Anatomical variations of the cerebral basal arterial network with special emphasis on morphometrics and their relation to cerebral aneurysms

A thesis presented by

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Dedication

This thesis is dedicated to my wife Rakchha, daughter Bindee, dad Guru and mum Binda, dad in law Deependra, mum in law Anita and my sisters Kalyani, Bina and Kranti for their continued support to keep going, being the biggest fans and being with me round the clock.

Declaration

I (Arjun Burlakoti) certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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6. Three-minute (3 - MT) thesis presentation, organising committee, The University of Adelaide, South Australia

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Thesis abstract

The components of cerebral basal arterial network (CBAN), comprising of inflowing internal carotid and vertebral arteries, outflowing hemispheric branches and arteries supplying the brain stem and the cerebellum, and the communicating segments present variations in >50% general population.[1,2,4] Cerebral aneurysms have been discussed to be related to the variations in the segments of CBAN but this relationship has not been quantitatively assessed. Cerebral aneurysms could rupture causing stroke, or compress the nearby brain surface, the cranial nerves and blood vessels.[2,5,6]

The main aim of the thesis was to assess the relationship of brain arterial variations, including asymmetries to the occurrence of cerebral aneurysms. The diameters of segments of CBAN from 51 dissected human brains and 166 cerebral angiography images were measured at specific regions and related to the locations of cerebral aneurysms. Furthermore, the study conducted the morphometric analysis of the incoming, and outgoing components of the CBAN, which influence the blood flow to the brain. The general hypothesis underlying this thesis is that the well-formed CBAN dampens peaks in blood pressure reaching the brain, which minimizes the formation of aneurysms.

The thesis consists of a series of four published and one submitted papers and six conference presentations. Paper one, following the idea presented by Vrselja and colleagues,[7] stated that the arrangement of incoming and outgoing arteries connected by communicating arteries of CBAN provides a mechanism for lowering peak pressures in cerebral circulation, thus decreasing the chances of formation of cerebral aneurysms.[1] Paper two clarified that the total blood supply to the left cerebral hemisphere is not different from that of the right and indicated that there is no total functional lateralization between the two cerebral hemispheres.[8] The anterior communicating artery complex (AcomAC) consists of the anterior communicating artery and the adjacent parts of left and right anterior cerebral arteries. Paper three established a quantitative index for the prediction of the chances of development anterior communicating artery complex aneurysms in the presence of size asymmetry of the first segments of anterior cerebral arteries (A1s).[9] Compared to

individuals with symmetric A1s, the relative risk (RR) of the development of AcomAC aneurysms was much greater (80% chance, RR = 17.4, odds ratio = 47.3) if one A1 had cross-sectional area two times greater than the other. This finding could be considered as a criterion for cerebral aneurysms screening, in addition to the currently accepted criteria of family history[10] of aneurysms.

Paper four presents how cerebral aneurysms adversely affect a person's health and wellbeing considering that cerebral aneurysms could compress the brain parenchyma, nearby cranial nerves, affect the surface of the brain, and rupture, leading to the stroke. This study demonstrated the significance of multidisciplinary approach in managing the clinical conditions resulting from a cerebral aneurysm.[11]

Finally, paper five investigated the effects of quantitative variance and asymmetry of CBAN components on hemodynamics based on the findings presented in previously published[1,8,9] papers of this thesis. Furthermore, this paper elaborated the double pressure dampening mechanism proximal to the second segment of posterior cerebral arteries (P2), which prevents the development of aneurysms at or distal to P2 segment.[12] Overall, the number of cerebral aneurysms occurring in the segments of CBAN varied with the ability of each arterial segment to dampen the peak systolic pressure.

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Introduction

Arteries supplying the human brain are derived from the vertebro-basilar and internal carotid arteries [1-3]. The basilar artery joins the vertebral arteries to the anteriorly located segments of arteries (circulus arteriosus cerebri) forming the cerebral basal arterial network (CBAN) [4]. The cerebral basal arterial network comprises of incoming, communicating and outgoing arterial segments [4, 5]. The incoming components of CBAN are made up of right and left internal carotid and vertebral arteries. Cerebral and cerebellar hemispheric branches and arteries supplying the brain stem and the spinal cord form outgoing parts of CBAN [6]. The hemispheric cerebral arteries are the major outgoing components [4, 5, 7]. The communicating segments consist of anterior, and a pair of posterior communicating, and the basilar artery [4]. The basilar artery is a communicating artery in this thesis, because it connects the vertebral arteries to the first segments of posterior cerebral arteries (PCAs). Furthermore, the basilar artery allows the arterial blood flow to the brain stem, the cerebellar hemispheres, posterior aspect of the cerebral hemispheres, as well as the reciprocal flow from one vertebral artery to the other, and one PCA to the other [5, 8]. The segments of circulus arteriosus cerebri (CAC) are made of cerebral part of bilateral internal carotid arteries (ICA) [9], the left and right first segment of anterior cerebral arteries (A1s), the anterior communicating artery (AcomA), left and right posterior communicating arteries (PcomAs), and the pre-communicating part of bilateral posterior cerebral arteries (P1s) [10]. The British physician Thomas Willis, in mid-1600 described that circulus arteriosus cerebri provides collateral blood flow in situations of arterial occlusions [3]. This arterial network is important in maintaining the cerebral blood flow [5, 10, 11] but may not be able to maintain the circulation adequately in the event of sudden occlusion of an arterial branch [12]. Vrselja and colleagues suggested that the network limits propagation of peak systolic pressure into cerebral arteries, serving as an energy dissipating system [12]. Variations in the length, diameter and the arrangement of parts of the vessels in the arterial network have been observed [13-15]. Such cerebral arterial variations have been described in human infants (i.e. preterm and term) and adults [16-19] and also in animals including monkeys and rabbits [20, 21]. Eighty-three different anatomical variations have been described in CBAN system [13, 16, 18, 22-27]. Eftekhar and colleagues presented that the most arterial variations in the CBAN occurred around the anterior and posterior communicating arteries [13]. The most common variation found

was the bilateral hypoplastic PcomAs (diameter <1 mm) [28, 29]). One hundred and ninety-three hypoplastic (i.e. size <1 mm) segments in addition to 127 variant components of CBAN were found in 225 dissected brains [29]. A recent Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans on 536 patients have shown that the complete foetal posterior cerebral arteries (PCAs) are less common (9.5%, n = 51 cases) compared to partial foetal posterior cerebral arteries (15.1%, n=81 cases) [30]. The complete foetal PCA refers to a condition where the posterior communicating artery (PcomA) continues as the posterior cerebral artery in the absence of the first segment of posterior cerebral artery (P1) [31]. Hypoplastic P1 segment of the PCA is termed the partial foetal PCA [31].

Anatomical variations in CBAN are clinically important, because of their association with cerebrovascular pathologies (i.e. aneurysms, cerebrovascular accidents and migraine) [19, 25, 32-40]. An arterial aneurysm is a vascular disorder, where the wall of an artery becomes thinner and weaker leading into a dilatation [41]. The mechanisms that are causing cerebral aneurysms are multifactorial, however arterial variations, altered arterial wall stress and hemodynamics in the cerebral arteries are the common etiological factors [42]. People with variations in cerebral arteries are thought to be more prone to cerebrovascular pathologies including cerebral aneurysms [19, 43]. This warrants further investigations. Cerebral aneurysms were reported to be more common among females (i.e. 3.4% in women compared to 2.1% in men) and frequently located in the middle cerebral, anterior cerebral and communicating arterial territories [44]. Eighty-one patients surgically treated for AcomA, middle cerebral artery (MCA) or internal carotid artery (ICA) abnormalities, revealed that individuals with shorter ICAs are more susceptible for the development of cerebral aneurysms [45]. Large cerebral aneurysms are pathological condition, that could compress the cranial nerves and be considered as one of the warning signs of an impending rupture leading to haemorrhagic stroke [46]. Variant components of CBAN have been strongly correlated with the occurrence of stroke [10, 47-49]. The risk of rupture of aneurysms located in the vertebrobasilar component of CBAN is higher [50]. Furthermore, rupture of cerebral aneurysm is associated with high mortality and morbidity [42, 51, 52]. Cerebral aneurysms and migraines have been linked with variations in cerebral arteries,

particularly with the variations in anterior and posterior communicating arteries [15, 26, 32, 53, 54]. Aneurysms could re-occur; thus, it is important to know the predisposing factors, in order to prevent the reoccurrence [32, 55-58].

Currently there is no comprehensive data allowing quantitative predictions of the risk of aneurysm formation and their rupture in various parts of the CBAN system. A systematic study of particular variations including vessel asymmetries in the CBAN is needed to explore the relations of specific cerebral arterial variations and asymmetries to the formation of aneurysms and their complications.

About three quarters of subarachnoid haemorrhages (i.e. the most hazardous type of strokes) were caused by cerebral aneurysms [42, 59]. Investigations of the haemodynamics of the blood flow in cerebral arterial network have revealed that the deviation from normal cerebral arterial anatomy gives rise to a high or low wall shear stress (WSS) at the arterial bifurcations and predisposes to development of aneurysmal dilatation [60, 61]. The role of peak blood pressures during cardiac cycles in creating arterial wall stress, the development of aneurysms and causing their complications in the CBAN system needs to be investigated. A CBAN system free of structural variations and asymmetries has the potential to dampen the peak blood pressures and minimise the development of aneurysms. Quantitation of the structural parameters of the arterial segments of the CBAN may help to understand the mechanisms involved in dampening of the peak blood pressures during cardiac cycles. This role of CBAN system in dampening peak pressures has been suggested very recently [4, 12], and requires further studies to better understand the concept. As a part of the puzzle, it is important to assess the relationship between the variations in the segments of CBAN and the occurrence of aneurysms [62]. As a consequence, the study of variations and asymmetries in segments of CBAN was conducted further in this thesis [62]. Findings of this research might also help to identify people at risk of developing cerebral aneurysms and cerebrovascular pathologies.

Cerebrovascular accidents (also known as stroke), are the second most leading cause of death worldwide, including Australia [63]. Severe and symptomatic cerebral aneurysms are associated with high mortality and morbidity rates, leading to a huge financial burden worldwide. [64, 65]

This thesis investigates the morphometry of the incoming, communicating and outgoing components of CBAN and the way they influence the blood flow in the brain. Furthermore, this thesis also investigates the relationship of variations of cerebral arteries to the locations of cerebral aneurysms. The focus of this research is to contribute to prediction (or risk assessment) of cerebrovascular aneurysms. The findings of this thesis have contributed to predicting the probability of developing cerebral aneurysms, that can rupture causing stroke.

Research questions and hypothesis

a) Since the function of the communicating arteries of the brain arterial network has been considered as lowering blood pressure variations [12], we hypothesize that the variant and asymmetric components of 'cerebral basal arterial network (CBAN)' will be leading to the formation of cerebral aneurysms.

b) The secondary hypothesis was that the locations of aneurysms (i.e. one of the cerebral pathologies), are related to anatomical variations of the specific arterial components of the cerebral basal arterial network. The hypothesis about dampening pressure variations was tested by comparing the sum of proximal cross sectional areas of the major cerebral arteries of the CBAN to the sum of communicating components of the network and proximal cross sectional areas of the arteries outgoing from the network. The proximal end of an artery is situated closer to the heart chambers, while the distal part is located farther away from the heart [66]. The assumption here was that greater size of communicating and outgoing components would dampen peak in pulse pressure coming through inflowing carotid and vertebral arteries.

The secondary hypothesis was tested by observing the effects of anatomical variations and asymmetries (i.e. in the size of different segments) of cerebral basal arterial network components on the location of aneurisms.

In addition to the above-mentioned aims, this PhD thesis also investigated and compared the sizes (in the form of cross-sectional areas) of cerebral arteries supplying the right and left cerebral hemispheres to estimate whether the blood flow to the right cerebral hemisphere is different from the left [67]. Since the volume of blood flowing through an artery is known to be proportional to the diameter of the artery, the measurement of the cross-sectional area of an artery reflects the amount of blood flowing through it [68-70]. The amount of blood flowing through a particular cortical area of a cerebral hemisphere has been investigated to be directly proportional to the measure of its function [71]. Hence, the size (cross-sectional area) of the arteries supplying the cerebral hemispheres in this study, does not indicate that the function of one hemisphere is greater compared to the other hemisphere [67].

I (Arjun Burlakoti) had an opportunity to collaborate with health professionals from different clinical backgrounds (such as dental and neurosurgeons) and to co-author a clinical patient-based journal paper during my PhD candidature [72]. The importance of investigating the variations of cerebral arteries and their relationship to the cerebral aneurysms has been highlighted in the paper that we published in 2019 [72]. Cerebral aneurysm can compress the brain parenchyma, nearby cranial nerves, inflame the brain surface, and rupture leading to the stroke. This paper highlighted how challenging it would be to treat a symptomatic case of cerebral neuralgic pain caused by the right MCA aneurysm irritating the right insular cerebral cortical area [72].

Aim and objective

The aims of this project are given below:

1) To determine how relations among the size (cross sectional area) of incoming (i.e. internal carotid and vertebral arteries), major outgoing (i.e. anterior, middle and posterior cerebral arteries) and communicating (i.e. anterior, two posterior communicating and basilar artery) arteries of the cerebral basal arterial network lower the peaks in blood pressure and maintain a stable blood flow to the brain.

2) To establish reference ranges for the relative size (diameters and cross sectional areas) of the incoming (i.e. internal carotid and vertebral arteries), major out-going (i.e. anterior, middle and posterior cerebral arteries) and the communicating (anterior, two posterior communicating and basilar) arteries of the cerebral basal arterial network using cerebral CT and MRA scans from a representative sample of adult humans. This was carried out by measuring the internal diameters of the above-mentioned arteries.

3) To access the anatomy of the first segment of anterior cerebral arteries (A1s) (e.g. asymmetric, hypoplastic, enlarged and absent A1s) and the association with the presence of aneurysms around anterior communicating artery complex (AcomAC) and elsewhere.

This PhD was carried out using donated and dissected human brains in the anatomy lab of the University of Adelaide, recorded MR and CT angiography images at Royal Adelaide Hospital, University of Adelaide from individuals with variant segments of CBAN. The external and the internal diameters of the components of CBAN were determined in cadaveric brains and angiographic brain images respectively.

Significance/Contribution to the discipline

The global burden of cerebrovascular accident (stroke) is increasing and studies showed that almost 81 out of 106 (76%) cases of subarachnoid haemorrhage (a form of stroke) resulted from spontaneous rupture of intracranial aneurysms [42, 59, 63, 73-75]. Furthermore, the incidence of cerebrovascular accidents varies from 4.2 to 11.7% per thousand persons per year in population aged 55 years or more. Intracranial aneurysm has been identified as one of the major causes of intracerebral haemorrhage [75]. It is projected that 920,000 Australians harbour cerebral aneurysm [42]. According to the Australian Government Research Council report, the incidence of stroke had increased by almost 6% in 2007-2010, because of the ageing of the population. Almost 9,000 Australians have died of stroke and its complications in 2010 [64, 65]. Almost 35,000 Australians were hospitalised in 2008 with a main diagnosis of stroke and about 282,600 (82%) Australians with a history of stroke also had different forms of disability [65]. Australian studies further indicated that cerebrovascular diseases were second and third leading causes of death among females and males, respectively. The lifetime cost for the management of patient with cerebrovascular disease (i.e. from the time of diagnosis) ranged from $49,995 to $57,106 [65, 76].

Above data, clearly indicate that cerebrovascular aneurysms substantially contribute to overall mortality and morbidity rate, leading to a huge financial burden worldwide. Studies including that done in Australia, have showed that the cost and the disabilities resulting from stroke are high and they vary according to patient's age, the presence of comorbid conditions. Hence, stroke causes a high financial burden both on the patient and the healthcare system. Findings of this PhD research may assist in predicting the development of cerebral vascular aneurysms, and clinical decision making. For instance, if a cerebral arterial variation (e.g. hypoplastic right first part of anterior cerebral artery is accidently detected during cerebral CT and MRA procedure), cerebral aneurysms might be predicted and variation could be corrected, and the clinical condition can be managed in a better way in such susceptible population group. Therefore, the suffering and financial burden on the patients, their family and the country could be reduced. Furthermore, the relationship between the

asymmetries in the segments of CBAN and the occurrence of aneurysms has been established. This was particularly performed by analysing the cerebral CT angiographic findings. Finally, the findings of this PhD project have contributed to better understanding on the haemodynamics of the cerebral blood circulation. This PhD on the CBAN underpins the function of the communicating arteries (including basilar artery) in distribution of pressure waves and lowering the hemodynamic stress. The correlation among the multiple components of CBAN analysed in this PhD helps to broaden the anatomical and clinical knowledge on this topic [4]. Furthermore, identification of the basilar artery, as the fourth communicating artery of CBAN is also, a novel contribution of this study.

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Manuscripts and conference presentations arising from this thesis

a) Published - four

b) Submitted - one

c) Conference and seminar presentations - six

a) Published manuscripts included in this thesis

Burlakoti, A, Kumaratilake, J, Taylor, J, Massy-Westropp, N & Henneberg, M 2017, 'The cerebral basal arterial network: morphometry of inflow and outflow components', Journal of Anatomy, vol. 230, no. 6, pp. 833-841.

Doi: https://doi.org/10.1111/joa.12604. This paper has been cited by six research articles till the date.

Burlakoti, A, Kumaratilake, J, Taylor, J & Henneberg, M 2019, 'Asymmetries of total arterial supply of cerebral hemispheres do not exist', Heliyon, vol. 5, no. 1, article no. e01086 pp. 1-14.

Doi: https://doi.org/10.1016/j.heliyon.2018.e01086. This paper has been cited by three research articles till the date

Burlakoti, A, Kumaratilake, J, Taylor, DJ & Henneberg, M 2020, 'Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm', BMJ Surgery, Interventions, & Health Technologies, vol. 2, no. 1, p. e000059.

Doi: http://dx.doi.org/10.1136/bmjsit-2020-000059

Mascarenhas, R, Hapangama, N, Mews, P, **Burlakoti, A** & Ranjitkar, S 2019, 'Orofacial neuralgia associated with a middle cerebral artery aneurysm', Australian Dental Journal, vol. 64, no. 1, pp. 106-110.

Doi: https://doi.org/10.1111/adj.12668

b) Submitted manuscripts included in this thesis

Arjun Burlakoti[1*], Jaliya Kumaratilake[2], Jamie Taylor[3], Maciej Henneberg[4], 'Prevalence of cerebral aneurysms is related to anatomical variations in cerebral basal arterial network: Investigation of cerebral Computed Tomography Angiography in a neurointerventional unit' The BMJ Open. [1]UniSA Allied Health and Human Performance, University of South Australia, Adelaide, Australia; [2]Discipline of Anatomy and Pathology, Adelaide Medical School, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia; [4]Institute of Evolutionary Medicine, The University of Zurich, Zurich, Switzerland.

Manuscript number: bmjopen-2021-051028.R1

c) Conference and seminar presentation

1. Conference one

The first conference poster on 'The cerebral basal arterial network: morphometry of inflow and outflow components' was presented by **Arjun Burlakoti** at the 13th Australian and New Zealand Association of Clinical Anatomists (ANZACA), Canberra, Australia, 7-9 December 2016.

2. Conference two

The second conference poster on 'Asymmetries of total arterial supply of cerebral hemispheres do not exist' was presented by **Arjun Burlakoti** at the 7th Australian Cognitive Neuroscience Society, Conference Adelaide, South Australia, 23-26 November 2017.

3. Conference three

The third conference poster titled 'role of cerebral basal arterial network in modulating arterial pressure in the brain and clinical consequences of anatomical variations in the cerebral arterial circle' was presented by **Arjun Burlakoti** at Florey Postgraduate Research Conference, University of Adelaide, National Wine Centre, South Australia, Australia on 24th of September 2019.

4. Conference four

The 4th conference poster related to this research, titled, "Well dampened blood pressure waves passing through the posterior cerebral artery prevent development of aneurysms", was presented by **Arjun Burlakoti** at Australian and New Zealand Association of Clinical Anatomists (ANZACA), 4-6 December 2019, University of Western Australia, Perth, Australia 2019.

5. South Australian Anatomy Practice Interest group meeting

One of the oral presentations related to this thesis, titled, "Circulus arteriosus cerebri and vertebrobasilar arterial system- research updates", was presented by **Arjun Burlakoti** at South Australian Anatomy Practice Interest group meeting on 14th of April 2016.

6. Australasian Nepalese Medical and Dental Association annual meeting

The second oral presentation related to this thesis, titled, "Relationship of the most severe types of the cerebral vascular accident to the variations of the cerebral basal arterial network", was presented by **Arjun Burlakoti** at fifth Australasian Nepalese Medical and Dental Association (ANMDA), annual meeting in Brisbane, Queensland, Australia on 30 of September 2019. (CBAN).

The details of the conference (including posters) and seminar presentations have been presented in chapter 7 of this thesis.

Abbreviations

Abbreviation	Full name
A1	First segment of anterior cerebral artery
ACA	Anterior cerebral artery
AcomA/ or AComA	Anterior communicating artery
AcomAC or AComAC	Anterior communicating artery complex
BA	Basilar artery
CAC	Circulus arteriosus cerebri
CBAN	Cerebral basal arterial network
CCTA	Cerebral Computed Tomography Angiography
CRP	C-reactive protein
CTA	Computed Tomography Angiography
ESR	erythrocyte sedimentation rate
ICA	Internal carotid artery
M1	First segment of middle cerebral artery
MAR	Magnetic resonance angiography
MCA	Middle cerebral artery
MRI	Magnetic Resonance Imaging
P2	Second segment of the posterior cerebral artery
PCA	Posterior cerebral artery
PcomA or PComA	Posterior communicating artery
RAH	Royal Adelaide Hospital
rTEM	Relative technical error of measurement
SAH	Subarachnoid haemorrhages

TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint
USA	United States of America
VA	Vertebral artery
VPM	Ventral postero-medial nucleus
P1	First segment of posterior cerebral arteries

Authors overall contribution to the manuscripts presented to this thesis

1. Contribution to the first manuscript

"The cerebral basal arterial network: morphometry of inflow and outflow components"- **Arjun Burlakoti-** prepared the first manuscript draft based on the analysed brain arterial data measured from the brain specimens that he dissected from the donated cadaveric head and neck. **Professor Maciej Henneberg, Dr Jaliya Kumaratilake, Dr Jamie Taylor and Dr Nicola Massy-Westropp** contributed in editing and shaping the manuscript for the submission to the Journal of Anatomy. **Arjun Burlakoti** dissected all the brain specimens at first, and **Professor Maciej Henneberg and Dr Jaliya Kumaratilake** assisted in reviewing the cerebral arterial measurements taken from the dissected brain specimens. The idea developed and the measurements obtained from the brain specimens were then conceptualized by Maciej Henneberg, Arjun Burlakoti, Jaliya Kumaratilake and Jamie Taylor. **Arjun Burlakoti**- dissected the cadaveric specimens, took pictures, recorded videos, contributed in conceptualization, collected and analysed the data, prepared and wrote the paper. **Maciej Henneberg**- initiated the idea, contributed to the concept, helped in data interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article. **Jaliya Kumaratilake**- contributed to the concept, data interpretation and collection, editing the manuscript, the critical revision of the manuscript and approving the article. **Jamie Taylor**- contributed to the concept, data interpretation, editing the manuscript, the critical revision of the manuscript and approving the article. **Nicola Massy-Westropp**- helped in starting the research project, contributed in editing the manuscript draft and approving the article.

2. Author contribution to the second manuscript

"Asymmetries of total arterial supply of cerebral hemispheres do not exist"

The primary manuscript draft was written by **Arjun Burlakoti** based on the brain arterial data that he obtained and analysed from the Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) digital images and the cadaveric brain specimens. Arjun Burlakoti, Professor Maciej Henneberg, and Dr Jaliya Kumaratilake put forward the concept of this research paper in exploring the symmetric hemispheric arteries supplying the cerebral hemispheres.

Arjun Burlakoti recorded the data from the brain specimens that he dissected from the donated human head and neck specimen. Arjun Burlakoti also collected the data from the cerebral Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) digital images in consultation with Consultant Neuroradiologist Dr Jamie Taylor from Magnetic Resonance Imaging (MRI) centre, Royal Adelaide Hospital, University of Adelaide. The idea developed and the data obtained were then conceptualized by Maciej Henneberg, Arjun Burlakoti, Jaliya Kumaratilake and Jamie Taylor. **Arjun Burlakoti**- conceived the idea and designed the analysis, dissected the cadaveric brains, collected and analysed the data from the cadaveric brains, CTA and MRA, took pictures, recorded videos, contributed in conceptualization, prepared and drafted the paper. **Maciej Henneberg**- conceived the idea, helped in data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article. **Jaliya Kumaratilake**- contributed to the concept, helped in data interpretation and collection, editing the manuscript, the critical revision of the manuscript and approving the article. **Jamie Taylor**- contributed in collecting and interpreting the data, editing the manuscript, helped in the critical revision of the manuscript and approving the article.

3. Author contribution to the third manuscript

"Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm"

Initial journal manuscript draft was prepared by **Arjun Burlakoti**. The manuscript draft was based on the data collected and analysed from the cerebral Computed Tomography Angiography (CTA) digital images. Arjun Burlakoti, Maciej Henneberg, Jamie Taylor, and Jaliya Kumaratilake put forward the concept of this research paper in exploring the relationship between the asymmetric first part of the anterior cerebral arteries and the presence of aneurysm in the anterior communicating artery complex. **Arjun Burlakoti** gathered the data from the cerebral Computed Tomography Angiography (CTA) digital images in consultation with **Consultant Neuroradiologist Dr Jamie Taylor** from Magnetic Resonance Imaging (MRI) centre, Royal Adelaide Hospital, University of Adelaide. The idea evolved and the CTA data collected were then conceptualized and brainstormed by Maciej Henneberg, Arjun Burlakoti, Jaliya Kumaratilake and Jamie Taylor. **Arjun Burlakoti**- conceived the idea, designed the analysis, collected and analysed the data from CTA, took pictures, recorded videos, contributed in conceptualization, prepared and drafted the manuscript. **Maciej Henneberg**- conceived the idea, helped in statistics, data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article. **Jaliya Kumaratilake**- conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article. **Jamie Taylor**- conceived the idea, contributed in collecting and interpreting the data, editing the manuscript, the critical revision of the manuscript and approving the article.

4. Author contribution to the fourth manuscript

"Orofacial neuralgia associated with a middle cerebral artery aneurysm"

Mascarenhas Raoul - reviewed patient over a number of years and helped manage dental care. Developed key concepts presented in this paper, wrote and edited the manuscript.

Hapangama ND- reviewed patient for differential diagnosis of facial pain. Contributed to records, guidance and editing the manuscript.

Peter J Mews - Performed neurosurgical procedure and was involved in subsequent follow-up. Contributed to records, guidance regarding neurosurgical concepts, and edited the paper.

Burlakoti A- contributed to developing and presenting neuroanatomical concepts published in this paper and edited the manuscript.

Sarbin Ranjitkar - contributed to developing key concepts in this manuscript, overall writing and editing of the paper.

5. Author contribution to the fifth manuscript

"Prevalence of cerebral aneurysms is related to anatomical variations in cerebral basal arterial network: Investigation of cerebral Computed Tomography Angiography in a neurointerventional unit"

The primary manuscript drafts were prepared by **Arjun Burlakoti**. The drafts were prepared on the data recorded and analysed from the cerebral CTA digital images.

Arjun Burlakoti, Maciej Henneberg, Jamie Taylor, and Jaliya Kumaratilake put forward the concept of this paper in exploring the relationship among the components of CBAN and the presence or absence of cerebral aneurysms. Arjun Burlakoti gathered data from the cerebral Computed Tomography Angiography (CTA) digital images in consultation with Consultant Neuroradiologist Dr Jamie Taylor from Magnetic Resonance Imaging (MRI) centre, Royal Adelaide Hospital, University of Adelaide. The idea evolved and the CTA data collected were then conceptualized and brainstormed by Maciej Henneberg, Arjun Burlakoti, Jaliya Kumaratilake and Jamie Taylor. **Arjun Burlakoti**- conceived the idea, designed the analysis, collected and analysed the data from CTA, took pictures, recorded videos, contributed in conceptualization, prepared and drafted the manuscript. **Maciej Henneberg**- conceived the idea, helped in statistics, data

analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article.

Jaliya Kumaratilake- conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.

Jamie Taylor- conceived the idea, contributed in collecting and interpreting the data, editing the manuscript, the critical revision of the manuscript and approving the article.

An official permission has been obtained from each co-author and included in the respective chapters of this thesis.

Chapter 1: The cerebral basal arterial network: morphometry of inflow and outflow components

Article DOI: 10.1111/joa.12604

This paper has been published in the **Journal of Anatomy** on 29 March 2017.

The Journal ranking = Q1 (2019 and 2018), comprises the quarter of the journals with the highest values.

The Journal of Anatomy, a peer reviewed journal is one of the highly ranked journals in the field of Anatomy with 2.720 impact factor (updated in 2020).

This paper has been cited by following five journal articles till the date

1 Blood flow rate and wall shear stress in seven major cephalic arteries of humans

RS Seymour, Q Hu, EP Snelling - Journal of Anatomy, 2020 - Wiley Online Library

Blood flow rate in relation to arterial lumen radius (ri) is commonly modelled according to theoretical equations and paradigms, including Murray's Law ($\propto$) and da Vinci's Rule ($\propto$). Wall shear stress (τ) is independent of ri with Murray's Law ($\tau\propto$) and decreases with da …

2 Identification and quantitative analysis of branching networks of the posterior intercostal arteries

LK Šaherl, M Gosak, M Rakuša - Anatomical Science International, 2020 - Springer

Morphological and anatomical characteristics of the posterior intercostal arteries have revived interest in their branching networks. Collateral supply between intercostal spaces is extensive due to anastomoses, although the data about the quantitative description of the …

3 Anatomical Variations of Arterial Cerebral Circle in an Amphitheater of a University in Bogota, Colombia/Variantes anatomicas del circulo arterial cerebral en un …

YQ Blanco, DG Orjuela - Revista Ciencias de la Salud, 2020 - go.gale.com

Introduction: The brain is a highly irrigated organ; this irrigation is supplied by the cerebral arterial circle: an anastomotic arterial network with frequent anatomical variations, some of which are associated with pathologies. This study aimed to describe the anthropometric …

4 Variantes anatómicas del círculo arterial cerebral en un anfiteatro universitario en Bogotá (Colombia)

YQ Blanco, DG Orjuela - Ciencias de la salud, 2020 - dialnet.unirioja.es

Introducción: el cerebro es un órgano altamente irrigado, y esta irrigación es suministrada por el círculo arterial cerebral: una red arterial anastomótica con frecuentes variaciones anatómicas, algunas asociadas con patologías. El objetivo es describir las características …

5 PROCJENA MOŽDANE VAZOREAKTIVNOSTI TRANSKRANIJSKIM DOPLEROM KOD BOLESNIKA S KRONIČNOM OPSTRUKTIVNOM PLUĆNOM BOLESTI

M Hlavati - 2020 - dr.nsk.hr

Sažetak Cilj istraživanja: Odrediti moždanu vazoreaktivnost u prednjoj i stražnjoj moždanoj cirkulaciji pomoću metode voljnog zadržavanja daha kod bolesnika s kroničnom opstruktivnom plućnom bolesti (KOPB) prema stupnju opstrukcije dišnog puta i moguću …

Context for the first paper

Anatomical variations occurring in cerebral arterial network supplying the brain are common and present in almost half of the total population (Crofton et al., 2019). Such commonly occurring variation of CBAN is clinically important because of its strong associations with cerebral vascular pathologies including aneurysms and strokes (Chuang et al., 2008, Malamateniou et al., 2009, Kapapa and König, 2015, Crofton et al., 2019).

This paper provided the statistical analysis of the arrangement of incoming, outgoing and communicating arteries of cerebral basal arterial network (CBAN). This arrangement could dampen peaks in blood pressure in human brain arterial network (Burlakoti et al., 2017).

Traditionally the role of the anterior part of CBAN (i.e. circulus arteriosus cerebri, CAC), first described by a Paduan anatomist Julius Casserius (1552-1616), and subsequently by Thomas Willis (1621-1675) (Bender et al., 2013, Feindel, 1962, Vasović et al., 2013, Rogers, 1947, De Silva et al., 2009), has been considered to serve for collateral circulation, when some arterial segments are missing or interrupted. However, the current study, taking base the idea forwarded by Vrselja and colleagues (Vrselja et al., 2014), explored that the arrangement of incoming, outgoing and communicating arteries of CBAN provides a mechanism for dissipating peak pressures in cerebral circulation, thus decreasing the chances of formation of aneurysms (Burlakoti et al., 2017).

Therefore, the arterial network and cross-sectional areas of the components of CBAN need to be investigated to elucidate the pressure gradients across the arterial network. The primary aim of this study was to investigate the cross-sectional area of incoming, communicating and outgoing cerebral basal arterial network components and determine their role in cerebral arterial circulation.

This study is clearly useful and has been cited 5 times already. The findings contribute to a change in the current concept that has been existing since early 1600. The novel concept summarised in this study helps to

understand the effects of disturbed pressure dampening mechanism resulting from variant segments of CBAN, which could predispose to cerebral pathologies including aneurysms.

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Vrselja Z, Brkic H, Mrdenovic S, Radic R, Curic G (2014) Function of circle of Willis. J Cereb Blood Flow Metab, 34, 578-84.

Statement of Authorship

Statement of Authorship

Title of Paper	The cerebral basal arterial network: morphometry of inflow and outflow components
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author	Arjun Burlakoti		
Contribution to the Paper	Dissecting the cadaveric specimens, taking pictures, recording videos, contributions to the concept, collecting and analyzing the data, preparing and writing the paper.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19th January 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jaliya Kumaratilake		
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Name of Co-Author	Maciej Henneberg		
Contribution to the Paper	Contributions to the concept, data interpretation, editing the manuscript, critical revision of the manuscript and approval of the article		
Signature		Date	19th January 2021

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Article:

The cerebral basal arterial network: morphometry of inflow and outflow components

Article DOI: 10.1111/joa.12604, Journal of Anatomy

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Abstract

The aim of this project was to study how the morphology of the incoming and outgoing arterial components of the cerebral basal arterial network influence the blood flow to the brain. Cerebral basal arterial network consists of the circulus arteriosus cerebri anteriorly and the basilar artery posteriorly. Diameters of inflow vessels (bilateral vertebral and internal carotid arteries), connecting vessels (anterior communicating, basilar and bilateral posterior communicating arteries) and outflow vessels (anterior, middle and posterior cerebral arteries) were measured and cross-sectional areas calculated in 51 cadaveric brain specimens. The individual and the average cross-sectional areas of inflow arteries (51.43 square millimetres) were significantly bigger than the major outflow arteries (37.76 square millimetres), but smaller than the combined cross-sectional areas of outflow (37.76 square millimetres) and connecting (25.33 square millimetres) arteries. The difference in the size of arterial cross-sectional area and the presence of the connecting arteries in the cerebral basal arterial network provides a mechanism for lowering peaks in pressure, and demonstrates a function of the cerebral basal arterial network.

Key words

cerebral arteries; circle of Willis; circulus arteriosus cerebri; internal carotid arteries; vertebral arteries.

Introduction

Stable perfusion of brain tissues at a high and constant rate is required due to high metabolic demands of the brain, while at the same time the high amplitude of cerebral perfusion pressure waves need to be reduced. The brain development occurs by expansion of three embryonic vesicles (O'Rahilly and Müller, 2006), thus the entire blood supply comes from a small set of closely related arteries (Menshawi et al., 2015). These exceptional circumstances are reflected in the structure of the origins of the arterial supply to the brain, an

anastomotic cerebral basal arterial network from which all major arteries branch from. The anterior portion of the cerebral arterial network, the circulus arteriosus cerebri (CAC) was first described by a Paduan anatomist Julius Casserius (1552-1616), and subsequently by Thomas Willis (1621-1675) includes the cerebral parts of right and left internal carotid arteries (ICA), pre-communicating parts of right and left anterior cerebral arteries (ACA), anterior communicating artery (AComA), right and left posterior communicating arteries (PComA) and the pre-communicating parts of the bilateral posterior cerebral arteries (PCA) (Bender et al., 2013, Feindel, 1962, Vasović et al., 2013, Rogers, 1947, De Silva et al., 2009). Traditionally the role of the circulus arteriosus cerebri at the base of the brain has been considered to serve for collateral circulation, when some feeding arteries are interrupted. However, it has recently been suggested that the anterior component of cerebral basal arterial network (i.e. circulus arteriosus cerebri) serves to limit peak systolic pressure propagating into cerebral arteries and serves as a passive energy dissipating system (Vrselja et al., 2014). A study of a mathematical model by Alastruey and colleagues showed that the arterial system supplying the brain does not require the collateral flow pathways through the posterior communicating arteries to effectively perfuse the brain in healthy people with complete circulus arteriosus cerebri (Alastruey et al., 2007). However, the increase in hemodynamic activities was noticed through the PComA that acted as an outflow vessel of the internal carotid artery in case of hypoplastic or absent first part of ACA or PCA (Vrselja et al., 2014). The blood flow through the communicating arteries could be both ways and that depends on the sites of variations (Alastruey et al., 2007).The data used by Alastruey and colleagues for their model were obtained from various tertiary resources that included different brains (Alastruey et al., 2007, Izzy and Muehlschlegel, 2014). They used the data provided by a number of sources including (Fahrig et al., 1999), who also took secondary random data from more than eight groups of authors. The objective of the current study is different from Alastruey's (Alastruey et al., 2007) investigation and present data from real cadaveric brains and sizes of components of cerebral basal arterial network have been statistically analysed. This analysis tests the hypothesis, (Vrselja et al., 2014) that the arterial circle of the brain provides a mechanism

for dampening peak cerebral perfusion pressures in brain arteries rather than just being a precaution against an eventual rare event of one of the main inflow or connecting arteries being blocked or absent.

The cerebral basal arterial networks show a number of variations in structure and arrangement (Hannequin et al., 2013, Gunnal et al., 2014, De Silva et al., 2011). Many of these variations are clinically important, because of their associations with aneurysms and cerebrovascular accidents (Sampath et al., 2010, Dell, 1982, Gunnal et al., 2014, Guerri-Guttenberg, 2009, Brown and Broderick, 2014, Bender et al., 2013, Alnæs et al., 2007, Leblanc et al., 2009). Cerebrovascular accidents are the second leading cause of death (Feigin et al., 2014) with increasing mortality and morbidity rates worldwide (D'Souza, 2015), including Australia and Sweden (Hankey et al., 2002, Nieuwkamp et al., 2014). Cerebrovascular aneurysms are associated with many factors such as tobacco smoking, hypertension, female sex and family history of cerebrovascular diseases (Ellamushi et al., 2001, D'Souza, 2015, Turan et al., 2016). In addition, variations in the anatomy of cerebral arteries are another important factor (Brown and Broderick, 2014, Alnæs et al., 2007). Shorter cranial part of the internal carotid artery and high hemodynamic stress acting across the variant cerebral arteries have been reported as a risk factor for the development of aneurysms (Kim and Kang, 2007, Alnæs et al., 2007, Zuleger et al., 2010). Pressure gradient across the arteries in which the blood flows is inversely proportional to the cross-sectional areas of the vessels (Zamir, 1977, Fung, 1997). Therefore, cross sectional areas of all components of the cerebral basal arterial network need to be investigated to elucidate the pressure gradients across the arterial network. The primary aim of this study was to investigate the cross-sectional area of incoming, communicating and outgoing cerebral basal arterial network components and determine their role in cerebral arterial circulation.

Materials and Methods

Ethics approval for the dissection and removal of brains from the cadavers and to use already dissected brains was obtained from the University of Adelaide (No. H-2014-176), before commencing the study. Fifty-one

prosected brains with complete arterial components were used in the study. Due to the process of de-identification of dissected brain specimens, the age and sex were available only for 26 brains. The external diameters of the arteries flowing into and leaving the cerebral basal arterial network were measured at specific sites (Figures 1 and 2), perpendicular to their long axis using a digital Vernier calliper. The digital Vernier callipers have been used to measure lengths and diameters of arteries in cadaveric brains (Siddiqi et al., 2013, Gellman et al., 2001, Lo et al., 2006, M. Mustafa Aldur 2006, Vázquez et al., 2009, Samuels et al., 2000, Kamath, 1981, Koppenhaver et al., 2009). Reliability of the measurements was verified by re-measuring the arterial diameters of 15 cadaveric brains (Table 1).

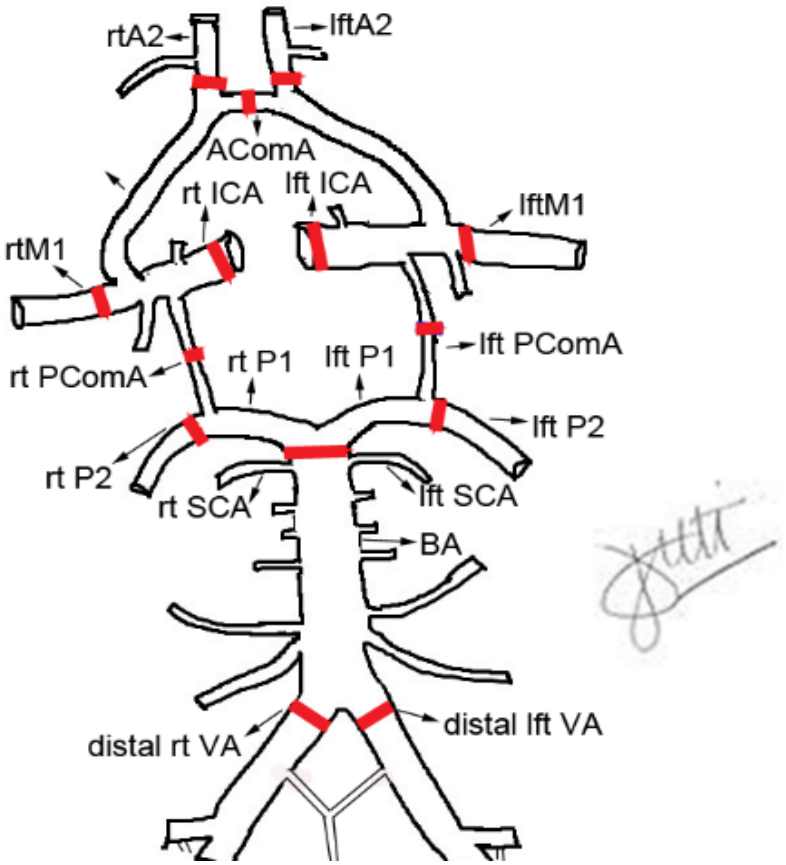

Figure 1: Schematic diagram of cerebral basal arterial network (CBAN). Red lines indicate the sites where the diameters were measured in millimetres (mm). BA = basilar artery, diameter measured at midway between SCA and PCA, rt VA = right vertebral artery, diameter measured at the most distal part, lft VA = left vertebral artery, diameter measured at the most distal portion, lft P2 = second part of the left posterior cerebral artery, diameter measured at the proximal portion, rt P2 = second part of the right posterior cerebral artery, diameter measured at the proximal portion, rt PComA = right posterior communicating artery, diameter measured at around the mid-point, lft PComA = left posterior communicating artery, diameter measured at around the mid-point, rt ICA = right internal carotid artery, diameter measured at the level of optic chiasm, lft ICA = left internal carotid artery, diameter measured at the level of optic chiasm, rt A2 = second part of the right anterior cerebral artery, diameter measured at the most proximal part, lft A2 = second part of right anterior cerebral artery, diameter measured at the most proximal part, AComA = anterior communicating artery, diameter measured around mid-point, rt M1 = first part of right middle cerebral artery, diameter measured at the most proximal part, lft M1 = first part of left middle cerebral artery, diameter measured at the most proximal part, SCA = superior cerebellar artery and PCA = posterior cerebral artery.

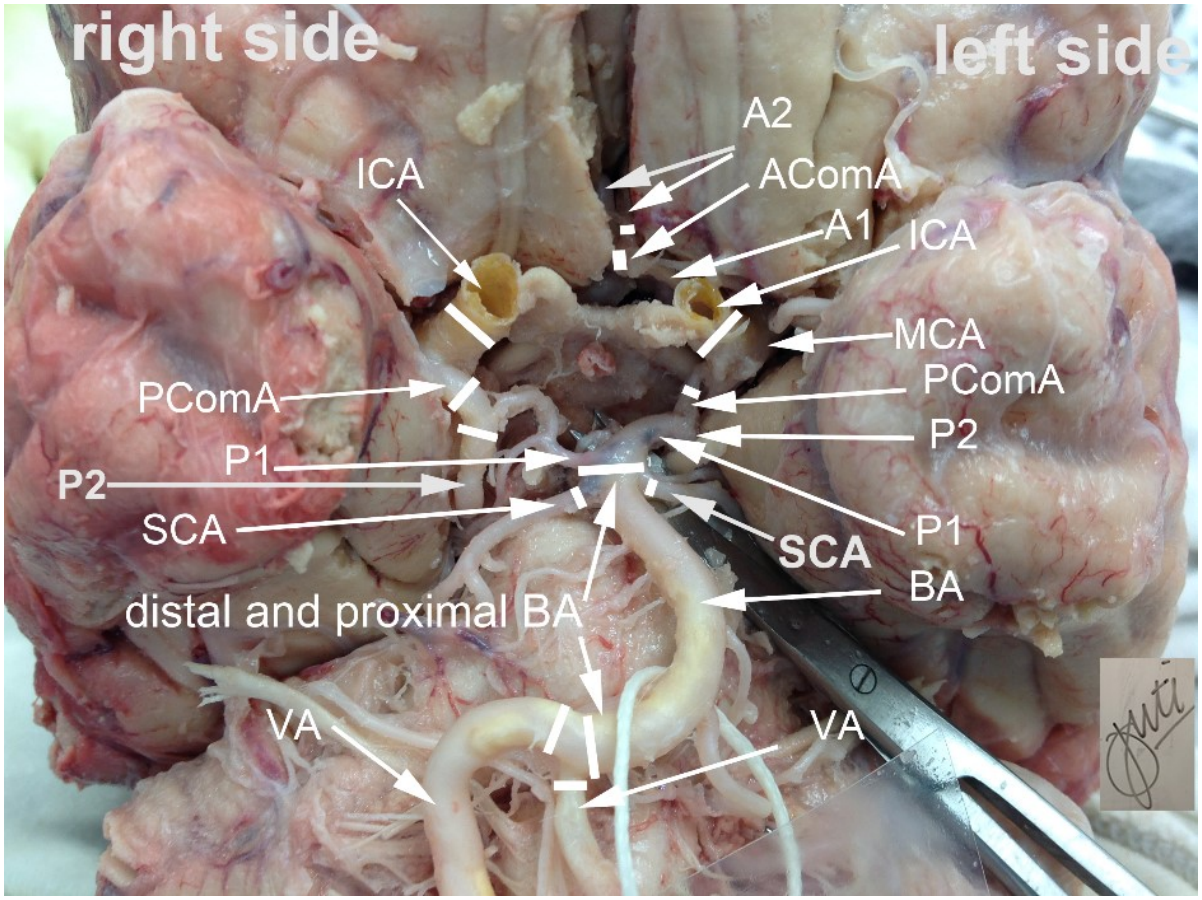

Figure 2: Base of the Brain, showing cerebral basal arterial network (CBAN). Measurements were taken in millimetres (mm) perpendicular to the long axis of the vessels at the sites indicated by the white lines. BA = basilar artery, VA = right vertebral artery, P1 = first part of the posterior cerebral artery, P2 = posterior cerebral artery second part, PComA = posterior communicating artery, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery, A1 = first part of the anterior cerebral artery, A2 = second part of anterior cerebral artery, AComA = anterior communicating artery, SCA = superior cerebellar artery

Cross sectional area of each artery was calculated using the formula $A = \pi r^2$, where A and r are cross sectional area and radius respectively.

Following are the sites of the measurements taken from the incoming, outgoing and communicating cerebral arterial components.

Arteries flowing into cerebral basal arterial network (incoming), Figures 1 and 2:

1. Cerebral part of the right internal carotid artery (ICA) - at the level of optic chiasm
2. Cerebral part of the left internal carotid artery (ICA - at the level of optic chiasm

3. Intracranial portion of the distal right vertebral artery (VA) - just proximal to the unification
4. Intracranial portion of the distal left vertebral artery (VA) - just proximal to the unification

Major arteries leaving cerebral basal arterial network (outgoing), Figures 1 and 2:

1. The most proximal portion of second part (A2) of the right anterior cerebral artery (ACA)
2. The most proximal portion of second part (A2) of the left anterior cerebral artery (ACA)
3. The most proximal portion of the first part (M1) of the right middle cerebral artery (MCA)
4. The most proximal portion of the first part (M1) of the left middle cerebral artery (MCA)
5. The most proximal portion of the second part (P2) of the right posterior cerebral artery (PCA)
6. The most proximal portion of the second part (P2) of the left posterior cerebral artery

Communicating arteries (Figures 1 and 2):

1. The mid-point of anterior communicating artery (AComA)
2. The mid-point of the right and left posterior communicating arteries (PComA)
3. Terminal portion of the basilar artery (BA) midway between posterior cerebral artery and superior cerebellar artery

Table 1: Inter-rater reliability measurement was performed from 15 specimens and the measurements were taken in millimetres (mm): technical errors of measurement (TEM), reliability (a square root of R squared value) and relative technical errors of measurement were calculated.

arterial components (in mm)	TEM	Reliability	Relative TEM (100*TEM/mean)
the distal diameter of BA	0.16	0.97	3.36
distal external diameter of rt VA	0.07	0.99	2.32
distal external diameter of lft VA	0.1	0.97	3.04
proximal external diameter of rt P2	0.06	0.97	2.33

proximal external diameter of lft P2	0.96	0.98	1.81
proximal external diameter of rt M1	0.08	0.96	2.76
proximal external diameter of lft M1	0.07	0.98	2.51
midpoint external diameter of rt PComA	0.07	0.99	5:00
midpoint external diameter of lft PComA	0.05	0.98	2.04
external diameter of lft ICA at the level of optic chiasma	0.09	0.98	2.02
external diameter of rt ICA at the level of optic chiasma	0.09	0.96	2.1
proximal external diameter of rt A2	0.07	0.94	2.89
proximal external diameter of lft A2	0.07	0.96	2.79
midpoint external diameter of AComA	0.06	0.99	3.13

rt = right, lft = left, BA = basilar artery, VA = right vertebral artery, P1 = first part of the posterior cerebral artery, P2 = posterior cerebral artery second part, PComA = posterior communicating artery, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery, A1 = first part of the anterior cerebral artery, A2 = second part of anterior cerebral artery, AComA = anterior communicating artery, SCA = superior cerebellar artery.

Statistical analysis

The data were analysed statistically using Microsoft excel 2013 and Statistical Package for Social Sciences (SPSS), version 22. The individual and average cross-sectional areas of incoming, outgoing and communicating arterial components were calculated. Descriptive statistics, Pearson product-moment correlation coefficient and Spearman rank-order non-parametric correlation procedures were used as SPSS analytical techniques. The assumed significant probability (P) value was set at <0.05.

Table 2: Descriptive Statistics: Means and standard deviations of individual diameter millimetres (mm) and the mean sum of cross-sectional areas in square millimetres (mm^2) of four incoming, six outgoings and four communicating arterial components.

