

Variations in the *Circulus Arteriosus Cerebri* in a South African Cadaveric Sample

by

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GRLJES001

Dissertation submitted to the University of Cape Town for the degree of
Master of Science (Applied Anatomy)

in the Division of Clinical Anatomy and Biological Anthropology

Department of Human Biology

Faculty of Health Sciences

University of Cape Town

Date of Submission: 10 February 2024

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Acknowledgements

I would like to express my sincere thanks to the following people for helping make the completion of this thesis possible.

To my ‘dream team’ supervisors, Emeritus Professor Graham Louw and Dr Kentse Mpolokeng, thank you for your hours of support, advice and reviewing. Thank you for challenging me throughout the study and sharing some of your vast wisdom and experience with me. I learnt much more than this thesis will reflect and am extremely grateful for all that I learnt.

To my extremely supportive family who helped keep me motivated when things got tough and provided endless support. Whether I asked you to proof-read, needed to talk, or a lift to campus because I was too tired to drive. Thank you, Dad, Mom, Ian, Nanna and Trace. This is as much my thesis as it is yours. To my dedicated partner, Ian, for your endless support, answering my statistics questions and allowing me to bounce ideas off you.

To those that offered advice and the use of equipment. Dr Supratim Biswas and Dr Ashwin Isaacs for lending us glassware. Ashwin, for your advice about using ImageJ effectively. Dr Sudesh Sivarasu, for your advice with imaging and for lending us a 3D handheld scanner. Thulisa and Nuraan for the use of the dissection microscope.

To the technical staff of HUB for the many hours of support and assistance. Thank you, Megan Petersen, Shirees Benjamin, Michael Cassar, Jacques Jacobs and Wilbur Van Niekerk for being so patient and assisting wherever possible: from helping remove brains to providing dissection equipment and the many chats that kept me motivated in the dissection halls. Your assistance is hugely appreciated.

To all those that reviewed my thesis at various stages. Dr Geney Gunston and Jeshika Luckrajh for taking time to be my internal reviewers for the proposal. To each member of CABA who attended my proposal presentation and to each member of the DRC, CRGC and HREC who reviewed my proposal and ensured my project met all the ethical requirements. I appreciate your time and input.

To all those that were involved from the Radiology Department at Groote Schuur Hospital. Professor Moosa for giving me access to the software, to Joshua Anirudhe for training me on the PACs system and Dr Robyn Wessels for your assistance with the images.

To all the fellow postgraduate students in HUB that helped keep me motivated and provided support in various ways. The comradery among students of the department made my masters experience easier and more memorable. In particular, thank you to Mbali Madolo for sharing a sample with me and assisting with some of the photographs, and Cailyn McFarlane, for your overall support and assistance with data collection.

Thank you to the University of Cape Town for funding my master's and providing me with the opportunity to complete this research.

Finally, thank you to the body donors and their families. This research would not be possible without our 'silent teachers'. I am deeply humbled and grateful that I was provided the opportunity to learn from the body donors of 2022 and 2023.

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List of abbreviations

Abbreviation	Meaning
ACA	Anterior cerebral artery
AcoA	Anterior communicating artery
A1	Pre-communicating segment of the anterior cerebral artery
A2	Post-communicating segment of the anterior cerebral artery
BA	Basilar artery
Body ID	Body identification number
CAC	Circulus arteriosus cerebri
CCA	Common carotid artery
CoW	Circle of Willis
C1	Atlas (first cervical vertebra)
C2	Axis (second cervical vertebra)
C3 - 7	Cervical vertebrae numbers 3 – 7
DRC	Departmental Research Committee
FTP	Fetal-type posterior configuration
fFTP	Full fetal-type posterior configuration
GSH	Groote Schuur Hospital
HUB	Department of Human Biology
HREC	Human Research Ethics Committee
IA	Intracranial aneurysm
ICA	Internal carotid artery
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRP	Magnetic resonance perfusion
n	Sample size or the number of observations
pFTP	Partial fetal-type posterior configuration
PCA	Posterior cerebral artery
PcoA	Posterior communicating artery
PCBAA	Persistent carotid-basilar artery anastomosis
PPOA	Persistent primitive olfactory artery
PTA	Persistent trigeminal artery
P1	Pre-communicating segment of the posterior cerebral artery
P2	Post-communicating segment of the posterior cerebral artery
P2A	Anterior portion of the P2 segment of the posterior cerebral artery
P2P	Posterior portion of the P2 segment of the posterior cerebral artery
P3	Quadrigeminal segment of the posterior cerebral artery
P4	Calcarine segment of the posterior cerebral artery
P5	Terminal branch of the posterior cerebral artery
RF pulse	Radiofrequency pulse
SAH	Subarachnoid haemorrhage
SCA	Superior cerebellar artery
sd	Standard deviation
TNP	Third nerve palsy
TOF	Time of flight angiography
T1	Time constant 1

T2	<i>Time constant 2</i>
UCT	<i>University of Cape Town</i>
VA	<i>Vertebral artery</i>
VAH	<i>Vertebral artery hypoplasia</i>
V1	<i>The preforaminal segment of the vertebral arteries</i>
V2	<i>The prevertebral segment of the vertebral arteries</i>
V3	<i>The third segment of the vertebral arteries</i>
V4	<i>The intradural segment of the vertebral arteries</i>
2D	<i>Two-dimensional</i>
3D	<i>Three-dimensional</i>

Glossary of terms

Term	Definition, as used in this study:
Accessory vessels	Additional vessels. These are arteries in the case of the CAC.
Anastomosis	The joining of arteries to form a single artery.
Aneurysm	An unusual outpouching or dilation of the arterial wall.
Aplasia	The absence of an artery.
Asymmetry of the CAC	The left and right sides of the CAC are not uniform owing to a variation being present on one side only.
Atherosclerosis	A medical condition whereby plaques cause arteries to become narrow.
Bifurcation	The division of an artery to form two terminal arteries.
Caudal	Positioned closer to the coccygeal vertebrae (embryology).
Collateral Circulation	Compensatory blood flow through the anterior and posterior communicating arteries.
Contralateral	Opposite side.
Conventional anatomical configuration	The traditional, 'textbook', 'standard' or 'normal' description of the circulus arteriosus cerebri.
Distal	An anatomical directional term meaning further away from the attachment site or midline of the body.
Duplication	There are two of the same arteries.
Fenestration	A vessel that divides into two or more channels that unite distally.
Fixation	Embalming of a deceased body.
Frequency	The number of observations or the percentage of observations.
Full FTP	The P1 segment is absent or hypoplastic and non-patent.
Haemorrhagic stroke	A stroke caused by rupture of a blood vessel with subsequent bleeding.
Hypoplasia	An artery with a very small diameter. In this study a diameter of less than 1mm is hypoplastic.
In vivo	Inside a living organism.
Ipsilateral	Same side.
Ischaemic stroke	A stroke caused by a blockage of one or more arteries resulting in little to no blood supply to a region of the brain.
Localised anaemia	Lack of blood supply to a region.
Partial FTP	The P1 segment is hypoplastic, but still patent.
Patent	An artery in which there is blood flow.
Plexiform	A network of arteries.
Proximal	An anatomical directional term meaning closer to the attachment site or midline of the body.
Rostral	Position closer to the front of the body (embryology).
Stenosis	Narrowing of blood vessels, commonly caused by atherosclerosis.
Thromboembolism	An embolism (blood clot) that has dislodged from an artery wall and enters circulation.
Triplication	The division of an artery to form three terminal arteries.

Sources for definitions: 2, 3, 14, 18, 19, 21, 36, 65, 68, 74.

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Abstract

The *circulus arteriosus cerebri* (CAC) or Circle of Willis is a highly variable arterial system at the base of the brain that allows for collateral blood flow, granting a protective effect during ischaemic events. Owing to variations, it may not compensate sufficiently during such events. Some CAC variations have been associated with aneurysm formation with subsequent rupture and subarachnoid haemorrhage. It is important to know the prevalence of these variations in a population.

This is a cross-sectional, observational and quantitative study approved by the UCT Human Research Ethics Committee (645/2022) and the Cadaver Research Governance Committee (2022/009) in the Department of Human Biology. The brains of 94 bodies were analysed. Patency of hypoplastic arteries was investigated and Fiji® software was used to measure the lengths and diameters of arteries. Brain volumes were compared to arterial lengths and diameters and a correction factor for human variation was determined.

The intact samples (n=40) were classified according to the 5-group system of Ayre *et al.* (2021) and 22.5% of the sample displayed the conventional anatomical pattern. The most common pattern of variation was group 5, comprising 15 different variations not matching the descriptions of groups 1-4. Individual variations were observed (n=64 brains; 81 variations). The most frequent variations were posterior communicating artery hypoplasia (17.3%) and aplasia (14.8%). The anterior communicating artery was the most variable artery (44.4% of individual variations). The narrowest artery was usually the right posterior communicating artery (PcoA) and the artery with the greatest variation in diameter was the left PcoA. Statistically significant associations were found for arterial diameter with age and length with age. Associations that were not statistically significant included variations with age, variations with sex and arterial dimensions with sex. There were too few intracranial aneurysms to perform analyses.

These variations may result in an increased risk and severity of stroke and intracranial aneurysm formation. Knowledge about CAC variations will aid neurosurgeons when planning and executing a range of neurosurgical procedures. There is little published data on this topic in a South African setting and further studies are recommended.

Key words: *circulus arteriosus cerebri*, cerebral arterial circle, Circle of Willis, cerebral arterial anastomosis, cerebral arterial configurations, Circle of Willis configurations, intracranial aneurysms, cerebral collateral circulation, dissection study, radiological study, correction factor for human variation, determining brain volume.

