THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE

CARDIAC DYSFUNCTION AND LACTIC ACIDOSIS DURING HYPERDYNAMIC AND HYPOVOLEMIC SHOCK

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Chapter 1

1.1 ABSTRACT

Lactic acidosis occurs during impaired tissue perfusion in both hyperdynamic and hypovolemic shock. Importantly, lactic acidosis is a key predictor of high mortality in patients. Cardiac dysfunction occurs during lactic acidosis but until recently had not been recognised to be important during hyperdynamic or hypovolemic shock.

This thesis details a series of studies in patients, in human volunteers and in large animals. Haemodynamics and left ventricular systolic and diastolic mechanics are reported during lactic acidosis, during therapies for lactic acidosis, and during hyperdynamic and hypovolemic shock. These studies do not address cardiogenic or obstructive shock.

The studies found in patients with shock and lactic acidosis, that infused bicarbonate does not improve cardiac function. In some patients, side effects of hypocalcemia and hypercapnia outweighed benefits. Transient haemodynamic effects of bicarbonate were due to the infusion of a hypertonic solution and not due to buffering. In lactic acidosis induced by hypovolemic shock (arterial pH 7.10), systolic left ventricular (LV) contractility was not decreased, perhaps due to endogenous catecholamines. Infusion of bicarbonate did not improve haemodynamics. In infused lactic acidosis (arterial pH 7.10), when catecholamines were blocked, systolic LV contractility was decreased and failed to increase after complete pH correction using bicarbonate. Histamine decreased LV contractility when measured using a non invasive technique in human volunteers (an H_1 mediated effect). Histamine may therefore be an important contributor to LV dysfunction reported during anaphylaxis. TNF - α decreased LV contractility in dogs suggesting that TNF - α may be an important contributor to LV dysfunction in the early hours of septic shock. Finally, hypovolemic shock was associated with profound LV diastolic stiffness which may account for failed resuscitation in patients with prolonged hypovolemic shock.

This thesis has the unifying hypothesis that cardiac dysfunction is important in hyperdynamic and hypovolemic shock and is not caused by lactic acidosis. Accordingly, clinical therapies intended to improve cardiac function and rapidly normalise tissue perfusion in patients with shock and lactic acidosis are more likely to be successful in improving patient outcome than therapies which are intended solely to correct the acidosis.

1.2 STATEMENT

This thesis contains no work that 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 has been made in the text.

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

14/11/1996

SIGNED **DATE**

1.3 CONTRIBUTION OF THE AUTHOR TO EACH STUDY

Each of the seven studies detailed in this thesis Chs (4.2.2 - 6.1) was conceived, designed and performed by myself, in each case with advice and assistance from my Critical Care Fellowship supervisors Dr Keith Walley and Dr Jim Russell. Data analysis was done with the assistance of Mr Barry Wiggs and Keith Walley. Manuscript writing and revision in Ch (4.2.1, 4.2.2, 4.3.2, and 5.2.2) was done by myself with the advice and assistance of co-authors. Manuscript writing for publication in Ch (4.3.1, 5.3.1, and 6.1) was done in collaboration with the co-authors, principally Keith Walley. The published review papers (4.4, and 2.2.1) which provide background and amplification for the original studies, and the two book chapters, (see Ch 1.5) were written by myself.

1.4 ACKNOWLEDGMENTS

This body of research would never have been completed, nor would this thesis have been written, without the support, assistance, guidance and encouragement of a large number of people. The work was done while an external postgraduate student of the University of Adelaide, predominantly during the tenure of a Critical Care Research Fellowship (1988 to 1990) at St. Paul's Hospital, University of British Colombia, Canada, in the Department of Critical Care Medicine and the Pulmonary Research Laboratory. Dr Jim Russell structured the Fellowship years and facilitated everything that I accomplished including the coordination of grant support. Dr Keith Walley was my model of scientific excellence and rigour, my teacher, and friend. Drs Jim Hogg and Dr Peter Pare nurtured the Pulmonary Research Laboratory to its present world class standing and endlessly provided grass roots support to me and the other Fellows. Dianne Minshall and Lisa Baile taught me laboratory skills and assisted with technical expertise for each of the animal studies. Prof WB Runciman supported the project with enthusiasm, provided encouragement, and kept at me with persistence until the thesis reached completion. Dr LIG Worthley, my earliest mentor, instilled both a love of Intensive Care and a need to always do better and provided constant encouragement. Finally, Cate Cooper gave unflagging support through nearly three years of the overseas Fellowship, three children, and a dislocated home life. My sincere thanks are due to all.

1.5 PUBLICATIONS ARISING FROM THIS THESIS

PAPERS

1. Cooper DJ, Worthley LIG. Adverse haemodynamic effects of sodium bicarbonate in metabolic acidosis. Intensive Care Med. 1987;13:425-427.

2. Cooper DJ, Walley KR, Russell JA. Bicarbonate does not improve haemodynamics in human lactic acidosis: a prospective, controlled study. Ann Intern Med 1990; 112:492-498.

3. Cooper DJ, and Worthley LIG. Buffer therapies for patients who have lactic acidosis? Intensive and Crit Care Digest 1990; 9:30-31. (Editorial).

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1. Cooper DJ: Shock. in Dziukas L (ed): Text Book of Emergency Medicine. 1st ed. McGraw Hill. (in press 1996).

2. Cooper DJ: Acidosis and sodium bicarbonate therapy, in Keneally J. (ed): Australasian Anaesthesia. 4th ed. Melbourne, Australian and New Zealand College of Anaesthetists,1994;39-47.

(Letters, Abstracts, and Invited Presentations arising from this Thesis, are detailed in Appendix 1)

Chapter 2

INTRODUCTION

2.1 Shock and lactic acidosis

2.1.1 Definition and Subtypes

Shock is a clinical syndrome in which decreased oxygen delivery to tissues causes cellular and organ dysfunction (1) (2). Oxygen delivery may be reduced following decreases in any its component parts - cardiac output, haemoglobin, arterial oxygen saturation, or at the tissue level, following impaired diffusion of oxygen to intracellular sites or following breakdown in the integrity of cellular mechanisms which utilise oxygen. Shock is traditionally divided into four broad subtypes: Hyperdynamic (or distributive), Hypovolemic, Cardiogenic, and Obstructive (2). Lactic acidosis occurs during shock when oxygen delivery is inadequate for aerobic metabolism to continue.

2.1.2 Hyperdynamic shock: occurs when there is inappropriate dilatation of arterioles and veins - decreasing blood pressure, decreasing afterload and increasing cardiac output. Despite increased cardiac output, hypotension may reduce perfusion pressure to vital organs below critical levels causing anaerobic metabolism and shock, despite a clinical picture of *increased* skin perfusion and vasodilatation. There are a number of causes of hyperdynamic shock and two of the most important are anaphylactic shock and septic shock.

Anaphylactic shock is usually the result of an immediate hypersensitivity reaction in which vasoactive mediators are released from mast cells and basophils. These mediators then cause the clinical picture recognised as anaphylactic shock. The clinical picture includes skin rash, bronchospasm, tissue oedema, and cardiovascular collapse. Cardiovascular collapse is thought to be primarily due to decreased preload (peripheral vascular dilatation, and extravascular fluid leak) and decreased afterload (arteriolar dilation) (3). In addition, myocardial dysfunction has recently been recognised to occur in some cases (4) (5). The cause of myocardial dysfunction during anaphylaxis however is unknown, and its significance in patients with anaphylaxis is controversial.

Septic shock has recently been defined as "sepsis induced hypotension, persisting despite adequate fluid resuscitation along with the presence of hypoperfusion abnormalities or organ dysfunction" (6). Hypotension by definition is a systolic blood pressure of less than 90 mmHg or its reduction by 40 mmHg or more from baseline in the absence of other causes of hypotension (6). Septic shock is associated with inappropriate peripheral vascular dilation due primarily to released mediators. Increased skin perfusion is noted clinically. Decreased afterload is associated with increased cardiac output, but the cardiac output increase is inadequate for demand and is inadequate to prevent hypotension. Decreased blood pressure below critical values for organ perfusion is a key factor causing shock during sepsis. However, during septic

shock, there is also thought to be dysfunction at a microvascular and cellular level. There are likely to be two primary contributors to this dysfunction (1) microvascular maldistribution of blood flow causing shunting, and (2) a cellular defect of oxygen extraction and oxygen utilisation. It is not known which of these factors is of primary importance, nor which of the many mediators released during sepsis are primarily responsible for each. However is likely that most of the pathophysiological disturbances during sepsis including the cellular and microvascular dysfunction, are mediated either directly or indirectly by cytokines. The cytokine, tumor necrosis factor (TNF - α) appears to be of early and pivotal importance. More recently, myocardial dysfunction has been clearly defined as contributing to cardiovascular compromise during septic shock (7), but its cause in these patients and the relative importance of systolic and diastolic left ventricular dysfunction, remain controversial.

2.1.3 Hypovolemic shock occurs when intravascular fluid loss (blood loss or fluid leakage out of vessels) decreases ventricular preload and decreases cardiac output to the point that physiologic compensation is inadequate and hypotension occurs. Perfusion pressures of important organs then decrease below levels essential for aerobic metabolism to continue. Although it is theoretically possible for hypovolemia to be associated with profound catecholamine induced vasoconstriction and resultant organ dysfunction without systemic hypotension, in practice hypovolemic shock is almost always hypotensive. Myocardial dysfunction has not previously been considered to be an important problem during hypovolemic shock but, in chapter 6, I report a study which demonstrated that in some cases of prolonged hypovolemic shock, myocardial dysfunction may be of critical importance for survival.

2.1.4 Cardiogenic shock: is due to decreased cardiac output following myocardial damage or damage to mechanical cardiac structures.

Obstructive shock: occurs when there is physical obstruction to blood flow toward the heart, as for example during a large pulmonary embolus. The pathophysiology of both cardiogenic and obstructive shock are reasonably well understood and are not further discussed in this thesis.

2.1.5 Lactic acidosis: Formation and metabolism of lactate in cells is catalysed by lactate dehydrogenase

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \quad \overset{\text{LDH}}{<\!\!-\!\!-\!\!-\!\!>} \quad \text{Lactate} + \text{NAD}^+$$

Whole body lactate production during health is about 0.8 mmol/kg/hr which results in blood lactate concentrations of < 1 mmol/L and basal lactate concentrations about 10 x pyruvate concentrations. Lactate formation is in part dependent upon pyruvate concentrations with pyruvate being sourced from lactate (via LDH), from proteolysis (about 15 %) and from glycolysis (about 85%). Glucose is obtained from absorbtion, from glycogen, and from gluconeogenesis and its glycolysis is

controlled by 3 unidirectional enzymes. The activity of one of these is increased by increasing intracellular pH. Alkalosis therefore increases, and acidosis decreases pyruvate and therefore lactate formation from glycolysis. During oxygen excess, pyruvate is oxidised (in cells with mitochondria) and lactate does not accumulate. The onset of anaerobic metabolism is associated with lactate accumulation and an increase in the lactate/pyruvate ratio. However, measurement of the lactate/pyruvate ratio (reflecting the cellular cytoplasmic redox state) is considered to be a poor indicator of the mitochondrial redox potential (8), and therefore of little clinical use.

Lactic acidosis has been variously defined as a blood lactate concentration of greater than 2 mmol/L or more commonly of greater than 5 mmol/L, in combination with acidemia - being an arterial pH of < 7.35 or of < 7.25 (9) (10) (11). One problem with these definitions is that although acidemia may be present it may be partially or completely compensated by preexisting alkalemia o by respiration.

Although most causes of lactic acidosis are acquired, some are congenital and are associated with defects in gluconeogenesis, pyruvate dehydrogenase, the TCA cycle or the respiratory chain. Cohen and Woods 1976 classification of lactic acidosis has been widely recognised (12). In this classification, Type A lactic acidosis includes patients with clinical evidence of tissue hypoxia and is by far the most common in critically ill patients. Causes include: shock, regional hypoperfusion, severe hypoxemia, severe anemia, carbon monoxide poisoning and severe asthma. Type B lactic acidosis includes patients with no clinical evidence of tissue hypoxia. The type B subgroups are: B1 (presence of an underlying disease state) including diabetes, liver disease, malignancy, sepsis, pheochromocytoma, thiamine deficiency; B2 (drug or toxin induced) including biguanides, ethanol, methanol, ethylene glycol, fructose, sorbitol, xylitol, salicylates, acetaminophin, adrenaline, salbutamol, cyanide, nitroprusside, isonaizid, propylene glycol; and B3 (inborn errors c metabolism including glucose-6 phosphatase deficiency, fructose 1,6 di-phosphatase deficiency, pyruvate carboxylase deficiency and oxidative phosphorylation defects (11).

In patients with cancer, there may be a high anaerobic glycolysis rate and hepatic lactate metabolism may also be impaired by tumor replacement. In non insulin dependent diabetes there may be a mild defect in pyruvate oxidation and in diabetic ketoacidosis there may be an inhibitory effect of ketones on hepatic lactate uptake. Thiamine and biotin are essential cofactors for pyruvate dehydrogenase activity and for conversion of pyruvate to oxaloacetate so chronic malnutrition may be associated with cofactor deficiency related lactic acidosis. Ethanol oxidation encourages conversion of pyruvate to lactate and inhibits other pathways of pyruvate metabolism. Phenformin increases glycolysis to lactate in peripheral tissues, inhibits pyruvate oxidation, increases splanchnic lactate production, and decreases hepatic lactate clearance. Interestingly although phenformin was considered a classic inducer of type B lactic acidosis and was used in frequently cited animal models, it was later realised to be a potent cardiac depressant which induce type A and B lactic acidosis concurrently. Catecholamines induce hepatic vasoconstriction and impair hepatic lactate clearance, and adrenaline also increases hepatic glycogenolysis (to lactate) (9).

Critically ill patients rarely have pure type A or B lactic acidosis. For example in sepsis there may be decreased myocardial preload and myocardial depression, both of which reduce cardiac function and may reduce oxygen delivery to tissues. In sepsis, hypotension may also reduce critical perfusion pressures to vital organs. However at the same time there are excess catecholamines which may impair hepatic lactate extraction (by reducing regional hepatic blood flow), and in addition, pyruvate dehydrogenase activity is reduced in both skeletal muscle and liver. There may also be defects in mitochondrial pyruvate oxidation.

During shock, type A lactic acidosis occurs when tissue perfusion is inadequate to sustain aerobic metabolism. Thus, an increasing blood lactate concentration in patients with shock suggests ongoing impaired tissue perfusion and is correlated with increased risk of a fatal outcome (13). More recent data reported from the placebo patients in a multicentre clinical trial confirms the relationship between increased blood lactate concentrations (mean 10.4 mmol/L) and a fatal outcome (83% mortality) (14). In these patients a blood lactate concentration of 5 mmol/L indicated a mortality approaching 80%. Survival was better in those whose hyperlactemia resolved, and in those without shock. However hyperlactemia may occur without tissue hypoperfusion - due to impaired lactate clearance (in cirrhotic patients), in hypermetabolic states where accelerated arobic glycolysis may contribute (sepsis, trauma, burns), in conditions with increased muscle activity (extreme excercise and seizures) or during exogenous lactate administration (intravenous hemofiltration fluid). Furthermore, there is recent evidence using NMR spectroscopy, that the hyperlactemia of sepsis may occur without tissue hypoxia (15). Clearly the genesis of hyperlactemia in sepsis is complex and requires further investigation.

Lactic acidosis may cause cardiac dysfunction, or instead lactic acidosis may be an epiphenomenon - an end result of tissue hypoperfusion due to cardiac dysfunction from other factors. Which of these alternatives is correct has been the subject of debate for many years.

2. 2 Cardiac dysfunction and therapies during lactic acidosis

In health lactate is continually produced as a metabolic product, predominantly in skeletal muscle, and at the same time is metabolised, primarily in the liver and kidneys. In health, owing to constant turnover, blood lactate concentrations remain low. However during shock when compensatory mechanisms are insufficient to maintain tissue oxygen delivery and aerobic metabolism, anaerobic metabolic processes commence and lactate production increases. Blood lactate concentrations then increase depending upon the capacity of the metabolising organs to accommodate the increased load. Shocked patients who have liver disease therefore often develop greater blood lactate concentrations than previously healthy subjects who have the same degree of tissue hypoxia. Production of acid is closely related to tissue hypoxia because hydrogen ions cannot easily be oxidised under anaerobic conditions. Production of lactate may also be directly related to tissue hypoxia but may also relate instead more closely to acceleration of the glycolytic pathway in situations unrelated to tissue hypoxia.

Nevertheless, absolute blood lactate concentrations are useful as a marker of shock severity and have been recognised to closely correlate with patient outcome (13). In patients with shock, if therapeutic measures are associated with decreasing blood lactate concentrations, then tissue perfusion is usually improving and patient survival is more likely.

Many patients who have shock and lactic acidosis also have decreased cardiac function. Therefore, for many years it was generally accepted that acidemia was a major contributor to cardiac dysfunction in these patients, and primarily for this reason, aggressive attempts to normalise arterial pH as rapidly as possible with buffer therapies - usually bicarbonate, were part of widespread clinical practice (16). This belief was based upon an extensive body of research in isolated muscle preparations, isolated heart preparations, in animal models and upon a handful of clinical case reports. Together these studies suggested that acidosis (respiratory, hydrochloric, ammonium chloride, and others) decreased cardiac function, decreased the haemodynamic response to catecholamines, increased arrhythmias, and shortened survival (16) (17).

However, for a number of reasons, this literature is in large part not generally applicable to critically ill patients who have lactic acidosis. First, respiratory and metabolic acidosis are more recently recognised to have different cardiovascular effects (18) (19) (20). Next, none of the animal models truly imitate human lactic acidosis; drugs and anaesthetics themselves known to decrease myocardial contractility were often used (20), many studies were uncontrolled, and interspecies differences are significant and difficult to interpret, making application from animal models to clinical practice hazardous. Furthermore in large part, studies that demonstrated significantly deceased cardiac function during metabolic acidosis did so at an arterial pH well below that which is seen clinically in critically ill patients - ie outside the physiologically observed range in humans. For example Yudkin et al (21) report decreased cardiac output in rats at a pH of 6.6 - 6.9 and Steenbergin et al report impaired LV pressure development in rats at a pH of 6.7 (22). By contrast, a group of critically ill patients with shock, lactic acidosis and a high mortality had a mean arterial pH of 7.22 (23). Clearly many factors including respiratory compensation which may be therapeutically applied by mechanical ventilation, combine to ensure that the arterial pH experienced by patients with lactic acidosis is usually within the range 7.1 - 7.30. Finally, many studies in large animals made inferences about changes in myocardial contractility without measuring myocardial contractility directly. Reliable load independent measurements of left ventricular contractility which are applicable to large animal models and to human studies have only been developed in recent years (24) (25) (26).

Bicarbonate has been a mainstay of therapy for patients with metabolic acidosis for many years. In recent years however, bicarbonate has been recognised to have significant side effects which must be weighed against possible benefits (27). Other potential therapies for patients include hyperventilation, carbicarb, dichloroacetate, and haemofiltration. Each of these will be considered in chapter 4.

2. 3 Cardiac dysfunction during hyperdynamic shock

2.3.1 Anaphylactic shock

Cardiovascular collapse during anaphylaxis is multifactorial in aetiology. It is predominantly caused by decreased preload which may be exacerbated by increased intrathoracic pressures during bronchospasm and positive pressure ventilation, and also by decreased afterload. Myocardial dysfunction had not been considered to be a major contributor to cardiovascular compromise during anaphylaxis until recently. In 1988, two cases (4) were reported which demonstrated that left ventricular ejection fraction can be severely and reversibly depressed during human anaphylaxis. The observation was confirmed by a different group in 1992 (5). Most cases of human anaphylaxis are not studied with echocardiography or radionuclide angiography and so the frequency of left ventricular dysfunction during anaphylaxis is unknown. Some evidence suggests that particular subgroups of anaphylactic reactions are associated with myocardial depression wheras others are not (28). When myocardial dysfunction occurs during anaphylaxis it may be due to mediators released during anaphylaxis, to adverse effects of high catecholamine levels, and/or may be exacerbated by beta receptor down regulation (5). In addition, decreased left ventricular (LV) function may be due to systolic dysfunction (decreased left ventricular contractility), to diastolic dysfunction (eg myocardial oedema), or to ventricular interaction (pulmonary hypertension and shift of the interventricular septum thereby impairing left ventricular filling). Because histamine is released in large amounts during anaphylaxis, is a key mediator of anaphylaxis and is known to cause all the clinical features of anaphylaxis, I decided to investigate myocardial LV function during anaphylactic shock by first determining the effect of histamine on left ventricular function in human volunteers. This study is detailed in Ch. (5.2.2).

2.3.2 Septic shock

Patients who have septic shock usually present with increased peripheral perfusion, increased cardiac output and hypotension. In this context, and using the measuring tools available to Intensive Care clinicians, cardiac dysfunction is difficult to recognise in patients. In 1984 however, Parker and Parrillo (7) first reported clear evidence of myocardial dysfunction in septic shock. Cardiac dysfunction was recognised through the use of more sophisticated non-invasive tools for assessing cardiac function which had previously been little used in critically ill patients - specifically, radionuclide angiography and echocardiography. Patients with septic shock were reported (most also had malignant diseases), and LV ejection fraction was measured at regular intervals throughout each patient's septic illness. Patients clearly separated into two groups - survivors and non survivors, based upon their LV function in the first 1-2 days of their illness. Those patients who later survived had ventricular dilatation and decreased ejection fraction during the first days of septic shock. As they recovered, these changes resolved. Those patients who later died received greater doses of catecholamines, but did not have ventricular dilatation nor decreased ejection fractions. The abnormal observations in the survivors were then

studied in detail. At a similar time, the same observations were made in an animal model of chronic septic shock (29). Furthermore, endotoxin infusion in humans produced similar cardiovascular findings (30), and a plasma filtrate from septic humans was isolated which depressed contractility in isolated cardiac muscle cells (31). The identity of this factor has not been identified. Tumor Necrosis Factor - α is a likely candidate because it is the right size, it depresses contractility in an isolated muscle cell preparation (31), and because it is released in critically ill patients who have sepsis and produces many of the cardiovascular abnormalities of sepsis. TNF - α infusion in animal models produces many of the cardiovascular abnormalities of septic shock.

The cardiovascular pathophysiology in the non-survivors of septic shock, remains inadequately explained. The working hypothesis from Parker et al (7) was that the peripheral vascular insult in non surviving patients was greater than that of the survivors - and may have been associated with myocardial capillary leak. Myocardial edema which resulted may then have accounted for loss of myocardial compliance (diastolic dysfunction) and failure of compensatory dilation which is observed in survivors and is essential for survival from severe septic shock. Diastolic LV dysfunction is difficult to study in critically ill patients and this concept (although appealing) remains hypothetical.

To provide more insight into the cardiovascular dysfunction of septic shock, I decided to infuse Tumor Necrosis Factor - α into a large animal preparation in which it was possible to objectively assess changes in systolic and diastolic left ventricular function. This study is detailed in Ch. (5.3). Future studies were then planned to investigate diastolic left ventricular function in ICU patients who have septic shock.

2. 4 Cardiac dysfunction during hypovolemic shock

In most circumstances, hypovolemic shock is best treated by rapid infusion of fluid. If resuscitation is prompt and depleted intravascular volume is rapidly replaced, no other immediate therapy is usually needed to normalise cardiovascular function. However if fluid resuscitation is delayed, hypovolemic shock may then not reverse with fluid alone, may become irreversible, and may progress to death despite otherwise adequate (although delayed) intravascular volume replacement (32). Such a sequence of events is well described in animal models and, I believe, is sometimes seen clinically in patients with ruptured aortic aneurysms in whom resuscitation is delayed, and who may not leave the operating table alive because of irreversible cardiac dysfunction. The cause of this irreversible shock state is unclear.

I therefore decided to investigate left ventricular systolic and diastolic function in a large animal model of prolonged hypovolemic shock, in an attempt to determine whether cardiac dysfunction contributed to irreversibility during hypovolemic shock. This study is detailed in Ch. (6).

2. 5 Cardiac dysfunction during ionised hypocalcaemia

Ionised hypocalcaemia occurs during shock and is being increasingly recognised as a common occurrence in critically ill patients (33). Studies suggest that there are multiple causes and that many patients have associated sepsis (34). In hypovolemic shock, hypocalcaemia may be worsened by chelation - for example by citrate contained in blood transfusions. Ionised hypocalcaemia is also recognised to decrease human cardiac function (35), and so might worsen shock by worsening cardiac dysfunction.

I reported ionised hypocalcaemia in critically ill patients with lactic acidosis and septic shock, and also identified an association with bicarbonate infusions (23). Furthermore, I was able to identify an association between blood lactate concentrations and ionised hypocalcaemia in patients with lactic acidosis (36). These observations are detailed in Ch (4.2.2)

Chapter 3

METHODS

3 .1 Left ventricular function assessment - introduction.

In critically ill patients who require Intensive Care, cardiac function is most usually and accurately assessed using a pulmonary artery catheter and an arterial catheter. As a result most studies which report cardiovascular function during critical illness do so in terms of the variables which are measurable by these invasive vascular catheters: pulmonary artery occlusion pressure mean arterial and pulmonary artery pressures, heart rate and cardiac output (by thermodilution). A number of other variables are commonly calculated from these basic measurements including systemic and pulmonary vascular resistances and oxygen delivery and consumption. Thermodilution cardiac output provides a reasonable overall indicator of cardiac function, especially when it is interpreted in terms of cardiac filling pressures, but is limited by being influenced by a number of factors other than cardiac function alone. These factors are well known and include preload, afterload and heart rate. Furthermore, cardiac function as expressed by cardiac output, is a combination of left ventricular systolic contractility and left ventricular diastolic function. Unfortunately many studies in the literature incorrectly equate changes in cardiac output in critically ill patients directly to changes in myocardial function (when in fact the changes may have been instead in preload or in afterload) or even more incorrectly equate changes in cardiac output directly with changes in systolic myocardial contractility.

All forms of shock are associated with changes in a number of the above determinants of cardiac output. Therefore critical analysis of changes in left ventricular function during shock requires very careful assessment of each of these factors. In the first study reported in this thesis Ch. (4.2.1) cardiac function is measured using standard clinical techniques - the best available at the time for that clinical study - and as a result, changes in left ventricular function in this study must be inferred from the measured changes in cardiac output, pulmonary capillary wedge pressure, and in mean arterial blood pressure.

Clinical assessment of cardiac function in patients can be improved by using intravenous fluid challenges in conjuction with thermodilution cardiac output measurements. Cardiac output measurements can then be obtained at several different left ventricular preloads (using pulmonary capillary wedge pressure as an approximation of LV preload). The cardiac function curves thus constructed from these measurements, are better than a single measure of cardiac output to describe cardiac function. Shifts in position of cardiac function curves classically describe changes in left ventricular function.

The maximum rate of LV pressure development (dP/dt_{max}) must also be mentioned as a very sensitive index of LV systolic contractility but its measurement requires a LV pressure catheter and so data recording is usually limited to cardiac catheter studies, or to laboratory studies. dP/dt_{max} also is limited in that it is a measurement which is dependent upon preload and

heart rate, and (like cardiac output) may therefore provide misleading information during shock and critical illness when loading conditions change markedly and unpredictably.

Over the last 8 -10 years, other techniques which were first exclusively used by cardiologists have been used in critically ill patients in general Intensive Care Units to more precisely measure changes in left ventricular function during shock. For example, radionuclide angiography reliably measures LV volumes and LV ejection fractions in shocked patients and both trans-thoracic echocardiography and trans-oesophageal echocardiography can deliver reliable assessments of global and regional LV function, LV fractional shortening and calculated LV ejection fraction. One of the major achievements from the use of these newer technologies in shocked critically ill patients in the mid 1980's was the unexpected realisation that LV function in patients with septic shock is decreased - not increased as had previously been believed. This understanding occurred because radionuclide or echo cardiographic ejection fraction gives a better assessment of LV function than does cardiac output. Cardiac output is dependent upon preload and afterload. Ejection fraction is largely independent of preload but also still quite dependent upon afterload. Increased afterload decreases ejection fraction, and decreased afterload increases ejection fraction. Furthermore measurements of ejection fraction do not distinguish systolic from diastolic LV dysfunction. There are now more precise methods of assessing LV function especially in large animals but also to some extent in patients, which do allow differentiation of systolic and diastolic LV dysfunction. The end-systolic pressure-volume relationship (ESPVR) is a very reliable method of assessing LV contractility (systolic function) in a load independent manner. The ESPVR is a good means of studying changes in LV contractility in situations where loading conditions may be constantly changing - specifically in animals and patients with shock. The ESPVR is defined by changing afterload and is almost completely independent of preload (37). It is not quite as sensitive to changes in contractility as dP/dt_{max} but this disadvantage is far outweighed during shock by load independence. In each of the large animal studies detailed in this thesis, the ESPVR is the primary measure of systolic LV contractility, although in each of the studies other measures are also included to enable comparisons with other studies in the literature.

In Ch. (5.2.2) a study is described in which LV function was assessed in human volunteers. There was a need for a precise but non-invasive assessment technique for LV function, and for this purpose, the end-systolic pressure-dimension relationship (ESPDR) was ideal as the primary measure of systolic LV contractility. The ESPDR is as valuable as the ESPVR but derives information about LV function from measurement of one LV dimension only, rather than three. This is a reliable derivation provided that regional LV dysfunction has been excluded (26) (38). In this study each subject had regional LV dysfunction excluded by two dimensional echocardiocardiography to avoid this problem.

3.2 Left ventricular function assessment in an animal model

3.2.1 Introduction

The studies done in large animals which are reported in the following chapters each employ similar methodology, and use a common large animal model. This open chest, ultrasonic crystal technique was developed and validated by Dr K.R. Walley at the University of Chicago on the basis of a great deal of previous work by others, including Dr S. Rankin, Duke NC, USA (39). I was fortunate in 1988 to be employed as a full time Critical Care Research Fellow at St. Paul's Hospital Vancouver BC Canada with Dr Walley as a primary research supervisor. I could therefore apply recently validated methodology to many questions about changes in LV function during shock and lactic acidosis. I did not develop, nor validate this methodology as this had already been meticulously done (18) (25).

3.2.2 Anaesthesia

All but one of the large animal studies that follow were done using pigs, which have cardiac physiology very similar to humans, were freely available in Vancouver from the University of British Columbia, and which compared to other animals were relatively cheap. In the sepsis study (5.3.1), dogs were used instead because all previous dose response studies that we had access to using TNF - α infusion, had been done in dogs. In each of the pig studies, anaesthesia was induced using ketamine 10 mg/kg intramuscularly, followed by thiopentone (10-20 mg/kg intravenously. Next, one of two anaesthetic regimens was used for maintenance of anaesthesia. In the endogenous lactic acidosis study Ch (4.3.1; (40)), the sepsis study Ch. (5.3.1; (41)) and the hypovolemic shock study Ch (6.2.1; (42)), I used alpha - chloralose (80 mg/kg iv followed by 25 mg/kg/hr infusion) plus morphine (0.5 mg/kg iv hourly as required) as this had been the anaesthesia successfully used during validation studies of the same animal model and of the methodology. In a later study (lactic acid infusion Ch 4.3.2; (43)), a different technique was used for maintenance of anaesthesia. For this study, I decided to improve on what had by then become a standard anaesthesia regimen. Isoflurane (0.75%) and ketamine (0.1 mg/kg/min by intravenous infusion) were chosen with the intention of maximising analgesic and anaesthetic efficacy while minimising undesirable depression of myocardial contractility, complexity of administration and cost. Alpha - chloralose is an effective anaesthetic in pigs but is associated with undesirable spontaneous paddling movements of the animals legs which necessitate animal paralysis to enable the sophisticated cardiac measurements to be done with precision. Furthermore alpha - chloralose must be heated to be dissolved for intravenous administration and rapidly crystallises on cooling. Many anaesthetists would consider that opioids might enable better cardiac anaesthesia, however, I investigated both morphine and fentanyl in a series of pilot studies and in my view, neither of these drugs alone is a very effective analgesic in this species.

After very large doses (morphine 100mg iv in a 25 kg animal), animals were poorly sedated and at times seemed responsive to painful stimuli. Further pilot studies confirmed that the combination of isoflurane and ketamine had little effect on LV contractility in this model and created a preparation which was stable for at least 6 hours.

In all studies the animals were paralysed using pancuronium (0.1 mg/kg IV and supplemented as necessary) to avoid reflex respiratory muscle movements, and to enable greater precision of the sonomicrometric measurements.

3.2.3 Instrumentation

In each of the pig studies, after induction of anaesthesia, a tracheostomy was performed through a midline neck incision. The pigs were mechanically ventilated using an inspired oxygen concentration of 40% to 45% to ensure adequate oxygenation and tidal volume was set at 12 mL/kg at a rate adjusted to maintain the arterial partial pressure of carbon dioxide (Pa_{CO2}) at approximately 40 mm Hg. Positive end-expiratory pressure of 4 cm H_20 was applied to maintain end-expired lung volume during the open thorocotomy. A left carotid arterial catheter was placed to sample arterial blood and to monitor arterial blood pressure. A left internal jugular venous catheter was placed for drug and fluid administration. Right atrial and pulmonary artery catheters were inserted via a right internal jugular vein for mixed venous blood sampling, pressure measurement, and cardiac output determination using thermodilution.

Following a midline thoracotomy, the pericardium was opened widely and sutured in place to form a support for the heart (25). Left ventricular pressure was measured using an intraventricular "Millar" catheter inserted through the apex of the left ventricle. The chest was left open so that no structures compressed the heart. Thus, left ventricular pressure measured with respect to atmospheric pressure equalled left ventricular transmural pressure. An inflatable cuff was placed around the inferior vena cava to allow for transient vena caval occlusion and the ascending aorta was exposed so that it could be briefly occluded when required using a vascular clamp.

The first pair of ultrasonic crystals was sewn to the anterior and posterior epicardium to measure an antero-posterior diameter ("D_{ap}"). The next ultrasonic crystal was then sewn to the apical epicardium and was paired with an ultrasonic crystal implanted at the base of the left ventricle to measure a long axis diameter ("D_{long}"). Finally, an ultrasonic crystal sewn to the free wall epicardium was paired with an ultrasonic crystal implanted in the septum to measure a septal-free wall diameter ("D_{sf}"). These three diameters were then measured continuously using a sonomicrometer (Sonomicrometer 120, Triton Technology, San Diego, CA). We assumed that the left ventricle was an ellipsoid and used these approximately orthogonal diameters to estimate left ventricular volume, V, as:

$$V = \pi/6 \times D_{ap} \times D_{long} \times D_{sf} \qquad \textit{Equation 1}$$

This volume estimate includes left ventricular chamber volume together with the volume of myocardium included by the placement of ultrasonic crystals. In these studies *absolute* volumes were not used to test any hypotheses and instead testing was done only to assess *changes* in left ventricular chamber volume. This methodology has been previously validated (18) (25).

3.2.4 Systolic Left Ventricular Contractility

In each of the large animal studies, left ventricular contractility was principally measured using the end-systolic pressure-volume relationship (ESPVR). The ESPVR was determined as the line of best fit through end-systolic pressure-volume points from two steady-state beats, two aortic cross-clamp beats, and four beats during the vena caval occlusion (Fig 1). The duration of vena caval occlusion was always short and the aorta was cross-clamped for only one to two beats to avoid reflex changes in LV contractility and the Anrep effect (44). End-systole for each analysed beat was defined as the point of maximum elastance, that is the point of maximum pressure divided by volume. The ESPVR is approximately linear within physiologic limits, yet it may be curvilinear outside this range (24) (45).

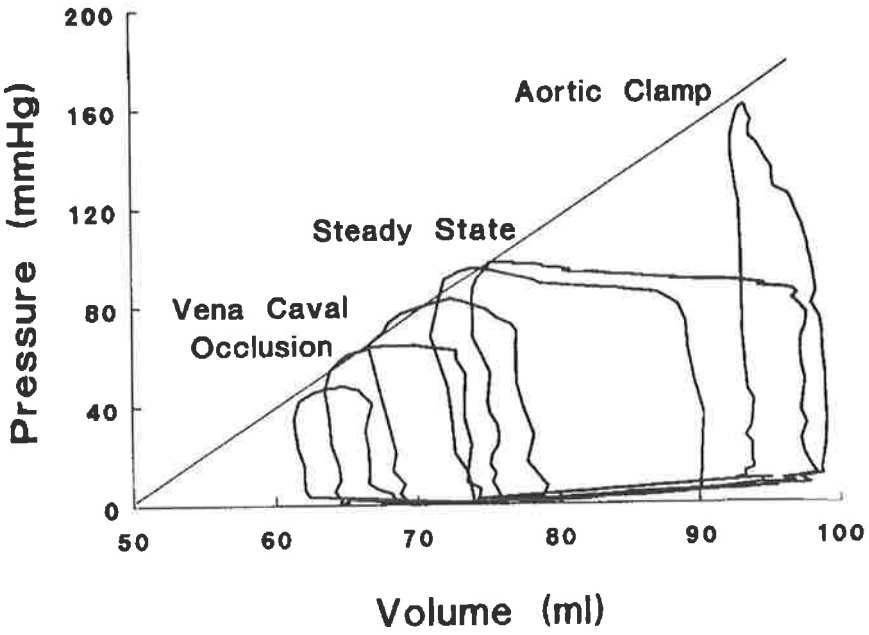

Figure 1. Points of maximum elastance from left ventricular pressure-volume loops during steady state, during a brief aortic clamp, and during transient inferior vena caval occlusion define the linear end-systolic pressure-volume relationship (ESPVR). The slope of the ESPVR is E_{max} and is a preload and afterload-insensitive index of left ventricular contractility

Since numeric estimate of the slope of a tangent line to a potentially curvilinear relationship requires data points below and above the tangent point (46), in each of the animal studies data is included from both vena caval occlusions and aortic cross clamps. The slope of the ESPVR is defined in most studies as E_{max} , (in (4.3.1) as m_{ESPVR}), and the volume axis intercept is defined

as V_d. E_{max} is a measure of left ventricular contractility which, compared with many other indices of contractility, is least sensitive to changes in preload and afterload (47) (48) V_d is determined by extrapolating the ESPVR to zero pressure and therefore has a potentially large 95% confidence interval. Therefore, in these studies, this value is not used in any calculations or conclusions. Another way to quantify a change in left ventricular contractility while avoiding extrapolations is to measure the shift in the ESPVR at a pressure of 100 mm Hg (δ_{ESPVR}) (10) (Fig 2). This approach has been suggested to be useful in some circumstances because it avoids extrapolation outside the range of the data and outside a physiologic range, and because it combines information from the coupled estimates of both m_{ESPVR} and V_d. δ_{ESPVR} may be more reliable than E_{max} alone (48). It was used in the studies described in Chapters (4.3.1) and (5.3.1).