Descriptive Statistics

	N	Mean	Standard Deviation
right vertebral artery- the most distal diameter	51	3.16	.69
right vertebral artery- the most distal cross-sectional area	51	8.20	3.45
left vertebral artery- the most distal diameter	51	3.46	.54
left vertebral artery- the most distal cross-sectional area	51	9.67	2.92
basilar artery diameter midway between SCA and PCA	51	4.57	.92
basilar artery- cross sectional area midway between SCA and PCA	51	17.08	6.84
right P2- the most proximal diameter	51	2.61	.33
right P2- the most proximal cross-sectional area	51	5.43	1.43
left P2- the most proximal diameter	51	2.59	.29
left P2- the most proximal cross-sectional area	51	5.33	1.19
right PComA- diameter around mid-point	51	1.59	.68
right PComA- cross sectional area around mid-point	51	2.35	1.94
left PComA- diameter around mid-point	51	1.42	.59
left PComA- cross sectional area around mid-point	51	1.85	1.50
right ICA diameter at the level of optic chiasm	51	4.56	.66
right ICA cross sectional area at the level of optic chiasm	51	16.68	4.99
left ICA diameter at the level of optic chiasm	51	4.59	.62
right ICA cross sectional area at the level of optic chiasm	51	16.85	4.74
right A2- the most proximal diameter	51	2.63	.42
right A2- the most proximal cross-sectional area	51	5.57	1.92

left A2- the most proximal diameter	51	2.61	.39
left A2- the most proximal cross-sectional area	51	5.47	1.56
AComA diameter around mid-point	51	2.05	.95
AComA cross sectional area around mid-point	51	4.03	3.61
right M1- the most proximal diameter	51	3.12	.40
right M1- the most proximal cross-sectional area	51	7.77	2.03
left M1- the most proximal diameter	51	3.19	.48
left M1- the most proximal cross-sectional area	51	8.17	2.33
cross sectional area of four incomings (left and right ICA and VA arteries)	51	51.42	10.58
cross sectional area of six outgoing (the most proximal part of bilateral A2, P2 and M1)	51	37.76	6.08
cross sectional area of four communicating (AComA, bilateral PComA and BA)	51	25.33	7.51
cross sectional area of six outgoing + four communicating arteries	51	63.09	11.66

BA = basilar artery, VA = vertebral artery, P1 = first part of the posterior cerebral artery, P2 = posterior cerebral artery second part, PComA = posterior communicating artery, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery, A1 = first part of the anterior cerebral artery, A2 = second part of anterior cerebral artery, AComA = anterior communicating artery, SCA = superior cerebellar artery

Results

Means and standard deviations of individual diameter and the mean sum of cross-sectional areas of four incoming arterial components (terminal right and left internal carotid arteries, distal portion of the right and left cranial vertebral arteries, six outgoing components (the most proximal portion of second part of right and left anterior cerebral artery , the most proximal portion of the first part of right and left middle cerebral artery and the most proximal portion of the second part of right and left posterior cerebral arteries) and four communicating branches including the basilar artery (the mid-point of anterior communicating artery, the

mid-point of the right and left posterior communicating arteries, terminal portion of the basilar artery midway between posterior cerebral and superior cerebellar arteries) are presented in Table 2, Table 4, Figures 1 and 2. Means and individual sums of cross-sectional areas of the arteries (in square millimetres) leaving the cerebral basal arterial network and communicating arteries were significantly bigger than those of the incoming arteries (Table 3 and Figure 3). The individual and average cross-sectional areas of four incoming arteries were correlated to six major outgoing arteries ($r = 0.63$, $p \leq 0.0001$, $N = 51$) and combined outgoing and communicating arteries ($r = 0.56$, $p \leq 0.0001$). The average communicating arterial cross-sectional area was correlated with the incoming components, although, less strongly ($r = 0.36$, $p \leq 0.04$, $N = 51$) was lower as compared to the outgoing ($r = 0.40$, $p \leq 0.0001$, $N = 51$). Statistically significant correlations in cross sectional areas of multiple, unilateral and bilateral cerebral arterial components are presented in a supplementary table (Table S1).

Table 3: Descriptive statistics of average cross-sectional area in square millimetres (mm^2) of four incoming (bilateral vertebral and internal carotid arteries), six outgoing (anterior, middle and posterior cerebral arteries) and four communicating (anterior communicating, basilar and bilateral posterior communicating) arteries.

	N	Mean	Std. Deviation
Four incoming	51	51.4	10.5
Six outgoing	51	37.7	6.0
Four communicating	51	25.3	7.5
six outgoing +four communicating	51	63.0	11.6

Discussion

Anatomists from Croatia (Vrselja et al., 2014), based on theoretical considerations, have advanced a hypothesis that circulus arteriosus cerebri has the function of stabilising the perfusion pressure across the two cerebral hemispheres more than maintaining the collateral circulation. Findings presented here are in agreement with the hypothesis and strongly favouring the incorporation of basilar artery into the circulus arteriosus cerebri as an additional communicating branch. This incorporation makes the cerebral basal arterial network (CBAN) supplied by internal carotids and vertebral arteries, the arterial circuit supplying the whole brain, including the brain stem and the cerebellum. Caplan and team indicated that the intervertebral arterial collateral blood flow (via the proximal basilar artery) and retrograde basilar arterial blood flow (via the distal basilar artery) might occur (Caplan, 1979). Internal carotid arteries may compensate insufficiencies of vertebral arterial blood flow via posterior communicating branches of circulus arteriosus cerebri into posterior cerebral arteries and from there into the basilar artery and its branches, such as superior cerebellar arteries. The bridging of circulus arteriosus cerebri anteriorly and vertebral arteries posteriorly by the BA would allow retrograde flow or blood flow from one vertebral artery to another. Therefore, basilar artery is considered as one of the communicating arteries in the cerebral basal arterial network system. The dimensions of arteries studied here compare well with those reported by other authors (Siddiqi et al., 2013) (Table 5). Variations in cerebral arteries, particularly in the interhemispheric anterior communicating artery (De Silva et al., 2009), posterior cerebral arteries, middle cerebral arteries (Gunnal et al., 2014), bilateral PComA (Chuang et al., 2008), and anterior cerebral arteries have been reported (Klimek-Piotrowska et al., 2013, Papantchev et al., 2013, Malamateniou et al., 2009). These cerebral arterial variations could alter the hemodynamics and cerebral perfusion pressure and affect the blood flow into right or left sides of the brain. A rapidly enlarged left PComA developed after the ipsilateral ICA aneurysm coiling procedure done in just four and half months' time (Jeck et al., 2002). This indicates that the PComA acts as one of the outflow arteries of the ICA.

Aneurysms may develop when high pressure encounters a weakened arterial wall. Therefore, altered haemodynamics may contribute to the development of aneurysms.

According to a French physician, Poiseuille's fluid dynamics model (Faber, 1995), longitudinal pressure gradient is required to pump fluid through a vessel, and it is inversely proportional to the fourth power of the radius of that vessel (Zamir, 1977). The deformation is not possible in viscoelastic fluid (like arterial blood) and the fluid pressure waves keep moving (Joseph, 2013), i.e. the pressure wave could be transmitted in either direction of communicating arteries of cerebral basal arterial network (CBAN).

In this study, the average incoming, outgoing and communicating cross-sectional areas correlated among themselves, however, a relatively weaker relationship was noticed between incoming and communicating components (Table 3 and Figure 3). The sample size of 51 brains is not very large in this study. However, our results compare reasonably well to data published by various authors on various arterial components (Alastruey et al., 2007, Fahrig et al., 1999, Siddiqi et al., 2013).

The combined greater cross sectional area of the arteries leaving the cerebral basal arterial network (efferent arteries) and communicating arteries compared to those of the incoming arteries (afferent arteries) indicates that there is a reduction in arterial pressure (MAP) gradient from the incoming to outgoing arteries. A computational hemodynamic study of the cerebral vasculature also considered PCA, MCA and ACA as the outflow components and has proven that blood flows towards the larger cross-sectional and low pressure region (Wiedeman, 1962, Fung, 1997).

Table 4: Spearman's rho correlations above diagonal and Pearson moment-product correlations below the diagonal among four incoming (bilateral vertebral and internal carotid arteries), six outgoing (anterior, middle and posterior cerebral arteries) and four communicating (anterior communicating, basilar and bilateral posterior communicating arteries) average arterial cross-sectional areas measured in square millimetres (mm^2)

	4 incoming	6 outgoing	4 communicating	outgoing+ + communicating
4 incoming	1	.670**	.420**	.614**
6 outgoing	.594**	1	.433**	.780**
4 communicating	.350*	.465**	1	.891**
outgoing + communicating	.535**	.822**	.887**	1

** Correlation is significant at the 0.01 level (2 - tailed).

* Correlation is significant at the 0.05 level (2 - tailed).

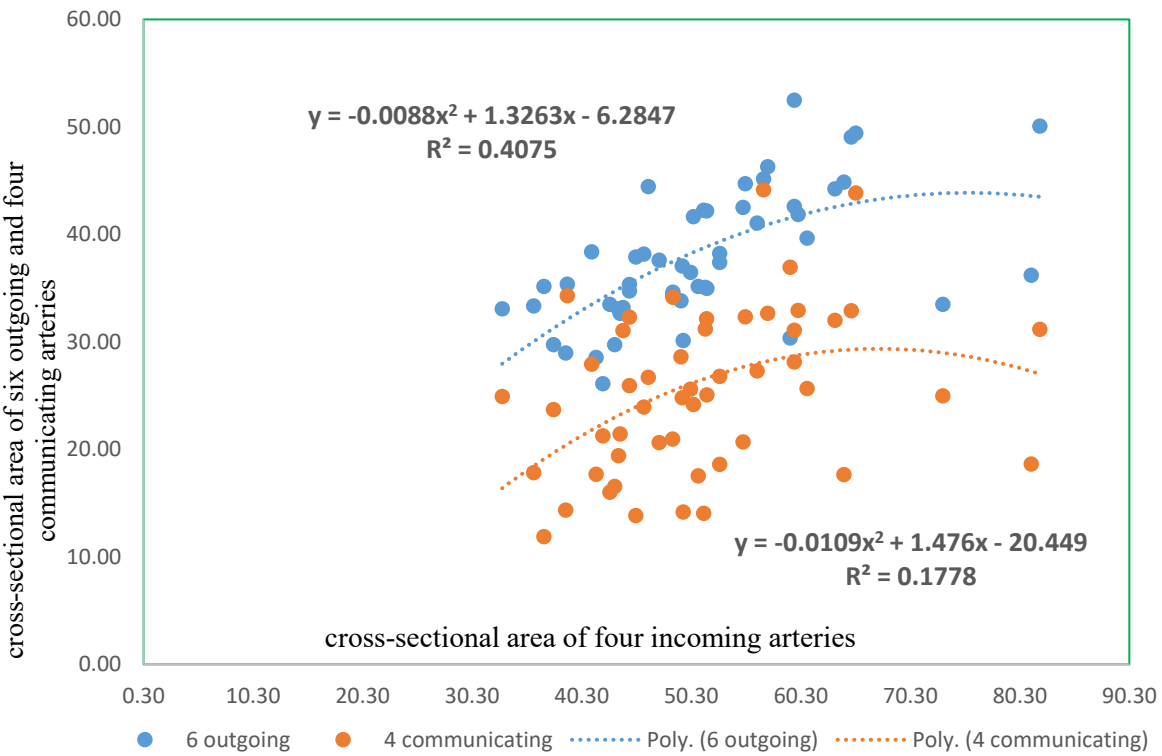

Figure 3: Correlations among four incoming, six outgoing and four communicating cerebral arterial components, X and Y axes show the cross-sectional area in squared millimetres (mm^2).

Table 5: Comparison of dimensions of proximal left (lft) and right (rt) anterior cerebral artery (A1) in multiple studies (Siddiqi et al., 2013) including our study, and the measurements were taken in millimetres (mm)

Author	Year	Mean Proximal diameter of rtA1	Mean Proximal diameter of lftA1
Our study (N = 51)	**2015**	**2.52**	**2.61**
Murray[6]	1964	1.47	1.42
Perlmutter and Rhoton[7]	1976	2.60	2.60
Kamath[3]	1981	2.20	2.40
Gomes et al[8]	1986	2.30	2.50
Stefani et al[9]	2000	2.61	2.61
Pai et al[10]	2005	2.80	2.90
Vohra et al[11]	2006	1.44	1.44
Mandiola et al[12]	2007	2.37	2.42

A study measuring arteries in bats and dogs showed a linear decrease in arterial diameter and increase in mean total cross-sectional area of the arteries and arterioles distally. Similarly, the arterial wall shear stress decreases as the total mean cross-sectional area increases along the distal arterial tree (Fung, 1997). Also, an increase in abdominal aortic arterial wave amplitude has been documented in the presence of decreased ratio between the cross-sectional area of the outgoing common iliac arteries and the parent vessel (Lasheras, 2010, Fung, 2013). The significant difference between incoming and outgoing cross-sectional areas of CBAN components (Figure 3 and Table 3) indicates the importance of having communicating arteries to normalise the cerebral perfusion pressure and to ensure adequate perfusion to the brain. A cerebral arterial network hemodynamic experiment revealed that the deviation from normal cerebral arterial anatomy gives rise to a high and low wall shear stress (WSS) around the bifurcation sites and predisposes to development of aneurysmal dilatation (Alnæs et al., 2007, Boussel et al., 2008). An uneven cerebral arterial blood flow found

among the participants in two studies done using Magnetic Resonance Angiography (MRA) (n=208) was attributed to the variant cerebral arterial anatomy, and indicated that variations in cerebral arterial anatomy could lead to uneven cerebral arterial blood flow and velocity (Van Laar et al., 2006, Hendrikse et al., 2005). The same studies found increased contralateral ICA blood flow in individuals with missing A1 (303ml/min ± SE56) compared to the normal ipsilateral flow (214 ml/ min ± SE94) without any variation.

The mean arterial pressure and the change in vessel diameter has been found to be linear from centre to periphery during the systolic and diastolic phase of a complete cardiac cycle (Sugawara et al., 2000). A recently published theoretical and mathematical model of cerebral arterial network (Vrselja et al., 2014) has provided a hemodynamic calculation, which contradicts the currently accepted concept of the compensatory flow function of the arterial network under physiological conditions. In another study, the vertebral MAP wave was observed to be dissipated once the bilateral vertebral arteries united forming the bigger cross-sectioned basilar artery in a computational experiment (Alnæs et al., 2007).

On this occasion, we have proposed the concept of having four connecting arteries (AComA, left and right PComA and BA) which serve as a perfusion pressure wave dampening communicating arterial system. The theoretical computational study done by the Vrselja team (Vrselja et al., 2014), previously discussed concept on arterial radii, shear stress, pressure flow relationship, normal relationship on smaller sum of proximal and greater sum of distal arterial cross-sectional area and flow rate (Fung, 1997, Zamir, 1977, Lasheras, 2010) and our cadaveric findings on greater sum of four incoming and smaller sum of six major outgoing cerebral arterial cross- sectional area support the cerebral arterial pressure easing role of communicating branches of cerebral basal arterial network system. We have now explained the reasons for introducing of this concept in more details and stated that it is based on a logical train of thought, not on an experiment. It should be noted that if the cross-sectional area of small outflowing arteries leaving the cerebral basal arterial network (such as anteromedial central, hypophyseal, posteromedial central, pontine, labyrinthine, posterior inferior cerebellar, labyrinthine and anterior inferior cerebellar arteries) were calculated, they would have been included within the sum of outgoing arteries leaving the cerebral basal arterial network in this study. Therefore, the positive

difference between cross-sectional areas of outgoing + communicating arteries and incoming arteries would be increased, which would further strengthen the conclusion that we reached in this study.

Contribution to the discipline

This study provides a novel concept that could contribute to the understanding of normal and pathological cerebral haemodynamics. The incidence of cerebrovascular accidents (CVA) is rapidly increasing, more particularly in elderly people (> 70 years of age), in developed nations (Feigin et al., 2003). Furthermore, it has been shown that the incidence of ischemic stroke, intracerebral, and subarachnoid haemorrhage varied from 4.2% to 11.7% per thousand persons per year among people aged 55 years or more (Feigin et al., 2003, Izzy and Muehlschlegel, 2014). The global burden of stroke is increasing and cerebral arterial variations leading to misbalanced cerebral hemodynamics and intracranial aneurysms have been identified as one of the major causes of ischemic stroke and spontaneous intracerebral haemorrhage (Qureshi et al., 2001, Izzy and Muehlschlegel, 2014, Feigin et al., 2014). A study in Sweden (Nilsson et al., 2000) has shown that almost 81 out of 106 (76%) cases of subarachnoid haemorrhage resulted from spontaneous rupture of intracranial aneurysm. Larger aneurysms were at greater risk of rupture (Mitchell and Jakubowski, 2000). The global burden of stroke is increasing (Feigin et al., 2014, Izzy and Muehlschlegel, 2014). A multinational study including Australia revealed that the complete cost of disabilities from CVA varies according to patient's age, the presence of other diseases and their severity (Caro et al., 2000) and worse stroke outcomes had been noticed in women(Phan et al., 2016). Each patient spent almost 14,000 USD on treatment in the first three months of acute CVA, 70% of the cost resulted during admission and initial treatment. An Australian study done in 2009 showed a very expensive ($49,995 to $57,106) lifetime cost per CVA case (Cadilhac et al., 2009). As aneurysms have been correlated to variant and hypoplastic arteries and abnormal cerebral hemodynamic resulted from the variations, our finding broadens the interpretation of the function of the communicating arteries to the distribution of pressure waves and hemodynamic stress lowering mechanism

in the cerebral basal arterial network. However, we strongly recommend to have further research and an additional study done such as in vivo pressure measurement while performing the cerebral surgical procedures and aneurysm coiling procedures.

Conclusion

Significant differences in cross-sectional areas of incoming and outgoing arteries, together with cross-sectional area of communicating arteries could provide a mechanism for lowering the peak pressures of arterial blood perfusion of the brain, thus lowering the incidence of aneurysms.

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Conflict of interest

All the authors of this study have no conflict of interest.

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Supplementary materials

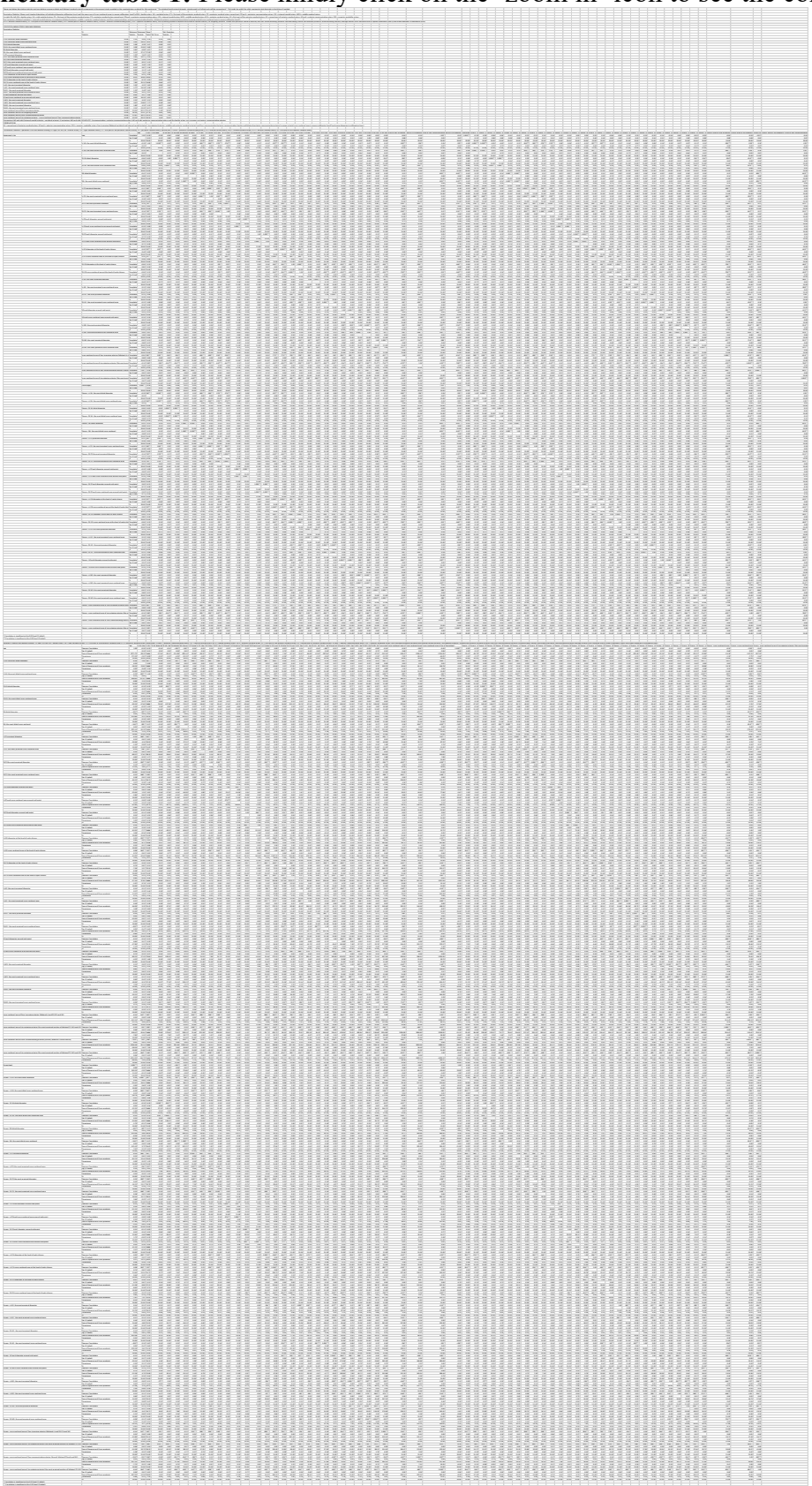
Supplementary Excel files related to this article have been published online at https://onlinelibrary.wiley.com/doi/full/10.1111/joa.12604, and supplied under 'supporting information' heading in the Journal of Anatomy webpage.

The supplementary files below are clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

Joa12604-supplementary file 1: Please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary file 1- Cerebral arterial data measured from dissected brain, measurements taken in millimeters (mm)																																		
dissectd brain no	rt VA dia		rt VA area	lft V dia		lft V area	ba ter dia	ba area	rt P2 dia		rt P2 area	lft P2 dia		lft P2 area	rt PComA cr	rt Pcom ar	lft PComA	lft Pcom ar	rt ICA dia	rt ICA area	lft ICA dia	lft ICA area	rt A2 dia		rt A2 area	lft A2 dia		lft A2 area	AComA dia	AComA ar	rt M1 dia		rt M1 area	lft M1 dia		lft M1 area	4 incoming	6 outgoing	4 commun	out +commu
4344.00	2.54	5.06	3.42	9.18	3.99	12.50	2.61	5.35	2.47	4.79	0.90	0.64	1.70	2.27	3.70	10.75	4.60	16.61	1.50	1.77	2.65	5.51	1.70	2.27	2.90	6.60	2.40	4.52	41.60	28.54	17.67	46.21
2.00	2.70	5.72	2.80	6.15	2.75	5.94	2.48	4.83	1.81	2.57	2.10	3.46	1.80	2.54	4.60	16.61	5.18	21.06	2.90	6.60	2.60	5.31	1.68	2.22	2.60	5.31	2.65	5.51	49.55	30.13	14.16	44.28
4319.00	3.34	8.76	3.42	9.18	3.40	9.07	2.50	4.91	2.56	5.14	2.45	4.71	1.10	0.95	4.15	13.52	4.79	18.01	2.70	5.72	2.80	6.15	3.58	10.06	3.11	7.59	3.10	7.54	49.47	37.06	24.80	61.86
3.00	3.95	12.25	3.23	8.19	4.19	13.78	2.70	5.72	2.80	6.15	1.64	2.11	0.89	0.62	5.85	26.86	4.53	16.11	4.25	14.18	1.10	0.95	4.44	15.48	3.60	10.17	3.00	7.07	63.41	44.24	31.99	76.23
4342/5	2.53	5.02	4.12	13.32	4.40	15.20	2.35	4.34	2.93	6.74	0.80	0.50	0.90	0.64	5.15	20.82	4.18	13.72	3.13	7.69	2.73	5.85	1.70	2.27	2.80	6.15	2.90	6.60	52.89	37.37	18.60	55.98
4.00	3.08	7.45	3.84	11.58	3.75	11.04	2.56	5.14	2.86	6.42	0.70	0.38	1.30	1.33	5.50	23.75	5.23	21.47	2.62	5.39	2.84	6.33	2.50	4.91	3.90	11.94	3.50	9.62	64.24	44.84	17.66	62.50
FGP82000	3.56	9.95	3.55	9.89	4.10	13.20	2.38	4.45	2.55	5.10	1.17	1.07	1.80	2.54	3.60	10.17	4.70	17.34	2.70	5.72	3.20	8.04	2.20	3.80	3.30	8.55	2.70	5.72	47.36	37.58	20.61	58.20
FGP72000	3.10	7.54	2.60	5.31	5.00	19.63	2.80	6.15	2.70	5.72	2.64	5.47	1.40	1.54	4.30	14.51	4.20	13.85	2.70	5.72	3.00	7.07	1.27	1.27	3.10	7.54	2.80	6.15	41.21	38.36	27.90	66.26
FGP62000	3.19	7.99	3.41	9.13	4.20	13.85	2.76	5.98	2.50	4.91	0.90	0.64	0.70	0.38	4.00	12.56	4.10	13.20	2.40	4.52	2.20	3.80	1.20	1.13	2.70	5.72	3.30	8.55	42.87	33.48	16.00	49.48
FGP52000	3.70	10.75	3.80	11.34	2.65	5.51	2.80	6.15	2.50	4.91	3.00	7.07	1.00	0.79	4.06	12.94	4.50	15.90	2.20	3.80	3.00	7.07	2.30	4.15	2.80	6.15	3.00	7.07	50.92	35.14	17.52	52.66
FGP32000	3.57	10.00	3.39	9.02	4.40	15.20	3.00	7.07	3.00	7.07	1.60	2.01	3.13	7.69	6.17	29.88	5.57	24.35	2.23	3.90	2.50	4.91	0.30	0.07	2.40	4.52	2.77	6.02	73.26	33.48	24.97	58.45
FGP52002	3.90	11.94	4.38	15.06	4.50	15.90	2.50	4.91	2.60	5.31	1.70	2.27	1.90	2.83	5.90	27.33	5.95	27.79	3.70	10.75	2.40	4.52	3.60	10.17	4.20	13.85	3.70	10.75	82.12	50.08	31.17	81.25
unisa1	3.54	9.84	3.40	9.07	4.40	15.20	2.48	4.83	2.45	4.71	0.71	0.40	1.40	1.54	4.04	12.81	3.90	11.94	2.00	3.14	2.20	3.80	1.70	2.27	3.20	8.04	3.30	8.55	43.66	33.07	19.40	52.47
unisa2	3.75	11.04	3.62	10.29	6.35	31.65	3.50	9.62	3.10	7.54	0.40	0.13	0.50	0.20	5.14	20.74	4.40	15.20	2.70	5.72	2.70	5.72	0.92	0.66	3.45	9.34	3.26	8.34	57.26	46.29	32.64	78.93
unisa3	1.14	1.02	4.04	12.81	2.90	6.60	2.40	4.52	2.24	3.94	1.98	3.08	2.20	3.80	4.26	14.25	3.70	10.75	2.42	4.60	2.10	3.46	1.05	0.87	3.10	7.54	2.50	4.91	38.83	28.97	14.34	43.31
Adel no labelling	4.76	17.79	2.80	6.15	4.50	15.90	2.90	6.60	2.80	6.15	2.10	3.46	1.90	2.83	4.90	18.85	4.80	18.09	2.50	4.91	2.36	4.37	2.10	3.46	3.49	9.56	3.20	8.04	60.87	39.63	25.65	65.29
Adel 13	2.94	6.79	3.13	7.69	4.80	18.09	2.50	4.91	2.40	4.52	0.80	0.50	1.30	1.33	4.40	15.20	4.00	12.56	2.36	4.37	2.38	4.45	1.30	1.33	2.60	5.31	1.80	2.54	42.23	26.10	21.24	47.34
Ade 5	3.70	10.75	3.80	11.34	3.76	11.10	2.99	7.02	3.30	8.55	3.40	9.07	0.80	0.50	5.01	19.70	4.30	14.51	2.60	5.31	2.70	5.72	2.90	6.60	2.90	6.60	3.16	7.84	56.30	41.04	27.28	68.31
Ade 11	2.40	4.52	3.98	12.43	5.49	23.66	2.04	3.27	2.40	4.52	0.70	0.38	1.22	1.17	4.39	15.13	4.00	12.56	2.50	4.91	3.00	7.07	3.00	7.07	3.38	8.97	2.90	6.60	44.64	35.33	32.28	67.61
Adel E6	2.80	6.15	4.26	14.25	3.50	9.62	2.71	5.77	2.77	6.02	1.37	1.47	0.00	0.00	3.30	8.55	3.17	7.89	2.63	5.43	2.56	5.14	1.00	0.79	2.70	5.72	3.00	7.07	36.84	35.15	11.87	47.02
Adel C7	3.00	7.07	2.80	6.15	4.90	18.85	2.10	3.46	2.41	4.56	2.23	3.90	1.10	0.95	4.00	12.56	3.90	11.94	2.25	3.97	2.27	4.05	0.00	0.00	2.80	6.15	3.10	7.54	37.72	29.74	23.70	53.44
Adel 10	4.45	15.54	1.98	3.08	6.20	30.18	2.54	5.06	2.61	5.35	1.35	1.43	1.70	2.27	5.62	24.79	4.50	15.90	2.80	6.15	2.60	5.31	1.97	3.05	2.25	3.97	2.40	4.52	59.31	30.37	36.92	67.29
Adl not labelled	2.50	4.91	2.50	4.91	5.79	26.32	2.17	3.70	2.25	3.97	2.27	4.05	1.25	1.23	4.00	12.56	4.60	16.61	2.60	5.31	2.74	5.89	1.85	2.69	3.30	8.55	3.18	7.94	38.98	35.36	34.27	69.63
Adel 5 repeated	3.26	8.34	4.30	14.51	3.80	11.34	2.64	5.47	2.34	4.30	0.85	0.57	1.20	1.13	5.44	23.23	6.70	35.24	2.15	3.63	3.10	7.54	2.67	5.60	3.00	7.07	3.23	8.19	81.33	36.20	18.63	54.83
unisa12.15.1	2.86	6.42	3.27	8.39	4.20	13.85	2.64	5.47	2.53	5.02	1.71	2.30	1.32	1.37	4.74	17.64	3.80	11.34	2.54	5.06	2.24	3.94	2.23	3.90	2.94	6.79	2.85	6.38	43.79	32.66	21.41	54.07
unisa12.15.2	3.00	7.07	3.12	7.64	4.30	14.51	1.90	2.83	2.10	3.46	0.86	0.58	0.54	0.23	4.73	17.56	3.75	11.04	2.45	4.71	2.53	5.02	1.25	1.23	3.58	10.06	2.15	3.63	43.31	29.72	16.55	46.27
unisa12.15.3	3.40	9.07	3.66	10.52	5.09	20.34	2.71	5.77	2.36	4.37	1.31	1.35	1.62	2.06	4.59	16.54	4.62	16.76	2.90	6.60	2.79	6.11	1.97	3.05	2.91	6.65	3.33	8.70	52.88	38.20	26.79	64.99
unisa12.15.4	4.96	19.31	3.11	7.59	5.69	25.42	3.02	7.16	2.67	5.60	1.34	1.41	1.42	1.58	4.59	16.54	4.60	16.61	2.16	3.66	2.80	6.15	2.40	4.52	3.65	10.46	3.35	8.81	60.05	41.84	32.93	74.77
unisa12.15.5	1.88	2.77	2.78	6.07	4.18	13.72	2.55	5.10	2.33	4.26	2.03	3.23	2.14	3.59	3.85	11.64	4.00	12.56	2.51	4.95	2.19	3.76	2.36	4.37	3.10	7.54	3.08	7.45	33.04	33.07	24.92	57.99
unisa12.15.6	3.76	11.10	2.93	6.74	4.48	15.76	2.58	5.23	2.56	5.14	1.08	0.92	1.20	1.13	4.40	15.20	4.45	15.54	2.90	6.60	2.50	4.91	2.00	3.14	2.70	5.72	2.94	6.79	48.58	34.39	20.94	55.33
unisa12.15.7	3.10	7.54	3.70	10.75	4.86	18.54	2.09	3.43	2.60	5.31	1.43	1.61	0.82	0.53	4.19	13.78	4.81	18.16	2.19	3.76	2.78	6.07	2.50	4.91	3.40	9.07	3.35	8.81	50.23	36.45	25.58	62.03
unisa12.15.8	2.59	5.27	3.59	10.12	5.08	20.26	2.66	5.55	2.71	5.77	2.64	5.47	2.66	5.55	6.25	30.66	4.90	18.85	2.70	5.72	3.05	7.30	1.43	1.61	3.83	11.52	4.10	13.20	64.89	49.06	32.89	81.94
unisa12.15.9	2.62	5.39	3.15	7.79	4.46	15.61	2.54	5.06	2.45	4.71	1.86	2.72	1.65	2.14	4.49	15.83	4.65	16.97	2.72	5.81	2.85	6.38	2.10	3.46	3.16	7.84	3.26	8.34	45.98	38.14	23.93	62.07
unisa	3.47	9.45	3.60	10.17	3.55	9.89	2.85	6.38	2.37	4.41	1.41	1.56	0.93	0.68	4.20	13.85	3.87	11.76	2.76	5.98	2.37	4.41	1.47	1.70	2.76	5.98	3.70	10.75	45.23	37.90	13.83	51.73
4419.00	3.18	7.94	4.36	14.92	6.90	37.37	3.10	7.54	2.61	5.35	0.99	0.77	1.01	0.80	4.32	14.65	4.97	19.39	2.46	4.75	3.27	8.39	2.57	5.18	3.23	8.19	3.73	10.92	56.90	45.15	44.13	89.28
4433.00	3.23	8.19	3.24	8.24	5.58	24.44	2.64	5.47	2.55	5.10	1.69	2.24	1.01	0.80	4.60	16.61	4.56	16.32	2.30	4.15	2.49	4.87	1.19	1.11	3.30	8.55	2.69	5.68	49.36	33.82	28.60	62.42
4418.00	2.66	5.55	3.62	10.29	5.24	21.55	2.50	4.91	2.75	5.94	1.51	1.79	1.70	2.27	4.39	15.13	4.43	15.41	3.10	7.54	2.52	4.99	1.17	1.07	3.22	8.14	4.06	12.94	46.38	44.45	26.69	71.14
4422.00	3.34	8.76	4.35	14.85	6.00	28.26	3.60	10.17	2.61	5.35	1.98	3.08	1.06	0.88	4.94	19.16	5.36	22.55	2.90	6.60	3.20	8.04	3.85	11.64	3.53	9.78	3.47	9.45	65.32	49.40	43.86	93.25
4458.00	2.89	6.56	3.88	11.82	3.31	8.60	2.76	5.98	2.86	6.42	1.43	1.61	1.97	3.05	4.30	14.51	4.86	18.54	2.98	6.97	2.87	6.47	1.00	0.79	3.01	7.11	3.44	9.29	51.43	42.24	14.04	56.28
4401.00	2.90	6.60	3.94	12.19	4.65	16.97	2.67	5.60	2.01	3.17	2.62	5.39	1.13	1.00	4.27	14.31	4.85	18.47	3.08	7.45	2.25	3.97	3.16	7.84	2.64	5.47	3.46	9.40	51.57	35.06	31.20	66.26
4433.00	3.59	10.12	4.01	12.62	4.81	18.16	3.29	8.50	3.15	7.79	2.23	3.90	1.41	1.56	4.58	16.47	5.11	20.50	3.07	7.40	3.20	8.04	2.39	4.48	3.35	8.81	3.90	11.94	59.70	52.47	28.11	80.58
4452.00	3.91	12.00	3.17	7.89	4.93	19.08	2.30	4.15	2.68	5.64	2.71	5.77	1.28	1.29	5.13	20.66	4.94	19.16	2.59	5.27	3.48	9.51	2.51	4.95	2.91	6.65	3.81	11.40	59.71	42.61	31.08	73.68
4432.00	3.67	10.57	3.47	9.45	5.56	24.27	2.45	4.71	2.61	5.35	1.70	2.27	2.02	3.20	4.72	17.49	4.25	14.18	2.67	5.60	1.99	3.11	1.75	2.40	3.76	11.10	3.96	12.31	51.69	42.17	32.14	74.32
4423.00	2.63	5.43	3.75	11.04	4.30	14.51	2.66	5.55	3.01	7.11	1.06	0.88	0.81	0.52	4.58	16.47	5.33	22.30	3.06	7.35	2.36	4.37	4.57	16.39	3.80	11.34	3.38	8.97	55.24	44.69	32.31	77.00
4439.00	3.35	8.81	4.21	13.91	4.25	14.18	2.38	4.45	3.05	7.30	1.45	1.65	1.46	1.67	4.32	14.65	4.74	17.64	3.01	7.11	2.56	5.14	2.01	3.17	3.08	7.45	3.75	11.04	55.01	42.49	20.67	63.17
4457.00	2.51	4.95	2.97	6.92	4.07	13.00	2.09	3.43	2.44	4.67	0.91	0.65	2.45	4.71	3.41	9.13	5.49	23.66	2.74	5.89	2.40	4.52	3.10	7.54	2.80	6.15	3.58	10.06	44.66	34.73	25.91	60.64
4411.00	3.15	7.79	2.86	6.42	4.52	16.04	2.34	4.30	2.68	5.64	2.11	3.49	2.25	3.97	4.47	15.69	4.25	14.18	2.18	3.73	2.32	4.23	3.10	7.54	2.92	6.69	3.31	8.60	44.07	33.19	31.05	64.24
4441.00	1.67	2.19	4.11	13.26	4.10	13.20	2.56	5.14	2.10	3.46	1.05	0.87	1.50	1.77	3.57	10.00	3.65	10.46	2.36	4.37	2.48	4.83	1.60	2.01	3.10	7.54	3.19	7.99	35.91	33.34	17.84	51.18
4437.00	3.28	8.45	3.42	9.18	6.06	28.83	2.61	5.35	2.59	5.27	1.35	1.43	1.65	2.14	4.15	13.52	4.72	17.49	2.32	4.23	2.85	6.38	1.49	1.74	2.89	6.56	2.95	6.83	48.64	34.60	34.14	68.74
4447.00	3.34	8.76	3.35	8.81	5.41	22.98	2.57	5.18	2.52	4.99	0.87	0.59	0.96	0.72	4.64	16.90	4.69	17.27	2.43	4.64	2.34	4.30	0.98	0.75	2.94	6.79	3.40	9.07	51.73	34.96	25.05	60.01
4456.00	2.83	6.29	2.72	5.81	4.02	12.69	2.69	5.68	2.87	6.47	2.25	3.97	2.39	4.48	4.83	18.31	5.06	20.10	2.58	5.23	2.73	5.85	1.96	3.02	3.10	7.54	3.72	10.86	50.51	41.63	24.16	65.79
Average	3.16	8.21	3.47	9.68	4.57	17.08	2.61	5.44	2.59	5.33	1.59	2.36	1.42	1.86	4.56	16.69	4.59	16.86	2.63	5.58	2.61	5.47	2.06	4.03	3.12	7.77	3.19	8.17	51.43	37.76	25.33	60.19
4 incoming= left and right (internal carotid arteries + vertebral arteries), 6 out going= left and right (A2+M1+P2), 4 communicating = anterior communicating artery, left and right posterior communicating artery and the basilar artery, out +commu= out going + communicating arteries																																		
rt/ Rt = right, lft lt = left, p2/ P2 = second segment of posterior cerebral artery, a/ A = area,																																		
rt P2 = right posterior cerebral artery P2 segment proximal internal diameter; rt p2a= right posterior cerebral artery P2 segment cross sectional area																																		
lt P2 = left posterior cerebral artery P2 segment proximal internal diameter; lft p2a= left posterior cerebral artery P2 segment cross sectional area																																		
rt A2 = right anterior cerebral artery A2 segment proximal internal diameter; rta2a= right anterior cerebral artery A2 segment proximal cross sectional area																																		
lft A2 = left anterior cerebral artery A2 segment proximal internal diameter; lfta2a= right anterior cerebral artery A2 segment proximal cross sectional area																																		
rt A2 = right anterior cerebral artery A2 segment proximal external diameter, A2 = second segment of anterior cerebral artery, lft A2 = left anterior cerebral artery A2 segment proximal external diameter																																		
M1 = first segment of middle cerebral artery																																		
Rt M1 = right middle cerebral artery M1 segment proximal external diameter; rtm1a= right middle cerebral artery M1 segment proximal cross sectional area																																		
Lt M1 =left middle cerebral artery M1 segment proximal internal diameter; lftm1a= left middle cerebral artery M1 segment proximal cross sectional area																																		
right p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area																																		
p2= second segment of posterior cerebral artery, a2/ A2 = second segment of anterior cerebral artery, m1/ M1 = first segment of middle cerebral artery																																		
left p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area																																		
BA ter dia = basilar artery external diameter at the distal point mid way between posterior cerebral and superior cerebral arteries																																		
rt VA dis = right vertebral artery distal external diameter																																		
dist = distal, l/ lt / lft/ Lft= left, rt/ Rt = right, Lt= left, ter = terminal, mid = mid point																																		
lft VA dis = left vertebral artery distal external diameter																																		
rt P2 = right posterior cerebral artery P2 segment proximal external diameter																																		
lt P2 = left posterior cerebral artery P2 segment proximal external diameter																																		
rt PComA= right posterior communicating artery external diameter at the mid point																																		
lft PcomA/PoCA mid dia = left posterior communicating artery external diameter at the mid point																																		
rt ICA / IntCA ext dia ocl = right internal carotid arterial external diameter around the optic chiasm level, ocl = optic chiasm level																																		
lft ICA / IintCA ext OCL = left internal carotid arterial external diameter around the optic chiasm level																																		
IntCA = ICA = internal carotid artery,																																		
rt A2 = right anterior cerebral artery A2 segment proximal external diameter, A2 = second segment of anterior cerebral artery, lft A2 = left anterior cerebral artery A2 segment proximal external diameter																																		
AcomA/ ACoA mid dia = anterior communicating artery external diameter around mid point																																		
r/ rt SCA prox dia = right superior cerebellar artery proximal external diameter																																		
l/ lft SCA prox dia = left superior cerebellar artery proximal external diameter																																		
Rt M1 = right middle cerebral artery M1 segment proximal external diameter																																		
Lt M1 prox dia = left middle cerebral artery M1 segment proximal exrternal diameter																																		
Measurements were taken from cadaveric brain specimens- Adelaide Medical School RayLastLab, University of Adelaide, Australia																																		

Joa12604-supplementary table 1: Please kindly click on the ‘zoom in’ icon to see the contents clearly.



Chapter 2: Asymmetries of total arterial supply of cerebral hemispheres do not exist

Article DOI: 10.1016/j.heliyon.2018. e01086.

This journal paper has been published in the **Heliyon** on 9 January 2019.

This Journal ranking = Q1 (2019 and 2020), comprises the quarter of the journals with the highest values.

The Heliyon, a peer reviewed journal is one of the highly ranked journals in the field of medicine with 1.650 impact factor (updated in 2020).

This paper has been cited by three following research articles till the date

1. Blood flow rate and wall shear stress in seven major cephalic arteries of humans

RS Seymour, Q Hu, EP Snelling - Journal of Anatomy, 2020 - Wiley Online Library

Blood flow rate in relation to arterial lumen radius (ri) is commonly modelled according to theoretical equations and paradigms, including Murray's Law ($\propto$) and da Vinci's Rule ($\propto$). Wall shear stress (τ) is independent of ri with Murray's Law ($\tau\propto$) and decreases with da …

2. Unilateral Relapsing Primary Angiitis of the CNS: An Entity Suggesting Differences in the Immune Response Between the Cerebral Hemispheres

MA AbdelRazek, JM Hillis, Y Guo… - Neurology …, 2021 - AAN Enterprises

Objective To determine whether studying patients with strictly unilateral relapsing primary angiitis of the CNS (UR-PACNS) can support hemispheric differences in immune response mechanisms, we reviewed characteristics of a group of such patients. Methods We surveiled …

3. АСИММЕТРИЯ БИЛАТЕРАЛЬНОГО КРОВОТОКА И ИНТЕГРАЛЬНАЯ ОЦЕНКА КОГНИТИВНЫХ ФУНКЦИЙ У БОЛЬНЫХ ДИСЦИРКУЛЯТОРНОЙ …

ВФ Фокин, РБ Медведев… - Journal of …, 2020 - search.ebscohost.com

Больные дисциркуляторной энцефалопатией (ДЭ) страдают хронической сосудистой недостаточность и в силу этого могут быть чувствительны к относительно небольшим, гемодинамически незначимым, колебаниям скорости кровотока. Оценивались …

Context for the second chapter

There is an interest and studies published on functional and structural lateralisation of human cerebral hemispheres extensively, however, most of the findings related to the hemispheric lateralization are ambiguous and have no definitive results [1-9]. Furthermore, the handedness has been taken as a common reflection of cerebral hemispheric lateralisation, and yet it can be easily altered by a training [8, 10-13]. Blood supply to each cerebral hemisphere comes from three major branches of the cerebral basal arterial network [14, 15].

It is a well-known scientific principle that the blood supply reflects the magnitude of the cerebral cortical function [16]. In addition, the cross-sectional area of an artery is directly proportional [17, 18] to the amount of blood flowing through the artery. It was possible to test whether totality of functions of one cerebral hemisphere is greater than the other one, since we have collected data on cross-sectional areas and sizes of all cerebral arteries, bringing blood to the hemispheres.

It follows that cross-sectional areas of the arteries supplying each cerebral hemisphere are good indicators of quantity of functions of cerebral hemispheres. Therefore, the research interest was expanded on investigating whether the asymmetricity in arteries supplying the two distinct cerebral hemispheres and the lateralisation of their total functions exists or not. The scientific finding turns out to be that there is no asymmetry in total functions of right and left cerebral hemispheres, since the arterial supply of each

hemisphere proportional to the function is the same. This finding [19] is useful and has already been cited a number of times.

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Principal Author

Name of Principal Author	Arjun Burlakoti		
Contribution to the Paper	Conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, contributed reagents, materials, analysis tools or data. Dissecting the cadaveric specimens, collected the Cerebral Computed Tomography Angiography (CCTA) and Magnetic resonance angiography (MRA) data, taking pictures, recording videos, preparing and wrote the main manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19th January 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jaliya Kumaratilake		
Contribution to the Paper	Conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, contributed reagents, materials, analysis tools or data and wrote and edit the paper		
Signature		Date	19th January 2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Jamie Taylor		
Contribution to the Paper	Conceived and designed the experiments, analysed and interpreted the data, contributed reagents, materials, analysis tools or data, and wrote and edit the paper.		
Signature		Date	25th January 2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Maciej Henneberg		
Contribution to the Paper	Conceived and designed the experiments, performed the experiments, analyzed and interpreted the data, contributed reagents, materials, analysis tools or data and wrote and edit the paper		
Signature		Date	19th January 2021

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Asymmetries of total arterial supply of cerebral hemispheres do not exist

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Article: Asymmetries of total arterial supply of cerebral hemispheres do not exist.

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Abstract

Background

Total blood supply to an organ, or its part, is proportional to its function. The aim of this project was to investigate whether there is a lateralisation of total functions of cerebral hemispheres by determining differences in the arterial blood supply to left and right cerebral hemispheres.

Methods

Diameters of right and left anterior, middle and posterior cerebral arteries were measured at specific sites and cross-sectional areas calculated in 203 adult brains (51 donated and dissected brain specimens and 152 cerebral arterial Computed Tomography Angiography and Magnetic Resonance Angiography images).

Findings

The sample size was large enough to provide a power of detecting as significant differences of 4%, but neither of the average cross-sectional areas of right anterior, middle and posterior cerebral arteries were significantly different from those of the anterior, middle and posterior cerebral arteries of the left side. Furthermore, combined areas of the three right cerebral arteries were not significantly different from combined areas of the left three arteries. This clearly indicates that the blood supply into the right cerebral hemisphere is not different from that of the left cerebral hemisphere. Therefore, there is no total functional lateralisation between the two cerebral hemispheres.

Conclusion

Brain lateralisation, frequently discussed in the literature, does not deferentially influence the total activity levels of cerebral hemispheres.

Keywords

Anatomy, Neuroscience

Introduction

Specialisation of neural functions of the brain to one hemisphere rather than the other hemisphere [1] has been referred to as lateralisation of a brain function. Pierre Paul Broca [2] (1861-1865) proposed the idea that the left hemisphere is functionally lateralised for language processes and many others expanded the idea of lateralization [3-5] of cerebral hemispheres regarding speech and language processes, and the handedness [4]. The concept of lateralization of some specific functions seems to hold true statistically, however, many individuals do not conform to this pattern. Music perception, rhythms and synthesis of pitches [2, 6, 7] are examples of functions that are not specialized to a cerebral hemisphere. Benton and colleagues [8] found that both cerebral hemispheres are involved in facial perception and the memory. A behavioural functional Magnetic Resonance Imaging (MRI) study done on 12 right-handed individuals suggested that the right frontal cortex mostly and sometimes bilateral frontal cortices [9] were involved in memory retrieval procedure.

It has been suggested that functional asymmetries are reflected in structural asymmetries between the two hemispheres of the brain. Structural symmetry and asymmetry of the brain, in relation to the function and the relationship of the structural asymmetry to lateralisation of the functions have been investigated extensively [10]. The structural asymmetry in right and left hemispheres has been discussed based on the depth of the central sulcus, larger anteriorly protruding right frontal lobe and the longer and posteriorly protruded left occipital lobe [10]. However, most of the findings related to the lateralization are ambiguous and have no definitive results [3, 11-16].

A book [16] on brain hemispheric lateralization has highlighted the cortical structural asymmetries, but the measured regions and the technique used to take measurements were not clear [16, 17]. This book has mentioned the handedness and behavioural functional lateralization in relation to the size of corpus callosum. However, the role of tracts of corpus callosum is to increase the interhemispheric connectivity and ensure involvement of cortical components of both cerebral hemispheres in specific functions [5]. A recent investigation of Magnetic Resonance Imaging (MRI) scans of brains obtained from more than 17000 healthy

individuals did not show bilateral variation in cerebral cortex thickness of most of the 39 regions of the cortex of the two hemispheres [18].

Furthermore, in cerebral regions where variations in cortical thickness between the hemispheres were evident, variations of the surface areas were also seen. That is, if the cortical thickness of one region was lesser than that of the same region of the contralateral hemisphere, the surface area of the thinner region was greater than that of thicker region of the contralateral hemisphere and vice versa [18]. This indicates that the volume of the cortical tissues of the brain regions of the two hemispheres remained similar. Therefore, this large study did not show structural evidence for variations in cortical function between hemispheres. A study, done in 54 adult donated brains, found that neither total dimensions of cerebral hemispheres (width, length and height), nor sizes of their major anatomical features (length of main sulci or height and length of lobes) showed any significant right-left differences [19]. The asymmetric patterns of dural venous sinuses result in the entire cerebral hemispheres to move anteriorly or posteriorly producing apparently asymmetric locations of occipital and frontal poles [20]. The arrangements and positions of posterior and lateral cerebral dural venous sinuses were studied in 58 brains and concluded that entire cerebral hemispheres moved in accordance with dural venous sinus asymmetries anteriorly or posteriorly producing asymmetric “petalia” [20]. Handedness has been considered as a common manifestation of cerebral lateralisation, and yet handedness can be easily changed by training [21-24].

Cross-sectional areas of nutrient foramina in mammalian long bones correlate with actual blood flow into the bone and its metabolic rate [25]. Arterial blood supply of a cortical area of the cerebral hemisphere has been shown to be directly proportional to the magnitude of its function [26]. Cross sectional area of an artery is directly proportional [27, 28] to the amount of blood flowing through the artery. It follows that cross-sectional areas of the arteries supplying each cerebral hemisphere are good indicators of functions in the hemispheres. Therefore, comparing sizes of arteries supplying right and left hemispheres should provide information about lateralisation of functions of areas they supply. Blood supply to each cerebral hemisphere comes from only three major branches of the cerebral basal arterial network (CBAN) comprising the vertebrobasilar component

(posterior part) and the circulus arteriosus cerebri (anterior part) [29]. Therefore, although cerebral hemispheres are complex entities, it is easy to measure their total blood supply by adding together areas of the three cerebral arteries: anterior, middle and posterior. This study determined the cross-sectional areas of arteries supplying each cerebral hemisphere of the human brain with the aim of testing whether one hemisphere is functionally dominant over the other by determining differences in their arterial blood supply.

Methods and materials

Data section

Arterial diameters were determined on Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) digital recordings obtained from 152 live adult patients at the Royal Adelaide Hospital documented in the Carestream database and in 51 adult brains dissected out from human bodies. Patients' documented in the Carestream database had given written permission to university clinicians and academics to use the data for research purposes after obtaining ethics approval. Patient's identities have not been recorded and documented. The dissected bodies were donated to Adelaide Medical School, the University of Adelaide for research. All measurements were taken after obtaining approval from the University of Adelaide ethics committee (Ethics approval No. H2014-176).

Data collection and measurement

Diameters of anterior, middle and posterior cerebral arteries were measured bilaterally in dissected brains and MRA and CTA scans [30] at the sites indicated in Figures 1, 2 and 3. In donated brains, external diameters of the arteries were measured using a digital Vernier caliper. In digital images of MRA and CTA scans obtained from live patients; the internal diameters of the three arteries were measured using image J software programme [30, 31].

