is ventilated with pure O_2 [Grulke & Hills 1978].

1.6.3. Stabilisation of bubbles

Amphipathic (surfactant) molecules have a strong affinity for interfaces. It is expected that intravascular bubbles will become coated with loosely bound surfactant molecules simply by passing over a surfactant coated surface such as the vascular endothelium [Butler & Hills 1983]. Bubbles crossing the pulmonary circulation, for example, may become stabilised by being coated with pulmonary surfactant [Hills 1977]. Surfactant coated bubbles exhibit different behaviour to uncoated bubbles and may cause less intravascular damage than uncoated bubbles [Hills & Barrow 1982]. Such surfactant coated bubbles may comprise a long lasting reservoir of circulating gas bubbles in the body after decompression [Butler & Hills 1979; Hills & Barrow 1982] and may persist at smaller sizes than would normally be expected [Weathersby *et al* 1982].

1.6.4. Effects of air dose

The actual dose of air entering any particular vascular bed will be depend on the size of the bubbles and orientation of the vascular tree during the process of embolisation [Catron *et al* 1984]. Bubbles produced by decompression are small so have different buoyancy and distribute differently to large emboli injected directly into a particular vessel. In studies which use decompression to generate gas embolism cannot be one certain of the amount of gas generated. Similarly, in studies in which air is injected into a vessel with many branches supplying the target organ one cannot be sure how much air actually enters the vascular bed under examination. In comparisons of

experiments one therefore needs to consider not only whether or not the gas embolism is venous or arterial and whether or not paradoxical gas embolism is occurring, but also the source of the air. Some authors believe that bubble size is an important determinant of effect and have utilised methods which produce microbubbles in the range 20-250 μm using fine hypodermic needles (measured using a Coulter Counter [Grulke *et al* 1973]).

1.7. EFFECTS OF GASEOUS PHASE GASES ON THE CIRCULATION

For the purpose of this discussion the circulation will include all the elements which provide nutrition and oxygen and which remove wastes and disease organisms from the tissues. These include the formed elements of the blood as well as the vessel wall and the endothelial cell layer. Special consideration will be given to the effects of intraluminal gaseous phase air (bubbles) on the cerebral circulation. Bubbles containing other gases may find their way into the cerebral circulation where they have similar effects to air embolism. This might be expected if it is the gas-blood/gas-vessel lumen phase differences which are producing the injury rather than the composition of the gas embolus.

1.7.1. Air in the circulation

Air is a mixture of gases containing mainly nitrogen (≈78%) which is inert, and O_2 (≈20%), which can be metabolised. Thus air bubbles will shrink as their O_2 dissolves and is removed from the circulation by being metabolised. Nitrogen bubbles tend to shrink much more slowly since nitrogen is less soluble and there is no active process absorbing dissolved nitrogen.

1.7.2. Oxygen bubbles in the circulation

The fatal dose of intravenous O_2 embolism is similar to the fatal dose of intravenous air embolism when the embolus is injected rapidly [Harkins & Harmon 1934]. Slow intra-arterial injection of O_2 produces the same qualitative effects on behaviour as air injected in the same way, although experimental animals demonstrate a greater tolerance for O_2. Some proportion of the dissolved O_2 is removed from the blood by diffusion into the tissues where it is consumed by oxidative metabolism [Fries *et al* 1957; Gorman *et al* 1987b] thus promoting further dissolution of the gaseous O_2 in the blood vessels. Oxygen injected into the carotid artery will open the blood brain barrier to protein tracers, an effect similar to that produced by air injection [Johansson 1978].

1.7.3. Carbon dioxide bubbles in the circulation

Carbon dioxide is sometimes used as a vascular contrast agent to displace flowing blood during angioscopy and is being used more frequently as a contrast agent in digital subtraction angiography [Silverman *et al* 1989]. It is believed to be a safe and effective radiographic contrast agent for examination of the venous circulation and the right side of the heart because it dissolves rapidly and is thought not to escape into the arterial circulation, being cleared by the lungs on the first pass [Silverman *et al* 1989].

However, experimental studies by Coffey *et al* [1984] have shown that intracarotid bolus injection of 50 to 400 µl/kg CO_2 will produce multifocal ischæmic cerebral infarcts with irreversible disruption of the blood-brain barrier. These effects are dose dependent and occur after passage of the CO_2 embolus. Electron microscopy showed the endothelial cell membranes (the anatomical site of the blood-brain barrier and the

pressure autoregulation response) damaged or completely disrupted. Swelling of the astrocyte end-feet was also observed [Coffey *et al* 1984]. Johansson has also reported that cerebral arterial CO_2 embolism produces similar but milder lesions to gas embolism [Johansson 1978].

1.7.4. Effects of gas bubbles on the blood constituents

Blood is a tissue comprised of a fluid plasma phase which contains a complex mixture of proteins and other chemicals as well as a number of formed elements. These include the erthyrocytes, the thrombocytes and the leukocytes (granulocytes and monocytes). Gas embolism has effects on all these blood constituents [Hallenbeck *et al* 1986; Kochanek *et al* 1988; Thorsen *et al* 1986; Warren *et al* 1973].

1.7.4.1. Effects of gas bubbles on complement factors

The consequences of complement activation and the symptoms of decompression sickness are similar. In rabbits, complement protein activity is essential for the development of neurological dysfunction after a hyperbaric exposure. In animal experiments the sensitivity and degree of activation of complement proteins correlates well with the risk of disease during and after decompression [Ward *et al* 1986; Ward *et al* 1990].

Anaphylatoxins C3a and C5a are produced in plasma by the presence of air bubbles but anaphylatoxin C4a is not, suggesting that air bubbles activate the complement system by the alternate pathway (see figure 1.6). One group of subjects produced 3.3 times more C3a and 5 times more C5a than expected. After being subjected to decompression profiles severe enough to produce air bubbles in their circulation (verified by ultrasonic Doppler

monitoring) this group was found to be more susceptible to DCI [Ward *et al* 1987].

Zymosan is an extract of killed yeast cells and is used to activate polymorphonuclear leukocytes. For rabbits whose leukocytes are zymosan sensitive both a plasma-air interface and a serum-air interface produce significant leukocyte aggregation. Removal of complement (by cobra venom activation of C3) inhibits this response [Ward *et al* 1986]. It would appear that the complement system is activated by the presence of an air interface in plasma.

Thus complement sensitive individuals may be susceptible to symptoms of DCI after exposure to small amounts of intravascular gas. Pulmonary filtration insufficiency or a patent foramen-ovale would not be required since complement factors move about the circulation freely. Insensitive individuals on the other hand may be able to tolerate comparatively large amounts of (Doppler detectable) intravascular air. Normal variations in complement sensitivity may explain much of the variability seen in the diving community and may even explain why certain individuals develop symptoms after non-provocative dives or do not develop symptoms even when Doppler detectable gas is present in the circulation.

1.7.4.2. Effects of gas bubbles on red blood cells

It was suggested as early as 1938 that aggregation of red blood cells was important in the ætiology of DCI [End 1939] although no histological evidence for this was available at that time [Catchpole & Gersh 1947].

FIGURE 1.6. ILLUSTRATING THE MAJOR COMPONENT PROTEINS OF BOTH THE CLASSICAL AND ALTERNATIVE COMPLEMENT ACTIVATION CASCADE

In the classic pathway, antigen-antibody complexes sequentially bind C1, C4 and C2. Binding is followed by activation (enzymatic activation is indicated by bold italics). Cleavage fragments are not indicated except in the case of B, C3 and C5.

In the alternative pathway, a high energy thiolester bond is hydrolysed in C3. It then binds factor B which is cleaved by factor D to form a convertase which is stabilised by properdin. The C3 cleavage product, C3b also has a cleaved thiolester bond and acts like a hydrolysed C3 to activate the alternative pathway.

The 2 pathways of complement activation converge to form a convertase that cleaves C3 (a convertase) which then undergoes sequential binding of each of the late-acting components until the Membrane Attack Complex (or MAC) is formed.

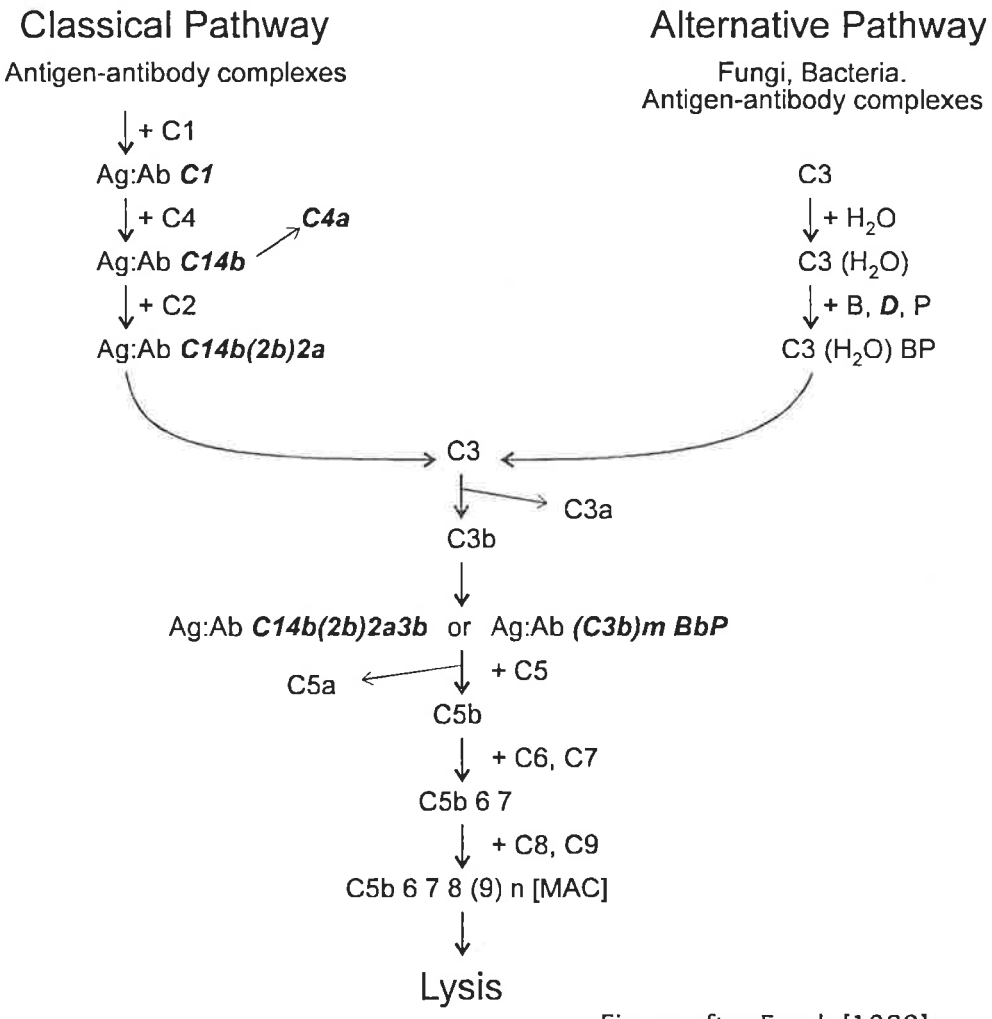


Figure after Frank [1989]

Wells *et al* have observed aggregations of erythrocytes in the mesenteric circulation of dogs after air embolism produced by decompression, maximum aggregation occurring 1 hour after bubbles were first observed. None of the observed intravascular bubbles arrested in the microcirculation [Wells *et al* 1971]. Similar data have been reported for the pial [Wagner 1945] and cheek microcirculation [Buckles 1968].

Euglobulin lysis (a measure of plasma activator of the fibrinolytic system) was significantly greater in animals surviving more than 1 hour after decompression [Wells *et al* 1971]. Euglobulin lysis was not increased in blood foamed *in vitro* which might be expected since the activator is derived from the vascular endothelial cells [Holemans & Silver 1969]. An increase in plasma activator levels usually occurs when there is vasodilation or when previously stagnant segments of the microcirculation open up [Holemans & Silver 1969]. These studies suggest that if flow in the microcirculation is compromised after air embolism it may not be due to air bubbles blocking the capillaries but may be due to aggregations of erythrocytes or other cells.

1.7.4.3. Effects of gas bubbles on platelets

In vitro, gas bubbles with a diameter in the range of 40-120 µm will cause platelet aggregation, an effect not attributable to citrate or free calcium, substances which normally promote aggregation of platelets. This effect appeared to be independent of the total gas bubble surface available for contact but required the platelets to be stirred [Thorsen *et al* 1986]. The platelet movements in platelet rich plasma and the bubble diameter (curvature of the N_2 microbubble surface) seemed more important for aggregation

than the total amount of gas surface available for contact [Thorsen *et al* 1986]. This suggests that stationary gas phases will have less effects on platelet aggregation than moving gas phases.

Experimental decompression sickness which produced significant intravascular gas embolism has been reported to deplete platelets in a time dependent manner, possibly due to platelets aggregating around bubbles in the blood [Tanoue *et al* 1987]. These authors suggested platelets left circulating after DCI are in a condition similar to those in acquired "*storage pool disease*", that is they have used up their stored adenine nucleotides [Fukami & Salganicoff 1977; Zahavi 1976]. Platelets are found in this condition in other clinical states including idiopathic thrombocytopenia purpura [Malpass *et al* 1981], collagen disease [Zahavi & Maeder 1974] and in disseminated intravascular coagulation [Pareti *et al* 1976].

Although accumulation of ^{111}In-labelled platelets in brain has been observed after CAGE, drugs which modify platelet function have a paradoxical effect on recovery of CBF and CSER after CAGE. Whereas the "*triple combination*" of prostaglandin I_2, indomethacin, and heparin promoted a significant recovery of CBF and CSER in dogs subjected to incremental CAGE [Hallenbeck *et al* 1982b] this was not accompanied by a reduction in the number of platelets accumulating in the embolised hemisphere [Kochanek *et al* 1988]. Interestingly, neither agent alone has a significant effect in this model [Hallenbeck *et al* 1982b; Obrenovitch & Hallenbeck 1985]. Platelet activating factor (PAF) is a powerful stimulus to platelet aggregation in rabbits, dogs and humans with an effective dose in the nanomolar range [Hwang *et al* 1983;

Kistler *et al* 1984a; Kistler *et al* 1984b]. Platelet activating factor has a specific membrane protein receptor on platelets, leukocytes and smooth muscle [Hwang *et al* 1983] and will activate leukocytes and cause platelets to aggregate [Kistler *et al* 1984a]. Kadsurenone is a platelet activating factor antagonist which significantly enhanced recovery of brain function and CBF after CAGE but, similar to the *"triple combination"*, did not reduce platelet accumulation in the brain [Kochanek *et al* 1987b]. It may be that this antagonist is interfering with adhesion of leukocytes to vascular endothelium after CAGE rather than preventing platelet accumulation.

1.7.4.4. Effects of gas bubbles on leukocytes

After erythrocytes, leukocytes are probably the most important determinant of microrheology in the circulation [Chien *et al* 1987; La Celle 1986]. Changes in behaviour of leukocytes might be expected to produce significant effects on the microcirculation and particularly to affect organs which have heterogenous microcirculatory flow patterns such as the brain.

Because of the comparatively small number of polymorphonuclear leukocytes in the blood it seems probable that substantial air embolism would be required to activate them directly. However, polymorphonuclear leukocytes have been shown to accumulate in either the brain substance or in brain microvessels after CAGE [Hallenbeck *et al* 1986; Kochanek *et al* 1987a]. It seems more likely that CAGE damages the vascular endothelium [Hills & James 1991] and this then exposes sites to which polymorphonuclear leukocytes can adhere [Chryssanthou *et al* 1977; Persson *et al* 1978; Hills & James 1991]. This adhesion has been shown to be

mediated by specific adhesion molecules such as CD11/18 [Argenbright *et al* 1991; Arnaout 1990; Bevilacqua *et al* 1987; Bevilacqua *et al* 1989] or GMP-140 [Geng *et al* 1990] and is potentiated under conditions in which the endothelial cells are damaged [Budd *et al* 1990]. These adhesive interactions can be inhibited by antibodies to CD11/18 [Argenbright *et al* 1991] or by platelet activating factor antagonists [Garcia *et al* 1988]. Indeed, inhibition of leukocyte-endothelial cell adhesion has been shown to be protective in certain types of cerebral ischæmia such as after aortic occlusion [Clark *et al* 1991a] or intracarotid injection of microspheres [Clark *et al* 1991b].

1.7.4.5. Ischæmia-reperfusion injury and CAGE

Ischæmia-reperfusion injury refers to cell death (or injury) caused by reperfusion after ischæmia in contrast to cell death (or injury) caused by the preceding ischæmic episode [Fox 1992]. Ischæmia-reperfusion injury is initiated by biochemical events which occur during ischæmia. These events result in the generation of reactive oxygen metabolites such as superoxide anion, hypochlorous acid and hydrogen peroxide [Welbourn *et al* 1991] but more importantly these substances appear to be generated by leukocytes which are adherent to the vascular endothelium [de la Ossa *et al* 1992]. Tissue damage is characterised by œdema and increased microvascular permeability to proteins. Numerous reviews of ischæmia-reperfusion injury are available [Welbourn *et al* 1991; de la Ossa *et al* 1992]. Some of the processes of ischæmia-reperfusion injury are summarised in figures 1.7 and 1.8.

FIGURE 1.7. EARLY BIOCHEMICAL CHANGES ASSOCIATED WITH *"ISCHÆMIA/REPERFUSION INJURY"*

Ischæmia leads to a build up of hypoxanthine and xanthine oxidase. When O_2 is reintroduced (with reperfusion) superoxide (O_2^-) and other reactive O_2 metabolites are generated in endothelial cells. The hydroxyl radical (OH^-) may be produced by the reaction of superoxide and H_2O_2 in the presence of Fe^{++} or Cu^{++} ions (the Haber Weiss Reaction) or H_2O_2 alone in the presence of Fe^{++} (the Fenton Reaction). After neutrophils are activated, myeloperoxidase (MPO) in the neutrophil itself generates HOCl.

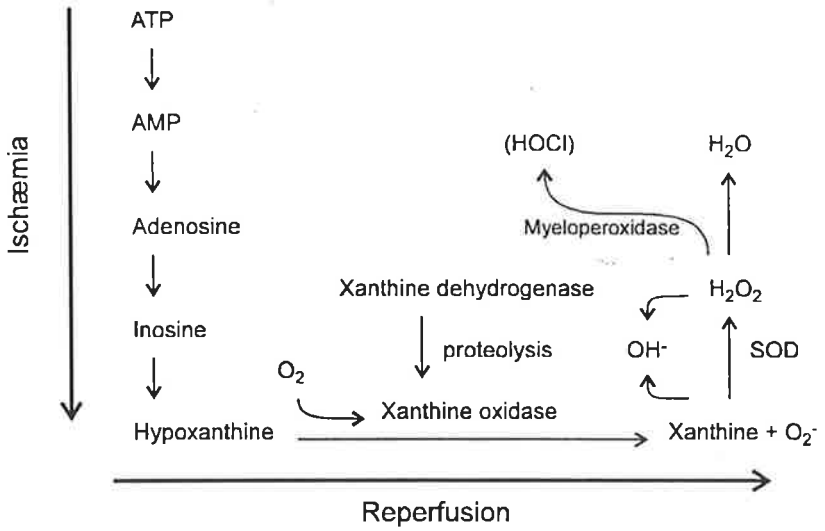


Figure after Granger [1988].

Experimental studies of ischæmia-reperfusion injury typically require at least 60 minutes of arrested blood flow in order to demonstrate an increase in reactive oxygen and other metabolites associated with ischæmia-reperfusion [Welbourn *et al* 1991; de la Ossa *et al* 1992]. As described above, air embolism typically produces a transient effect on the circulation as emboli pass into the veins. It may be that the second stage of an ischæmia-reperfusion injury is initiated by air embolism when bubbles damage the vascular endothelium which then promotes leukocyte

adhesion. The adherent leukocytes then activate and generate tissue damaging quantities of hypochlorous acid.

FIGURE 1.8. SCHEMATIC DIAGRAM OF LEUKOCYTE (NEUTROPHIL)-INTERACTIONS WITH ENDOTHELIUM IN *"ISCHÆMIA/REPERFUSION INJURY"*

Following binding of its adhesion receptors (the CD11/18 complex) to endothelial ligands, the activated neutrophil releases proteolytic enzymes and reactive oxygen metabolites into the extracellular space resulting in increased tissue permeability and œdema.

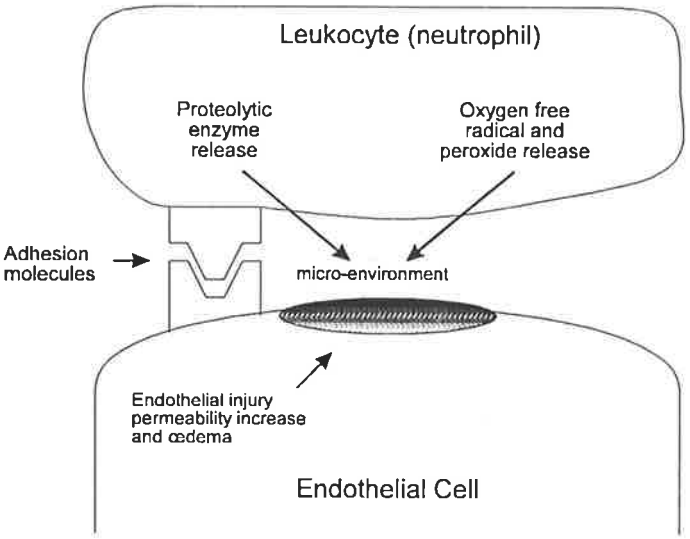


Figure after Welbourn *et al* [1991]

1.7.4.6. Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a syndrome which encompasses a wide spectrum of clinically important coagulation disorders [Bick 1988; Lasch *et al* 1967; Mersky *et al* 1967]. DIC is associated with a significant amount of microvascular (and sometimes large vessel) thrombosis. This vessel thrombosis impairs blood flow and often leads to significant morbidity and mortality [Bick 1988]. It has been described as a *"consumptive coagulopathy"* [Lasch *et al* 1967] or *"defibrination syndrome"* [Mersky *et al* 1967] although a better term might be *"de-*

fibrinogenation syndrome" [Bick 1988]. Disorders associated with endothelial cell damage can initiate DIC, including intravascular damage (by air bubbles) tissue damage of any type, platelet and erythrocyte damage, endotoxemia or any pathological process which causes release of tissue pro-coagulant enzymes [Deykin 1970; Evanson *et al* 1973]. The presence of plasmin and thrombin in the circulation has been used by some as a working definition of the presence of a DIC type process [Bick 1992; Flute 1972; Haragawa *et al* 1976; Heyes *et al* 1975].

1.7.4.7. Is CAGE a disseminated intravascular coagulopathy?

Although similarities between DCI and DIC have been reported previously this avenue of investigation has been largely unexplored except for a few studies [Albano *et al* 1971; Hart 1976; Novomesky 1982; Philp *et al* 1971]. Kochanek *et al* [1988] reported that treatment of dogs with the "*triple combination*" demonstrated a significant (but not sustained) improvement in CSER and CBF although they failed to inhibit platelet accumulation in the air-embolised hemisphere. Because the coagulation pathways are so complex it is possible that some other component of the air embolism induced injury process is inhibited by the "*triple combination*".

Thus arterial air embolism may initiate DIC or ischæmia-reperfusion or a similar process. Because there is considerable misunderstanding as to what exactly is happening in air embolism and to avoid confusing well established pathologies with the model proposed here it is suggested the term *gas embolism related coagulopathy* be used to refer to the damage caused by air bubbles to the vascular endothelium which then initiates

erythrocyte and/or platelet aggregation and/or leukocyte adhesion to the vascular endothelium.

FIGURE 1.9. SCHEME OF THE TRIGGERING MECHANISMS OF DISSEMINATED INTRAVASCULAR COAGULATION

A wide variety of seemingly unrelated pathophysiological insults can give rise to the same common pathway. In many instances the pathways leading from the initial pathophysiological insult to the generation of systemic thrombin and plasmin are different. Regardless of the activation pathway, once triggered, the resulting DIC-type pathophysiology is the same.

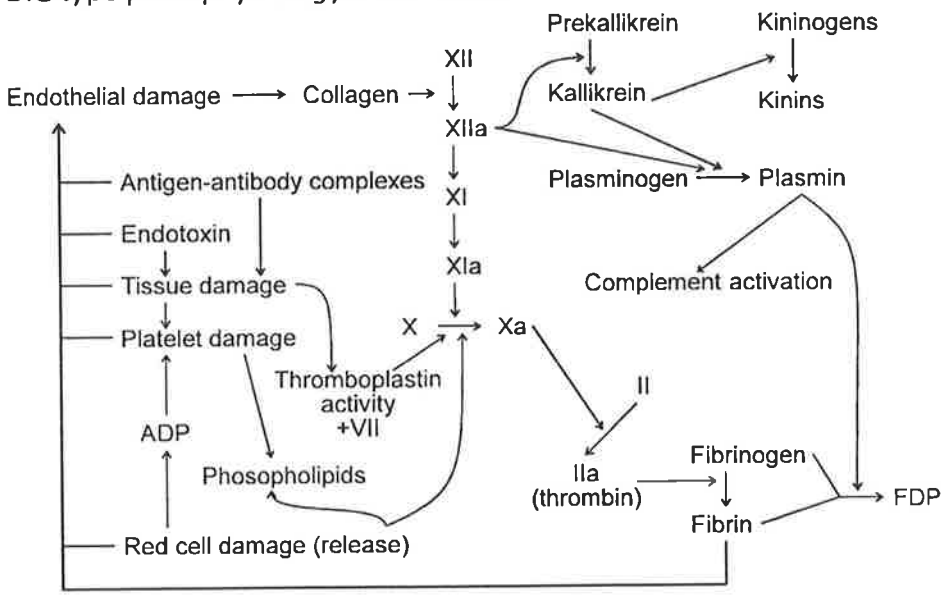


Figure after Bick [1988].

1.8. PATHOPHYSIOLOGICAL EFFECTS OF CAGE

A remarkable account of the clinical effects, suggested pathological mechanisms and treatment for gas embolism was presented in 1829 by Bichat in his paper *"Determining how the cessation of the functions of the right side of the heart interrupts those of the brain"* [Bichat 1829]. Bichat reviewed many early anecdotal reports on gas embolism in patients as well as conducting experiments in which air was introduced into the carotid arteries of horses. He concluded from these studies that gas embolism was lethal only when air entered the cerebral circulation [Bichat 1829].

The principle neurological signs of CAGE appear rapidly and possibly more quickly than one would expect if air embolism was producing cerebral ischæmia. These signs vary according to the distribution of the air in the vertebrobasilar and carotid arteries [Neuman & Hallenbeck 1987]. There may be loss of consciousness (with or without convulsions), confusion, aphasia, incoordination, focal weakness and or hemiparesis, unilateral paræsthesia, headache, blindness or other visual disturbance, dizziness and vertigo, deafness, sensorial or personality changes and other changes in neuropsychological status [Gillen 1968; Menkin & Schwartzman 1977]. Gas embolism of the brain-stem causes respiratory depression [De la Torre *et al* 1962b; Fries *et al* 1957; Meldrum *et al* 1971; Pate 1957], prolonged apnœa [Van Allen *et al* 1929], cardiac dysrhythmias [Cales *et al* 1981; Catron *et al* 1984; De la Torre *et al* 1962b; Evans *et al* 1981; Greene 1978], and a transient increase in arterial blood pressure [De la Torre *et al* 1962b; Evans *et al* 1981; Fries *et al* 1957] that may surpass the limit of cerebrovascular autoregulation [Dutka *et al* 1987; Evans & Kobrine 1987; Evans *et al* 1984; Shurubura *et al* 1976a; Shurubura *et al* 1976b; Simms *et al* 1971b]. Brain-stem symptoms are usually followed by death of the subject.

Massive air locking in the heart will produce cardiac arrest due to coronary artery gas embolism [Clayton *et al* 1985; Geoghegan & Lom 1953]. Cardiac arrest can also be a secondary effect of brain stem embolisation which produces neurogenically mediated cardiac arrhythmia [Cales *et al* 1981; Catron *et al* 1984; De la Torre *et al* 1962b; Evans *et al* 1981; Greene 1978].

1.8.1. Damage to vascular endothelial cells caused by CAGE

Circulating gas bubbles are endothelial irritants [Broman *et al* 1966; Johansson 1978; Nishimoto *et al* 1978] and may induce endothelial damage which is not due to hypoxia or ischæmia [Nishimoto *et al* 1978; Haller *et al* 1987], but which can lead to intravascular coagulation and

occlusion [Hallenbeck & Furlow 1977]. This will then further impair microvascular perfusion. After gas embolism endothelial cells showed flattening of their nuclei and acquired a wrinkled appearance and degradation of the intercellular junctions [Haller *et al* 1987]. This type of damage suggests surface mechanical damage that could be due to "*abrasive*" effects of an air-blood interface [Grulke *et al* 1973; Haller *et al* 1987].

The circulation contains a number of surfactant-like (amphipathic) molecules and it could be predicted that these would coat the vessel lumen making it hydrophilic. However, measurement of the contact angle between a vessel lumen and a drop of water has shown the lumena of cerebral and many other vessels are hydrophobic [Hills & James 1991; Hills 1992a]. Indeed, many other surfaces in the body have been found to be hydrophobic [Butler *et al* 1983; Cotton & Hills 1984; Hills *et al* 1983]. Amphipathic molecules have a strong affinity for phase interfaces, such as bubbles and thus bubble passage across endothelial cells could result in surfactant migrating from the outer membranes of the endothelial cells to bubbles in transit [Butler & Hills 1983]. Bubbles are drawn towards hydrophobic surfaces in aqueous environments. Therefore it would be expected that bubbles in the circulation would stick to endothelial cells and rupture the fluid film which normally separates the bubble surface from the endothelial cell membrane [Grulke & Hills 1978]. They then carry away the surfactant coating of the endothelial cells. The force for doing this could be provided by the "*disjoining pressure*" [Hills 1992a] which adsorbed layers of phospholipid have been shown to exert *ex vivo* on lawns of cultured endothelial cells [Hills 1984]. The *disjoining pressure* is that pressure exerted by low energy surfaces which cause spontaneous rupture of any supernatant

liquid layer. This effect can be seen on a surface polished with silicone wax where water forms beads surrounded by dry areas. A *"dirty"* surface will retain a thin film of water. Peeling can occur when any particle in the blood adsorbs to the vascular endothelium [Israelachvili 1985]. It is a phenomenon dependent on a force perpendicular to the surface and has been suggested as a possible mechanism for exfoliation of endothelial cells and opening of the blood-brain barrier after CAGE [Broman 1947; Johansson 1978; Israelachvili 1985].

In vitro studies of air bubble passage across an endothelial cell monolayer cultured in a flow chamber show that bubbles cause profound damage to some individual cells but not others. When the flow of medium was high there was no damage to endothelial cells yet the passage of even one air bubble resulted in the lifting and loss of those cells from the monolayer which the bubble had contacted. Thus, bubbles *in vivo* may exert a shearing stress on the endothelial cells during gas embolism due to surface tension phenomena at the liquid-air interface [see APPENDIX A.5].

1.8.2. Cerebral vessel dilation caused by CAGE

When gas emboli enter cerebral vessels the affected vessel segment dilates [Atkinson 1963; Fritz & Hossmann 1979; Gorman 1987a; Grulke & Hills 1978; Simms *et al* 1971a], an effect possibly due to endothelial cell damage, since it is the endothelial cells which mediate pressure autoregulation [Broman *et al* 1966; Fritz & Hossmann 1979; Hossmann & Fritz 1978; Johansson 1978; Nishimoto *et al* 1978; Simms *et al* 1971a].

Whereas hypoxia does not normally disturb pial arterial reactivity to H^+ or K^+ or adenosine [Haller & Kuschinsky 1985], gas embolism will attenuate reactivity to H^+ and adenosine while K^+ reactivity is largely

preserved [Haller & Kuschinsky 1981] suggesting that embolism of vessels with air does not produce effects typical of "*pure*" hypoxia.

Both nicotinic [Haller & Kuschinsky 1981] and muscarinic [Haller *et al* 1987] induced dilation are abolished after air embolism, presumably because the cholinergic response is mediated by the vascular endothelium which is damaged by the passage of the air embolus.

1.8.3. Damage to the blood-brain barrier caused by CAGE

The deleterious effect of gas embolism on the blood-brain barrier was first reported by Broman in 1940 using Trypan Blue as a tracer dye for cerebral œdema. In 1966 he enlarged upon these earlier experiments and reported that;

1. the same kind of damage was seen in pial and intracerebral arteries;
2. passage of dye into perivascular tissue (œdema) required persistent gas embolism (10 or more minutes);
3. gas embolism of saline perfused animals (after death) produced the same kind of effects as those seen in living animals [Broman *et al* 1966].

More recent experimental studies have further validated and expanded these findings [Ah-See 1977b; Chryssanthou *et al* 1977; Garcia *et al* 1981; Hossmann & Olsson 1971; Hossmann 1976; Johansson 1978; Lee & Olszewski 1959; Schuier *et al* 1978; Vorbrodt *et al* 1986].

The damage caused by gas embolism is not the same as that seen after ischæmia. Several minutes of ischæmia will not cause a blood-brain barrier leakage of dye-albumin complexes [Broman 1944; Johansson & Steinwall 1972] whereas even a very short exposure to intravascular gas

will cause a blood-brain barrier disturbance [Johansson 1978]. Ischæmia inhibits cerebral energy production and so œdema, if present, is generally of the cytotoxic type (even in the presence of other blood-brain barrier damaging conditions such as hypertension [Hossmann & Olsson 1971]).

Brain swelling seen after ischæmia is often reversible if flow is restored within a few hours of the ischæmic insult [Hossmann 1976; Olsson *et al* 1971]. Johansson found that 100 to 500 µl of air (or O_2 or CO_2) injected into the left common carotid artery produces a unilateral embolism of the brain. Flow must have been restored because, after a few seconds, fluorescent protein bound tracer could be seen in arteries, arterioles and capillaries. A larger dose of air produced extravasation of Evans Blue tracer into brain parenchyma, a disturbance which lasted 24 to 48 hours. The lesions occur much more rapidly than ischæmic or anoxic blood-brain barrier lesions and appear quite different from those seen in solid and fat embolism [Johansson 1978].

Shearing stresses induced by embolus passage will cause increases in endothelial histidine decarboxylase and thus accelerate endothelial cell histamine production [Rosen *et al* 1974]. This release of histamine will increase the rate of trans-endothelial passage of plasma proteins and other molecules [Cotran & Karnovsky 1967].

1.8.4. Cerebral œdema caused by CAGE

An increase in brain-water content will only occur when the rate of fluid extravasation exceeds the capacity of the brain interstitial water homeostatic mechanism to absorb the fluid produced [North & Reilly 1990; Sung *et al* 1992]. Blood-brain barrier damage is almost always absent during global CBF arrest [Hossmann & Olsson 1971] and yet embolism of a small

number of capillaries with 15 µm microspheres is followed by severe blood-brain barrier damage [Schuier *et al* 1978]. Thus, the relationship between ischæmia and blood-brain barrier lesions must depend on the site and mode of vascular occlusion. Air embolism produces a lesion between these 2 extremes which is still variable in its degree. An increase in brain-water (often restricted to grey matter) has been demonstrated in some experimental animals with CAGE [Garcia *et al* 1981; Hallenbeck *et al* 1984; Hekmatpanah 1978; Nishimoto *et al* 1978], but has not been shown in others [Fritz & Hossmann 1979; Hossmann & Fritz 1978; Leitch *et al* 1984d]. Similar variable degrees of brain œdema have been reported in some post-mortem examinations of humans with lethal CAGE [Ah-See 1977a; De la Torre *et al* 1962b; Fries *et al* 1957; Greene 1978; Ward *et al* 1971]. The increase in intracranial pressure and volume of intracranial contents after CAGE has been shown to occur without any increase in brain-water. Thus intracranial pressure increases in these cases must be due to an increase in brain blood volume due to cerebral vasodilation [Fritz & Hossmann 1979; Hossmann & Fritz 1978].

The brain-water content in experimental animals with CAGE does not correlate well with outcome [Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984; Leitch *et al* 1984d]. Furthermore, it has been shown that significant blood-brain barrier disruption and brain œdema can co-exist with normal levels of CBF and neurological function [Gresham *et al* 1992; Ichikawa *et al* 1992; Penn 1980; Sung *et al* 1992; Varney *et al* 1992]. Brain œdema only impairs neurological function when either the intracranial pressure reduces the cerebral perfusion pressure to ischæmic levels, or when focal cerebral œdema causes brain shift due to a mass-effect [Go 1984; Kety *et al* 1948; Penn 1980; Varney *et al* 1992]. Thus, brain œdema does not appear to have an important

role in CAGE mechanisms except when brain swelling has compromised brain blood flow.

1.8.5. Effects of CAGE on CBF

Although the effects of CAGE on CBF are variable the available data suggest a significant and progressive impairment of cerebral perfusion after CAGE which may be the result of endothelial cell œdema further exacerbated by the intravascular accumulation of formed elements from the circulation (*gas embolism related coagulopathy*) [Hallenbeck *et al* 1979; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984; Obrenovitch *et al* 1984].

The pathophysiological sequence of events following CAGE have been described as being very similar to those seen after transient but complete interruption of blood flow [Hossmann & Fritz 1978; Hossmann *et al* 1976]. Some authors have reported pronounced but transient hyperæmia when reperfusion occurs after CAGE [Fritz & Hossmann 1979; Simms *et al* 1971a; Simms *et al* 1971b; Waite *et al* 1967]. Increasing the dose of gas can increase the size of an embolus and so affect its rate of passage. Multiple repeat embolism of the same vessels may also occur due to recirculation of the embolus. Indeed one group of investigators have found it was necessary to infuse gas in multiple increments in order to suppress the EEG [Leitch *et al* 1984a].

Pressure autoregulation is mediated by the vascular endothelium [Hishikawa *et al* 1992; Silver 1978; Willette & Sauermelch 1990] and so CAGE induced vasodilation might be considered an inappropriate response to the increased transmural pressure due to the presence of the bubble. Increases in arterial blood pressure are thus accompanied by disproportionate increases in CBF [Grulke & Hills 1978; Hossmann & Fritz

1978; Simms *et al* 1971a]. Progress of air emboli through the cerebral circulation is then influenced both by arterial blood pressure and vessel dilation.

Regional brain ischæmia [Brierley *et al* 1970; De la Torre *et al* 1962b; Eriksson *et al* 1992; Fries *et al* 1957; Garcia *et al* 1981; Kogure *et al* 1988], platelet accumulation [Kubes *et al* 1990], thrombus formation [Hallenbeck *et al* 1979; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984; Kubes *et al* 1990] and increased blood-brain barrier permeability [Ah-See 1977b; Garcia *et al* 1981; Hekmatpanah 1978; Johansson & Steinwall 1972; Kogure *et al* 1988; Lee 1974; Nishimoto *et al* 1978] seen after CAGE are all thought to be secondary effects [Catron *et al* 1984; Fries *et al* 1957; Grulke & Hills 1978; Hekmatpanah 1978] of CAGE and thus may not be ameliorated by recompression alone. Hyperbaric O_2 therapy may, however, modify these effects of CAGE, but may also need to be applied over multiple treatments to be properly effective.

1.8.6. Damage to the brain parenchyma caused by CAGE

Histological examination of brain parenchyma after CAGE reveals disturbances of capillary permeability and substantial alterations to cell membranes [Hekmatpanah 1978]. Unilateral CAGE in gerbils will cause obvious multifocal brain lesions and widening of the extracellular spaces within 10 minutes. Three hours after CAGE, astrocytes were swollen and although there was considerable shrinkage and necrosis of the neuronal soma, neurones, oligodendrocytes and myelin sheaths appeared to be largely unchanged [Garcia *et al* 1981]. Similar results have been reported for dogs [De la Torre *et al* 1962a]. These delayed effects of CAGE are

similar to those observed after unilateral carotid ligation in gerbils [Garcia *et al* 1981].

Subarachnoid hæmorrhage in association with a marked impairment of the circulation has been observed after CAGE, mainly in the lateral parietal area of the cerebral cortex [Fries *et al* 1957]. For this reason alone the use of aspirin and other anti-coagulants has been discouraged by clinicians treating suspected CAGE, although it is possible that the beneficial effects on coagulation and leukocyte adhesion may transcend these possible harmful effects.

1.8.7. Relapse after initial improvement from CAGE.

Regardless of ætiology, about 30% of patients with CAGE relapse after an initial improvement or resolution of symptoms [Ah-See 1977a; Brooks *et al* 1986; Foote *et al* 1977; Hallenbeck 1977; Hallenbeck *et al* 1984; Kubes *et al* 1990; Pearson 1984]. Explanations for this phenomenon include re-embolism, brain œdema, progressive impairment of perfusion by endothelial œdema with platelet thrombus formation, and regeneration and regrowth of *in situ* gas emboli during decompression [Hallenbeck 1977; Hallenbeck *et al* 1982a; Van Allen *et al* 1929]. Sources of re-embolism have been sought in accordance with the conventional physical explanation for CAGE. Emboli that arose during the original decompression trauma could redistribute from the thoracic vessels to the brain, from regions of the cerebral circulation to other parts of the brain and to the spinal cord. New emboli might be forming as tissues saturated with inert gas continue to contribute to the gas bubble pool [Eriksson *et al* 1992; Grulke & Hills 1978; Leitch *et al* 1984b; Van Allen *et al* 1929].

Another explanation does not require the presence of intravascular bubbles. *Gas embolism related coagulation* may have been unsuccessfully or only partially treated with hyperbaric O_2. Further treatments are usually initiated if symptoms of DCI re-emerge and frequently these additional sessions of hyperbaric O_2 eventually cure the symptoms. The mechanisms by which hyperbaric O_2 may exert these effects is discussed below.

1.9. OUTCOME AND TREATMENT AFTER CAGE

Outcome after CAGE has been shown to correlate with CBF and so treatment of CAGE has been aimed at trying to re-establish satisfactory cerebral perfusion or increase the supply of O_2 to supposedly ischæmic tissues [Hallenbeck *et al* 1982a; Hallenbeck *et al* 1984; Leitch *et al* 1984c; Leitch *et al* 1984b; Meldrum *et al* 1971]. Thus, hyperbaric O_2 therapy has been used to treat CAGE both because it is believed bubbles obstruct the circulation (and so must be compressed) and to provide hypoxic tissue with O_2. It has been the obvious choice for the Navies of the world which have air compressors and hyperbaric pressure vessels at their ready disposal. Although the symptoms of some patients resolve without hyperbaric treatment, compression within 5 minutes of onset of symptoms frequently results in rapid and frequently complete recovery [Baskin & Wozniak 1975; Catron *et al* 1984; Gorman 1984; Kinsey 1954; Thiede & Manley 1976]. However, many patients deteriorate later, often progressively, and often with different neurological manifestations to those of the initial presentation [Dutka 1990]. This may occur even after apparently successful recompression treatment [Greene 1978; Leitch *et al* 1984c; Nishimoto *et al* 1978; Pearson & Goad 1982]. A mechanistic explanation for this deterioration invokes re-embolism due to redistribution of emboli from elsewhere in the body to the cerebral circulation (*viz;* from the pulmonary vascular bed) or expansion of

other *in situ* residual gas reservoirs on decompression. An alternative explanation is that secondary deterioration is due to local circulatory obstruction and progressive impairment of microperfusion due to endothelial damage and accumulation of formed elements from the circulation [Hallenbeck *et al* 1979]. Polymorphonuclear leukocytes may further release vasoactive or other substances such as free radicals which damages the neural tissue. Platelets and erythrocytes may also aggregate around damaged endothelium and further exacerbate the *gas embolism related coagulopathy.*

1.9.1. Treatment of CAGE

Appropriate first aid may reduce the morbidity and mortality after CAGE [Comet 1989]. Thus, the immediate problem for the clinician is that, left alone some patients may exhibit deteriorating brain function, often [Broman *et al* 1966; De la Torre *et al* 1962b; Ring & David 1969; Lee & Olszewski 1959], but not always [Fritz & Hossmann 1979; Hossmann & Fritz 1978] thought to be due to the progressive development of cerebral œdema.

Aggressive, multiple treatments with hyperbaric O_2 therapy are considered essential for any manifestation of CAGE [Armon *et al* 1991; Bove *et al* 1982; Hart 1974]. This is in spite of the limited evidence from prospective randomised studies demonstrating that standard hyperbaric treatment protocols improve recovery of brain function after CAGE [Dutka 1992].

1.9.1.1. Trendelenburg position

Victims of arterial gas embolism are initially managed by placing the patient in a 15° head-down (Trendelenburg) position to prevent further air bubbles reaching the brain [Butler *et al* 1988; Butler *et al* 1987; Roe 1988; Greene 1978]. Lowering the head has

been reported to promote passage of stationary or slowly moving air emboli, presumably because of venous dilation [Atkinson 1963] whereas other studies have shown the forces of buoyancy do not overcome the force of arterial blood flow if the bubbles are small [Butler *et al* 1988]. Provided the patient is not inclined at an angle greater than 30°, the right-to-left ventricular pressure differential should not be high enough to allow shunting *via* a patent foramen ovale. The Trendelenburg position should be considered as no more than a first aid response to suspected air embolism.

1.9.1.2. Hyperbaric therapy

Recompression by itself will reduce the volume of any gas-filled space in the body in direct proportion to the increase in pressure (Boyle's law). However, reduction in the diameter of a spherical bubble is not linear and little is gained by compression above 6 BAR. In blood vessels, gas emboli tend to form cylindrical plugs [Fries *et al* 1957; Grulke & Hills 1978; Hekmatpanah 1978]. Recompression will reduce embolus length and so reduce gas-vessel interface friction forces [Grulke *et al* 1973]. In combination with a reactive vasodilation beyond the obstruction, arterial pressure may then force these air columns through to the post-capillary venules. Thus embolus removal with compression could be explained by embolus volume reduction and bubble redistribution [Catron *et al* 1984; De la Torre *et al* 1962b; Fries *et al* 1957; Fritz & Hossmann 1979; Grulke & Hills 1978; Pate 1957; Van Allen *et al* 1929]. Indeed, embolus redistribution from cerebral and pial arterioles to the venous circulation [Grulke & Hills 1978], other areas of the brain [Grulke & Hills 1978], and

from the spinal cord [Leitch *et al* 1984b] has been demonstrated after compression of experimental animals.

Another explanation for embolus removal during compression is based on the increase in the pressure due to surface tension (P_γ), such that the gas molecules leave the gas phase and enter solution in plasma. The magnitude of P_γ acting on the embolus is given by La Place's law. P_γ can only act on the proximal and distal gas-blood interfaces of a cylindrical gas embolus occupying a small arteriole [Fries *et al* 1957; Grulke & Hills 1978; Hekmatpanah 1978], (see figure 1.5). Although compression will reduce the length of these emboli in a specific vessel, the radii of the gas-blood interfaces will not change, and the contact angle will not be lost until after the embolus becomes spherical at which point P_γ will increase. Thus an embolus 500 μm long and trapped in an arteriole 100 μm in diameter would have to be compressed from atmospheric pressure to an ambient pressure of 8.5 BAR before it would become spherical [Gorman 1987a].

Furthermore, it has been suggested that spherical bubbles will remain stable in plasma even when their radii have been reduced to less than 1 μm [Weathersby *et al* 1982] since the stability of these natural emboli may be further increased by attracting the hydrophobic portions of surfactants to their surfaces [Butler & Hills 1983]. Such surfactant coated bubbles may not initiate *gas embolism related coagulation* and may account for Doppler detected intravascular air in patients with suspected air embolism who are otherwise asymptomatic.

1.9.1.3. Hyperbaric oxygen therapy

Although compression to 2.8 BAR reduces bubble volume by about 30%, breathing pure O_2 establishes a high diffusion gradient for inert gas between the inside and outside of the bubble (see below). This will facilitate diffusion of nitrogen from the emboli [Grulke & Hills 1978] and hence increase dissolution rates by up to 5 times [Kindwall 1973; Van Liew *et al* 1965].

Hyperbaric O_2 therapy is applied by subjecting the patient to a compression under air and then providing breathing O_2 *via* a mask (Built In Breathing System [BIBS]; *viz;* hyperbaric therapy plus O_2). Thus bubbles are compressed and a gas gradient is applied to any bubbles present.

The use of breathing masks reduces the chance of a fire in the hyperbaric chamber and allows other staff in the chamber to breath hyperbaric air only. A typical treatment will include "*air breaks*" in which the O_2 supply is discontinued for 5 minutes every hour under pressure. Air breaks reduce the chances of O_2 toxicity (O_2 induced epileptiform convulsions, nausea, dizziness, disturbance of vision, or muscular twitching [Butler & Knafelc 1986; Dutka 1985; Norkool & Kirkpatrick 1985] and pulmonary toxicity [Smith 1899]. During hyperbaric O_2 therapy, large amounts of O_2 dissolved in plasma may maintain viability of brain tissue in areas where perfusion is compromised. There are other effects of increased O_2 concentration which are discussed below.

Sukoff *et al* [1968] showed a drop in cerebrospinal fluid pressure of 50% with hyperbaric O_2, probably due to cerebral vaso-constriction. This effect of hyperbaric O_2 treatment on the

cerebral vessels appears to be locally mediated and does not reduce blood flow in ischæmic tissue [Bird & Telfer 1966; Lambertsen 1965; Stalker & Ledingham 1973; Sukoff *et al* 1968]. Hyperbaric O_2 induced vasoconstriction lowers intracranial pressure substantially [Isakov & Romasenko 1986; Thiede & Manley 1976; Hollin *et al* 1968; Sukoff *et al* 1968]. The effects of various combinations of time between 2 and 20 minutes and between pressures of 2.8 and 10 BAR (60 and 300 ft) breathing air or O_2 at 2.8 BAR (equivalent to 60 feet of sea water), on the continued recovery of CSER, CBF, and water content of the brain have been studied in a dog CAGE model. In this model outcome was independent of the pressure of treatment at pressures greater than 2.8 BAR but O_2 at these pressures enhanced treatment [Leitch *et al* 1984b]. Thus it appears the partial pressure of O_2 and not the absolute pressure during treatment is an important determinant of outcome.

While rapid recovery occurs with early compression of patients with CAGE in a recompression chamber [Baskin & Wozniak 1975; Catron *et al* 1984; Gorman 1984; Higgs *et al* 1978; Kinsey 1954; Thiede & Manley 1976; Van Genderen & Waite 1968], delays of several hours are associated with treatment failure rates as high as 50% [Hart 1974; Murphy & Cramer 1984].

Following treatment with hyperbaric O_2 as many as 30% of patients relapse, and up to 10% die. A review of 43 cases of surgical arterial gas embolism treated with hyperbaric O_2 showed complete relief of symptoms in only 65%, partial relief in 21% and no benefit whatsoever in 14% of patients. Five patients (12%) died [Murphy & Cramer 1984]. In spite of these shortcomings, hyper-

baric O_2 is currently the most effective therapy for CAGE, and it is one that is comparatively simple to apply in the appropriately equipped Navy or shore based hospital.

1.9.1.4. How does hyperbaric oxygen treatment work?

Besides DCI and CAGE, hyperbaric O_2 therapy is also used to treat carbon monoxide poisoning [Gorman & Runciman 1991] and is used as an adjuvant in the treatment of necrotising fasciitis [Kranz *et al* 1986], selected chronic wounds [Cohn 1986] including burn wounds [Milione & Kanat 1985; Wiseman & Grossman 1985], ischæmic skin flaps [Kindwall *et al* 1991; Meltzer & Myers 1986] and gangrene [Eltorai *et al* 1986]. Chronic infections of various types have been shown to respond well to hyperbaric O_2 therapy [Esterhai *et al* 1987; Kindwall 1992; Riseman *et al* 1990]. (See table 1.1.). Since many of these illnesses do not involve intravascular bubbles it is probable hyperoxia induces novels states in other systems in the body.

Some of the effects of hyperbaric O_2 therapy appear inconsistent. For example, killing efficiency of neutrophils is increased during hyperoxia [Hohn *et al* 1976; Knighton *et al* 1986] and the production of superoxide, hydrogen peroxide and other O_2 radicals also increases [Hohn 1977]. On the other hand, prolonged periods of *in vivo* hyperbaric O_2 therapy result in decreased phagocytosis and adherence by guinea pig alveolar macrophages [Rister 1982]. Similarly, 24 hours of hyperbaric O_2 inhibits *in vitro* mouse peritoneal cell phagocytosis of latex beads and adherence to glass by mouse splenic macrophages [Mehm & Pimsler 1986]. Hansbrough and Eisman have reported hyperbaric O_2 depletes monocyte numbers in the circulation [Eiseman *et al*

1980; Hansbrough & Eiseman 1979] and possibly leukocyte numbers as well [Hansbrough *et al* 1980].

Other studies have shown that prolonged daily exposure to hyperbaric O_2 suppresses the tuberculin reaction, prevents the manifestations of encephalomyelitis and extends allograft acceptance, all effects which are consistent with hyperbaric O_2 therapy inducing a delayed hypersensitivity response [Jacobs *et al* 1978; Touhey *et al* 1987; Warren *et al* 1978a]. Repeated hyperbaric O_2 exposure [eight 90-min exposures twice daily to 2.4 BAR and 100% O_2] does not affect polymorphonuclear leukocyte phagocytosis and oxidative burst although lymphocyte proliferation was decreased, and an activated population of CD8 activated T cells appeared after mitogen stimulation [Gadd *et al* 1990].

1.9.1.5. Pharmacological and other treatments

If the pathophysiological effects of CAGE are mediated by a *gas embolism related coagulopathy* involving the formed elements of the circulation then it would be expected that agents which modify the coagulation cascade, the complement system or the behaviour of the formed elements would improve either CBF or outcome or both after CAGE.

Early investigations centred on limiting brain œdema after CAGE [Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984; Kubes *et al* 1990; Leitch *et al* 1984d] although none of these studies show specific prophylactic or therapeutic effects for any of the treatments tried. Hypocarbia has been advocated by some as a way of reducing cerebral œdema, while others emphasise the importance of hydration [Ah-See 1977b; Pearson 1984] on the

basis that perfusion pressure will increase. Hydration may work simply because it lowers blood viscosity.

TABLE 1.1. USES OF HYPERBARIC O_2 APPROVED BY THE UNDERSEA AND HYPERBARIC MEDICAL SOCIETY

After Kindwall 1993.

Gas embolism
Decompression sickness
Clostridial myonecrosis (gas gangrene)
Crush injury, the compartment syndrome and other acute traumatic ischæmia
Carbon monoxide poisoning and smoke inhalation
Enhancement of healing in selected problem wounds
Exceptional anæmia from blood loss
Necrotising soft tissue infections (of subcutaneous tissue, muscle or fascia)
Refractory osteomyelitis
Radiation tissue damage (osteoradionecrosis)
Compromised skin grafts and flaps
Thermal burns

Reducing platelet thrombus formation and promoting vasodilation by using the *"triple combination"* of prostaglandin I_2, heparin, and indomethacin, has been shown to improve outcome after CAGE in an animal model [Dutka 1985; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984].

Evans *et al* induced CAGE by infusion of 400 µl of air into a vertebral artery of chloralose-anæsthetised cats. CAGE reduced the CSER to 28% ± 9% (mean ± standard error) of baseline before it recovered to 73% ± 12% after 2 hours. Pre-treatment with 5 mg/kg lignocaine protected the CSER such that it was only suppressed to

68% ± 9% of baseline after CAGE and recovered almost completely [Evans *et al* 1984]. Similarly, if air was introduced into the carotid artery in increments of 80 µl until the CSER was reduced to 10% or less of baseline values a post-CAGE lignocaine infusion accelerated recovery of the CSER from 32.6% ± 4.7% in the CAGE group to 77.3% ± 6.2% in the CAGE/lignocaine treated group. The acute hypertension and the increase in intracranial pressure following air embolism were also reduced by lignocaine pre-treatment. More recently, Dutka *et al* [1992a] repeated these studies measuring CBF as well as CSER in dogs given repeated doses of lignocaine or equivalent volumes of saline during hyperbaric therapy after CAGE. To simulate symptoms often seen in divers with CAGE a transient hypertension was induced with 10 µg/kg noradrenaline during compression. The CSER of lignocaine/hyperbaric O_2 treated dogs recovered to 60 ± 10% (± confidence limits) of the baseline CSER 220 minutes after CAGE whereas the CSER of saline/hyperbaric O_2 treated dogs only recovered to 30 ± 10% of baseline ($p < 0.01$). Furthermore, CBF was higher in the lignocaine/hyperbaric O_2 treated dogs, a factor which may account for the preservation of CSER in these animals [Dutka *et al* 1992a].

These data suggest lignocaine administration will facilitate return of neural function after CAGE [Evans *et al* 1989; Dutka *et al* 1992a], possibly by increasing CBF [Dutka *et al* 1992a]. Activated leukocytes can increase vascular resistance and may account for 50-60% of the total resistance [Sutton & Schmidschonbein 1992]. It is therefore possible the effectiveness of lignocaine for treating experimental CAGE may be due to it inhibiting the accumulation

of platelets and leukocytes in the microcirculation so that blood flow is not compromised.

Leukocyte accumulation occurs either in the brain substance or in the brain microvessels after CAGE [Hallenbeck *et al* 1986; Kochanek *et al* 1987a]. Leukocyte depletion before CAGE leads to amelioration of the post-embolus hypoperfusion [Dutka *et al* 1989]. However, administration of anti-neutrophil serum has not been effective in improving cerebral reperfusion after cerebral ischæmia produced by bilateral carotid artery occlusion in rats [Grogaard *et al* 1989]. Neither has it been shown to improve neurological recovery after cerebral ischæmia produced by 10 minutes of cardiac arrest in dogs [Schott *et al* 1989]. The anti-neutrophil serum used in both of these studies produced severe leukocytopenia. This suggests that CAGE and definite ischæmia are different injuries.

A strategy for evaluating leukocyte involvement in ischæmia/re-perfusion injury (see figure 1.8) in spinal cord [Clark *et al* 1991b; Lindsberg *et al* 1991], intestine [Hernandez *et al* 1987], skin [Vedder *et al* 1990] and heart [Simpson *et al* 1990] uses an anti-body which is not leukocytopenic, but which inhibits leukocyte adhesion to endothelial cells. The human leukocyte differentiation antigen CD11b/CD18 is a glycoprotein expressed on the plasma membrane of neutrophils and monocytes (but which is absent from T and B lymphocytes) [Todd *et al* 1981; Arnaout 1990]. Patients deficient in this antigen are susceptible to recurrent bacterial infections because of leukocyte adhesion deficiency [Beatty *et al* 1984; Klebanoff *et al* 1985]. Monoclonal antibody 60.3 binds to CD11b/CD18 (β-chain of the CD18

complex) and inhibits neutrophil aggregation, adhesion, *in vitro* chemotaxis and spreading on natural and synthetic substrates [Price *et al* 1987; Schwartz *et al* 1985; Wallis *et al* 1986]. The observation that neurological recovery is improved by administration of anti-CD18 antibody before [Clark *et al* 1991b] or after 30 minutes of reperfusion following transient spinal cord ischæmia [Lindsberg *et al* 1991] suggests the CD18 glycoprotein complex may be involved in leukocyte adhesion to ischæmia-damaged endothelium [Takeshima *et al* 1992].

The possible protective effects of antibodies such as monoclonal antibody 60.3 after CAGE have not been reported.

1.10. EXPERIMENTAL METHODS USED TO STUDY CAGE

Approaches to the study of CAGE have involved either the measurement of neurophysiological parameters including CBF and indicators of brain function, or studies of post-mortem cerebral histopathology [Fries *et al* 1957; Leitch *et al* 1984a; Leitch *et al* 1984b; Leitch *et al* 1984c; Leitch *et al* 1984d; Thiede & Manley 1976].

As discussed previously, the effects of gas embolism are not limited to the presence of bubbles alone. Many investigators have thus studied treatments other than those which attempt to re-distribute bubbles and prevent bubble induced ischæmia. While there is ongoing debate about which is the best hyperbaric profile to use many investigators are also examining the efficacy of agents such as lignocaine in conjunction with hyperbaric O_2 therapy.

1.10.1. Studies in humans

Many studies of CAGE in humans have involved factorial analyses of case-report data from patients with CAGE as well as post-mortem neuro-

pathological examination of patients after fatal CAGE [Ah-See 1977a; Baskin & Wozniak 1975; Behnke 1932; Bristow *et al* 1985; Brooks *et al* 1986; Cales *et al* 1981; Catron *et al* 1984; Foote *et al* 1977; Gorman 1984; Greene 1978; Hart 1974; Kinsey 1954; Murphy & Cramer 1984; Pearson & Goad 1982; Ward *et al* 1971].

Many analyses of case-report data from patients with CAGE used varied data sources, particularly for inert gas loads and delays prior to treatment [Catron *et al* 1984; Murphy & Cramer 1984; Pearson & Goad 1982; Pearson 1984; Van Genderen & Waite 1968]. The presence of any pre-existing illnesses increases the heterogeneity of studies of patients with iatrogenic CAGE [Baskin & Wozniak 1975; Bristow *et al* 1985; Hart 1974; Herbst 1978; Ireland *et al* 1985; Justice *et al* 1972; Kent & Blades 1942; Murphy & Cramer 1984; Ward *et al* 1971; Schlaepfer 1922]. Casualties of submarine escape training are one source of potentially homogeneous data [Ah-See 1977a; Brooks *et al* 1986; Greene 1978; Liebow *et al* 1959; Jones 1988; Polak & Adams 1932]. However, when groups from this source have been matched with respect to the decompression insult, the inert gas level, delay prior to treatment and adjuvant therapy, the group sizes have been too small for a formal statistical analysis of the data [Brooks *et al* 1986; Gorman 1984].

Experimental studies in humans have used ultrasonic Doppler to study intravascular bubble formation and resolution during decompression or some other procedure with a risk of gas embolism [Belcher 1980; Catron *et al* 1986; Deverall *et al* 1988; Gillis *et al* 1968b; Gillis *et al* 1968a; Karuparthy *et al* 1989; Tikuisis *et al* 1990]. Several studies have been conducted by anæsthetists or surgeons using ultrasonic Doppler investigating paradoxical gas embolism [Fong *et al* 1990; Matjasko *et al* 1987; Muzzi *et al* 1990; Spiess *et al* 1988b; Teague & Sharma 1991].

The ideal hyperbaric treatment regime is still disputed, since some efficacy of treatment has been shown both by using the United States Navy Table 6A (recompression to 6 BAR) even after a delay of one-half to 29 hours [Calverley *et al* 1971; Mader & Hulet 1979; Newman & Manning 1980; Thiede & Manley 1976] whereas others advocate hyperbaric O_2 at 2.8 BAR [Bove *et al* 1982; Hart 1974; Leitch *et al* 1984a; Leitch *et al* 1984b; Leitch *et al* 1984c]. The latter regime may be more appropriate in patients presenting with a several hour history of anoxic brain injury, with its associated cerebral œdema causing reduced perfusion pressure and aggravated by the gas embolism related coagulopathy. The compression only regime may simply be treating tissue bound autochthonous bubbles [Hills 1993].

The evidence for lignocaine improving outcome after arterial gas embolism (especially in combination with hyperbaric therapy [McDermott *et al* 1990]) is now so strong that a multicentre trial has been proposed [Drewry & Gorman 1992; Dutka 1990].

1.10.2. Studies in animals

Experimental studies of gas embolism in animals allow the deliberate production of gas embolism either by rapid decompression or by infusion of the gas of interest into the vascular bed under study. Investigations have been performed on a variety of animal-models including cats [Atkinson 1963; Evans *et al* 1984; Evans *et al* 1981; Hossmann & Fritz 1978; Fritz & Hossmann 1979], dogs [De la Torre *et al* 1962a; Fries *et al* 1957; Hallenbeck *et al* 1979; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Leitch *et al* 1984a; Leitch *et al* 1984b; Leitch *et al* 1984c; Leitch *et al* 1984d; Persson *et al* 1978; Simms *et al* 1971a], gerbils

[Garcia *et al* 1981], baboons [Meldrum *et al* 1971], rats [Kogure *et al* 1988] and rabbits [Malhotra & Wright 1960].

These studies have produced air embolism by injection of air [Evans *et al* 1981; Evans *et al* 1984; Fries *et al* 1957; Garcia *et al* 1981; Hallenbeck *et al* 1979; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Leitch *et al* 1984a; Leitch *et al* 1984b; Leitch *et al* 1984d; Ring & David 1969; Simms *et al* 1971a], blood foam [Fritz & Hossmann 1979], by pulmonary over inflation [Atkinson 1963; Malhotra & Wright 1960; Schaefer *et al* 1958] or by decompression after a hyperbaric exposure [Leitch *et al* 1984c]. Some authors have advocated the injection of bubbles which are of uniform size [Grulke *et al* 1973; Hills & Grulke 1975] and others have foamed air with plasma in order to create air emboli coated with surfactant [Fritz & Hossmann 1979].

Widespread and gross pulmonary damage is not often seen in human patients with CAGE suggesting that the pulmonary over inflation models may not be very useful [Baskin & Wozniak 1975; Behnke 1932; Brooks *et al* 1986; Cales *et al* 1981; Catron *et al* 1984; Eriksson *et al* 1992; Gorman 1984; Greene 1978; Hart 1974; Ingvar *et al* 1973; Ireland *et al* 1985; James 1968; Kinsey 1954; Malhotra & Wright 1960; Pearson 1984; Polak & Adams 1932; Powell & Miller 1992; Schaefer *et al* 1958; Schlaepfer 1922; Van Genderen & Waite 1968; Ward *et al* 1971].

1.11. CAGE PATHOPHYSIOLOGY

The evidence presented thus far suggests that CAGE has an acute phase (during bubble passage) and a chronic post-embolus phase. This ignores any other injury evolving due to formation or collection of autochthonous bubbles. The effects of CAGE have not been fully susceptible to the conventional treatments

used although hyperbaric O_2 appears to be partially effective. Injecting air into the carotid artery will model the effects of the acute phases of DCI when air bubbles pass through the circulation. It also represents what may happen after pulmonary barotrauma, iatrogenic accidents and paradoxical embolism.

1. Bubbles pass through the cerebral vessels; they may or may not be trapped for a period of time.

2. Bubble passage initiates some change or damage in;

    2.1. The coagulation system;

    2.2. The complement system;

    2.2. Endothelial cells [including damage to the surfactant layers and exposure of adhesion molecules];

    2.3. Leukocytes, platelets and/or erythrocytes.

3. Leukocytes and/or platelets adhere to the vascular endothelium and alter the microrheology (especially boundary flow [La Celle 1986].

    3.1 Treatments which modify leukocyte and/or platelet levels or behaviour will improve outcome after CAGE. It may be that the interaction between all 3 cell types [endothelial cells, leukocytes and platelets] may be required to produce effects on the central nervous system;

CAGE is a disease process which involves bubbles entering and subsequently passing though the brain circulation (either spontaneously or due to hyperbaric therapy). These bubbles initiate a pathological process which includes reduction of CBF, transient disruption of the blood-brain barrier and cessation of brain function.

1.12. PROPOSED STUDIES

From the preceding discussion it is clear that the consequences of CAGE to the cerebral function and circulation are complex. However, a number of common features emerge;

1. Air bubbles in the cerebral circulation typically produce effects on the brain circulation which are not necessarily due to bubbles blocking arteries. Large doses of air and conditions which favour ongoing production of air (such as DCI) may have an additive effect on subsequent processes.

2. Formed elements in the circulation play a role in the progressive nature of CAGE and may be important in the relapse phenomena.

3. Agents such as prostaglandin I_2, indomethacin and heparin [Dutka 1985; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1984] improve outcome after CAGE, possibly by modifying the behaviour of the formed elements of the circulation.

4. A single hyperbaric treatment (either with or without O_2) is not usually effective whereas multiple treatments with hyperbaric O_2 at 2.8 BAR usually are. This dose of O_2 has diverse effects on the immune system as well as on granulocytes and macrophages.

It seems likely that small bubbles are stabilised by coatings of surfactant (such as are formed during DCI) and these may be less damaging than a large embolus of intracarotid air (such as may occur after redistribution of air from a large vessel reservoir in the body). These stabilised bubbles may not activate the *gas embolism related coagulation* proposed here, or they may provide a surface for

an evolving coagulopathy which then manifests as a delayed response to a dysbaric exposure.

1.12.1. Hypothesis and aims

The primary aim of these studies was to investigate the mechanisms that underlie the decline in both CBF and cerebral function after gas embolism. A secondary aim was to identify therapies that modify these mechanisms.

The studies reported in this thesis set out to test the hypotheses;

1. That CAGE does not cause cerebral ischæmia.
2. That CAGE produces progressive damage to the cental nervous system (even when intravascular air is not visible)
3. That the effects of CAGE can be altered by modifying the blood composition (*viz;* by inducing leukocytopenia)
4. That the effects of CAGE can be altered by modifying the adhesiveness of the formed elements of the blood (without producing leukocytopenia).

Accordingly experiments to study CAGE in anæsthetised male New Zealand White rabbits were undertaken;

1. A dose response study in which amounts of 25, 50 100, 200 and 400 and 1600 µl of air were injected into the left side of the cerebral circulation of urethane anæsthetised rabbits.
2. A dose of air which produced measurable and significant decrements in CBF and brain function was chosen for study. Rabbits were then either;

2.1. made leukocytopenic by pre-treatment with mechlorethamine;

2.2. treated with dextran 500 sulphate (mw 500,000) to reduce leukocyte adhesiveness.

During these experiments measurements of CBF, CSER and pial arteriolar diameter were undertaken. Several other studies which further characterise the behaviour of air in the brain circulation are described in APPENDIX A.

CHAPTER 2.

METHODS AND MATERIALS USED

2.1. ANIMALS

The experiments reported here were performed on anæsthetised male New Zealand White rabbits with weights ranging from 2.1 to 2.4 kg. The animals were purpose bred by the South Australian Department of Agriculture at a field station near Adelaide before being moved to animal holding facilities on campus. The animals were housed individually and maintained on a 12/12 hour day/night cycle with access to food and water *ad libitum*. These animals are a convenient size and weight for CBF experiments. They tolerate urethane anæsthesia well and there is evidence that the behaviour of pial vessels in this species corresponds to that of intraparenchymal brain vessels of similar size [Tuor & Farrar 1984].

All experiments were approved by the Animal Ethics Committees of both the University of Adelaide and of the Institute of Medical and Veterinary Sciences, Adelaide.

Details of manufacturers, model numbers and supplier addresses for all of the materials and instruments used can be found in APPENDIX E. In the text only the common names and manufacturer are mentioned.

2.2. ANÆSTHESIA

Urethane is a general anæsthetic agent suitable for studying neural function in both central and peripheral nervous systems since a number of reflex responses are preserved [Maggi & Meli 1986a]. Urethane in doses of 0.5 to 1.0 g/kg induces prolonged anæsthesia suitable for surgery without affecting neuro-transmission in the peripheral nervous system and various subcortical areas of

the brain. Sympathetic drive is increased slightly and in studies involving pharmacological stimulation of peripheral adrenoceptors urethane increases the magnitude of the response under study [Maggi & Meli 1986b]. Urethane will decrease the global rate of cerebral glucose metabolism by up to 33%, but this effect is not homogeneous throughout the brain. The habenula-interpeduncular system for example, is unaffected [Ito *et al* 1984].

Urethane anæsthesia produces no changes in resting pial arteriole diameter or in mean arterial blood pressure, but will increase end-expiratory P_aCO_2 (and produce pronounced hyperglycæmia [Collado *et al* 1987]) during room air breathing. Thus it is usually necessary to ventilate urethane anæsthetised animals to maintain blood gas concentrations in the normal range. The responsiveness of cerebral arterioles to hypercarbia is reduced, possibly due to the decrease in cerebral metabolism [Levasseur & Kontos 1989].

Urethane is eliminated from the body either *via* an alcohol dehydrogenase, an aldehyde dehydrogenase, or an alcohol preferring isoenzyme of cytochrome P_{450}. This metabolism can be inhibited either by ethanol or by dimethyl-sulphoxide [Waddell *et al* 1989].

The experiments reported in this thesis were undertaken using a single infusion of urethane administered at a dose of 1.0 g/kg infused over 30 to 45 minutes. This treatment induced surgical anæsthesia for 8 to 10 hours within 45 minutes of starting the infusion.

2.3. SURGERY

Both the preparative surgery and the experiments were carried out on a steel slab which was heated by circulating water through a heating pad. The temperature of the water was varied between 40 and 50°C so as to maintain rectal temperature of the animal at 38 to 39°C.

Each rabbit was lightly restrained and a 22 G × 25 mm teflon intravenous catheter (Johnson & Johnson; JELCO) introduced into a medial ear vein. Urethane (Ajax Chemicals; ethyl carbamate) was prepared as 0.25 gm/ml in water and infused over 30 - 45 minutes using a syringe pump (Terumo; STC-521). This produced a level of anæsthesia appropriate for surgery. A 5 cm long midline incision was made over the cricothryroid membrane and the trachea isolated from its adventitia. Two (2) 3.0 silk threads were placed around the trachea, one proximal and one distal to an incision made between the tracheal rings. A 5 cm long polypropylene tracheostomy tube was introduced into this incision and tied into place (Portex; 3.0 100/141/030). The urethane infusion was then replaced with an infusion of gallamine triethiodide (Rhône-Poulenc; FLAXEDIL) in saline (5 mg/ml). After loading the rabbit with gallamine triethiodide to induce paralysis the tracheostomy tube was connected to a ventilator (Harvard; RODENT VENTILATOR MODEL 683) and the lungs ventilated with a mixture of oxygen in air adjusted to maintain normocarbia (P_aCO_2 35 - 40 mmHg). Oxygen was added to the inspired gases to keep P_aO_2 between 100 - 130 mmHg (normal physiological ranges are listed in table 2.1). The gallamine triethiodide infusion was maintained at a rate of 7.5 mls/hour throughout the experiment (*viz;* 37.5 mg/hr).