Chapter 1: Introduction

The brain is a metabolically active organ that requires a continuous supply of oxygenated, nutrient-rich blood. As a result, the vasculature supplying the brain is unique¹ and consists of four main arteries: two internal carotid and two vertebral arteries that are joined by a central anastomosis at the base of the brain.² The anastomosis is situated in the subarachnoid space of the interpeduncular fossa and extends anteriorly to a point below the hypothalamus,³⁻⁵ as seen in *Figure 1.1*. This arterial anastomosis has been known about, at least in part, for a very long time. Knowledge of the *circulus arteriosus cerebri* (CAC), more commonly known as the Circle of Willis (CoW), dates to the Greco-Roman Antiquity starting in approximately eighth century BC.⁶ Thomas Willis, whom the CoW is named after, was the first to prepare a complete and detailed description of this arterial system and determine its function and significance in his publication of *De Cerebri Anatome* in 1664.⁶⁻⁸ Although, the CAC has been familiar to people for an extensive period, there is still much to learn about its functioning and anatomy.

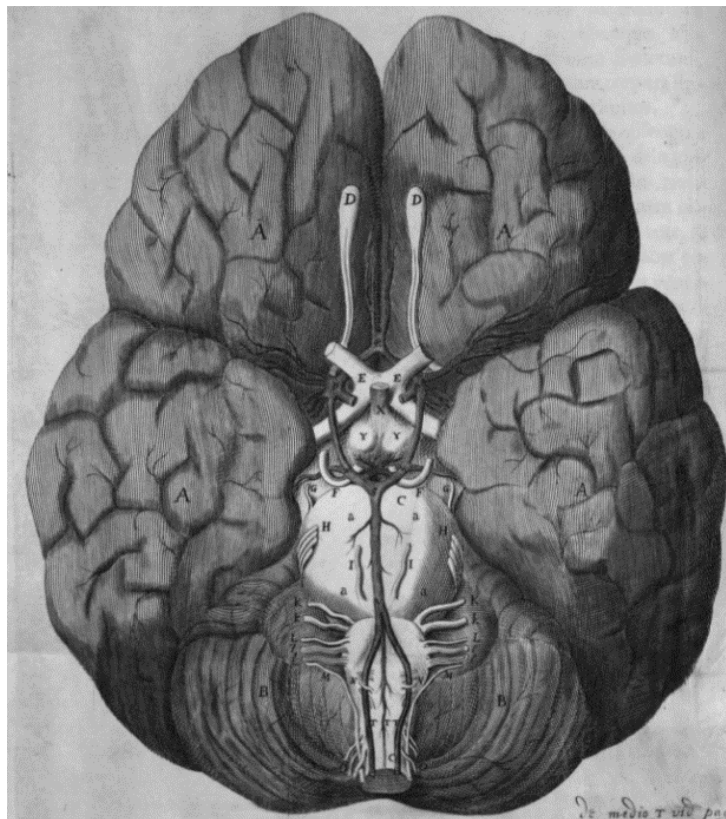


Figure 1.1: An illustration of the *circulus arteriosus cerebri* on the base of the brain, from ‘*De Cerebri Anatome*’ (page 25) published by Thomas Willis in 1664 and illustrated by his associate Christopher Wren. Image reproduced from The Medical History Library*.⁹ Note: The features labelled with letters of the alphabet cover a range of anatomical structures as identified by the original author.

*An open access site.

1.1 Problem Statement

The CAC is highly variable with many studies reporting that less than 50% of their samples had the configuration described by Thomas Willis.^{3,10} Consequently, every individual has a CAC but it may present one or more variations that make it asymmetrical or incomplete. As a result, different configurations arise that deviate from the conventional anatomical configuration. The high prevalence of variations and the inadequately documented prevalence of variations in South Africa is the reason for this study being conducted. Furthermore, variations of the CAC have been associated with aneurysm development, location and rupture^{11,12} with most intracranial aneurysms (IAs) being in the CAC or closely related arteries.¹³ Therefore, it is important to know the prevalence of variations in a specific population and to understand the potential effects of these variations on patients.

1.2 Research aims

To help make this information more available to other researchers and clinicians, the primary aims of this study were to:

1. Determine the prevalence of variations in the *circulus arteriosus cerebri* present in a sample at the University of Cape Town and record those presenting with aneurysms.
2. Examine the impact of brain size/volume on arterial dimensions and implement correction factors to account for human variation.

1.3 Research objectives

To achieve these aims, the following objectives were determined:

1. To observe and record the proportion of *circulus arteriosus cerebri* samples with the conventional anatomical configuration and those with variations present in a cadaveric sample.
2. To observe and record variations present in a radiographic sample.
3. To observe and record the presence of intracranial aneurysms.
4. To measure the length and diameter of *circulus arteriosus cerebri* arteries.
5. Test the patency of hypoplastic arteries and those with unusual branching patterns.
6. Measure the volumes of brains, using a water displacement method, to calculate correction factors to determine if these should be applied to account for human variation in the cadaveric sample.

7. To conduct and present statistical analyses to determine potential associations in the data.
8. Compare data from this study to other local and international studies.

Chapter 2: Literature review

The CAC has a protective function by permitting rapid compensation of blood flow when there is hindered movement of blood through one of the component or closely related arteries.^{8,12} Thus, reducing the effects of an ischaemic event^{2,14,15} by allowing for greater perfusion of the affected regions.^{14,16,17} This collateral pathway is possible because of the presence of the anterior communicating arteries (AcoAs) and posterior communicating arteries (PcoAs) completing the ring-like structure of the CAC and allowing for multi-directional diversion of blood.^{14,18} Therefore, the communicating arteries permit compensatory flow between the anterior circulation (carotid system) and posterior circulation (vertebrobasilar system) of the CAC via the PcoAs and the left and right sides through the AcoA and PcoAs.^{19,20} Thus, the communicating arteries stabilise blood flow through the CAC.⁴ However, collateral circulation is not always able to compensate sufficiently during ischaemic events owing to the diameter of arteries or the number of functional arteries before and after such events.¹⁴ Thus, the collateral function of the CAC relies on the highly variable pattern and dimensions of the anastomosed arteries forming this system.^{5,12}

Whilst, the protective function of the CAC is accepted, it does not fully explain the physiological or day-to-day function of this system. The current prevailing theory is that the CAC minimises the harmful effects of fluctuations in blood flow to the brain, thereby ensuring constant perfusion of the brain.^{8,15} High fluctuations of blood through one or more of the CAC arteries are diverted to reduce the pressure within each component artery and their branches.^{8,15} Accordingly, the CAC passively distributes pressure during stress-scenarios, such as flight or fight scenarios. The pressure within the internal carotid arteries (ICAs) is almost equal to that in the posterior cerebral arteries (PCAs) and there is usually very little blood flow through the PcoAs.²¹ Generally, compensation through the collateral pathway is the only time a larger volume of blood flows through the PcoAs. For example, Muskat *et al.*¹⁵ conducted a haemodynamic experiment whereby cardiovascular stress was induced in young participants. In those that had a complete CAC, there was a greater perfusion of the cerebellum and brain stem resulting from the multidirectional blood flow through the communicating arteries.^{14,18} The multidirectional flow was present owing to pressure changes in these arteries: anteriorly the pressure decreased and posteriorly the pressure increased. Consequently, perfusion of the cerebellum and brain stem was faster and aided the organism in a survival setting.¹⁵ Therefore,

the CAC provides a collateral pathway for blood flow and passively distributes pressure during stress scenarios.

2.1 Conventional anatomical configuration

To understand variations, the textbook or standard configuration of the CAC must be understood. Textbooks and published journal articles describe the conventional anatomical configuration of the CAC as a complete, polygonal ring that displays bilateral symmetry.^{3,6,22} In this description, the four main arteries include a left and right ICA and a left and right vertebral artery (VA).^{3,12,19} Anteriorly, each ICA gives rise to an anteriorly projecting anterior cerebral artery (ACA) and a laterally projecting middle cerebral artery (MCA) on the ipsilateral side.³ The ACAs are connected by the AcoA and posteriorly the two VAs fuse and become known as the basilar artery (BA).³ The BA bifurcates to form the left and right PCAs that project laterally.³ The PcoA, usually originating from the ICA, connects the PCA to the ipsilateral ICA.³ Therefore, a complete ‘ring’ is formed (*Figure 2.1*). Only the first segments of the ACA and PCA, pre-communicating segment of the ACA (A1) and pre-communicating segment of the PCA (P1) segments respectively, form part of the CAC.¹² Thus, the component arteries of the CAC are the ICA, A1, AcoA, PcoA, and the P1.^{5,7}