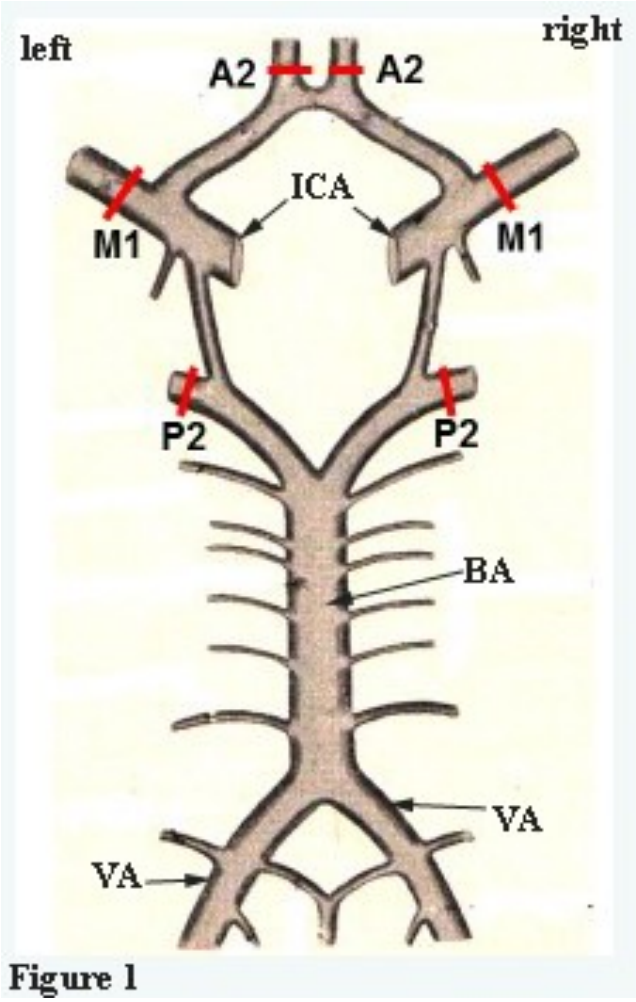

Figure 1

Figure 1: Schematic diagram. Red lines perpendicular to the long axis of the vessels indicate measurement sites, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, rt = right, lft = left, A2= the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA

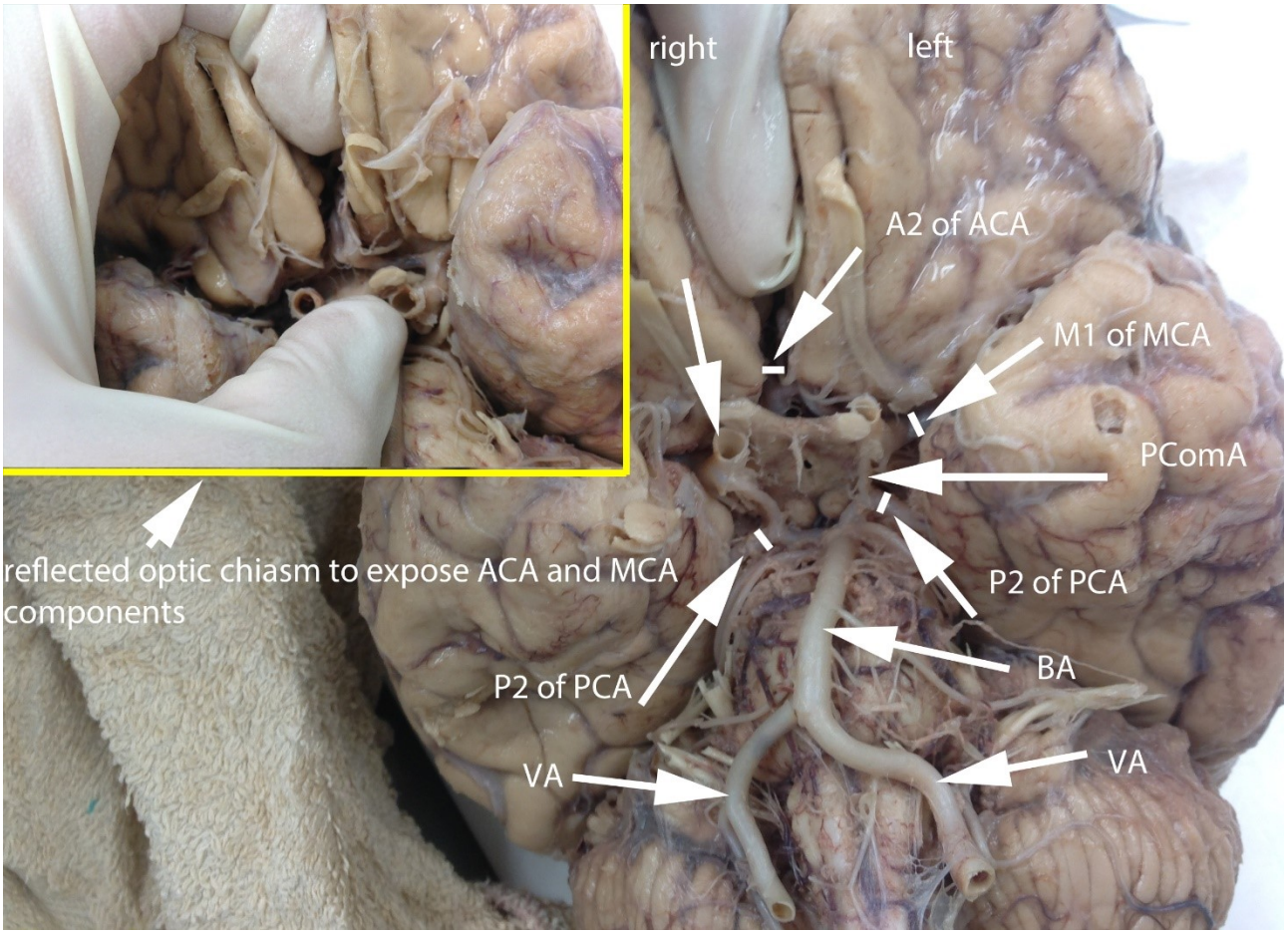

Figure 2: Basal view of the brain, white lines without arrows showing the measurement sites of vessel diameter, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, rt = right, lft = left, A2= the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA, BA = basilar artery, ICA = internal carotid artery, VA = vertebral artery

External diameters of the arteries in donated brains and internal diameters in MRA and CTA digital scans are the only diameters that could be measured accurately. The digital Vernier calipers have been commonly used [32-36] to measure the arterial diameter in cadaveric brains. Magnetic Resonance Angiography and CTA have been used for morphometry of different components of brain and they seem to be more accurate [30] than measurements taken physically on brains. The accuracy and the reliability of the measurements were determined by repeating the procedure in 15 cadavers, and 10 MRA and CTA digital scans. Technical errors of measurement (TEM) and reliability coefficients (r) are presented in Table 1. This project is designed to

observe the differences in the blood supply between the left and right cerebral hemispheres of each brain comparing the left and right arteries of the same individuals, thus the arterial measurements were not subdivided into groups according to the method of measurement nor according to the age and sex.

Statistical analysis

A priori power analysis with a power 0·80 and two-tailed probability 0·05 indicated that to detect in a paired t-test a difference of about 10% in mean arterial diameters (Cohen's effect size of 0·5), the minimum sample size is 33. Both samples exceeded this size. A sample size of 128 was required to detect 5% mean difference with the same assumed parameters.

Figure 3a and 3b: Figure showing the sites of arterial diameter measurement in reconstructive cerebral arterial Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), rt = right, lft = left, green lines showing the measurement sites of vessel diameters, A2 = the most proximal portion of second part of anterior cerebral artery and M1 = the most proximal portion of the first part of middle cerebral artery.

This sample size was exceeded by our scan data (N = 152) and by joined samples (N = 203). A sample of 198 was needed to detect 4% size differences, that is about 0·3 mm^2 in the size of the single artery or 0·7 mm^2 in the total size of arteries. Our total sample size (n = 203) exceeded the calculated 198.

Table 1: Accuracy and reliability of the measurements in Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) scans and cadaveric brains. The coefficients of variation of the measurements are presented:

Arterial components measured	Measurements in cadaveric brains (n = 15)		Measurements in CTA and MRA scans (n = 10)	
	TEM	Reliability (r)	TEM	Reliability (r)
Rt P2	0.13	0.97	0.02	0.99
Lft P2	0.10	0.97	0.04	0.98
Rt M1	0.11	0.97	0.03	0.99
Lft M1	0.07	0.97	0.02	0.99
Rt A2	0.07	0.97	0.07	0.96
Lft A2	0.21	0.97	0.04	0.98

TEM = Technical errors of measurement, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, Rt = right, Lft = left, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA.

Descriptive statistics and paired t-test were used to compare the calculated cross-sectional areas of the arteries supplying the right and left cerebral hemispheres. Probability (P) values less than 0·05 were taken as significant. Statistical analyses were conducted using SPSS v 25. Linear regressions of right on left arterial sizes were run to observe any deviation of residuals to the right or left (Figure 4). Paired t-tests were applied to each artery and to the total size of arteries. We also counted how many brains had a particular artery larger on the right and how many on the left. These numbers were compared using chi-squared sign test. The same

comparison was performed for the sum of arterial sizes dominating on the right or on the left (Tables 2 and 3).

Results

The tests were conducted separately and combinedly for data obtained from prosected brains and CTA and MRA images. Mean cross sectional areas of right and left, anterior, middle and posterior cerebral arteries of donated brains and CTA and MRA scans are presented in Table 2.

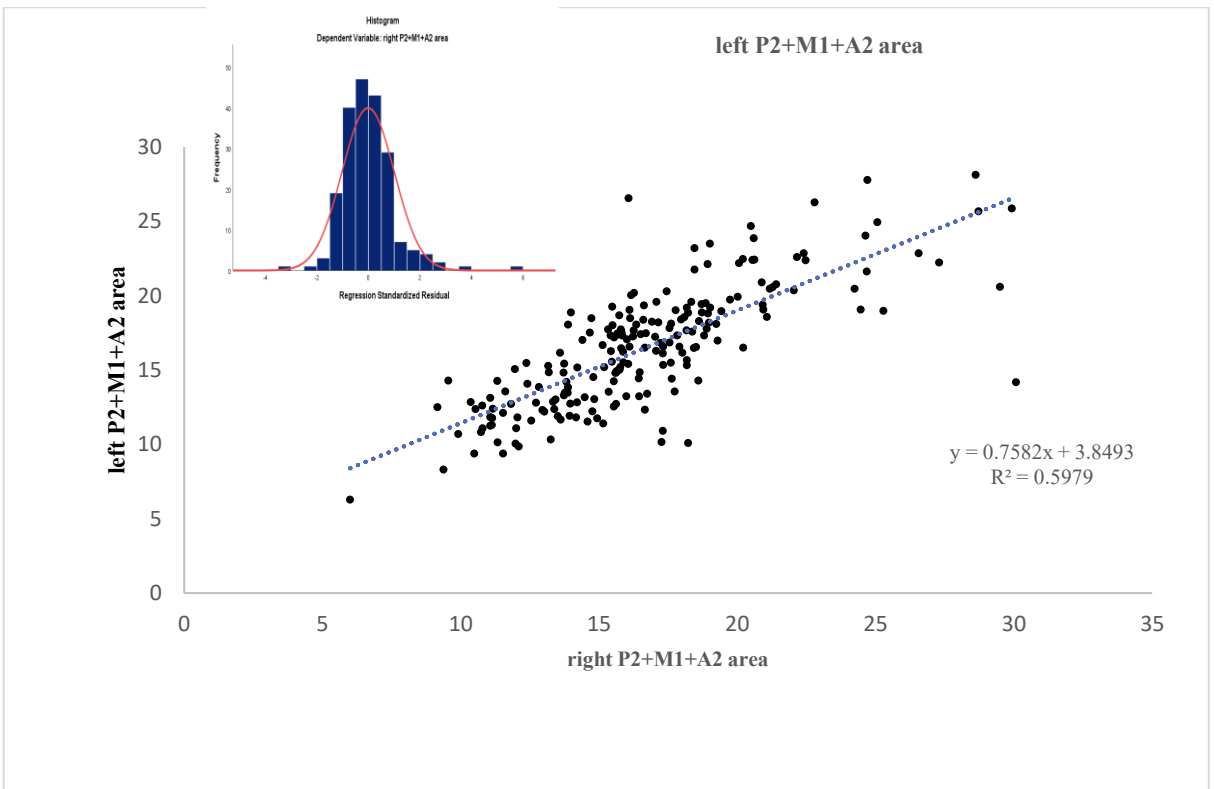

Figure 4: Sum total of cross-sectional areas (mm^2) of left anterior, posterior and middle cerebral arteries regressed on sum total of cross-sectional areas of right anterior, posterior and middle cerebral arteries. Arterial data taken from cadaveric brains and Computed Tomography Angiography and Magnetic Resonance Angiography (n = 203). Right- scattergram and left- distribution of residuals around

the regression line. Observe symmetrical distribution of residuals around zero. This distribution does not differ significantly from the normal distribution.

The average combined cross-sectional area of right anterior, middle and posterior cerebral arteries supplying the right cerebral hemisphere of dissected brains (18·8 mm^2) did not differ significantly (t = 0·6) from the relevant value for the left hemisphere (19·0 mm^2).

Table 2: Means and standard deviations (mm^2), and paired samples t-test results comparing right and left anterior, middle and posterior cerebral arterial cross sectional areas determined from dissected cadaveric brains, Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) data.

Items	**cadaveric paired sample test, N=51**				**CTA and MRA scan- paired sample test, N=152**				**Total (cadaveric and scans) paired sample test, N=203**			
	right	**left**			**right**	**left**			**right**	**left**		
	mean *(Std.Dev)*	**mean** *(Std.Dev)*	**paired t-test** *t- value*	**sign.**	**mean** *(Std.Dev)*	**mean** *(Std.Dev)*	**paired t-test** *t- value*	**sign.**	**mean** *(Std.Dev)*	**mean** *(Std.Dev)*	**paired t-test** *t- value*	**sign.**
ACA A2a	5.6	5.5	0.3	ns	4.5	4.4	1.8	ns	4.8	4.6	1.2	ns
	1.9	*1.6*			*1.5*	*1.4*			*1.7*	*1.5*		
MCA M1a	7.8	8.3	-1.7	ns	6.7	6.7	0.3	ns	7.0	7.1	-0.8	ns
	2.0	*2.3*			*2.1*	*2.1*			*2.1*	*2.2*		
PCA P2a	5.4	5.3	0.5	ns	4.7	4.5	1.3	ns	4.9	4.7	1.4	ns
	1.4	*1.2*			*1.6*	*1.4*			*1.6*	*1.4*		
ACA A2a+ MCA M1a+PCA P2a	18.8	19.0	-0.6	ns	15.9	15.6	1.8	ns	16.6	16.5	0.9	ns
	3.6	*3.5*			*4.0*	*3.8*			*4.1*	*4.0*		

N = 203, PCA= posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, rt = right, lft = left, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA, ns = not significant

In CTA and MRA study, the average combined cross-sectional area of three right cerebral arteries was 15·9 mm^2 while on the left it was 15·6 mm^2 (t = 1·8). Dissected brains indicated that the arteries were larger on the left and the MRA and CTA scans data showed that the arteries were larger on the right side. These differences were random and fell within the insignificant range.

Table 3: Cross-sectional area measured on left and right cerebral arteries from cadaveric and Computed Tomography Angiography and Magnetic Resonance Angiography scans data and their comparison using formula; χ^2 = (left-right)^2/(left +right), n = 203. lft = left, rt = right, P2a = posterior cerebral artery second part (P2 proximal segment) cross sectional area, A2a= anterior cerebral artery second part (A2 segment) proximal cross-sectional area, M1a = middle cerebral artery first part (M1 segment) proximal cross-sectional area in mm^2 , ns = not significant

arterial area	arterial cross-sectional area	larger on:		χ^2
	equal	left	right	
A2a	5	93	105	ns
M1a	7	100	96	ns
P2a	9	93	101	ns

In the combined cadaveric and the scanned samples, the average difference between the total right and left areas of arteries was 0·09 mm^2. It was not significant (t = 0·5). The results for the left and right differences of individual arteries- anterior, middle and posterior, were small and all statistically insignificant. The residuals of regressions of right cerebral arterial cross-sectional areas on corresponding arterial cross-sectional areas of the left were normally symmetrically distributed around a mode of zero (Figures 4). The number of

the brains showing larger arteries on the right was similar to that on the left, statistically these numbers were indistinguishable because the test, $\chi 2$ = (left-right)2/(left +right) did not provide the significant results (Table 3).

Discussion

Current study shows that there are no right and left differences in cross sectional areas of arteries supplying the cerebral hemispheres (Tables 2 and 3). These clearly indicate that in the left cerebral hemisphere, there are no additional functional areas in the territories supplied by the anterior, middle and posterior cerebral arteries compared to the same territories of the right hemisphere. Lateralisation of one or more functions to a cerebral hemisphere is expected to associate with increase in the volume of cortical tissues of the respective area/areas (i.e. thickness or surface area or both of the specific region/regions) compared to the contralateral hemisphere. This will result in increased need for blood supply, thus the cross-sectional area of an artery supplying the region, and the total cross-sectional areas of arteries supplying a cerebral hemisphere should increase. Dominance of one hemisphere should lead to the asymmetry of the size of arteries. Where there is no laterization of the function, blood flow to each hemisphere would be the same.

Another interpretation is also possible: if the lateralization of the brain functions were such that exactly half of all functions were located in the left and another half in the right hemisphere, then the blood flow, and the cross-sectional areas of arteries to both hemispheres would be the same. Some of the human functions such as language, handedness, logical reasoning have been generally accepted to be located in the left hemisphere [3, 11, 14, 37-39] in most people and the left occipital petalia present in most human beings were cited as an indication of the enlargement of the left hemisphere.

The handedness and behavioural functional lateralization have been studied in relation to the size of corpus callosum. However, the role of corpus callosum tracts is to increase the interhemispheric connectivity and

ensure the need of having bilateral cortical components to perform some specific functions together and support the functional relationship between the adjacent components of the cerebral hemispheres [5].

Recent studies on lateralization have revealed that some functions are mastered particularly well by one hemisphere [15, 16], while other functions might be mastered by the other hemisphere so that the total functional output of each hemisphere is similar. In other words, the idea of hemispheric specialization may apply to specific function, but not to all functions [4]. Any tissue and organ in the body, including a part of the brain performing particular function, requires more blood flow. If, however, function occurs intermittently for short periods, the amount of blood flow may increase but the flow is not large enough to cause permanent change to the arterial structures. Brain works continuously, and especially during wakefulness performs number of functions simultaneously, so that both hemispheres require constant flow of blood. It may be that each hemisphere performs different functions, but the sum total is the same as in the contralateral hemisphere, or that many functions use both hemispheres communicating via corpus callosum, anterior and posterior commissures. Results of the current study cannot distinguish between these two possibilities.

Since each cerebral hemisphere is entirely supplied by the three arteries-anterior cerebral artery (ACA), posterior cerebral artery (PCA) and middle cerebral artery (MCA) [27, 28, 40], thus the total cross-sectional areas of these arteries are a good indicator of the function of a cerebral hemisphere. The total size of a cerebral hemisphere is the size of the cerebral cortex and its subcortical connections. Therefore, if a cortex of a given hemisphere is larger due to its functional dominance, the entire hemisphere should be larger.

In another study, dimensions of right cerebral hemispheres of 54 donated brains were compared with those of the left hemispheres and no significant size differences between the two hemispheres were found [19]. Furthermore, the arrangements of asymmetric posterior and lateral cerebral dural venous sinuses (in 58 brains) were found to be correlated with the petalial patterns. Larger volume of blood in dural venous sinuses in the posterior aspect of the right of the cranial cavity might move the entire right cerebral hemisphere anteriorly [20]. This produces larger occipital extent of the left hemisphere, and larger anterior extent of the right hemisphere, a pattern found in approximately 60% of people [41]. This difference in appearance does not

indicate there is real difference in size [20]. The cortical thicknesses of 39 functional areas of one cerebral hemisphere has been compared with those of the same 39 functional areas of the other hemisphere in MRI scans obtained from 17,000 healthy individuals [18]. No significant differences between the two cerebral hemispheres were found. These three studies mentioned in in this paragraph, investigated different indicators of cerebral lateralization and found no differences between two cerebral hemispheres.

Most of the findings related to the lateralization are ambiguous and have no definitive results, structural asymmetry exists only statistically, there are no specific criteria to prove it. Current study examined the arterial cross-sectional areas supplying the cerebral hemispheres and the findings show small and uniformly insignificant differences between left and right cerebral arterial cross-sectional areas. Functional predominance and different cognitive functions between the two hemispheres have been reported [16], however the size of the arteries supplying the two hemispheres in this study, does not indicate greater function of one hemisphere compared to the other hemisphere.

Conclusion

Blood supply from anterior, posterior and middle cerebral arteries to the right and left cerebral hemispheres is the same. Since the blood supply is proportional to the function, we suggest that there is no asymmetry in total functions of cerebral hemispheres.

Authors contribution statement

Arjun Burlakoti: Conceived and designed the analysis; analysed and interpreted the data; wrote the paper.

Jaliya Kumaratilake: Conceived and designed the analysis; interpreted the data and edited the paper.

Taylor Jamie: Contributed the analysis tools and data; edited the paper and interpreted the data.

Maciej Henneberg: Conceived and designed the analysis; analysed and interpreted the data; edited the paper.

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Competing interest statement

The authors declare no conflict of interest.

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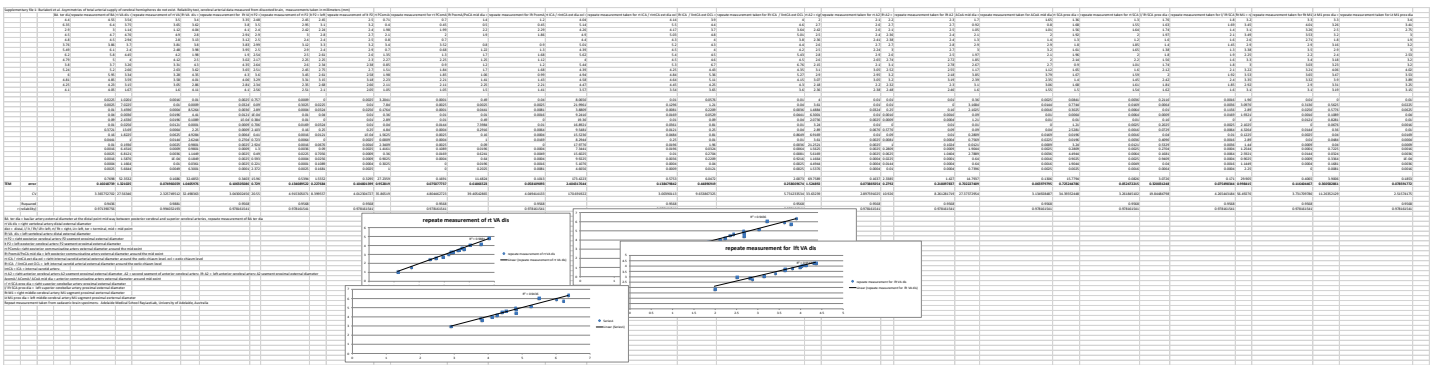
Supplementary materials

Supplementary Excel files related to this article have been published online at https://doi.org/10.1016/j.heliyon.2018.e01086, and also supplied under 'supplementary content' heading in the Heliyon Journal webpage.

Supplementary file 1: The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.



Supplementary file 2: The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary File 2- Burlakoti et al. Asymmetries of total arterial supply of cerebral hemispheres do not exist; dissected brain data. Cerebral arterial data measured from dissected brain, measurements taken in millimeters (mm)

rt P2 = righ	rt p2a= rig	lt P2 = left	lft p2a= left	rt A2 = righ	rta2a= righ	lft A2 = lef	lfta2a= rigl	Rt M1 = rig	rtm1a= rigl	Lt M1 =left	lftm1a= lef	right p2+m1+a2 area=	left p2+m1+a2 area=	(left p2+m1+a2) area - (right p2+m1+a2) area
2.30	4.15	2.68	5.64	2.59	5.27	3.48	9.51	2.91	6.65	3.81	11.40	16.07	26.54	-10.47
2.69	5.68	2.87	6.47	2.58	5.23	2.73	5.85	3.10	7.54	3.72	10.86	18.45	23.18	-4.73
2.38	4.45	3.05	7.30	3.01	7.11	2.56	5.14	3.08	7.45	3.75	11.04	19.01	23.49	-4.48
3.10	7.54	2.61	5.35	2.46	4.75	3.27	8.39	3.23	8.19	3.73	10.92	20.48	24.66	-4.18
2.09	3.43	2.60	5.31	2.19	3.76	2.78	6.07	3.40	9.07	3.35	8.81	16.27	20.18	-3.91
2.64	5.47	2.34	4.30	2.15	3.63	3.10	7.54	3.00	7.07	3.23	8.19	16.16	20.03	-3.87
2.09	3.43	2.44	4.67	2.74	5.89	2.40	4.52	2.80	6.15	3.58	10.06	15.48	19.26	-3.78
2.34	4.30	2.68	5.64	2.18	3.73	2.32	4.23	2.92	6.69	3.31	8.60	14.72	18.46	-3.74
2.66	5.55	2.71	5.77	2.70	5.72	3.05	7.30	3.83	11.52	4.10	13.20	22.79	26.26	-3.47
2.50	4.91	2.75	5.94	3.10	7.54	2.52	4.99	3.22	8.14	4.06	12.94	20.59	23.86	-3.27
2.99	7.02	3.30	8.55	2.60	5.31	2.70	5.72	2.90	6.60	3.16	7.84	18.93	22.11	-3.18
3.29	8.50	3.15	7.79	3.07	7.40	3.20	8.04	3.35	8.81	3.90	11.94	24.71	27.77	-3.06
2.80	6.15	2.50	4.91	2.20	3.80	3.00	7.07	2.80	6.15	3.00	7.07	16.11	19.04	-2.93
2.10	3.46	2.41	4.56	2.25	3.97	2.27	4.05	2.80	6.15	3.10	7.54	13.59	16.15	-2.56
3.00	7.07	3.00	7.07	2.23	3.90	2.50	4.91	2.40	4.52	2.77	6.02	15.49	17.99	-2.50
2.61	5.35	2.59	5.27	2.32	4.23	2.85	6.38	2.89	6.56	2.95	6.83	16.13	18.47	-2.34
2.76	5.98	2.86	6.42	2.98	6.97	2.87	6.47	3.01	7.11	3.44	9.29	20.06	22.18	-2.11
2.57	5.18	2.52	4.99	2.43	4.64	2.34	4.30	2.94	6.79	3.40	9.07	16.61	18.36	-1.75
2.71	5.77	2.77	6.02	2.63	5.43	2.56	5.14	2.70	5.72	3.00	7.07	16.92	18.23	-1.32
2.85	6.38	2.37	4.41	2.76	5.98	2.37	4.41	2.76	5.98	3.70	10.75	18.34	19.57	-1.23
2.61	5.35	2.47	4.79	1.50	1.77	2.65	5.51	2.90	6.60	2.40	4.52	13.72	14.82	-1.11
2.48	4.83	2.45	4.71	2.00	3.14	2.20	3.80	3.20	8.04	3.30	8.55	16.01	17.06	-1.05
2.04	3.27	2.40	4.52	2.50	4.91	3.00	7.07	3.38	8.97	2.90	6.60	17.14	18.19	-1.05
2.76	5.98	2.50	4.91	2.40	4.52	2.20	3.80	2.70	5.72	3.30	8.55	16.22	17.25	-1.03
2.35	4.34	2.93	6.74	3.13	7.69	2.73	5.85	2.80	6.15	2.90	6.60	18.18	19.19	-1.01
2.54	5.06	2.45	4.71	2.72	5.81	2.85	6.38	3.16	7.84	3.26	8.34	18.71	19.43	-0.72
2.50	4.91	2.56	5.14	2.70	5.72	2.80	6.15	3.11	7.59	3.10	7.54	18.22	18.84	-0.62
1.90	2.83	2.10	3.46	2.45	4.71	2.53	5.02	3.58	10.06	3.50	9.62	17.61	18.10	-0.50
2.17	3.70	2.25	3.97	2.60	5.31	2.74	5.89	3.30	8.55	3.18	7.94	17.55	17.81	-0.25
2.71	5.77	2.36	4.37	2.90	6.60	2.79	6.11	2.91	6.65	3.33	8.70	19.01	19.19	-0.17
2.38	4.45	2.55	5.10	2.70	5.72	3.20	8.04	3.30	8.55	2.70	5.72	18.72	18.87	-0.15
2.54	5.06	2.61	5.35	2.80	6.15	2.60	5.31	2.25	3.97	2.40	4.52	15.19	15.18	0.02
2.56	5.14	2.86	6.42	2.62	5.39	2.84	6.33	3.90	11.94	3.50	9.62	22.47	22.37	0.10
2.80	6.15	2.70	5.72	2.70	5.72	3.00	7.07	3.10	7.54	2.80	6.15	19.42	18.94	0.48
2.45	4.71	2.61	5.35	2.67	5.60	1.99	3.11	3.76	11.10	3.96	12.31	21.41	20.77	0.64
2.58	5.23	2.56	5.14	2.90	6.60	2.50	4.91	2.70	5.72	2.94	6.79	17.55	16.84	0.71
3.02	7.16	2.67	5.60	2.16	3.66	2.80	6.15	3.65	10.46	3.35	8.81	21.28	20.56	0.72
2.56	5.14	2.10	3.46	2.36	4.37	2.48	4.83	3.10	7.54	3.19	7.99	17.06	16.28	0.78
2.67	5.60	2.01	3.17	3.08	7.45	2.25	3.97	2.64	5.47	3.46	9.40	18.51	16.54	1.97
2.64	5.47	2.53	5.02	2.54	5.06	2.24	3.94	2.94	6.79	2.85	6.38	17.32	15.34	1.98
2.55	5.10	2.33	4.26	2.51	4.95	2.19	3.76	3.10	7.54	3.08	7.45	17.59	15.47	2.12
2.90	6.60	2.80	6.15	2.50	4.91	2.36	4.37	3.49	9.56	3.20	8.04	21.07	18.56	2.50
2.64	5.47	2.55	5.10	2.30	4.15	2.49	4.87	3.30	8.55	2.69	5.68	18.17	15.65	2.52
3.50	9.62	3.10	7.54	2.70	5.72	2.70	5.72	3.45	9.34	3.26	8.34	24.68	21.61	3.07
2.50	4.91	2.40	4.52	2.36	4.37	2.38	4.45	2.60	5.31	1.80	2.54	14.58	11.51	3.07
2.48	4.83	1.81	2.57	2.90	6.60	2.60	5.31	2.60	5.31	2.65	5.51	16.74	13.39	3.35
3.60	10.17	2.61	5.35	2.90	6.60	3.20	8.04	3.53	9.78	3.47	9.45	26.56	22.84	3.72
2.66	5.55	3.01	7.11	3.06	7.35	2.36	4.37	3.80	11.34	3.38	8.97	24.24	20.45	3.79
2.40	4.52	2.24	3.94	2.42	4.60	2.10	3.46	3.10	7.54	2.50	4.91	16.66	12.31	4.36
2.50	4.91	2.60	5.31	3.70	10.75	2.40	4.52	4.20	13.85	3.70	10.75	29.50	20.57	8.93
2.70	5.72	2.80	6.15	4.25	14.18	1.10	0.95	3.60	10.17	3.00	7.07	30.08	14.17	15.91

rt/ Rt = right, lft lt = left, p2/ P2 = second segment of posterior cerebral artery, a/ A = area

rt P2 = right posterior cerebral artery P2 segment proximal internal diameter; rt p2a= right posterior cerebral artery P2 segment cross sectional area

lt P2 = left posterior cerebral artery P2 segment proximal internal diameter; lft p2a= left posterior cerebral artery P2 segment cross sectional area

rt A2 = right anterior cerebral artery A2 segment proximal internal diameter; rta2a= right anterior cerebral artery A2 segment proximal cross sectional area

lft A2 = left anterior cerebral artery A2 segment proximal internal diameter; lfta2a= right anterior cerebral artery A2 segment proximal cross sectional area

rt A2 = right anterior cerebral artery A2 segment proximal external diameter, A2 = second segment of anterior cerebral artery, lft A2 = left anterior cerebral artery A2 segment proximal external diameter

M1 = first segment of middle cerebral artery

Rt M1 = right middle cerebral artery M1 segment proximal external diameter; rtm1a= right middle cerebral artery M1 segment proximal cross sectional area

Lt M1 =left middle cerebral artery M1 segment proximal internal diameter; lftm1a= left middle cerebral artery M1 segment proximal cross sectional area

right p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area

p2= second segment of posterior cerebral artery, a2/ A2 = second segment of anterior cerebral artery, m1/ M1 = first segment of middle cerebral artery

left p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area

Supplementary file 3: Please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary file 3: Burlakoti et al. Asymmetries of total arterial supply of cerebral hemispheres do not exist; data taken from cerebral Computed Tomography Angiography = CTA and magnetic resonance angiography = MRA

age	Sex	rt P2 = righ	rt p2a= rig	lt P2 = left	lftp2a= lef	rt A2 = rig	rta2a= righ	lft A2 = lef	lfta2a= rig	Rt M1 = ri	rtm1a= rig	Lt M1 =lefi	lftm1a= lef	right p2+m1+a2 area= ri	left p2+m1+a2 area
58.00	m	1.83	2.63	1.99	3.11	2.45	4.71	1.68	2.22	2.46	4.75	2.40	4.52	12.09	9.85
70.00	m	1.29	1.31	1.66	2.16	1.27	1.27	1.16	1.06	2.09	3.43	1.97	3.05	6.00	6.27
38.00	f	2.45	4.71	2.81	6.20	2.93	6.74	2.40	4.52	3.16	7.84	2.82	6.24	19.29	16.96
62.00	f	2.57	5.18	2.29	4.12	1.64	2.11	2.02	3.20	2.21	3.83	2.25	3.97	11.13	11.29
54.00	m	2.35	4.34	2.71	5.77	2.14	3.59	2.15	3.63	2.83	6.29	2.71	5.77	14.22	15.16
73.00	m	2.50	4.91	2.82	6.24	2.27	4.05	2.62	5.39	3.29	8.50	3.32	8.65	17.45	20.28
26.00	m	2.33	4.26	1.74	2.38	1.93	2.92	1.73	2.35	2.05	3.30	2.43	4.64	10.48	9.36
71.00	f	2.48	4.83	2.26	4.01	1.80	2.54	1.81	2.57	2.43	4.64	2.39	4.48	12.01	11.07
62.00	m	2.76	5.98	2.32	4.23	1.64	2.11	2.04	3.27	3.04	7.25	2.77	6.02	15.35	13.52
79.00	m	2.39	4.48	2.23	3.90	2.52	4.99	2.17	3.70	2.69	5.68	2.20	3.80	15.15	11.40
46.00	m	2.01	3.17	2.01	3.17	2.67	5.60	2.19	3.76	3.47	9.45	2.00	3.14	18.22	10.08
79.00	m	2.36	4.37	2.59	5.27	2.79	6.11	3.02	7.16	2.54	5.06	2.46	4.75	15.55	17.18
47.00	f	2.59	5.27	1.83	2.63	2.02	3.20	1.98	3.08	2.64	5.47	2.81	6.20	13.94	11.90
100.00	m	2.16	3.66	2.32	4.23	2.13	3.56	2.36	4.37	3.08	7.45	3.37	8.92	14.67	17.51
58.00	m	2.29	4.12	2.39	4.48	2.47	4.79	2.08	3.40	2.45	4.71	2.19	3.76	13.62	11.65
69.00	f	2.04	3.27	2.04	3.27	2.14	3.59	2.06	3.33	1.97	3.05	2.28	4.08	9.91	10.68
47.00	f	2.68	5.64	2.27	4.05	2.79	6.11	2.73	5.85	2.84	6.33	3.32	8.65	18.08	18.55
60.00	m	2.47	4.79	2.49	4.87	2.26	4.01	2.42	4.60	2.84	6.33	3.03	7.21	15.13	16.67
26.00	m	2.09	3.43	1.85	2.69	2.09	3.43	2.22	3.87	2.22	3.87	2.33	4.26	10.73	10.82
89.00	m	2.71	5.77	3.14	7.74	2.51	4.95	2.48	4.83	3.14	7.74	3.42	9.18	18.45	21.75
56.00	m	1.96	3.02	2.57	5.18	1.81	2.57	2.08	3.40	2.94	6.79	2.96	6.88	12.37	15.46
71.00	f	1.96	3.02	2.32	4.23	2.29	4.12	2.19	3.76	2.39	4.48	2.66	5.55	11.62	13.54
18.00	f	1.65	2.14	2.00	3.14	2.52	4.99	2.30	4.15	2.24	3.94	2.40	4.52	11.06	11.81
85.00	m	2.25	3.97	2.93	6.74	2.73	5.85	2.72	5.81	3.22	8.14	2.73	5.85	17.96	18.40
45.00	f	1.65	2.14	1.96	3.02	2.05	3.30	1.92	2.89	2.24	3.94	1.74	2.38	9.37	8.29
48.00	m	2.73	5.85	2.22	3.87	2.90	6.60	2.84	6.33	2.94	6.79	3.17	7.89	19.24	18.09
60.00	m	2.09	3.43	1.95	3.08	2.85	6.38	2.38	4.45	2.72	5.81	2.59	5.27	15.61	12.70
63.00	m	2.25	3.97	1.94	2.95	2.47	4.79	2.33	4.26	2.70	5.72	2.75	5.94	14.49	13.15
70.00	m	2.41	4.56	2.19	3.76	2.18	3.73	2.66	5.55	3.39	9.02	2.94	6.79	17.31	16.10
61.00	f	2.19	3.76	2.80	6.15	2.52	4.99	2.35	4.34	3.18	7.94	2.98	6.97	16.69	17.46
77.00	m	2.96	6.88	3.03	7.21	2.45	4.71	2.22	3.87	2.82	6.24	2.82	6.24	17.83	17.32
85.00	f	2.36	4.37	2.47	4.79	2.53	5.02	2.42	4.60	2.39	4.48	3.32	8.65	13.88	18.04
60.00	m	2.48	4.83	2.41	4.56	2.80	6.15	2.52	4.99	2.91	6.65	2.49	4.87	17.63	14.41
63.00	f	2.42	4.60	2.43	4.64	2.04	3.27	2.75	5.94	3.23	8.19	2.48	4.83	16.05	15.40
52.00	m	2.16	3.66	2.60	5.31	2.56	5.14	2.69	5.68	2.67	5.60	2.77	6.02	14.40	17.01
69.00	f	2.08	3.40	2.50	4.91	2.16	3.66	2.50	4.91	2.33	4.26	2.38	4.45	11.32	14.26
63.00	f	2.73	5.85	2.33	4.26	1.91	2.86	2.10	3.46	2.97	6.92	3.03	7.21	15.64	14.93
63.00	m	2.32	4.23	2.12	3.53	1.88	2.77	1.73	2.35	3.47	9.45	3.06	7.35	16.45	13.23
79.00	m	2.58	5.23	2.71	5.77	2.06	3.33	1.84	2.66	2.48	4.83	2.24	3.94	13.38	12.36
53.00	f	1.86	2.72	1.87	2.75	2.38	4.45	2.51	4.95	2.23	3.90	2.63	5.43	11.07	13.12
33.00	f	2.33	4.26	2.59	5.27	2.35	4.34	1.97	3.05	3.16	7.84	2.79	6.11	16.44	14.42
58.00	m	2.23	3.90	2.53	5.02	2.56	5.14	2.13	3.56	3.05	7.30	3.47	9.45	16.35	18.04
52.00	f	1.80	2.54	2.46	4.75	1.93	2.92	2.26	4.01	2.28	4.08	2.65	5.51	9.55	14.27
50.00	m	2.30	4.15	2.10	3.46	2.80	6.15	2.10	3.46	3.30	8.55	4.00	12.56	18.86	19.48
69.00	f	2.80	6.15	2.10	3.46	1.90	2.83	2.70	5.72	3.20	8.04	3.20	8.04	17.03	17.22
74.00	m	3.60	10.17	2.60	5.31	3.00	7.07	3.00	7.07	3.20	8.04	2.90	6.60	25.28	18.97
91.00	m	2.30	4.15	2.30	4.15	2.70	5.72	2.80	6.15	3.30	8.55	2.80	6.15	18.42	16.46
80.00	f	2.60	5.31	2.80	6.15	3.00	7.07	2.80	6.15	3.30	8.55	3.00	7.07	20.92	19.37
20.00	f	2.60	5.31	2.60	5.31	3.20	8.04	3.10	7.54	3.10	7.54	3.20	8.04	20.89	20.89
73.00	f	2.30	4.15	2.20	3.80	1.90	2.83	1.65	2.14	3.30	8.55	2.90	6.60	15.54	12.54
75.00	f	2.80	6.15	2.30	4.15	1.90	2.83	1.60	2.01	2.40	4.52	2.70	5.72	13.51	11.88
78.00	m	1.90	2.83	2.20	3.80	2.70	5.72	2.10	3.46	3.50	9.62	3.20	8.04	18.17	15.30
73.00	m	3.90	11.94	3.60	10.17	2.90	6.60	2.60	5.31	3.60	10.17	3.60	10.17	28.72	25.65
65.00	m	2.80	6.15	2.70	5.72	2.60	5.31	2.80	6.15	3.30	8.55	3.20	8.04	20.01	19.92
55.00	m	2.10	3.46	2.10	3.46	2.70	5.72	2.60	5.31	3.50	9.62	3.30	8.55	18.80	17.32
49.00	m	1.90	2.83	1.90	2.83	1.90	2.83	2.30	4.15	2.80	6.15	2.70	5.72	11.82	12.71
60.00	f	2.30	4.15	2.20	3.80	2.40	4.52	2.30	4.15	3.00	7.07	3.00	7.07	15.74	15.02
84.00	m	2.20	3.80	2.30	4.15	2.30	4.15	2.10	3.46	1.90	2.83	2.10	3.46	10.79	11.08
64.00	f	2.10	3.46	2.10	3.46	2.10	3.46	2.10	3.46	3.00	7.07	3.90	11.94	13.99	18.86
72.00	m	2.00	3.14	2.30	4.15	2.50	4.91	2.50	4.91	3.10	7.54	2.70	5.72	15.59	14.78
80.00	m	2.20	3.80	1.90	2.83	2.30	4.15	1.90	2.83	3.20	8.04	3.10	7.54	15.99	13.21
55.00	m	2.60	5.31	2.10	3.46	2.90	6.60	2.80	6.15	3.00	7.07	3.30	8.55	18.97	18.16
55.00	m	1.50	1.77	1.90	2.83	2.50	4.91	2.10	3.46	2.80	6.15	3.10	7.54	12.83	13.84
53.00	m	2.30	4.15	2.10	3.46	2.10	3.46	2.60	5.31	3.50	9.62	3.20	8.04	17.23	16.81
74.00	m	2.80	6.15	3.00	7.07	2.50	4.91	2.80	6.15	3.80	11.34	3.50	9.62	22.40	22.84
70.00	f	1.90	2.83	1.60	2.01	2.20	3.80	1.90	2.83	2.40	4.52	3.10	7.54	11.15	12.39
54.00	m	3.20	8.04	3.20	8.04	3.20	8.04	3.00	7.07	4.20	13.85	3.70	10.75	29.92	25.85
66.00	m	1.90	2.83	2.10	3.46	2.30	4.15	2.30	4.15	2.30	4.15	2.30	4.15	11.14	11.77
38.00	m	2.92	6.69	2.53	5.02	2.77	6.02	2.54	5.06	2.74	5.89	3.23	8.19	18.61	18.28
73.00	f	2.89	6.56	3.07	7.40	2.69	5.68	2.70	5.72	3.09	7.50	2.90	6.60	19.73	19.72
76.00	f	1.83	2.63	2.52	4.99	1.95	2.98	2.16	3.66	2.46	4.75	2.31	4.19	10.36	12.84
68.00	f	2.44	4.67	1.75	2.40	1.77	2.46	2.15	3.63	2.95	6.83	2.92	6.69	13.96	12.73
29.00	f	2.60	5.31	1.90	2.83	2.95	6.83	3.00	7.07	2.40	4.52	2.90	6.60	16.66	16.50
59.00	f	2.40	4.52	2.12	3.53	1.86	2.72	1.94	2.95	2.60	5.31	2.55	5.10	12.54	11.59
40.00	m	2.97	6.92	2.35	4.34	1.98	3.08	1.40	1.54	3.04	7.25	2.33	4.26	17.26	10.14
69.00	f	2.96	6.88	2.72	5.81	1.85	2.69	2.69	5.68	2.71	5.77	2.82	6.24	15.33	17.73
70.00	f	2.03	3.23	2.10	3.46	1.76	2.43	1.87	2.75	2.49	4.87	2.80	6.15	10.53	12.36
83.00	f	2.46	4.75	2.75	5.94	2.30	4.15	2.20	3.80	2.94	6.79	3.12	7.64	15.69	17.38
35.00	f	1.83	2.63	2.09	3.43	2.31	4.19	2.28	4.08	2.67	5.60	2.89	6.56	12.41	14.07
65.00	m	2.33	4.26	2.08	3.40	2.27	4.05	2.18	3.73	2.74	5.89	2.69	5.68	14.20	12.81
83.00	m	2.34	4.30	2.33	4.26	2.30	4.15	2.11	3.49	2.70	5.72	2.27	4.05	14.17	11.80
65.00	f	2.61	5.35	2.32	4.23	2.64	5.47	1.98	3.08	1.97	3.05	2.80	6.15	13.87	13.46
86.00	f	2.23	3.90	2.09	3.43	2.31	4.19	2.58	5.23	2.54	5.06	2.90	6.60	13.16	15.26
76.00	m	2.58	5.23	2.10	3.46	2.60	5.31	2.21	3.83	2.34	4.30	2.70	5.72	14.83	13.02
52.00	f	1.98	3.08	2.40	4.52	2.56	5.14	2.93	6.74	3.11	7.59	2.83	6.29	15.81	17.55
71.00	f	2.39	4.48	2.80	6.15	2.50	4.91	2.18	3.73	3.48	9.51	3.17	7.89	18.90	17.77
61.00	f	2.56	5.14	2.07	3.36	2.10	3.46	1.90	2.83	2.97	6.92	3.04	8.04	15.53	14.24
70.00	f	2.08	3.40	2.22	3.87	2.14	3.59	2.28	4.08	2.81	6.20	2.96	6.88	13.19	14.83
53.00	m	1.98	3.08	2.07	3.36	2.06	3.33	2.09	3.43	2.36	4.37	2.72	5.81	10.78	12.60
42.00	f	2.59	5.27	2.89	6.56	2.74	5.89	2.23	3.90	3.03	7.21	3.01	7.11	18.37	17.57
63.00	f	2.02	3.20	1.68	2.22	2.33	4.26	2.18	3.73	2.66	5.55	2.82	6.24	13.02	12.19
41.00	f	1.79	2.52	2.09	3.43	1.98	3.08	2.03	3.23	2.75	5.94	2.63	5.43	11.53	12.09
74.00	f	2.70	5.72	2.33	4.26	1.95	2.98	2.04	3.27	3.39	9.02	2.77	6.02	17.73	13.55
65.00	f	2.66	5.55	2.28	4.08	1.98	3.08	1.74	2.38	2.55	5.10	3.38	8.97	13.74	15.43
56.00	f	1.95	2.98	1.84	2.66	2.27	4.05	2.01	3.17	2.34	4.30	2.34	4.30	11.33	10.13
47.00	f	2.25	3.97	2.28	4.08	1.92	2.89	1.93	2.92	2.57	5.18	2.47	4.79	12.05	11.79
65.00	m	2.59	5.27	2.20	3.80	2.38	4.45	2.72	5.81	3.28	8.45	3.20	8.04	18.16	17.65
85.00	f	2.12	3.53	2.13	3.56	2.25	3.97	1.81	2.57	2.39	4.48	2.23	3.90	11.99	10.04
48.00	m	2.54	5.06	2.30	4.15	2.14	3.59	2.20	3.80	2.55	5.10	2.65	5.51	13.76	13.46
68.00	f	2.33	4.26	2.55	5.10	2.75	5.94	2.76	5.98	2.96	6.88	3.29	8.50	17.08	19.58
81.00	m	2.01	3.17	2.31	4.19	2.61	5.35	2.39	4.48	3.01	7.11	2.80	6.15	15.63	14.83
66.00	m	2.55	5.10	2.16	3.66	1.92	2.89	2.03	3.23	2.63	5.43	2.79	6.11	13.43	13.01
65.00	f	2.43	4.64	2.35	4.34	2.67	5.60	2.83	6.29	2.68	5.64	2.67	5.60	15.87	16.22
69.00	m	2.99	7.02	2.56	5.14	2.63	5.43	2.77	6.02	3.29	8.50	3.17	7.89	20.94	19.06
78.00	m	3.02	7.16	2.70	5.72	2.56	5.14	2.50	4.91	3.24	8.24	3.87	11.76	20.54	22.39
65.00	f	2.26	4.01	2.14	3.59	2.85	6.38	2.10	3.46	2.97	6.92	2.21	3.83	17.31	10.89
72.00	m	2.83	6.29	2.91	6.65	2.77	6.02	2.73	5.85	3.17	7.89	3.56	9.95	20.20	22.45
82.00	m	2.37	4.41	2.57	5.18	1.89	2.80	2.20	3.80	2.46	4.75	2.78	6.07	11.96	15.05
59.00	f	2.71	5.77	2.69	5.68	2.01	3.17	2.24	3.94	2.95	6.83	2.66	5.55	15.77	15.17
74.00	f	1.96	3.02	2.19	3.76	2.81	6.20	2.62	5.39	3.04	7.25	2.69	5.68	16.47	14.83
50.00	f	2.63	5.43	2.44	4.67	1.83	2.63	1.89	2.80	2.96	6.88	2.33	4.26	14.94	11.74
60.00	f	2.58	5.23	2.86	6.42	2.19	3.76	2.39	4.48	3.56	9.95	3.17	7.89	18.94	18.79
83.00	m	2.22	3.87	2.47	4.79	2.90	6.60	2.07	3.36	3.10	7.54	3.19	7.99	18.01	16.14
48.00	f	2.72	5.81	2.35	4.34	2.59	5.27	2.43	4.64	2.95	6.83	3.11	7.59	17.91	16.56
76.00	f	2.93	6.74	2.88	6.51	2.36	4.37	2.89	6.56	3.48	9.51	3.45	9.34	20.62	22.41
48.00	f	2.60	5.31	2.77	6.02	2.11	3.49	2.22	3.87	2.53	5.02	2.34	4.30	13.83	14.19
69.00	f	2.86	6.42	2.50	4.91	2.28	4.08	2.31	4.19	3.21	8.09	2.57	5.18	18.59	14.28
65.00	f	2.38	4.45	2.06	3.33	1.90	2.83	1.53	1.84	2.76	5.98	2.56	5.14	13.26	10.31
61.00	m	2.61	5.35	2.82	6.24	2.00	3.14	2.17	3.70	3.05	7.30	3.15	7.79	15.79	17.73
50.00	m	2.01	3.17	2.17	3.70	2.84	6.33	2.77	6.02	2.84	6.33	3.11	7.59	15.83	17.31
50.00	f	2.40	4.52	2.60	5.31	2.51	4.95	2.20	3.80	2.94	6.79	3.30	8.55	16.25	17.65
23.00	m	2.33	4.26	2.72	5.81	2.22	3.87	2.07	3.36	3.29	8.50	3.60	10.17	16.63	19.34
79.00	m	2.34	4.30	2.49	4.87	2.85	6.38	2.99	7.02	2.46	4.75	2.63	5.43	15.43	17.31
50.00	m	2.81	6.20	2.31	4.19	2.60	5.31	2.40	4.52	3.33	8.70	3.15	7.79	20.21	16.50
72.00	f	1.90	2.83	1.86	2.72	2.28	4.08	2.36	4.37	2.86	6.42	2.71	5.77	13.34	12.85
52.00	m	2.25	3.97	2.75	5.94	2.54	5.06	2.64	5.47	2.92	6.69	3.04	7.25	15.73	18.66
48.00	f	2.44	4.67	2.35	4.34	2.60	5.31	2.91	6.65	2.69	5.68	2.87	6.47	15.66	17.45
39.00	f	2.51	4.95	2.04	3.27	2.55	5.10	2.44	4.67	2.45	4.71	2.33	4.26	14.76	12.20
51.00	f	2.10	3.46	2.81	6.20	2.16	3.66	2.11	3.49	3.34	8.76	2.72	5.81	15.88	15.50
66.00	f	3.02	7.16	2.55	5.10	2.26	4.01	2.48	4.83	2.90	6.60	3.40	9.07	17.77	19.01
74.00	m	3.22	8.14	2.27	4.05	2.85	6.38	2.71	5.77	3.56	9.95	3.43	9.24	24.46	19.05
50.00	f	2.57	5.18	2.71	5.77	1.65	2.14	2.25	3.97	2.89	6.56	2.28	4.08	13.88	13.82
80.00	m	3.22	8.14	3.06	7.35	3.13	7.69	2.90	6.60	3.43	9.24	3.74	10.98	25.07	24.93
64.00	m	2.61	5.35	2.83	6.29	3.57	10.00	2.64	5.47	3.90	11.94	3.65	10.46	27.29	22.22
48.00	f	1.86	2.72	2.09	3.43	2.02	3.20	2.30	4.15	2.03	3.23	2.50	4.91	9.15	12.49
79.00	m	2.08	3.40	1.95	2.98	1.64	2.11	1.88	2.77	2.66	5.55	2.64	5.47	11.06	11.23
60.00	f	2.08	3.40	1.85	2.69	1.99	3.11	1.78	2.49	2.53	5.02	2.31	4.19	11.53	9.36
54.00	f	2.63	5.43	2.46	4.75	2.30	4.15	2.45	4.71	2.97	6.92	3.18	7.94	16.51	17.40
62.00	f	1.68	2.22	1.80	2.54	2.82	6.24	2.60	5.31	2.59	5.27	2.63	5.43	13.72	13.28
55.00	m	2.41	4.56	2.38	4.45	2.13	3.56	2.08	3.40	2.48	4.83	2.38	4.45	12.95	12.29
77.00	f	2.66	5.55	2.52	4.99	2.46	4.75	2.41	4.56	2.99	7.02	2.99	7.02	17.32	16.56
69.00	m	3.09	7.50	2.83	6.29	2.74	5.89	2.71	5.77	3.32	8.65	3.25	8.29	22.04	20.34
69.00	m	3.17	7.89	3.14	7.74	2.56	5.14	2.51	4.95	3.41	9.13	3.55	9.89	22.16	22.58
85.00	f	2.02	3.20	2.03	3.23	2.11	3.49	2.08	3.40	2.77	6.02	2.80	6.15	12.72	12.79
77.00	f	2.85	6.38	2.80	6.15	2.95	6.83	2.98	6.97	4.43	15.41	4.37	14.99	28.61	28.12
66.00	m	2.80	6.15	2.75	5.94	2.41	4.56	2.38	4.45	3.65	10.46	3.58	10.06	21.17	20.44
70.00	f	2.23	3.90	2.17	3.70	2.25	3.97	2.23	3.90	3.11	7.59	3.18	7.94	15.47	15.54
70.00	F	2.37	4.41	2.41	4.56	2.68	5.64	2.69	5.68	2.62	5.39	2.77	6.01	15.44	16.25
48.00	f	2.73	5.85	2.66	5.55	2.49	4.87	2.53	5.02	2.28	4.08	2.24	3.94	14.80	14.52
54.00	F	2.55	5.10	2.67	5.60	2.56	5.14	2.59	5.27	2.66	5.55	2.67	5.60	15.80	16.46
56.00	f	2.26	4.01	2.28	4.08	2.23	3.90	2.25	3.97	3.23	8.19	3.29	8.50	16.10	16.55
44.00	m	3.12	7.64	3.06	7.35	3.11	7.59	3.08	7.45	3.46	9.40	3.43	9.24	24.63	24.03

M= male, F= female, rt/ Rt = right, lft/ lt = left, p2/ P2 = second segment of posterior cerebral artery, a/ A = area.
rt P2 = right posterior cerebral artery P2 segment proximal internal diameter
rt p2a= right posterior cerebral artery P2 segment cross sectional area
lt P2 = left posterior cerebral artery P2 segment proximal internal diameter
lftp2a= left posterior cerebral artery P2 segment cross sectional area
rt A2 = right anterior cerebral artery A2 segment proximal internal diameter
rta2a= right anterior cerebral artery A2 segment proximal cross sectional area
lft A2 = left anterior cerebral artery A2 segment proximal internal diameter
lfta2a= right anterior cerebral artery A2 segment proximal cross sectional area
Rt M1 = right middle cerebral artery M1 segment proximal internal diameter
rtm1a= right middle cerebral artery M1 segment proximal cross sectional area
Lt M1 =left middle cerebral artery M1 segment proximal internal diameter
lftm1a= left middle cerebral artery M1 segment proximal cross sectional area
right p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area
left p2+m1+a2 area= right posterior cerebral artery P2 segment cross sectional area + middle cerebral artery (M1) cross sectional area+ anterior cerebral artery A2 cross sectional area
p2= second segment of posterior cerebral artery, a2/ A2 = second segment of anterior cerebral artery, m1/ M1 = first segment of middle cerebral artery

Chapter 3: Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm

Article DOI: 10.1136/bmjsit-2020-000059

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Context for the third paper

This study aimed to link the findings presented in the first paper included in this thesis, on effects of anatomical variation of cerebral arterial network on imbalanced hemodynamics and formation of cerebral aneurysms.[1] The fluctuation in peak cerebral arterial pressure predisposes to the formation of cerebral aneurysms in the presence of variant arterial segments, as we suggested in paper one. We now specifically studied, this idea by considering anterior communicating artery complex (AcomAC) aneurysms and variations in the first segment of anterior cerebral artery (A1). The anterior communicating artery complex (AcomAC) consists of the anterior communicating artery and the adjacent portions of anterior cerebral arteries.[2]

Variations in cerebral arterial segments have ranged from missing arterial segments to asymmetry between contralateral arterial segments.[1 3] Asymmetry could change or alter the peak pressure dampening effects and causes aneurysms, and we tested the concept in the study.