The femoral arteries and one femoral vein were exposed and cuffed cannulæ (Dow-Corning; SILICONE TUBE 602-175) were introduced. Ligatures were placed proximal and distal to the arterial incision. These incisions were then closed with silk and the ear vein infusion was transferred to the femoral vein. One femoral arterial cannula was used to monitor blood pressure and the other used for sampling blood for arterial blood gas analysis. For arterial blood gas analysis 50 µl samples were collected in heparinised glass capillary tubes and analysed immediately using an automatic blood gas analyser (Corning; MODEL 178).

FIGURE 2.1. DETAIL VIEW OF CAROTID ARTERY ANATOMY OF THE RABBIT

Variations in the origin of the internal carotid artery from the common carotid artery. The medial aspect of the vessels on the left side is shown; dorsal is to the left and rostral is at the top of the figure. After Scremin *et al* [1982].

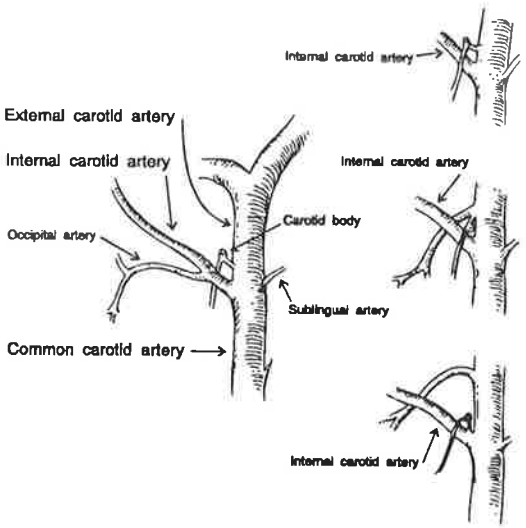
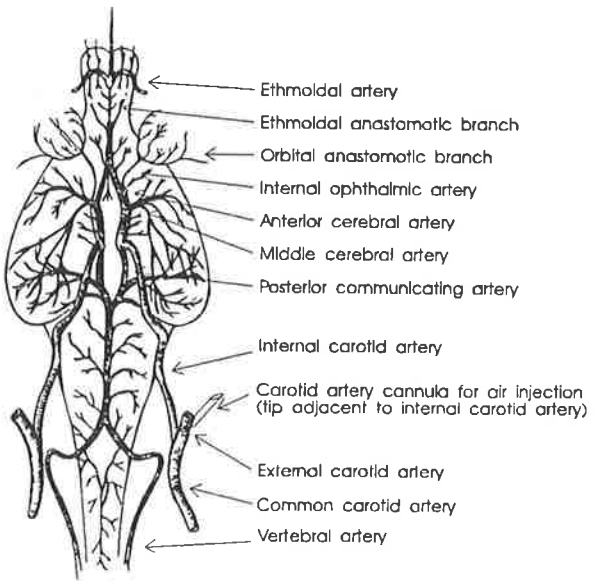


FIGURE 2.2. OVERVIEW OF CAROTID ARTERY ANATOMY OF THE RABBIT

Outline of the arterial supply of the rabbit brain (after Scremin *et al* [1982]). The cannula for injection of intracarotid air was placed in the external carotid artery so that its tip lay adjacent to the internal carotid artery. Care was always taken to ensure the internal carotid artery was never stretched nor traumatised in any way. Manipulations to the external carotid artery were kept to a minimum.



The left common carotid artery was then exposed through the tracheostomy incision. The internal carotid artery was identified [figure 2.1] before isolating and clearing the adventitia from the external carotid artery. A cuffed silicone cannula was introduced retrogradely into the external carotid artery so that its tip was adjacent to the lumen of the still patent internal carotid artery [figure 2.2]. The external carotid artery was tied off.

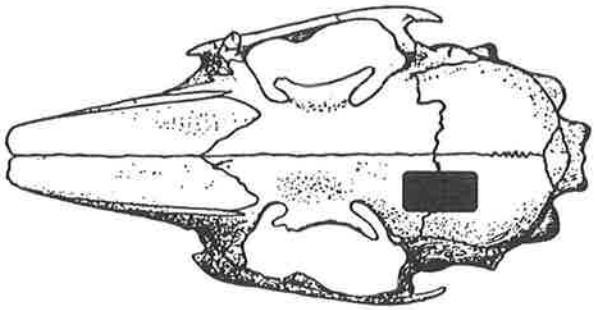
The rabbit was then placed in the sphinx position and fixed into a stereotaxic frame using a Rabbit adaptor (Kopf Instruments; MODEL 900 and 1240 Rabbit adaptor).

The scalp was reflected and the skull cleared of periosteum. A 1 mm burr hole was made 3 cm anterior to bregma on the midline cranial suture and a stainless steel screw (Laubman & Pank; TECSOL DV40) implanted as an indifferent electrode for the somatosensory evoked response recording. A 1 mm burr hole was made over the right sensorimotor cortex to provide access for a platinum electrode. Two additional 1 mm burr holes were made and fitted with stainless steel screws on the left side to provide mechanical support for the cranial reservoir. A high speed diamond burr (Meisinger; ISO 806 104) was irrigated with saline and a square craniotomy made over the left sensorimotor cortex in between these screws [figure 2.3].

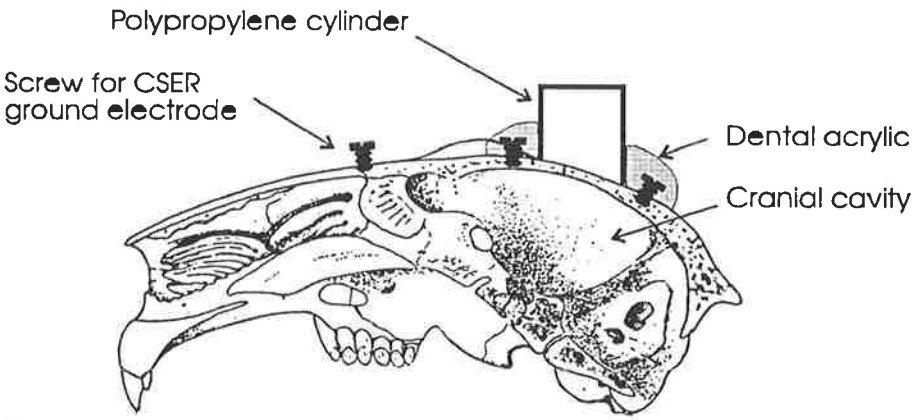
After all bleeding from the bone was stopped using bone wax, an incision was made in the dura using the sharp edge of a 25 G needle. The dura was then reflected back over the edges of the craniotomy and cemented down to the skull using dental acrylic (Dentsply DeTrey; SELF CURE ACRYLIC RR). A 1 cm diameter polypropylene cylinder was then cemented to this and to the screws adjacent to the craniotomy with dental acrylic. This cylinder was then filled with paraffin oil (Delta West; LIQUID PARAFFIN B.P.) to a depth of 1 cm so as to maintain pial-surface pH within the normal range [Kuschinsky & Wahl 1980].

FIGURE 2.3. VIEW OF SKULL SHOWING CRANIOTOMY

Dorsal view showing the approximate site of the craniotomy (shaded area).



Detail view of the craniotomy in cross section showing the approximate site of the CSER ground electrode.



2.4. CORTICAL SOMATOSENSORY EVOKED RESPONSES

Evoked responses can be used to assess central nervous system function in experimental situations [Desmedt *et al* 1990; Grundy 1990]. By electrical stimulation of peripheral sensory (or mixed nerves) a *cortical-somatosensory evoked response* (CSER) can be recorded from the primary sensory area of the contralateral cerebral cortex [Cohen *et al* 1981; Chiappa & Ropper 1982a; Chiappa & Roper 1982b; Dimitrijevic *et al* 1978; Grundy 1990].

For these studies, far field potentials arising from stimuli to the rabbit's forepaw were measured. Changes in the CSER induced by CAGE could then be measured [Cusick *et al* 1979; Desmedt & Noel 1973; Dorfman *et al* 1980; Hattori *et al* 1979]

2.4.1. Method for cortical somatosensory evoked responses

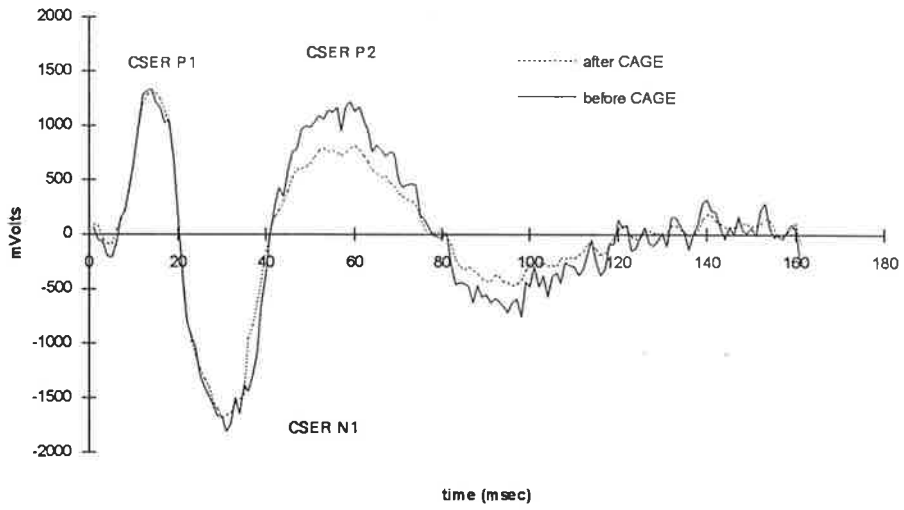
A 3 cm length of 99% pure silver wire was heated at one end until the approximately 0.25 cm of the wire melted and a 0.75 mm diameter ball was formed. The other end of this wire was then soldered onto an insulated lead which was mounted on a stereotaxic carrier (Kopf Instruments; MODEL 1460 ELECTRODE MANIPULATOR). The ball was then placed on the left cerebral hemisphere approximately on the somatosensory focus for the right forepaw. A stainless steel screw fixed to the skull was used as a ground electrode. The cortical and ground leads were then connected to a head stage preamplifier (Neomedix; NEOTRACE ACTIVE HEADSTAGE NT462) which was in turn connected to an AC amplifier (Neomedix; NEOTRACE AC AMPLIFIER NT114A). The high pass filter was set to 2 KHz, the low pass filter to 5 KHz and the gain set to 2K. The output from this amplifier was charted using a chart recorder (Neomedix NEOTRACE WR3701) and the signal also sent to a digital storage oscilloscope (Gould Instruments; DIGITAL STORAGE OSCILLOSCOPE TYPE 4035) as well as to a analog to digital board (National Instruments; AT-MIO-16). Details of the analog to digital data acquisition system can be found in APPENDIX B.

Stainless steel needle electrodes were placed subcutaneously in the right forepaw of the rabbit. The stimulator was triggered by the data acquisition computer. An electric pulse of approximately 7 - 9 volts (a voltage three times the level that produces a detectable response) was

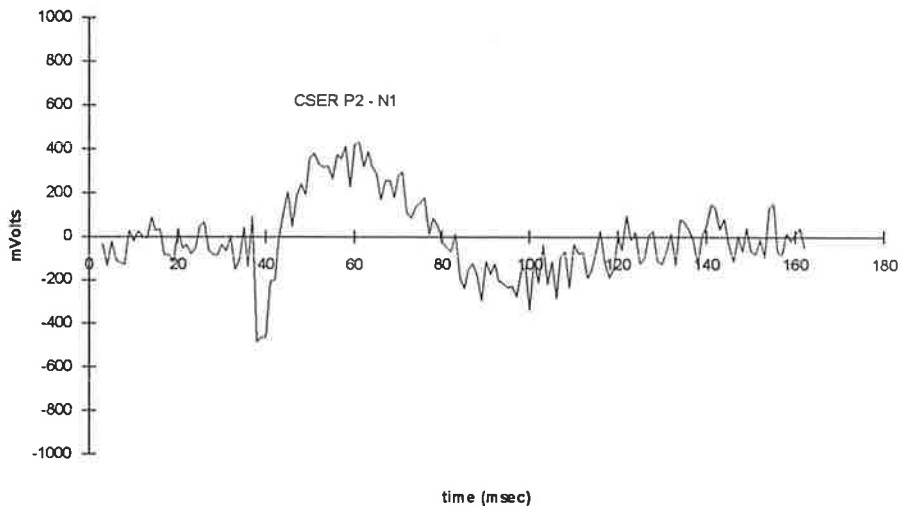
applied for a duration of 0.5 ms at a frequency of approximately 1 Hz to the forepaw electrode (Digitimer Stimulator; DIGISTIM DS9A).

FIGURE 2.4. CORTICAL SOMATOSENSORY EVOKED RESPONSES

(CSER P_1 = First positive wave, CSER N_1 = First negative wave, CSER P_2 = Second positive wave, stimulus artefact not shown)



Showing plot of difference between CAGE and control.



The cortical somatosensory electrode was then positioned so as to record the maximum signal from the left somatosensory area I, [Iragui-Madoz & Wiederholt 1977]. The average of 64 stimulations was calculated by the

data acquisition computer and the resulting waveform called a cortical somatosensory evoked response (CSER; see figure 2.4). Pilot studies showed the second positive wave (CSER P_2) of this CSER to be the most sensitive to air embolism and so the maximum voltage amplitude (CSER AP_2) of this wave was measured and recorded. The latency of this wave (CSER LP_2) was defined as the time from the stimulus artefact to the peak responses for P_1, N_1 or P_2 (see figure 2.4). This latency was unaffected by air embolism.

2.4.2. Spreading depression

Laser-Doppler flowmetry has been used to measure CBF during cortical spreading depression induced by cortical pinprick in anæsthetised cats. This pinprick stimulus induced a transient cortical hyperæmia (215 ± 48% peak increase in cortical blood flow lasting for 2.7 ± 0.4 min) followed by prolonged cortical oligemia, with a reduction in flow of 20 ± 4% at 1 hour and 28 ± 4% at 2 hours [Piper *et al* 1991]. After cortical spreading depression, cerebrovascular reactivity to the inhalation of CO_2 was abolished and did not fully recover for at least 10 hours. Spontaneous vasomotor activity in the cerebral microcirculation was significantly reduced after cortical spreading depression ($p < 0.05$), and autoregulation of cortical blood flow in response to hypotension was preserved [Piper *et al* 1991].

In early pilot studies, before the paraffin oil reservoir method, episodes of spreading depression could sometimes be seen on the continuous CSER traces. However, spreading depression was never seen when using the paraffin oil reservoir method.

2.5. CEREBRAL BLOOD FLOW

CBF is comparatively high (mean of 50 mls/min/100 g) to cover metabolic and energy requirements of the brain. Below defined flow thresholds the various functions of the nervous tissue is abolished. Global CBF stays constant while the blood pressure is in the range 50 - 150 mmHg (pressure autoregulation) and varies according to arterial and tissue CO_2 tension and to the metabolic needs of brain tissue resulting from functional activation (functional autoregulation). Due to robust regulatory mechanisms only a few drugs are able to directly affect CBF; their effects depending on the resting blood supply to small regions which may lead to heterogeneous responses [Heiss 1981].

The technique for measuring CBF should be selected according to the requirements of the study and according to the limitations of the various methods available. For the studies reported in this thesis a technique that allowed multiple readings was required. An invasive method was acceptable. Consideration was given to the microsphere method, laser Doppler flowmetry, tracer accumulation and tracer clearance methods. The advantages and disadvantages of each of these methods are briefly considered.

2.5.1. Microsphere method

The microsphere method for measuring blood flow utilises radioactive latex beads, 10 - 12 µm in diameter. These are injected into the right atrium and accumulate in end capillaries according to the rate of blood flow. The spatial resolution of this technique is limited and the number of measurements is constrained by the number of radioisotopes which can be discriminated, usually only 5 to 8 depending on the sophistication of the radioactive counter available. CBF values obtained using this method in anæsthetised cats under various experimental conditions

typically correlate well with those obtained with the hydrogen clearance method (75 ± 23.5 mls/min/100 g for the hydrogen clearance and 67 ± 26.2 mls/min/100 g for microsphere the technique) [Heiss & Traupe 1981]. However, during ischæmia (induced by middle cerebral artery occlusion) the microsphere technique did not indicate severe ischæmia in 6 out of 20 instances and after restoration of flow. Hyperperfusion was observed by the microsphere technique in 2 cases only while hydrogen clearance indicated hyperæmia in 6 instances. This limited comparability between the 2 methods during ischæmia was also expressed in a low correlation coefficient (0.486) calculated from 139 flow values obtained simultaneously with both methods [Heiss & Traupe 1981]. The discrepancy between the microsphere and hydrogen clearance methods under pathological conditions might be due mainly to the different recording volumes. Hydrogen clearance methods generally record blood flow in a few mm^3 or less of tissue (less than 10 mg) whereas tissue samples of 300 - 700 mg are necessary for the microsphere technique. Thus microvascular flow variations in the brain may be below the spatial resolution of the microsphere method [Heiss & Traupe 1981].

2.5.2. Laser Doppler flowmetry

Laser-Doppler flowmetry combines a measurement of the Doppler shift of low power laser light, with the amount of light reflected to calculate a *"red cell flux"* (often wrongly referred to as flow). A linear relationship between relative changes of the Doppler signal and blood flow over a wide range of pharmacological as well as pathological flow alterations, including cerebral ischæmia has been demonstrated [Haberl *et al* 1989a; Haberl *et al* 1989b]. Whereas it is impossible to get absolute flow values

and the method is sensitive to artefacts it does have a high spatial and temporal resolution [Frerichs & Feuerstein 1990].

Changes in flux measured by Doppler flowmetry have been reported to correlate linearly with flow measured by hydrogen clearance laser (r = 0.78) [Lindsberg *et al* 1989] and with changes in pial arteriolar diameter (measured with a microscope in rabbits equipped with a closed cranial window; r = 0.94, slope = 0.97) [Haberl *et al* 1989b]. Other studies have shown that hydrogen clearance and laser Doppler methods exhibit a linear relationship between relative values of blood flow changes, the coefficients being 0.658, 0.876 and 0.878 for the correlations between the laser-Doppler data and relative changes in the fast, slow and mean flow compartments detected by hydrogen clearance respectively (compartmental clearance is discussed below). All three regression lines were significantly different from the line of identity. These discrepancies between the two methods may be related to limitations inherent in each of them. For example, the depth sensitivity of laser-Doppler in the brain may be greater than expected [Skarphedinsson *et al* 1988].

2.5.3. Tracer accumulation methods

Instantaneous CBF can be measured with a freely diffusible tracers such as ^{14}C iodoantipyrene if, after injection of the tracer, the animal is killed and the brain rapidly removed and frozen. The amount of radiation in a tissue is proportional to the blood flow immediately before death. Excellent spatial resolution can be obtained with the ^{14}C iodoantipyrene method if the tissue is sectioned and autoradiographs prepared [Tamura *et al* 1981]. Whereas, the ^{14}C iodoantipyrene method gives results which correlate well with other tracer clearance methods such as $^{133}Xenon$

[Tuor *et al* 1986] the disadvantage of this method for the studies reported in this thesis is that only a single reading can be obtained from each animal.

2.5.4. Clearance methods, particularly hydrogen clearance

The ideal diffusible tracer for measurement of CBF will have the following properties;

1. Clearance of the tracer must be exclusively due to the rate of arterial flow;
2. A tracer with a short half life will minimise recirculation (and so complex calculations can be avoided);
3. Blood flow in the region of interest must be homogeneous and constant during the period of measurement;
4. The indicator must be inert (not metabolised or pharmacologicaly active), and
5. Tracer and tissue must equilibrate rapidly and independently of the tracer concentration.

Substances suitable for clearance measurements include xenon, krypton and hydrogen gas. Xenon and krypton are difficult to detect and so are typically used as their radioactive isotopes. Being radio-opaque, some attempts to measure CBF using X ray tomography equipment have been made [Kishore *et al* 1984; Webster *et al* 1986]. The hydrogen clearance method was selected for these studies since it allows repeated CBF measurements from a known volume of cerebral cortex and is simple to apply.

Hydrogen gas is metabolically inert and not normally present in body tissues. It has a high diffusion coefficient and therefore will achieve

rapid diffusion equilibrium with the tissues. It is has a very low water-gas partition coefficient (0.018) and so recirculation can be ignored [Kety 1951]. It is readily soluble in lipids and is easily detectable using polarographic methods. These properties make it an almost ideal tracer for measuring blood flow.

Regional CBF can be calculated from a clearance curve made after administration of a bolus of hydrogen gas although this method of hydrogen administration is less accurate for CBF measurements [Young 1980]. The equations for calculating blood flow from clearance curve data are described in detail by Kety [1951] and will only be summarised here.

The Fick principle states that *"if the quantity of a tracer increases or decreases during passage through a vascular bed, the blood flow can be calculated by dividing the amount taken up or added to the blood in a given time by the arteriovenous difference"* (*viz;* except for losses through lymphatic drainage, matter is conserved) [Fick 1870]. The concentration of a tracer in a tissue is thus given as;

$$C(t)=fe^{-Kt}.\int_{0}^{t} C_a(u)e^{Ku}du$$

$C(t)$	tissue concentration of the tracer at time t
$C_a(u)$	arterial concentration of the tracer at time u
f	blood flow per unit mass of tissue
λ	partition coefficient ($\lambda = 1$)
K	clearance constant ($K = f/\lambda$)

If the arterial input function is carefully controlled two special cases arise. When C_a is constant and positive during saturation the equation can be reduced to;

$$C(t) = \lambda C_a [1 - e^{-Kt}]$$

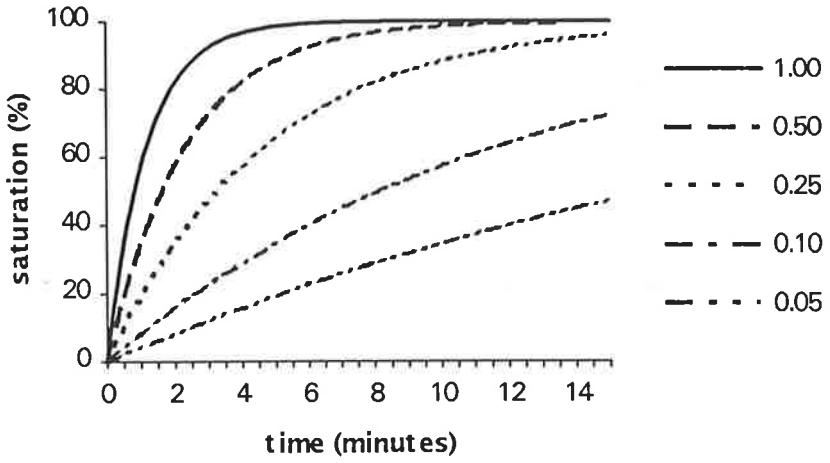
and when C_a is constant during desaturation,

$$C(t) = C(0)\, e^{-Kt}$$

where *C(0)* is the concentration at time zero.

FIGURE 2.5. GRAPH OF TISSUE SATURATION VERSUS TIME FOR VARIOUS FLOW RATES

Tissue saturation [*C(t)*] as a function of time for various flow rates ranging from 0.05 to 1.00 mls/min/g. Arterial hydrogen concentration (C_a) was assumed to be constant. At 100% saturation $C(t) = C_a$. After Farrar [1987].



Since the partition coefficient for hydrogen is approximately 1, the equation for tissue saturation given above indicates the tissue concentration will eventually equal the arterial concentration and that the rate of saturation depends only on the tissue blood flow.

A graph of tissue saturation versus time for various flow rates is shown in figure 2.5. At flow rates of 100 mls/min/100 g (approximately that of grey matter) 99% saturation is achieved within 5 minutes whereas at flow rates of 20 mls/min/100 g (typical for white matter) the tissue is only 63% saturated at 5 minutes and almost 25 minutes would be required to achieve a 99% saturation. Thus grey matter flows can be recorded as often as every 10 minutes while white matter flows can only be measured every 50 minutes. If a recording electrode is detecting hydrogen in both grey and white matter, then the clearance curve will be at least biexponential. The experiments reported in this thesis are thus constrained to a measurement of CBF by hydrogen clearance every 15 minutes (to allow a preinjection baseline reading). All other measurements were also made at 15 minute intervals .

Clearance curves from brain tissue typically indicate several rates of blood flow. CBF for the whole brain is often considered bimodal with a fast component for grey matter and a slower component for white matter [Kety 1965; Harper 1967; Reivich *et al* 1969]. The brain can also be regarded as consisting of a number of homogenous compartments with different flow levels arranged in parallel [Ingvar & Lassen 1962]. Curves obtained by measuring tracer clearance from exposed cerebral cortex can generally be made to fit the sum of 2 exponentials. The fast and slow components may overlap at low flow rates (such as during anæsthesia or low P_aCO_2 levels) and so the fast component may not always be visible. If the device for measuring tracer concentration occupies 2 or more flow compartments then an average concentration value will be obtained, masking any compartmental differences. (This may actually represent consecutive as opposed to simultaneous flows but may not be a problem if the electrodes are in one microvascular region, *viz;* make the electrode

tip as small as possible [von Kummer & Kries 1985]. Horton *et al* used ^{14}C 2-iodoantipyrene as a tracer and found that, in the cerebral cortex of rats, several discrete flow levels exist [Horton *et al* 1980], probably reflecting the different flow levels of each cortical layer. Similar data have been reported for the cat [Sakurada *et al* 1978] and dog [Harper *et al* 1961].

The extreme diffusibility of hydrogen, compared with xenon or krypton, may create artefacts when it is used to measure local blood flow with a tissue electrode. The errors are greatest when hydrogen is given as an intra-arterial bolus, or if the electrode is within 2 mm of another tissue compartment, CSF, or air. These errors are greatest when inter-compartmental diffusion occurs at rates of the same order of magnitude as clearance from the tissue by blood flow. A simple check for this error is to saturate the tissue under investigation and then arrest blood flow. There should be an insignificant clearance of hydrogen (less than 5% over 10 minutes). No matter how small the electrode, the ultimate spatial resolution of the method appears to be about 2 mm unless quantitative account is taken of diffusion. An important precaution in use of the method is to obtain homogeneous tissue saturation by prolonged inhalation [Halsey *et al* 1977].

CBF may be calculated from clearance data by any of 3 methods.

2.5.4.1. Compartmental analysis

Two or more components may be derived by plotting the log of the tracer concentration against time and directly reading off the $t_{½}$ for each. Knowing the tissue partition coefficients for grey matter (D_g) and white matter (D_w) for the tracer, flow can be calculated from the general equation;

$$Blood\ flow = \frac{D.log_e.60.100}{t_{½}}$$

2.5.4.2. Stochastic analysis

Sometimes called height over area analysis this method gives an average CBF;

$$Blood\ flow = \frac{D_b.(H-H_{10}).60.100}{A_{10}}$$

D_b is the tissue to blood partition coefficient for the whole brain, hours is the maximum height of the clearance curve, H_{10} is the height of the clearance curve at 10 minutes and A_{10} is the area under the curve at 10 minutes [Zierler 1965]. This method of calculation is generally used when the tracer is a radioactive isotope.

2.5.4.3. Initial slope index analysis

Errors due to rebreathing of hydrogen can be avoided if the first 30 seconds of the clearance are ignored. If the next 2 minutes of data are log transformed a value biased toward the faster components is obtained using an equation of the general form;

$$Blood\ flow = \frac{D_g.log_2.60.100}{t_{½}}$$

Equation after [Sveinsdottir et al 1969].

This is the method preferred for flow calculations in hydrogen clearance experiments.

2.5.4.4. The virtual ground circuit

Polarography is used to measure the hydrogen concentration in the tissue of interest. The polarising voltage can be set to

measure the reactive species of choice; +350 mV for H_2 or -750 mV for O_2. In the case of hydrogen clearance the polarograph measures the numbers of electrons collected by an electrically polarised collector surface (such as platinum) according to the reaction;

$$H_2 \rightarrow 2H^+ + 2e^-$$

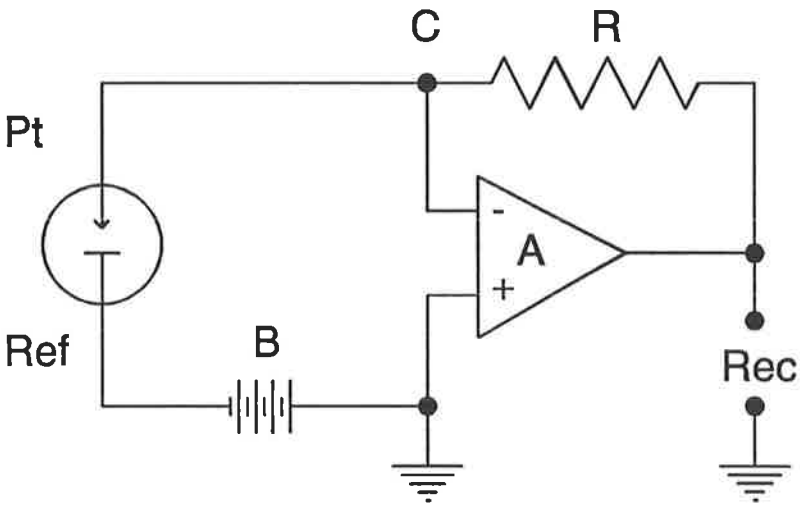
The system used to amplify and display the currents from the platinum wire hydrogen electrodes is shown in figure 2.6. Up to 4 electrodes could be monitored simultaneously using a multi-channel recorder (RIKADENKI B-4021). Each amplifier had its own baseline setting control and offset balance control. The balance control was adjusted for zero hydrogen in the tissue until the recorder pens were at baseline for any setting of the gain control. The chopper stabilised operational amplifiers used in this system (Analog Devices; 233J) have a very low drift rate, less than ± 2 pA per ^{o}C in the bias current, so the contribution toward total drift from this source was negligible compared to that arising from the electrode system itself. Ordinary chloride-silver wire has been shown to produce a variable reference voltage [Young 1980] and a sintered Ag/AgCl electrode (Tektronix; ECG electrode) is preferred.

2.5.4.5. Application of the hydrogen clearance technique

The methods used here are essentially the same as those described by Aukland *et al* [1964]. Details of the theory, instrument design and construction and the procedure for calculating CBF can be found in APPENDIX C.

FIGURE 2.6. VIRTUAL GROUND CIRCUIT

The reference electrode (Ref) is connected to the negative terminal of a -375 mV polarising battery so that Pt becomes positive with respect to the reference. The other terminal is grounded and connected to (in this case) an operational amplifier (Analog Devices; AMPLIFIER 233J). The negative input of the amplifier (A) is connected to the platinum electrode and fed back to the amplifier output through a resistor (R). Current generated at the platinum electrode will change the potential of the negative input with respect to ground. The amplifier will than produce a voltage at its output sufficient to feed back through the resistor and return the negative input to ground (*viz;* the voltage difference is cancelled) The amplifier output (Rec) is charted. Figure from Pasztor *et al* [1973].

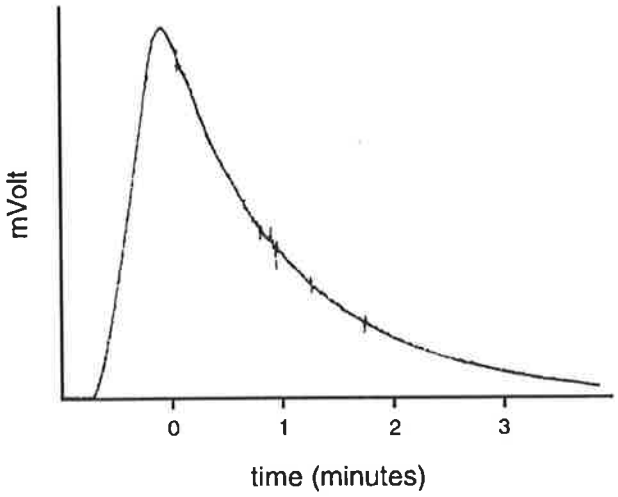


Electrodes were prepared from sharpened 125 µm teflon-coated platinum wire. The bare platinum tips were placed in the right and left cerebral cortex to a depth of 1 mm using microelectrode manipulators (Kopf Instruments MODEL 1460). An indifferent electrode of silver-silver chloride was placed subcutaneously in the animal's back. A 2 channel polarographic amplifier system (APSF POLAROGRAPH MK II) was used to measure the hydrogen concentration; hydrogen gas (approximately 10% by volume) was added to the ventilator inlet for at least 5 minutes.

When hydrogen gas is introduced in the breathing mixture the arterial concentration rises rapidly while tissue hydrogen concentration equilibrates more slowly. When the supply of hydrogen gas is discontinued, venous hydrogen concentration drops by 90% on the first passage through the lungs and the arterial concentration falls to 15% within 40 seconds. Re-circulation effects can be minimised and CBF calculations simplified by ignoring data from the first 30 seconds of the clearance curves [Griffiths *et al* 1975; Pasztor *et al* 1973].

FIGURE 2.7. HYDROGEN CLEARANCE CURVE FROM TYPICAL CORTICAL ELECTRODE SHOWING RAW DATA PLOT

It takes approximately 5 to 10 minutes for hydrogen to completely clear from the brain. Thus, in these experiments CBF can be measured every 15 minutes.



A small region of tissue damage around the electrode tip is sometimes seen however this will only delay clearance and does not alter the shape of the curve [Aukland *et al* 1964].

CBF (mls/min/100 g) was calculated using the initial slope index method. The brain blood partition coefficient for hydrogen (D_h)

has been shown to be very nearly 1 and so by the initial slope index CBF is given by;

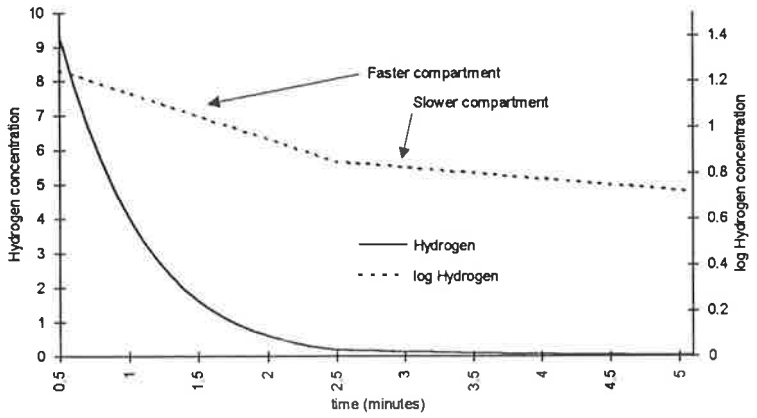
$$CBF = \frac{D_h \log_2 .60.100}{t_{½}}$$

$$CBF = \frac{4158}{t_{½}}$$

This gives a value for CBF in mls/minute/100 g tissue [Aukland *et al* 1964].

FIGURE 2.8. CURVE STRIPPING SHOWING MULTIPLE CLEARANCE COMPARTMENTS DETECTED BY THE SAME ELECTRODE

Biexponential hydrogen clearance (ideal data) log transformed to illustrate 2 compartment clearance.



2.6. PIAL ARTERIOLAR DIAMETER

The brain surface was photographed at regular intervals through the craniotomy using a single lens reflex camera equipped with a data back (Contax; 35 mm 139 QUARTZ) which was mounted on the stereo operating microscope.

Black and white film (Ilford; FP-4) was used exposed at an effective ASA of 100 and developed for 10 minutes (Ilford; MICROPHEN diluted 1:1 from stock) before washing and fixing for 3 minutes (Ilford HYPAM). The individual frames were

mounted and projected onto a screen using a projector (Kodak; CAROUSEL). This process magnified the images of the brain pial arterioles approximately 100,000 times.

If bubbles do become trapped it is in arterioles of between 40 and 100 µm [Gorman 1987a; Gorman *et al* 1987a; Gorman *et al* 1987b]. Thus an arteriole with an external diameter of 40 to 100 µm (before treatment) was selected and its external diameter measured in successive frames on the projected image using a vernier calliper. The system was calibrated against a 35 µm suture thread.

Some studies were recorded using a video camera (Sony; CCD DCX101) connected to a video recorder (JCV; Video Cassette Recorder BR64000JR) and television monitor (JVC; 93 SYSTEM PLUS AV-20ME).

2.7. ANALYSIS OF RESULTS

For each parameter, preinjection baseline data for each animal were averaged and all subsequent data were expressed as a percentage of this mean value. Data were tested by analyses of variance, regression analyses, t-tests or by the Wilcoxon-Mann-Whitney test [Siegel & Castellan 1988] where appropriate.

Because simultaneous multiple comparisons were to be performed a procedure to control the error rate associated with the entire set of comparisons was required. Such a set could consist of all comparisons to control, an arbitrary preplanned number of comparisons or more complex comparisons. For a given set of comparisons the probability of falsely declaring one or more differences to be significant (when all means may be equal) should be set at a small value, usually 5% ($p < 0.05$).

Tukey's test is best suited to the case for which all pairwise comparisons are of interest. Dunnett's test should only be used when comparing the control group to each of the other groups. Sheffe's test is intended to evaluate arbitrary combinations of groups against each other.

The Bonferroni procedure is usually recommended for general use since it is easy to apply and has a wide range of applications [Ludbrook 1991; Wallenstein *et al* 1980]. If the investigator is able to limit the number of comparisons it gives critical values that are lower than those of other procedures. If many comparisons must be made only slightly larger critical values will be obtained.

2.7.1. The Bonferroni method

Based on an elementary inequality (called Bonferroni's inequality), a conservative critical factor for the modified t-statistic can be obtained from tables of the t distribution using a significance level of P/m where m is the number of comparisons to be performed. The degrees of freedom are those for the mean square for the within group variation of the ANOVA. For example, if only 4 comparisons were to be made and P = 0.05, the Bonferroni corrected P would be 0.05/4 = 0.0125. If 10 comparisons were to be made P would be 0.05/10 = 0.005. A decision as to which set of comparisons is to be tested must be decided beforehand and not by inspection of the results [Miller 1966].

2.8. EXPERIMENTAL PLAN

Blood pressure, heart rate, arterial blood gas tensions, CBF, pial arteriolar diameter, brain oxygen and an averaged somatosensory evoked response was recorded every 15 minutes.

2.8.1. Sequencing of experiments

The studies reported in this thesis have been published as a series of papers. As the various studies were undertaken "internal control" experiments were undertaken from time to time in order to qualitatively evaluate whether or not the essential qualities of the model were changing. Accordingly, when the 400 µl CAGE studies were published, only 5 studies of this dose of intracarotid air had been done although 3 more were done subsequently. These 8 400 µl CAGE experiments are presented as one contiguous series in CHAPTER 4. Thus the published data vary slightly from the data reported in this thesis although it is emphasised the essential conclusions have not changed.

2.8.2. Sequence of steps

Experiments were conducted according to the following sequence of steps;

1. Collect rabbit from animal house (generally before 9:00 a.m.);
2. induce anæsthesia with urethane; shave neck, scalp and groin;
3. tracheostomise and install femoral catheters; take blood sample for blood gas analysis and every 15 minutes until end of study; also record MABP, rectal temperature and respiration rate;
4. install carotid arterial line;
5. turn animal over and place in stereotaxic frame, deflect scalp and perform craniotomy; deflect dura; cement plastic reservoir to skull and fill with paraffin oil

6. insert CSER stimulation electrodes in forepaw; position CSER recording electrode to record maximum signal (several CSER recordings are taken to test this);

7. insert electrodes for measuring CBF by hydrogen clearance;

8. begin preinjection baseline recording; measurements of CBF, CSER and pial arterial diameter are taken every 15 minutes;

9. if 90 - 120 minutes of stable preinjection baseline data are recorded then randomise into control or CAGE and perform carotid artery injection of air/saline or saline accordingly;

10. monitor for 3 hours;

11. kill rabbit with an intravenous injection of 10 mls 0.1 KCl (Ajax Chemicals; potassium chloride).

TABLE 2.1. NORMAL PHYSIOLOGICAL VALUES FOR THE RABBIT

After Green 1982.

pH	7.300
P_aCO_2 (mmHg)	38
P_aO_2 (mmHg)	110
MABP (mmHg)	100
Temperature °C	38.5
minute volume (mls/minutes)	675
grey matter CBF (mls/min/100g)	60
white matter CBF (mls/min/100g)	20

TABLE 2.2. EXPERIMENT CODES

Each rabbit was assigned to one of the following groups. For each group code, pretreatment and dose of CAGE are shown.

GROUP CODE	PRETREATMENT (IF ANY)	CAGE DOSE
CAGE Control	nil	100 or 1000 µl saline
CAGE 25µl	nil	Intracarotid injections of 25 µl air and 100 µl saline
CAGE 50µl	nil	Intracarotid injections of 25 µl air and 100 µl saline
CAGE 100µl	nil	Intracarotid injections of 100 µl air and 400 µl saline
CAGE 200µl	nil	Intracarotid injections of 200 µl air and 800 µl saline
CAGE 400µl	nil	Intracarotid injections of 400 µl air and 600 µl saline
CAGE Control granulo-cytopenic	Mechlorethamine (1.5 mg/kg) 72 hours prior to anæsthesia	Intracarotid injections of 1000 µl saline
CAGE 400µl granulo-cytopenic	Mechlorethamine (1.5 mg/kg) 72 hours prior to anæsthesia	Intracarotid injections of 400 µl air and 600 µl saline
CAGE Control dextran 500	Dextran 500 (200 mg/kg) 15 minutes before CAGE	Intracarotid injections of 1000 µl saline
CAGE Control dextran sulphate 500	Dextran 500 sulphate (200 mg/kg) 15 minutes before CAGE	Intracarotid injections of 1000 µl saline
CAGE 400µl dextran 500	Dextran 500 (200 mg/kg) 15 minutes before CAGE	Intracarotid injections of 400 µl air and 600 µl saline
CAGE 400µl dextran sulphate 500	Dextran 500 sulphate (200 mg/kg) 15 minutes before CAGE	Intracarotid injections of 400 µl air and 600 µl saline

TABLE 2.3. SEQUENCING OF EXPERIMENTS FOR CHAPTERS 3 & 4

Experiments were performed in 4 separate series. The list here shows the date on which experiments for CHAPTERS 3 & 4 were done. The experiment codes are explained in Table 2.2.

EXPERIMENT	DATE
CAGE 100µl	20-Apr-88
CAGE 200µl	21-Apr-88
CAGE 100µl	22-Apr-88
CAGE 100µl	1-Jun-88
CAGE 50µl	2-Jun-88
CAGE 50µl	3-Jun-88
CAGE 25µl	8-Jun-88
CAGE 25µl	15-Jun-88
CAGE 25µl	20-Jul-88
CAGE 25µl	4-Aug-88
CAGE 25µl	9-Aug-88
CAGE 25µl	16-Aug-88
CAGE Control	17-Aug-88
CAGE Control	25-Aug-88
CAGE Control	6-Sep-88
CAGE Control	7-Sep-88
CAGE Control	8-Sep-88
CAGE 200µl	19-Oct-88
CAGE 200µl	9-Nov-88
CAGE 400µl	30-Nov-88
CAGE 400µl	24-Apr-89
CAGE 400µl	27-Apr-89
CAGE Control	7-Jun-89
CAGE Control	9-Jun-89
CAGE Control	15-Jun-89
CAGE Control	22-Jun-89
CAGE Control	30-Jun-89
CAGE Control	7-Jul-89
CAGE 400µl	25-Jul-89
CAGE 400µl	3-Aug-89
CAGE 400µl	10-Aug-89
CAGE 400µl	11-Aug-89
CAGE 400µl	14-Aug-89
CAGE Control	15-Nov-89

TABLE 2.4. SEQUENCING OF EXPERIMENTS FOR CHAPTER 5

Experiments were performed in 4 separate series. The list here shows the date on which experiments for CHAPTER 5 were done. The experiment codes are explained in Table 2.2.

EXPERIMENT	DATE
CAGE Control granulocytopenic	7-Dec-89
CAGE 400µl granulocytopenic	13-Dec-89
CAGE 400µl granulocytopenic	20-Dec-89
CAGE 400µl granulocytopenic	25-Jan-90
CAGE 400µl granulocytopenic	2-Mar-90
CAGE Control granulocytopenic	15-Mar-90
CAGE Control granulocytopenic	16-Mar-90
CAGE 400µl granulocytopenic	30-Mar-90
CAGE Control granulocytopenic	24-Apr-90
CAGE Control granulocytopenic	27-Apr-90
CAGE Control granulocytopenic	1-May-90
CAGE Control granulocytopenic	7-Jun-90
CAGE Control granulocytopenic	13-Jun-90

TABLE 2.5. SEQUENCING OF EXPERIMENTS FOR CHAPTER 6

Experiments were performed in 4 separate series. The list here shows the date on which experiments for CHAPTER 6 were done. The experiment codes are explained in Table 2.2.

EXPERIMENT	DATE
CAGE Control	16-May-91
CAGE Control	17-May-91
CAGE Control	22-May-91
CAGE Control	23-May-91
CAGE 400µl dextran sulphate 500	20-Nov-91
CAGE 400µl dextran 500	4-Dec-91
CAGE Control dextran 500	10-Dec-91
CAGE 400µl dextran sulphate 500	20-Dec-91
CAGE 400µl dextran sulphate 500	8-Jan-92
CAGE 400µl dextran 500	5-Feb-92
CAGE 400µl dextran 500	11-Mar-92
CAGE 400µl dextran sulphate 500	12-Mar-92
CAGE 400µl dextran sulphate 500	18-Mar-92
CAGE 400µl dextran 500	19-Mar-92
CAGE Control dextran 500	25-Mar-92
CAGE Control dextran sulphate 500	26-Mar-92
CAGE Control dextran sulphate 500	1-Apr-92
CAGE Control dextran 500	2-Apr-92
CAGE Control dextran 500	23-Apr-92
CAGE Control dextran sulphate 500	29-Apr-92
CAGE Control dextran sulphate 500	30-Apr-92
CAGE Control dextran sulphate 500	18-Jun-92
CAGE Control dextran sulphate 500	1-Jul-92
CAGE 400µl dextran 500	5-Aug-92

TABLE 2.6. OTHER EXPERIMENTS DONE

Experiments performed but not included in the analysis presented here. After surgery these animals were monitored for a period of time but were exclude from analysis for the reasons shown. Equipment failure means either camera, CSER, MABP or other monitoring equipment failure. Animals which became acidotic or hypotensive are indicated as such as are experiments in which a stable preinjection baseline could not be established.

This list does not include studies described in APPENDIX A.

EXPERIMENT	DATE
Blood gas analyser failure	1-Sep-88
Acidotic	15-Nov-88
Very noisy pre-injection baseline data	16-Nov-88
Equipment failure	17-Nov-88
Not injured? internal carotid artery trauma	1-Dec-88
Equipment failure	22-Mar-89
Blood gas analyser failure	23-Mar-89
Acidotic/hypoxic	21-Apr-89
No pre-injection baseline established	26-Apr-89
No pre-injection baseline established	28-Apr-89
Equipment failure	3-Jul-89
No CAGE visible, carotid ligation	26-Jul-89
CAGE 1600µl	13-Sep-89
CAGE 1600µl	21-Sep-89
Acidotic	19-Jun-90
CAGE 1600µl	20-Sep-90
Equipment failure	5-Jun-91
Equipment failure	6-Jun-91
Hypotensive	26-Jun-92
Acidotic	2-Jul-92
Hypoxic	6-Aug-92
Hypotensive	26-Aug-92
Equipment failure	27-Aug-92

TABLE 2.7. DAY SHEET USED FOR RECORDING DATA

Data from individual experiments were logged in a *"daysheet"*. These data were then keyed into EXCEL for analysis (see APPENDIX H). The numbers in italics are calculated by EXCEL or are references to other parts of the worksheet. (Data from an experiment performed on 16-Aug-1988 are shown for illustration only).

Group	Date	Clock	ETime	MABP	Temp	MinVol	pH	PaCO2	PaO2	HCO3	O2sat	rCBF	ICBF	VDiam	ADiam	ERa1	ERI1	ERa2	ERI2	ERa3	ERI3	ERa2a3
CAGE 25µl	16-Aug-88	12:00	-120	90	38.3	675	7.42	37.9	117.4	24.5	98.3	43.3	61.3		35	147	15.8	136	41	21	76	*157*
CAGE 25µl	*16-Aug-88*	*12:15*	*-105*	85	38.0	675	7.42	36.7	102.3	23.8	97.8	39.68	54.19		35	126	16.8	161	46	21	79.6	*182*
CAGE 25µl	*16-Aug-88*	*12:30*	*-90*	90	38.0	675	7.39	39.1	129.8	23.6	98.6	42	66	1200	35	129	15	143	43	7	85	
CAGE 25µl	*16-Aug-88*	*12:45*	*-75*	90	38.0	675										185	15	154	32	67	76	*220.5*
CAGE 25µl	*16-Aug-88*	*13:00*	*-60*	90	38.0	675	7.42	32.3	155.3	20.9	99.0	45	53	1240	35	206	15	150	36	49	73	*199*
CAGE 25µl	*16-Aug-88*	*13:15*	*-45*	90	38.0	675	7.35	40.1	161.2	21.9	99.0	39	70	1160	35	213	16	161	39	53	77	*213.5*
CAGE 25µl	*16-Aug-88*	*13:30*	*-30*	90	38.0	675	7.35	35.8	152.3	19.9	98.9	41	68	1200	35	147	16	142	43	60	74	*201.5*
CAGE 25µl	*16-Aug-88*	*13:45*	*-15*											1260		185	14	98	28	14	86	
CAGE 25µl	*16-Aug-88*	*14:00*	*0*	90	38.0	675	7.38	44.1	147.3	25.9	98.8	43	101	1250	65	119	14	129	27	28	92	*157*
CAGE 25µl	*16-Aug-88*	*14:15*	*15*	90	38.0	675	7.33	42.7	138.9	22.6	98.6	53	68	1290	55	161	17	161	41	21	75	*182*
CAGE 25µl	*16-Aug-88*	*14:30*	*30*	90	38.0	675	7.32	39.4	145.2	20.3	98.0	41	67	1270		122	16	122	40	39	73	*160.5*
CAGE 25µl	*16-Aug-88*	*14:45*	*45*	95	38.0	675	7.38	34.8	158.2	20.4	99.0	57	65	1240	50	147	17	77	41	67	66	
CAGE 25µl	*16-Aug-88*	*15:00*	*60*	95	38.0	675	7.37	40.2	166.0	23.0	99.1	58	95	1300	50	203	14	84	27	70	73	
CAGE 25µl	*16-Aug-88*	*15:15*	*75*	95	38.3	675	7.34	44.5	177.0	23.8	99.1	61	87	1280	45	318	14	192	28	150	76	
CAGE 25µl	*16-Aug-88*	*15:30*	*90*	97	38.8	750	7.40	33.6	181.3	20.2	99.2	47	87		40	378	14	255	26	203	79	
CAGE 25µl	*16-Aug-88*	*15:45*	*105*	98	39.0	710	7.40	31.3	147.0	19.5	98.9	48	52	1270	40	364	15	115	39	136	72	
CAGE 25µl	*16-Aug-88*	*16:00*	*120*	98	38.5	675	7.40	35.8	175.6	22.2	99.2	42	54	1180	35	392	14	238	27	150	76	
CAGE 25µl	*16-Aug-88*	*16:15*	*135*	95	38.0	675	7.38	28.8	173.3	16.1	99.1	66	48	1180		430	17	318	37	217	69	
CAGE 25µl	*16-Aug-88*	*16:30*	*150*	95	38.5	675						47	67	1090	35							
CAGE 25µl	*16-Aug-88*	*16:45*	*165*	95	39.0	675	7.36	39.0	153.9	22.1	98.9	47	39	1160	35							
CAGE 25µl	*16-Aug-88*	*17:00*	*180*	95	39.0	675	7.42	39.6	179.0	21.5	99.3	45	55	1280								
transit time	fast																					
CAGE 25µl 16-Aug-88			Mean	*89.3*	*38.0*	*675.0*	*7.4*	*37.0*	*136.4*	*22.4*	*98.6*	*41.6*	*62.0*	*1212.0*	*35.0*	*167.3*	*15.5*	*143.1*	*38.4*	*44.9*	*78.3*	*195.6*
CAGE 25µl % baseline 16-Aug-88			SD	*1.89*	*0.11*	*0.00*	*0.03*	*2.77*	*23.63*	*1.82*	*0.48*	*2.48*	*7.05*	*38.99*	*0.00*	*34.25*	*0.71*	*20.33*	*6.15*	*19.48*	*4.92*	*23.07*
CAGE 25µl % baseline	*16-Aug-88*	*13:45*	Baseline	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
CAGE 25µl % baseline	*16-Aug-88*	*14:00*	*5*	*100.8*	*99.9*	*100.0*	*99.8*	*119.2*	*108.0*	*115.5*	*100.2*	*103.6*	*162.8*	*103.1*	*185.7*	*71.2*	*89.2*	*90.1*	*69.8*	*62.3*	*117.5*	*80.3*
CAGE 25µl % baseline	*16-Aug-88*	*14:15*	*15*	*100.8*	*99.9*	*100.0*	*99.2*	*115.5*	*101.8*	*100.7*	*100.0*	*127.9*	*109.7*	*106.4*	*157.1*	*96.3*	*109.9*	*112.5*	*107.8*	*46.8*	*96.0*	*93.1*
CAGE 25µl % baseline	*16-Aug-88*	*14:30*	*30*	*100.8*	*99.9*	*100.0*	*99.0*	*106.5*	*106.5*	*90.5*	*99.4*	*97.5*	*108.3*	*104.8*		*72.9*	*102.1*	*85.2*	*104.2*	*85.7*	*93.5*	*82.1*
CAGE 25µl % baseline	*16-Aug-88*	*14:45*	*45*	*106.4*	*99.9*	*100.0*	*99.8*	*94.1*	*116.0*	*90.9*	*100.4*	*135.9*	*104.8*	*102.3*	*142.9*	*87.9*	*108.6*	*53.8*	*106.8*		*84.5*	
CAGE 25µl % baseline	*16-Aug-88*	*15:00*	*60*	*106.4*	*99.9*	*100.0*	*99.7*	*108.7*	*121.7*	*102.5*	*100.5*	*138.8*		*107.3*	*142.9*	*121.4*	*87.9*	*58.7*	*69.3*		*93.0*	
CAGE 25µl % baseline	*16-Aug-88*	*15:15*	*75*	*106.4*	*100.7*	*100.0*	*99.2*	*120.3*	*129.8*	*106.1*	*100.5*	*147.1*		*105.6*	*128.6*	*190.1*	*93.1*	*134.1*	*71.9*		*96.8*	
CAGE 25µl % baseline	*16-Aug-88*	*15:30*	*90*	*108.6*	*102.0*	*111.1*	*100.1*	*90.9*	*132.9*	*90.0*	*100.6*	*113.8*			*114.3*	*226.0*	*87.9*	*178.2*	*68.8*		*101.1*	
CAGE 25µl % baseline	*16-Aug-88*	*15:45*	*105*	*109.8*	*102.5*	*105.2*	*100.2*	*84.6*	*107.8*	*86.9*	*100.3*	*115.1*	*84.1*	*104.8*	*114.3*	*217.6*	*96.9*	*80.3*	*101.6*		*92.0*	
CAGE 25µl % baseline	*16-Aug-88*	*16:00*	*120*	*109.8*	*101.2*	*100.0*	*100.1*	*96.8*	*128.8*	*99.0*	*100.6*	*101.6*	*87.2*	*97.4*	*100.0*	*234.4*	*87.9*	*166.3*	*69.3*		*97.6*	
CAGE 25µl % baseline	*16-Aug-88*	*16:15*	*135*	*106.4*	*99.9*	*100.0*	*99.8*	*77.9*	*127.1*	*71.8*	*100.5*	*158.7*	*77.9*	*97.4*		*257.1*	*108.6*	*222.2*	*96.9*		*87.9*	
CAGE 25µl % baseline	*16-Aug-88*	*16:30*	*150*	*106.4*	*101.2*	*100.0*						*112.6*		*89.9*	*100.0*							#
CAGE 25µl % baseline	*16-Aug-88*	*16:45*	*165*	*106.4*	*102.5*	*100.0*	*99.5*	*105.5*	*112.8*	*98.5*	*100.3*	*113.7*	*62.4*	*95.7*	*100.0*							
CAGE 25µl % baseline	*16-Aug-88*	*17:00*	*180*	*106.4*	*102.5*	*100.0*	*100.3*	*107.1*	*131.2*	*95.8*	*100.7*	*107.5*	*87.9*	*105.6*								

CHAPTER 3.
A MODEL OF CAGE

3.1. EFFECTS OF GAS EMBOLISM ON BRAIN BLOOD FLOW AND FUNCTION

Although it has been demonstrated that prolonged obstruction of the pial circulation by air bubbles is lethal for rabbits [Gorman *et al* 1987b], dogs [Leitch *et al* 1984b; Leitch *et al* 1984c], baboons [Meldrum *et al* 1971] and rats [Johansson 1980] it was widely believed that non-lethal CAGE is associated with air bubble trapping and obstruction to blood flow in the brain circulation [Catron *et al* 1984]. However, regional CBF recovers after non-lethal CAGE, suggesting that air bubbles do not block blood flow through brain capillaries completely [Fritz & Hossmann 1979; Van Allen *et al* 1929]. Bubble passage through the cerebral vessels is the best explanation for the need to repeatedly infuse gas into the internal carotid artery to maintain a constant decrement in neural function in dogs [Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Kochanek *et al* 1988; Obrenovitch *et al* 1984].

To test the hypothesis that bubbles pass through the brain circulation but still disrupt CBF and brain function, experiments were conducted in which rabbits were subjected to CAGE with a non-lethal dose of air.

3.2. METHODS

Rabbits were prepared as described in CHAPTER 2. Pilot studies established that the smallest dose of air which could be infused and reliably viewed was 25 µl and so this dose was chosen for study. All rabbits were maintained within the physiological ranges [Green 1982] for P_aO_2 and P_aCO_2 for at least 90 minutes before either 25 µl of air and 100 µl of saline (embolism group; n=5 rabbits), or 100 µl of saline alone (control group; n=6 rabbits) was injected into the carotid artery cannula over one second. Table 2.3 shows the sequence in which studies

were undertaken. Control (intracarotid saline) rabbits were randomised with 25 µl CAGE rabbits at the time the studies were undertaken. Additional controls were subsequently done and these have been included in the data presented here.

All groups were monitored for 3 hours following the intracarotid saline (control) or gas (CAGE 400 µl) injection, and then killed by an intravenous injection of KCl. All parameters were recorded 2 and 15 minutes after the injection and then every 15 minutes. For analysis of the data, the mean of the pre-injection data for each parameter was assigned a value of 100%. For statistical analysis, all post-injection results were then expressed as a percentage of the pre-injection mean.

3.3. RESULTS

The rabbits remained well throughout the experiment. No brain swelling or other signs of diffuse brain injury were observed.

3.3.1. General observations

The MABP, temperature, P_aCO_2 and P_aO_2 did not change significantly from pre-injection baseline at any time in either group (see table 3.1 for mean data). Similarly, there were no significant pre-injection changes in CBF, CSER AP_2, pial artery diameter or pial vein diameter (data not graphed but listed in APPENDIX H).

Following injection of 25 µl of air (approximately 10 µl/kg) into the left internal carotid artery, bubbles appeared in the pial arteries of all rabbits within 10 seconds. Typically, these bubbles were displaced by the blood-gas interface and advanced with each cardiac systole so that no gas remained in view after 30 seconds of injection. For some rabbits it was

necessary to play the video tape recording of the gas embolism at slow speed to be certain that CAGE had occurred.

3.3.2. Right CBF

There were no significant differences in the right CBF data either between the embolism and control groups or between pre- and post-injection mean values. These data are graphed as percentage of pre-injection baseline after CAGE in figure 3.1 ($F = 1.241$; $df = 65$; $p = 0.279$).

3.3.3. Left CBF

Before saline injection into the internal carotid artery, left CBF in the control group was 53.0 ± 3.07 mls/min/100 g (n = 75 observations; mean ± SEM). ANOVA of left CBF as percent of control showed no change with time after injection of intracarotid saline ($F = 1.060$; $df = 173$; $p = 0.392$). Thus left CBF was not affected by intracarotid saline injection.

In the CAGE group, left CBF was 64.8 ± 3.51 mls/min/100 g (n = 39 observations; mean ± SEM) before CAGE. After CAGE, left CBF showed a progressive decline as compared to pre-injection baseline ($F = 3.029$; $df = 53$; $p = 0.003$). Left CBF in the CAGE group was significantly different from the intracarotid saline group at 30, 45, 75, 90, 105, 120 and 180 minutes ($p < 0.05$; see figure 3.2).

The reason for a statistically significant difference in left CBF for the control and CAGE groups is unknown although the difference is likely to have little physiological significance. The animals were prepared in an identical way and were randomly assigned to either the control or CAGE group. Analysis of the data as a percentage of pre-injection baseline eliminates any systematic contribution this difference may have had on the actual changes induced by CAGE.

3.3.4. Pial artery diameter

The control group pial arterial diameter was 409 ± 39.8 µm (n = 63 observations; mean ± SEM) before saline injection. When the data were compared to pre-injection baseline as a percent of control, there was no statistically significant variation in pial artery diameter throughout the course of the experiments (F = 0.938; df = 129; p = 0.516).

In the 25 µl CAGE group, pial artery diameter was 392 ± 61.5 µm (n = 32 observations; mean ± SEM) before air injection into the internal carotid artery. Immediately after the air injection there was an increase compared to control by 5 minutes of 22.6% (t = 3.315; p = 0.005) which was maximal by 15 minutes, 26.7% greater than control (t = 3.315; p = 0.005). This change was however, not sustained, pial artery diameter slowly returned to the pre-injection values so that by 90 minutes the diameters of the two groups were similar ((F = 1.104; df = 54; p = 0.0457; see figure 3.3).

3.3.5. Pial venous diameter

Pial venous diameter was 180 ± 5.6 µm (n = 64 observations; mean ± SEM) before saline injection in the control group and although the pial veins constricted to 91.1% of pre-injection baseline at the by the end of the experiment this small change is not likely to be physiologically important (F = 2.02; df = 144; p = 0.023). Similarly, pial venous diameter was 141 ± 93.4 µm (n = 18 observations; mean ± SEM) before air embolism but did not change throughout the course of the experiment (F = 0.67; df = 36 p = 0.770; see figure 3.4).

3.3.6. CSER AP_2

The measurements of CSER AP_2 performed 2 minutes after the gas-saline or saline injection showed no significant changes from the pre-injection means in either the embolism or the control group and no significant difference existed between the two groups at this time. Thereafter, the CSER AP_2 measurements showed a progressive decrease of amplitudes in the embolism compared to pre-injection baseline ($F = 2.25$; $df = 51$; $p = 0.025$) and this difference became significant at 90 minutes when the mean decrease in the embolism group was 50 ± 13% ($p < 0.05$; mean ± SEM). The control group CSER AP_2 never differed from the pre-injection mean value ($F = 1.00$; $df = 168$; $p = 0.45$). These data are shown as % pre-injection baseline after CAGE in figure 3.5.

3.3.7. Relationship between CSER AP_2 and CBF

The CSER AP_2 wave is produced by stimulation of a rabbit's right forepaw and recording the generated signal on the surface of the left cerebral hemisphere [Iragui-Madoz & Wiederholt 1977]. The hydrogen clearance technique measures the CBF of a small region (approximately 8 mm^3) of brain [Halsey *et al* 1977; Pearce & Adams 1982]. In order to see if CBF and brain function remain coupled during the decline in CSER AP_2 regression analyses was performed. A linear relationship between left CBF and CSER AP_2 in the embolism group could be demonstrated ($r^2 = 0.47$; $F = 9.97$; $p = 0.009$) over the data range expressed by the equation;

$$\text{left CBF} = 1.00 \times \text{CSER } AP_2 + 12.55$$

(see figure 3.6)

3.4. DISCUSSION

A gas volume of 25 µl was the smallest that would reliably embolise the exposed pial vessels. Bubbles appeared in pial arteries within 10 seconds of injection and were rapidly displaced by blood. The injection of gas into the left internal carotid artery had no effect on right CBF suggesting there was little or no embolism of the contralateral hemisphere, an observation consistent with other reports [Furlow 1982; Lee 1974].

The decrease in CBF cannot be explained by changes in MABP, P_aCO_2 or P_aO_2, all of which remained stable, or by changes in intracranial pressure which cannot increase in this open-brain model. The stable MABP in the embolism group suggests that the circulation to the brain-stem was not affected, [Evans *et al* 1981; Fritz & Hossmann 1979; Gorman & Browning 1986; Nagao *et al* 1987].

The embolised vessels underwent a transient vasodilation, a event probably not due to brain-stem reflexes [Nagao *et al* 1987] or to changes in MABP, P_aO_2 or P_aCO_2 which remained constant throughout the experiment. Although the calculated pressure in bubbles trapped in pial arteries is less than 870 mmHg [Gorman 1987a] absolute pressures greater than 935 mmHg are needed to overcome pressure autoregulation [Vinall & Simeone 1981]. Furthermore, the characteristic *"sausage"* or *"bead-string"* dilation caused by such elevated pressures [Vinall & Simeone 1981] was not seen in these experiments. The increase in transmural pressure caused by these intra-arterial bubbles should cause the vessels to constrict rather than dilate (pressure autoregulation) [Bayliss 1902; Harder 1987]. However, the normal vasoconstrictor response to increases in transmural pressure requires an intact endothelium [Harder 1987] and bubble transit has been shown to damage endothelial cells [Kuroiwa *et al* 1988; Persson *et al* 1978; Warren *et al* 1973]. The initial vasodilation seen in

this model may therefore be an inappropriate vascular response to the transit of the embolus.

Despite a stable MABP the 27% increase in external diameter of embolised pial arteries was not associated with any change in regional CBF. If the internal vessel diameter also increased by 27% then in the absence of any other changes and assuming Newtonian flow [Rothe 1971], there should have been a 260% increase in CBF [Ganong 1983]. Of course, blood flow in these small vessels may not be Newtonian [La Celle 1986] in which case the immediate post-embolus maintenance of CBF may be due to an increase in resistive pressure secondary to bubbles in the capillaries or intraparenchymal arterioles. After embolus transit the pial arteries then constricted to their pre-embolism size over 90 minutes accompanied by a reduction in CBF to 60% of control values.

The CSER AP_2 also decreased after CAGE, indicating that cortical sensorimotor cortex function was impaired. This impairment correlated well with the reduced CBF. A coupling of brain function and CBF has also been demonstrated in the cats after CAGE [Fritz & Hossmann 1979], and in dogs the CSER recovery after air embolism correlates well with the blood flow in the sensorimotor cortex [Dutka *et al* 1987].

Although it has been suggested that bubbles can pass to the cerebral veins and be cleared from the brain after CAGE in rabbits [Gorman *et al* 1987b; Gorman & Browning 1986] no venous bubbles were observed in these experiments. It has also been suggested the local vascular architecture at the junction of the grey and white matter makes bubble entrapment likely [Dutka *et al* 1988]. Whereas such bubbles cannot be detected by this model bubble trapping at the grey-white junction may not relevant here. Mechanical blockage of intraparenchymal blood vessels should have been detected with the first measurement of CBF after embolism. However 15 minutes post-injection, the left CBF in the

embolism group did not differ significantly from either the pre-injection value for this group, or from the left CBF of the control group. Furthermore, brief periods (5-30 seconds) of arrested brain blood flow are normally followed by a reactive hyperaemia [Gourley & Heistad 1984; Symon *et al* 1972], a phenomenon not seen in this model. CBF after air embolism showed a progressive and significant decline of greater than 40% over 90 minutes. If bubble trapping at the grey-white junction was important in this model then its effects should have been measurable immediately after embolism. The reason for progressive fall in CBF cannot be identified by these studies but it seems unlikely to be caused by bubble trapping.

Others have reported that bubbles have acute effects on vascular endothelium [Haller *et al* 1987; Persson *et al* 1978; Warren *et al* 1973] and blood constituents [Hallenbeck *et al* 1986; La Celle 1986; Obrenovitch *et al* 1984; Thorsen *et al* 1986; Warren *et al* 1973] such that blood vessel wall thickness will increase. Thus, a better explanation would invoke secondary gas-induced changes in blood and/or blood vessels.

In order to further characterise this model rabbits were treated with increasing doses of intracarotid air.

FIGURE 3.1. RIGHT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (INTRACAROTID SALINE INJECTION) [MEAN ± SEM]

Right CBF was measured by hydrogen clearance from a platinum electrode inserted through a burr hole over the right somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (mean ± SEM) from this pre-injection baseline value.

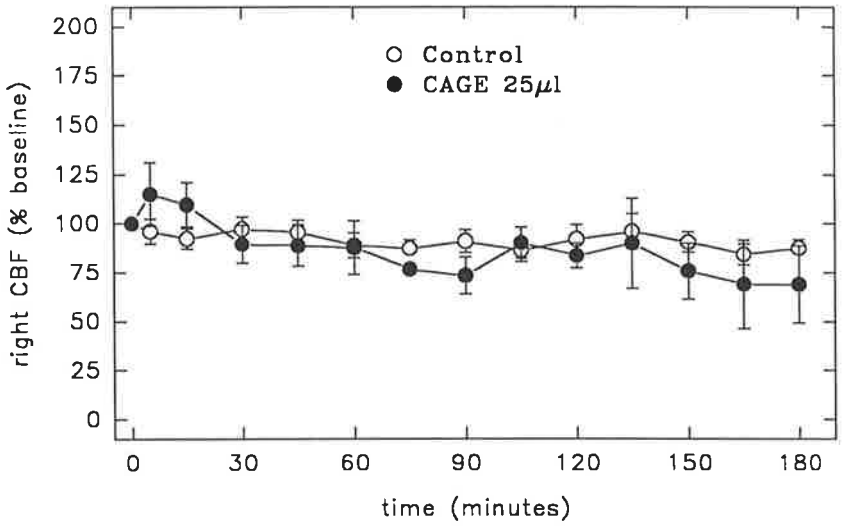


FIGURE 3.2. LEFT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (INTRACAROTID SALINE INJECTION) [MEAN ± SEM]

Left CBF was measured by hydrogen clearance from a platinum electrode inserted through the craniotomy made over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (mean ± SEM) from this pre-injection baseline value.

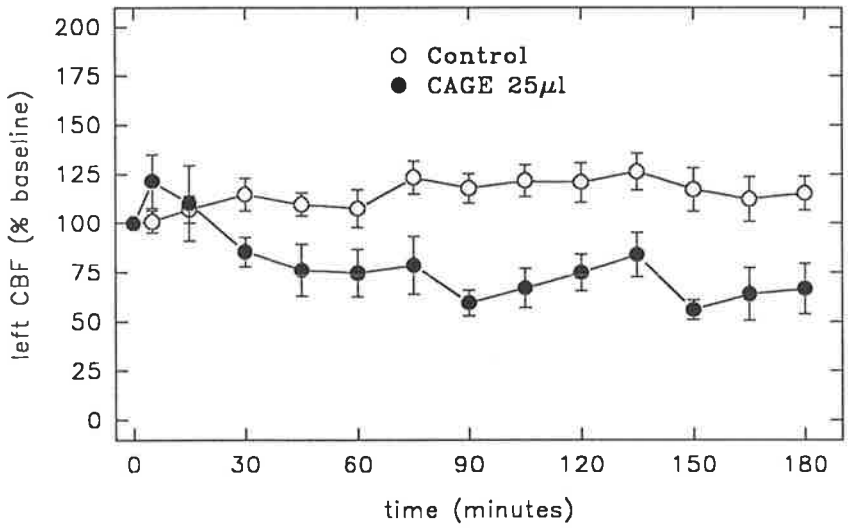


FIGURE 3.3. PIAL ARTERIAL DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (INTRACAROTID SALINE INJECTION) [MEAN ± SEM]

Pial arterial diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (mean ± SEM) from this pre-injection baseline value.

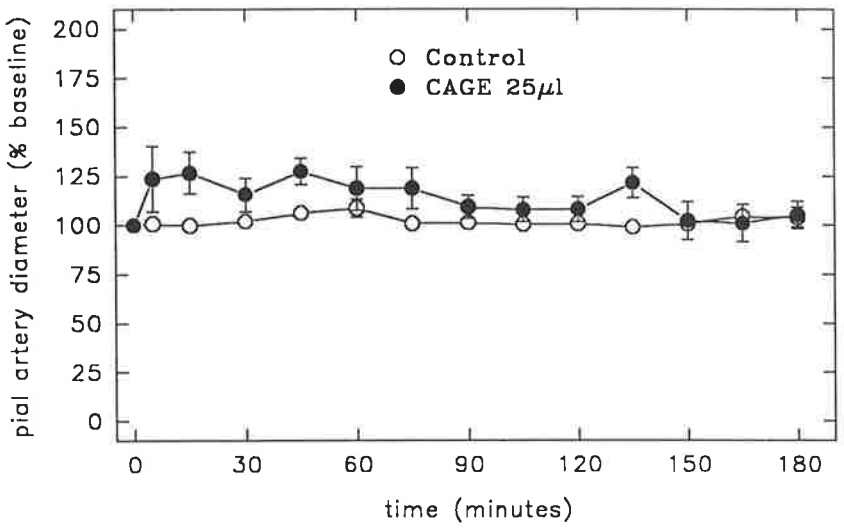


FIGURE 3.4. PIAL VENOUS DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (INTRACAROTID SALINE INJECTION) (MEAN ± SEM)

Pial venous diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (mean ± SEM) from this pre-injection baseline value.