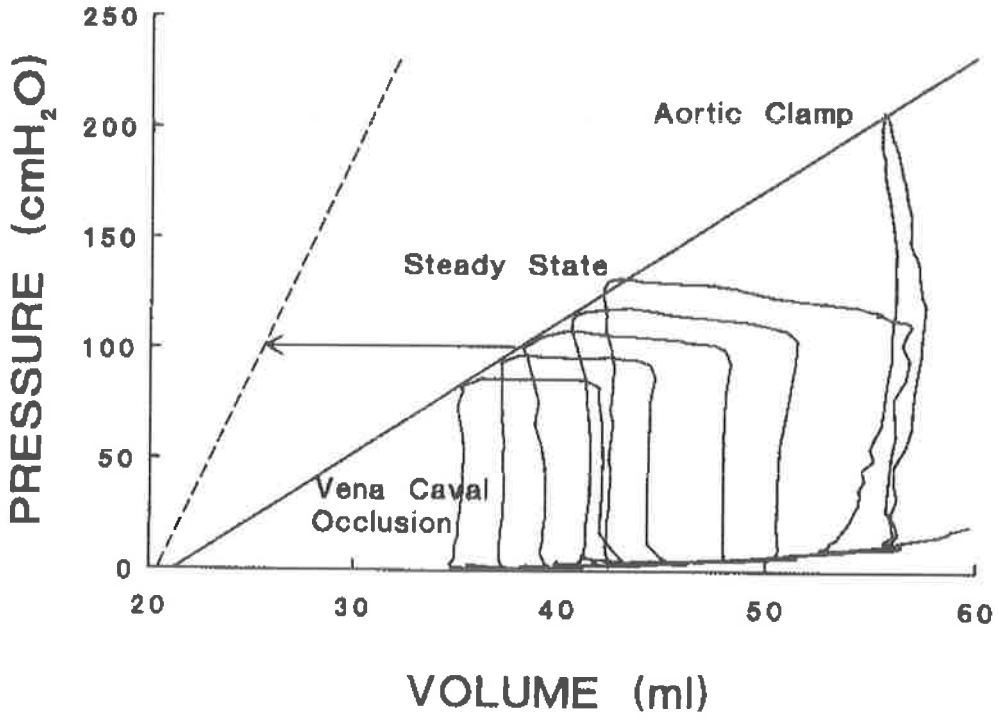

Figure 2. Pressure-volume trajectories from one representative pig at baseline in Ch. (4.3.1) to illustrate how left ventricular contractility was measured. The ESPVR is the best fit solid line through end-systolic points (maximum elastance) from four beats during a vena caval occlusion, two beats during steady state (only one beat shown in this figure), and two beats during aortic cross clamping (only one beat shown in this figure). In this study, m_{ESPVR} is the slope of the ESPVR. m_{ESPVR} of the dashed line is increased, indicating increased contractility. The left shift of the ESPVR at 100 cm H_20 (δ_{ESPVR}) from the solid to the dashed line, is shown by the bold arrow and is another measure of increased contractility.

Other measurements of left ventricular function used in the following studies include the maximum rate of left ventricular pressure development (dP/dt_{max}), and left ventricular stroke work. dP/dt was calculated from steady-state pressure-volume data sampled at 250 Hz using the Lagrange five-point formula (46) and the maximum (dP/dt_{max})) was determined. LV stroke

work was calculated as mean arterial pressure times LV stroke volume. In the study (Ch 4.3.2; (43)) dP/dt_{max} divided by LVEDP and left ventricular ejection fraction (LV stroke volume divided by LV end diastolic volume above V_0) were also calculated. In the sepsis study (Ch 5.3.1; (41)) and to avoid the incorrect assumption in that study that the ESPVR is linear at high and low pressures, the left shift in the ESPVR at a pressure of 100 mmHg (δESPVR) (Figure 2) was also measured. Finally, the reviewers of the hypovolemic shock study (Ch 6.2; (42) for Am J Physiol requested that the relationship between left ventricular stroke work and end-diastolic volume be calculated as an additional measure of intrinsic myocardial performance that is potentially independent of loading, geometry, and heart rate(49). This relationship was determined as described by Glower et al. (49) from the pressure volume data measured during all vena caval occlusions. In this study the slope and intercept of this relationship changed during this experiment, the value of stroke work was calculated at a single typical end-diastolic volume of 25 ml above V_d (average diastolic volume for all sets in this study was 24.5 ml). Interestingly, in no case did the results of these alternative measures add information not already determined by the ESPVR, E_{max} and V_0.

3.2.5 Left ventricular diastolic mechanics

In the lactic acid infusion study (Ch 4.3.2; (43)) measurements of LV diastolic pressure-volume relationships were included to account for changes in left ventricular diastolic function caused by pulmonary hypertension and ventricular interaction. In this study some animals developed severe pulmonary hypertension early in the study and in the immediate pre terminal minutes in these animals, the measured septal free-wall dimensions indeed decreased markedly. It seemed likely that in the animals that died early, pulmonary hypertension increased right ventricular pressure which then terminally shifted the intraventricular septum sufficiently to decrease left ventricular stroke volume and that this initiated demise. All of the animals included in this paper were studied to determine whether there was any evidence of ventricular interaction which might have influenced the measurements of contractility; none was identified. First, the diastolic pressure-volume relationships were examined in all animals. By least squares analysis, points from diastasis were best fit using the equation:

$$P = Ae^{BV} \quad (37) \qquad \textit{Equation 2}$$

where A and B are parameters determined by a best fit procedure. To determine whether there was a significant change in the diastolic pressure-volume relationship we tested for changes in these parameters. If the interventricular septum had shifted from right to left due to right ventricular pressure overload, then the left ventricle should have been less compliant in diastole - a shift of the relationship upwards and to the left. We also tested for changes in the ratios

between D_{long}/D_{sf}, D_{ap}/D_{sf}, and D_{ap}/D_{long} during the course of the experiment. If the interventricular septum had shifted from right to left, then these ratios would have changed.

In the sepsis study (Ch 5.3.1; (41)) the left ventricular diastolic pressure-volume relationship was determined from pressure-volume points during diastasis (42) as follows. Diastasis was defined as starting five exponential pressure decay time constants, tau (calculated as TD in (50)), after end-systole and ending at atrial contraction. Diastasis points were included from two steady state beats, two beats during aortic occlusion, and four beats during vena caval occlusion. These points were then best fit (Quasi-Newton non linear best fitting procedure, SYSTAT, Evanston, IL) these points using:

$$P = S \times \ln \{(V_m - V)/(V_m - V_0) \qquad \textit{Equation 3}$$

where S, V_m, and V_0 are parameters determined by the best fit procedure (44). *Equation 3* has advantages over the previously used exponential equation in that the best fit parameters can be readily interpreted in physiological terms.

In the hypovolemic shock study Ch. (6.1; (35)), *equation 3* was also used to define the diastolic pressure-volume relationship. In this study the equation had the advantage of accurately describing the diastolic pressure-volume relationship at low volumes and negative pressures (51). Furthermore, as illustrated in Figure 3, the best fit parameters can also be readily interpreted in physiological terms. Specifically, V_m represents the maximum volume that is approached asymptotically as pressure rises, the yield volume of the diastolic left ventricle. V_0 is simply the equilibrium diastolic volume at which pressure is zero. Finally, S is suggested to be a size-independent chamber stiffness parameter having the units of stress (51).

To obtain the best representation of the relaxed diastolic pressure-volume relationship in the hypovolemic shock study, diastolic points were chosen from diastasis from beats spanning a wide range of diastolic volume. To ensure that the diastolic pressure-volume points lay on the relaxed diastolic pressure-volume relationship (51) (52), diastolic pressure-volume points starting five exponential pressure decay time constant periods, tau (calculated as TD in (50)), after end systole (defined as the point of maximum elastance) were included and diastolic pressure-volume points occurring during atrial contraction were excluded. To obtain a wide range of data along the volume axis, points from diastasis from two steady-state beats, four vena caval occlusion beats, and two aortic clamp beats were included. To further broaden the spread of data along the volume axis, and thereby optimise our fitting procedure, diastolic data from the two data sets at the start of the experiment (both before and after haemorrhage) were combined and compared with the two data sets at the end of the experiment (both before and after volume resuscitation) (Fig. 3).

3.2.6 Ventricular function curves

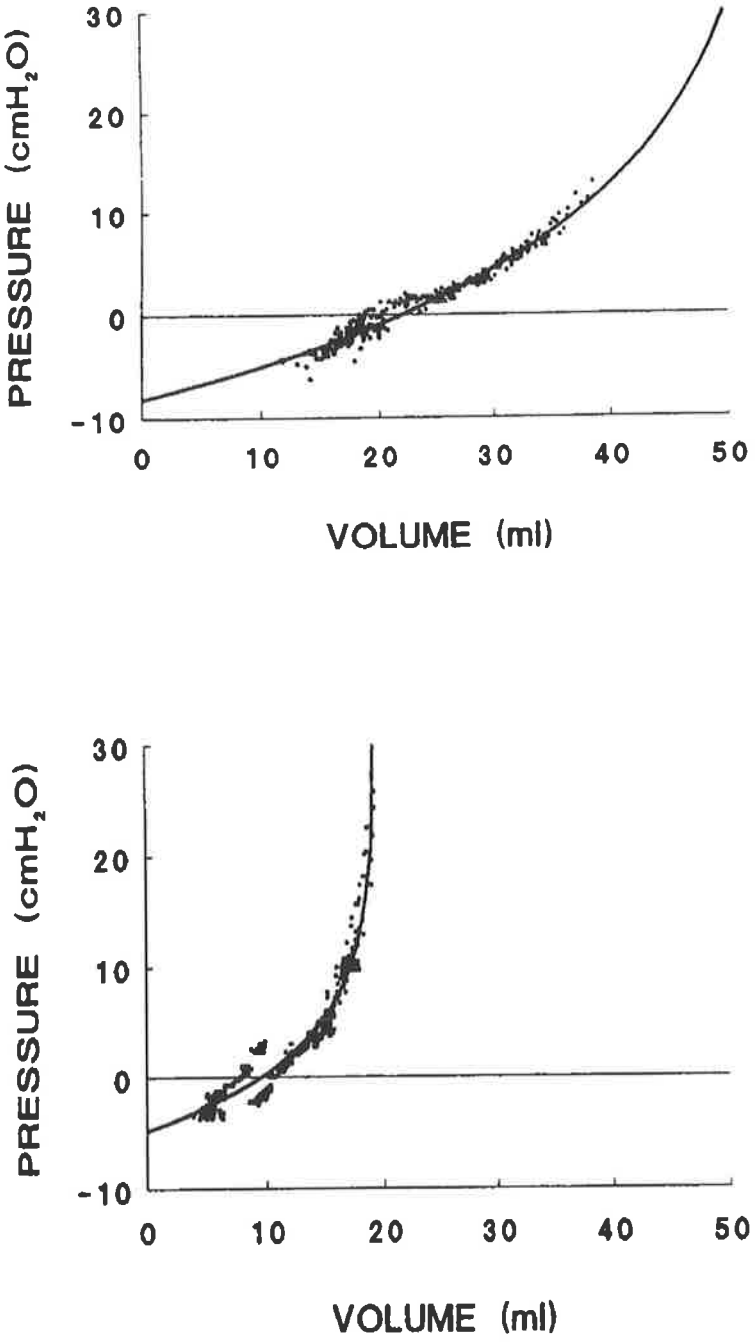

Figure 3. Data from study Ch (6.1) (30). *Equation 3* (smooth curve) is best fit to typical diastolic pressure-volume data at start of experiment (top: sets 1 and 2) and after a period of hypovolemic shock (bottom: sets 3 and 4) in one representative pig. Wide spread of data along x-axis improves fitting procedure and is accomplished by taking diastolic points from beats at steady state, during aortic clamping, and during vena caval occlusion. Wider spread still is obtained by combining data from 2 data sets before and after volume removal or infusion (points before volume removal in this example lie mainly to the right and points after volume removal lie mainly to the left). Volume at zero pressure (intersection of the smooth curve and dotted line) is equilibrium volume. Maximum volume approached asymptotically as pressure rises.

In the hypovolemic shock study (Ch 6.1; (42), in order to clearly define the unusual observation that overall left ventricular function was decreased despite increased systolic contractility, left ventricular function curves were also calculated. To determine a left ventricular function curve from the diastolic and end-systolic pressure-volume relationships, afterload, and heart rate at each experimental condition, cardiac output was calculated for a range of end-diastolic filling pressures (Fig. 4).

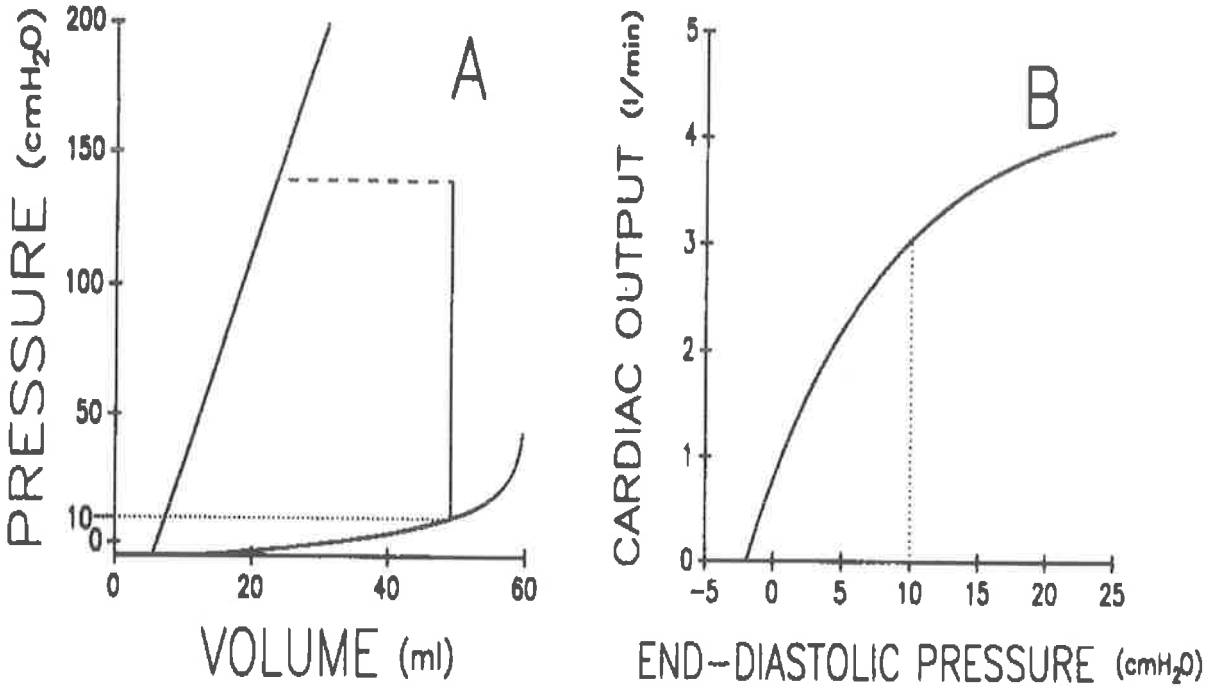

Figure 4. Left ventricular function curve (B) is derived from left ventricular diastolic and end systolic pressure-volume relationships (ESPVR) (A) at given afterloads and heart rates. For example, at end-diastolic pressure of 10, end-diastolic volume is determined from diastolic pressure-volume relationship (horizontal dotted line in A). Then stroke volume (horizontal dotted line in A) is determined for known pressure afterload and ESPVR. Finally, stroke volume times heart rate is cardiac output for an end-diastolic pressure of 10 (vertical dotted line in B). Complete cardiac function curve in B is determined by repeating this calculation at many different end-diastolic pressures using constant diastolic pressure-volume relationship, ESPVR and heart rate.

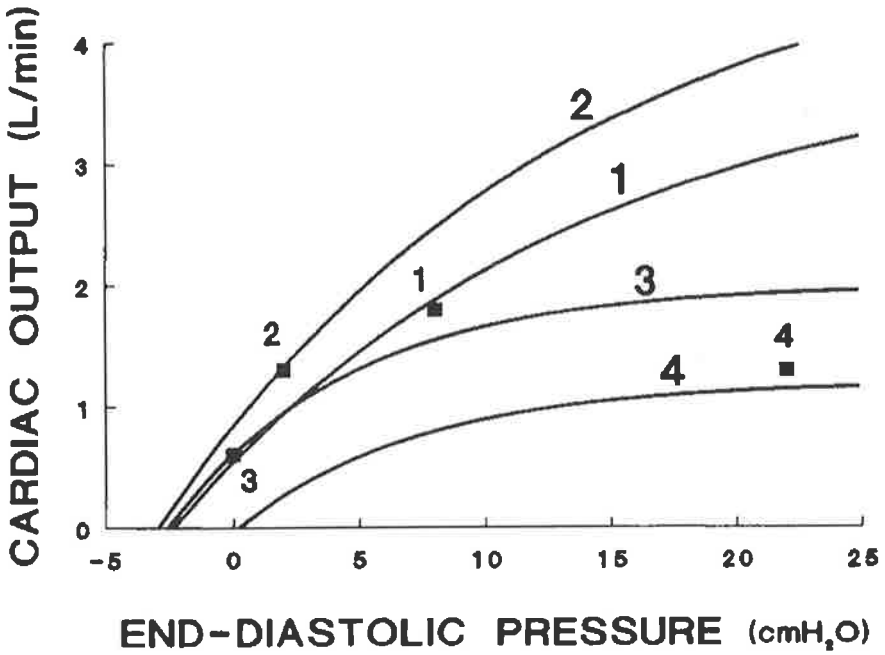

Figure 5. Data from Ch (6.1) (30). Typical left ventricular function curves calculated as in Fig 4 at four experimental sets (large numbers) are illustrated for 1 representative pig. Independently measured end-diastolic pressure and cardiac output (thermodilution) points for each set. (solid square labelled with small numbers) lie close to corresponding calculated curves. Left ventricular function improves from baseline (curve 1) to immediately after phlebotomy (curve 2) because contractility and heart rate increase while afterload decreased. Left ventricular function is markedly impaired after a period of hypovolemic shock (curves 3 and 4) because increased diastolic stiffness impairs diastolic filling.

First, the end-diastolic volume for a given filling pressure was determined from the diastolic pressure-volume relationship. Then, the end-systolic volume was determined from the end-systolic pressure-volume relationship and the pressure afterload. Stroke volume was then determined as the difference between end-diastolic and end-systolic volume. Finally, cardiac output was determined as heart rate times stroke volume. Repeating this calculation, using the same diastolic and end-systolic pressure-volume relationships as well as constant pressure afterload and heart rate, for many different end-diastolic filling pressures within the experimentally observed range, generated the ventricular function curves (Figs. 4 and 5).

3.2.7 Limitations of the animal model

The fact that the chest was held widely open in this animal model makes it quite different from critically ill patients with shock and sepsis. Lack of pericardial and chest wall constraint decreases the coupling between right ventricular and left ventricular mechanics, particularly at the relatively low pressures of diastole. Thus right to left septal shift, which could contribute to decreased diastolic compliance (or prevent increased diastolic compliance) in severe human shock, could be missed in this animal model. Another problem is that if myocardial volume had changed during the course of the experiments, then the LV volume estimates would have been affected. In the following studies however we did not find find a difference in post mortem wet-to-dry weight ratios or in myocardial weight. Therefore, it is unlikely that myocardial volume changes were significant, or an important source of methodological error.

3.3 Left ventricular function assessment in human volunteers

In the histamine infusion study (Ch 5.2.2; (53), left ventricular systolic mechanics were assessed non-invasively in humans using the following previously reported methodology (38). Mean arterial blood pressure was first measured using an automated sphygmomanometer. A carotid arterial pressure tracing was simultaneously measured using a carotid transducer, a trans-thoracic echocardiogram was done to enable measurements of systolic and diastolic LV dimensions and an electrocardiogram and phonocardiogram were continually recorded.

All pressure, dimension, and RR interval measurements taken from the echo cardiographic and electrocardiographic records (Fig 6) were repeated on 5 beats during each intervention, and then averaged. The coefficient of variation for these repeated measures for pressure was 6.7 ± 1.2%, for dimension was 1.3 ± 0.4%, and for RR interval was 0.8 ± 0.5%. All measurements were performed independently by two observers blinded to the haemodynamic intervention. Identical effects were identified by these two independent measurement sets and the mean correlation coefficient for dimension measurements between these two sets was 0.95.

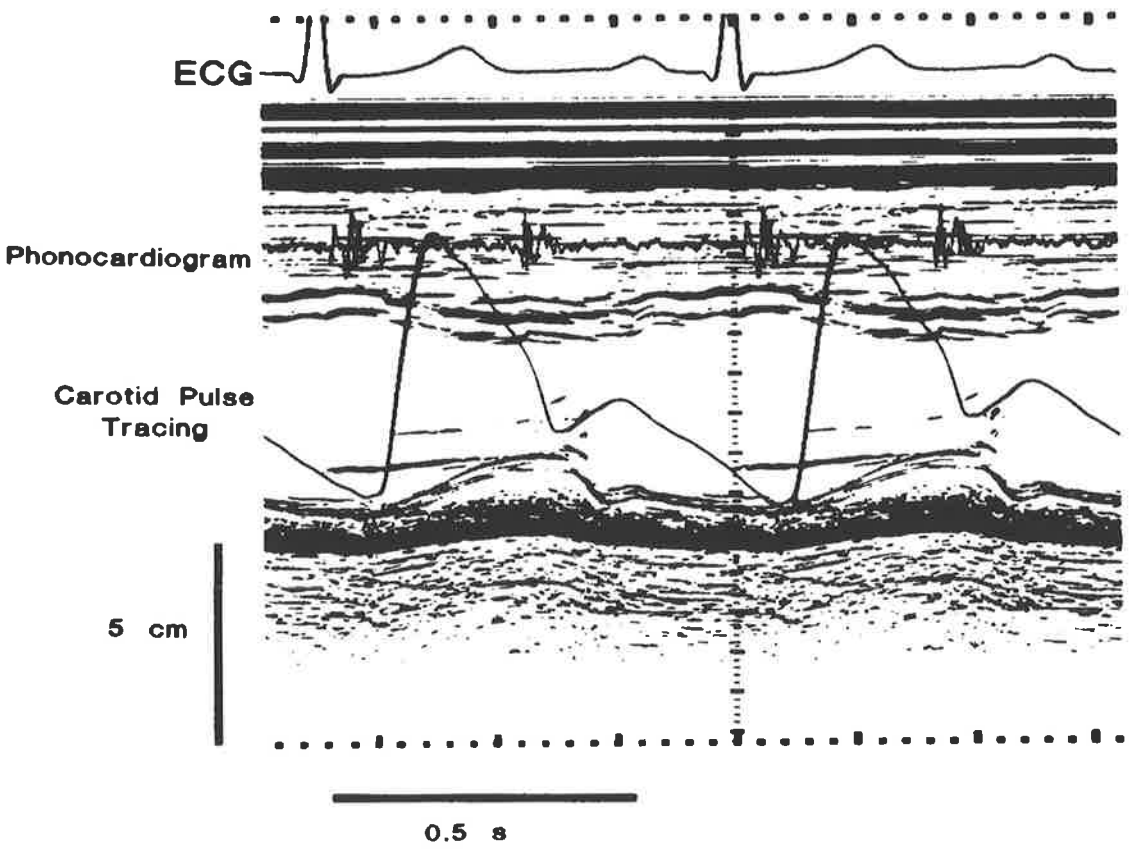

Figure 6. Typical raw data for one measurement in one subject (study in Ch 5.2.2). Electrocardiogram (ECG), phonocardiogram, and carotid pulse tracings were superimposed on targeted M -mode echocardiogram so that all measurements could be made simultaneously from this permanent record.

3.3.1 Left ventricular end-systolic pressure measurement

Indirect carotid arterial pulse pressure was measured (HP 21 050A Transducer, Hewlett Packard, Andover, MA) from the right carotid artery by an experienced technologist (Figure 6). Each tracing was then linearly calibrated by assigning simultaneously measured automated brachial cuff systolic and diastolic pressures (Dinamap^R monitor, Johnson and Johnson, Tampa, FL) to the peak and to the nadir of the tracing respectively. The dicrotic notch pressure was determined by linear interpolation and has been shown to closely approximate end-systolic pressure (54) (38). This method has been previously validated and has been found to be accurate over a wide range of systemic pressures and cardiac outputs (38).

3.3.2 Left ventricular dimension measurement

The echocardiograms were obtained by an independent echocardiographer experienced with the methodology but unaware of the sequence of haemodynamic interventions. Left parasternal two-dimensional left ventricular cross sectional echo cardiographic images were obtained using a 2.5 MHz transducer (HP Sonos 1000, Hewlett Packard, Andover, MA). The position and angle of the echo transducer was maintained by directing the beam just off the tip of the anterior leaflet of the mitral valve and by maintaining internal anatomic landmarks constant. From the two-dimensional image, derived M-mode echocardiograms were obtained (Fig 6). All recordings were done at held end expiration with the glottis open. Left ventricular internal dimensions and left ventricular posterior wall thickness were measured at end-diastole (defined as the onset of the QRS complex in lead 11 of the simultaneously obtained electrocardiogram), and end-systole (defined as the first high frequency component of the aortic second heart sound, from the simultaneously obtained phonocardiogram).

The following calculations were done to enable comparisons of the results with those from the Dr K.M. Borow laboratory at University of Chicago where the technique was first described and validated.

3.3.3 Rate corrected velocity of circumferential fibre shortening ($V_{cf,c}$)

The left ventricular percent fractional shortening was calculated as end-diastolic dimension minus end-systolic dimension, divided by end-diastolic dimension. Left ventricular ejection time was measured from the simultaneous carotid artery pulse tracing. The ejection time was rate corrected to a heart rate of 60 beats per minute by dividing by the square root of the R-R interval measured in seconds. The rate corrected velocity of circumferential fibre shortening ($V_{cf,c}$) was calculated by dividing the fractional shortening by the rate-corrected ejection time (38).

3.3.4 Left ventricular end-systolic meridional wall stress (σ_{es})

The left ventricular end-systolic meridional wall stress (σ_{es}) in g/cm^2 was calculated using the method of Grossman et al. (55).

$$\sigma_{es} = \frac{(1.35)\,(P_{es})\,(D_{es})}{(4)(h_{es})[1 + (h_{es}/D_{es}]}$$

where P_{es} is left ventricular end-systolic pressure in mmHg, D_{es}, is end-systolic internal dimension in cm and h_{es} is end-systolic posterior wall thickness in cm. 1.35 is a conversion factor (mmHg to g/cm^2), and 4 is a geometric factor that results from conversion of radius to internal dimension. Changes in minor axis dimension may be greater than associated changes in left ventricular long axis dimension and therefore meridional wall stress changes may overestimate circumferential wall stress changes. Nevertheless, since each normal subject was used as his own control, changes in wall stress were reliably detected using this technique to assess meridional wall stress (38) (33).

Chapter 4

CARDIAC DYSFUNCTION DURING LACTIC ACIDOSIS

4.1 Introduction

The research detailed in this chapter was stimulated during 1987 by a clinical case report done when I was a registrar at the Royal Adelaide Hospital. This report identified cardiac dysfunction during sodium bicarbonate infusion in a patient who had shock and metabolic acidosis (56). The case was significant because bicarbonate was being infused intravenously in this patient with the intention of *improving* cardiovascular function. The case report suggested that therapies for acidosis in critically ill patients might have side effects which outweigh potential benefits, and initiated the thinking behind other studies in this chapter.

4.1.1 Case report *Intensive Care Med 1987;13:425-427* (56)

A 66-year-old scrap metal merchant was admitted to the Royal Adelaide Hospital with a 2-day history of increasing cough, dyspnoea and generalised myalgia. On examination he was agitated, cyanotic and anuric and had poor peripheral perfusion. His temperature was 40.5 °C, blood pressure 100/90 mmHg, pulse rate 144 per minute, and respiratory rate 48 per minute. The CXR revealed diffuse bilateral alveolar and interstitial opacities and arterial blood gas results were Pa_{O2} 48 mmHg, Pa_{CO2}, 25 mmHg and pH 7.34. Serum biochemical results were sodium 125 mmol/l, potassium 4.1 mmol/l, calcium 2.03, creatinine 0.24 mmol/l and urea 18.0 mmol/l.

A diagnosis of viral pneumonitis with acute respiratory failure was made and was later confirmed by positive serological studies. Treatment consisted of endotracheal intubation, mechanical ventilation and intravenous corticosteroids. A pulmonary artery catheter was inserted and 1500 ml of a colloid solution was infused, increasing the pulmonary artery occlusion pressure from 7 mmHg to 15 mmHg and blood pressure from 100/90 mmHg to 140/90 mmHg.

Table 1. *Haemodynamic and blood gas changes in a patient with lactic acidosis (n=1).*

$NaHCO_3$ 100 mmol	BP mmHg	PAOP mmHg	CO $l.min^{-1}$	SV ml	SVR $dyne.s.cm^{-5}.m^{-2}$	LVSW $g.m.beat^{-1}$	pH	BE $mmol.l^{-1}$	$PaCO_2$ kPa	PaO_2 kPa	PvO_2 kPa
Before	140/90	16	8.70	85.3	891	106	7.20	-11	5.7	7.9	4.8
After	130/90	16	6.09	55.4	1194	65.5	7.31	-6	5.5	7.3	3.9
Before	120/80	12	6.07	61.9	1172	68.2	7.28	-7	5.7	6.9	4.1
After	95/60	13	5.76	57.6	874	46.2	7.37	-1	5.6	7.1	4.1
Before	140/90	10	8.84	92.1	877	121	7.18	-10	6.7	7.7	5.1
After	145/80	13	9.09	94.7	791	115	7.25	-5	6.8	7.5	4.8

However the patient remained anuric. Twenty four hours later the arterial blood gas results were Pa_{O2}, 60 mmHg, Pa_{CO2} 43 mmHg, and pH 7.20, with an inspired oxygen concentration of 50%. Blood tested for ketones was negative and serum biochemical results were lactate 2.5 mmol/l, sodium 129 mmol/1, potassium 4.1 mmol/l, urea 29.7 mmol/l, creatinine 0.55 mmol/l and creatinine phosphokinase was greater than 10,000 U/l. One hundred millilitres of 8.4% sodium bicarbonate (100 mmol) were administered intravenously over 10 min, and cardiac output unexpectedly decreased. Intravenous sodium bicarbonate 100mmol) was administered again 12 hours later and again 36 hours later. Blood pressure (BP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), arterial pH, base excess (BE), carbon dioxide (Pa_{CO2}, and oxygen (Pa_{O2}) tensions and mixed venous oxygen tension (Pv_{O2}) measurements were performed, and stroke volume (SV), left ventricular stroke work (LVSW) and systemic vascular resistance (SVR) indices were derived (51) immediately before and after the three infusions of sodium bicarbonate (Table 1). On each occasion the cardiac output measurement was done in triplicate by the same operator and the mean value was recorded as the cardiac output.

With each of the three infusions of 100 mmol of sodium bicarbonate, LVSW decreased. Blood pressure, CO and SV decreased with the first and second infusions, whereas $Pv0_2$ decreased with the first and final infusions of sodium bicarbonate. The patient subsequently received no further intravenous alkali and was treated with daily haemodialysis to maintain a normal acid-base status.

Discussion

While adverse cardiovascular effects associated with metabolic acidosis had been well described, the ability of sodium bicarbonate to reverse these effects and to improve patient outcome had not been convincingly documented (57). In this patient, a reduction in LVSW was consistently observed with the infusion of sodium bicarbonate. While the BP, CO, and SV decreased with the first and second infusions, they increased with the third infusion. This increase may have been due to bicarbonate increasing preload. Apart from the constant reduction in LVSW, the cardiovascular responses to sodium bicarbonate were varied with each infusion.

This case report demonstrated that the cardiovascular effects of bicarbonate infusion during acidosis may be unpredictable and at times may be detrimental. Furthermore this case report highlighted the need for a randomised controlled clinical trial to address the issues raised.

4.2 Human Studies

My Critical Care Research Fellowship concerning myocardial dysfunction during lactic acidosis and shock then followed at St Paul's Hospital, University of British Columbia, Vancouver, Canada. It seemed clear that the major reason for an ongoing controversy about the value of bicarbonate infusions for patients who had lactic acidosis was the absence of a prospective controlled clinical trial. The following study was therefore designed and performed.

4.2.1 Bicarbonate in critically ill patients with lactic acidosis

(Ann Intern Med 1990;112:492-498) (23)

4.2.1 Introduction

Because metabolic acidosis was believed to decrease cardiovascular function, patients with lactic acidosis were often treated with sodium bicarbonate to correct acidemia, to improve myocardial contractility and cardiac output, and to increase the cardiovascular response to circulating catecholamines (16) (17) (58) (11) (12). However, until this study had been completed, the ability of sodium bicarbonate therapy to achieve these goals had never been tested in a controlled clinical study and indeed was actively debated (16) (27). Many adverse effects of sodium bicarbonate therapy have been described (27). Some of the potentially more important adverse effects include hypercapnia and aggravation of intracellular acidosis (59) (60), hyperosmolality (61), congestive cardiac failure, and ionised hypocalcaemia (56) (62). Hypercapnia is likely to occur during sodium bicarbonate therapy when the normally compensating respiratory reflexes are obtunded, which may occur during sedation and mechanical ventilation. Hypercapnia may increase intracellular acidosis because carbon dioxide crosses cell membranes rapidly and thus may decrease myocardial cell function (59) (61) (63) (64) (22). Sodium bicarbonate is usually infused as a hypertonic solution and therefore may decrease myocardial contractility (65), increase preload, and alter afterload. Any of these changes may alter cardiac output. Finally, sodium bicarbonate may decrease plasma ionised calcium. By increasing pH, sodium bicarbonate increases the binding between calcium ions and albumin (66) (67) and also directly binds calcium (67). A decrease in plasma ionised calcium may then decrease myocardial contractility (35). This prospective, randomised, placebo controlled clinical study was therefore designed to determine whether the positive or negative haemodynamic effects of sodium bicarbonate therapy predominate when it is used to treat patients who have lactic acidosis. I questioned whether correction of acidemia using sodium bicarbonate infusion improves cardiac output, blood pressure, or other haemodynamic variables or changes plasma ionised calcium and partial pressure of CO_2 in arterial blood (Pa_{CO2}) in critically ill patients who have lactic acidosis.

4.2.1 Patients and Methods

Fourteen critically ill patients in the intensive care unit of St. Paul's Hospital, Vancouver BC, Canada were studied according to a protocol approved by the Human Ethics Committee of St. Paul's Hospital and the University of British Columbia. Consecutive patients, who had pulmonary and systemic arterial catheters inserted for clinical purposes, were studied if they had metabolic acidosis (arterial bicarbonate < 17 mmol/L and base excess < -10) and increased arterial blood lactate (> 2.5 mmol/L). Arterial pH was not used as an inclusion criterion because of the dependence of pH on Pa_{C02} which is affected by ventilator settings (68). All patients were being mechanically ventilated, 13 were receiving infusions of dopamine, dobutamine, adrenaline, or noradrenaline, or a combination, and 11 had a proven site of infection (Table 2). Eight patients had renal dysfunction (mean creatinine, 336 mmol/L; range, 175 to 672 mmol/L). The mean blood lactate concentration was 7.8 mmol/L (n= 14) and the mean baseline Pa_{CO2} was 32 mm Hg, reflecting hyperventilation.

Protocol

To avoid patient variability, all patients were studied after their haemodynamic status had stabilised. For the same reason, ventilator settings and fluid infusion rates were kept constant during the 2-hour study period, no new medications were administered, and nursing interventions, particularly patient turning and endotracheal suctioning, were minimised.

Each patient received sequentially both sodium bicarbonate (0.9 M, 2 mmol/kg body weight infused over 15 minutes via either a peripheral or a central line) and sodium chloride (equal dose, volume, and time) during the 2-hour study period. The infusion order was randomised using cards in sealed envelopes, so that 7 patients received sodium bicarbonate first and 7 received sodium chloride first. An assistant was aware of the code and labelled each infusion numerically. When each patient's study was completed the infusions were identified to allow ongoing analysis. The infusions were identical in appearance and the investigator, the patient's nurse, and the patient were all blind to solution identity. Because the patients were all heavily sedated and mechanically ventilated they were unaware of the crossover point between infusions. Because the investigator was aware of the end tidal CO_2 measurements, however, he was no longer effectively blinded after the infusions had started.

All measurements were done immediately before, immediately after, and 30 minutes after the first infusion. After a 20 minute break the protocol was repeated with the second infusion.

Table 2. *Characteristics of 14 patients who had lactic acidosis*

Patient	Sex, Age	Diagnoses	Inotropic Drugs	Site of Infection	Lactate	Creatinine	Outcome
	y				*mmol/L*	*μmol/L*	
1	M, 26	Chronic renal failure, ischemic bowel	dopamine, dobutamine, norepinephrine	Blood (gram-negative bacillus)	2.5	672	Died
2	F, 75	Pneumonia, ischemic bowel	dobutamine, epinephrine	Sputum (*Staphylococcus aureus*)	5.0	68	Died
3	M, 75	Empyema	dobutamine, epinephrine, norepinephrine	Pleural fluid (*Staphylococcus aureus*)	5.7	206	Died
4	M, 35	Septic shock	dopamine, epinephrine, norepinephrine	Blood (*Streptococcus pneumoniae*)	18	400	Died
5	F, 63	Septic shock, cirrhosis	dopamine, epinephrine	Blood (gram-negative bacillus)	21	226	Died
6	F, 65	Septic shock	dopamine, dobutamine, epinephrine	Blood (*Streptococcus pneumoniae*)	2.9	350	Died
7	F, 78	Hemicolectomy	dopamine, dobutamine	Peritoneum (*Bacteroides fragilis*)	4.4	123	Died
8	M, 57	Pneumonia, ethylene glycol	dopamine, epinephrine	Sputum (*Staphylococcus aureus*, gram-negative bacillus)	6.5	389	Survived
9	M, 37	Pneumonia	dopamine, dobutamine, epinephrine	Lavage (*Pneumocystis carinii*)	14	180	Died
10	F, 82	Hypovolemic shock	dopamine, dobutamine	No infection	8.4	101	Died
11	M, 67	Septic shock, acute myeloid leukemia	dopamine, epinephrine	Blood (gram-negative bacillus)	6	93	Died
12	M, 29	Pneumonia	dopamine, dobutamine, epinephrine	Lavage (*Pneumocystis carinii*)	4.7	379	Died
13	M, 61	Cardiac arrest, alcoholism	dopamine, dobutamine, epinephrine	No infection	8	175	Died
14	F, 34	Hypovolemic shock	No inotropic drugs	No infection	4.5	124	Survived

Thus the total study duration for each patient was less than 2 hours. A 2 hour study period was chosen because it proved to be the maximum time during which medical and nursing interventions could be avoided and constant study conditions could be maintained. Every patient was studied using the same protocol with the same interval between infusions. There were no dropouts.

Arterial and mixed venous blood gases (including measured oxygen saturations), arterial ionised calcium, haemodynamics (Table 3) and end tidal CO_2 (Engstrom Eliza, Bromma, Sweden) were measured. Haemodynamics comprised mean arterial, pulmonary artery, pulmonary capillary wedge and central venous pressures, heart rate, and cardiac output

Table 3. *Additional haemodynamic and blood gas variables of 14 patients who had lactic acidosis.*

Variable	HCO_3 Infusion			NaCl Infusion		
	Before	Immediately after	30 Minutes after	Before	Immediately after	30 Minutes after
Heart rate, (*beats/min*)	111 ± 18	116 ± 24	112 ± 20	112 ± 22	114 ± 22	111 ± 19
Central venous pressure, (*mmHg*)	13 ± 5	15 ± 6	13 ± 6	11 ± 6	15 ± 7	13 ± 6
Pulmonary artery pressure, (*mmHg*)	30 ± 8	32 ± 8	30 ± 9	30 ± 8	31 ± 8	30 ± 9
Arterial oxygen saturation, (*measured %*)	92 ± 6	91 ± 6	92 ± 7	91 ± 7	92 ± 6	91 ± 7
Mixed venous oxygen saturation, (*measured %*)	69 ± 10	69 ± 11	65 ± 12	68 ± 10	69 ± 10	68 ± 11
End tidal CO_2, (*mm Hg*)	23 ± 6	29 ± 6†	25 ± 6†	22 ± 6	22 ± 6	22 ± 6
Oxygen delivery, (*mL/min*)	1067 ± 574	1188 ± 517	1023 ± 452	1036 ± 485	1150 ± 456	1055 ± 509
Oxygen consumption, (*mL/min*)	230 ± 66	256 ± 72	266 ± 92	234 ± 64	261 ± 59	242 ± 69

* All values are expressed as mean ± SD.
† $P \leq 0.01$ compared with values measured before HCO_3.

using the thermodilution technique. All measurements were done at end expiration. Cardiac output was measured in triplicate using 10-mL injections of 5% dextrose at room temperature and a cardiac output computer (Marquette Electronics Inc, Milwaukee, Wisconsin). Oxygen delivery and oxygen consumption were calculated using standard formulas (69). Plasma ionised calcium was measured using an ICA I analyzer (Radiometer, Copenhagen, Denmark) and was not corrected for pH.