The arterial measurements were taken, and the position of the cerebral aneurysms were observed. We picked up and measured the specific components of cerebral basal arterial network (i.e. A1 segment) and observed the location of aneurysms in AcomAC and elsewhere in the cranial cavity.

This study produced a quantitative anatomical index for the prediction of the chances of having AcomAC aneurysms.4 A highly significant statistical relationship between the A1 asymmetry and the occurrences of AcomAC aneurysms has been stablished. Patients with A1 asymmetry detected in their CT or MR scans, should be closely followed up, because of a greater risk of developing aneurysms in the AcomAC region.

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Statement of Authorship

Statement of Authorship

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Principal Author

Name of Principal Author	Arjun Burlakoti		
Contribution to the Paper	Conceived the idea, collected the data, designed the analysis, collected and analysed the data taken from Cerebral Computed Tomography Angiography (CCTA), took pictures, recorded videos, contributed in conceptualisation, prepared and drafted the main manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	22nd January 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jaliya Kumaratilake		
Contribution to the Paper	Conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.		
Signature		Date	22nd January 2021

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Name of Co-Author	Jamie Taylor		
Contribution to the Paper	Conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.		
Signature		Date	25th January 2021

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Name of Co-Author	Maciej Henneberg		
Contribution to the Paper	Conceived the idea, contributed to the concept, helped in statistics, data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article.		
Signature		Date	22nd January 2021

Please cut and paste additional co-author panels here as required.

Article:

Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm

Article DOI: 10.1136/bmjsit-2020-000059, BMJ Surgery, Interventions, & Health Technologies

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Keywords

Health Technology, Minimally Invasive Surgical Procedures, Neurointerventional Devices, Vascular Access Devices

Abbreviations

Anterior communicating arterial complex = AcomAC, anterior cerebral artery = ACA, Cerebral Computed

Tomography Angiography = CCTA, Computed Tomography Angiography = CTA proximal segment of ACA = A1, subarachnoid haemorrhages = SAH, magnetic resonance angiography = MRA, cerebral basal arterial network = CBAN, Royal Adelaide Hospital = RAH, relative technical error of measurement = rTEM, Magnetic Resonance Imaging = MRI, and United State Dollar = USD

Abstract

Objectives

The aim of this study was to establish an anatomical index for early prediction of the risk of development of aneurysms in anterior communicating arterial complex (AcomAC). The asymmetric diameter of one anterior cerebral artery (ACA) to other could alter hemodynamics and may contribute to formation of aneurysms in AcomAC and be a reliable predictor of the risk of development of aneurysms.

Design and setting

This is a retrospective, observational and quantitative study, which used Cerebral Computed Tomography Angiography (CCTA) scans in South Australia.

Participants

Cerebral CTA scans of 166 adult patients of both sexes were studied.

Main outcome measures

The internal diameters of the proximal segments of ACAs (A1s) were measured. Position, and presence or absence of aneurysms in AcomAC were determined. The ratio of A1 diameters was taken as a measure of A1 asymmetry.

Results

The ratio of diameters of A1s, correlated with the occurrence of AcomAC aneurysms. The risk of development of aneurysms in AcomAC was much greater (80%, odds ratio = 47.3) when one A1 segment's radius was at least 50% larger (i.e. 2.25 times cross-sectional area) than the other.

Conclusion

The general information on asymmetric A1 has been published previously. The present findings have significant contribution since the A1s asymmetry ratios have been categorised in ascending order and matched with the presence of AcomAC aneurysms. The asymmetry ratio of the A1 is a good predictor for the development of AcomAC aneurysms. Reconstruction of the asymmetric A1 could be done if the technology gets advanced.

Summary

What is already known about this subject?

Relationship of asymmetry of A1 segment of anterior cerebral artery (ACA) to the occurrence of aneurysms in anterior communicating artery complex (AcomAC) has been observed in literature but has not been explained nor quantified.

What are the new findings?

Asymmetry of the A1 of ACA was quantified, and a mathematical model has been established to predict the likelihood of developing AcomAC aneurysms depending on the degree of asymmetry.

How might these results affect future research or surgical practice?

Patients with asymmetry of A1 found in their brain scans, should be closely followed up, because of the

high risk of developing aneurysms in the AcomAC complex. Reconstruction of the asymmetric A1 can be done to prevent the development of AcomAC aneurysms, if ethically justified.

Introduction

Rupture of cerebral aneurysms causes subarachnoid haemorrhages leading to high mortality and morbidity. The incidence of subarachnoid haemorrhages (SAH) has been 10 – 36 per 100,000 people per year and about 3/4 of them resulted from spontaneous rupture of cerebral aneurysms.[1 2] Large cerebral aneurysms may also compress adjacent cranial nerves.[3] The mortality and morbidity rates resulting from ruptured cerebral aneurysms remain high, with around 1/3rd dying at the time, 1/3rd suffering a major stroke and 1/3rd making a reasonable recovery.[4] An aneurysm is a dilatation and outpouching of the wall of a blood vessel.[5 6] The action of fluctuating blood pressure on vascular walls has been identified as the main cause for the development of aneurysms.[7] The risk of aneurysm rupture is 6 to 8 in 100,000 per year in most developed countries.[8] In South Australia, where the total population is 1.7 Millions, radiologists involved in the treatment observed approximately 170 ruptured aneurysm cases per year (i.e.1 in every 10,000 cases per year). Another study revealed that about one in thirty adults likely to have intracranial aneurysms and in 25% of them, the aneurysms could rupture and produce SAHs or compression of surrounding structures.[7] Anterior communicating artery complex has been the most common location of ruptured cerebral aneurysms.[9] Un-ruptured aneurysms have been observed in 2.8% of patients investigated by magnetic resonance angiography (MRA).[10] People with variations in cerebral arteries, particularly, in anterior cerebral arterial territory are thought to be subjected to imbalance in cerebral blood flow leading to cerebrovascular pathologies, including cerebral aneurysms.[11]

Variations in cerebral basal arterial network (CBAN) have ranged from missing arterial segments to asymmetry between collateral arterial segments and the later was more common.[12 13] Some of the most variant and asymmetric patterns of arteries were seen in relation to anterior cerebral and anterior

communicating arterial territories.[11 14] Fluctuation in arterial blood flow, and thus the blood pressure, has been observed in asymmetric A1 segments.[15 16] Such variations in blood flow could predispose the arterial wall for aneurysmal dilatations.[17-22] Genetics, smoking, trauma and medications are factors that could weaken the walls of arteries and predispose them to the development of aneurysms, particularly when subjected to alteration in hemodynamics or chronic hypertension.[22] Prediction and early detection of aneurysms allow treatment, thus could prevent or reduce the incidences of cerebral stroke, including reoccurrences of aneurysms. The aim of this research was to investigate the relationship of asymmetry between A1s and the development of AcomAC aneurysms. As far as we know, no studies have been done on quantifying and calculating the degree of A1 asymmetry to the occurrences of AcomAC aneurysms. A method to predict the risk of occurrence of aneurysms in AcomAC using the degree of asymmetry between right and left A1s has been established.

Methods

Study design

Internal diameters of A1s were measured on CCTA digital images obtained from 166 (80 males and 86 females) adult individuals (average age = 60 years, SD =16) (see supplementary file 1). The same images were used to determine the presence or the absence of AcomAC aneurysms. The source of the CCTA images were the Carestream (Vue RIS version 11.0.14.35) database of the Royal Adelaide Hospital, University of Adelaide, South Australia. The CCTA images were taken between January 2011 and December 2018. The use of these information for research was approved by the University of Adelaide Human Research Ethics Board (approval number: H2014-176). Patient's personal details, have not been copied, documented, or included in this research. The CCTA images studied were those taken for the clinical investigation of different cranial pathologies. These included 51 cases out of 166 patients who had a history of previously diagnosed cerebral aneurysms (Supplementary file 1).

Data collection and extraction

Data collection was carried out by the corresponding author in consultation with radiologists from the Royal Adelaide Hospital (RAH), South Australia who were involved in patients' care. Cases with severe cerebral vasospasm diagnosed by radiologists and recorded in the data system were excluded from the study.

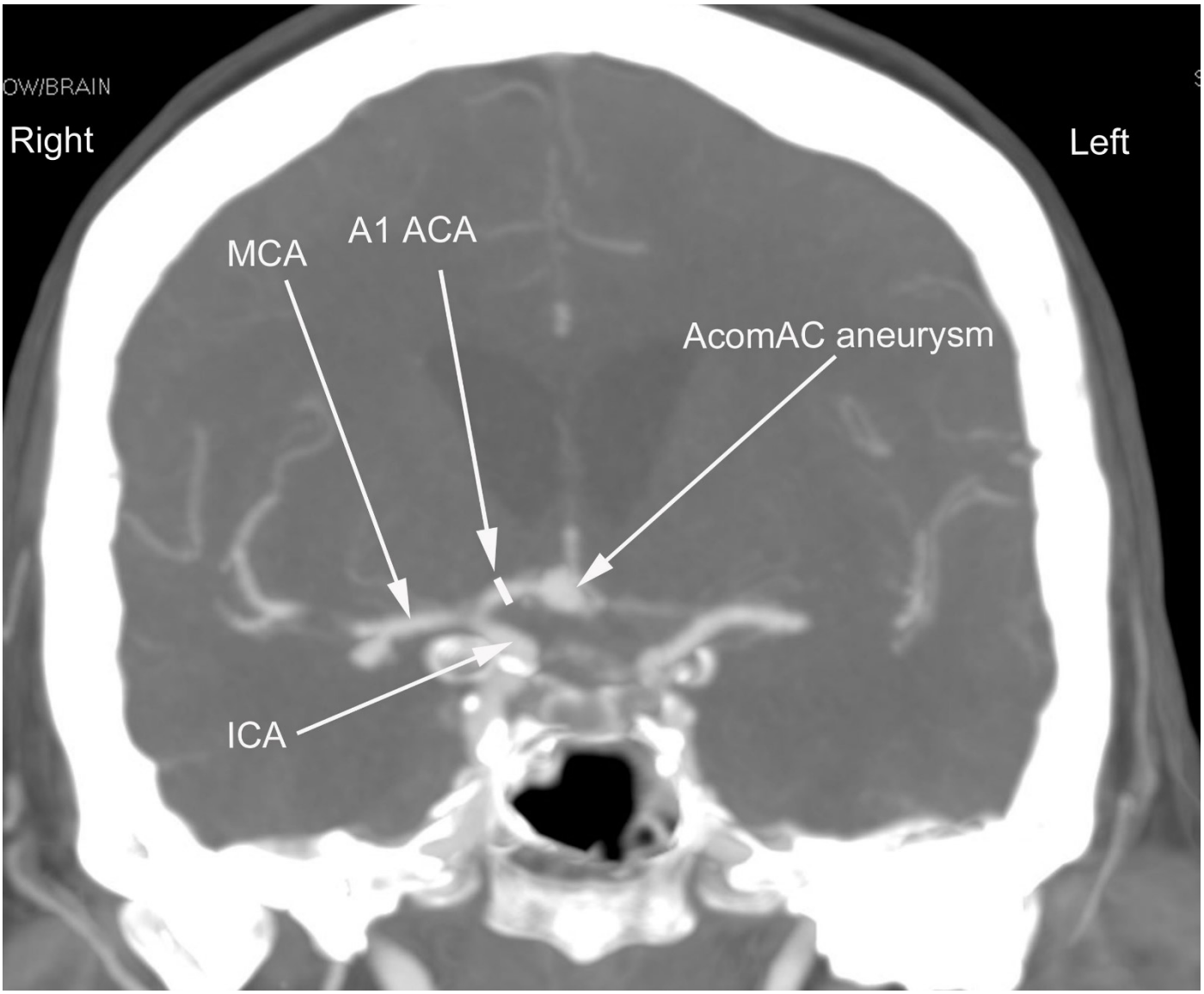

Figure 1: Cerebral Computed Tomography Angiography (CTA) scan with AcomAC aneurysm in coronal view, white line perpendicular to the long axis of the vessel (A1 ACA) indicates measurement site. A1 ACA = the first part of anterior cerebral artery; MCA = middle cerebral artery; ICA = internal carotid artery, and AcomAC = anterior communicating arterial complex.

The internal diameters were measured at the midpoint of the left and right A1s were measured perpendicular to the long axis of the vessels at the narrowest possible sites (in the coronal and axial CCTA images) using image J software (Figures 1, supplementary figure 1 and supplementary figure 2). Measurements taken by the image J software have been proven accurate and reliable in previous studies.[23] The reliability and the accuracy of the measurements were confirmed by repeating measurements of 30 cases at 15 months interval by the same person and determined the intra-observer errors (Table 1 and supplementary file 2). Comparison of first and repeated measurements gave a 10% relative technical error of measurement (rTEM) without adjustment and less than 5% rTEM with minor correction and adjustment (Table 1 and supplementary file 2). These reliabilities and the accuracy calculations were statistically acceptable.[24]
The selection of measurement sites was consistent throughout the data collection. Data were taken only from the electronic files stored in the Carestream software at the Royal Adelaide Hospital, University of Adelaide. Occurrence of AcomAC aneurysms with or without the presence of aneurysm elsewhere and prior history of aneurysms anywhere in the brain were included from each individual case.

Table 1: Accuracy and reliability of the measurements of the first part of the anterior cerebral artery (A1) in Cerebral Computed Tomography Angiography (CCTA) scans.

	Reliability (R)	Technical error of measurement (TEM) in mm	Relative technical error of measurement(rTEM) in %
Repeat A1 measurement in axial CTA images (not adjusted*)	0.93	0.24	11.00
Repeat A1 measurement in axial CTA images (adjusted*)	0.98	0.12	5.39
Repeat A1 measurement in axial and coronal CTA images (adjusted*)	0.98	0.10	4.77
Repeat A1 measurement in coronal CTA images (not adjusted)	0.94	0.22	10.45
Repeat A1 measurement in coronal CTA images (adjusted*)	0.96	0.14	6.55

The coefficients of variation of the measurements (rTEM) are presented. Technical errors of measurement = TEM. Reliability is the correlation among the previous 1st measurement done in coronal and axial CTA slices and the 2nd measurement performed in axial and coronal cerebral CTA after 15 months of the initial measurement taken of the same artery, A1= first part of anterior cerebral artery, n = 30. * adjustment made by excluding two outliers from the previous and the corresponding repeat measurements of right A1 (file supplied in supplementary file 2).

The asymmetry ratios of right and left or left and right (i.e. bigger to smaller ratio) A1 arteries were computed for all 166 CCTA cases (see supplementary file 1). The calculated bigger to smaller A1 asymmetry ratios were categorised into three groups (i.e. mild to moderate asymmetry ≤1.5, substantial asymmetry >1.5 to ≤2 and severe asymmetry ≥2, (Table 2 and supplementary file 3). The rationale for this classification was for easy application and interpretation. The diameter (and hence also the radius) ratio of 1.5 corresponds to the 2.25 times difference in the cross-sectional area of the vessel's lumen, while the ratio of 2.0 reflects four times difference in the cross-sectional area of the vessel lumen.

Statistical analysis

A cross-sectional observational design and Statistical Package for the Social Sciences (SPSS IBM, version 25) program were used in the study. Measurement error analysis has been described in Table 1. In the main analysis, non-parametric statistics (Chi-squared) were used and odds ratios were calculated to observe the strength of association between the A1 asymmetries and the AcomAC aneurysms (Table 2 and supplementary file 3).

Table 2: Probability (out of 1.00) to have anterior communicating artery complex aneurysms in relation to the degree of right and left asymmetricity of A1 ACA.

	A1 asymmetry ratio (right and left bigger to smaller A1)	AcomA complex aneurysm			% Chance	Odds ratio	Chi-squared (Asymptotic Significance); P <
		No	**Yes**	**Total**			
Number of cases; n = 166	**Mild to moderate (≤1.5)**	130	11	141	7·8	0.02	0.0001
	Substantial to severe (>1.5)	5	20	25	80.0	47.3	0.0001
	Total	135	31	166			
Number of cases without history of aneurysm (n = 115)	**Mild to moderate (≤1.5)**	93	7	100	7.0	0.027	0.0001
	Substantial to severe (>1.5)	4	11	15	73.3	36.53	0.0001
	Total	97	18	115			
Number of cases with history of aneurysm (n = 51)	**Mild to moderate (≤1.5)**	37	4	41	9.6	0.012	0.0001
	Substantial to severe (>1.5)	1	9	10	90.0	83.25	0.0001

Total	38	13	51

A1 ACA = first segment of the anterior cerebral artery, AcomA = anterior communicating artery (n = 166), without history of aneurysms (n = 115), with the previous history of aneurysm (n = 51).

Results

The asymmetry ratios of right and left A1 segments of ACA together with the presence and absence of AcomAC aneurysms are presented in Table 2, and supplementary files 1 and 3 (in ascending order, n =166). Amongst 141 patients with mild to moderate A1 asymmetry (≤1.5), 11 had AcomAC aneurysms. Out of 13 patients with substantial asymmetry (>1.5 to ≤2.0), 10 had AcomAC aneurysms. In 12 patients with severe type of asymmetric ratios (>2.0), 10 were affected with AcomAC aneurysms (Table 2, supplementary file 3). Amongst the people with A1 asymmetry ratios of less than 1.5 just 7.8% had aneurysms while in those with ratios of >1.5 to ≤2 and >2, the risks of developing AcomAC aneurysm were 77% and 83% respectively. In summary, patients with asymmetry ratios greater than 1.5 had 80% risk of developing aneurysms (odds ratio = 47.3), while those with asymmetry ratios below 1.5 had 7.8% AcomAC aneurysms (odds ratio = 0.02), (Table 2, supplementary files 1, 3 and 4).

Table 3: Presence or absence of anterior communicating artery complex (AcomAC) aneurysms and cerebral aneurysms elsewhere in the current study. AcomAC = anterior communicating artery complex, n = 166; without history of aneurysms, n = 115; and with the previous history of aneurysm, n = 51.

			AcomAC region		
		Presence or absence of aneurysms	**Yes**	**No**	**Total**
Total number of cases; n = 166	**Aneurysms elsewhere in the cerebrum**	**Yes**	9	68	77
		No	22	67	89
		Total	31	135	166
Cases without history of aneurysm (n = 115)	**Aneurysms elsewhere in the cerebrum**	**Yes**	3	30	33
		No	15	67	82
		Total	18	97	115
Cases with history of aneurysm (n = 51)	**Aneurysms elsewhere in the cerebrum**	**Yes**	6	38	44
		No	7	0	7
		Total	13	38	51

The chances of developing AcomAC aneurysms in the presence of substantial and severe A1 asymmetries were statistically similar between people with or without a previous history of aneurysms (Table 2 and supplementary file 3). In patients with no previous history of aneurysms (n = 115), the incidences, risks and odds ratios (Table 2 and supplementary file 3) of AcomAC aneurysms were similar to the entire sample and to the patients with previous history of aneurysm.

The prevalence of AcomAC aneurysms between sexes and among age groups was statistically not different. Altogether, 31 out of 166 cases had AcomAC aneurysms and 77 out of 166 cases had cerebral aneurysms

elsewhere (i.e. other than the AcomAC aneurysm). Seven out of 11 cases with AcomAC aneurysms that had only mild asymmetry of A1 also had aneurysms elsewhere in the brain other than AcomAC location (Table 3). However, there was no significant relationship between the presence of AcomAC aneurysms and aneurysms elsewhere in the brain (Chi-squared 3.7, $p = 0.05$). Furthermore, statistical relationship between A1 asymmetricity and the presence of cerebral aneurysms elsewhere was not found ($p>0.05$). All patients with AcomAC aneurysms had 1.66 median asymmetry ratio, while the patients without the presence of AcomAC aneurysms had 1.09 median asymmetry ratio. The median A1 asymmetry ratio for all the cases included in this study was just 1.10 (Table 3, supplementary files 1 and 3).

Discussion

The current study quantified for the first time, A1 asymmetry and the likelihood of occurrences of AcomAC aneurysms. Previously the co-occurrence of AcomAC aneurysms with A1 asymmetry has been observed but not quantified.[11 25 26] The study included random CCTA cases accessing the data at a specialized tertiary centre. Obviously, we would assume to see cases of suspected cerebral pathologies in a specialised tertiary medical centre. We examined fairly a large number of 166 CTA evaluating individual A1 asymmetry and aneurysms. The findings (odds ratio and risk percentage) on A1 asymmetry ratio (≥1.42) were extremely significant in relation to the AcomAC aneurysms.

The findings of the study indicate that, the prevalence of aneurysms in AcomAC was greater with increasing asymmetry between left and right A1s (Table 2 and supplementary file 3). The asymmetry ratio of 1.5 indicates that the cross-sectional area of an A1 segment is twice as large as that of the other one (1.52 = 2.25). Furthermore, such asymmetry would likely to have significant haemodynamic effects that could produce 80% risk of AcomAC aneurysms (Table 2, supplementary file 3 and supplementary file 4). The exact mechanism involved in causing aneurysms in AcomAC is not well understood.[27] The development of aneurysm could be due to the altered haemodynamics resulting from the increased blood flow and the

greater peak systolic pressure in the larger anterior cerebral artery.[12 27 28] Imbalanced hemodynamics originating from the larger anterior cerebral artery may weaken and dilate the wall of the AcomAC at branching points, resulting in an aneurysmal formation.[12 21 29] Thus, the extent of the asymmetry in A1s may allow to predict the occurrence of the AcomAC aneurysms. Current sample included patients presenting with various cerebral problems, including strokes and aneurysms. However, when patients were divided into two subsamples: those with a history and without known history of aneurysms, the results did not differ significantly between these sub samples (Table 2 and supplementary file 3). This lack of difference indicates that prior history of aneurysms did not influence the overall results of the study. Therefore, the observed correlation between asymmetry of A1s and AcomAC aneurysms is independent of the prior history of any cerebral aneurysms, because in the current sample there is no correlation between presence of AcomAC aneurysms and aneurysms elsewhere ((Table 2 and supplementary file 3).

The A1 asymmetry ratio was just below 1.5 in 11 out of 31 AcomAC aneurysms cases. However, 3 out of those 11 cases had A1 asymmetry ratios of more than 1.42 (indicating double the cross-sectional area of one A1 artery compared to the other). Furthermore, all others (i.e. 8 out of those 11 cases with asymmetry ratio below 1.5) had asymmetry ratios above the median of 1.09 and represented the “mild to moderate asymmetry” category. Seven of those eleven cases had also aneurysms elsewhere (Table 2, 3 and supplementary file 3). These may indicate that causes for the development of AcomAC aneurysms in the lower A1 asymmetry (<1.40) cases may be because of the quality of vessel’s walls and high blood pressure, in addition to altered hemodynamics resulting from the asymmetry.

Since the CCTA data were taken from the specialised medical centre, it is true that we get to see symptomatic individuals with different pathologies. That approach is even better to see the connection between A1 asymmetry and the presence or absent of aneurysms rather than trying to scan many innocent people in the community, exposing them to the radiation unnecessarily. Modifiable known risk factors, such as history of smoking and hypertension were not quantified in this study. These could have been supplementary factors promoting AcomAC aneurysms, however literature suggests hypertension is not

related to the cerebral aneurysms.[30] Furthermore, there is no reason to assume that A1 asymmetry is related to the smoking and hypertension. This research found a coincidence of A1 asymmetry and AcomAC aneurysms. This coincidence could result from: a) AcomAC aneurysm altering the blood flow and remodelling the size of A1 segments. b) Asymmetry of A1 arteries causing altered blood flow in AcomAC and affecting the walls and producing the aneurysm. Remodelling of the size of arteries in the vicinity or proximal to an aneurysm is not known, therefore it is more likely that A1 asymmetry causes aneurysms. A longitudinal prospective study would likely confirm vessel asymmetry as the cause of aneurysms rather than the reverse. We are not aware of such a study being conducted and there may be significant ethical impediments. Treatment and the management of patients after strokes are costly to the affected family as well as to the country. A multinational study has shown that, the cost of management of a patient after a stroke ranged from USD 18,538 to $228,038. [31] The procedure of treatment of unruptured aneurysms is safe, and the risk of development of stroke is approximately 3% and the mortality is less than 1%, therefore, there is great advantage in identifying and treating aneurysms before they rupture.[32 33]

The ability to predict the likelihood of the development of aneurysms in AcomAC using the asymmetry ratio between right and left A1s could enhance the viability of a national screening programme. Undertaking CCTA screening in the general population is not recommended due to ethical reason. However, if A1 asymmetry is noticed in cranial investigation done for other reasons, clinicians should be cautious as it could indicate the possibility of future development of aneurysms. Therefore, MRI screening of older individuals may be beneficial, and has been recommended.[20] These findings make significant contribution to existing knowledge, since the A1 asymmetry index has been categorised in ascending order and matched with the presence or absence of AcomAC aneurysms in each of the 166 cases. This type of study has not been done before. General anatomical variations of A1 could be corrected with the advancement of medical and surgical technologies. This would prevent unequal blood flow and pressure contributing to the occurrences of AcomAC aneurysms. Patients who have A1 asymmetry (especially the A1 asymmetry with ≥1.42) on scans should be monitored regularly by follow up imaging and angiograms.

Reconstruction of A1 asymmetry is a future possibility with technological advancement.

Conclusion

The asymmetry of the diameters of A1s should be routinely assessed in all patients undergoing cerebral imaging, which includes these vessels. Patients with asymmetry of the A1 should be closely followed up, because of the high risk of development of aneurysms in the AcomAC complex. Reconstruction of the asymmetric A1 could be done if the technology gets advanced in the future.

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Authors' contribution

Arjun Burlakoti- conceived the idea, designed the analysis, collected and analysed the data from CTA, took pictures, recorded videos, contributed in conceptualization, prepared and drafted the manuscript.
Jaliya Kumaratilake- conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.
David J Taylor- conceived the idea, contributed in collecting and interpreting the data, editing the manuscript, the critical revision of the manuscript and approving the article.
Maciej Henneberg- conceived the idea, helped in statistics, data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article.

Conflict of interest statements

There is no conflict of interests

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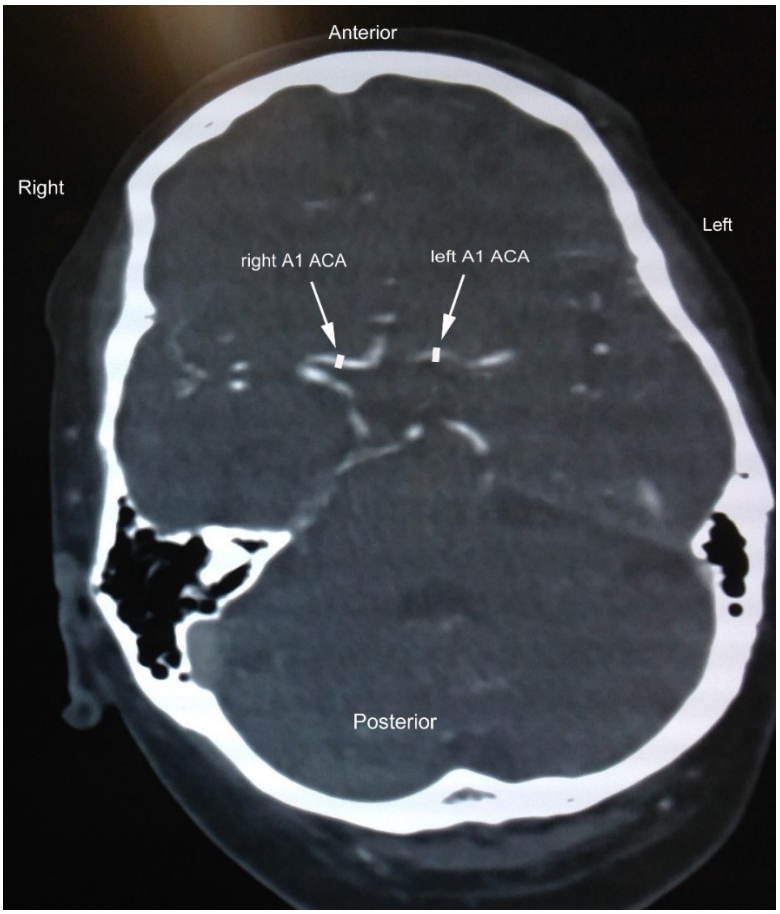
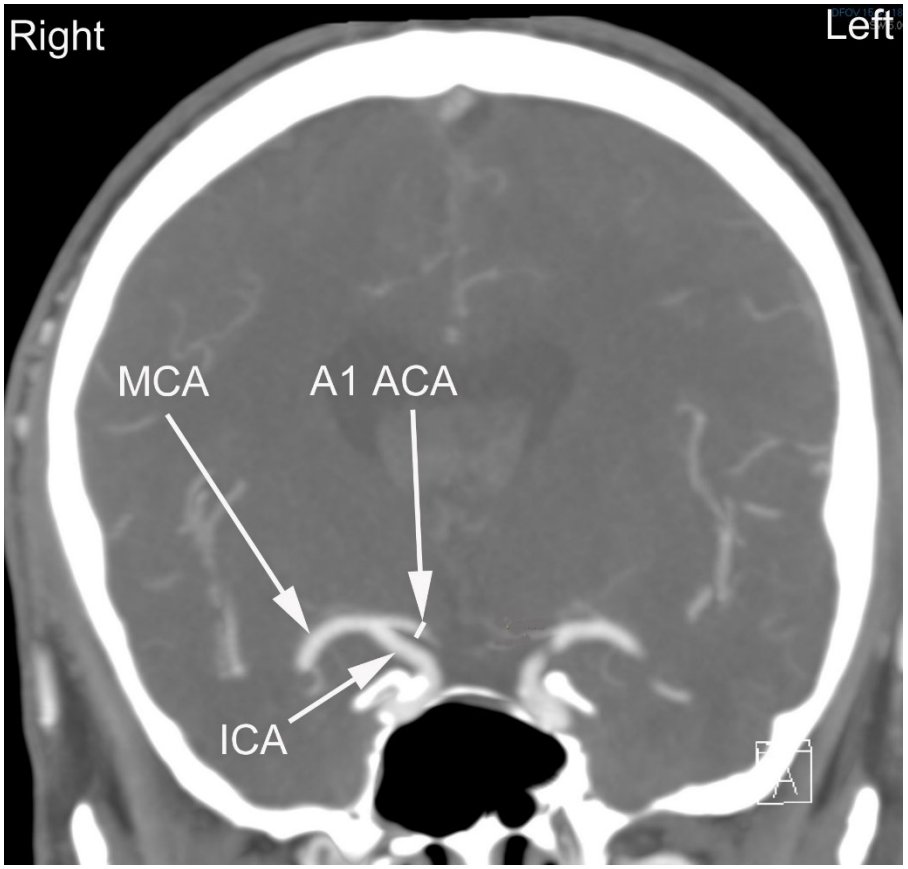
Supplementary figures and files:



Supplementary figure 1: Sites of arterial diameter measurement in cerebral arterial Computed Tomography Angiography (CTA). White lines showing the measurement sites of vessel (A1 ACA) diameters, A1 ACA= the first part of anterior cerebral artery and MCA= the middle cerebral artery.



Supplementary figure 2: Cerebral Computed Tomography Angiography (CTA) scan in coronal view. White line perpendicular to the long axis of the vessel (A1 ACA) indicates the measurement site. A1 ACA= the first part of anterior cerebral artery; MCA= middle cerebral artery; and ICA= internal carotid artery.

Supplementary file 1:

The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary file 1: Presenting the data file (abbreviations with their definitions have been listed in the last page)

With/H	Without/H	Age range in years	rt A1	lft A1	rt A1/lft A1	Asymmetry ratio	AcomAC aneurysm	Aneurysm elsewhere
	0	15-19	3.96	2.38	1.66	1.66	n	n
	0	15-19	2.05	1.96	1.05	1.05	n	y
	0	20-29	1.87	1.91	0.98	1.02	n	n
1		20-29	2.32	2.34	0.99	1.01	n	y
	0	20-29	1.51	1.51	1.00	1.00	n	n
1		20-29	2.51	2.72	0.92	1.08	n	y
	0	20-29	1.63	2.20	0.74	1.35	n	n
	0	20-29	2.22	2.39	0.93	1.08	n	n
	0	20-29	2.13	1.76	1.21	1.21	n	n
	0	20-29	2.60	2.70	0.96	1.04	n	n
1		30-39	2.46	2.50	0.98	1.02	n	y
	0	30-39	2.46	1.88	1.31	1.31	n	n
1		30-39	2.01	2.10	0.96	1.04	n	y
	0	30-39	2.03	3.20	0.63	1.58	n	n
	0	30-39	2.40	2.10	1.14	1.14	n	y
	0	30-39	2.13	2.14	1.00	1.00	n	y
	0	40-49	0.00	2.15	0.00	215.00	y	n
	0	40-49	1.20	2.60	0.46	2.89	y	n
	0	40-49	2.75	2.49	1.10	1.10	n	y
1		40-49	3.51	1.67	2.10	2.10	y	n
1		40-49	2.88	1.01	2.85	2.85	y	n
1		40-49	1.72	1.55	1.11	1.11	n	y
1		40-49	0.00	2.70	0.00	270.00	y	n
1		40-49	3.29	3.16	1.04	1.04	n	y
1		40-49	1.49	3.70	0.40	2.48	y	n
	0	40-49	2.31	2.33	0.99	1.01	n	n
1		40-49	1.51	1.69	0.89	1.12	n	y
1		40-49	1.82	2.37	0.77	1.30	y	y
	0	40-49	2.25	2.38	0.95	1.06	n	y
1		40-49	2.27	2.45	0.93	1.08	n	y
1		40-49	2.14	2.20	0.97	1.03	n	y
	0	40-49	0.00	2.63	0.00	263.00	n	n
	0	40-49	2.56	2.57	1.00	1.00	n	y
1		40-49	2.34	1.72	1.36	1.36	n	y
1		40-49	2.32	2.29	1.01	1.01	n	y
1		40-49	2.29	2.28	1.00	1.00	n	y
	0	40-49	2.19	2.63	0.83	1.20	y	y
	0	40-49	1.84	1.83	1.01	1.01	y	y
	0	50-59	2.22	2.03	1.09	1.09	n	y
	0	50-59	2.42	2.31	1.05	1.05	n	y
1		50-59	2.15	2.72	0.79	1.27	n	y
1		50-59	2.90	2.69	1.08	1.08	n	y
1		50-59	2.37	2.48	0.96	1.05	n	y
	0	50-59	2.64	1.49	1.77	1.77	y	n
1		50-59	2.50	2.60	0.96	1.04	n	y
	0	50-59	2.39	2.05	1.17	1.17	n	n
	0	50-59	2.53	2.27	1.11	1.11	n	n
	0	50-59	1.28	1.36	0.94	1.07	n	n
	0	50-59	2.57	2.26	1.14	1.14	n	y
1		50-59	2.42	2.63	0.92	1.09	n	y
	0	50-59	0.85	2.56	0.33	3.00	y	n
1		50-59	2.99	1.83	1.63	1.63	y	n
	0	50-59	1.98	2.15	0.92	1.09	n	n
	0	50-59	2.37	1.92	1.23	1.23	n	n
	0	50-59	2.52	2.49	1.01	1.01	n	n
1		50-59	2.71	2.66	1.02	1.02	n	y
	0	50-59	2.18	2.17	1.00	1.00	n	n
	0	50-59	2.55	1.52	1.68	1.68	y	n
	0	50-59	3.14	2.14	1.47	1.47	n	n
	0	50-59	2.17	2.48	0.88	1.14	n	n
	0	50-59	2.03	2.00	1.02	1.02	n	n
	0	50-59	0.88	2.14	0.41	2.44	n	y
	0	50-59	2.24	2.33	0.96	1.04	n	y
1		50-59	2.38	2.34	1.02	1.02	n	y
1		50-59	2.14	1.92	1.11	1.11	n	y
	0	50-59	2.27	1.86	1.22	1.22	n	n
	0	50-59	1.96	1.53	1.28	1.28	n	y
	0	50-59	2.99	2.38	1.26	1.26	n	y
	0	50-59	2.80	0.00	#DIV/0!	280.00	y	n

	0	50-59	1.75	2.00	0.87	1.15	n	n
	0	50-59	3.03	2.95	1.03	1.03	n	y
1		50-59	2.34	2.17	1.08	1.08	n	y
	0	60-69	2.56	2.11	1.21	1.21	n	n
	0	60-69	2.20	2.54	0.87	1.15	n	n
	0	60-69	1.81	1.80	1.01	1.01	n	n
	0	60-69	2.03	2.08	0.98	1.02	n	y
1		60-69	2.76	2.91	0.95	1.05	n	y
1		60-69	2.68	2.19	1.22	1.22	y	y
	0	60-69	2.70	2.24	1.21	1.21	n	n
	0	60-69	2.75	2.47	1.11	1.11	n	n
1		60-69	1.49	2.02	0.74	1.35	n	y
1		60-69	2.59	2.38	1.09	1.09	n	y
1		60-69	2.31	2.30	1.00	1.00	n	y
	0	60-69	2.45	2.34	1.05	1.05	n	y
1		60-69	2.17	1.32	1.64	1.64	n	y
1		60-69	2.08	2.03	1.02	1.02	n	y
	0	60-69	1.13	1.93	0.59	1.71	y	n
	0	60-69	1.63	1.94	0.84	1.19	y	n
1		60-69	2.38	1.28	1.86	1.86	y	y
	0	60-69	2.31	2.41	0.96	1.04	n	n
	0	60-69	2.08	2.17	0.96	1.04	n	n
	0	60-69	1.97	2.02	0.98	1.03	n	n
1		60-69	2.19	2.40	0.91	1.10	n	y
1		60-69	2.36	2.46	0.96	1.04	n	y
1		60-69	3.15	1.56	2.02	2.02	y	n
	0	60-69	3.58	2.27	1.58	1.58	y	n
	0	60-69	2.25	1.75	1.29	1.29	n	n
	0	60-69	1.96	2.17	0.90	1.11	n	n
	0	60-69	2.60	2.42	1.07	1.07	n	n
	0	60-69	2.03	1.91	1.06	1.06	n	n
	0	60-69	1.72	2.25	0.76	1.31	n	y
	0	60-69	1.80	2.05	0.88	1.14	n	y
	0	60-69	1.70	2.74	0.62	1.61	y	n
1		60-69	2.00	3.23	0.62	1.62	y	y
1		60-69	1.58	2.48	0.64	1.07	y	y
	0	60-69	2.11	2.40	0.88	1.14	n	n
	0	60-69	2.74	2.60	1.05	1.05	n	n
	0	60-69	2.65	2.70	0.98	1.02	n	y
1		60-69	2.80	2.34	1.20	1.20	n	y
	0	60-69	2.48	2.14	1.16	1.16	n	y
	0	60-69	2.47	2.69	0.92	1.09	n	y
	0	60-69	2.43	2.49	0.98	1.02	n	y
	0	60-69	2.00	2.38	0.84	1.19	n	n
	0	60-69	2.37	2.49	0.95	1.05	n	y
	0	60-69	2.25	2.36	0.95	1.05	n	y
1		60-69	2.80	2.11	1.33	1.33	n	y
1		60-69	1.70	1.74	0.98	1.02	n	y
	0	60-69	2.47	1.49	1.66	1.66	y	n
1		60-69	2.30	4.04	0.57	1.76	y	n
	0	70-79	1.96	1.62	1.21	1.21	n	n
	0	70-79	1.89	2.06	0.92	1.09	n	n
	0	70-79	1.98	1.95	1.02	1.02	n	n
	0	70-79	2.24	2.14	1.05	1.05	n	y
1		70-79	1.16	1.43	0.81	1.23	n	y
1		70-79	2.44	2.16	1.13	1.13	n	y
1		70-79	1.95	1.94	1.01	1.01	n	y
	0	70-79	1.97	2.91	0.68	1.48	y	n
1		70-79	2.50	3.31	0.76	1.32	y	y
	0	70-79	1.85	1.41	1.31	1.31	n	n
	0	70-79	2.67	2.45	1.09	1.09	n	n
	0	70-79	1.53	1.81	0.85	1.18	n	y
	0	70-79	2.82	3.03	0.93	1.07	n	y
	0	70-79	2.06	1.89	1.09	1.09	y	y
	0	70-79	2.50	2.18	1.15	1.15	n	n
	0	70-79	2.27	2.22	1.02	1.02	n	n
	0	70-79	2.57	2.58	1.00	1.00	n	y
1		70-79	2.87	2.56	1.12	1.12	n	y
1		70-79	1.89	2.04	0.93	1.08	n	y
	0	70-79	2.10	1.82	1.15	1.15	n	n
	0	70-79	2.03	1.95	1.04	1.04	n	n

1		70-79	2.64	2.54	1.04	1.04	n	y
	0	70-79	2.22	1.91	1.16	1.16	n	n
	0	70-79	3.20	2.90	1.10	1.10	n	n
	0	70-79	2.35	2.20	1.07	1.07	n	y
	0	70-79	2.13	2.37	0.90	1.11	n	n
	0	70-79	1.76	1.93	0.91	1.10	n	n
	0	70-79	2.28	2.78	0.82	1.22	n	n
	0	70-79	2.61	2.29	1.14	1.14	n	n
	0	70-79	2.02	2.05	0.99	1.01	n	n
	0	70-79	0.88	2.28	0.39	2.59	y	n
	0	80-89	2.19	2.10	1.04	1.04	n	n
	0	80-89	2.29	2.69	0.85	1.17	n	y
	0	80-89	2.54	2.65	0.96	1.04	n	n
	0	80-89	1.92	2.00	0.96	1.04	n	n
	0	80-89	1.81	2.57	0.70	1.42	y	n
	0	80-89	2.45	2.54	0.96	1.04	n	n
	0	80-89	2.08	2.11	0.99	1.01	n	n
	0	80-89	1.77	3.10	0.57	1.44	y	n
	0	80-89	2.79	2.44	1.14	1.14	n	n
	0	80-89	2.29	2.55	0.90	1.11	n	n
	0	80-89	1.90	1.75	1.09	1.09	n	n
	0	80-89	1.87	1.79	1.04	1.04	n	n
	0	80-89	2.40	2.12	1.13	1.13	n	n
	0	80-89	2.74	3.06	0.90	1.12	n	n
	0	90-99	2.49	2.29	1.09	1.09	n	n
	0	100-109	2.25	2.20	1.02	1.02	n	n
					X	1.66		
					Y	1.09		
					Z	1.11		

X= median A1 asymmetry for patients with AcomAC aneurysm= 1.66
Y= median A1 asymmetry for patients without AcomAC aneurysm= 1.09
Z= median A1 asymmetry for all patients with or without AcomAC aneurysms= 1.11

Sex (m= male, f= female)
rt A1 = right sided first part of anterior cerebral artery
lft A1 = left sided first part of anterior cerebral artery
With/H= with history of aneurysm elsewhere
Without/H= without history of aneurysm

Asymmetry ratio= bigger to smaller asymmetry ratio calculation
AcomAC aneurysm= Aneurysm positioned at Anterior communicating artery complex (AcomAC) region, y = present, and n = absent
Aneurysm elsewhere= Aneurysm positioned elsewhere (otherthan AcomAC region), y = present, and n = absent

Supplementary file 2:

The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary file 2: Repeate measurement for reliability calculation (abbreviations with their definitions have been listed in the last page)

rt A1 repeat coronal	lft A1 repeat coronal	coronal A1 ratio left /right	rt A1 Axial repeat	lft A1 Axial repeat	Axial A1 ratio left /right	rt A1 primary CTA measurement in mm	left A1 primary CTA measurement in mm
1.76	2.84	1.61	1.53	2.63	1.72	1.63	1.94
1.93	2.31	1.20	1.92	2.38	1.24	1.82	2.37
2.69	0.00	0.00	2.77	0.00	0.00	2.80	0.00
2.62	1.56	0.60	2.53	1.53	0.60	2.47	1.49
1.00	2.45	2.45	1.06	2.51	2.37	0.85	2.56
0.74	2.70	3.65	0.90	2.56	2.84	0.90	2.60
2.58	1.58	0.61	2.65	1.52	0.57	2.64	1.49
2.40	1.29	0.54	2.45	1.68	0.69	2.38	1.28
1.30	2.51	1.93	1.27	2.35	1.85	1.13	1.93
0.10	2.20	2.20	0.10	2.20	2.20	0.00	2.15
2.90	1.00	0.34	2.80	1.00	0.36	2.88	1.01
1.80	2.70	1.50	1.80	2.70	1.50	1.70	2.74
2.00	2.00	1.00	1.90	1.90	1.00	1.84	1.83
2.20	3.60	1.64	2.50	4.20	1.68	2.30	4.04
1.90	2.80	1.47	1.80	2.70	1.50	1.81	2.57
2.80	2.30	0.82	2.70	2.20	0.81	2.68	2.19
2.00	3.10	1.55	2.10	3.00	1.43	2.16	3.10
2.10	2.50	1.19	2.20	2.60	1.18	2.19	2.63
1.50	2.50	1.67	1.00	2.50	2.50	2.66	2.48
2.20	2.00	0.91	2.20	2.00	0.91	2.06	1.85
3.30	2.50	0.76	3.40	2.40	0.71	3.58	2.27
1.60	2.50	1.56	1.60	2.70	1.69	0.88	2.28
2.60	1.50	0.58	2.60	1.50	0.58	2.55	1.52
3.20	2.10	0.66	3.20	2.10	0.66	2.99	1.83
0.10	2.70	27.00	0.10	2.70	27.00	0.00	2.70
2.10	3.10	1.48	2.10	3.20	1.52	2.00	3.23
2.60	3.00	1.15	2.70	3.10	1.15	2.50	3.31
0.10	3.60	36.00	0.10	3.70	37.00	1.49	3.70
3.40	1.80	0.53	3.50	1.70	0.49	3.51	1.67
3.20	1.60	0.50	3.10	1.50	0.48	3.15	1.56

rt A1 coronal= repeat diameter measured in millimeter (mm) at mid point of the right first segment (A1) of anterior cerebral artery (ACA) in coronal Computed Tomography Angiography (CTA)
lft A1 coronal=repeat diameter measured in millimeter (mm) at mid point of the left A1 of ACA in coronal CTA

rt A1 Axial= repeat diameter measured in millimeter (mm) at mid point of the right A1 of ACA in axial CTA
lft A1 Axial= repeat diameter measured in millimeter (mm) at mid point of the left A1 of ACA in axial CTA

lft= left
rt= right
CTA= Computed Tomography Angiography
A1= first segment of anterior cerebral artery

Supplementary file 3:

The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

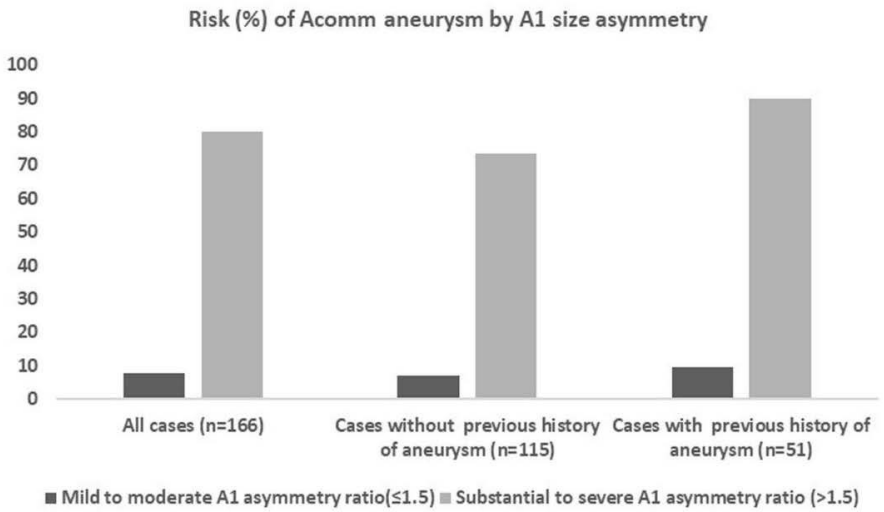
1

Supplementary file 3: Probability (out of 1.00) to have anterior communicating artery complex aneurysms in relation to the degree of right and left asymmetricity of A1 ACA. A1ACA = first segment of the anterior cerebral artery, AComA= anterior communicating artery (n=166), without history of aneurysms (n = 115), with the previous history of aneurysm (n = 51).