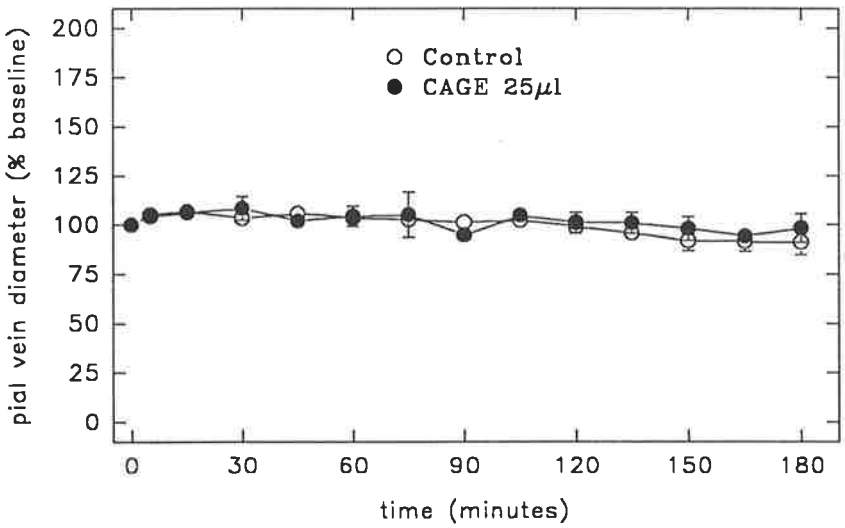


FIGURE 3.5. CSER AP_2 AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (INTRACAROTID SALINE INJECTION) (MEAN ± SEM)

The CSER AP_2 was measured from the mean of 80 average evoked responses from the somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (mean ± SEM) from this pre-injection baseline value.

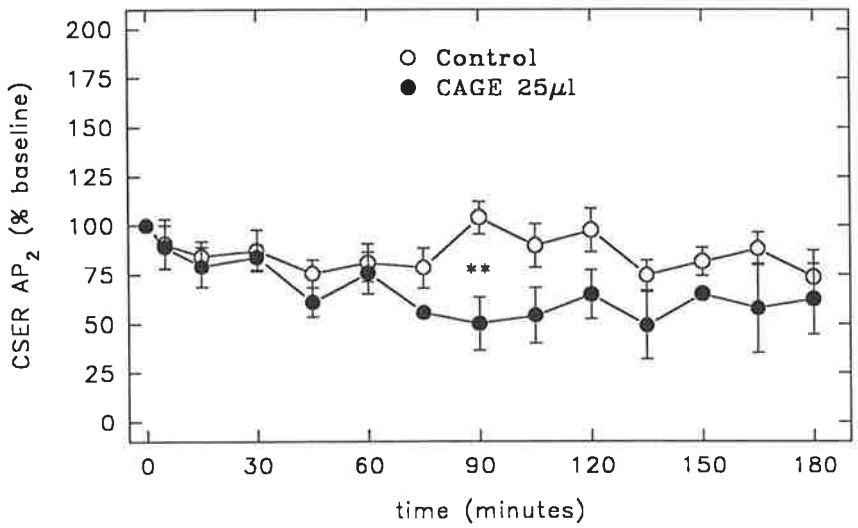


FIGURE 3.6. REGRESSION ANALYSIS OF CSER AP_2 AND LEFT CBF IN THE 25 µl CAGE GROUP

Least squares regression analysis was performed on left CBF (percent of the pre-injection mean value) versus CSER AP_2 (percent of the pre-injection mean value). The line shows the equation of best fit (r^2 = 0.47; F = 9.97; p = 0.009);

$$\text{left CBF} = 1.00 \times \text{CSER } AP_2 + 12.55$$

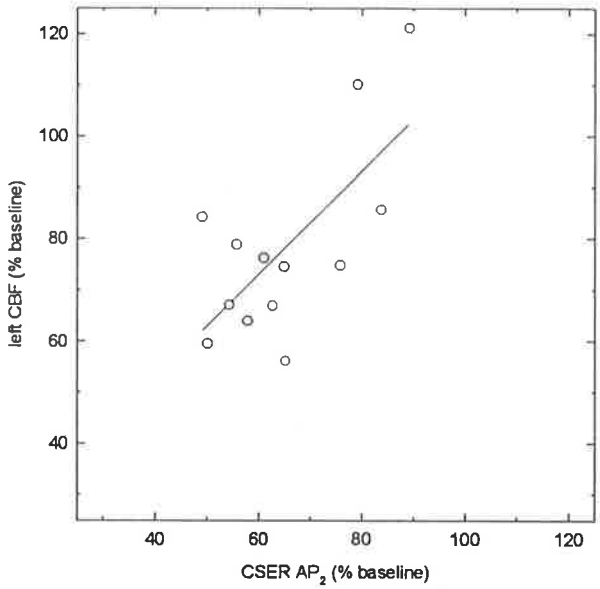


TABLE 3.1 MABP, TEMPERATURE, P_aCO_2 AND P_aO_2 BEFORE CAGE OR INTRACAROTID SALINE

MABP (mmHg)	mean	SD	SEM	n
Control	94.4	12.79	0.73	302
CAGE 25µl	95.5	12.67	1.19	112

Temperature °C	mean	SD	SEM	n
Control	38.2	0.66	0.03	298
CAGE 25µl	38.4	0.53	0.05	110

P_aCO_2	mean	SD	SEM	n
Control	38.6	4.59	0.26	294
CAGE 25µl	38.2	4.45	0.42	110

P_aO_2	mean	SD	SEM	n
Control	142.6	25.76	1.50	292
CAGE 25µl	144.7	24.39	2.32	110

CHAPTER 4.

INCREASING DOSES OF AIR

4.1. EFFECTS OF INCREASING DOSES OF INTRACAROTID AIR ON CEREBRAL BLOOD FLOW AND BRAIN FUNCTION

Studies described in CHAPTER 3 have shown that small amounts of air injected into the internal carotid artery appear in and then pass rapidly through the pial arteries. Measurements of both local brain blood flow and brain function (CSER AP_2) performed immediately after this bubble transit show normal values. However, brain blood flow and function then slowly but progressively deteriorate over the next 90 minutes. Effects on pial arterial diameter were transient.

The aim of the next series of experiments was to identify and study an intermediate bubble insult, that is a dose of air which caused bubbles to be trapped temporarily in the pial arteries, but which would allow the bubbles to be cleared eventually and the rabbits to survive. The dose range above that chosen for this series of studies blocks pial arteries and has been shown to be lethal [Gorman & Browning 1986; Gorman *et al* 1987b].

4.2. METHODS

Rabbits were prepared as described in CHAPTER 2. In the first stage of the study, bubble transit times (measured from the first appearance of a bubble until complete bubble clearance) through the exposed pial vessels were determined for the following volumes of air injected into the left internal carotid artery: 50 µl (2 rabbits) 100 µl (3 rabbits), 200 µl (3 rabbits) and 400 µl (8 rabbits). All doses of intracarotid air caused CAGE, but only in animals given 400 µl air injections were bubbles temporarily trapped (*viz;* bubbles were nearly

stationary) in the pial vessels. Thus a 400 µl dose of air was chosen for the second phase of the study.

Rabbits were maintained within the physiological ranges [Green 1982] for P_aO_2 and P_aCO_2 for at least 90 minutes. After this time either 400 µl of air and 600 µl of saline (embolism group; n = 8 rabbits), or 1000 µl of saline alone (control group; n = 16 rabbits) were injected into the carotid artery cannula at a rate of 400 µl/60 seconds.

Both groups were monitored for 3 hours following the air/saline or saline injection, and then killed by a barbiturate overdose. All parameters were recorded 2 and 15 minutes after the insult and then every 15 minutes for 3 hours.

For each parameter, the mean of the pre-injection data was assigned a value of 100%. All subsequent data were recorded as percentages of the pre-injection mean values. Data were tested by analyses of variance, regression analyses and t-tests. A significance level of $p < 0.05$ was chosen and when simultaneous multiple comparisons were performed the Bonferroni Method was used [Wallenstein *et al* 1980].

4.3. RESULTS

4.3.1. General observations

The MABP, temperature, P_aCO_2, P_aO_2 and heart rate did not change significantly from pre-injection baseline at any time in any rabbit (see table 4.1). Similarly, there were no significant changes in CBF, CSER AP_2, pial artery diameter or pial vein diameter (data not graphed but listed in APPENDIX H).

Following injection of 400 µl of air into the left internal carotid artery, bubbles appeared in the pial arteries of all rabbits within 10 seconds (approximately 150 µl/kg). These bubbles became trapped in pial arteries of between 50 and 200 µm diameter, but were eventually displaced by blood. Bubble transit times through the exposed vessels ranged from 60 to 405 seconds with a mean of 231.4 ± 64.5 seconds (± SEM). In all rabbits, most of the air had cleared from view within 120 seconds of embolism.

Data from the 25 µl CAGE studies are shown for purposes of comparison.

4.3.2. Right CBF

There were no significant differences in the right CBF data either between the embolism and control groups or between pre-injection baseline and post-injection mean values. These data are shown as percentages of pre-injection baseline in figure 4.1 ($F = 0.687$; $df = 64$; $p = 0.766$).

4.3.3. Left CBF

In the 400 µl CAGE group, left CBF was 87.1 mls/min/100 g ± 4.51 ($n = 38$) before CAGE. After CAGE, left CBF showed a progressive decline as compared to pre-injection baseline ($F= 3.022$; $df = 72$; $p = 0.002$). Left CBF in the 400 µl CAGE group was significantly different from the intracarotid saline group from 45 minutes onward ($p < 0.05$, see figure 4.2) but was at no time different from the 25 µl CAGE group.

4.3.4. Pial arterial diameter

The control group showed no significant variation in pial arterial diameter throughout the course of the experiments, whereas the embolism groups showed significant increases in external diameter

immediately after the gas/saline injection (F = 1.191; df = 71; p = 0.046). Arterial dilatation was maximal at 5 minutes after CAGE when it reached 126 ± 13.7% (n = 5; ± SEM) of control (CAGE 400 µl compared to control at 5 minutes; t = 2.85; p = 0.011). The initial percentage dilatation in the 25 and 400 µl embolism groups was not significantly different (126.0 ± 13.7% compared to 126.0 ± 16.6% ; df = 9; t = 0.11; p = 0.910). These diameters then slowly returned to the pre-injection values so that by 90 (25 µl) and 30 (400 µl) minutes those of the embolism groups were similar to the controls (figure 4.3).

4.3.5. Pial venous diameter

In the 400 µl CAGE group the pial veins exhibited a slight but statistically significant constriction compared to the control value (F = 2.107; df = 81; p = 0.024). Compared to control the veins had recovered 105 minutes after 400 µl CAGE (figure 4.4).

4.3.6. CSER AP_2

As bubbles appeared in the pial vessels, the CSER AP_2 was suppressed. In the 25 µl embolism group this was brief and as the bubbles passed out of the exposed vessels the cortical response returned to normal (see figure 4.6). The CSER AP_2 measured 2 minutes after the 25 µl air injection (CSER AP_2 = 89 ± 10.8% SEM) was not significantly different from either the pre-injection mean value in these animals or the CSER AP_2 in the control group at the same time (CSER AP_2 = 90 ± 12.7% SEM). Thereafter, the CSER AP_2 measurements showed a progressive decrease of amplitudes in the 25 µl embolism group.

CSER AP_2 in the 400 µl CAGE group however exhibited a catastrophic reduction to 29 ± 11.0% SEM of pre-injection baseline within 5 minutes of CAGE. Thereafter the CSER AP_2 in this group remained suppressed, never

properly recovering (see figure 4.5). The continuous CSER trace for one animal is shown in figure 4.6. The amplitude of the CSER is immediately suppressed but by 25 minutes after CAGE has only recovered slightly.

4.3.7. Relationship between CSER AP_2 and CBF

In the 400 µl embolism group the CSER AP_2 persisted even after the bubbles passed out of view. Although almost all bubbles had cleared by 5 minutes (transit time average 231 ± 63 seconds) and the mean left CBF at this time was similar to that in the pre-injection and control group values (figure 4.2), the CSER AP_2 in these rabbits was still significantly reduced (CSER AP_2 = 29 ± 11.1% SEM). This had recovered slightly when the CSER AP_2 was measured again 15 minutes after the injection (CSER AP_2 = 55% ± 7.6 SEM). Thereafter there were no further changes in the mean CSER AP_2 in this group (figure 4.5). At all times after embolism these 400 µl CSER AP_2 values were significantly lower than the pre-injection mean value for this group and from the control group, and were also significantly lower than the CSER AP_2 in the 25 µl embolism group for the first 60 minutes after embolism.

Regression analysis showed there was no direct relationship between left CBF and CSER AP_2, indicating an uncoupling of brain blood flow and function (r^2 = 0.001; F = 0.005; p = 0.940; see figure 4.7).

4.4. DISCUSSION

A single intracarotid air dose of 400 µl (approximately 150 µl/kg) was needed to produce CAGE in which there was temporary bubble trapping. In none of the other doses of air up to 300 µl [10-125 µl/kg] did bubbles become trapped in the exposed pial vessels. Bubble typically took less than 30 seconds to transit the field of view and blood flow was restored immediately. Others have shown

that when air injection is continued until bubbles permanently block pial vessels, rabbits survive only for about 20 minutes [Gorman & Browning 1986; Gorman *et al* 1987b].

The progressive reductions in CBF seen after 400 µl CAGE cannot be explained by changes in MABP, P_aCO_2 or P_aO_2, all of which remained stable, or by changes in intracranial pressure which cannot increase in this open-brain model. This 400 µl dose of air was associated with an inhibition of both neural function and CBF ipsilateral but not contralateral to the injection, an effect that has been described previously [Furlow 1982; Lee 1974]. Within 5 minutes of embolism however, 80% of all visible air had cleared from view, and the measured CBF was 97.2% of the pre-injection mean. This was not significantly different from that in the 25 µl embolism group (121.4%) or the controls (100.8%). The progressive decline in CBF during the subsequent 45 minutes to about half of the pre-injection mean in the 400 µl embolism group did not differ from that seen in the 25 µl embolism group. The effect of air embolism on CBF (as measured by hydrogen clearance) and pial arterial diameter appears therefore to be independent of dose.

The external diameters of the embolised vessels increased significantly, but again, the 25 and 400 µl embolism groups showed similar changes. Indeed, the dilatation seen in both groups was not significantly different from that which follows a lethal air dose [Gorman & Browning 1986; Gorman *et al* 1987b].

The somatosensory response produced by stimulation of a rabbit's right forepaw is projected to a small area on the surface of the left cerebral hemisphere [Iragui-Madoz & Wiederholt 1977]. Analysis of the initial slope of a hydrogen clearance graph measures the fastest blood flow in a small region (approximately 8 mm^3) of brain [Halsey *et al* 1977; Pearce & Adams 1982]. Therefore it was possible to observe the changes in CBF and CSER AP_2 in the very

localised region through which bubble passage was observed. Gas embolism suppressed the CSER AP_2 indicating that sensorimotor cortex function was impaired [Iragui-Madoz & Wiederholt 1977]. This effect was dose-dependent. In the 25 µl embolism group, there was a very brief suppression of the CSER continuous trace that recovered almost immediately (see figure 4.6). This was followed by a progressive decline in the CSER AP_2 which correlated well with the falling CBF ($r = 0.67$). A coupling of function and CBF has also been demonstrated in the cat brain after air embolism [Hossmann & Fritz 1978], and in dogs recovery of the cortical somatosensory evoked response after air embolism also correlated well with blood flow in the sensorimotor cortex [Dutka *et al* 1987]. In contrast, 2 minutes after the 400 µl air injection, although CBF was 100.2% of the pre-injection mean and most bubbles had cleared, the CSER AP_2 remained at less than 30% of the pre-injection mean value. This was followed by an improvement during the next 13 minutes to 50% of the pre-injection mean, but no further improvement was seen after this time. This profound post-embolic inhibition of the cortical somatosensory evoked response was significantly greater than after a 25 µl injection and neural function and CBF were clearly uncoupled. The reasons for this uncoupling of function and flow or for the sustained suppression of function were not identified in these studies. While these measurements of CBF may underestimate areas of low CBF within the sampled tissue it is noteworthy that the evoked response voltages and the initial slope index of CBF correlated well with each other after the 25 µl air injection. Loss of this correlation after the 400 µl air embolism is worthy of further investigation.

These effects of intracarotid air (25 µl to 400 µl) are consistent with the natural history of air embolism of the brain in divers [Gorman 1984; Greene 1978; Stonier 1985]. In about 5% of divers there is a cardiorespiratory arrest and death [Gorman 1984; Greene 1978]. This is analogous to a lethal continuous air

dose. In about 35% of divers there is a sustained interruption of neural function [Stonier 1985] analogous to the 400 µl air dose (temporary bubble trapping but sustained inhibition of brain function). Finally, in the remaining 60% there is a spontaneous recovery [Stonier 1985], often complete. This is analogous to the 25 µl air dose (rapid bubble transit and recovery of brain function). The subsequent decline in CBF and neural function following this 25 µl insult may explain why some of these divers recover only to relapse later [Pearson 1984]. Indeed, the observed time-frame in these rabbits is comparable with the peak occurrence of relapses in those patients with air embolism who initially respond to recompression therapy [Leitch & Green 1986; Green & Leitch 1987]. This model of air embolism of the brain would therefore appear to be suitable for further study including the testing of potential therapeutic regimens.

Bubbles in the pial arterioles interfered with the signal from a laser Doppler flowmeter used in some studies. The laser Doppler signal returned to normal when the bubbles were no longer visible suggesting bubbles had in fact left the cerebral cortex (see APPENDIX A.3.). Similarly the signal from an ultrasonic Doppler crystal over the sagittal sinus changes in a characteristic way when intracarotid air is injected. This signal returns to normal after several minutes, suggesting that some proportion of the intracarotid gas escapes into the venous circulation (APPENDIX A.2.2.). Attempts to measure tissue O_2 tension using a polarographic electrode showed that CAGE in this model was not producing substantial tissue hypoxia (APPENDIX A.4.). Thus it seems probable that bubbles do not trap in the brain circulation to any significant degree and neither do they cause substantial tissue hypoxia.

The changes in CBF, neural function and pial arterial diameter might be explained by the effects of gas on the blood itself or on blood vessels. This hypothesis has two important consequences for the treatment of patients with CAGE. Firstly, although compression in a recompression chamber will reduce

air embolus volume and so help to redistribute trapped emboli to the venous circulation [Gorman *et al* 1987a], treatment by compression alone could be expected to have a significant failure rate because it takes no account of these secondary effects. Indeed, a significant failure rate has been shown for compression treatment alone for CAGE in both animals (30-50%) [Gorman *et al* 1987a; Leitch *et al* 1984a; Leitch *et al* 1984b; Leitch *et al* 1984c; Leitch *et al* 1984d] and divers (22%) [Kizer 1987]. Secondly, a post-CAGE, gas-induced fall in CBF to neuron disabling levels [Dutka *et al* 1987; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b; Hallenbeck *et al* 1986] may explain why many patients who appear to have recovered from CAGE subsequently relapse [Pearson 1984]. If this model is a reasonable predictor for humans this should occur within two hours of embolism. While the speed of endothelial damage and the response of the blood system may be different in man, this predicted time-frame is consistent with the peak occurrence of relapses in those patients with CAGE who initially respond to recompression therapy [Leitch & Green 1986; Green & Leitch 1987].

FIGURE 4.1. RIGHT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Right CBF was measured by hydrogen clearance from a platinum electrode inserted through a burr hole over the right somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

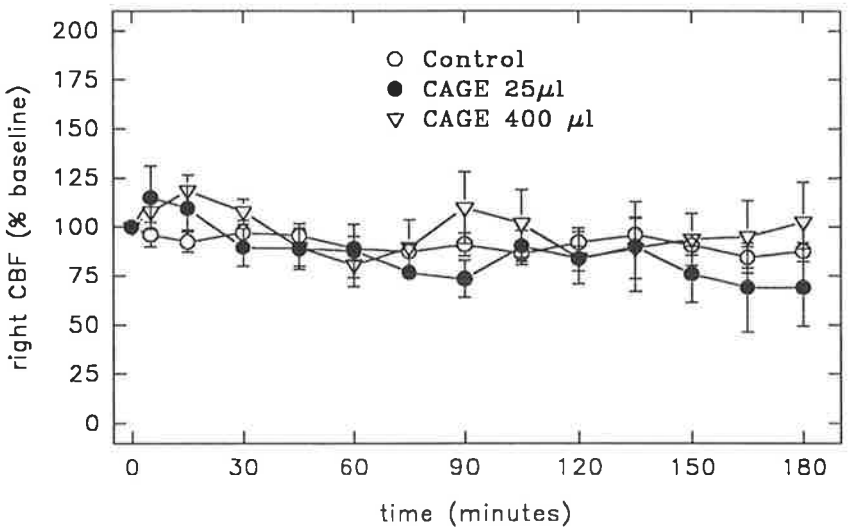


FIGURE 4.2. LEFT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Left CBF was measured by hydrogen clearance from a platinum electrode inserted through a burr hole over the right somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

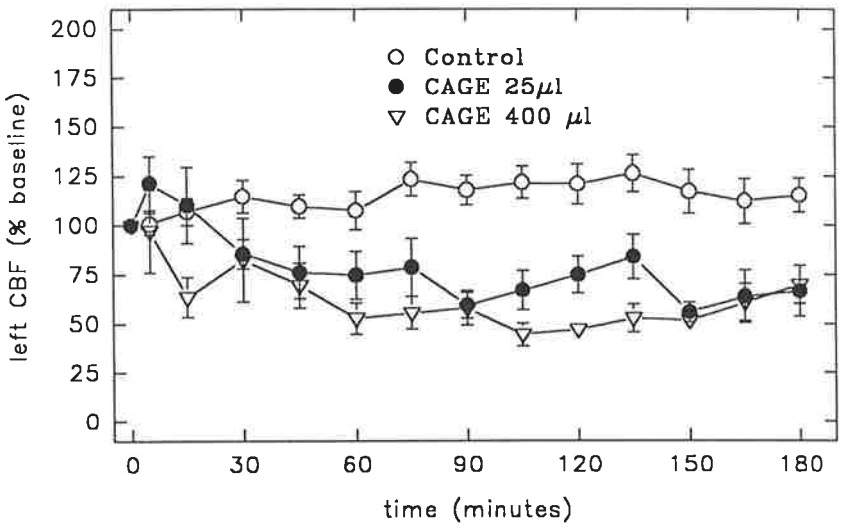


FIGURE 4.3. PIAL ARTERIAL DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Pial arterial diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

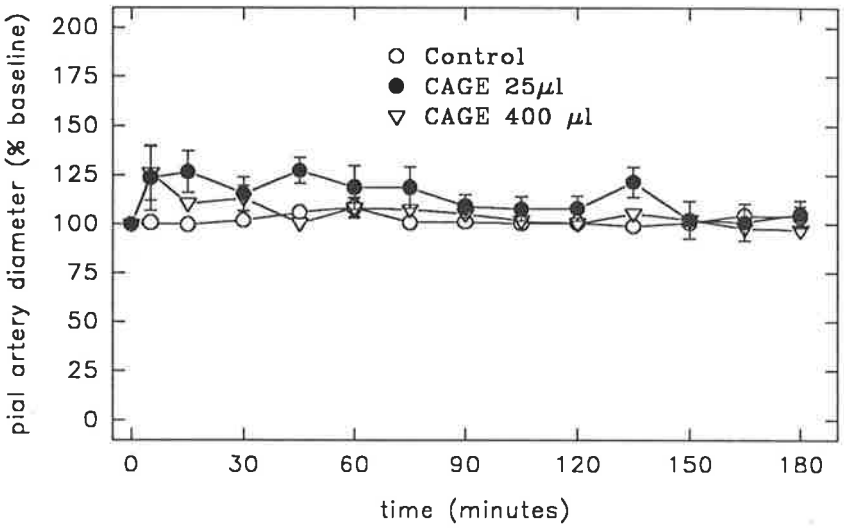


FIGURE 4.4. PIAL VENOUS DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Pial venous diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

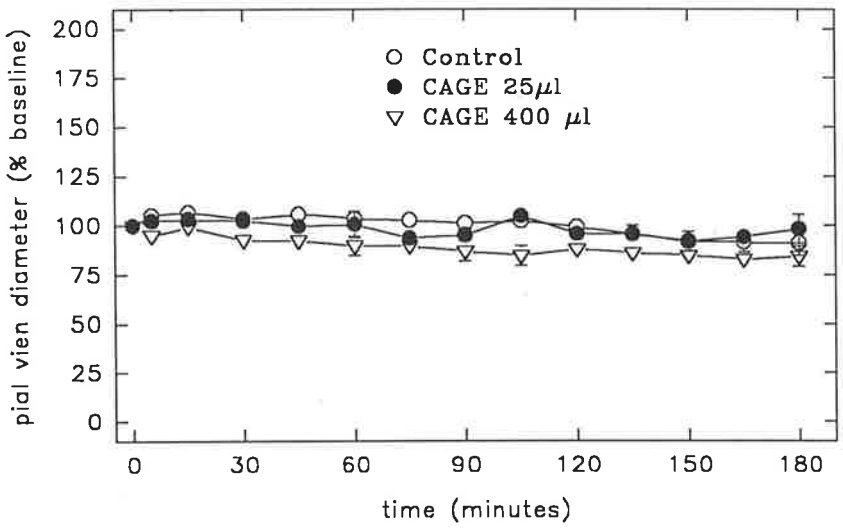


FIGURE 4.5. CSER AP_2 AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

The CSER AP_2 was measured from the mean of 80 average evoked responses from the somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

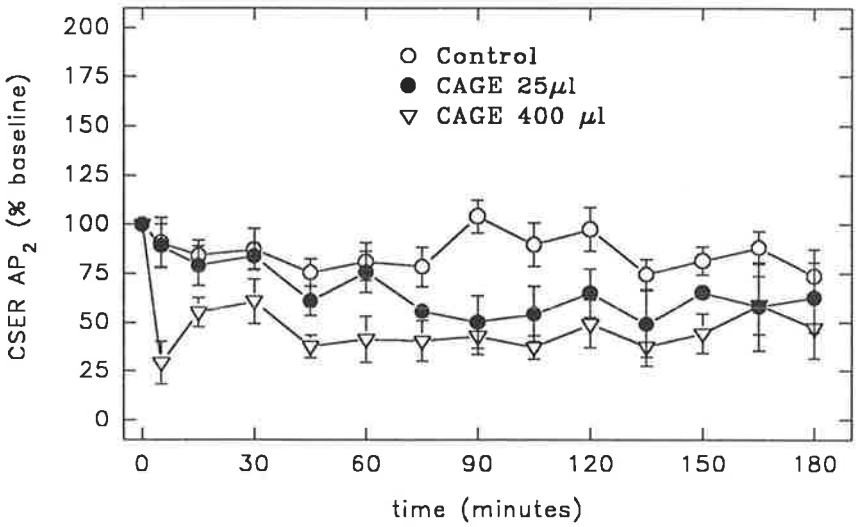


FIGURE 4.6. TYPICAL CONTINUOUS TRACING OF THE CSER SIGNAL IN RABBITS

The shaded bar indicates time air was visible in the pial arteries.

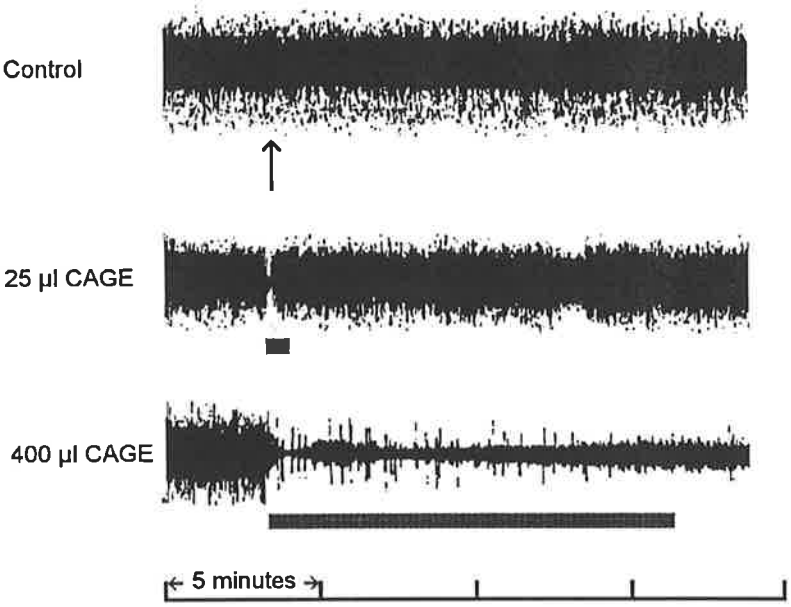


FIGURE 4.7. REGRESSION ANALYSIS OF THE CSER AP_2 AND LEFT CBF IN THE 400 µl CAGE GROUP

The equation was not statistically significant (r^2 = 0.00; F = 0.005; p = 0.940).

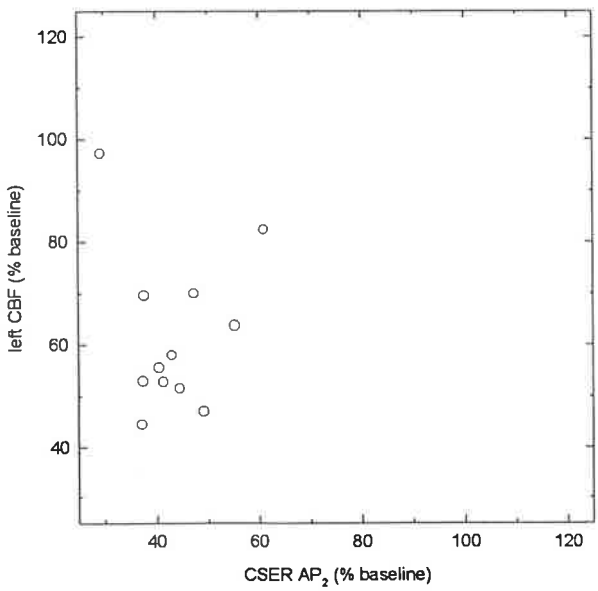


TABLE 4.1 MABP, TEMPERATURE, P_aCO_2 AND P_aO_2 BEFORE CAGE OR INTRACAROTID SALINE

MABP (mmHg)	mean	SD	SEM	n
Control	94.4	12.79	0.73	302
CAGE 400µl	89.2	13.28	1.84	52

Temperature °C	mean	SD	SEM	n
Control	38.2	0.66	0.03	298
CAGE 400µl	38.7	0.51	0.07	52

P_aCO_2	mean	SD	SEM	n
Control	38.6	4.59	0.26	294
CAGE 400µl	37.7	3.92	0.54	52

P_aO_2	mean	SD	SEM	n
Control	142.6	25.76	1.50	292
CAGE 400µl	156.4	28.19	3.95	51

CHAPTER 5.

EFFECTS OF GRANULOCYTE DEPLETION

5.1. AIR EMBOLISM OF THE BRAIN IN RABBITS PRE-TREATED WITH MECHLORETHAMINE

Air injected into an internal carotid artery of rabbits causes significant decrements in CBF and brain function (as measured by CSER AP_2). These changes occur both when bubble transit is rapid (25 µl CAGE) and when bubbles are temporarily trapped in pial arteries (400 µl CAGE). The effects of CAGE on CBF are independent of dose and develop gradually over the 3 hours of the experiment. The CSER AP_2 is suppressed gradually after 25 µl CAGE, presumably due to the progressive impairment of CBF whereas 400 µl CAGE produces a profound and sustained decrement in CSER AP_2.

For all doses of gas studied the effects on CBF and brain function persist after all bubbles have cleared from the observed field. It seems likely bubbles do not trap in the brain circulation to any significant extent. The nature of the interactions which produce the sudden depression of CSER AP_2 after 400 µl CAGE are not obvious from these experiments, but since CBF is not different from control until at least 45 minutes after CAGE it seems unlikely to be due to cerebral ischæmia. It is also unlikely there is substantial tissue hypoxia in this model of CAGE (see APPENDIX A). Thus, the decrements in brain function and blood flow seen in this model may not be due to bubbles directly occluding blood vessels but may be due to vessel occlusion caused by interactions between bubbles, blood vessels and blood cells.

Granulocytes accumulate either in the brain substance or in the brain microvessels after CAGE [Hallenbeck *et al* 1986; Kochanek *et al* 1987a] and granulo-

cyte depletion before CAGE leads to amelioration of post embolus hypoperfusion [Dutka *et al* 1989].

To further test the hypothesis that brain dysfunction and reduced blood flow after CAGE in this model was due to mobile bubbles activating granulocytes, rabbits were treated with mechlorethamine to make them granulocytopenic prior to a 400 µl CAGE.

5.2. METHODS

Seventy two hours prior to study 13 rabbits were treated with an intravenous injection of 1.5 mg/kg mechlorethamine [Boots Pharmaceutical; *2-Chloro-N-(2-choroethyl)-N-methylethanamine* (nitrogen mustard)]. Mechlorethamine is a potent alkylating agent with a short half life in the circulation (less than 30 minutes) and has its effects primarily on cells which are rapidly synthesising nucleic acids (*viz;* are dividing rapidly). Depletion of white cells (leukocytopenia) was monitored by periodically taking blood anticoagulated with EDTA di-potassium for cell analysis on a cell counter (either a Coulter Electronics; COULTER S & 6 CELL COUNTER [with Cash modification] or on a Technicon; TECHNICON H•1 HEMATOLOGY SYSTEM; see APPENDIX E). Neither of these cell counters give reliable animal platelet counts. However, other studies treating animals with mechlorethamine have reported no effect on platelet numbers in dogs [Dutka *et al* 1989], sheep [Flick *et al* 1981] or rabbits [Freed *et al* 1989]. Blood samples for cell counts were taken before and after mechlorethamine treatment and on the day of the CAGE studies (*viz;* after the preparative surgery). None of the animals treated with mechlorethamine showed a decline in condition or body weight.

Rabbits treated with mechlorethamine were randomly assigned to either the mechlorethamine control group (n = 8 rabbits) or the mechlorethamine 400 µl

CAGE group (n = 5 rabbits; see table 2.4). The untreated rabbits from previous studies were used for comparison as [control group (n = 16 rabbits) or the untreated 400 µl CAGE group (n = 8 rabbits); see table 2.3].

All animals were prepared as described in CHAPTER 2. After a stable pre-injection baseline had been established, all monitored parameters were recorded for at least 90 minutes. Either 400 µl of air and 600 µl of saline (embolism groups) or 1000 µl of saline (control groups) was then infused into the carotid artery cannula.

All groups were monitored for 3 hours following the intracarotid saline (control) or gas (CAGE 400 µl) injection, and then killed by an intravenous injection of KCl. All parameters were recorded 2 and 15 minutes after the injection and then every 15 minutes. For analysis of the data, the mean of the pre-injection data for each parameter was assigned a value of 100%. For statistical analysis, all post-injection results were then expressed as a percentage of the pre-injection mean.

TABLE 5.1. NUMBER OF RABBITS ASSIGNED TO EACH GROUP FOR GRANULOCYTOPENIA STUDIES.

See tables 2.3 and 2.4 for the sequence in which studies were undertaken. Animals treated with mechlorethamine were randomised as one series. Animals not treated with mechlorethamine were randomised as a separate series.

	GRANULOCYTOPENIC (MECHLORETHAMINE TREATED)	UNTREATED
Control (intracarotid saline)	8	8
CAGE 400 µl	5	16

5.3. RESULTS

5.3.1. General observations

The MABP, temperature, P_aCO_2, P_aO_2 and heart rate did not change significantly at any time in either any group (see table 5.2). Similarly, there were no significant pre-injection baseline changes in CBF, CSER AP_2, pial artery diameter or pial vein diameter (data not graphed but listed in APPENDIX H).

Prior to mechlorethamine treatment hæmatological values were consistent with published data (see table 5.3). Seventy two hours following mechlorethamine administration there was no significant change in red blood cell numbers. White blood cells were depleted to a mean of 10% of pre-mechlorethamine levels (Wilcoxon rank test, $p < 0.01$). The differential of the white blood cell count was also changed from 11:4:1 to 7:21:1 (lymphocytes : granulocytes : monocytes), that is, relative to the number of monocytes there were more lymphocytes than granulocytes after mechlorethamine treatment. Thus the rabbits were rendered granulocytopenic by mechlorethamine treatment.

Following injection of 400 µl (150 - 200 µl/kg) air into the left internal carotid artery, bubbles appeared in the pial arteries of all rabbits within 5 seconds. These bubbles were observed in pial arteries of between 50 and 200 µm diameter, and were displaced by blood. The time taken for air to appear and then be washed out of the field of view (transit time) was 108 ± 24 seconds (n = 5 rabbits; ± SEM) for the 400 µl CAGE granulocytopenic rabbits. This was not significantly different ($t = 1.82$; $p = 0.103$) to the transit time for the 400 µl CAGE group (231 ± 63 seconds [n = 5 rabbits; ± SEM]).

5.3.2. Right CBF

In the control granulocytopenic group, right CBF did not change compared to pre-injection mean values (F = 0.96; df = 81; p = 0.490; [see lower panel of figure 5.1]).

In the 400 µl CAGE granulocytopenic group, right CBF showed an increase to 134 ± 12.6% (n = 5 rabbits; ± SEM) compared to pre-injection mean values, (F = 2.625; df = 41; p = 0.015) but this recovered to pre-injection mean values 5 minutes after CAGE.

5.3.3. Left CBF

In the control granulocytopenic group, left CBF did not change compared to pre-injection baseline, F = 0.65; df = 71; p = 0.798; [see lower panel of figure 5.2]).

In the 400 µl CAGE granulocytopenic group, left CBF did not change (compared to pre-injection baseline) (F = 0.96; df = 81; p = 0.490; [see lower panel of figure 5.2]).

5.3.4. Pial arterial diameter

In the control granulocytopenic group no statistically significant vaso-dilatation was seen after CAGE (F = 1.46; df = 51; p = 0.177; [see lower panel of figure 5.3]).

Although vasodilation was observed in the 400 µl CAGE granulocytopenic group this did not achieve statistical significance (F = 0.96; df = 45; p = 0.500; [see lower panel of figure 5.3]). This is in contrast to what was seen in the 400 µl CAGE group which show a pronounced, transient vasodilation which reverts to pre-injection baseline after 45 minutes [see upper panel of figure 5.3].

5.3.5. Pial venous diameter

In the control granulocytopenic group no change in pial venous diameter was seen after CAGE ($F = 0.59$; $df = 48$; $p = 0.841$). Similarly in the 400 µl CAGE granulocytopenic group no statistically significant venodilation could be identified after CAGE ($F = 1.16$; $df = 40$; $p = 0.356$; [see lower panel of figure 5.4]).

5.3.6. CSER AP_2

The control granulocytopenic group exhibited a slight but not significant reduction in CSER AP_2 during the course of the experiment ($F = 1.73$; $df = 77$; p 0.074).

Similarly in the 400 µl CAGE granulocytopenic animals given there was no suppression of CSER AP_2 ($F = 0.75$; $df = 37$; $p = 0.698$; [see lower panel of figure 5.5]).

5.4. DISCUSSION

The data reported here show granulocytopenia to be protective of the effects of CAGE in this rabbit model. Whereas the data from granulocytopenic rabbits is noisier than in earlier studies, the protective effect is clearly demonstrated, especially for the CSER AP_2 data shown in figure 5.5. Although not achieving statistical significance, the accelerated transit time for the granulocytopenic rabbits may have been due to reduced viscosity at the level of the micro-circulation.

Mechlorethamine is a potent alkylating agent with a short half life in the circulation (less than 30 minutes). Mechlorethamine exerts its cytotoxic effects through covalent linkage of alkyl groups to DNA and so affects cells which rapidly synthesise nucleic acids [Hall & Tilby 1992]. Mechlorethamine treatment

was tolerated very well by the rabbits and granulocytopenia was established prior to CAGE. Other studies treating dogs [Dutka *et al* 1989], sheep [Flick *et al* 1981] or rabbits [Freed *et al* 1989] with mechlorethamine have either not reported platelet levels or reported no effect on platelet numbers [Albertine 1988; Laughlin *et al* 1986; Freed *et al* 1989].

In a canine model, labelled granulocytes [Hallenbeck *et al* 1986] and platelets [Obrenovitch & Hallenbeck 1985] have been shown to accumulate in the brain after air embolism and in a subsequent study, recovery of brain function was accelerated in those dogs made granulocytopenic by pre-treatment with mechlorethamine [Dutka *et al* 1989]. Interestingly, treatment with the "triple combination" of prostaglandin I_2, indomethacin and heparin will improve recovery of the CSER after CAGE but does not alter the number of ^{111}In-labelled platelets accumulating in the brain [Hallenbeck *et al* 1982b; Kochanek *et al* 1988; Obrenovitch & Hallenbeck 1985]. Treatment with kadsurenone, a platelet activating factor (PAF) antagonist significantly enhances recovery of CSER and CBF after CAGE but did not reduce platelet accumulation in the brain either [Kochanek *et al* 1987b]. This paradoxical result may be due to the ^{111}In-labelling process activating granulocytes and platelets obstructing flow without actually plugging in the blood vessels [Grogaard *et al* 1989].

The possibility that bubbles have trapped in the grey white sub-cortical junction [Dutka *et al* 1988] cannot be eliminated by these experiments although if mechlorethamine treatment protects the brain against the effects of air embolism the influence of bubbles trapped in this layer, on CBF and CSER, is likely to be unimportant.

Leukocytes, however, are known to profoundly affect the microrheology of capillary beds [La Celle 1986; Sutton & Schmidschonbein 1992]. They are also important mediators of local inflammatory responses which may further alter

blood flow [La Celle 1986]. Any damage to the vascular endothelial cells which retards movement of leukocytes may therefore impose a significant hæmodynamic resistance [Sutton & Schmidschonbein 1992]. Indeed, hypoperfusion seen after reversible ischæmia in a rat model of reversible carotid ligation may be due to granulocytes obstructing but not actually plugging the microcirculation [Grogaard *et al* 1989].

Taken together with other studies, the experiments reported here strongly suggest that the significant deterioration in both CBF and CSER AP_2 which occur after CAGE might be due to granulocyte accumulation in the microcirculation. Bubbles passing through the blood vessels may damage vascular endothelial cells which then allows adhesion of granulocytes. This accumulation of granulocytes then leads to altered microvascular flow resulting in reduced CBF and impaired brain function [Dutka *et al* 1989; Hallenbeck *et al* 1986; La Celle 1986; Obrenovitch *et al* 1984]. Bubbles are unlikely to stimulate granulocytes directly because of their comparatively small number in the total circulation but it seems probable bubble passage could damage the vascular endothelium. Vascular endothelium thus damaged then binds leukocytes (specifically granulocytes in the model used here).

In order to examine whether or not the pathophysiology of CAGE is due to granulocyte adhesion, experiments were conducted in which granulocyte adhesion was inhibited and rabbits given a 400 µl CAGE.

FIGURE 5.1 RIGHT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (MEAN ± SEM)

Right CBF was measured by hydrogen clearance from a platinum electrode inserted through a burr hole over the right somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The upper part of the figure shows data from untreated control rabbits plotted with data from untreated rabbits given a 400 µl CAGE (data from CHAPTER 4).

The lower part of the figure shows data from granulocytopenic control rabbits plotted with granulocytopenic rabbits given a 400 µl CAGE.

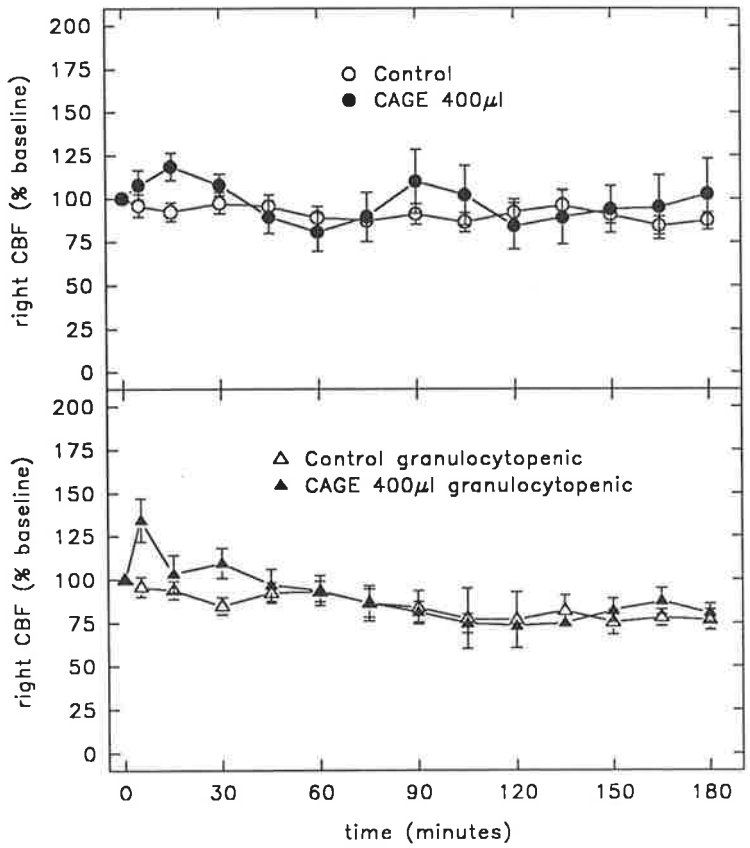


FIGURE 5.2. LEFT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (MEAN ± SEM)

Left CBF was measured by hydrogen clearance from a platinum electrode inserted through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The upper part of the figure shows data from untreated control rabbits plotted with data from untreated rabbits given a 400 µl CAGE (data from CHAPTER 4).

The lower part of the figure shows data from granulocytopenic control rabbits plotted with granulocytopenic rabbits given a 400 µl CAGE.

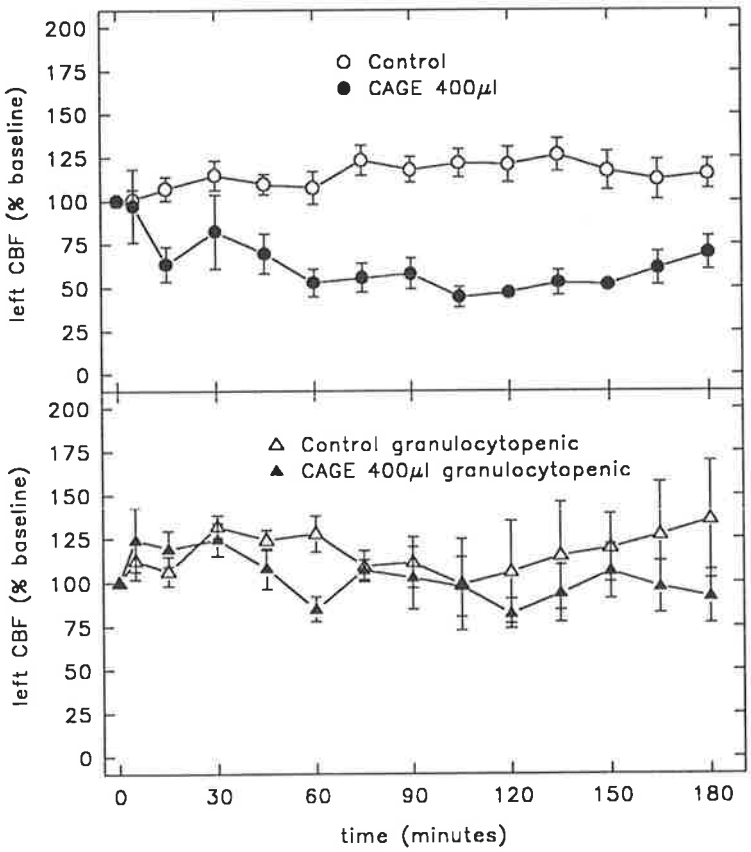


FIGURE 5.3. PIAL ARTERIAL DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (MEAN ± SEM)

Pial arterial diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The upper part of the figure shows data from untreated control rabbits plotted with data from untreated rabbits given a 400 µl CAGE (data from CHAPTER 4).

The lower part of the figure shows data from granulocytopenic control rabbits plotted with granulocytopenic rabbits given a 400 µl CAGE.

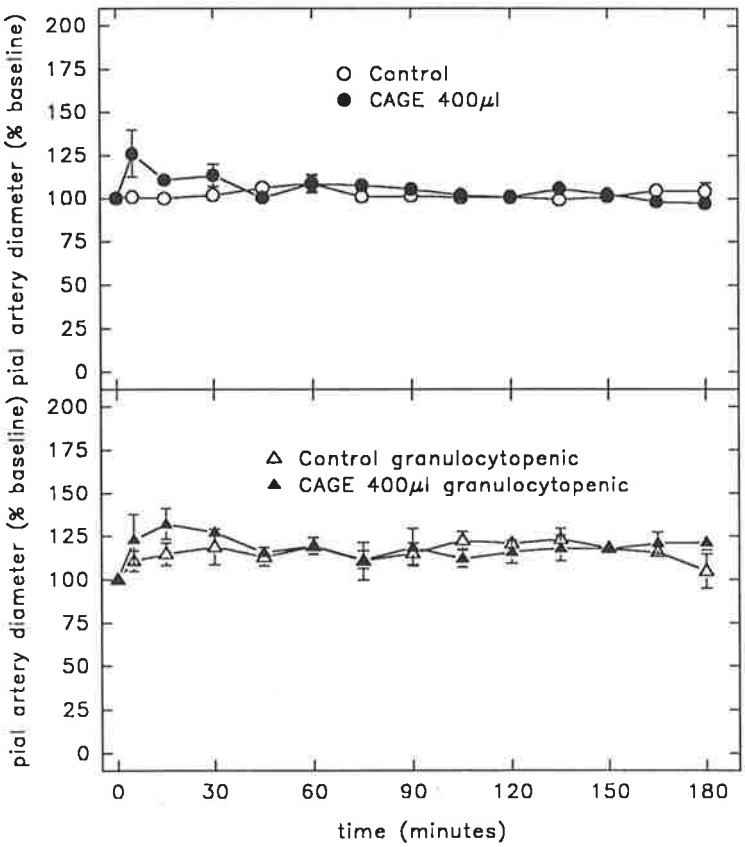


FIGURE 5.4. PIAL VENOUS DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (MEAN ± SEM)

Pial venous diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The upper part of the figure shows data from untreated control rabbits plotted with data from untreated rabbits given a 400 µl CAGE (data from CHAPTER 4).

The lower part of the figure shows data from granulocytopenic control rabbits plotted with granulocytopenic rabbits given a 400 µl CAGE.

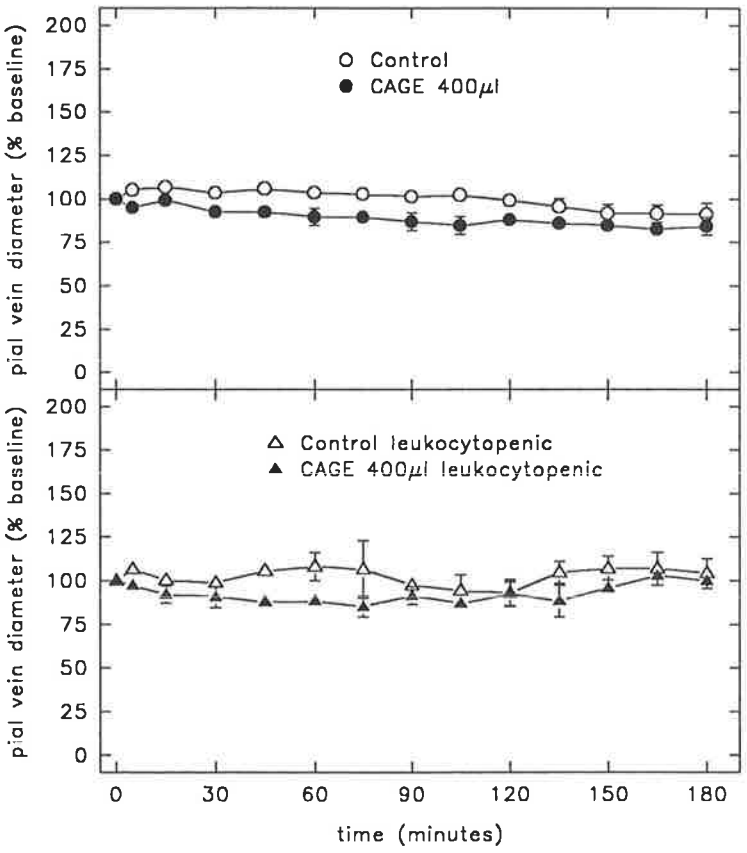


FIGURE 5.5. CSER AP_2 AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR CONTROL (MEAN ± SEM)

The CSER AP_2 was measured from the mean of 80 average evoked responses from the somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The upper part of the figure shows data from untreated control rabbits plotted with data from untreated rabbits given a 400 µl CAGE (data from CHAPTER 4).

The lower part of the figure shows data from granulocytopenic control rabbits plotted with granulocytopenic rabbits given a 400 µl CAGE.

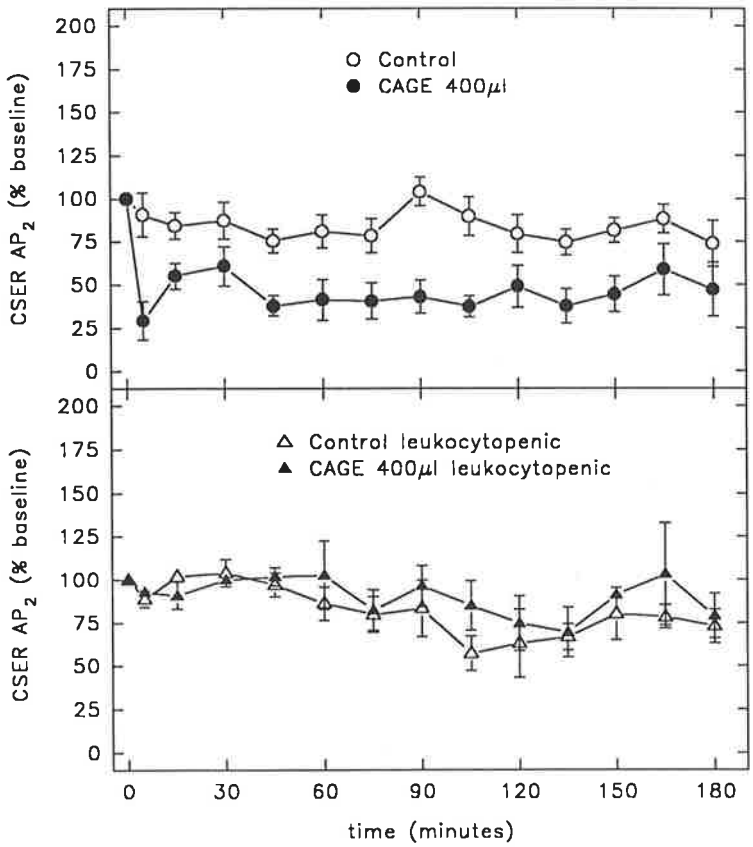


TABLE 5.2. MABP, TEMPERATURE, P_aCO_2 AND P_aO_2 BEFORE CAGE OR INTRACAROTID SALINE IN THE GRANULOCYTOPENIC CONTROL AND GRANULOCYTOPENIC 400 µl CAGE GROUPS

Granulocytopenic Control	mean	SD	SEM	n
MABP (mmHg)	96.7	14.25	1.69	71
Temperature °C	38.6	0.74	0.09	71
P_aCO_2	36.8	3.09	0.37	70
P_aO_2	128.1	18.99	2.27	70

Granulocytopenic 400 µl CAGE	mean	SD	SEM	n
MABP (mmHg)	93.6	15.21	2.27	45
Temperature °C	39.3	0.44	0.07	44
P_aCO_2	37.0	3.82	0.57	45
P_aO_2	132.0	21.37	3.19	45

TABLE 5.3. HÆMATOLOGICAL VALUES BEFORE AND AFTER MECHLORETHAMINE TREATMENT

	BEFORE MECHLOR-ETHAMINE TREATMENT	AFTER MECHLOR-ETHAMINE TREATMENT
RBC (cells/µl)	$5.84 \pm 0.103 \times 10^6$	$5.53 \pm 0.213 \times 10^6$
WBC** (cells/µl)	$7.40 \pm 0.609 \times 10^3$	$0.75 \pm 0.102 \times 10^3$
granulocytes	$25.73 \pm 3.86\%$	$0.28^* \pm 0.28\%$
lymphocytes	$68.07 \pm 3.98\%$	$8.41^* \pm 8.40\%$
monocytes	$6.20 \pm 1.21\%$	$0.40^* \pm 0.40\%$

* Errors in the differential count occurred in the mechlorethamine treated group because of the small numbers of cells being counted

** different from pre-treatment $p < 0.001$ by Wilcoxon test

CHAPTER 6.

MODIFICATION OF LEUKOCYTE ADHESION

6.1. STUDIES WITH DEXTRAN SULPHATE

CAGE is a transient insult the effects of which can be largely prevented by mechlorethamine treatment [CHAPTER 5; Dutka *et al* 1989]. Furthermore it has been shown that granulocytes [Hallenbeck *et al* 1986; Kochanek *et al* 1987a] and platelets [Obrenovitch & Hallenbeck 1985] accumulate in either the brain substance or in the brain microvessels after CAGE. If leukocytes and/or platelets are mediating the pathophysiological effects of CAGE then therapies which inhibit normal leukocyte and platelet adhesion to vascular endothelial surfaces may protect the brain from the effects of CAGE.

Sulphated polysaccharides, in particular polysulphated dextran (mw 500,000; dextran 500 sulphate) inhibit leukocyte adhesion to vascular endothelium [Tangelder & Arfors 1991] and prevent leukocyte migration across vascular endothelium at sites of inflammation [Parish *et al* 1990].

To further investigate the possible role leukocytes may have in the pathophysiology of CAGE and to test the hypothesis that brain dysfunction and reduced blood flow after air embolism is due to leukocyte adhesion to vascular endothelium the effects of dextran 500 sulphate treatment after CAGE were studied.

6.2. MATERIALS AND METHODS

The methods used were the same as those described in CHAPTER 2. The rabbits were randomly assigned to either CAGE dextran 500 sulphate, CAGE dextran 500, control dextran 500 sulphate, control dextran 500 or control. An intracarotid dose of 400 µl of air was used to induce CAGE. All animals were

monitored until at least 90 minutes of stable recordings were established (pre-injection baseline). Either polysulphated dextran (Pharmacia; dextran 500 sulphate, mw 500,000 substitution 17%) or DEAE dextran (Pharmacia; dextran 500; mw 500,000) were prepared as a 20 mg/ml solution dissolved in saline and injected into the femoral venous line 10 minutes before CAGE at a dose of 20 mg/kg. Either 400 µl of air and 600 µl of saline (embolism groups) or 1000 µl of saline (control groups) were infused into the carotid artery cannula. All parameters were recorded 2 and 15 minutes after the injection and then every 15 minutes. All groups were monitored for 3 hours following the gas/saline or saline injection and killed by a KCl injection without ever recovering from anæsthesia.

Blood samples were anticoagulated with EDTA for cell analysis on a COULTER S & 6 CELL COUNTER [with Cash modification] (Coulter Electronics) or on a TECHNICON H•1 HEMATOLOGY SYSTEM (Technicon). Samples were taken before dextran treatment, before CAGE, after CAGE and at the end of the experiment. It was found that dextran 500 sulphate causes platelets to clump together. Since neither of these cell counters give reliable animal platelet counts no platelet data are reported.

TABLE 6.1. NUMBER OF RABBITS ASSIGNED TO EACH GROUP FOR DEXTRAN 500 SULPHATE STUDIES

	DEXTRAN 500 SULPHATE	DEXTRAN 500
Control (saline)	6	5
CAGE 400 µl	5	4

6.3. RESULTS

6.3.1. General observations

The MABP, P_aCO_2, P_aO_2 and heart rate did not change significantly at any time in any rabbits studied except that a brief period of hypotension sometimes followed the injection of dextran 500 sulphate. Similarly, there were no significant pre-injection changes in CBF, CSER AP_2, pial artery diameter or pial vein diameter (data not graphed but listed in APPENDIX H).

Bubbles appeared in the pial arteries within 5 seconds of injection of 400 µl (150 to 200 µl/kg) air into the left internal carotid artery. These bubbles were observed in pial arterioles of between 50 and 200 µm diameter, and were displaced by blood. Transit time for air in the 400 µl CAGE dextran 500 sulphate group was 178 ± 50 seconds (n = 4) which was significantly different (t = 3.54; p = 0.016) to the 400 µl CAGE dextran 500 group which had a transit time of 622 ± 132 seconds (n = 3) but not significantly different (t = 0.63; p = 0.552) to the 400 µl CAGE group (231 ± 63 seconds [n = 5; ± SEM])

Mean leukocyte counts increased from $4.62 \times 10^3 \pm 247$ /mm^3 to 12,925 ± 1,108 /mm^3 (F = 3.29; p = 0.038) without any change in leukocyte differential or red blood cell counts. Red blood cell counts did not change (F = 0.75; p = 0.532). Platelet counts are not reliable in this cell counter if blood samples contain dextran 500 sulphate.

The combined treatment of dextran 500 and CAGE was lethal for 4 of 5 rabbits. This series was stopped although data from this group are shown and discussed no formal analysis was done.

6.3.2. Right CBF

The dextran 500 sulphate control group showed slight but not statistically significant decline in CBF for the 180 minutes after injection of intracarotid saline ($F = 1.28$; $df = 56$; $p = 0.258$).

In the dextran 500 sulphate CAGE group, CBF showed a rapid but transient increase at 5 minutes after injection of 400 µl of intracarotid air ($F = 1.69$; $df = 69$; $p = 0.087$). Right CBF at 5 minutes after CAGE was not statistically higher compared to all other times but was clearly increased compared to studies reported previously in which right CBF did not change after CAGE [see figure 6.1]. This is in contrast to all the studies done up till now where the effects of CAGE have been ipsilateral to the injection of intracarotid air.

6.3.3. Left CBF

Left CBF did not change in the dextran 500 sulphate control group at any time ($F = 1.42$; $df = 57$; $p = 0.188$).

However, in the dextran 500 sulphate CAGE group left CBF showed a transient increase at 5 minutes which reached statistical significance ($F = 2.30$; $df = 69$; $p = 0.015$). Except for the flow at 5 minutes after embolism, there was no change in left CBF. These data contrast with previous studies which show 400 µl CAGE produces a progressive reduction in CBF over the 3 hours of the study [see figure 6.1].

6.3.4. Pial arteriolar diameter

Dextran 500 sulphate treatment by itself produced no systematic changes in pial arteriolar diameter ($F = 1.81$; $df = 67$;$p = 0.065$).

In the dextran 500 sulphate group given a 400 µl CAGE there was a vasodilation to approximately 120% of control of pre-injection baseline which persisted for the duration of the experiment ($F = 0.77$; $df = 48$; $p = 0.681$). These diameter increases were significantly higher than for the dextran 500 sulphate group given intracarotid saline. Differences between dextran 500 sulphate saline and dextran 500 sulphate CAGE are shown on figure 6.3.

This result contrasts with the CAGE 400 µl data also shown in figure 6.3 which shows CAGE produces a transient vasodilation only.

6.3.5. Pial venous diameter

The pial venous diameters showed a slight but not statistically significant venoconstriction over the course of the experiment in the control dextran 500 sulphate ($F = 2.162$; $df = 67$; $p = 0.024$).

Pial venous diameter in the CAGE dextran 500 sulphate group did not change ($F = 0.727$; $df = 52$; $p = 0.725$).

6.3.6. CSER AP_2

The control dextran 500 sulphate group did not demonstrate any significant or systematic change in CSER AP_2 ($F = 0.695$; $df = 83$; $p = 0.762$).

On the other hand the dextran 500 sulphate CAGE group exhibited a transient reduction in CSER AP_2 to 52 ± 18% of pre-injection baseline ($t = 2.65$; $p = 0.021$ compared to pre-injection baseline). This then recovered and was not different from pre-injection baseline thereafter. Previous experiments have shown that a 400 µl CAGE produces a sudden and

profound reduction in CSER AP_2 to 29.3 ± 11.0% of pre-injection baseline which did not recover over the next 180 minutes.

6.3.7. Relationship between CSER AP_2 and CBF

Regression analyses of left CBF against CSER AP_2 in the dextran 500 sulphate embolism group failed to demonstrate a convincing linear relationship ($r = 0.52$; $F = 4.65$; $p = 0.05$) over the data range studied [see figure 6.6].

6.4. DISCUSSION

Studies reported in CHAPTERS 3 and 4 have shown that intracarotid air in doses ranging from 25 to 400 µl produces transient pial arteriolar dilatation which was followed by a progressive deterioration in CBF and CSER AP_2 in rabbits. Treatment with mechlorethamine to induce granulocytopenia affords significant protection against these effects of CAGE (CHAPTER 5). In the experiments reported here granulocyte numbers were not depleted but their ability to adhere to surfaces was impaired by pre-treatment of the rabbits with dextran 500 sulphate. This treatment afforded significant protection against these effects of CAGE in this rabbit model.

Leukocytes affect the microrheology of capillary beds and are important mediators of local inflammatory responses [La Celle 1986]. Leukocytes [Hallenbeck *et al* 1986; Kochanek *et al* 1987a] and platelets [Obrenovitch & Hallenbeck 1985] have been shown to accumulate in either the brain substance or in brain microvessels after CAGE and leukocyte depletion before CAGE has been shown to ameliorate post embolus hypoperfusion [Dutka *et al* 1989].

Leukocyte adhesion is thought to be due to some change in the vascular wall rather than to a change in the leukocytes which adhere to it [Jones & Hurley 1984; Allison *et al* 1955]. Endothelial cell damage can cause granulocytes to

adhere to specific adhesion receptors such as leukocyte adhesion molecule (LAM) [Argenbright *et al* 1991; Giddon & Lindhe 1972; Gorog *et al* 1980; Lewinsohn *et al* 1987]. Endothelial cell exfoliation and damage to the endothelial cell surfactant layer may promote leukocyte adhesion to vascular endothelium which then obstructs flow.

Surfactant-like (amphipathic) molecules coat the vessel lumen of cerebral and other vessels making the lumen hydrophobic [Hills & James 1991; Hills 1992a]. Amphipathic molecules have a strong affinity for phase interfaces, such as bubbles. Bubbles in the circulation have been shown to stick to endothelial cells and rupture the fluid film which normally separates the bubble surface from the endothelial cell membrane [Grulke & Hills 1978]. Bubble passage across endothelial cells could collect surfactant from the outer membranes of the endothelial cells [Butler & Hills 1983]. Electron microscope studies have shown lipid droplets, which may be endothelial cell associated surfactants [Hills 1992a] attached to surface associated protein on the air side of the air-blood interface as well as incorporated in the interface [Warren *et al* 1973]. Furthermore, passage of air bubbles has been shown to produce herniation of endothelial cells through fenestrations in more rigid structures of the vessel wall [Warren *et al* 1973].

Modification of leukocyte adhesiveness might be expected to have a profound effect on the microcirculation. Experiments conducted in this rabbit model have not affected CBF contralateral to the side of air injection up until these studies. It is possible the microcirculatory resistance was reduced to the point where air could now distribute across the Circle of Willis to invade both cerebral hemispheres. Lowering the dose of gas to one cerebral hemisphere might in itself afford some protection of the brain except that a progressive decline in CBF and CSER AP_2 is always seen in rabbits given CAGE. Such a decline was not seen in rabbits pre-treated with dextran 500 sulphate.

Sulphated polysaccharides have been shown to inhibit leukocyte binding to vascular endothelial cells *in vivo* [Ohkubo *et al* 1991; Tangelder & Arfors 1991] and *in vitro* [Ley *et al* 1989]. The effectiveness of inhibition of leukocyte adhesion was dependent on the degree of sulphate substitution and the duration of action depended on the molecular weight [Tangelder & Arfors 1991]. Dextran 500 sulphate will also inhibit granulocyte adhesion to vascular endothelium in the presence of shear stress [Ley *et al* 1989]

Fluid resuscitation is an important step in treating decompression illness and although solutions of dextran (typically m.w. 70,000) are not in common use, further studies of the combined effects of dextran and CAGE are indicated. It may be that the additive effects of the rouleaux properties of dextran [Sewchand & Canham 1979] and CAGE may cause a massive, fatal coagulopathy similar to disseminated erythrocyte aggregation [Sewchand & Canham 1979].

These studies taken together with the work of Hallenbeck *et al* [Hallenbeck *et al* 1986] and Dutka *et al* [Dutka *et al* 1989] provide compelling evidence for a leukocyte/endothelial cell interaction producing the decrements in brain blood flow and function seen after CAGE.

FIGURE 6.1. RIGHT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Right CBF was measured by hydrogen clearance from a platinum electrode inserted through a burr hole over the right somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The top figure shows the effects of dextran 500 sulphate pre-treatment (20 mg/kg), the middle figure the effects of dextran 500 pre-treatment (20 mg/kg) and the bottom figure the effects of no treatment. CAGE was fatal after dextran 500 pre-treatment in all except one animal.

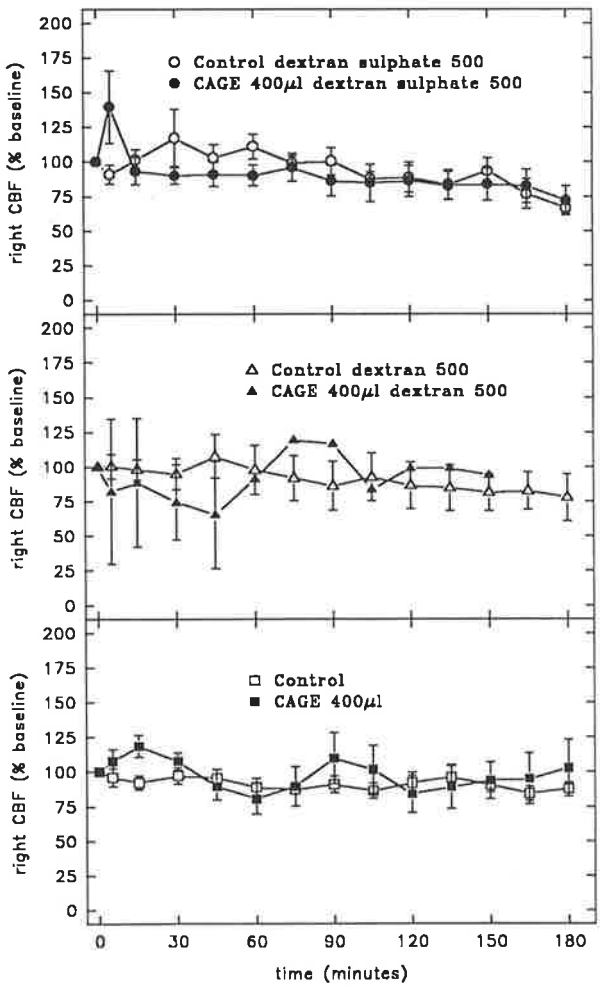


FIGURE 6.2. LEFT CBF AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Left CBF was measured by hydrogen clearance from a platinum electrode inserted through the craniotomy made over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The top figure shows the effects of dextran 500 sulphate pre-treatment (20 mg/kg), the middle figure the effects of dextran 500 pre-treatment (20 mg/kg) and the bottom figure the effects of no treatment. CAGE was fatal after dextran 500 pre-treatment in all except one animal.

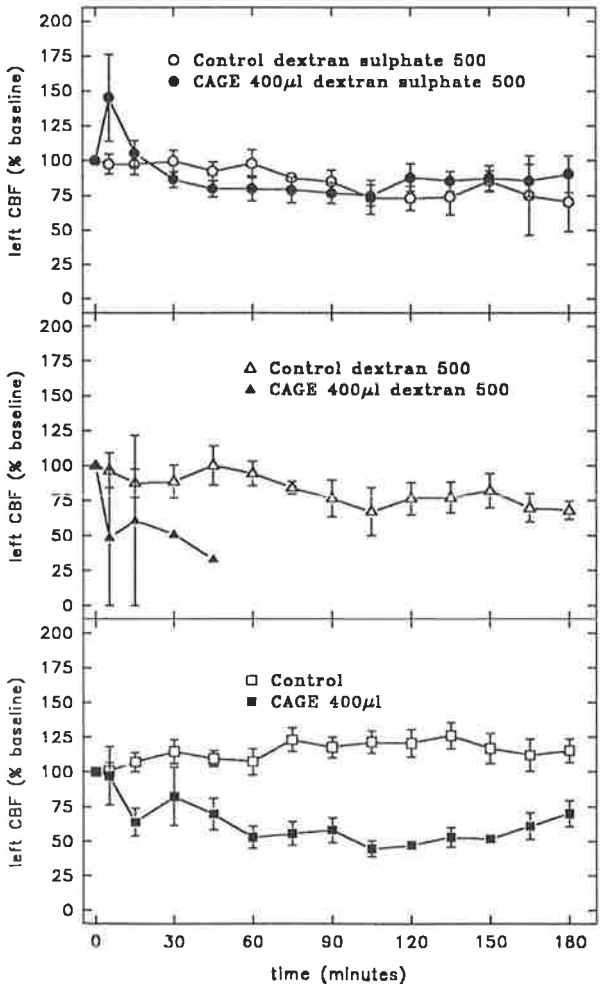


FIGURE 6.3. PIAL ARTERIOLE DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Pial arterial diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The top figure shows the effects of dextran 500 sulphate pre-treatment (20 mg/kg), the middle figure the effects of dextran 500 pre-treatment (20 mg/kg) and the bottom figure the effects of no treatment. CAGE was fatal after dextran 500 pre-treatment in all except one animal. The * indicates $p < 0.05$.