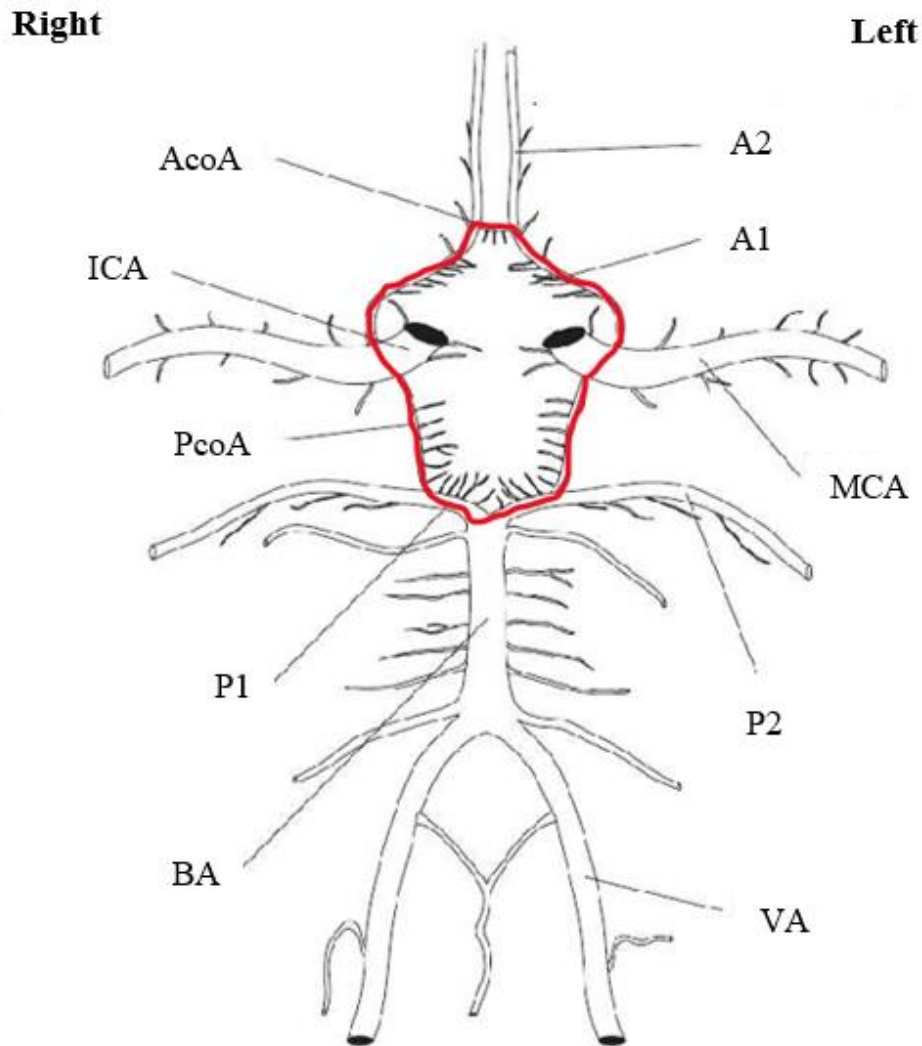


Figure 2.1: An illustration depicting the conventional anatomical configuration of the circulus arteriosus cerebri and closely associated arteries. The circulus arteriosus cerebri is highlighted in red. [AcoA: Anterior communicating artery; ICA: internal carotid artery; PcoA: posterior communicating artery; P1: pre-communicating branch of the PCA; BA: basilar artery; A2: post-communicating branch of the ACA; A1: pre-communicating of the ACA; MCA: middle cerebral artery; P2: post-communicating branch of the PCA]. The image is adapted from Valen-Sendstad et al.²³.

2.1.1 Internal carotid artery

Each ICA arises from the bifurcation of the common carotid artery (CCA) at the level of the fourth cervical vertebra (C4) and projects upwards in the neck to enter the cranial cavity through the carotid canal of the temporal bone,²⁴ as illustrated in *Figure 2.2*.

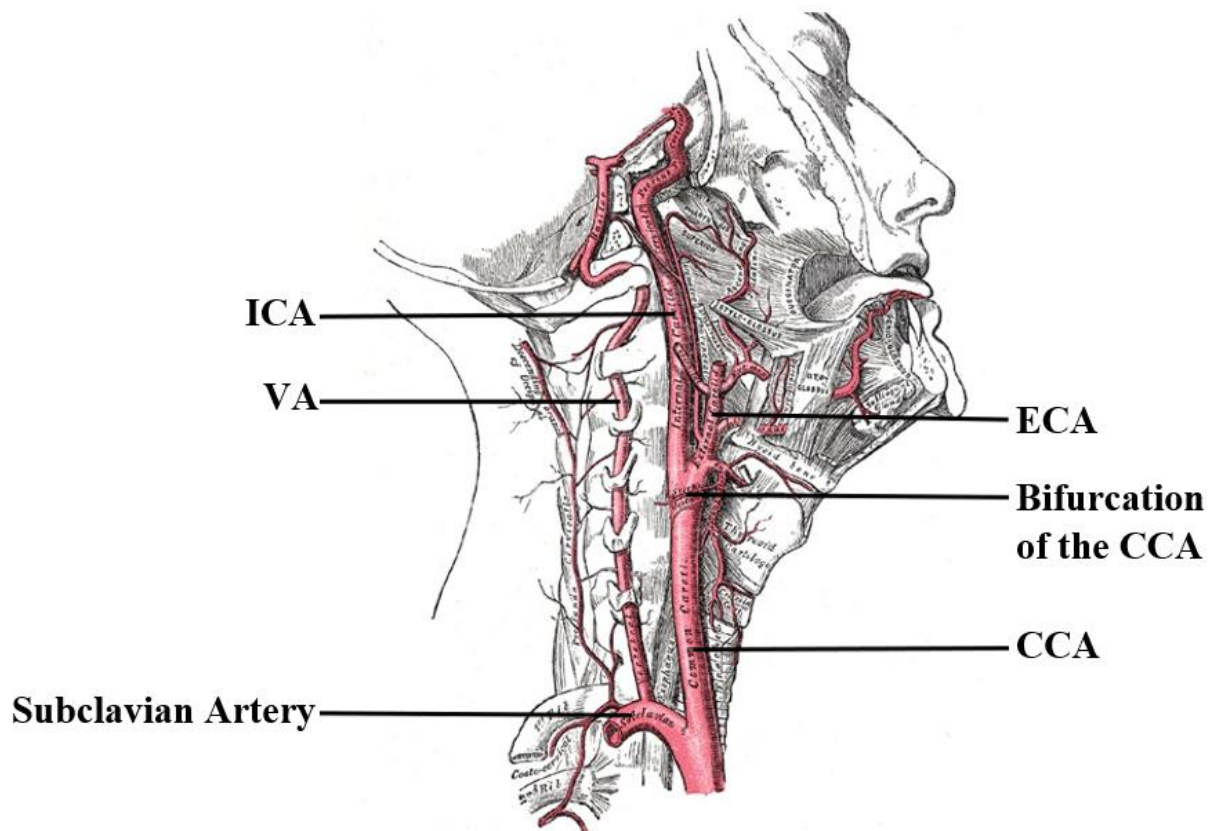


Figure 2.2: An illustration depicting the cervical pathway of the right internal carotid artery from the arch of the aorta to its entry into the cranial cavity. [ICA: internal carotid artery; VA: vertebral artery; ECA: external carotid artery; CCA: common carotid artery]. Image adapted from Jones et al.²⁵.

Through their branches, the ICAs provide 80% of the blood supply to the brain.²¹ The ophthalmic artery originates distal to the cavernous sinus and supplies the eye, internal and external muscles of the eye, lacrimal gland, superior portions of the nose, levator palpebrae superioris muscle and portions of the forehead.²⁴ After giving off the ophthalmic artery, the ICAs bifurcate at the medial border of the lateral fissure,³ which separates the frontal and parietal lobes from the temporal lobe, and gives rise to the ACAs and MCAs.

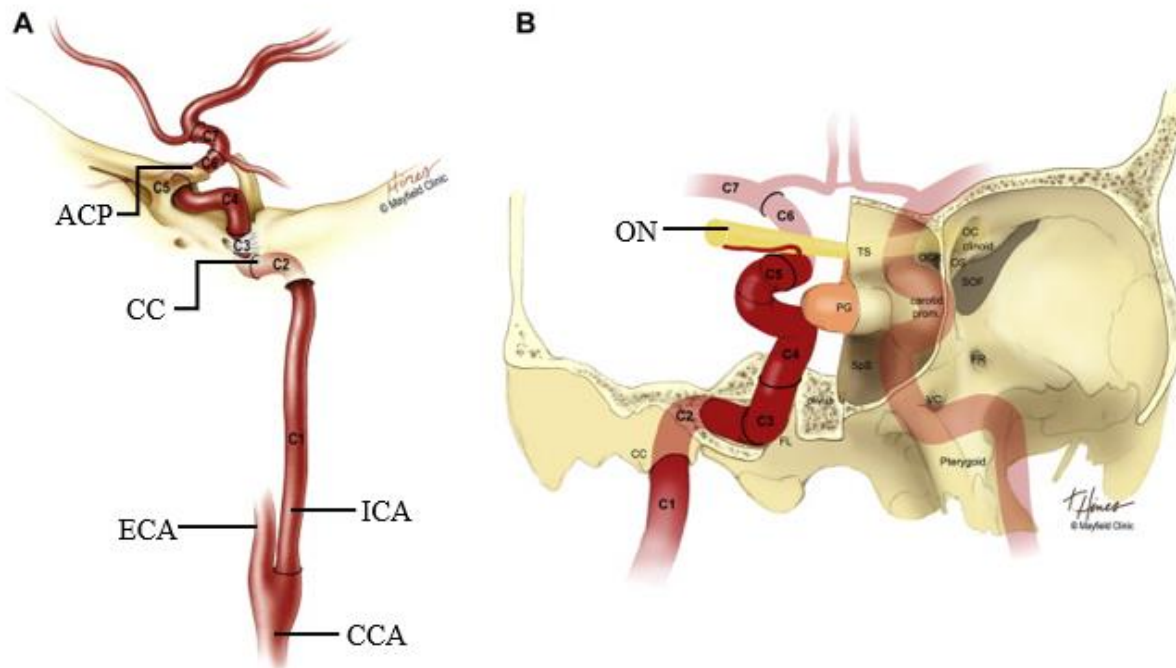


Figure 2.3: An illustration depicting the Bouthillier classification of the seven segments of the internal carotid artery (C1 - C7). A: The course of the internal carotid artery from its origin at the bifurcation of the common carotid artery. B: The intracranial course of the internal carotid artery in greater detail than figure 2.3A. The relative position of each segment to bony structures is shown. [ACP: anterior clinoid process; CC: carotid canal; ECA: external carotid artery; ICA: internal carotid artery; CCA: common carotid artery; ON: optic nerve; C1-7: segments of the ICA; FL: foramen lacerum; FR: foramen rotundum; SOF: superior orbital fissure; OS: optic strut; OC: optic canal TS: tuberculum sellae; PG: pituitary gland; VC: vidian canal; SpS: sphenoid sinus]. Image adapted from Depowell et al.²⁶.