	A1 asymmetry ratio (right and left bigger to smaller A1)	AcomA complex aneurysm			% Chance	Odds ratio	Chi-squared (Asymptotic Significance); P <
		No	Yes	Total			
Number of cases; n=166	Mild to moderate (≤1.5)	130	11	141	7.8	0.02	0.0001
	substantial (>1.5 to ≤2)	3	10	13	76.9	20.95	0.0001
	Severe (≥2)	2	10	12	83.3	31.67	0.0001
	substantial to severe (>1.5)	5	20	25	80.0	47.3	0.0001
	Total	135	31	166			
Number of cases without history of aneurysm (n=115)	Mild to moderate (≤1.5)	93	7	100	7.0	0.027	0.0001
	substantial (>1.5 to ≤2)	2	6	8	75	23.75	0.0001
	Severe (≥2)	2	5	7	71.4	18.26	0.0001
	substantial to severe (>1.5)	4	11	15	73.3	36.53	0.0001
	Total	97	18	115			
Number of cases with history of aneurysm (n=51)	Mild to moderate (≤1.5)	37	4	41	9.6	0.012	0.0001
	substantial (>1.5 to ≤2)	1	4	5	20.0	16.44	0.012
	Severe (≥2)	0	5	5	100	infinite	0.001
	substantial to severe (>1.5)	1	9	10	90.0	83.25	0.0001
	Total	38	13	51			

Supplementary file 4 for chapter 3:

Supplementary file 4: Showing the risk (%) of AcomAC aneurysms associated with mild to moderate A1 asymmetry ratio (≤1.5) and substantial A1 asymmetry ratios (>1.5). A1= the first segment of anterior cerebral artery, AcomAC = anterior communicating artery complex



Chapter 4: Orofacial neuralgia associated with a middle cerebral artery aneurysm

Article DOI: 10.1111/adj.12668

This journal paper has been published in the **Australian Dental Journal** on 7th December 2018.
The Journal ranking = Q1 (2019 and 2020), comprises the quarter of the journals with the highest values.
The Australian Dental Journal, a peer reviewed journal is one of the highly ranked journals in the field of dentistry with 1.401 impact factor (updated in 2019).

I (Arjun Burlakoti's) am one of the co-authors of this journal paper, and the permission has been received from all authors involved and please see below signed statement of authorship.

Context for the fourth paper

The PhD candidate had an opportunity to get involved with health professionals from different clinical backgrounds and co-author journal paper using his PhD-related knowledge during his candidature.[1] The diagnosis and management of pain related to the head and neck regions is very challenging and needs an interdisciplinary approach to tackle such conditions. One of the significances of exploring variant cerebral arteries and their relationship to the cerebral aneurysms has been highlighted in the paper published in Australian Dental Journal in 2019 and I was one of the co-authors of this publication. [1] Cerebral aneurysm can compress the brain parenchyma, nearby neurons, irritate the brain surface, get ruptured leading to the

stroke. [2] This paper highlighted on how challenging it would be to treat a complicated case of cerebral neuralgic pain caused by the right MCA aneurysm irritating the right insular cerebral cortical area.

References cited for the context

1. Mascarenhas R, Hapangama N, Mews P, Burlakoti A, Ranjitkar S. Orofacial neuralgia associated with a middle cerebral artery aneurysm. Aust Dent J 2019; 64(1): 106-10.

2. Van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. The Lancet 2007; 369(9558): 306-18.

Statement of Authorship

Statement of Authorship

Title of Paper	Orofacial neuralgia associated with a middle cerebral artery aneurysm
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Mascarenhas, R, Hapangama, N, Mews, P, Burlakoti, A & Ranjitkar, S 2019, 'Orofacial neuralgia associated with a middle cerebral artery aneurysm', Australian Dental Journal, vol. 64, no. 1, pp. 106-110. Doi: https://doi.org/10.1111/adj.12668

Principal Author

Name of Principal Author	Raoul Mascarenhas		
Contribution to the Paper	Reviewed patient over a number of years and helped manage dental care. Developed key concepts presented in this paper, wrote and edited the paper.		
Overall percentage (%)	35%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	04/12/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	ND Hapangama		
Contribution to the Paper	10% Contribution Reviewed patient for differential diagnosis of facial pain. Contributed to records, guidance and editing of the paper.		
Signature		Date	10/12/2020

Name of Co-Author	Peter J Mews		
Contribution to the Paper	10% Contribution Performed neurosurgical procedure and was involved in subsequent follow-up. Contributed to records, guidance regarding neurosurgical concepts, and edited the paper.		
Signature		Date	10/12/2020

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Arjun Burlakoti		
Contribution to the Paper	15% Contribution Contributed to developing and presenting neuroanatomical concepts published within this paper and edited it.		
Signature		Date	30th November 2020

Name of Co-Author	Sarbin Ranjitkar		
Contribution to the Paper	30% contribution Contributed to developing key concepts in this paper, overall writing and editing of the paper.		
Signature		Date	13th December 2020

Please cut and paste additional co-author panels here as required.

Article:

Orofacial neuralgia associated with a middle cerebral artery aneurysm

Article DOI: 10.1111/adj.12668, Australian Dental Journal

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Abbreviation and acronyms

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCA = middle cerebral artery; MRI = magnetic resonance imaging; TMD = temporomandibular joint disorder; TMJ = temporomandibular joint; VPM = ventral postero-medial nucleus.

Abstract

Chronic orofacial pain of neuropathic origin can present diagnostic and management dilemmas to dental practitioners and also affects the patient's quality of life. Intracranial aneurysms are a potential cause of stroke (e.g. sub-arachnoid haemorrhage) that is usually associated with, high rates of mortality and morbidity. A patient who had been previously managed for symptoms of temporomandibular joint disorder (TMD) presented with sharp, shooting pain of moderate intensity. It was precipitated by swallowing, and radiated to the right throat, posterior border of the mandible, ear and temporomandibular joint. Clinical and radiological investigations ruled out odontogenic pain, TMD and other more common types of facial pain. Magnetic resonance imaging revealed a 7 X 6 mm aneurysm in the right middle cerebral artery (MCA) which was subsequently surgically clipped. Interestingly, the facial pain resolved after this procedure. Compression of the insular region of the brain innervated by the trigeminal, glossopharyngeal and vagus nerves provides a plausible explanation for the pain reported. To our knowledge, this is the first case of facial neuralgia associated with an aneurysm in the MCA which emphasizes the importance of a multidisciplinary approach in the diagnosis and management of unusual cases of chronic orofacial pain.

Keywords

Orofacial pain, Intracranial aneurysm, Middle cerebral artery, Neuropathic pain, Multidisciplinary.

Introduction

Intracranial aneurysms are localized dilations of cerebral artery walls that commonly occur as saccular outpouchings at bifurcations.[1] A meta-analysis of 68 studies in 94912 patients from 21 countries

reported the prevalence of 3.2% of unruptured intracranial aneurysms in the general population with a mean age of 50 years.[2] Risk factors for intracranial aneurysms include age, female gender, smoking, hypertension, cerebral arterial variations and familial history of sub- arachnoid haemorrhage, as well as hereditary and congenital syndromes (such as the autosomal dominant form of polycystic kidney disease) and connective tissue disorders (such as the Ehlers–Danlos syn- drome).[3] Aneurysm size, morphology and location within posterior cerebral arteries are associated with increased risk of rupture.[4] Intracranial aneurysm is responsible for approximately 85% of subarachnoid haemorrhages, making it a leading cause of haemorrhagic stroke.[5]

The middle cerebral artery (MCA) is a branch of the internal carotid artery and is the largest and most complex of the cerebral vessels, supplying the basal ganglia (basal nuclei) and the lateral surfaces of the frontal, parietal and temporal lobes of the brain.[6] The artery is typically divided into four segments, including the sphenoidal (M1), insular (M2), opercular (M3) and the cortical (M4) regions of the brain.[7] As many as 14% - 43% of cerebral aneurysms occur within these blood vessels,[8] accounting for up to 55% of all aneurysm-related haematomas following rupture.[9] The rupture of MCA aneurysms results in both subarachnoid and intracerebral haemorrhages in 30% - 50% of cases, with high mortality rates (up to 41%); of those who survive, many suffer permanent neurological deficits including hemiparesis, epilepsy and visual field defects.[10]

A large proportion of unruptured cerebral aneurysms is clinically asymptomatic and is only detected incidentally during radiological and clinical examination. Clinical signs and symptoms associated with cerebral aneurysms include cerebral ischemia and cranial nerve palsy, commonly affecting the oculomotor nerve.[11] Thrombosis, and expansion or inflammation of the aneurysm can also result in severe headache, visual deficits, cranial nerve neuropathies and sei- zures.[12] There are few reports of orofacial pain being associated with posterior communicating artery aneurysms and posterior cerebral artery aneurysms, resulting in trigeminal neuralgia-like symptoms from compression of trigeminal nerve fibers.[13-15] A large proportion of trigeminal neuralgia (approximately 80% - 90%) is caused by

compression of the trigeminal nerve by blood vessels in the cerebellopontine angle, and a smaller proportion of cases is believed to be associated with other intracranial pathologies.[16] However the relationship between the occurrence of aneurysms and facial neuralgia is complex and poorly understood. This report describes a case of unusual chronic facial pain associated with an MCA aneurysm, a presentation that, to our knowledge, has not previously been documented in the literature.

Case report

A 62-year-old female patient presented for a general dental examination with a chief concern of mild pain around the right mandible. Medical history included hypertension, asthma and gastric regurgitation (commonly termed gastric reflux) that were well-controlled by medication. Dental history revealed nocturnal bruxism, for which the patient had been wearing an occlusal splint for 20 years. The most recent occlusal splint had been fabricated 3 months earlier and it showed cracks and significant wear. The masseter and temporalis muscles as well as the lateral pole of the right mandibular condyle were tender to palpation. There was no clicking or significant deviation or limitation to mandibular opening, closing and lateral movements. Furthermore, multiple carious teeth and failing restorations were identified, for which a management plan was formulated. The patient was counselled with regard to the role of bruxism in the aetiology of facial pain, and her symptoms were monitored over the course of restorative care.

Three months after the initial appointment, the pattern and severity of the pain changed. The pain became moderately intense and stabbing in nature. It was precipitated by swallowing, and radiated through the right throat, posterior border of the mandible, ear and temporomandibular joint (TMJ).

Dental radiographs and clinical examination did not reveal an odontogenic source of pain and a subsequent referral was made to an oral and maxillofacial surgeon.

The oral and maxillofacial surgeon organized blood tests including assessment of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) titres. These common markers of vasculitis and inflammation were all within normal limits. Following the lack of osseous pathology evident on cone-beam computerized tomography, magnetic resonance imaging (MRI) of the TMJs and cranial base was obtained which did not reveal any TMJ pathology. However, the MRI displayed an aneurysm in the right MCA. Subsequently an MRI scan of the head was obtained, which revealed a 7 mm x 6 mm aneurysm in the M2 segment of the MCA (Figure 1). The second MRI did not reveal any other pathology within the cranial cavity. This case was referred to a neurosurgeon who con- firmed the aneurysm with computed tomography angiography (Figure 2) and proceeded to clip it surgically. Interestingly, the facial pain resolved postoperatively, and patient's recovery was uneventful. The patient was free of symptoms at the one-month postoperative review and at the time of preparation of this manuscript at six-month post-operative review.

Discussion

Generally, differential diagnoses of chronic facial pain (in decreasing order of occurrence) include odontogenic pain, temporomandibular joint disorders (TMD), temporal arteritis, cranial nerve neuropathies, salivary gland pathology and Eagle's Syndrome.[17] Odontogenic pain is the most common cause of pain[18] but it was excluded during clinical assessment. TMD can present with reduced mandibular movement, muscle and joint pain, disc displacement, arthralgia/arthritis and arthroses,[19] affecting up to half of the population.[20] Radiological and clinical investigations excluded it as well. Giant cell arteritis is a common form of vasculitis with a predilection for the temporal arteries.[21] Signs and symptoms include temporal headache, jaw claudication, scalp tenderness, visual disturbances, fever, weight loss and polymyalgia, as well as increases in CRP and ESR.[22] The blood tests excluded this condition. Eagle's syndrome is characterized by an

elongated styloid process or calcified stylohyoid ligament that compresses on the structures in the neck. When the glossopharyngeal nerve is involved, pain radiates to the throat, base of the tongue and ear when swallowing.[23] Radiological examination excluded this condition, along with salivary gland malignancy that can mimic the symptoms of TMD.[24] Neuropathic pain can occur from disturbances to the sensory pathways of the nervous system either centrally (within the brain and spinal cord), peripherally (vascular compression of nerves) or at both levels. Peripheral neuropathic pain presentations can occur centrally (within the brain and spinal cord), peripherally (vascular compression of nerves) or at both levels. Peripheral neuropathic pain presentations can occur from neuralgia of the trigeminal, glossopharyngeal and vagus nerves which typically present as unilateral sharp, shooting pain triggered by stimulation of the regions distributed by these nerves.[25–27] This condition is often associated with demyelination of the affected nerves closer to their roots secondary to com- pression by adjacent vascular pathology.[28] The patient's symptoms resembled those caused by combined trigeminal, glossopharyngeal and vagal neuralgia, which has been reported to occur on rare occasions.[27] The MRI however did not show evidence of nerve compression, excluding neurovascular conflict as a cause.

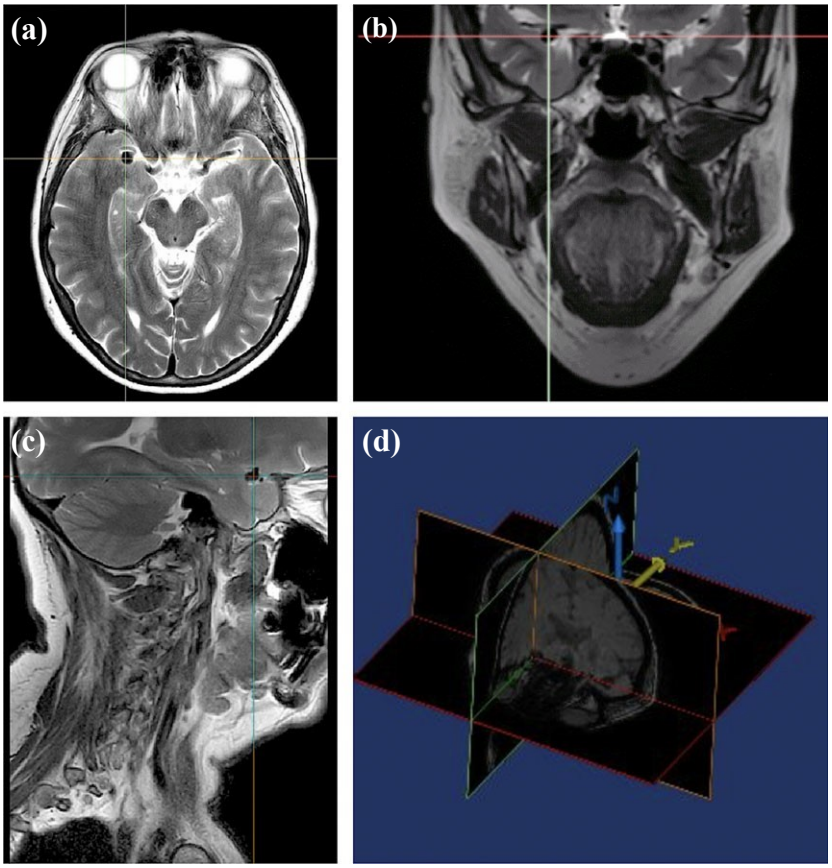

Figure 1: (a) Inferior transverse, (b) Anterior coronal and (c) Right sagittal Magnetic Resonance Images (sections) showing the middle cerebral artery (MCA) aneurysm, and (d) A three-dimensional reconstruction showing the aneurysm in the right MCA within the insula. The location of the aneurysm is shown by the point of intersection of the perpendicular planes.

Figure 2: Anterior coronal view of computed tomography angiography demonstrating the right middle cerebral artery aneurysm (red arrow).

The most plausible explanation for pain in the pre- sent case is central neuropathic pain exerted by aneurysmal compression around the frontal and the parietal opercula of the insula corresponding to the sensory and motor homunculus of the pharynx and the TMJ.[29] The M2 segment of the MCA courses through the insular region around the Sylvian cistern. The enlargement of the aneurysm in the right MCA over time is likely to have compressed areas of this region corresponding to the innervation of the trigeminal, glossopharyngeal and vagus nerves to cause facial neuralgia.

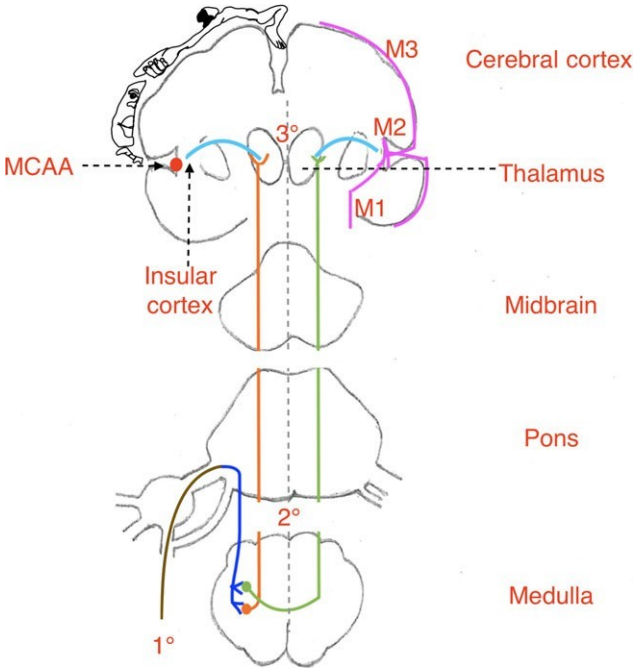

Figure 3: Convergence of first-order trigeminal, glossopharyngeal and vagus pain neurons represented by the brown line (1°) occurs within the spinal nucleus of the trigeminal nerve (dark blue line). The second-order neurons (2°) predominantly project to the contralateral ventral posteromedial nucleus (VPM) in the thalamus via the ventral trigeminothalamic tract (green line), with a degree of projection to the ipsilateral VPM via the dorsal trigeminothalamic tract (orange line). The third-order neurons (3°) then project to the cerebral cortex, including the insular cortex, corresponding to the homunculus regions of the lower face and oro-pharynx. The course of the middle cerebral artery including the M1, M2 and M3 segments is shown by a pink line. The location of the aneurysm (MCAA) adjacent to the insular cortex corresponding to the lower face and pharynx provides the most plausible explanation for ipsilateral manifestation of pain.

Sensory processing of pain and other modalities (e.g. temperature, crude touch and vibration) from the peripheral organs to the brain involve three sets of neurons. First-order neurons carrying pain in the trigeminal, glossopharyngeal and vagus nerves synapse at the spinal nucleus of the trigeminal nerve (nucleus caudalis).[30,31] Second order neurons primarily project to the contralateral (opposite side) ventral posteromedial nucleus (VPM) in the thalamus.[32] Some second-order pain neurons also project to the ipsilateral VPM (on the same side).[33,34] Third order neurons project from the VPM to the cerebral cortex, including the insula (insular cortex). Because of significant crossing-over of pain neurons, a central lesion is typically expected to affect the opposite side of the body. However, ipsilateral projection of trigeminal pain neurons is likely to be responsible for ipsilateral neuralgia associated with insular compression from the right MCA aneurysm in the present case (Figure 3).The need for improving the interface between medical and dental professionals is being increasingly realized.[35] As management of orofacial pain is also common to both fields, appropriate referral and additional investigations (e.g. brain scans) can be necessary for appropriate management. Referral to multidisciplinary pain centers specializing in orofacial pain might also be a pathway to manage unusual cases of facial pain.[36] This could not only help resolve the symptoms in a timely manner but also avoid complications of underlying pathologies, which is important amid growing concerns of litigation against negligent professional behaviour and malpractice.

Conclusion

Differentiating between TMD and other causes of facial pain can be a diagnostic challenge. To our knowledge, this is the first case of orofacial pain that was relieved by surgical clipping of an MCA aneurysm that was not initially considered to be related to

the pain. It is important for the dental practitioner to be aware of these conditions when presented with unusual facial pain of a similar nature as timely medical referral and treatment are crucial. Further studies are required to better elucidate the complex relationship between intracranial aneurysms and pain in the orofacial region.

Conflicts of interest

The authors have no conflicts of interest to declare. The patient provided consent for the use of their records for publication within this article.

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Chapter 5: Prevalence of cerebral aneurysms is related to anatomical variations in cerebral basal arterial network: Investigation of cerebral Computed Tomography Angiography in a neurointerventional unit

Manuscript number: bmjopen-2021-051028.R1

This revised manuscript has been submitted to '**The BMJ Open' journal** for publication on 6th of June 2021.

The Journal ranking = Q1 (2019), comprises the quarter of the journals with the highest values. The BMJ Open, a peer reviewed journal is one of the highly ranked journals in the field of medicine.

Context for the fifth paper

A proof of the concept, about the general study on the importance of cerebral basal arterial network (CBAN) described in paper one, has been presented in the third paper of the thesis which quantified the relationship of anterior communicating artery complex (AcomAC) aneurysm to the degree of asymmetry in the first segment of anterior cerebral artery (A1).[1]

Now, all the cerebral aneurysmal cases were taken in consideration to investigate whether the variant segments of CBAN were linked to the occurrences of aneurysms everywhere in the CBAN or not. The significant findings of this study suggested that the size of individual components of CBAN differed within a person who had an aneurysm more than in persons without aneurysms. This paper has tested the effect of dual pressure dampening mechanism that occurred in the presence of basilar communicating artery[2] in the CBAN system.

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1. Burlakoti A, Kumaratilake J, Taylor DJ, Henneberg M. Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm. BMJ Surgery, Interventions, & Health Technologies 2020; 2(1): e000059.

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Statement of Authorship

Statement of Authorship

Title of Paper	Prevalence of cerebral aneurysms is related to anatomical variations in cerebral basal arterial network: Investigation of cerebral Computed Tomography Angiography in a neurointerventional unit
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscriot style
Publication Details	Arjun Burlakoti, Jaliya Kumaratilake, David J Taylor, Maciej Henneberg, 2021, 'Well-formed segmental cerebral arteries dampen the peak systolic pressure lowering the chances of aneurysms', The Lancet,

Principal Author

Name of Principal Author	Arjun Burlakoti		
Contribution to the Paper	Conceived the idea, collected the data, designed the analysis, collected and analysed the data taken from Cerebral Computed Tomography Angiography (CCTA), took pictures, recorded videos, contributed in conceptualisation, prepared and drafted the main manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	22nd January 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jaliya Kumaratilake		
Contribution to the Paper	Conceived the idea, contributed to the concept, contributed in conceptualisation, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.		
Signature		Date	22nd January 2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Jamie Taylor		
Contribution to the Paper	Conceived the idea, contributed to the concept, contributed in conceptualisation, helped in data collection and interpretation, editing and the critical revision of the manuscript and approving the article.		
Signature		Date	25th January 2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Maciej Henneberg		
Contribution to the Paper	Conceived the idea, contributed to the concept, contributed in conceptualisation, helped in statistics, data analysis and interpretation, edited the manuscript, helped in the critical revision of the manuscript and approving the article.		
Signature		Date	22nd January 2021

Please cut and paste additional co-author panels here as required.

Article:

Prevalence of cerebral aneurysms is related to anatomical variations in cerebral basal arterial network: Investigation of cerebral Computed Tomography Angiography in a neurointerventional unit

Manuscript number: bmjopen-2021-051028.R1

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Abstract

Objective

The segments of cerebral basal arterial network (CBAN) dampen the peak pressure in blood flowing through these arteries, minimizing the chances of development of cerebral aneurysms. The objective of this research was to find the relationship of intracranial aneurysms to variations of the components of the CBAN.

Design and setting

This is an observational, quantitative, and retrospective research, which used Computed Tomography Angiography (CTA) images.

Participants

Cerebral CTA scans of 145 adult patients of both sexes were studied.

Main outcome measures

Diameters of segments of CBAN were measured in cerebral CTA images and the relative size of each vessel was calculated to standardise for differences in overall arterial sizes among patients. Relationships among sizes of CBAN components were analysed. Presence of aneurysms in different parts of the CBAN was recorded.

Results

Forty-six aneurysms in right internal carotid artery (ICA) and middle cerebral artery (MCA) and 32 aneurysms in left ICA and MCA segments were noted in 42 and 30 patients, respectively. Aneurysms in anterior communicating artery complex (AcomAC) and vertebral-basilar (VB) arterial segments were seen in 27 and 8 patients respectively, while they were not detected in parts of posterior cerebral artery (PCA). The significant ($p<0.0001$) inverse relationships between sizes of posterior communicating artery (PcomA) and the first segment

of PCA on both sides indicated that blood inputs to the second part of PCA were similar. Differences in means of the index of arterial size variation for people with aneurysms (0.96) and without aneurysms (0.86) was significant ($p<0.015$). Aneurysms in AcomAC, PCA and VB arteries were less and was proposed that it is due to dampening of peak systolic blood pressures.

Conclusion

Variation in segments of CBAN has been quantified. The peak pressure dampening mechanism in such arterial segments reduces the chances of development of aneurysms.

Key words

subarachnoid haemorrhage; aneurysm; stroke; hemodynamics; cerebral basal arterial network

Funding

None

Strengths and limitations of this study

The relationship of cerebral arterial variations to aneurysms has been quantitatively assessed for the first time.

A method for standardising size of individual cerebral arteries in relation to the total size of the cerebral basal arterial system has been introduced.

Parametric and non-parametric statistical methods were used.

Patients from neurointerventional unit are not a random representation of the general population.

A cross-sectional, not a longitudinal study.

Introduction

Cerebral aneurysms are a common cause of haemorrhagic stroke. Diagnosis, management, prediction and prevention of aneurysms are challenging.[1] The middle cerebral artery (MCA) and anterior communicating artery complex (AcomAC) regions have been identified as the most common locations for the occurrence of intracranial aneurysms.[2-5] However, the occurrence of more than two thirds of the total intracranial aneurysms has been reported in relation to internal carotid artery (ICA) territory.[6] Therefore, most of the cerebral aneurysms occur in ICA, MCA and AcomAC territories.[2-6] Pia and Fontana have described posterior cerebral artery (PCA) aneurysms, but the rate of prevalence of cerebral aneurysms in PCA and vertebrobasilar (VB) arterial components is the least.[7-9] The prevalence of intracranial aneurysms of various sizes ranged from 0.2 to 6.8 %, and approximately 6-10/100,000 people suffered from ruptured intracranial aneurysms per year.[4,10] These individuals had poor prognosis and more than a third of the mortalities occurred within a month of the illness.[4,10] Most of the ruptured aneurysms (85.6% cases) were reported to be symptomatic and were from the MCA and AcomAC territories.[4,5] Therefore, studying the relationship of relative sizes of cerebral arteries, sites of location of cerebral aneurysms and their relationship to the variant segments of CBAN would help to understand the risk factors, and maximise the management of strokes.

The blood flow to the cranial cavity through the four main incoming arteries is asynchronous.[11] The asynchronous blood pressure gradients in the incoming intracranial arteries combine via segments of the CBAN. This maintains a continuous, smooth blood flow through the arteries leaving the arterial network, thus minimises peaks in pressure and reduces the chances of development of cerebral aneurysms. [11,12] However, the blood flowing through the asymmetric and variant segments of CBAN, alters the hemodynamics and peaks in pressure and predisposes to the development of aneurysms in the associated “arterial

complexes".[11,13] A relationship for the development of AcomAC aneurysms to the degree of asymmetry between left and right first segments of ACA (A1s) has been shown to occur.[14] The current study, investigated the relationship of locations of intracranial aneurysms to relative sizes of all arterial segments of CBAN and their individual variations. The concept that the mechanisms involved in dampening peak systolic pressures in arterial segments of CBAN, reduce the chances of the development of aneurysms in the ACA and PCA territories, justified the current investigation.

Material and method

Patient and public involvement

The cerebral computed tomography angiography (CCTA) images used in this study were taken from patients who visited the Royal Adelaide Hospital (RAH) for a variety of reasons related to cranial pathologies and screening purposes. Personal information of patients recorded in the data system has not been included in this study. Human Research Ethics Board granted permission (approval number: H2014 -176) to access and use data from the Carestream data registry system (Vue RIS version 11.0.14.35).

Study design

Randomly selected CCTA images of 145 patients archived in the Carestream data registry system at RAH, South Australia between January 2011 and December 2019, were used in the study (age range 18 to 100 years, male = 67, female = 78, mean age = 60.9 years) (Supplementary file 1).The CCTA images with severe artefacts or from patients with severe cerebral vasospasm (i.e. diagnosed by radiologists) were excluded from the study. Missing arterial components or those not seen in the CCTA images (e.g. PcomA and proximal segment of ACA) were considered to have 0.1 mm diameter for the purpose of statistical analysis (Supplementary file 1). The components of CBAN in some CCTA were not visible

due to artefacts and such cases were excluded. Therefore, the number of arterial components measured in CCTA varied to a moderate extent.

Data collection

The position, presence or absence of aneurysms of any sizes were recorded from CCTA of 145 patients based on the diagnosis made by radiologists and clinicians. The position of aneurysms associated with the AcomAC, MCA, ICA, PCA and VB arterial regions were recorded. Some cases had multiple aneurysms. The internal diameters of intracranial segment of ICA at the level of anterior clinoid processes, the first segment of ACA (A1) at the mid-point, PcomAs at the mid-point, the proximal end of the first segment of MCA (M1), anterior communicating artery (AcomA) at the mid-point, the proximal end of the second part of ACA (A2), the first segment of PCA (P1) at the mid-point, the proximal segment of PCA (P2) at the level of dorsum sellae, the distal end of basilar artery just proximal to the origin of superior cerebellar artery (SCA), and the distal vertebral arteries (AV) just proximal to the formation of basilar artery (BA) were measured at right angles to the longitudinal axis of arteries in each individual (Figure 1). The measured internal diameters (in millimetre, mm) were converted into the "relative sizes" of the vessels using the formula, "measured diameter of each vessel / the average size of all the CBAN components measured" (Supplementary file 1) and transferred into the SPSS v. 25 software, before the statistical analysis. The diameters of arteries were converted into "relative sizes" to neutralize the individual differences in sizes of CBAN components among patients.

The diameter of each artery was measured at the narrowest region of the selected site, perpendicular to the long axis of the vessel (Figure 1), to make the measurements consistent across all CCTA images. Furthermore, the CCTA arterial data taken from all the patients were divided into two groups (see below) in order to observe the relationship of aneurysms to

the variation in the components of CBAN. This was achieved by analysing the average standard deviation (SD) of arterial sizes in each individual, and coefficients of variation of CBAN components.

Group a: patients with one and more than one cerebral aneurysms; group b: patients without cerebral aneurysm (see columns number 44 to 53 in Supplementary file 1).

Three variables (shown below) characterising each patient's CBAN were constructed for the analysis of the variation of the sizes of all left and right segments of the CBAN (i.e. left and right ICA, first segment of MCA, A1, A2, P1, P2, AcomA, PcomA, and BA):

1. Average sizes (Av) of all CBAN arteries
2. Standard deviation (SD) of sizes of the same CBAN components
3. Coefficient of variation (CV) of CBAN segments = 100*SD/Av

The average size of CBAN, SD and CV of all components of CBAN were calculated to determine the degree of variation in the CBAN segments for each individual patient (columns 23 to 25 in Supplementary file 1)

The accuracy of the measurements was determined by repeating measurements in CCTA of 10 cases, a week after the first measurement (Table 1 and Supplementary file 2). The relative technical error of the measurement (rTEM) was calculated and found to be within the statistically acceptable limits (i.e., ≤10%).

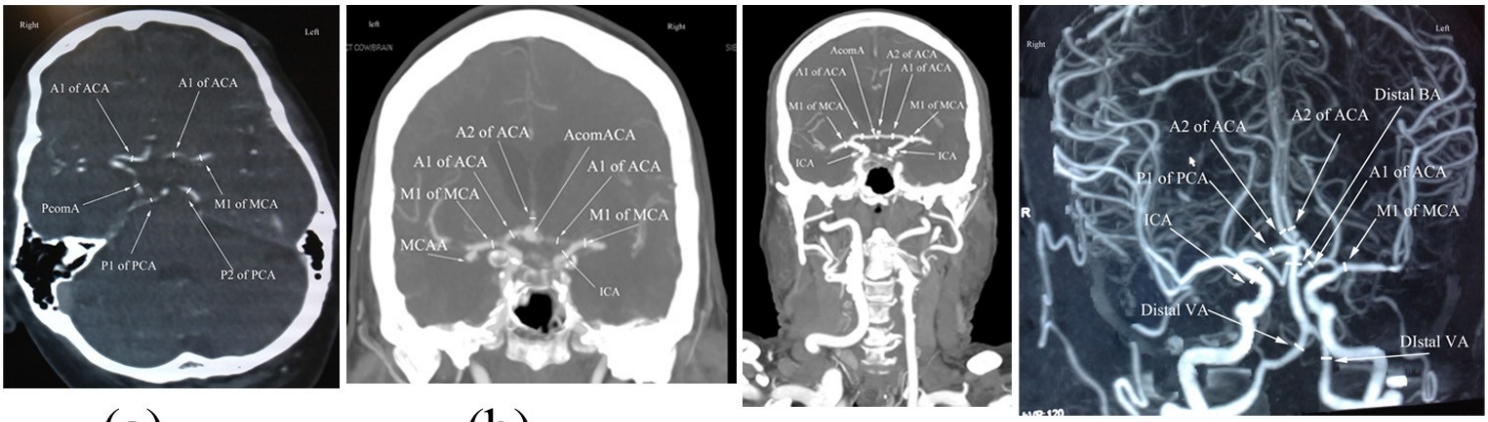

Figure 1

Figure 1: Sites of arterial diameter measurement in cerebral angiography images.

White lines perpendicular to the long axes of vessels show the measurement sites and white arrows depict the components of cerebral basal arterial network (CBAN). (a) = axial image showing the sites of measurement, (b) = coronal image showing the sites of measurement and location of aneurysms, (c) = coronal angiography showing the sites of vessel measurement, (d) = digital subtraction angiography showing the sites of vessel measurement. ACA = anterior cerebral artery, MCA = middle cerebral artery, ICA = cranial component of internal carotid artery, PCA = posterior cerebral artery, A1 of ACA = the first segment of ACA, A2 of ACA = the second segment of ACA, AcomA = anterior communicating artery, PcomA = posterior communicating artery, M1 of MCA = the first segment of middle cerebral artery, P1 of PCA = first segment of PCA, P2 of PCA = second segment of PCA, BA = basilar artery, VA = vertebral artery, AcomACA= AcomA complex aneurysm, and MCAA = MCA aneurysm.

Table 1: The reliability of the measurements taken in Cerebral Computed Tomography Angiography (CCTA) images.

	rt VA	lft VA	BA	rt P2	lft P2	rt Pco mA	lft Pco mA	rt ICA	lft ICA	rt A2	lft A2	Acom A	rt M1	lft M1	rt P1	lft P1	rt A1	lft A1
TEM error	0.025	0.021	0.019	0.018	0.017	0.003	0.004	0.023	0.055	0.020	0.069	0.070	0.020	0.003	0.008	0.007	0.006	0.015
rTem (CV)	0.982	0.767	0.644	0.793	0.697	0.708	0.909	0.533	1.305	0.751	2.783	3.623	0.684	0.805	0.842	0.755	3.732	5.825
R reliability	0.998	0.999	0.999	0.997	0.996	0.99	0.99	0.998	0.988	0.998	0.948	0.971	0.998	0.98	0.99	0.98	0.991	0.982

Reliability, the coefficients of variation (CV) or the relative technical error of cerebral vessel internal diameter measurements (rTEM) and the technical error of measurements (TEM) are presented. Reliability is the correlation among the first measurements and the second measurements taken from the same artery, n = 10. rt = right, lft = left, dia = internal diameter, ACA = anterior cerebral artery, MCA = middle cerebral artery, ICA = cranial component of internal carotid artery, PCA = posterior cerebral artery, A1 = first segment of ACA, PcomA = posterior communicating artery, AcomA = anterior communicating artery, M1 = first segment of MCA, P1 = first segment of PCA, P2 = second segment of PCA, BA = basilar artery, and VA = vertebral artery (Supplementary file 2).

Statistical analysis

This is a cross-sectional observational study. The data were analysed using excel data file and descriptive, parametric and non-parametric statistical methods, independent sample t – test, linear regression, logistic regression, and custom tables from Statistical Package for the Social Sciences (SPSS IBM, version 25) program. The p values less than 0.05 were considered statistically significant (Table 1, Table 2, Table 3, Table 4, Supplementary files 1, 2, 3 and 4).

Findings

The majority of the cerebral aneurysms detected in the current study were in association with bilateral ICA and MCA (columns number 45 to 53 in Supplementary file 1, pages 2-4 in Supplementary file 3, Supplementary file 4, Supplementary table 1 and 2). Statistically strong inverse relationships were found between relative sizes of ipsilateral PcomA, and P1 segments on the right and left sides (Table 2). The relative sizes of right and left PcomA were found to be inversely correlated with the relative size of basilar artery (Table 2 and Supplementary file 3). Furthermore, significant positive correlations were found between relative sizes of left and right cranial ICA, left and right first part of MCA (M1), left and right second part of ACA (A2), and left and right second part of PCA (P2) (Table 2, Supplementary table 1 and page number 4 to 8 in Supplementary file 3). The differences in averages of standard deviation (std. Dev) and Coefficient of variation (CV) analysed by means of logistic regression and independent sample t – test in groups with or without aneurysms were statistically significant (Table 3 and 4). The variation in the sizes of CBAN segments was found to be greater in people with aneurysms compared to those without aneurysms (Table 3, Table 4, and column number 23 to 25 in Supplementary file 1).

Eighty-three patients out of 145 had cerebral aneurysms in various locations (Supplementary tables 1 and 2, columns number 45 to 53 in Supplementary files 1, page 2 in Supplementary files 3). Some individuals had multiple aneurysms, thus a total of 113 aneurysms were found in the 83 patients (Supplementary table 1 and 2, columns number 45 to 53 in Supplementary file 1, and Supplementary file 4). Out of the total number of 113 aneurysms, 32 (28.31%), 14 (12.4%), 24 (21.24%) and 8 (7%) aneurysms were found in right MCA, right ICA, left MCA and left ICA regions respectively. Seventy-eight out of the 113 aneurysms in the 83 patients (i.e. 69% of the total) were in the right and left MCA and ICA regions (Supplementary table 1, columns number 45 to 53 in Supplementary file 1 and page 2 to 4 in Supplementary file 3). Furthermore, 27 aneurysms (23.9% of the total) were in AcomAC regions, one in each of 27 patients (Supplementary table 1 and columns number 45 to 53 in Supplementary file 1). In addition, 8 aneurysms (7% of the total) were located in the VB arterial regions (Supplementary table 1). Ten and 2 patients had bilateral MCA and ICA aneurysms respectively (Supplementary table 1). Out of the 27 patients with AcomAC aneurysms, 19 of them had aneurysms only in the AcomAC regions (Supplementary table 1). Eight patients with AcomAC aneurysms also had coexisting left MCA (n = 4), right MCA (n = 4), and right ICA (n = 4) aneurysms. Out of those eight patients with multiple coexisting aneurysms, one of them had aneurysms in AcomAC, right MCA and left MCA, while another had coexisting aneurysms in AcomAC, right ICA and right MCA (Supplementary table 1). The third patient with AcomAC aneurysm also had coexisting aneurysms in right ICA and left MCA (Supplementary table 1). Ten cases also had coexisting aneurysms in bilateral MCA territories (Supplementary table 1 and columns 45 to 53 in Supplementary file 1). Out of eight patients with VB aneurysms, one, three, one, and one also had coexisting right ICA, right MCA, left ICA and left MCA aneurysms respectively. No aneurysms were detected at

or distal to P2 segments of PCA (column 45 to 53 in Supplementary file 1, Supplementary table 1 and 2).

Table 2: Spearman's rho nonparametric correlation among the relative size of CBAN components.

Correlations - Spearman's rho

		RsBA	RsRt P2	RsLft P2	RsRtPcomA mid dia	RsLftPcomA mid dia	RsRt P1	RsLft P1
RsBA	**Correlation Coefficient**	**1.000**	**.169***	**-.017**	**-.390****	**-.447****	**.245***	**.293****
	Sig. (2-tailed)	.	<.043	.839	<.000	<.000	<.015	<.003
	N	145	145	145	145	145	98	98
RsRt P2	**Correlation Coefficient**	**.169***	**1.000**	**.357****	**-.350****	**-.286****	**.234***	**.168**
	Sig. (2-tailed)	<.043	.	<.000	<.000	<.000	<.020	.098
	N	145	145	145	145	145	98	98
RsLft P2	**Correlation Coefficient**	**-.017**	**.357****	**1.000**	**-.206***	**-.140**	**.301****	**.191**
	Sig. (2-tailed)	.839	<.000	.	<.013	.093	<.003	.059
	N	145	145	145	145	145	98	98
RsRtPcomA mid dia	**Correlation Coefficient**	**-.390****	**-.350****	**-.206***	**1.000**	**.456****	**-.600****	**-.388****

	Sig. (2-tailed)	<.000	<.000	<.013	.	<.000	<.000	<.000
	N	145	145	145	145	145	98	98
RsLftPcomA mid dia	**Correlation Coefficient**	**-.447****	**-.286****	**-.140**	**.456****	**1.000**	**-.315****	**-.639****
	Sig. (2-tailed)	<.000	<.000	.093	<.000	.	<.002	<.000
	N	145	145	145	145	145	98	98
RsRtP1	**Correlation Coefficient**	**.245***	**.234***	**.301****	**-.600****	**-.315****	**1.000**	**.352****
	Sig. (2-tailed)	<.015	<.020	<.003	<.000	<.002	.	<.000
	N	98	98	98	98	98	98	98
RsLft P1	**Correlation Coefficient**	**.293****	**.168**	**.191**	**-.388****	**-.639****	**.352****	**1.000**
	Sig. (2-tailed)	<.003	.098	.059	<.000	<.000	<.000	.
	N	98	98	98	98	98	98	98

***. Correlation is significant at the <0.05 level (2-tailed), **. Correlation is significant at the <0.01 level (2-tailed).**

Cerebral basal arterial network = CBAN, Rs = relative size, Rt = right, Lft = left, PCA = posterior cerebral artery, PcomA = posterior communicating artery, BA = distal basilar artery, P2 = second part of PCA, PcomA = posterior communicating artery, P1 = first part of PCA, RsBA= relative size of distal basilar artery, RsRt P2 = relative size of right proximal P2, RsLft P2 = relative size of left proximal P2, RsRtPcomA mid dia = relative size of right

PcomA at the mid-point, RsLftPcomA mid dia = relative size of left PcomA at mid-point, RsRt P1 = relative size of right P1 at mid-point, RsLft P1 = relative size of left P1 at mid-point.

Table 3: Comparison of average SD and CV of cerebral basal arterial network (CBAN) measurement in patients with and without cerebral aneurysms (Independent sample t – test). Analysis of standard deviation (SD) of CBAN measurement, Coefficient of variation (CV), and an average size of CBAN in mm.

	Standard deviation of CBAN measurement (SD, mm) average (SD)	Coefficient of variation (CV) average (SD)	Size of CBAN (mm) average (SD)
Patients without cerebral aneurysms (n = 62)	0.86 (0.22)	34.9 (10.0)	2.50 (0.24)
Patients with one or multiple cerebral aneurysms (n = 83)	0.96 (0.23)	38.2 (9.1)	2.52 (0.26)
Significant (2- tailed, p value)	0.015	0.038	0.708

The table 3 shows the variation in the components of CBAN in everyone in relation to the presence or absence of aneurysms. CBAN = cerebral basal arterial network.

Table 4: Comparison of average standard deviation (std. Dev) and Coefficient of variation (CV) of cerebral basal arterial network (CBAN) measurement in patients with and without cerebral aneurysms (using a logistic regression model for the presence of cerebral aneurysms).

Variables	B	Constant	p
CV	0.037	-1.071	<0.040
Std. Dev	1.822	-1.368	<0.017

Cerebral aneurysms = CV. 0.037-1.071, significant $p<0.040$

Cerebral aneurysms = std. Dev. 1.822-1.368, significant $p<0.017$

Discussion

The significant differences in the means of variation measures of segments of CBAN in people with aneurysms and without aneurysms suggest that the size of individual vessels of the CBAN differs within a person who had an aneurysm (Table 3 and 4 and columns number 23 to 26 in Supplementary file 1). Furthermore, the analysis also confirmed that the occurrences of aneurysms did not depend on the average size of the segments of CBAN (columns number 23 to 26 in Supplementary file 1 and Table 3). However, the overall variation in the size of individual segments of CBAN determined the probability of having the cerebral aneurysms (Table 3). Therefore, these statistically significant differences in the variation of segments of CBAN suggested that the minimally variant segments of CBAN served to best equalize the blood pressure preventing the development of cerebral aneurysms (Table 3). Similar distribution patterns of intracranial aneurysms have been described in the literatures.[3,4,6,15] Aneurysms less than 3 mm in diameter could be missed in commonly used CCTA imaging techniques.[16] The findings of the current study, on more than 4 mm in

diameter sized ICA aneurysms compared well with Imaizumi and colleagues findings.[6] Approximately, 3% of the general population develop cerebral aneurysms and may not be diagnosed, until they enlarge sufficiently to cause symptoms or rupture.[17] However, more than 70 % of aneurysms detected by Imaizumi and colleagues[6] using advanced imaging technique were ≤3mm in diameter.[16] The current study, collected data from patients with complicated and ruptured aneurysmal cases, who were referred to the Neuro-interventional Centre in RAH for treatment. Imaizumi and colleagues[6] conducted the study on healthy and asymptomatic adults and detected the right ICA territory as the most common location (78%) for the development intracranial aneurysms. Almost 83% of the detected ICA aneurysms in the latter study were ≤3.9mm in diameter[6], thus individuals with these aneurysms would not have displayed aneurysm related symptoms. The chances for the rupture of an aneurysm is minimal, when the size is ≤4mm in diameter.[2,6] Most of the CCTA images with AcomAC aneurysms (19 cases) in the current study, had no other coexisting aneurysms located elsewhere in the intracranial regions (Supplementary file 1). The frequency of aneurysms was lower in AcomAC and PCA territories in comparison to the aneurysms found in the MCA and ICA territories in the current study and in a study published recently.[6]

The absence of aneurysms elsewhere in 19 out of 27 (i.e., 70.04%) AcomAC aneurysmal cases (Supplementary files 1 and 3) may indicate that the causes of aneurysms were not due to generalised weakness of the CBAN arterial wall, hypertension, smoking and familial reasons. Vrselja and colleagues suggested that the communicating arteries divert the blood flow and dampen the peaks in systolic pressure in the CBAN system to reduce the occurrence of aneurysms.[18] The chances of the development of AcomAC aneurysms have been predicted to be ≥80% when the asymmetric ratio between right and left A1 segments is 1.42 or more (i.e., larger diameter /smaller diameter).[14] Furthermore, the effect of fluctuating peak systolic pressure in causing aneurysms in AcomAC territories would be lower in the presence

of symmetrical A1 arterial segments.[14] Therefore, these 19 cases of AcomAC aneurysms could have resulted from the altered haemodynamics caused by the asymmetry between right and left A1 segments.[14]

Fluctuation of peak systolic pressure may contribute to the occurrence and rupture of cerebral aneurysm.[19] In addition, the amount of blood flowing through a MCA had been found to be increased in the presence of the hypoplastic or absent A1 segment or PcomA on that side of CBAN.[20] Therefore, the 8 cases of AcomAC aneurysms that cooccurred with aneurysms elsewhere (i.e. AcomAC aneurysms cooccurred with right ICA, right MCA and left MCA regions) might have been associated with the presence of hypoplastic or absent A1 segments or PcomA (Supplementary file 1). These variations of A1 and PcomA segments would increase the resistance to the outflow of blood from the ICA, thus increase the flow and peak systolic pressure through the MCA. Therefore, the greater incidence (≥85% cases) of cerebral aneurysms found in the ICA and MCA territories, [3,4,15] could be linked to the altered haemodynamic in the presence of variant segments of CBAN.[21-23] A significant amount of wall shear stress has been noticed on the stent placed next to the aneurysmal sac suggesting increased peaks in systolic pressure would result in the development of aneurysm.[24] This indicates that symmetrical A1 segments, and PcomA could act as the flow diverting segments of CBAN and reduce or dampen the peak systolic pressure in the ICA and MCA reducing the incidence of aneurysms in these regions. The PCA aneurysms are rare.[7,25] The i) significant positive correlations between right and left PcomA, ipsilateral P1 and P2 segments and BA with right and left P1 segments, and ii) inverse correlations between PcomA with ipsilateral and contralateral P1 segments and BA with right and left PcomA (Table 2 and supplementary file 3) indicate that these arterial segments help to balance and maintain optimal blood flow in P2 segments. Thus, the peak systolic pressures may not reach levels that could injure the arterial wall and cause aneurysms in P2 segment and beyond.[26]

This is particularly important, because the blood flow in P2 segment is maintained by two inversely correlated ($p \leq 0.01$) ipsilateral PcomA and P1 vessels (Table 2). Thus the prevalence of aneurysms in the P2 segment territory of PCA is zero or minimal (Supplementary file 1 and 3).[7] The peak systolic pressures of the blood flowing via the vertebral arteries would get dissipated in the basilar artery (which is also considered as a communicating artery [27]), and then in P1 before reaching the P2 segment. In a similar way, blood flowing from the ICA is dampened in PcomA before reaching the P2 segments, which ensures the less fluctuating peak systolic pressures in P2 and distal to the P2 segments. Therefore, pressure dampening mechanisms could smoothen the arterial pressure distal to P2 segments and reduce the chances of developing aneurysms in PCA compared to ICA, MCA and AcomAC territories.

In vertebrate brain evolution, brainstem evolved first, whereas the telencephalon (specially the frontal lobes) was a later addition to the brain.[28] Therefore, the arterial supply in the brainstem and the posterior part of telencephalon had more time to be well established. The recently evolved large telencephalon is predominantly supplied by ICA.[29] The anterior part of CBAN evolved along with the telencephalon and has had less evolutionary time to develop, compared to the posterior segments.[28] Thus, the natural selection did not have adequate time to minimise the variations and asymmetries of the anterior segments of the CBAN. Furthermore, a larger blood volume has to flow through the less evolved anterior segments of CBAN to meet the demand of the large telencephalon.[30] Therefore; the chances of development of aneurysms in the arteries supplied by the anterior segments of CBAN are higher compared to the posterior part. Asymmetry between antimere segments of CBAN could result from the mutations of genes involved in the development of cerebral arterial segments (e.g., development of hypoplastic right or left A1 segment of ACA) in the embryo. However, in some, the embryo has the ability to enlarge the collateral segment of a

hypoplastic segment of CBAN and maintain adequate blood supply to the affected right or left side of the brain. Establishment of this compensatory blood flow also requires the enlargement of respective communicating arteries (i.e. anterior and posterior communicating arteries, or the basilar artery). Therefore, the brain develops normally and maintains normal function. However, the increase in blood flow in the enlarged arterial segments, could lead to the formation of aneurysms later in life. Asymmetry between antimere A1 is a good example. In these arterial segments, the risk of development of aneurysms in AcomAC is ≥80%, when the A1 asymmetry ratio remains ≥1.42.[14]

This study was not designed to examine the shape and characteristics of aneurysms, but the focus was on the relationship of the relative size of the blood vessels to the formation of aneurysms in different regions of the brain. Further investigations of cerebral blood flow and the changes in the blood pressure in the presence of asymmetric and variant arteries may help to understand the mechanisms involved in the development of aneurysms. Limitations: The data for this study were obtained from the cases treated at a highly specialised neurointerventional centre, thus the prevalence rate of cerebral aneurysms was higher compared to the general population. It is unethical to expose general population to CTA related radiation purely for research purposes. This study is a pure cross-sectional study, since the repeated CTA from the same patient could not be obtained at different time points. The timeframe of the current study did not allow us to follow up the patients and continue as a longitudinal study.