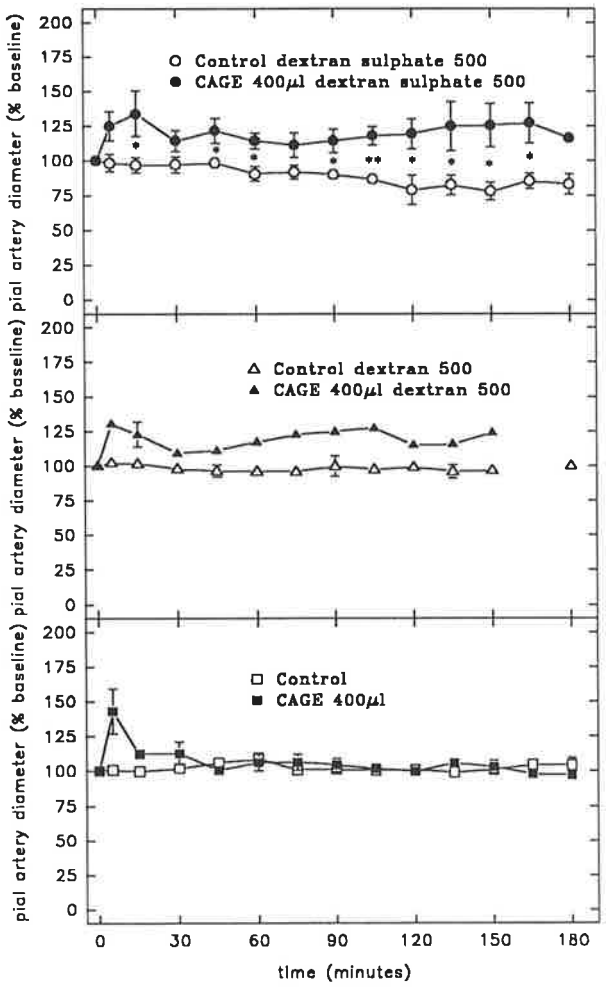


FIGURE 6.4. PIAL VENOUS DIAMETER AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

Pial venous diameter was measured from photographs of the brain surface made through the craniotomy over the left somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The top figure shows the effects of dextran 500 sulphate pre-treatment (20 mg/kg), the middle figure the effects of dextran 500 pre-treatment (20 mg/kg) and the bottom figure the effects of no treatment in all except one animal.

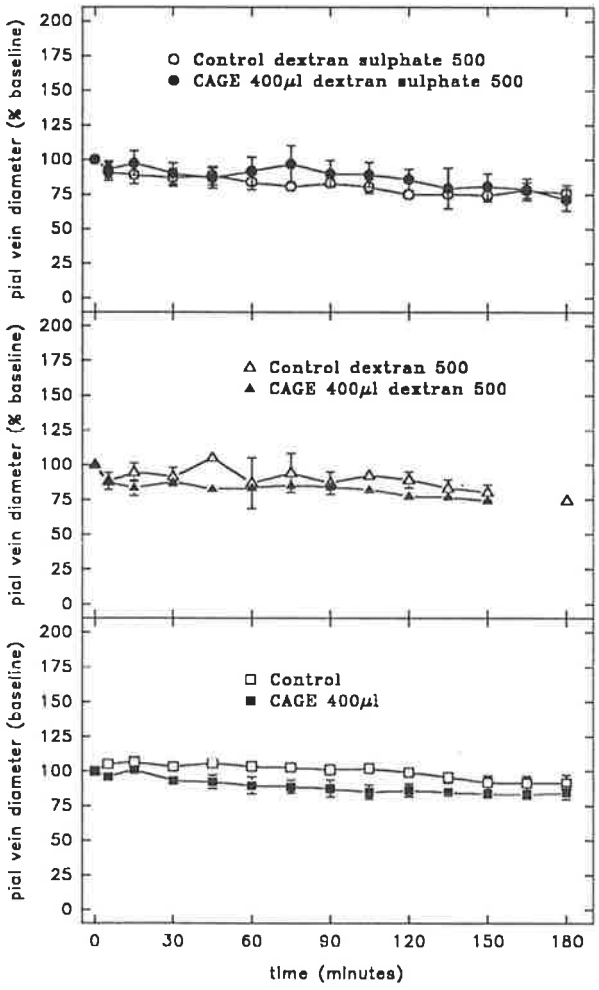


FIGURE 6.5. CSER AP_2 AS A PERCENTAGE OF THE PRE-INJECTION MEAN VALUE IN THE CAGE AND CONTROL GROUPS FOR THE 3 HOURS POST CAGE OR INTRACAROTID SALINE INJECTION (MEAN ± SEM)

The CSER AP_2 was measured from the mean of 80 average evoked responses from the somatosensory cortex. Measurements were made every 15 minutes for approximately 90 minutes prior to CAGE or intracarotid saline injection. For individual rabbits the percentage change from pre-injection baseline was calculated. The graph shows the mean percentage change (± SEM) from this pre-injection baseline value.

The top figure shows the effects of dextran 500 sulphate pre-treatment (20 mg/kg), the middle figure the effects of dextran 500 pre-treatment (20 mg/kg) and the bottom figure the effects of no treatment in all except one animal. The * indicates $p < 0.05$.

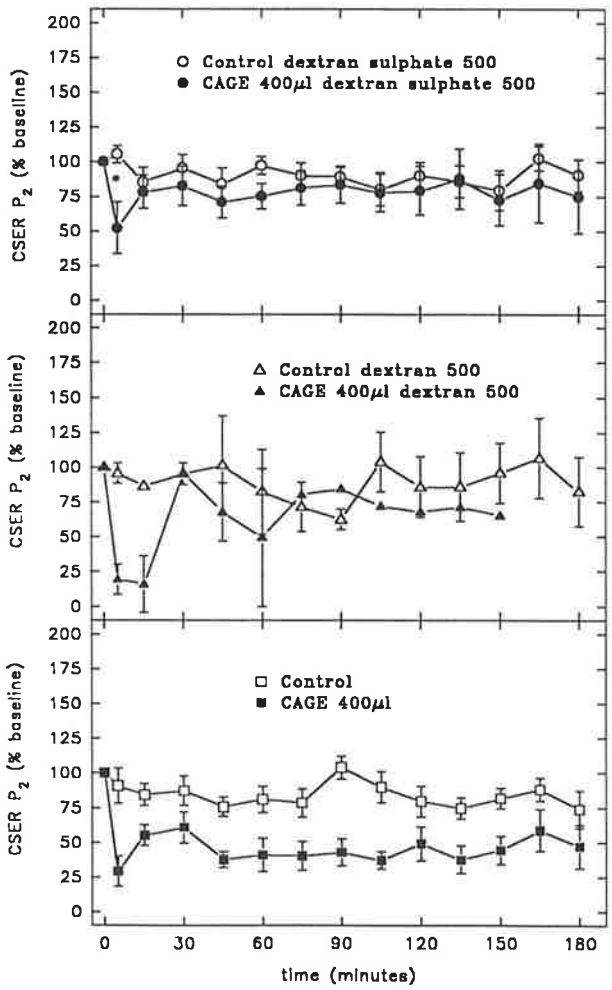


FIGURE 6.6. REGRESSION ANALYSIS OF THE CSER AP_2 AND LEFT CBF IN THE 400 µl CAGE DEXTRAN 500 SULPHATE GROUP

The equation was not statistically significant ($r^2 = 0.27$; $F = 4.48$; $p = 0.055$)

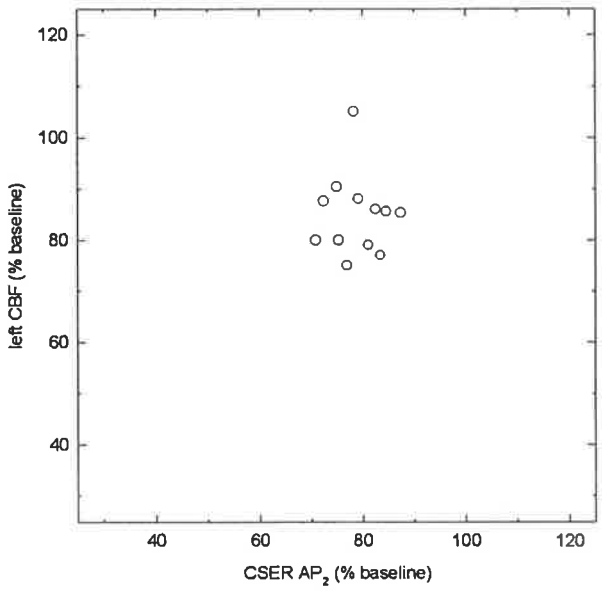


TABLE 6.2. MABP, TEMPERATURE, P_aCO_2 AND P_aO_2 BEFORE CAGE OR INTRACAROTID SALINE IN THE DEXTRAN 500 CONTROL, DEXTRAN 500 SULPHATE CONTROL, DEXTRAN 500 400 µl CAGE AND DEXTRAN 500 SULPHATE 400 µl CAGE GROUPS

Control Dextran 500	**mean**	**SD**	**SEM**	**n**
MABP (mmHg)	90.5	12.53	2.22	32
Temperature °C	38.6	0.42	0.07	32
P_aCO_2	36.2	1.85	0.33	32
P_aO_2	117.5	11.83	2.09	32

Control dextran 500 sulphate	**mean**	**SD**	**SEM**	**n**
MABP (mmHg)	88.5	11.30	1.63	48
Temperature °C	39.0	0.13	0.02	48
P_aCO_2	37.3	2.48	0.36	48
P_aO_2	110.9	8.04	1.16	48

CAGE dextran 500	**mean**	**SD**	**SEM**	**n**
MABP (mmHg)	83.9	18.62	2.94	40
Temperature °C	38.6	0.43	0.07	40
P_aCO_2	36.2	2.00	0.32	40
P_aO_2	128.8	16.64	2.63	40

CAGE dextran 500 sulphate	**mean**	**SD**	**SEM**	**n**
MABP (mmHg)	89.2	10.17	1.52	45
Temperature °C	38.8	0.59	0.09	45
P_aCO_2	36.3	2.97	0.45	43
P_aO_2	126.5	19.75	2.94	45

TABLE 6.3. HÆMATOLOGICAL VALUES BEFORE AND AFTER DEXTRAN 500 SULPHATE TREATMENT

	RBC (CELLS/µL)
PRE-INJECTION BASELINE	$6.05 \pm 0.147 \times 10^6$ (7)
AFTER DEXTRAN 500 SULPHATE	$5.76 \pm 0.193 \times 10^6$ (7)
AFTER CAGE	$5.70 \pm 0.197 \times 10^6$ (7)
END OF EXPERIMENT	$5.84 \pm 0.169 \times 10^6$ (7)

	WBC (CELLS/µL)
PRE-INJECTION BASELINE	$4.62 \pm 0.656 \times 10^3$ (7)
AFTER DEXTRAN 500 SULPHATE	$7.20 \pm 1.249 \times 10^3$ (7)
AFTER CAGE	$9.89 \pm 2.398 \times 10^3$ (6)
END OF EXPERIMENT	$12.93 \pm 2.933 \times 10^3$ (7)

	LYMPHOCYTES	MONOCYTES	GRANULOCYTES
PRE-INJECTION BASELINE	62 ± 8.6 (6)	14 ± 2.9 (6)	22 ± 8.6 (6)
AFTER DEXTRAN 500 SULPHATE	60 ± 4.9 (6)	21 ± 6.4 (6)	16 ± 2.4 (6)
AFTER CAGE	68 ± 3.5 (5)	15 ± 2.4 (5)	14 ± 2.4 (5)
END OF EXPERIMENT	79 ± 3.5 (6)	11 ± 3.1 (6)	8 ± 2.3 (6)

CHAPTER 7.
DISCUSSION AND CONCLUSIONS

7.1. THE CONVENTIONAL VIEW

Once the presence of CAGE (or DCI) has been established, the accepted treatment involves recompression with breathing of O_2 under pressure. The aim of recompression (based on Boyle's Law) is to mechanically reduce the bubble volume and so promote bubble passage to the venous circulation. Hyperbaric O_2 is used because it increases the diffusion gradient for nitrogen (which is thought to be the main gas in intravascular bubbles) and to promote bubble dissolution. Hyperbaric O_2 also reduces cerebral œdema by vasogenic constriction [Hollin *et al* 1968; Kohshi *et al* 1991; Miller 1973; Torbati *et al* 1978] and increases the distance O_2 will diffuse from the capillary [Dutka 1985], which is thought to promote survival of tissue in watershed areas of the circulation. Taken together with the large number of anecdotal reports of successful hyperbaric O_2 therapy [Armon *et al* 1991; Bove *et al* 1982; Hart 1974] these reasons might suggest hyperbaric O_2 is the definitive treatment for CAGE or DCI. There is, however, limited evidence from prospective randomised studies demonstrating standard hyperbaric O_2 protocols improve recovery of brain blood flow or brain function after CAGE.

Submarine escape trainees who suffer CAGE can be treated effectively and often completely by a single 6 BAR recompression provided it is initiated immediately. Indeed placing the recompression chamber at the top of a submarine escape training tank (instead of having it at ground level) to shorten the time between CAGE first being recognised and treatment being started has itself reduced the mortality and morbidity of CAGE in this group of people [Van Genderen & Waite 1968]. Once this time "*window*" is past however, multiple treatments with hyperbaric O_2 are required to treat CAGE. A recent animal study by McDermott

et al has shown that initiating treatment of CAGE with 2.8 BAR of hyperbaric O_2 is as good as the currently accepted practise used for treating patients with 6 Bar air for 30 minutes followed by hyperbaric O_2 treatment at 2.8 and 1.9 BAR [McDermott *et al* 1992a]. Hyperbaric O_2 at 6 BAR is very likely to induce convulsions and death [Criborn *et al* 1987; Criborn *et al* 1986; Torbati & Lambertsen 1985; Torbati & Lambertsen 1983].) Although reducing bubble size is important, clearly, 2.8 BAR of O_2 is affecting some other specific processes initiated by CAGE. Whatever this process is, it has been shown to be further alleviated by other therapies adjunctive to, or in place of, hyperbaric O_2. Many investigations into such treatments have been undertaken [Catron *et al* 1984; Dutka 1985; Evans *et al* 1984; Evans *et al* 1989; Kochanek *et al* 1987b; Lindsberg *et al* 1991; McDermott *et al* 1990; Menasche *et al* 1985; Spiess *et al* 1988a] and some hyperbaric practitioners are already advocating use of agents such as lignocaine as an adjunct to hyperbaric O_2 [Drewry & Gorman 1992; Dutka *et al* 1992a; Dutka 1990] even though the exact mode of action is unknown.

7.2. PREVIOUS STUDIES

Outcome after CAGE has been shown to correlate with CBF and therefore treatment of CAGE has tried to re-establish satisfactory cerebral perfusion or increase supplies of O_2 to ischæmic tissues [Hallenbeck *et al* 1982a; Hallenbeck *et al* 1984; Leitch *et al* 1984b; Leitch *et al* 1984c; Meldrum *et al* 1971]. Alternative therapies have also attempted to re-establish CBF and reduce brain swelling and intracranial pressure to increase perfusion pressure.

7.2.1. Prevention of CAGE

Although evidence exists for intravascular bubbles being associated with any decompression [Ornhagen *et al* 1988], appropriate decompression, which minimises the amount of intravascular and autochthonous bubble formation, avoids CAGE and DCI [Francis & Smith 1991; Lee *et al* 1991].

The studies reported here show that different doses of intravascular gas produce different effects on brain function. The critical dose is different for different people and may even be different for the same person on different days [Hills 1969; How *et al* 1990]. Long term acclimatisation may also occur [Hills 1969; How *et al* 1990]. A critical threshold surface area (*viz;* dose of intravascular gas) may be needed to initiate the *gas embolism related cell adhesion* proposed by this author. Decompression schedules that are conservative in regard to time at depth might be expected to produce lower rates of DCI by restricting the inert gas load and thus minimising the amounts of intravascular gas formed on decompression. Such conservative decompression tables minimise the likelihood of any single hyperbaric exposure producing DCI in normal healthy individuals. Even so, minimal hyperbaric excursions have been reported to produce symptoms of CAGE which require hyperbaric O_2 treatment [Weien & Baumgartner 1990; Ikeda *et al* 1993].

Thus decompression schedules are expected to minimise DCI but may never eliminate it completely. Certain individuals may not be protected from DCI by decompression schedules at all if their threshold total bubble surface area is low enough to initiate *gas embolism related cell adhesion* after a modest dysbaric episode.

7.2.2. The patent foramen ovale

A controversial subject amongst diving physicians is whether the presence of a right-to-left inter-atrial shunt is a possible risk factor for the development of DCI in SCUBA divers. From the studies reported in CHAPTERS 3 and 4 it can be concluded that even small amounts of air which enter the cerebral circulation will pass through. A diver who has a patent foramen ovale is likely to undergo CAGE after every dive, since

venous bubbles are almost always found after diving [Bayne *et al* 1985; Eatock & Nishi 1987; Evans *et al* 1972; Gardette 1979; Nashimoto & Gotoh 1976; Neuman *et al* 1976; Ornhagen *et al* 1988; Powell & Johanson 1978; Spencer 1976]. This may have some kind of cumulative effect on the central nervous system, even if a particular diver is resistant to the presence of intravascular bubbles [Ward *et al* 1986; Ward *et al* 1990; Walder 1968]. Also, bubbles formed during a non-provocative decompression (normal ascent after a shallow dive) can be surfactant coated [Hills 1989a; Hills 1989b; Hills & James 1991] and thus possibly benign. A diver with a patent foramen ovale may have difficulty if the amount of venous gas is higher than usual. If the pulmonary filter is bypassed, non-surfactant coated air may embolise the cerebral vessels. The dose response effect seen in this model shows there can be a profound effect on brain function if a threshold dose of CAGE is exceeded.

7.2.3. Hyperbaric oxygen therapy

Repeated hyperbaric O_2 therapy is the currently accepted treatment for CAGE and DCI even though there have been few studies of the mechanisms by which hyperbaric O_2 exerts its effects.

It has been shown that hyperbaric O_2 treatment may protect the micro-circulation in an *ex vivo* model of skeletal muscle ischæmia-reperfusion injury by reducing venular leukocyte adherence and inhibiting progressive adjacent arteriolar vasoconstriction [Zamboni *et al* 1993]. Furthermore, hyperbaric O_2 therapy causes immune suppression [Eiseman *et al* 1980; Hansbrough *et al* 1980; Hansbrough & Eiseman 1979; Warren *et al* 1978b] and will interfere with granulocyte function [Rister 1982] and granulocyte adhesion to glass wool [Rister 1982]. The

mechanisms by which hyperbaric O_2 exerts these effects are unknown [Rister 1982] although it is possible that 2.8 BAR of O_2 inhibits with upregulation of adhesion molecules on either the vascular endothelial cells or leukocytes or both.

The studies reported here show that modification of granulocyte numbers or adhesiveness was protective of the early effects of CAGE. It therefore seems reasonable to expect that hyperbaric O_2 exerts at least some of its effects by reducing granulocyte adhesiveness.

7.2.4. Pharmacological treatment of CAGE

Pharmacological treatment of CAGE or DCI is difficult to reconcile with the stationary intravascular bubble model of CAGE. The studies reported in this thesis provide evidence that bubbles can pass through the arteries and capillaries and into the veins and initiate changes that may then be treated by non-hyperbaric therapy. If granulocytes are important mediators of the pathophysiological process of CAGE then other treatments which have been shown to be protective may also affect granulocyte adhesion and/or granulocyte function.

7.2.4.1. CAGE and lignocaine

Lignocaine improves rate of recovery after CAGE [Evans *et al* 1984; Drewry & Gorman 1992; Dutka *et al* 1992a] and will also protect the spinal cord from ischæmia [Kobrine *et al* 1984]. How it does this is not clear although it has been shown to prevent granulocytes from releasing superoxide anion [Goldstein *et al* 1977a; Peck *et al* 1985] which suggests that any marginating or trapped granulocytes may be prevented from damaging adjacent tissue. The most important effect of lignocaine may be to increase prostacyclin levels [Casey *et al* 1980] which then inhibits

granulocyte adhesion to damaged vascular endothelium [Giddon & Lindhe 1972; Jones & Hurley 1984], finding which are consistent with the results reported in this thesis.

Paradoxically, lignocaine has been shown to inhibit EDRF-mediated vasodilatation [Johns 1989; Johns *et al* 1985] but will induce pial arterial dilatation [Altura & Lassoff 1981]. This suggests Lignocaine may have direct effects on the vascular smooth muscle and may be able to induce vessel dilatation even if the vascular endothelium is damaged.

7.2.4.2. CAGE and steroids

Steroids have been used as an adjunct to hyperbaric O_2 in the treatment of DCI and CAGE [Kindwall & Margolis 1975; Leitch & Green 1986]. Dexamethasone reduces œdema around tumours and sites of inflammation [Anderson & Cranford 1978; Klatzo 1987] but it takes several hours to be effective [Shapiro 1975]. Typically CAGE causes a vasogenic œdema [Klatzo 1987] which only lasts 20 to 180 minutes [Fritz & Hossmann 1979; Garcia *et al* 1981; Lee & Olszewski 1959] and thus corresponds to the period of time the blood-brain barrier is open after CAGE [Hills & James 1991]. In a skin model of ischæmia-reperfusion, dexamethasone was shown to prevent activated neutrophils from accumulating in the microcirculation [Yarwood *et al* 1993] which raises the possibility that it may act similarly in brain after CAGE. However, there are no reports of such studies.

7.2.4.3. CAGE and the "*triple combination*"

Hallenbeck, Dutka, Kochanek *et al* have published several studies demonstrating the efficacy of the so called "*triple combination*"

(prostaglandin I_2, indomethacin and heparin) in protecting the brain against the effects of CAGE. Prostaglandin I_2 has been shown to inhibit granulocyte adherence to vascular endothelium [Jones & Hurley 1984]. However, although it has been shown this "*triple combination*" accelerates recovery of CSER without reducing brain œdema [Hallenbeck *et al* 1982a] and that it increases CBF [Hallenbeck *et al* 1982b] after CAGE, it did not prevent the accumulation of granulocytes [Kochanek *et al* 1987a] or platelets in the brain [Kochanek *et al* 1988]. These authors concluded that platelets and granulocytes may still adhere to damaged endothelium despite aggressive "*anti-adhesion*" therapy. The "*triple combination*" may be protective of the effects of CAGE in this model by inhibiting cyclic nucleotide metabolism [Goldstein *et al* 1977b] which then inhibits the ability of granulocytes to release superoxides.

The conclusions drawn from these experiments may also be influenced by the methods used to identify platelet or leukocyte accumulation. These authors removed blood, isolated the granulocytes by centrifugation and washing before radio-labelling with ^{111}Indium. Almost any isolation procedure will damage granulocytes [Glasser & Fiederlein 1990; Gruber *et al* 1990]. Although such procedures have not been reported to up-regulate cell adhesion molecules, other surface antigens, such as CD16 (the functional receptor structure for performing antibody-dependent cellular cytotoxicity) are up-regulated by isolation methods [Watson *et al* 1992]. Platelets or leukocytes so treated may not adhere to damaged vascular endothelium as would unhandled cells.

7.2.4.4. CAGE and kadsurenone

Platelet activating factor [1-*O*-hexa-decyl-2-acetyl-*sn*-glyceryl-phosphorylcholine, PAF], is a substance which has attracted some attention as a possible mediator of platelet adhesiveness in various injury states. Kadsurenone is a specific inhibitor of PAF which was found to improve the rate of recovery after incremental CAGE but without preventing platelets accumulating in the brain [Kochanek *et al* 1987b]. Thus, the beneficial effects of kadsurenone may be related to effects other than those on platelets. Receptors for PAF are found on granulocytes and smooth muscle cells [Zahavi & Maeder 1974] and PAF antagonists may exert their protective effects by modifying granulocyte rather than platelet adhesion after CAGE.

7.2.4.5. CAGE and granulocytopenia

Dogs treated with mechlorethamine before being subjected to incremental CAGE recovered faster than dogs with normal granulocyte counts [Dutka *et al* 1989]. Other models of ischæmia [Freed *et al* 1989] and endothelial cell damage [Laughlin *et al* 1986] are similarly protected by granulocytopenia.

Such results are consistent with the findings reported here. Granulocytes can block blood vessels and reduce blood flow by adhesion to the vascular endothelium or by increasing their rigidity. Once the granulocytes have adhered they can marginate and release superoxides and other cytotoxic products. Studies in which granulocytes are depleted demonstrate these cells are important mediators of the pathophysiology of CAGE but they do not show that granulocyte adhesion to vascular endothelium is required as part of this process. The studies reported in CHAPTER 6

of this thesis demonstrate the protective effects of dextran 500 sulphate in CAGE and strongly suggest granulocyte adhesion is required for the effects of CAGE on brain blood flow and function.

7.2.4.6. Adenosine and granulocyte adhesion

Adenosine has been shown to reduce post-ischæmia reperfusion injury in different organ systems [Dux *et al* 1990; Grisham *et al* 1989]. These effects of adenosine have been attributed to its vasodilator effects [Berne 1980] as well as its potential to decrease granulocyte activation [Cronstein *et al* 1985], which it does presumably by activating the cyclic AMP pathway [Iannone *et al* 1987; Fessatidis *et al* 1991]. Most of the physiological effects of adenosine are mediated through membrane bound receptors and there is evidence that activation of the adenosine A_2 receptor will decrease granulocyte superoxide [Cronstein *et al* 1985] and H_2O_2 production as well as inhibit release of myeloperoxidase and other cytotoxic enzymes [Riches *et al* 1985; Iannone *et al* 1987]. Adhesion of stimulated granulocytes to cultured endothelial cells and granulocyte-induced endothelial damage are also mediated by adenosine A_2 receptors [Nolte *et al* 1992]. Indeed Nolte *et al* have suggested that the most important of the beneficial effects of adenosine are due to its inhibitory actions on post-ischæmic granulocyte adhesion [Nolte *et al* 1991a]. They have further demonstrated that these effects are mediated *via* adenosine A_2 and not adenosine A_1 receptors.

7.3. THE STUDIES REPORTED HERE

In the model of CAGE described and studied here a bolus of air is injected into one internal carotid artery. This model attempts to mimic the situation

expected after pulmonary barotrauma or other iatrogenic accident or after decompression in which large amounts of intra-arterial air may be produced by gas shunting through a patent foramen ovale (or other atrial septal defect). Large boluses of gas may be expected to be produced if small bubbles produced by decompression coalesce. Whereas a steady stream of small bubbles may also damage the brain circulation, this has not been examined by the studies in this thesis.

The doses of air studied (25 µl and 400 µl) produced effects characteristic of CAGE seen in divers [Gorman 1984; Greene 1978; Stonier 1985]. In about 5% of divers with CAGE there is a cardiorespiratory arrest and death [Gorman 1984; Greene 1978] such as are produced by a continuous injection of air into the cerebral vessels [Gorman 1987a; Gorman & Browning 1986; Gorman *et al* 1987b]. In about 35% of divers with CAGE there is a sustained interruption of neural function [Stonier 1985] such as was produced by the 400 µl air dose (temporary bubble trapping but sustained inhibition of brain function). In the remaining 60% there are symptoms of neurological dysfunction [Stonier 1985] which may resolve. This is analogous to situations produced by the 25 µl air dose (rapid bubble transit and partial suppression of the CSER AP_2).

7.3.1. Do intravascular bubbles pass through the cerebral circulation?

In all doses of gas studied, blood flow declined during the 3 hours post-embolism. There was no evidence of bubbles blocking the circulation producing profound ischæmia or hypoxia. Bubbles embolised many of the arteries on view although the full extent or nature of bubble distribution could not be studied in this model.

Air embolism of the contralateral hemisphere was negligible (except in the dextran 500 sulphate studies). This might be expected since air was injected into the ipsilateral carotid artery only and it has previously been

shown that bubble distribution is influenced largely by bubble buoyancy and blood flow [Gorman *et al* 1987b]. The bilateral distribution of air in the dextran 500 sulphate group cannot be explained by these data. If dextran 500 sulphate is inhibiting leukocyte adhesion to the vascular endothelium changes in the local microviscocity may influence streaming or induce other flow effects which then influence bubble distribution.

If bubble trapping had produced ischæmia it would have been evident in the first measurement of brain blood flow after the gas infusion. In the 400 µl group, bubbles were typically visible within 2 minutes of CAGE and yet CBF was normal or slightly higher than pre-injection baseline in all the experiments, suggesting that sufficient collateral blood vessels were open to maintain CBF. The progressive loss of flow to approximately 40% of baseline over the next 75 minutes can be explained by granulocytes interfering with the microcirculation. In rabbits treated with mechlorethamine or dextran 500 sulphate, CBF was largely preserved.

The degree of embolism of other areas of brain is not critical to this study as these measurements of CBF and neural function are limited to the small area of exposed cerebral cortex. Thus, it is not necessary to invoke trapping of bubbles at the gray-white junction in the subcortex [Dutka *et al* 1988] to explain the results reported here unless the accumulation was massive and caused cortical ischæmia which it clearly does not..

In some of the later studies CBF was measured using a laser Doppler flowmeter (see APPENDIX A.3). The laser Doppler signal was attenuated during the passage of air but red cell flux returned to normal after

bubble passage suggesting that for at least the area under the laser Doppler probe, bubbles were not causing any vessel blockage. Bubble passage has been reported by Gorman *et al* in rabbit pial arteries [Gorman *et al* 1987b; Gorman *et al* 1987a; Gorman & Browning 1986] and a number of other workers have shown bubbles transit retinal arteries [Ring & David 1969], rat carotid artery [Guyton *et al* 1984], and the pulmonary vascular bed [Vik *et al* 1991; Butler & Hills 1985].

7.3.2. CBF after CAGE

In the model used here, CAGE causes progressive, delayed reductions of CBF, an effect which appears to be independent of dose. This is not characteristic of short periods (5 to 30 seconds) of ischæmia which are normally followed by a reactive hyperæmia [Gourley & Heistad 1984; Symon *et al* 1972] suggesting that CAGE does not produce ischæmia in the accepted sense.

Despite stable MABP, the increase in external diameter of embolised pial arteries was not associated with any change in regional CBF. Flow in these small vessels is probably not Newtonian [La Celle 1986] although if it is then a vessel diameter increase of 27% in the absence of any other changes should have produced a 260% increase in flow [Ganong 1983]. Such an increase in CBF was not seen, suggesting that although the outer diameter was increased, there was no change in the luminal diameter. It is thus necessary to postulate alternative mechanisms for these reductions in CBF.

Endothelial cell and astrocyte swelling has been described after brain trauma [Maxwell *et al* 1988] and bubbles have been shown to damage endothelial cells [Haller *et al* 1987; Kuroiwa *et al* 1988; Persson *et al* 1978; Warren *et al* 1973]. Since granulocytopenia protects the brain from

these effects it is likely granulocytes are involved. Furthermore, dextran 500 sulphate treatment (which inhibits granulocyte adhesiveness) was also protective. An explanation for this protection would be that granulocytes attach to air embolus-damaged endothelium and interfere with microrheology. Either depletion of granulocytes or modification of their adhesiveness thus protects the brain from blood flow impairments due to granulocytes interfering with the microcirculation.

7.3.3. Pial arterial diameter after CAGE

The external diameters of air embolised vessels increased significantly and transiently in all studies. This dilatation is unlikely to be due to brain-stem reflexes [Nagao *et al* 1987] since there was no simultaneous increase MABP often seen after air embolism of the brain stem [Evans & Kobrine 1987]. It is also unlikely the diameter changes were due to variations in P_aO_2 or P_aCO_2 which remained constant throughout the experiment.

The calculated absolute gas pressure in bubbles trapped in pial arteries is less than 870 mmHg [Gorman 1987a], not enough to overcome pressure autoregulation [Vinall & Simone 1981]. Although bubbles in the capillaries or intraparenchymal arterioles may cause an increase in transmural pressure, the response of normal vessels should be to constrict rather than dilate due to pressure autoregulation [Bayliss 1902; Harder 1987]. However, the normal vasoconstrictor response to increases in transmural pressure may require intact endothelium [Harder 1987; Hishikawa *et al* 1992] and bubble passage has been shown to damage endothelial cells [Persson *et al* 1978; Warren *et al* 1973; Kuroiwa *et al* 1988]. The pial artery dilatation seen in these experiments may

thus be an inappropriate response by an air embolus damaged vascular endothelium.

Studies with nitric oxide (NO) synthase inhibitors have shown endothelium-derived NO is an important endogenous modulator of leukocyte adherence [Kubes *et al* 1991]. Impairment of NO production results in leukocyte adhesion to cat mesentery similar to that seen in acute inflammation [Kubes *et al* 1991]. Endothelium damaged by bubble passage may not be able to keep granulocytes from adhering because NO synthesis is reduced. Treatment with nitro-L-arginine (L-NA) might be protective of the effects of CAGE by preventing granulocyte adherence [Iadecola 1992].

7.3.4. CSER AP_2 after CAGE

Regression analysis of left CBF against CSER AP_2 showed that after a 25 µl CAGE brain blood flow and function are still coupled since there is still a demonstrable relationship between blood flow and brain function (figure 3.6). After a 400 µl CAGE, brain blood flow and function become uncoupled as shown by a complete loss of any relationship between blood flow and brain function (figure 4.7). Thus CAGE has a dose threshold effect on the relationship between CBF and CSER AP_2. The mechanism for the sudden loss of function in the 400 µl group cannot be identified by these studies although since granulocytopenia or treatment with dextran 500 sulphate protects the brain it is likely that granulocytes are involved in some way.

The progressive decline in CSER AP_2 seen in the 25 µl CAGE group is likely due to a progressive impairment of the circulation by accumulating granulocytes. Furthermore, superoxides could be released from arrested

granulocytes which may further damage neurons [Garcia & Anderson 1989].

More difficult to explain is how the 400 µl CAGE produces such a sudden impairment of CSER AP_2. Possible explanations include the role of endothelin, a vasoconstrictor polypeptide which can be released from endothelial cells and which can also suppress somatosensory evoked potentials when administered *via* the carotid artery in rats [Todorova *et al* 1992]. Whereas this response is most likely to be due to cerebral vasoconstriction, it is tempting to speculate that vascular endothelial cells are able to send signals to the brain, perhaps *via* the astrocytic foot processes to which they are closely apposed.

Another hypothesis to explain the interaction between the endothelial cells and the brain involves the neuropeptide innervation of the cerebral vessels. It has been shown that endothelial leukocyte adhesion molecule (ELAM-1) is rapidly induced on post-capillary dermal venules after degranulation of adjacent mast cells and that the principle endogenous mediator of mast cell degranulation is the neuropeptide substance P [Klein *et al* 1989]. Substance P release from dermal nerve fibres degranulates mast cells and promotes upregulation of ELAM-1 [Matis *et al* 1990]. Similarly, calcitonin gene related peptide (CGRP), which is co-distributed and released with substance P, stimulates adhesion of granulocytes to vascular endothelial cells [Sung *et al* 1992]. This theory is speculative but mechanisms such as these may provide a link between reflex control of CBF and brain function and the means by which granulocytes sequester in the circulation.

7.3.5. Studies with mechlorethamine

Mechlorethamine pre-treatment afforded significant protection against the effects of CAGE on CBF and CSER AP_2. Treating the rabbits with mechlorethamine reduced the granulocyte numbers so that even if the cerebral vascular endothelium was damaged by air embolism, there were insufficient granulocytes available to reduce CBF.

7.3.6. Studies with dextran 500 sulphate

Rabbits pre-treated with dextran 500 sulphate were protected from the effects on CBF and CSER AP_2 effects induced by CAGE.

Sulphated polysaccharides have been shown to inhibit granulocyte binding to vascular endothelial cells *in vivo* [Ohkubo *et al* 1991; Tangelder & Arfors 1991] and *in vitro* [Ley *et al* 1989]. The effectiveness of inhibition of granulocyte adhesion was dependent on the degree of sulphate substitution and the duration of action depended on the molecular weight [Tangelder & Arfors 1991]. Dextran 500 sulphate will also inhibit granulocyte adhesion to vascular endothelium in the presence of shear stress [Ley *et al* 1989].

The effects of dextran 500 sulphate treatment on complement has not been reported although it may inhibit complement activation by coating the cell surface and preventing secretion of C3 [Botto *et al* 1992].

Modification of granulocyte adhesiveness might be expected to have a profound effect on the microcirculation. CBF contralateral to the side of air injection was not affected in any experiments except those in which the rabbits were treated with dextran 500 sulphate. It is possible dextran 500 sulphate treatment reduced the blood viscosity at the level of the microcirculatory resistance vessels such that air could now distribute

across the Circle of Willis to invade both cerebral hemispheres. Lowering the dose of gas to one cerebral hemisphere might in itself afford some protection of the brain. However a progressive decline in CBF and CSER AP_2 was always seen in rabbits given even a 25 µl CAGE whereas a decline was not seen in rabbits pre-treated with dextran 500 sulphate.

7.3.7. Conclusions of the studies performed here

The formed elements of the blood, most probably the granulocytes, mediate many of the effects of air embolism. The progressive effects on brain blood flow and function induced by CAGE could be due to granulocytes accumulating in and obstructing the microcirculation. That the immediate effects of CAGE are abolished by granulocytopenia or by interfering with granulocyte adhesion with dextran 500 sulphate suggests that granulocytes somehow interfere with the brain function very rapidly. Long term damage to the brain by granulocytes could be due to superoxide damage of neural elements [Kontos & Povlishock 1986] but it is not clear how enough granulocytes to cause instantaneous shutdown can get at the brain in less than 2 minutes.

These studies, taken together with the work of Hallenbeck *et al* [Hallenbeck *et al* 1986] and Dutka *et al* [Dutka *et al* 1989], provide good evidence for a granulocyte/endothelial cell interaction producing the decrements in brain blood flow and function seen after CAGE. It also seems likely that granulocyte adhesion to the endothelium is required for the pathology of CAGE to evolve. In CHAPTER 1 the idea of a *"gas embolism related coagulopathy"* was discussed. A more appropriate term for the phenomenon observed in these studies might be a *"gas embolism related cell adhesion"*.

7.4. THE *GAS EMBOLISM INITIATED INTRAVASCULAR CELL ADHESION* HYPOTHESIS

Surfactant-like (amphipathic) molecules coat the lumenal surface of the vascular endothelium of cerebral and other vessels making the lumen hydrophobic [Hills & James 1991; Hills 1992a]. Amphipathic molecules have a strong affinity for phase interfaces, such as bubbles. Bubbles in the circulation have been shown to stick to endothelial cells and rupture the fluid film which normally separates the bubble surface from the endothelial cell membrane [Grulke & Hills 1978]. A bubble passing across endothelial cells could collect surfactant from the outer membranes of the endothelial cells [Butler & Hills 1983]. Electron microscope studies have shown lipid droplets which could be endothelial cell associated surfactants [Hills 1992a], attached to surface associated protein on the air side of the air-blood interface as well as incorporated in it [Warren *et al* 1973]. Furthermore, passage of air bubbles has been shown to produce herniation of endothelial cells through fenestrations in more rigid structures of the vessel wall [Warren *et al* 1973].

Surfactants may be also be important in spinal cord decompression sickness as extracellular lamellar bodies may act as bubble forming surfaces [Hills 1993]. Interestingly, lamellar bodies are found on the luminal side of the cerebral circulation [Hills 1993] where they may cause local intravascular bubble formation after decompression.

As bubbles pass through the cerebral circulation, they collect surfactant from the endothelial cells and damage them. This damage may then expose adhesion molecules such as E-Selectin [Kotovuori *et al* 1993] or may even upregulate synthesis of late acting leukocyte bound adhesion molecules such as CD11/18 [Kotovuori *et al* 1993] causing granulocytes

to adhere to endothelial cells and plug small vascular channels [La Celle 1986]. It is well established that granulocytes affect the microrheology of capillary beds [La Celle 1986] and adhesion of the formed element of the circulation to the vascular endothelium has been shown to alter microvascular flow [La Celle 1986; Obrenovitch *et al* 1984; Hallenbeck *et al* 1986; Dutka *et al* 1989].

7.4.1. Where are the granulocytes adhering?

Leukocyte adhesion to vascular endothelium has only been observed in post-capillary venules [Lipowsky *et al* 1988; Granger *et al* 1993; Ley *et al* 1991; Ikeda *et al* 1993; Kubes *et al* 1991]. Leukocytes are seen rolling along the vascular endothelium in veins because in arteries flow rates are too high and shear forces are too great for the *"loose"* adhesion interactions to take place [Lawrence & Springer 1991]. If flow of arterial blood is slowed by introducing an intra-arterial air bubble and the endothelium is damaged by the presence or transit of this air bubble adhesion molecules may then be up-regulated so that leukocytes then adhere to the arterial endothelium. When blood flow is restored a zone of vascular obstruction is formed. This zone may then become larger as more leukocytes bind to vascular endothelium around the turbulent zone in the area of initial damage until eventually, brain function is affected. If the initial dose of intravascular air is high enough (*viz;* 400 µl in these studies) the brain *"shuts down"* immediately and does not *"switch on"* again before CBF has dropped to neuron disabling levels. Granulocytopenic rabbits do not exhibit the brain shut down because their blood microviscosity is so low that after bubble transit nutrient supplies are restored almost immediately. The reduced viscosity of blood at the level of the microcirculation may also promote bubble passage (although there was no significantly shorter transit time for the

leukocytopenic rabbits). Dextran 500 sulphate treated rabbits do exhibit a transient reduction in brain function. However, it may be postulated that this recovers quickly because there are no granulocytes adhering to damaged vascular endothelium affecting the microcirculation.

The following sequence of events are proposed. CAGE initiates damage to the vascular endothelium. This damage may simply involve stripping of surfactant layers from the vascular endothelial cells. Granulocytes adhere to this damaged endothelium and release superoxides and further upregulate the complement system promoting accumulation of more granulocytes. It may be that normal homeostatic systems take control of this "*inflammatory*" response if small amounts of damage are involved. Prompt hyperbaric treatment with 6 BAR of air may keep the total amount of endothelial damage and complement activation at low levels by reducing the total intravascular gas surface area. If treatment is delayed, larger amounts of intravascular gas may then evolve and more extensive and thorough damage is caused. The mainstay for CAGE treatment, hyperbaric O_2 may have its most important effects on granulocyte function although improving O_2 carriage to flow impaired tissues would also be expected to improve outcome for victims of CAGE. Therapies which further reduce granulocyte adhesion would be useful adjuncts to hyperbaric O_2 or may reduce morbidity and mortality if used as a first aid treatment for CAGE or DCI. Indeed, intravenous lignocaine is being promoted both as an adjunctive or first aid treatment for DCI [Dutka 1990].

7.4.2. Complement activation

In rabbits, complement protein activity is essential for the development of neurological dysfunction after a hyperbaric exposure and the

sensitivity and degree of activation of complement proteins correlates with the risk of DCI after decompression [Ward *et al* 1986; Ward *et al* 1990]. Removal of complement (by cobra venom activation of C3) inhibits aggregation of leukocytes exposed to a phase interface suggesting the complement system is activated by the presence of an air interface in plasma [Ward *et al* 1986].

Thus complement sensitive individuals are susceptible to symptoms of DCI after exposure to small amounts of intravascular gas. Failure of the lungs to trap any circulating air or a patent foramen ovale would not be required since complement factors move about the circulation freely. Insensitive individuals on the other hand are able to tolerate comparatively large amounts of (Doppler detectable) intravascular air. Normal variations in complement sensitivity may explain much of the variability seen in the diving community and may explain why certain individuals develop symptoms after non-provocative dives or do not develop symptoms when Doppler detectable gas is present in the circulation.

7.4.3. Does CAGE produce an ischæmia - reperfusion injury?

This model of CAGE was not associated with blood flow reduction to near zero flow levels nor was there any measurable tissue hypoxia (see APPENDIX A). Animal studies of ischæmia - reperfusion injury typically arrest flow by ligating arteries for more than one hour [Nolte *et al* 1991a; Nolte *et al* 1991b; Nolte *et al* 1992; Iwayama *et al* 1986; Siemionow *et al* 1991]. Although granulocyte adhesion to vascular endothelium is a feature of ischæmia-reperfusion injury and certainly is important in CAGE, it may be that bubble passage is considerably more damaging than even extended periods of ischæmia. Inhibition of complement activation

is protective after 4 hours of ischæmia followed by reperfusion [Pemberton *et al* 1993]. Activated granulocytes express complement C3 [Botto *et al* 1992] and so inhibition of complement activation would be expected to be protective of the effects of CAGE [Ward *et al* 1986; Ward *et al* 1987; Ward *et al* 1990].

7.4.4. The formed elements of the blood and CAGE

Granulocytes are large, stiff viscoelastic cells that adhere naturally to the vascular endothelium. On their passage through the capillary network they have to be deformed, and recent evidence indicates that they may impose a significant hæmodynamic resistance. The residence time of granulocytes in the capillaries is about three orders of magnitude longer than that for red cells. Inside a capillary, granulocytes move with a lower velocity than red cells. When the capillary perfusion pressure is reduced and/or elevated levels of inflammatory products are present that increase the adhesion stress to the endothelium, granulocytes may become stuck in the capillary. In such a situation, the granulocytes form a large contact area with the capillary endothelium and may obstruct the vascular lumen, and initiate tissue injury. After the restoration of the perfusion pressure the granulocytes may not be removed from the capillary owing to adhesion to endothelium. Capillary plugging by granulocytes appears to be the mechanism responsible for the no-reflow phenomenon, and together with O_2 free radical formation and lysosomal enzyme activity may constitute the origin of ischæmic injury as well as other microvascular occlusive diseases.

7.4.5. The molecular mechanisms of formed cell mediation of CAGE

The actual molecular entity which mediates this process can only be determined by considerably more sophisticated experiments. Although

it is likely than more than one class of molecule is involved CAGE may produce a particularly "clean" insult to the cerebral circulation and thus it is possible that only a small class of compounds is involved.

7.4.5.1. Possible roles of CD11/18 and/or GMP-140

It is possible that CAGE induced endothelial cell-granulocyte attachment is mediated by specific granulocyte-endothelial cell adhesion molecules. These are typically surface glycoproteins that promote adhesive interactions with circulating granulocytes. This group of molecules includes the so called *endothelial-granulocyte adhesion molecule-1* (ELAM-1), *inducible cell adhesion molecule 110* (INCAM-110) or GMP-140 (Granule Membrane Protein-140; identical to P-Selectin, PADGEM or CD62) [Luscinskas *et al* 1989; Ley 1992; Tonnesen 1989; Yong & Khwaja 1990].

Rapid neutrophil adhesion to activated endothelium has been shown to be mediated by GMP-140. This only takes minutes and does not require active granulocyte metabolism, although it is Ca^{++} dependent [Geng *et al* 1990; Hamburger & McEver 1990].

The adhesion substance (or substances) cannot be identified by these studies although it is tempting to suggest GMP-140 as a likely candidate since its adhesive effects can be reduced by dextran 500 sulphate [Handa *et al* 1991b], it is found on platelets, granulocytes and endothelial cells [McEver 1991; Moore *et al* 1991] and because it is expressed on the cell surface rapidly [Moore *et al* 1991] after damage to the circulation.

Both dextran 500 sulphate and heparin have the apparently paradoxical effect of activating Factor XII [Hageman factor] [Silverberg & Diehl 1987; Silverberg 1989] as well as being anticoagulants

[Hocking *et al* 1992]. Terminal components of the complement system are not essential for dextran 500 sulphate activity [Bellavia *et al* 1984]. Dextran 500 sulphate has also been shown to cause platelets to sequester in lung where they degranulate [Wiggins *et al* 1985]. It was not established whether or not there was a dextran 500 sulphate-induced thrombocytopenia because dextran 500 sulphate interferes with the platelet assay used in these studies.

7.5. POSSIBLE FUTURE THERAPIES FOR CAGE

A promising potential therapy for injury-states which involve granulocyte adhesion uses monoclonal antibodies against the specific cell surface molecules involved in granulocyte adhesion. Studies *in vitro* [Yoshida *et al* 1992] as well as *in vivo* in brain [Martin *et al* 1992; Huitinga *et al* 1993] and other tissues [Argenbright *et al* 1991] have shown specific antibodies against CD11/18 to be protective of the effects of ischæmia followed by reperfusion. The promise has not been without detraction however. Some models of cerebral ischæmia have been found to be resistant to treatment with monoclonal antibodies [Takeshima *et al* 1992].

It might be expected that if the pathophysiology of CAGE is mediated by the formed elements of the circulation adhering to the vascular endothelium then antibodies against specific adhesion molecules would be protective of the progressive decline in brain blood flow and brain function seen after CAGE. It is unclear how such agents might protect against the acute mechanical effects of intravascular air although the studies reported here provide good evidence that they should.

Other agents such as buflomedil, which make neutrophils more elastic, [Boisseau *et al* 1991] have been shown to reduce post-ischæmic reperfusion injury [Nolte *et al* 1991b]. Substances such as N,N,N-trimethyl-sphingosine (a specific protein kinase C inhibitor) prevent early upregulation of P-selectin [Handa *et al* 1991a] and are also worthy of investigation.

A systematic study of how hyperbaric O_2 therapy exerts its effects is also long overdue. It would be useful to conduct intravital microscopic studies of the cerebral circulation during hyperbaric O_2 therapy for CAGE or DCI. The adhesiveness or not of granulocytes under hyperbaric conditions could be modified further by non-specific agents such as dextran 500 sulphate.

7.6. CONCLUSIONS AND FUTURE DIRECTIONS

There is considerable evidence that a granulocyte/endothelial cell interaction produces the decrements in CBF and brain function seen after CAGE. Future research could investigate a variety of compounds or specific antibodies which modulate adhesion molecule function. Studies which further characterise the mode of action of hyperbaric O_2 therapy may provide insight into the important components of the pathology of CAGE.

APPENDIX A.

MISCELLANEOUS STUDIES WHICH FURTHER CHARACTERISE THE MODEL

A.1. CHARACTERISATION OF THE EFFECTS OF CAGE ON THE BRAIN

The studies reported in CHAPTERS 3 and 4 demonstrate that CAGE can produce effects on CBF which are not dose dependent as well as effects on brain function which are dose dependent. Whereas passage of bubbles through pial arterioles is observed for all the doses of intracarotid air studied it was considered important to try to establish whether or not bubbles were escaping into the venous circulation and at what rate and for how long. It was also of interest to get some idea of whether the brain was becoming ischæmic in the early period or not. Accordingly, studies of bubble passage and brain tissue oxygen concentration were undertaken. These pilot studies were intended to effect a decision as to what studies to conduct next, rather than being comprehensive experiments in their own right.

A.2. BUBBLE TRAPPING STUDIES

There was always the possibility that air bubbles were trapped in the brain somewhere, possibly the grey/white junction under the cerebral cortex [Dutka *et al* 1988]. Fritz and Hossman looked at the distribution of carbon black after CAGE *via* the innominate artery in cats [Fritz & Hossmann 1979]. One minute after CAGE, air was distributed all over the brain. After 3 minutes the pial vasculature and the middle part of the lateral gyrus was still completely embolised and the middle of the pyriform lobe partly embolised, both of the last 2 regions are border zones between arterial territories and perfusion pressure is low. The rest of the hemispheres showed no filling with air. Fifteen minutes after air embolism the whole brain was reperfused with the exception

of a few vessels in the lateral gyrus [Fritz & Hossmann 1979]. In dogs given CAGE Fries *et al* observed a gradual accumulation of air in the pial veins. A few small bubbles in a vessel appeared to pass readily from artery to vein, sometimes in less than a minutes [Fries *et al* 1957].

Thus an attempt to quantify trapping of 400 µl of air (the most commonly studied dose in these experiments) was undertaken. The sagittal sinus was cannulated in an attempt to collect air which may have passed through the brain circulation after CAGE in this model. In another set of experiments an ultrasonic Doppler was used to detect bubbles in the sagittal sinus after CAGE.

A.2.1. Collection of air from the sagittal sinus

A.2.1.1. Surgical preparation for air collection

Four rabbits were anæsthetised and the femoral vessels cannulated. The internal carotid artery was prepared as described in CHAPTER 2. The animals were placed in a stereotaxic frame and the scalp deflected before a radical bilateral craniotomy was performed. Bleeding from the cranium was stopped by topical application of cyanoacrylate glue (Selleys BONDZA GLUE). A 5.0 ligature was passed under the most posterior segment of the sagittal sinus. A small incision was made in the transverse sinus whereupon air was seen to drain into the saggital sinus. A 23G stainless steel cannula with smoothed ends was introduced in a rostral direction through this incision and the ligature tightened. Any tubing connected to the steel cannula caused a sufficient increase in back-pressure that flow almost stopped so the circulation was simply allowed to drain from the cannula.

A.2.1.2. Results of air collection studies

Air introduced into the internal carotid artery was rapidly distributed throughout the pial arterioles of the ipsilateral hemisphere (one rabbit exhibited a bilateral embolism; possibly due to the bilateral craniotomy). Whereas no air bubbles were seen in the sagittal sinus cannula, small bubbles could be seen in the pial veins. These were stationary and their movement appeared to be restricted because they had risen to the highest point in the local venous circulation. Review of some of the earlier videotapes showed that stationary air bubbles could sometimes be seen in larger pial veins. Because air was seen to entrain into the draining sinus, sagittal sinus pressure must be sub-atmospheric and so it might be expected that in the intact animal not only arterial pressure but the negative sagittal sinus pressure would promote the passage of gas after CAGE.

A.2.2. Ultrasonic Doppler detection of air in the sagittal sinus

Ultrasonic Doppler is used to measure blood flow in vessels by reflecting an ultrasonic sound wave into the blood vessel at an angle. The output from the ultrasonic Doppler is normally charted although it can also be connected to a speaker whereupon the Doppler signal makes a characteristic hissing sound. Ultrasonic Doppler is used to test for the presence of a patent foramen ovale [Moon *et al* 1989; Teague & Sharma 1991] and works best if a "*contrast*" of shaken saline (*viz;* saline containing bubbles) is used. It was thus considered a most appropriate tool to see if air bubbles could be found in the sagittal sinus after CAGE in this rabbit model.

A.2.2.1. Surgical preparation for ultrasonic Doppler studies

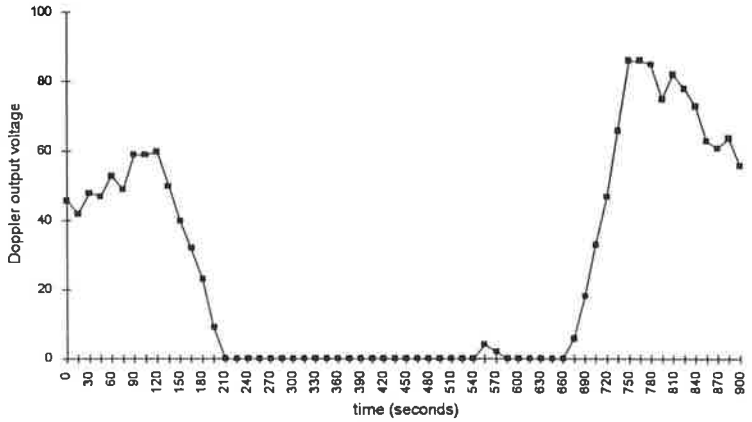
Two rabbits were anæsthetised and the femoral vessels cannulated. The internal carotid artery was prepared as described in CHAPTER 2. The animals were placed in a stereotaxic frame and the scalp deflected before a radical bilateral craniotomy was performed. Bleeding from the cranium was stopped by topical application of cyanoacrylate glue (Selleys BONDZA). A 20 MHz suture down crystal ultrasonic Doppler crystal (Titronics Medical Instruments; "FIGURE F" 20 MHz) was glued to the sagittal sinus in the most posterior position so that the signal would reflect from blood draining the sagittal sinus. The leads from the crystal were then connected to a directional pulsed Doppler flowmeter (Bioengineering Department of the University of Iowa; MODEL 545C-4) and the output charted.

A.2.2.2. Results of ultrasonic Doppler bubble trapping studies

After 30 minutes of stable recording, 800 µl of air was injected into the internal carotid artery. A change in the signal output sound indicating emboli (probably air emboli) were draining into the sagittal sinus. The charted signal is shown in figure A.1. After a period of time the signal recovered suggesting that no more air emboli were passaging the circulation.

FIGURE A.1 EFFECTS OF CAGE ON ULTRASONIC DOPPLER SIGNAL FROM SAGITTAL SINUS

The bubbles were detected by the ultrasonic Doppler 150 seconds after infusion of 800 µl air into the internal carotid artery. After 780 seconds the signal was higher than pre-injection baseline.



A.2.3. Conclusions of bubble trapping studies

Air introduced into the internal carotid artery was rapidly distributed throughout the pial arterioles of the ipsilateral hemisphere (one rabbit exhibited a bilateral embolism). The unilateral distribution of air normally observed may be due to the craniotomy providing a region of decompressed brain. Whereas no air bubbles were seen in the sagittal sinus cannula, small bubbles were seen in the pial veins. These were stationary and their movement appeared to be restricted because they had risen to the highest point in the local venous circulation, *viz;* they were distributed according to their buoyancy.

Bubble passage may be promoted because sagittal sinus pressure appears to be sub-atmospheric. Although no air could be collected from the sagittal sinus ultrasonic Doppler clearly demonstrates the presence of emboli in the sagittal sinus of the intact rabbit given CAGE.

A.3. CEREBRAL BLOOD FLOW MEASURED BY LASER DOPPLER FLOWMETRY

Laser Doppler flowmetry is a technique for noninvasive and continuous measurement of local blood flow. The flow estimate by this technique is based an assessment of the Doppler shift of low power laser light, which is scattered by moving red blood cells. Laser Doppler flowmetry has been validated for various organs, including brain. There is a linear relationship between relative changes of the Doppler signal and blood flow over a wide range of pharmacological as well as pathological flow alterations, including cerebral ischæmia. Whereas it is impossible to get absolute flow values and the method is sensitive to artefacts it does have a good spatial and temporal resolution [Frerichs & Feuerstein 1990]. Laser Doppler flowmetry is a useful technique for continuous assessment of cortical blood flow in response to topically applied agents [Haberl *et al* 1989a].

Changes in flow measured by hydrogen clearance have been reported to correlate linearly ($r = 0.94$, slope = 0.97) with laser Doppler flowmetry and with changes in pial arteriolar diameter (measured with a microscope in rabbits equipped with a closed cranial window). When pial arterioles are dilated 19 ± 4% (mean ± SE) by increasing arterial P_aCO_2 from 28 to 48 mmHg laser Doppler flow increased by 74 ± 9%, as would be predicted by a third power relationship of diameter to flow [Haberl *et al* 1989b].

Data from hydrogen clearance and laser Doppler, show a linear relationship between relative values of blood flow changes, the coefficients being 0.658, 0.876 and 0.878 for the correlation between the laser Doppler data and relative changes in the fast, slow and mean H_2 CBF respectively. All three regression lines were significantly different from the line of identity. The discrepancy between the two methods may be related to limitations inherent in each of them, despite efforts to minimise these limitations. Thus the depth sensitivity

of laser Doppler in the brain may be greater than expected but laser Doppler nevertheless appears to be a useful method for continuous estimations of CBF [Skarphedinsson *et al* 1988].

A.3.1. Method used for laser Doppler flowmetry

A Perimed laser Doppler device (PERIFLUX PF2B) was used. It was calibrated according to the instructions supplied with the machine. The tip of the optical fibre bundle was mounted on a micromanipulator and its tip placed close to the cerebral cortex though the craniotomy. The output from the PERIFLUX PF2B was connected to a chart recorder.

A.3.2.1. Surgical preparation for laser Doppler studies

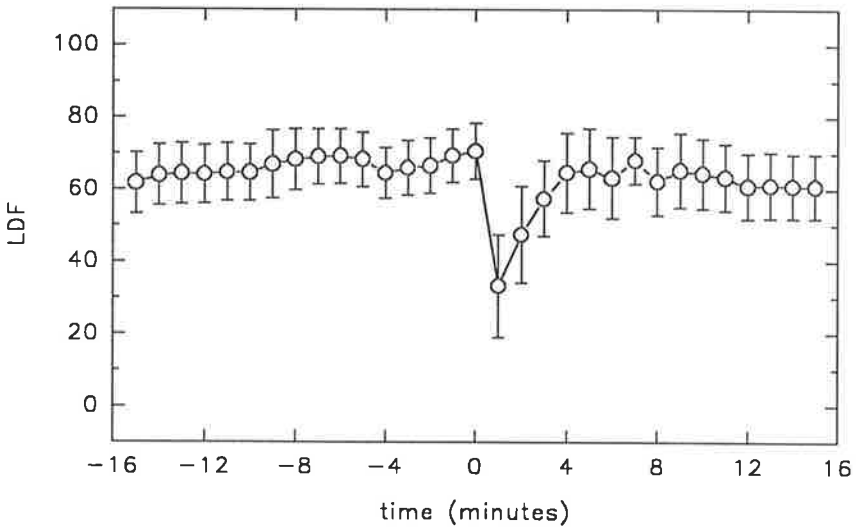
Laser Doppler flowmetry was performed in during the dextran sulphate studies only. The animals were prepared as described in CHAPTER 2 before being placed in a stereotaxic frame and craniotomy performed.

A.3.2.2. Results and conclusions of laser Doppler studies

Data sampled every 15 minutes is presented as a mean ± SEM (not as a % of pre-injection baseline). The data exhibit a similar pattern to that obtained by hydrogen clearance except that when air bubbles are in the pial vessels the laser Doppler signal becomes attenuated. It recovers after bubble passage suggesting that passage of air emboli had stopped. . The charted signal is shown in figure A.2.

FIGURE A.2 EFFECTS OF CAGE ON LASER DOPPLER SIGNAL FROM EXPOSED CEREBRAL CORTEX

The laser Doppler signal was recorded once a minute. After 400 µl air was injected into the internal carotid artery (at time = 0) the laser Doppler signal was immediately attenuated. Over the next 300 seconds it recovered to approximately pre-injection baseline.



A.4. CEREBRAL TISSUE OXYGEN AND CAGE

If bubbles were trapping in the brain long enough to produce ischæmia then it was expected a substantial reduction in tissue oxygen concentration could be measured.

A.4.1. Methods used to study hypoxia

The polarograph normally used for measuring hydrogen concentration was modified to measure tissue oxygen concentration as detailed in APPENDIX C.

Electrodes were prepared from sharpened 125 µm teflon-coated platinum wire. The tips were bared and then coated with styrene (Ajax Chemicals; $C_6H_5.CH{:}CH_2$) to create a membrane semi-permeable to oxygen. These

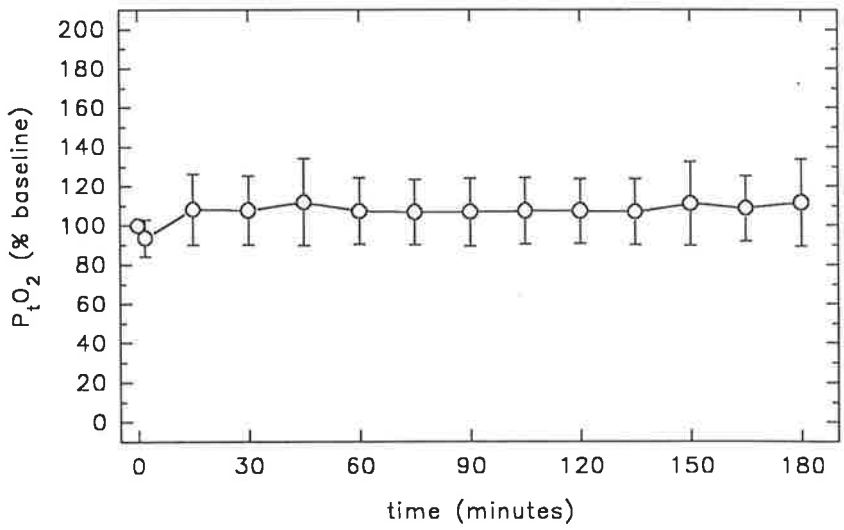
were placed 1 mm in the cerebral cortex. A Ag/AgCl indifferent electrode was implanted subcutaneously in the rabbit. The oxygen concentration was charted and calibrated *in vivo* during hypoxia (P_aO_2 = 20 mmHg), normoxia (P_aO_2 = 100 mmHg) and hyperoxia (P_aO_2 = 200 mmHg; after [Spokane *et al* 1990; Clark & Becattini 1967]).

Tissue oxygen was measured in the 8 rabbits subjected to a 400 µl CAGE described in CHAPTER 4.

During administration of hydrogen for CBF measurements the electrode current decreased as much as 25% of pre-injection baseline. After 400 µl CAGE, the electrode current would sometimes be reduced but always recovered by the end of the hydrogen clearance, even if bubbles were still visible in the pial arterioles. There was no systematic or significant hypoxia as measured using a polarographic method and it was concluded no significant cerebral hypoxia was occurring.

FIGURE A.3 EFFECTS OF CAGE ON CEREBRAL TISSUE OXYGEN MEASURED USING A POLAROGRAPHIC METHOD

P_tO_2 is shown as a % of pre-injection baseline.



A.5. *IN VITRO* STUDIES OF GAS EMBOLISM

These studies were undertaken in collaboration with Dr. Paul Drew and Eric Smith using a flow chamber to model the effects of shear stress on an endothelial cell monolayer. Their method and results briefly described below are presented here because the findings are very significant for the studies of CAGE as well as for completeness of the discussion. (A complete description of the method and results have been submitted to *British Journal of Pharmacology.* A draft (or reprint) of the paper is available from Dr. Paul Drew, School of Nursing, Flinders University, BEDFORD PARK, South Australia, 5048)

A.5.1. Preparation of endothelial cells

Human umbilical cords of at least 15 cm in length were stored at 4°C and used within 36 hours of collection. The umbilical vein was cannulated and flushed with 100 mls of sterile Hanks balanced salt solution pre-warmed to 37°C. The vein was then filled with a solution of collagenase in Hanks balanced salt solution to final concentration 0.1% (142 unit/ml) and incubated for 5 minutes. The resulting cell suspension was collected and the vein flushed twice with Hanks balanced salt solution. These washings were pooled and centrifuged at 150 × *g* for 10 minutes and the pellet resuspended in complete culture medium (containing RPMI 1640) supplemented with foetal bovine serum to 20% final v/v, streptomycin 100 IU/ml, Penicillin 100 µg/ml, heparin 10 µ/ml, 1% non-essential amino acids, 2.5 µg/ml Fungizone, 10 mM sodium pyruvate, 20 mM glutamine and 10 mM HEPES. For maintenance subculture, the complete culture medium was supplemented with 25 µg/ml ECGS supplemented with endothelial cell growth supplement for culture. The cells harvested from each cord were cultured at 37°C in a humidified incubator gassed with a mixture of air and CO_2 to a final concentration of 5%, and grown to

confluence before being subcultured by enzyme detachment with trypsin-EDTA. Cells were used in the 4th or 5th subculture and were seeded at a higher density in the flow chamber than in the subcultures.

A.5.2. Flow Chamber

The flow chamber consisted of a polished perspex block with three inlet/outlet ports, clamped into a 60 mm Petri dish in which was cultured an endothelial cell monolayer, and separated from the endothelial cells by a gasket of 25 μm thickness. The inlet and outlet ports at the ends of the block were used to create a flow of medium over the monolayer, while the third port, between these two, allowed the introduction of a gas bubble of known volume into the flowing medium, using a glass micro-syringe. The rate of the introduction and withdrawal of the gas bubble and its volume was reproducible. The endothelial cell monolayer in the Petri dish formed the base of the flow chamber created, the depth of which was determined by the thickness of the gasket material. The assembly was mounted on the stage of an inverted phase contrast microscope, and warmed to 37°C. The media was maintained at 37°C in an adjacent water bath. A 35 mm camera mounted on the microscope was used to record the experiments for later analysis. The flow rate was controlled by fixing the height of the inlet and outlet reservoirs relative to each other, and maintained so that the bubble moved relatively slowly over the endothelial cells. The use of gravity feed ensured smooth flow of medium. By observing red blood cells introduced into the flowing medium, it was shown that the flow was lamina.

A.5.3. Simulation of air embolism *in vitro*

The cultures were checked microscopically to ensure that they were confluent, and were then washed 3 times in RPMI 1640 buffered with

20 mM HEPES (pH 7.4). The gasket and perspex block were assembled to create the flow chamber, the reservoir of warmed medium connected and the glass micro-syringe put in place. The medium was allowed to flow for a period of 4 minutes to allow equilibration. A gas bubble was then slowly introduced into the chamber and then withdrawn over a period of 30 seconds. The volume of the bubble was sufficient to ensure that the field of view was covered approximately 75%, to enable the comparison of areas over which the bubble travelled and unaffected areas. The rate of movement of the bubble interface was controlled to be similar to that observed for a large percentage of bubbles which move through rabbit pial vessels *in vivo* in experiments reported in CHAPTER 4. Photographs were taken immediately before the introduction of the first bubble, as soon as each bubble was withdrawn, and 3 minutes after each bubble, following which another bubble was introduced. For most experiments a total of 4 bubbles were passed over the monolayer. The rate of flow of the medium over the endothelial cells monolayer did not vary during the whole of the experiment. The shear rate of the medium applied was not sufficient to separate the bubble from its entry port and wash it to the exit port, nor to prevent it from being withdrawn back into the syringe against the flow of medium.

Shear rate was set at a rate which enabled complete control of the gas bubble so that the bubble was introduced to the monolayer and withdrawn back, against the flow of the medium, through the gas inlet port

A.5.4. Results of *in vitro* studies of gas embolism studies

The images were captured from the developed negatives into a computerised image analysis system. A region of interest was defined

and the number of cells counted in that region in each of the negatives taken during the experimental run. The region of interest was approximately the same position in relation to the bubble inlet port in each experiment.

The flow of medium only across endothelial cells, even at high shear rates damaged very few cells. The passage of one air bubble over a confluent monolayer of endothelial cells resulted in lifting and loss of cells. Endothelial cells dislodged only from the area that the embolus travelled over and from no other part of the monolayer. Damage occurred in the total absence of blood components such as complement, platelets or white blood cells.

A.5.5. Discussion of *in vitro* studies of gas embolism studies

Ultrastructural studies of blood vessels after gas embolism *in vivo* indicate that the endothelial cells sustain early and significant damage. Air embolism of vessels has been reported to damage to endothelial cells *in vivo*, producing a flattening of the endothelial nuclei whereupon they acquired a wrinkled appearance [Haller *et al* 1987] or herniated [Warren *et al* 1973]. The sub-endothelial basement layer intact is left intact after air embolism [Guyton *et al* 1984). The experiment described here shows that these effects can be reproduced *in vitro*, in the absence of any blood elements.

The higher the shear force the greater the number of endothelial cells stripped from the monolayer. The curvature of the embolus interface (varied by adjusting the gasket thickness) did not influence the number of endothelial cells removed suggesting the effect is independent of surface tension force. The number of endothelial cells removed increases as more emboli pass over an area, and as the emboli move

faster. The effect is not due to the time that embolus remains above an area of the monolayer. One which sits for 30 seconds before being moved on causes the loss of similar number of cells as one stationary for 10 minutes. The time that the endothelial cells have been in culture, the number of subcultures in the same dish, or the age of the endothelial cells line, do not affect the outcome.

These observations, that the movement of a gas bubble across an endothelial cells monolayer can damage and mechanically detach cells, may provide part of the explanation for the pathological effects of gas emboli *in vivo*.

A.6. DISCUSSION

The studies described in this appendix provide evidence that;

1. Some proportion (possibly all) of the intracarotid air bubbles passage the cerebral circulation. These bubble are small and can sometimes be seen after coalescence in small pial veins. Passage of these bubble to the sagittal sinus can be detected using ultrasonic Doppler or laser Doppler.
2. CAGE is not producing any significant or sustained cerebral hypoxia as measured by a polarographic electrode.
3. Initial damage caused by gas embolism is due to the bubble moving across the endothelial cell lining of the blood vessels.

Other models if ischæmia/reperfusion typically arrest blood flow for periods of at least 10 minutes and often longer [Dereski *et al* 1992; Del Zoppo *et al* 1991; Meno *et al* 1991]. Indeed, in order to produce a satisfactory suppression of CSER AP_2 in dogs, Hallenbeck and Dutka *et al* repeatedly inject boluses of air into the carotid artery to produce ischæmia [Dutka *et al* 1988; Kochanek *et al*

1988; Dutka *et al* 1987; Dutka *et al* 1989; Hallenbeck *et al* 1982a; Hallenbeck *et al* 1982b]. In the studies performed here a single bolus of gas was used. Some proportion was detected in the sagittal sinus, but it produced no substantial hypoxia in the acute phases. Thus it seems probable that in this model of CAGE, temporary occlusion is followed by reperfusion in the accepted sense.

APPENDIX B.