4.2.1 Data Analysis

In this study the principal null hypothesis that there was no difference between sodium bicarbonate and sodium chloride infusions was tested for cardiac output, mean arterial pressure, and ionised calcium using a 2 X 2 crossover design with repeat baseline measurements (70). The measurements after baseline were done both immediately and 30 minutes after each infusion. We also examined the other variables using the same analysis. Because no statistically significant differences in haemodynamics were observed between sodium bicarbonate and sodium chloride, we tested the power of our data (71) to detect a difference of 0.5 and 1.0 L/min between the changes in cardiac output after sodium bicarbonate compared with sodium chloride. These differences are 7% and 15%, respectively, of the mean cardiac output measurements (n = 14). We chose to test for a 15% change in cardiac output because previous investigators have accepted this change as clinically significant (72). We also chose to test for a smaller change in cardiac output (7%) because we recognise that the change considered to be "clinically significant" is dependent on clinical judgment.

Crossover designs with repeat baseline measurements differ from the more traditional crossover design, the weaknesses of which have been recently discussed (73). A 2 X 2 crossover design with repeat baseline measurements has only two possible carryover effects. First, a difference in baseline measurements can occur, and second, the treatment effect may be altered by treatment order. Kenward and Jones (70) have described a method that has a high power to test for carryover effects. In contrast, the method used to test for carryover effects in a traditional crossover design has a low power (70). Therefore, following the method of Kenward and Jones, we tested for both types of carryover. In the event that carryover was detected, only first-period data were used. In addition, because some investigators hesitate to use crossover analyses at all (73), we also tested for treatment effect using all the first-period data only. In this analysis we avoided any potential carryover problems but lost some of the statistical power of the crossover design. Finally, in order to search for a benefit for bicarbonate in very acidemic patients, we also separately examined the subgroup of seven patients who had an initial pH of 7.20 or less. Crossover study results are presented as estimates of the effect and with 95% confidence intervals (CI).

4.2.1 Results

There was no difference at any time between the effects of sodium bicarbonate and sodium chloride infusions on cardiac output, blood pressure, or pulmonary capillary wedge pressure (Fig 7). Immediately after both infusions pulmonary capillary wedge pressure increased (15 to 17 mm Hg and 14 to 17 mm Hg; both $P < 0.001$) and cardiac output increased (6.7 to 7.5 L/min and 6.6 to 7.3 L/min; both $P < 0.01$), whereas mean arterial pressure and heart rate were unchanged. The differences in effects between sodium bicarbonate and sodium chloride at 30 minutes were 0.15 L/min (CI, - 0.06 to 0.36) for cardiac output, - 0.29 mm Hg (CI, - 2.43 to 1.85) for mean

arterial pressure, and 0.44 mm Hg (CI, - 1.10 to 0.46) for pulmonary capillary wedge pressure. None of these differences at 30 minutes was statistically significant.

In this study, the dose of sodium bicarbonate used (2 mmol/kg) was adequate to significantly improve acidemia throughout the study period. After sodium bicarbonate infusion, the mean arterial pH increased from 7.22 to 7.36 ($P < 0.001$) and the mean serum bicarbonate

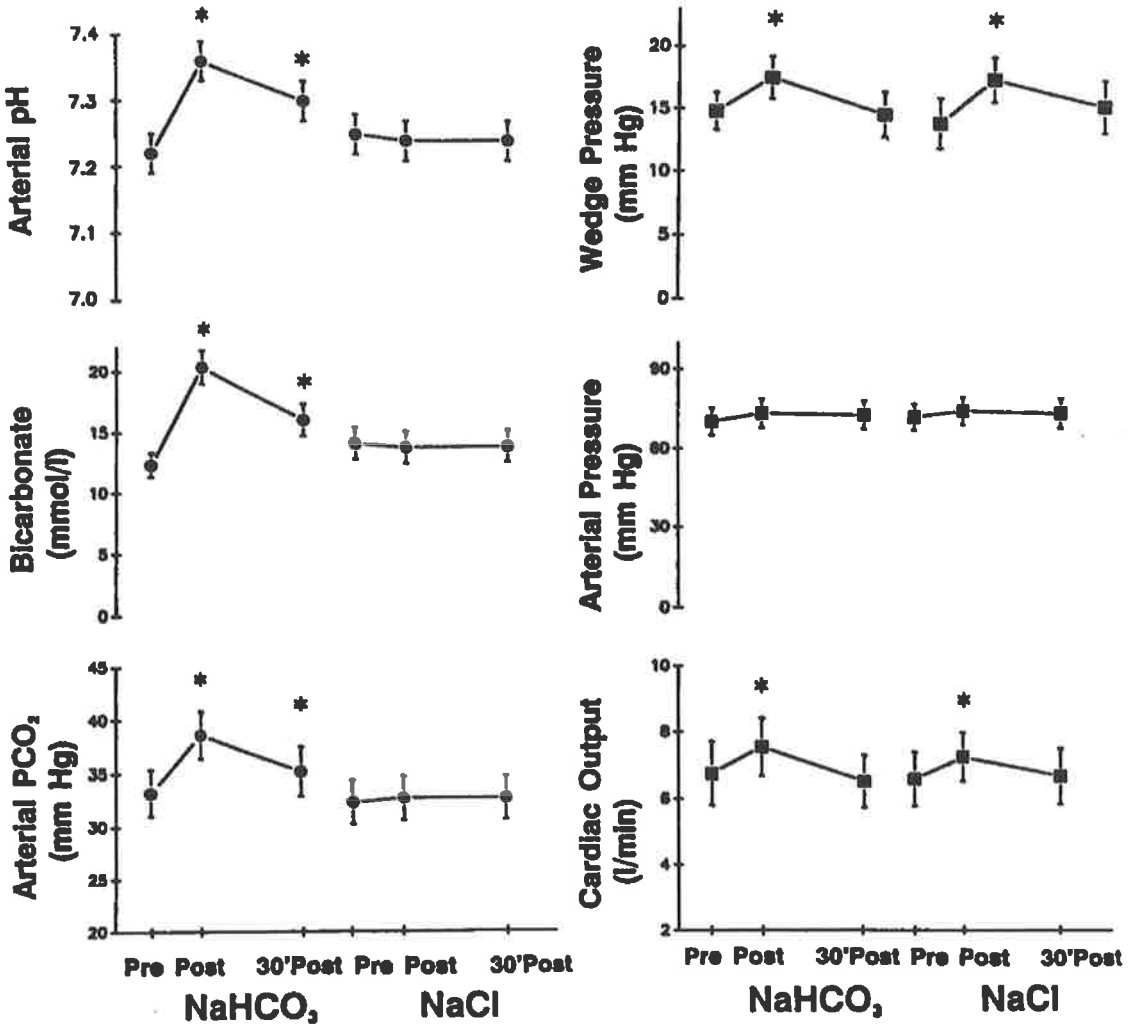

Figure 7. Acid-base (*left*) and haemodynamic (*right*) measurements before (*Pre*) and after (*Post*) sodium bicarbonate and sodium chloride in critically ill patients who had lactic acidosis (n=14). The increases in pulmonary capillary wedge pressure and cardiac output were not caused by pH correction because identical changes were seen after sodium chloride. All values are mean ± SE. Asterisk indicates $P < 0.01$ compared with Pre.

increased from 12 to 18 mmol/L ($P < 0.001$). Both measurements then gradually decreased (Fig. 7). At 30 minutes, however, both were still increased compared with their baseline values ($P < 0.001$). Unlike the haemodynamic measurements, the baseline measurements of serum bicarbonate in the sodium bicarbonate and sodium chloride groups were not identical. I therefore also present the data by order of infusion (Figure 8) to demonstrate that the haemodynamic effects were the same regardless of the infusion order.

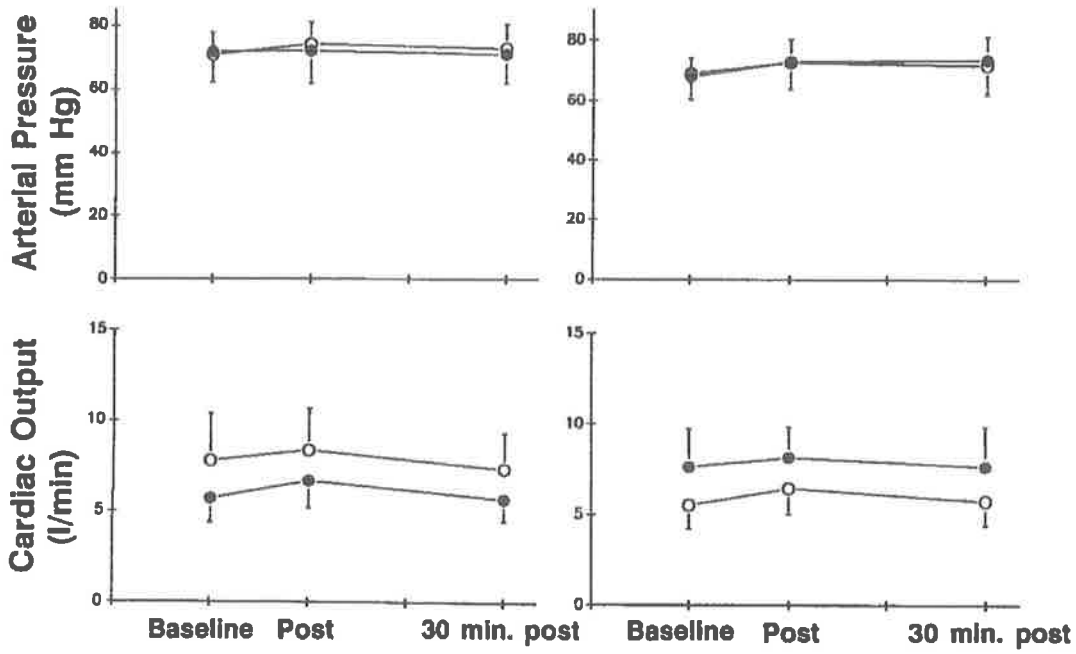

Figure 8. Influence of infusion order on haemodynamic measurements before (Baseline) and after (Post) sodium bicarbonate and sodium chloride infusion in 14 patients who had lactic acidosis. In each case patients who received an infusion first are represented by open circles and those who received an infusion second are represented by closed circles. There were no changes in cardiac output or in blood pressure and the trends were the same regardless of infusion order. All values are mean ± SE.

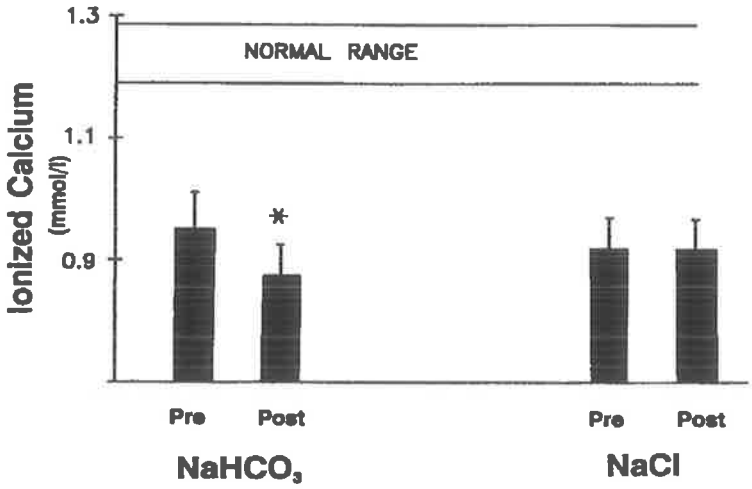

Figure 9. Changes in plasma ionised calcium after sodium bicarbonate and sodium chloride infusion in critically ill patients who had lactic acidosis (n=10). Ionised calcium decreased after sodium bicarbonate but not after sodium chloride infusion. All values are mean ± SE. Asterisk indicates $P < 0.001$ compared with Pre.

Bicarbonate decreased plasma ionised calcium (Figure 9). Plasma ionised calcium was low in all patients at baseline (mean, 0.95 mmoL; normal range for the St. Paul's laboratory, 1.17 to 1.29 mmol/L). After sodium bicarbonate infusion, plasma ionised calcium decreased further (to 0.87 mmol/L, $P < 0.001$) but after sodium chloride infusion, it was unchanged.
Bicarbonate increased Pa_{C02} (Fig 7). During the sodium bicarbonate infusion, Pa_{CO2} increased from 33 to 39 mm Hg ($P < 0.001$). End tidal CO_2 increased from 23 to 29 mm Hg ($P < 0.001$) over the same time and peaked toward the end of the infusion. Arterial and end tidal CO_2 then decreased, but both were still elevated at 30 minutes. None of these changes were seen after sodium chloride.

The power of the design to detect a difference in cardiac output between sodium bicarbonate and sodium chloride infusions was 99.9% to detect a difference of 1.0 L/min, and over 90% to detect a difference of 0.5 L/min. When the first period only was examined (no crossover), seven patients received sodium bicarbonate and seven received sodium chloride. The conclusions are the same as in the larger study - no difference was seen between sodium bicarbonate and sodium chloride for any haemodynamic response. In this more restricted analysis, the power was 95% to detect a 1.0 L/min difference but less than 50% to detect a 0.5 L/min difference. Finally, the seven most acidemic patients (arterial pH < 7.20; Fig 10) were separately analysed. These patients had a mean arterial pH of 7.13 (range, 6.9 to 7.2) and a mean arterial lactate of 10.1 mmol/L (range, 2.6 to 21 mmol/L). Even in these patients however, although bicarbonate increased arterial pH significantly (Fig 10, left), it did not increase cardiac output or mean arterial pressure. The haemodynamic responses (Fig 10, right) were the same as those for the whole group.

Discussion

This prospective randomised controlled study shows that in critically ill patients who have metabolic acidosis and increased blood lactate, correction of acidemia using sodium bicarbonate does not increase cardiac output, blood pressure, or change other haemodynamic variables. The study also shows that sodium bicarbonate infusion does not increase the cardiovascular response to circulating catecholamines in these patients. Two side effects of sodium bicarbonate infusion that may explain its lack of efficacy were identified. Sodium bicarbonate decreases plasma ionised calcium and increases Pa_{CO2}. Finally, this study suggests that transient haemodynamic responses to sodium bicarbonate infusion are not caused by increases in pH, but instead are caused by the infusion of a hypertonic, sodium-containing solution.

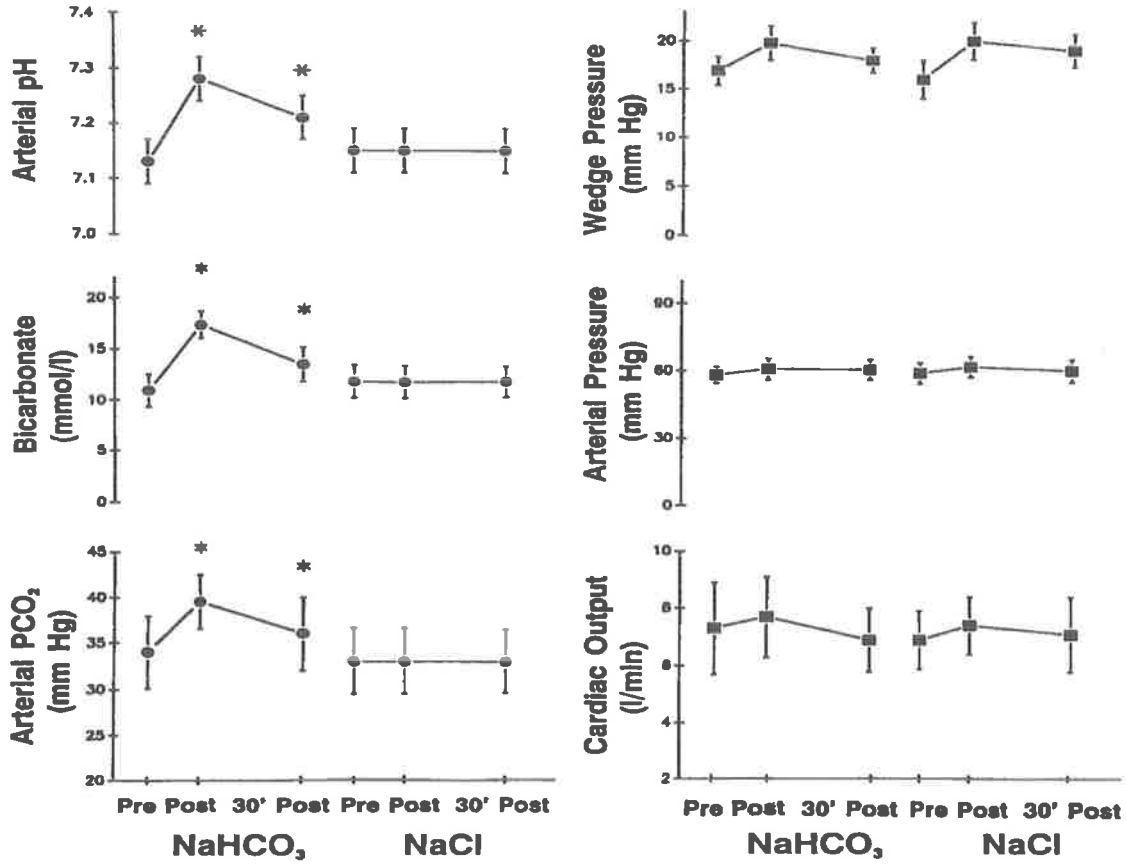

Figure 10. Acid-base (left) and haemodynamic (right) measurements before (Pre) and after (Post) sodium bicarbonate and sodium chloride infusions in seven critically ill patients who had severe lactic acidosis (arterial pH < 7.20). The changes and the trends were the same as in the larger group (Figure 7). All values are mean ± SE. Asterisk indicates $P < 0.05$ compared with Pre.

Many clinicians believe that correction of acidemia using sodium bicarbonate is most likely to improve haemodynamics in patients who have a very low pH, and an arterial pH of 7.20 is often the point at which sodium bicarbonate therapy is recommended (74). However, in the critically ill patients in this study who had an arterial pH less than 7.20, there was no difference between the haemodynamic effects of sodium bicarbonate and sodium chloride. Thus, it appears that even in very acidemic patients, an increase in pH using sodium bicarbonate does not improve haemodynamics.

Because 13 of these 14 patients were receiving catecholamine infusions, I was also able to examine the hypothesis that correction of acidemia increases the cardiovascular response to circulating catecholamines (75) (76). In this study it did not. The notion that acidemia decreases the cardiovascular response to circulating catecholamines is widely held among clinicians and is based largely on animal models using extremely severe acidosis (77) which is more severe than acidoses which are encountered clinically in patients. I measured no differences in the haemodynamic responses after sodium bicarbonate and sodium chloride in the patients who were receiving catecholamines, despite a large increase in pH using sodium bicarbonate. Therefore, I

concluded that in critically ill patients who have lactic acidosis, sodium bicarbonate infusion does not improve the cardiovascular response to catecholamines.

This study identifies two important side effects of sodium bicarbonate therapy: decreased ionised calcium and increased Pa_{CO2}. Sodium bicarbonate may decrease ionised calcium by two mechanisms. First, an increase in pH increases the binding between ionised calcium and proteins and thereby decreases the physiologically active, ionised fraction (66). Second, bicarbonate may directly complex calcium in vivo as it does in vitro (66) (67). Although several investigators (56) (62) have recently raised this issue as potentially important in humans, prior to this study there were no data that had been published on the effect of sodium bicarbonate therapy on plasma ionised calcium in either animals or patients with lactic acidosis. A decrease in plasma ionised calcium in these patients may decrease myocardial contractility as it did in a recent study (35) in which myocardial contractility, measured non-invasively in humans, decreased as plasma ionised calcium decreased. In that study plasma ionised calcium decreased by 24%. In the present study, patients' mean plasma ionised calcium at baseline was 20% below the normal range for the St Paul's Hospital laboratory. Sodium bicarbonate infusion further decreased plasma ionised calcium by 8.5% ($P < 0.001$). Thus, the low ionised calcium levels in these patients may have decreased myocardial contractility, and it is also possible that sodium bicarbonate administered to our patients before the study may have contributed to the baseline plasma ionised calcium levels observed. A number of associations of ionised hypocalcaemia in critically ill patients have been described (78) (34). This study identifies another - sodium bicarbonate therapy - in critically ill patients who have lactic acidosis. The other important side effect of sodium bicarbonate infusion in these mechanically ventilated patients was hypercapnia, which may also decrease myocardial contractility. Intracellular pH was not measured in this study but an increase in extracellular P_{CO2} may decrease intracellular pH and thus decrease myocardial cell function (59) (64) (22).

This study also suggests that anecdotal reports (79) of sodium bicarbonate improving haemodynamics during acidosis may be explained by effects common to both sodium bicarbonate and sodium chloride infusions, and not to pH changes. An increase in extracellular fluid osmolality and in sodium content can both affect myocardial contractility (65). Furthermore, the increase in intravascular volume after hypertonic solutions may be much greater than the infused volume owing to fluid shifts from the extravascular compartment. Thus, increased preload may increase cardiac output. The equimolar sodium chloride control was received by all patients, and therefore effects of increased pH could be separated from these other factors. All the changes in haemodynamics observed were accounted for by factors common to both solutions and not to changes in pH.

The conclusions from this study differed from previously published reports that suggest a beneficial effect of sodium bicarbonate. There are three likely reasons for these differences. First, most previous studies have not been in humans, and because large interspecies differences exist (80) these studies may not be directly extrapolated to humans. A prospective, controlled human study had not previously been reported. Second, most previous studies did not examine

endogenous lactic acidosis (81) (82) and those studies that did examine endogenous lactic acidosis used drugs and anaesthetic agents (in the animal models) which are known to depress myocardial contractility (20) (83). Finally, of those studies that have examined sodium bicarbonate therapy, most had been unable to reach a definitive conclusion about haemodynamics because of difficulty increasing pH with the dose and regimen of sodium bicarbonate used (20) (84).

The patients in this study are typical of those who currently receive sodium bicarbonate therapy in many critical care settings. The patients had severe cardiac dysfunction. Despite high preload (mean pulmonary capillary wedge pressure, 14 mm Hg), low afterload (mean arterial pressure, 70 mm Hg), and infusion of inotropic drugs in 13 patients, cardiac output was only marginally above normal (mean, 6.7 L/ min, Fig 7). In contrast, a healthy person who had no cardiac dysfunction but who had the same high preload, low afterload, and inotrope infusions would be expected to have a much greater cardiac output. Cardiac dysfunction may have been caused by acidemia but there are other possible causes. These patients had a very high mortality (86%, Table 3). However, the mean survival time of non survivors after the study was 48 hours. Therefore, although these patients were all critically ill, had cardiac dysfunction and had a high mortality they were stable at the time of the study. It is exactly this type of patient who commonly received sodium bicarbonate therapy in many different Intensive Care Units in 1990.

In conclusion, correction of acidemia using sodium bicarbonate infusion did not improve cardiac output, blood pressure, or other haemodynamic variables in critically ill patients who had lactic acidosis. Correction of acidemia also did not improve the cardiovascular response to circulating catecholamines in these patients. Sodium bicarbonate infusion decreased plasma ionised calcium and increased Pa_{CO2}, and it is possible that these side effects overrode any beneficial effects that pH correction may have on haemodynamics.

In 1991 (12 months following the publication of this study), an independent group in France reported a remarkably similar and confirmatory study, in 10 mechanically ventilated, critically ill patients with lactic acidosis (85). In this paper at no time was there any difference in haemodynamic measurements between equimolar sodium bicarbonate and sodium chloride infusions. This paper replicates and confirms the results of (Ch 4.2.1; (23)).

4.2.2 Plasma ionised calcium and lactate in patients with lactic acidosis

Intensive Care Med 1992;18:286-289 (36))

Following the observation that blood ionised calcium concentrations are often decreased in patients with lactic acidosis and shock and recognising that hypocalcaemia may be one of the factors decreasing cardiac function in patients who had lactic acidosis, the following study was initiated. I wished to investigate whether an apparent relationship between blood ionised calcium and blood lactate concentrations truly existed in critically ill patients.

4.2.2 Introduction

Decreased blood ionised calcium [Ca^{++}] concentrations and lactic acidosis are both important problems in critically ill patients (78). Lactic acidosis has for many years been associated with a high mortality (13). Decreased [Ca^{++}] may cause tetany and arrhythmia's, decreased diaphragm strength (86), decreased myocardial contractility (35), and recently in critically ill patients decreased [Ca^{++}] concentrations have also been associated with increased mortality (87). In these critically ill patients, decreased [Ca^{++}] concentrations have also been associated with hypotension (88) (34), with sepsis (34), and reported in patients having lactic acidosis (23) and in others having out of hospital cardiac arrest (89). In contrast, [Ca^{++}] usually *increases* during acidemia when hydrogen ions bind to albumin and displace calcium ions from their protein binding sites. However, in most clinical studies concerning [Ca^{++}] concentrations in critically ill patients, blood lactate concentrations were not measured, and in consequence an association between [Ca^{++}] and blood lactate concentrations in patients having lactic acidosis had not previously been reported.

To test the hypothesis that decreased plasma ionised calcium concentrations are associated with increased blood lactate concentrations in critically ill patients, arterial blood samples were taken for simultaneous measurement of [Ca^{++}] and lactate concentrations in nine critically ill patients.

4.2.2 Materials and methods

Nine patients having lactic acidosis who were admitted to the Intensive Care Unit of St. Paul's Hospital, Vancouver BC, Canada were studied. Lactic acidosis was defined as a serum bicarbonate < 17 mmol/l, base excess < -10, blood lactate concentration > 2.5 mmol/l and arterial pH was not used as an admission criterion because of its dependence on arterial P_{CO2}. Five of these patients were included in a previous study (23) but on that occasion only data from the first 2 hr study period was reported. In this report, patients were not included if intravenous calcium had been infused in the previous 12 hours, or if a possible cause of decreased [Ca^{++}]

(Hypomagnesemia, blood transfusion in the previous 24 hours) was recognised. Clinical characteristics of the patients are described in Table 4. All patients were receiving infusions of inotropic drugs and sodium bicarbonate as part of their therapeutic regimens. The study was approved by the Human Ethics Committees of St. Paul's Hospital and of the University of British Columbia.

Blood was withdrawn from the arterial catheter (10 ml) and discarded, and then arterial blood was drawn for measurement of arterial pH, P_{CO2}, and plasma [Ca^{++}], lactate, creatinine, magnesium and albumin. Each patient then had arterial blood sampled for [Ca^{++}] and lactate concentrations every 6 hours until the attending physicians infused calcium, the acidosis resolved, or the patient died.

Table 4. *Clinical and biochemical characteristics of nine critically ill patients having lactic acidosis.*

Age	Sex	Diagnosis/etiology of lactic acidosis	Creatinine (mol/l)	Mg^{++} (mmol/l)	Albumin (mmol/l)	pH	PCO_2 (mmol/l)	HCO_3^- (mmol/l)
71	M	Lung cancer, pneumonia, septic shock	229	0.91	25	7.12	24	8
39	M	Wegener's granulomatosis, ARDS, pneumonia, septic shock	668	1.01	29	7.31	26	15
65	F	Colectomy, ARDS, septic shock	74	1.11	23	7.34	21	16
79	F	Hematemesis, cardiogenic shock	99	0.71	18	7.28	18	8
37	F	Pneumonia, septic shock	202	0.70	27	7.29	20	9
57	F	Pneumonia, ethylene glycol poisoning	462	1.06	20	7.32	31	16
65	F	Septic shock	342	0.70	13	7.29	23	11
63	F	Cirrhosis, septic shock	255	1.2	28	7.14	22	7
35	F	Meningitis, septic shock	421	0.82	18	6.91	42	7

Normal ranges in our laboratory: Creatinine 40–120 µmol/l; Mg^{++} (0.7–1.05 mmol/l); albumin 36–42 mmol/l; arterial pH, 7.35–7.42; PCO_2, 36–42 mmol/l; HCO_3^-, 24±2 mmol/l

A total of 34 paired samples for blood [Ca^{++}] and lactate measurements were taken (range 1-7 for each patient). Six patients had 3 or more paired samples collected. Arterial blood for [Ca^{++}] measurement was collected anaerobically into sealed serum separator tubes and placed immediately on ice. All samples were centrifuged within 60min. [Ca^{++}] concentrations were measured using an ionised calcium analyzer (ICA 1, Radiometer, Copenhagen, Denmark) and the results were not corrected for pH. Arterial blood for lactate determination was placed immediately on ice and lactate concentrations were measured within 1hr of collection using an

enzymatic spectrophotometric technique (Sigma, St. Louis, USA). The tubes containing blood for lactate measurement contained a glycolytic inhibitor. Magnesium, albumin, and creatinine concentrations were measured using a colorimetric method (Ektachem 700, Kodak. Rochester, USA). Arterial pH and PCO_2 were measured anaerobically using a Radiometer blood gas analyzer (ABL 3, Radiometer, Copenhagen). Base excess was calculated using a standard formulae and arterial bicarbonate was calculated using formula 16 from Siggaard-Anderson O, 1974 (90).

4.2.2 Statistics

The hypothesis that there was an association between plasma $[Ca^{++}]$ and lactate concentrations was tested using linear regression analysis for the group. Then to confirm that the association did not arise through the use of pooled data, the data for each of the six patients who had three or more data points was also analysed using random effects regression (91). In each case the slopes and intercepts are reported, together with the standard error of the estimates. $P < 0.05$ was considered to be significant.

4.2.2 Results

In 9 critically ill patients who had lactic acidosis, there was a strong association (r-=0.78, $p \leq 0.001$) between decreased plasma $[Ca^{++}]$ and increased blood lactate concentrations. The association was present for the group (slope = -0.025, intercept 1.196; Fig. 11a), and also when the patients were considered individually [slope= -0.018 (SE 0.005), intercept 1.11 (SE 0.08); Fig. 11b].

The association between $[Ca^{++}]$ and arterial pH (r- = 0.21) was weak (Fig. 12).

The clinical and biochemical characteristics of the patients are found in Table 4. The plasma $[Ca^{++}]$ blood lactate and arterial pH results are found in Table 5. All patients were hypoalbuminemic (mean plasma albumin 22mmol/1). Six patients had renal dysfunction, but there was no relationship between $[Ca^{++}]$ and creatinine concentrations.

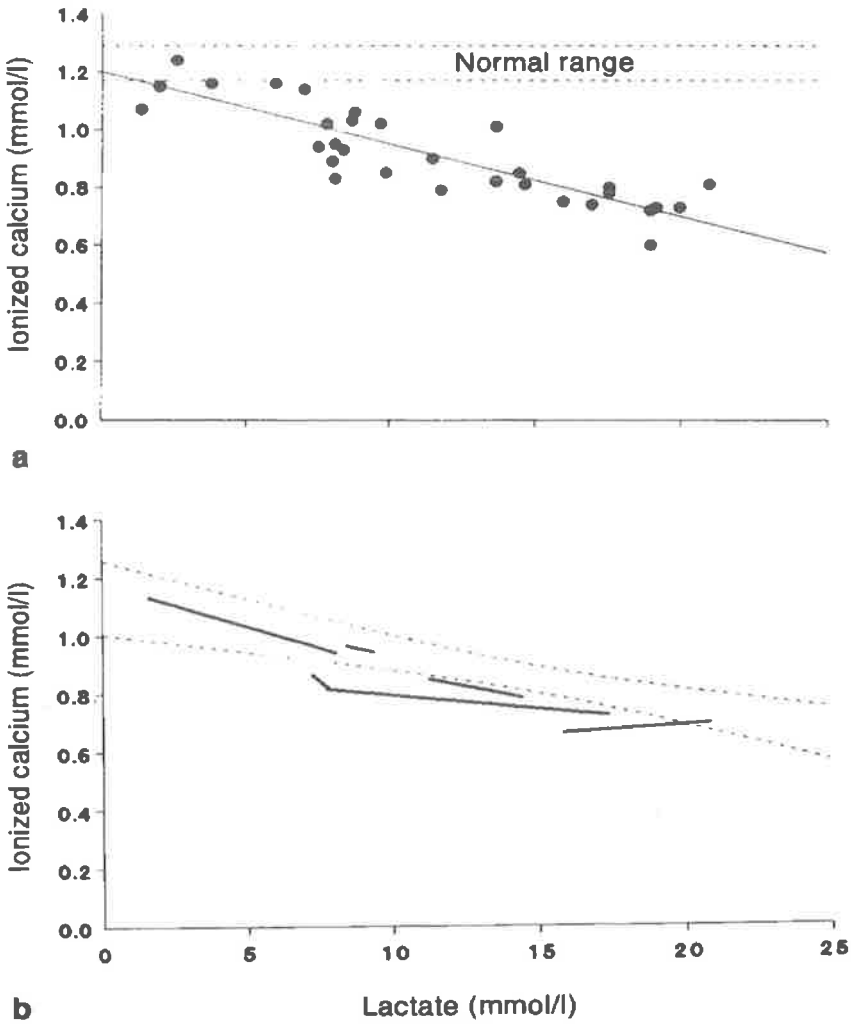

Figure 11 a,b. Relationship between [Ca^{++}] and plasma lactate concentrations in nine critically ill patients who had metabolic acidosis. [Ca^{++}] decreased as lactate increased. **a** Linear regression analysis for the group ($r2 = 0.78$, $P < 0.001$). **b** random effects regression and 95% CI for the 6 patients who had 3 or more data points [slope - 0.018 (SE 0.005); intercept 1.11 (SE 0.08)].

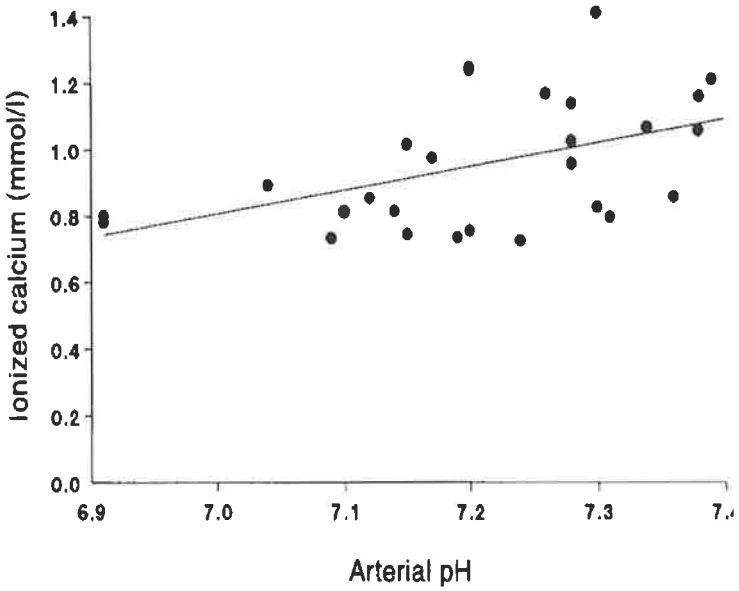

Figure 12. Relationship between [Ca^{++}] and arterial pH in 9 critically ill patients who had lactic acidosis. Linear regression analysis for the group ($r^2 = 0.21$, $P < 0.01$)

Table 5. *Plasma ionised calcium, blood lactate and arterial pH results in 9 critically ill patients having lactic acidosis.*

Age	Sex	Ca^{++}	Lactate	Arterial pH
71	M	0.72 ± 0.03	17.6 ± 0.27	7.10 ± 0.06
39	M	0.87 ± 0.15	10.3 ± 0.99	7.33 ± 0.03
65	F	1.08 ± 0.06	9.3 ± 0.45	7.36 ± 0.03
79	F	0.86 ± 0.03	7.3 ± 1.5	7.28 ± 0.04
37	F	0.81 ± 0.07	13.4 ± 1.3	7.28 ± 0.02
57	F	0.79 ± 0.07	6.2 ± 0.4	7.28 ± 0.15
65	F	0.96 ± 0.06	8.8 ± 0.9	7.31 ± 0.09
63	F	0.79 ± 0.05	22 ± 3.1	7.16 ± 0.05
35	F	0.65 ± 0.09	20.9 ± 6.4	7.00 ± 0.08

Normal ranges in our laboratory: Ca^{++} (1.17 – 1.29 mmol/l), lactate < 2.0 mmol/l. All values are reported as mean ± SD

All patients were mechanically ventilated, were hypotensive and were receiving infusions of inotropic drugs. Haemodynamic measurements were not done specifically as part of this study. Eight patients had sepsis as a significant contributor to lactic acidosis and nine patients died.

In this study a strong and unexpected association between decreased blood [Ca^{++}] and increased blood lactate concentrations was identified in critically ill patients who had lactic acidosis. It was unexpected because [Ca^{++}] usually increases when acidemia increases owing to decreased binding between calcium ions and proteins during acidemia. The mechanism of the association was not revealed by this study, but there are a number of possible explanations. Abnormalities of the parathyroid/vitamin D axis have been described in critically ill patients who have sepsis (34). Of these, renal 1-a hydroxylase insufficiency may be less likely to be the explanation because there was no relationship between [Ca^{++}] and one index of renal function (serum creatinine) in these patients. However in this study the parathyroid/vitamin D axis was not specifically investigated. Changes in blood magnesium, albumin or phosphate concentrations over time may each influence plasma [Ca^{++}] concentrations and these were all measured once only (at baseline) in this report. All patients had received bicarbonate therapy as part of their clinical management and bicarbonate is also likely to have contributed to hypocalcaemia. Next, lactate ions could be important calcium chelators in critically ill patients. Although this possibility had not previously been reported, lactate chelates calcium in vitro (87), in animals, and in healthy human volunteers (92). Furthermore, lactate chelates calcium in healthy humans to a greater extent than been previously believed (92). Other factors particular to critically ill patients (for example hypoalbuminemia, which increases binding between calcium and lactate) might also be important. Finally, it is also possible that increasing shock in these patients was a common factor causing both decreased [Ca^{++}] and increased blood lactate concentrations. In this regard it is well recognised that shock is often associated with increased blood lactate concentrations, and it has also been reported that hypotension is associated with decreased [Ca^{++}] in medical intensive care patients (83) (r^2=0.18 - a relatively weak association). These authors however did not measure blood lactate concentrations. Against this possibility of shock being the unifying factor, is the very strong correlation observed between decreased [Ca^{++}] and increased blood lactate. On statistical grounds, the correlation (r^2 = 0.78) strongly suggests that 78% of the observed correlation is due to lactate and not to other factors. Therefore although decreased [Ca^{++}] in these patients is highly likely to be multifactorial in nature, the blood lactate concentration is likely to be one of the important contributing factors. Only a weak association between [Ca^{++}] and arterial pH was observed. It is likely that decreasing [Ca^{++}] was associated with increasing blood lactate concentrations but not with increasing acidemia, primarily because of the therapies used concurrently in these patients to increase pH. Therapies included hyperventilation and bicarbonate infusion. In addition, it is possible that these patients had impaired lactate clearance mechanisms in association with shock, and therefore had increasing blood lactate concentrations greater than would have expected for the increase in acidemia. Despite the therapies however, patients remained acidemic and so would not have been expected to have the decreased [Ca^{++}] observed unless factors other than pH changes were also operating.

The clinical relevance of this association between [Ca^{++}] and blood lactate concentrations has not yet been established. However, if further investigations suggest that lactate does chelate

calcium to an important extent in critically ill patients, therapies intended to reduce blood lactate concentrations might conceivably be investigated. Calcium infusions to correct ionised hypocalcaemia, could also be investigated in patients. Intravenous calcium supplementation may increase $[Ca^{++}]$ and thereby increase myocardial contractility, but there is also ongoing concern about the role that increasing extracellular calcium may have in exacerbating cell injury and cell death. Thus the desirabilitv of increasing blood calcium concentrations in hypocalcemic critically ill patients continues to be actively debated.

In conclusion, in this study a strong association between decreased plasma ionised calcium and increased blood lactate concentrations was reported in critically ill patients who had lactic acidosis. Many factors might have contributed to this unexpected association, and it was suggested that the mechanism deserves further investigation.