Conclusion

The number of cerebral aneurysms vary with the sizes of arteries constituting the cerebral basal arterial network. Variation of those arteries is said to affect hemodynamics, thus predisposing to aneurysms. Patients who have asymmetric and variant cerebral arterial

segments and communicating arteries in CBAN should be monitored regularly. This finding could be considered as one of the criteria for screening the cerebral aneurysms.

Data sharing statement

Extra data is available by emailing to Arjun.Burlakoti@unisa.edu.au

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None

Author contribution statement

Arjun Burlakoti- conceived the idea, designed the analysis, collected and analysed the data from CCTA, took pictures, recorded videos, contributed in conceptualization, prepared and drafted the manuscript.

Jaliya Kumaratilake- conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article.

Jamie Taylor- conceived the idea, contributed in collecting and interpreting the data, editing the manuscript, the critical revision of the manuscript and approving the article.

Maciej Henneberg- conceived the idea, helped in statistics, data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article.

Conflict of interest statements

There is no conflict of interest with any of the authors.

Ethical Approval Statement

The University of Adelaide, Human Research Ethics Board granted permission to access and use data for this research project (Ethics Approval Number: H2014 -176).

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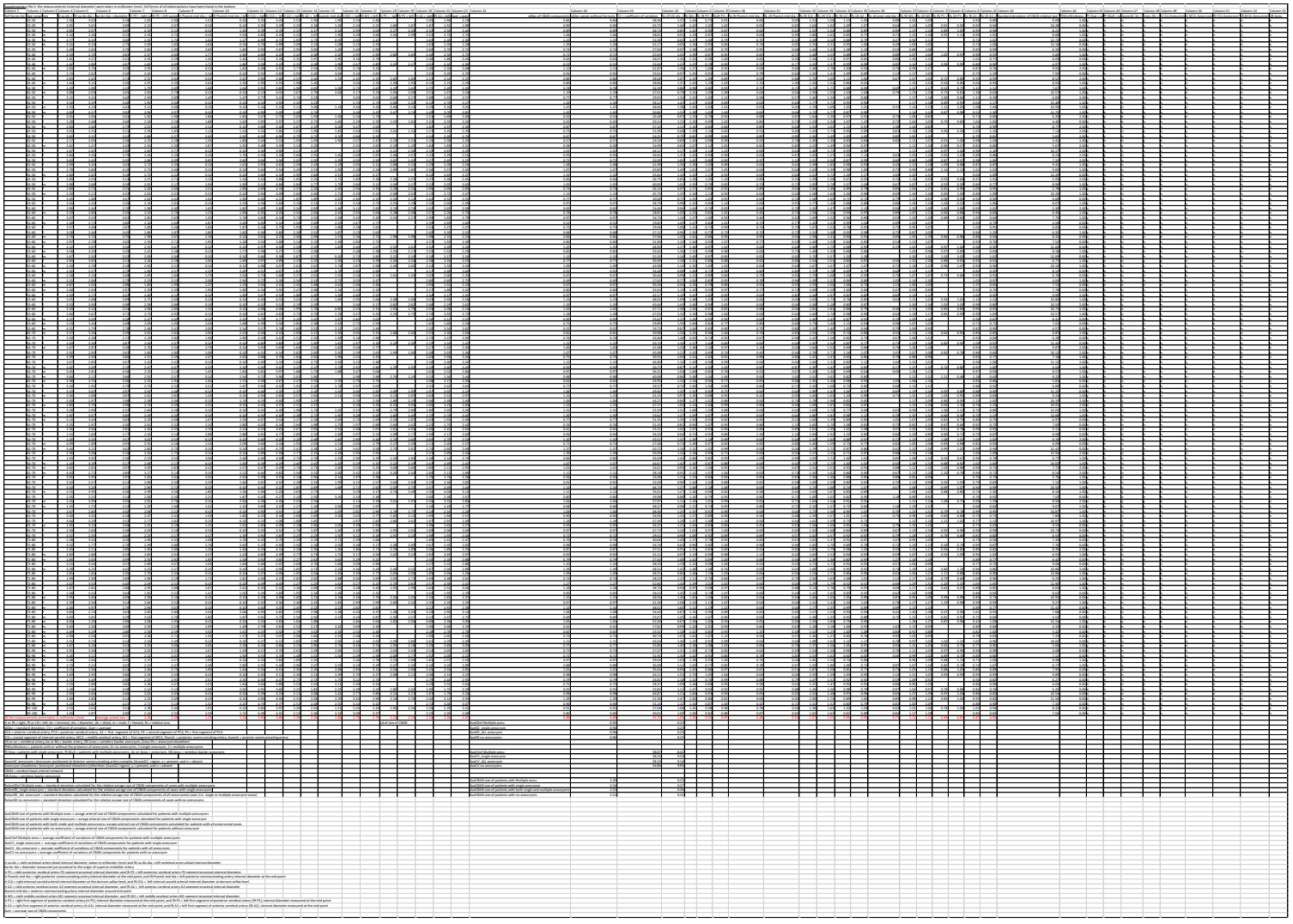
Supplementary files:

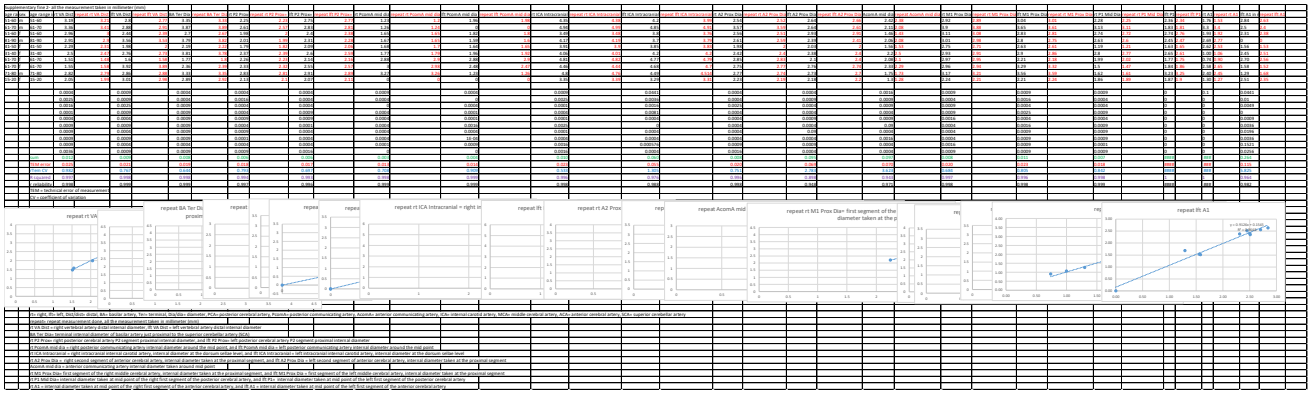
Supplementary file 1:

The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.



Supplementary file 2:

The supplementary file below is clearly readable and please kindly click on the ‘zoom in’ icon to see the contents clearly.



Supplementary file 3: The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.

Supplementary file 3

Abbreviations and full forms

- All the measurements were taken in millimetre (mm)
- SCA = superior cerebellar artery
- rt or Rt = right, lft or Lft = left, ter = terminal, dia = diameter, dis = distal, m = male, f = female, Rs = relative size,
- stDev = standard deviation, CV = coefficient of variation, Aver = average
- ACA = anterior cerebral artery, PCA = posterior cerebral artery, A1 = first segment of ACA, A2= second part of ACA, P2 = second segment of PCA, P1 = first segment of PCA
- ICA = internal carotid artery, MCA = middle cerebral artery, M1 = first segment of MCA, PcomA = posterior communicating artery, AcomA = anterior communicating artery
- VA or va = vertebral artery, ba or BA = basilar artery, VB Aneu = vertebro basilar aneurysm, Aneu Els = elsewhere aneurysm
- ba ter dia = diameter measured just proximal to the origin of superior cerebellar artery
- AcomAC = Anterior communicating artery complex
- AcomAC aneurysm= Aneurysm positioned at Anterior communicating artery complex (AcomAC) region, y = present, and n = absent
- Aneurysm elsewhere= Aneurysm positioned elsewhere (other than AcomAC region), y = present, and n = absent
- CBAN = cerebral basal arterial network,
- VB Aneu = vertebro basilar aneurysm, rt= right, lft= left, Dist/dist = distal, BA= basilar artery, Ter= terminal, Dia/dia= diameter
- PCA= posterior cerebral artery, PcomA= posterior communicating artery, AcomA= anterior communicating artery, ICA= internal carotid artery, MCA= middle cerebral artery, ACA= anterior cerebral artery, and SCA= superior cerebellar artery

Frequency Table

Sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	f	78	53.8	53.8	53.8
	m	67	46.2	46.2	100.0
	Total	145	100.0	100.0	

AcomAC An = aneurysms at AcomAC junction, y=yes and n=no

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	n	118	81.4	81.4	81.4
	y	27	18.6	18.6	100.0
	Total	145	100.0	100.0	

rt ICA Aneurysm

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	n	131	90.3	90.3	90.3
	y	14	9.7	9.7	100.0
	Total	145	100.0	100.0	

rt MCA Aneurysm

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	n	113	77.9	77.9	77.9
	y	32	22.1	22.1	100.0
	Total	145	100.0	100.0	

lft ICA Aneurysm

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	n	137	94.5	94.5	94.5
	y	8	5.5	5.5	100.0
	Total	145	100.0	100.0	

lft MCA Aneurysm

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	**n**	121	83.4	83.4	83.4
	y	24	16.6	16.6	100.0
	Total	145	100.0	100.0	

vertebro basilar aneurysm

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	**n**	137	94.5	94.5	94.5
	y	8	5.5	5.5	100.0
	Total	145	100.0	100.0	

Spearman's rho Correlations

Correlations

			RsRtVA dis = relative size of right vertebral artery distal internal diameter	RsLftVA dis = relative size left vertebral artery distal internal diameter	RsBA= relative size of terminal basilar artery just proximal to SCA	RsRt P2 = relative size of proximal right 2nd part of posterior cerebral artery (P2) internal diameter	RsLft P2 = relative size of proximal left 2nd part of posterior cerebral artery (P2) internal diameter	RsRtPcomA mid dia = relative size of right posterior communicating artery external diameter around the mid-point	RsLftPcomA mid dia = relative size of left posterior communicating artery external diameter around the mid-point	RsRt IntCA = relative size of right internal carotid arterial internal diameter at the dorsum sellae level
Spearman's rho	RsRtVA dis = relative size of right vertebral artery distal internal diameter	Correlation Coefficient	1.000	-.235**	.172*	.044	-.129	-.108	-.059	-.011
		Sig. (2-tailed)	.	.005	.039	.597	.122	.196	.478	.894
		N	145	145	145	145	145	145	145	145
	RsLftVA dis = relative size left vertebral artery distal internal diameter	Correlation Coefficient	-.235**	1.000	.337**	.070	.078	-.379**	-.389**	.050
		Sig. (2-tailed)	.005	.	.000	.401	.351	.000	.000	.550
		N	145	145	145	145	145	145	145	145
	RsBA= relative size of terminal basilar artery proximal to SCA	Correlation Coefficient	.172*	.337**	1.000	.169*	-.017	-.390**	-.447**	-.062
		Sig. (2-tailed)	.039	.000	.	.043	.839	.000	.000	.460
		N	145	145	145	145	145	145	145	145
	RsRt P2 = relative size of proximal right 2nd part of posterior cerebral artery (P2) internal diameter	Correlation Coefficient	.044	.070	.169*	1.000	.357**	-.350**	-.286**	-.066
		Sig. (2-tailed)	.597	.401	.043	.	.000	.000	.000	.431
		N	145	145	145	145	145	145	145	145
	RsLft P2 = relative size of	Correlation Coefficient	-.129	.078	-.017	.357**	1.000	-.206*	-.140	-.150

proximal left	Sig. (2-tailed)	.122	.351	.839	.000	.	.013	.093	.072
2nd part of	N	145	145	145	145	145	145	145	145
posterior									
cerebral artery									
(P2) internal									
diameter									
RsRtPcomA mid	Correlation	-.108	-.379**	-.390**	-.350**	-.206*	1.000	.456**	-.170*
dia = relative	Coefficient								
size of right	Sig. (2-tailed)	.196	.000	.000	.000	.013	.	.000	.041
posterior	N	145	145	145	145	145	145	145	145
communicating									
artery internal									
diameter around									
the mid point									
RsLftPcomA	Correlation	-.059	-.389**	-.447**	-.286**	-.140	.456**	1.000	-.277**
mid dia =	Coefficient								
relative size of	Sig. (2-tailed)	.478	.000	.000	.000	.093	.000	.	.001
left posterior	N	145	145	145	145	145	145	145	145
communicating									
artery internal									
diameter around									
the mid point									
RsRt IntCA =	Correlation	-.011	.050	-.062	-.066	-.150	-.170*	-.277**	1.000
relative size of	Coefficient								
right internal	Sig. (2-tailed)	.894	.550	.460	.431	.072	.041	.001	.
carotid arterial	N	145	145	145	145	145	145	145	145
internal diameter									
at the dorsum									
sellae level									
RsLft IntCA =	Correlation	-.018	-.014	.002	.198*	-.132	-.225**	-.160	.462**
relative size of	Coefficient								
left internal	Sig. (2-tailed)	.826	.868	.981	.017	.114	.006	.055	.000
carotid arterial	N	145	145	145	145	145	145	145	145
internal diameter									
at the dorsum									
sellae level									
RsRt A2 =	Correlation	-.162	.114	-.152	-.074	-.170*	.002	-.068	-.016
relative size of	Coefficient								
proximal right	Sig. (2-tailed)	.052	.173	.069	.380	.041	.979	.417	.847
2nd part of	N	145	145	145	145	145	145	145	145
anterior cerebral									
artery (A2)									
internal diameter									

RsLft A2 = relative size of proximal left 2nd part of anterior cerebral artery (A2) internal diameter	Correlation Coefficient	-.181*	.162	.006	-.014	-.031	-.154	-.230**	.034
	Sig. (2-tailed)	.029	.051	.941	.865	.713	.065	.005	.684
	N	145	145	145	145	145	145	145	145
RsAComA mid dia = relative size of anterior communicating artery internal diameter around mid-point	Correlation Coefficient	-.264**	-.061	-.059	-.184*	-.086	.151	.112	-.221*
	Sig. (2-tailed)	.003	.492	.508	.037	.335	.088	.209	.012
	N	128	128	128	128	128	128	128	128
RsRt M1 = relative size of proximal right 1st part of middle cerebral artery (M1) internal diameter	Correlation Coefficient	-.185*	-.074	-.040	.206*	.165*	-.203*	-.205*	.126
	Sig. (2-tailed)	.026	.376	.636	.013	.047	.014	.013	.131
	N	145	145	145	145	145	145	145	145
RsLft M1 = relative size of proximal left 1st part of middle cerebral artery (M1) internal diameter	Correlation Coefficient	-.139	.023	-.026	.194*	.021	-.296**	-.198*	.155
	Sig. (2-tailed)	.096	.782	.756	.019	.805	.000	.017	.062
	N	145	145	145	145	145	145	145	145
RsRt P1 = relative size of proximal right first segment of posterior cerebral artery (PCA) internal diameter taken at mid-point	Correlation Coefficient	.107	.152	.245*	.234*	.301**	-.600**	-.315**	-.164
	Sig. (2-tailed)	.295	.134	.015	.020	.003	.000	.002	.107
	N	98	98	98	98	98	98	98	98
RsLft P1 = relative size of proximal left	Correlation Coefficient	.015	.290**	.293**	.168	.191	-.388**	-.639**	.060
	Sig. (2-tailed)	.883	.004	.003	.098	.059	.000	.000	.554

	first segment of posterior cerebral artery (PCA) internal diameter taken at mid-point	N	98	98	98	98	98	98	98	98
	RsRt A1 = relative size of proximal right 1st part of anterior cerebral artery (A1) internal diameter	Correlation Coefficient	-.115	-.029	-.008	.060	.222**	-.326**	-.043	-.037
		Sig. (2-tailed)	.169	.729	.922	.470	.007	.000	.604	.655
		N	145	145	145	145	145	145	145	145
	RsLft A1 = relative size of proximal left 1st part of anterior cerebral artery (A1) internal diameter	Correlation Coefficient	-.176*	-.087	.026	.088	.044	-.143	-.233**	.048
		Sig. (2-tailed)	.034	.300	.754	.290	.599	.086	.005	.568
		N	145	145	145	145	145	145	145	145

Correlations

			RsLft IntCA = relative size of left internal carotid arterial internal diameter at the dorsum sellae level	RsRt A2 = relative size of proximal right 2nd part of anterior cerebral artery (A2) internal diameter	RsLft A2 = relative size of proximal left 2nd part of anterior cerebral artery (A2) internal diameter	RsACom A mid dia = relative size of anterior communicating artery internal diameter around mid-point	RsRt M1 = relative size of proximal right 1st part of middle cerebral artery (M1) internal diameter	RsLft M1 = relative size of proximal left 1st part of middle cerebral artery (M1) internal diameter	RsRt P1 = relative size of proximal right 1st part of posterior cerebral artery (P1) internal diameter taken at midpoint	RsLft P1 = relative size of proximal left 1st part of posterior cerebral artery (P1) internal diameter taken at midpoint
Spearman's rho	RsRtVA dis = relative size of right vertebral artery distal internal diameter	Correlation Coefficient	-.018	-.162	-.181*	-.264**	-.185*	-.139	.107	.015
		Sig. (2-tailed)	.826	.052	.029	.003	.026	.096	.295	.883
		N	145	145	145	128	145	145	98	98
	RsLftVA dis = relative size left	Correlation Coefficient	-.014	.114	.162	-.061	-.074	.023	.152	.290**

vertebral artery distal internal diameter	Sig. (2-tailed)	.868	.173	.051	.492	.376	.782	.134	.004
	N	145	145	145	128	145	145	98	98
RsBA= relative size of terminal basilar artery, proximal to the origin of SCA	Correlation Coefficient	.002	-.152	.006	-.059	-.040	-.026	.245*	.293**
	Sig. (2-tailed)	.981	.069	.941	.508	.636	.756	.015	.003
	N	145	145	145	128	145	145	98	98
RsRt P2 = relative size of proximal right 2nd part of posterior cerebral artery (P2) internal diameter	Correlation Coefficient	.198*	-.074	-.014	-.184*	.206*	.194*	.234*	.168
	Sig. (2-tailed)	.017	.380	.865	.037	.013	.019	.020	.098
	N	145	145	145	128	145	145	98	98
RsLft P2 = relative size of proximal left 2nd part of posterior cerebral artery (P2) internal diameter	Correlation Coefficient	-.132	-.170*	-.031	-.086	.165*	.021	.301**	.191
	Sig. (2-tailed)	.114	.041	.713	.335	.047	.805	.003	.059
	N	145	145	145	128	145	145	98	98
RsRtPcomA mid dia = relative size of right posterior communicating artery internal diameter around the mid point	Correlation Coefficient	-.225**	.002	-.154	.151	-.203*	-.296**	-.600**	-.388**
	Sig. (2-tailed)	.006	.979	.065	.088	.014	.000	.000	.000
	N	145	145	145	128	145	145	98	98
RsLftPcomA mid dia = relative size of left posterior communicating artery internal diameter around the mid point	Correlation Coefficient	-.160	-.068	-.230**	.112	-.205*	-.198*	-.315**	-.639**
	Sig. (2-tailed)	.055	.417	.005	.209	.013	.017	.002	.000
	N	145	145	145	128	145	145	98	98
RsRt IntCA = relative size of right internal	Correlation Coefficient	.462**	-.016	.034	-.221*	.126	.155	-.164	.060
	Sig. (2-tailed)	.000	.847	.684	.012	.131	.062	.107	.554

	carotid arterial internal diameter at the dorsum sellae level	N	145	145	145	128	145	145	98	98
	RsLft IntCA = relative size of	Correlation Coefficient	1.000	-.139	-.024	-.435**	.100	.218**	-.088	-.052
	left internal	Sig. (2-tailed)	.	.094	.776	.000	.231	.008	.387	.612
	carotid arterial internal diameter at the dorsum sellae level	N	145	145	145	128	145	145	98	98
	RsRt A2 = relative size of	Correlation Coefficient	-.139	1.000	.579**	.173	-.071	-.030	-.134	-.156
	proximal right	Sig. (2-tailed)	.094	.	.000	.051	.393	.720	.188	.126
	2nd part of anterior cerebral artery (A2) internal diameter	N	145	145	145	128	145	145	98	98
	RsLft A2 = relative size of	Correlation Coefficient	-.024	.579**	1.000	-.009	-.041	.061	-.054	.017
	proximal left	Sig. (2-tailed)	.776	.000	.	.917	.624	.465	.598	.867
	2nd part of anterior cerebral artery (A2) internal diameter	N	145	145	145	128	145	145	98	98
	RsAComA mid dia = relative	Correlation Coefficient	-.435**	.173	-.009	1.000	-.050	-.178*	-.159	-.237*
	size of anterior	Sig. (2-tailed)	.000	.051	.917	.	.578	.045	.156	.033
	communicating artery internal diameter around mid-point	N	128	128	128	128	128	128	81	81
	RsRt M1 = relative size of	Correlation Coefficient	.100	-.071	-.041	-.050	1.000	.521**	.060	.012
	proximal right	Sig. (2-tailed)	.231	.393	.624	.578	.	.000	.558	.910
	1st part of middle cerebral artery (M1) internal diameter	N	145	145	145	128	145	145	98	98
	RsLft M1 = relative size of	Correlation Coefficient	.218**	-.030	.061	-.178*	.521**	1.000	.031	.114
	proximal left 1st	Sig. (2-tailed)	.008	.720	.465	.045	.000	.	.764	.262

part of middle cerebral artery (M1) internal diameter	N	145	145	145	128	145	145	98	98
RsRt P1 = relative size of proximal right	Correlation Coefficient	-.088	-.134	-.054	-.159	.060	.031	1.000	.352**
	Sig. (2-tailed)	.387	.188	.598	.156	.558	.764	.	.000
1st part of posterior cerebral artery (P1) internal diameter taken at midpoint	N	98	98	98	81	98	98	98	98
RsLft P1 = relative size of proximal left 1st part of posterior cerebral artery (P1) internal diameter taken at midpoint	Correlation Coefficient	-.052	-.156	.017	-.237*	.012	.114	.352**	1.000
	Sig. (2-tailed)	.612	.126	.867	.033	.910	.262	.000	.
	N	98	98	98	81	98	98	98	98
RsRt A1 = relative size of proximal right	Correlation Coefficient	-.056	.026	.071	-.200*	.180*	.137	.164	.053
	Sig. (2-tailed)	.501	.755	.397	.024	.031	.101	.106	.605
1st part of anterior cerebral artery (A1) internal diameter	N	145	145	145	128	145	145	98	98
RsLft A1 = relative size of proximal left 1st part of anterior cerebral artery (A1) internal diameter	Correlation Coefficient	.248**	-.073	.129	-.143	.164*	.102	.029	.222*
	Sig. (2-tailed)	.003	.383	.121	.107	.049	.221	.777	.028
	N	145	145	145	128	145	145	98	98

Correlations

		RsRt A1 = relative size of proximal right 1st part of anterior cerebral artery (A1) internal diameter	RsLft A1 = relative size of proximal left 1st part of anterior cerebral artery (A1) internal diameter

Spearman's rho	RsRtVA dis = relative size of right vertebral artery distal internal diameter	Correlation Coefficient	-.115	-.176*
		Sig. (2-tailed)	.169	.034
		N	145	145
	RsLftVA dis = relative size left vertebral artery distal internal diameter	Correlation Coefficient	-.029	-.087
		Sig. (2-tailed)	.729	.300
		N	145	145
	RsBA= relative size of terminal basilar artery, internal diameter measured proximal to the SCA	Correlation Coefficient	-.008	.026
		Sig. (2-tailed)	.922	.754
		N	145	145
	RsRt P2 = relative size of proximal right 2nd part of posterior cerebral artery (P2) internal diameter	Correlation Coefficient	.060	.088
		Sig. (2-tailed)	.470	.290
		N	145	145
	RsLft P2 = relative size of proximal left 2nd part of posterior cerebral artery (P2) internal diameter	Correlation Coefficient	.222**	.044
		Sig. (2-tailed)	.007	.599
		N	145	145
	RsRtPcomA mid dia = relative size of right posterior communicating artery internal diameter at the mid point	Correlation Coefficient	-.326**	-.143
		Sig. (2-tailed)	.000	.086
		N	145	145
	RsLftPcomA mid dia = relative size of left posterior communicating artery internal diameter at the mid point	Correlation Coefficient	-.043	-.233**
		Sig. (2-tailed)	.604	.005
		N	145	145
	RsRt IntCA = relative size of right internal carotid arterial internal diameter at the dorsum sellae level	Correlation Coefficient	-.037	.048
		Sig. (2-tailed)	.655	.568
		N	145	145
	RsLft IntCA = relative size of left internal carotid arterial internal diameter at the dorsum sellae level	Correlation Coefficient	-.056	.248**
		Sig. (2-tailed)	.501	.003
		N	145	145
	RsRt A2 = relative size of proximal right 2nd part of anterior cerebral artery (A2) internal diameter	Correlation Coefficient	.026	-.073
		Sig. (2-tailed)	.755	.383
		N	145	145
	RsLft A2 = relative size of proximal left 2nd part of anterior cerebral artery (A2) internal diameter	Correlation Coefficient	.071	.129
		Sig. (2-tailed)	.397	.121
		N	145	145
	RsAComA mid dia = relative size of anterior communicating artery internal diameter around mid point	Correlation Coefficient	-.200*	-.143
		Sig. (2-tailed)	.024	.107
		N	128	128
	RsRt M1 = relative size of proximal right 1st part of middle	Correlation Coefficient	.180*	.164*
		Sig. (2-tailed)	.031	.049

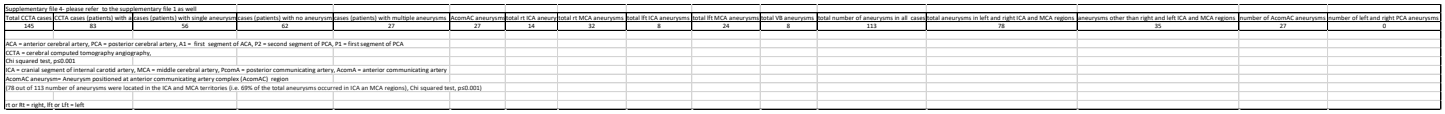
cerebral artery (M1) internal diameter	N	145	145
RsLft M1 = relative size of proximal left 1st part of middle cerebral artery (M1) internal diameter	Correlation Coefficient	.137	.102
	Sig. (2-tailed)	.101	.221
	N	145	145
RsRt P1 = relative size of proximal right first segment of posterior cerebral artery (PCA) internal diameter taken at mid-point	Correlation Coefficient	.164	.029
	Sig. (2-tailed)	.106	.777
	N	98	98
RsLft P1 = relative size of proximal left first segment of posterior cerebral artery (PCA) internal diameter taken at mid-point	Correlation Coefficient	.053	.222*
	Sig. (2-tailed)	.605	.028
	N	98	98
RsRt A1 = relative size of proximal right 1st part of anterior cerebral artery (A1) internal diameter	Correlation Coefficient	1.000	.106
	Sig. (2-tailed)	.	.204
	N	145	145
RsLft A1 = relative size of proximal left 1st part of anterior cerebral artery (A1) internal diameter	Correlation Coefficient	.106	1.000
	Sig. (2-tailed)	.204	.
	N	145	145

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Supplementary file 4:

The supplementary file below is clearly readable and please kindly click on the 'zoom in' icon to see the contents clearly.



Supplementary file 4- please refer to the supplementary file 1 as well

Total CCTA cases	CCTA cases (patients) with a	cases (patients) with single aneurysm	cases (patients) with no aneurysm	cases (patients) with multiple aneurysms	AcomAC aneurysms	total rt ICA aneury	total rt MCA aneurysms	total lft ICA aneurysms	total lft MCA aneurysms	total VB aneurysms	total number of aneurysms in all cases	total aneurysms in left and right ICA and MCA regions	aneurysms other than right and left ICA and MCA regions	number of AcomAC aneurysms	number of left and right PCA aneurysms
145	83	56	62	27	27	14	32	8	24	8	113	78	35	27	0

ACA = anterior cerebral artery, PCA = posterior cerebral artery, A1 = first segment of ACA, P2 = second segment of PCA, P1 = first segment of PCA
CCTA = cerebral computed tomography angiography,
Chi squared test, p≤0.001
ICA = cranial segment of internal carotid artery, MCA = middle cerebral artery, PcomA = posterior communicating artery, AcomA = anterior communicating artery
AcomAC aneurysm= Aneurysm positioned at anterior communicating artery complex (AcomAC) region
(78 out of 113 number of aneurysms were located in the ICA and MCA territories (i.e. 69% of the total aneurysms occurred in ICA an MCA regions), Chi squared test, p≤0.001)

rt or Rt = right, lft or Lft = left

Supplementary Table 1: Anatomical locations of intracranial cerebral aneurysms in the current Cerebral Computed Tomography Angiography scans study (n = 145, age range = 18 to 100 years, female = 79, male = 67). Total 113 aneurysms were recorded in 83 patients. rt = right, lft = left, AcomAC = anterior communicating artery complex, MCA= middle cerebral artery, ICA = internal carotid artery, y = aneurysms present, n = aneurysms absent, MCA = middle cerebral artery, PCA = posterior cerebral artery, VBA = vertebra basilar arteries. P1 = first segment of PCA, and P2 = second segment of PCA.

		Aneurysms at AcomAC		rt ICA Aneurysm		rt MCA Aneurysm		lft ICA Aneurysm		lft MCA Aneurysm		Vertebro basilar aneurysm		PCA aneurysm
		n	y	n	y	n	y	n	y	n	y	n	y	n
		Count	Count	Count	Count	Count	Count	Count	Count	Count	Count	Count	Count	Count
Aneurysms at	**n**	118	0	108	10	90	28	110	8	98	20	110	8	118
AcomAC	**y**	0	27	23	4	23	4	27	0	23	4	27	0	27
rt ICA	**n**	108	23	131	0	102	29	125	6	108	23	124	7	131
Aneurysm	**y**	10	4	0	14	11	3	12	2	13	1	13	1	14
rt MCA	**n**	90	23	102	11	113	0	105	8	99	14	108	5	113
Aneurysm	**y**	28	4	29	3	0	32	32	0	22	10	29	3	32
lft ICA	**n**	110	27	125	12	105	32	137	0	115	22	130	7	137
Aneurysm	**y**	8	0	6	2	8	0	0	8	6	2	7	1	8
lft MCA	**n**	98	23	108	13	99	22	115	6	121	0	114	7	121
Aneurysm	**y**	20	4	23	1	14	10	22	2	0	24	23	1	24
	n	110	27	124	13	108	29	130	7	114	23	137	0	137

Vertebro basilar aneurysm	**y**	8	0	7	1	5	3	7	1	7	1	0	8	8
PCA aneurysm	**n**	118	27	131	14	113	32	137	8	121	24	137	8	145

Supplementary Table 2:

Average relative sizes of cerebral arteries and aanatomical locations of cerebral aneurysms in the current Cerebral Computed Tomography Angiography scans studies (total cases, n = 145, age range = 18 to 100 years, female = 79, male = 67). Total 113 aneurysms were recorded in 83 patients. VBA = vertebral basilar arteries; ACA = anterior cerebral artery, AcomAC = anterior communicating artery complex; A1 = first segment of ACA; P2 of PCA = second part of PCA; ICA = internal carotid arterial; A2 of ACA = second part of ACA, and M1 of MCA= first part of MCA.

	Aneurysms		**Average relative artery size (internal diameter)**		**Average artery size in mm (internal diameter)**	
	Right	**Left**	**Right**	**Left**	**Right**	**Left**
A1 of ACA	27 aneurysms in AcomAC		0.87	0.95	2.36	2.47
ICA	14	8	1.57	1.55	3.9	3.86
M 1 of MCA	32	24	1.12	1.11	2.78	2.76
P2 of PCA	0	0	0.95	0.95	2.36	2.36
A2 of ACA	0	0	0.96	0.95	2.39	2.36
VBA aneurysms		8				

Chapter 6: Published version of papers related to this thesis.

Paper 1: Journal published version

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The cerebral basal arterial network: morphometry of inflow and outflow components

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Abstract

The aim of this project was to study how the morphology of the incoming and outgoing arterial components of the cerebral basal arterial network influence the blood flow to the brain. The cerebral basal arterial network consists of the circulus arteriosus cerebri anteriorly and the basilar artery posteriorly. Diameters of inflow vessels (bilateral vertebral and internal carotid arteries), connecting vessels (anterior communicating, basilar and bilateral posterior communicating arteries) and outflow vessels (anterior, middle and posterior cerebral arteries) were measured and cross-sectional areas calculated in 51 cadaveric brain specimens. The individual and the average cross-sectional areas of inflow arteries (51.43 mm^2) were significantly bigger than the major outflow arteries (37.76 mm^2) but smaller than the combined cross-sectional areas of outflow (37.76 mm^2) and connecting (25.33 mm^2) arteries. The difference in the size of arterial cross-sectional area and the presence of the connecting arteries in the cerebral basal arterial network provides a mechanism for lowering peaks in pressure, and demonstrates a function of the cerebral basal arterial network.

Key words: cerebral arteries; circle of Willis; circulus arteriosus cerebri; internal carotid arteries; vertebral arteries.

Introduction

Stable perfusion of brain tissues at a high and constant rate is required due to high metabolic demands of the brain, while at the same time the high amplitude of cerebral perfusion pressure waves needs to be reduced. The brain development occurs by expansion of three embryonic vesicles (O'Rahilly & Müller, 2006), thus the entire blood supply comes from a small set of closely related arteries (Menshawi et al. 2015). These exceptional circumstances are reflected in the structure of the origins of the arterial supply to the brain, an anastomotic cerebral basal arterial network from which all major arteries branch. The anterior portion of the cerebral arterial network, the circulus arteriosus cerebri (CAC), first described by a Paduan anatomist Julius Casserius (1552–1616) and subsequently by Thomas Willis (1621–1675), includes the cerebral parts of right and left internal carotid arteries (ICA), pre-communicating parts of right and left anterior cerebral arteries (ACA), anterior communicating artery (AComA), right and left posterior communicating arteries (PComA), and the pre-communicating parts of the bilateral posterior cerebral arteries (PCA) (Rogers, 1947; Feindel, 1962; De Silva et al. 2009; Bender et al. 2013; Vasović et al. 2013). Traditionally the role of the circulus arteriosus cerebri at the base of the brain has been considered to serve for collateral circulation when some feeding arteries are interrupted. However, it has been suggested recently that the anterior component of the cerebral basal arterial network (i.e. circulus arteriosus cerebri) serves to limit peak systolic pressure propagating into cerebral arteries and serves as a passive energy-dissipating system (Vrselja et al. 2014). A study of a mathematical model by Alastruey and colleagues showed that the arterial system supplying the brain does not require the collateral flow pathways through the posterior communicating arteries to effectively perfuse the brain in healthy people with complete circulus arteriosus cerebri (Alastruey et al. 2007). However, the increase in haemodynamic activities was noticed through the PcomA, which acted as an outflow vessel off the internal carotid artery in case of hypoplastic or absent first part of ACA or PCA (Vrselja et al. 2014). The blood flow through the communicating arteries could be both

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ways, depending on the sites of variations (Alastruey et al. 2007).The data used by Alastruey and colleagues for their model were obtained from various tertiary resources that included different brains (Alastruey et al. 2007; Izzy & Muehlschlegel, 2014). They used the data provided by a number of sources including Fahrig et al. (1999), who also took secondary random data from more than eight groups of authors. The objective of the current study is different from Alastruey et al.'s (2007) investigation and we present data from real cadaveric brains and sizes of components of cerebral basal arterial network, which have been statistically analyzed. This analysis tests the hypothesis (Vrselja et al. 2014) that the arterial circle of the brain provides a mechanism for dampening peak cerebral perfusion pressures in brain arteries rather than just being a precaution against the possible rare event of one of the main inflow or connecting arteries being blocked or absent.

The cerebral basal arterial networks show a number of variations in structure and arrangement (De Silva et al. 2011; Hannequin et al. 2013; Gunnal et al. 2014). Many of these variations are clinically important because of their associations with aneurysms and cerebrovascular accidents (Dell, 1982; Alnæs et al. 2007; Guerri-Guttenberg, 2009; Leblanc et al. 2009; Sampath et al. 2010; Bender et al. 2013; Brown & Broderick, 2014; Gunnal et al. 2014). Cerebrovascular accidents are the second leading cause of death (Feigin et al. 2014) with increasing mortality and morbidity rates worldwide (D'Souza, 2015), including Australia and Sweden (Hankey et al. 2002; Nieuwkamp et al. 2014). Cerebrovascular aneurysms are associated with many factors such as tobacco smoking, hypertension, female sex and family history of cerebrovascular diseases (Ellamushi et al. 2001; D'Souza, 2015; Turan et al. 2016). Variations in the anatomy of cerebral arteries are another important factor (Alnæs et al., 2007; Brown & Broderick, 2014). A shorter cranial part of the internal carotid artery and high haemodynamic stress acting across the variant cerebral arteries have been reported as a risk factor for the development of aneurysms (Alnæs et al., 2007; Kim & Kang, 2007; Zuleger et al. 2010). Pressure gradient across the arteries in which the blood flows is inversely proportional to the cross-sectional areas of the vessels (Zamir, 1977; Fung, 1997). Therefore, cross-sectional areas of all components of the cerebral basal arterial network need to be investigated to elucidate the pressure gradients across the arterial network. The primary aim of this study was to investigate the cross-sectional area of incoming, communicating and outgoing cerebral basal arterial network components and to determine their role in cerebral arterial circulation.

Materials and methods

Ethics approval for the dissection and removal of brains from the cadavers and use of already dissected brains was obtained from the University of Adelaide (No. H-2014-176) before commencing the study. Fifty-one prosected brains with complete arterial components were used in the study. Due to the process of de-identification of dissected brain specimens, the age and sex were only available for 26 brains. The external diameters of the arteries flowing into and leaving the cerebral basal arterial network were measured at specific sites (Figs 1 and 2) perpendicular to their long axis, using digital Vernier callipers. The digital Vernier callipers have been used to measure lengths and diameters of arteries in cadaveric brains (Kamath, 1981; Samuels et al. 2000; Gellman et al. 2001; Aldur, 2006; Lo et al. 2006; Koppenhaver et al. 2009; Vázquez et al. 2009; Siddiqi et al. 2013). Reliability of the measurements was verified by re-measuring the arterial diameters of 15 cadaveric brains (Table 1).

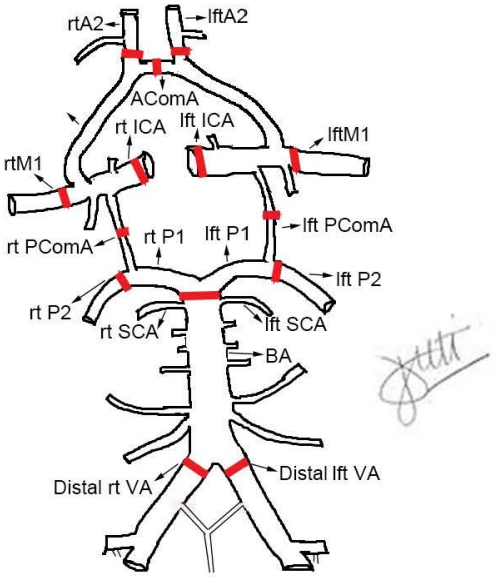

Fig. 1 Schematic diagram of cerebral basal arterial network (CBAN). Red lines indicate the sites where the diameters were measured in millimetres (mm). BA, basilar artery, diameter measured at midway between SCA and PCA; rt VA, right vertebral artery, diameter measured at the most distal part; lft VA, left vertebral artery, diameter measured at the most distal portion; lft P2, second part of the left posterior cerebral artery, diameter measured at the proximal portion; rt P2, second part of the right posterior cerebral artery, diameter measured at the proximal portion; rt PComA, right posterior communicating artery, diameter measured at around the mid-point; lft PComA, left posterior communicating artery, diameter measured at around the mid-point; rt ICA, right internal carotid artery, diameter measured at the level of optic chiasm; lft ICA, left internal carotid artery, diameter measured at the level of optic chiasm; rt A2, second part of the right anterior cerebral artery, diameter measured at the most proximal part; lft A2, second part of right anterior cerebral artery, diameter measured at the most proximal part; AComA, anterior communicating artery, diameter measured around mid-point; rt M1, first part of right middle cerebral artery, diameter measured at the most proximal part; lft M1, first part of left middle cerebral artery, diameter measured at the most proximal part; SCA, superior cerebellar artery and PCA, posterior cerebral artery.

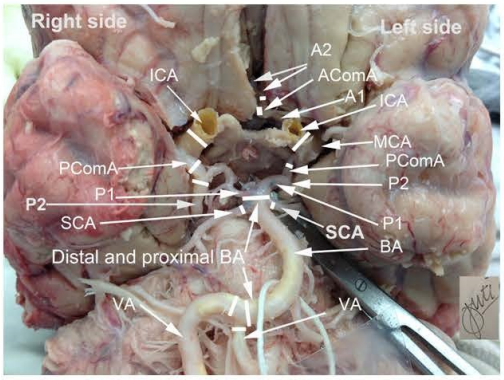

Fig. 2 Base of the brain, showing cerebral basal arterial network (CBAN). Measurements were taken in millimetres (mm) perpendicular to the long axis of the vessels at the sites indicated by the white lines. BA, basilar artery; VA, right vertebral artery; P1, first part of the posterior cerebral artery; P2, posterior cerebral artery second part; PComA, posterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; A1, first part of the anterior cerebral artery; A2, second part of anterior cerebral artery; AComA, anterior communicating artery; SCA, superior cerebellar artery.

Cross-sectional area of each artery was calculated using the formula $A = \pi r^2$, where A and r are cross-sectional area and radius, respectively.

The following are the sites of the measurements taken from the incoming, outgoing and communicating cerebral arterial components.

Arteries flowing into cerebral basal arterial network (incoming) (Figs 1 and 2):

1 cerebral part of the right internal carotid artery (ICA) at the level of optic chiasm
2 cerebral part of the left internal carotid artery (ICA) at the level of optic chiasm
3 intracranial portion of the distal right vertebral artery (VA) just proximal to the unification
4 intracranial portion of the distal left vertebral artery (VA) just proximal to the unification

Major arteries leaving cerebral basal arterial network (outgoing) (Figs 1 and 2):

1 the most proximal portion of second part (A2) of the right anterior cerebral artery (ACA)
2 the most proximal portion of second part (A2) of the left anterior cerebral artery (ACA)
3 the most proximal portion of the first part (M1) of the right middle cerebral artery (MCA)
4 the most proximal portion of the first part (M1) of the left middle cerebral artery (MCA)
5 the most proximal portion of the second part (P2) of the right posterior cerebral artery (PCA)
6 the most proximal portion of the second part (P2) of the left posterior cerebral artery

Communicating arteries (Figs 1 and 2):

1 the mid-point of anterior communicating artery (AComA)
2 the mid-point of the right and left posterior communicating arteries (PComA)
3 terminal portion of the basilar artery (BA) midway between posterior cerebral artery and superior cerebellar artery

Table 1 Inter-rater reliability measurement was performed from 15 specimens and the measurements were taken in millimetres (mm): technical errors of measurement (TEM), reliability (a square root of *R*-squared value) and relative technical errors of measurement were calculated.

Arterial components (in mm)	TEM	Reliability	Relative TEM (100*TEM mean^{-1})
The distal diameter of BA	0.16	0.97	3.36
Distal external diameter of rt VA	0.07	0.99	2.32
Distal external diameter of lft VA	0.1	0.97	3.04
Proximal external diameter of rt P2	0.06	0.97	2.33
Proximal external diameter of lft P2	0.96	0.98	1.81
Proximal external diameter of rt M1	0.08	0.96	2.76
Proximal external diameter of lft M1	0.07	0.98	2.51
Midpoint external diameter of rt PComA	0.07	0.99	5:00
Midpoint external diameter of lft PComA	0.05	0.98	2.04
External diameter of lft ICA at the level of optic chiasma	0.09	0.98	2.02
External diameter of rt ICA at the level of optic chiasma	0.09	0.96	2.1
Proximal external diameter of rt A2	0.07	0.94	2.89
Proximal external diameter of lft A2	0.07	0.96	2.79
Midpoint external diameter of AComA	0.06	0.99	3.13

Rt, right; lft, left; BA, basilar artery; VA, right vertebral artery; P1, first part of the posterior cerebral artery; P2, posterior cerebral artery second part; PComA, posterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; A1, first part of the anterior cerebral artery; A2, second part of anterior cerebral artery; AComA, anterior communicating artery; SCA, superior cerebellar artery.

Statistical analysis

The data were analyzed statistically using Microsoft EXCEL 2013 and Statistical Package for Social Sciences (SPSS), version 22. The individual and average cross-sectional areas of incoming, outgoing and communicating arterial components were calculated. Descriptive statistics, Pearson product-moment correlation coefficient and Spearman rank-order non-parametric correlation procedures were

Table 2 Descriptive statistics: Means and standard deviations of individual diameter millimetres (mm) and the mean sum of cross-sectional areas in square millimetres (mm^2) of four incoming, six outgoings and four communicating arterial components.

Descriptive statistics	*n*	Mean	SD
Right vertebral artery the most distal diameter	51	3.16	0.69
Right vertebral artery the most distal cross-sectional area	51	8.20	3.45
Left vertebral artery the most distal diameter	51	3.46	0.54
Left vertebral artery the most distal cross-sectional area	51	9.67	2.92
Basilar artery diameter midway between SCA and PCA	51	4.57	0.92
Basilar artery cross-sectional area midway between SCA and PCA	51	17.08	6.84
Right P2 the most proximal diameter	51	2.61	0.33
Right P2 the most proximal cross-sectional area	51	5.43	1.43
Left P2 the most proximal diameter	51	2.59	0.29
Left P2 the most proximal cross-sectional area	51	5.33	1.19
Right PComA diameter around mid-point	51	1.59	0.68
Right PComA cross-sectional area around mid-point	51	2.35	1.94
Left PComA diameter around mid-point	51	1.42	0.59
Left PComA cross-sectional area around mid-point	51	1.85	1.50
Right ICA diameter at the level of optic chiasm	51	4.56	0.66
Right ICA cross-sectional area at the level of optic chiasm	51	16.68	4.99
Left ICA diameter at the level of optic chiasm	51	4.59	0.62
Right ICA cross-sectional area at the level of optic chiasm	51	16.85	4.74
Right A2 the most proximal diameter	51	2.63	0.42
Right A2 the most proximal cross-sectional area	51	5.57	1.92
Left A2 the most proximal diameter	51	2.61	0.39
Left A2 the most proximal cross-sectional area	51	5.47	1.56
AComA diameter around mid-point	51	2.05	0.95
AComA cross-sectional area around mid-point	51	4.03	3.61
Right M1 the most proximal diameter	51	3.12	0.40
Right M1 the most proximal cross-sectional area	51	7.77	2.03
Left M1 the most proximal diameter	51	3.19	0.48
Left M1 the most proximal cross-sectional area	51	8.17	2.33
Cross-sectional area of four incomings (left and right ICA and VA arteries)	51	51.42	10.58
Cross-sectional area of six outgoing (the most proximal part of bilateral A2, P2 and M1)	51	37.76	6.08
Cross-sectional area of four communicating (AComA, bilateral PComA and BA)	51	25.33	7.51
Cross-sectional area of six outgoing + four communicating arteries	51	63.09	11.66

BA, basilar artery; VA, vertebral artery; P1, first part of the posterior cerebral artery; P2, posterior cerebral artery second part; PComA, posterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; A1, first part of the anterior cerebral artery; A2, second part of anterior cerebral artery; AComA, anterior communicating artery; SCA, superior cerebellar artery.

used as SPSS analytical techniques. The assumed significant probability (P) value was set at < 0.05.

Results

Means and standard deviations of individual diameter and the mean sum of cross-sectional areas of four incoming arterial components (terminal right and left internal carotid arteries, distal portion of the right and left cranial vertebral arteries), six outgoing components (the most proximal portion of second part of right and left anterior cerebral artery, the most proximal portion of the first part of right and left middle cerebral artery and the most proximal portion of the second part of right and left posterior cerebral arteries) and four communicating branches including the basilar artery (the mid-point of anterior communicating artery, the mid-point of the right and left posterior communicating arteries, terminal portion of the basilar artery midway between posterior cerebral and superior cerebellar arteries) are presented in Tables 2 and 3, Figs 1 and 2. Means and individual sums of cross-sectional areas of the arteries (in square millimetres) leaving the cerebral basal arterial network and communicating arteries were significantly bigger than those of the incoming arteries (Table 4, Fig. 3). The individual and average cross-sectional areas of four incoming arteries were correlated to six major outgoing arteries ($r = 0.63$, $P \leq 0.0001$, $n = 51$) and combined outgoing and communicating arteries ($r = 0.56$, $P \leq 0.0001$). The average communicating arterial cross-sectional area was correlated with the incoming components, although less strongly ($r = 0.36$, $P \leq 0.04$, $n = 51$), less than the outgoing arteries ($r = 0.40$, $P \leq 0.0001$, $n = 51$).

Statistically significant correlations in cross-sectional areas of multiple, unilateral and bilateral cerebral arterial components are presented in Supporting Information Table S1.

Table 3 Descriptive statistics of average cross-sectional area in square millimetres (mm^2) of four incoming (bilateral vertebral and internal carotid arteries), six outgoing (anterior, middle and posterior cerebral arteries) and four communicating (anterior communicating, basilar and bilateral posterior communicating) arteries.

	n	Mean	SD
Four incoming	51	51.4	10.5
Six outgoing	51	37.7	6.0
Four communicating	51	25.3	7.5
Six outgoing + four communicating	51	63.0	11.6

Discussion

Anatomists from Croatia, on the basis of theoretical considerations, have advanced a hypothesis that circulus arteriosus cerebri has the function of stabilizing the perfusion pressure across the two cerebral hemispheres, more than maintaining the collateral circulation. Findings presented here are in agreement with the hypothesis and strongly favor the incorporation of basilar artery into the circulus arteriosus cerebri as an additional communicating branch. This incorporation implies that the cerebral basal arterial network (CBAN) is supplied by internal carotids and vertebral arteries, the arterial circuit supplying the whole brain, including the brain stem and the cerebellum. Caplan and team indicated that intervertebral arterial collateral blood flow (via the proximal basilar artery) and retrograde basilar arterial blood flow (via the distal basilar artery) might occur (Caplan, 1979). Internal carotid arteries may compensate for insufficiencies of vertebral arterial blood flow via posterior communicating branches of circulus arteriosus cerebri into posterior cerebral arteries and from there into the basilar artery and its branches, such as superior cerebellar arteries. The bridging of circulus arteriosus cerebri anteriorly and vertebral arteries posteriorly by the BA would allow retrograde flow or blood flow from one vertebral artery to another. Therefore, basilar artery is considered one of the communicating arteries in the cerebral basal arterial network system. The dimensions of arteries studied here compare well with those reported by other authors (Siddiqi et al. 2013) (Table 5). Variations in cerebral arteries, particularly in the interhemispheric anterior communicating artery (De Silva et al. 2009), posterior cerebral arteries, middle cerebral arteries (Gunnal et al. 2014), bilateral PComA (Chuang et al. 2008) and anterior cerebral arteries have been reported (Malamateniou et al. 2009; Klimek-Piotrowska et al. 2013; Papantchev et al. 2013). These cerebral arterial variations could alter the hemodynamics and cerebral perfusion pressure and affect the blood flow into the right or left sides of the brain. A rapidly enlarged left PComA developed just 4½ months after an ipsilateral ICA aneurysm coiling procedure (Jeck et al. 2002). This indicates that the PComA acts as one of the outflow arteries off the ICA. Aneurysms may develop when high pressure encounters a weakened arterial wall. Therefore, altered haemodynamics may contribute to the development of aneurysms.

According to a French physician, Poiseuille's fluid dynamics model (Faber, 1995), longitudinal pressure gradient is required to pump fluid through a vessel and it is inversely proportional to the fourth power of the radius of that vessel (Zamir, 1977). The deformation is not possible in viscoelastic fluid (such as arterial blood) and the fluid pressure waves keep moving (Joseph, 2013), i.e. the pressure wave could be transmitted in either direction of communicating arteries of the CBAN.