A COMPUTERISED DATA ACQUISITION SYSTEM FOR AVERAGING SOMATOSENSORY EVOKED RESPONSES

B.1. DATA ACQUISITION REQUIREMENTS

A digital oscilloscope with the ability to average more than 16 evoked responses was not available when the experiments were conducted so a computerised system was constructed using off the shelf components.

B.2. DATA ACQUISITION HARDWARE

A National Instruments AT-MIO-16 high performance multifunction analog to digital (with timing input/output functions) board was used. This board uses a 12 bit analog to digital converter which can be multiplexed to 16 inputs among other functions.

The AT-MIO-16 board was installed in a MicroBits (Adelaide, South Australia) 80386 SX [16 MHz] computer with 4 megabytes of random access memory (RAM), a 20 megabyte hard disk drive and a monochrome, medium resolution graphics monitor (Hercules type).

All inputs to the AT-MIO-16 were shielded.

B.3. DATA ACQUISITION SOFTWARE

National Instruments provide a software library to simplify programming the AT-MIO-16 analog to digital board. This library contains additional functions for accessing graphic and other hardware in the host computer. The program listed below was written using the LabWindows interactive program and compiled using the Microsoft Quick Basic v4.5 compiler to create a stand alone executable file.

B.3.1. Algorithm for data acquisition software

Load LabWindows libraries

Dimension data arrays to hold data

Declare common variables

Set aside memory for graphics functions

Set constants (number of averages to do; gain on A/D board; use Hercules adaptor; etc)

Define graphics ports [LabWindows requirement]

Number of samples to collect (about 0.5 seconds)

Acquire and plot data for specified average scans

Reset trigger and throw away the first acquisition

Set up plot window

Acquire data

    WHILE

        Calculate moving average

        Plot moving average

    WEND

Finished getting data so write the date and time on the screen

Hardcopy

Cursor function

Re-Define numeric ports

Put a cursor on the plot

Move cursor with each key press

WHILE

Write latency and amplitude on plot

up arrow (move 10 increments forward)

down arrow (move 10 increments backward)

left arrow (move 2 increments forward)

right arrow (move 2 increments backward)

WEND

Display amplitude

Display latency

Go back to plot, because we want to see a new average

Actually draw cursor on plot

Stop and end

B.3.2. Program for data acquisition software

Comments in the code explain what each section does.

```
REM   $INCLUDE: 'C:\LW\INCLUDE\LWSYSTEM.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\GPIB.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\FORMATIO.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\GRAPHICS.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\ANALYSIS.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\DATAACQ.INC'
REM   $INCLUDE: 'C:\LW\INCLUDE\RS232.INC'
' $INCLUDE libraries for compiler use
'=============================================================================
'CSER6.BAS,'Asynchronous averaging oscilloscope, Stephen Helps, December 1990
'=============================================================================
dim cser.data%(1000)
dim plot.data#(1000)
dim mean.data#(1000)
dim cursor as integer
dim dat as string * 11
dim tim as string * 11

common shared /cser.data/cser.data%()
common shared /plot.data/plot.data#()
common shared /mean.data/mean.data#()

CALL getmem(10000 &)            'Set aside memory for graphics functions

average.scans#=64               'number of averages to do
gain%=2                         'gain on A/D board

pause%=0                        'don't pause
prt%=0                          'don't print
reset.attr%=0                   'no attribute reset
reset.graphics%=2               'close library on exit
CALL GrfLReset(pause%,prt%,reset.attr%,reset.graphics%)
CALL SetAdapter (1, 30, t%)     'use hercules adaptor
```

```
'----------------------
'Define graphics ports
'----------------------
x%=0 :y%=0                'port is in the lower left of screen
format%=0                 'format values integer
val.width%=4              'maximum width of values
val.precision%=2          '2 digits precision
units$="Scans"            'port displays scans done
title$=""
num.port%=CreateNumericPort(x%,y%,format%,val.width%,val.precision%,units$,title$)
CALL SetPortFrame (0)
CALL SetGrdFrame (1)

'--------------------------
'Port 2 for average display
'--------------------------
x%=0:y%=10:wwidth%=100:hheight%=90:port%=2
port%=CreatePort(x%,y%,wwidth%,hheight%)
mean.data.port%=port%

data.count#=250          'number of samples to collect (viz; about 0.5 seconds)
dat1.count%=data.count#
conversions#=data.count#

'-------------------------------------------------
'Acquire and plot data for specified average.scans
'-------------------------------------------------
t% = DIG.Prt.Config (1, 0, 0 1)
t% = DIG.Out.Port (1, 0 1)                      'external on trigger for stimulator
t% = DIG.Out.Port (1, 0, 0)                     'external off trigger for stimulator
t% = DAQ.Op (1, 0 1, cser.data%() 1000, 5000.0)'throw away the first acquistion

'-------------------
'Set up plot window
'-------------------
      CALL SetActivePort (11%)
      CALL SetPlotMode (0)                'immediate
      CALL SetYDataType (4)               '8 byte integer
      CALL SetAxName (0, "mSecs")
      CALL SetAxGridVis (0, 0)
      CALL SetAxAuto (0, 0)
      CALL SetAxRange (0, 0.0, data.count# 10)
      CALL SetAxName (1, "average mVolt")
      CALL SetAxGridVis (0 1)
      CALL SetAxAuto (1, 0)
      CALL SetAxRange (1, -2500.0, 2500.0, 5)
      CALL SetPortFrame (0)
      CALL SetGrdFrame (1)


'============
'Do the deed
'============
WHILE count% < average.scans#

      t% = DIG.Out.Port (1, 0 1)'external on trigger for stimulator
      t% = DIG.Out.Port (1, 0, 0)'external off trigger for stimulator
      t% = DAQ.Op (1, 0, gain%, cser.data%(),  1000, 2000.0)'acquire data


      count%=count%+1:n.scans#=n.scans# + 1
      CALL GrfNumeric(num.port%,n.scans#) 'display number of scans so far in port ?
      '-----------------------------------
      'Calculate moving average
      '-----------------------------------
      FOR i%=0 TO dat1.count%                          'sum cser.data
            plot.data#(i%)=plot.data#(i%)+cser.data%(i%)
            mean.data#(i%)=plot.data#(i%)/count%
      NEXT i%
      '--------------------
      'Plot moving average
      '--------------------
      CALL GrfWaveform (mean.data#(), dat1.count% 1.0, 0.0, 0.0 1.0)
      CALL RemovePlots (mean.data.port%)  'we want to see a new average

WEND

'-------------------------------------------------------------
'Finished getting data so write the date and time on the screen
'-------------------------------------------------------------
n%=fmt(tim$,time$):CALL GrfPrint (85, 0, tim$)
n%=fmt(dat$,date$):CALL GrfPrint (85, 5, dat$)

'----------------------------
'Hardcopy then cursor function
'----------------------------
CALL SetActivePort (mean.data.port%)
```

```
CALL GrfWaveform (mean.data#(), dat1.count% 1.0, 0.0, 0.0 1.0)
CALL Hardcopy

'-------------------------
'Re-Define numeric ports
'-------------------------
x%=20 :y%=0              'port is in the lower left of screen
format%=0                'format values integer
val.width%=5             'maximum width of values
val.precision%=2         '2 digits precision
units$="latency"         'port displays latency
title$=""
num.port%=CreateNumericPort(x%,y%,format%,val.width%,val.precision%,units$,title$)
latency.port%=num.port%

x%=20 :y%=5              'port is in the lower left of screen
format%=0                'format values integer
val.width%=5             'maximum width of values
val.precision%=2         '2 digits precision
units$="amplitude"       'port displays amplitude
title$=""
num.port%=CreateNumericPort(x%,y%,format%,val.width%,val.precision%,units$,title$)
amplitude.port%=num.port%

'-------------------------
'Put a cursor on the plot
'-------------------------
BEEP

CALL SetActivePort (mean.data.port%)  'go back to plot
CALL RemovePlots (mean.data.port%)    'because we want to see a new average
CALL GrfWaveform (mean.data#(), dat1.count% 1.0, 0.0, 0.0 1.0)

increment%=2                          'amount to move cursor with each key press
WHILE KeyHit% < 12

      k%=GetKey%                      'ASCII value of keypress

      IF k%=13 THEN                   'write latency and amplitude on plot
            curse!=cursor%
            CALL GrfText2D (curse!, mean.data#(cursor%)+10,  "doesn't work")
      END IF

      IF k%=18432 THEN                                    'up arrow
            cursor%=cursor%+increment%*10
            IF cursor% < 0 THEN
                  cursor%=0
            END IF
      END IF

      IF k%=20480 THEN                                    'down arrow
            cursor%=cursor%-increment%*10
            IF cursor% < 0 THEN
                  cursor%=0
            END IF
      END IF

      IF k%=19712 THEN                                    'left arrow
            cursor%=cursor%+increment%
            IF cursor% > 500 THEN
                  cursor%=500
            END IF
      END IF

      IF k%=19200 THEN                                        'right arrow
            cursor%=cursor%-increment%
            IF cursor% < 0 THEN
                  cursor%=0
            END IF
      END IF

      IF k%=27 THEN                                           'get off
            CALL GrfLReset (0, 0, 0 1)
            CALL SetDisplayMode (0)
            STOP                                              'this is where we end
      END IF

            y.position#=mean.data#(cursor%)
            CALL SetActivePort (amplitude.port%)
            CALL GrfNumeric(amplitude.port%,y.position#)    'display amplitude
            x.position#=cursor%
            CALL SetActivePort (latency.port%)
            CALL GrfNumeric(latency.port%,x.position#)      'display latency
            CALL SetActivePort (mean.data.port%)            'go back to plot
            CALL RemovePlots (mean.data.port%)     'because we want a new average
            CALL GrfWaveform (mean.data#(), dat1.count% 1.0, 0.0, 0.0 1.0)

      CALL SetActivePort (mean.data.port%)         'actually draw cursor on plot
```

```
            CALL SetPointStyle (2)                          'point style, asterisk
            curse!=cursor%                                  'math for bloody LW
            CALL GrfPoint2D (curse!, mean.data#(cursor%))   'put a cursor on the plot

        WEND

        STOP
```

APPENDIX C.

CALCULATION OF CBF FROM HYDROGEN CLEARANCE DATA

C.1. EXCEL WORKSHEET FOR CBF CALCULATION FROM HYDROGEN CLEARANCE DATA

A Microsoft EXCEL worksheet was used to calculate CBF from the hydrogen clearance data. TABLE C.1. shows EXCEL formulæ in italics and text in bold. Polarographic voltages are entered into the shaded area and the double border surrounds the part of the sheet where the answers are displayed.

The worksheet does a *"log least squares regression analysis"* of the hydrogen levels against time. The $t_{½}$ for the clearance of hydrogen is calculated from the equation of the line. CBF (mls/min/100 g) is calculated using the *initial slope index method* [Aukland *et al* 1964]. The brain blood partition coefficient for hydrogen (D_h) has been shown to be very nearly 1 and so by the initial slope index CBF is given by;

$$CBF = \frac{D_h \log_2 .60.100}{t_{½}}$$

$$CBF = \frac{4158}{t_{½}}$$

This gives a value for CBF in mls/minute/100 g tissue [Aukland *et al* 1964].

TABLE C.1 EXCEL WORKSHEET FOR CALCULATION OF CBF FROM HYDROGEN CLEARANCE DATA

	A	B	C	D	E	F	G
1	Notes	Decimal time (1.5 minutes = 90					
2							
3	r^2=	=B26					
4	T½=	=(LOG10((10^$B$25)/2)-	in minutes				
5	CBF=	=4158/$B$29	mls/min/100gm				
6							
7		Time	log H_2	H_2	X*Y	X^2	Y^2
8		0.5	=LOG10(D8)	40	=B8*C8	=B8^2	=C8^2
9		=B8+0.5	=LOG10(D9)	18	=B9*C9	=B9^2	=C9^2
10		=B9+0.5	=LOG10(D10)	10	=B10*C10	=B10^2	=C10^2
11		=B10+0.5	=LOG10(D11)	5.5	=B11*C11	=B11^2	=C11^2
12		=B11+0.5	=LOG10(D12)	3.5	=B12*C12	=B12^2	=C12^2
13				=AVERAGE(D8:D12)			
14	meanX	=AVERAGE(B8:B13)	=AVERAGE(C8:C13)				
15	sumX	=SUM(B8:B13)	=SUM(C8:C13)				
16	sum(X)2	=SUM(B8:B13)^2	=SUM(C8:C13)^2		sumX2	=SUM(F8:F13)	=SUM(G8:G13)
17	varX	=VAR(B8:B13)	=VAR(C8:C13)				
18	nX	=COUNT(B8:B13)	=COUNT(C8:C13)				
19	sumXY				=SUM(E8:E13)		
20							
21	P=	=E19-(B15*C15/B18)					
22	Q=	=F16-B15^2/B18					
23	R2=	=$G$16-$C$16/$C$18					
24	a1=	=B21/B22	constant				
25	a0=	=C14-B14*B24	intercept				
26	r2=	=B21^2/B22/B23					
27							
28	T½=	=(LOG10((10^$B$25)/2)-	in minutes				
29		=$B$28*60	in seconds				
30	CBF=	=4158/$B$29	mls/min/100gm				

APPENDIX D.

THE CLASSIFICATION OF DYSBARISM

D.1. CURRENT AND NEW CLASSIFICATION SYSTEMS

Gases dissolve in body fluids and tissues in direct proportion to their pressure. After decompression from higher to lower pressures inert gases dissolved in body tissues form bubbles which may then migrate into the circulation. Arterial bubbles in divers can either arise either in the veins, or from pulmonary barotrauma or secondarily from the arterialisation of venous bubbles. Once formed, gas may also escape into other body cavities such as the pleural space or joints. Thus the distinction between arterial air embolism induced by decompression or barotrauma is not always apparent.

The dysbaric disorders are currently classified (and so diagnosed) according to Table D.1. This classification is unsatisfactory because of the need to identify a presumed site of injury (*viz;* the spinal cord or inner ear). Furthermore, many of the dysbaric disorders (particularly those involving the central nervous system) are the result of multifocal injuries. The classification of DCS as type I or type II is arbitrary and symptoms may overlap.

A new system which does not require an interpretative step between observation and diagnosis has been proposed by the UNDERSEA AND HYPERBARIC MEDICAL SOCIETY. Using the new system a patient may be described as having;

> *progressive neurological dysbarism with an onset time of 15 minutes after surfacing, a high gas burden and no evidence of barotrauma;*

or a different patient may be described as;

spontaneously resolving neurological dysbarism with onset 5 minutes after surfacing, a low gas burden and evidence of pulmonary barotrauma.

Each case may be further described using descriptions (as yet not defined). A definition of terms used can be found in ANNEX B of Describing Decompression Illness [Francis & Smith 1990].

TABLE D.1. CONVENTIONAL SYSTEM FOR CLASSIFICATION OF DYSBARIC DISORDERS

Barotrauma	Pulmonary	Arterial gas embolism Interstitial emphysema Pneumothorax
	Sinus Inner ear Middle ear Outer ear Dental Gastrointestinal	
Decompression sickness	Type I (moderate)	Pain only (niggles and so on) Skin Lymphatic
	Type II (severe)	Cerebral Spinal cord Vestibular (Staggers) Cardiopulmonary (Chokes)
	Type III	Central nervous system

TABLE D.2. PROPOSED SYSTEM FOR CLASSIFICATION OF DYSBARIC DISORDERS

Evolution	Spontaneous recovery Static Relapsing Progressive
Organ system	Neurological Cardiopulmonary Limb pain exclusively Skin Lymphatic Vestibular
Time of onset	Minutes (after reaching the surface)[a]
Gas burden	
Pulmonary barotrauma	Yes or no Pulmonary[c] Ear Sinus Other

NOTES

a Exact timing may not be possible

b Calculated from the maximum likelihood analysis of a select US Navy diving accident database, repetitive dive group from any decompression table or simply low, medium or high

c Pneumothorax, surgical emphysema or radiological evidence of extra-pulmonary gas

APPENDIX E.

MANUFACTURERS AND SUPPLIERS

The tables shows brand and generic names and sources of supply for all the principle specialised materials and equipment used in this thesis;

EQUIPMENT	MODEL	MANUFACTURER/SUPPLIER
Analog/digital board	AT-MIO-16	National Instruments (Australia) PO Box 466 RINGWOOD, 3134 Australia
Blood cell analyser	H•2 HEMATOLOGY SYSTEM	Technicon Equipment (Australia) 24 Taminga Street Regency Park, SA 5010 Australia
Blood cell analyser	COULTER S & 6 CELL COUNTER [with Cash modification]	Coulter Electronics 1-45 Walkins Street NORTH FITZROY, Vic 3068 Australia
Blood gas analyser	CORNING MODEL 178	Ciba Corning Australian Diagnostic Corporation PO Box 158 FERNTREE GULLY, 3156 Australia
Camera 35mm	CONTAX 139 QUARTZ	Photographic Wholesalers 151 Hutt Street ADELAIDE, SA 5000 Australia
Chopper stabilised amplifiers	ANALOG DEVICES 239K	Trio Elextrix Pty.Ltd. 10 James Street THEBARTON, 5031 Australia
Circulation heater	HAAKE D1	HAAKE Goerzalle 249 1000 BERLIN(W) Germany

Craniotomy burrs	MEISINGER ISO 806 104	Ivoclar Pty.Ltd. 43-45 King William Street KENT TOWN, SA 5067 Australia
Craniotomy Drill	FARO MODEL 000485	Ivoclar Pty.Ltd. 43-45 King William Street KENT TOWN, SA 5067 Australia
Cyanoacrylate adhesive	BONDZA GLUE	Selleys 1 Gow Street PADSTOW, NSW Australia
Dental acrylic	SELF CURE RR	Dentsply Ltd (DeTrey Division) Weybridge, Surrey England KT15 2SE
dextran 500 sulphate dextran sulphate	DEXTRAN SULPHATE (SODIUM) DEAE-Dextran	Pharmacia (Australia) Pty.Ltd. 4 Byefield Street NORTH RYDE, NSW 2113 Australia
Directional pulsed Doppler flowmeter	MODEL 545C-4	Department of Bioengineering College of Medicine, 56 M.R.F. The University of Iowa Iowa City, IO 52242 USA
Doppler crystal	"FIGURE F" 20 MHZ	Department of Bioengineering College of Medicine, 56 M.R.F. The University of Iowa Iowa City, IO 52242 USA
Film 35mm	ILFORD FP4	Ilford Antec 5 Valetta Road KIDMAN PARK, SA 5025 Australia
Gallamine triethiodide	FLAXEDIL *2,2',2"-[1,2,3-Benzene-triyltris(oxy)tris[N,N,N-triethyethanaminium] triiode*	Rhône-Poulenc Rorer Australia Pty.Ltd. 19-23 Paramount Road WEST FOOTSCRAY, 3012 Australia

Hydrogen clearance polarographic amplifier	MARK II	A.P.S.F. GPO Box 400 ADELAIDE, SA 5000 Australia
Indifferent electrode for hydrogen clearance	ECG ELECTRODE	Tektronix Australia Pty.Ltd. 128 Gilles Street ADELAIDE, 5001 Australia
Infusion pump	TERUMO STC-521	Terumo Corporation Tokyo Japan
Intravenous cannula (Jelco)	22 G x 25 mm	Johnson & Johnson (Australia) 358 Findon Road KIDMAN PARK, SA 5025 Australia
Laser Doppler Flowmeter	PERIFLUX PF2B	Perimed Inc. 200 Centenial Avenue PISCATAWAY, NJ 08854-3910 U.S.A.
Mechlorethamine	NITROGEN MUSTARD *2-Chloro-N-(2-choroethyl)-N-methylethanamine*	Boots Pharaceutical (Australia) 21 Loyalty Road NORTH ROCKS, NWS 2151 Australia
Medical gases	OXYGEN HYDROGEN MEDICAL AIR	Commonwealth Industrial Gases Cnr Ashwin & Jervois Streets TORRENSVILLE, SA 5031 Australia
Micro-surgical instruments	various	Fine Science Tools 277 Mountain Highway North Vancouver, BC V7J 3P2 Canada
NeoMedix Intruments	NEOTRACE 400 DC AMPLIFIER NT 218 AC AMPLIFIER NT 114A	Neomedix Systems 2 Villiers Place DEE WHY WEST, NSW 2099 Australia

Operating microscope	ZEISS OMPI	Carl Zeiss Pty.Ltd. 287 Burbridge Road BROOKLYN PARK, SA 5032 Australia
Oscilloscope	DIGITAL STORAGE OSCILLOSCOPE TYPE 4035	Tech Rentals (Gould Intruments) 241 Churchill Road PROSPECT 5082 Australia
Paraffin oil	Liquid paraffin B.P.	Delta West 15 Brodie Hall Drive BENTLEY, 6012 Australia
Projector	CAROUSEL S-AV 1030 PROJECTOR	Kodak Australasia 19 Fullarton Road KENT TOWN, 5067 Australia
Rectilinear chart recorder	KA622	Rikadenki Kogyo Co.Ltd. Tokyo Japan
Rodent Ventilator	MODEL 683	Harvard Bioscience (An Ealing Division) Pleasant Street South Natick, MA 01760 U.S.A.
Silastic tube (for cannulæ)	602-175	Dow Corning Corporation Medical Products Midland, MI 48686-0994 U.S.A.
Stainless steel screws (for canial fixation)	TECSOL DV40	Laubman & Pank (Tecsol Industries) 62 Gawler Place ADELAIDE, 5001 Australia
Stereotaxic frame	FRAME 1430 RABBIT ADAPTOR MODEL 1460 ELECTRODE MANIPULATORS	Kopf Instruments 7324 Elmo Street Tijuana, CA 91042-0636 U.S.A.

Terumo syringe pump	STC-521	Terumo (Australia) 77 Fullarton Road KENT TOWN, SA 5067 Australia
Urethane	ETHYL CARBAMATE $NH_2COO.C_2H_5$	Ajax Chemicals 22 Pambula Street REGENCY PARK 5010 Australia
Video Camera	SONY CCD DCX101	SONY Australia Lum Street Export Park Adelaide Airport Australia
Video Monitor	JVC 93 SYSTEM PLUS AV-20ME	Japan Victor Company Ltd Tokyo Japan
Video Recorder	JCV VIDEO CASSETTE RECORDER BR64000JR	Japan Victor Company Ltd Tokyo Japan

APPENDIX F.

OTHER PAPERS AND ABSTRACTS PUBLISHED DURING CANDIDATURE

Chapman M, Helps SC, Russell WJ (1992) Laser Doppler flowmetry compared with hydrogen clearance for the measurement of cerebral blood flow in the rabbit. *Anaesthesia & Intensive Care* (Supplement)

Ludbrook GL, Helps SC, Gorman DF (1992) The relative effects of nitrogen and carbon monoxide hypoxia on brain function in rabbits *Undersea Biomedical Research* 19:s48

Ludbrook GL, Helps SC, Gorman DF (1992) Cerebral blood flow response to increases in arterial CO_2 tension during alfentanil anesthesia in the rabbit *Journal of Cerebral Blood Flow & Metabolism* 12:529-532

Ludbrook GL, Helps SC, Gorman DF, Reilly PL, North JB, Grant C (1992) The relative effects of hypoxic hypoxia and carbon monoxide on brain function in rabbits *Toxicology* 75:71-80

Meyer-Witting M, Helps SC, Gorman DF (1990) The effect of an acute CO exposure on cerebral blood flow in the rabbit *Undersea Biomedical Research* 19(supplement)

Meyer-Witting M, Helps SC, Gorman DF (1991) Acute carbon monoxide exposure and cerebral blood flow in rabbits *Anaesthesia & Intensive Care* 19:373-377

Webb RK, Vanderwalt JH, Runciman WB, Williamson JA, Cockings J, Russell WJ, Helps SC (1993) Which monitor? an analysis of 2000 incident reports *Anaesthesia & Intensive Care* 21:529-542

APPENDIX G.

DEFINITION OF OTHER TERMS USED

TABLE G.1 TERMS COMMONLY USED IN THE TEXT

"triple combination"	Prostaglandin I_2, indomethacin and heparin (administered intravenously).
autochthonous bubbles	Bubbles which form in the non-mobile tissues from dissolved gases (after decompression).
1 BAR	100 kilopascals (100,000 Newton/m^2) or 0.987 atmospheres or the pressure under 10 metres of seawater.
baseline or pre-injection baseline	Baseline data are those collected prior to intracarotid air or saline injection; they are generally referred to as a mean ± SEM.
dextran 500	DEAE dextran m.w. 500,000
dextran 500 sulphate	dextran sulphate (sodium salt) m.w. 500,000
EDTA di-potassium	Used as an anticoagulant; *N,N' - 1,2-Ethanediylbis[N-carboxymethyl)glycine] dipotassium salt*
granulocytes	A *leukocyte* containing characteristic granules in its cytoplasm (includes the neutrophils, eosinophils and basophils).
granulocytopenic	When *granulocyte* counts are reduced to less than 10% of pre-mechlorethamine treatment levels.
ischæmia-reperfusion injury	Damage to the circulation resulting from arrest of the circulation for a period of time followed by re-perfusion; after re-perfusion *leukocytes* accumulate in the blood vessels of the affected tissue.
leukocytes	Any of several nucleated cells that occur in blood or tissues fluid (exclusive of erythrocytes and their precursors). Includes the lymphocytes, monocytes, and *granulocytes* (neutrophils, eosinophils and basophils).
leukocytopenic	When *leukocyte* counts are reduced to less than 10% of pre-mechlorethamine treatment levels.
percent of control	Data collected after the intracarotid air or saline injection are expressed as a percentage of the *baseline* value.
platelet	A fragment of megakaryocyte cytoplasm that is normally present in large numbers in the blood and which plays an important role in blood clotting.

TABLE G.2. TERMS USED TO DESCRIBE CELL ASSOCIATED MOLECULES

Terms for equivalent molecules are given where possible to assist the reader who may not be familiar with this terminology.

C3	Compliment factor 3
C3a	Compliment factor 3 activated form
C5	Compliment factor 5
C5a	Compliment factor 5 activated form
CD11	A family of 3 leukocyte associated single chain molecules comprising 2 polypeptide chains; the larger (a) being different for each member of the family
CD11a	Common β chain plus an **"a"** chain of the leukocyte function associated antigen (LFA-1). Binds to ICAM-1 (CD54) and ICAM-2.
CD11b	Common β chain plus an **"a"** chain of Mac-1. It is present on granulocytes, monocytes and NK cells.
CD11c	Common β chain plus an **"a"** chain of the p150,95 molecule. It is present on granulocytes, monocytes and NK cells.
CD16	The functional receptor structure for performing antibody-dependent cellular cytotoxicity
CD18	This antigen is an integral membrane glycoprotein non-covalently linked to CD11a, CD11b or CD11c. It is expressed on leukocytes and is important for cell adhesion
CD62	Cluster of Differentiation antigen 62 is a membrane glycoprotein found in secretory granules of platelets and endothelial cells (also called GMP-140, PADGEM or P-selectin).
ELAM-1	Endothelial-granulocyte adhesion molecule-1 (identical to E-selectin)
GMP-140	Granule Membrane Protein-140 is a membrane glyco-protein found in secretory granules of platelets and endothelial cells (also called P-selectin, PADGEM or CD62)
INCAM-110	Inducible cell adhesion molecule 110
P-selectin	Platelet Selectin is a membrane glycoprotein found in secretory granules of platelets and endothelial cells (also called GMP-140, PADGEM or CD62)
PADGEM	Platelet Activation-Dependent Granule External Membrane Protein is a membrane glycoprotein found in secretory granules of platelets and endothelial cells (also called GMP-140, P-selectin or CD62)

APPENDIX H.

RAW DATA

Data from individual experiments were entered into separate EXCEL worksheets. These were then linked together and saved as a dBase III file for importing into STATGRAPHICS. The data listed below are the raw data for all studies reported in this thesis.

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 400µl dextran sulphate 500	8-Jan-92	-120	100	39.4	540	7.33	36.0	100.0	18.8	59.0	58.0	2350.0	975.0	[1189]	12.0	[1367]	26.0	827.0	48.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-105	90	39.5	540	7.32		99.3		66.0	58.0	2360.0	980.0	[1184]	14.0	[1487]	28.0	[956]	52.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-90	90	39.5	540	7.35		95.0		72.0	59.0	2200.0	990.0	[1072]	14.0	[1317]	28.0	806.0	50.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-75	90	39.5	540	7.36	33.0	172.0	17.7	64.0	60.0	2180.0	1100.0	804.0	10.0	1196.0	22.0	480.0	42.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-60	90	39.6	540	7.37	34.0	172.0	19.1	71.0	54.0	2290.0	1080.0	911.0	12.0	1143.0	24.0	452.0	54.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-45	85	39.6	540	7.36	33.0	149.0	18.4	71.0	60.0			788.0	10.0	1071.0	22.0	376.0	38.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-30	90	39.6	420	7.35	35.0	122.0	19.2	73.0	67.0	2080.0	1220.0	526.0	10.0	780.0	24.0	308.0	40.0
CAGE 400µl dextran sulphate 500	8-Jan-92	-15	95	39.5	420	7.37	35.0	128.0	20.2	73.0	73.0	2020.0	1250.0	505.0	10.0	636.0	24.0	211.0	40.0
CAGE 400µl dextran sulphate 500	8-Jan-92	0	110	39.3	420	7.36	41.0	119.0	23.5	60.0	69.0	1930.0	1350.0	0.0		0.0		0.0	
CAGE 400µl dextran sulphate 500	8-Jan-92	15	95	39.3	480	7.36	37.0	123.0	20.7	70.0	61.0			467.0	10.0	630.0	24.0	269.0	46.0
CAGE 400µl dextran sulphate 500	8-Jan-92	30	90	39.3	480	7.37	35.2	136.0	20.4	61.0	57.0	2090.0	1300.0	761.0	14.0	1093.0	26.0	535.0	48.0
CAGE 400µl dextran sulphate 500	8-Jan-92	45	85	39.2	480	7.36	35.0	124.2	19.6	85.0	56.0	2030.0	1450.0	649.0	14.0	888.0	28.0	400.0	48.0
CAGE 400µl dextran sulphate 500	8-Jan-92	60	85	39.1	480	7.35	40.0	93.0	23.8	80.0	55.0			740.0	14.0	974.0	28.0	519.0	48.0
CAGE 400µl dextran sulphate 500	8-Jan-92	75	85	39.0	480	7.36	38.4	98.0	21.5	92.0	57.0			604.0	14.0	1023.0	26.0	581.0	46.0
CAGE 400µl dextran sulphate 500	8-Jan-92	90	80	38.8	480	7.34	35.0	96.0	18.7	87.0	53.0			651.0	14.0	969.0	26.0	484.0	48.0
CAGE 400µl dextran sulphate 500	8-Jan-92	105	85	38.8	480	7.33	40.0	97.0	22.8	92.0	56.0	1960.0	1470.0	587.0	14.0	957.0	26.0	509.0	46.0
CAGE 400µl dextran sulphate 500	8-Jan-92	120	85	38.8	480	7.33	39.3	99.1	24.1	83.0	57.0	1990.0	1530.0	544.0	12.0	937.0	24.0	520.0	46.0
CAGE 400µl dextran sulphate 500	8-Jan-92	135	85	38.8	480	7.33	35.5	104.4	18.9	82.0	57.0	2080.0	1550.0	580.0	12.0	981.0	24.0	544.0	46.0
CAGE 400µl dextran sulphate 500	8-Jan-92	150	85	38.8	480	7.35	42.0	97.0	23.5	86.0	58.0	2000.0	1535.0	556.0	12.0	947.0	24.0	476.0	44.0
CAGE 400µl dextran sulphate 500	8-Jan-92	165	85	38.8	480	7.35	35.0	99.1	19.1	85.0	61.0	1990.0	1540.0	535.0	10.0	821.0	24.0	458.0	44.0
CAGE 400µl dextran sulphate 500	8-Jan-92	180	90	38.9	480	7.35	39.6	98.3	21.8	68.0	64.0			543.0	10.0	789.0	24.0	456.0	44.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-120	95	38.1	315	7.36	40.0	136.0	23.0	88.0	77.0	2280.0	900.0	1554.0	18.0	1752.0	30.0	1088.0	54.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-105	95	38.1	315	7.35	35.3	118.0	19.4	75.0	96.0			1009.0	16.0	1349.0	30.0	944.0	52.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-90	95	38.1	315	7.38	38.3	143.0	22.5	82.0	81.0			1385.0	18.0	1689.0	28.0	1153.0	52.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-75	90	38.1	315	7.43	36.3	132.0	23.8	77.0	80.0			1374.0	18.0	1620.0	28.0	1022.0	52.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-60	90	38.1	315	7.39	38.1	173.0	23.1	66.0	82.0	2250.0	850.0	1219.0	20.0	1613.0	32.0	942.0	56.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-45	80	38.0	315	7.32	42.0	104.0	21.9	57.0	77.0	2500.0	880.0	1418.0	16.0	1617.0	28.0	956.0	52.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-30	80	38.0	315	7.33	39.5	115.0	21.0	62.0	82.0	2380.0	880.0	1328.0	16.0	1431.0	28.0	836.0	50.0
CAGE 400µl dextran sulphate 500	20-Dec-91	-15	90	37.9	315	7.33	39.9	91.8	21.0	53.0	69.0	1840.0	790.0	1668.0	16.0	1803.0	28.0	1251.0	48.0
CAGE 400µl dextran sulphate 500	20-Dec-91	0	110	37.9	315	7.32	42.0	93.0	21.7	110.0	108.0	1705.0	940.0	401.0	16.0	529.0	36.0	411.0	60.0
CAGE 400µl dextran sulphate 500	20-Dec-91	15	80	37.9	315	7.34	38.1	100.0	20.4	58.0	76.0	1630.0	1070.0	721.0	20.0	1533.0	36.0	863.0	58.0
CAGE 400µl dextran sulphate 500	20-Dec-91	30	70	38.0	315	7.31	35.0	154.0	17.3	83.0	78.0	1540.0	1030.0	757.0	14.0	1210.0	32.0	666.0	58.0
CAGE 400µl dextran sulphate 500	20-Dec-91	45	65	38.1	315	7.31	38.5	105.0	19.5	53.0	74.0	1545.0	1050.0	746.0	16.0	1189.0	32.0	656.0	56.0
CAGE 400µl dextran sulphate 500	20-Dec-91	60	60	38.1	315	7.38	35.8	95.0	19.3	49.0	78.0	1550.0	970.0	718.0	14.0	1112.0	32.0	593.0	54.0
CAGE 400µl dextran sulphate 500	20-Dec-91	75	60	38.1	315	7.28	35.0	111.0	15.1	53.0	74.0	1590.0	980.0	710.0	14.0	990.0	32.0	523.0	56.0
CAGE 400µl dextran sulphate 500	20-Dec-91	90	55	38.2	315	7.28	36.9	92.0	17.1	46.0	76.0	1500.0	950.0	590.0	14.0	766.0	32.0	441.0	56.0
CAGE 400µl dextran sulphate 500	20-Dec-91	105	55	38.1	315	7.26	35.1	138.0	14.2	39.0	63.0	1420.0	930.0	493.0	14.0	583.0	34.0	401.0	60.0
CAGE 400µl dextran sulphate 500	20-Dec-91	120	55	38.2	315	7.23	35.6	112.0	13.4	40.0	78.0	1420.0	915.0	413.0	14.0	373.0	34.0	295.0	60.0
CAGE 400µl dextran sulphate 500	20-Dec-91	135	55	38.2	297	7.21	33.0	134.7	13.1	43.0	71.0	1455.0	920.0	412.0	14.0	422.0	32.0	231.0	58.0
CAGE 400µl dextran sulphate 500	20-Dec-91	150	55	38.3	297	7.17	35.2	127.9	11.9	40.0	72.0	1400.0	945.0	377.0	14.0	320.0	34.0	188.0	56.0
CAGE 400µl dextran sulphate 500	20-Dec-91	165	50	38.3	270	7.11	36.1	120.4	10.7	39.0	75.0	1440.0	970.0	457.0	14.0	393.0	30.0	220.0	54.0
CAGE 400µl dextran sulphate 500	20-Dec-91	180	40	38.3	270	7.06	34.9	117.3	11.2	31.0	64.0	1420.0	1000.0	133.0	18.0	194.0	38.0	112.0	60.0
CAGE 400µl dextran sulphate 500	12-Mar-92	-120	85	39.0	600	7.31	38.0	126.0	19.0	43.0	54.0	2620.0	620.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	-105	80	39.2	600	7.30	35.0	125.0	17.0	41.0	49.0								
CAGE 400µl dextran sulphate 500	12-Mar-92	-90	80	39.2	600	7.30	35.0	125.0	16.0	40.0	49.0								
CAGE 400µl dextran sulphate 500	12-Mar-92	-75	80	39.2	600	7.32	33.0	137.0	17.0	40.0	47.0	2370.0	620.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	-60	80	39.3	600	7.33	34.0	125.0	18.0	37.0	47.0	2250.0	620.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	-45	80	39.3	600	7.33	35.0	122.0	18.0	33.0	40.0	2230.0	645.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	-30	80	39.3	600	7.32	33.0	125.0	17.0	30.0	37.0	2255.0	645.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	-15	80	39.3	600	7.35	35.0	126.0	19.0	36.0	44.0	2360.0	630.0	438.0	30.0	645.0	38.0	287.0	54.0
CAGE 400µl dextran sulphate 500	12-Mar-92	0	80	39.2	600	7.28	36.0	117.0	17.0	36.0	22.0	2100.0	940.0	62.0	28.0	214.0	40.0	92.0	54.0
CAGE 400µl dextran sulphate 500	12-Mar-92	15	90	39.2	600	7.26	35.0	126.0	16.0	28.0	65.0	2300.0	970.0	268.0	32.0	402.0	38.0	135.0	54.0
CAGE 400µl dextran sulphate 500	12-Mar-92	30	90	39.1	600	7.28	37.0	121.0	17.0	28.0	30.0	2150.0	790.0	296.0	32.0	360.0	40.0	106.0	58.0
CAGE 400µl dextran sulphate 500	12-Mar-92	45	85	39.1	600	7.30	36.0	123.0	18.0	33.0	30.0	1950.0	850.0	265.0	32.0	319.0	40.0	118.0	64.0
CAGE 400µl dextran sulphate 500	12-Mar-92	60	85	39.1	600	7.30	36.0	119.0	17.0	32.0	28.0	1900.0	770.0	308.0	32.0	287.0	40.0	155.0	62.0
CAGE 400µl dextran sulphate 500	12-Mar-92	75	85	39.0	600	7.30	35.0	118.0	17.0	35.0	29.0			465.0	30.0	672.0	38.0	296.0	52.0
CAGE 400µl dextran sulphate 500	12-Mar-92	90	85	39.0	600	7.27	36.0	123.0	17.0	32.0	33.0	1910.0	830.0	471.0	32.0	603.0	40.0	357.0	58.0
CAGE 400µl dextran sulphate 500	12-Mar-92	105	85	39.0	600	7.28	36.0	125.0	17.0	25.0	29.0	1800.0	800.0	263.0	32.0	330.0	48.0	321.0	62.0
CAGE 400µl dextran sulphate 500	12-Mar-92	120	80	39.0	600	7.21	35.4	123.0	16.0	36.0	43.0	1770.0	845.0						
CAGE 400µl dextran sulphate 500	12-Mar-92	135	85	39.0	600	7.24	33.0	121.0	14.9	28.0	41.0								
CAGE 400µl dextran sulphate 500	12-Mar-92	150	75	39.0	600	7.25	33.0	128.0	14.7	29.0	49.0								
CAGE 400µl dextran sulphate 500	12-Mar-92	165	65	39.0	600	7.25	29.0	129.0	12.0	29.0	49.0								
CAGE 400µl dextran sulphate 500	12-Mar-92	180	65	39.0	600	7.20	34.0	121.0	14.0	22.0	59.0								

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 400µl dextran sulphate 500	18-Mar-92	-120	100	38.8	600	7.36	37.0	120.0	21.0	67.0	66.0	2695.0	750.0	[417]	[20]	[1168]	[36]	[477]	[58]
CAGE 400µl dextran sulphate 500	18-Mar-92	-105	100	38.8	600	7.33	38.0	120.0	20.0	56.0	70.0	2740.0	745.0	249.0	20.0	1019.0	36.0	430.0	60.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-90	100	38.8	600	7.37	36.0	114.0	20.0	51.0	68.0			221.0	20.0	985.0	36.0	456.0	60.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-75	100	38.8	600	7.36	39.0	113.0	23.0	60.0	68.0	2700.0	730.0	349.0	16.0	1000.0	30.0	235.0	50.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-60	100	38.8	600	7.38	38.0	110.0	22.0	56.0	64.0	2800.0	760.0	265.0	16.0	1052.0	30.0	377.0	48.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-45	100	38.8	600	7.38	35.0	110.0	20.0	55.0	59.0	2850.0	790.0	302.0	16.0	932.0	30.0	212.0	50.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-30	95	38.8	600	7.36	39.0	110.0	22.0	58.0	58.0	2860.0	780.0	340.0	16.0	974.0	30.0	210.0	50.0
CAGE 400µl dextran sulphate 500	18-Mar-92	-15	75	38.9	600	7.37	35.0	115.0	20.0	45.0	49.0	2770.0		[530]	[16]	[1236]	[30]	[280]	[48]
CAGE 400µl dextran sulphate 500	18-Mar-92	0	115	38.9	600	7.31	42.0	116.0	21.0	130.0	153.0	2830.0	720.0			324.0	46.0	284.0	74.0
CAGE 400µl dextran sulphate 500	18-Mar-92	15	100	38.8	600	7.29	39.0	101.0	19.0	72.0	59.0	2930.0	700.0	415.0	12.0	810.0	28.0	320.0	66.0
CAGE 400µl dextran sulphate 500	18-Mar-92	30	100	38.8	600	7.30	38.0	112.0	19.0	59.0	53.0	2940.0	700.0	404.0	12.0	629.0	26.0	293.0	64.0
CAGE 400µl dextran sulphate 500	18-Mar-92	45	100	38.8	600	7.33	41.0	100.0	21.0	50.0	41.0	2880.0	730.0	388.0	10.0	592.0	26.0	190.0	62.0
CAGE 400µl dextran sulphate 500	18-Mar-92	60	90	38.8	600	7.32	41.0	108.0	21.0	49.0	35.0	2920.0	750.0	438.0	12.0	637.0	26.0	268.0	58.0
CAGE 400µl dextran sulphate 500	18-Mar-92	75	90	38.8	600	7.35	40.0	109.0	22.0	46.0	32.0	2900.0	720.0	363.0	10.0	597.0	26.0	224.0	48.0
CAGE 400µl dextran sulphate 500	18-Mar-92	90	85	38.8	600	7.33	37.0	113.0	20.0	38.0	31.0	2890.0	700.0	459.0	12.0	655.0	26.0	236.0	48.0
CAGE 400µl dextran sulphate 500	18-Mar-92	105	85	38.8	600	7.33	42.0	103.0	21.0	43.0	33.0	2955.0	740.0	416.0	12.0	593.0	26.0	251.0	54.0
CAGE 400µl dextran sulphate 500	18-Mar-92	120	85	38.7	600	7.35	40.0	98.0	22.0	38.0	31.0	2945.0	730.0	469.0	12.0	624.0	26.0	320.0	50.0
CAGE 400µl dextran sulphate 500	18-Mar-92	135	85	38.7	600	7.35	39.0	104.0	22.0	41.0	36.0			461.0	12.0	646.0	20.0	350.0	48.0
CAGE 400µl dextran sulphate 500	18-Mar-92	150	85	38.6	600	7.33	42.0	105.0	22.0	39.0	34.0			531.0	12.0	586.0	26.0	298.0	48.0
CAGE 400µl dextran sulphate 500	18-Mar-92	165	85	38.6	600	7.34	39.0	106.0	21.0	35.0	25.0			805.0	14.0	908.0	28.0	502.0	54.0
CAGE 400µl dextran sulphate 500	18-Mar-92	180	85	38.6	600	7.34	40.0	109.0	22.0	37.0	31.0			701.0	18.0	757.0	32.0	436.0	56.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-120	80	38.7	750	7.32	34.9	132.0	18.0	72.0				1150.0	18.0	1144.0	38.0	701.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-105	90	38.4	750	7.34	35.1	135.0	18.0	57.0		1530.0	500.0	927.0	20.0	1002.0	38.0	670.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-90	80	38.1	675	7.38	34.1	138.0	18.9	58.0	31.0	1490.0	485.0	796.0	16.0	803.0	34.0	637.0	92.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-75	75	38.0	675	7.32	33.3	143.0	17.0	68.0	38.0			870.0	16.0	838.0	32.0	397.0	80.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-60	80	38.0	600	7.31	34.3	148.0	17.1	78.9	46.8	1450.0	495.0	722.0	20.0	879.0	30.0	353.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-45	80	38.0	600	7.31	33.0	150.0	17.0	56.0	36.0			1015.0	16.0	934.0	36.0	514.0	84.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-30	80	38.1	525	7.33	28.5	157.8	14.9			1460.0	525.0	1326.0	18.0	1361.0	36.0	777.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	-15	75	38.0	525	7.29	35.8	138.7	17.0	77.0	35.0			1073.0	16.0	1238.0	36.0	683.0	82.0
CAGE 400µl dextran sulphate 500	20-Nov-91	0	100	38.3	525	7.29	41.0	133.0	19.0	84.0	58.0	1640.0	740.0	457.0	14.0	369.0	34.0	595.0	90.0
CAGE 400µl dextran sulphate 500	20-Nov-91	15	90	38.3	525	7.38	37.0	124.0	19.0	53.0	36.0	1695.0	830.0	1137.0	18.0	981.0	32.0	629.0	84.0
CAGE 400µl dextran sulphate 500	20-Nov-91	30	90	38.3	525	7.31	37.0	126.0	19.0	64.0	35.0			780.0	18.0	998.0	38.0	659.0	82.0
CAGE 400µl dextran sulphate 500	20-Nov-91	45	90	38.3	525	7.35	37.1	132.1	20.4	52.0	32.0			803.0	18.0	938.0	38.0	649.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	60	90	38.3	525	7.30	35.8	139.7	17.6	61.0	36.0	1670.0	820.0	687.0	14.0	747.0	34.0	451.0	84.0
CAGE 400µl dextran sulphate 500	20-Nov-91	75	85	38.3	525	7.52	35.0	127.1	18.0	63.0	36.0	1710.0	625.0	649.0	14.0	637.0	30.0	381.0	82.0
CAGE 400µl dextran sulphate 500	20-Nov-91	90	85	38.3	525	7.33	35.8	125.0	18.6	57.0	30.5	1600.0	615.0	707.0	16.0	762.0	36.0	467.0	84.0
CAGE 400µl dextran sulphate 500	20-Nov-91	105	80	38.3	525	7.32	35.1	121.5	17.6	60.9	33.3	1650.0	610.0	608.0	14.0	494.0	34.0	333.0	82.0
CAGE 400µl dextran sulphate 500	20-Nov-91	120	85	38.2	525	7.33	38.5	146.3	20.2	59.3	39.8	1395.0		777.0	14.0	785.0	34.0	491.0	80.0
CAGE 400µl dextran sulphate 500	20-Nov-91	135	90	38.2	525	7.33	35.0	138.0	18.1	56.8	36.7			623.0	20.0	976.0	38.0	640.0	86.0
CAGE 400µl dextran sulphate 500	20-Nov-91	150	85	38.1	525	7.34	35.0	139.7	17.8	60.1	34.6	1330.0		729.0	16.0	853.0	34.0	487.0	80.0
CAGE 400µl dextran sulphate 500	20-Nov-91	165	85	38.1	525	7.31	38.2	138.1	19.2	62.0	33.0	1210.0		801.0	14.0	670.0	34.0	400.0	74.0
CAGE 400µl dextran sulphate 500	20-Nov-91	180	85	38.1	525	7.34	36.1	132.5	19.2	62.0	33.4	1180.0		808.0	14.0	687.0	30.0	358.0	70.0
CAGE 400µl dextran 500	19-Mar-92	-120	75	39.7	480	7.30	34.0	131.0	17.0	33.0	46.0	950.0	1200.0	1245.0	20.0	1482.0	32.0	896.0	52.0
CAGE 400µl dextran 500	19-Mar-92	-105	75	39.2	480	7.31	34.0	126.0	17.0	32.0	41.0	990.0	1260.0	1112.0	22.0	1478.0	34.0	834.0	52.0
CAGE 400µl dextran 500	19-Mar-92	-90	75	38.9	480	7.30	35.0	132.0	18.0	35.0	45.0	1070.0	1210.0	[834]	[19]	[817]	[32]	[637]	[50]
CAGE 400µl dextran 500	19-Mar-92	-75	75	38.9	480	7.35	35.0	127.0	18.0	35.0	46.0	1020.0	1200.0	1070.0	18.0	1083.0	32.0	835.0	50.0
CAGE 400µl dextran 500	19-Mar-92	-60	80	38.9	480	7.34	34.0	120.0	18.0	36.0	47.0	935.0	1100.0	1198.0	20.0	1625.0	30.0	956.0	52.0
CAGE 400µl dextran 500	19-Mar-92	-45	85	38.9	480	7.35	35.0	119.0	18.0	36.0	47.0	1020.0	1060.0	1458.0	22.0	1616.0	34.0	902.0	52.0
CAGE 400µl dextran 500	19-Mar-92	-30	90	38.9	480	7.35	35.0	121.0	19.0	36.0	47.0	1000.0	1130.0	1239.0	24.0	1704.0	34.0	774.0	54.0
CAGE 400µl dextran 500	19-Mar-92	-15	70	38.9	480	7.27	33.0	123.0	16.0	27.0	43.0	960.0	1090.0	1627.0	22.0	1924.0	34.0	1664.0	54.0
CAGE 400µl dextran 500	19-Mar-92	0	105	39.0	400	7.22	37.0	105.0	15.0	74.0	66.0	810.0	1530.0	-271.0	20.0	177.0	34.0	0.0	54.0
CAGE 400µl dextran 500	19-Mar-92	15	85	39.0	400	7.15	36.0	111.0	13.0	53.0	55.0	900.0	1580.0	963.0	16.0	82.0	34.0	-164.0	54.0
CAGE 400µl dextran 500	19-Mar-92	30	85	38.9	400	7.12	34.0	124.0	11.0	16.0	23.0			354.0	26.0	1581.0	38.0	936.0	60.0
CAGE 400µl dextran 500	19-Mar-92	45	70	38.9	400	7.10	27.0	135.0		9.0	15.0			393.0	18.0	1182.0	38.0	460.0	60.0
CAGE 400µl dextran 500	19-Mar-92	60	70	38.9	400										18.0	0.0	40.0	0.0	60.0
CAGE 400µl dextran 500	19-Mar-92	75	50	38.9	400	7.05	19.0	140.0	5.5										
CAGE 400µl dextran 500	19-Mar-92	90																	
CAGE 400µl dextran 500	19-Mar-92	105																	
CAGE 400µl dextran 500	19-Mar-92	120																	
CAGE 400µl dextran 500	19-Mar-92	135																	
CAGE 400µl dextran 500	19-Mar-92	150																	
CAGE 400µl dextran 500	19-Mar-92	165																	
CAGE 400µl dextran 500	19-Mar-92	180																	
CAGE 400µl dextran 500	4-Dec-91	-120	100	39.1	600	7.23	40.9	154.0	19.6	46.0	62.0								
CAGE 400µl dextran 500	4-Dec-91	-105	105	39.1	675	7.30	39.5	132.0	19.3	44.5	53.0			1371.0	18.0	1426.0	40.0	1163.0	84.0
CAGE 400µl dextran 500	4-Dec-91	-90	100	39.1	675	7.30	40.1	156.7	20.9	45.6	47.3			1462.0	16.0	1612.0	40.0	1175.0	82.0
CAGE 400µl dextran 500	4-Dec-91	-75	105	39.0	750	7.34	36.0	165.2	19.1	50.4	62.9								
CAGE 400µl dextran 500	4-Dec-91	-60	105	39.0	750	7.33	35.2	160.9	17.3	55.0	67.0			1609.0	18.0	1683.0	40.0	1201.0	82.0
CAGE 400µl dextran 500	4-Dec-91	-45	105	39.0	750	7.34	35.1	159.2	19.0	42.5	59.3			1371.0	16.0	1319.0	38.0	837.0	78.0
CAGE 400µl dextran 500	4-Dec-91	-30	100	38.9	750	7.33	35.7	157.7	18.0	48.6	66.2			1325.0	14.0	1243.0	34.0	639.0	74.0
CAGE 400µl dextran 500	4-Dec-91	-15	100	38.9	750	7.34	35.4	159.3	17.6	56.0	77.0			1169.0	16.0	1108.0	38.0	803.0	82.0
CAGE 400µl dextran 500	4-Dec-91	0	95	38.9	750	7.35	28.0	144.0	15.8	0.0	0.0			517.0	20.0	576.0	46.0	366.0	92.0
CAGE 400µl dextran 500	4-Dec-91	15	0	38.9	750									0.0	0.0	0.0	0.0	0.0	0.0
CAGE 400µl dextran 500	4-Dec-91	30																	
CAGE 400µl dextran 500	4-Dec-91	45																	
CAGE 400µl dextran 500	4-Dec-91	60																	
CAGE 400µl dextran 500	4-Dec-91	75																	
CAGE 400µl dextran 500	4-Dec-91	90																	
CAGE 400µl dextran 500	4-Dec-91	105																	
CAGE 400µl dextran 500	4-Dec-91	120																	
CAGE 400µl dextran 500	4-Dec-91	135																	
CAGE 400µl dextran 500	4-Dec-91	150																	
CAGE 400µl dextran 500	4-Dec-91	165																	
CAGE 400µl dextran 500	4-Dec-91	180																	
CAGE 400µl dextran 500	5-Feb-92	-120	105	38.3	450	7.35	33.0	107.0	18.0	42.0	50.0	2100.0	820.0	1296.0	20.0	1746.0	36.0	1034.0	64.0
CAGE 400µl dextran 500	5-Feb-92	-105	105	38.2	450	7.37	36.0	100.0	21.0	39.0	47.0	2020.0	1000.0	1219.0	20.0	1764.0	34.0	1011.0	60.0
CAGE 400µl dextran 500	5-Feb-92	-90	105	38.2	450	7.38	36.0	101.0	20.0	38.0	50.0	2030.0	1010.0	847.0	20.0	1744.0	32.0	1055.0	60.0
CAGE 400µl dextran 500	5-Feb-92	-75	105	38.2	450	7.39	36.0	121.0	20.0	35.0	46.0	2000.0	900.0	961.0	16.0	1395.0	32.0	724.0	50.0
CAGE 400µl dextran 500	5-Feb-92	-60	105	38.3	450	7.35	35.0	116.0	19.0	32.0	47.0			1178.0	18.0	1585.0	34.0	810.0	56.0
CAGE 400µl dextran 500	5-Feb-92	-45	105	38.3	270	7.34	36.0	118.0	19.0	34.0	47.0			1050.0	14.0	1427.0	30.0	964.0	54.0
CAGE 400µl dextran 500	5-Feb-92	-30	105	38.3	270	7.35	36.0	118.0	18.0	38.0	47.0			1225.0	14.0	1471.0	30.0	920.0	52.0
CAGE 400µl dextran 500	5-Feb-92	-15	100	38.2	270	7.33	39.0	113.0	20.0	37.0	42.0			818.0	14.0	1130.0	32.0	700.0	54.0
CAGE 400µl dextran 500	5-Feb-92	0	130	38.3	270	7.32	35.0	109.0	16.0	0.0	0.0	1790.0	1200.0	190.0	16.0	199.0	40.0	58.0	58.0
CAGE 400µl dextran 500	5-Feb-92	15	70	38.4	270	7.44	15.0	111.0	10.0	0.0	0.0	1480.0	990.0	0.0		0.0		0.0	
CAGE 400µl dextran 500	5-Feb-92	30	0		270														
CAGE 400µl dextran 500	5-Feb-92	45																	
CAGE 400µl dextran 500	5-Feb-92	60																	
CAGE 400µl dextran 500	5-Feb-92	75																	
CAGE 400µl dextran 500	5-Feb-92	90																	
CAGE 400µl dextran 500	5-Feb-92	105																	
CAGE 400µl dextran 500	5-Feb-92	120																	
CAGE 400µl dextran 500	5-Feb-92	135																	
CAGE 400µl dextran 500	5-Feb-92	150																	
CAGE 400µl dextran 500	5-Feb-92	165																	
CAGE 400µl dextran 500	5-Feb-92	180																	

Group	Date	time	MABP	Temp	Min.Vol	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	ICBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 400µl dextran 500	11-Mar-92	-120	70	38.1	900	7.31	33.0	137.0	17.0	42.0	[23]	2150.0	835.0	1768.0	18.0	1997.0	52.0	1225.0	52.0
CAGE 400µl dextran 500	11-Mar-92	-105	75	38.1	900	7.29	34.0	110.0	16.0	40.0	[23]	2150.0	700.0	1845.0	18.0	2015.0	30.0	1419.0	54.0
CAGE 400µl dextran 500	11-Mar-92	-90	75	38.0	825	7.29	36.0	121.0	17.0	41.0	[24]	2200.0	750.0	1869.0	18.0	1951.0	30.0	1638.0	50.0
CAGE 400µl dextran 500	11-Mar-92	-75	65	38.1	825	7.28	36.0	122.0	21.0	41.0	[24]	2100.0	700.0	1937.0	16.0	2008.0	30.0	1886.0	50.0
CAGE 400µl dextran 500	11-Mar-92	-60	65	38.1	825	7.27	36.0	134.0	17.0	37.0	[22]	2250.0	720.0	1829.0	14.0	1968.0	30.0	1861.0	48.0
CAGE 400µl dextran 500	11-Mar-92	-45	60	38.1	825	7.29	37.0	128.0	18.0	38.0	[18]			1860.0	16.0	1993.0	30.0	1720.0	50.0
CAGE 400µl dextran 500	11-Mar-92	-30	50	38.1	825	7.25	37.0	130.0	16.0	37.0	[19]			1789.0	14.0	1930.0	28.0	1543.0	48.0
CAGE 400µl dextran 500	11-Mar-92	-15	50	38.0	825	7.26	35.0	130.0	16.0	39.0	[20]	2090.0	745.0	1822.0	14.0	1960.0	30.0	1591.0	54.0
CAGE 400µl dextran 500	11-Mar-92	0	80	38.0	825	7.22	33.0	110.0	14.0	43.0		2000.0		1129.0	20.0	1697.0	34.0	846.0	58.0
CAGE 400µl dextran 500	11-Mar-92	15	55	38.0	825	7.13	35.0	90.0	12.0	43.0	27.0	1880.0	930.0	1747.0	16.0	1946.0	32.0	1544.0	54.0
CAGE 400µl dextran 500	11-Mar-92	30	50	38.1	825	7.08	38.0	135.0	11.0	40.0	24.0	1890.0	810.0	1617.0	16.0	1868.0	30.0	1549.0	50.0
CAGE 400µl dextran 500	11-Mar-92	45	45	38.2	825	7.10	36.0	145.0	11.0	41.0	22.0	1780.0	825.0	1661.0	12.0	1620.0	28.0	1432.0	50.0
CAGE 400µl dextran 500	11-Mar-92	60	45	38.2	825	7.13	34.0	150.0	11.0	36.0	24.0	1800.0	870.0	1755.0	14.0	1868.0	28.0	1596.0	48.0
CAGE 400µl dextran 500	11-Mar-92	75	45	38.3	750	7.11	35.0	148.0	12.0	47.0	21.0	1840.0	910.0	1373.0	16.0	1613.0	30.0	1294.0	50.0
CAGE 400µl dextran 500	11-Mar-92	90	45	38.4	750	7.17	33.0	146.0	11.0	46.0	19.0	1815.0	925.0	1523.0	16.0	1711.0	30.0	1361.0	52.0
CAGE 400µl dextran 500	11-Mar-92	105	45	38.4	675	7.15	35.0	157.0	11.0	33.0	21.0	1770.0	945.0	1546.0	14.0	1584.0	30.0	1161.0	52.0
CAGE 400µl dextran 500	11-Mar-92	120	45	38.4	675	7.16	35.0	155.0	11.0	39.0	12.0	1670.0	855.0	1131.0	16.0	1663.0	32.0	1096.0	52.0
CAGE 400µl dextran 500	11-Mar-92	135	45	38.6	675	7.14	20.0	162.0	8.0	39.0	11.0	1660.0	860.0	1297.0	14.0	1674.0	30.0	1147.0	54.0
CAGE 400µl dextran 500	11-Mar-92	150	45	38.6	825	7.11	24.0	163.0	10.0	37.0		1600.0	920.0	722.0	16.0	1527.0	36.0	1049.0	66.0
CAGE 400µl dextran 500	11-Mar-92	165																	
CAGE 400µl dextran 500	11-Mar-92	180																	
CAGE 400µl dextran 500	5-Aug-92	-120	85	39.0	540	7.35	36.0	119.0	18.0	43.0	53.0			877.0	24.0	1156.0	44.0	1256.0	80.0
CAGE 400µl dextran 500	5-Aug-92	-105	80	38.8	540	7.37	35.0	134.0	20.0	47.0	60.0			498.0	26.0	923.0	46.0	1039.0	82.0
CAGE 400µl dextran 500	5-Aug-92	-90	75	38.8	540	7.33	39.0	127.0	21.0	56.0	67.0	1320.0	825.0	602.0	22.0	791.0	44.0	832.0	80.0
CAGE 400µl dextran 500	5-Aug-92	-75	75	38.8	540	7.33	38.0	109.0	19.0	51.0	67.0	1300.0	680.0	720.0	20.0	914.0	40.0	909.0	74.0
CAGE 400µl dextran 500	5-Aug-92	-60	75	38.8	540	7.33	39.0	122.0	21.0	52.0	65.0	1220.0	700.0	628.0	22.0	1026.0	46.0	1009.0	78.0
CAGE 400µl dextran 500	5-Aug-92	-45	75	38.8	540	7.34	38.0	125.0	21.0	51.0	71.0	1250.0	680.0	745.0	20.0	821.0	34.0	690.0	74.0
CAGE 400µl dextran 500	5-Aug-92	-30	60	38.8	540	7.33	36.0	126.0	19.0	58.0	74.0	1350.0	710.0	835.0	22.0	946.0	38.0	929.0	74.0
CAGE 400µl dextran 500	5-Aug-92	-15	40	38.8	540	7.35	38.0	139.0	21.0	73.0	85.0	1380.0	690.0	888.0	20.0	919.0	34.0	951.0	72.0
CAGE 400µl dextran 500	5-Aug-92	0	140	38.8	540	7.23	39.0	85.0	18.0			1300.0	930.0	0.0		0.0		0.0	
CAGE 400µl dextran 500	5-Aug-92	15	5	39.3	540	7.00						1210.0	800.0	0.0		0.0		0.0	
CAGE 400µl dextran 500	5-Aug-92	30																	
CAGE 400µl dextran 500	5-Aug-92	45																	
CAGE 400µl dextran 500	5-Aug-92	60																	
CAGE 400µl dextran 500	5-Aug-92	75																	
CAGE 400µl dextran 500	5-Aug-92	90																	
CAGE 400µl dextran 500	5-Aug-92	105																	
CAGE 400µl dextran 500	5-Aug-92	120																	
CAGE 400µl dextran 500	5-Aug-92	135																	
CAGE 400µl dextran 500	5-Aug-92	150																	
CAGE 400µl dextran 500	5-Aug-92	165																	
CAGE 400µl dextran 500	5-Aug-92	180																	
Control dextran 500	10-Dec-91	-120	100	38.0	450	7.43	36.6	127.6	24.2	25.2	180.0	1245.0	845.0	674.0	26.0	689.0	66.0	483.0	112.0
Control dextran 500	10-Dec-91	-105	100	38.0	450	7.43	35.7	131.0	23.9	22.0	61.5	1320.0	770.0	513.0	24.0	466.0	64.0	306.0	108.0
Control dextran 500	10-Dec-91	-90	100	38.0	450	7.45	35.2	130.5	24.2	21.8	42.5	1280.0	755.0	489.0	24.0	408.0	64.0	296.0	110.0
Control dextran 500	10-Dec-91	-75	95	38.0	450	7.43	35.5	140.0	23.6	18.1	37.9	1270.0		398.0	24.0	422.0	60.0	330.0	110.0
Control dextran 500	10-Dec-91	-60	95	38.0	450	7.44	36.2	137.8	24.6	22.0	38.3			466.0	20.0	390.0	48.0	255.0	255.0
Control dextran 500	10-Dec-91	-45	95	38.0	450	7.44	36.4	125.6	24.5	28.2	30.6			627.0	26.0	604.0	60.0	466.0	110.0
Control dextran 500	10-Dec-91	-30	90	38.0	450	7.43	36.0	136.7	23.7	24.6	30.6			599.0	20.0	468.0	48.0	293.0	100.0
Control dextran 500	10-Dec-91	-15	95	38.1	450	7.44	35.5	139.4	24.0	24.3	22.6			663.0	18.0	520.0	42.0	368.0	108.0
Control dextran 500	10-Dec-91	0	90	38.1	450	7.43	38.9	107.4	26.2	29.8	34.9			769.0	18.0	648.0	40.0	388.0	104.0
Control dextran 500	10-Dec-91	15	90	38.1	450	7.43	36.1	136.0	23.8	26.9	36.5			409.0	20.0	395.0	52.0	329.0	106.0
Control dextran 500	10-Dec-91	30	90	38.1	450	7.41	38.2	114.8	24.1	25.3	31.0			523.0	18.0	420.0	38.0	318.0	98.0
Control dextran 500	10-Dec-91	45	90	38.1	450	7.41	38.9	120.7	24.7	31.4	34.6			576.0	16.0	450.0	38.0	312.0	100.0
Control dextran 500	10-Dec-91	60	90	38.1	450	7.44	38.3	119.8	25.8	31.0	44.0			509.0	18.0	414.0	38.0	296.0	98.0
Control dextran 500	10-Dec-91	75	90	38.1	450	7.42	36.1	119.6	23.2	29.0	42.0			511.0	16.0	505.0	36.0	296.0	104.0
Control dextran 500	10-Dec-91	90	90	38.1	450	7.41	37.0	122.0	24.0	28.0	47.0			393.0	24.0	416.0	58.0	229.0	100.0
Control dextran 500	10-Dec-91	105	90	38.0	450	7.43	40.0	111.7	26.8	30.4	31.4			299.0	20.0	400.0	54.0	259.0	100.0
Control dextran 500	10-Dec-91	120	95	38.0	450	7.42	39.8	118.7	26.0	31.0	37.1			340.0	20.0	365.0	50.0	195.0	98.0
Control dextran 500	10-Dec-91	135	90	37.9	450	7.41	39.5	116.3	27.4	31.1	36.7			369.0	22.0	504.0	56.0	299.0	100.0
Control dextran 500	10-Dec-91	150	90	37.9	450	7.41	40.0	136.8	25.8	26.3	34.2			478.0	24.0	593.0	56.0	367.0	102.0
Control dextran 500	10-Dec-91	165	90	37.9	450	7.44	35.5	137.9	23.9	25.2	33.6			702.0	22.0	653.0	48.0	342.0	110.0
Control dextran 500	10-Dec-91	180	95	37.9	450	7.42	35.0	128.0	22.0	28.5	32.8			811.0	20.0	656.0	46.0	315.0	106.0
Control dextran 500	25-Mar-92	-120	100	39.2	660	7.31	37.0	99.0	19.0	71.0	78.0	2840.0	775.0	524.0	20.0	939.0	32.0	533.0	60.0
Control dextran 500	25-Mar-92	-105	100	39.2	660	7.33	36.0	109.0	19.0	64.0	65.0	2910.0	730.0						
Control dextran 500	25-Mar-92	-90	100	39.2	660	7.34	36.0	102.0	19.0	71.0	76.0	2900.0	690.0	707.0	18.0	1246.0	30.0	723.0	56.0
Control dextran 500	25-Mar-92	-75	100	39.1	660	7.34	35.0	104.0	19.0	65.0	83.0	2990.0	720.0	791.0	18.0	1292.0	32.0	851.0	56.0
Control dextran 500	25-Mar-92	-60	95	39.1	660	7.31	33.0	109.0	17.0	53.0	66.0	3090.0	700.0	715.0	18.0	1322.0	32.0	834.0	52.0
Control dextran 500	25-Mar-92	-45	95	39.0	660	7.34	36.0	96.0	19.0	54.0	85.0	3040.0	700.0	677.0	16.0	1359.0	30.0	738.0	54.0
Control dextran 500	25-Mar-92	-30	90	39.0	660	7.35	33.0	104.0	18.0	51.0	67.0			664.0	16.0	1160.0	30.0	678.0	56.0
Control dextran 500	25-Mar-92	-15	85	39.1	660	7.34	33.0	110.0	17.0	46.0	70.0	2860.0	670.0	683.0	16.0	1076.0	30.0	567.0	54.0
Control dextran 500	25-Mar-92	0	85	39.1	600	7.39	34.0	117.0	20.0	55.0	90.0	2840.0	730.0	618.0	18.0	1295.0	30.0	733.0	58.0
Control dextran 500	25-Mar-92	15	85	39.1	600	7.34	34.0	87.0	19.0	48.0	57.0	2990.0	750.0	637.0	16.0	1134.0	30.0	644.0	54.0
Control dextran 500	25-Mar-92	30	90	39.0	600	7.35	40.0	84.0	23.0	71.0	83.0	3080.0	670.0	706.0	16.0	1347.0	30.0	727.0	56.0
Control dextran 500	25-Mar-92	45	90	39.0	600	7.28	36.0	115.0	17.0	80.0	94.0	3010.0	720.0	647.0	18.0	1369.0	30.0	760.0	54.0
Control dextran 500	25-Mar-92	60	95	38.9	600	7.29	43.0	106.0	21.0	91.0	109.0	3015.0	700.0	721.0	20.0	1152.0	32.0	711.0	56.0
Control dextran 500	25-Mar-92	75	95	38.9	600	7.30	43.0	109.0	21.0	78.0	90.0	2460.0	680.0	1049.0	20.0	1497.0	32.0	812.0	54.0
Control dextran 500	25-Mar-92	90	95	38.9	600	7.29	43.0	110.0	21.0	65.0	81.0	2560.0	700.0	1060.0	24.0	1590.0	36.0	1012.0	58.0
Control dextran 500	25-Mar-92	105	95	38.9	600	7.28	40.0	124.0	19.0	65.0		2650.0	670.0	944.0	22.0	1644.0	34.0	1179.0	56.0
Control dextran 500	25-Mar-92	120	95	38.9	660	7.32	38.0	114.0	20.0	52.0	75.0	2460.0	680.0	868.0	20.0	1462.0	32.0	1058.0	54.0
Control dextran 500	25-Mar-92	135	95	38.9	660	7.29	38.0	126.0	19.0	40.0	75.0	2270.0	650.0	746.0	16.0	1662.0	30.0	1051.0	54.0
Control dextran 500	25-Mar-92	150	95	38.9	660	7.32	29.0	124.0	15.0	38.0	59.0	2200.0	690.0	777.0	16.0	1734.0	30.0	1074.0	52.0
Control dextran 500	25-Mar-92	165	95	38.9	660	7.32	39.0	132.0	19.0	37.0	43.0			1052.0	22.0	1614.0	34.0	1127.0	54.0
Control dextran 500	25-Mar-92	180	95	38.9	660	7.32	35.0	132.0	18.0	39.0	47.0	2130.0	700.0	688.0	18.0	1421.0	32.0	1034.0	52.0
Control dextran 500	2-Apr-92	-120	70	38.7	540	7.37	36.0	113.0	21.0	114.0	67.0	1330.0	800.0	704.0	20.0	1002.0	40.0	395.0	64.0
Control dextran 500	2-Apr-92	-105	70	38.7	540	7.38	35.0	106.0	21.0	96.0	76.0			681.0	20.0	922.0	40.0	462.0	60.0
Control dextran 500	2-Apr-92	-90	70	38.7	540	7.37	36.0	111.0	21.0	111.0	71.0			678.0	18.0	613.0	38.0	328.0	62.0
Control dextran 500	2-Apr-92	-75	70	38.8	540	7.36	34.0	115.0	19.0	109.0	73.0	1385.0	800.0	612.0	18.0	625.0	34.0	321.0	58.0
Control dextran 500	2-Apr-92	-60	70	38.8	540	7.37	36.0	117.0	22.0	98.0	61.0	1300.0	845.0	566.0	18.0	482.0	32.0	[178]	52.0
Control dextran 500	2-Apr-92	-45	70	38.8	540	7.39	39.0	115.0	24.0	128.0	69.0			471.0	18.0	507.0	30.0	[205]	54.0
Control dextran 500	2-Apr-92	-30	70	38.8	540	7.37	33.0	126.0	19.0	128.0	75.0	1350.0	820.0	813.0	18.0	731.0	30.0	325.0	50.0
Control dextran 500	2-Apr-92	-15	70	38.9	540	7.38	35.0	121.0	20.0	109.0	91.0			577.0	18.0	622.0	38.0	338.0	58.0
Control dextran 500	2-Apr-92	0	75	38.9	540	7.42	33.0	110.0	21.0	99.0	77.0	1230.0	830.0	586.0	18.0	574.0	34.0	319.0	60.0
Control dextran 500	2-Apr-92	15	75	38.9	540	7.41	37.0	121.0	23.0	115.0	81.0	1160.0	800.0	659.0	18.0	652.0	30.0	282.0	56.0
Control dextran 500	2-Apr-92	30	70	38.8	540	7.39	38.0	114.0	23.0	85.0	70.0	1120.0	790.0	701.0	18.0	814.0	34.0	402.0	58.0
Control dextran 500	2-Apr-92	45	75	38.8	540	7.37	34.0	112.0	17.0	96.0	84.0	1450.0	750.0	915.0	18.0	1054.0	34.0	691.0	60.0
Control dextran 500	2-Apr-92	60	75	38.8	480	7.34	33.0	105.0	18.0	90.0	80.0	1410.0	750.0	816.0	18.0	840.0	38.0	484.0	60.0
Control dextran 500	2-Apr-92	75	75	38.8	480	7.32	35.0	109.0	18.0	82.0	62.0	1450.0	800.0	888.0	18.0	787.0	34.0	338.0	60.0
Control dextran 500	2-Apr-92	90	70	38.9	480	7.34	40.0	98.0	21.0	68.0	37.0	1275.0	875.0	755.0	16.0	705.0	28.0	265.0	52.0
Control dextran 500	2-Apr-92	105	75	39.0	480	7.36	39.0	99.0	22.0	57.0	32.0	1275.0	825.0	737.0	18.0	857.0	32.0	339.0	56.0
Control dextran 500	2-Apr-92	120	75	39.1	480	7.34	44.0	105.0	24.0	59.0	36.0	1275.0	837.5	650.0	18.0	600.0	30.0	231.0	58.0
Control dextran 500	2-Apr-92	135	75	39.1	480	7.34	39.0	105.0	21.0	68.0	38.0	1200.0	825.0	517.0	16.0	417.0	32.0	102.0	54.0
Control dextran 500	2-Apr-92	150	75	39.1	480	7.36	38.0	99.0	20.0	62.0	[25]	1150.0	790.0	579.0	16.0	506.0	32.0	195.0	54.0
Control dextran 500	2-Apr-92	165	75	39.1	480					45.0		1045.0	815.0	496.0	16.0	527.0	28.0	304.0	46.0
Control dextran 500	2-Apr-92	180	70	39.0	480	7.34	39.0	119.0	21.0	46.0	[36]	1030.0	830.0	353.0	16.0	338.0	40.0	235.0	64.0