The Bouthillier classification indicates that there are seven ICA segments described according to the region the segment passes through and supplies.²⁴ These segments have been summarised in Table 2.1 and are illustrated in Figure 2.3. Only the C6 and C7 segments are components of the CAC.

Table 2.1: A summary of the seven segments of the internal carotid artery according to the Bouthillier Classification, as laid out by Charlick & Das²⁴.

Segment Name	Arises	Terminates
Cervical (C1)	Bifurcation of CCA	Start of the carotid canal
Petrous (C2)	End of the carotid canal	Posterior border of the foramen lacerum
Lacerum (C3)	Posterior border of the foramen lacerum	Superior border of the petrolingual ligament
Cavernous (C4)	Superior border of the petrolingual ligament	Anterior clinoid process
Clinoid (C5)	Anterior clinoid process	Roof of the cavernous sinus
Ophthalmic (C6)*	Roof of the cavernous sinus	Proximal to the origin of the PcoA
Communicating (C7)*	Proximal to the origin of the PcoA	Bifurcation of the ICA

**Segments of the internal carotid artery that are components of the circulus arteriosus cerebri.*

2.1.2 Middle cerebral artery

The MCAs originate from the bifurcation of the ipsilateral ICA and continue to the lateral sulcus.²⁷ Here they give rise to branches that supply areas of the lateral and inferior frontal lobe, lateral surface of the parietal lobe and lateral surface of the temporal lobe,^{21,24} including the Broca's area, Wernicke's area and the sensory and motor cortex that corresponds to the upper limb and face.²⁴ Other branches supply the insula, head of the caudate nucleus, putamen and globus pallidus²¹. The origin of this artery is seen in *Figure 2.1* and the cortical branches are seen in *Figure 2.4*. The MCAs are closely related to the CAC but do not form one of its component arteries.

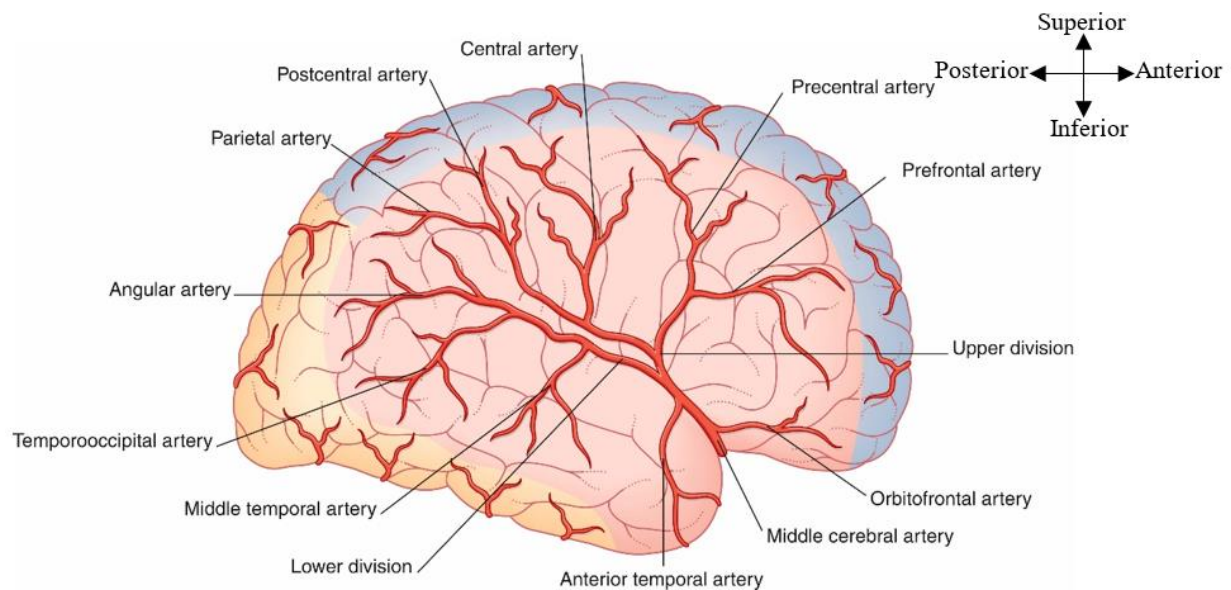


Figure 2.4: A lateral view of the right cerebral hemisphere, where the cortical branches of the middle cerebral artery are visible. The pink area is supplied by branches of the middle cerebral artery. The blue area is supplied by branches of the anterior cerebral artery and the orange area is supplied by the posterior cerebral artery. Image adapted from Mtui & Gruener²⁸.

2.1.3 Anterior cerebral artery

Through branches on the medial and inferior surface of the frontal lobe and medial surface of the parietal lobe (Figure 2.5), the ACAs supply the motor and sensory regions corresponding to the lower limbs,^{21,24,29} the corpus callosum (excluding the splenium), hypothalamus, anterior 2/3 of the cingulate gyrus and other structures therein.^{21,29}

Usually, the left and right ACAs are connected by the AcoA approximately 2 - 3.5mm from their origin.⁷ The A1 segment is from the origin of the ACA to the junction of the ACA with the AcoA,^{5,7} where it continues as the A2 segment. There are different segment schemes for the ACA,²⁹ but for simplicity the three-segment scheme is as follows: the A1 segment passes over the optic nerve and chiasm of the ipsilateral side.²⁹ The A2 segment continues into the interhemispheric fissure at a point anterior to the lamina terminalis.²⁹ The final, or distal segment, courses around the splenium of the corpus callosum and ends in the choroid plexus of the third ventricle.²⁹ The A1 segment forms part of the CAC and is seen in Figures 2.2 and 2.3.

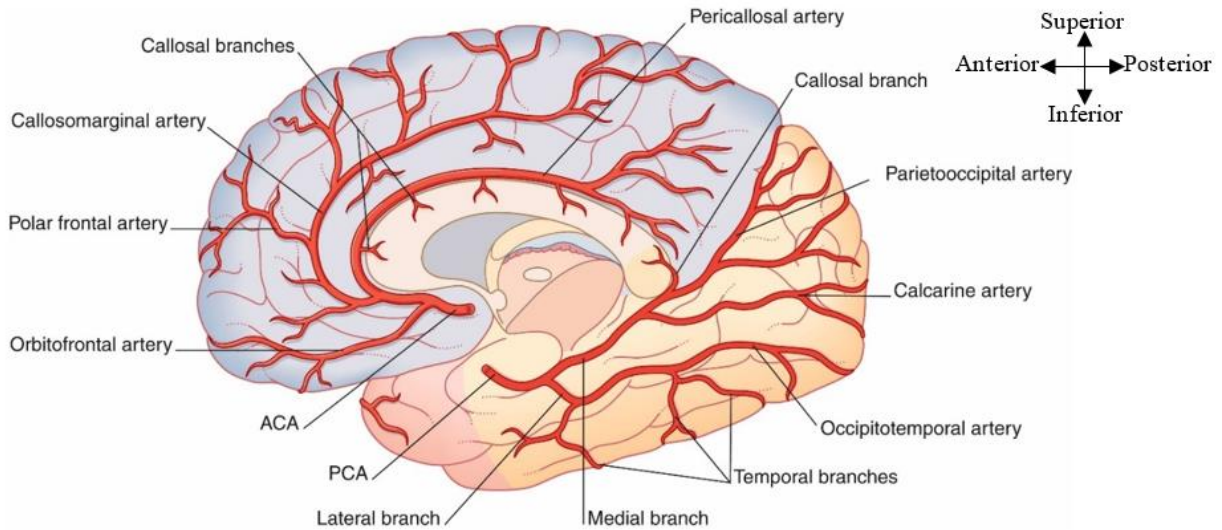


Figure 2.5: A medial view of the right cerebral hemisphere, showing the cortical branches of the anterior and posterior cerebral arteries. The blue area is supplied by the anterior cerebral artery, the orange area by the posterior cerebral artery and the pink area is supplied by the middle cerebral artery. [ACA: anterior cerebral artery; PCA: posterior cerebral artery]. The image is adapted from Mtui & Gruener²⁸.

2.1.4 Anterior communicating artery

The two ACAs are connected by the AcoA at the anterior border of the longitudinal fissure.³ The AcoA is located anterior to the optic chiasm,³⁰ as seen in Figures 2.2, 2.3 and 2.6.