In this study, the average incoming, outgoing and communicating cross-sectional areas were correlated with each other; however, a relatively weaker relationship was noticed between incoming and communicating components (Table 3, Fig. 3). The sample size of 51 brains is not very large in this study. However, our results compare reasonably well with data published by various authors on various arterial components (Fahrig et al. 1999; Alastruey et al. 2007; Siddiqi et al. 2013).

The combined greater cross-sectional area of the arteries leaving the cerebral basal arterial network (efferent arteries) and communicating arteries compared with those of the incoming arteries (afferent arteries) indicates that there is a reduction in mean arterial pressure (MAP) gradient from incoming to outgoing arteries. A computational haemodynamic study of the cerebral vasculature also

Table 4 Spearman's rho correlations above diagonal and Pearson product-moment correlations below the diagonal among four incoming (bilateral vertebral and internal carotid arteries), six outgoing (anterior, middle and posterior cerebral arteries) and four communicating (anterior communicating, basilar and bilateral posterior communicating arteries) average arterial cross-sectional areas measured in square millimetres (mm^2).

	4 incoming	6 outgoing	4 communicating	Outgoing + communicating
4 incoming	1	0.670*	0.420*	0.614*
6 outgoing	0.594*	1	0.433*	0.780*
4 communicating	0.350**	0.465*	1	0.891*
Outgoing + communicating	0.535*	0.822*	0.887*	1

*Correlation is significant at the 0.01 level (2-tailed).
**Correlation is significant at the 0.05 level (2-tailed).

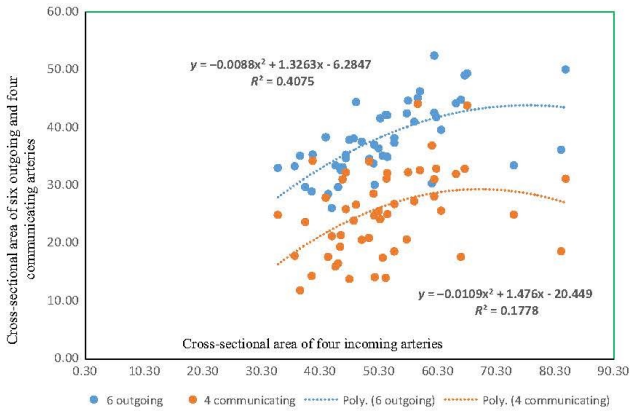

Fig. 3 Correlations among four incoming, six outgoing and four communicating cerebral arterial components, X- and Y-axes show the cross-sectional area in squared millimetres (mm^2).

Table 5 Comparison of dimensions of proximal left (lft) and right (rt) anterior cerebral artery (A1) in multiple studies (Siddiqi et al. 2013) including our study, and the measurements were taken in millimetres (mm).

Author	Year	Mean proximal diameter of rtA1	Mean proximal diameter of lftA1
Our study (n = 51)	2015	2.52	2.61
Murray[6]	1964	1.47	1.42
Perlmutter & Rhoton[7]	1976	2.60	2.60
Kamath[3]	1981	2.20	2.40
Gomes et al.[8]	1986	2.30	2.50
Stefani et al.[9]	2000	2.61	2.61
Pai et al.[10]	2005	2.80	2.90
Vohra et al.[11]	2006	1.44	1.44
Mandiola et al.[12]	2007	2.37	2.42

considered PCA, MCA and ACA as the outflow components and has proven that blood flows towards the larger cross-sectional and low pressure region (Wiedeman, 1962; Fung, 1997). A study measuring arteries in bats and dogs showed a linear decrease in arterial diameter and an increase in mean total cross-sectional area of the arteries and arterioles distally. Similarly, the arterial wall shear stress decreases as the total mean cross-sectional area increases along the distal arterial tree (Fung, 1997). Also, an increase in abdominal aortic arterial wave amplitude has been documented in the presence of a decreased ratio of cross-sectional area of the outgoing common iliac arteries to the parent vessel (Lasheras, 2010; Fung, 2013). The significant difference between incoming and outgoing cross-sectional areas of CBAN components (Fig. 3, Table 3) indicates the importance of having communicating arteries to normalize the cerebral perfusion pressure and ensure adequate perfusion to the brain. A cerebral arterial network haemodynamic experiment revealed that the deviation from normal cerebral arterial anatomy gives rise to a high and low wall shear stress (WSS) around the bifurcation sites and predisposes to development of aneurysmal dilation (Alnæs et al., 2007; Boussel et al. 2008). An uneven cerebral arterial blood flow found among the participants in two studies done using magnetic resonance angiography (MRA) (n = 208) was attributed to the variant cerebral arterial anatomy, and indicated that variations in cerebral arterial anatomy could lead to uneven cerebral arterial blood flow and velocity (Hendrikse et al. 2005; van Laar et al. 2006). The same studies found increased contralateral ICA blood flow in individuals with missing A1 (303 mL min^{-1} ± 56 SE) compared with the normal ipsilateral flow (214 mL min^{-1} ± 94 SE) without any variation.

The mean arterial pressure and the change in vessel diameter has been found to be linear from centre to periphery during the systolic and diastolic phases of a complete cardiac cycle (Sugawara et al. 2000). A recently published theoretical and mathematical model of cerebral arterial network has provided a haemodynamic calculation which contradicts the currently accepted concept of the compensatory flow function of the arterial network under physiological conditions. In another study, the vertebral MAP wave was observed to be dissipated once the bilateral vertebral arteries united, forming the bigger cross-sectioned basilar artery in a computational experiment (Alnæs et al., 2007).

On this occasion, we have proposed the concept of having four connecting arteries (AComA, left and right PComA and BA) which serve as a perfusion pressure wave dampening communicating arterial system. The theoretical computational study done by Vrselja et al. (2014) previously,

discussed the concept of arterial radii, shear stress, pressure flow relationship, normal relationship on smaller sum of proximal and greater sum of distal arterial cross-sectional area and flow rate (Fung, 1997; Zamir, 1977; Lasheras, 2010); our cadaveric findings on a larger sum of four incoming and a smaller sum of six major outgoing cerebral arterial cross-sectional area support the cerebral arterial pressure-easing role of communicating branches of the cerebral basal arterial network system. We have now explained the reasons for introducing of this concept in more detail and stated that it is based on a logical train of thought, not on an experiment. It should be noted that if the cross-sectional area of small outflowing arteries leaving the cerebral basal arterial network (such as anteromedial central, hypophyseal, posteromedial central, pontine, labyrinthine, posterior inferior cerebellar, labyrinthine and anterior inferior cerebellar arteries) was calculated, it would have been included within the sum of outgoing arteries leaving the cerebral basal arterial network in this study. Therefore, the positive difference between cross-sectional areas of outgoing + communicating arteries and incoming arteries would be increased, which would further strengthen the conclusion reached in this study.

Contribution to the discipline

This study provides a novel concept that could contribute to the understanding of normal and pathological cerebral haemodynamics. The incidence of cerebrovascular accidents (CVA) is rapidly increasing, more particularly in elderly people (> 70 years of age), in developed nations (Feigin et al. 2003). Furthermore, it has been shown that the incidence of ischaemic stroke, intracerebral and subarachnoid haemorrhage varied from 4.2 to 11.7% per thousand persons per year among people aged 55 years or more (Feigin et al. 2003; Izzy & Muehlschlegel, 2014). The global burden of stroke is increasing and cerebral arterial variations leading to misbalanced cerebral haemodynamics and intracranial aneurysms have been identified as one of the major causes of ischaemic stroke and spontaneous intracerebral haemorrhage (Qureshi et al. 2001; Feigin et al. 2014; Izzy & Muehlschlegel, 2014). A study in Sweden (Nilsson et al. 2000) has shown that almost 81 of 106 cases (76%) of subarachnoid haemorrhage resulted from spontaneous rupture of an intracranial aneurysm. Larger aneurysms were at greater risk of rupture (Mitchell & Jakubowski, 2000). The global burden of stroke is increasing (Feigin et al. 2014; Izzy & Muehlschlegel, 2014). A multinational study including Australia revealed that the complete cost of disabilities from CVA varies according to patient's age, the presence of other diseases and their severity (Caro et al. 2000) and worse stroke outcomes have been noticed in women (Phan et al. 2016). Each patient spent almost US$ 14,000 on treatment in the first 3 months of acute CVA; 70% of the cost resulted during admission and initial treatment. An Australian study done in 2009 showed a very expensive (AU$49,995 to AU$57,106) lifetime cost per CVA case (Cadilhac et al. 2009). As aneurysms have been correlated to variant and hypoplastic arteries and abnormal cerebral haemodynamics resulted from the variations, our finding broadens the interpretation of the function of the communicating arteries to the distribution of pressure waves and the haemodynamic stress-lowering mechanism in the cerebral basal arterial network. However, we strongly recommend further research and an additional study done such as *in vivo* pressure measurement while performing the cerebral surgical procedures and aneurysm-coiling procedures.

Conclusion

Significant differences in cross-sectional areas of incoming and outgoing arteries, together with cross-sectional area of communicating arteries could provide a mechanism for lowering the peak pressures of arterial blood perfusion of the brain, thus lowering the incidence of aneurysms.

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Conflict of interest

None the authors of this study has any conflict of interest.

Author contributions

Arjun Burlakoti: dissecting the cadaveric specimens, taking pictures, recording videos, contributions to the concept, collecting and analyzing the data, preparing and writing the paper. Maciej Henneberg: contributions to the concept, data interpretation, editing the manuscript, critical revision of the manuscript and approval of the article. Jaliya Kumaratilake: contributions to the concept, data collection and interpretation, editing the manuscript, critical revision of the manuscript and approval of the article. Jamie Taylor: contributions to the concept, data interpretation, editing the manuscript, critical revision of the manuscript and approval of the article. Nicola Massy-Westropp: editing the manuscript and approval of the article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Descriptive statistics.

Appendix S1. Descriptive and correlation statistics among multiple and bilateral arterial components of the cerebral basal arterial network.

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Asymmetries of total arterial supply of cerebral hemispheres do not exist

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Abstract

Background: Total blood supply to an organ, or its part, is proportional to its function. The aim of this project was to investigate whether there is a lateralisation of total functions of cerebral hemispheres by determining differences in the arterial blood supply to left and right cerebral hemispheres.

Methods: Diameters of right and left anterior, middle and posterior cerebral arteries were measured at specific sites and cross-sectional areas calculated in 203 adult brains (51 donated and dissected brain specimens and 152 cerebral arterial Computed Tomography Angiography and Magnetic Resonance Angiography images).

Findings: The sample size was large enough to provide a power of detecting as significant differences of 4%, but neither of the average cross-sectional areas of right anterior, middle and posterior cerebral arteries were significantly different from those of the anterior, middle and posterior cerebral arteries of the left side. Furthermore, combined areas of the three right cerebral arteries were not significantly different from combined areas of the left three arteries. This clearly indicates that the blood supply into the right cerebral hemisphere is not different

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from that of the left cerebral hemisphere. Therefore, there is no total functional lateralisation between the two cerebral hemispheres.

Conclusion: Brain lateralisation, frequently discussed in the literature, does not deferentially influence the total activity levels of cerebral hemispheres.

Keywords: Anatomy, Neuroscience

1. Introduction

Specialisation of neural functions of the brain to one hemisphere rather than the other hemisphere [1] has been referred to as lateralisation of a brain function. Pierre Paul Broca [2] (1861−1865) proposed the idea that the left hemisphere is functionally lateralised for language processes and many others expanded the idea of lateralization [3, 4, 5] of cerebral hemispheres regarding speech and language processes, and the handedness [4]. The concept of lateralization of some specific functions seems to hold true statistically, however, many individuals do not conform to this pattern. Music perception, rhythms and synthesis of pitches [2, 6, 7] are examples of functions that are not specialized to a cerebral hemisphere. Benton and colleagues [8] found that both cerebral hemispheres are involved in facial perception and the memory. A behavioural functional Magnetic Resonance Imaging (MRI) study done on 12 right handed individuals suggested that the right frontal cortex mostly and sometimes bilateral frontal cortices [9] were involved in memory retrieval procedure.

It has been suggested that functional asymmetries are reflected in structural asymmetries between the two hemispheres of the brain. Structural symmetry and asymmetry of the brain, in relation to the function and the relationship of the structural asymmetry to lateralisation of the functions have been investigated extensively [10]. The structural asymmetry in right and left hemispheres has been discussed based on the depth of the central sulcus, larger anteriorly protruding right frontal lobe and the longer and posteriorly protruded left occipital lobe [10]. However, most of the findings related to the lateralization are ambiguous and have no definitive results [3, 11, 12, 13, 14, 15, 16].

A book [16] on brain hemispheric lateralization has highlighted the cortical structural asymmetries, but the measured regions and the technique used to take measurements were not clear [16, 17]. This book has mentioned the handedness and behavioural functional lateralization in relation to the size of corpus callosum. However, the role of tracts of corpus callosum is to increase the interhemispheric connectivity and ensure involvement of cortical components of both cerebral hemispheres in specific functions [5]. A recent investigation of Magnetic Resonance Imaging (MRI) scans of brains obtained from more than 17000 healthy individuals did not show bilateral variation in cerebral cortex thickness of most of the 39 regions of the cortex of the two hemispheres [18].

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Furthermore, in cerebral regions where variations in cortical thickness between the hemispheres were evident, variations of the surface areas were also seen. That is, if the cortical thickness of one region was lesser than that of the same region of the contralateral hemisphere, the surface area of the thinner region was greater than that of thicker region of the contralateral hemisphere and vice versa [18]. This indicates that the volume of the cortical tissues of the brain regions of the two hemispheres remained similar. Therefore, this large study did not show structural evidence for variations in cortical function between hemispheres. A study, done in 54 adult donated brains, found that neither total dimensions of cerebral hemispheres (width, length and height), nor sizes of their major anatomical features (length of main sulci or height and length of lobes) showed any significant right-left differences [19]. The asymmetric patterns of dural venous sinuses result in the entire cerebral hemispheres to move anteriorly or posteriorly producing apparently asymmetric locations of occipital and frontal poles [20]. The arrangements and positions of posterior and lateral cerebral dural venous sinuses were studied in 58 brains and concluded that entire cerebral hemispheres moved in accordance with dural venous sinus asymmetries anteriorly or posteriorly producing asymmetric "petalia" [20]. Handedness has been considered as a common manifestation of cerebral lateralisation, and yet handedness can be easily changed by training [21, 22, 23, 24].

Cross-sectional areas of nutrient foramina in mammalian long bones correlate with actual blood flow into the bone and its metabolic rate [25]. Arterial blood supply of a cortical area of the cerebral hemisphere has been shown to be directly proportional to the magnitude of its function [26]. Cross sectional area of an artery is directly proportional [27, 28] to the amount of blood flowing through the artery. It follows that cross-sectional areas of the arteries supplying each cerebral hemisphere are good indicators of functions in the hemispheres. Therefore, comparing sizes of arteries supplying right and left hemispheres should provide information about lateralisation of functions of areas they supply. Blood supply to each cerebral hemisphere comes from only three branches of the cerebral basal arterial network (CBAN) comprising the vertebrobasilar component and the anterior arterial circle of the brain [29] (circulus arteriosus cerebri). Therefore, although cerebral hemispheres are complex entities, it is easy to measure their total blood supply by adding together areas of the three cerebral arteries: anterior, middle and posterior. This study determined the cross-sectional areas of arteries supplying each cerebral hemisphere of the human brain with the aim of testing whether one hemisphere is functionally dominant over the other by determining differences in their arterial blood supply.

2. Materials & methods

2.1. Data section

Arterial diameters were determined on Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA) digital recordings obtained from

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152 live adult patients at the Royal Adelaide Hospital documented in the Carestream database and in 51 adult brains dissected out from human bodies. Patients' documented in the Carestream database had given written permission to university clinicians and academics to use the data for research purposes after obtaining ethics approval. Patient's identities have not been recorded and documented. The dissected bodies were donated to Adelaide Medical School, the University of Adelaide for research. All measurements were taken after obtaining approval from the University of Adelaide ethics committee (Ethics approval No. H2014-176).

2.2. Data collection/measurement

Diameters of anterior, middle and posterior cerebral arteries were measured bilaterally in dissected brains and MRA and CTA scans [30] at the sites indicated in Figs. 1, 2, and 3. In donated brains, external diameters of the arteries were measured using a digital Vernier caliper. In digital images of MRA and CTA scans obtained from live patients; the internal diameters of the three arteries were measured using image J software programme [30, 31]. External diameters of the arteries in donated brains and internal diameters in MRA and CTA digital scans are the only diameters that could be measured accurately. The digital Vernier calipers have been commonly

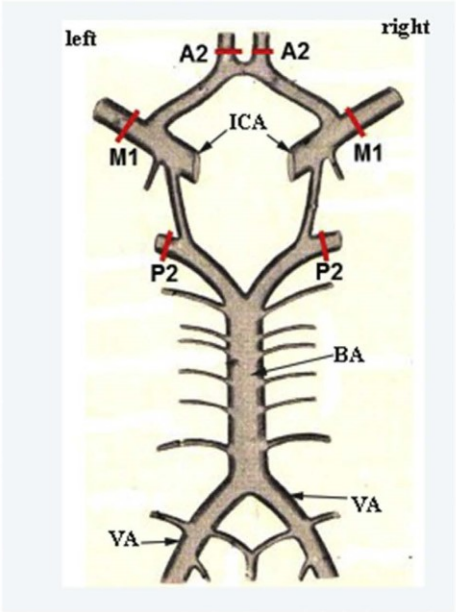

Fig. 1. Schematic diagram. Red lines perpendicular to the long axis of the vessels indicate measurement sites, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, rt = right, lft = left, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA.

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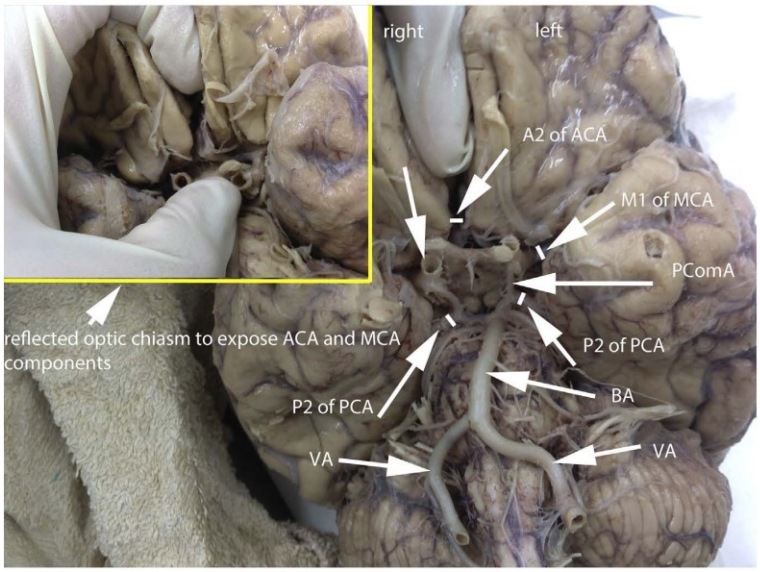

Fig. 2. Basal view of the brain, white lines without arrows showing the measurement sites of vessel diameter, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, rt = right, lft = left, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA, BA = basilar artery, ICA = internal carotid artery, VA = vertebral artery.

used [32, 33, 34, 35, 36] to measure the arterial diameter in cadaveric brains. Magnetic Resonance Angiography and CTA have been used for morphometry of different components of brain and they seem to be more accurate [30] than measurements taken physically on brains. The accuracy and the reliability of the measurements were determined by repeating the procedure in 15 cadavers, and 10 MRA and CTA digital scans. Technical errors of measurement (TEM) and reliability coefficients (r) are presented in Table 1. This project is designed to observe the differences in the blood supply between the left and right cerebral hemispheres of each brain comparing the left and right arteries of the same individuals, thus the arterial measurements were not subdivided into groups according to the method of measurement nor according to the age and sex.

2.3. Statistical analysis

A priori power analysis with a power 0·80 and two-tailed probability 0·05 indicated that to detect in a paired t-test a difference of about 10% in mean arterial diameters (Cohen's effect size of 0·5), the minimum sample size is 33. Both samples exceeded this size. A sample size of 128 was required to detect 5% mean difference with the same assumed parameters. This sample size was exceeded by our scan data

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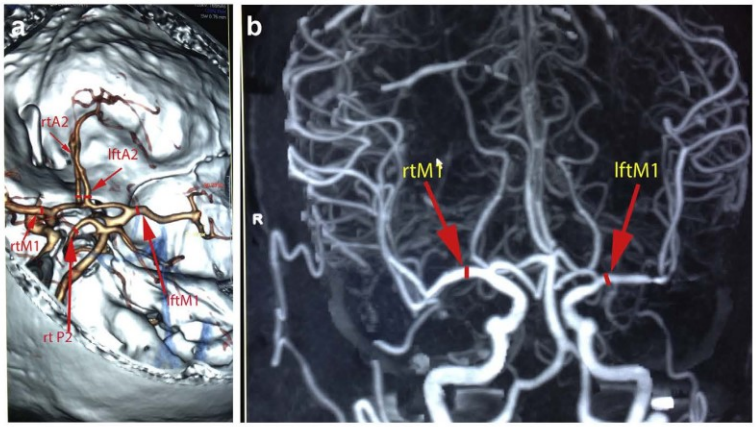

Fig. 3. a and b: Figure showing the sites of arterial diameter measurement in reconstructive cerebral arterial Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), rt = right, lft = left, green lines showing the measurement sites of vessel diameters, A2 = the most proximal portion of second part of anterior cerebral artery and M1 = the most proximal portion of the first part of middle cerebral artery.

(N = 152) and by joined samples (N = 203). A sample of 198 was needed to detect 4% size differences, that is about 0·3 mm^2 in the size of the single artery or 0·7 mm^2 in the total size of arteries. Our total sample size (n = 203) exceeded the calculated 198.

Table 1. Accuracy and reliability of the measurements in Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) scans and cadaveric brains. The coefficients of variation of the measurements are presented: TEM = Technical errors of measurement, PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, Rt = right, Lft = left, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA.

Arterial components measured	Measurements in cadaveric brains (n = 15)		Measurements in scans (n = 10)	
	TEM	Reliability (r)	TEM	Reliability (r)
Rt P2	0.13	0.97	0.02	0.99
Lft P2	0.1	0.97	0.04	0.98
Rt M1	0.11	0.97	0.03	0.99
Lft M1	0.07	0.97	0.02	0.99
Rt A2	0.07	0.97	0.07	0.96
Lft A2	0.21	0.97	0.04	0.98

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Descriptive statistics and paired t-test were used to compare the calculated cross-sectional areas of the arteries supplying the right and left cerebral hemispheres. Probability (P) values less than 0·05 were taken as significant. Statistical analyses were conducted using SPSS v 25. Linear regressions of right on left arterial sizes were run to observe any deviation of residuals to the right or left (Fig. 4). Paired t-tests were applied to each artery and to the total size of arteries. We also counted how many brains had a particular artery larger on the right and how many on the left. These numbers were compared using chi-squared sign test. The same comparison was performed for the sum of arterial sizes dominating on the right or on the left (Tables 2 and 3).

3. Results

The tests were conducted separately and combinedly for data obtained from prosected brains and CTA and MRA images. Mean cross sectional areas of right and left, anterior, middle and posterior cerebral arteries of donated brains and CTA and MRA scans are presented in Table 2. The average combined cross-sectional area of right anterior, middle and posterior cerebral arteries supplying the right cerebral hemisphere of dissected brains (18.8 mm^2) did not differ significantly (t = 0.6) from the relevant value for the left hemisphere (19.0 mm^2). In CTA and MRA study, the average combined cross-sectional area of three right cerebral

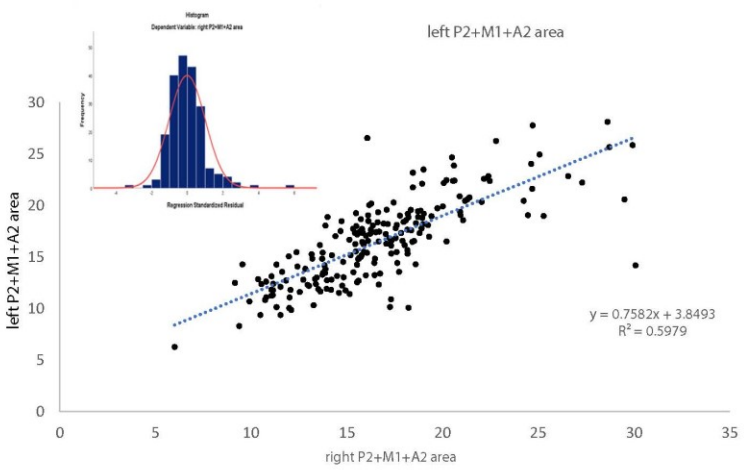

Fig. 4. Sum total of cross-sectional areas (mm^2) of left anterior, posterior and middle cerebral arteries regressed on sum total of cross-sectional areas of right anterior, posterior and middle cerebral arteries. Arterial data taken from cadaveric brains and Computed Tomography Angiography and Magnetic Resonance Angiography (n = 203). Right- scattergram and left- distribution of residuals around the regression line. Observe symmetrical distribution of residuals around zero. This distribution does not differ significantly from the normal distribution.

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Table 2. Means and standard deviations (mm^2), and paired samples t-test results comparing right and left anterior, middle and posterior cerebral arterial cross sectional areas determined from dissected donated **brains, Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) data, N=203,** PCA = posterior cerebral artery, ACA = anterior cerebral artery, MCA = middle cerebral artery, A2 = the most proximal portion of second part ACA, P2 = the most proximal portion of the second part of PCA, M1 = the most proximal portion of the first part of MCA, ns = not significant, ACA A2a = cross sectional area measured at the most proximal portion of second part of ACA, MCA M1a = cross sectional area measured at the most proximal portion of the first part of MCA and PCA P2a = cross sectional area measured at the most proximal portion of the second part of PCA.

Items	cadaveric paired sample test, N = 51				CTA and MRA scan- paired sample test, N = 152				Total (cadaveric and scans) paired sample test, N = 203			
	Right	Left	Paired t-test	sign.	Right	Left	Paired t-test	sign.	Right	Left	Paired t-test	sign.
	Mean (Std.Dev)	Mean (Std.Dev)	t- value		Mean (Std.Dev)	Mean (Std.Dev)	t- value		Mean (Std.Dev)	Mean (Std.Dev)	t- value	
ACA A2a	5.6 *1.9*	5.5 *1.6*	0.3	ns	4.5 *1.5*	4.4 *1.4*	1.8	ns	4.8 *1.7*	4.6 *1.5*	1.2	ns
MCA M1a	7.8 *2.0*	8.3 *2.3*	−1.7	ns	6.7 *2.1*	6.7 *2.1*	0.3	ns	7.0 *2.1*	7.1 *2.2*	−0.8	ns
PCA P2a	5.4 *1.4*	5.3 *1.2*	0.5	ns	4.7 *1.6*	4.5 *1.4*	1.3	ns	4.9 *1.6*	4.7 *1.4*	1.4	ns
ACA A2a + MCA M1a + PCA P2a	18.8 *3.6*	19.0 *3.5*	−0.6	ns	15.9 *4.0*	15.6 *3.8*	1.8	ns	16.6 *4.1*	16.5 *4.0*	0.9	ns

arteries was 15.9 mm^2 while on the left it was 15.6 mm^2 (t = 1.8). Dissected brains indicated that the arteries were larger on the left and the MRA and CTA scans data showed that the arteries were larger on the right side. These differences were random and fell within the insignificant range.

Table 3. Cross-sectional area measured on left and right cerebral arteries from cadaveric and Computed Tomography Angiography and Magnetic Resonance Angiography scans data and their comparison using formula; χ^2 = (left − right)^2/(left + right), n = 203, lft = left, rt = right, P2a = posterior cerebral artery second part (P2 proximal segment) cross sectional area, A2a = anterior cerebral artery second part (A2 segment) proximal cross-sectional area, M1a = middle cerebral artery first part (M1 segment) proximal cross-sectional area in mm^2, ns = not significant.

Arterial area	Arterial cross-sectional area	Larger on:		χ^2
	Equal	Left	Right	
A2a	5	93	105	ns
M1a	7	100	96	ns
P2a	9	93	101	ns

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In the combined cadaveric and the scanned samples, the average difference between the total right and left areas of arteries was 0.09 mm^2. It was not significant ($t = 0.5$). The results for the left and right differences of individual arteries- anterior, middle and posterior, were small and all statistically insignificant. The residuals of regressions of right cerebral arterial cross-sectional areas on corresponding arterial cross-sectional areas of the left were normally symmetrically distributed around a mode of zero (Fig. 4). The number of the brains showing larger arteries on the right was similar to that on the left, statistically these numbers were indistinguishable because the test, $\chi^2 = (\text{left} - \text{right})^2/(\text{left} + \text{right})$ did not provide the significant results (Table 3).

4. Discussion

Current study shows that there are no right and left differences in cross sectional areas of arteries supplying the cerebral hemispheres (Tables 2 and 3). These clearly indicate that in the left cerebral hemisphere, there are no additional functional areas in the territories supplied by the anterior, middle and posterior cerebral arteries compared to the same territories of the right hemisphere. Lateralisation of one or more functions to a cerebral hemisphere is expected to associate with increase in the volume of cortical tissues of the respective area/areas (i.e. thickness or surface area or both of the specific region/regions) compared to the contralateral hemisphere. This will result in increased need for blood supply, thus the cross-sectional area of an artery supplying the region, and the total cross-sectional areas of arteries supplying a cerebral hemisphere should increase. Dominance of one hemisphere should lead to the asymmetry of the size of arteries. Where there is no laterization of the function, blood flow to each hemisphere would be the same.

Another interpretation is also possible: if the lateralization of the brain functions were such that exactly half of all functions were located in the left and another half in the right hemisphere, then the blood flow, and the cross-sectional areas of arteries to both hemispheres would be the same. Some of the human functions such as language, handedness, logical reasoning have been generally accepted to be located in the left hemisphere [3, 11, 14, 37, 38, 39] in most people and the left occipital petalia present in most human beings were cited as an indication of the enlargement of the left hemisphere.

The handedness and behavioural functional lateralization have been studied in relation to the size of corpus callosum. However, the role of corpus callosum tracts is to increase the interhemispheric connectivity and ensure the need of having bilateral cortical components to perform some specific functions together and support the functional relationship between the adjacent components of the cerebral hemispheres [5].

Recent studies on lateralization have revealed that some functions are mastered particularly well by one hemisphere [15, 16], while other functions might be mastered by

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the other hemisphere so that the total functional output of each hemisphere is similar. In other words, the idea of hemispheric specialization may apply to specific function, but not to all functions [4]. Any tissue and organ in the body, including a part of the brain performing particular function, requires more blood flow. If, however, function occurs intermittently for short periods, the amount of blood flow may increase but the flow is not large enough to cause permanent change to the arterial structures. Brain works continuously, and especially during wakefulness performs number of functions simultaneously, so that both hemispheres require constant flow of blood. It may be that each hemisphere performs different functions, but the sum total is the same as in the contralateral hemisphere, or that many functions use both hemispheres communicating via corpus callosum, anterior and posterior commissures. Results of the current study cannot distinguish between these two possibilities.

Since each cerebral hemisphere is entirely supplied by the three arteries-anterior cerebral artery (ACA), posterior cerebral artery (PCA) and middle cerebral artery (MCA) [27, 28, 40], thus the total cross-sectional areas of these arteries are a good indicator of the function of a cerebral hemisphere. The total size of a cerebral hemisphere is the size of the cerebral cortex and its subcortical connections. Therefore, if a cortex of a given hemisphere is larger due to its functional dominance, the entire hemisphere should be larger.

In another study, dimensions of right cerebral hemispheres of 54 donated brains were compared with those of the left hemispheres and no significant size differences between the two hemispheres were found [19]. Furthermore, the arrangements of asymmetric posterior and lateral cerebral dural venous sinuses (in 58 brains) were found to be correlated with the petalial patterns. Larger volume of blood in dural venous sinuses in the posterior aspect of the right of the cranial cavity might move the entire right cerebral hemisphere anteriorly [20]. This produces larger occipital extent of the left hemisphere, and larger anterior extent of the right hemisphere, a pattern found in approximately 60% of people [41]. This difference in appearance does not indicate there is real difference in size [20].The cortical thicknesses of 39 functional areas of one cerebral hemisphere has been compared with those of the same 39 functional areas of the other hemisphere in MRI scans obtained from 17,000 healthy individuals [18]. No significant differences between the two cerebral hemispheres were found. These three studies mentioned in in this paragraph, investigated different indicators of cerebral lateralization and found no differences between two cerebral hemispheres.

Most of the findings related to the lateralization are ambiguous and have no definitive results, structural asymmetry exists only statistically, there are no specific criteria to prove it. Current study examined the arterial cross-sectional areas supplying the cerebral hemispheres and the findings show small and uniformly insignificant differences between left and right cerebral arterial cross-sectional areas. Functional

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predominance and different cognitive functions between the two hemispheres have been reported [16], however the size of the arteries supplying the two hemispheres in this study, does not indicate greater function of one hemisphere compared to the other hemisphere.

5. Conclusion

Blood supply from anterior, posterior and middle cerebral arteries to the right and left cerebral hemispheres is the same. Since the blood supply is proportional to the function, we suggest that there is no asymmetry in total functions of cerebral hemispheres.

Declarations

Author contribution statement

Arjun Burlakoti, Jaliya Kumaratilake, Maciej Henneberg: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jamie Taylor: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm

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ABSTRACT

Objectives The aim of this study was to establish an anatomical index for early prediction of the risk of development of aneurysms in anterior communicating arterial complex (AcomAC). The asymmetric diameter of one anterior cerebral artery (ACA) to other could alter haemodynamics and may contribute to formation of aneurysms in AcomAC and be a reliable predictor of the risk of development of aneurysms.

Design and setting This is a retrospective, observational and quantitative study, which used cerebral computed tomography angiography (CCTA) scans in South Australia.

Participants CCTA scans of 166 adult patients of both sexes were studied.

Main outcome measures The internal diameters of the proximal segments of ACAs (A1s) were measured. Position and presence or absence of aneurysms in AcomAC were determined. The ratio of A1 diameters was taken as a measure of A1 asymmetry.

Results The ratio of diameters of A1s correlated with the occurrence of AcomAC aneurysms. The risk of development of aneurysms in AcomAC was much greater (80%, OR=47.3) when one A1 segment's radius was at least 50% larger (ie, 2.25 times cross-sectional area) than the other.

Conclusion The general information on asymmetric A1 has been published previously. The present findings have significant contribution since the A1s asymmetry ratios have been categorised in ascending order and matched with the presence of AcomAC aneurysms. The asymmetry ratio of the A1 is a good predictor for the development of AcomAC aneurysms. Reconstruction of the asymmetric A1 could be done if the technology gets advanced.

Key messages

What is already known about this subject?

► Relationship of asymmetry of A1 segment of anterior cerebral artery (ACA) to the occurrence of aneurysms in anterior communicating arterial complex (AcomAC) has been observed in literature but has not been explained nor quantified.

What are the new findings?

► Asymmetry of the A1 of ACA was quantified, and a mathematical model has been established to predict the likelihood of developing AcomAC aneurysms depending on the degree of asymmetry.

How might these results affect future research or surgical practice?

► Patients with asymmetry of A1 found in their brain scans should be closely followed up, because of the high risk of developing aneurysms in the AcomAC complex. Reconstruction of the asymmetric A1 can be done to prevent the development of AcomAC aneurysms, if ethically justified.

INTRODUCTION

Rupture of cerebral aneurysms causes subarachnoid haemorrhages (SAH) leading to high mortality and morbidity. The incidence of SAH has been 10–36 per 100 000 people per year and about 3/4 of them resulted from spontaneous rupture of cerebral aneurysms.[1 2] Large cerebral aneurysms may also compress adjacent cranial nerves.[3] The mortality and morbidity rates resulting from ruptured cerebral aneurysms remain high, with around one-third dying at the time, one-third suffering a major stroke and one-third making a reasonable recovery.[4] An aneurysm is a dilatation and outpouching of the wall of a blood vessel.[5 6] The action of fluctuating blood pressure on vascular walls has been identified as the main cause for the development of aneurysms.[7] The risk of aneurysm rupture is 6–8 in 100 000 per year in most developed countries.[8] In South Australia, where the total population is 1.7 millions, radiologists involved in the treatment observed approximately 170 ruptured aneurysm cases per year (ie, 1 in every 10 000 cases per year). Another study revealed that about 1 in 30 adults likely to have intracranial aneurysms and in 25% of them, the aneurysms could rupture and produce SAHs or compression of surrounding structures.[7] Anterior communicating artery complex (AcomAC) has been the most common

location of ruptured cerebral aneurysms.[9] Unruptured aneurysms have been observed in 2.8% of patients investigated by magnetic resonance (MR) angiography.[10] People with variations in cerebral arteries, particularly, in anterior cerebral arterial (ACA) territory are thought to be subjected to imbalance in cerebral blood flow leading to cerebrovascular pathologies, including cerebral aneurysms.[11]

Variations in cerebral basal arterial network have ranged from missing arterial segments to asymmetry between collateral arterial segments and the later was more common.[12 13] Some of the most variant and asymmetric patterns of arteries were seen in relation to anterior cerebral and anterior communicating arterial territories.[11 14] Fluctuation in arterial blood flow, and thus the blood pressure, has been observed in asymmetric A1 segments.[15 16] Such variations in blood flow could predispose the arterial wall for aneurysmal dilatations.[17–22] Genetics, smoking, trauma and medications are factors that could weaken the walls of arteries and predispose them to the development of aneurysms, particularly when subjected to alteration in haemodynamics or chronic hypertension.[22] Prediction and early detection of aneurysms allow treatment, thus could prevent or reduce the incidences of cerebral stroke, including reoccurrences of aneurysms. The aim of this research was to investigate the relationship of asymmetry between A1s and the development of AcomAC aneurysms. As far as we know, no studies have been done on quantifying and calculating the degree of A1 asymmetry to the occurrences of AcomAC aneurysms. A method to predict the risk of occurrence of aneurysms in AcomAC using the degree of asymmetry between right and left A1s has been established.

METHODS

Study design

Internal diameters of A1s were measured on cerebral CT angiography (CCTA) digital images obtained from 166 (80 males and 86 females) adult individuals (average age=60 years, SD=16) (see online supplemental file 1). The same images were used to determine the presence or the absence of AcomAC aneurysms. The source of the CCTA images were the Carestream (Vue RIS V.11.0.14.35) database of the Royal Adelaide Hospital (RAH), University of Adelaide, South Australia. The CCTA images were taken between January 2011 and December 2018. Patient's personal details have not been copied, documented or included in this research.

The CCTA images studied were those taken for the clinical investigation of different cranial pathologies. These included 51 cases out of 166 patients who had a history of previously diagnosed cerebral aneurysms (see online supplemental file 1).

Data collection and extraction

Data collection was carried out by the corresponding author in consultation with radiologists from the RAH, South Australia who were involved in patients' care. Cases with severe cerebral vasospasm diagnosed by radiologists and recorded in the data system were excluded from the study. The internal diameters were measured at the midpoint of the left and right A1s were measured perpendicular to the long axis of the vessels at the narrowest possible sites (in the coronal and axial CCTA images) using image J software (figure 1, online supplemental figure 1 and online supplemental figure 2). Measurements taken by the image J software have been proven accurate and reliable in previous studies.[23] The reliability and the accuracy of the measurements were confirmed by repeating measurements of 30 cases at 15 months interval by the same person and determined the intra-observer errors (table 1 and online supplemental file 2). Comparison of first and repeated measurements gave a 10% relative technical error of measurement (rTEM) without adjustment and less than 5% rTEM with minor correction and adjustment (table 1 and online supplemental file 2). These reliability and the accuracy calculations were statistically acceptable.[24]

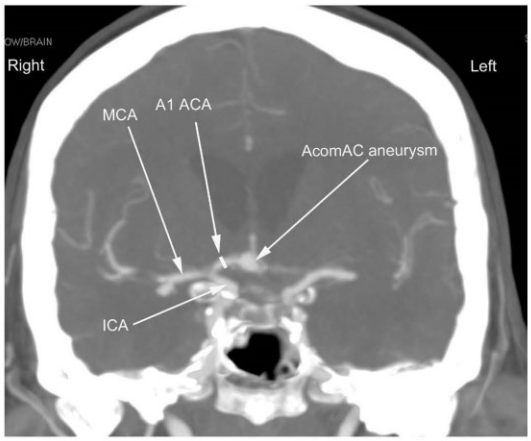

Figure 1 Cerebral CT Angiography scan with AcomAC aneurysm in coronal view, white line perpendicular to the long axis of the vessel (A1 ACA) indicates measurement site. A1 ACA, the first part of anterior cerebral artery; AcomAC=anterior communicating arterial complex; ICA, internal carotid artery; MCA, middle cerebral artery.

The selection of measurement sites was consistent throughout the data collection. Data were taken only from the electronic files stored in the Carestream software at the RAH, University of Adelaide. Occurrence of AcomAC aneurysms with or without the presence of aneurysm elsewhere and prior history of aneurysms anywhere in the brain were included from each individual case.

The asymmetry ratios of right and left or left and right (ie, bigger to smaller ratio) A1 arteries were computed for all 166 CCTA cases (see online supplemental file 1). The calculated bigger to smaller A1 asymmetry ratios were categorised into three groups (ie, mild to moderate asymmetry ≤1.5, substantial asymmetry >1.5 to ≤2 and

Table 1 Accuracy and reliability of the measurements of the first part of the anterior cerebral artery (A1) in cerebral CT angiography (CTA) scans

	Reliability (R)	Technical error of measurement (TEM) in mm	Relative TEM (rTEM) in %
Repeat A1 measurement in axial CTA images (not adjusted*)	0.93	0.24	11.00
Repeat A1 measurement in axial CTA images (adjusted*)	0.98	0.12	5.39
Repeat A1 measurement in axial and coronal CTA images (adjusted*)	0.98	0.10	4.77
Repeat A1 measurement in coronal CTA images (not adjusted)	0.94	0.22	10.45
Repeat A1 measurement in coronal CTA images (adjusted*)	0.96	0.14	6.55

The coefficients of variation of the measurements (rTEM) are presented. Reliability is the correlation among the previous first measurement done in coronal and axial CTA slices and the second measurement performed in axial and coronal cerebral CTA after 15 months of the initial measurement taken of the same artery, computed tomography = CT, A1=first part of anterior cerebral artery, n=30
*Adjustment made by excluding two outliers from the previous and the corresponding repeat measurements of right A1 (file supplied in online supplemental file 2).

severe asymmetry ≥2, (table 2 and online supplemental file 3). The rationale for this classification was for easy application and interpretation. The diameter (and hence also the radius) ratio of 1.5 corresponds to the 2.25 times difference in the cross-sectional area of the vessel's lumen, while the ratio of 2.0 reflects four times difference in the cross-sectional area of the vessel lumen.

STATISTICAL ANALYSIS

A cross-sectional observational design and SPSS V.25 (IBM) program were used in the study. Measurement error analysis has been described in table 1. In the main analysis, non-parametric statistics (χ^2) were used and ORs were calculated to observe the strength of association between the A1 asymmetries and the AcomAC aneurysms (table 2 and online supplemental file 3).

RESULTS

The asymmetry ratios of right and left A1 segments of ACA together with the presence and absence of AcomAC aneurysms are presented in table 2, and online supplemental files 1 and 3 (in ascending order, n=166). Among 141 patients with mild to moderate A1 asymmetry (≤1.5), 11 had AcomAC aneurysms. Out of 13 patients with substantial asymmetry (>1.5 to≤ 2.0), 10 had AcomAC aneurysms. In 12 patients with severe type of asymmetric ratios (>2.0), 10 were affected with AcomAC aneurysms

Table 2 Probability (out of 1.00) to have anterior communicating artery complex aneurysms in relation to the degree of right and left asymmetricity of A1 ACA

A1 asymmetry ratio (right and left bigger to smaller A1)	AcomA complex aneurysm					χ^2 (asymptotic significance); p value
	No	Yes	Total	% Chance	OR	
No of cases; n=166						
Mild to moderate (≤1.5)	130	11	141	7.8	0.02	0.0001
Substantial to severe (>1.5)	5	20	25	80.0	47.3	0.0001
Total	135	31	166			
No of cases without history of aneurysm (n=115)						
Mild to moderate (≤1.5)	93	7	100	7.0	0.027	0.0001
Substantial to severe (>1.5)	4	11	15	73.3	36.53	0.0001
Total	97	18	115			
No of cases with history of aneurysm (n=51)						
Mild to moderate (≤1.5)	37	4	41	9.6	0.012	0.0001
Substantial to severe (>1.5)	1	9	10	90.0	83.25	0.0001
Total	38	13	51			

n=166, without history of aneurysms (n=115), with the previous history of aneurysm (n=51).
A1 ACA, first segment of the anterior cerebral artery; AcomA, anterior communicating artery.

Table 3 Presence or absence of anterior communicating artery complex (AcomAC) aneurysms and cerebral aneurysms elsewhere in the current study

	Presence or absence of aneurysms	AcomAC region		
		Yes	No	Total
Total no of cases; n=166				
Aneurysms elsewhere in the cerebrum	Yes	9	68	77
	No	22	67	89
	Total	31	135	166
Cases without history of aneurysm (n=115)				
Aneurysms elsewhere in the cerebrum	Yes	3	30	33
	No	15	67	82
	Total	18	97	115
Cases with history of aneurysm (n=51)				
Aneurysms elsewhere in the cerebrum	Yes	6	38	44
	No	7	0	7
	Total	13	38	51

n=166; without history of aneurysms, n=115; and with the previous history of aneurysm, n=51.

(table 2, online supplemental file 3). Among the people with A1 asymmetry ratios of less than 1.5 just 7.8% had aneurysms while in those with ratios of >1.5 to ≤2 and >2, the risks of developing AcomAC aneurysm were 77% and 83%, respectively. In summary, patients with asymmetry ratios greater than 1.5 had 80% risk of developing aneurysms (OR=47.3), while those with asymmetry ratios below 1.5 had 7.8% AcomAC aneurysms (OR=0.02), (table 2, online supplemental files 1, 3 and 4).

The chances of developing AcomAC aneurysms in the presence of substantial and severe A1 asymmetries were statistically similar between people with or without a previous history of aneurysms (table 2 and online supplemental file 3). In patients with no previous history of aneurysms (n=115), the incidences, risks and ORs (table 2 and online supplemental file 3) of AcomAC aneurysms were similar to the entire sample and to the patients with previous history of aneurysm.

The prevalence of AcomAC aneurysms between sexes and among age groups was statistically not different. Altogether, 31 out of 166 cases had AcomAC aneurysms and 77 out of 166 cases had cerebral aneurysms elsewhere (ie, other than the AcomAC aneurysm). Seven out of 11 cases with AcomAC aneurysms that had only mild asymmetry of A1 also had aneurysms elsewhere in the brain other than AcomAC location (table 3). However, there was no significant relationship between the presence of AcomAC aneurysms and aneurysms elsewhere in the brain (χ^2 3.7, p=0.05). Furthermore, statistical relationship between A1 asymmetricity and the presence of cerebral aneurysms elsewhere was not found (p>0.05). All patients with AcomAC aneurysms had 1.66 median asymmetry ratio, while the patients without the presence of AcomAC aneurysms had 1.09 median asymmetry ratio. The median A1 asymmetry ratio for all the cases included in this study was just 1.10 (table 3, online supplemental files 1 and 3).

DISCUSSION

The current study quantified for the first time, A1 asymmetry and the likelihood of occurrences of AcomAC aneurysms. Previously the co-occurrence of AcomAC aneurysms with A1 asymmetry has been observed but not quantified.[11 25 26] The study included random CCTA cases accessing the data at a specialised tertiary centre. Obviously, we would assume to see cases of suspected cerebral pathologies in a specialised tertiary medical centre. We examined fairly a large number of 166 CTA evaluating individual A1 asymmetry and aneurysms. The findings (OR and risk percentage) on A1 asymmetry ratio (≥1.42) were extremely significant in relation to the AcomAC aneurysms.

The findings of the study indicate that, the prevalence of aneurysms in AcomAC was greater with increasing asymmetry between left and right A1s (table 2 and online supplemental file 3). The asymmetry ratio of 1.5 indicates that the cross-sectional area of an A1 segment is twice as large as that of the other one (1.5^2=2.25). Furthermore, such asymmetry would likely to have significant haemodynamic effects that could produce 80% risk of AcomAC aneurysms (table 2, online supplemental file 3 and online supplemental file 4). The exact mechanism involved in causing aneurysms in AcomAC is not well understood.[27] The development of aneurysm could be due to the altered haemodynamics resulting from the increased blood flow and the greater peak systolic pressure in the larger ACA.[12 27 28] Imbalanced haemodynamics originating from the larger ACA may weaken and dilate the wall of the AcomAC at branching points, resulting in an

aneurysmal formation.[12 21 29] Thus, the extent of the asymmetry in A1s may allow to predict the occurrence of the AcomAC aneurysms. Current sample included patients presenting with various cerebral problems, including strokes and aneurysms. However, when patients were divided into two subsamples: those with a history and without known history of aneurysms, the results did not differ significantly between these sub samples (table 2 and online supplemental file 3). This lack of difference indicates that prior history of aneurysms did not influence the overall results of the study. Therefore, the observed correlation between asymmetry of A1s and AcomAC aneurysms is independent of the prior history of any cerebral aneurysms, because in the current sample there is no correlation between presence of AcomAC aneurysms and aneurysms elsewhere ((table 2 and online supplemental file 3).

The A1 asymmetry ratio was just below 1.5 in 11 out of 31 AcomAC aneurysms cases. However, 3 out of those 11 cases had A1 asymmetry ratios of more than 1.42 (indicating double the cross-sectional area of one A1 artery compared with the other). Furthermore, all others (ie, 8 out of those 11 cases with asymmetry ratio below 1.5) had asymmetry ratios above the median of 1.09 and represented the 'mild to moderate asymmetry' category. Seven of those 11 cases had also aneurysms elsewhere (tables 2 and 3 and online supplemental file 3). These may indicate that causes for the development of AcomAC aneurysms in the lower A1 asymmetry (<1.40) cases may be because of the quality of vessel's walls and high blood pressure, in addition to altered haemodynamics resulting from the asymmetry.

Since the CCTA data were taken from the specialised medical centre, it is true that we get to see symptomatic individuals with different pathologies. That approach is even better to see the connection between A1 asymmetry and the presence or absent of aneurysms rather than trying to scan many innocent people in the community, exposing them to the radiation unnecessarily. Modifiable known risk factors, such as history of smoking and hypertension were not quantified in this study. These could have been supplementary factors promoting AcomAC aneurysms, however, literature suggests hypertension is not related to the cerebral aneurysms.[30] Furthermore, there is no reason to assume that A1 asymmetry is related to the smoking and hypertension. This research found a coincidence of A1 asymmetry and AcomAC aneurysms. This coincidence could result from: (A) AcomAC aneurysm altering the blood flow and remodelling the size of A1 segments, (B) Asymmetry of A1 arteries causing altered blood flow in AcomAC and affecting the walls and producing the aneurysm. Remodelling of the size of arteries in the vicinity or proximal to an aneurysm is not known, therefore, it is more likely that A1 asymmetry causes aneurysms. A longitudinal prospective study would likely confirm vessel asymmetry as the cause of aneurysms rather than the reverse. We are not aware of such a study being conducted and there may be significant ethical impediments. Treatment and the management of patients after strokes are costly to the affected family as well as to the country. A multinational study has shown that, the cost of management of a patient after a stroke ranged from US$18 538–US$228 038.[31] The procedure of treatment of unruptured aneurysms is safe, and the risk of development of stroke is approximately 3% and the mortality is less than 1%, therefore, there is great advantage in identifying and treating aneurysms before they rupture.[32 33]

The ability to predict the likelihood of the development of aneurysms in AcomAC using the asymmetry ratio between right and left A1s could enhance the viability of a national screening programme.

Undertaking CCTA screening in the general population is not recommended due to ethical reason. However, if A1 asymmetry is noticed in cranial investigation done for other reasons, clinicians should be cautious as it could indicate the possibility of future development of aneurysms. Therefore, MRI screening of older individuals may be beneficial, and has been recommended.[20] These findings make significant contribution to existing knowledge, since the A1 asymmetry index has been categorised in ascending order and matched with the presence or absence of AcomAC aneurysms in each of the 166 cases. This type of study has not been done before. General anatomical variations of A1 could be corrected with the advancement of medical and surgical technologies. This would prevent unequal blood flow and pressure contributing to the occurrences of AcomAC aneurysms. Patients who have A1 asymmetry (especially the A1 asymmetry with ≥1.42) on scans should be monitored regularly by follow up imaging and angiograms. Reconstruction of A1 asymmetry is a future possibility with technological advancement.