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	ICBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
Control dextran 500	23-Apr-92	-120	100	38.4	600	7.33	40.0	115.0	21.0	48.0	52.0	1360.0	555.0	743.0	22.0	1004.0	34.0	388.0	58.0
Control dextran 500	23-Apr-92	-105	100	38.4	600	7.34	38.0	118.0	21.0	43.0	61.0	1400.0	550.0	983.0	22.0	1180.0	34.0	550.0	56.0
Control dextran 500	23-Apr-92	-90	100	38.4	600	7.30	37.0	123.0	17.0	47.0	53.0	1300.0	600.0	871.0	22.0	1108.0	32.0	459.0	54.0
Control dextran 500	23-Apr-92	-75	100	38.5	600	7.33	39.0	114.0	21.0	46.0	58.0	1340.0	740.0	742.0	20.0	981.0	32.0	401.0	54.0
Control dextran 500	23-Apr-92	-60	100	38.5	600	7.34	38.0	121.0	20.0	42.0	60.0	1265.0	755.0	659.0	20.0	984.0	30.0	379.0	52.0
Control dextran 500	23-Apr-92	-45	100	38.5	600	7.35	38.0	113.0	21.0	43.0	54.0	1500.0	700.0	634.0	18.0	984.0	30.0	390.0	50.0
Control dextran 500	23-Apr-92	-30	100	38.5	600	7.33	39.0	110.0	21.0	39.0	55.0	1150.0	610.0	588.0	18.0	890.0	30.0	325.0	50.0
Control dextran 500	23-Apr-92	-15	100	38.5	600	7.35	37.0	121.0	20.0	43.0	51.0	1150.0	680.0	618.0	18.0	868.0	30.0	318.0	50.0
Control dextran 500	23-Apr-92	0	80	38.5	600	7.35	35.0	135.0	19.0	41.0	53.0	1000.0	670.0	588.0	18.0	766.0	30.0	318.0	46.0
Control dextran 500	23-Apr-92	15	90	38.4	600	7.27	35.0	95.0	18.0	41.0	53.0			600.0	18.0	790.0	28.0	330.0	46.0
Control dextran 500	23-Apr-92	30	100	38.4	600	7.35	37.0	100.0	20.0	33.0	50.0	1130.0	670.0	561.0	18.0	748.0	28.0	304.0	48.0
Control dextran 500	23-Apr-92	45	100	38.4	600	7.34	38.0	129.0	21.0	33.0	53.0			464.0	18.0	459.0	30.0	67.0	46.0
Control dextran 500	23-Apr-92	60	95	38.3	600	7.36	36.0	121.0	20.0	35.0	52.0	900.0	650.0	478.0	18.0	467.0	30.0	115.0	44.0
Control dextran 500	23-Apr-92	75	95	38.3	600	7.35	36.0	126.0	20.0	34.0	51.0	1050.0	610.0	445.0	18.0	527.0	28.0	145.0	42.0
Control dextran 500	23-Apr-92	90	95	38.3	600	7.36	35.0	115.0	20.0	34.0	52.0	1030.0	600.0	483.0	18.0	567.0	28.0	194.0	44.0
Control dextran 500	23-Apr-92	105	90	38.3	600	7.31	37.0	117.0	19.0	35.0	56.0			439.0	18.0	604.0	30.0	322.0	44.0
Control dextran 500	23-Apr-92	120	90	38.3	600	7.36	35.0	119.0	20.0	32.0	49.0			441.0	18.0	630.0	30.0	294.0	46.0
Control dextran 500	23-Apr-92	135	90	38.3	600	7.36	36.0	119.0	21.0	34.0	49.0			435.0	18.0	704.0	30.0	323.0	46.0
Control dextran 500	23-Apr-92	150	90	38.2	600	7.34	37.0	118.0	21.0	41.0	58.0			394.0	18.0	578.0	30.0	289.0	44.0
Control dextran 500	23-Apr-92	165	95	38.2	600	7.34	39.0	121.0	21.0	34.0	50.0			312.0	18.0	509.0	30.0	247.0	44.0
Control dextran 500	23-Apr-92	180	100	38.2	600	7.35	37.0	103.0	21.0	38.0	45.0			334.0	18.0	431.0	30.0	111.0	46.0
Control dextran sulphate 500	26-Mar-92	-120	90	39.1	660	7.28	40.0	117.0	19.0				850.0	1468.0	18.0	1648.0	36.0	522.0	68.0
Control dextran sulphate 500	26-Mar-92	-105	85	39.2	660	7.26	36.0	118.0	17.0				770.0	1620.0	18.0	1765.0	34.0	921.0	58.0
Control dextran sulphate 500	26-Mar-92	-90	90	39.3	660	7.24	38.0	112.0	19.0					1311.0	20.0	1816.0	34.0	897.0	58.0
Control dextran sulphate 500	26-Mar-92	-75	90	39.3	660	7.28	35.0	113.0	17.0					1580.0	18.0	1868.0	34.0	860.0	58.0
Control dextran sulphate 500	26-Mar-92	-60	90	39.3	660	7.29	35.0	124.0	17.0			2570.0	790.0	1506.0	16.0	1690.0	30.0	880.0	52.0
Control dextran sulphate 500	26-Mar-92	-45	85	39.3	660	7.32	36.0	110.0	18.0					1419.0	16.0	1507.0	30.0	856.0	54.0
Control dextran sulphate 500	26-Mar-92	-30	85	39.3	660	7.33	38.0	100.0	20.0					1306.0	16.0	1554.0	32.0	829.0	56.0
Control dextran sulphate 500	26-Mar-92	-15	80	39.3	600	7.28	35.0	119.0	16.0					1573.0	18.0	1705.0	32.0	933.0	54.0
Control dextran sulphate 500	26-Mar-92	0	90	39.4	600	7.32	38.0	111.0	17.0			2680.0	820.0	1507.0	18.0	1545.0	32.0	834.0	52.0
Control dextran sulphate 500	26-Mar-92	15	90	39.4	600	7.30	33.0	122.0	16.0			2680.0	770.0	1472.0	18.0	1840.0	32.0	839.0	54.0
Control dextran sulphate 500	26-Mar-92	30	90	39.4	600	7.30	38.0	109.0	19.0			2690.0	750.0	1516.0	16.0	1704.0	30.0	788.0	52.0
Control dextran sulphate 500	26-Mar-92	45	90	39.2	600	7.28	37.0	110.0	17.0			2745.0	720.0	1599.0	16.0	1809.0	28.0	808.0	48.0
Control dextran sulphate 500	26-Mar-92	60	85	39.0	600	7.27	37.0	115.0	17.0			2630.0	750.0	1622.0	16.0	1900.0	28.0	849.0	48.0
Control dextran sulphate 500	26-Mar-92	75	90	38.8	600	7.31	37.0	120.0	18.0			2500.0	750.0	1478.0	18.0	1622.0	30.0	919.0	54.0
Control dextran sulphate 500	26-Mar-92	90	90	38.6	600	7.27	36.0	118.0	19.0			2390.0	750.0	1463.0	19.0	1574.0	30.0	704.0	50.0
Control dextran sulphate 500	26-Mar-92	105	90	38.6	600	7.32	32.0	120.0	17.0			2330.0	750.0	1568.0	18.0	1766.0	32.0	958.0	50.0
Control dextran sulphate 500	26-Mar-92	120	90	38.5	600	7.32	34.0	124.0	18.0					1628.0	18.0	1791.0	32.0	896.0	52.0
Control dextran sulphate 500	26-Mar-92	135	95	38.5	600	7.29	37.0	117.0	19.0			2300.0	775.0	1522.0	18.0	1856.0	32.0	983.0	52.0
Control dextran sulphate 500	26-Mar-92	150	95	38.5	600	7.32	38.0	112.0	20.0			2250.0	740.0	1423.0	18.0	1698.0	30.0	742.0	50.0
Control dextran sulphate 500	26-Mar-92	165	90	38.8	600	7.33	34.0	118.0	17.0			2290.0	740.0	1446.0	18.0	1722.0	30.0	839.0	50.0
Control dextran sulphate 500	26-Mar-92	180	90	38.9	600	7.32	36.0	110.0	19.0					1470.0	18.0	1661.0	32.0	860.0	52.0
Control dextran sulphate 500	1-Apr-92	-120	100	38.9	480	7.38	43.0	112.0	24.0	99.0	95.0		480.0						
Control dextran sulphate 500	1-Apr-92	-105	100	38.9	540	7.36	41.0	108.0	24.0	87.0	98.0	2795.0	470.0						
Control dextran sulphate 500	1-Apr-92	-90	100	38.9	540	7.35	43.0	117.0	24.0	89.0	76.0	2800.0	490.0						
Control dextran sulphate 500	1-Apr-92	-75	90	39.0	540	7.33	41.0	117.0	22.0	80.0	68.0	3250.0	450.0						
Control dextran sulphate 500	1-Apr-92	-60	95	39.0	540	7.34	39.0	122.0	21.0	90.0	78.0	2940.0	450.0						
Control dextran sulphate 500	1-Apr-92	-45	95	39.0	540	7.36	40.0	117.0	23.0	88.0	70.0								
Control dextran sulphate 500	1-Apr-92	-30	95	39.0	540	7.35	40.0	126.0	22.0	96.0	78.0	2900.0	630.0	1035.0	16.0	1491.0	32.0	1453.0	56.0
Control dextran sulphate 500	1-Apr-92	-15	95	39.0	540	7.35	35.0	104.0	19.0	87.0	71.0	2850.0		1193.0	16.0	1505.0	32.0	1475.0	56.0
Control dextran sulphate 500	1-Apr-92	0	80	39.0	540	7.32	36.0	100.0	20.0	67.0	70.0			1128.0	20.0	1868.0	34.0	1863.0	58.0
Control dextran sulphate 500	1-Apr-92	15	80	38.9	540	7.30	39.0	119.0	19.0	76.0	70.0			1015.0	18.0	1835.0	34.0	1846.0	56.0
Control dextran sulphate 500	1-Apr-92	30	80	38.9	540	7.32	38.0	115.0	19.0	80.0	73.0			1064.0	16.0	1651.0	34.0	1723.0	56.0
Control dextran sulphate 500	1-Apr-92	45	80	38.9	540	7.32	36.0	128.0	18.0	85.0	73.0	2340.0	490.0	932.0	16.0	1496.0	34.0	1587.0	54.0
Control dextran sulphate 500	1-Apr-92	60	80	38.9	540	7.33	39.0	107.0	20.0	89.0	84.0			1138.0	16.0	1686.0	30.0	1551.0	56.0
Control dextran sulphate 500	1-Apr-92	75	80	38.9	540	7.32	39.0	109.0	20.0	80.0	73.0			966.0	16.0	1493.0	32.0	1571.0	56.0
Control dextran sulphate 500	1-Apr-92	90	80	38.9	540	7.32	37.0	111.0	19.0	74.0	84.0			979.0	16.0	1492.0	30.0	1421.0	54.0
Control dextran sulphate 500	1-Apr-92	105	80	38.9	540	7.33	37.0	105.0	18.0	70.0	84.0			992.0	16.0	1586.0	30.0	1517.0	52.0
Control dextran sulphate 500	1-Apr-92	120	90	38.9	540	7.34	35.0	107.0	19.0	66.0	67.0			825.0	16.0	1458.0	34.0	1539.0	58.0
Control dextran sulphate 500	1-Apr-92	135	90	38.9	540	7.33	36.0	109.0	19.0	73.0	67.0			773.0	18.0	1630.0	34.0	1652.0	56.0
Control dextran sulphate 500	1-Apr-92	150	90	38.9	540	7.34	37.0	110.0	19.0	60.0	72.0			967.0	20.0	1783.0	36.0	1760.0	58.0
Control dextran sulphate 500	1-Apr-92	165	90	39.0	540	7.33	35.0	124.0	18.0	59.0	82.0	2910.0	470.0	916.0	18.0	1672.0	34.0	1678.0	56.0
Control dextran sulphate 500	1-Apr-92	180	90	39.0	540	7.33	41.0	93.0	21.0	55.0	73.0	2870.0	470.0	940.0	18.0	1695.0	34.0	1723.0	56.0
Control dextran sulphate 500	29-Apr-92	-120	110	38.9	600	7.37	39.0	100.0	22.0	43.0	44.0	1630.0	860.0	1785.0	26.0	1824.0	40.0	1488.0	68.0
Control dextran sulphate 500	29-Apr-92	-105	110	38.9	600	7.36	36.0	91.0	20.0	49.0	41.0	1550.0	900.0	1346.0	22.0	1705.0	36.0	1086.0	58.0
Control dextran sulphate 500	29-Apr-92	-90	110	38.9	600	7.37	36.0	98.0	21.0	48.0	37.0	1690.0	860.0	1293.0	20.0	1460.0	30.0	1169.0	64.0
Control dextran sulphate 500	29-Apr-92	-75	100	38.9	600	7.39	35.0	107.0	22.0	51.0	39.0	1700.0	850.0	1044.0	24.0	1361.0	30.0	1006.0	68.0
Control dextran sulphate 500	29-Apr-92	-60	100	39.0	600	7.37	37.0	101.0	23.0	52.0	40.0			998.0	26.0	1514.0	38.0	1086.0	80.0
Control dextran sulphate 500	29-Apr-92	-45	100	39.0	600	7.32	39.0	103.0	23.0	54.0	41.0	1700.0	800.0	1572.0	26.0	1591.0	48.0	504.0	76.0
Control dextran sulphate 500	29-Apr-92	-30	100	39.0	600	7.34	40.0	97.0	22.0	50.0	35.0	1600.0	840.0	895.0	28.0	1375.0	44.0	965.0	88.0
Control dextran sulphate 500	29-Apr-92	-15	100	39.0	600	7.37	40.0	100.0	23.0	54.0	35.0	1640.0	780.0	1316.0	26.0	1537.0	52.0	763.0	78.0
Control dextran sulphate 500	29-Apr-92	0	95	39.0	600	7.34	36.0	100.0	19.0	46.0	30.0	1410.0	800.0	1217.0	26.0	1270.0	46.0	966.0	92.0
Control dextran sulphate 500	29-Apr-92	15	100	39.0	600	7.38	41.0	94.0	25.0	46.0	29.0	1350.0	820.0	1197.0	28.0	1269.0	50.0	797.0	92.0
Control dextran sulphate 500	29-Apr-92	30	95	39.0	600	7.37	40.0	95.0	23.0	52.0	29.0	1225.0	790.0	1465.0	22.0	1519.0	40.0	1235.0	96.0
Control dextran sulphate 500	29-Apr-92	45	95	39.0	600	7.38	41.0	106.0	24.0	43.0	27.0	1170.0	820.0	1238.0	24.0	1396.0	50.0	895.0	72.0
Control dextran sulphate 500	29-Apr-92	60	95	39.0	600	7.39	37.0	106.0	22.0	62.0	26.0	1220.0	750.0	1381.0	24.0	1337.0	44.0	959.0	92.0
Control dextran sulphate 500	29-Apr-92	75	95	38.9	600	7.39	41.0	104.0	25.0	57.0	30.0	1230.0	830.0	1358.0	22.0	1424.0	42.0	593.0	82.0
Control dextran sulphate 500	29-Apr-92	90	90	38.8	600	7.38	38.0	105.0	25.0	57.0	26.0			698.0	26.0	817.0	52.0	1021.0	84.0
Control dextran sulphate 500	29-Apr-92	105	90	38.8	600	7.41	39.0	110.0	24.0	44.0	19.0	1160.0	710.0	1281.0	26.0	1311.0	48.0	804.0	74.0
Control dextran sulphate 500	29-Apr-92	120	90	38.8	600	7.36	38.0	106.0	22.0	40.0	19.0			670.0	22.0	788.0	42.0	1096.0	82.0
Control dextran sulphate 500	29-Apr-92	135	90	38.8	600	7.39	39.0	105.0	24.0	27.0	16.0	1110.0	700.0	914.0	20.0	848.0	40.0	675.0	72.0
Control dextran sulphate 500	29-Apr-92	150	90	38.8	600	7.30	39.0	110.0	19.0	47.0	27.0	1205.0	720.0	1649.0	22.0	1649.0	42.0	990.0	98.0
Control dextran sulphate 500	29-Apr-92	165	90	38.8	600	7.37	40.0	114.0	24.0	44.0	18.0	1100.0	715.0	1468.0	20.0	1554.0	40.0	1342.0	94.0
Control dextran sulphate 500	29-Apr-92	180	90	38.8	600	7.37	39.0	107.0	22.0	36.0	19.0	1010.0	710.0	1176.0	20.0	1310.0	40.0	1037.0	68.0
Control dextran sulphate 500	30-Apr-92	-120	85	39.1	600	7.39	36.0	113.0	21.0	31.0	37.0	1100.0	960.0	837.0	34.0	894.0	68.0	863.0	128.0
Control dextran sulphate 500	30-Apr-92	-105	85	39.1	600	7.43	35.0	108.0	22.0	29.0	32.0	1330.0	1050.0	554.0	32.0	709.0	66.0	577.0	110.0
Control dextran sulphate 500	30-Apr-92	-90	80	39.2	600	7.46	35.0	107.0	25.0	30.0	33.0	1300.0	955.0	545.0	32.0	672.0	52.0	480.0	112.0
Control dextran sulphate 500	30-Apr-92	-75	80	39.1	600	7.34	35.0	115.0	18.0	30.0	33.0	1550.0		621.0	30.0	693.0	50.0	480.0	122.0
Control dextran sulphate 500	30-Apr-92	-60	80	39.0	600	7.42	35.0	118.0	22.0	31.0	34.0	1500.0	970.0	898.0	24.0	1120.0	44.0	462.0	84.0
Control dextran sulphate 500	30-Apr-92	-45	80	39.0	600	7.42	33.0	115.0	21.0	29.0	33.0	1380.0	865.0	688.0	26.0	972.0	46.0	486.0	96.0
Control dextran sulphate 500	30-Apr-92	-30	80	39.0	480	7.41	35.0	113.0	22.0	36.0	37.0	1550.0	870.0	806.0	22.0	816.0	44.0	384.0	86.0
Control dextran sulphate 500	30-Apr-92	-15	80	39.1	480	7.41	35.0	111.0	22.0	35.0	33.0	1430.0	930.0	636.0	20.0	640.0	46.0	334.0	92.0
Control dextran sulphate 500	30-Apr-92	0	80	39.1	480	7.39	35.0	110.0	22.0	34.0	33.0	1513.3	975.0	683.0	20.0	805.0	46.0	548.0	98.0
Control dextran sulphate 500	30-Apr-92	15	80	39.2	480	7.37	35.0	112.0	20.0	36.0	34.0	1455.0	1000.0	749.0	20.0	741.0	44.0	429.0	92.0
Control dextran sulphate 500	30-Apr-92	30	80	39.2	480	7.57	35.0	108.0	32.0	35.0	37.0	1400.0	1080.0	876.0	20.0	838.0	40.0	311.0	78.0
Control dextran sulphate 500	30-Apr-92	45	85	39.1	480	7.36	36.0	117.0	20.0	33.0	30.0	1400.0	960.0	826.0	20.0	799.0	40.0	153.0	70.0
Control dextran sulphate 500	30-Apr-92	60	85	39.1	480	7.36	35.0	115.0	20.0	32.0	29.0	1240.0	780.0	867.0	22.0	963.0	44.0	560.0	92.0
Control dextran sulphate 500	30-Apr-92	75	85	39.0	480	7.37	36.0	112.0	21.0	30.0	29.0	1150.0	795.0	725.0	20.0	769.0	42.0	447.0	88.0
Control dextran sulphate 500	30-Apr-92	90	85	39.0	480	7.36	37.0	113.0	22.0	38.0	27.0	1170.0	835.0	851.0	22.0	878.0	40.0	296.0	66.0
Control dextran sulphate 500	30-Apr-92	105	85	39.0	480	7.37	35.0	113.0	26.0	32.0	22.0	1300.0	785.0	761.0	20.0	806.0	42.0	197.0	70.0
Control dextran sulphate 500	30-Apr-92	120	85	39.0	480	7.36	36.0	111.0	20.0	36.0	24.0	1100.0	650.0	738.0	22.0	1043.0	46.0	474.0	80.0
Control dextran sulphate 500	30-Apr-92	135	85	38.9	480	7.36	36.0	112.0	21.0	33.0	23.0	1070.0	590.0	760.0	20.0	693.0	42.0	238.0	80.0
Control dextran sulphate 500	30-Apr-92	150	85	38.9	480	7.38	35.0	100.0	21.0	33.0	26.0	970.0	620.0	633.0	20.0	569.0	40.0	82.0	70.0
Control dextran sulphate 500	30-Apr-92	165	85	38.9	480	7.37	36.0	101.0	22.0			1030.0	680.0	652.0	22.0	707.0	42.0	361.0	84.0
Control dextran sulphate 500	30-Apr-92	180	85	38.9	480	7.35	36.0	105.0	20.0			1050.0	610.0	576.0	22.0	583.0	46.0	294.0	106.0

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
Control dextran sulphate 500	18-Jun-92	-120	90	39.0	520	7.31	39.0	105.0	20.0	53.0	51.0	1960.0	700.0						
Control dextran sulphate 500	18-Jun-92	-105	90	39.0	520	7.31	35.0	105.0	18.0	52.0	55.0	1845.0	800.0						
Control dextran sulphate 500	18-Jun-92	-90	90	39.0	520	7.28	40.0	104.0	19.0	58.0	54.0	1980.0	790.0						
Control dextran sulphate 500	18-Jun-92	-75	90	39.0	520	7.31	38.0	102.0	19.0	49.0	48.0	2070.0	820.0						
Control dextran sulphate 500	18-Jun-92	-60	95	39.0	520	7.33	37.0	106.0	20.0	48.0	68.0	2260.0	790.0						
Control dextran sulphate 500	18-Jun-92	-45	85	38.9	520	7.33	37.0	105.0	19.0	48.0	62.0	2500.0	820.0						
Control dextran sulphate 500	18-Jun-92	-30	80	38.9	520	7.39	35.0	110.0	20.0	42.0	48.0	2500.0	830.0						
Control dextran sulphate 500	18-Jun-92	-15	80	38.9	520	7.28	35.0	114.0	18.0	37.0	51.0	2070.0	920.0	1104.0	24.0	1367.0	42.0	1485.0	78.0
Control dextran sulphate 500	18-Jun-92	0	80	38.9	520	7.30	37.0	113.0	18.0	43.0	65.0	1770.0	925.0	1164.0	28.0	1612.0	46.0	1726.0	82.0
Control dextran sulphate 500	18-Jun-92	15	85	38.9	520	7.32	35.0	120.0	18.0	44.0	60.0	1760.0	870.0	531.0	28.0	864.0	46.0	1038.0	82.0
Control dextran sulphate 500	18-Jun-92	30	85	38.9	520	7.35	38.0	110.0	21.0	41.0	65.0	1735.0	845.0	638.0	28.0	1150.0	44.0	1170.0	84.0
Control dextran sulphate 500	18-Jun-92	45	80	38.9	520	7.37	36.0	115.0	20.0	43.0	57.0	1800.0	850.0	998.0	30.0	1425.0	48.0	1436.0	86.0
Control dextran sulphate 500	18-Jun-92	60	80	38.9	520	7.35	33.0	126.0	19.0	44.0	58.0	1740.0	880.0	1007.0	28.0	1525.0	46.0	1556.0	86.0
Control dextran sulphate 500	18-Jun-92	75	80	38.9	520	7.37	34.0	119.0	20.0	47.0	53.0	1630.0	860.0	1060.0	28.0	1584.0	44.0	1618.0	82.0
Control dextran sulphate 500	18-Jun-92	90	85	38.9	520	7.37	36.0	116.0	20.0	41.0	48.0	1630.0	800.0	962.0	24.0	1293.0	44.0	1419.0	80.0
Control dextran sulphate 500	18-Jun-92	105	80	38.9	520	7.36	37.0	123.0	21.0	40.0	41.0	1610.0	800.0	990.0	24.0	1298.0	42.0	1362.0	80.0
Control dextran sulphate 500	18-Jun-92	120	80	38.9	520	7.35	35.0	112.0	19.0	39.0	48.0	1555.0	810.0	882.0	22.0	1254.0	38.0	1162.0	76.0
Control dextran sulphate 500	18-Jun-92	135	80	38.9	520	7.32	36.0	110.0	19.0	45.0	56.0	1560.0	810.0	951.0	22.0	1420.0	40.0	1451.0	76.0
Control dextran sulphate 500	18-Jun-92	150	80	38.9	520	7.31	37.0	110.0	19.0	52.0	57.0			940.0	20.0	1205.0	38.0	1028.0	78.0
Control dextran sulphate 500	18-Jun-92	165	85	38.9	520	7.37	35.0	120.0	20.0			1550.0	825.0	752.0	20.0	1177.0	44.0	1341.0	78.0
Control dextran sulphate 500	18-Jun-92	180	80	38.9	520	7.35	38.0	129.0	22.0			1570.0	830.0	880.0	20.0	1113.0	36.0	752.0	74.0
Control dextran sulphate 500	1-Jul-92	-120	80	39.0	600	7.35	41.0	112.0	23.0			2200.0	880.0						
Control dextran sulphate 500	1-Jul-92	-105	80	39.0	600	7.35	39.0	112.0	22.0	11.0	44.0			906.0	28.0	1047.0	44.0	1342.0	82.0
Control dextran sulphate 500	1-Jul-92	-90	80	39.0	600	7.44	36.0	115.0	21.0		53.0	2180.0	970.0	984.0	24.0	1239.0	40.0	1332.0	78.0
Control dextran sulphate 500	1-Jul-92	-75	85	39.0	600	7.35	37.0	116.0	22.0		48.0			737.0	26.0	996.0	40.0	1359.0	82.0
Control dextran sulphate 500	1-Jul-92	-60	80	39.0	600	7.33	39.0	115.0	23.0		46.0	1915.0	565.0	[1087]	[24]	[1375]	[40]	[1522]	[78]
Control dextran sulphate 500	1-Jul-92	-45	80	38.9	600	7.39	34.0	127.0	20.0	13.0	54.0	1950.0	580.0	714.0	22.0	965.0	38.0	1161.0	74.0
Control dextran sulphate 500	1-Jul-92	-30	90	38.9	600	7.39	35.0	118.0	21.0	17.0	63.0			673.0	20.0	905.0	36.0	1030.0	74.0
Control dextran sulphate 500	1-Jul-92	-15	50	38.9	600	7.34	38.0	123.0	20.0		53.0			603.0	22.0	968.0	38.0	1032.0	76.0
Control dextran sulphate 500	1-Jul-92	0	80	39.0	600	7.31	36.0	116.0	18.0		55.0	1550.0	580.0	621.0	22.0	999.0	36.0	1041.0	76.0
Control dextran sulphate 500	1-Jul-92	15	90	39.0	600	7.33	33.0	119.0	17.0	17.0	59.0	1500.0	580.0	435.0	22.0	611.0	36.0	650.0	76.0
Control dextran sulphate 500	1-Jul-92	30	85	39.0	600	7.39	33.0	143.0	19.0	27.0	54.0	1545.0	600.0	714.0	22.0	1051.0	40.0	1197.0	78.0
Control dextran sulphate 500	1-Jul-92	45	80	38.8	600	7.38	34.0	126.0	19.0	19.0	56.0			700.0	24.0	1011.0	40.0	1010.0	74.0
Control dextran sulphate 500	1-Jul-92	60	80	38.8	600	7.36	34.0	123.0	19.0	19.0	65.0	1500.0	590.0	551.0	22.0	675.0	38.0	804.0	74.0
Control dextran sulphate 500	1-Jul-92	75	80	38.8	600	7.36	34.0	122.0	19.0			1500.0	580.0	556.0	20.0	728.0	36.0	833.0	70.0
Control dextran sulphate 500	1-Jul-92	90	90	38.8	600	7.37	34.0	117.0	19.0			1630.0	600.0	663.0	22.0	1023.0	38.0	1197.0	74.0
Control dextran sulphate 500	1-Jul-92	105	80	38.8	600	7.38	34.0	121.0	20.0			1510.0	550.0	395.0	20.0	497.0	38.0	642.0	74.0
Control dextran sulphate 500	1-Jul-92	120	90	38.8	600	7.37	34.0	115.0	19.0			1500.0	510.0	548.0	24.0	751.0	40.0	590.0	78.0
Control dextran sulphate 500	1-Jul-92	135	90	38.8	600	7.37	33.0	117.0	19.0			1430.0	525.0	587.0	20.0	769.0	36.0	678.0	74.0
Control dextran sulphate 500	1-Jul-92	150	80	38.8	600	7.34	36.0	100.0	19.0			1385.0	510.0	631.0	22.0	916.0	38.0	1015.0	76.0
Control dextran sulphate 500	1-Jul-92	165	80	38.8	600	7.35	34.0	104.0	19.0			1380.0	500.0	843.0	22.0	1156.0	38.0	1283.0	76.0
Control dextran sulphate 500	1-Jul-92	180	80	38.3	600	7.34	36.0	118.0	18.0			1460.0	515.0	745.0	22.0	1172.0	38.0	1343.0	76.0
CAGE 25µl	4-Aug-88	-120	120	40.0	675	7.43	31.6	88.3	21.0										
CAGE 25µl	4-Aug-88	-105	120	40.0	675	7.40	31.4	114.7	19.5										
CAGE 25µl	4-Aug-88	-90	120	40.0	675	7.37	28.6	125.3	16.6										
CAGE 25µl	4-Aug-88	-75	110	40.0	600	7.38	37.1	117.0	21.6	62.6	74.5	1670.0	85.0	318.0	18.8	217.0	43.4	143.0	77.0
CAGE 25µl	4-Aug-88	-60	110	40.0	600	7.33	42.8	124.1	22.7	59.1	57.8	1660.0	85.0	343.0	17.4	245.0	43.4	168.0	75.8
CAGE 25µl	4-Aug-88	-45	110	40.0	600	7.35	39.3	125.9	21.8	61.0	54.7	1670.0	85.0	196.0	16.8	147.0	42.2	182.0	82.8
CAGE 25µl	4-Aug-88	-30	100		600	7.35	41.1	129.9	22.7	55.9	64.9	1600.0	85.0	220.0	13.2	339.0	44.2	115.0	83.0
CAGE 25µl	4-Aug-88	-15	100		600	7.37	43.1	116.6	24.9	50.6	82.8		105.0	164.0	12.6	297.0	46.4	129.0	85.6
CAGE 25µl	4-Aug-88	0	100	39.3	600	7.40	42.7	120.0	26.2	67.9	93.9	1680.0	115.0	255.0	16.4	336.0	42.6	108.0	78.6
CAGE 25µl	4-Aug-88	15	100	39.3	615	7.42	40.6	127.1	26.3	74.1	116.8	1655.0	125.0	224.0	17.6	276.0	41.2	133.0	83.4
CAGE 25µl	4-Aug-88	30	100	39.5	675	7.37	41.5	92.9	24.0	63.2	68.7	1655.0	120.0	294.0	18.4	311.0	40.4	119.0	80.6
CAGE 25µl	4-Aug-88	45	100	39.5	675	7.38	38.1	139.8	22.7	59.1	[127]	1600.0	120.0	262.0	17.2	339.0	44.2	101.0	86.0
CAGE 25µl	4-Aug-88	60	100	39.5	675	7.37	35.3	131.4	20.2	53.1	[108]	1550.0	115.0	283.0	18.0	294.0	46.0	133.0	83.6
CAGE 25µl	4-Aug-88	75	95	39.0	675	7.28	43.8	107.2	20.6	46.0		1545.0	115.0	304.0	18.6	213.0	38.4	[182]	82.2
CAGE 25µl	4-Aug-88	90	95	39.0	675	7.35	42.1	145.4	22.9	44.7		1570.0	115.0	297.0	17.4	336.0	45.2	98.0	82.2
CAGE 25µl	4-Aug-88	105	95	39.0	675	7.36	41.1	156.7	23.2	59.5			115.0	248.0	17.8	325.0	44.2	77.0	77.2
CAGE 25µl	4-Aug-88	120										1555.0	115.0	224.0	17.0	266.0	48.6	73.5	88.2
CAGE 25µl	4-Aug-88	135	95	38.8	675	7.32	40.5	144.3	20.8	37.4		1550.0	115.0	206.0	17.4	220.0	38.8	105.0	80.2
CAGE 25µl	4-Aug-88	150	97	38.3	675	7.34	43.1	144.7	23.3	35.6	43.2	1555.0	115.0	248.0	17.4	248.0	43.6	98.0	80.2
CAGE 25µl	4-Aug-88	165	96	38.0	675	7.37	38.7	146.0	22.8	30.7	62.2	1530.0	105.0	231.0	13.2	220.0	45.8	119.0	89.2
CAGE 25µl	4-Aug-88	180	96	38.2	675	7.33	47.8	141.2	25.2	30.6	49.0	1500.0	100.0	262.0	19.4	182.0	39.2	119.0	75.8
CAGE 25µl	8-Jun-88	-120	100	38.5	900	7.37	40.2	175.1	22.9	64.5	182.9	n/a	733.0	182.0	19.8	199.0	40.6	129.0	73.6
CAGE 25µl	8-Jun-88	-105	100	38.5	900	7.36	33.5	172.4	18.9	89.2	179.9	n/a	823.0	182.0	16.6	154.0	42.2	129.0	73.4
CAGE 25µl	8-Jun-88	-90	100	38.5	900	7.36	35.5	166.1	20.2	76.0	167.5	n/a	832.0	203.0	17.6	192.0	43.4	126.0	71.8
CAGE 25µl	8-Jun-88	-75	100	38.5	900	7.35	42.9	158.8	23.7	75.9	161.6	n/a	846.0	199.0	14.4	210.0	23.4	112.0	61.4
CAGE 25µl	8-Jun-88	-60	100	38.5	900	7.36	39.1	161.1	22.1	66.1	210.6	n/a	848.0	150.0	17.4	154.0	40.8	73.5	69.6
CAGE 25µl	8-Jun-88	-45	95	38.5	900	7.34	40.3	164.3	21.7	72.7	218.4	n/a	861.0	150.0	13.6	101.0	33.6	73.5	83.0
CAGE 25µl	8-Jun-88	-30	95	38.0	900	7.33	41.6	164.1	22.0	70.5	209.7	n/a	841.0	175.0	18.0	147.0	41.2	115.0	71.0
CAGE 25µl	8-Jun-88	-15	90	38.0	900	7.35	38.3	163.7	21.2	61.6	195.9	n/a	897.0	199.0	18.0	203.0	42.0	119.0	74.4
CAGE 25µl	8-Jun-88	0	85	38.0	900	7.33	40.6	161.0	21.6	62.9	147.3	n/a	910.0	206.0	16.4	122.0	36.4	94.5	68.6
CAGE 25µl	8-Jun-88	15	90	38.5	900	7.35	42.3	162.4	23.2	59.0	157.5	n/a	1040.0	157.0	16.4	87.5	38.6	80.5	70.0
CAGE 25µl	8-Jun-88	30	85	38.5	900	7.34	43.6	157.2	23.9	49.6	157.6	n/a	1024.0	147.0	17.6	115.0	40.2	84.0	71.6
CAGE 25µl	8-Jun-88	45	85	38.5	900	7.35	35.7	163.8	19.9	49.5	142.2	n/a	974.0	84.0	13.8	98.0	27.4	75.0	70.0
CAGE 25µl	8-Jun-88	60	70	38.5	900	7.25	40.4	167.0	17.6	43.5	96.7	n/a	936.0	164.0	16.2	119.0	36.4	80.5	67.8
CAGE 25µl	8-Jun-88	75	80	38.5	900	7.36	39.8	159.1	22.4	48.4	124.7	n/a		171.0	17.6	119.0	34.6	83.0	71.6
CAGE 25µl	8-Jun-88	90	75	38.5	900	7.35	29.3	162.5	16.1	45.5	112.0	n/a	908.0	154.0	15.4	87.5	28.4	66.5	67.0
CAGE 25µl	8-Jun-88	105	75	38.5	900	7.39	37.6	166.7	23.7	52.7	118.4	n/a	832.0	161.0	15.4	115.0	29.4	87.5	66.8
CAGE 25µl	8-Jun-88	120	75	38.5	900	7.39	42.4	168.2	25.3	58.6	129.0	n/a	967.0	135.0	16.2	101.0	30.4	87.5	69.2
CAGE 25µl	8-Jun-88	135	75	38.5	900	7.37	38.5	170.9	22.4	46.3	130.6	n/a	950.0	147.0	16.4	105.0	29.6	66.5	63.4
CAGE 25µl	8-Jun-88	150	70	38.5	900	7.36	37.2	170.3	21.0	33.2	97.3	n/a	709.0	157.0	15.4	136.0	30.2	70.0	66.2
CAGE 25µl	8-Jun-88	165	70	38.5	900	7.36	40.1	175.9	22.8	28.9	79.4	n/a	710.0	150.0	15.6	122.0	30.4	38.5	71.6
CAGE 25µl	8-Jun-88	180	60	38.5	900	7.32	41.3	162.1	21.1	33.5	82.7	n/a	821.0	140.0	16.5	115.0	31.6	49.0	67.2
CAGE 25µl	9-Aug-88	-120	125	38.0	675	7.39	34.0	141.3	20.4										
CAGE 25µl	9-Aug-88	-105	110	38.0	675	7.30	46.3	142.5	22.7										
CAGE 25µl	9-Aug-88	-90	110	38.0	750	7.37	41.3	158.8	23.8	83.5	75.1								
CAGE 25µl	9-Aug-88	-75	110	38.0	750	7.37	41.5	165.7	24.0	123.9	138.3			255.0	19.6	192.0	41.0	63.0	83.0
CAGE 25µl	9-Aug-88	-60	110	38.0	750	7.42	36.3	150.3	23.7	115.2	86.7			217.0	19.0	154.0	39.0	45.0	83.0
CAGE 25µl	9-Aug-88	-45	105	38.5	750	7.43	35.7	158.6	23.7	110.3	55.4			199.0	19.0	154.0	41.2	28.0	91.4
CAGE 25µl	9-Aug-88	-30	100	38.5	675	7.34	36.1	156.7	19.3	120.0	133.7			220.0	19.0	122.0	41.0	35.0	91.0
CAGE 25µl	9-Aug-88	-15	110	38.5	600	7.38	29.2	133.1	17.4	64.1	69.9			178.0	18.4	175.0	38.8	38.5	79.0
CAGE 25µl	9-Aug-88	0	100	38.5	600	7.32	44.2	148.4	22.5	77.3		2755.0	865.0	122.0	16.4	59.5	38.0	52.0	67.0
CAGE 25µl	9-Aug-88	15	100	38.5	600	7.30	48.0	149.5	23.6	86.3	105.4	2480.0	890.0	122.0	16.0	59.0	38.0	52.0	67.0
CAGE 25µl	9-Aug-88	30	100	38.5	675	7.30	43.8	157.1	20.0	62.4	59.3	2350.0	980.0	245.0	13.6	136.0	19.8	[133]	72.6
CAGE 25µl	9-Aug-88	45	100	38.0	675	7.34	39.6	160.4	21.2	73.4	78.1	2220.0	970.0	80.5	18.2	129.0	42.0	[280]	83.4
CAGE 25µl	9-Aug-88	60	90	38.0	675	7.28	44.0	89.5	20.6	69.7	77.8	2080.0	956.0	38.5	17.2	101.0	42.8	17.5	75.6
CAGE 25µl	9-Aug-88	75	80	38.0	675	7.28	49.2	59.5	23.4	53.2	45.3	2265.0	1000.0	105.0	13.2	140.0	35.4	0.0	67.0
CAGE 25µl	9-Aug-88	90	70	38.0	750	7.30	41.3	73.2	20.4	45.2	39.3	2200.0	980.0	171.0	14.0	185.0	30.4	3.5	70.0
CAGE 25µl	9-Aug-88	105	70	38.0	750	7.23	48.9	67.3	20.4			2370.0	900.0	308.0	14.4	238.0	26.4	129.0	71.0
CAGE 25µl	9-Aug-88	120																	
CAGE 25µl	9-Aug-88	135																	
CAGE 25µl	9-Aug-88	150																	
CAGE 25µl	9-Aug-88	165																	
CAGE 25µl	9-Aug-88	180																	

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	ICBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 25µl	15-Jun-88	-120	80	38.0	900	7.33	35.9	164.0	19.0	43.1	48.6	n/a	561.0	42.0	12.0	52.5	38.2	[28]	65.6
CAGE 25µl	15-Jun-88	-105	85	38.0	900	7.34	36.9	157.3	19.8	46.8	51.5	n/a	545.0	42.0	11.4	10.5	19.0	[7]	25.0
CAGE 25µl	15-Jun-88	-90	90	38.0	900	7.36	39.0	158.2	22.2	46.0	40.5	n/a	645.0	143.0	13.2	80.5	23.2	101.0	62.2
CAGE 25µl	15-Jun-88	-75	90	38.0	900	7.39	40.2	157.3	24.2	48.2	44.2	n/a	616.0	98.0	16.2	147.0	38.0	49.0	69.6
CAGE 25µl	15-Jun-88	-60	95	38.0	900	7.40	33.5	157.5	20.9	40.9	36.1	n/a	648.0	105.0	14.8	136.0	31.2	80.5	57.8
CAGE 25µl	15-Jun-88	-45	95	38.0	900	7.41	36.2	158.8	22.7	36.1	36.9	n/a	601.0	171.0	17.8	140.0	40.2	87.5	63.4
CAGE 25µl	15-Jun-88	-30	95	38.0	900	7.40	37.7	159.8	23.2	30.1	30.1	n/a	652.0	230.0	12.8	136.0	23.0	94.5	62.0
CAGE 25µl	15-Jun-88	-15	80	38.0	900	7.40	36.0	157.5	22.2	33.7	35.3	n/a	645.0	115.0	14.2	157.0	35.8	112.0	63.2
CAGE 25µl	15-Jun-88	0	80	38.0	900	7.38	37.6	160.0	22.3	47.7	46.9	n/a	606.0	115.0	11.8	129.0	36.0	87.5	70.2
CAGE 25µl	15-Jun-88	15	80	38.0	900	7.39	37.8	155.9	23.0	40.8	34.1	n/a	710.0	87.5	12.8	161.0	34.4	94.5	58.8
CAGE 25µl	15-Jun-88	30	85	38.0	900	7.40	36.7	158.9	22.4	32.5	28.6	n/a	675.0	45.5	19.6	126.0	39.8	59.5	67.2
CAGE 25µl	15-Jun-88	45	85	38.5	900	7.39	37.2	157.3	22.8	31.7	16.8	n/a	708.0	101.0	16.6	175.0	38.0	[112]	76.0
CAGE 25µl	15-Jun-88	60	85	38.5	900	7.38	36.5	159.6	21.6			n/a	558.0	147.0	15.0	178.0	31.4	91.0	70.6
CAGE 25µl	15-Jun-88	75	85	38.5	900	7.40	33.5	161.7	20.6	30.6	25.3	n/a	664.0	112.0	13.2	87.5	27.6	[171]	61.8
CAGE 25µl	15-Jun-88	90	90	38.5	900	7.37	37.9	161.0	21.8	30.7	26.2	n/a	609.0	126.0	11.6	150.0	22.2	73.5	58.6
CAGE 25µl	15-Jun-88	105	90	38.5	900	7.36	34.8	156.3	19.4	31.3	16.5	n/a	620.0	112.0	13.8	164.0	40.6	[101]	68.8
CAGE 25µl	15-Jun-88	120	85	38.5	900	7.34	38.6	152.1	20.8	29.5	21.2	n/a	620.0	110.0	13.8	130.0	42.0	80.0	64.0
CAGE 25µl	15-Jun-88	135										n/a							
CAGE 25µl	15-Jun-88	150										n/a							
CAGE 25µl	15-Jun-88	165										n/a							
CAGE 25µl	15-Jun-88	180										n/a							
CAGE 25µl	16-Aug-88	-120	90	38.3	675	7.42	37.9	117.4	24.5	43.3	61.3		35.0	147.0	15.8	136.0	41.0	21.0	76.0
CAGE 25µl	16-Aug-88	-105	85	38.0	675	7.42	36.7	102.3	23.8	39.7	54.2		35.0	126.0	16.8	161.0	46.0	21.0	79.6
CAGE 25µl	16-Aug-88	-90	90	38.0	675	7.39	39.1	129.8	23.6	42.4	66.2	1200.0	35.0	129.0	15.2	143.0	42.6	[7]	84.8
CAGE 25µl	16-Aug-88	-75	90	38.0	675									185.0	15.0	154.0	32.0	66.5	76.0
CAGE 25µl	16-Aug-88	-60	90	38.0	675	7.42	32.3	155.3	20.9	45.2	53.2	1240.0	35.0	206.0	15.2	150.0	36.4	49.0	73.2
CAGE 25µl	16-Aug-88	-45	90	38.0	675	7.35	40.1	161.2	21.9	38.5	69.9	1160.0	35.0	213.0	15.6	161.0	38.6	52.5	76.6
CAGE 25µl	16-Aug-88	-30	90	38.0	675	7.35	35.8	152.3	19.9	40.7	67.5	1200.0	35.0	147.0	15.8	142.0	43.0	59.5	73.8
CAGE 25µl	16-Aug-88	-15										1260.0		185.0	14.4	98.0	27.6	[14]	86.4
CAGE 25µl	16-Aug-88	0	90	38.0	675	7.38	44.1	147.3	25.9	43.1	101.0	1250.0	65.0	119.0	13.8	129.0	26.8	28.0	92.0
CAGE 25µl	16-Aug-88	15	90	38.0	675	7.33	42.7	138.9	22.6	53.2	68.1	1290.0	55.0	161.0	17.0	161.0	41.4	21.0	75.2
CAGE 25µl	16-Aug-88	30	90	38.0	675	7.32	39.4	145.2	20.3	40.6	87.2	1270.0		122.0	15.8	122.0	40.0	38.5	73.2
CAGE 25µl	16-Aug-88	45	95	38.0	675	7.38	34.8	158.2	20.4	58.6	85.0	1240.0	50.0	147.0	16.8	77.0	41.0	[67]	66.2
CAGE 25µl	16-Aug-88	60	95	38.0	675	7.37	40.2	166.0	23.0	57.8	[95]	1300.0	50.0	203.0	13.6	84.0	26.6	[70]	72.8
CAGE 25µl	16-Aug-88	75	95	38.3	675	7.34	44.5	177.0	23.8	61.2	[87]	1280.0	45.0	318.0	14.4	192.0	27.6	[150]	75.8
CAGE 25µl	16-Aug-88	90	97	38.8	750	7.40	33.6	181.3	20.2	47.4	[87]		40.0	378.0	13.6	255.0	28.4	[203]	79.2
CAGE 25µl	16-Aug-88	105	98	39.0	710	7.40	31.3	147.0	19.5	47.9	52.2	1270.0	40.0	364.0	15.0	115.0	39.0	[136]	72.0
CAGE 25µl	16-Aug-88	120	98	38.5	675	7.40	35.8	175.6	22.2	42.3	54.1	1180.0	35.0	392.0	13.6	238.0	26.6	[150]	76.4
CAGE 25µl	16-Aug-88	135	95	38.0	675	7.38	28.8	173.3	18.1	66.1	48.3	1180.0		430.0	16.8	318.0	37.2	[217]	68.8
CAGE 25µl	16-Aug-88	150	95	38.5	675					46.9	[87]	1090.0	35.0						
CAGE 25µl	16-Aug-88	165	95	39.0	675	7.36	39.0	153.9	22.1	47.3	38.7	1160.0	35.0						
CAGE 25µl	16-Aug-88	180	95	39.0	675	7.42	39.6	179.0	21.5	44.8	54.6	1280.0							
CAGE 25µl	20-Jul-88	-120	100	38.0	675	7.27	35.7	157.7	16.2										
CAGE 25µl	20-Jul-88	-105	100	38.5	675	7.42	38.4	141.8	16.5	56.2	69.7			147.0	19.8	231.0	49.0	84.0	78.8
CAGE 25µl	20-Jul-88	-90	100	38.5	675	7.23	38.9	119.5	16.3	48.1	71.2	1140.0	75.0	147.0	19.4	140.0	45.4	98.0	83.4
CAGE 25µl	20-Jul-88	-75	100	38.5	675	7.32	38.6	133.3	18.8	34.5	52.7	1140.0	60.0	294.0	19.8	238.0	43.8	126.0	89.4
CAGE 25µl	20-Jul-88	-60																	
CAGE 25µl	20-Jul-88	-45	100	38.5	675	7.28	30.2	124.5	14.0	38.2	56.0	1180.0	60.0	210.0	15.8	161.0	39.8	91.0	83.4
CAGE 25µl	20-Jul-88	-30	100	38.5	675	7.26	26.4	116.2	11.9	37.0	48.0	1200.0	60.0	182.0	18.6	182.0	47.0	77.0	82.4
CAGE 25µl	20-Jul-88	-15	100	38.5	675	7.33	33.0	112.3	17.4	38.2	75.4	1160.0	60.0	175.0	17.0	154.0	45.2	70.0	85.2
CAGE 25µl	20-Jul-88	0	115	38.5	675	7.40	36.1	138.0	22.2	79.1	73.6	1260.0	60.0						
CAGE 25µl	20-Jul-88	15	110	38.5	675	7.33	28.6	120.3	15.4	[54]	[105]	1300.0	60.0	181.0	17.4	147.0	46.0	70.0	81.8
CAGE 25µl	20-Jul-88	30	110	38.5	675	7.30	38.2	139.7	18.9	50.5	59.4	1400.0	60.0	203.0	18.6	168.0	44.2	98.0	81.6
CAGE 25µl	20-Jul-88	45	115	38.0	675	7.31	38.6	128.3	19.6	32.0	[78]	1240.0		147.0	18.0	154.0	42.2	42.0	74.4
CAGE 25µl	20-Jul-88	60	105	38.0	675	7.40	31.3	126.5	19.2	33.6	56.0	1300.0		161.0	17.0	119.0	44.8	63.0	78.4
CAGE 25µl	20-Jul-88	75	120	37.9	650	7.33	37.3	117.4	19.5	35.5	67.1	1360.0		203.0	18.0	161.0	49.8	49.0	80.6
CAGE 25µl	20-Jul-88	90	120	38.0	650	7.36	41.0	116.3	22.9	27.6	45.1	1100.0	60.0	112.0	18.0	126.0	43.6	28.0	82.4
CAGE 25µl	20-Jul-88	105	115	38.0	665	7.39	38.6	115.5	23.5	34.8	50.4	1220.0	60.0	112.0	15.0	147.0	46.8	28.0	74.8
CAGE 25µl	20-Jul-88	120	115	38.0	675	7.37	35.1	149.7	20.0	32.9	57.3	1300.0	60.0	161.0	14.4	126.0	47.0	35.0	80.2
CAGE 25µl	20-Jul-88	135	110	38.0	675	7.41	35.2	158.6	22.3	30.5	65.9	1300.0		105.0	16.2	147.0	45.2	14.0	80.0
CAGE 25µl	20-Jul-88	150	110	38.0	675	7.42	38.5	129.2	25.0	34.9	[77]	1280.0	60.0						
CAGE 25µl	20-Jul-88	165																	
CAGE 25µl	20-Jul-88	180																	
CAGE 50µl	3-Jun-88	-120	95	38.0	1200	7.27	40.6	125.2	18.5	44.3	47.2	n/a							
CAGE 50µl	3-Jun-88	-105	90	38.0	1200	7.25	40.7	127.1	17.9	39.5	58.7	n/a	346.0	91.0	18.2	175.0	41.8	56.0	63.2
CAGE 50µl	3-Jun-88	-90	100	38.0	1050	7.26	41.2	129.3	18.6	47.2	54.4	n/a	322.0	203.0	16.0	196.0	38.8	180.0	65.2
CAGE 50µl	3-Jun-88	-75	100	38.0	1050	7.26	34.3	133.6	15.2	40.7	55.8	n/a	371.0	157.0	12.8	189.0	36.4	66.5	63.4
CAGE 50µl	3-Jun-88	-60	80	38.0	900	7.25	45.5	131.0	19.7	37.6	52.6	n/a	353.0	210.0	13.0	126.0	37.2	105.0	68.2
CAGE 50µl	3-Jun-88	-45	75	37.5	900	7.28	45.4	132.8	21.3	61.4	39.5	n/a	391.0	143.0	12.6	154.0	39.2	84.0	66.6
CAGE 50µl	3-Jun-88	-30	90	37.0	900	7.28	59.0	126.6	27.8	55.5	48.3	n/a	366.0	129.0	19.6	203.0	40.6	52.5	64.0
CAGE 50µl	3-Jun-88	-15	80	37.0	900	7.31	48.7	129.3	24.2	57.5	66.6	n/a	360.0	108.0	18.0	192.0	36.8	87.5	66.8
CAGE 50µl	3-Jun-88	0	80	37.5	900	7.25	51.7	117.8	22.8	99.4	113.2	n/a	365.0	168.0	19.0	171.0	37.0	129.0	67.8
CAGE 50µl	3-Jun-88	15	70	37.0	1200	7.27	51.7	112.0	23.8	42.7	57.9	n/a	420.0	42.0	11.6	315.0	17.4	28.0	24.6
CAGE 50µl	3-Jun-88	30	60	37.0	1200	7.29	47.8	124.0	22.8	21.4	30.9	n/a	421.0	52.5	12.0	175.0	19.0	31.5	25.0
CAGE 50µl	3-Jun-88	45	60	37.0	900	7.27	50.4	127.7	23.1			n/a	345.0	31.5	10.8	115.0	16.2	87.5	25.6
CAGE 50µl	3-Jun-88	60	65	37.0	900	7.28	47.7	126.8	22.2	35.6	41.0	n/a	350.0	17.5	11.0	875.0	17.8	59.5	26.6
CAGE 50µl	3-Jun-88	75	80	37.0	900	7.24	47.7	128.0	20.4	50.8	58.4	n/a	336.0	21.0	10.8	150.0	16.8	101.0	29.2
CAGE 50µl	3-Jun-88	90	80	37.0	900	7.24	49.8	131.5	21.2	53.0	60.6	n/a	328.0	10.5	9.6	203.0	15.0	140.0	24.4
CAGE 50µl	3-Jun-88	105	80	37.0	1050	7.25	49.2	127.8	21.2	53.9	75.7	n/a	332.0	-7.0	9.6	255.0	16.2	147.0	27.4
CAGE 50µl	3-Jun-88	120	80	37.5	1050	7.25	50.6	128.7	22.1	40.4	61.0	n/a	365.0	28.0	10.0	140.0	16.8	133.0	29.8
CAGE 50µl	3-Jun-88	135	60	37.5	1500	7.26	47.5	131.2	21.3	27.6	40.5	n/a	334.0	10.5	10.8	164.0	16.4	63.0	26.8
CAGE 50µl	3-Jun-88	150	75	38.0	900	7.23	47.3	118.8	19.9	47.2	84.5	n/a	377.0	28.0	9.6	122.0	13.8	105.0	23.0
CAGE 50µl	3-Jun-88	165	75	38.0	900	7.23	51.2	124.2	21.5	39.9	[87]	n/a	357.0	42.0	9.8	161.0	16.8	101.0	25.8
CAGE 50µl	3-Jun-88	180										n/a							
CAGE 50µl	2-Jun-88	-120	95	39.0	900	7.38	40.6	169.4	23.9	157.0		n/a							
CAGE 50µl	2-Jun-88	-105	95	39.0	900	7.34	39.4	169.5	21.3	103.1		n/a							
CAGE 50µl	2-Jun-88	-90	95	39.0	900	7.37	40.3	173.0	23.2	85.1		n/a	406.0	63.0	20.4	119.0	39.0	52.5	72.4
CAGE 50µl	2-Jun-88	-75	95	39.0	900	7.36	42.3	173.0	23.6	77.6	[221]	n/a							
CAGE 50µl	2-Jun-88	-60	95	39.0	900	7.38	40.6	173.6	24.2	101.5	114.2	n/a	437.0	38.5	12.8	140.0	40.8	77.0	77.2
CAGE 50µl	2-Jun-88	-45	90	39.0	900	7.38	38.5	156.7	22.5	83.2	89.6	n/a	419.0	35.0	12.6	91.0	40.2	59.5	73.0
CAGE 50µl	2-Jun-88	-30	90	39.0	900	7.32	34.4	164.3	20.2	77.7	68.7	n/a	403.0	94.5	16.8	84.0	38.8	105.0	73.4
CAGE 50µl	2-Jun-88	-15	90	38.5	900	7.36	43.2	148.2	24.6	83.3	89.3	n/a	384.0	101.0	17.4	52.5	40.0	112.0	68.6
CAGE 50µl	2-Jun-88	0	95	38.5	900	7.35	45.1	147.7	24.9	77.2		n/a	420.0	59.5	12.2	38.4	39.8	42.0	68.4
CAGE 50µl	2-Jun-88	15	95	38.5	900	7.37	41.3	152.9	23.6	68.3	66.4	n/a	414.0	60.0	18.0	70.0	48.0	15.0	80.0
CAGE 50µl	2-Jun-88	30	100	39.0	900	7.38	43.8	153.5	24.9	64.3	99.8	n/a	432.0	28.0	18.2	80.5	50.4	28.0	75.6
CAGE 50µl	2-Jun-88	45	100	39.0	900	7.36	44.2	150.5	24.8	60.4	100.4	n/a	431.0	35.0	19.6	77.0	40.8	[7]	71.0
CAGE 50µl	2-Jun-88	60	100	39.0	900	7.36	45.1	147.8	25.7	68.9	86.6	n/a	441.0	10.5	11.4	[3.5]	42.4	38.5	69.4
CAGE 50µl	2-Jun-88	75	100	38.5	900	7.36	44.8	139.4	25.4	65.0	109.8	n/a	445.0	105.0	11.8	101.0	40.8	45.5	68.6
CAGE 50µl	2-Jun-88	90	100	38.5	1050	7.36	44.7	146.1	25.3	58.2	77.6	n/a	402.0						
CAGE 50µl	2-Jun-88	105	100	39.0	1200	7.33	44.1	148.1	23.1	52.5		n/a	444.0						
CAGE 50µl	2-Jun-88	120	100	39.0	1200	7.33	42.5	148.5	22.2	49.5	65.4	n/a	420.0						
CAGE 50µl	2-Jun-88	135	100	39.0	1200	7.33	38.2	151.1	20.2	47.0	77.7	n/a	446.0						
CAGE 50µl	2-Jun-88	150	100	39.0	1200	7.37	42.7	149.0	23.8	50.7	62.9	n/a	437.0						
CAGE 50µl	2-Jun-88	165	100	39.0	1200	7.34	42.2	147.4	22.7	47.4	60.3	n/a	422.0						
CAGE 50µl	2-Jun-88	180	95	39.0	1200	7.35	42.0	154.0	23.2	44.7	62.0	n/a	429.0						

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 100µl	1-Jun-88	-120			1050	7.29	41.5	133.0	19.9	86.5		n/a	n/a						
CAGE 100µl	1-Jun-88	-105	100	39.0	1200	7.30	38.9	149.0	19.2	77.3		n/a	n/a						
CAGE 100µl	1-Jun-88	-90	105	39.0	1200	7.32	35.3	151.0	18.1	81.3		n/a	n/a	287.0	22.8	189.0	45.0	133.0	83.4
CAGE 100µl	1-Jun-88	-75	90	39.0	1200	7.32	39.4	147.0	20.2	51.5	83.7	n/a	n/a	198.0	17.6	273.0	43.0	133.0	81.8
CAGE 100µl	1-Jun-88	-60	90	38.5	1200	7.30	41.4	155.0	20.4	104.9	116.8	n/a	n/a	286.0	21.8	119.0	47.6	168.0	88.8
CAGE 100µl	1-Jun-88	-45	90	38.0	1200	7.32	39.3	157.0	20.1	98.4	100.8	n/a	n/a	315.0	18.4	252.0	47.8	105.0	92.4
CAGE 100µl	1-Jun-88	-30	90	38.5	1200	7.30	38.5	152.0	18.8	77.5	84.0	n/a	n/a	188.0	19.6	322.0	47.2	91.0	81.0
CAGE 100µl	1-Jun-88	-15	90	38.5	1200	7.30	40.5	158.0	19.9	81.7	85.0	n/a	n/a	343.0	17.8	203.0	45.4	42.0	81.6
CAGE 100µl	1-Jun-88	0	95	38.0	1200	7.31	39.3	158.0	19.7	78.0	73.0	n/a	n/a						
CAGE 100µl	1-Jun-88	15	90	38.0	1200	7.29	36.9	154.0		83.6	84.0	n/a	n/a						
CAGE 100µl	1-Jun-88	30	90	38.0	1200					93.1	86.0	n/a	n/a						
CAGE 100µl	1-Jun-88	45	90	38.0	1200	7.29	44.3	156.0	21.3	91.9	82.0	n/a	n/a						
CAGE 100µl	1-Jun-88	60	95	38.0	1200	7.30	45.5	158.0	22.4	71.4	78.0	n/a	n/a						
CAGE 100µl	1-Jun-88	75	90	37.5	1350	7.31	42.2	164.0	21.2	82.8	83.0	n/a	n/a						
CAGE 100µl	1-Jun-88	90										n/a	n/a						
CAGE 100µl	1-Jun-88	105	90			7.36	31.9	161.0	18.2			n/a	n/a						
CAGE 100µl	1-Jun-88	120										n/a	n/a						
CAGE 100µl	1-Jun-88	135										n/a	n/a						
CAGE 100µl	1-Jun-88	150										n/a	n/a						
CAGE 100µl	1-Jun-88	165										n/a	n/a						
CAGE 100µl	1-Jun-88	180										n/a	n/a						
CAGE 100µl	20-Apr-88	-120	80	36.0	825	7.31	29.5	156.6	15.0										
CAGE 100µl	20-Apr-88	-105	75	75.0	825	7.31	33.0	164.2	16.5		85.7								
CAGE 100µl	20-Apr-88	-90	85	85.0	825	7.30	33.3	158.2	16.3										
CAGE 100µl	20-Apr-88	-75	80	80.0	825	7.33	28.9	164.0	15.2	[107]	50.7	n/a	n/a						
CAGE 100µl	20-Apr-88	-60	90	90.0	750	7.29	35.9	174.3	17.1	77.1		n/a	n/a						
CAGE 100µl	20-Apr-88	-45	80	80.0	750	7.26	32.5	160.3	14.6		46.9	n/a	n/a						
CAGE 100µl	20-Apr-88	-30	80	80.0	675	7.21	37.8	160.1	15.2	76.4	82.7	n/a	n/a						
CAGE 100µl	20-Apr-88	-15	80	80.0	675	7.22	34.3	153.0	14.6	69.2	71.3	n/a	n/a						
CAGE 100µl	20-Apr-88	0	80	80.0	675	7.23	34.4	147.2	14.4		111.4	n/a	n/a						
CAGE 100µl	20-Apr-88	15	94	94.0	675	7.24	32.2	184.4	13.8	50.5	130.1	n/a	n/a						
CAGE 100µl	20-Apr-88	30	90	90.0	675	7.25	43.9	155.9	19.0	56.0	91.1	n/a	n/a						
CAGE 100µl	20-Apr-88	45	90	37.5	675	7.20	52.8	141.3	20.8	62.1	136.6	n/a	n/a						
CAGE 100µl	20-Apr-88	60	160	37.0	675	7.25	48.2	157.5	21.1			n/a	n/a						
CAGE 100µl	20-Apr-88	75										n/a	n/a						
CAGE 100µl	20-Apr-88	90										n/a	n/a						
CAGE 100µl	20-Apr-88	105										n/a	n/a						
CAGE 100µl	20-Apr-88	120										n/a	n/a						
CAGE 100µl	20-Apr-88	135										n/a	n/a						
CAGE 100µl	20-Apr-88	150										n/a	n/a						
CAGE 100µl	20-Apr-88	165										n/a	n/a						
CAGE 100µl	20-Apr-88	180										n/a	n/a						
CAGE 100µl	22-Apr-88	-120	100	38.0	650	7.38	41.2	170.6	24.2			n/a	n/a						
CAGE 100µl	22-Apr-88	-105	98	37.5	650	7.38	39.4	179.8	23.1			n/a	n/a						
CAGE 100µl	22-Apr-88	-90	80	38.0	1000	7.38	32.9	169.6	19.5	37.1	41.7	n/a	n/a						
CAGE 100µl	22-Apr-88	-75	90	37.8	1050	7.36	31.4	135.7	17.7	44.7	67.8	n/a	n/a						
CAGE 100µl	22-Apr-88	-60	70	38.5	1500	7.39	27.6	118.3	16.7	51.3	35.8	n/a	n/a						
CAGE 100µl	22-Apr-88	-45	90	37.0	1500	7.36	26.6	134.7	15.0	46.0	60.9	n/a	n/a						
CAGE 100µl	22-Apr-88	-30	80	37.5	900	7.33	28.9	115.9	15.3	61.7	64.2	n/a	n/a						
CAGE 100µl	22-Apr-88	-15	80	37.5	750	7.33	34.5	131.1	18.1	82.1	111.4	n/a	n/a						
CAGE 100µl	22-Apr-88	0	80	37.5	525	7.35	34.6	133.9	19.0	80.7	83.9	n/a	n/a						
CAGE 100µl	22-Apr-88	15	105	37.5	525	7.34	39.6	108.0	21.4	146.6		n/a	n/a						
CAGE 100µl	22-Apr-88	30	90	37.0	300	7.25	42.8	56.0	18.9	86.0	79.5	n/a	n/a						
CAGE 100µl	22-Apr-88	45	90	37.0	900	7.42	26.3	140.5	16.9	53.3	46.8	n/a	n/a						
CAGE 100µl	22-Apr-88	60	90	37.0	750	7.42	29.6	110.2	18.8	66.7	57.4	n/a	n/a						
CAGE 100µl	22-Apr-88	75	90	37.0	500	7.32	39.1	163.1	20.3	110.2	115.7	n/a	n/a						
CAGE 100µl	22-Apr-88	90										n/a	n/a						
CAGE 100µl	22-Apr-88	105										n/a	n/a						
CAGE 100µl	22-Apr-88	120										n/a	n/a						
CAGE 100µl	22-Apr-88	135										n/a	n/a						
CAGE 100µl	22-Apr-88	150										n/a	n/a						
CAGE 100µl	22-Apr-88	165										n/a	n/a						
CAGE 100µl	22-Apr-88	180										n/a	n/a						
CAGE 200µl	21-Apr-88	-120	110	39.0		7.44	40.6	176.5	27.9	76.3		n/a	n/a						
CAGE 200µl	21-Apr-88	-105	100	39.0		7.44	37.4	175.3	25.8	91.9		n/a	n/a						
CAGE 200µl	21-Apr-88	-90	100	39.0		7.47	37.9	176.6	27.4	81.3		n/a	n/a						
CAGE 200µl	21-Apr-88	-75	100	39.0		7.45	40.3	179.1	27.8	65.0		n/a	n/a						
CAGE 200µl	21-Apr-88	-60	100	39.0		7.46	33.5	187.0	23.9	84.6	113.0	n/a	n/a						
CAGE 200µl	21-Apr-88	-45	100	39.0		7.45	33.2	182.0	23.2	115.1		n/a	n/a						
CAGE 200µl	21-Apr-88	-30	90	39.0		7.46	40.4	185.0	28.4	99.6	133.5	n/a	n/a						
CAGE 200µl	21-Apr-88	-15	100	39.0		7.45	36.5	191.8	26.4	68.9	99.4	n/a	n/a						
CAGE 200µl	21-Apr-88	0	100	38.5		7.45	37.2	152.5	25.5			n/a	n/a						
CAGE 200µl	21-Apr-88	15	100	38.5		7.47	32.8	168.5	23.8	92.1		n/a	n/a						
CAGE 200µl	21-Apr-88	30	100	38.5		7.43	36.8	166.5	24.6	98.1	[294]	n/a	n/a						
CAGE 200µl	21-Apr-88	45	100	38.5		7.43	38.3	167.9	26.0	54.3	141.1	n/a	n/a						
CAGE 200µl	21-Apr-88	60	100	38.5		7.43	41.6	158.4	27.5	55.9	142.9	n/a	n/a						
CAGE 200µl	21-Apr-88	75	100	38.5		7.46	31.7	174.1	22.5	45.4	106.8	n/a	n/a						
CAGE 200µl	21-Apr-88	90										n/a	n/a						
CAGE 200µl	21-Apr-88	105										n/a	n/a						
CAGE 200µl	21-Apr-88	120										n/a	n/a						
CAGE 200µl	21-Apr-88	135										n/a	n/a						
CAGE 200µl	21-Apr-88	150										n/a	n/a						
CAGE 200µl	21-Apr-88	165										n/a	n/a						
CAGE 200µl	21-Apr-88	180										n/a	n/a						
CAGE 200µl	9-Nov-88	-120										n/a	n/a						
CAGE 200µl	9-Nov-88	-105										n/a	n/a						
CAGE 200µl	9-Nov-88	-90										n/a	n/a						
CAGE 200µl	9-Nov-88	-75	110	39.0	600	7.21	[52]	169.0	20.6	157.0	143.0	n/a	n/a	406.0	18.0	518.0	33.0	217.0	65.0
CAGE 200µl	9-Nov-88	-60	115	38.6	600	7.33	48.3	164.0	25.6	88.0	139.0	n/a	n/a	441.0	19.0	336.0	38.0	126.0	75.0
CAGE 200µl	9-Nov-88	-45	110	38.5	600	7.37	39.0	197.0	22.4	117.0	154.0	n/a	n/a	497.0	19.0	357.0	43.0	147.0	73.0
CAGE 200µl	9-Nov-88	-30	110	38.5	600	7.31	41.5	144.0	21.0	71.0	95.0	n/a	n/a	511.0	18.0	398.0	36.0	238.0	71.0
CAGE 200µl	9-Nov-88	-15	100	38.4	600	7.32	47.4	171.0	24.5	67.0	110.0	n/a	n/a	525.0	19.0	483.0	38.0	42.0	69.0
CAGE 200µl	9-Nov-88	0	100	38.1	600					170.0	131.0	n/a	n/a	546.0	18.0	441.0	37.0	126.0	65.0
CAGE 200µl	9-Nov-88	15	100	38.5	600	7.31	44.0	160.0	22.2	223.0	135.0	n/a	n/a	245.0	18.0	147.0	32.0	175.0	61.0
CAGE 200µl	9-Nov-88	30	100	38.5	600	7.36	36.1	199.4	20.5	75.0	105.0	n/a	n/a	210.0	19.0	168.0	36.0	91.0	70.0
CAGE 200µl	9-Nov-88	45	100	38.5	575	7.36	43.9	193.4	25.0	80.0	104.0	n/a	n/a						
CAGE 200µl	9-Nov-88	60	100	38.5	575	7.34	39.6	198.7	21.7	91.0	128.0	n/a	n/a	112.0	18.0	182.0	37.0	56.0	60.0
CAGE 200µl	9-Nov-88	75	100	38.5	575	7.34	41.0	186.7	22.1	76.0	107.0	n/a	n/a	126.0	18.0	308.0	39.0	49.0	68.0
CAGE 200µl	9-Nov-88	90	100	38.5	575	7.33	39.4	191.1	20.5	76.0	112.0	n/a	n/a	105.0	18.0	84.0	37.0	84.0	67.0
CAGE 200µl	9-Nov-88	105	100	38.5	575	7.32	41.5	192.0	21.5	69.0	113.0	n/a	n/a	119.0	19.0	91.0	35.0	35.0	73.0
CAGE 200µl	9-Nov-88	120	90	38.5	575	7.32	44.4	184.1	22.8	81.0	121.0	n/a	n/a	49.0	15.0	182.0	28.0	49.0	78.0
CAGE 200µl	9-Nov-88	135	90	38.5	575	7.31	42.3	185.8	21.2	68.0	94.0	n/a	n/a	63.0	16.0	147.0	35.0	98.0	66.0
CAGE 200µl	9-Nov-88	150	85	38.5	575	7.32	43.4	181.8	22.5	64.0	103.0	n/a	n/a						
CAGE 200µl	9-Nov-88	165	85	38.5	575	7.30	45.3	182.0	22.3	55.0	90.0	n/a	n/a						
CAGE 200µl	9-Nov-88	180										n/a	n/a						