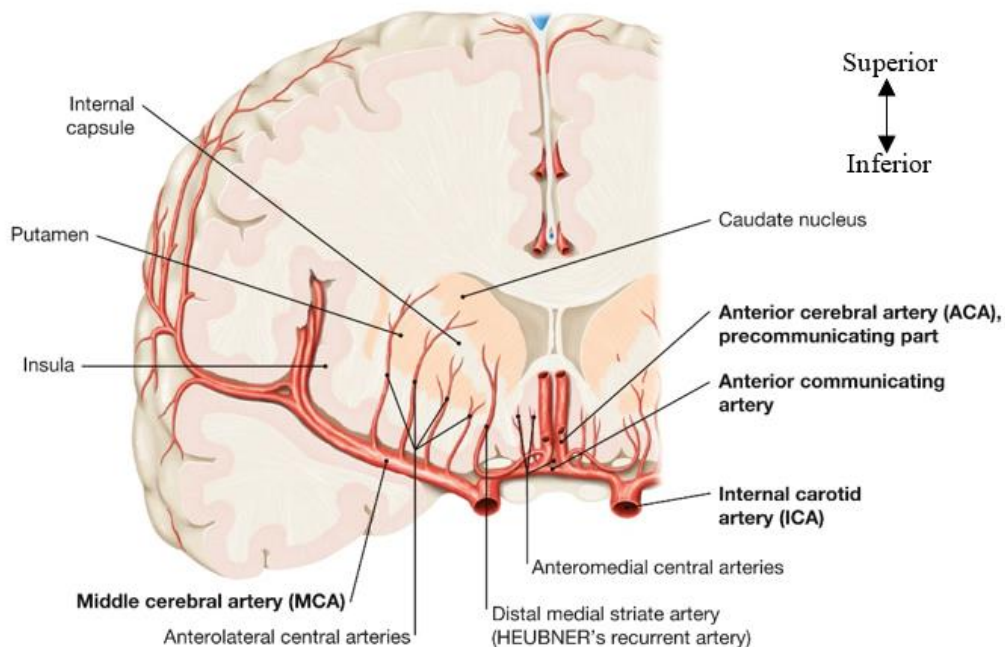


Figure 2.6: A frontal section of the cerebral hemispheres showing the pathway of the anterior communicating artery, branches of the middle cerebral artery and the anterior cerebral artery. The image is adapted from Hombach-Klonisch et al.³¹.

2.1.5 Vertebral artery

The VA is the first branch of the subclavian artery and passes anterior to the transverse foramen of the seventh cervical vertebra (C7).^{32,33} Thereafter, the VA enters the transverse foramen of the sixth cervical vertebra (C6) and continues through the transverse foraminae of C5 to C3.³³ At the axis (C2), the VA travels posteriorly to enter the foramen transversarium of the atlas (C1), where it continues through the atlantoaxial membrane and enters the cranial cavity through the foramen magnum.^{32,33} The left and right VAs anastomose and form the BA at the medullo-pontine junction.^{33,34} The VAs provide 20% of the blood supply to the brain, including supply to the medulla oblongata.²¹

The four segments of the VAs are divided into three extra-cranial (V1 - V3) and one intracranial (V4) segment.³² The preforaminal segment (V1) originates from the subclavian artery and continues until the artery enters the first transverse foramen.³² The second or vertebral segment (V2) runs through the transverse foramina of C6 - C3 and lies anterior to the cervical nerve roots in the region.³² The third segment (V3) passes from the foramen transversarium of C1 to the point of entry to the foramen magnum.³² V3 has a complicated course because it crosses the craniovertebral junction³² and must prevent damage during movements of the head allowed by this junction. The intradural segment (V4) runs through the dura mater from the foramen magnum to the anastomosis of the VAs.³² These arteries and their divisions are illustrated in *Figure 2.7*. The VAs are not component arteries of the CAC but are closely related to the CAC.

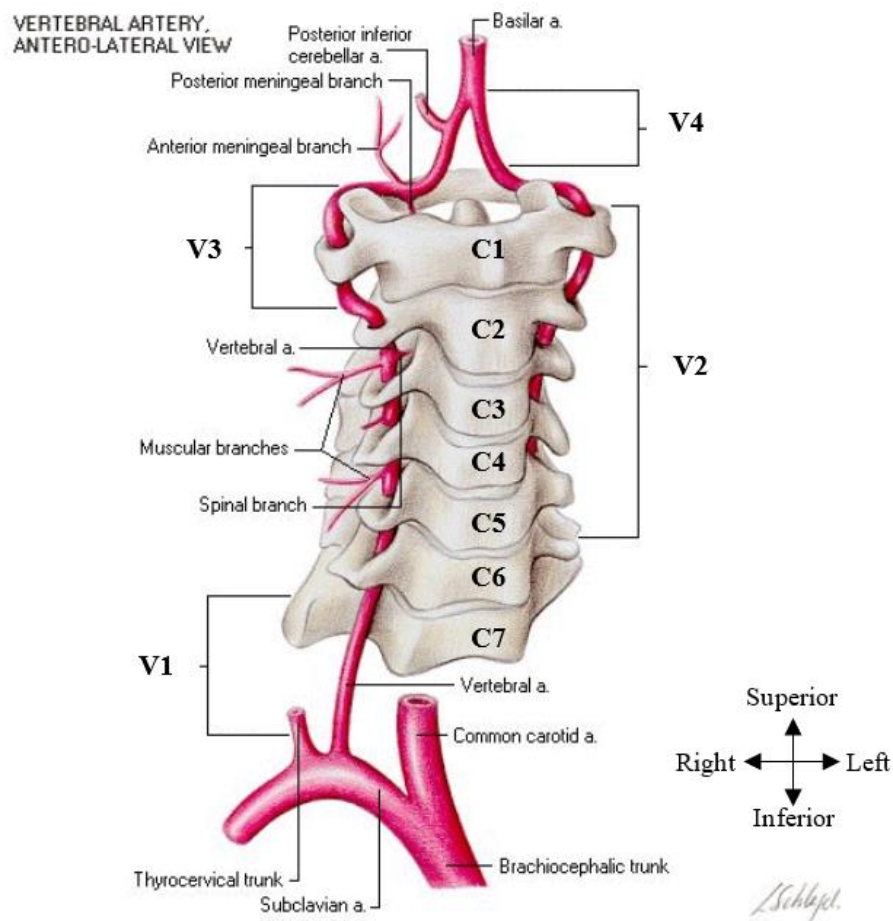


Figure 2.7: An anterior view of the cervical vertebrae and the course of the right vertebral artery from its origin at the subclavian artery to its termination as the basilar artery. The four segments of the vertebral artery are demarcated (V1-4). [V1: preforaminal part of the VA; V2: vertebral part of the VA; V3: third segment of the VA; V4: intradural segment of the VA; C1-7: Cervical vertebrae 1-7; a.: artery]. The image is adapted from Cagnie et al.³⁵.

2.1.6 Basilar artery

The large, unpaired BA gives rise to the posterior circulation of the CAC and arises from the anastomosis of the VAs³³ in the pontine cistern.³⁶ The BA travels along the basilar sulcus, located on the ventral surface of the pons, and gives rise to branches that supply the cerebellum^{33,34}; anterior inferior cerebellar arteries arise from the inferior aspect of the BA and the superior cerebellar arteries arise from the superior aspect of the BA.^{12,34} Other branches of the BA supply the brainstem^{33,34,37} and thalamus.³⁷ The BA also gives rise to numerous, small perforating arteries that supply the pons^{21,34} namely, the pontine arteries. At the ponto-mesencephalic junction, the BA bifurcates to give rise to the left and right PCAs^{3,34} and is seen in *Figures 2.3, 2.8 and 2.9*. The BA is not a component of the CAC but is a closely associated artery since it gives rise to the PCAs.

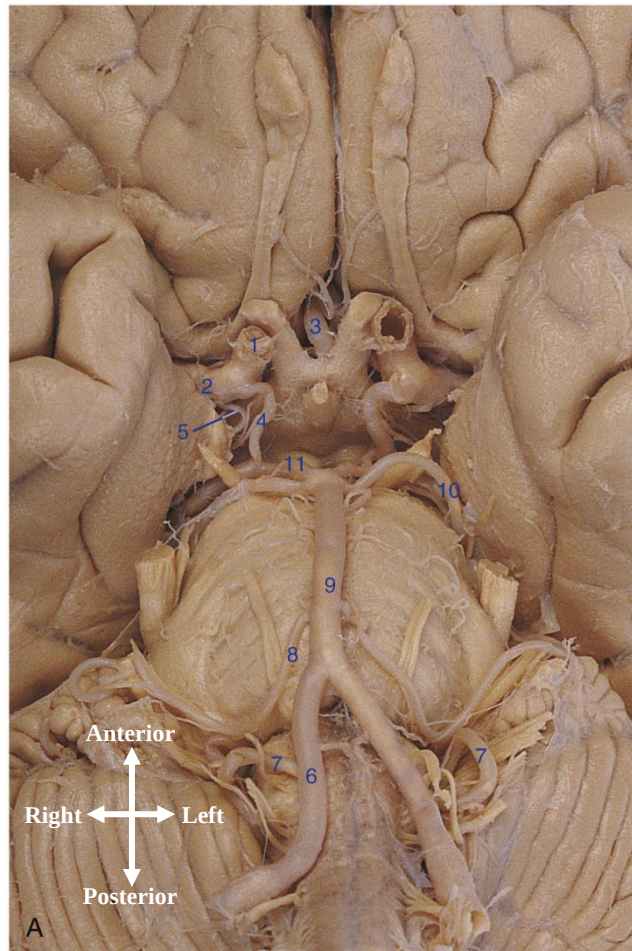


Figure 2.8: The arterial components of the *circulus arteriosus cerebri* on the ventral surface of the brain. The visible arteries include the right internal carotid artery (1), right middle cerebral artery (2), right anterior cerebral artery (3), right posterior communicating artery (4), right anterior choroidal artery (5), right vertebral artery (6), posterior inferior cerebellar arteries (7), right anterior inferior cerebellar artery (8), basilar artery (9), left superior cerebellar artery (10) and the right posterior cerebral artery (11). The image is adapted from Vanderah & Gould²¹.