4.3 Animal Studies

The next phase of this research was to take the questions generated in the clinical studies, and to address them in the large animal laboratory. Specifically I planned to examine the effects of lactic acidosis and therapies for lactic acidosis upon left ventricular function in an animal model because it is extremely difficult to study left ventricular systolic and diastolic mechanics in critically ill patients. Furthermore the facilities and expertise were available to study haemodynamics and cardiac mechanics with great precision in the laboratory using already validated methodology. Therefore I next took these questions to the large animal laboratory in the Pulmonary Research Laboratory University of British Columbia, at St. Paul's Hospital Vancouver, Canada and the following two studies were completed and published. The first examines cardiac function during lactic acidosis caused by hypovolemic shock and the second examines lactic acidosis due to lactic acid infusion. In both situations, pH correction using bicarbonate is carefully assessed.

4.3.1 Endogenous lactic acidosis

J Crit Care 1992;7:14-21 (40)

During hypovolemic shock, lactic acidosis due to tissue hypoperfusion, may impair cardiac function. This possibility is supported by reports that lactic acid decreases contractility of isolated myocardial muscle (64) (93) decreases contractility of whole hearts (94) (22) and that infused lactic acid decreases left ventricular contractility in intact large animals (19). Bicarbonate infusion to correct acidemia (pH less than 7.20) is a common therapy in patients during resuscitation from hypovolemic shock (95) in part because it is thought to reverse decreased left ventricular contractility associated with acidemia (16). However, there are no data available to directly support this hypothesis. In fact, bicarbonate therapy during metabolic acidosis is possibly of no benefit (23) and may at times be detrimental (27).

Accordingly, this study tested the hypothesis that correction of acidemia using a bicarbonate infusion would increase left ventricular contractility in acidemic animals during resuscitation from hypovolemic shock. To test this hypothesis 12 anaesthetised, mechanically ventilated pigs were studied following phlebotomy (approximately 40% of their circulating blood volume removed for 4 ± 1 hours to reduce arterial pH below 7.15) and following reinfusion of all shed blood. Six pigs then received infused bicarbonate, which corrected acidemia, and six control pigs received an equivalent infusion of infused saline. Left ventricular contractility was assessed using the end-systolic pressure-volume relationship (ESPVR). This index of LV contractility is least sensitive to changes in preload and afterload (37).

4.3.1 Methods

Anaesthesia was induced in 12 pigs weighing 22 ± 3 kg using ketamine (10 mg/kg intramuscularly) and thiopentone (10 to 20 mg/kg intravenously). Anaesthesia was then maintained using alpha-chloralose (80 mg/kg IV followed by 25 mg/kg/hr infusion) and morphine (5 mg/kg IV followed by supplemental doses as necessary). The pigs were paralysed using pancuronium (0.1 mg/kg IV and supplemented as necessary) to avoid reflex respiratory muscle movement during hypovolemic shock. A tracheostomy was created through a midline neck incision. The pigs were ventilated using an inspired oxygen concentration of 40% to 45% to ensure adequate oxygenation and tidal volume was set at 12 mL/kg at a rate adjusted to maintain PCO_2 at approximately 40 mm Hg. Positive end-expiratory pressure of 4 cm H_20 was applied to maintain end-expired lung volume.

The pigs were then instrumented according to the procedures described in Ch. (3.2) .

4.3.1 Experimental Protocol

Following instrumentation, the animals were allowed to stabilise for 30 minutes. A baseline set of data was collected. The animals were then bled to a mean aortic pressure of approximately 45 cm H_20. Shed blood was anticoagulated using heparin and chilled on ice. Prior to any reinfusion the blood was warmed to body temperature. The animals were maintained at a mean aortic pressure of approximately 45 cm H_20 by occasional small phlebotomy or by reinfusion of shed blood. Arterial blood gas analysis was repeated every hour until arterial pH had fallen below 7.15. Then all remaining shed blood was infused and, after a 10-minute stabilisation period, a "pretreatment" set of data was collected. At this point the pigs were randomised using cards in sealed envelopes to receive either an infusion of bicarbonate (6 mmol/kg of 1 mol/L $NaHCO_3$) or a control infusion of saline (6 mmol/kg of 1 mol/L NaCl) over 20 minutes. Twenty minutes after completing the infusion a final post treatment set of data was collected. Final measurements were not done beyond this point for two reasons. First, if measurements were delayed further following bicarbonate infusion, additional bicarbonate was necessary as the pH fell by more than 50% toward the pre bicarbonate level over the next 30 minutes. This effect had previously been observed in humans following bicarbonate infusion (23). Second, a third of the pigs died in the subsequent 30 minutes, reflecting the irreversibility of shock.

Data collected at each set included arterial and mixed venous blood gases (ABL30; Radiometer, Copenhagen, Denmark), haematocrit, arterial lactate (enzymatic determination; Sigma, St Louis, MO), and temperature. At each set, measurements of aortic pressure, left ventricular pressure, ultrasonic crystal diameters, and thermodilution cardiac output (repeated three times) at end-expiration were done. Left ventricular pressure and diameters were sampled using an analog to digital converter (LabMaster DMA; Scientific Solutions, Solon, OH) and

stored in digital format using a microcomputer. Left ventricular pressure and diameters were sampled during steady-state and during a one-beat aortic cross-clamp, repeated twice, at 250 Hz and during an 8-second vena caval occlusion at 100 Hz.

This level of haemorrhage resulted in a moderately unstable preparation and worsening bradycardia and indicated imminent cardiac arrest. Of the 12 experiments reported here, six pigs (two in the bicarbonate group and four in the saline group) received atropine (1 mg IV) or epinephrine (maximum, 0.5 mg IV) to increase heart rate during a bradycardic episode. Experimental measurements were not taken for at least 30 minutes after any drug administration. Three animals died prior to randomisation and are not included in this data analysis. Five of the 12 pigs had additional measurements taken during the period of hypovolemic shock to examine the course of changes in systolic and diastolic left ventricular mechanics (42).

4.3.1 Systolic left ventricular contractility

In this study, left ventricular contractility was principally measured using the end-systolic pressure-volume relationship (ESPVR). Measurement of this relationship is described in detail in Ch (3.2.4). The mean correlation coefficient for all ESPVR estimates in this study was $r^2 = 0.93 \pm 0.04$, suggesting that the ESPVR was quite linear throughout the range of the data. In this study the slope of the ESPVR is defined as m_{ESPVR} and the volume axis intercept is defined as V_d. Another way to quantify an increase in contractility while avoiding extrapolations is to measure the left shift in the ESPVR at a pressure of 100 mm Hg (δ_{ESPVR}). This measurement is also described in Ch. (3.2.4) and Fig. 2. For comparison to other studies reported in the literature the maximum rate of left ventricular pressure development (dP/dt_{max}) and left ventricular stroke work were additionally determined in this study. These are not used as principle measures of contractility because these indices are greatly influenced by changes in preload and afterload.

4.3.1 Data Analysis

To determine m_{ESPVR} each set of end-systolic pressure-volume points was fit individually using a measurement error model for regression because this takes into account error in both the pressure and volume measurement by calculating the reduced major axis through the data (16)). A repeated measures analysis of variance was used with one grouping factor to test the principle null hypotheses that (1) m_{ESPVR} did not change from "baseline" to the acidemic "pretreatment" set to "post treatment" (the repeated measures in each animal) and (2) that there was no difference in left ventricular contractility between the bicarbonate and control saline groups (the grouping factor). When a difference was found in the repeated measures analysis ($P \leq 0.05$) individual differences between the experimental sets were identified using paired t-tests weighted

by the inverse of the variance and 95% confidence intervals of the differences were calculated. Multiple comparisons were corrected for using an improved sequentially rejective Bonferroni test procedure (96) ($P \leq 0.05$). The same analysis was performed on m_{ESPVR} and other variables listed in the tables to highlight changes in measured parameters. Data are summarised as mean ± standard deviation throughout.

4.3.1 Results

After 4 ± 1 hours of hypovolemic shock and following reinfusion of all shed blood, all animals had lactic acidosis (pH decreased from 7.42 ± 0.04 to 7.08 ± 0.07, $P \leq .05$; lactate levels increased from 0.9 ± 0.3 to 9.3 ± 4.0 mmol/L, $P \leq .05$) (Table 6). Left ventricular end-diastolic pressure and right atrial pressure increased compared with baseline ($P \leq 0.05$), but mean arterial pressure was decreased by 57% ($P \leq 0.05$) and cardiac output was decreased by 35% ($P \leq .05$) (Table 7). Heart rate increased by 36% ($P \leq 0.05$) so that stroke volume decreased by 51% ($P \leq 0.05$) (Table 7). Thus following reinfusion of all shed blood to correct the primary volume deficit, significant secondary problems of metabolic acidosis and cardiovascular dysfunction remained.

Following the period of hypovolaemic shock, m_{ESPVR} was increased from baseline to pretreatment levels ($P \leq 0.05$) (Figs 13, 14, and 15). The mean increase in m_{ESPVR} was 7.2 cm H_20/mL with a 95% confidence interval from 2.9 to 11.4 cm H_20/mL. The associated left shift of the ESPVR (δ_{ESPVR} 2.9 ± 5.9 mL) was not statistically significant (Figs 14 and 15). There was no significant change in dP/dt_{max} even though preload and afterload had decreased substantially and LV stroke work decreased ($P \leq 0.05$) (Table 7).

Table 6. *Blood gas analysis in 12 Pigs.*

	Bicarbonate			Saline		
	Baseline	Pretreatment	Posttreatment	Baseline	Pretreatment	Posttreatment
Temperature (°C)	37.0 ± 0.5	36.7 ± 0.7	36.5 ± 0.9	37.0 ± 0.6	37.2 ± 0.5	37.0 ± 0.5
Hematocrit (%)	29 ± 5	31 ± 7	24 ± 3	28 ± 5	26 ± 5	23 ± 6
Arterial						
pH	7.40 ± 0.04	7.05 ± 0.08	7.46 ± 0.08	7.43 ± 0.04	7.11 ± 0.07	7.12 ± 0.09*†
Pco_2 (mm Hg)	41 ± 5	41 ± 5	40 ± 4	40 ± 5	48 ± 9	43 ± 3
Po_2 (mm Hg)	340 ± 60	280 ± 130	320 ± 180	370 ± 80	300 ± 130	370 ± 90
Lactate (mmol/L)	0.9 ± 0.4	10.9 ± 5.0	14.5 ± 7.5	0.8 ± 0.3	7.6 ± 2.2	7.7 ± 2.5*
Mixed venous						
pH	7.33 ± 0.5	6.97 ± 0.09	7.30 ± 0.12	7.38 ± 0.06	7.03 ± 0.09	7.02 ± 0.10*†
Pco_2 (mm Hg)	50 ± 6	57 ± 12	54 ± 9	47 ± 5	69 ± 9	58 ± 7*
Po_2 (mm Hg)	48 ± 3	51 ± 16	36 ± 5	45 ± 3	38 ± 7	45 ± 8†

Note: Values are expressed as mean ± standard deviation.

*Baseline different from pretreatment (both bicarbonate and saline groups combined): $P \leq .05$.

†Postbicarbonate different from post saline: $P \leq .05$.

Table 7. *Haemodynamics in 12 pigs.*

	Bicarbonate			Saline		
	Baseline	Pretreatment	Posttreatment	Baseline	Pretreatment	Posttreatment
Heart rate (beats/min)	108 ± 14	136 ± 19	146 ± 26	99 ± 10	146 ± 29	135 ± 29*
Cardiac output (L/min)	2.87 ± 0.76	1.99 ± 0.94	1.87 ± 0.79	3.00 ± 0.68	1.85 ± 0.41	1.87 ± 0.25*
Stroke volume (mL)	27.0 ± 8.9	14.9 ± 7.5	13.8 ± 8.5	30.7 ± 7.3	13.4 ± 5.2	15.0 ± 6.5*
Mean arterial pressure (cm H_2O)	133 ± 20	64 ± 23	49 ± 10	123 ± 35	47 ± 9	48 ± 9*
Right atrial pressure (cm H_2O)	6.0 ± 2.6	9.2 ± 4.2	9.0 ± 3.6	6.3 ± 1.6	11.3 ± 2.7	11.3 ± 2.5*
End-diastolic pressure (cm H_2O)	6.8 ± 3.5	16.5 ± 8.1	19.5 ± 12.4	9.5 ± 6.4	14.3 ± 7.6	21.5 ± 9.0*
Change in end-diastolic volume (mL) from previous set	0	−15.7 ± 7.3	−2.3 ± 5.0	0	−29.1 ± 9.5	3.7 ± 4.8*
dP/dt_{max} (cm H_2O/s)	2,890 ± 740	3,900 ± 1,610	2,000 ± 1,200	2,670 ± 330	1,440 ± 570	1,360 ± 450
Stroke work (cm H_2O/mL)	3,590 ± 1,210	960 ± 580	680 ± 430	3,680 ± 1,290	630 ± 290	680 ± 140*

Note: Values are expressed as mean ± standard deviation.

*Baseline different from pretreatment (both bicarbonate and saline groups combined): $P \leq .05$.

†Postbicarbonate different from postsaline: $P \leq .05$.

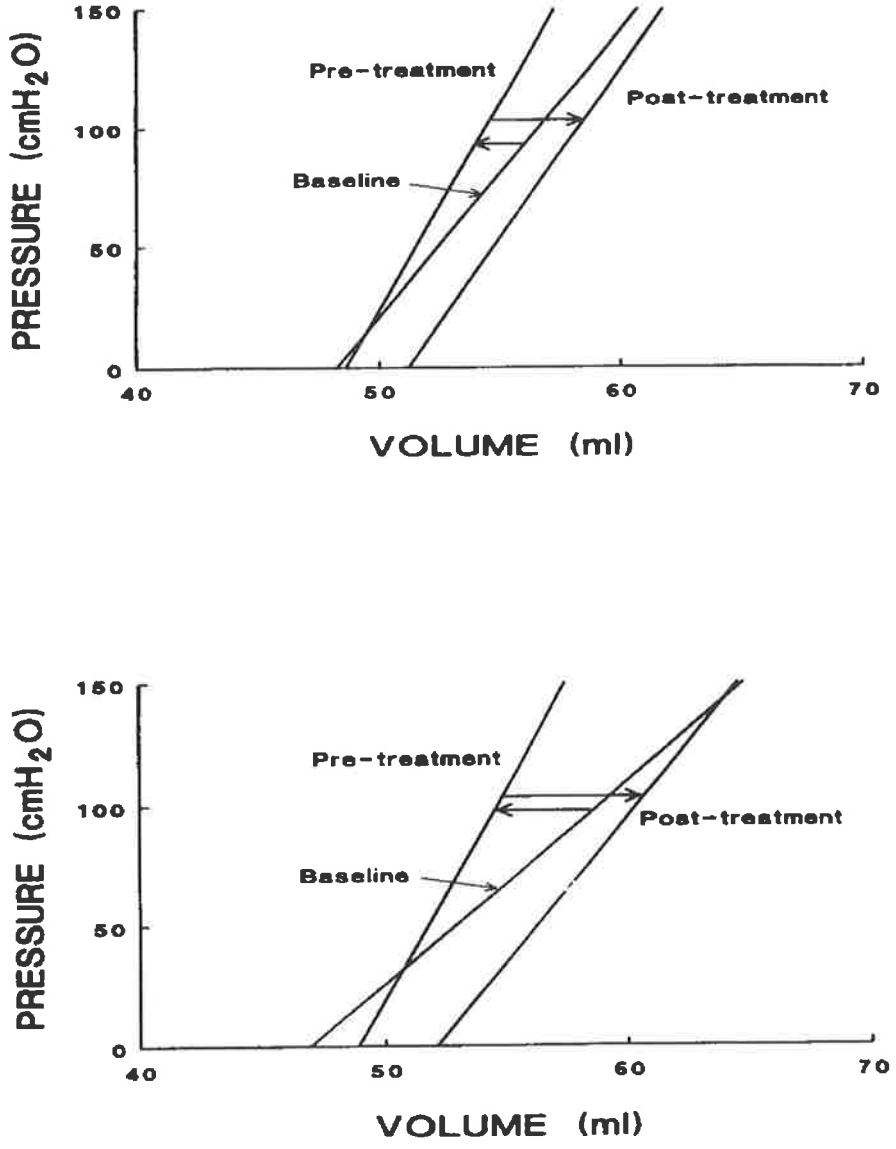

Fig 13. The average ESPVRs for all animals in all three experimental sets are shown. Shift of the ESPVR at a pressure of 100 cm H_2O (δ_{ESPVR}) is illustrated by the bold arrows. There is no difference between bicarbonate (top) and control saline (bottom). For both groups there is a significant increase in contractility from baseline to pretreatment (m_{ESPVR} increased; $P < 0.05$) and a decrease in contractility from pretreatment to post treatment (δ_{ESPVR} decreased; $P < 0.05$).

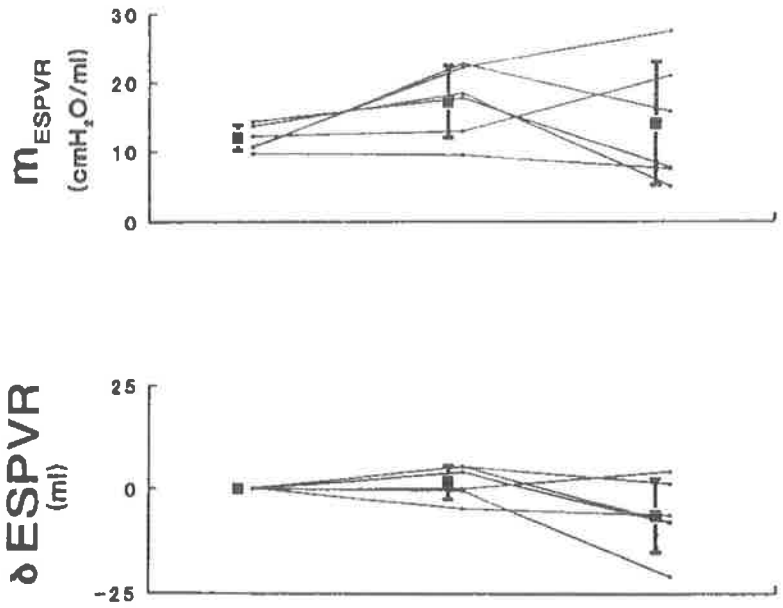

Fig 14. Measures of left ventricular contractility are illustrated for six pigs receiving bicarbonate. The average values and standard deviations are shown by the large squares bounded by error bars. There are no significant differences between bicarbonate and control saline infusions (Fig 15)

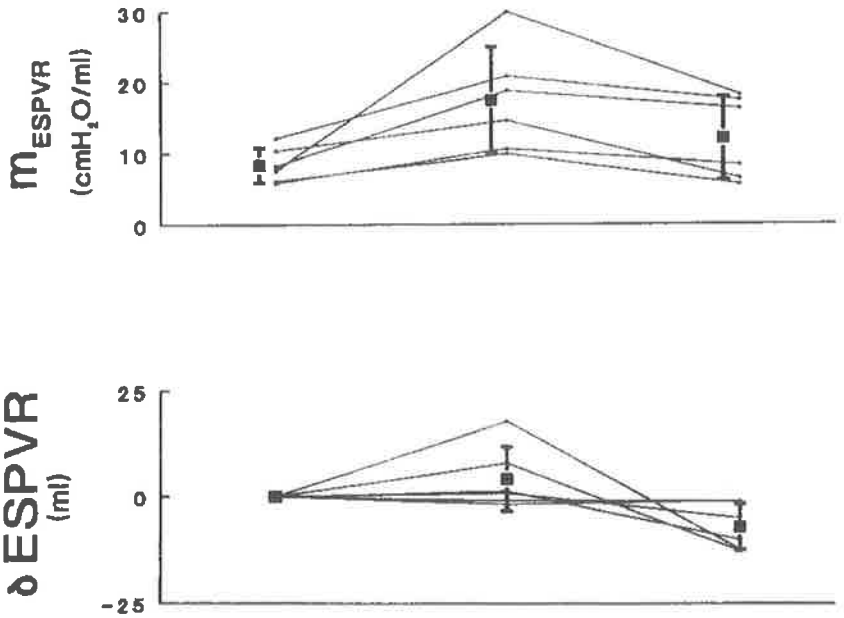

Figure 15. Measures of left ventricular contractility are illustrated for six control pigs receiving saline as in Fig 14. There are no significant differences between bicarbonate and saline infusions (Fig 14)

Infusion of 6 mmol/kg of 1 mol/L bicarbonate completely reversed the arterial acidemia, while similar infusion of saline did not alter arterial pH (Table 6). The lactate level increased by 33% ($P \leq 0.05$) following bicarbonate infusion but only by 1% (P = NS) following saline infusion. Both infusions had similar haemodynamic effects, with similar changes in right atrial and left ventricular end-diastolic pressures as well as little effect on blood pressure and cardiac output (Table 7). Thus, there were no haemodynamic findings that distinguished between the infusions of bicarbonate and saline (Table 7).

The main finding from this study is that bicarbonate infusion did not increase the two primary indices of contractility, m_{ESPVR} and δE_{SPVR}; these were no different from the control saline infusion. In fact, δE_{SPVR} decreased ($P \leq 0.05$) from pretreatment to post treatment levels in similar fashion for both bicarbonate (δE_{SPVR} -6.3 ± 8.8 mL) and saline (δE_{SPVR} -7.1 ± 5.4 mL), indicating a right shift of the ESPVR (Figs 13 and 14. On average, m_{ESPVR}, decreased by 4.3 ± 6.4 cm H_20/ mL, but this decrease was not statistically significant and there was no difference between bicarbonate and control saline infusion. Since there were no significant changes in preload and afterload from the pretreatment to post treatment sets (Table 7), dP/dt_{max} and LV stroke work become better indicators of contractility (15). dP/dt_{max} decreased by 37% ($P < 0.05$) and LV stroke work decreased by 14% (P = NS) (Table 7). Again there were no differences between bicarbonate and the saline control .

4.3.1 Discussion

These results from this study in pigs with endogenous lactic acidosis, indicate that after volume resuscitation from hypovolemic shock, correction of moderately severe acidemia using bicarbonate does not improve left ventricular contractility. In this model of lactic acidosis induced by hypovolemic shock, decreased left ventricular contractility was not observed at all, even at low arterial pH. Possibly increased circulating catecholamines obscured any depressant effect of acidemia or perhaps acidemia did not contribute substantially to decreased left ventricular contractility. Because correction of the acidemia using bicarbonate did not increase contractility compared with the control saline group, the latter possibility seems likely.

In isolated cardiac muscle experiments and isolated heart experiments acidosis decreases left ventricular contractility (64) (93) (94) (22) (59). However, the cardiovascular effects of lactic acidosis in whole animal preparations are more complicated because the direct myocardial depressant effects of acidosis may be obscured by a compensatory sympathetic response or by vascular changes altering preload and afterload. Thus, although some large animal studies suggest that metabolic acidosis has an important cardiac effect (97) (80) others do not (98) (99). A limitation of most of these large animal studies is that indexes of contractility that vary in response to changes in preload and afterload were used. However, in one recent sophisticated

study in dogs, lactic acid infusion to a pH of 7.10 decreased left ventricular contractility when load-independent indexes of contractility were used (19).

Previous studies of the cardiovascular changes observed during resuscitation from hypovolemic shock using bicarbonate have measured and reported changes only in haemodynamics (84), and have not included measurements of ventricular mechanics. Specifically, the effect of potential therapies on preload and afterload insensitive indexes of contractility had not been reported. Therefore in this study, to determine the effect of bicarbonate on ventricular mechanics during resuscitation from hypovolemic shock, left ventricular dimensions and pressure were measured directly. From these measurements left ventricular contractility using the ESPVR was assessed as the best available preload and afterload insensitive measurement (37). Thoracotomy and pericardiotomy alter the diastolic pressure-volume relationship by removing the mechanical interaction of the heart with surrounding structures. Systolic function however, is much less altered (100). Furthermore, the results of this study, focus on the difference between bicarbonate and control saline infusions; both were given after identical surgical preparation. Therefore, the results from this study are not likely to be an artefact of the surgical preparation.

In this model of endogenous lactic acidosis, left ventricular contractility was not decreased despite severe acidemia: (pH, 7.08 ± 0.07; lactate, 9.3 ± 4.0 mmol/L). Furthermore and most importantly, correction of the acidemia using bicarbonate did not improve left ventricular contractility in this model. A number of recent studies suggest reasons why bicarbonate infusion may not improve contractility (23) (27). During cardiac arrest, bicarbonate infusion may be detrimental because bicarbonate may increase arterial and venous P_{CO2} and thus lower intracellular pH (83) (101). However in this study, unlike the first study in this thesis, in critically ill patients (23), hypercapnia was avoided by adjusting the mechanical ventilator to maintain constant arterial P_{CO2} during bicarbonate infusion. In contrast to cardiac arrest studies (102) we found in this study that mixed venous P_{CO2} was no different during bicarbonate and control saline infusions (Table 6), possibly because the cardiac output was never excessively low. Therefore, in this study, it seems unlikely that increased intracellular acidosis (due to increased arterial or venous P_{CO2}) accounts for the lack of effect of bicarbonate infusion. Bicarbonate infusions have been shown to decrease extracellular ionised calcium (23). Although blood ionised calcium was not measured in this experiment, it seems plausible that blood ionised calcium decreased during bicarbonate infusion and thereby offset any potential benefit gained by correcting the acidemia.

Bicarbonate infusions are hyperosmolar, which potentially could alter contractility (61) (103). However, the control saline infusion was identical in dose and osmolarity. Therefore, even if changes in plasma osmolality accompanying bicarbonate infusion are important, the equimolar saline infusion controlled for these effects. It is interesting to note in addition that the control hypertonic saline solution was also not effective in improving left ventricular contractility. A number of recent studies have reported that hypertonic saline is beneficial in resuscitation from haemorrhagic shock (104) (105). While hypertonic solutions may increase

contractility in some isolated muscle preparations, (106) to my knowledge, no studies have reported the effect of hypertonic saline solutions on preload, and afterload - insensitive indices of contractility in intact large animals. This study was not designed specifically to measure the effects of hypertonic solutions on LV contractility. However, the data suggest that any benefit of hypertonic saline is not due to increased left ventricular contractility.

This study demonstrates that left ventricular contractility is not decreased during severe endogenous lactic acidosis in anaesthetised pigs. No beneficial effects on left ventricular mechanics could be determined during bicarbonate infused to correct acidemia in these animals despite sophisticated measurements. Therefore it seemed likely (although unproven at this stage) that lactic acidosis also does not significantly depress myocardial contractility in patients who have lactic acidosis, and this may be one of the prime reasons why bicarbonate is an ineffective therapy in these patients (23).

4.3.2 Infused lactic acidosis in pigs

Am Rev Resp Dis 1993;148:317-322 (43)

4.3.2 Introduction

The following study was designed and completed because several aspects of the endogenous lactic acidosis study (Ch 4.3.1; (40)) made interpretation of the results and their application to patients difficult. Firstly, in Ch (4.3.1) cardiac function was depressed in the animals with hypovolemic shock, and although not caused by the acidosis, this depression may have influenced the results. Secondly, in Ch (4.3.1) left ventricular contractility actually tended to increase during lactic acidosis and it seemed likely that this increase was a response to endogenous catecholamines released in response to hypovolemic shock. Although this may mimic the clinical picture seen in some patients when shock and catecholamine release do usually accompany lactic acidosis, it made interpretation of the cardiovascular effects of the acidosis more difficult. Essentially it seemed likely that the sympathoadrenal response to shock had increased contractility and perhaps masked a true underlying affect of acidosis on myocardial function.

Therefore I decided it would be worthwhile to use the same sophisticated methodology to study left ventricular mechanics during lactic acidosis induced without shock, and to block catecholamine influences which may have masked direct effects of the acidosis upon left ventricular function.

Sympathoadrenal responses clearly modify the cardiovascular response to shock and to acidosis. In isolated myocardium, acidemia decreases contractility (40) (94) (107) (22). In animals, if sympathoadrenal responses are intact, acidemia has variable effects on cardiac output and contractility (80) (97) (98) (99) (108) but when sympathoadrenal responses are removed,

decreased contractility has usually been reported (109) (98). These studies however, all used indices of contractility (LV stroke volume, dP/dt_{max}, and LV stroke work) which are dependent upon loading conditions, and because lactic acidemia may also have major effects upon pulmonary and peripheral vascular tone, load dependent indices of contractility may be misleading. A recent study (19) measured the LV end-systolic pressure-volume relationship (ESPVR) to study DL - lactic acid infusion in dogs whose sympathoadrenal responses were intact. This study reported decreased LV contractility, but "L-lactic" acid is instead the endogenously produced isomer which is active in patients and animals and "DL lactic" acid may not have the same effects. Therefore it remained unresolved whether bicarbonate reversed negative cardiovascular effects when infused during lactic acidosis.

To answer this question and to minimise any indirect effects of acidosis on left ventricular contractility, including beta-adrenergic stimulation and tachycardia, L-lactic acid was infused into 15 beta-blocked, atrially paced pigs. Haemodynamics and LV contractility were measured during lactic acidosis and while maintaining Pa_{CO2} constant either after infusing bicarbonate to normalise arterial pH or after infusing an equivalent amount of saline. In this study we did not attempt to model the very heterogenous disorder of clinical lactic acidemia and the associated respiratory compensation. Instead this study was carefully designed to measure the direct in vivo effect of bicarbonate on left ventricular contractility during a constant Pa_{CO2}. Endogenous models of lactic acidosis which more closely mimic the clinical situation are difficult to interpret because the intervention used to cause lactic acidosis may itself have significant indirect effects upon left ventricular contractility. Thus cytokines released during sepsis (110), changes in diastolic function during hypovolemic shock (42) and drugs used to induce acidosis may all independently alter LV function. Exactly as in Ch (4.3.1) left ventricular dimensions and pressures were measured and then, by changing afterload, the left ventricular end-systolic pressure-volume relationship (ESPVR) was measured as the primary index of LV contractility. In this study, to enable comparisons with other similar studies, LV contractility was also assessed using several other commonly reported indices of LV contractility. Potentially confounding effects of catecholamines were avoided by pretreating all animals with propranolol (2 mg/kg iv), and heart rate was kept constant using overdrive pacing with a right atrial epicardial pacemaker.

4.3.2 Methods

4.3.2 Instrumentation

Eleven pigs (25.5 ± 3.5 kg) were induced using ketamine (10 mg/kg i.m.) and then thiopentone (10 - 20 mg/kg i.v.). Anaesthesia was maintained using isoflurane 0.75% and ketamine (0.1 mg/kg/min.). Pancuronium (0.1 mg/kg iv) was infused as necessary to prevent reflex respiratory muscle movement, and the pancuronium was always infused at least 15 minutes prior to any measurements. The animals were then intubated, ventilated, and instrumented as described in the methods Ch (3.2).

4.3.2 Measurements of systolic LV contractility

The primary index of LV contractility, the ESPVR, was determined as follows: Simultaneous left ventricular pressure and volume measurements were digitally sampled at 250Hz during steady state and during brief aortic cross clamping, and at 100 Hz during an eight second vena caval occlusion. The ESPVR was determined as the line of best fit through end systolic pressure volume points (defined as points of maximal elastance) from two steady state beats, two aortic cross clamp beats, and from four beats during the caval occlusion, as described in Ch 3.2 (Figure 1). In this study, several of the other commonly reported indices of LV contractility were also calculated. First the end-systolic volume above V_0 was determined at an end-systolic pressure of 100 cm H_20, ($ESV_{P=100}$), interpolated from the ESPVR. This index avoids extrapolation of data beyond the physiologic range and may be useful because it incorporates changes both in E_{max} and in V_0 (49). The maximum rate of LV pressure development (dP/dt_{max}) was calculated from the steady state pressure-volume data sampled at 250Hz using the Lagrange 5 point formula (46). dP/dt_{max} varies with LV end diastolic pressure (LV_{EDP}) and so dP/dt_{max} divided by LV_{EDP} was also calculated. Finally LV Ejection Fraction was calculated as stroke volume divided by end diastolic volume (EDV) above V_0.

4.3.2 Measurements of diastolic LV function

Measurements of diastolic LV pressure-volume relationships are included because some animals in this study developed early severe pulmonary hypertension and in the immediate pre terminal minutes in these animals, the measured septal free-wall dimensions decreased markedly. Thus it seemed likely that in these animals pulmonary hypertension increased right ventricular pressure which then terminally shifted the intraventricular septum sufficiently to decrease left ventricular stroke volume and initiate demise. These animals are not included in our analysis because they died before the arterial pH had decreased to 7.10 and only baseline

measurements were obtained. Having made these observations however, all the animals were then tested to determine whether there was any evidence of ventricular interaction which might have influenced the measurements of contractility. First, the diastolic pressure-volume relationships were examined in all animals, using methodology described in Ch (3.2).

4.3.2 Experimental protocol

Following instrumentation the animals were allowed to stabilise for one half hour and then received propranolol 2 mg/kg i.v. followed by propranolol infusion (40 μg/kg/min). Beta blockade was tested (isoproteronol 6 μg/kg/min, for three minutes) (105) both after the loading dose of propranolol and again near the end of the experiment. At no time did isoproteronol cause any visible change in heart rate, (pacemaker turned off), left ventricular or mean arterial pressures, or LV diameters. Thus we are confident that beta blockade was adequate during each experiment.

Fifteen minutes later an "preacidemia; (1)" set of data was collected. 0.2 molar L-lactic acid was then infused via a femoral artery at 0.3 ml/min. The infusion rate was increased by increments of 0.3 ml/min each 10 minutes until the arterial pH reached 7.10. This occurred after a mean of 90 mins. We increased the lactic acid infusion rate gradually because in preliminary studies more rapid infusion rates were associated with pulmonary hypertension, right ventricular dilatation and early demise. A second set of data "baseline; (2)" was collected when the arterial pH was less than 7.10. Animals were then randomly assigned, using cards in sealed envelopes, to receive either sodium bicarbonate (1M, n=6) or sodium chloride (1M, n=5). 1M bicarbonate was infused at 3.5 ml/min for 10 mins, and then at 9.0 ml/min until arterial pH approached 7.40 (approximately twenty minutes). The control animals received 1M sodium chloride for the same rates and times. A third and final set of data ("post bicarbonate; (3)" or "post saline; (3)") was then collected.

During each set arterial blood gases (Radiometer, ABL 30), arterial blood lactate concentrations (enzymatic determination, Sigma), and arterial plasma ionised calcium concentrations (ICA 1, Radiometer) were measured. During each set aortic pressures, left ventricular pressures, ultrasonic crystal diameters, and thermodilution cardiac output (repeated four times with first measurement discarded) at end expiration were also measured. Left ventricular pressures and dimensions were sampled during steady state, during a one beat aortic clamp repeated twice, and during an eight second vena caval occlusion.

Four further "control" animals were anaesthetised and instrumented exactly as above. These animals did not receive lactic acid infusion. Instead they received 0.2 molar sodium chloride infused for the same time as the animals which received lactic acid. These animals controlled for any measurable time or anaesthesia related changes in the surgical preparation. Measurements were done at 3 time points: (1) pre-acidemia, (2) baseline, and (3) 2.5 hours post

baseline. Over the 2.5 hour time period there were no changes in arterial blood gases, in the ESPVR, or in other indices of contractility (Table 8).

4.3.2 Data Analysis

The principal null hypothesis that there was no change in any measure of LV contractility during lactic acidosis and following bicarbonate or hypertonic saline infusions, was tested using a two way analysis of variance. When $P \leq 0.05$ individual data sets were compared using t-tests corrected for multiple comparisons using a sequentially rejective Bonferroni procedure. The same analyses were used to illustrate changes in haemodynamics and other measured

Table 8. *Four time and anaesthesia control experiments*[*]

	1	2	3
Arterial pH	7.44 ± 0.07	7.39 ± 0.04	7.36 ± 0.04
Mean arterial pressure, mm Hg	77 ± 12	85 ± 14	86 ± 17
Cardiac output, L/min	3.7 ± 0.06	3.8 ± 0.7	4.4 ± 0.9
Left ventricular end-diastolic pressure, mm Hg	4.9 ± 2.8	6.3 ± 3.8	9.7 ± 6.6
E_{max}, mm Hg	6.3 ± 1.8	6.1 ± 1.8	5.9 ± 1.7
δ_{ESPVR}, ml	0.5 ± 2.5	0	-0.9 ± 4.0

[*] All values are mean ± SD except E_{max}, which is mean ± standard error of the estimate (random effects regression).

variables. All data in the text and tables are reported as mean ± standard deviation with one exception. Because E_{max} and V_0 are co-variant parameters of the ESPVR it is incorrect to examine them as independent parameters. Therefore the average ESPVR was determined using random effects regression (81) and the 95% confidence interval was computed.

4.3.2 Results

During lactic acid infusion, arterial pH decreased (7.42 ± 0.02 to 7.04 ± 0.06), and arterial lactate concentrations increased (0.5 ± 0.2 to 12.8 ± 4.8 mmol/L). Arterial PCO_2 was unchanged

owing to frequent ventilator adjustments. Arterial oxygen saturations were also unchanged from baseline measurements (Table 9).

All cardiovascular measurements were compared to the baseline set measured after beta adrenoreceptor blockade. Lactic acid infusion increased left ventricular end diastolic pressure (6.2 ± 2.9 to 11.7 ± 3.5 cm H_2O, $P<0.05$), but did not change cardiac output (Table 10).

Table 9. *Blood gas and lactate concentrations* *

	Saline Infusion (n = 7)			Bicarbonate Infusion (n = 8)		
	1 Preacidemia	2 Baseline	3 Postsaline	1 Preacidemia	2 Baseline	3 Postbicarbonate
Arterial pH	7.41 ± 0.02†	7.06 ± 0.05	7.07 ± 0.06	7.42 ± 0.04†	7.04 ± 0.06	7.45 ± 0.11†
$Paco_2$, mm Hg	42 ± 4	44 ± 3	40 ± 4	40 ± 4	44 ± 4	42 ± 9
Bicarbonate, mmol/L	27 ± 3†	12 ± 1	11 ± 2	26 ± 4†	11 ± 2	29 ± 8†
Sao_2, %	97 ± 1	98 ± 1	98 ± 1	96 ± 3	96 ± 6	96 ± 2
Lactate, mmol/L	0.9 ± 0.1†	12.6 ± 3.6	11.0 ± 3.4	0.9 ± 0.4†	13 ± 5.6	15.2 ± 7.6

* All values mean ± SD.
† $p < 0.05$ compared with baseline.

Table 10. *Haemodynamic changes* *

	Saline Infusion (n=7)			Bicarbonate Infusion (n=8)		
	1 Preacidemia	2 Baseline	3 Postsaline	1 Preacidemia	2 Baseline	3 Postbicarbonate
Mean arterial pressure, (mm Hg)	78 ± 24†	106 ± 29	85 ± 32†	78 ± 27†	105 ± 20	95 ± 40†
Heart rate, (beats/min)	141 ± 8	142± 6	142 ± 6	137 ± 4	134 ± 5	139± 6
Cardiac output, L/min	3.3 ± 1.1	3.1± 0.9	3.8 ± 1.5	3.5 ± 0.8	3.3 ± 1.4	3.5 ± 1.9
Left ventricular end-diastolic pressure, (mm Hg)	4.8 ± 2.1†	9.4 ± 3.1	9.7± 4.0	4.3 ± 2.0†	7.2 ± 3.2	8.3 ± 4.6
Mean right atrial pressure, (mm Hg)	4.0 ± 2.5†	8.0 ± 2.6	8.7 ± 2.4	3.2 ± 1.4†	7.3 ± 2.5	9.0 ± 4.4
Mean pulmonary arterial pressure, (mm Hg)	12.2 ± 3.2†	28.4 ± 9.2	23.1 ± 4.2	12.9 ± 2.6†	26.0± 6.6	27.0 ± 8.8
Systemic vascular resistance, (mm Hg/L/min)	25.7 ± 15.7	34.6 ± 17.7	27.0 ± 28.6	21.6 ± 7.6	35.8 ± 22.2	31.5 ± 20.6

*All values mean ± SD

†P < 0.05 compared to baseline

Because cardiac output and stroke volume did not change despite increased preload, it is clear that cardiac function was depressed. This may have been due to increased afterload, because lactic acid increased pulmonary and systemic mean arterial pressures (mean pulmonary artery pressure increased from 17 ± 2.9 to 38 ± 10.5 cm H_20, P<0.05), and mean aortic pressure increased from 92 ± 19 to 133 ± 28 cm H_20, P<0.05, Table 10), suggesting a generalised increase in arterial vascular tone, or it may have been due to decreased LV contractility. When the results from all eleven pigs were combined, decreased left ventricular contractility was confirmed by decreased E_{max} (6.9 to 4.8 cm H_20/ml, P < 0.05), and decreased ejection fraction (0.53 ± 0.07 to 0.36 ± 0.09, P < 0.05). dP/dt_{max} did not change although preload increased, and since increased preload normally increases dP/dt_{max}, decreased left ventricular contractility is also suggested by this index. Indeed, $dP/dt_{max}/LV_{EDP}$ decreased (295 ± 163 to 157 ± 41, P < 0.05).