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 200µl	19-Oct-88	-120																	
CAGE 200µl	19-Oct-88	-105																	
CAGE 200µl	19-Oct-88	-90	110	38.0	500	7.38	40.3	141.8	21.3	52.6	52.8	2730.0	1065.0	[19]	[392]	[40]	[2]	[7]	[73]
CAGE 200µl	19-Oct-88	-75	110	38.0	500	7.37	40.4	160.4	23.3	59.7	[23.17]	2440.0	1030.0	[378]	[19]	[280]	[42]	[154]	[78]
CAGE 200µl	19-Oct-88	-60	105	38.0	500	7.37	44.4	141.1	25.4	45.6	[24.63]		392.0	[19]	[301]	[39]	[18]	[71]	[71]
CAGE 200µl	19-Oct-88	-45	100	38.0	500	7.36	44.9	139.7	25.3	50.7	46.4	2675.0	1145.0	[19]	[301]	[38]	[16]	[79]	[79]
CAGE 200µl	19-Oct-88	-30	100	38.0	500	7.36	39.0	150.9	22.0	42.0	47.8	2645.0	1530.0						
CAGE 200µl	19-Oct-88	-15	100	38.0	500	7.39	32.7	178.9	19.7	68.5	51.2	2650.0	1300.0	[581]	[19]	[43]	[40]	[175]	[69]
CAGE 200µl	19-Oct-88	0	100	37.5	500	7.36	37.0	155.3	20.3	68.0	61.8	2790.0	1205.0	189.0	12.6	175.0	27.4	84.0	70.8
CAGE 200µl	19-Oct-88	15	100	37.5	500	7.33	40.9	155.7	21.5	50.7	51.5	2700.0	1200.0	357.0	16.0	357.0	28.8	126.0	71.8
CAGE 200µl	19-Oct-88	30	100	37.5	500	7.31	38.1	154.8	19.1	43.6	51.8	2685.0	1240.0	420.0	15.4	364.0	28.0	77.0	62.0
CAGE 200µl	19-Oct-88	45	100	37.5	500	7.32	38.5	158.0	19.7	57.2	63.3	2860.0	1260.0	469.0	16.0	392.0	29.8	119.0	66.2
CAGE 200µl	19-Oct-88	60	100	37.5	500	7.35	38.4	155.0	21.0	56.1	71.2	2870.0	1265.0	392.0	15.6	273.0	29.0	189.0	67.2
CAGE 200µl	19-Oct-88	75	95	37.5	500	7.31	38.2	156.7	19.0	54.2	75.8	2440.0	1265.0	455.0	15.8	350.0	29.0	168.0	71.8
CAGE 200µl	19-Oct-88	90	95	37.5	500	7.36	36.2	181.5	20.4	58.4	45.8	2245.0	1220.0	490.0	16.4	322.0	30.4	119.0	63.6
CAGE 200µl	19-Oct-88	105	90	37.5	500	7.37	42.9	168.5	24.7	74.0	60.4	2090.0	1245.0	371.0	19.0	336.0	35.8	147.0	68.6
CAGE 200µl	19-Oct-88	120	90	37.5	500	7.34	42.2	161.2	22.9	36.7	35.4	1520.0	1285.0	490.0	17.0	371.0	29.6	154.0	63.8
CAGE 200µl	19-Oct-88	135	85	38.0	500	7.34	44.0	161.0	23.4	43.6	59.8	1700.0		287.0	16.2	245.0	28.6	105.0	72.4
CAGE 200µl	19-Oct-88	150	85	38.0	500	7.34	39.5	160.4	21.1			1700.0		231.0	16.4	210.0	29.0	126.0	73.0
CAGE 200µl	19-Oct-88	165	90	38.0	500	7.34	41.4	160.8	20.0										
CAGE 200µl	19-Oct-88	180	90	38.0	500	7.28	42.8	156.7	20.0										
CAGE 400µl	27-Apr-89	-120																	
CAGE 400µl	27-Apr-89	-105																	
CAGE 400µl	27-Apr-89	-90																	
CAGE 400µl	27-Apr-89	-75																	
CAGE 400µl	27-Apr-89	-60																	
CAGE 400µl	27-Apr-89	-45	90	39.0	825	7.24	36.1	126.7	15.5				470.0	602.0	15.0	357.0	35.0	175.0	81.0
CAGE 400µl	27-Apr-89	-30	92	38.5	825	7.30	44.2	132.8	21.8			1490.0	440.0	273.0	16.0	329.0	40.0	259.0	78.0
CAGE 400µl	27-Apr-89	-15	92	39.0	825	7.32	40.0	124.8	20.6			1616.0	320.0	[168]	17.8	[203]	43.0	[105]	97.4
CAGE 400µl	27-Apr-89	0	90	39.0	825	7.39	30.6	124.3	18.6			1395.0	410.0	147.0	12.8	175.0	43.0	70.0	86.8
CAGE 400µl	27-Apr-89	15	90	38.0	825	7.34	44.0	135.0	24.0					140.0	19.0	203.0	43.0	98.0	73.0
CAGE 400µl	27-Apr-89	30	80	37.0	825	7.31	42.1	134.5	21.1					91.0	20.0	203.0	42.0	91.0	80.0
CAGE 400µl	27-Apr-89	45	76	37.0	825	7.28	35.3	132.2	16.5					49.0	20.0	112.0	44.0	63.0	27.0
CAGE 400µl	27-Apr-89	60	80	37.0	825	7.34	44.0	136.0	24.0					21.0	15.0	49.0	32.0	21.0	90.0
CAGE 400µl	27-Apr-89	75	80	37.0	825	7.29	47.0	122.0	23.0			1300.0	440.0	21.0	21.0	14.0	45.4	28.0	66.2
CAGE 400µl	27-Apr-89	90	76	37.0	900	7.37	34.0	123.0	20.0			1310.0	450.0	21.0	14.0	28.0	37.0	14.0	86.0
CAGE 400µl	27-Apr-89	105	80	37.0	900	7.29	42.7	118.5	20.3					14.0	13.0	28.0	17.2	42.0	36.4
CAGE 400µl	27-Apr-89	120	84	37.5	900	7.27	44.7	133.2	20.5					-7.0	12.0	49.0	18.0	28.0	42.0
CAGE 400µl	27-Apr-89	135	78	37.0	900	7.37	39.0	126.3	22.2					21.0	9.4	70.0	16.0	42.0	36.0
CAGE 400µl	27-Apr-89	150	84	37.0	900	7.36	34.1	129.4	19.2					0.0	9.2	91.0	16.0	28.0	38.0
CAGE 400µl	27-Apr-89	165	90	37.0	900	7.37	40.6	127.9	23.3					0.0	9.6	84.0	15.0	77.0	38.0
CAGE 400µl	27-Apr-89	180	82	37.0	900	7.38	41.9	134.6	24.5							35.0	32.0	7.0	68.0
CAGE 400µl	11-Aug-89	-120	75	38.7	936	7.28	35.0	174.7	16.1	40.0	98.0	1490.0	410.0	436.3	14.9	394.0	34.2	125.2	78.4
CAGE 400µl	11-Aug-89	-105	75	38.6	900	7.23	35.5	175.4	14.7	34.0	75.0	1500.0	340.0	437.0	15.5	407.0	33.1	136.2	85.2
CAGE 400µl	11-Aug-89	-90	75	38.5	810	7.34	35.0	177.0	18.6	27.9	103.0	1510.0		460.7	14.3	365.0	31.5	186.6	80.3
CAGE 400µl	11-Aug-89	-75	75	38.6	774	7.32	35.4	177.4	19.1	35.7	85.0	1470.0		449.0	16.1	338.0	33.7	150.2	94.8
CAGE 400µl	11-Aug-89	-60	75	38.6	774	7.46	35.0	176.0	18.3	31.4		1490.0	400.0	346.3	14.5	263.3	36.7	142.6	43.8
CAGE 400µl	11-Aug-89	-45	75	38.6	774	7.31	35.6	175.9	19.0	27.6	52.0	1410.0		456.0	15.5	354.3	32.6	146.7	91.0
CAGE 400µl	11-Aug-89	-30	75	38.6	756	7.30	38.5	171.1	19.4	35.1	54.0	1020.0	390.0	371.0	15.0	243.7	32.9	139.8	84.2
CAGE 400µl	11-Aug-89	-15	75	38.6	756	7.30	36.9	167.9	18.2	37.4	125.0	1470.0	400.0	433.7	13.5	253.0	38.3	148.0	94.8
CAGE 400µl	11-Aug-89	0	75	38.4	756	7.24	39.1	117.1	16.8	32.4	73.0			0.0	0.0	0.0	0.0	0.0	0.0
CAGE 400µl	11-Aug-89	15	75	38.3	720	7.20	49.4	109.8	19.6	47.8	39.5	1590.0		143.3	12.1	76.8	37.4	56.7	98.0
CAGE 400µl	11-Aug-89	30	75	38.6	720	7.25	45.0	150.7	19.0	37.5	28.8	1170.0	550.0	89.8	17.9	9.9	41.0	58.8	97.8
CAGE 400µl	11-Aug-89	45	75	39.0	720	7.28	39.9	172.5	18.5	30.5	27.4	1140.0		84.0	19.6	91.0	41.9	51.1	100.2
CAGE 400µl	11-Aug-89	60	75	39.2	810	7.33	38.2	181.1	19.9	21.8	15.4	1070.0	500.0	68.3	21.3	59.5	48.7	31.5	114.8
CAGE 400µl	11-Aug-89	75	75	38.8	810	7.28	36.2	188.2	16.9	25.1	25.1	1200.0	500.0	45.5	19.8	45.5	34.2	14.0	120.2
CAGE 400µl	11-Aug-89	90	75	38.5	810	7.33	35.3	193.6	18.7	35.1	30.5	1170.0	475.0	92.2	18.5	66.5	42.5	63.6	98.4
CAGE 400µl	11-Aug-89	105	75	38.3	774	7.29	36.9	193.6	17.8	26.8	27.4	1180.0		73.5	15.1	473.8	41.2	43.4	94.6
CAGE 400µl	11-Aug-89	120	75	38.4	774	7.31	39.2	192.1	19.7	28.8	28.8	1200.0		85.2	11.9	66.6	42.3	40.6	96.0
CAGE 400µl	11-Aug-89	135	75	38.5	756	7.31	37.0	195.2	18.4	20.6	20.1	1230.0	470.0	103.7	11.9	82.8	40.0	49.0	98.0
CAGE 400µl	11-Aug-89	150	75	38.6	756		35.0			30.9	30.0	1220.0	470.0	66.5	14.6	77.0	39.4	37.1	99.4
CAGE 400µl	11-Aug-89	165	75	38.6	756	7.32	38.1	185.0	19.5	26.2	26.2	1250.0		78.2	13.3	58.3	38.1	49.0	89.6
CAGE 400µl	11-Aug-89	180	75	38.7	720	7.37	35.5	182.1	20.4			1350.0		30.0	9.0	36.0	26.0	24.5	49.0
CAGE 400µl	14-Aug-89	-120	80	39.4	900	7.37	40.8	173.7	23.4	[60]	[52]	2870.0	550.0	368.0	14.0	233.0	32.0	149.0	66.0
CAGE 400µl	14-Aug-89	-105	75	39.3	900		38.0					2865.0		297.0	13.0	251.0	29.0	132.0	80.0
CAGE 400µl	14-Aug-89	-90	75	39.3	900	7.39	36.7	183.3	21.9	[35]	[26]	2875.0	520.0	375.0	15.0	287.0	31.0	163.0	80.0
CAGE 400µl	14-Aug-89	-75	75	39.3	900	7.42	40.0	157.0	23.8	[45]	[33]	2865.0	520.0	406.0	15.0	316.0	30.0	184.0	79.0
CAGE 400µl	14-Aug-89	-60	70	39.5	900	7.42	35.0	167.0		[28]	[24]	2900.0	545.0	337.0	13.0	260.0	25.0	168.0	88.0
CAGE 400µl	14-Aug-89	-45	70	39.2	900	7.44	33.4	128.5	22.8	[35]	[24]	2870.0	525.0	353.0	14.0	305.0	30.0	174.0	79.0
CAGE 400µl	14-Aug-89	-30	75	39.2	900	7.40	37.2	177.8	22.8	[39]	[37]	2870.0	520.0	408.0	14.0	309.0	28.0	161.0	90.0
CAGE 400µl	14-Aug-89	-15	75	39.2	900	7.49	36.7	175.3	27.6	[45]	[47]	2850.0	540.0	468.0	15.0	351.0	33.0	196.0	86.0
CAGE 400µl	14-Aug-89	0	75	39.2	882	7.49	38.4	181.4	29.2	[99]	[44]	2590.0	870.0	73.5	14.0	80.5	33.0	0.0	0.0
CAGE 400µl	14-Aug-89	15	75	39.2	882	7.41	37.3	174.9	23.6	59.3	60.1	2870.0	635.0	291.0	17.0	288.0	33.0	99.0	99.0
CAGE 400µl	14-Aug-89	30	70	39.2	882	7.41	35.0	172.2	21.7	52.0	60.0	2790.0	600.0	312.0	17.0	253.0	34.0	91.0	96.0
CAGE 400µl	14-Aug-89	45	60	39.2	882	7.40	38.6	171.5	23.6	50.3	58.0	2745.0	510.0	270.0	17.0	280.0	32.0	43.0	91.0
CAGE 400µl	14-Aug-89	60	60	39.2		7.44	36.0	167.7	24.4	62.8	53.9	2850.0	510.0	269.0	16.0	240.0	33.0	91.0	103.0
CAGE 400µl	14-Aug-89	75	60	39.2		7.44	37.7	176.5	25.3	61.1	69.3	2680.0	520.0	263.3	14.0	223.0	31.0	82.0	82.0
CAGE 400µl	14-Aug-89	90	65	39.1		7.45	37.7	190.1	26.1	40.5	65.0	2600.0	520.0	338.0	16.3	263.3	31.6	106.9	80.3
CAGE 400µl	14-Aug-89	105	50	39.1		7.39	36.7	179.1	22.4	69.3	59.3	2500.0	535.0	346.3	12.5	334.7	25.3	103.6	85.5
CAGE 400µl	14-Aug-89	120	50	39.1		7.40	38.0	173.4	23.6	52.1	63.6	2550.0	535.0	399.0	13.0	253.0	28.0	172.0	71.0
CAGE 400µl	14-Aug-89	135	50	39.1	864	7.41	39.7	160.0	25.0			2530.0	540.0	422.0	13.0	342.0	28.0	143.0	76.0
CAGE 400µl	14-Aug-89	150	50	39.1	900	7.41	39.0	172.7	24.5			2515.0	510.0	431.0	14.0	322.0	30.0	158.0	67.0
CAGE 400µl	14-Aug-89	165	50	39.1	900	7.47	36.7	178.0	26.6			2520.0	510.0	358.0	14.0	317.0	29.0	137.0	68.0
CAGE 400µl	14-Aug-89	180	50	39.0		7.69	42.7	138.3				2500.0		316.0	13.0	308.0	27.0	137.8	75.8
CAGE 400µl	25-Jul-89	-120	80	38.4	720	7.34	42.8	177.1	23.1	[24]	110.0			436.0	12.4	404.3	37.2	255.4	82.1
CAGE 400µl	25-Jul-89	-105	80	38.8	774	7.36	42.5	172.0	23.8	[28]	105.0	1280.0	600.0	376.6	14.3	320.7	36.5	262.4	83.6
CAGE 400µl	25-Jul-89	-90	80	39.3	810	7.38	38.1	174.2	22.4	40.5	134.3	1350.0	610.0	352.0	13.0	266.0	32.0	198.0	87.0
CAGE 400µl	25-Jul-89	-75	80	39.5	810	7.36	38.3	158.9	21.4	34.1	97.2	1430.0	615.0	409.3	15.9	346.3	37.1	184.0	78.0
CAGE 400µl	25-Jul-89	-60	80	39.3	810	7.34	42.0	150.6	22.6	32.8	129.2	1300.0	610.0	380.0	15.3	315.7	34.0	184.0	84.0
CAGE 400µl	25-Jul-89	-45	80	39.0	810	7.32	46.0	152.0	24.0	43.0	123.2	1250.0	612.5	313.2	17.2	315.4	43.6	119.0	84.0
CAGE 400µl	25-Jul-89	-30	80	39.0	756	7.34	35.4	155.1	19.1	47.3	102.9	1270.0	615.0	291.3	15.7	220.3	40.2	149.6	82.3
CAGE 400µl	25-Jul-89	-15	80	39.0	774	7.32	44.6	155.5	22.7	60.6	96.1	1300.0	622.5	274.0	13.5	228.3	39.0	146.3	83.8
CAGE 400µl	25-Jul-89	0	90	38.9	810	7.28	44.7	134.0	21.0		75.8	1220.0	945.0	0.0	0.0	0.0	0.0	0.0	0.0
CAGE 400µl	25-Jul-89	15	85	38.7	810	7.34	41.3	166.0	22.4	52.8	91.6	1220.0	700.0	204.0	19.7	152.7	44.1	71.4	104.9
CAGE 400µl	25-Jul-89	30	80	38.7	810	7.33	39.6	170.0	20.9	45.9	72.0	1205.0	810.0	192.0	15.2	213.0	39.6	65.8	71.0
CAGE 400µl	25-Jul-89	45	80	38.6	810	7.37	41.0	167.9	23.7		75.6	1090.0	625.0	178.3	16.0	140.7	40.5	65.1	85.5
CAGE 400µl	25-Jul-89	60	70	38.4	810	7.39	35.0	175.7	20.9	49.2	71.7	1080.0	650.0	198.3	15.2	141.0	35.0	75.5	72.5
CAGE 400µl	25-Jul-89	75	75	38.4	774	7.35	39.0	167.0	21.2	60.0	61.1	1040.0	645.0	169.0	14.5	191.0	33.9	59.5	85.2
CAGE 400µl	25-Jul-89	90	70	38.5	774	7.36	40.1	168.0	22.3	67.5	78.4	1010.0	647.5	223.7	12.9	201.7	33.1	98.1	73.4
CAGE 400µl	25-Jul-89	105	70	38.8	774					62.9	44.5	980.0	645.0	115.0	12.0	154.0	42.0	47.3	85.4
CAGE 400µl	25-Jul-89	120	60	39.0	774					49.7	57.5	1020.0	620.0	232.0	12.0	177.0	34.0	93.1	79.8
CAGE 400µl	25-Jul-89	135	70	39.4	774	7.38	41.0	168.0		55.5	50.1	1040.0	640.0	304.0	13.0	203.0	37.0	91.5	39.9
CAGE 400µl	25-Jul-89	150	70		774	7.36	41.2	163.0		56.6	53.9	1000.0	625.0	329.0	11.0	220.0	33.0	117.0	83.1
CAGE 400µl	25-Jul-89	165	70	39.1	774		41.0			61.9	49.5	980.0	615.0	360.0	10.0	[307]	31.0	117.0	76.7
CAGE 400µl	25-Jul-89	180	70	39.0	774		41.0			60.9	47.4	1010.0	615.0	352.0	11.0	265.0	31.0	117.0	75.0

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 400µl	10-Aug-89	-120	110	38.1	828	7.33	38.4	162.1	19.3	102.1	98.1	1605.0	685.0	449.0	18.7	361.0	40.0	187.0	70.0
CAGE 400µl	10-Aug-89	-105	110	38.3	828	7.36	38.2	184.7	21.5	129.9	100.3		680.0	428.0	19.0	367.0	40.0	160.0	75.0
CAGE 400µl	10-Aug-89	-90	110	38.5	828	7.36	37.2	186.3	21.0	102.9	91.8	1755.0	685.0	418.7	19.0	352.0	41.5	159.5	74.0
CAGE 400µl	10-Aug-89	-75	110	38.7	828	7.37	37.9	181.7	21.9	121.6	116.9	1820.0	685.0	[363]	18.7	[284]	41.7	[106]	72.7
CAGE 400µl	10-Aug-89	-60	110	38.8	828	7.36	37.8	175.8	21.4	109.8	119.4	1780.0	682.5	452.7	19.0	320.7	39.9	134.0	73.9
CAGE 400µl	10-Aug-89	-45	110	39.0	828	7.36	37.9	170.2	21.3	102.9	109.8	1800.0	677.5	365.0	17.9	256.3	38.7	110.4	73.3
CAGE 400µl	10-Aug-89	-30	110	39.0	828	7.36	36.0	171.6	20.1	107.0	113.1	1920.0	670.0	354.3	17.5	254.0	383.3	101.3	69.3
CAGE 400µl	10-Aug-89	-15	110	39.0	828	7.37	37.9	169.5	22.0	112.6	129.9	1900.0	680.0	349.7	17.3	252.0	38.5	168.4	67.2
CAGE 400µl	10-Aug-89	0	110	39.0	828	7.40	38.3	169.6	23.8	138.6	151.8	1830.0		271.7	13.8	177.0	42.9	77.0	91.4
CAGE 400µl	10-Aug-89	15	100	38.9	828	7.38	36.9	165.0	21.7	109.8	69.3	1830.0	790.0	245.0	16.0	157.3	34.8	62.3	68.2
CAGE 400µl	10-Aug-89	30	95	38.8	828	7.38	38.1	169.0	22.5	109.8	76.8	1870.0	767.5	287.7	18.0	270.7	37.5	83.8	63.5
CAGE 400µl	10-Aug-89	45	100	38.8	828	7.39	39.1	168.9	23.8	69.3	64.7	1980.0	720.0	277.3	17.6	191.3	39.3	35.0	63.3
CAGE 400µl	10-Aug-89	60	95	38.5	828	7.38	41.5	154.0	24.6	77.3	82.1	1950.0	710.0	313.7	17.5	186.3	38.7	33.6	78.2
CAGE 400µl	10-Aug-89	75	95		828		35.0			78.8	91.6	1900.0	687.5	269.0	16.2	206.3	34.9	88.7	63.3
CAGE 400µl	10-Aug-89	90	90	38.3	828	7.40	42.9	153.0	26.6	74.2	94.4	1980.0	665.0	167.7	17.4	156.3	34.7	36.4	75.5
CAGE 400µl	10-Aug-89	105	95	38.3	828	7.40	41.4	151.1	25.9	78.0	67.0	1850.0	700.0	144.3	17.5	160.7	35.0	46.2	72.0
CAGE 400µl	10-Aug-89	120	90	38.3	828	7.39	45.0	145.4	27.1	63.6	54.2	1845.0	685.0	174.7	17.9	123.3	37.1	47.6	63.8
CAGE 400µl	10-Aug-89	135	80	38.2	828	7.39	44.9	145.0	27.3	69.3	72.4	1750.0	690.0	109.3	15.4	90.8	55.0	29.8	81.5
CAGE 400µl	10-Aug-89	150	85	38.2	828	7.40	43.1	133.2	26.8	71.7	54.4	1680.0	680.0	43.2	20.9	80.3	69.2	58.1	139.5
CAGE 400µl	10-Aug-89	165	85	38.5	828	7.42	36.3	140.3	23.7	78.8	69.3	1600.0	665.0	53.7	26.9	59.5	70.8	44.8	124.0
CAGE 400µl	10-Aug-89	180	90	38.7	828	7.38	41.1	131.0	24.3	84.7	80.6	1640.0	665.0	129.0	28.0	57.0	85.0	55.9	140.4
CAGE 400µl	3-Aug-89	-120	85	38.4	954	7.37	35.9	122.9				1940.0	662.5	338.0	16.0	316.0	35.0	115.0	72.0
CAGE 400µl	3-Aug-89	-105	90	38.3	954	7.31	43.9	102.9	22.2	58.0		2030.0	630.0	366.0	17.0	337.0	32.0	106.0	71.0
CAGE 400µl	3-Aug-89	-90	100	38.2	954	7.33	43.8	121.7	23.3		74.2	2100.0	665.0	327.0	16.7	242.0	32.0	133.0	77.0
CAGE 400µl	3-Aug-89	-75	100	38.3	972	7.31	43.5	120.9	21.8	58.8	69.3	2050.0	670.0	458.3	18.0	357.7	36.7	130.2	74.0
CAGE 400µl	3-Aug-89	-60	95	38.4	972	7.33	44.7	94.9	23.3	44.2	53.9	2145.0	660.0	235.5	17.5	252.0	36.5	[90]	83.0
CAGE 400µl	3-Aug-89	-45	95	38.6	990	7.38	40.1	97.7	23.7	45.2	50.0	2180.0	670.0	403.3	17.5	286.7	34.2	[90]	81.0
CAGE 400µl	3-Aug-89	-30	95	38.6	990	7.35	39.3	99.0	21.8	49.2	58.8	2100.0	670.0	373.0	17.4	288.0	34.0	127.8	75.1
CAGE 400µl	3-Aug-89	-15	95	38.6	990	7.34	39.1	107.3	21.0	35.7	53.1	2130.0	670.0	395.3	17.1	298.3	32.3	144.1	78.8
CAGE 400µl	3-Aug-89	0	105	38.7	990	7.34	45.0	126.0	27.2	49.6	[57]	2070.0	735.0	225.0	16.3	234.3	31.3	80.4	68.7
CAGE 400µl	3-Aug-89	15	100	38.6	1044	7.38	37.7	142.1	22.2	50.0	[66]	2060.0	660.0	449.5	17.0	286.5	31.8	99.4	78.0
CAGE 400µl	3-Aug-89	30	90	38.6	1008	7.42	35.0	155.8	22.3	45.2	48.5	1900.0	640.0	411.7	16.4	249.7	32.8	101.3	69.3
CAGE 400µl	3-Aug-89	45	98	38.8	1008	7.40	42.0	168.0	26.0	49.2	61.3	1920.0	650.0	429.3	17.0	277.3	31.7	94.4	74.9
CAGE 400µl	3-Aug-89	60	90	38.8	1008	7.38	35.8	122.6		48.0	27.8	1720.0	635.0	249.3	14.4	161.7	35.5	72.8	125.8
CAGE 400µl	3-Aug-89	75	85	38.8	1008	7.37	40.8	159.9	23.3	49.6	32.5	1680.0	650.0	179.7	13.7	84.0	35.7	41.3	107.9
CAGE 400µl	3-Aug-89	90	85	38.8	1008	7.38		163.4	22.2	53.9	26.8	1600.0	645.0	218.0	13.9	125.7	34.9	37.8	97.2
CAGE 400µl	3-Aug-89	105	80	38.8	1026	7.37	39.5	165.6	22.8	53.9	33.6	1580.0	650.0	142.0	13.8	76.8	33.0	47.8	109.8
CAGE 400µl	3-Aug-89	120	80	38.9	1026	7.34	40.1	166.0	21.4	53.9	30.5	1590.0	640.0	209.7	14.6	167.7	33.5	47.6	82.1
CAGE 400µl	3-Aug-89	135	80	38.8	1026	7.35	39.3	153.9	21.5	60.6	43.0	1510.0	655.0	246.0	14.1	119.0	34.9	58.8	76.6
CAGE 400µl	3-Aug-89	150	75	38.8	1026	7.41	40.9	174.9	25.7	56.0	34.4	1550.0	632.5	208.3	14.1	110.8	36.1	43.4	86.0
CAGE 400µl	3-Aug-89	165	80	38.7	1026	7.31	45.0			64.7	54.6	1540.0		154.6	12.3	47.8	36.5	40.7	87.1
CAGE 400µl	3-Aug-89	180	80	38.7	1026	7.32	41.5	145.1	21.5	64.7	54.6	1545.0	615.0	146.7	12.9	85.0	32.9	67.2	86.4
CAGE 400µl	30-Nov-88	-120																	
CAGE 400µl	30-Nov-88	-105																	
CAGE 400µl	30-Nov-88	-90																	
CAGE 400µl	30-Nov-88	-75	100	38.5	585	7.31	31.5	182.0	15.7	79.0	63.0			4.0	18.0	66.0	52.0	52.0	72.0
CAGE 400µl	30-Nov-88	-60	100	38.2	585	7.35	33.5	194.0	18.3		61.0			35.0	19.0	46.0	38.0	38.0	83.0
CAGE 400µl	30-Nov-88	-45	100	38.0	585	7.34	31.0	191.0	16.7		48.0			24.0	17.0	63.0	49.0	49.0	75.0
CAGE 400µl	30-Nov-88	-30	100	37.0	575	7.37	35.3	186.0	16.5		47.0			56.0	20.0	52.0	73.0	73.0	82.0
CAGE 400µl	30-Nov-88	-15	100	37.0	575	7.32	30.0	179.0	15.5		51.0			35.0	14.0	77.0	66.0	66.0	83.0
CAGE 400µl	30-Nov-88	0	100	37.0	575														
CAGE 400µl	30-Nov-88	15	100	37.0	575	7.31	42.5	163.0	21.2										
CAGE 400µl	30-Nov-88	30	100	37.0	575	7.31	40.5	173.4	20.3		87.0								
CAGE 400µl	30-Nov-88	45	90	37.0	575	7.36	36.1	181.4	20.1		29.0			7.0	15.0	21.0	18.0	18.0	84.0
CAGE 400µl	30-Nov-88	60	90	37.0	575	7.34	38.5	173.3	20.8		28.0			0.0	15.0	38.0	7.0	7.0	70.0
CAGE 400µl	30-Nov-88	75	90	37.0	575	7.31	30.0	170.5	15.2		19.0			[3]	[14]	[56]	[56]		[84]
CAGE 400µl	30-Nov-88	90	95	37.0	570	7.31	40.6	160.9	20.3		29.0			56.0	14.0	24.0	65.0	45.0	110.0
CAGE 400µl	30-Nov-88	105	90	37.0	570	7.31	34.5	158.6	17.5		18.0			24.0	16.0	25.0	50.0	31.0	85.0
CAGE 400µl	30-Nov-88	120	85	37.0	570	7.29	32.5	111.7	15.5										
CAGE 400µl	30-Nov-88	135	70	37.5	570	7.31	41.5	164.8	20.7		26.0								
CAGE 400µl	30-Nov-88	150	80	37.5	550	7.33	47.5	166.2	24.9		32.0								
CAGE 400µl	30-Nov-88	165	80	37.5	550	7.29	35.8	172.4	17.2		46.0								
CAGE 400µl	30-Nov-88	180	80	37.0	550	7.31	37.7	179.4	19.1		48.0								
CAGE 400µl	24-Apr-89	-120																	
CAGE 400µl	24-Apr-89	-105																	
CAGE 400µl	24-Apr-89	-90																	
CAGE 400µl	24-Apr-89	-75																	
CAGE 400µl	24-Apr-89	-60	105	38.5	825	7.32	30.7	132.5	16.0	166.0	67.0	980.0	850.0	290.0	16.0	262.0	35.0	199.0	66.0
CAGE 400µl	24-Apr-89	-45	100	39.0	825	7.34	37.5	135.0	16.0	142.0	84.0	1010.0	870.0	406.0	16.0	311.0	36.0	133.0	82.0
CAGE 400µl	24-Apr-89	-30	95	39.0	870	7.36	34.1	125.9	20.1		69.0	1000.0	830.0	395.0	15.0	297.0	35.0	105.0	70.0
CAGE 400µl	24-Apr-89	-15	95	39.0	870	7.33	30.2	126.7	19.2	97.0	52.0	1010.0	860.0	588.0	15.0	490.0	33.0	217.0	76.0
CAGE 400µl	24-Apr-89	0	110	39.0	870	7.31	38.2	116.6	16.0			955.0	860.0	287.0	15.0	238.0	38.0	98.0	92.0
CAGE 400µl	24-Apr-89	15	100	38.5	870	7.19	44.3	106.8	18.4	171.0		900.0	880.0	602.0	15.0	364.0	38.0	140.0	82.0
CAGE 400µl	24-Apr-89	30	104	38.5	870	7.17	46.0	94.0	16.9	175.0		890.0	990.0	448.0	16.0	392.0	34.0	196.0	74.0
CAGE 400µl	24-Apr-89	45	92	38.0	870	7.31	36.0	131.9	16.5	139.0	70.0	930.0		357.0	15.8	427.0	34.2	77.0	68.4
CAGE 400µl	24-Apr-89	60	88	37.0	930	7.33	40.0	161.0	18.0	75.0	42.0	900.0	1020.0	623.0	14.8	539.0	33.0	182.0	70.0
CAGE 400µl	24-Apr-89	75	70	37.0	930	7.37	36.2	145.0	21.0	81.0	40.0	990.0	970.0	618.0	15.0	574.0	34.0	147.0	77.2
CAGE 400µl	24-Apr-89	90	80	37.0	930	7.40	[28.6]	113.6	17.7	69.0	36.0	955.0	940.0	609.0	15.0	532.0	34.0	147.0	71.0
CAGE 400µl	24-Apr-89	105	80	37.0	900	7.41	[27.7]	110.1	17.7	71.0	37.0	980.0	880.0	620.0	15.0	427.0	31.0	161.0	72.0
CAGE 400µl	24-Apr-89	120	80	37.0	825	7.39	33.0	123.1	20.4	69.0	34.0	980.0	880.0	560.0	17.0	413.0	39.0	133.0	90.0
CAGE 400µl	24-Apr-89	135	80	37.0	825	7.39	35.0	144.0	21.0	91.0	43.0	920.0		434.0	16.0	553.0	35.0	14.0	71.0
CAGE 400µl	24-Apr-89	150	78	37.0	825	7.35	35.1	141.8	19.3	88.0	41.0	910.0	840.0	455.0	16.0	434.0	33.0	70.0	69.0
CAGE 400µl	24-Apr-89	165	80	37.0	825	7.39	34.3	140.2	20.8	68.0	35.0			588.0	16.0	448.0	35.0	224.0	71.0
CAGE 400µl	24-Apr-89	180	80	37.0	825	7.38	34.1	176.6	20.3	80.0	37.0			588.0	16.0	448.0	34.0	182.0	81.0
CAGE Control	6-Sep-88	-120																	
CAGE Control	6-Sep-88	-105																	
CAGE Control	6-Sep-88	-90																	
CAGE Control	6-Sep-88	-75	100	39.0	500	7.37	32.3	154.6	18.5	[110]	[101]	1150.0	64.8	68.2	17.8	98.0	44.6	35.0	86.0
CAGE Control	6-Sep-88	-60	100	39.0	450	7.30	37.3	157.1	18.2	[115]	[81]	1290.0	68.8	82.2	19.2	122.0	48.2	49.0	85.8
CAGE Control	6-Sep-88	-45	100	39.0	450	7.32	37.1	152.5	18.9	56.8	51.5	1340.0	79.2	63.0	19.4	203.0	47.6	14.0	90.2
CAGE Control	6-Sep-88	-30	105	39.0	450	7.34	28.6	162.3	15.4	64.6	59.0	1310.0	79.2	40.2	12.4	103.0	45.4	28.0	90.2
CAGE Control	6-Sep-88	-15	100	39.0	450	7.31	39.1	143.2	19.6	55.2	55.8	1270.0	74.4	38.5	12.8	115.0	44.8	17.5	89.8
CAGE Control	6-Sep-88	0	100	39.0	450	7.29	36.3	157.8	17.3	40.6	46.1	1240.0	64.8	38.5	13.0	101.0	43.2	42.0	85.8
CAGE Control	6-Sep-88	15	95	39.0	450	7.30	37.9	147.8	18.5	43.8	46.4	1225.0	67.2	31.5	12.4	141.0	44.0	14.0	89.2
CAGE Control	6-Sep-88	30	95	38.5	450	7.28	38.5	156.4	18.1	61.8	28.8	1090.0	67.2	33.2	12.2	[66]	48.6	[11]	76.8
CAGE Control	6-Sep-88	45	95	38.5	450	7.29	45.9	156.4	22.1	76.1	47.4			36.7	12.8	101.0	48.4	[-7]	86.8
CAGE Control	6-Sep-88	60	100	38.5	450	7.31	49.5	158.4	25.0	47.0	44.7	1100.0	67.2						
CAGE Control	6-Sep-88	75	100	38.5	450	7.27	44.1	155.4	20.4	67.4	61.9	1180.0	71.2	17.5	12.6	54.2	47.2	19.2	76.4
CAGE Control	6-Sep-88	90	100	38.5	475	7.35	32.8	142.8	18.0	48.9	36.6	1420.0	66.4	7.0	13.2	129.0	44.6	42.0	92.0
CAGE Control	6-Sep-88	105	100	38.5	475	7.32	38.5	153.2	19.6	44.2	51.4	1415.0	67.2	8.8	13.2	64.7		38.7	85.8
CAGE Control	6-Sep-88	120	95	38.5	475	7.32	42.2	158.0		74.7	53.2	1500.0	64.0	[46]	[12]			[40]	[73]
CAGE Control	6-Sep-88	135	100	38.5	475	7.36	39.0	156.4	20.3	50.2	49.3	1510.0	64.8	66.5	12.8	120.0	43.4	14.0	84.6
CAGE Control	6-Sep-88	150	90	38.5	475	7.29	43.3	162.2	20.9	49.9	45.5	1520.0	83.2	45.5	12.6	96.2	42.0	15.7	76.6
CAGE Control	6-Sep-88	165	95	38.5	475	7.31	37.3	155.6	18.7	50.0	47.0	1480.0	90.4	49.0	12.4	105.0	48.8	[5]	72.4
CAGE Control	6-Sep-88	180	95	38.5	475	7.38	35.9	162.8	17.4	55.8	59.5	1580.0	87.2	45.5	16.2	197.0	42.4	[4]	86.0

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE Control	7-Jun-89	-120																	
CAGE Control	7-Jun-89	-105																	
CAGE Control	7-Jun-89	-90																	
CAGE Control	7-Jun-89	-75																	
CAGE Control	7-Jun-89	-60	90	37.0	1080	7.35	39.8	140.0			55.0	1650.0	957.5	672.0	19.8	364.0	44.0	420.0	85.0
CAGE Control	7-Jun-89	-45	85	37.0	1080	7.34	37.0	148.0	19.9		41.0	1680.0	937.5	728.0	20.0	287.0	50.0	413.0	81.0
CAGE Control	7-Jun-89	-30	75	37.0	1080	7.38	38.0	150.0	22.0		[33]	1750.0	900.0	672.0	19.0	189.0	44.0	336.0	80.0
CAGE Control	7-Jun-89	-15	75	37.0	1080	7.36	37.5	151.6	20.7		[28]	2000.0	890.0	672.0	19.8	294.0	43.0	322.0	94.2
CAGE Control	7-Jun-89	0	85	37.0	1080	7.38	36.9	151.8	21.7		61.0	2090.0	882.5	546.0	18.0	140.0	43.8	308.0	94.0
CAGE Control	7-Jun-89	15	80	37.5	1080	7.37	38.1	150.7	20.7		78.0	2090.0	945.0	609.0	18.0	119.0	39.0	364.0	78.0
CAGE Control	7-Jun-89	30	80	38.0	1080	7.35	35.4	149.5	20.0		59.0	2090.0	865.0	511.0	18.0	252.0	43.2	203.0	89.8
CAGE Control	7-Jun-89	45	75	38.0	1080	7.38	31.7	140.3	18.8		87.0	2020.0	865.0	497.0	12.0	77.0	29.8	399.0	80.0
CAGE Control	7-Jun-89	60	85	38.0	1080	7.28	51.0	91.0	24.0		50.0	2180.0	910.0	378.0	138.0	210.0	50.0	259.0	105.0
CAGE Control	7-Jun-89	75	85	38.0	1170	7.39	43.0	142.0	25.0		82.0	2230.0	870.0	434.0	17.0	105.0	44.0	287.0	85.0
CAGE Control	7-Jun-89	90	80	38.0	1170	7.41	37.0	154.0	23.2		58.0	2180.0	897.5	476.0	17.4	231.0	42.0	196.0	81.0
CAGE Control	7-Jun-89	105	80	38.0	1170	7.40	35.0	162.3	21.3		61.0	2000.0	870.0	567.0	17.0	224.0	43.0	210.0	100.0
CAGE Control	7-Jun-89	120	80	38.0	1170	7.40	37.0	158.1	23.1		60.0	2030.0	845.0	511.0	12.0	126.0	30.0	259.0	83.0
CAGE Control	7-Jun-89	135	80	38.0	1026	7.40	29.4	140.0	18.4		75.0	2000.0	885.0	532.0	11.6	113.0	30.4	259.0	91.0
CAGE Control	7-Jun-89	150	80	38.0	900	7.35	36.0	147.8	19.8		73.0	1980.0	875.0	525.0	13.2	168.0	31.4	301.0	77.0
CAGE Control	7-Jun-89	165	85	37.5	900	7.38	43.7	143.0	25.0		79.0	2000.0	895.0	490.0	11.2	280.0	27.0	301.0	77.0
CAGE Control	7-Jun-89	180	80	37.0	900	7.42	36.1	154.1	23.4		56.0	1820.0	830.0	469.0	11.8	217.0	28.8	168.0	98.0
CAGE Control	7-Jul-89	-120	75	39.0	1008	7.29	40.8	161.6	19.4	[17]	[26]			452.7	20.5	459.7	43.3	134.4	83.0
CAGE Control	7-Jul-89	-105	75	39.0	1008	7.27	41.2	177.0	19.0	18.2	29.6	1080.0	650.0	502.0	20.8	467.0	44.8	134.4	87.4
CAGE Control	7-Jul-89	-90	60	38.5	1062	7.26	39.9	179.8	17.8	21.4	30.7	2000.0	670.0	606.7	18.3	515.7	45.1	145.6	87.9
CAGE Control	7-Jul-89	-75	60	38.5		7.31	40.4	173.0	20.2	19.6	29.3	1800.0	690.0	711.7	17.3	529.7	43.5	145.6	87.9
CAGE Control	7-Jul-89	-60	65	38.5	1080	7.28	40.6	167.0	19.2	18.1	31.0	1870.0	685.0	585.7	18.6	583.3	42.9	135.8	94.6
CAGE Control	7-Jul-89	-45	65	38.5	1118	7.29	41.0	164.0	19.5	21.8	39.1	1840.0	670.0	607.0	18.5	467.0	44.9	165.2	108.0
CAGE Control	7-Jul-89	-30	65	38.5	1170	7.28	38.2	169.3	17.8	17.5	26.2	1800.0	665.0	767.7	16.7	450.3	37.0	183.4	91.2
CAGE Control	7-Jul-89	-15	70	38.5	1206	7.30	38.5	149.5	18.9	20.5	34.4	1840.0	650.0	688.3	15.8	443.3	39.9	147.0	88.1
CAGE Control	7-Jul-89	0	70	38.5	1206	7.30	38.1	167.8	17.6	21.9	36.3	1835.0	665.0	709.6	16.9	485.3	40.6	196.0	95.0
CAGE Control	7-Jul-89	15	70	38.5	1170	7.29	35.5	171.1	16.9	18.2	31.5	1940.0	670.0	557.7	17.9	457.3	41.9	163.8	101.4
CAGE Control	7-Jul-89	30	70	38.5	1080	7.31	39.0	168.2	19.8	19.2	42.3	1910.0	705.0	672.0	14.9	450.0	40.5	187.6	93.0
CAGE Control	7-Jul-89	45	70	39.0	1134	7.31	37.0	175.2	18.7	15.0	29.7	1920.0	685.0	438.7	14.9	340.7	44.6	152.6	86.9
CAGE Control	7-Jul-89	60	65	39.0	1134	7.31	35.7	184.8	17.9	17.9	38.9	1890.0	700.0	672.0	15.7	529.7	40.5	147.0	82.6
CAGE Control	7-Jul-89	75	70	39.0	1080	7.31	37.6	184.9	18.8	14.6	35.2	1850.0	720.0	553.0	15.7	499.3	42.4	212.8	87.7
CAGE Control	7-Jul-89	90	70	39.0	1080	7.31	36.6	187.4	18.5	16.8	38.8	1830.0		583.3	14.6	504.0	42.0	183.4	92.2
CAGE Control	7-Jul-89	105	65	39.0	1080	7.31	35.3	180.3	17.8	15.9	43.2			494.7	14.8	410.7	43.3	165.2	89.7
CAGE Control	7-Jul-89	120	65	39.0	990	7.32	36.4	187.8	18.8	17.9	42.3			576.3	14.9	391.7	40.9	151.2	95.9
CAGE Control	7-Jul-89	135	65	39.0	990	7.33	38.3	185.1	20.0	21.0	43.7			518.0	18.7	352.3	44.4	124.6	126.1
CAGE Control	7-Jul-89	150	65	39.0	990	7.31	38.4	184.4	19.4	20.4	48.8			763.0	17.4	599.7	41.5	205.8	104.4
CAGE Control	7-Jul-89	165	70	39.0	954	7.27	41.0	181.7	19.0	22.3	43.3			415.3	16.4	388.0	43.3	156.8	104.9
CAGE Control	7-Jul-89	180																	
CAGE Control	7-Sep-88	-120																	
CAGE Control	7-Sep-88	-105																	
CAGE Control	7-Sep-88	-90																	
CAGE Control	7-Sep-88	-75	100	38.5	500	7.37	36.3	126.7	20.7	99.4	88.3			[84]	[16]	[89]	[36]	[63]	[71]
CAGE Control	7-Sep-88	-60	100	38.5	500	7.41	38.0	120.4	23.9	83.3	78.0	2000.0	59.2	150.0	18.0	64.0	42.6	94.5	79.8
CAGE Control	7-Sep-88	-45	100	38.5	500	7.38	43.8	124.0	25.7	67.5	59.5	2080.0	47.2	122.0	17.4	131.0	40.4	40.2	83.0
CAGE Control	7-Sep-88	-30	100	38.5	525	7.36	43.5	127.7	23.8	67.8	65.9	2080.0	47.2	101.0	17.2	96.2	39.4	45.5	83.8
CAGE Control	7-Sep-88	-15	100	38.5	525	7.38	41.5	129.8		61.3	64.1	2180.0	47.2	141.0	16.8	127.0	39.0	98.0	88.6
CAGE Control	7-Sep-88	0	100	38.5	500	7.45	28.3	137.7	19.8	73.6	61.7	2145.0	51.2	150.0	17.0	101.0	39.0	99.7	75.4
CAGE Control	7-Sep-88	15	100	38.5	500	7.36	42.4	133.4	24.1	69.3	58.1	2000.0	51.2	108.0	15.8	77.0	37.4	78.7	70.6
CAGE Control	7-Sep-88	30	100	38.5	500	7.36	43.1	141.7	24.0	70.0	61.2	2190.0	51.2	119.0	17.2	166.0	38.4	19.0	78.8
CAGE Control	7-Sep-88	45	95	38.5	500	7.35	39.2	136.4	21.5	89.5	57.9	2250.0	54.4	113.0	14.6	131.0	40.0	14.0	78.6
CAGE Control	7-Sep-88	60	100	38.5	500	7.44	32.6	126.8	22.1	54.6	60.1	2180.0	54.4	126.0	16.8	157.0	40.0	24.5	74.0
CAGE Control	7-Sep-88	75	100	38.5	500	7.32	36.9	136.6	19.1	57.0	67.1	2180.0		8.1	14.2	128.0	34.4	5.3	77.6
CAGE Control	7-Sep-88	90	100	38.5	500	7.40	47.2	133.1	28.9	55.1	64.0	2170.0	54.4	47.0	17.0	148.0	41.0	38.5	77.4
CAGE Control	7-Sep-88	105	100	38.5	500	7.41	47.4	128.4	30.0	48.4	64.6	2060.0	53.6	89.2	16.8	185.0	38.4	10.5	83.0
CAGE Control	7-Sep-88	120	100	38.0	500	7.36	32.0	137.8	17.9	81.8	73.4	2020.0		94.5	18.0	175.0	40.0	3.5	73.0
CAGE Control	7-Sep-88	135	100	38.0	500	7.30	39.0	136.7	18.1	70.0	77.7	1790.0	58.2	89.2	14.6	168.0	36.2	26.2	85.0
CAGE Control	7-Sep-88	150	100	38.0	500	7.35	42.9	136.3	23.5	79.9	70.9	1780.0	56.8	45.5	12.4	129.0	38.0	56.0	85.2
CAGE Control	7-Sep-88	165	100	38.0	500	7.37	44.3	131.8	25.3	77.3	67.7	1740.0	55.2	75.2	14.8	159.0	37.2	24.5	85.0
CAGE Control	7-Sep-88	180	100	38.0	500	7.33	46.7	132.3	24.4	75.8	70.8	1740.0	59.2	43.7	14.8	119.0	37.2	0.0	87.0
CAGE Control	8-Sep-88	-120																	
CAGE Control	8-Sep-88	-105																	
CAGE Control	8-Sep-88	-90																	
CAGE Control	8-Sep-88	-75	95	37.5	525	7.37	45.2	124.6	25.9	55.3	51.7	2040.0	55.2	182.0	17.2	120.0	35.4	82.2	79.8
CAGE Control	8-Sep-88	-60	95	37.5	550	7.36	38.0	139.3	21.4	53.7	51.7	2130.0	55.2	178.0	18.6	87.5	43.4	71.7	79.6
CAGE Control	8-Sep-88	-45	95	37.5	550	7.36	43.9	126.2	24.9	40.7	70.4	2075.0	55.2	168.0	14.8	105.0	28.6	98.0	73.2
CAGE Control	8-Sep-88	-30	95	37.5	550	7.33	45.9	128.7	23.9	57.8	[104]	2030.0	55.2	152.0	14.8	[79]	30.8	84.0	75.2
CAGE Control	8-Sep-88	-15	95	38.0	600	7.34	33.0	142.3	17.7	[132]	65.0	2080.0	55.2	176.0	15.0	126.0	33.6	77.0	80.4
CAGE Control	8-Sep-88	0	90	38.0	600	7.21	42.2	134.2	16.7	48.3	81.2	2140.0	56.8	190.0	16.8	129.0	38.4	77.0	80.6
CAGE Control	8-Sep-88	15	90	38.0	600	7.31	42.1	145.0	20.9	49.3	76.2	2380.0	54.4	164.0	16.6	115.0	43.8	[47]	85.4
CAGE Control	8-Sep-88	30	90	38.0	600	7.31	36.2	139.7	18.0	38.5	57.5	2140.0	55.2	164.0	17.2	128.0	38.4	78.7	82.6
CAGE Control	8-Sep-88	45	90	38.0	600	7.31	30.7	130.4	15.6	42.7	59.8	2120.0	74.4	178.0	15.2	124.0	32.4	45.5	76.8
CAGE Control	8-Sep-88	60	80	38.0	600	7.34	37.6	134.2	20.0	34.1	37.4	2130.0	76.8	168.0	16.6	192.0	40.4	50.7	79.2
CAGE Control	8-Sep-88	75	90	37.5	600	7.28	35.5	130.8	16.5	32.2	43.9	1890.0	58.4	197.0	15.2	127.0	39.6	80.5	80.8
CAGE Control	8-Sep-88	90	80	37.5	600	7.26	44.7	136.2	20.1	32.1	80.9	1700.0	56.8	182.0	15.6	133.0	34.8	84.0	80.4
CAGE Control	8-Sep-88	105	85	37.5	600	7.33	44.3	148.8	23.3	38.6	44.0	1750.0	62.4						
CAGE Control	8-Sep-88	120	85	37.5	600	7.31	41.4	143.7	21.0	33.2	37.4	1760.0	64.0	204.0	16.8	162.0	36.0	57.7	80.2
CAGE Control	8-Sep-88	135	85	37.5	600	7.37	30.8	153.8	17.8	41.8	66.8	1730.0	56.0	220.0	16.2	105.0	36.6	105.0	75.4
CAGE Control	8-Sep-88	150	85	37.5	600	7.35	34.3	152.4	16.9	33.0	29.5	1500.0	55.2	173.0	14.6	122.0	38.4	64.7	85.2
CAGE Control	8-Sep-88	165	80	37.5	600	7.29	26.2	166.0	12.5	38.1	29.2	1490.0		197.0	15.4	129.0	34.0	108.0	85.0
CAGE Control	8-Sep-88	180																	
CAGE Control	9-Jun-89	-120																	
CAGE Control	9-Jun-89	-105																	
CAGE Control	9-Jun-89	-90																	
CAGE Control	9-Jun-89	-75										2290.0	755.0						
CAGE Control	9-Jun-89	-60										2290.0	740.0						
CAGE Control	9-Jun-89	-45										2280.0	735.0						
CAGE Control	9-Jun-89	-30	110	38.5	702	7.36	39.8	128.2	22.4		38.0	2280.0	745.0	[609]	[16]	[35]	[40]	[350]	[73]
CAGE Control	9-Jun-89	-15	110	38.0	756	7.39	40.4	115.8	23.9		41.0	2380.0	735.0	[504]	[16]	[14]	[41]	[350]	[88]
CAGE Control	9-Jun-89	0	110	38.0	810	7.34	43.3	124.6	23.5		47.0	2300.0	710.0	504.0	16.2	14.0	41.0	350.0	87.0
CAGE Control	9-Jun-89	15	110	38.0	810	7.37	38.7	138.5	22.5		50.0	2350.0	680.0	623.0	14.8	21.0	39.6	336.0	85.0
CAGE Control	9-Jun-89	30	105	38.0	810	7.38	41.9	140.8	23.6		53.0	2300.0	715.0	518.0	17.4	105.0	42.0	350.0	82.0
CAGE Control	9-Jun-89	45	110	38.0	828	7.36	40.9	150.8	23.0		47.0	2320.0	740.0	532.0	15.2	0.0	40.0	252.0	71.0
CAGE Control	9-Jun-89	60	110	38.0	828	7.36	41.0	140.0	23.0		44.0	2300.0	710.0	609.0	15.0	49.0	31.0	343.0	67.0
CAGE Control	9-Jun-89	75	110	38.0	846	7.39	39.0	150.0	21.4		56.0	2160.0	715.0	434.0	14.0	21.0	27.0	252.0	72.0
CAGE Control	9-Jun-89	90	105	38.0	846	7.38	37.0	149.0	21.4		55.0	2090.0	745.0	420.0	13.0	14.0	254.0	287.0	82.0
CAGE Control	9-Jun-89	105	100	38.0	846	7.36	38.4	141.0	21.8		56.0	2070.0	740.0	581.0	15.4	7.0	36.0	308.0	76.0
CAGE Control	9-Jun-89	120	100	38.0	792	7.37	35.0	145.0	19.3		53.0	2070.0	775.0	420.0	13.8		28.4	392.0	140.0
CAGE Control	9-Jun-89	135	100	37.5	792	7.36	38.0	146.0			58.0	2000.0	710.0	567.0	11.0	63.0	22.0	329.0	70.0
CAGE Control	9-Jun-89	150	100	37.5	792	7.37	40.0	148.9	22.0		62.0	1760.0	725.0	672.0	12.4	161.0	26.4	399.0	7.5
CAGE Control	9-Jun-89	165	100	37.5	792	7.37	41.6	147.0	24.0		62.0	1770.0	715.0	672.0	12.4	35.0	23.0	434.0	62.2
CAGE Control	9-Jun-89	180	100	37.5	792	7.39	37.9	138.0	22.7		62.0	1790.0	685.0	647.0	12.8	161.0	23.4	399.0	71.2

Group	Date	time	MABP	Temp	Min.Vol	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE Control	15-Jun-89	-120										[1400]	[750]						
CAGE Control	15-Jun-89	-105										[1500]	[615]						
CAGE Control	15-Jun-89	-90										[1550]	[810]						
CAGE Control	15-Jun-89	-75																	
CAGE Control	15-Jun-89	-60	80	36.0	1044	7.33	43.8	126.3	23.1	32.0	53.0	1530.0	590.0	504.0	14.4	336.0	35.2	203.0	84.0
CAGE Control	15-Jun-89	-45	80	37.5	1044	7.31	43.9	118.1	21.9	32.0	69.0	1580.0	595.0	548.0	18.0	448.0	41.0	112.0	85.0
CAGE Control	15-Jun-89	-30	80	37.5	1116	7.35	43.5	172.3	24.1	38.0	82.0	1550.0	595.0	406.0	17.0	336.0	42.0	133.0	86.0
CAGE Control	15-Jun-89	-15	80	37.0	1134	7.34	42.1	129.3	22.5	33.0	92.0	1550.0	600.0	399.0	17.4	308.0	40.6	168.0	74.4
CAGE Control	15-Jun-89	0	80	37.5	1134	7.31	41.8	126.2	21.2	37.0	[143]	1970.0	620.0	791.0	17.2	588.0	42.0	210.0	88.0
CAGE Control	15-Jun-89	15	80	38.0	1170	7.35	43.9	120.6	23.9	[58]	[197]	1680.0	622.5	548.0	13.4	329.0	35.2	133.0	81.0
CAGE Control	15-Jun-89	30	70	38.0	1170					32.0	[150]	1650.0	630.0	700.0	16.6	497.0	39.0	245.0	91.0
CAGE Control	15-Jun-89	45	80	37.5	1170	7.29	42.2	55.0		29.0	[116]	1630.0	627.5	553.0	16.8	441.0	39.4	126.0	85.4
CAGE Control	15-Jun-89	60	80	37.5	1170	7.34	43.0	57.0	22.0	26.0	[105]	1670.0	625.0	602.0	13.8	441.0	32.0	210.0	76.4
CAGE Control	15-Jun-89	75	70	37.5	1170	7.35	39.0	164.0	21.4	28.0	90.0	1800.0	645.0	434.0	12.6	329.0	40.0	161.0	80.0
CAGE Control	15-Jun-89	90	70	37.5	1170	7.33	40.5	137.8	21.4	21.0	86.0	1700.0	615.0	546.0	13.0	385.0	33.0	154.0	82.0
CAGE Control	15-Jun-89	105	70	37.5	1188	7.33	40.5	134.9	21.5	25.0	[111]	1780.0	590.0	686.0	17.2	546.0	42.0	266.0	81.2
CAGE Control	15-Jun-89	120	80	37.0	1188	7.32	38.5	138.7	19.8	23.0	[42]	1645.0	600.0	637.0	17.0	462.0	43.0	245.0	92.0
CAGE Control	15-Jun-89	135	70	37.0	1188	7.31	38.4	137.0	19.2	25.0	84.0	1410.0	585.0						
CAGE Control	15-Jun-89	150	70		1188	7.35	35.8	125.0	20.0	34.0	85.0	1405.0	515.0	329.0	15.8	245.0	40.0	161.0	95.0
CAGE Control	15-Jun-89	165	70	38.0	1152	7.35	38.2	135.4	20.9	26.0	66.0	1430.0	572.5	497.0	11.6	245.0	42.0	210.0	86.0
CAGE Control	15-Jun-89	180	70	38.5	1152	7.36	37.2	112.2	21.1	29.0	83.0			553.0	14.0	462.0	41.6	175.0	82.0
CAGE Control	15-Nov-89	-120	105	39.2	1080	7.39	39.8	122.9	24.1										
CAGE Control	15-Nov-89	-105	105	39.2	1080	7.41	37.7	126.9	23.8			940.0							
CAGE Control	15-Nov-89	-90	105	39.1	1080	7.40	35.0	122.8	21.6		[71]	940.0	440.0	[434]	[18]	[283]	[39]	[262]	[71]
CAGE Control	15-Nov-89	-75	100	39.1	1080	7.40	34.0	121.9	21.1	24.0	57.0	1010.0	437.5	262.0	19.0	248.0	41.6	213.0	86.0
CAGE Control	15-Nov-89	-60	100	39.1	1080	7.38	32.3	117.5	19.2	[16]	41.0	1000.0	425.0	227.0	17.6	259.0	40.0	178.0	83.0
CAGE Control	15-Nov-89	-45	100	39.3	1080	7.39	35.8	118.5	21.9	23.0	38.0	990.0	455.0	347.3	17.1	262.3	38.0	249.6	85.4
CAGE Control	15-Nov-89	-30	95	39.3	1080	7.39	35.0	109.0	20.8	24.0	59.0	980.0	495.0	326.7	16.7	225.0	37.3	197.2	84.7
CAGE Control	15-Nov-89	-15	100	39.3	1080	7.38	36.6	103.4	23.6	32.0	59.0			284.3	15.1	226.0	37.7	170.4	83.4
CAGE Control	15-Nov-89	0	100	39.4	1080	7.40	37.9	87.4	23.1	36.0	51.0	920.0	485.0	315.7	14.7	213.0	36.7	181.0	84.0
CAGE Control	15-Nov-89	15	100	39.4	1080	7.39	42.4	141.2	25.6	[42]	59.0	940.0	520.0	241.3	14.0	176.0	35.0	207.4	72.0
CAGE Control	15-Nov-89	30	90	39.5	1080	7.37	38.0	147.0	21.7	35.0	66.0	960.0	550.0	215.3	13.5	154.8	35.3	159.2	71.6
CAGE Control	15-Nov-89	45	90	39.5	1080	7.39	35.3	162.3	21.2	[62]	52.0			234.0	18.0	283.3	40.0	174.0	86.2
CAGE Control	15-Nov-89	60	90	39.3	1080	7.38	38.7	160.8	22.9	[21]	[74]			193.3	18.0	193.3	40.0	136.2	86.8
CAGE Control	15-Nov-89	75	90	39.3	1080	7.40	41.8	156.1	25.5	25.0	69.0			145.7	15.3	142.0	42.3	109.0	91.0
CAGE Control	15-Nov-89	90	90	39.1	1080	7.38	40.5	148.3	24.0	29.0	75.0			274.0	14.6	217.0	38.0	184.8	92.6
CAGE Control	15-Nov-89	105		39.1	1080	7.37	38.5	157.1	22.2	31.0	71.0			238.7	14.5	208.3	44.3	160.8	90.4
CAGE Control	15-Nov-89	120	100	38.8	1080	7.39	42.4	161.6	25.7	28.0	[76]								
CAGE Control	15-Nov-89	135	100	38.7						[53]	64.0								
CAGE Control	15-Nov-89	150	100	38.7		7.27	63.4	139.1	29.3	[38]	[72]			244.7	14.8	239.0	38.3	168.4	88.0
CAGE Control	15-Nov-89	165								[40]	[92]								
CAGE Control	15-Nov-89	180																	
CAGE Control	25-Aug-88	-120																	
CAGE Control	25-Aug-88	-105	110	37.0	600	7.42	35.8	181.4	23.4	96.0	85.0	2350.0	73.0	203.0	21.0	171.0	44.6	129.0	87.4
CAGE Control	25-Aug-88	-90	110	37.0	600	7.44	34.3	179.7	23.4	131.0	150.0	2380.0	72.0	220.0	20.2	252.0	46.0	87.5	81.8
CAGE Control	25-Aug-88	-75	100	37.0	600	7.45	34.3	149.7	23.6	104.4	77.8	2300.0	71.0	119.0	12.2	129.0	42.2	126.0	77.0
CAGE Control	25-Aug-88	-60	100	37.0	600	7.41	35.5	148.1	22.5	112.8	92.2	2665.0	71.0	105.0	18.4	108.0	42.0	91.0	76.2
CAGE Control	25-Aug-88	-45	90	37.0	600	7.47	36.6	127.5	26.7	86.0	73.0	2630.0	73.0	241.0	19.4	199.0	46.2	140.0	85.4
CAGE Control	25-Aug-88	-30	90	37.0	525	7.43	34.3	134.1	22.7	135.6	69.0	2310.0	75.0	199.0	21.0	276.0	47.8	105.0	84.5
CAGE Control	25-Aug-88	-15	90	37.0	525	7.37	42.0	105.5	24.4	117.3	96.6	2310.0	71.0	154.0	19.0	171.0	48.2	101.0	85.6
CAGE Control	25-Aug-88	0	90	37.0	525	7.33	35.8	137.0	19.0	138.3	94.6	2470.0	73.0	115.0	20.6	133.0	50.2	52.5	85.4
CAGE Control	25-Aug-88	15	90	37.0	525	7.41	38.5	140.8	24.0	132.4	125.0	2570.0	69.0	101.0	19.2	87.5		31.5	82.4
CAGE Control	25-Aug-88	30	90	37.0	525	7.38	38.9	144.4	23.0	86.7	143.0	2500.0	71.0						
CAGE Control	25-Aug-88	45	100	37.2	275	7.38	40.1	146.3	23.9	135.5	134.0	2630.0	70.0	185.0	19.6	161.0	45.6	70.0	76.0
CAGE Control	25-Aug-88	60	100	37.0	525	7.43	37.2	152.1	24.8	116.8	148.0	2580.0		213.0	20.3	192.0	47.4	108.0	77.2
CAGE Control	25-Aug-88	75	100	37.0	525	7.40	38.5	153.0	23.8	90.2	171.0	2400.0	71.0	108.0	20.0	150.0	47.8	70.0	77.6
CAGE Control	25-Aug-88	90	100	37.0	525	7.40	37.2	150.0	22.8	106.3	120.0	2400.0	69.0	136.0	12.4	161.0	35.2	112.0	76.2
CAGE Control	25-Aug-88	105	100	37.0	525	7.42	33.5	162.3	21.6	91.3	119.0	2280.0	71.0	136.0	14.0	147.0	43.4	84.0	79.0
CAGE Control	25-Aug-88	120	105	37.0	525	7.43	41.3	150.5	27.2	110.7	141.0	2210.0	71.0	119.0	13.0	143.0	45.4	49.0	85.4
CAGE Control	25-Aug-88	135	100	37.0	525	7.40	39.0	171.1	23.8	83.8	93.0	2220.0	71.0	136.0	15.6	101.0	42.0	80.5	80.0
CAGE Control	25-Aug-88	150	100	37.0	525	7.34	39.0	171.8	21.1	97.2	85.0	2070.0	73.0	94.5	19.6	182.0	45.6	45.5	81.2
CAGE Control	25-Aug-88	165	100	37.0	525	7.44	30.4	167.1	20.5	101.1	78.0	1900.0	72.0	122.0	15.4	122.0	46.2	87.5	91.4
CAGE Control	25-Aug-88	180	90	37.0	525	7.44	34.6	171.1	23.3	93.4	69.0	1910.0	71.0	143.0	12.2	112.0	43.6	126.0	78.6
CAGE Control	22-Jun-89	-120	110	39.0	900	7.55	37.2	97.2	32.5	42.0	45.0	2250.0	490.0	[724]	16.0	[720]	41.0	[201]	72.0
CAGE Control	22-Jun-89	-105	110	39.0	900	7.41	44.0	136.3	27.5	50.0	39.0	1980.0	500.0	[721]	17.0	[630]	43.2	[243]	75.4
CAGE Control	22-Jun-89	-90	95	39.0	990	7.46	39.0	125.2	27.5	36.0	[25]	1910.0	495.0	[696]	17.0	[647]	45.6	[147]	74.5
CAGE Control	22-Jun-89	-75	95	39.0	990	7.46	38.7	148.0	26.8	30.0	[21]	1910.0	490.0	[554]	14.8	[421]	44.8	[160]	82.0
CAGE Control	22-Jun-89	-60	95	39.0	990	7.48	33.0	145.8	24.2	[27]	[21]	2000.0	475.0	[554]	16.0	[377]	43.6	[134]	81.3
CAGE Control	22-Jun-89	-45	95	39.0	990		38.4			[27]	[26]	2140.0	475.0	[635]	15.4	[398]	40.1	[158]	85.6
CAGE Control	22-Jun-89	-30	95	39.0	954	7.40	37.3	148.9	23.2	29.0	35.0	2150.0	510.0	[650]	15.4	[365]	38.8	[137]	79.3
CAGE Control	22-Jun-89	-15	100	39.0	954	7.41	37.5	153.1	23.6	45.0	44.0	2190.0	500.0	[565]	15.0	[323]	38.9	[128]	78.0
CAGE Control	22-Jun-89	0	100	39.0	954	7.42	34.5	148.9	22.3	[57]	[96]	2230.0	490.0	312.7	14.7	116.7	31.1	96.6	75.0
CAGE Control	22-Jun-89	15	100	39.0	900	7.41	35.6	128.6	22.5	35.0	32.0	2700.0		303.3	13.7	175.0	28.7	78.4	75.3
CAGE Control	22-Jun-89	30	100	38.5	846	7.40	36.6	134.5	22.5	46.0	41.0	2520.0	480.0	324.3	14.3	193.7	30.7	81.2	69.7
CAGE Control	22-Jun-89	45	95	38.5	846	7.35	36.9	136.0	20.5	47.0	39.0	2540.0	520.0	282.0	14.1	177.0	29.9	64.4	70.3
CAGE Control	22-Jun-89	60	95	38.5	846	7.41	36.3	134.4	23.1	50.0	45.0	2420.0	510.0	242.7	13.5	149.3	27.7	79.8	74.6
CAGE Control	22-Jun-89	75	100	38.5	846	7.39	39.1	128.4	23.8	43.0	50.0	2410.0	470.0	221.7	14.4	158.7	28.6	67.2	71.5
CAGE Control	22-Jun-89	90	100	38.5	846	7.38	37.9	132.8	22.1	55.0	63.0	2400.0	490.0	287.0	13.7	147.0	27.8	92.4	73.1
CAGE Control	22-Jun-89	105	95	38.5	846	7.39	35.0	135.2	21.1	[55]	[62]	2330.0	455.0	324.3	14.3	186.7	28.7	58.8	69.3
CAGE Control	22-Jun-89	120	95	38.5	826	7.38	38.5	137.0	22.9	[58]	[65]	2300.0	500.0	235.7	13.7	156.3	29.7	70.0	71.6
CAGE Control	22-Jun-89	135	90	38.5	826	7.38	41.6	133.4	24.9	[57	[53]	2380.0	475.0	242.7	13.7	121.3	27.6	72.8	72.3
CAGE Control	22-Jun-89	150	90	38.0	826	7.38	36.3	129.8		[63]	[63]	2200.0	480.0	226.3	13.7	156.3	29.2	51.8	79.9
CAGE Control	22-Jun-89	165										2200.0							
CAGE Control	22-Jun-89	180																	
CAGE Control	17-Aug-88	-120	120		675	7.45	36.5	106.1	25.2										
CAGE Control	17-Aug-88	-105	120	38.0	675	7.32	43.5	242.7	22.4										
CAGE Control	17-Aug-88	-90	110	38.0	675	7.36	43.0	202.6	24.2	110.0	105.0			182.0	18.6	199.0	44.2	87.5	80.0
CAGE Control	17-Aug-88	-75	110	38.2	700	7.35	40.2	216.7	21.9	94.8	94.4	1500.0	61.0	227.0	18.2	213.0	45.6	101.0	76.8
CAGE Control	17-Aug-88	-60	110	38.2	700	7.39	36.9	196.3	22.2	78.1	94.2	1510.0	63.0	182.0	18.8	185.0	44.4	77.0	76.0
CAGE Control	17-Aug-88	-45	110	38.0	700	7.35	37.1	207.8	20.3	80.2		1560.0	62.0	217.0	19.2	234.0	46.8	87.5	79.0
CAGE Control	17-Aug-88	-30	110	38.0	675	7.39	32.0	171.6	19.3	62.5		1580.0	64.0	143.0	17.8	157.0	46.6	56.0	81.8
CAGE Control	17-Aug-88	-15	110	38.0	675	7.35	33.0	179.9	18.2	99.5	106.9	1520.0	66.0						
CAGE Control	17-Aug-88	0	110	38.0	675	7.36	33.2	170.5	18.8	64.8		1520.0	70.0	220.0	16.0	182.0	44.4	49.0	83.6
CAGE Control	17-Aug-88	15	110	38.0	600	7.37	31.8	163.1	18.3	101.8	84.4	1520.0	68.0	168.0	17.6	136.0	47.0	56.0	81.0
CAGE Control	17-Aug-88	30	110	38.0	600	7.32	39.2	165.4	19.9	65.5		1500.0	68.0	182.0	14.6	87.5	41.8	70.0	81.0
CAGE Control	17-Aug-88	45	110	38.0	600	7.30	42.9	165.9	21.2	90.3		1430.0	68.0	115.0	14.8	94.5	44.0	59.5	86.6
CAGE Control	17-Aug-88	60	110	38.0	675	7.31	37.6	168.3	19.0	80.7	85.0	1400.0	68.0	178.0	15.8	108.0	37.6	70.0	81.6
CAGE Control	17-Aug-88	75	110	38.0	675	7.28	43.1	171.5	20.3	80.5	84.1	1390.0		115.0	17.8	98.0	46.0	38.5	86.4
CAGE Control	17-Aug-88	90	110	38.0	675	7.33	38.0	170.0	20.0	80.3	84.1	1350.0	68.0	206.0	15.8	119.0	44.0	84.0	81.6
CAGE Control	17-Aug-88	105	110	38.0	675	7.34	35.7	163.8	19.0	81.1	88.4	1330.0	68.0	154.0	14.8	94.5	39.6	80.5	84.8
CAGE Control	17-Aug-88	120	110	38.0	675	7.36	38.1	168.0	21.3	[46]	61.1	1325.0	64.0	150.0	15.4	101.0	42.4	42.0	79.0
CAGE Control	17-Aug-88	135	110	37.0	675	7.37	36.7	159.5	21.2	[46]	70.3	1235.0	64.0	157.0	18.0	122.0	44.0	56.0	85.8
CAGE Control	17-Aug-88	150	110	37.0	675	7.34	39.8	171.4	21.4	[38]	78.1	1235.0		157.0	18.0	122.0	44.0	56.0	85.8
CAGE Control	17-Aug-88	165	100	37.0	675	7.36	37.2	170.1	21.1	54.1	89.2	1200.0	68.0	133.0	14.8	122.0	40.6	49.0	88.0
CAGE Control	17-Aug-88	180	110	37.0	675	7.37	38.1	163.2	22.0	[46]	94.7	1240.0						63.0	83.2