2.1.7 Posterior cerebral artery

The PCAs originate at the bifurcation of the BA and travel posteriorly over the tentorium cerebelli and around the cerebral peduncles.^{2,21} The PCAs supply the medial-inferior surface of the occipital lobe, midbrain, and various structures along their path, including the thalamus and parahippocampal gyrus.^{2,21} Some of the branches on the lateral aspect of the cortex are seen in *Figure 2.4* and the branches on the medial aspect are seen in *Figure 2.5*. The PCA segments can be divided either anatomically or surgically (*Figure 2.9*). This is an anatomical study and only the anatomical divisions of the PCA are outlined. According to the Krusen and Yasargil classification, the P1 segment is from the bifurcation of the BA to the anastomosis with the PcoA.^{1,7,11,38} The P2 segment continues from the anastomosis with the PcoA^{1,11} and is

divided into two parts: the anterior P2A and posterior P2P segments.³⁸ The division between P2A and P2P has been debated to be from the lateral cerebellar peduncle or the posterior margin of the cerebellar peduncle or the lateral mesencephalic sulcus.³⁸ The third portion or quadrigeminal segment (P3) continues until the quadrigeminal cistern.¹ Thereafter, the PCA continues as the calcarine segment (P4) that terminates in the calcarine sulcus of the occipital lobe and gives rise the terminal branches of the PCA (P5).¹ These are the calcarine and parieto-occipital arteries respectively.³⁸ Only the P1 segment is a component of the CAC.

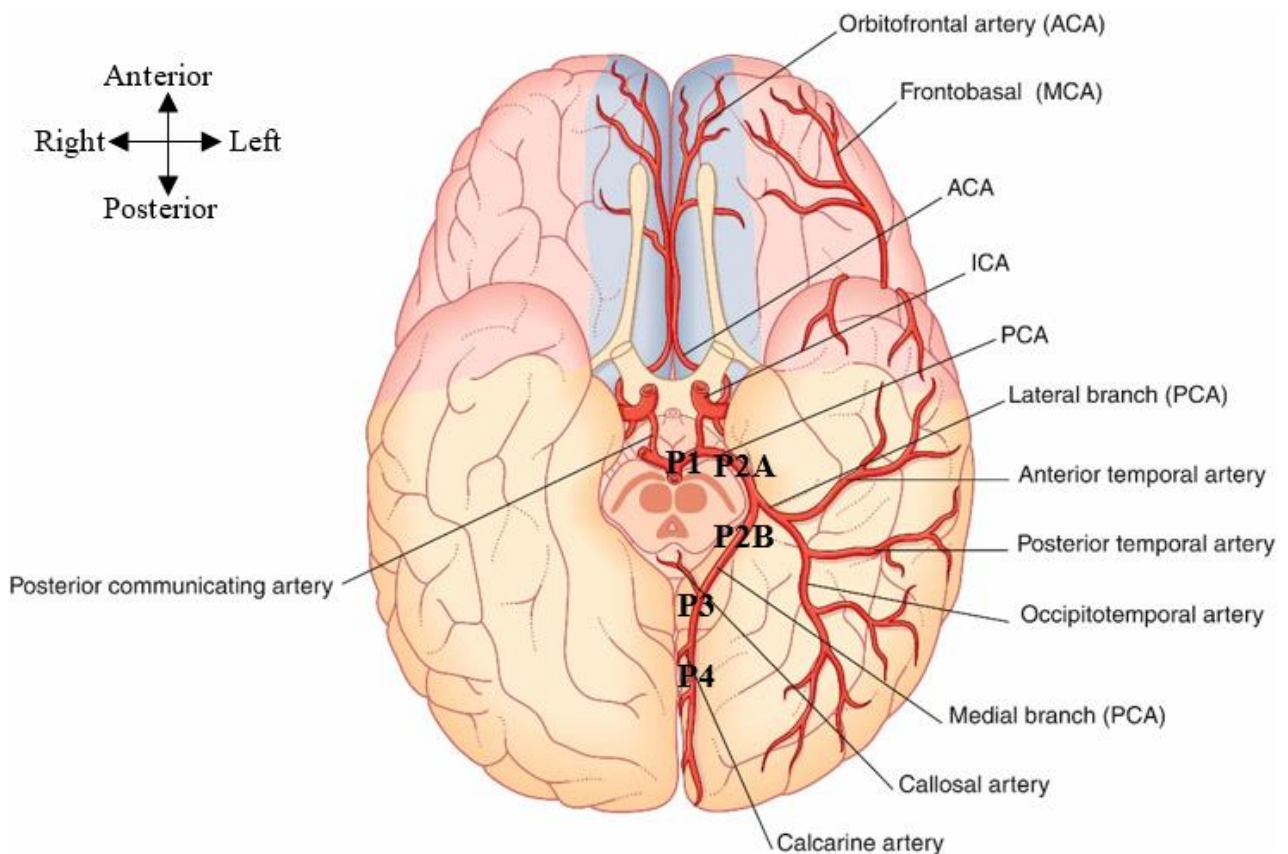


Figure 2.9: An illustration depicting the anatomical segments of the right posterior cerebral artery on the ventral surface of the brain. The posterior communicating arteries are seen joining the posterior cerebral artery to the ipsilateral internal carotid artery. The yellow-orange indicates areas supplied by the posterior cerebral arteries. The pink areas are supplied by the middle cerebral arteries and the blue areas are supplied by the anterior cerebral arteries. [ACA: anterior cerebral artery; ICA: internal carotid artery; PCA: posterior cerebral artery; P1: pre-communicating segment of the PCA; P2A: anterior post-communicating segment of the PCA; P2B: posterior post-communicating segment of the PCA; P3: quadrigeminal segment of the PCA; P4: calcarine segment of the PCA]. Image adapted from Mtui & Gruener²⁸.

2.1.8 Posterior communicating artery

The PcoAs arise from the communicating segment (C7) of the ICAs and anastomoses with the ipsilateral PCA^{3,11, 24} (*Figure 2.9*). Therefore, the PcoAs connect the anterior and posterior circulations of the CAC.¹ Branches of these arteries supply the thalamus.²¹

2.2 Embryological development

The cardiovascular system forms early in embryological development and is the first major system to be active in the developing embryo³⁹. In the initial stages of development, the vasculature of the embryo is in the form of various plexuses. These plexuses give rise to larger arteries, primarily through fusion of several branches, later in development.¹⁶ The resulting arteries either persist in some form or gradually disappear throughout development.¹⁶ The resulting six aortic arches, which are not present simultaneously, and intersegmental arteries will give rise to the cerebral circulation observed in adults.¹⁶ There are numerous arteries during vasculogenesis and these merge and regress into the pattern of the mature CAC configuration present in individuals.

The pharyngeal arch arteries develop from the aortic sac and terminate in the ipsilateral dorsal aorta³⁹ (*Figure 2.10*). The significance of each pharyngeal arch artery pair is described in *Table 2.2*.

Table 2.2: A summary of the significance of each pair of pharyngeal arch arteries in the development of mature arteries in the developing embryo.

Artery pair	Significance in development
First	Remnants contribute to the formation of the maxillary arteries that supply the stapes. ³⁹
Second	Contribute to the development of the stapediaal arteries. ¹⁶
Third	Forms the CCAs and ICAs. ³⁹ The proximal portion forms the CCAs, and the distal portion forms the ICAs by merging with the dorsal aorta. ³⁹
Fourth	Different origins: the proximal portion of the left artery is derived from the aortic sac and the distal portion develops from the left dorsal aorta. The left artery contributes to the formation of the arch of the aorta. ³⁹ The distal portion of the right artery develops from the right dorsal aorta and right seventh intersegmental artery. ³⁹ The right pharyngeal arch artery forms the proximal portion of the right subclavian artery. ³⁹ The left subclavian artery develops from the left seventh intersegmental artery. ³⁹
Fifth	Develop in approximately 50% of embryos and does not have a significant impact on vascular development as these arteries degenerate without contributing to the mature vasculature. ³⁹
Sixth	Have different origins: the proximal portion of the left artery remains as the proximal portion of the left pulmonary artery and the distal portion of the left artery forms the ductus arteriosus. ³⁹ The proximal portion of the right artery remains as the proximal portion of the right pulmonary artery and the distal portion of the right artery degenerates since there is only one ductus arteriosus. ³⁹
Seventh	Usually degenerate or give rise to small vessels in the areas surrounding the pulmonary arteries. ¹⁶

The first cerebral artery to develop is the ICA at approximately day 24 of development and arises from the merging of three arteries of the branchial arch.^{5, 24} The ICA initially supplies the entire developing brain.^{24,34,40} By day 28 of development, the ICA bifurcates to give rise to the anterior and posterior divisions.^{2,24} Later during development, these divisions give rise to various arteries and the anterior division forms the anterior choroidal, anterior cerebral and middle cerebral arteries^{2,24} observed in the mature CAC. While the posterior cerebral and posterior choroidal arteries form the posterior division.²⁴

Initially, the posterior circulation is mostly supplied by the primitive carotid-vertebrobasilar anastomosis, that arises from the primitive trigeminal, primitive hypoglossal and primitive proatlantal arteries.^{2,34} However, as the posterior portions of the brain develop at a rapid rate, the ICA becomes insufficient, and the posterior circulation develops from the anterior

circulation.^{24,40} The primitive carotid-vertebrobasilar anastomosis disintegrates³⁴ resulting in the PcoAs being the only mature connection between the anterior and posterior circulations.¹ Around day 29 of development, the primitive arteries of either side of the hindbrain, the longitudinal neural arteries, merge to form the BA plexus.^{34,41,42} Anteriorly, this plexus communicates with the PcoAs and posteriorly, with the VAs.³⁴ From days 30 to 35 of development, the mature BA and VAs develop and the remaining plexuses regress.^{34,40} The two vertebral arteries form from the fusion of the intersegmental arteries on either side of the cervical region³⁹ and formation is complete around day 40 of development.^{41,42} If, however, the complete regression of the arteries forming the plexuses fails, this will result in persistent embryological arteries in the mature CAC, such as the fetal PCA configuration.^{7,40} Around day 40 of development, there is a plexus between the two ACAs^{41,42} and by day 44, the MCA and ACAs are extending across the cerebral hemispheres.^{41,42} Also, around day 44, the development of the AcoA completes the anterior circulation of the CAC.^{41,42} By day 52, both PCAs have completed their formation.^{41,42}