Bicarbonate infusion normalised arterial pH (7.03 ± 0.07 to 7.47 ± 0.12, n=6) while normocapnia was maintained using ventilator adjustments (P_{CO2} 43 to 41 mm Hg) and arterial lactate concentrations did not change (13 ± 5.6 to 15.2 ± 7.6 P=NS). Bicarbonate decreased afterload (mean arterial pressure decreased from 137 ± 26 to 110 ± 31 cm H_20, P<0.05), and did not change preload (left ventricular end diastolic pressure and volume, Table 10). Despite these changes which normally would have increased cardiac output, cardiac output was not changed. These observations do not suggest that bicarbonate improved LV contractility, and indeed dP/dt_{max} and E_{max} were also unchanged (Table 11; Figure 12). The animals that received 1M sodium chloride remained acidemic (arterial pH 7.05 ± 0.05 to 7.10 ± 0.04, P=NS), but the haemodynamic (Table 10 and ventricular mechanics (Table 11, Figure 12) changes following saline were indistinguishable from those following bicarbonate.

Table 11. *Other indices of left ventricular contractility*

	Saline Infusion (*n* = 7)			Bicarbonate Infusion (*n* = 8)		
	1 Preacidemia	2 Baseline	3 Postsaline	1 Preacidemia	2 Baseline	3 Postbicarbonate
$\delta ESPVR$, ml	-0.8 ± 4.2	0	1.6 ± 4.1	1.4 ± 4.3	0	4.4 ± 7.1
Ejection fraction, %	0.47 ± 0.16	0.36 ± 0.10	0.45 ± 0.14	0.47 ± 0.12	0.36 ± 0.12	0.40 ± 0.13
dP/dt_{max}, mm Hg/s	1,690 ± 390	1,770 ± 320	1,810 ± 410	1,840 ± 510	1,860 ± 620	1,990 ± 790
$dP/dt_{max}/LVEDP$, s^{-1}	360 ± 330	160 ± 70	160 ± 80	480 ± 550	230 ± 130	210 ± 100

* All values mean ± SD.

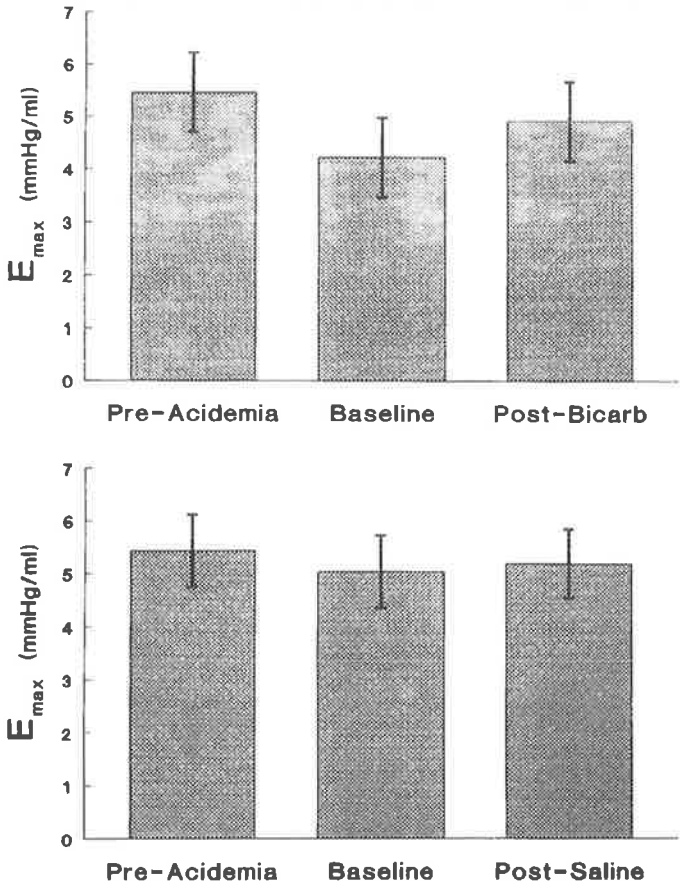

Figure 12. The principal index of contractility, Emax, is shown at each set for the bicarbonate group (top panel) and the saline group (bottom panel). Error bars indicates standard error of the estimate. There is no significant difference between the two groups.

To determine whether ventricular interaction may have influenced the results, the diastolic pressure-volume relationships were also analysed. First there was no change in the parameters A and B (Table 13), indicating no shift in the position of the mean diastolic pressure-volume relationship after bicarbonate (A 0.70 ± 1.16 to 0.50 ± 0.85; B 0.109 ± 0.077 to 0.106 ± 0.065) or after saline (A 0.51 ± 0.8 to 0.74 ± 0.93; B 0.079 ± 0.028 to 0.077 ± 0.022). Second there was no change at any time in the septum-free wall LV diameter in relation to the long axis diameter (D_{long}/D_{sf} 1.56 ± 0.24 at baseline to 1.57 ± 0.24 after bicarbonate). Thus, at the time we were making our measurements of LV contractility, septal shift had not occurred.

4.3.2 Discussion

In this study, L - lactic acid infusion (to an arterial pH of 7.04), significantly decreased left ventricular contractility in beta blocked atrially paced pigs. Despite this severe acidemia, this decrease in contractility, although statistically significant was small. The main finding of the study is that bicarbonate infusion normalised arterial pH but did not increase left ventricular contractility and did not improve left ventricular function. Normocapnia was maintained at all times by ventilator adjustments.

Previous studies have reported changes in cardiovascular function during lactic acidosis. Unfortunately however, these previous experiments were designed such that their conclusions regarding left ventricular contractility were inconclusive. Graf et al studied lactic acidosis induced by phenformin, hepatectomy, and hypoxia (60) in dogs. Cardiac output decreased during lactic acidosis but either pentobarbital anaesthesia, phenformin, or myocardial hypoxia could have been responsible. Graf et al (60) also report that lactic acid infusion did not change cardiac output in dogs, but because preload was not reported in this study, no conclusions about cardiac function can be made.

Studies reporting changes in cardiovascular function during bicarbonate infusion for lactic acidosis suffer, from similar problems. Bicarbonate therapy decreased cardiac output in diabetic dogs treated with phenformin (60), and in dogs having lactic acidosis caused by hypoxaemia (60), but preload was not reported and therefore it is not clear whether cardiac function had changed. In these studies, dogs became hypercapnic during bicarbonate infusion and so increasing intracellular acidosis may have decreased cardiac muscle function (18). Bicarbonate did not change haemodynamics in dogs having lactic acidosis induced by hypovolemic shock (84) but the dose of bicarbonate infused in this study was not sufficient to change arterial pH and so the results are inconclusive. Pentobarbital anaesthesia and a failure to include controls, further confound this study.

The present study (43) therefore provides new information. When arterial pH was normalised from severe acidemia (7.03) to normal (7.47), even when hypercapnia was prevented, bicarbonate did not increase left ventricular contractility. To determine whether LV contractility changed during lactic acidosis and after bicarbonate infusion, several indices of left ventricular contractility were used and each of these may have different advantages. Ejection fraction is commonly reported in studies of cardiovascular performance but is highly dependent upon afterload, which changed considerably in the study animals. dP/dt_{max} is highly sensitive to changes in LV contractility, but is also very dependent upon changes in preload and heart rate. In this experiment, heart rate was kept constant using an atrial pacemaker, but preload changed markedly as a result of the fluid infusion required to dilute lactic acid. Therefore left ventricular volumes were measured using three pairs of epicardial ultrasound crystals, and end-systolic pressure-volume relationships (Fig 1) were defined.

In this study, lactic acidosis decreased E_{max} by 24.5%. All eleven animals were required for the change to reach statistical significance. However the bicarbonate question was answered

using six animals. Therefore it is possible that our study did not have sufficient power to detect a small beneficial effect of bicarbonate on left ventricular contractility. However the change in LV contractility after 1M bicarbonate was almost identical to that observed after 1M saline (Table 11, Figure 12) and therefore it is most unlikely that increasing the number of study animals would alter our conclusions.

Although in this study, lactic acid infusion increased afterload and decreased left ventricular contractility, stroke volume was unchanged. It is most likely that the large volume required to dilute lactic acid solution to 0.2 M, increased preload (left ventricular end diastolic volume increased by 6.5 ml, and left ventricular end diastolic pressure increased from 7.9 to 12.2 cm H_20) which prevented a decrease in stroke volume. I avoided greater concentrations of lactic acid as these may be associated with structural damage to membranes and cellular components of the blood. Although lactic acid decreased left ventricular contractility in this study, the magnitude of change was not large (24.5% decrease in E_{max}, 32% increase in ESV_{P100}). Therefore it may also be true that relatively small changes in contractility do not have important effects upon overall left ventricular function in vivo. Teplinski et al found that DL - lactic acid infusion decreased both left ventricular contractility *and* stroke volume in dogs (14) but in this study, more concentrated (0.5M) lactic acid requiring less volume, was infused and no change in left ventricular end diastolic volume was observed. Therefore in this study, although increased preload may have maintained stroke volume, an alternative explanation is that DL-lactic acid may have different effects to L-lactic acid, the isomer which is used in this study and which is released endogenously in man and in animals. Nevertheless we confirmed Teplinski's fundamental observation - that when normocapnia is maintained, lactic acid infusion decreases load independent measures of left ventricular contractility.

This model of lactic acid infusion in beta blocked, atrially paced, anaesthetised, open chest pigs is of course, far removed from clinical practice in critically ill patients, but the conclusions may nevertheless have clinical application. First, although lactic acidaemia decreased left ventricular contractility the decrease was small even when sympathoadrenal responses were blocked. In patients with shock and lactic acidosis, sympathoadrenal responses are usually not blocked. Thus decreased contractility during lactic acidaemia in patients although probably present, is not likely to contribute importantly to cardiovascular dysfunction. Furthermore, although it has not yet been studied in vivo, it remains possible that appropriately compensated lactic acidosis (by "compensated" I mean hyperventilation during lactic acidosis to cause physiologically appropriate hypocapnia) may not decrease left ventricular contractility at all. In support of this concept, in vitro hypocapnia prevents intracellular acidosis until extracellular pH reaches 6.90 (111). Second, bicarbonate therapy does not improve decreased left ventricular contractility even when hypercapnia is prevented. For these reasons bicarbonate may not be effective for its primary indication in patients who have lactic acidosis - decreased left ventricular contractility.

In conclusion, L-lactic acid infusion decreases left ventricular contractility in normocapnic, atrially paced, beta blocked pigs. Bicarbonate infusion however does not then improve left

ventricular contractility in these animals. The many side effects of bicarbonate infusion that we now recognise may negate improved left ventricular contractility during normalisation of arterial pH.

4.4 Management strategies for patients with acidosis

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General principles

On the basis of the foregoing studies and on the other relevant literature, a number of general points can be made amount management strategies for critically ill patients with shock and acidosis. We recognise that the onset of lactic acidosis in critically ill patients is an ominous clinical sign, because despite many advances in intensive care practice over the last thirty years, the very high mortalities first documented in patients having lactic acidosis in the 1960's (13), are little changed in the 1990's. In accordance with this observation, present management strategies for patients having lactic acidosis are often ineffective and as a result, optimal management for patients having lactic acidosis remains highly controversial (16) (27). It may be that one of the reasons for therapeutic failure in this condition is that management strategies are often directed at the acidosis, although it is well recognised that lactic acidosis (in most critically ill patients) is really a secondary problem - an end result of inadequate tissue perfusion - and not a primary disease entity.

Management of the commonly encountered forms of metabolic acidosis other than lactic acidosis is in contrast, well established, relatively straightforward, and in each case is focussed upon treatment of the underlying condition. Metabolic acidosis due to renal failure is efficiently treated using dialysis (haemodialysis, continuous arteriovenous haemofiltration (CAVH), or peritoneal dialysis). Bicarbonate losing conditions (renal tubular acidosis, pancreatic fistulae) are optimally managed using bicarbonate replacement. Diabetic keto acidosis is effectively treated using insulin, appropriate fluid and electrolytes, and importantly, early treatment of the precipitating condition. Even relatively severe metabolic acidosis during diabetic keto acidosis (arterial pH >6.90), is best managed without using bicarbonate. There are two well designed, prospective clinical studies (57) (113) which demonstrate not only that bicarbonate does not have any measurable beneficial effects when infused during diabetic keto acidosis but also that bicarbonate infusion delays the clearance of important metabolites (ketones, lactate and the lactate/pyruvate ratio). Finally, low cardiac output states which may cause lactic acidosis, including cardiac arrest , are best treated by supporting an adequate cardiac output. The interventions which are recognised to improve outcome during cardiac arrest are oxygenation, electrical defibrillation, and alpha agonists (adrenaline) to restore coronary perfusion pressures. Each of these interventions addresses aspects of the primary underlying problem - inadequate cardiac function. By contrast, bicarbonate infusions, which are intended to correct the secondary problem of pH disturbance, have not been demonstrated to be of any benefit to patients during cardiac arrest. When infused during cardiac arrest, bicarbonate also has significant side effects causing profound mixed venous hypercapnia (102) (114), whilst failing to reverse increasing myocardial tissue acidosis (115) (116). Bicarbonate therefore has been effectively withdrawn from the American Heart Association recommendations for cardiac arrest management (ACLS)

since 1986 (117). In each of the above examples of metabolic acidosis, the effective therapy is the one that is directed at the primary problem, not that which is directed solely at the acidosis.

4.4 Lactic Acidosis

In critically ill patients who do not have cardiac arrest, lactic acidosis usually results from tissue hypoxia. In some patients this is a result of inadequate preload, and in some it is a result of inadequate left ventricular function. In others, (including critically ill patients having sepsis), the primary abnormalities are probably at the microvascular and cellular level, although there are also concurrent abnormalitites of cardiac function during sepsis and septic shock (7) (30). In all of these patients, lactic acidosis is a secondary event following primary abnormalities in oxygen delivery or in cellular oxygen utilisation. Perhaps inappropriately, for many years there has been a clinical focus upon buffer therapies, particularly bicarbonate to normalise arterial pH in patients.

4.4 Bicarbonate

Bicarbonate enjoyed considerable popularity as a therapy for lactic acidosis over 30 years, and the logic behind its usage deserves critical examination. The rationale for using bicarbonate (and in fact any metabolic buffer therapy) during lactic acidosis originates from isolated muscle and animal studies which suggested that many experimental forms of acidosis decreased cardiac function, decreased the haemodynamic response to catecholamines, increased arrhythmias, and shortened survival (77) (109) (80).

There are many reasons why this literature must be very carefully interpreted, and many of them have been discussed in the foregoing studies. The reasons are summarised as follows: *First*, respiratory and metabolic acidosis although sometimes considered the same in studies, are quite different in many respects. The effects of respiratory acidosis on haemodynamics and cardiac mechanics in critically ill patients have not been well studied, and indeed controlled hypoventilation (called "permissive hypercapnia") is part of 1990's clinical practice in many centres in several clinical situations including asthma and ARDS. *Second*, there are few animal models which truly imitate human lactic acidosis. One of the most prolific laboratories has developed models of lactic acidosis including hypoxic hypoxia, hepatectomy, and phenformin (20) (83) but each of these interventions is recognised to have its own independent effects upon left ventricular function. Thus extrapolation of results to humans may at best be unwise. *Third*, the majority of large animal experiments in this field have used anaesthetic drug regimens which include long acting barbiturates. These are known to have a cumulative and unpredictable, depressant effect upon left ventricular function, so correct interpretations of observed changes in cardiac function may be difficult. *Fourth*, most studies reporting changes in cardiac function

during acidosis, do not consider the load dependence of their measurements. Thus conclusions from some of the earlier studies may be misleading. *Fifth*, many studies have not been controlled, although we now recognise that bicarbonate may have many other important effects other than the changes in pH. *Sixth*, there are significant recognised differences between species in their cardiovascular responses to acidosis (80), and these differences must make extrapolation of laboratory observations to patients, more difficult. *Finally*, and quite importantly, the degrees of acidosis which are easily achieved in the laboratory and which are associated with important physiological changes in animal studies, are rarely encountered in critically ill humans.

Nevertheless, despite all these all these shortcomings of the available data, for many years clinicians adopted the view that because acidosis had important detrimental effects, then correction of acidosis must be beneficial to the patient. In many cases, the reality that buffer therapies may have important side effects was often not appreciated, although the agent in common clinical usage - sodium bicarbonate - had never been subjected to a controlled clinical trial in patients. It is unusual to have an agent in such common usage, which has not been critically examined in human clinical trials - but until 1990, such was the case with bicarbonate.

The arguments against using bicarbonate therapy in patients have been well summarised (27). However, the presence or importance of each of these factors has been convincingly debated (16). Polarisation of views on this issue has lead to large regional and international differences in clinical practice - in parts of North America very large doses of bicarbonate were often been used in patients who had lactic acidosis, while in other regions, particularly in many parts of Australia, bicarbonate had been infrequently used in these patients (118).

The bicarbonate controversy developed and persisted because controlled data from critically ill patients was not available. Clinicians therefore based management decisions upon laboratory data and upon clinical case reports. The difficulties inherent in completing a meaningful clinical trial in critically ill patients having lactic acidosis are considerable and are emphasised by a recently published clinical study (119). On this occasion bicarbonate therapy was studied in humans by infusing bicarbonate into volunteer patients who had normal acid base status, had cardiac failure and who were undergoing cardiac catheterisation. Thus, to obtain clinical data about therapies for metabolic acidosis, metabolic alkalosis was induced in patients having normal acid-base status. Clearly extrapolation of results from this study to acidotic critically ill patients would be unwise.

The first study detailed in this thesis Ch. (4.2.1) is however the first prospective, controlled study of bicarbonate therapy in critically ill patients having lactic acidosis and in this study bicarbonate did not improve haemodynamics in patients with lactic acidosis and had two identifiable side effects which are likely to have been detrimental.

This study has now been repeated by a different group and the results have been confirmed (85). Ideally future studies should aquire data over longer time periods, and if possible patients with more severe acidosis should be included to extend the findings to these groups. Nevertheless, both studies provide substantial clinical evidence against using a therapy which has no measurable benefits in patients and which has important measurable side effects.

The two large animal studies described in this thesis Chapters (4.3.1) and (4.3.2) add several important pieces of information. If taken together with the clinical results these suggest that bicarbonate was not an effective therapy in critically ill patients for two reasons. First because lactic acidosis has less influence upon left ventricular function than the many other factors which compete to alter left ventricular function during shock, and second because the side effects of bicarbonate infusion outweigh the potential benefits.

4.4 Alternative therapies for lactic acidosis

It seems to me that it is unlikely that alternative metabolic buffer therapies will be demonstrated to have important clinical advantages not seen with bicarbonate, because buffers do not correct the underlying pathological disorder. Nevertheless, at present, there is considerable experimental interest in several of these alternatives. **Carbicarb** and **dichloroacetate** are the two most actively studied agents at present. Carbicarb (an equimolar combination of sodium carbonate and sodium bicarbonate) generates 30% less carbon dioxide than bicarbonate, but is otherwise indistinguishable. There was at this time no clinical study to support its usage in patients, although studies in organ preparations (120) and in whole animals (121) do suggest advantages. In langendorff preparations of rat hearts, carbicarb improves intracellular acidosis and cellular function whereas bicarbonate does not (120). In the hypoxic dog model (121), similar conclusions were obtained - carbicarb improved both arterial blood pressure and cardiac output - improvements that were not obtained with bicarbonate. Carbicarb will therefore need to be carefully studied in patients before it can be determined whether the differences translate into measurable clinical benefits.

Dichloroacetate (DCA) is not a buffer, and acts by increasing the activity of phosphate dehydrogenase. DCA thus is intended to decrease lactate production, and accumulating data suggests that DCA does indeed lower blood lactate levels, normalise pH and in some cases improve haemodynamic measurements. In the hepatectomy, phenformin and hypoxia (122) (123) models, DCA decreases lactate production, increases liver lactate extraction and increases arterial pH. In one study (122), short term mortality was also improved. During E Coli endotoxemia in dogs (124), DCA also rapidly normalises blood lactate concentrations, but in this study had no measurable effect upon haemodynamics. Owing to the accumulating laboratory data, DCA has been the subject of an multicentre prospective clinical trial in North America. When interpreting clinical studies which concerning the cardiovascular effects of DCA during acidosis it will be important to consider the recent observations that DCA also increases haemodynamic performance when it is infused into healthy human volunteers who do not have acidosis (125). This haemodynamic effect is independent of the effects of DCA upon acid base balance, and so studies which report important haemodynamic effects of DCA during metabolic acidosis should be carefully interpreted with this in mind. Importantly to patients, and like each of the buffers, DCA does not do anything to improve the cellular hypoxia which initiates and

maintains most forms of lactic acidosis, and which almost certainly determines patient outcome. There is only one (uncontrolled) study in which DCA was infused into patients having lactic acidosis (68). In these thirteen patients, DCA effectively lowered blood lactate concentrations, increased arterial pH and was associated in some of the patients with improved haemodynamic status. However, all but one of these patients died rapidly from their underlying disease process. DCA was effective at improving acid-base status but had no effect upon the underlying disease - which determined eventual outcome.

Another approach to therapy for patients who have lactic acidosis is to consider the lactate ions as potentially important toxins and therefore to adopt measures intended to increase lactate elimination. There is little data to support this concept, although it has been suggested that lactate ions may contribute to ionised hypocalcaemia and so may indirectly contribute to decreased LV contractility (36). Case reports suggest that peritoneal dialysis can effectively eliminate lactate (126) and haemofiltration (CAVH) is probably similarly effective. Unfortunately, like all the therapies discussed to this point, lactate removal does not correct the underlying problem in most patients. It does not improve cellular hypoxia and so is also unlikely to influence patient survival.

4.4 Future Directions

Improved survival for critically ill patients who have lactic acidosis is likely instead to depend on a number of factors. Most important perhaps will be increased recognition of the fundamental importance of improving tissue perfusion, and a more aggressive focus upon correcting the underlying disorder. Reliable techniques to measure tissue perfusion and cellular acidosis are being developed (127) and need to be further refined before widespread clinical use. If such monitors are shown to be reliable indicators of tissue perfusion in patients (and present studies suggest that some may be), they may prove extremely useful in guiding effective resuscitation and vasoactive therapies. Therapies which improve tissue pH are far more likely to benefit tissue function and outcome than therapies which simply alter the blood pH. Furthermore, present therapeutic protocols must be carefully re-examined with the cellular function of critical organ systems (particularly gut and liver) used as specific end points.

Next, more effective and more specific therapies for patients who have sepsis (which might include presently investigational therapies like Tumor Necrosis Factor monoclonal antibodies and selective Platelet Activating Factor antagonists) may enable early correction of the cellular dysfunction of sepsis which causes anaerobic metabolism and lactic acidosis. With a similar intent in mind, new vasodilators or combinations of vasoactive agents including vasodilatation, are now being developed and used clinically in an attempt to improve the organ specific oxygen delivery in patients who have sepsis, but without compromising critical organ perfusion pressures. For many years, clinicians have been acutely aware that hypotension has always been the major problem associated with using presently available vasodilators during sepsis in patients.

In conclusion, lactic acidosis is an important marker of impaired tissue perfusion during cardiovascular dysfunction and shock. In my view, it is most likely that improved cardiovascular function and improved patient outcome are most likely to come from therapies which improve tissue perfusion rather than from those that simply normalise arterial pH.

Chapter 5

CARDIAC DYSFUNCTION DURING HYPERDYNAMIC SHOCK

5.1 Introduction

In this chapter several aspects of myocardial function during hyperdynamic shock are investigated. The chapter is divided into two sections - anaphylactic shock and septic shock. In the first section, literature relevant to cardiovascular collapse during anaphylaxis is first reviewed and histamine is highlighted as a key mediator. Then the effect of histamine on myocardial function in human volunteers is reported in detail.

5.2 Anaphylactic Shock

5.2.1 Cardiac Dysfunction during Anaphylaxis

(Applied Cardiopulmonary Pathophysiology. 1993;5:9-18) (128)

5.2.1 Introduction

Human anaphylaxis is a symptom complex characterised particularly by skin rash, oedema, bronchospasm, cardiovascular collapse, and gastrointestinal disturbance. Virtually every other organ system in the body can at times also be affected. The most common precipitants are antibiotics and iodinated radiocontrast media, with an incidence of about 1:5000 exposures and a fatality rate of 5-10%. There are also many other less common precipitants including muscle relaxants, nonsteroidal anti-inflammatory drugs, venoms and stings, human proteins, hypertonic solutions, exercise and foods.

5.2.1 Pathophysiology of Anaphylaxis

Most commonly human anaphylaxis is a type one, immediate hypersensitivity reaction - resulting from re exposure to an antigen, and thereby antigen exposure to preformed IgE (and IgG) attached to mast cells and basophils. These cells then de granulate and the symptoms we recognise clinically are caused by the released mediators. Some of these mediators (histamine, bradykinin, serotonin and various chemotactic factors) are preformed and act immediately, wheras others are released as precursors (leukotrienes, platelet activating factor) and their effects therefore onset more slowly. There are two other mechanisms which sometimes apply. First,

antigen-antibody complexes can activate the complement cascade directly (aggregate anaphylaxis) forming C3a and C5a which can then trigger the release of the same mediators from mast cells and basophils, and second, some hypertonic solutions can stimulate the release of mediators directly by as yet unknown mechanisms (129) (130) (131) (3). Anaphylactic mediators have many direct effects, but they also act in synergy with each other and furthermore have many of their effects modified by the concomitant release of catecholamines. Catecholamines are released indirectly by hypotension and stress and also by direct adrenal gland stimulation by mediators, including histamine. In accordance with this pathophysiology, case reports indicate that anaphylactic reactions are associated with marked rises in plasma histamine. For example, Moss et al(132) reported plasma histamine concentrations of to 20 - 40,000 pg/ml within minutes of the onset of a reaction to succinylcholine. In this particular case in which catecholamines were also measured, plasma concentrations of noradrenaline and adrenaline of 1500 - 2250 pg/ml respectively were reported.

5.2.1 Cardiovascular collapse during human anaphylaxis

Owing to the unpredictable and frequently catastrophic nature of human anaphylaxis, present knowledge of the cardiovascular changes occurring during these reactions in man is not based upon controlled clinical studies. There are however a number of case reports from patients in which haemodynamic changes during anaphylaxis have been reported. Silverman et al (133) documented a marked decrease in filling pressures in association with hypotension and with decreased cardiac output in a patient undergoing an anaphylactic reaction to penicillin. Nicolas et al (134) (135) studied a patient during anaphylaxis following intravenous infusion of a modified gelatin solution. This patient maintained an increased cardiac output during hypotension until intravascular volume replacement was ceased. At that point decreased cardiac output and then cardiac arrest supervened. In a patient having antibiotic related anaphylaxis, Beauropre (135) confirmed using two dimensional echocardiography, that cardiovascular collapse was associated with marked reductions in preload. In this case preload was measured as left ventricular end diastolic area. There were no changes in regional cardiac function and left ventricular ejection fraction was increased - a change which may have been due solely to decreased afterload or alternatively due to increased left ventricular function. In most of the cases which document increased cardiac output during anaphylaxis, the increase is primarily due to increased heart rate with little change, and at many times actually a decrease, in left ventricular stroke volume (132). These cases and others reinforce the view that the major cardiovascular changes occurring during anaphylaxis are threefold. First there is tachycardia, second arteriolar dilation which decreases afterload and therefore tends to increase cardiac output when preload is maintained, and third decreased preload due both to venodilation and also to fluid flux from the intravascular compartment to the interstitium. Decreased preload decreases cardiac output and in many patients this is the primary cardiovascular abnormality. In critically ill patients who are

also being mechanically ventilated for other or for associated reasons, increased intrathoracic pressure may aggravate the decrease in venous return and decrease cardiac output further.

However cardiovascular collapse during anaphylaxis does not always respond readily to standard therapy. During the course of a controlled study to evaluate different forms of immunotherapy for subjects with insect sting hypersensitivity, Smith et al (136) had the opportunity to prospectively study three patients having severe systemic anaphylactic reactions. In each of these cases the major dysfunction was cardiovascular, the hypotension was severe, and in two cases was very resistant to fluid and adrenaline therapy. The extent and timing of hypotension correlated closely with plasma histamine levels, but the only cardiovascular variables monitored were heart rate and blood pressure and these did not allow differentiation of whether in each case the primary dysfunction was in the peripheral vasculature or the heart.

There is little doubt that catecholamines released during anaphylaxis modify the clinical response in many patients. Furthermore, there are an increasing number of case reports in the literature which detail exceptionally severe and prolonged anaphylaxis in patients who are already receiving beta adrenergic blocking drugs (137) (33) (138) (139). These cases reinforce the view that both exogenous and endogenous catecholamines considerably modify the cardiovascular changes induced by mediators of anaphylaxis, and may mask important changes in myocardial function in many patients.

Although myocardial function could be depressed during human anaphylaxis, this possibility has never been clearly explored, for several reasons. First there is an obvious difficulty with organising controlled studies of left ventricular function during such an uncommon, unpredictable and often catastrophic clinical event. Secondly is the problem that most of the techniques which might be used to carefully assess left ventricular contractility (both in animals and in humans) are inadequate, and at times misleading in the context of altered preload and heart rate (37). For example, increased stroke volume or ejection fraction which is documented at times during anaphylaxis could be due solely to decreased afterload, and altered dP/dt_{max} (usually measured in the cardiac catheter laboratory) is readily influenced by changes in heart rate and in preload. Load independent techniques enable contractility assessments to be made much more directly and precisely but their importance in settings like anaphylaxis has only been recognised in recent years.

Nevertheless, and despite these reservations about many assessment techniques, decreased left ventricular contractility has recently been described in two separate case reports during human anaphylaxis. In the first paper, two patients experiencing severe anaphylaxis (one to anaesthesia and another to bee sting) were studied using two dimensional echocardiography and radionuclide angiography (4). In both patients, although hypoxia and acidosis had been treated and were not complicating the clinical picture, there was profound systolic myocardial dysfunction. Both patients were supported using intra-aortic balloon counterpulsation. After anaphylaxis had resolved, both patients had normal left ventricular function so preexisting left ventricular dysfunction was not responsible for these findings. Although the same authors have studied a number of other cases (MM Fisher, personal communication) which did not

demonstrate these changes, this data strongly suggests that in some patients having anaphylaxis there is life threatening depression of left ventricular function in addition to the other more widely recognised cardiovascular changes. Two years later another case was reported by a second group (5), and on this occasion improved myocardial function followed infusion of the non-catecholamine inotrope amrinone. The authors suggest that down regulaton of catecholamine receptors during severe anaphylaxis may unmask negative inotropic effects of anaphylactic mediators which would otherwise be masked by catecholamines.

5.2.1 Animal studies

There are many animal studies in different species which report changes in cardiovascular function during anaphylaxis, and this chapter does not intend to detail all of them. In general, the animal studies have been difficult to apply to humans because of considerable interspecies variation, of difficulties accurately modelling human anaphylaxis, and because load independent techniques have until recently not been utilised. It is however appropriate to mention two studies. First, Pavek et al determined in monkeys (140) that the same species could respond to anaphylactic challenge in different ways - in some animals cardiovascular collapse was entirely due to decreased preload and pulmonary hypertension, and in others the decrease in cardiac output was more severe and was additionally due to decreased myocardial contractility. This work was later extended in dogs (28) and it seemed probable that it was the animals with high titres of serum IgG antibodies and therefore "aggregate anaphylaxis" that displayed myocardial depression, wheras those with predominantly IgE mediated "cytotropic anaphylaxis" had predominantly a peripheral vascular problem, and little cardiac depression. These workers hypothesised that SRSA (now known as the leukotrienes) might be the mediators mainly responsible for cardiac depression in these models. These studies however suffered from an inability to precisely measure left ventricular (LV) contractility in vivo. Much more recently , Correa et al (141) (142) placed sub endocardial ultrasound crystals in ragweed pollen sensitised dogs, to measure LV contractility changes during anaphylaxis. This technology enabled the measurement of load independent end-systolic pressure-dimension relationships and thereby the careful assessment of changes in left ventricular function during anaphylaxis. Some animals were anaesthetised, others were awake during study. In this model, anaphylaxis caused hypotension and also caused significant depression of left ventricular systolic contractility . This depression was not due to decreased coronary flow (which increased) nor to hypoxia or acidosis, and left ventricular contractility was not changed in controls made hypotensive using vasodilator infusions. Therefore in this model, cardiovascular collapse during anaphylaxis was due to decreased left ventricular contractility in addition to and in association with the decreased preload and pulmonary hypertension that has been recognised for many years. In a following study the same group now suggest that decreased left ventricular contractility during anaphylaxis in this model is due to histamine, acting via H_1 histamine receptor stimulation (143).

5.2.1 Histamine

Although many mediators are released during human anaphylaxis, histamine is probably responsible more than any other for the clinical symptoms (144). Histamine is measured in large quantities in many patients having anaphylaxis, and when infused into animals and volunteer humans can alone cause all the clinical findings observed during anaphylaxis. In humans, the symptoms and signs following histamine infusion are dose related. Low levels (1-3 ng/ml) are associated with tachycardia, flushing, and increased pulse pressure (145). Hypotension (5 ng/ml) and shock (>10 ng/ml) are associated with higher plasma histamine concentrations (3).

The effects of histamine on the in vivo human heart are not well elucidated. Both H_1 and H_2 receptors are present on atrial and ventricular muscle (146) and in many animals intracardiac mast cells exist which directly release histamine. In animal and human isolated cardiac muscle preparations, histamine increases contractility by H_2 histamine receptor stimulation (147) (26). In different models histamine has different effects on coronary flow, however in humans with normal coronary vessels the predominant effect is H_1 receptor mediated vasodilatation (145), so that is unlikely that myocardial ischaemia due to histamine mediated coronary vasoconstriction is an important contributor to myocardial dysfunction during human anaphylaxis.

Because histamine infusion so closely imitates human anaphylaxis, in several prospective investigations histamine has been infused into human volunteers in an attempt to precisely quantitate the cardiovascular effects. Vigorito et al (148) infused histamine over short time periods into four patients receiving cardiac catheterisation. Histamine decreased blood pressure, left ventricular end diastolic pressure, and stroke index, and increased heart rate. Histamine also increased LV dP/dt_{max} and this change could have been due to increased LV contractility. LV dp/dt_{max} is commonly used to assess LV contractility when the facilities for placement of a LV catheter are available, but unfortunately LV dp/dt_{max} is considerably influenced by changes in preload and in heart rate. Thus despite careful assessment, this reservation meant that the authors were unable to make definitive conclusions about changes in left ventricular contractility. Watkins et al (149) similarly infused histamine in six normal men, and in each case compared the haemodynamic effects after histamine with those occurring after equally hypotensive doses of nitroprusside. In this study and in each of these subjects, histamine was infused following pretreatment with H_1 receptor blockade and thus their conclusions were limited to observations on unopposed H_2 receptor stimulation. Histamine (H_2 stimulation) increased LV percentage fractional shortening (measured by trans-thoracic echocardiography) compared to nitroprusside, and so increased LV contractility. Quite large doses of histamine were required (1.5 mg/kg/min). Since no data was gathered during histamine infusion without histamine H_1 receptor blockade it is impossible to know whether in the lower doses of histamine which normally cause hypotension and flushing in humans whether H_1 receptor stimulation would negate or override the increased contractility.

In order to clarify the question of histamine effect on human left ventricular contractility the study detailed in Ch (5.2.2); (53) was designed. Central to the conduct of this study was the

ability to measure left ventricular contractility precisely but non-invasively using a technique which was not affected by concurrent changes in left ventricular preload and afterload. This study demonstrated that histamine decreased left ventricular contractility in healthy human volunteers and that the effect probably involved H_1 receptors.

In a following study, (150) the effects of histamine on LV mechanics were also studied using 10 anaesthetised (6 histamine and 4 control) pigs and the methodology described in Ch (3.2). In this study the intention was to block catecholamines in a manner which would not be ethically acceptable in humans. Because catecholamines are both directly and indirectly released by histamine (probably more so in many animal species than occurs in humans), and because catecholamine effects are difficult to separate from the effects of histamine itself, catecholamines were blocked in all animals from the start of each experiment with alpha (phentolamine) and beta (propranolol) adrenoceptor blockade. To ensure that all measurements were done at the same heart rate, animals were paced using a right atrial pacemaker. Histamine was infused in graded doses, and after each dose increase, measurements of haemodynamics and LV mechanics were done. Owing to the results in the human study (53), we were primarily interested in determining the effects of H_1 receptor stimulation, so all measurements were then repeated after H_2 histamine receptor blockade (ranitidine). In high doses, histamine transiently increased LV contractility. This effect was blocked by ranitidine and so was caused by H_2 receptor stimulation. In low doses histamine decreased LV contractility and after histamine had ceased, decreased left ventricular contractility was both marked and prolonged. Decreased LV contractility was not observed in the controls and was not blocked by ranitidine and was therefore H_1 mediated. Since decreased LV contractility was such a long lasting effect and because histamine has a short elimination half life, it is possible that another mediator released by initial H_1 stimulation was the cause. Recent data suggests Platelet Activating Factor as a possible candidate for this mediator (151) (152) (153) (154).

5.2.1 Other important mediators

Several other mediators released along with histamine, may also be important causes of cardiac dysfunction during anaphylaxis. These include Platelet Activating Factor (PAF), leukotrienes, serotonin, and bradykinin. There is unfortunately little data from human volunteers or from patients with anaphylaxis to clarify the possible roles of these other mediators in patients.

The data that is available is as follows. PAF has been studied in several in-vitro and in-vivo animal models and many of the now numerous PAF antagonists have been investigated in small animal models of anaphylaxis. PAF mediates several aspects of the anaphylactic response in animals (153) and decreases carefully measured left ventricular contractility when infused into dogs (152). PAF antagonists block hypotension during anaphylactic shock in rodents (155) and also block fluid and protein extravasation in the same species. However the effects of PAF

antagonists on left ventricular contractility and on cardiac function during anaphylaxis have not yet been established. It is known that both histamine and bradykinin induce a rapid synthesis of PAF from cultured endothelial cells (151). If this occurs in vivo in humans, it might be the mechanism by which histamine initiates a longer lasting impact upon left ventricular function than its short half life would suggest possible. However it is clear that the true importance of PAF and PAF antagonists during human anaphylaxis has not yet been determined. **Leukotrienes** are released during anaphylaxis and have also been suggested as causes of depressed cardiac contractility in laboratory models of anaphylaxis (156) (157). In many small animal models the major cardiac effect of the leukotrienes is to induce coronary vasoconstriction and myocardial ischaemia. In sensitised dogs with anaphylaxis however, coronary vasoconstriction is not usually observed and in case reports of human anaphylaxis electrocardiographic changes of myocardial ischaemia are not commonly reported. Therefore although leukotrienes are likely important during human anaphylaxis, there is little evidence at this time linking leukotrienes with decreased left ventricular function during anaphylaxis in patients. **Serotonin and bradykinin** are released during anaphylaxis but there is not good evidence to link these mediators with left ventricular dysfunction.