CONCLUSION

The asymmetry of the diameters of A1s should be routinely assessed in all patients undergoing cerebral imaging, which includes these vessels. Patients with asymmetry of the A1 should be closely followed up, because of the high risk of development of aneurysms in the AcomAC complex. Reconstruction of the asymmetric A1 could be done if the technology gets advanced in the future.

Contributors AB conceived the idea, designed the analysis, collected and analysed the data from cerebral CT angiography (CCTA), took pictures, recorded videos, contributed in conceptualisation, prepared and drafted the manuscript. JK conceived the idea, contributed to the concept, helped in data interpretation, editing and the critical revision of the manuscript and approving the article. DJT conceived the idea, contributed in collecting and interpreting the data, editing the manuscript, the critical revision of the manuscript and approving the article. MH conceived the idea, helped in statistics, data analysis and interpretation, editing the manuscript, the critical revision of the manuscript and in approving the article.

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Paper 4: Journal published version

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Orofacial neuralgia associated with a middle cerebral artery aneurysm

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ABSTRACT

Chronic orofacial pain of neuropathic origin can present diagnostic and management dilemmas to dental practitioners and also affects the patient's quality of life. Intracranial aneurysms are a potential cause of stroke (e.g. sub-arachnoid haemorrhage) that is usually associated with, high rates of mortality and morbidity. A patient who had been previously managed for symptoms of temporomandibular joint disorder (TMD) presented with sharp, shooting pain of moderate intensity. It was precipitated by swallowing, and radiated to the right throat, posterior border of the mandible, ear and temporomandibular joint. Clinical and radiological investigations ruled out odontogenic pain, TMD and other more common types of facial pain. Magnetic resonance imaging revealed a 7 × 6 mm aneurysm in the right middle cerebral artery (MCA) which was subsequently surgically clipped. Interestingly, the facial pain resolved after this procedure. Compression of the insular region of the brain innervated by the trigeminal, glossopharyngeal and vagus nerves provides a plausible explanation for the pain reported. To our knowledge, this is the first case of facial neuralgia associated with an aneurysm in the MCA which emphasizes the importance of a multidisciplinary approach in the diagnosis and management of unusual cases of chronic orofacial pain.

Keywords: Orofacial pain, Intracranial aneurysm, Middle cerebral artery, Neuropathic pain, Multidisciplinary.

Abbreviation and acronyms: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCA = middle cerebral artery; MRI = magnetic resonance imaging; TMD = temporomandibular joint disorder; TMJ = temporomandibular joint; VPM = ventral posteromedial nucleus.

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INTRODUCTION

Intracranial aneurysms are localized dilations of cerebral artery walls that commonly occur as saccular outpouchings at bifurcations.[1] A meta-analysis of 68 studies in 94 912 patients from 21 countries reported the prevalence of 3.2% of unruptured intracranial aneurysms in the general population with a mean age of 50 years.[2] Risk factors for intracranial aneurysms include age, female gender, smoking, hypertension, cerebral arterial variations and familial history of subarachnoid haemorrhage, as well as hereditary and congenital syndromes (such as the autosomal dominant form of polycystic kidney disease) and connective tissue disorders (such as the Ehlers–Danlos syndrome).[3] Aneurysm size, morphology and location within posterior cerebral arteries are associated with increased risk of rupture.[4] Intracranial aneurysm is responsible for approximately 85% of subarachnoid haemorrhages, making it a leading cause of hemorrhagic stroke.[5]

The middle cerebral artery (MCA) is a branch of the internal carotid artery and is the largest and most complex of the cerebral vessels, supplying the basal ganglia (basal nuclei) and the lateral surfaces of the frontal, parietal and temporal lobes of the brain.[6] The artery is typically divided into four segments, including the sphenoidal (M1), insular (M2), opercular (M3) and the cortical (M4) regions of the brain.[7] As many as 14%–43% of cerebral aneurysms occur within these blood vessels,[8] accounting for up to 55% of all aneurysm-related haematomas following rupture.[9] The rupture of MCA aneurysms results in both subarachnoid and intracerebral haemorrhages in 30%–50% of cases, with high mortality rates (up to 41%); of those who survive, many suffer permanent

neurological deficits including hemiparesis, epilepsy and visual field defects.[10]

A large proportion of unruptured cerebral aneurysms is clinically asymptomatic and is only detected incidentally during radiological and clinical examination. Clinical signs and symptoms associated with cerebral aneurysms include cerebral ischemia and cranial nerve palsy, commonly affecting the oculomotor nerve.[11] Thrombosis, and expansion or inflammation of the aneurysm can also result in severe headache, visual deficits, cranial nerve neuropathies and seizures.[12] There are few reports of orofacial pain being associated with posterior communicating artery aneurysms and posterior cerebral artery aneurysms, resulting in trigeminal neuralgia-like symptoms from compression of trigeminal nerve fibers.[13–15] A large proportion of trigeminal neuralgia (approximately 80%–90%) is caused by compression of the trigeminal nerve by blood vessels in the cerebello-pontine angle, and a smaller proportion of cases is believed to be associated with other intracranial pathologies.[16] However the relationship between the occurrence of aneurysms and facial neuralgia is complex and poorly understood. This report describes a case of unusual chronic facial pain associated with an MCA aneurysm, a presentation that, to our knowledge, has not previously been documented in the literature.

CASE REPORT

A 62-year-old female patient presented for a general dental examination with a chief concern of mild pain around the right mandible. Medical history included hypertension, asthma and gastric regurgitation (commonly termed gastric reflux) that were well-controlled by medication. Dental history revealed nocturnal bruxism, for which the patient had been wearing an occlusal splint for 20 years. The most recent occlusal splint had been fabricated 3 months earlier and it showed cracks and significant wear. The masseter and temporalis muscles as well as the lateral pole of the right mandibular condyle were tender to palpation. There was no clicking or significant deviation or limitation to mandibular opening, closing and lateral movements. Furthermore, multiple carious teeth and failing restorations were identified, for which a management plan was formulated. The patient was counselled with regard to the role of bruxism in the aetiology of facial pain, and her symptoms were monitored over the course of restorative care.

Three months after the initial appointment, the pattern and severity of the pain changed. The pain became moderately intense and stabbing in nature. It was precipitated by swallowing, and radiated through the right throat, posterior border of the mandible, ear and temporomandibular joint (TMJ). Dental radiographs and clinical examination did not reveal an odontogenic source of pain and a subsequent referral was made to an oral and maxillofacial surgeon.

The oral and maxillofacial surgeon organized blood tests including assessment of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) titres. These common markers of vasculitis and inflammation were all within normal limits. Following the lack of osseous pathology evident on cone-beam computerized tomography, magnetic resonance imaging (MRI) of the TMJs and cranial base was obtained which did not reveal any TMJ pathology. However, the MRI displayed an aneurysm in the right MCA. Subsequently an MRI scan of the head was obtained, which revealed a 7 mm × 6 mm aneurysm in the M2 segment of the MCA (Fig. 1). The second MRI did not reveal any other pathology within the cranial cavity. This case was referred to a neurosurgeon who confirmed the aneurysm with computed tomography angiography (Fig. 2) and proceeded to clip it surgically. Interestingly, the facial pain resolved postoperatively, and patient's recovery was uneventful. The patient was free of symptoms at the one-month post-operative review and at the time of preparation of this manuscript at six-month post-operative review.

DISCUSSION

Generally, differential diagnoses of chronic facial pain (in decreasing order of occurrence) include odontogenic pain, temporomandibular joint disorders (TMD), temporal arteritis, cranial nerve neuropathies, salivary gland pathology and Eagle's Syndrome.[17] Odontogenic pain is the most common cause of pain[18] but it was excluded during clinical assessment. TMD can present with reduced mandibular movement, muscle and joint pain, disc displacement, arthralgia/arthritis and arthroses,[19] affecting up to half of the population.[20] Radiological and clinical investigations excluded it as well. Giant cell arteritis is a common form of vasculitis with a predilection for the temporal arteries.[21] Signs and symptoms include temporal headache, jaw claudication, scalp tenderness, visual disturbances, fever, weight loss and polymyalgia, as well as increases in CRP and ESR.[22] The blood tests excluded this condition. Eagle's syndrome is characterized by an elongated styloid process or calcified stylohyoid ligament that compresses on the structures in the neck. When the glossopharyngeal nerve is involved, pain radiates to the throat, base of the tongue and ear when swallowing.[23] Radiological examination excluded this condition, along with salivary gland malignancy that can mimic the symptoms of TMD.[24]

Neuropathic pain can occur from disturbances to the sensory pathways of the nervous system either

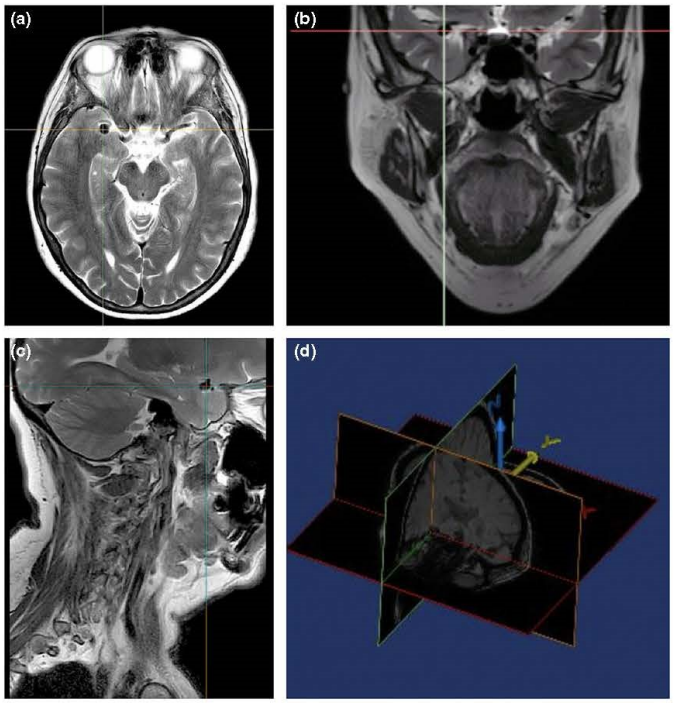

Fig. 1 (a) Inferior transverse, (b) Anterior coronal and (c) Right sagittal Magnetic Resonance Images (sections) showing the middle cerebral artery (MCA) aneurysm, and (d) A three-dimensional reconstruction showing the aneurysm in the right MCA within the insula. The location of the aneurysm is shown by the point of intersection of the perpendicular planes.

Fig. 2 Anterior coronal view of computed tomography angiography demonstrating the right middle cerebral artery aneurysm (red arrow).

centrally (within the brain and spinal cord), peripherally (vascular compression of nerves) or at both levels. Peripheral neuropathic pain presentations can occur from neuralgia of the trigeminal, glossopharyngeal and vagus nerves which typically present as unilateral sharp, shooting pain triggered by stimulation of the regions distributed by these nerves.[25–27] This condition is often associated with demyelination of the affected nerves closer to their roots secondary to compression by adjacent vascular pathology.[28] The patient's symptoms resembled those caused by combined trigeminal, glossopharyngeal and vagal neuralgia, which has been reported to occur on rare occasions.[27] The MRI however did not show evidence of nerve compression, excluding neurovascular conflict as a cause.

The most plausible explanation for pain in the present case is central neuropathic pain exerted by aneurysmal compression around the frontal and the parietal opercula of the insula corresponding to the sensory and motor homunculus of the pharynx and the TMJ.[29] The M2 segment of the MCA courses through the insular region around the Sylvian cistern. The enlargement of the aneurysm in the right MCA over time is likely to have compressed areas of this region corresponding to the innervation of the trigeminal, glossopharyngeal and vagus nerves to cause facial neuralgia.

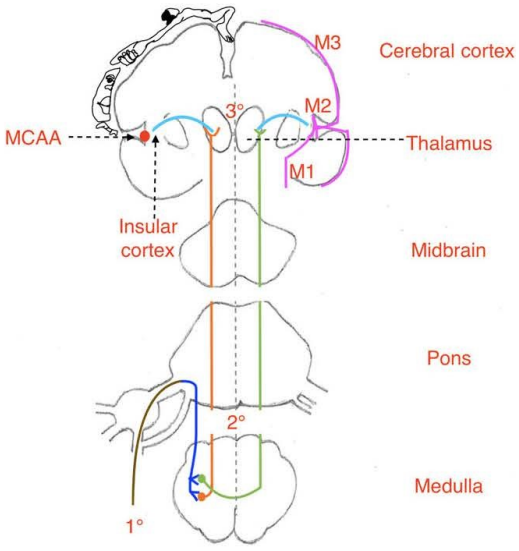

Fig. 3 Convergence of first-order trigeminal, glossopharyngeal and vagus pain neurons represented by the brown line (1°) occurs within the spinal nucleus of the trigeminal nerve (dark blue line). The second-order neurons (2°) predominantly project to the contralateral ventral posteromedial nucleus (VPM) in the thalamus via the ventral trigeminalothalamic tract (green line), with a degree of projection to the ipsilateral VPM via the dorsal trigeminalothalamic tract (orange line). The third-order neurons (3°) then project to the cerebral cortex, including the insular cortex, corresponding to the homunculus regions of the lower face and oro-pharynx. The course of the middle cerebral artery including the M1, M2 and M3 segments is shown by a pink line. The location of the aneurysm (MCAA) adjacent to the insular cortex corresponding to the lower face and pharynx provides the most plausible explanation for ipsilateral manifestation of pain.

Sensory processing of pain and other modalities (e.g. temperature, crude touch and vibration) from the peripheral organs to the brain involve three sets of neurons. First-order neurons carrying pain in the trigeminal, glossopharyngeal and vagus nerves synapse at the spinal nucleus of the trigeminal nerve (nucleus caudalis).[30,31] Second order neurons primarily project to the contralateral (opposite side) ventral posteromedial nucleus (VPM) in the thalamus.[32] Some second-order pain neurons also project to the ipsilateral VPM (on the same side).[33,34] Third order neurons project from the VPM to the cerebral cortex, including the insula (insular cortex). Because of significant crossing-over of pain neurons, a central lesion is typically expected to affect the opposite side of the body. However, ipsilateral projection of trigeminal pain neurons is likely to be responsible for ipsilateral neuralgia associated with insular compression from the right MCA aneurysm in the present case (Fig. 3).

The need for improving the interface between medical and dental professionals is being increasingly realized.[35] As management of orofacial pain is also common to both fields, appropriate referral and additional investigations (e.g. brain scans) can be necessary for appropriate management. Referral to multidisciplinary pain centers specializing in orofacial pain might also be a pathway to manage unusual cases of facial pain.[36] This could not only help resolve the symptoms in a timely manner but also avoid complications of underlying pathologies, which is important amid growing concerns of litigation against negligent professional behaviour and malpractice.

CONCLUSION

Differentiating between TMD and other causes of facial pain can be a diagnostic challenge. To our knowledge, this is the first case of orofacial pain that was relieved by surgical clipping of an MCA aneurysm that was not initially considered to be related to the pain. It is important for the dental practitioner to be aware of these conditions when presented with unusual facial pain of a similar nature as timely medical referral and treatment are crucial. Further studies are required to better elucidate the complex relationship between intracranial aneurysms and pain in the orofacial region.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. The patient provided consent for the use of their records for publication within this article.

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Chapter 7: The details of posters and oral presentations at conferences and seminars

1 Conference one

The first conference poster on **"The cerebral basal arterial network: morphometry of inflow and outflow components"** was presented by **Arjun Burlakoti** at the 13th Australian and New Zealand Association of Clinical Anatomists (ANZACA), Canberra, Australia, 7-9 December 2016. Arjun Burlakoti[1,2], Jaliya Kumaratilake[2], David J Taylor[3], Nicola Massy-Westropp[1], Maciej Henneberg[2]. [1]University of South Australia; [2]University of Adelaide Australia; [3]Royal Adelaide Hospital, South Australia (SA) Medical Imaging, Adelaide, Australia. This conference granted me a great opportunity to talk about the research findings that we conducted on exploring peak systolic pressure dampening function of communicating and segmental arteries of CBAN on human brain. I received constructive feedback from different health professionals.

Poster PDF - Please see below the first poster related to this thesis presented in the conference

The cerebral basal arterial network: morphometry of inflow and outflow components

Authors: Arjun Burlakoti[1, 2]*, Jaliya Kumaratilake[2], Jamie Taylor[3], Nicola Massy-Westropp[1] Maciej Henneberg[2]
[1] School of Health Sciences University of South Australia, [2] Adelaide Medical School, The University of Adelaide and [3]Magnetic Resonance Imaging centre, Royal Adelaide Hospital.

Introduction

Stable perfusion of brain tissues at a high and constant rate is required due to high metabolic demands of the brain, while at the same time the high amplitude of pressure waves need to be distributed. The blood vessels supplying the brain come from a small set of closely related arteries located at the base of three embryonic brain vesicles (1,2). These exceptional circumstances are reflected in the structure of the origins of the arterial supply to the brain, an anastomotic cerebral basal arterial network from which all major arteries branch from. The anterior portion of the cerebral arterial network, the circulus arteriosus cerebri (CAC), was first described by a Paduan anatomist Julius Casserius (1552-1616), and subsequently by Thomas Willis (1621-1675) (3, 4, 5-8). Traditionally, the role of the communicating arteries has been considered to serve for collateral circulation(3, 4). However, some researchers suggest that the anterior component of cerebral basal arterial network (CBAN) serves to limit peak systolic pressures propagating into cerebral arteries. Variation of the cerebral arterial network structure and arrangement, is associated with aneurysm and cerebrovascular accident with increasing mortality and morbidity rates worldwide (9-11, 3, 9-21, 13, 14, 22, 23, 24, 25). Pressure gradient across the arteries in which the blood flows is inversely proportional to the cross sectional areas of the vessels(11, 24, 25-27). Therefore, it may be valuable to investigate cross sectional areas of all components of the cerebral basal arterial network and pressure gradients across the cerebral basal arterial network. The primary aim of this study was to investigate the cross sectional area of incoming, communicating and outgoing cerebral basal arteries and discuss their role in cerebral arterial circulation.

Materials and methods

- Ethics approval- (No. H-2014-176)
- 51 brains, male +female
- Complete arterial components.
- External diameters of the arteries measured (Figures 1 and 2)
- Cross-sectional area of arterial components calculated
- Excel 2013 and SPSS used for data analysis
- Descriptive statistics and correlation procedures were used
- Assumed significant probability (P) value was set at ≤0.05

Incoming arteries: (Figures 1 and 2)
Cerebral part- right and left internal carotid artery (ICA)- at the level of optic chiasm
Distal portion of the right and left cranial vertebral artery (VA) - just proximal to the unification
Outgoing arteries (Figures 1 and 2):
The most proximal portion of second part (A2) of right and left anterior cerebral artery (ACA)
The most proximal portion of the first part (M1) of right and left middle cerebral artery (MCA)
The most proximal portion of the second part (P2) of right and left posterior cerebral arteries (PCA)
Communicating arteries (Figures 1 and 2):
The mid-point of anterior communicating artery (AComA)
The mid-point of the right and left posterior communicating arteries (PComA)

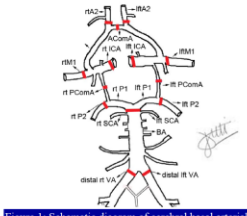


Figure 1: Schematic diagram of cerebral basal arterial network indicating measurement sites of vessel diameter

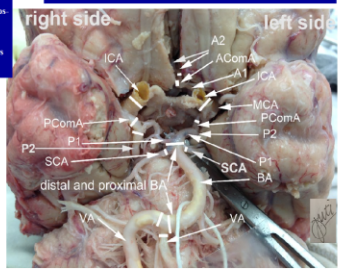


Figure 2: Base of the brain, showing cerebral basal arterial network. and measurements sites of vessel diameter.

Results

The average summarised cross-sectional areas of inflow arteries (51.43 mm^2) were significantly bigger than those of the major outflow arteries (37.76 mm^2) but smaller than the combined cross-sectional areas of connecting (25.33 mm^2) and outflow arteries (37.76 mm^2). The increase in the pressure in the cerebral basal arterial network as a result of the smaller cross-sectional area in major outflow vessels compared to the greater inflow cross-sectional area, should be dampened to and from those communicating blood vessels. This is the area where communicating arteries play a crucial role to transmit the pressure around and make sure to let blood flow in a continuous way during the cardiac cycle without hampering feeding the brain parenchyma.

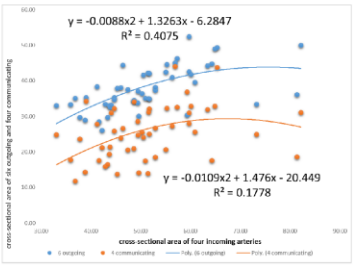


Figure 3- Correlations among four incoming, six outgoing and four communicating cerebral arterial components, X and Y axes show the cross-sectional area in squared millimetres (mm^2).

Table 1: Descriptive statistics

	N	Mean	Std. Deviation	Std. Error Mean
4 incoming	51	51.4	10.5	1.4
6 outgoing	51	37.7	6.0	.8
4 incoming	51	51.4	10.5	1.4
4 communicating	51	25.3	7.5	1.0
4 outgoing +communicating	51	63.0	11.6	1.6

Table 2: Correlations between the cross-section of four incoming, six outgoing and four communicating cerebral arterial components

	N	Correlation	Sig.
4 incoming & 6 outgoing	51	.594	.000
4 incoming & 4 communicating	51	.350	.012
4 incoming & outgoing +communicating	51	.535	.000
4 communicating & 4 incoming	51	.350	.012
4 communicating & 6 outgoing	51	.465	.001

Conclusion

Differences in cross-sectional areas of incoming and outgoing arteries, together with cross-sectional area of communicating arteries could provide a mechanism for lowering peak pressures of arterial blood perfusion of the brain, thus lowering the incidence of aneurysms

References

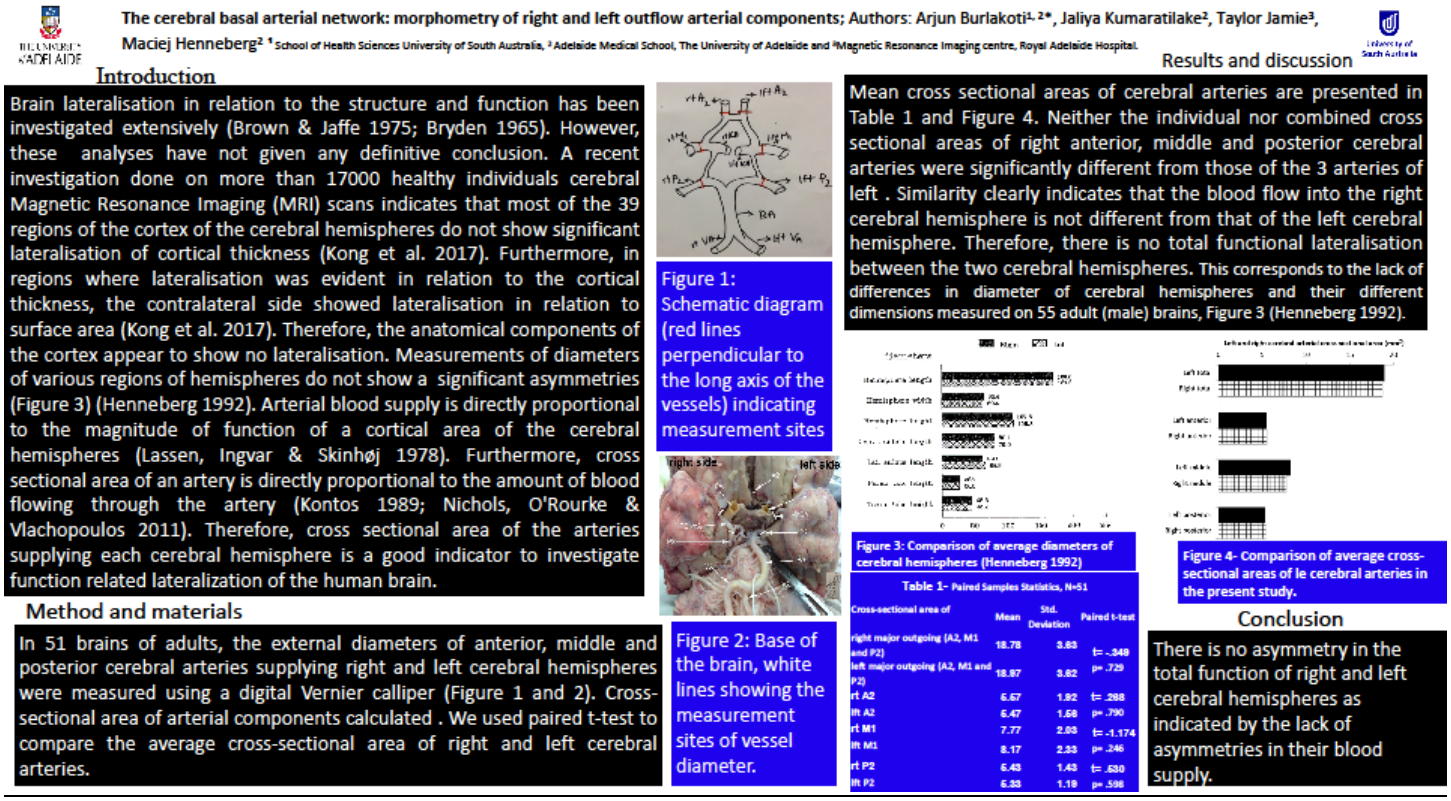
Reference

(ANZACA), AaNZaoca 2016, 'Meeting abstracts: Abstracts presented at the Australian and New Zealand association of clinical anatomists (ANZACA) 12th annual meeting “anatomy: virtual or real,” 9th-11th December 2015, Adelaide, South Australia', Clinical Anatomy, vol. 29, no. 2, pp. 217-236.

2 Conference two

The second conference poster on "**Asymmetries of total arterial supply of cerebral hemispheres do not exist"** was **presented by Arjun Burlakoti** at the 7th Australian Cognitive Neuroscience Society, Conference Adelaide, South Australia, 23-26 November 2017. Arjun Burlakoti[1,2], Jaliya Kumaratilake[2], David J Taylor[3], Maciej Henneberg[2]. [1]University of South Australia; [2]University of Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia). This conference provided me a platform to discuss my PhD research findings on the cerebral hemispheric symmetricity in relation to the differences in size of cerebral arteries supplying the right and left cerebral hemispheres. I presented my findings as "neither the individual nor the combined cross-sectional areas of right cerebral arteries were significantly different from those of the left and there is no total functional lateralisation between the two cerebral hemispheres". Medical researchers and health professionals from different facets of health were interested on the findings and provided me constructive feedback.

Poster PDF - Please see below the second poster related to this thesis presented in the conference



3 Conference three

The third conference poster titled "**Role of cerebral basal arterial network in modulating arterial pressure in the brain and clinical consequences of anatomical variations in the cerebral arterial circle"** was **presented by Arjun Burlakoti** at Florey Postgraduate Research Conference, University of Adelaide, National Wine Centre, South Australia, Australia on 24th of September 2019. Arjun Burlakoti[1,2], Jaliya Kumaratilake[2], David J Taylor[3], Maciej Henneberg[2]. The role of cerebral basal arterial network in modulating arterial pressure in the brain and clinical consequences of anatomical variations in the cerebral arterial circle. [1]University of South Australia; [2]University of Adelaide, Adelaide, Australia; Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia.

Poster PDF - Please see below the third poster related to this thesis presented in the conference

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The role of cerebral basal arterial network in modulating arterial pressure in the brain and clinical consequences of anatomical variations in the cerebral arterial circle; Authors:

Arjun Burlakoti[1,2*], Juliya Kumarotilake[1], Taylor Jamie[1], Maciej Henneberg[1] [1] School of Health Sciences University of South Australia, [2] Adelaide Medical School, The University of Adelaide and [3]Magnetic Resonance Imaging centre, Royal Adelaide Hospital.

University of South Australia

Introduction

The aim of this research project was to study whether the size asymmetry of the first segment of the anterior cerebral artery predicts the risk of anterior communicating arterial complex aneurysm.

Method and materials

-The internal diameters of first segments of right and left anterior cerebral arteries were determined at specific sites and cross-sectional areas calculated on 163 cerebral Computed Tomography (CT) and Magnetic Resonance (MR) scans of adult patients of both sexes.
-Positions, presence or absence of anterior communicating artery complex aneurysms were noted.
-The asymmetricity calculated

Figure 1: Diagram (white lines perpendicular to the long axis of the vessels) indicating measurement sites, Magnetic Resonance Angiography

Figure 2: Figure showing the sites of arterial diameter measurement in cerebral arterial 3D Reconstructive Computed Tomography Angiography (CTA), red lines showing the measurement sites of vessel diameters, A1 ACA= the first part of anterior cerebral artery and MCA= the middle cerebral artery.

Results and discussion

The risk of having anterior communicating artery complex aneurysms is 44 % and more than 80 % higher in the presence of asymmetric index between 25 to 50 and more than 50 respectively. Adult population (>18 years of age) with more than 50% asymmetric first segment of anterior cerebral arteries develop anterior communicating artery complex aneurysms 27 times more than those with asymmetricity less than 5%.

Table: Probability (out of 1.00) to have anterior communicating artery complex aneurysms (with the history of cerebral aneurysms elsewhere) in sliding scale has been presented. Risk and odds ratio of developing aneurysms have been tabulated when the asymmetry of the right and left first part of anterior cerebral artery varies, n=163, A1= first segment of the anterior cerebral artery, AComA= anterior communicating artery

A1s asymmetry (index)	**AComA complex aneurysm**		**% Chance/ Risk**	**Odds ratio against <5%**	**Chi-square (Asymptotic Significance)**
	Yes	No			P <
<5	2	47	4.1	0.1	0.001
5 to <25	7	*69*	*9.2*	*0.3*	0.005
25 to <50	*10*	*13*	*43.5*	*4.4*	0.003
≥50	12	3	80	27.2	0.0001
Sum	31	132			

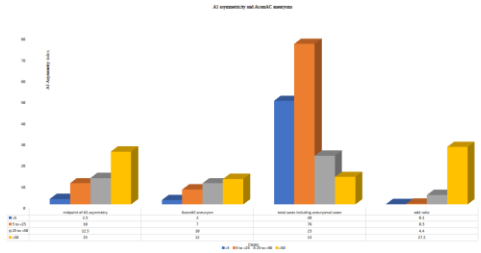


Figure : Bar diagram showing the A1 asymmetricity, the presence of AcomAC aneurysms and the odd ratio: A1= first part of anterior cerebral artery, AcomAC= anterior communicating artery complex

Conclusion

The size asymmetry of anterior cerebral arteries is a good predictor of anterior communicating artery complex aneurysms.

CRICOS PROVIDER NUMBER 00123M

4 Conference four

The 4th conference poster related to this research, titled, **"Well dampened blood pressure waves passing through the posterior cerebral artery prevent development of aneurysms"**, was **presented by Arjun Burlakoti** at Australian and New Zealand Association of Clinical Anatomists (ANZACA), 4-6 December 2019, University of Western Australia, Perth, Australia 2019. Arjun Burlakoti[1,2], Jaliya Kumaratilake[2], David J Taylor[3], Maciej Henneberg[2]. Well dampened blood pressure waves passing through the posterior cerebral artery prevent development of aneurysms. [1]University of South Australia; [2]University of Adelaide, Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia). This conference has granted me another opportunity to highlight an interesting study that we conducted on exploring perfusion pressure dampening function of CBAN on human brain and the delegates seemed to be interested on research findings. The size asymmetry of anterior cerebral arteries is a good predictor of anterior communicating artery complex aneurysms.

Poster PDF - Please see below the fourth poster related to this thesis presented in the conference

"The connecting segments of the cerebral basal arterial network act as pressure smoothening mechanism."

The pressure dampening mechanism proximal to the second segment of posterior cerebral artery favours a significant reduction in the risk of development of posterior cerebral artery aneurysms.

Well dampened blood pressure waves passing through the posterior cerebral artery prevent development of aneurysms

Arjun Burlakoti[1, 2]*, Jaliya Kumaratilake[2], Jamie Taylor[3], Maciej Henneberg[2]
[1] School of Health Sciences University of South Australia, [2] Adelaide Medical School, The University of Adelaide and [3]Magnetic Resonance Imaging centre, Royal Adelaide Hospital.

INTRODUCTION

- Posterior cerebral artery (PCA) aneurysms are rare [1,2]
- The PCA has been divided into four segments.[2,3]
- Aneurysms are not common in PCA (<1% of all intracranial aneurysms) and even less commonly found distal to the second segment of PCA (P2) segment.[1,2,4]
- The aim was to determine the effects of size differences between the right and left first segment of the PCAs (P1) and the posterior communicating arteries (PcomA) in causing aneurysm distal to the second part of the PCA.

METHODS

- N=97 (male= 39, female= 58).
- Cerebral Computed Tomography Angiography (CTA).
- Diameters measured perpendicular to the long axis of the vessels- bilateral P1 and P2 and PcomA
- Calculated P1/P2 and PcomA/P2 ratios.
- Relationships determined
- Positions and presence or absence of PCA aneurysms and aneurysms elsewhere were noted.

RESULTS AND DISCUSSION

- A significant inverse relationship between right and left PcomA/P2 ratio and P1/P2 ratio was found (n=98, r= -0.32, p<0.05 and r=-0.42, p<0.05 respectively).
- When one of the input arteries was smaller, the other was larger and maintained a smooth blood flow into the posterior cerebral artery and reduced pressure fluctuations.
- Aneurysms were noted in multiple locations, Aneurysms were noted in various locations, around right middle cerebral artery (N= 26), right internal carotid artery (N= 12), left middle cerebral artery (N= 17), left internal carotid artery (N= 5), anterior communicating artery complex (N= 21) and vertebrobasilar region (N= 7).
- No aneurysm was detected distal to P2 of PCA.
- The connecting segments of the cerebral basal arterial network act as pressure smoothening mechanism.[5-7]
- Pressure waves are well dampened before reaching the second part of PCA bilaterally preventing the development of aneurysms.

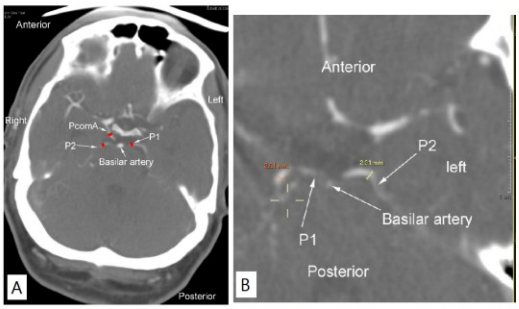
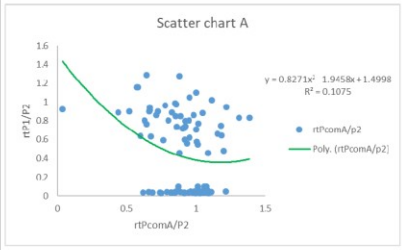
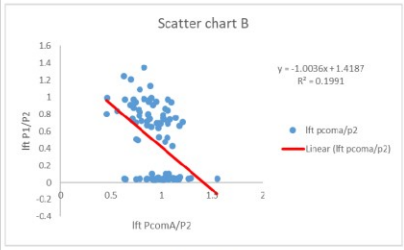


Figure 1: A) Axial Computed Tomography Angiography (red lines perpendicular to the long axis of the vessels) indicate measurement sites, PcomA= posterior communicating artery, P1= first part of posterior cerebral artery, P2= 2nd part of posterior cerebral artery.
B) Axial Computed Tomography Angiography (enlarged view), yellow and red lines showing the measurement sites of P2 diameter, P1= first part of posterior cerebral artery, P2= 2nd part of posterior cerebral artery





Scatter chart A and chart B- Relationship between left and right PcomA/P2 and P1/P2 ratio. PcomA= posterior communicating artery, P1= first part of posterior cerebral artery, P2= 2nd part of posterior cerebral artery, rt= right, lft= left

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1. Drake CG, Amacher A. Aneurysms of the posterior cerebral artery. J Neurosurg 1969; 30(4): 468-74.
2. Ciceri EF, Klucznik RP, Grossman RG, Rose JE, Mawad ME. Aneurysms of the posterior cerebral artery: classification and endovascular treatment. American journal of neuroradiology 2001; 22(1): 27-34.
3. eal AA, Rhoton AL. Microsurgical anatomy of the posterior cerebral artery. J Neurosurg 1978; 48(4): 534-59.
4. Pia H, Fontana H. Aneurysms of the posterior cerebral artery. Acta Neurochir (Wien) 1977; 38(1-2): 13-35.
5.Burlakoti A, Kumaratilake J, Taylor J, Massy-Westropp N, Henneberg M. The cerebral basal arterial network: morphometry of inflow and outflow components. J Anat 2017; 230(6): 833-41.
6. Vrselja Z, Brkic H, Mrdenovic S, Radic R, Curic G. Function of circle of Willis. J Cereb Blood Flow Metab 2014; 34(4): 578-84.
7. Alastruey J, Parker KH, Peiro J, Byrd SM, Sherwin SJ. Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. Journal of biomechanics 2007; 40(8): 1794-805.

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5 South Australian Anatomy Practice Interest group seminar presentation

I **(Arjun Burlakoti)** delivered an oral presentation at South Australian Anatomy Practice Interest group meeting on 14th of April 2016. Title, **"Circulus arteriosus cerebri and vertebrobasilar arterial system- research updates".** Arjun Burlakoti[1,2*], Jaliya Kumaratilake[2], David J Taylor[3], Maciej Henneberg[2]. [*]corresponding author, [1]University of South Australia; [2]University of Adelaide, Adelaide, Australia; Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia.

This anatomy expert group meeting granted me an invaluable platform to expose my initial findings related to this research project on exploring peak systolic pressure dampening function of cerebral basal arterial network (CBAN) on human brain and received constructive professional feedback.

6 Australasian Nepalese Medical and Dental Association annual meeting

I **(Arjun Burlakoti)** delivered an oral presentation at fifth Australasian Nepalese Medical and Dental Association (ANMDA), Conference in Brisbane, Queensland, Australia on 30 of September 2019. Title, **"Relationship of the most severe types of the cerebral vascular accident to the variations of the cerebral basal arterial network (CBAN)"**. Arjun Burlakoti[1,2*], Jaliya Kumaratilake[2], David J Taylor[3], Maciej Henneberg[2]. [*]corresponding author, [1]University of South Australia; [2]University of Adelaide, Adelaide, Australia; Adelaide, Australia; [3]Royal Adelaide Hospital, SA Medical Imaging, Adelaide, Australia.

Chapter 8: Thesis summary

Cerebral aneurysms could compress on the brain surface, or cranial nerves and nearby blood vessels, creating serious health problems, and even rupture leading to haemorrhagic stroke. This PhD studied inflowing, communicating, and outflowing components of cerebral basal arterial network (CBAN) from 217 brains which included 51 donated human brains and cerebral angiograms of 166 hospital-based patients.

The study showed and quantified that there is a relationship between occurrence of aneurysms and the variations (including asymmetries) in the sizes of arteries forming the CBAN which supplies the arterial blood to the brain. Furthermore, the study measured the quantitative relationship among the different components of CBAN.

The observation of variations (including asymmetries) of the sizes of different segments of CBAN allows to predict patients that are at risk of having cerebral aneurysms and require regular follow up clinical appointments. This study can eventually contribute to reducing the burden of stroke on the health system.

Chapter 9: Future directions

Future investigations are needed measuring and recording the rate of cerebral blood flow, and the fluctuation in peak systolic arterial pressure in the presence of asymmetric and variant segments of cerebral basal arterial network and the development of aneurysms.

Appendix 1: Please see below additional peer reviewed and published journal articles by me (Arjun Burlakoti)

Burlakoti, A, Westropp, NM- & Wechalekar, H 2013, 'Variant third and fourth lumbrical muscles of the left hand', International Journal of Anatomical Variations, vol. 6, p. 3.

Burlakoti, A & Massy-Westropp, N 2015, 'Bilateral variant thyroid arteries', International Journal of Anatomical Variations, vol. 8, pp. 43-46.

Burlakoti, A, Lee, J & Massy-Westropp, N 2016, 'An unusual presentation of tibialis anterior', Int J Anat Var (IJAV), vol. 9, pp. 1-2.

Abbas, B, **Burlakoti, A**, Westropp, N & Wechalekar, H 2017, 'The existence of an additional extensor of the little toe arising from the plantar surface of the calcaneus', Int J Anat Var Vol, vol. 10, no. 3, p. 37.

Massy-Westropp, N, Giles, E, Dantu, R, Wechalekar, H & **Burlakoti, A** 2019, 'Developing and evaluating virtual anatomy resources for teaching allied health disciplines', Research in Learning Technology, vol. 27. Link: https://journal.alt.ac.uk/index.php/rlt/article/view/2125

Appendix 2: Three-minute (3 - MT) thesis participation

I (Arjun Burlakoti) successfully presented the 3 - MT thesis twice (August 2017 and 2019) in three-minute timeframe during the university wide 3 - MT thesis competition and received constructive feedback on my presentation (see below PDF attached).

Presentation details

Full title of presentation = Relationship of stroke to variations of brain arterial network

Presenter name = Arjun Burlakoti

Presenter's University = The University of Adelaide, South Australia

Presenter's School = Adelaide Medical School, School of Health and Medical Sciences

Presenter's department = Anatomy and Pathology

Time and date = 1:25 pm, 21st August 2019

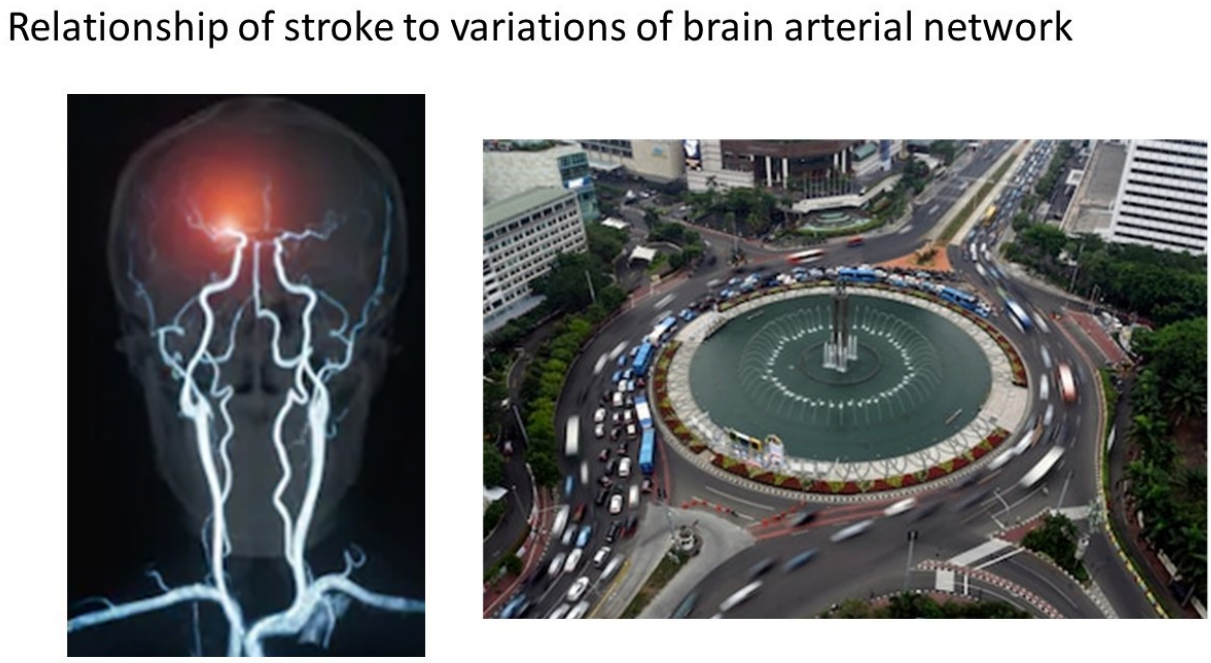
Supervisory team

Professor Dr Maciej Henneberg; e-mail - maciej.henneberg@adelaide.edu.au

Dr Jaliya Kumaratilake; e-mail - Jaliya.kumaratilake@adelaide.edu.au

Dr Jamie Taylor; e-mail - Jamie.Taylor@health.sa.gov.au

3 - MT Presented slide



1,2, https://pixabay.com/

References

1. Burlakoti A, Kumaratilake J, Taylor J, Massy-Westropp N, Henneberg M. The cerebral basal arterial network: morphometry of inflow and outflow components. J Anat 2017; 230(6): 833-41.

2. Burlakoti A, Kumaratilake J, Taylor DJ, Henneberg M. Quantifying asymmetry of anterior cerebral arteries as a predictor of anterior communicating artery complex aneurysm. BMJ Surgery, Interventions, & Health Technologies 2020; 2(1): e000059.

Feedback on 3 - MT received (below)

3MT® THREE MINUTE THESIS
FOUNDED BY THE UNIVERSITY OF QUEENSLAND

Relationship of stroke to variations of brain arterial network

PRESENTER: Dr Arjun Burlakoti

SCHOOL/INSTITUTE/FACULTY: Adelaide Medical School

UNIVERSITY: The University of Adelaide

3MT TITLE: Relationship of stroke to variations of brain arterial network

CATEGORY 1: COMPREHENSION AND CONTENT

Strong 7 6 (5) 4 3 2 1 Weak

(Y) / N	Did the presentation provide an understanding of the background and significance to the research question being addressed while explaining terminology and avoiding jargon?
(Y) / N	Did the presentation clearly describe the impact and/or results of the research, including conclusions and outcomes?
(Y) / N	Did the presentation follow a clear and logical sequence?
(Y) / N	Was the thesis topic, research significance, results/impact and outcomes communicated in language appropriate to a non-specialist audience?
(Y) / N	Did the presenter spend adequate time on each element of their presentation - or did they elaborate for too long on one aspect or was the presentation rushed?

CATEGORY 2: ENGAGEMENT AND COMMUNICATION

Strong 7 (6) 5 4 3 2 1 Weak

(Y) / N	Did the oration make the audience want to know more?
(Y) / N	Was the presenter careful not to trivialise or generalise their research?
(Y) / N	Did the presenter convey enthusiasm for their research?
(Y) / N	Did the presenter capture and maintain their audience's attention?
(Y) / N	Did the speaker have sufficient stage presence, eye contact and vocal range; maintain a steady pace, and have a confident stance?
(Y) / N	Did the PowerPoint slide enhance the presentation - was it clear, legible, and concise?

TOTAL SCORE

Category 1 + Category 2 = 11 / 14

ADDITIONAL NOTES:

Great eye contact & engagement
clearly articulated a complex problem

3MT® THREE MINUTE THESIS
FOUNDED BY THE UNIVERSITY OF QUEENSLAND

Relationship of stroke to variations of brain arterial network

PRESENTER: Dr Arjun Burlakoti

SCHOOL/INSTITUTE/FACULTY: Adelaide Medical School

UNIVERSITY: The University of Adelaide

3MT TITLE: Relationship of stroke to variations of brain arterial network

CATEGORY 1: COMPREHENSION AND CONTENT

Strong 7 (6) 5 4 3 2 1 Weak

(Y)/ N	Did the presentation provide an understanding of the background and significance to the research question being addressed while explaining terminology and avoiding jargon?
(Y) N	Did the presentation clearly describe the impact and/or results of the research, including conclusions and outcomes?
(Y)/ N	Did the presentation follow a clear and logical sequence?
(Y)/ N	Was the thesis topic, research significance, results/impact and outcomes communicated in language appropriate to a non-specialist audience?
(Y)/N	Did the presenter spend adequate time on each element of their presentation - or did they elaborate for too long on one aspect or was the presentation rushed?

CATEGORY 2: ENGAGEMENT AND COMMUNICATION

Strong 7 (6) 5 4 3 2 1 Weak

(Y)/ N	Did the oration make the audience want to know more?
(Y)/ N	Was the presenter careful not to trivialise or generalise their research?
(Y)/ N	Did the presenter convey enthusiasm for their research?
(Y)/ N	Did the presenter capture and maintain their audience's attention?
(Y)/ N	Did the speaker have sufficient stage presence, eye contact and vocal range; maintain a steady pace, and have a confident stance?
(Y)/ N	Did the PowerPoint slide enhance the presentation - was it clear, legible, and concise?

TOTAL SCORE

Category 1 + Category 2 = 12 / 14

ADDITIONAL NOTES:

Logical flow from the start. Ballooning - good term.
Not sure about "intact wound sac".
Engaging style. Good examples - giving the percentages, 27 times
Just work on your - start a little bit.

3MT® THREE MINUTE THESIS
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Relationship of stroke to variations of brain arterial network

PRESENTER: Dr Arjun Burlakoti

SCHOOL/INSTITUTE/FACULTY: Adelaide Medical School

UNIVERSITY: The University of Adelaide

3MT TITLE: Relationship of stroke to variations of brain arterial network

CATEGORY 1: COMPREHENSION AND CONTENT

Strong 7 6 (5) 4 3 2 1 Weak

(Y) / N	Did the presentation provide an understanding of the background and significance to the research question being addressed while explaining terminology and avoiding jargon?
(Y) / N	Did the presentation clearly describe the impact and/or results of the research, including conclusions and outcomes?
(Y) N	Did the presentation follow a clear and logical sequence?
Y / N	Was the thesis topic, research significance, results/impact and outcomes communicated in language appropriate to a non-specialist audience?
Y / N	Did the presenter spend adequate time on each element of their presentation - or did they elaborate for too long on one aspect or was the presentation rushed? -> consequences not clear

CATEGORY 2: ENGAGEMENT AND COMMUNICATION

Strong 7 (6) 5 4 3 2 1 Weak

(Y) / N	Did the oration make the audience want to know more?
(Y) / N	Was the presenter careful not to trivialise or generalise their research?
(Y) N	Did the presenter convey enthusiasm for their research?
(Y) / N	Did the presenter capture and maintain their audience's attention?
(Y) / N	Did the speaker have sufficient stage presence, eye contact and vocal range; maintain a steady pace, and have a confident stance?
(Y) / N	Did the PowerPoint slide enhance the presentation - was it clear, legible, and concise?

TOTAL SCORE

Category 1 + Category 2 = 11 / 14

ADDITIONAL NOTES:

* Suggest outcomes that could happen.

3MT® THREE MINUTE THESIS
FOUNDED BY THE UNIVERSITY OF QUEENSLAND

Relationship of stroke to variations of brain arterial network

PRESENTER: Dr Arjun Burlakoti

SCHOOL/INSTITUTE/FACULTY: Adelaide Medical School

UNIVERSITY: The University of Adelaide

3MT TITLE: Relationship of stroke to variations of brain arterial network

CATEGORY 1: COMPREHENSION AND CONTENT

Strong 7 6 (5) 4 3 2 1 Weak

Y / (N)	Did the presentation provide an understanding of the background and significance to the research question being addressed while explaining terminology and avoiding jargon?
(Y) / N	Did the presentation clearly describe the impact and/or results of the research, including conclusions and outcomes?
(Y) / N	Did the presentation follow a clear and logical sequence?
(Y) / N	Was the thesis topic, research significance, results/impact and outcomes communicated in language appropriate to a non-specialist audience?
(Y) / N	Did the presenter spend adequate time on each element of their presentation - or did they elaborate for too long on one aspect or was the presentation rushed?

CATEGORY 2: ENGAGEMENT AND COMMUNICATION

Strong 7 (6) 5 4 3 2 1 Weak

(Y) / N	Did the oration make the audience want to know more?
(Y) / N	Was the presenter careful not to trivialise or generalise their research?
(Y) / N	Did the presenter convey enthusiasm for their research?
(Y) / N	Did the presenter capture and maintain their audience's attention?
(Y) / N	Did the speaker have sufficient stage presence, eye contact and vocal range; maintain a steady pace, and have a confident stance?
(Y) / N	Did the PowerPoint slide enhance the presentation - was it clear, legible, and concise?

TOTAL SCORE

Category 1 + Category 2 = 11 / 14

ADDITIONAL NOTES: great! metaphors a little incomplete.

Appendix 3: Professional membership and affiliation

Member of the Australian and New Zealand Association of Clinical Anatomists (ANZACA) - (2015 to ongoing).

Appendix 4: Award and recognition

Academic staff of the year 2018, Division of Health Sciences, University of South Australia:

I was the recipient of the "2018 Academic Staff of the year Recognition Award, page 6 in the newsletter" announced by former Pro-Vice Chancellor (Division of Health) Professor Bob Vink, from the University of South Australia (UniSA), Division of Health Sciences at the 'Celebrating Success Function'.

Former Head of School, School of Health Sciences, Professor Roger Eston (present Executive Dean, UniSA Allied Health and Human Performance) and colleagues were very delighted that I had received this lovely recognition from my peers in the Division of Health Sciences.

Ten years of Staff Service Award to the University of South Australia:

I was one of the lecturers at The University of South Australia, who received a '10-Year Staff Service Award' in December 2020.