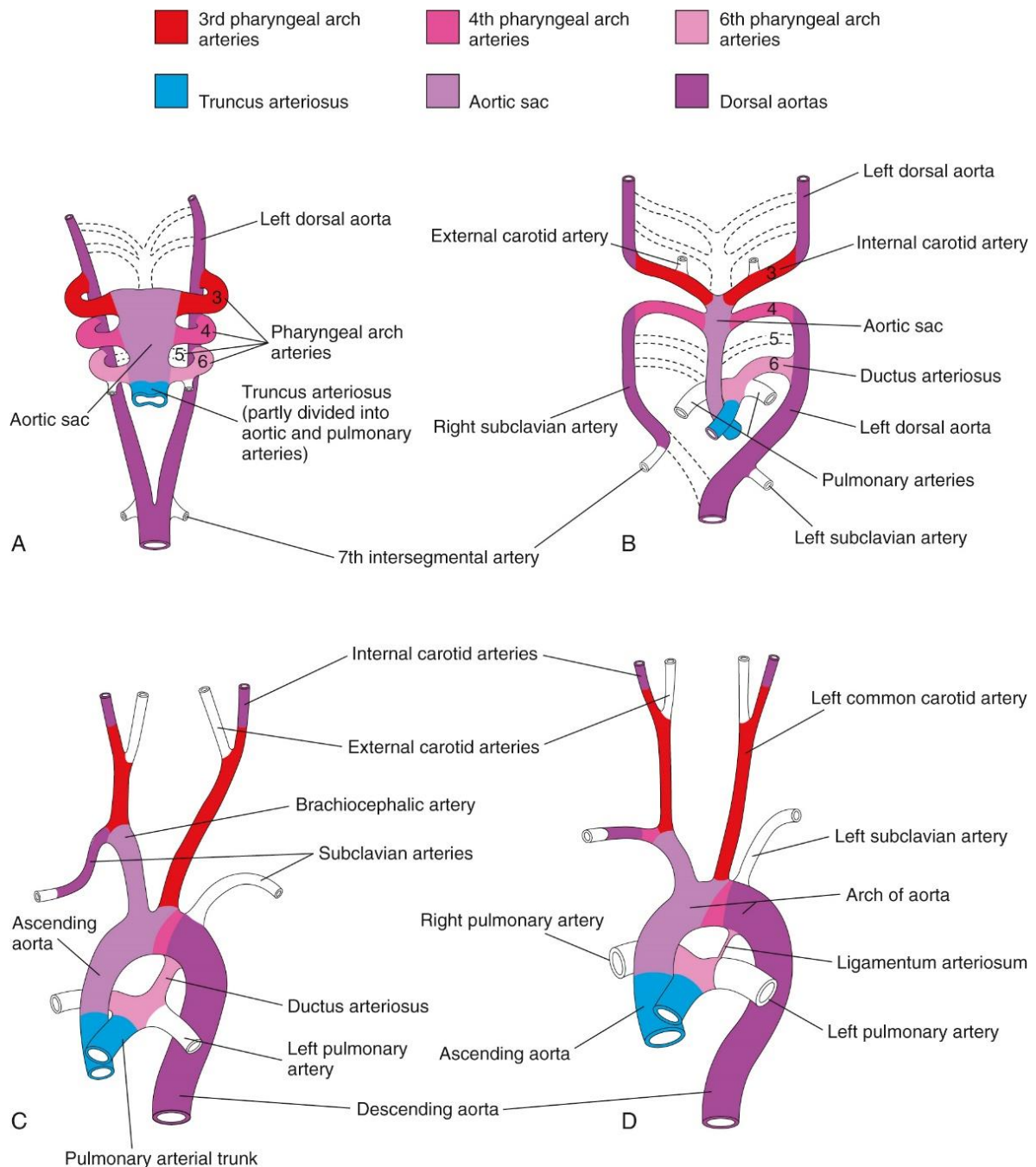


Figure 2.10: A schematic illustration showing the development of the truncus arteriosus, aortic sac, the six pairs of pharyngeal arch arteries and the dorsal aortae into the arterial pattern observed in adults. The white vessels do not develop from the above structures. A: Pairs 3-6 of the pharyngeal arch arteries at 6 weeks. Pairs 1 – 2 have mostly disappeared by this stage. B: The remaining pharyngeal arch arteries at 7 weeks. The dotted lines indicate the dorsal aortae and pharyngeal arch arteries that have normally disappeared by this stage. C: Arteries at 8 weeks. D: The arterial pattern usually observed in a 6-month-old child. It can be noted that the ascending aorta and pulmonary arteries are significantly larger in D than in C because of the differential flow of blood through these vessels at different developmental stages. In D, the ductus arteriosus (observed in C) has become the ligamentum arteriosus. The image is reproduced [†] from Moore, et al.³⁹.

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Variations may arise during embryological development when triggers or events result in the vascular construction programme being altered temporarily or permanently.^{5,24} If the trigger allows for uninterrupted development and does not result in repair processes or apoptosis, then the prevailing variation has the potential to become a congenital variation.⁵ This is partly why variations in the CAC may have regional or ancestral patterns.⁵

Additionally, triggers or events could result in the incomplete development of the arterial wall, which could result in a fenestration, or the fusion of arteries.⁵ These patterns usually result in weaker connections between endothelial cells to develop and a weaker arterial wall to form.⁵ Thus, potentially predisposing patients to aneurysm development. Incomplete cell selection is evident when an artery is absent, plexiform, doubled or tripled.^{5,7} A plexiform configuration is when a small network of arteries is present. As an example, if a trigger causes the AcoA to remain in its more fetal form, then the plexus or part thereof, would remain in the adult CAC in the form of a plexiform, duplicate or triplicate AcoA.^{41,42} Therefore, variations in the CAC may arise owing to alterations during embryonic development.

Not only could variations be formed during embryonic development, but postnatally and throughout life too. During postnatal development, changes to the CAC may occur owing to environmental factors, genetic influence or disease.^{7,43,44} Other causes for the development of CAC variations could include the extent of neck movements throughout life⁴⁵ and the resulting haemodynamic changes and factors that may favour the growth of certain arteries or arterial segments.⁴³ Therefore, there are many factors to consider when determining the cause of variations in the CAC.

2.3 Anatomical variations of the *circulus arteriosus cerebri*

In 1994 the perceptive, South African president Nelson Mandela^{46(p.271)} said, “[i]f you wait for textbook conditions, they will never occur”. To an extent, the CAC can be held to this, since studies consistently indicate that less than 50% of their samples had the conventional anatomical configuration described in section 2.1 (*Figure 2.1*) and recorded in *Table 2.3*. Several variations observed include one or more arteries being hypoplastic,^{5,7} aplastic,^{5,7,47} the presence of fenestrations,²⁴ or additional arteries being present, including duplications and triplications.^{3,7} The origin of arteries may also vary from the conventional description with Kuybu *et al.*⁴⁸ determining that 70% of the PCAs in their sample arose from the BA, which agrees with the conventional description. However, the PCA arose from the PcoA and both the

BA and PcoA in 20% and 10% of their sample respectively.⁴⁸ There may also be ‘persistence of the embryonic pattern’⁷ with certain embryonic origins or arteries remaining in the mature CAC.

Table 2.3: The reported prevalence of circulus arteriosus cerebri samples with anterior circulation variations, posterior circulation variations, variations in both the anterior and posterior circulations, and a complete circulus arteriosus cerebri in the current literature.

Author, year	Sample size	Study type	Country	Anterior variations	Posterior variations	Variations in both circulations	Standard CAC
Windle, 1888 ⁴⁹	200	D	UK	-	-	-	38%
Fawcett & Blachford 1905 ⁴⁷	700	D	UK	11%	-	26.43%	72.8%
Alpers <i>et al.</i> , 1959 ⁵⁰	350	D	USA	-	-	-	52%
Riggs & Rupp, 1963 ⁵¹	994	D	USA	12.98%	29.58%	38.13%	19.3%
Fisher, 1965 ⁵²	414	D	USA	1.45%	42.27%	49.03%	4.8%
Puchades-Orts, <i>et al.</i> , 1976 ⁵³	62	D	Spain	-	-	-	13%
Ozaki <i>et al.</i> , 1977 ⁴¹	153	D(e)	China	-	-	-	46.3%
Lazorthes <i>et al.</i> , 1979 ⁴⁵	200	D	France	-	-	-	14.5%
Kayembe <i>et al.</i> , 1984 ⁵⁴	148	D(e)	Japan	-	-	-	46.3%
el Khamlichi <i>et al.</i> 1985 ⁵⁵	100	D	Morocco	13%	42%	27%	18%
Al-Hussain <i>et al.</i> , 2001 ¹¹	50	D	Jordan	-	-	-	20%
Eftekhar <i>et al.</i> , 2006 ⁴⁴	102	D	Iran	-	48.04%	12.75%	28.43%
Kapoor <i>et al.</i> , 2008 ⁷	1000	D(e)	India	23.4%	31.4%	7.4%	45.2%
Ghanbari <i>et al.</i> , 2008 ¹⁰	100	D(e)	Iran	-	79%	-	21%
De Silva <i>et al.</i> 2011 ⁵⁶	225	D(e)	Sri Lanka	-	-	-	14.2%
Iqbal, 2013 ³	50	D(e)	India	20%	32%	-	48%
Cilliers & Page, 2016 ⁵⁷	60	D(e)	South Africa	-	-	-	15.4%
Cilliers <i>et al.</i> , 2017 ⁴³	39	D(e)	South Africa	10.26%	33.4%	15.34%	41%
Pascalau <i>et al.</i> , 2019 ¹²	10	D(e)	Romania	34.8%	65.2%	-	-
Saikai <i>et al.</i> , 2014 ⁵	140	D (e) TOF	India	47.86%	25%	-	22.14%

Krabbe-Harkamp et al., 1998²⁰	150	TOF	Netherlands	26%	48%	-	42%
Macchi et al., 2002⁵⁸	118	TOF	Italy	10%	51.5%	-	47%
Chen et al., 2004⁵⁹	507	TOF	Taiwan	22%	85.6%	-	21.3%
Papantchev et al., 2007⁶⁰	99	CTA	Bulgaria	-	-	-	57.6%
He et al., 2007⁶¹	153	TOF	China	47.7%	34.6%	-	17.7%
Jeton et al., 2018⁴	513	TOF	Kosovo	22.3%	72.35%	-	23.4%
Hindenes et al., 2020⁶²	1864	TOF	Norway	2.63%	59.12%	23.18%	11.9%
Dhakal et al., 2020⁶³	95	CTA	Nepal	7.37%	50.52%	-	45.3%

The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. The table was divided into dissection studies and radiological studies. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection of embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; UK: United Kingdom; USA: United States of America.