5.2.1 Conclusions and Practical Applications

In many patients, cardiovascular collapse during anaphylaxis is due primarily to severe vasodilatation and to extravascular fluid leak. These patients frequently respond to conventional therapeutic measures - intravascular volume replacement and adrenaline. Steroids probably prevent relapse and should be used early. We now recognise however that some patients also have decreased cardiac function, and this is likely due to decreased left ventricular systolic contractility. Left ventricular diastolic dysfunction may also occur but has not yet been demonstrated in patients. Decreased cardiac function may be due to histamine, to platelet activating factor, or to the leukotrienes and recent work suggests that histamine H_1 receptors are involved. Present data suggests that H_1 antagonists should be therefore also be used during anaphylaxis, and platelet activating factor antagonists may have a future therapeutic role. The use of H_2 receptor antagonists is more controversial. In patients demonstrating depressed cardiac function, full supportive measures including (if necessary) cardiac assist devices and non-catecholamine inotropes, should be used because depressed left ventricular function during anaphylaxis is reported to be completely reversible.

5.2.2 Cardiac dysfunction during histamine infusion in humans

(J Appl Physiol 1992;73:2530-2537) (53)

Introduction

Histamine is a major mediator of human anaphylaxis. Although other mediators are released during anaphylaxis, histamine alone can produce all of the clinical manifestations (158). Although there are few data carefully evaluating cardiac function during human anaphylaxis, several reports suggest that severe left ventricular dysfunction may occur (4) (136) despite marked increases in circulating catecholamines (159) (149). Smith et al, (136) documented severe cardiovascular dysfunction in a human subject during bee-sting anaphylaxis which was difficult to reverse using intravenous fluids and catecholamine therapy. Raper and Fisher (4) described two cases of severe, but eventually reversible, left ventricular dysfunction during anaphylaxis using echocardiography and radionuclide angiography.

In contrast to these findings in anaphylaxis, studies evaluating histamine alone have suggested that it increases left ventricular contractility. Histamine infusion in human volunteers increases dP/dt_{max}, (148) but in this study histamine also decreased preload, decreased afterload, and increased heart rate. Because dP/dt_{max}, varies considerably with changes in both heart rate and preload (37), conclusions about changes in left ventricular contractility could not be made. In another study, histamine infusion in subjects pretreated with a histamine H_1 receptor antagonist increased left ventricular contractility, when compared with an equally hypotensive infusion of nitroprusside (149). These results suggested that selective stimulation of H_2 receptors increased left ventricular contractility. Because the relative effects of H_1 and H_2 receptors upon the human heart in vivo are unknown, this result may not accurately reflect the overall effects of histamine on human left ventricular contractility.

Accordingly, the present study was undertaken to test the hypothesis that histamine increases left ventricular contractility in humans and to determine if this effect is mediated by H_1 receptors. To circumvent the problem of changes in load upon left ventricular contractility we used the left ventricular end-systolic pressure-dimension relationship (ESPDR) (26) (160) and the left ventricular end-systolic meridional wall stress - rate corrected velocity of circumferential fibre shortening (σ_{es}-$V_{cf,c}$) relationship (38) (54) which are both relatively load independent. By establishing these linear relationships over a wide range of afterloads, it is possible to determine if an intervention such as histamine infusion changes left ventricular contractility by quantitating the deviation of the one intervention point from the baseline linear relationship (161).

5.2.2 Methods

5.2.2 Subjects

Nine healthy male volunteers (age 36 ± 4 years) who responded to a posted advertisement were studied. Subjects had no clinical history suggestive of ischaemic heart disease, asthma, anaphylaxis, or ulcer disease. No subject had recently taken any medications. All subjects had a normal physical examination and a normal echo cardiographic examination with no regional wall motion abnormalities. The study was approved by the University of British Colombia Clinical Screening Committee For Human Research and by the Ethics Committee of St Paul's Hospital. Written informed consent was obtained from all subjects.

5.2.2 Measurements and calculations

All pressure, dimension, and RR interval measurements taken from the echo cardiographic records (Fig 6) were repeated on 5 beats in each condition and averaged. The coefficient of variation for these repeated measures for pressure was 6.7 ± 1.2%, for dimension was 1.3 ± 0.4%, and for RR interval was 0.8 ± 0.5%. All measurements were performed independently by two observers blinded to the haemodynamic intervention. Identical effects were identified by these two independent measurement sets and the mean correlation coefficient for dimension measurements between these two sets was 0.95.

5.2.2 Left ventricular end-systolic pressure

Indirect carotid arterial pulse pressure was measured (HP 21 050A Transducer, Hewlett Packard, Andover, MA) from the right carotid artery by an experienced technologist (Fig 6). as described in Ch (3.3.1). This method has been previously validated and has been found to be accurate over a wide range of systemic pressures and cardiac outputs (38) (54).

5.2.2 Left ventricular dimensions

The echocardiograms were obtained by an independent echocardiographer unaware of the sequence of haemodynamic interventions, as described in Ch (3.3.2).

5.2.2 Protocol

Previously all subjects had been studied to determine the dose of histamine which decreased mean arterial pressure by 20% (159) (median dose 0.6mg/kg/min). During histamine infusion all subjects experienced cutaneous flushing, 1 experienced headache, and all experienced the sensation of forceful cardiac contractions. These side effects did not influence data acquisition in any way. The norepinephrine response to this dose of histamine is approximately three times that of an equally hypotensive dose of nitroglycerine (159) or nitroprusside (162) (163). To the extent that higher catecholamine levels during histamine-induced hypotension increase contractility, any negative inotropic effect of histamine observed in this study would underestimate the true negative inotropic effect of histamine. This dose range of intravenous histamine infusion has also been demonstrated to produce plasma levels of approximately 4,000 to 10,000 pg/ml histamine (164) (159). Plasma histamine values, although elevated, have poor correlation with systemic hypotension. In one report of 3 subjects with hypotension following insect stings, plasma histamine values ranged from less than 20,000 pg/ml to greater than 140,000 pg/ml (159) (154). Therefore any effect of histamine on left ventricular contractility observed in this study may underestimate the effect during anaphylaxis. To define the baseline left ventricular ESPDR (Fig 13) and σ_{es}-V_{cfc} relationship, multiple measurements were made in each subject before drug infusions and then over a wide range of left ventricular loading conditions.

Afterload was first increased using intravenous phenylephrine (Winthrop Laboratories, Aurora, ON) 0.1 to 0.15 mg/min, and then, after allowing the mean arterial pressure to return to within 5% of the baseline values, afterload was decreased using sodium nitroprusside (La Roche, Etobicoke, ON) 0.5 - 3.0 Mch/kg/min. During each infusion, at least three sets of measurements were taken. Subjects were all pretreated with atropine sulphate (Abbott Laboratories, Montreal, PQ) 1.0 mg i.v. before these measurements and then 0.5 mg i.v. repeated half hourly) to depress baseline vagal tone and to allow all measurements to be done at similar heart rates (38).

At the start of the experiment in 7 of the 9 subjects we infused dobutamine hydrochloride (Eli Lilly, Scarborough, ON) intravenously at 5 mg/kg/min for five minutes to ensure that the methodology was adequate and sensitive enough to detect the change in left ventricular contractility occurring with a moderate dose of a known positive inotropic agent, and also to provide an index of magnitude of changes in left ventricular contractility, for comparison with histamine. After dobutamine, all subjects rested for 20 minutes to permit a return to baseline conditions prior to the administration of other drugs.

After obtaining data defining the baseline left ventricular ESPDR and the σ_{es}-V_{cfc} relationship, subjects rested until mean arterial pressure returned to within 5% of the baseline value. Histamine phosphate (Allen and Hanburys, Toronto, ON) was then infused intravenously for 3 - 5 minutes in doses previously established to safely decrease mean arterial pressure by 20% in the same subjects (median dose 0.6 mg/kg/min, range 0.4 to 0.8 mg/kg/min). After repeating all measurements during histamine infusion subjects again rested until mean arterial

pressure returned to within 5% of the baseline value (10 ± 2 minutes). Finally, following pretreatment with the H1 receptor antagonist diphenhydramine hydrochloride (Parke-Davis, Scarborough, ON) 50 mg i.v. over 10 minutes, histamine was infused a second time (same dose and time) and all measurements were repeated.

5.2.2 Statistical Analysis

The left ventricular ESPDR and the σ_{es}-V_{cfc} relationship at baseline were determined using linear regression analysis and the 95% confidence intervals for the relationships were computed. The end-systolic pressure-dimension and σ_{es}-V_{cfc} points during histamine infusion, during histamine infusion following H_1 histamine receptor antagonist pretreatment, and during dobutamine infusion were then compared to the baseline relationship for each subject using the method of Rajfer et al (161). This approach is feasible and safe but does not determine whether a change in contractility was associated with a change in slope or intercept of the end-systolic relationship.

To determine if interventions changed contractility we first visually assessed whether end-systolic points during interventions lay within or outside the 95% confidence intervals for the baseline relationships. Next, in each subject we measured the vertical and horizontal distances of each of these points from the baseline relationships and tested the null hypothesis that there was no difference between the points and the baseline relationships using paired T-tests. Finally, we compared the end-systolic pressure-dimension and the σ_{es}-$V_{cf,c}$ points at baseline with those during histamine infusion and with those during an equally hypotensive nitroprusside infusion (nitroprusside dose chosen to most closely approximate the decrease in end-systolic pressure observed during histamine infusion), using a repeated measures analysis of variance (Table 12). When a significant difference was found ($p < 0.05$) we then identified specific differences between baseline, nitroprusside, histamine after H_1 blockade, histamine, and using paired t-tests corrected for multiple comparisons using a sequentially rejective Bonferroni test procedure (96). We used the same analysis (ANOVA plus multiple comparison test) to highlight differences in other variables in Table 12. All results are reported as mean ± standard deviation.

Table 12. *Changes in haemodynamics and left ventricular mechanics in 9 normal human subjects.*

	Baseline	Nitroprusside	Histamine	Histamine After H_1 Blockade
Heart rate, beats/min	95±22	116±17	106±19	105±27
Systolic blood pressure, mmHg	120±10†	91±15	92±18	116±23†
Diastolic blood pressure, mmHg	68±6†	48±11	46±14	70±19†
End-systolic blood pressure, mmHg	86±11†	53±18	54±17	84±28†
End-diastolic dimension, mm	49.3±1.7	46±3.2*	48.1±3.1	49.5±2.9*
End-systolic dimension, mm	30.1±3.3	24.7±5.1*	29.0±4.3	30.8±4.5*
Fractional shortening, %	0.39±0.06	0.46±0.09	0.40±0.07	0.40±0.05
$V_{cf,c}$, circumferences/s	1.34±0.26	1.65±0.46	1.35±0.31	1.24±0.24
σ_{es}, g/cm^2	31.3±7.4†	13.9±6.9	18.3±8.4	33.1±15.7†

Values are means ± SD. $V_{cf,c}$, rate-corrected velocity of circumferential fiber shortening. * Different from histamine ($P < 0.05$). † Different from histamine ($P < 0.01$).

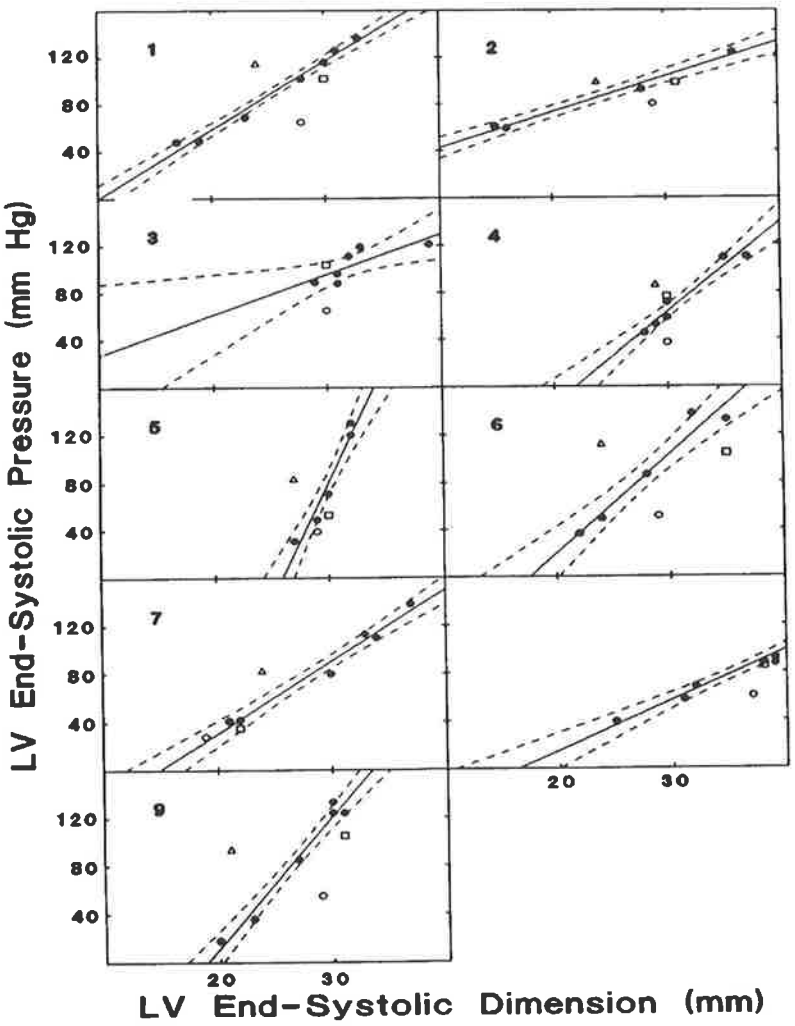

Figure 13. All end-systolic pressure-dimension relationship (ESPDR) measurements from all 9 subjects are shown. Baseline ESPDR (solid lines) is determined by linear regression to baseline points (solid circles) and 95% confidence intervals are shown (dashed lines). Wide range of afterload for baseline points was accomplished by phenylephrine and the nitroprusside infusions. In 7 subjects who received dobutamine infusion contractility increased (open triangles lie to left and above ESPDR). Histamine infusion decreased contractility (open circles lie to right and below ESPDR). After H_1 antagonist pretreatment histamine infusion had less effect on contractility (open squares lie close to ESPDR).

5.2.2 Results

Histamine decreased mean arterial pressure from 86 ± 8 to 62 ± 13 mmHg ($p<0.05$) and (owing to atropine pretreatment) did not significantly change heart rate (95 ± 22 to 106 ± 19, P = NS) (Table 12). Compared to baseline, left ventricular end-diastolic dimension decreased slightly after both histamine and an equally hypotensive dose of nitroprusside but only the nitroprusside induced decrease was significant ($p < 0.05$). Despite decreased afterload, end-systolic dimension did not decrease after histamine (30.1 ± 3.3 to 29.0 ± 4.3 mm). However, end-systolic dimension was significantly decreased after an equally hypotensive dose of nitroprusside (30.1 ± 3.3 to 24.7 ± 5.1 mm, $p < 0.05$). Fractional shortening during nitroprusside infusion increased compared to baseline ($p < 0.05$) but did not increase compared to baseline during histamine infusion. Thus, left ventricular ejection was decreased during histamine infusion compared to nitroprusside, even though afterload (end-systolic pressure) was similar to that measured during nitroprusside infusion (Table 12). H_1 antagonist pretreatment prevented all of these changes (Fig. 13 and Table 12).

In all subjects we obtained linear baseline left ventricular end-systolic pressure-dimension relationships (mean correlation coefficient = 0.96) (Fig. 13). In each of the seven subjects in whom dobutamine was infused, the end-systolic pressure-dimension point was shifted to the left and above the ESPDR, indicating increased left ventricular contractility. The end-systolic pressure-dimension point during dobutamine infusion was different from the baseline ESPDR in both vertical and horizontal directions, ($P < 0.01$) (Fig. 13) . By contrast, during histamine infusion, the end-systolic pressure-dimension point was shifted to the right and below the baseline ESPDR. In seven subjects the histamine points lay outside the 95% confidence intervals for the baseline data and, for all subjects taken together, the histamine points were different from the baseline ESPDR in both their horizontal and vertical directions ($P < 0.01$) (Fig. 13). Following H_1 antagonist pretreatment, end-systolic pressure-dimension points were not significantly different from the baseline ESPDR in either the horizontal or vertical direction (Fig 14).

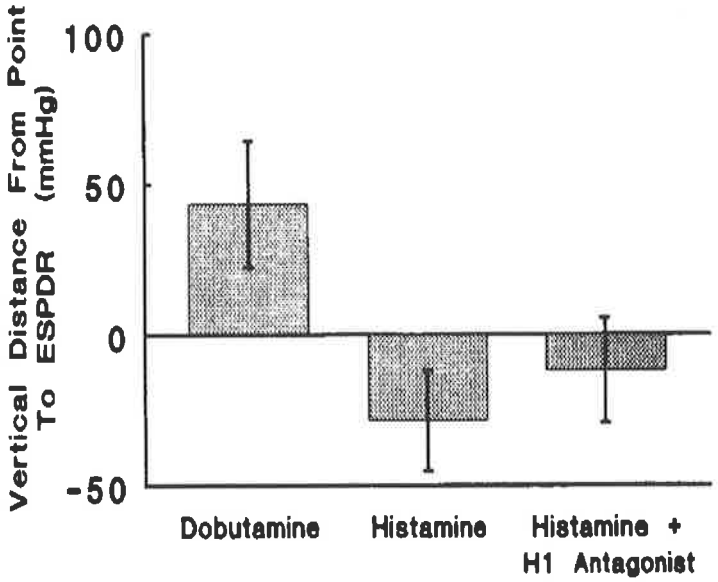

Figure 14. To quantitate changes in left ventricular contractility vertical distance from end-systolic points to ESPDR is shown for dobutamine, histamine, and histamine after H1 antagonist pretreatment. vertical distance of zero is baseline contractility. Error bars are SDs. Dobutamine significantly increased contractility ($P < 0.001$) while histamine alone decreased contractility ($P<0.001$) to a similar extent. After H1 antagonist pretreatment, histamine did not significantly alter contractility (P=NS).

We also obtained linear baseline σ_{es}-$V_{cf,c}$ relationships in all subjects (mean $r = 0.978$). Dobutamine infusion resulted in σ_{es}-$V_{cf,c}$ points lying above the baseline σ_{es}-$V_{cf,c}$ relationships ($p < 0.05$) (Figs 15 &16). During histamine infusion the σ_{es}-$V_{cf,c}$ points fell below the baseline σ_{es}-V_{cfc} relationship ($p < 0.05$) (Figs15 &16). These data also indicate that histamine decreases left ventricular contractility.

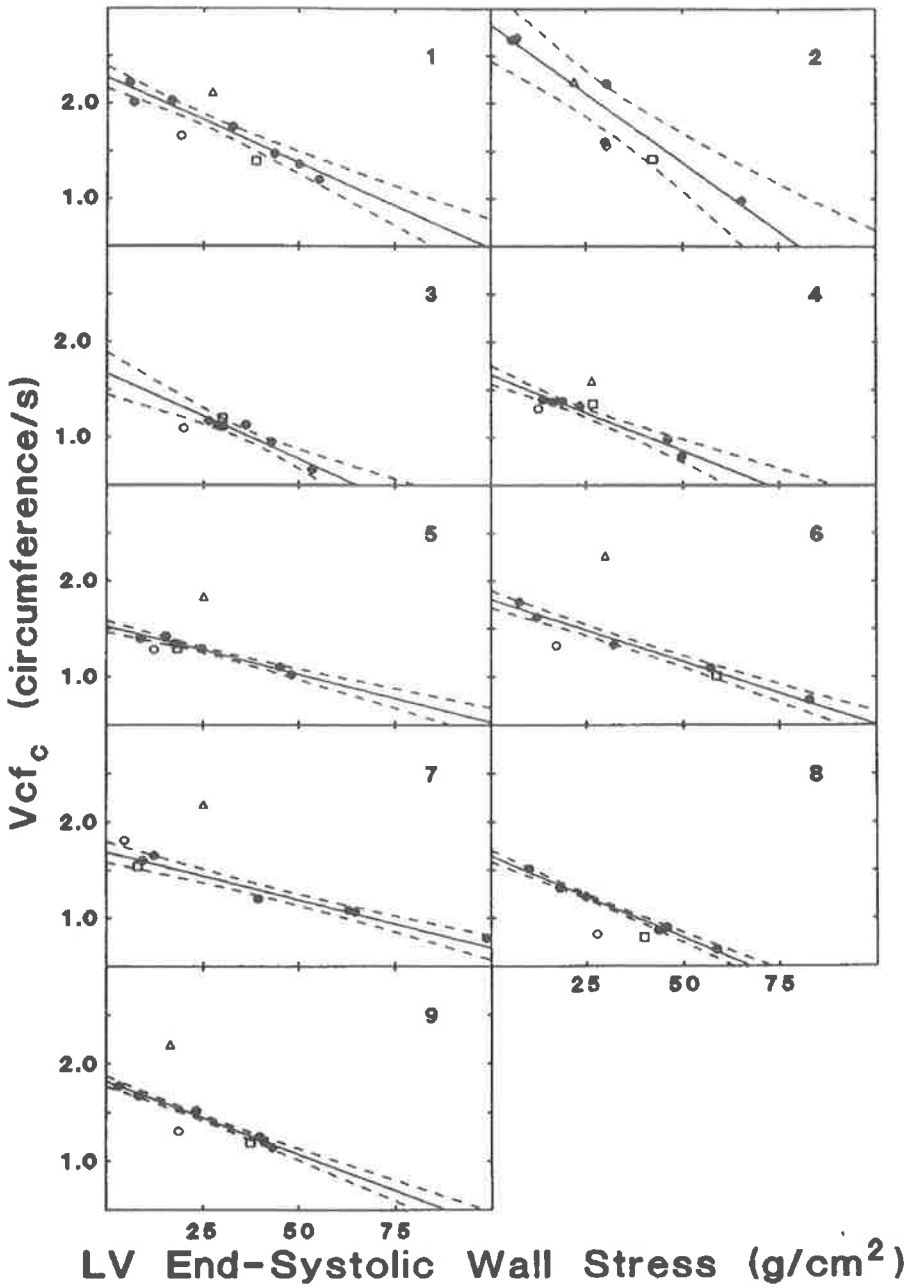

Figure 15. LV end-systolic wall stress-rate-corrected velocity of circumferential fibre shortening (V_{cfc}) relationships at baseline for all 9 subjects are shown as regression lines fit to baseline points (solid circles) with 95% confidence intervals (dashed lines). Dobutamine points (open triangles) lie above lines so that V_{cfc} is increased at same wall stress compared with baseline relationship, indicating increased left ventricular contractility. Histamine infusion decreased contractility (open circles lie below lines). After pretreatment with an H_1 - receptor antagonist, histamine infusion had less effect on contractility (open squares lie close to lines).

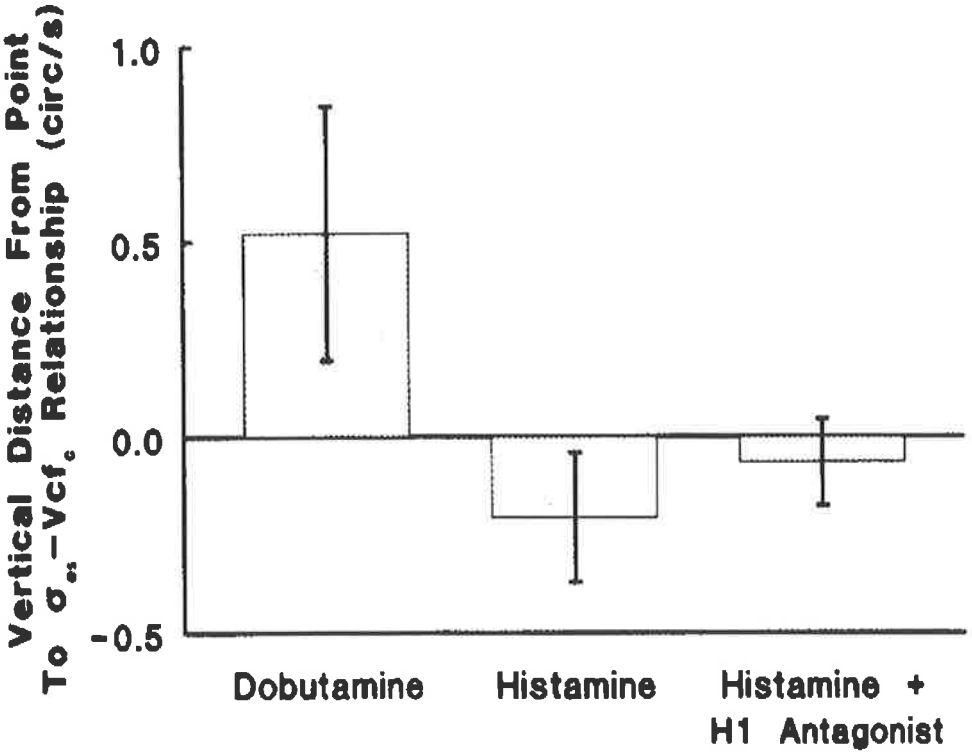

Figure 16. Vertical distance from end-systolic points to wall stress (σ_{es}) - ($V_{cf,c}$) relationship is shown for dobutamine, histamine, and histamine after H1 antagonist pretreatment. Vertical distance of zero is baseline contractility. Error bars are SE's. Dobutamine significantly increased contractility ($P < 0.01$) while histamine alone decreased contractility ($P < 0.01$). After H_1-receptor antagonist pretreatment, histamine did not significantly alter contractility (P = NS).

5.2.2. Discussion

The major findings from this study are that, in normal human subjects, histamine infusion decreases left ventricular contractility and that this decrease is inhibited at least partially, by H_1 antagonist pretreatment. The decrease in left ventricular contractility during histamine infusion was statistically significant and possibly haemodynamically important, despite the presence of catecholamines released during histamine infusion (159).

Cardiovascular collapse during anaphylaxis is thought to be primarily caused by decreased preload as a result of venodilation, plasma leakage from the intravascular space (159) (158) and, if mechanical ventilation is employed, decreased venous return due to increased intrathoracic pressure. Cardiovascular changes may also occur as a consequence of hypoxaemia, acidosis, and dilation of both arteries and veins. Thus, anaphylaxis and histamine are associated with large changes in preload and afterload. Furthermore, catecholamines are released during anaphylaxis indirectly in response to hypotension or stress and also as a direct effect of histamine (159) (149).

Catecholamines may modulate the cardiovascular changes observed during anaphylaxis and may be responsible for some of the cardiovascular effects which have been attributed to histamine. Therefore, to determine if histamine infusion altered contractility a measure of left ventricular contractility was needed that was insensitive to the anticipated large changes in preload and afterload and it was important to consider the effects of catecholamines released during histamine infusion.

To measure contractility in this study the ESPDR was used. Comparable to the ESPVR, this index is least sensitive to changes in preload and afterload (54) (160) (38). Furthermore we largely prevented changes in heart rate during histamine infusion by pretreating with atropine, a vagal antagonist. As a second index of contractility we also used the σ_{es}-$V_{cf,c}$ relationship which is a clinically useful approximation of the left ventricular force-velocity relationship (38). The σ_{es}-$V_{cf,c}$ relationship has been proposed as a more useful measure of left ventricular contractility because it also takes into account changes in heart rate and left ventricular wall thickness (26). Because the subjects were healthy volunteers, because each subject was compared to himself, and because heart rate was controlled using atropine, we did not expect changes in wall thickness or heart rate to alter the results. Both the ESPDR and the σ_{es}-$V_{cf,c}$ relationship demonstrate that histamine decreases contractility in this study. Perhaps because these relationships could be defined using almost entirely non-invasive methods a larger sample size of healthy subjects was obtained than in previous studies. Use of the ESPDR and the σ_{es}-$V_{cf,c}$ relationship enabled definition of decreased left ventricular contractility due to histamine that might well have been obscured by methodological constraints in previous studies.

In addition to the analysis based on these measures of contractility, the effect of histamine infusion was compared to an equally hypotensive dose of nitroprusside. Histamine decreased contractility compared to nitroprusside. Increased circulating catecholamines secondary to the hypotension caused by nitroprusside could increase the left ventricular contractile state and shift both the ESPDR and the σ_{es}-$V_{cf,c}$ relationship upward. However, previous workers in the UBC Pulmonary Research Laboratory have shown that histamine infusion results in a 3-fold greater increase in circulating norepinephrine levels than does an equally hypotensive dose of nitroglycerine (154). Similar data are available for nitroprusside (162) (163). Therefore, the catecholamine response to histamine infusion should have increased contractility and shifted the ESPDR and σ_{es}-$V_{cf,c}$ relationships even further upward than the equally hypotensive dose of nitroprusside. Notably this did not happen and instead both the end-systolic pressure-dimension points and the end-systolic σ_{es}-$V_{cf,c}$ points were shifted downward (Figs 14 and 16). This suggests that the myocardial depressant effect of histamine may be substantial; first to overcome a marked increase in circulating catecholamines and then to significantly decrease both measures of contractility.

Most previous studies measuring left ventricular end-systolic pressure-volume relationships show that the slope (E_{max}) of the relationship increases with increasing contractility (24). However, studies of left ventricular end-systolic pressure-dimension relationships show that the dimension intercept also changes when contractility changes (161) (148) as would be expected

on purely mathematical grounds. In this study because a single end-systolic pressure-dimension point was measured after histamine in each subject it is not possible to determine whether the change we observed was due to a change in slope, in dimension intercept, or in both. Nevertheless it is clear that during histamine infusion the left ventricle ejects less completely than it does at equivalent afterload under baseline conditions (baseline ESPDR), and therefore left ventricular contractility is decreased.

Ventricular interaction is not likely to have influenced the measurements. Although pulmonary artery pressures were not measured in this study, histamine has been shown to increase pulmonary artery pressures (148) and therefore might have induced right ventricular pressure overload, shifted the interventricular septum, and thereby impaired left ventricular function. Because two-dimensional cross sectional echocardiograms were used to target our M-mode measurements, we were able to check for any evidence of interventricular septal shift at every set. We observed no evidence of deviation of the interventricular septum and therefore are convinced that it was not an important factor in this study. Furthermore, if such a shift had occurred it would affect the left ventricular diastolic pressure-volume relationship much more than the systolic left ventricular function.

The finding that histamine decreased left ventricular contractility was contrary to my initial hypothesis formulated on the basis of data from other investigators (148) (149). Decreased contractility was probably due to histamine because the other factors which may have been operating either have no effect or instead increase contractility. Catecholamines released by baroreceptor - mediated sympathetic stimulation and by a direct effect of histamine (159) increase contractility. Histamine causes coronary artery dilation in humans (165) which is not likely to have decreased contractility.

The well documented cases of reversibly decreased left ventricular contractility accompanying anaphylaxis (148) (136) (4) are in keeping with our findings for histamine, although we recognise that other allergic mediators, in particular leukotrienes (148), have negative inotropic effects. From our study it is difficult to evaluate the relative importance of histamine compared to these other mediators of anaphylaxis in decreasing left ventricular contractility. However, Correa et al (142) found that the end-ejection diameter did not decrease significantly during antigen-induced anaphylaxis in sensitised dogs, even though blood pressure fell by 30%. During nitroprusside infusion in control dogs Correa et al (142) found that end-ejection diameter decreased by 18% when blood pressure decreased by 31%. Similarly, in this study, during histamine infusion in normal human subjects, end-systolic dimension did not decrease significantly when end-systolic pressure fell by 37% and during control nitroprusside infusion, end-systolic dimension decreased by 18% when end-systolic pressure fell by 38%. Thus the present findings during histamine infusion in humans are very similar to the animal anaphylaxis data, suggesting that histamine is an important, or possibly the main, mediator released during anaphylaxis resulting in decreased contractility.

These results demonstrate that the decreased contractility produced by histamine is mediated, at least in part, via H_1 receptor activation since the H_1 antagonist diphenhydramine

inhibits the effect of histamine on left ventricular contractility. Whether a higher dose of antagonist would have produced complete inhibition was not evaluated. Watkins et al (149) found that selective H_2 stimulation increased left ventricular contractility in humans. Human heart tissue in vitro contains both H_1 and H_2 receptors but the physiological responses have varied. Using atrial biopsy samples, Gristwood et al (166) provided evidence for an H_2 - mediated positive inotropic effect whereas H_1 antagonism had no effect. A similar conclusion was reached by Ginsburg et al (146) using recipient heart tissue from cardiac transplant subjects. The lack of H_1 effects are contrary to the findings of Guo et al (167) who demonstrated decreased contractility related to H_1 receptor activation. These investigators also demonstrated an H_2 mediated positive inotropic effect. Thus, H_1 stimulation decreases myocardial contractility due to direct myocardial activity (167) or due to an indirect non-cardiac H_1 agonist effect which decreases left ventricular contractility via an unknown intermediate. In contrast H_2 receptor stimulation increases myocardial contractility in vitro and in vivo and it is intriguing to speculate that H_2 effects may be mediated by release of norepinephrine from cardiac adrenergic nerves. Although the present study did not evaluate the effects of H_2 receptor inhibition directly, the finding that histamine decreased left ventricular contractility suggests that any positive inotropic function of H_2 receptor activation is overwhelmed by the negative inotropic H_1 activity.

Although systemic hypotension and resultant decreased perfusion to vital organs is the primary concern during anaphylaxis, it is obvious that decreased myocardial contractility would accentuate the problem. Since both of these histamine effects appear to be H_1 dependent, it is rational to include an H_1 antagonist in the treatment regimen of anaphylactic shock. The use of H_2 antagonists during anaphylaxis to prevent adverse cardiovascular responses is controversial (168) (169) (170). Whether H_2 antagonists prevent histamine-induced decreases in left ventricular contractility is not supported by previous studies which show that H_2 receptors may increase contractility (146) (148) (166), and not directly addressed by our finding that H_1 antagonist pretreatment largely abolished the decrease in contractility during histamine infusion.

In conclusion, histamine infusion in healthy human volunteers, in doses adequate to cause supine hypotension, significantly decreases left ventricular contractility by apparent H_1 receptor activation. This decrease in contractility may be an important contributor to decreased left ventricular function reported during human anaphylaxis.

5.3 Septic shock

5.3.1 Cardiac dysfunction during Tumor Necrosis Factor Infusion

J Appl Physiol. 1994;76:1060-1067 (41)

5.3.1 Introduction

Sepsis occurs in about 1% of all hospitalised patients (171) . In 40% of these patients sepsis is complicated by cardiovascular dysfunction leading to septic shock (172) (173). When significant cardiovascular dysfunction occurs, the mortality rate rises from 20 to 30% in sepsis shock (172) (174) to approximately 40 to 70% in septic shock (172) (175). Cardiovascular dysfunction is therefore a critically important feature of sepsis and appears to be related at least in part to the release of a complex cascade of multiple cytokines and other inflammatory mediators of sepsis (175) (176). Tumor Necrosis Factor alpha (TNF - α) is a cytokine with a short half life that is released by macrophages and monocytes early in the mediator cascade of sepsis. TNF - α has been suggested to be important in causing cardiovascular dysfunction (176) (177).

TNF - α has been shown to decrease left ventricular ejection fraction in dogs (177) (110) over a time course similar to the decrease in ejection fraction (7) (178) observed during human septic shock. As shown in figure 17, ejection fraction changes with changes in systolic contractility, diastolic compliance, and afterload. All of these factors change during sepsis and may change after TNF - α infusion. A decrease in ejection fraction could be accounted for by a decrease in left ventricular contractility but could also be accounted for by decreased diastolic compliance, whereas the decrease in afterload that occurs will tend to ameliorate these effects. In studies where end-diastolic volume decreases after TNF - α infusion (179), a decrease in ejection fraction would be expected to occur even in the absence of a change in contractility. Therefore ejection fraction measurements have not fully elucidated the separate effects of TNF - α on systolic contractility, diastolic compliance, and afterload.

It is not known whether the in-vivo effect of TNF - α is direct or whether TNF - α acts indirectly my triggering a multiple cascade of multiple cytokines and other inflammatory mediators (176) that affect the heart. One important study of the cardiovascular effects of TNF - α infusion and of endotoxin clot implantation in dogs(110) demonstrated that both TNF - α and endotoxin did not decrease ejection fraction for two days, long after peak TNF - α blood levels. Indeed endotoxin, which rapidly initiates endogenous TNF - α release, did not decrease ejection fraction at 1 day after infusion. One possible explanation for the delayed effect on left ventricular ejection fraction is that neither TNF - α nor other early mediators of sepsis are myocardial depressant factors in vivo. Instead TNF - α may initiate release of other myocardial depressant factors much further along in the mediator cascade of sepsis. A second possibility is that TNF - α decreases left ventricular contractility early during sepsis, but this decrease is not accurately quantified by ejection fraction due to the concomitant decrease in afterload or change in end-diastolic volume (179).

To address these issues left ventricular contractility was measured using the end-systolic pressure-volume relationship (ESPVR) and its slope (E_{max}) which, among many potential indices of contractility. is the least sensitive to the changes in preload and afterload (37) anticipated to occur.

Likewise the diastolic pressure-volume relationship was measured over a wide range of diastolic volumes. These measurements were repeated hourly for 5 hours after TNF - α infusion in dogs to test the hypotheses that preload and afterload insensitive measures of left ventricular contractility and diastolic compliance change soon after TNF- α infusion.

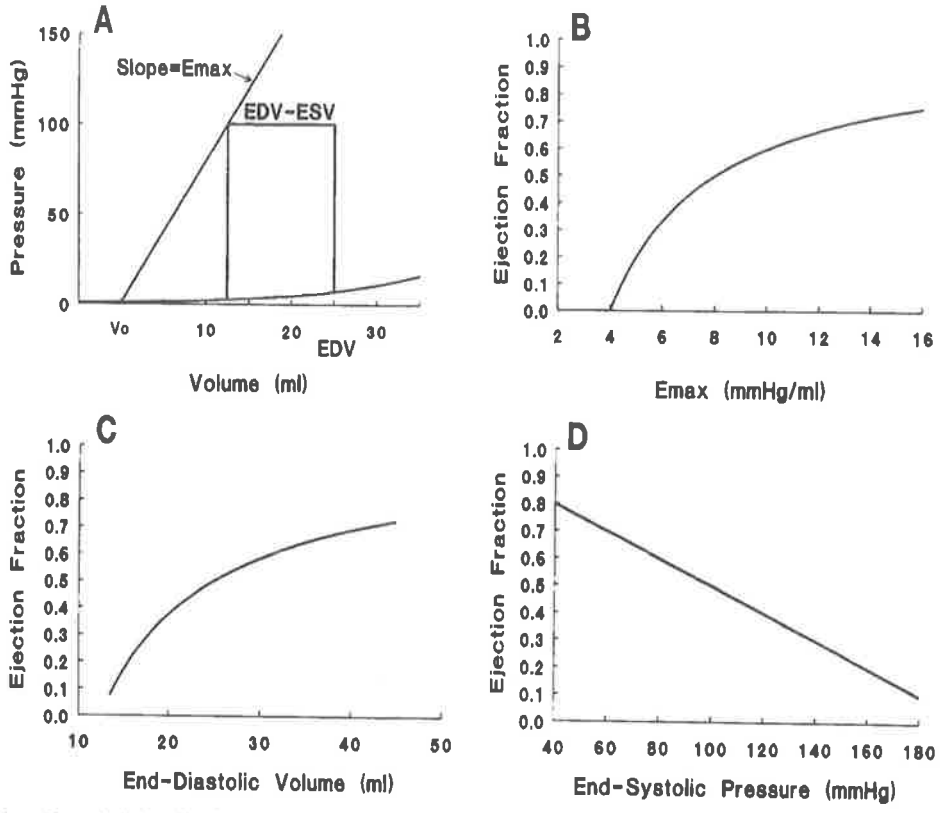

Figure 17. Dependence of ejection fraction on contractility (Emax: B), end-diastolic volume (EDV; C), and end-systolic pressure (D). These relationships were determined from pressure-volume loops in A (typical values from this study) by varying each variable separately. Ejection fraction was calculated as difference between EDV and end-systolic volume (ESV) divided by EDV. Ejection fraction changes as Emax changes. However, influence of EDV and end-systolic pressure are also very important. Therefore, measurement of ejection fraction alone does not fully elucidate separate effects of TNF - α on systolic contractility and diastolic compliance. V_0, volume at zero diastolic pressure.