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
AGE Control	30-Jun-89	-120	95	39.0	1062	7.38	42.3	150.0	25.0	120.0	94.0			760.0	17.2	735.0	41.5	380.6	81.0
CAGE Control	30-Jun-89	-105	105	38.5	1062	7.37	37.7	162.7	23.2					774.7	18.6	709.3	43.9	333.2	83.4
CAGE Control	30-Jun-89	-90	100	38.5	1062	7.44	38.9	125.9	26.1	78.8	76.2			700.0	18.0	660.0	42.3	301.0	81.6
CAGE Control	30-Jun-89	-75	100	38.5	1062	7.40	41.0	[98]	25.0	96.1				620.7	18.5	446.0	41.3	225.4	88.8
CAGE Control	30-Jun-89	-60	100	38.5	1062	7.39	35.7	155.2	21.0	75.8	51.1	1550.0	890.0	730.3	18.0	506.3	43.3	225.4	88.8
CAGE Control	30-Jun-89	-45	100	38.5	1062	7.45	34.0	175.0	23.3	90.3	[46]	1560.0	885.0	665.0	17.4	436.6	40.8	219.8	81.0
CAGE Control	30-Jun-89	-30	105	38.5	1044	7.35	35.8	177.3	19.5	94.4	53.5	1520.0	825.0	560.0	16.9	408.0	41.2	156.8	79.2
CAGE Control	30-Jun-89	-15	105	38.5	1044	7.42	35.2	176.8	22.6	93.4	50.3	1505.0	840.0	625.0	16.9	480.7	39.5	200.0	86.0
CAGE Control	30-Jun-89	0	95	38.5	1008	7.39	35.7	177.8	21.7	[122]		1630.0	880.0	485.3	17.3	343.0	42.1	185.2	84.6
CAGE Control	30-Jun-89	15	105	38.5	990	7.39	37.0	171.0	22.1		[116]	1600.0		480.7	17.3	317.3	42.3	149.8	81.3
CAGE Control	30-Jun-89	30	105	38.5	990	7.40	36.9	169.1	22.5			1430.0	875.0	534.0	16.8	317.3	40.8	175.0	82.5
CAGE Control	30-Jun-89	45	110	38.5	990	7.36	40.5	170.3	22.9	[123]	76.2	1450.0		581.0	16.2	301.0	39.0	142.8	83.6
CAGE Control	30-Jun-89	60	100	38.5	990	7.35	39.8	175.8	22.0			1450.0	900.0	667.3	16.3	427.0	37.1	201.8	85.8
CAGE Control	30-Jun-89	75	100	38.5	990	7.35	38.2	184.6	21.0			1300.0		569.3	16.7	315.0	40.6	165.2	82.2
CAGE Control	30-Jun-89	90	100	38.5	1062	7.39	35.0	185.0	20.7	[123]	78.0	1300.0	920.0	520.3	17.2	394.3	43.3	152.6	88.4
CAGE Control	30-Jun-89	105	100	38.5	1062	7.37	36.6	185.3	21.2	[132]	92.4	1790.0		518.0	16.4	340.7	42.5	189.0	85.4
CAGE Control	30-Jun-89	120	80	38.0	1026	7.39	35.1	177.0	20.6	[132]	91.0	1420.0	910.0	527.0	16.3	306.0	43.2	187.0	84.4
CAGE Control	30-Jun-89	135	80	38.0	1026	7.42	36.3	183.9	23.3	[139]	[104]	1390.0		459.7	14.9	221.7	38.3	127.4	86.8
CAGE Control	30-Jun-89	150	70	38.0	1026	7.40	35.0	173.2	21.4	99.3	82.1	1360.0	890.0	448.0	15.8	256.7	42.7	158.2	86.2
CAGE Control	30-Jun-89	165	80	38.0	990	7.33	36.6	187.0	19.4	[124]	[101]	1500.0	910.0	618.3	15.9	270.7	40.8	214.2	88.6
CAGE Control	30-Jun-89	180	100	38.0	990	7.36	35.2	189.9	19.6	[118]	85.7	1380.0	920.0	422.0	11.9	189.0	37.6	198.8	87.3
CAGE Control	16-May-91	-120	95	38.6	825	7.34	35.0	133.0	19.0					1064.0	18.0	1076.0	50.0	548.0	90.0
CAGE Control	16-May-91	-105	105	38.5	825	7.32	42.0	141.0	21.0	63.0	56.0								
CAGE Control	16-May-91	-90	105	38.7	825	7.36	39.0	136.0	22.0	79.0	67.0			809.0	18.0	1185.0	56.0	621.0	104.0
CAGE Control	16-May-91	-75			825														
CAGE Control	16-May-91	-60	90	39.0	825	7.31	42.0	130.0	21.0	47.0	36.0			949.0	16.0	268.0	56.0	912.0	110.0
CAGE Control	16-May-91	-45	95	39.1	825	7.34	39.0	131.0	21.0	49.0	38.0								
CAGE Control	16-May-91	-30	95	39.1	825	7.30	40.0	127.0	20.0	61.0	46.0								
CAGE Control	16-May-91	-15	100	39.1	825	7.33	43.0	128.0	23.0	42.0	33.0			465.0	14.0	720.0	50.0	468.0	98.0
CAGE Control	16-May-91	0	100	39.1	825	7.30	42.0	119.0	20.0	57.0	38.0			507.0	14.0	14.0	749.0	52.0	527.0
CAGE Control	16-May-91	15	100	38.9	825	7.30	46.0	120.0	23.0	55.0	41.0			603.0	14.0	724.0	50.0	580.0	90.0
CAGE Control	16-May-91	30	100	38.8	825	7.30	43.0	128.0	22.0	71.0	65.0			526.0	14.0	728.0	48.0	536.0	84.0
CAGE Control	16-May-91	45	100	38.8	825	7.30	51.0	121.0	24.0	57.0	48.0			700.0	14.0	828.0	50.0	574.0	86.0
CAGE Control	16-May-91	60	105	38.2	825	7.30	47.0	128.0	22.0	49.0	48.0			617.0	14.0	845.0	48.0	705.0	86.0
CAGE Control	16-May-91	75	95	37.9	825	7.25	48.0	127.0	21.0	60.0	57.0			870.0	14.0	848.0	48.0	705.0	86.0
CAGE Control	16-May-91	90	105	37.7	825	7.27	52.0	130.0	24.0	54.0	54.0			978.0	16.0	1186.0	48.0	906.0	86.0
CAGE Control	16-May-91	105	100	37.6	825	7.29	44.0	134.0	21.0	70.0	64.0			753.0	12.0	1013.0	48.0	641.0	80.0
CAGE Control	16-May-91	120	105	37.7	825	7.28	46.0	125.0	22.0	61.0	63.0			600.0	14.0	787.0	48.0	548.0	86.0
CAGE Control	16-May-91	135	95	38.1	825	7.28	52.0	126.0	24.7	68.0	75.0			508.0	12.0	675.0	48.0	517.0	88.0
CAGE Control	16-May-91	150	95	38.2	900	7.28	49.0	125.0	23.0					477.0	10.0	655.0	48.0	441.0	86.0
CAGE Control	16-May-91	165	90	38.5	900	7.27	44.0	119.0	20.0					651.0	14.0	762.0	42.0	584.0	84.0
CAGE Control	16-May-91	180																	
CAGE Control	22-May-91	-120	110	39.5	60	7.36	34.0	125.0	19.0	34.0				722.0	10.0	693.0	34.0	517.0	70.0
CAGE Control	22-May-91	-105	110	39.5	60	7.37	31.7	130.0	18.0	19.0	12.0			855.0	12.0	862.0	32.0	535.0	68.0
CAGE Control	22-May-91	-90	110	39.2	55	7.37	29.0	137.0	17.0					870.0	12.0	853.0	32.0	508.0	64.0
CAGE Control	22-May-91	-75	110	39.3	50	7.35	33.0	124.0	18.0	19.0	11.0			588.0	12.0	568.0	32.0	368.0	68.0
CAGE Control	22-May-91	-60	100	39.5	50	7.33	33.0	124.0	16.7	19.0	14.0			588.0	12.0	592.0	30.0	402.0	66.0
CAGE Control	22-May-91	-45	100	39.6	60	7.34	33.0	75.0	18.0	15.0	17.0			530.0	10.0	421.0	26.0	306.0	60.0
CAGE Control	22-May-91	-30	100	39.5	60	7.26	34.0	141.0	15.0					530.0	10.0	774.0	50.0	615.0	84.0
CAGE Control	22-May-91	-15		39.2	60	7.30	30.0	137.0	14.0					725.0	15.0	913.0	50.0	667.0	86.0
CAGE Control	22-May-91	0	100	39.0	60	7.26	35.0	144.0	16.0	15.0	10.0			666.0	12.0	982.0	52.0	724.0	84.0
CAGE Control	22-May-91	15	90	39.0	60	7.29	35.0	146.0	16.8	14.0	13.0			691.0	12.0	725.0	30.0	477.0	64.0
CAGE Control	22-May-91	30	90	38.9	60									674.0	10.0	624.0	28.0	371.0	58.0
CAGE Control	22-May-91	45	90	38.7	60	7.26	34.0	138.0	15.0	17.0	12.0			751.0	10.0	721.0	28.0	436.0	62.0
CAGE Control	22-May-91	60	90	38.5	60	7.27	32.0	128.0	15.0					739.0	10.0	715.0	26.0	450.0	60.0
CAGE Control	22-May-91	75	90	38.5	60	7.24	35.0	148.0	15.0	18.0	15.0			789.0	10.0	812.0	26.0	448.0	58.0
CAGE Control	22-May-91	90	90	38.4	60	7.26	33.0	148.0	15.0	18.0	10.0			901.0	12.0	1001.0	30.0	651.0	62.0
CAGE Control	22-May-91	105	80	38.4	60	7.25	33.0	140.0	14.0	18.0	18.0			728.0	10.0	581.0	28.0	350.0	64.0
CAGE Control	22-May-91	120	80	38.3	55	7.24	31.0	113.0	13.0	11.0	17.0			774.0	10.0	802.0	26.0	406.0	58.0
CAGE Control	22-May-91	135	80	38.2	55	7.20	29.0	125.0	12.0	18.0	16.0			810.0	10.0	847.0	26.0	498.0	62.0
CAGE Control	22-May-91	150	80	38.1	55	7.22	35.0	129.0	14.0	15.0	17.0			778.0	12.0	977.0	28.0	592.0	62.0
CAGE Control	22-May-91	165	80	38.0	55	7.26	35.0	137.0	16.0	16.0	17.0			871.0	10.0	1030.0	28.0	534.0	60.0
CAGE Control	22-May-91	180	75	37.9	55	7.25	35.0	141.0	15.0	15.0	21.0			934.0	10.0	1032.0	28.0	578.0	60.0
CAGE Control	17-May-91	-120	110	39.2	900	7.35	42.0	103.0	24.0					1214.0	12.0	1338.0	50.0	964.0	104.0
CAGE Control	17-May-91	-105	117	39.4	900	7.33	39.0	109.0	21.0	40.0	16.0			850.0	14.0	1100.0	54.0	800.0	110.0
CAGE Control	17-May-91	-90	117	39.3	900	7.39	33.0	117.0	20.0	34.0	15.0			369.0	18.0	690.0	56.0	385.0	98.0
CAGE Control	17-May-91	-75	117	38.8	900	7.40													
CAGE Control	17-May-91	-60	110	38.7	900	7.38	35.0	118.0	21.0	35.0	21.0			581.0	10.0	604.0	48.0	520.0	100.0
CAGE Control	17-May-91	-45	110	38.7	900	7.36	37.0	106.0	22.0	34.0	15.0			623.0	18.0	873.0	58.0	607.0	106.0
CAGE Control	17-May-91	-30	105	38.7	900														
CAGE Control	17-May-91	-15	105	38.7	900	7.36	38.0	86.0	20.9	26.0	18.0			741.0	14.0	708.0	54.0	352.0	94.0
CAGE Control	17-May-91	0	110	38.7	900	7.31	46.0	114.0	24.0	28.0	16.0			1192.0	14.0	1176.0	50.0	80.0	108.0
CAGE Control	17-May-91	15	110		900														
CAGE Control	17-May-91	30	110	38.3	900	7.31	42.0	124.0	21.0	29.0	16.0								
CAGE Control	17-May-91	45	110		900														
CAGE Control	17-May-91	60	110	38.2	900	7.26	45.0	132.0	20.0					717.0	14.0	1176.0	50.0	80.0	108.0
CAGE Control	17-May-91	75	110		900														
CAGE Control	17-May-91	90	110	38.2	900	7.27	47.0	119.0	22.0	31.0	15.0			1132.0	16.0	1330.0	54.0	806.0	110.0
CAGE Control	17-May-91	105	110	38.3	900	7.29	44.0	125.0	21.0	23.0	15.0								
CAGE Control	17-May-91	120	110	38.3	900	7.28	49.0	123.0	23.0					1080.0	14.0	1121.0	54.0	692.0	114.0
CAGE Control	17-May-91	135	110	38.3	1050	7.30	44.0	83.0	21.0										
CAGE Control	17-May-91	150	110		1050									645.0	12.0	632.0	52.0	467.0	110.0
CAGE Control	17-May-91	165	110	38.4	1050	7.30	42.0	124.0	19.0					764.0	14.0	801.0	52.0	400.0	92.0
CAGE Control	17-May-91	180	110	38.8	1050	7.26	48.0	118.0	22.0					447.0	10.0	513.0	50.0	376.0	98.0
CAGE Control	23-May-91	-120	95	39.0	825	7.33	35.0	133.0	18.0	99.0	46.0			877.0	20.0	1195.0	46.0	910.0	82.0
CAGE Control	23-May-91	-105	95	39.0	825	7.36	35.0	119.0	20.0	63.0	37.0			721.0	20.0	1064.0	44.0	832.0	80.0
CAGE Control	23-May-91	-90	85	38.8	825	7.34	38.0	89.0	20.0	74.0	43.0			743.0	20.0	1036.0	46.0	792.0	82.0
CAGE Control	23-May-91	-75	85	38.8	825	7.34	40.0	108.0	21.0	69.0	36.0			727.0	16.0	957.0	46.0	717.0	74.0
CAGE Control	23-May-91	-60	95	38.6	825	7.35	35.0	132.0	19.0	69.0	36.0			865.0	16.0	973.0	46.0	719.0	80.0
CAGE Control	23-May-91	-45	90	38.6	825	7.29	37.0	133.0	18.0	62.0	38.0			1047.0	16.0	1104.0	40.0	785.0	78.0
CAGE Control	23-May-91	-30	90	38.7	825	7.35	36.0	124.0	20.0	57.0	36.0			890.0	18.0	1011.0	44.0	702.0	78.0
CAGE Control	23-May-91	-15	90	38.6	825	7.37	38.0	121.0	20.0	57.0	43.0			1179.0	16.0	117.0	38.0	785.0	78.0
CAGE Control	23 May-91	0	85	38.7	825	7.32	38.0	98.0	18.0	55.0	35.0			1408.0	14.0	1259.0	34.0	824.0	72.0
CAGE Control	23-May-91	15	85	38.6	825	7.29	35.0	101.0	17.0	56.0	44.0			1280.0	16.0	1099.0	36.0	845.0	72.0
CAGE Control	23-May-91	30	85	38.6	825	7.27	39.0	93.0	18.0	55.0	51.0			1359.0	14.0	1262.0	34.0	817.0	72.0
CAGE Control	23-May-91	45	85	38.6	825	7.27	42.0	86.0	19.0	45.0	51.0			1013.0	14.0	806.0	30.0	647.0	70.0
CAGE Control	23-May-91	60	85	38.5	825	7.26	40.0	85.0	18.0	57.0	49.0			1196.0	14.0	1072.0	34.0	751.0	72.0
CAGE Control	23-May-91	75	90	38.4	825					68.0	66.0			1002.0	14.0	846.0	34.0	627.0	72.0
CAGE Control	23-May-91	90	90	38.4	825	7.25	41.8	92.0	18.0	71.0	66.0			1282.0	14.0	1170.0	34.0	892.0	72.0
CAGE Control	23-May-91	105	90	38.4	825	7.27	39.9	112.0	18.0	68.0	72.0			1106.0	14.0	914.0	34.0	730.0	70.0
CAGE Control	23-May-91	120	90	38.4	825	7.25	39.5	101.4	17.0	65.0	71.0			1275.0	14.0	1043.0	32.0	758.0	70.0
CAGE Control	23-May-91	135	90	38.0	825	7.27	37.0	110.0	17.0	65.0	78.0			806.0	14.0	840.0	30.0	621.0	70.0
CAGE Control	23-May-91	150	90	37.9	825	7.26	35.0	106.0	16.0	63.0	69.0			935.0	14.0	980.0	28.0	663.0	64.0
CAGE Control	23-May-91	165	90	37.9	825	7.28	36.0	144.0	18.0	55.0	62.0			837.0	14.0	803.0	30.0	627.0	70.0
CAGE Control	23-May-91	180	90	37.9	825	7.24	40.6	149.0	17.0	51.0	58.0			1281.0	14.0	1201.0	34.0	794.0	70.0

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE Control Leucocytopenic	1-May-90	-120	115	37.8	450	7.29	37.0	140.0	18.0			1530.0	817.5	440.0	12.0	361.0	26.0	212.0	65.0
CAGE Control Leucocytopenic	1-May-90	-105	110	37.8	450	7.28	36.6	131.0	17.0	57.0	20.0	1600.0	607.5	367.0	12.0	324.0	25.0	141.0	74.0
CAGE Control Leucocytopenic	1-May-90	-90	113	37.8	450	7.27	35.0	114.8	16.1	72.0		1590.0	605.0	414.0	11.0	323.0	28.0	180.0	69.0
CAGE Control Leucocytopenic	1-May-90	-75	112	37.7	450	7.29	31.2	125.6	14.8	72.0	16.0	1560.0		428.0	11.0	296.0	28.0	174.0	74.0
CAGE Control Leucocytopenic	1-May-90	-60	115	37.7	450	7.27	35.0	133.0	16.1	69.0	18.0	1645.0	625.0	455.0	11.0	339.0	27.0	205.0	70.0
CAGE Control Leucocytopenic	1-May-90	-45	111	37.7	450	7.28	33.1	133.7	15.4	59.0	16.0			461.0	11.0	325.0	28.0		70.0
CAGE Control Leucocytopenic	1-May-90	-30	103	37.6	405	7.28	35.0	128.8	16.1	54.0	23.0			437.0	11.0	332.0	25.0	208.0	69.0
CAGE Control Leucocytopenic	1-May-90	-15	106	37.7	450	7.27	33.0	128.0	15.0	57.0	38.0	1630.0	655.0	405.0	12.0	333.0	31.0	213.0	71.0
CAGE Control Leucocytopenic	1-May-90	0	107	37.7	450	7.26	37.0	123.0	17.0	65.0	20.0	1660.0	635.0	395.0	11.0	312.0	26.0	166.0	73.0
CAGE Control Leucocytopenic	1-May-90	15	110	37.7	450	7.27	39.0	124.0	18.0	61.0	26.0	1615.0	648.0	402.0	11.0	247.0	28.0	188.0	75.0
CAGE Control Leucocytopenic	1-May-90	30	110	37.8	450	7.27	37.3	120.0	17.0	57.0	33.0			408.0	11.0	279.0	26.0	167.0	70.0
CAGE Control Leucocytopenic	1-May-90	45	99	38.0	450	7.28	42.3	116.0	20.0	68.0	29.0	1600.0	662.0	368.0	11.0	253.0	24.0	141.0	69.0
CAGE Control Leucocytopenic	1-May-90	60	101	38.0	450	7.27	40.5	117.0	18.7	64.0	29.0	1630.0	686.0	319.0	11.0	184.0	23.0	118.0	72.0
CAGE Control Leucocytopenic	1-May-90	75	110	38.3	450	7.28	35.5	110.0	16.7	56.0	30.0			284.0	10.0	177.0	24.0	103.0	72.0
CAGE Control Leucocytopenic	1-May-90	90	95	38.3	450	7.28	37.5	108.0	17.7	55.0	28.0	1665.0	692.0	267.0	10.0	199.0	20.0		74.0
CAGE Control Leucocytopenic	1-May-90	105	101	38.5	450	7.27	37.1	102.4	17.3	54.0	37.0	1660.0	825.0	268.0	9.0	164.0	21.0	99.0	70.0
CAGE Control Leucocytopenic	1-May-90	120	102	38.7	450	7.28	47.2	119.0	22.6	60.0	41.0	1645.0	775.0	289.0	10.0	191.0	21.0	110.0	75.0
CAGE Control Leucocytopenic	1-May-90	135	100	38.7	450	7.32	39.0	106.0	22.5	60.0	35.0	1665.0	765.0	312.0	11.0	199.0	23.0	112.0	71.0
CAGE Control Leucocytopenic	1-May-90	150	101	39.0	400	7.32	38.2	109.0	18.8	55.0	34.0	1675.0	742.0	351.0	10.0	212.0	23.0	111.0	73.0
CAGE Control Leucocytopenic	1-May-90	165	93	39.1	400	7.32	37.3	108.0	19.5	52.0	38.0	1715.0	740.0	383.0	10.0	239.0	24.0	131.0	71.0
CAGE Control Leucocytopenic	1-May-90	180	91	39.1	400	7.31	34.1	110.5	17.4	54.0	40.0	1710.0	715.0	386.0	10.0	201.0	22.0	122.0	71.0
CAGE Control Leucocytopenic	7-Jun-90	-120	108	40.6	360	7.33	38.2	133.5	19.0		40.0	74.0	510.0	256.0	10.0	291.0	18.0	189.0	35.0
CAGE Control Leucocytopenic	7-Jun-90	-105	105	40.5	360	7.35	38.7	129.6	21.2	76.0	33.0	780.0	400.0	294.0	10.0	292.0	19.0	201.0	36.0
CAGE Control Leucocytopenic	7-Jun-90	-90	105	40.4	360	7.36	38.3	132.8	21.4	80.0	42.0	800.0		276.0	10.0	205.0	18.0	157.0	34.0
CAGE Control Leucocytopenic	7-Jun-90	-75	97	40.1	360	7.36	38.3	135.0	22.0	65.0	37.0	750.0	380.0	156.0	8.0	131.0	17.0		36.0
CAGE Control Leucocytopenic	7-Jun-90	-60	101	39.9	360	7.37	38.3	136.1	22.1	65.0	39.0	810.0	400.0	215.0	9.0	252.0	18.0	186.0	36.0
CAGE Control Leucocytopenic	7-Jun-90	-45	92	39.7	360	7.39	37.7	137.9	22.6	63.0	48.0	800.0	450.0	170.0	9.0	164.0	18.0	155.0	37.0
CAGE Control Leucocytopenic	7-Jun-90	-30	99	39.6	360	7.40	39.8	144.6	24.5	66.0	48.0	780.0	487.5	231.0	9.0	209.0	18.0	176.0	35.0
CAGE Control Leucocytopenic	7-Jun-90	-15	94	39.5	360	7.37	36.1	139.3	21.0	74.0	59.0	810.0	525.0	237.0	9.0	210.0	18.0	166.0	35.0
CAGE Control Leucocytopenic	7-Jun-90	0	94	39.3	360	7.39	37.8	143.0	22.8	82.0	67.0	760.0	550.0	239.0	9.0	211.0	18.0	164.0	36.0
CAGE Control Leucocytopenic	7-Jun-90	15	94	39.2	360	7.39	33.7	110.1	20.1			770.0	540.0	217.0	9.0	185.0	17.0	150.0	38.0
CAGE Control Leucocytopenic	7-Jun-90	30	100	39.0	360	7.38	36.9	147.5	21.7	59.0	59.0	750.0	632.5	294.0	10.0	292.0	18.0	208.0	36.0
CAGE Control Leucocytopenic	7-Jun-90	45	94	38.8	360	7.38	37.5	149.3	22.1	61.0	60.0	820.0	542.5	270.0	10.0	248.0	18.0	178.0	36.0
CAGE Control Leucocytopenic	7-Jun-90	60	93	38.7	360	7.37	39.1	148.0	22.3	60.0	56.0	870.0	570.0	120.0	10.0	104.0	18.0	78.0	35.0
CAGE Control Leucocytopenic	7-Jun-90	75	89	38.5	360	7.36	39.0	142.3	21.4			860.0		112.0	10.0	116.0	17.0	78.0	32.0
CAGE Control Leucocytopenic	7-Jun-90	90	87	38.4	360	7.33	40.3	154.4	21.4				575.0	108.0	9.0	121.0	17.0	94.0	31.0
CAGE Control Leucocytopenic	7-Jun-90	105	87	38.4	360	7.33	39.9	153.0	21.1			870.0	545.0	114.0	9.0	151.0	17.0	94.0	31.0
CAGE Control Leucocytopenic	7-Jun-90	120		38.4	360	7.31	39.3	151.8	19.8			810.0	565.0	118.0	9.0	124.0	16.0	82.0	28.0
CAGE Control Leucocytopenic	7-Jun-90	135	78	38.4	360	7.31	39.6	154.9	19.9			810.0	635.0	128.0	9.0	144.0	17.0	89.0	31.0
CAGE Control Leucocytopenic	7-Jun-90	150	87	38.4	360	7.33	34.3	145.6	18.0			840.0	532.5	142.0	11.0	216.0	18.0	127.0	33.0
CAGE Control Leucocytopenic	7-Jun-90	165	84	38.7	360	7.32	32.6	157.3	16.7			860.0		154.0	10.0	212.0	17.0	122.0	32.0
CAGE Control Leucocytopenic	7-Jun-90	180	85	38.8	360	7.29	35.2	150.0	17.0			820.0		130.0	9.0	142.0	17.0	86.0	31.0
CAGE Control Leucocytopenic	7-Dec-89	-120																	
CAGE Control Leucocytopenic	7-Dec-89	-105	104	37.7		7.44	36.6	153.1	25.1					147.0	19.0	234.0	35.0	171.0	62.0
CAGE Control Leucocytopenic	7-Dec-89	-90	108	37.7		7.41	41.4	112.4	26.4		110.0	520.0	740.0	154.0	19.0	204.0	33.0	144.0	59.0
CAGE Control Leucocytopenic	7-Dec-89	-75	108	37.6		7.40	36.3	104.8	22.3		95.0			166.0	19.0	240.0	36.0		60.0
CAGE Control Leucocytopenic	7-Dec-89	-60	100	37.5		7.44	42.7	99.7	29.0	65.0	69.0	530.0	830.0	173.0	18.0	184.0	35.0	185.0	59.0
CAGE Control Leucocytopenic	7-Dec-89	-45	108	37.5		7.48	37.1	102.9	27.3	70.0	80.0	490.0	790.0	135.0	19.0	188.0	35.0	156.0	59.0
CAGE Control Leucocytopenic	7-Dec-89	-30	110	37.7	720	7.37	38.0	81.0	22.0	69.0	94.0	490.0	800.0	142.0	19.0	176.0	35.0	148.0	61.0
CAGE Control Leucocytopenic	7-Dec-89	-15	110	37.6	720	7.41	40.0	93.0	26.0	52.0	102.0	520.0	800.0	144.0	18.8	184.0	35.0	160.0	58.6
CAGE Control Leucocytopenic	7-Dec-89	0	104	37.8		7.42	47.9	96.1	30.7	65.0	96.0			128.0	18.3	217.0	33.0	141.0	57.0
CAGE Control Leucocytopenic	7-Dec-89	15	100	37.9	720	7.40	41.9	134.5	26.1	49.0	70.0	490.0		135.0	18.4	179.0	35.1	165.0	57.6
CAGE Control Leucocytopenic	7-Dec-89	30	100	38.0	720	7.42	37.0	137.0	24.0	44.0	122.0	480.0	785.0	103.8	17.9	176.0	32.7	158.0	56.3
CAGE Control Leucocytopenic	7-Dec-89	45	100	38.0	792	7.38	44.0	125.0	26.0	70.0	96.0	510.0	805.0	131.0	15.9	137.0	32.9	162.8	54.2
CAGE Control Leucocytopenic	7-Dec-89	60	96	38.5	792	7.42	42.0	135.0	27.0	48.0	80.0	500.0		123.0	15.3	142.0	32.9	159.0	53.6
CAGE Control Leucocytopenic	7-Dec-89	75	96	38.6	792	7.45	43.0	127.0	30.0	52.0	72.0	460.0	790.0	142.0	14.0	156.0	32.0	131.0	53.0
CAGE Control Leucocytopenic	7-Dec-89	90	100	38.7	840	7.43	40.0	129.0	27.0	54.0	61.0	470.0	770.0	149.0	15.5	157.0	32.3	127.0	55.0
CAGE Control Leucocytopenic	7-Dec-89	105	100	38.8	840	7.45	36.0	138.0	25.0	62.0	55.0	440.0	825.0	128.0	13.0	114.0	32.0	130.0	54.0
CAGE Control Leucocytopenic	7-Dec-89	120	100	38.8	840	7.45	41.0	130.0	29.0	71.0	63.0	430.0	895.0	121.0	13.0	160.0	29.0	167.0	55.0
CAGE Control Leucocytopenic	7-Dec-89	135	100	38.8	840	7.44	38.0	135.0	26.0	54.0	52.0	480.0	880.0	107.0	13.0	112.0	32.1	116.0	50.2
CAGE Control Leucocytopenic	7-Dec-89	150	108	38.3	840	7.43	41.0	131.0	27.0	48.0	82.0	490.0	920.0						
CAGE Control Leucocytopenic	7-Dec-89	165	100	38.4	840	7.44	41.0	133.0	28.0	53.0	64.0	460.0	890.0	114.0	14.6	156.0	32.0	124.0	51.2
CAGE Control Leucocytopenic	7-Dec-89	180	104	38.2	840	7.43	40.0	130.0		50.0	65.0	450.0	750.0	143.0	14.9	149.0	31.9	134.0	53.9
CAGE Control Leucocytopenic	13-Jun-90	-120	82	38.9	540	7.13	35.1	140.6	11.6	89.0	123.0		520.0						
CAGE Control Leucocytopenic	13-Jun-90	-105	79	38.9	540	7.14	32.6	144.6	11.0	57.0	98.0		575.0	405.0	12.0	423.0	18.0	257.0	36.0
CAGE Control Leucocytopenic	13-Jun-90	-90	75	38.8	540	7.13	31.7	156.0	13.2	44.0	73.0			381.0	11.0	419.0	19.0	288.0	33.0
CAGE Control Leucocytopenic	13-Jun-90	-75	57	38.7	480	7.25	36.6	171.3	15.9	76.0	88.0		630.0	363.0	11.0	433.0	16.0	296.0	30.0
CAGE Control Leucocytopenic	13-Jun-90	-60	68	38.6	480	7.23	32.3	165.3	13.4	61.0	88.0		630.0	310.0	9.0	439.0	17.0	245.0	30.0
CAGE Control Leucocytopenic	13-Jun-90	-45	75	38.5	420	7.15	42.3	169.6	14.8	69.0	103.0		575.0	297.0	9.0	436.0	17.0	245.0	29.0
CAGE Control Leucocytopenic	13-Jun-90	-30	79	38.6	420	7.17	42.4	167.3	15.3	75.0	125.0		605.0	322.0	9.0	436.0	18.0	263.0	30.0
CAGE Control Leucocytopenic	13-Jun-90	-15	73	38.7	480	7.19	37.9	173.4	14.3	67.0	123.0		610.0	352.0	10.0	426.0	17.0	238.0	30.0
CAGE Control Leucocytopenic	13-Jun-90	0	56	38.9	480	7.23	33.1	175.5	13.7	54.0	105.0		640.0	355.0	10.0	455.0	17.0	240.0	29.0
CAGE Control Leucocytopenic	13-Jun-90	15	48	38.8	480	7.18	43.0	95.0	16.0	65.0	131.0		770.0	309.0	10.0	445.0	18.0	263.0	29.0
CAGE Control Leucocytopenic	13-Jun-90	30	48	38.7	540	7.14	40.4	116.0	13.8	55.0	116.0		785.0	298.0	11.0	433.0	16.0	205.0	30.0
CAGE Control Leucocytopenic	13-Jun-90	45	50	38.7	540	7.11	40.3	113.2	12.7	43.0	106.0		730.0	397.0	9.0	432.0	18.0	253.0	31.0
CAGE Control Leucocytopenic	13-Jun-90	60	55	38.7	540	7.14	43.0	104.0	14.0	49.0	131.0		715.0	364.0	10.0	434.0	19.0	290.0	31.0
CAGE Control Leucocytopenic	13-Jun-90	75	44	38.6	540	7.07	38.4	113.0	11.0	31.0	99.0		720.0	381.0	10.0	440.0	19.0	311.0	31.0
CAGE Control Leucocytopenic	13-Jun-90	90	33	38.6	540	7.06	33.0	128.0	9.3	19.0	83.0		775.0	447.0	10.0	437.0	21.0	418.0	34.0
CAGE Control Leucocytopenic	13-Jun-90	105	28	38.6	540	7.08	30.6	120.7	9.0	8.0	60.0		790.0	63.0	16.0	127.0	27.0	62.0	44.0
CAGE Control Leucocytopenic	13-Jun-90	120	26	38.6	540	7.04	27.3	112.4	7.4	13.0	61.0		760.0						
CAGE Control Leucocytopenic	13-Jun-90	135																	
CAGE Control Leucocytopenic	13-Jun-90	150																	
CAGE Control Leucocytopenic	13-Jun-90	165																	
CAGE Control Leucocytopenic	13-Jun-90	180																	
CAGE Control Leucocytopenic	16-Mar-90	-120	110	39.0	675	7.15	33.2	140.9	12.3										
CAGE Control Leucocytopenic	16-Mar-90	-105	110	38.5	675	7.16	33.6	120.0	11.9					231.0	15.0	287.0	40.0		96.0
CAGE Control Leucocytopenic	16-Mar-90	-90	110	38.5	675	7.09	39.5	117.0	12.3	58.0	46.0			168.0	13.0	248.0	39.0	42.0	62.0
CAGE Control Leucocytopenic	16-Mar-90	-75	110	38.5	675					53.0	44.0			247.0	14.0	203.0	43.0	74.0	79.0
CAGE Control Leucocytopenic	16-Mar-90	-60	110	38.1	675	7.12	36.7	121.7	12.1	56.0	50.0			243.0	13.0	234.0	38.0	115.0	80.0
CAGE Control Leucocytopenic	16-Mar-90	-45	110	38.1	675	7.22	37.0	109.0	15.4	45.0	45.0			224.0	13.0	196.0	36.0	156.0	75.0
CAGE Control Leucocytopenic	16-Mar-90	-30	115	38.1	675	7.18	30.0	130.0	11.5		42.0			198.0	9.0	156.0	27.0	184.0	84.0
CAGE Control Leucocytopenic	16-Mar-90	-15	115	38.1	675	7.27	39.0	112.0	17.0	34.0	38.0			175.0	12.0	183.0	37.0	140.0	78.0
CAGE Control Leucocytopenic	16-Mar-90	0	115	38.1	675	7.32	36.0	113.0	19.0	37.0	34.0			153.0	12.0	188.0	40.0	115.0	102.0
CAGE Control Leucocytopenic	16-Mar-90	15	115	38.1	675	7.14	38.0	106.0	13.0	36.0	54.0			162.0	12.0	205.0	38.0		86.0
CAGE Control Leucocytopenic	16-Mar-90	30	115	38.1	675	7.28	36.0	113.0	16.0	35.0	50.0			125.0	8.0	85.0	31.0	120.0	75.0
CAGE Control Leucocytopenic	16-Mar-90	45	115	38.5	675	7.17	35.4	115.6	13.0	44.0	59.0			188.0	10.0	202.0	40.0	95.0	82.0
CAGE Control Leucocytopenic	16-Mar-90	60	110	38.5	675	7.11	33.3	109.0	10.7	44.0	48.0			206.0	12.0	211.0	35.0	122.0	93.0
CAGE Control Leucocytopenic	16-Mar-90	75	100	38.5	825	7.12	30.1	120.7	9.8	44.0	49.0			207.0	12.0	171.0	39.0	101.0	81.0
CAGE Control Leucocytopenic	16-Mar-90	90	100	38.7	825	7.16	33.8	116.5	12.1	44.0	49.0			248.0	11.0	305.0	40.0	64.0	87.0
CAGE Control Leucocytopenic	16-Mar-90	105			825														
CAGE Control Leucocytopenic	16-Mar-90	120			825														
CAGE Control Leucocytopenic	16-Mar-90	135																	
CAGE Control Leucocytopenic	16-Mar-90	150																	
CAGE Control Leucocytopenic	16-Mar-90	165																	
CAGE Control Leucocytopenic	16-Mar-90	180																	

APPENDIX H

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	lCBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE Control Leucocytopenic	27-Apr-90	-120	95	38.5	405	7.22	34.1	128.9	13.9										
CAGE Control Leucocytopenic	27-Apr-90	-105	95	38.5	405	7.21	35.0	131.5	13.9	33.0	17.0			444.0	12.0	379.0	31.0		78.0
CAGE Control Leucocytopenic	27-Apr-90	-90	95	38.2	405	7.20	36.1	125.0	14.0	29.0	19.0			423.0	13.0	388.0	27.0		80.0
CAGE Control Leucocytopenic	27-Apr-90	-75	95	38.1	405	7.20	36.0	133.8	13.9	26.0	23.0			414.0	13.0	342.0	29.0	153.0	72.0
CAGE Control Leucocytopenic	27-Apr-90	-60	90	38.2	405	7.19	37.9	129.2	14.5	25.0	26.0			357.0	12.0	329.0	34.0	127.0	71.0
CAGE Control Leucocytopenic	27-Apr-90	-45	85	38.5	405	7.20	33.1	114.2	12.8	30.0	29.0			310.0	12.0	280.0	37.0	152.0	79.0
CAGE Control Leucocytopenic	27-Apr-90	-30	75	38.5	405	7.18	39.0	117.3	14.6	27.0	28.0			304.0	12.0	202.0	39.0	127.0	75.0
CAGE Control Leucocytopenic	27-Apr-90	-15	70	38.9	405	7.20	35.8	107.2	13.9	31.0	31.0			188.0	10.0	167.0	38.0	135.0	66.0
CAGE Control Leucocytopenic	27-Apr-90	0	70	38.9	405	7.20	41.2	112.9	16.2	33.0	36.0			247.0	10.0	239.0	36.0	124.0	67.0
CAGE Control Leucocytopenic	27-Apr-90	15	60	39.1	405	7.23	35.6	115.3	14.9	31.0	22.0			253.0	12.0	197.0	31.0	159.0	69.0
CAGE Control Leucocytopenic	27-Apr-90	30	70	39.2	405	7.25	34.0	115.0	14.9	31.0	36.0			399.0	11.0	241.0	29.0	205.0	68.0
CAGE Control Leucocytopenic	27-Apr-90	45	75	39.0	405	7.27	36.4	118.5	16.6	25.0	34.0			392.0	11.0	299.0	29.0	180.0	68.0
CAGE Control Leucocytopenic	27-Apr-90	60	75	39.0	405	7.25	36.0	115.0	16.0	27.0	44.0			388.0	11.0	294.0	32.0	148.0	81.0
CAGE Control Leucocytopenic	27-Apr-90	75	65	39.3	405	7.27	35.0	103.2	11.0	24.0	25.0			350.0	11.0	235.0	33.0	158.0	76.0
CAGE Control Leucocytopenic	27-Apr-90	90	65	39.3	405	7.24	29.0	96.5	12.5	27.0	41.0			352.0	11.0	304.0	29.0	173.0	82.0
CAGE Control Leucocytopenic	27-Apr-90	105																	
CAGE Control Leucocytopenic	27-Apr-90	120																	
CAGE Control Leucocytopenic	27-Apr-90	135																	
CAGE Control Leucocytopenic	27-Apr-90	150																	
CAGE Control Leucocytopenic	27-Apr-90	165																	
CAGE Control Leucocytopenic	27-Apr-90	180																	
CAGE Control Leucocytopenic	24-Apr-90	-120	100	38.5	480	7.32	34.6	140.8	17.6	44.0	48.0	580.0	505.0	246.0	13.0	241.0	25.0		45.0
CAGE Control Leucocytopenic	24-Apr-90	-105	95	38.5	480	7.33	36.2	136.5	19.0	39.0	44.0	580.0	500.0	202.0	12.0	262.0	23.0		45.0
CAGE Control Leucocytopenic	24-Apr-90	-90	95	38.6	480	7.35	32.0	127.1	17.3	35.0	53.0	510.0	480.0	289.0	12.0	289.0	22.0	121.0	44.0
CAGE Control Leucocytopenic	24-Apr-90	-75	95	38.6	420	7.32	36.3	126.8	18.8	30.0	40.0	510.0	480.0	188.0	14.0	149.0	32.0	123.0	97.0
CAGE Control Leucocytopenic	24-Apr-90	-60	105	38.0	420	7.30	38.0	129.0	19.0	34.0	39.0	530.0	490.0	203.0	14.0	152.0	35.0	99.0	91.0
CAGE Control Leucocytopenic	24-Apr-90	-45	105	39.1	420	7.29	37.0	129.0	18.0	35.0	43.0	520.0	490.0	111.0	13.0	157.0	32.0	108.0	83.0
CAGE Control Leucocytopenic	24-Apr-90	-30	95	39.1	420	7.31	39.0	129.0	20.0	41.0	62.0	520.0	510.0	234.0	13.0	205.0	33.0	116.0	91.0
CAGE Control Leucocytopenic	24-Apr-90	-15	95	39.2	420	7.32	35.0	120.7	15.9	34.0	51.0	530.0		226.0	12.0	197.0	34.0	119.0	94.0
CAGE Control Leucocytopenic	24-Apr-90	0	100	39.2	420	7.33	35.0	120.0	18.0	30.0	53.0			190.0	13.0	139.0	37.0	122.0	86.0
CAGE Control Leucocytopenic	24-Apr-90	15	100	39.4	420	7.33	36.9	126.7	19.7	36.0	49.0	520.0	515.0	161.0	12.0	169.0	32.0	130.0	82.0
CAGE Control Leucocytopenic	24-Apr-90	30	95	39.5	420	7.32	34.0	125.2	17.1			510.0	510.0	184.0	12.0	186.0	32.0	130.0	86.0
CAGE Control Leucocytopenic	24-Apr-90	45	95	39.5	420	7.32	36.4	128.8	18.5	29.0	56.0	560.0		315.0	13.0	196.0	33.0	135.0	107.0
CAGE Control Leucocytopenic	24-Apr-90	60	95	39.5	420	7.30	39.2	129.3	19.1	37.0	62.0			231.0	13.0	169.0	33.0	87.0	79.0
CAGE Control Leucocytopenic	24-Apr-90	75	95	39.5	420	7.30	43.4	124.0	21.5	36.0	62.0			196.0	12.0	207.0	33.0	107.0	92.0
CAGE Control Leucocytopenic	24-Apr-90	90	85	39.2	480	7.29	44.1	121.0	21.3	36.0	55.0	510.0	530.0	197.0	14.0	172.0	33.0	85.0	83.0
CAGE Control Leucocytopenic	24-Apr-90	105	80	39.1	540	7.30	40.3	150.5	19.9	33.0	51.0	410.0	600.0	220.0	13.0	245.0	33.0	103.0	101.0
CAGE Control Leucocytopenic	24-Apr-90	120	90	39.0	540	7.32	39.9	157.5	20.4	24.0	51.0	480.0	550.0	169.0	14.0	236.0	33.0	122.0	92.0
CAGE Control Leucocytopenic	24-Apr-90	135	90	38.6	540	7.36	35.0	141.4	19.1	24.0	61.0		580.0	272.0	13.0	201.0	32.0	97.0	84.0
CAGE Control Leucocytopenic	24-Apr-90	150	80	38.7	540	7.35	33.0	138.9	18.2	23.0	54.0			294.0	13.0	227.0	32.0	125.0	99.0
CAGE Control Leucocytopenic	24-Apr-90	165	80	38.7	480	7.34	35.0	144.5	15.5	25.0	65.0			248.0	13.0	231.0	32.0	112.0	96.0
CAGE Control Leucocytopenic	24-Apr-90	180	90	38.9	480	7.30	36.0	140.0	18.0	24.0	73.0			141.0	13.0	255.0	36.0	107.0	94.0
CAGE Control Leucocytopenic	15-Mar-90	-120	105	38.9	600	6.99	32.6	127.2	7.8	57.0		590.0	890.0	399.0	14.0	430.0	43.0		98.0
CAGE Control Leucocytopenic	15-Mar-90	-105	90	38.9	600	7.15	41.6	108.3	14.5	56.0		770.0		375.0	12.0	382.0	39.0		90.0
CAGE Control Leucocytopenic	15-Mar-90	-90	85	38.9	600	7.20	37.0	119.7	14.4			790.0	845.0	374.0	13.0	306.0	38.0	138.0	90.0
CAGE Control Leucocytopenic	15-Mar-90	-75	90	39.2	600	7.15	37.3	111.5	12.9	48.0		760.0		342.0	13.0	321.0	41.0	108.0	97.0
CAGE Control Leucocytopenic	15-Mar-90	-60	90	39.1	600	7.19	38.2	118.4	14.4	46.0			720.0	314.0	13.0	320.0	40.0		98.0
CAGE Control Leucocytopenic	15-Mar-90	-45	90	39.2	600	7.10	38.5	116.0	11.9	49.0		820.0	820.0	387.0	13.0	373.0	37.0	158.0	91.0
CAGE Control Leucocytopenic	15-Mar-90	-30	90	39.2	600	7.10	38.4	107.8	11.8	39.0		790.0	980.0	360.0	12.0	302.0	36.0	123.0	93.0
CAGE Control Leucocytopenic	15-Mar-90	-15	90	38.8	600	7.14	39.6	117.6	13.4	34.0		680.0		255.0	14.0	266.0	43.0	118.0	101.0
CAGE Control Leucocytopenic	15-Mar-90	0	90	38.7	600	7.12	38.0	120.6	12.4	43.0				232.0	15.0	227.0	44.0	75.0	97.0
CAGE Control Leucocytopenic	15-Mar-90	15	90	38.5	600	7.06	34.0	115.8	9.4	50.0		720.0		267.0	15.0	267.0	44.0	126.0	93.0
CAGE Control Leucocytopenic	15-Mar-90	30	80	38.4	600	7.05	39.4	112.8	10.8	41.0				317.0	14.0	254.0	42.0	112.0	100.0
CAGE Control Leucocytopenic	15-Mar-90	45	80	38.4	600	6.99	33.4	120.3	7.9	53.0				319.0	14.0	282.0	42.0	97.0	89.0
CAGE Control Leucocytopenic	15-Mar-90	60	80	38.4	600	7.05	41.3	114.5	11.4	58.0				246.0	12.0	232.0	40.0		96.0
CAGE Control Leucocytopenic	15-Mar-90	75	95	38.4	600	7.23	37.0	110.3	15.4	55.0				174.0	12.0	133.0	44.0	58.0	91.0
CAGE Control Leucocytopenic	15-Mar-90	90	75	38.5	600	7.11	41.6	111.0	13.3	49.0				146.0	16.0	189.0	43.0	48.0	93.0
CAGE Control Leucocytopenic	15-Mar-90	105	80	38.6	600	7.13	44.9	69.6	14.9	49.0		600.0		91.0	16.0	96.0	49.0	55.0	102.0
CAGE Control Leucocytopenic	15-Mar-90	120	70	38.7	750	7.12	37.3	152.3	12.0	43.0		530.0		119.0	16.0	99.0	44.0		100.0
CAGE Control Leucocytopenic	15-Mar-90	135																	
CAGE Control Leucocytopenic	15-Mar-90	150																	
CAGE Control Leucocytopenic	15-Mar-90	165																	
CAGE Control Leucocytopenic	15-Mar-90	180																	
CAGE 400µl Leucocytopenic	25-Jan-90	-120	65	39.1	1170	7.38	37.4	128.0	22.6	56.0	59.0			475.0	14.0	394.0	27.0	266.0	66.0
CAGE 400µl Leucocytopenic	25-Jan-90	-105	70	39.1	1080	7.37	37.7	128.9	21.9	52.0	51.0	800.0	900.0	496.0	14.0	387.0	25.0	271.0	58.0
CAGE 400µl Leucocytopenic	25-Jan-90	-90	65	39.3	1080	7.37	38.2	131.1	22.5	49.0	52.0	900.0	897.5	458.0	13.7	426.7	27.0	235.8	64.6
CAGE 400µl Leucocytopenic	25-Jan-90	-75	70	39.4	1080	7.39	35.6	139.4	21.3	51.0	68.0			450.0	15.0	422.0	29.0	325.0	63.0
CAGE 400µl Leucocytopenic	25-Jan-90	-60	65	39.5	990	7.37	37.0	134.6	21.4	45.0	60.0	820.0	940.0	485.0	14.0	378.0	26.0	215.0	67.0
CAGE 400µl Leucocytopenic	25-Jan-90	-45	65	39.5	990	7.39	35.3	149.4	21.2	49.0	69.0	830.0	920.0	417.0	14.0	415.0	27.0	317.0	63.0
CAGE 400µl Leucocytopenic	25-Jan-90	-30	65	39.6	990	7.40	35.4	162.9	21.7	46.0	63.0	780.0	950.0						
CAGE 400µl Leucocytopenic	25-Jan-90	-15	65	39.6	900	7.37	38.2	177.4	22.2	75.0									
CAGE 400µl Leucocytopenic	25-Jan-90	0	65	39.6	900	7.44	38.1	175.3	25.8	89.0	108.0	800.0	928.0						
CAGE 400µl Leucocytopenic	25-Jan-90	15	70	39.6	900	7.37	40.4	165.1	23.4	50.0	86.0								
CAGE 400µl Leucocytopenic	25-Jan-90	30	70	39.6	900	7.39	36.3	150.5	21.7	46.0	85.0								
CAGE 400µl Leucocytopenic	25-Jan-90	45	70	39.5	900	7.40	36.6	164.0	22.5	54.0	89.0	790.0	1040.0						
CAGE 400µl Leucocytopenic	25-Jan-90	60	65	39.5	900	7.40	35.4	165.2	21.8	55.0	67.0	800.0	1130.0						
CAGE 400µl Leucocytopenic	25-Jan-90	75	70	39.4	810	7.38	36.6	170.0	20.8	48.0	71.0	800.0	1120.0						
CAGE 400µl Leucocytopenic	25-Jan-90	90	70	39.4	810	7.37	37.4	169.4	21.6	42.0	73.0	820.0	1090.0						
CAGE 400µl Leucocytopenic	25-Jan-90	105	65	39.4	810	7.40	36.9	165.7	22.7	43.0	90.0	790.0	1107.5						
CAGE 400µl Leucocytopenic	25-Jan-90	120	70	39.5	810	7.41	35.7	169.8	22.4	42.0	68.0	810.0	1100.0						
CAGE 400µl Leucocytopenic	25-Jan-90	135	65	39.7	810	7.39	36.9	180.6	22.1	41.0	86.0	800.0	1065.0						
CAGE 400µl Leucocytopenic	25-Jan-90	150	65	39.7	810	7.40	36.9	165.2	23.0	32.0	93.0	830.0	1100.0						
CAGE 400µl Leucocytopenic	25-Jan-90	165	70	39.7	810	7.40	36.6	174.3	22.8	58.0	82.0	860.0	1120.0						
CAGE 400µl Leucocytopenic	25-Jan-90	180	70	39.7	810	7.39	37.1	176.5	22.6	37.0	69.0	820.0	1135.0						
CAGE 400µl Leucocytopenic	2-Mar-90	-120	90	38.7	900	7.18	28.6	116.0	10.7			680.0	665.0						
CAGE 400µl Leucocytopenic	2-Mar-90	-105	90	38.7	810	7.21	31.1	126.2	12.3	82.0	70.0	730.0	690.0	325.0	15.0	220.0	42.0	126.0	95.0
CAGE 400µl Leucocytopenic	2-Mar-90	-90	95	38.7	720	7.13	33.2	123.6	10.9	65.0	57.0	720.0	615.0	322.0	15.0	189.0	46.0	136.0	103.0
CAGE 400µl Leucocytopenic	2-Mar-90	-75	95	38.7	720	7.12	38.3	114.0	12.4	63.0	65.0	720.0	675.0	220.0	15.0	162.0	43.0	148.0	96.0
CAGE 400µl Leucocytopenic	2-Mar-90	-60	95	38.7	720	7.22	35.7	114.6	14.7	110.0	69.0	710.0	635.0	360.0	15.0	262.0	43.0	148.0	99.0
CAGE 400µl Leucocytopenic	2-Mar-90	-45	95	38.7	720	7.22	40.9	114.1	16.7	75.0	65.0	720.0	635.0	412.0	15.0	255.0	42.0	147.0	93.0
CAGE 400µl Leucocytopenic	2-Mar-90	-30	95	38.7	720	7.20	38.2	113.4	15.0	81.0	76.0	730.0	720.0	340.0	15.0	158.0	43.0	105.0	102.0
CAGE 400µl Leucocytopenic	2-Mar-90	-15	95	38.6	720	7.19	43.0	115.5	18.4	66.0	71.0	720.0	675.0	233.0	14.0	165.0	43.0	143.0	91.0
CAGE 400µl Leucocytopenic	2-Mar-90	0	95	38.6	720	7.17	49.9	46.9	18.0	89.0	75.0	700.0	1075.0	323.0	14.0	185.0	52.0	116.0	114.0
CAGE 400µl Leucocytopenic	2-Mar-90	15	90	38.6	1080	7.21	38.0	141.0	15.3	60.0	74.0	650.0	925.0	331.0	17.0	208.0	44.0	145.0	109.0
CAGE 400µl Leucocytopenic	2-Mar-90	30	80	38.7	1080	7.21	35.4	158.1	14.2	72.0	81.0	600.0	860.0	276.0	16.0	266.0	44.0	141.0	99.0
CAGE 400µl Leucocytopenic	2-Mar-90	45	75	38.7	990	7.22	34.1	162.8	13.8	55.0	58.0	650.0	820.0	340.0	15.0	257.0	44.0	149.0	110.0
CAGE 400µl Leucocytopenic	2-Mar-90	60	65	38.0	900	7.13	37.7	153.7	12.6	50.0	49.0	610.0	860.0	357.0	15.0	141.0	43.0	185.0	103.0
CAGE 400µl Leucocytopenic	2-Mar-90	75	65	38.4	900	7.26	35.0	164.3	14.3	57.0	74.0			353.0	16.0	253.0	43.0	130.0	100.0
CAGE 400µl Leucocytopenic	2-Mar-90	90	65	38.0	810	7.25	33.0	141.0	14.4	53.0	49.0	670.0	990.0	415.0	16.0	252.0	44.0	157.0	110.0
CAGE 400µl Leucocytopenic	2-Mar-90	105	70	39.2	810	7.22	33.4	157.4	13.5	50.0	38.0			402.0	15.0	252.0	43.0	144.0	106.0
CAGE 400µl Leucocytopenic	2-Mar-90	120	65	39.2	720	7.21	35.8	143.4	14.4	52.0	53.0	720.0	880.0	358.0	13.0	218.0	44.0	145.0	106.0
CAGE 400µl Leucocytopenic	2-Mar-90	135	60	39.1	720	7.17	36.4	153.0	13.2	50.0	48.0	700.0	875.0	310.0	14.0	158.0	43.0	114.0	101.0
CAGE 400µl Leucocytopenic	2-Mar-90	150	60	38.8	720	7.16	35.8	147.6	12.6	55.0	47.0	710.0	820.0	188.0	14.0	163.0	43.0	124.0	102.0
CAGE 400µl Leucocytopenic	2-Mar-90	165	60	38.5	720	7.16	37.4	148.1	13.4	62.0	55.0	730.0	875.0	250.0	14.0	73.0	40.0	181.0	98.0
CAGE 400µl Leucocytopenic	2-Mar-90	180	60	38.5	720	7.13	35.2	148.0	12.8	59.0	57.0	720.0	850.0	199.0	13.0	101.0	41.0	125.0	104.0

Group	Date	time	MABP	Temp	Min.Vol.	pH	P_aCO_2	P_aO_2	HCO_3	rCBF	ICBF	vDiam	ADiam	AP_1	LP_1	AN_2	LN_2	AP_2	LP_2
CAGE 400µl Leucocytopenic	30-Mar-90	-120	115	39.6	750	7.35	32.3	142.5	17.8										
CAGE 400µl Leucocytopenic	30-Mar-90	-105	110	39.6	750	7.33	39.0	145.0	20.0					305.0	8.5	258.0	21.0		45.0
CAGE 400µl Leucocytopenic	30-Mar-90	-90	110	39.6	750	7.33	35.0	147.0	19.0	113.0	56.0			356.0	11.0	364.0	22.0		45.0
CAGE 400µl Leucocytopenic	30-Mar-90	-75	105	39.1	750	7.34	35.2	140.9	18.9	110.0	67.0			275.0	10.0	345.0	21.0		44.0
CAGE 400µl Leucocytopenic	30-Mar-90	-60	105	39.1	750	7.35	34.2	141.6	19.0	104.0	49.0			324.0	10.0	340.0	19.0		43.0
CAGE 400µl Leucocytopenic	30-Mar-90	-45	105	39.1	750	7.37	30.0	151.0	17.0	129.0	42.0			325.0	9.0	342.0	20.0		46.0
CAGE 400µl Leucocytopenic	30-Mar-90	-30	105	39.1	750	7.36	35.0	133.0	19.0	104.0	56.0			292.0	8.0	302.0	23.0		40.0
CAGE 400µl Leucocytopenic	30-Mar-90	-15	105	39.1	675	7.36	34.0	137.0	19.0	117.0	53.0			245.0	8.5	236.0	17.9		43.6
CAGE 400µl Leucocytopenic	30-Mar-90	0	100	39.1	675	7.36	35.0	122.0	20.0	142.0	56.0			152.0	8.0	113.0	18.0		44.0
CAGE 400µl Leucocytopenic	30-Mar-90	15	100	39.1	675	7.35	39.0	126.0	21.0	127.0	76.0			112.0	8.0	111.0	19.0		45.0
CAGE 400µl Leucocytopenic	30-Mar-90	30	100	39.1	675	7.36	36.0	129.0	20.0	126.0	74.0			125.0	8.4	126.0	19.0		43.0
CAGE 400µl Leucocytopenic	30-Mar-90	45	100	39.1	675	7.36	37.5	130.0	22.0	110.0	55.0			140.0	9.0	130.0	18.0		42.0
CAGE 400µl Leucocytopenic	30-Mar-90	60	85	39.0	675	7.38	37.7	133.1	22.5	92.0	46.0			114.0	9.0	133.0	18.0		43.0
CAGE 400µl Leucocytopenic	30-Mar-90	75	85	39.0	675	7.39	36.0	133.0	21.0	62.0	46.0			107.0	9.0	107.0	22.0		48.0
CAGE 400µl Leucocytopenic	30-Mar-90	90	85	39.0	675	7.42	35.0	107.0	21.4	84.0	47.0			85.0	9.0	102.0	19.0		38.0
CAGE 400µl Leucocytopenic	30-Mar-90	105	80	38.8	675	7.41	38.6	150.4	24.5	79.0	40.0			190.0	8.8	168.0	18.0		34.0
CAGE 400µl Leucocytopenic	30-Mar-90	120	80	38.8	675	7.41	35.4	151.7	22.2	71.0	40.0			143.0	8.8	98.0	18.5		31.0
CAGE 400µl Leucocytopenic	30-Mar-90	135	95	38.5	675	7.37	38.4	132.1	22.2	75.0	44.0			128.0	8.5	102.8	16.8		32.8
CAGE 400µl Leucocytopenic	30-Mar-90	150	95	38.3	675	7.37	41.4	133.7	23.8	88.0	42.0			111.0	9.0	111.0	17.0		32.0
CAGE 400µl Leucocytopenic	30-Mar-90	165	85	38.2	675	7.36	40.4	135.4	22.8	81.0	37.0			106.0	9.0	113.0	18.0		32.0
CAGE 400µl Leucocytopenic	30-Mar-90	180	80	38.0	675	7.34	38.7	135.9	21.0	81.0	28.0			140.0	8.5	92.0	19.0		32.0
CAGE 400µl Leucocytopenic	13-Dec-89	-120	110	39.9	804	7.38	38.4	148.4	22.7	85.0	56.0			346.0	14.1	329.0	22.7		50.4
CAGE 400µl Leucocytopenic	13-Dec-89	-105	110	39.9	804	7.38	40.6	147.8	23.8	103.0			720.0	399.0	14.5	311.0	22.5		50.0
CAGE 400µl Leucocytopenic	13-Dec-89	-90	100	39.9	840	7.39	39.5	142.5	23.9	82.0	71.0	710.0		351.0	14.1	249.7	21.6		50.8
CAGE 400µl Leucocytopenic	13-Dec-89	-75	100	40.0	840	7.40	43.8	133.6	26.9	133.0	40.0	720.0		389.0	14.0	283.0	22.3		51.6
CAGE 400µl Leucocytopenic	13-Dec-89	-60	100	39.9	1050	7.41	40.8	140.2	25.6	131.0	33.0		650.0	311.0	14.3	227.3	22.0		51.0
CAGE 400µl Leucocytopenic	13-Dec-89	-45	100	39.9	1050	7.43	38.0	140.7	25.4	81.0	86.0			313.7	13.6	202.7	21.0		48.4
CAGE 400µl Leucocytopenic	13-Dec-89	-30	90	39.9	1050	7.43	38.1	142.4	25.1	110.0	50.0	700.0	670.0	216.7	12.7	169.0	19.7	116.0	50.8
CAGE 400µl Leucocytopenic	13-Dec-89	-15	90	39.9	1050	7.44	35.7	148.2	24.1	95.0	38.0			206.0	13.0	222.7	21.3	116.0	48.4
CAGE 400µl Leucocytopenic	13-Dec-89	0	90	39.9	1050	7.43	38.0	151.7	25.4	151.0			870.0	209.7	13.8	194.8	29.0	113.0	50.2
CAGE 400µl Leucocytopenic	13-Dec-89	15	90	39.9	1050	7.42	35.2	156.8	22.9	132.0	48.0	720.0	970.0	153.7	14.3	121.0	27.3	99.0	50.4
CAGE 400µl Leucocytopenic	13-Dec-89	30	90	39.9	1050	7.44	35.7	144.1	24.3	134.0	63.0	730.0	850.0	216.0	15.0	249.0	27.0	113.0	55.0
CAGE 400µl Leucocytopenic	13-Dec-89	45	80	39.9	1050	7.42	35.5	149.7	23.2	123.0	47.0	590.0		167.7	12.3	220.3	24.0	106.0	57.0
CAGE 400µl Leucocytopenic	13-Dec-89	60	96	39.9	1050	7.42	35.0	138.0	22.6	119.0	40.0		810.0	138.7	12.5	142.3	21.3	78.0	54.5
CAGE 400µl Leucocytopenic	13-Dec-89	75	100	39.8	1050	7.44	36.1	146.0	24.6	125.0	57.0	560.0	730.0	128.0	11.3	138.7	22.7	68.0	55.2
CAGE 400µl Leucocytopenic	13-Dec-89	90	90	39.8	1050	7.42	35.7	151.5	22.9	104.0	37.0	580.0	680.0	155.0	14.0	187.7	22.7	86.0	54.0
CAGE 400µl Leucocytopenic	13-Dec-89	105	80	39.6	1050	7.45	35.6	150.0	24.7	91.0	45.0	590.0	700.0	158.3	11.7	92.2	21.0	106.0	51.0
CAGE 400µl Leucocytopenic	13-Dec-89	120	80	39.7	1050	7.42	34.0	117.8	22.0	79.0	33.0	560.0	700.0	137.3	14.0	133.0	24.7	66.0	57.4
CAGE 400µl Leucocytopenic	13-Dec-89	135	90	39.7		7.42	40.2	135.1	25.8	72.0	30.0	500.0		82.8	11.3	100.3	21.5		44.0
CAGE 400µl Leucocytopenic	13-Dec-89	150	90	39.6	1050	7.43	39.0	131.5	25.2	96.0	56.0			93.0	12.0	91.0	24.3		42.8
CAGE 400µl Leucocytopenic	13-Dec-89	165																	
CAGE 400µl Leucocytopenic	13-Dec-89	180																	
CAGE 400µl Leucocytopenic	20-Dec-89	-120	100			7.45	38.9	129.0	27.0			930.0							
CAGE 400µl Leucocytopenic	20-Dec-89	-105	110	39.0	900	7.41	37.5	116.0	24.0			820.0		323.0	19.0	294.0	40.0	112.0	83.0
CAGE 400µl Leucocytopenic	20-Dec-89	-90	100	39.0	900	7.43	37.0	117.0	25.0	77.0	70.0	830.0	650.0	297.0	19.0	300.0	43.0	150.0	86.0
CAGE 400µl Leucocytopenic	20-Dec-89	-75	105	39.0	900	7.46	37.5	118.0	27.0	66.0	56.0	820.0	600.0	276.0	18.0	265.0	42.0	124.0	89.0
CAGE 400µl Leucocytopenic	20-Dec-89	-60	105	39.0	900	7.43	32.0	103.0	22.0	54.0	55.0		620.0	273.0	16.0	272.0	45.0	99.0	89.0
CAGE 400µl Leucocytopenic	20-Dec-89	-45	105	39.0	900	7.43	36.1	126.4	24.0	67.0	78.0	860.0	640.0	210.0	17.0	243.0	42.0	91.0	84.0
CAGE 400µl Leucocytopenic	20-Dec-89	-30	105	39.0	900	7.38	32.2	139.1	19.1	62.0	87.0	850.0		227.0	15.0	259.0	41.0	137.0	91.0
CAGE 400µl Leucocytopenic	20-Dec-89	-15	95	39.0	810	7.42	38.2	130.4	24.9	75.0	77.0	860.0	680.0	254.0	17.0	203.0	39.0	155.0	90.0
CAGE 400µl Leucocytopenic	20-Dec-89	0	95	39.0	810	7.39	43.4	94.7	26.4	65.0	73.0		650.0	228.0	17.0	175.0	37.0	119.0	88.0
CAGE 400µl Leucocytopenic	20-Dec-89	15	100	38.9	900	7.41	41.3	104.3	26.3	58.0	80.0	720.0	730.0	246.0	18.0	259.0	41.3	100.0	85.4
CAGE 400µl Leucocytopenic	20-Dec-89	30	95	38.9	990	7.39	41.1	104.0	25.0	73.0	96.0	730.0		267.0	17.0	135.0	39.0	122.0	81.0
CAGE 400µl Leucocytopenic	20-Dec-89	45	95	39.0	990	7.39	45.1	90.2	27.0	53.0	82.0	700.0	700.0	296.0	17.0	220.0	39.0	129.0	82.0
CAGE 400µl Leucocytopenic	20-Dec-89	60	80	38.9	990	7.39	35.0	113.2	21.0	60.0	56.0	710.0	680.0	324.0	15.0	208.0	43.0	130.0	82.0
CAGE 400µl Leucocytopenic	20-Dec-89	75	90	38.9	990	7.45	33.0	119.0	23.0	55.0	82.0	680.0	670.0	242.0	17.0	225.0	37.0	115.0	86.0
CAGE 400µl Leucocytopenic	20-Dec-89	90	90	39.0	990	7.43	37.4	119.1	24.9	57.0	115.0		680.0	274.0	16.0	184.0	40.0	123.0	84.0
CAGE 400µl Leucocytopenic	20-Dec-89	105	90	39.0	990	7.44	34.1	130.0	23.0	39.0	87.0	700.0	720.0	176.0	14.0	164.0	37.0	71.0	78.0
CAGE 400µl Leucocytopenic	20-Dec-89	120	90	39.2	990	7.42	35.0	112.1	14.3	47.0	59.0		690.0	175.0	14.0	156.0	38.0	75.0	75.0
CAGE 400µl Leucocytopenic	20-Dec-89	135	90	39.3	990	7.45	37.0	132.0	25.0	57.0	84.0		680.0	160.0	15.0	131.0	37.0	68.0	74.0
CAGE 400µl Leucocytopenic	20-Dec-89	150	90	39.3	990	7.44	39.0	104.0	26.0	64.0	88.0	750.0	700.0	[227]	[16]	[132]	[37]	[129]	[89]
CAGE 400µl Leucocytopenic	20-Dec-89	165	90	39.3	990	7.44	39.0	102.0	27.0	52.0	73.0		700.0	142.0	12.0	123.0	35.0	91.0	90.0
CAGE 400µl Leucocytopenic	20-Dec-89	180	90	39.3	990	7.46	37.0	109.0	27.0	63.0	82.0		720.0	174.0	12.0	163.0	37.0	82.0	84.0

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NOTES

This thesis was prepared on a number of MS-DOS computers but was mostly accomodated on a COMPAQ III portable microcomputer donated to this research project by John Freidrichs, former Managing Director of the NATIONAL SAFETY COUNCIL OF AUSTRALIA (Victorian Division). This computer is based on an INTEL 80286 microprocessor running at an internal clock speed 12 megahertz and supported by an INTEL 80287 math co-processor. This computer uses a gas plasma display with a resolution of 600 by 400 pixels. It was further equipped with 6.7 megabytes of random access memory (RAM) deployed as 640 kilobytes DOS addresable and 6104 kilobytes expanded memory. Mass storage was accomplished with a 1.44 megabyte (3.5 inch) TEAC floppy disk drive and a 110 megabyte hard disk drive. Microsoft DOS versions 3.3 through 6.0 were used. In the later stages of preparation, STAC Corporation STACKER software was used to increase the amount of effective disk space to approximately 200 megabytes.

References were maintained with REFERENCE MANAGER version 5 (up to 5.05 for DOS) and in the latter stages with REFERENCE MANAGER FOR WINDOWS.

Data collation and analysis was done using EXCEL (Microsoft Corporation [versions 2.0, 3.0 and 4.0]) running under WINDOWS (Microsoft Corporation [versions 2.0, 2.1, 3.0 and 3.1]).

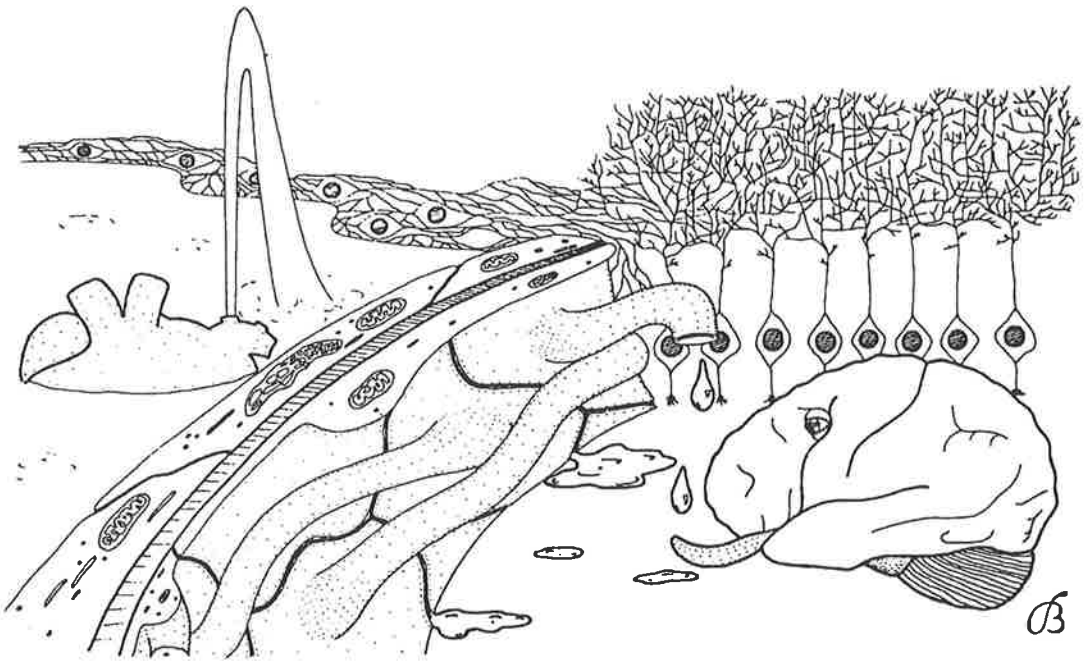
Statistical analysis was performed with either STAGRAPHICS (STSC Corporation) or MSTATS (my own code written in QBASIC (Microsoft Corporation [version 4.0 or 4.5]).

Figures were prepared by scanning on a SCANJET (Hewlet Packard) and further editing of the TIF (tagged image format file) was done with either Corel PAINT! or Corel DRAW! (Corel Corporation [version 2.0 or 3.0]) before being embedded in the document files.

Graphs were drawn with SIGMAPLOT (Jandel) and combined with the text of the thesis as CGM Graphics metafiles.

The text was prepared using WORD FOR WINDOWS (Microsoft Corporation [version 1.0 1.1 and 2.0]). Each chapter or section was prepared separately before being combined and printed to produce the final draft on a BROTHER HL-10V Laser printer (Brother).

Backups were maintained with DSBackup (DS [version 1.0 or 2.0] or Norton Backup or MICROSOFT BACKUP (DOS 6.0).



"Nothing in this world can take the place of persitence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination alone are omnipotent."

Calvin Coolidge