5.3.1 Methods

5.3.1 Instrumentation

In 12 mongrel dogs (24 ± 4 kg) anaesthesia was induced using thiopentone (20 mg/kg). Anaesthesia was maintained using alpha-chloralose (60 mg/kg) and morphine (5 mg/kg over 1 hour) followed by an infusion of alpha-chloralose (20 mg/kg/hr) and morphine (0.5 mg/kg as needed every hour). Depth of anaesthesia was tested every hour by monitoring heart rate blood pressure, and limb withdrawal response to painful stimuli and was supplemented as necessary. The dogs were intubated and mechanically ventilated and intravenous lines were placed as in (Ch 3.2). A midline sternotomy was performed and ultrasonic crystals placed on the heart as described in (Ch 3.2). A bipolar pacemaker electrode was sutured to the left atrial appendage. The pacing rate was set at approximately 140 beats per minute.

Separate measurements of diaphragmatic function were also made and are reported elsewhere (177). To accomplish this a right lateral thoracotomy was performed through the 7th intercostal space and 2 pairs of ultrasonic crystals and EMG electrodes were inserted onto the costal surface of the diaphragm. To keep the diaphragm at constant length, 1.5 litres of normal saline were instilled into the abdomen through a small midline laparotomy and the abdomen was bound with casting material. The chest remained widely open so that neither the diaphragm nor the lungs compressed the heart.

5.3.1 Left ventricular contractility

Left ventricular contractility was assessed using the ESPVR (Fig 1) and the δ_{ESPVR} (Fig 2) as detailed in Ch (3.2.4). For comparison to other studies reported in the literature dP/dt_{max} and LV ejection fraction were also calculated.

5.3.1 Left ventricular diastolic pressure-volume relationships

The left ventricular diastolic pressure-volume relationship was determined from pressure-volume points during diastasis (42), as in Ch (3.2.5).

5.3.1 Protocol

Following instrumentation, the animals were allowed to stabilise for one half hour. A baseline set of data was measured. A dose of 60 μg/kg of human recombinant TNF - α was then infused over 1 hour in 6 dogs and an equivalent volume of saline was infused over 1 hour in 6 control dogs. Left ventricular end-diastolic pressure was maintained constant between 5 and 8 mmHg in all dogs by normal saline infusion. Typically, in the TNF - α group this required 20 ml/kg normal saline during the first hour and 10-20 ml/kg each hour for the rest of the experiment. Repeat data sets were measured immediately following the TNF - α or control infusion and then hourly for 5 hours.

Measurements at each set included arterial blood gases (Radiometer ABL30, Copenhagen, Denmark), core temperature, right atrial pressure, mean pulmonary artery pressure, mean aortic pressure, and thermodilution cardiac output repeated 3 times at end-expiration. At each set left ventricular pressure and dimension measurements were digitally sampled at 250 Hz for 4 seconds during steady state and during a 2 beat aortic occlusion and at 100 Hz during an 8 second vena caval occlusion. The short duration of aortic and vena caval occlusions were chosen to avoid reflex changes in contractility. At the end of the experiment the left ventricle was excised, weighed, and wet to dry weight ratios of 3 representative samples of myocardium were determined. One sample was taken from the anterior wall, one from the poster-lateral wall and one from the septum. Each sample was transmural and was taken from a site remote from ultrasonic crystal placement.

5.3.1 Data Analysis

Using multivariate general linear hypothesis analysis software (SYSTAT, Evanston, IL) a repeated measures analysis of variance with one grouping factor was used to test the null hypothesis that E_{max} did not change during the seven experimental sets (tested using the first order polynomial) and that there was no difference between the TNF - α and control groups (the grouping factor). A similar analysis was used to test the null hypothesis that diastolic stiffness did not change (S, V_m, and V_0) during the seven experimental sets and that there was no difference between the TNF - α and control groups. When a significant difference was found ($p < 0.05$) changes from baseline to 1 and 5 hours after completion of control or TNF - α infusion were identified using paired t-tests and differences between groups were identified using unpaired t-tests corrected for multiple comparisons using an improved sequentially rejective Bonferroni test procedure (96) (using $p < 0.05$). The same analysis was performed on variables listed in the figures and table to highlight changes in measured parameters. Data are summarised as mean ± standard deviation throughout.

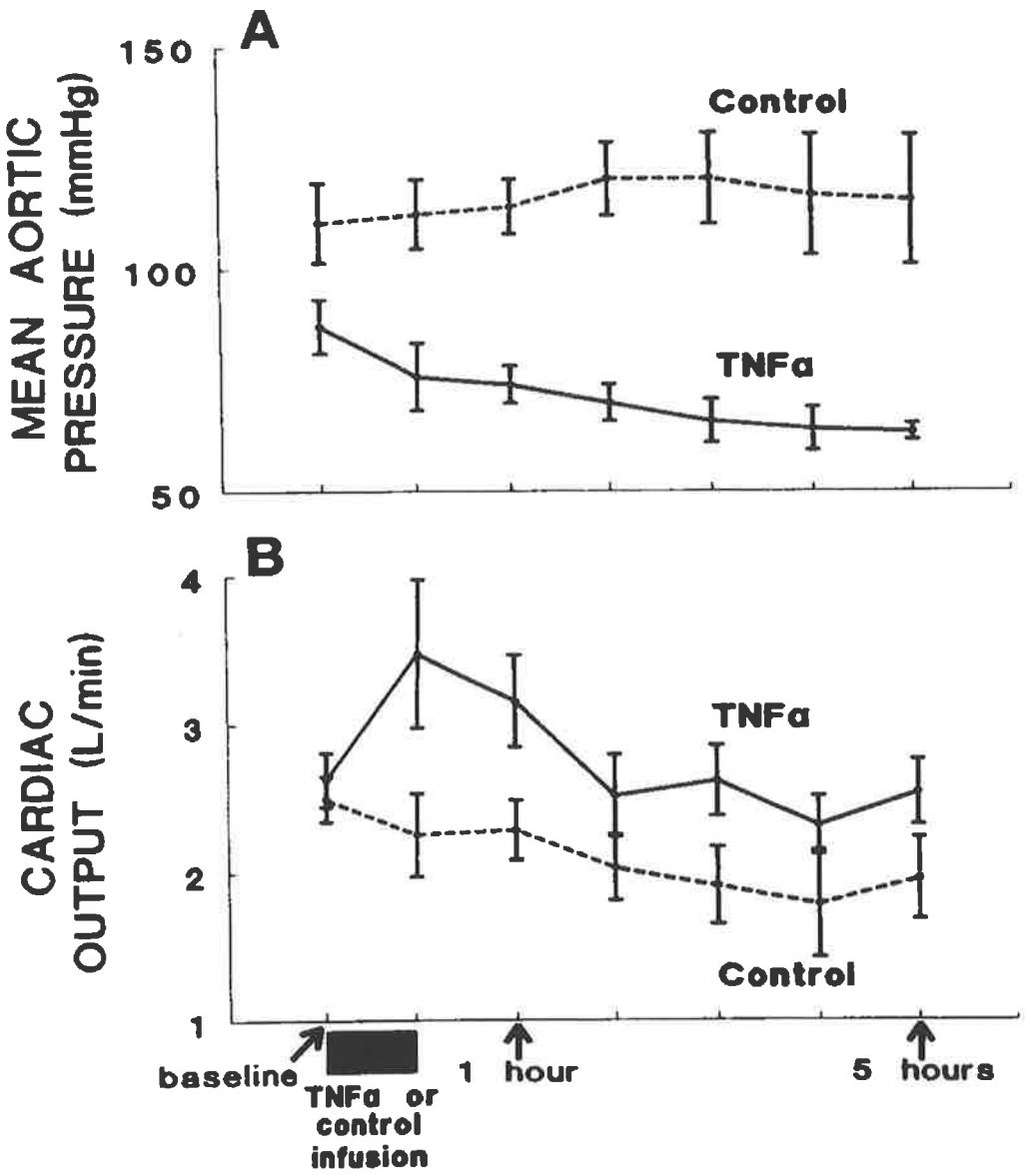

Figure 18. A: mean aortic pressure vs time for TNF - α group and control group. Error bars, SE. Variables are measurement at baseline, TNF - α or control is infused over 1 hr, and measurements are repeated immediately after infusion and hourly thereafter with statistical comparisons at 1 and 5 hr after infusion. Slope of 1st order polynomial is significantly negative in TNF - α group, indicating that mean aortic pressure decreases over course of experiment. Decrease in blood pressure is significant 1 hr after TNF - α infusion and persists throughout experiment. B: cardiac output vs time for TNF - α group and control group. Cardiac output is significantly higher at 1 and 5 hrs after TNF - α infusion than in control group.

5.3.1 Results

At baseline there were no significant differences in haemodynamic variables, measures of left ventricular contractility, or diastolic pressure-volume relationships between the and control groups. Mean aortic pressure at baseline was slightly, but not significantly ($P > 0.23$), lower in the in the control group. The significant difference was that mean aortic pressure decreased over the course of the experiment after TNF - α infusion ($p<0.05$) but did not change after the control infusion. One hour after TNF - α infusion mean aortic pressure decreased by 22%, and this decrease persisted until the end of the experiment ($p < 0.05$) (Fig. 18).

Table 13. Haemodynamic and left ventricular mechanics variables.

	TNF-α			Control		
	Baseline	1 h	5 h	Baseline	1 h	5 h
End-diastolic volume, ml	22.2±3.8	21.4±4.1	22.6±5.8	25.6±7.1	25.1±5.5	23.6±11.7
End-systolic volume, ml	9.0±2.6	8.7±2.7	9.1±3.0	12.2±5.7	13.9±4.2	13.7±8.8
Right atrial pressure, mmHg	10.9±1.9	7.5±1.0	8.8±5.8	13.0±3.8	9.7±2.5	12.2±1.5
Mean pulmonary arterial pressure, mmHg	16.6±5.3	14.8±4.6	16.5±5.8	15.0±2.9	16.0±2.5	17.0±5.1
Maximum dP/dt, mmHg/s	2,210±220	2,090±340	1,530±280*	2,260±560	2,560±850	2,140±360
τ, ms	28.1±7.7	27.3±5.0	26.6±3.9	29.0±4.6	29.4±5.4	31.0±8.5
Ejection fraction, %	58±13	58±17	58±13	53±17	44±13	44±14

Values are means ± SD for 6 tumor necrosis factor-α (TNF-α) and 6 control dogs. dP/dt, rate of change of left ventricular pressure during isovolumic systole; τ, time constant. * $P < 0.05$ compared with baseline.

One hour after TNF - α infusion cardiac output increased by 19% which was significantly greater than the cardiac output after control infusion ($p < 0.05$). Cardiac output remained higher in the TNF - α group than the control group throughout the experiment ($p < 0.05$) . Because right atrial pressure did not change significantly in either the TNF - α or control groups (Table 13) the calculated systemic vascular resistance (the difference between mean blood pressure and right atrial pressure divided by cardiac output) decreased by 38% one hour after TNF - α infusion ($p < 0.05$) and remained decreased, but did not change significantly in the control group. Thus, TNF - α resulted in a hypotensive, hyperdynamic circulation as early as one hour after infusion.

E_{max} decreased significantly after TNF - α infusion ($p < 0.01$) but not after the control infusion (p = NS) (Fig. 19). By one hour after TNF - α infusion E_{max} had decreased by 23% ($p < 0.05$) and by the end of the experiment E_{max} had decreased by 52% ($p < 0.01$). δ_{ESPVR} also decreased significantly after TNF - α infusion ($p < 0.05$) but not after the control infusion (p = NS) (Fig.19).

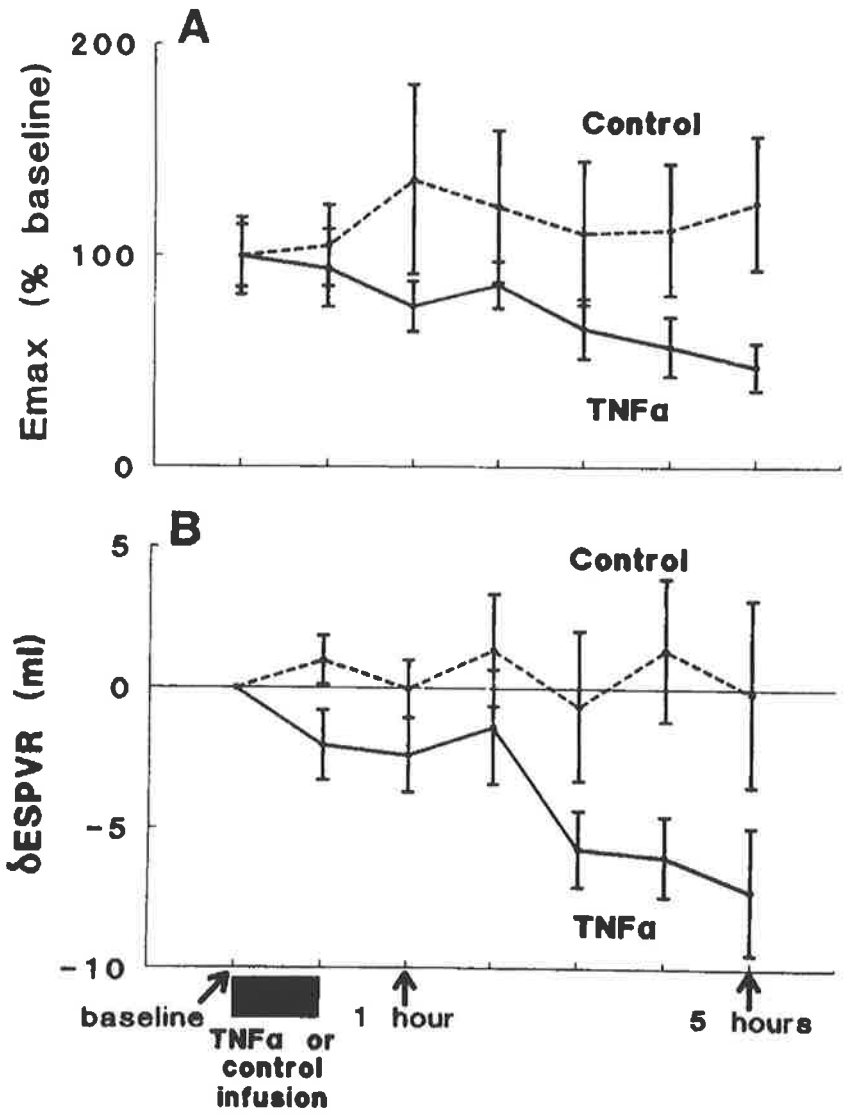

Figure 19. A: E_{max} vs time for TNF - α group and control group. B: δ_{ESPVR} vs time for TNF - α group and control group. Error bars, SE. E_{max} decreases significantly in TNF - α group, as indicated by significant slope of 1st order polynomial ($P < 0.01$); this decrease is significant at 1($P < 0.05$) and 5 ($P < 0.01$) hr after TNF - α infusion. E_{max} does not change in control group. Similarly δ_{ESPVR} decreases significantly in TNF - α group but not in control group.

At the constant left ventricular end-diastolic pressure, end-diastolic volume did not change significantly in either the TNF - α or control groups (Table 13). Left ventricular end-systolic pressure mirrored mean aortic pressure in both TNF - α and control groups, decreasing significantly after TNF - α infusion. Left ventricular end-systolic volume did not change significantly in either the TNF - α or control groups (Table 13). Since there was no change in preload, the decrease in dP/dt_{max} after TNF - α infusion ($p < 0.001$) (Table 13) reflects a decrease in contractility and may partially reflect a decrease in afterload as well. dP/dt_{max} did not change after control infusion (p = NS). While E_{max}, δ_{ESPVR}, and dP/dt_{max} decreased, ejection fraction did not change significantly after TNF - α infusion. (Table 13). Figure 19 illustrates that

ejection fraction does not decrease after TNF - α infusion despite the decrease in E_{max} and δ_{ESPVR} because end-systolic pressure decreases so that end-systolic volume does not change. The diastolic pressure-volume relationship did not change significantly in either the TNF - α or control groups during the experiment. Specifically, there was no change in S, V_m, or V_0 with time and there was no significant difference between the TNF - α and control groups. In addition there was no difference in systolic relaxation measured by tau (Table 13) or disproportionate septal-freewall shortening in either the TNF - α or control groups. Post mortem left ventricular wet-to-dry weight ratios were not different between the TNF - α and the control groups. Thus, myocardial water content was not different between TNF - α (0.78 ± 0.07%) and control (0.81 ± 0.04%) groups.

5.3.1 Discussion

The key new finding of this study was that, within 1 hour, TNF - α infusion results in a hypotensive, hyperdynamic circulation and a significant decrease in left ventricular contractility. These cardiovascular changes persisted, but no change in the diastolic pressure-volume relationship occurred. Because contractility is decreased soon after TNF - α infusion, these results suggest that TNF - α, or more likely, other mediators released very soon after TNF - α, may be myocardial depressant factors of early sepsis. During the course of these measurements, which model the very early stages of fluid resuscitated septic shock, ejection fraction did not decrease because the decrease in afterload allowed stroke volume to be maintained even though left ventricular contractility was decreased.

5.3.1 Mechanism of decreased left ventricular contractility

These results show that TNF - α decreases left ventricular contractility and therefore TNF - α may account for part of the decreased left ventricular contractility observed during human septic shock (7) (178) (31), in whole animal models of sepsis (180), and in isolated myocardial preparations (31).

The mechanism whereby left ventricular contractility is decreased during sepsis is not known and therefore the role of TNF - α is not known. However, it is known that the time course of decreased left ventricular ejection fraction after TNF - α infusion in dogs (110) is similar to that observed in septic humans. Therefore TNF - α may be a very important contributor.

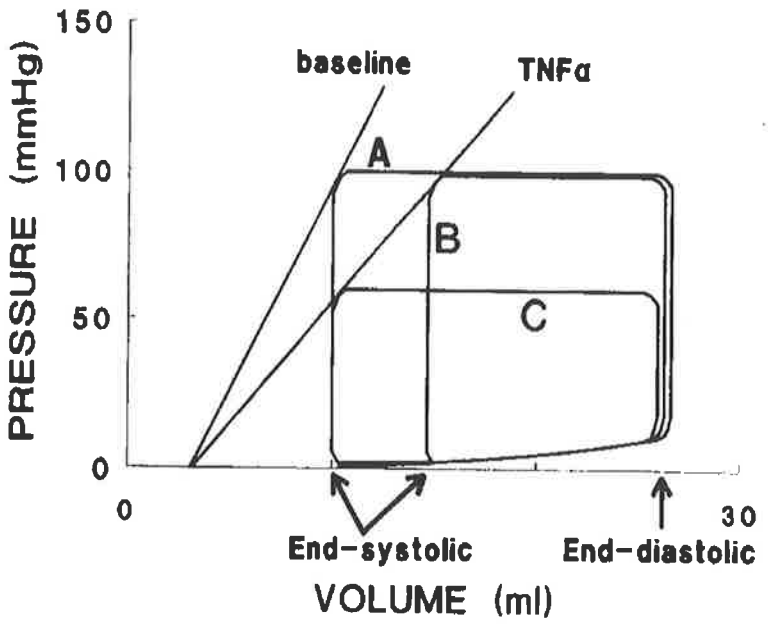

Figure 20. Reason ejection fraction did not decrease in TNF - α group despite decrease in contractility. *Loop A,* stylised pressure-volume trajectory at baseline. When contractility decreases after TNF - α infusion, slope of ESPVR decreases and ESV would increase if afterload were maintained (*loop B*). In this case ejection fraction (difference between EDV and ESV divided by EDV) would decrease reflecting decrease in contractility. However, after TNF - α infusion, afterload decreases (loop C). Because EDV did not change and ESV is now equal to baseline value, ejection fraction does not change despite decrease in contractility.

Preliminary reports suggest that TNF - α may directly decrease myocardial contractility (181). However, a direct myocardial depressant effect of TNF - α cannot be fully accounted for by our results because TNF - α is rapidly cleared from the circulation. TNF - α injected into humans (182) or rats (183) is rapidly cleared with a half life in the range of 0.5 hr. After induction of endotoxemia or bacteraemia in many animal species (175), rapid increase and decrease in circulating TNF - α occur with return to baseline levels within 4-5 hours (173) (184) (182) (185). In this study one would expect that by one hour after the end of the infusion circulating TNF - α levels would be rapidly decreasing and that by five hours after the infusion, when the greatest decrease in left ventricular contractility was observed, TNF - α levels would be very low. Therefore, the decrease in contractility observed at five hours must have been caused by mediators or processes initiated as a result of the TNF - α infusion rather than by TNF - α itself.

A number of mediators released soon after TNF - α potentially could cause the decrease in contractility. Interleukin (IL) -1 serum levels peak at 2 to 5 hours (173) (184) and IL-6 serum levels peak several hours (173) after maximum TNF - α levels after endotoxin infusion. Because both IL-1 and IL-6 cause some of the circulatory manifestations of sepsis in animal models (176) they could contribute to decreased left ventricular contractility. Infusion of IL-1

into dogs (29) did not decrease left ventricular contractility making IL-1 a less likely candidate as a myocardial depressant factor. The cardiovascular effects of TNF - α infusion are diminished by pretreatment with cyclooxygenase inhibitors (186) suggesting a possible role for prostaglandins and thromboxanes. TNF - α induces nitric oxide release, which may contribute to both the vascular abnormality and the decreased left ventricular contractility (172) (187). Indeed, there may be contributions by a number of mediators of sepsis to decreased left ventricular contractility. Because the serum levels of all of these mediators of sepsis rise and fall more rapidly than the 7 to 10 day time course of decreased left ventricular contractility in human sepsis (7) (31) (178) and following TNF - α infusion (179) (110), we suspect that decreased left ventricular contractility is due to a combination of mechanisms comprising the inflammatory response triggered by TNF - α infusion, and not just by TNF - α alone.

Another possibility is that systemic hypotension with coronary hypoperfusion and myocardial ischaemia may have caused decreased left ventricular contractility. We think that this is less likely for several reasons. By measuring coronary venous blood, Cunnion et al (174) and Dhainaut et al (188) have concluded that in humans having septic shock and hypotension there is no evidence of myocardial anaerobic metabolism. In pigs, systemic hypotension alone to a much greater degree than observed here did not result in evidence of myocardial ischaemia and, if anything, increased left ventricular systolic contractility as measured by ESPVR (42). In this study, τ of systolic relaxation which increases during myocardial ischaemia was measured. There was no change in τ. Therefore on the basis of previous findings and the current data, systemic hypotension and coronary hypoperfusion are unlikely to have contributed importantly to the observed decrease in left ventricular contractility.

5.3.1 **Relationship of ejection fraction to contractility**

Kass et al (37) have carefully investigated the preload and afterload dependence of many indexes of contractility, including E_{max}, LV ejection fraction, and maximum dP/dt. E_{max} and other indexes derived from the ESPVR such as δ_{ESPVR}, are least sensitive to changes in preload and afterload. Therefore E_{max} and δ_{ESPVR} were chosen as the principle measures of left ventricular contractility in this study where loading conditions were expected to change. However, particularly in human studies, ESPVR measurements are much more difficult to obtain than radionuclide ventriculography - determined ejection fraction. Thus, ejection fraction has been used frequently in sepsis studies (7) (37) (178) (189). For comparison to these studies and in order to assess the effects of the changes in loading conditions, we also measured ejection fraction. LV ejection fraction did not decrease after TNF – α infusion with volume resuscitation, even though left ventricular contractility decreased, because afterload decreased enough to maintain stroke volume (Fig 20). In this study, volume resuscitation was titrated to maintain a constant LV end-diastolic pressure and volume. Had this not been done, ejection fraction measurements would have decreased as observed by Eichenolz et al. (179). We conclude that

ejection fraction is not a sensitive measure of decreases in contractility during sepsis because afterload decreases and preload changes. Despite these limitations, if ejection fraction decreases in the presence of decreased afterload with no change in preload, then ventricular contractility must be very significantly decreased. It follows that, in studies of sepsis that demonstrate decreased left ventricular ejection fraction (7) (178) the decrease in contractility may be underestimated, and therefore the decrease in ventricular contractility during sepsis may be even more severe than has previously been considered.

5.3.1 Diastole

Diastolic compliance changes during human septic shock (178) (7) and in animal models of sepsis. In some animal models and in humans, administered endotoxin, end-diastolic volumes tend to increase. In contrast, in a canine peritonitis model, Stahl et al observed late but not early increases in diastolic unstressed volume associated with decreased diastolic compliance. Non-survivors of septic shock and septic adult respiratory distress syndrome (189) have relatively normal LV end-diastolic volumes that are much less than the initial end-diastolic volumes of survivors. Thus the change in diastolic compliance during sepsis is complex and may depend on the severity of the septic insult, the degree of volume resuscitation, time, and other factors. For example some degree of hypovolaemia and hypotension often accompany septic shock, and hypovolemic shock has been shown to decrease LV diastolic compliance (42). Therefore one conceivable explanation for the difference between non-survivors and survivors of septic shock is that the usual response of decreased diastolic compliance in septic shock may be prevented in severe septic shock by a greater contribution of hypovolemic shock pathophysiology. The balance between septic mechanisms resulting in increased end-diastolic volume and hypovolemic pathophysiology causing decreased diastolic compliance could conceivably also account for the results of Stahl et al.

On the basis of the literature, we expected either increased diastolic compliance, or because our animal model was designed to mimic severe septic shock, no change or even decreased diastolic compliance. Possible mechanisms of decreased diastolic compliance during sepsis that we tested for were myocardial oedema due to inflammation, and right-to-left septal shift due to pulmonary hypertension. There was no change in the left ventricular diastolic pressure-volume relationship after TNF - α infusion. Wet-to-dry weight ratios and myocardial water content were not different between the TNF - α and control groups and disproportionate shortening of the septal-freewall diameter did not occur.

The difference between the lack of change in diastolic compliance observed here and the decreased diastolic compliance observed in non-survivors in human sepsis studies (178) (189) may reflect a number of differences between this animal study and human sepsis. In particular it may be that changes in diastolic compliance take much longer to develop than the time course of this acute study. In this study, changes in diastolic compliance do not occur as rapidly as the

decrease in left ventricular systolic contractility, consistent with the study of Stahl et al. (190), who found late but not early changes in diastolic compliance. Given the limitations in extrapolating these data to human sepsis, it follows from these data that the mechanism of decreased left ventricular contractility and the mechanism of decreased diastolic compliance are likely to be different.

5.3.1 Limitations in extrapolating these data

This experiment was designed to determine whether TNF - α altered systolic contractility and diastolic compliance within hours of infusion. Out of the large set of inflammatory mediators of sepsis only TNF - α was infused. Thus, this is not a model designed to mimic the more complex human condition of sepsis and may not model closely the changes in cardiac function in other septic animal models or in septic humans. This may account for the differences between diastolic compliance changes observed in human sepsis studies and the lack of change observed in this study. Our results apply only to the very early stages of the septic process, whereas human clinical studies document diastolic abnormalities days after the initial septic insult. Although these results depend on the difference between TNF - α and control groups, which were identically instrumented, a number of methodological issues arise in this highly instrumented animal model. The anaesthetic agents and surgical preparation used conceivably could have contributed to the findings. For example, cardiac output decreased over time, in the control group. However the same anaesthetic agents were used in the TNF - α and control groups, so that the difference between these groups is not explained by the anaesthetic agents. The fact that the chest was held widely open in this animal model makes it quite different from human sepsis. Lack of pericardial and chest wall constraint decreases the coupling between right ventricular and left ventricular mechanics, particularly at the relatively low pressures of diastole. Thus, right to left septal shift, which could contribute to decreased diastolic compliance (or prevent increased diastolic compliance) in severe human septic shock, could be missed in this animal model. Another problem is that if myocardial volume had changed during the course of the experiment, then the LV volume estimates would have been affected. We did not find a difference in post mortem wet-to-dry weight ratios or in myocardial weight. Therefore, it is unlikely that this accounts for the results. Finally, in the acute animal preparation, instrumentation alone will induce TNF - α release which may decrease the response to subsequent TNF - α infusion (191) as early as one hour after first exposure. Thus the early decrease in contractility observed here may be less than that observed after exposure to TNF - α for the first time.

5.3.1 Summary

In conclusion, TNF - α results in a hypotensive, hyperdynamic circulation and decreased left ventricular contractility soon after infusion. Diastolic compliance did not change. Ejection fraction did not decrease because afterload decreases enough to maintain stroke volume. Because contractility decreases early, TNF - α or other mediators such as nitric oxide or IL-6, which are released soon after TNF - α, may be myocardial depressant factors.

Chapter 6

HYPOVOLEMIC SHOCK

6.1 Cardiac dysfunction during hypovolemic shock in pigs

Am J Physiol 1991;260:H702-H712 (42)

6.1 Introduction

Cardiovascular collapse during hypovolemic shock is primarily due to loss of intravascular volume. However it has also been reported that left ventricular function may be impaired after a period of severe hypovolemic shock (192) (193) (194) (195). The cause of impaired ventricular function is however not clearly established. This is important because impaired ventricular function during hypovolemic shock may explain why mortality rates remain high (196) and why shock becomes irreversible after several hours (195) (197) (198) (32) when resuscitation with fluid and blood fails to restore normal cardiovascular function. Generally, left ventricular function depends on both systolic contractility and the diastolic pressure-volume relationship (49) (199). Specifically in hypovolemic shock, impaired left ventricular function has most commonly been thought to be due to decreased systolic contractility (200) (201) possibly due to ischaemia (200) (202) or to a myocardial depressant factor of hypovolaemia (192) (203) (204). However, other studies have found little evidence of ischaemia (205) (205-207) or depressed systolic contractility from any cause (208) (209). Forrester et al. (203) report a confusing dissociation between impaired ventricular function and increased contractility within the same data, they believe due to competition between stimulating catecholamines and a myocardial depressant factor. Whether altered diastolic pressure-volume relationships impair left ventricular function in hypovolemic shock is uncertain. One group (208) (210) has found evidence of increased LV diastolic stiffness, although their single LV dimension data do not exclude shape changes of the ventricle, such as septal shift, as the explanation for their findings. In contrast, another group reports no change in diastolic compliance (211). Finally, altered cardiovascular function has been suggested to be due to peripheral vascular changes (209) (212) instead of cardiac abnormalities.

During the design of this study it was reasoned that the cause of impaired left ventricular function could be more clearly identified by measuring the effect of hypovolemic shock on all of the basic determinants of left ventricular function: diastolic and end-systolic pressure-volume relationships, aortic pressure, and heart rate. The left ventricular function curve, here defined as the relationship between left ventricular input (end-diastolic pressure) and output (cardiac output) can be calculated from, and is therefore uniquely defined by, these basic determinants (Fig. 4). It became clear that aortic pressure and heart rate were less important determinants in this setting so that, essentially, we sought to determine whether decreased ventricular function was caused by increased diastolic stiffness or decreased systolic contractility.

In a porcine model diastolic stiffness was assessed during hypovolemic shock by measuring left ventricular pressure-volume points during diastasis and by fitting a logarithmic equation to these points (51). This equation has been proposed to be superior to previously used exponential equations (213) (214) because it provides a better fit at low volumes and pressures and because its fitted parameters can be interpreted simply as maximum left ventricular diastolic volume, equilibrium left ventricular diastolic volume at zero pressure and a material property of the myocardium. Systolic LV contractility was assessed during during hypovolemic shock by measuring end-systolic pressure-volume points during a vena caval occlusion and during brief aortic cross clamping to define the end-systolic pressure-volume relationship (ESPVR). The ESPVR is least sensitive to changes in preload and afterload (37), an essential characteristic for this study of hypovolemic shock. The relationship between stroke work and end-diastolic volume has also been proposed as an index of contractility that is independent of preload and insensitive to changes in afterload (49); however, the limitations of this index of contractility have not been as clearly defined as those of the more extensively studied ESPVR(215) (216). Nevertheless, we computed this index from our data and found that it supports the conclusions derived from the ESPVR but is somewhat less sensitive to changes in contractility in this setting.

Consistent with previous studies, during prolonged hypovolemic shock profound depression in left ventricular function was observed. Surprisingly however, enhanced systolic contractility was measured at the same time. The depressed left ventricular function was completely accounted for by marked diastolic stiffness. The shape of the diastolic pressure-volume relationships suggests that diastolic stiffness was increased by a decrease in maximum and equilibrium left ventricular diastolic volumes, but the myocardial muscle stress-strain characteristics had not necessarily changed.

6.1 Methods

6.1 Instrumentation

In this study, six pigs (22 ± 2 kg) were induced using ketamine (10 mg/kg i.m.) and subsequently using thiopentone (10-20 mg/kg iv). Anaesthesia was then maintained using α-chloralose (80 mg/kg iv followed by 25mg/ kg/hour infusion) and morphine (5 mg/kg iv followed by supplemental doses as necessary). The pigs were paralysed using pancuronium (0.1 mg/kg iv and supplemented as necessary) to avoid reflex respiratory muscle movement during hypovolemic shock. Mechanical ventilator settings, vascular catheters, thoracotomy, ultrasonic crystal placement, left ventricular Millar catheter placement were done as in previous studies and as described in Ch (3.2).

6.1 Systolic and diastolic pressure-volume relationships

As before, the left ventricle was assumed to be approximately an ellipsoid and the approximately orthogonal diameters were measured by the ultrasound crystals, to estimate left ventricular volume (V) as:

$$V = \pi/6 \times D_{ap} \times D_{long} \times D_{sf} - V_{myo} \qquad \textit{(Equation 2)}$$

where V_{myo} is the volume of myocardium included by the placement of ultrasonic crystals. V_{myo} correlates with, but does not exactly equal, the measured volume of the postmortem myocardium (18) (25) and therefore the value of V_{myo} could not be determined exactly. Thus, in this study, we tested only for *changes* in left ventricular chamber volume that are accurately detected using this approach (18) (25). Absolute volumes based on a "best estimate" of V_{myo} are reported to illustrate the relative size of the changes in chamber volume that we observed. At the start of each experiment V_{myo} was estimated for each animal using the previous observation in intact and isolated hearts that the volume axis intercept of the ESPVR is a relatively constant value of 6 ml/100 g LV weight above zero chamber volume (25) (215, 216). At the start of the experiment, before any experimental interventions, it follows from (Eq. 1) that 0.06 x LV weight = the ultrasonic crystal measurement of the volume axis intercept of the ESPVR - V_{myo}. Therefore, a best estimate V_{myo} can be calculated.

The ESPVR was determined in this study as previously described. The relationship between stroke work and end-diastolic volume has been proposed to be an additional measure of intrinsic myocardial performance that is potentially independent of loading, geometry, and heart rate (49). Following recommendations of the reviewers for *Am J Physiol* this relationship was therefore also determined exactly as described by Glower et al. (49) from pressure volume data measured during all vena caval occlusions. Both the slope and intercept of this relationship changed during the experiment. Therefore, to compare the different experimental conditions, the value of LV stroke work was calculated at a single typical end-diastolic volume of 25 ml above V_d (average diastolic volume for all sets was 24.5 ml).

The left ventricular *diastolic* pressure volume relationship was determined by best fit (Quasi-Newton non linear best fitting procedure, SYSTAT, Evanston, IL) of points from diastasis using:

$$P = S \times I_n [(V_m - V)/(V_m - V_0)] \qquad \textit{(equation 3)}$$

where S, V_m, and V_0 are parameters determined by the best fit procedure (51). *Equation 3* has distinct advantages over the previous use of exponential equations (211) (212). In particular, the diastolic pressure-volume relationship at low volumes and negative pressures are inadequately described by current exponential equations (51). Furthermore, as illustrated in (Fig. 22), the best fit parameters can be readily interpreted in physiological terms. Specifically, V_m represents the

maximum volume that is approached asymptotically as pressure rises, the yield volume of the diastolic left ventricle. V_0 is simply the equilibrium diastolic volume at which pressure is zero. Finally, S is suggested to be a size-independent chamber stiffness parameter having the units of stress (51).

To obtain the best representation of the relaxed diastolic pressure-volume relationship diastolic points from diastasis were chosen from beats spanning a wide range of diastolic volume. To ensure that the diastolic pressure-volume points lie on the relaxed diastolic pressure-volume relationship (51) (52) diastolic pressure-volume points were included starting five exponential pressure decay time constant periods, tau (calculated as τ_D in (50), after end systole (defined as the point of maximum elastance) and diastolic pressure-volume points occurring during atrial contraction were excluded. To obtain a wide range of data along the volume axis, diastasis from two steady-state beats, four vena caval occlusion beats, and two aortic clamp beats were included. To further broaden the spread of data along the volume axis, and thereby optimise the fitting procedure, diastolic data from the two data sets at the start of the experiment (both before and after haemorrhage) were combined and compared with the two data sets at the end of the experiment (both before and after volume resuscitation) (Fig. 3).

6.1 Ventricular function curves

To determine the left ventricular function curve from the diastolic and end-systolic pressure-volume relationships, afterload, and heart rate at each experimental condition, cardiac output for a range of end-diastolic filling pressures (Fig. 4) was calculated. First, the end-diastolic volume for a given filling pressure was determined from the diastolic pressure-volume relationship. Then, the end-systolic volume was determined from the end-systolic pressure-volume relationship and the pressure afterload. Stroke volume is the difference between end-diastolic and end-systolic volume. Finally, cardiac output is heart rate times stroke volume. Repeating this calculation, using the same diastolic and end-systolic pressure-volume relationships as well as constant pressure afterload and heart rate, for many different end-diastolic filling pressures within the experimentally observed range, the ventricular function curves were generated (Figs. 4 and 5).

6.1 Experimental protocol.

After instrumentation, the animals were allowed to stabilise for 0.5 hour. A baseline set of data was collected *(set 1)*. The animal was then bled to a mean aortic pressure of 50 cm H_20. Shed blood was anticoagulated using heparin and chilled on ice. Before any reinfusion the blood was warmed to body temperature. After a 10-min stabilisation period a second set of data was collected in this hypovolemic state *(set 2)*. After this, the animals were maintained at a

mean aortic pressure of 50 cmH_20 by occasional small phlebotomy or reinfusion of shed blood. After 6-8 hours I repeatedly needed to reinfuse blood to maintain mean aortic pressure. As suggested by previous authors (192) (195), haemorrhagic shock could not be maintained at this level when >15% of the shed blood was retransfused. When this critical 15% retransfusion point was reached or when 8 h were reached, a data collection *(set 3)* was repeated. The pigs were then volume resuscitated with all remaining shed blood, and after a 10-min stabilisation period a final data collection *(set 4)* was done.

Data collected at each set included arterial blood gases (Radiometer ABL30, Copenhagen), haematocrit, arterial lactate (enzymatic determination, Sigma Chemical), and temperature. At each set, aortic pressure, left ventricular pressure, ultrasonic crystal diameters, and thermodilution cardiac output (repeated 3 times) at end expiration were also measured. Left ventricular pressure and diameters were sampled during steady state, during a one-beat aortic cross clamp repeated twice, and during an 8-sec vena caval occlusion.

In preliminary experiments we found that greater levels of haemorrhage and lower mean aortic pressures resulted in an unstable preparation with animals dying from arrhythmia's before completion of the experiments. Preliminary experiments also verified previous authors' reports of irreversible shock rapidly leading to death if fluid resuscitation was not initiated when >15% of the shed blood was reinfused (195) (198). In preliminary experiments worsening bradycardia indicated imminent cardiovascular arrest. As a result, three of the six pigs received atropine (1 mg iv) or adrenaline (maximum 0.5 mg iv) to increase heart rate during a bradycardic episode. Experimental measurements were not made for at least 0.5 hr after any drug administration.

6.1 Time and anaesthesia controls

Two additional animals were instrumented exactly as described above, bled to a mean pressure of 50 cmH_20, but then, after *set 2,* immediately reinfused with all shed blood. They were then observed for 8 hr to rule out major time or anaesthesia-related changes in the surgical preparation. Over the course of an 8-hr period there was no significant changes in the ESPVR, in diastolic stiffness, or in haemodynamics.

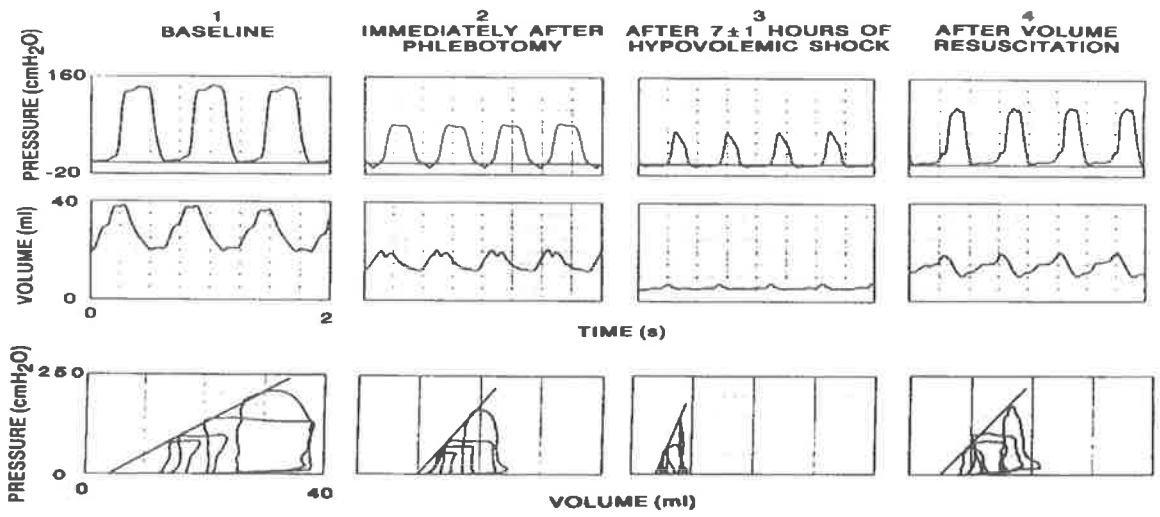

Figure 21. Pressure vs time and volume vs time are illustrated in top 2 rows for al 4 experimental conditions in 1 representative pig (same pig as in Figs 3 and 5). Pressure vs volume for 1 beat of this steady state data plus 1 aortic clamp beat and 2 vena caval occlusion beats is shown in bottom row. ESPVR (determined from 8 beats) is shown and shifts to left after onset of hypovolemic shock. Therefore compared with baseline, systolic contractility increases and remains increased after volume resuscitation.

6.1 Data analysis

A repeated measures analysis of variance was used to test the null hypothesis that E_{max} and V_d did not change during the four experimental sets. The same analysis was used to test the null hypothesis that diastolic stiffness did not change from before *(sets 1* and *2)* to after *(sets 3 and 4)* the period of hypovolemic shock. Specifically, the parameters S, V_m and V_0 were tested for changes. When a significant difference was found ($P < 0.05$) individual differences between sets were identified using a *t* test corrected for multiple comparisons using an improved sequentially rejective Bonferroni test procedure (96) $P < 0.05$). The same analysis was done on variables listed in tables and figures to highlight changes in measured parameters. Data are summarised as means ± SD throughout.

6.1 Results

Complete results in one representative pig are shown in Figs. 3-5 and 21-22 to demonstrate how the measurements and calculations were made and to illustrate typical findings. On average in all six pigs ventricular function was enhanced 10 min after phlebotomy *(set 2*) to a mean aortic pressure of 50 cmH_20 (Fig. 5). Left ventricular end-diastolic pressure decreased from 8.7 to 1.0 cmH_20 ($P < 0.01$) associated with a decrease by one-half of end-diastolic volume ($P <$

0.01). Heart rate increased by 26% ($P < 0.01$), and cardiac output decreased by 43% ($P < 0.01$) so that stroke volume decreased 54% ($P < 0.01$) (Table 14). The ESPVR was shifted to the left (Figs. 21 and 23 and Table 15, conventionally interpreted as enhanced contractility, by an increase in E_{max} from 7.9 to 11.3 cmH_20/ml ($P < 0.05$) with no change in V_d. Stroke work at a diastolic volume of 25 ml increased but not significantly (Fig. 22 and Table 14).

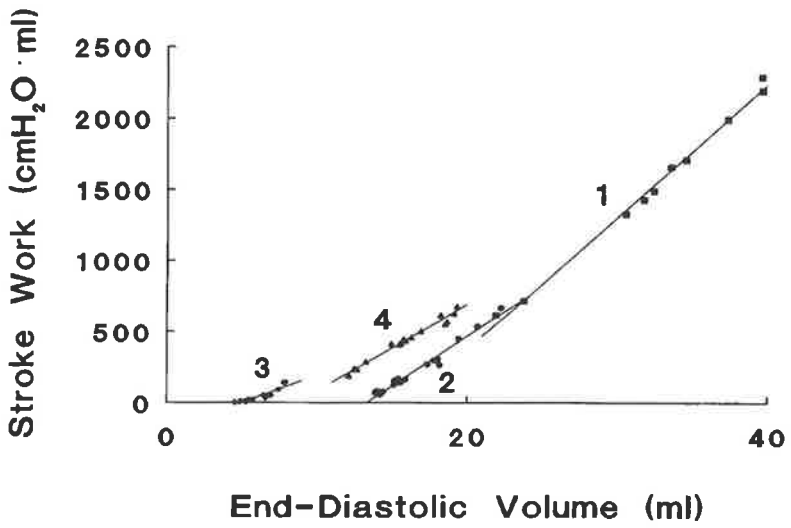

Figure 22. Relationship between stroke work and end-diastolic volume for each of 4 experimental sets is shown for 1 representative pig (same pig as in Figs 3, 5, 21). Individual points comprising each of 4 lines are measured from single beat during vena caval occlusion. Relationship is shown to shift to left after onset of hypovolemic shock indicating that ventricle generates greater stroke work than extrapolation of baseline set 1 line would have predicted. In particular at average end-diastolic volume of 25 ml (all animals) stroke work increased from baseline to sets 2-4 (P=NS). This index is consistent with but not as sensitive as ESPVR in detecting increased systolic contractility during hypovolemic shock.

At the end of 6-8 hours of haemorrhagic shock *(set 3),* left ventricular function was impaired (Fig. 5). Mean arterial pressure remained low and end-diastolic volume decreased by one half compared with its value immediately after phlebotomy despite a rise in end-diastolic pressure to 9.2 cmH_20 (Table 14). Heart rate remained elevated and cardiac output decreased by one-half again so that stroke volume decreased to 31% of the baseline value ($P < 0.01$). The ESPVR was significantly left-shifted compared with baseline by an increase in E_{max} to 18.5 cmH_20/ml ($P < 0.05$) and by a decrease in V_0 of 3.9 ml compared with baseline (P = NS) (Figs. 21 and 23 and Table 15). This increase in contractility was also reflected by an increase in the stroke work at an end-diastolic volume of 25 ml (Fig. 22 and Table 14), although this increase was not significant because the variability of this measurement was large.

Table 14. *Left ventricular mechanics and haemodynamics in 6 pigs*

	Set 1	*Set 2*	*Set 3*	*Set 4*
Heart rate, beats/min	112±8	141±16†	147±18†	132±10†
Mean arterial pressure, cmH_2O	131±23	58±14†	39±7†	47±14†
End-diastolic pressure, cmH_2O	8.7±6.9	1.0±2.4†	7.2±10.7	20.3±6.1†
End-diastolic volume, ml	44.8±8.6	20.6±4.2†	10.6±8.7†	21.8±8.4†
Cardiac output, l/min	2.5±0.6	1.5±0.2†	1.0±0.4†	1.5±0.4†
Stroke volume, ml	22.4±4.7	10.4±1.7†	6.9±2.5†	11.3±3.0†
Stroke work at diastolic volume of 25 ml, cmH_2O/ml	850±630	1,050±420	1,310±890	1,240±680
τ, ms	42.2±9.8	41.2±7.1	36.7±21.1	42.6±11.0

Values are means ± SD. *Set 1*, baseline; *Set 2*, immediately after phlebotomy; *Set 3*, after 7 ± 1 h of hypovolemic shock; *Set 4*, after volume resuscitation. Different from *set 1*, † $P < 0.01$.

Volume resuscitation from this shocked state *(set 4)* confirmed the presence of impaired left ventricular function (Fig. 23). Aortic pressure rose only to 47 cmH_2O ($P < 0.01$ compared with baseline). End-diastolic pressure rose dramatically to more than double its baseline value ($P < 0.05$), although end-diastolic volume remained less than one-half of its baseline value ($P < 0.01$) (Table 14). Cardiac output and stroke volume increased slightly but remained decreased compared with baseline ($P < 0.01$) (Table 14). The ESPVR shifted rightward after volume resuscitation but was still to the left of the baseline ESPVR (Figs. 21 and 23 and Table 15) due to increased E_{max} ($P < 0.05$). Stroke work at an end-diastolic volume of 25 ml changed in the same direction as E_{max} indicating increased contractility, but these changes were not statistically significant (Fig. 22 and Table 14). Thus markedly impaired left ventricular function (high diastolic pressures with low aortic pressure and low cardiac output) was not accounted for by depressed systolic contractility.

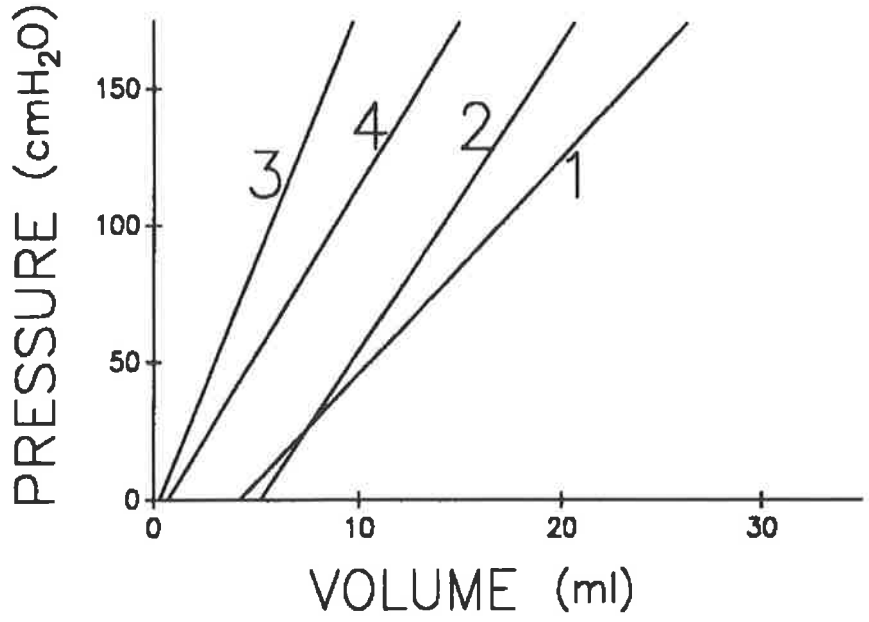

Figure 23. Average ESPVRs (n=6 pigs) are illustrated at all 4 sets using same axes as Fig 4. ESPVR shifts to left from baseline (line 1) to immediately after phlebotomy (line 2) due to increase in slope ($P < 0.05$). ESPVR shifts further to left after period of hypovolemic shock (line 3). After fluid resuscitation (line 4) ESPVR is still left shifted compared with baseline (line 1) ($P < 0.05$), conventionally interpreted as enhanced contractility.

The diastolic pressure-volume relationship after the period of haemorrhagic shock (sets 3 and 4) was shifted significantly to the left and upward compared with before a period of shock (sets 1 and 2), a marked increase in diastolic stiffness (Figs. 3 and 24 and Table 16). The change in diastolic stiffness resulted in a 23.0-ml decrease in end-diastolic volume compared with baseline ($P < 0.01$) accounting for all of the decrease in stroke volume. As determined by fitting the diastolic pressure-volume points to *Eq. 2,* the V_m decreased by 52% ($P < 0.01$) and the V_0 decreased by 57% ($P < 0.01$) (Table 16). There was no significant change in S (Table 16), although the power of this data to exclude a significant change in S is low.

Table 15. *End-systolic pressure-volume relationships in 6 pigs*

Pig	*Set 1*		*Set 2*		*Set 3*		*Set 4*	
	E_{max}	V_d	E_{max}	V_d	E_{max}	V_d	E_{max}	V_d
1	7.6	4.1	15.9	10.0	38.2	4.2	15.9	5.1
2	10.4	3.9	11.2	0.8	19.3	3.2	13.2	1.3
3	4.3	4.3	5.7	6.1	12.7	−18.3	7.5	−5.9
4	7.8	4.5	12.8	7.3	15.7	4.0	16.2	3.1
5	10.0	4.7	13.6	6.9	15.6	1.2	13.4	6.8
6	7.5	3.9	8.3	0.0	9.6	7.7	7.4	−6.1
Means ± SD	7.9±2.2	4.2±0.3	11.3±3.7*	5.2±3.9	18.5±10.2*	0.3±9.4	12.3±3.9*	0.7±5.5

Values are means ± SD in cmH_2O for slope (E_{max}) and ml for volume axis intercept (V_d). See Table 1 for set descriptions. Different from *set 1*, * $P < 0.05$.

Table 16. *Diastolic pressure-volume relationship parameters in 6 pigs*

Pig	*Sets 1* and *2*				*Sets 3* and *4*			
	Before prolonged hypovolemic shock				After 7 ± 1 h of hypovolemic shock			
	S	V_m	V_o	$(V_m - V_o)V_o$	S	V_m	V_o	$(V_m - V_o)V_o$
1	−22.7	53.2	17.0	0.68	−8.1	19.4	8.0	0.59
2	−5.4	40.8	24.7	0.39	−24.2	24.3	15.6	0.36
3	−8.9	61.3	34.4	0.44	−7.9	25.9	21.1	0.19
4	−5.1	55.7	22.8	0.59	−16.8	20.9	3.0	0.86
5	−10.5	73.5	35.7	0.51	−5.4	35.0	16.6	0.53
6	−8.9	52.1	30.2	0.42	−12.6	49.8	29.1	0.42
Means ± SD	−10.2±6.5	56.1±10.8	27.5±7.2	0.51±0.11	−12.5±7.0	29.2±11.5†	15.6±9.3†	0.49±0.23

Values are means ± SD in cmH_2O for stress (S) and ml for maximum volume (V_m) and equilibrium volume (V_o). *Sets 1* and *2*, before prolonged hypovolemic shock; *sets 3* and *4*, after 7 ± 1 h of hypovolemic shock. Different from *sets 1* and *2*, † $P < 0.01$.

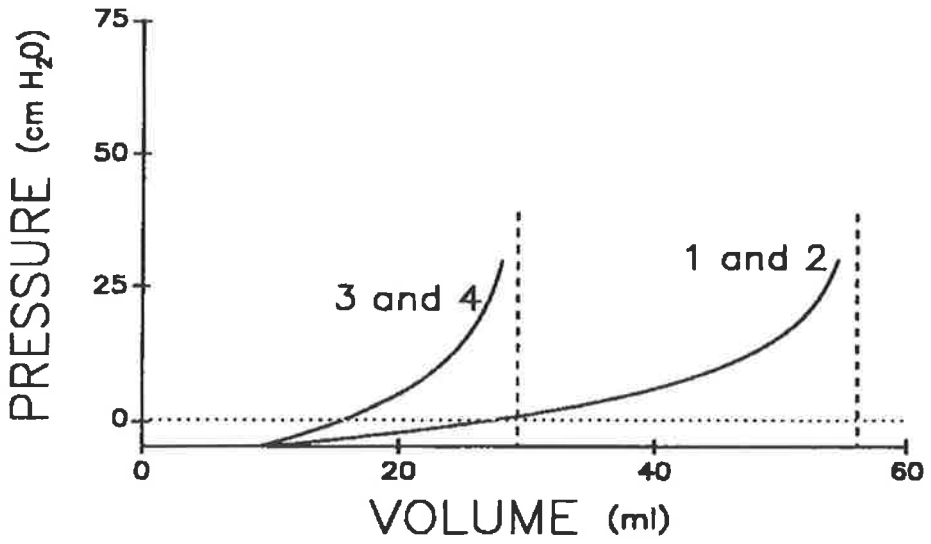

Figure 24. Average diastolic pressure-volume relationships (n = 6 pigs) are illustrated comparing data before, (sets 1 and 2) and after prolonged period of hypovolemic shock (sets 3 and 4). Diastolic left ventricle is much stiffer after period of shock due to decrease in equilibrium volume (intersection of smooth curves and horizontal dotted zero pressure line), and to decrease in maximum volume (asymptotically approached vertical dashed lines).

Table 17. *Variables related to arterial blood gas measurements in 6 pigs*

	Set 1	*Set 2*	*Set 3*	*Set 4*
pH	7.42±0.03	7.40±0.04	7.12±0.04†	7.03±0.07†
P_{CO_2}, mmHg	39±3	39±3	42±4	46±7
P_{O_2}, mmHg	360±40	320±100	300±20	270±140
Lactate, mmol/l	0.9±0.4	2.4±0.8*	10.4±4.6†	10.5±4.3†
Hematocrit, %	28±4	26±3	25±3	27±5

Values are means ± SD. See Table 1 for set description. Different from *set 1*, * $P < 0.05$, † $P < 0.01$.

Systemic vascular resistance was no different after the period of haemorrhagic shock [32 ± 10 $cmH_20/(l/min)$ at set 3] compared with the start of haemorrhagic shock [34 ± 13 $cmH_20/(l/min)$ at set 2] suggesting no marked change in arterial tone during the period of haemorrhagic shock. There was no significant change in the rate constant of r during hypovolemic shock (Table 14), although after a period of haemorrhagic shock the variability of r increased, possibly reflecting decreased accuracy of the measurement at high heart rates and low pressures. Arterial pH decreased due to a mounting lactic acidosis during hypovolemic shock (Table 17). Whole body oxygen delivery decreased in parallel with cardiac output because arterial Pa_{O2} and haematocrit did not change. Minute ventilation required to maintain Pa_{CO2} decreased during haemorrhagic shock suggesting that CO_2 production decreased. Because the ratio of CO_2 production to oxygen consumption did not decrease during shock it follows that whole body oxygen consumption also decreased.

These data taken together show that during hypovolaemia the pigs were below the critical level of oxygen delivery needed to maintain aerobic metabolism, thereby fulfilling the definition of shock.

6.1 Discussion

These results confirm that impaired left ventricular function develops during a period of hypovolemic shock. However, impaired left ventricular function was not due to decreased systolic contractility because the ESPVR shifted to the left, conventionally interpreted as enhanced contractility. Instead, the main finding was that the diastolic pressure-volume relationship shifted dramatically up and to the left indicating a much stiffer diastolic ventricle (Fig. 24). This increase in diastolic stiffness accounts for all of the observed decrease in stroke volume and therefore for all of the depression in left ventricular function. These findings shift the focus of understanding and treating impaired left ventricular function during hypovolemic shock to diastole.

6.1 Effect of hypovolemic shock on systolic contractility

We tested for changes in systolic contractility using the ESPVR and also using the relationship between stroke work and end-diastolic volume. Even though the ESPVR is not a perfect index of contractility (47), it is the least sensitive of all available indexes of contractility to changes in preload and afterload (37). It is also one of the basic determinants of left ventricular function and is therefore particularly useful in this study of hypovolemic shock. The relationship between stroke work and end-diastolic volume has also been proposed to be potentially independent of loading, geometry, and heart rate (49) (199). The present use of these relatively load independent measures of contractility may explain a number of apparent

discrepancies in and among previous studies. That is, the data confirm that left ventricular function is decreased after a period of severe haemorrhagic shock (192) (193) (194) (195) despite increased systolic contractility (203) (205) (208). Although these results may have been interpreted as discrepant we suggest that they are not and instead are accounted for by increased diastolic stiffness. The confusing finding of Forrester et al. (203) that there was an association between cardiac function and measures of contractility is now easily understood as the effect of increased diastolic stiffness and does not require their difficult hypothesis that their results were due to a complex competition between catecholamines enhancing function and a factor depressing myocardial contractility.

It has been suggested that ischaemia accounts for the depressed cardiac function of hypovolemic shock (202) (200) and other data refute this (205) (207) (206). Our data do not support the hypothesis that ischaemia accounts for depressed cardiac function. We did not observe slowed diastolic relaxation (τ did not change) that accompanies ischaemia. Also, we did not observe decreased systolic contractility that occurs during ischaemia. We conclude that while it is possible that myocardial hypoperfusion may contribute to development of the abnormalities of left ventricular mechanics observed here, ischaemia is not the primary event.

In this model of hypovolemic shock, initially the E_{max} of the ESPVR increased with no change in the V_d. This type of enhanced contractility is consistent with the effect of catecholamines (47). Over the ensuing 6-8 h E_{max} increased further and the V_d decreased slightly (P = NS). This progressive left shift of the end-systolic pressure-volume relationship means that the left ventricle is able to eject further at a given afterload, conventionally interpreted as enhanced contractility. It may be that the progressive left shift of the ESPVR over time is due to a gradually increasing level of circulating catecholamines or gradually increasing efficacy of a stable level of catecholamines. Although possible, neither of these explanations seems likely. The end-systolic length of myocardial muscle is set by the length of the contractile element, length of the passive series elastic element, and the number of these "Hill" units linked in series. Therefore, the progressive left shift of the ESPVR is not necessarily due to increased contractility of the contractile element. Alternatively, shortening of the passive series elastic element or a decrease in the number of Hill units linked in series could also account for a left shift in ESPVR. It is possible to show mathematically that the left shift of the ESPVR in this study can be accounted for by a 20% reduction in the number of Hill units in series and this 20% reduction in muscle length concurrently can account for the altered diastolic properties.

6.1 Effect of hypovolemic shock on diastolic pressure-volume relationship

The main finding of this study is that diastolic stiffness increased dramatically during a period of hypovolemic shock and that increased diastolic stiffness (Fig. 24), not decreased systolic contractility, accounts for all of the decrease in left ventricular function. Furthermore, diastolic stiffness increased in an interesting way. The V_m and the V_0 decreased by one-half,

whereas the parameter reflecting muscle S did not change (Table 16). To arrive at this description of how diastolic stiffness changed an equation recently proposed by Nikolic et al. (29) was used to fit the diastolic pressure-volume data. This new equation was chosen because it offered potential for substantial improvement in physiological understanding. First, this new equation allows for elastic recoil and negative pressures at finite volumes. This is important in the present study of hypovolemic shock because diastolic pressures well below zero were frequently observed. Second, the parameters in previously used exponential equations "have been ad hoc empirical descriptions of data with little or no theoretical base in the mechanics of the heart" (214). The equation used in this study avoids this problem because the parameters V_m, V_0, and S have a clear physiological interpretation. V_m estimates the maximum volume or yield volume of the ventricle above which the structural elements of the left ventricle are altered, associated with a physical change such as rupture of the ventricle. V_0 is simply the equilibrium volume of the diastolic left ventricle at zero transmural pressure. S is a size-independent chamber stiffness parameter having the units of stress reflecting a material property of the myocardium (51).

The pericardium was open, and care was taken to ensure that surrounding structures did not compress the heart. Therefore, our results only apply to the left ventricular myocardium. If the percardium and chest wall were intact it is possible that the results would be altered. However, because hypovolaemia results in smaller heart volumes the effects of the pericardium and chest wall would be minimised. We did not observe pulmonary hypertension or disproportionate shortening of the septal-free wall dimension (septal shift) so that the effect of coupling with the right ventricle probably did not markedly affect our results.

The degree of diastolic stiffness observed in this study explains the "irreversibility" of haemorrhagic shock first characterised by Wiggers (32). The previous observations of (1) depressed cardiac function and (2) irreversibility of the shock state, strongly suggest that increased diastolic stiffness was the cause. Systolic dysfunction can be treated or reversed using fluid infusion (Frank-Starling mechanism) or vasopressor drugs and therefore could not have accounted for irreversibility. Changes in peripheral arterial or venous tone can also be countered by fluid infusion or vasopressor drugs. On the other hand, there is no known acute treatment of diastolic stiffness, other than fluid resuscitation, in an attempt to fill the stiff diastolic left ventricle. These findings of decreased yield volume suggest that even extremely high diastolic pressures may not result in an end-diastolic volume that allows for an adequate stroke volume. In fact, V_{max} which represents the maximum volume or yield volume of the ventricle, is lower after haemorrhagic shock than baseline end-diastolic volume. This suggests that it is possible that no amount of volume resuscitation could restore end-diastolic volume as the ventricle would yield (rupture or undergo an irreversible deformation) before this could be accomplished. The consequence of a very stiff diastolic ventricle was observed in several animals when acute pulmonary oedema developed at high end-diastolic pressures when diastolic volume was extremely small so that the shock state was still not reversed. To conclude, increased diastolic

stiffness is the only cardiovascular abnormality that could reasonably account for decreased cardiac function and irreversibility of the shock state in these animals.

Our data do not demonstrate why the diastolic ventricles became stiffer after a period of hypovolemic shock, but a number of explanations seem possible. A change in passive diastolic elastic characteristics when diastolic volume is increased has been well described (217) and is termed "stress relaxation" of the diastolic left ventricle. It is conceivable that the reverse process may occur when diastolic volume is decreased leading to a stiff diastolic ventricle after several hours. Alternatively, myocardial oedema or changes in supporting structures surrounding and within the myocytes could also account for a change in passive diastolic elastic characteristics. If either of these explanations were true we would have expected muscle stress-strain characteristics (S from *Eq. 2)* to change. However, these alternatives cannot be excluded because physiological interpretation of parameters of a fitting equation is always uncertain and because our data cannot exclude a change in S with substantial power. Finally, increased myocardial vascular volume having an erectile effect (218) at low left ventricular chamber volumes could conceivably account for our observation. It is not known whether S would change under these conditions.

It is interesting to note that normal dogs with different size ventricles have approximately the same value of S (51). Our results are therefore similar to this observation and this similarity suggests an alternative mechanistic explanation for the observation of a decrease in diastolic yield and equilibrium volumes despite no change in S.

This explanation is that a reduction of muscle length by decreasing the number of Hill units in series by 20% would account for the observed changes in diastolic and end-systolic pressure-volume relationships (see appendix 2). Previously distensible myocardium may have become indistensible in series with normal myocardium so that it effectively no longer contributed to measured stiffness. These data do not show how this may have occurred. Yet, it is plausible that the rest length is reduced as a result of the effects of prolonged shock, conceivably due to an increase in residual calcium in the myocardium(218) (207) or some other process. How could a 20% reduction in muscle length occur morphologically without changing muscle stiffness? A review of Hackel et al. (207) of the morphology of the heart in hypovolemic shock, specifically zonal lesions, may shed some light on this problem. "This type of lesion consists of a zone of apparent hypercontraction at the end of a myocyte, adjacent to an intercalated disc, with local scalloping of the sarcolemma, marked shortening of the sarcomeres adjacent to the intercalated disc, fragmentation of the Z bands, bizarre bending and distortion of the myofilaments, and displacement of the mitochondria away from the intercalated disc." We speculate that because our measurements of systolic and diastolic pressure-volume relationships can be accounted for by decreased length (fewer Hill units in series) they are simply the physiological expression of these anatomically observed zonal lesions.

6.1 Clinical implications

Although the present surgical preparation merely models human hypovolemic shock, we believe information from this study may be clinically important. Specifically, increased diastolic stiffness observed here likely occurs in humans during a period of hypovolemic shock because the haemodynamic and cardiac function abnormalities observed here resemble human data. Certainly, zonal lesions and irreversibility are also observed in humans (205) (207) (206). To the extent that increased diastolic stiffness probably occurs in humans, difficulty in volume resuscitation due to diastolic stiffness may well complicate human hypovolemic shock. Currently there is considerable interest in the efficacy of different resuscitation regimens for hypovolemic shock (104) (219). These results suggest that reported differences in outcome of these various studies may be partly due to unmeasured differences in diastolic stiffness. Furthermore, it is likely that successful resuscitation from established hypovolemic shock will require attention to the diastolic pressure-volume relationship. Currently, there is no therapy that will acutely improve diastolic stiffness in patients with hypovolemic shock.

Chapter 7
CONCLUSIONS

This thesis details a number of studies investigating cardiac dysfunction during lactic acidosis and during hyperdynamic and hypovolemic shock.

In the first study (Ch 4.1.1) a patient with rhabdomolysis, renal failure, lactic acidosis and shock received acute bicarbonate infusions on 3 occasions with the intent of improving cardiac dysfunction. The effects were variable, but on each occasion cardiac function decreased, suggesting that bicarbonate may have had adverse side effects which outweighed advantages.

In the next study (Ch 4.2.1) 14 patients with shock and lactic acidosis received 20 minute infusions of bicarbonate and of hypertonic saline. Cardiac function was measured using pulmonary and systemic arterial catheters. Bicarbonate transiently increased preload and cardiac output but the same transient changes were observed after hypertonic saline. No effect of pH correction on cardiac function could be detected, either in all patients (arterial pH = 7.22) or in the most severe (arterial pH = 7.10). Side effects of hypercapnia and ionised hypocalcemia were observed. This study suggested that previous anecdotal reports of bicarbonate improving haemodynamics were likely to be due to the infusion of a hypertonic solution, not pH correction.

Nine patients (Ch. 4.2.2) with lactic acidosis were then studied. A close association between ionised hypocalcemia and hyperlactemia was observed. Possible causes were considered including lactate being a calcium chelator, and shock being a common cause of both hypocalcemia and hyperlactemia.

Twelve anaesthetised ventilated pigs were then studied (Ch. 4.3.1) to assess the effect of endogenous lactic acidosis and its correction on precise measures of LV function. Lactic acidosis was induced by progressive hemmorrhage. When an arterial pH of 7.10 was reached, normovolemia was restored and the animals were studied. Complete, acute correction of acidosis did not improve excellent measures of LV contractility, in part because LV contractility was not decreased. It was concluded that endogenous lactic acidosis was likely to be associated with endogenous catecholamine release which more than compensated for any decrease in LV systolic contractility. Bicarbonate therapy was therefore not logical and not effective.

The final study in this lactic acidosis series involved 15 anaesthetised, mechanically ventilated pigs (Ch. 4.3.2). In order to study "pure" lactic acidosis without the confounding influences of shock, sympathoadrenal resposes, and therapy related hypercapnia, lactic acid was infused to a pH of 7.05, the animals were beta - blocked, and hypercapnia was prevented with ventilator adjustments. At an arterial pH of 7.05 a small decrease in LV contractility was observed. Despite optimal circumstances in this study to identify a benefit of bicarbonate therapy, complete acute correction of acidosis with bicarbonate failed to improve LV contractility.

Investigations then turned to hyperdynamic shock. To learn more about cardiac dysfunction in human anaphylaxis, histamine was infused in 9 healthy human volunteers (Ch. 5.2.2). Left ventricular contractility was measured noninvasively using echocardiographic assessment of LV

dimensions and LV pressures measured indirectly from carotid arterial pulse tracings. Histamine decreased LV contractility, despite the effects of catecholamines known to be released at the same time. Decreased contractilty was in large part reversed by H_1 receptor blockade and was therefore considered to be H_1 mediated.

To study sepsis, 12 anaesthetised dogs received intravenous TNF - α infusions. Hypotensive, hyperdynamic sepsis associated with decreased LV contractility was observed within 1 hour. There were no changes in diastolic compliance during the 5 hour study period.

Finally, 8 anaesthetised pigs (6 study animals and 2 controls) had hypovolemic shock induced by hemorrhage and maintained for 6-8 hours (Ch. 6.1). Increased LV diastolic stiffness was observed and accounted for marked impairment of overall LV function. We speculated that the profound decrease in diastolic LV function may account for previous observations of failed resuscitation during prolonged hypovolemic shock.

These studies, together with the many others referenced in this thesis, provide conclusive evidence that left ventricular dysfunction occurs during both hyperdynamic (anaphylactic and septic) and hypovolaemic shock. In hyperdynamic shock, left ventricular dysfunction seems to be due primarily to mediators, whereas in hypovolaemic shock, although left ventricular dysfunction is clearly described, the cause is still uncertain. These studies taken together also suggest that although lactic acidosis frequently occurs during hyperdynamic and hypovolaemic shock, and may contribute to left ventricular dysfunction during severe shock, the contribution is minor, is probably over-ridden by other factors, and is of little clinical importance. In future therefore, therapy for patients with shock and lactic acidosis should be focussed on the causes of shock and the inflammatory mediators which cause left ventricular dysfunction, and not on the acidosis which is of secondary importance. Bicarbonate therapy is not therefore a useful therapy for most patients with shock and lactic acidosis.

Finally and in conclusion, the linking hypothesis – that cardiac dysfunction is important in hyperdynamic and hypovolemic shock and is not caused by lactic acidosis – has been upheld by this thesis.

APPENDIX 1

PUBLISHED LETTERS AND ABSTRACTS BASED ON THE WORK CONTAINED IN THIS THESIS

LETTERS

1. Cooper DJ, Walley KR, Russell JA. Lactic acidosis. Ann Intern Med 1990; 113:255-256. (authors reply).

2. Cooper DJ. Association between plasma ionised calcium and blood lactate concentrations in critically ill patients. Intensive Care Med 1993;19: 362-363. (authors reply) .

3. Cooper DJ. Haemodynamic effects of sodium bicarbonate. Intensive Care Med 1994;20: 306-307.

4. Cooper DJ, Walley KR. Bicarbonate does not increase left ventricular contractility during L- lactic acidemia in pigs (authors reply) Am J Resp Crit Care Med 1994;149:1054-1055

ABSTRACTS

1. Cooper DJ, Walley KR. Left ventricular diastolic stiffness and systolic elastance increase during hypovolemic shock. Fed Proc 1989; 3:A5491. **Presented:** Federation of American Societies of Experimental Biology. New Orleans, Louisiana, USA. March 1989.

2. Walley KR, Cooper DJ, Russell JA. Sodium bicarbonate does not improve haemodynamics and ventricular mechanics during hemorrhagic shock induced lactic acidosis. Am Rev Resp Dis 1989;139:A18. **Presented:** International Scientific Meeting of the American Thoracic Society. Cincinatti, Ohio USA. May 1989.

3. Cooper DJ, Walley KR, Russell JA. Sodium bicarbonate does not improve haemodynamics in human metabolic acidosis. Am Rev Resp Dis 1989;139:A18. **Presented:** International Scientific Meeting of the American Thoracic Society. Cincinatti, Ohio USA. May 1989.

4. Cooper DJ, Walley KR. Diastolic stiffness completely accounts for left ventricular dysfunction during hemorrhagic shock. Clin Invest Med 1989;12:B19. **Presented:** Annual National Meeting of the Royal College of Physicians and Surgeons of Canada. Edmonton, Alberta, Canada. September 1989.

5. Cooper DJ, Walley KR, Russell JA. Sodium bicarbonate does not improve haemodynamics and ventricular mechanics during hemorrhagic shock induced lactic acidosis. Clin Invest Med 1989;12:B20. **Presented:** National Meeting: Royal College Physicians and Surgeons of Canada. Edmonton, Alberta. September 1989.

6. Russell JA, Cooper DJ, Walley KR, Dodek P. Ionized hypocalcemia and elevated serum lactate correlate closely in human lactic acidosis. Clin Invest Med 1989;12:B20. **Presented:** National Meeting of the Royal College of Physicians and Surgeons of Canada. Edmonton, Alberta, Canada. September 1989.

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12. Cooper DJ, Walley KR, Wiggs B, Russell JA. Bicarbonate does not improve haemodynamics in critically ill patients who have lactic acidosis. Intern Medicine 1990;10: 18-19.

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17. Cooper DJ, Schellenberg RR, Walley KR. Effects of histamine on left ventricular contractility in pigs. Anaesth Intensive Care 1992;2:A237. **Presented:** 16th Australian and New Zealand Annual Scientific Meeting on Intensive Care, Canberra ACT, September 1991.

18. Cooper DJ, Herbert PC, Wakai Y, Wilcox P, Road J., Walley KR. Tumor necrosis factor (TNF alpha) decreases systolic left ventricular contractility. Anaesth Intensive Care. 1992;20:A238. **Presented:** 16th Australian and New Zealand Annual Scientific Meeting on Intensive Care, Canberra ACT, September 1991.

19. Herbert PC, Cooper DJ, Wakai Y, Wilcox PG, Road JD, Walley KR. Early decrease in left ventricular contractiliity after TNF-α infusion. Am Rev Resp Dis 1992;144: A74.

APPENDIX 2

THEORETICAL EXPLANATION FOR CHANGES IN DIASTOLIC AND END-SYSTOLIC PRESSURE-VOLUME RELATIONSHIPS DURING HYPOVOLEMIC SHOCK. (Conceived by K.R. Walley) (37)

In this appendix, it will be shown that a 20% reduction in extendible muscle length accounts for the observed changes in diastolic stiffness and systolic elastance reported in Ch. 6.1. That is, the ventricle behaved as if the length of each myocardial cell shortened by 20% so that the number of Hill units in series had been reduced by 20%, with no change in diastolic or systolic stress-strain characteristics of the remaining 80% of the myocardium. How does a 20% shortening of muscle length account for these observations ?

1) V_m decreased from 56.1 to 27.5 ml. V_m is the maximum volume asymptote from Equation 2 (Ch 6.1), the yield volume. A change in muscle stiffness will not alter yield volume (it will simply increase the pressure as yield volume is approached) but a shortening of muscle fibre length will. To calculate the amount of muscle shortening necessary to produce the observed decrese in V_m we made the simplifying assumption that the ventricle is a sphere. We then calculated the change in circumferential length (l_c) as a measure of the true muscle shortening

$$l_c = 2\pi \text{ . radius} = 2\pi (3V/4\pi)^{1/3} \quad \textit{(Equation 4)}$$

Using V = 56.1 ml and then 29.2 ml we found that l_c and therefore muscle length decreased by 21%.

2) V_0 decreased from 27.5 to 15.6 ml. V_0 is unlike V_m in that it depends on muscle stiffness as well as muscle length. Therefore if the same decrease in muscle length calculated from V_m accounts for the observed decrease in V_0 it suggests that there was no change in muscle stiffness of the remaining muscle. We again used Eq 3 to calculate the muscle shortening associated with the observed decrease in V_0 using V = 27.5 and then 15.6 ml. We found that the muscle length (l_c) shortening required to account for the observed decrease in V_0 is 17%, similar to that calculated for V_m.

3) S does not change. Nicolic et al (46) coinclude that S is a material property of the myocardium related to chamber stiffness so that in this experiment if myocardial stiffness had changed to account for the diastolic stiffness we would have expected to observe a change in S.

4) Systolic V_d decreased by 3.9 ml and E_{max} increased from 7.9 to 18.5 cm H_2O/ml. If muscle length decreased then end-systolic volume (V_{es}) and V_d would decrease according to Eq 3. At baseline V_{es} = 21.4 so that l_c = 10.8 cm. Reducing l_c by 20% yields new values for l_c, V_{es}, V_d, and E_{max}, which are all indicated by the prime superscript V_{es}' = 11.0 ml. Likewise, for V_d = 4.2 ml at baseline a 20% muscle length shortening reduces V_d' = 2.1 ml. Because E_{max} = $P_{es}/(V_{es} - V_0)$ we calculate that after the 20 % reduction in muscle fibre length E_{max}' = E_{max} x $(V_{es} - V_d)/ (V_{es}' - V_d')$ = 15.3. The increases in E_{max} from 7.9 to 15.3 and decrease in Vd by 2.1 ml predicted from a 20% reduction in muscle length closely match the experimental measured values.

Therefore a reduction of muscle length by decreasing the number of Hill units in series by 20% accounts for the observed changes in diastolic and end-systolic pressure-volume relationships.

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