The '-' indicates that the relevant information was not specified by the study.

'Complete' and 'standard' configurations are not necessarily used interchangeably and variations may be found in both the anterior and posterior circulations combined. Therefore, depending on the study, the sum of percentages may exceed 100%.

2.3.1 Hypoplasia

Hypoplasia is a common variation of the CAC and is defined as an attenuated vessel.³ These vessels can be patent, meaning there is blood flow through the small diameter vessel,³ or non-patent (no blood flow). According to the study conducted by Iqbal,³ 52% of their sample had anatomical variations of the CAC, and of these variations patent hypoplasia of one or more arteries represented 24% of their sample. Hypoplasia was the most common variation reported by Iqbal³ and hypoplastic arteries included the PcoA (10%), P1 (6%), A1 (4%) and ACA (4%). It is difficult to compare the frequency of hypoplasia and make reliable conclusions from the literature since there is no consensus on the diameter that determines a hypoplastic artery. Furthermore, not every study notes whether hypoplastic arteries are patent or not. Therefore, it is difficult to make reliable and accurate predictions about the frequency of hypoplastic arteries in a population, as well as the potential haemodynamic changes in these arteries when making inferences on the effects of hypoplasia on CAC function.

Unilateral hypoplasia would result in asymmetry and the larger artery is referred to as the dominant artery of the pair. Dominance can have an influence on other arteries, for instance VA dominance can result in the BA becoming longer and gravitating towards the non-dominant side³⁷ (*Figure 2.11*). The curvature is a result of altered haemodynamics in the posterior circulation,^{37,64} as explained in *Figure 2.11*. According to the haemodynamic study conducted by Hong *et al.*⁶⁴, hypoplasia of one VA potentially predisposes patients to posterior circulation stroke; especially pontine infarction on the side of the dominant VA.

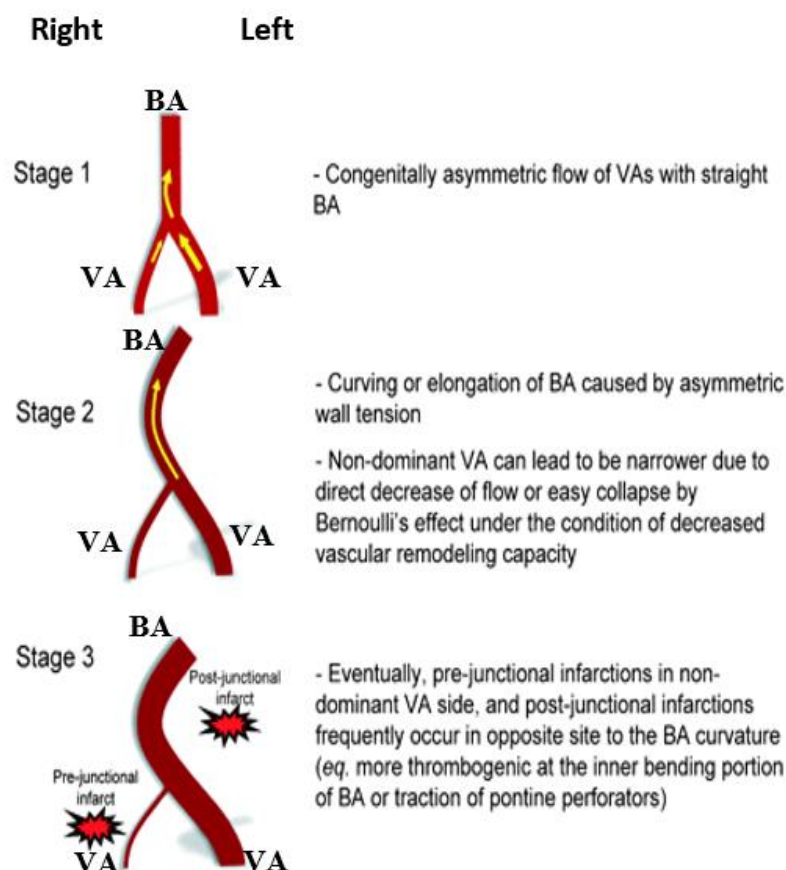


*Figure 2.11: A schematic showing dominance in the vertebral arteries and the development of a curved and elongated basilar artery. In this scenario, the left vertebral artery is dominant and results in the basilar artery curving to the right. [BA: basilar artery; VA: vertebral artery]. Image adapted from Hong *et al.*⁶⁴.*

2.3.2 Accessory vessels

There may be additional arteries, called accessory vessels, present in the CAC. Iqbal³ noted that in duplication of the AcoA, one of the ACAs was hypoplastic, but patent. Two of the samples had a triplicate AcoA, where there was a midline corpus callosal branch from the ACA.³ In these samples, the third AcoA was approximately the same diameter as the other two. Furthermore, in 10% of their sample, the embryonic origin of the PCA remained visible and

was joined to the BA by a small unnamed artery.³ Therefore, accessory vessels can vary in length, diameter and location.

2.3.3 Fenestrations

Fenestrations are defined as the branching of a vessel into two or more channels that unite distally to have a single lumen for the rest of the course of the vessel.⁶⁵ The channels of a fenestrated artery share the adventitia layer but have separate endothelial and muscular layers.⁶⁵ Saikia *et al.*⁵ reported that 6.4% and 4.3% of their sample had a fenestrated A1 and AcoA, respectively. However, according to Kwon *et al.*⁶⁶, fenestrations are more common in the posterior circulation than in the anterior circulation.

2.3.4 Variations in the anterior and posterior circulation

The common types of variations have been described and more detail about variations in the anterior, posterior or both the anterior and posterior circulations is provided in the following sections.

2.3.4.1 Posterior circulation

Fawcett & Blachford⁴⁷ analysed 700 CACs and reported that 96.1% of these had complete CACs and only 3.8% had an incomplete CAC owing to unilateral PcoA aplasia (right: 1.8%; left: 1.4%), bilateral PcoA aplasia (0.4%) and AcoA aplasia (0.2%). Thus, the causes of an incomplete CAC were mostly due to aplasia in the posterior circulation. Fawcett & Blachford⁴⁷ also observed symmetry of the CAC and reported that it was complete and symmetrical in 72.8% of their samples. Asymmetry, which occurs when a variation only appears on one side of the CAC, was caused by discrepancies in the size of the left and right PcoA in relation to one another with the right being larger in 12.4% and left being larger in 9.1% of their sample. Other causes of asymmetry included ACA duplications (right 0.85% and left 0.57%) or a non-typical origin of the PCA.⁴⁷ Therefore, variations in the posterior circulation tended to be the cause of asymmetry and the PcoA appeared to be the most variable artery. This agrees with the data in *Tables 2.4 and 2.5*, where variations in the posterior circulation are reported more frequently.

The posterior circulation is usually described as having an adult, transitional or embryonic/fetal configuration,^{11,40} as illustrated in *Figure 2.12*. However, the definitions are not agreed upon throughout the literature and some terms are used interchangeably by some researchers, but not others. For instance, fetal PCA and fetal PcoA seem to be used interchangeably even though

these are two different configurations. Therefore, it is again difficult to compare the literature. The current study agrees with definitions that classify adult, and fetal configurations according to the diameter of P1 relative to the diameter of the ipsilateral PcoA.^{11,40} However, some studies refer to a fetal PCA and fetal PcoA depending on the origin of the arteries.

The adult configuration is the most frequently occurring posterior configuration in the mature CAC.^{18,40,67} In this configuration the diameter of P1 is greater than the diameter of the ipsilateral PcoA,^{11,40,68} which may be aplastic.⁶⁸ The smaller diameter or aplasia of the PcoA results in limited blood flow to P2 via the PcoA compared to blood flow from P1.¹¹ In a transitional configuration, the diameters of P1 and the PcoA are approximately equal and blood flow to P2 on each side is approximately the same.^{11,40,68}

In a fetal-type posterior configuration (FTP), the P1 is smaller than the ipsilateral PcoA.^{56,68} Named so because over 60% of fetal brains have the FTP configuration.⁷ A persistent FTP in a mature CAC results in the patient having a higher probability of developing vascular deficiencies.⁶⁸ For instance, Gaigalaite *et al.*⁴⁰ noted that FTP could result in more severe ischaemic strokes if there is reduced blood flow through the ICA because more of the brain relies on the ICA for supply. The ICA is the dominant source of blood because the origin of P1 is mostly from the ICA via the ipsilateral PcoA.^{5,11,40,56} Furthermore, the smaller diameter of P1 results in a decrease in blood flow through this artery. The incidence of FTP has been reported by three studies, as follows:

- Unilateral: left 28% and right 26% according to Eftekhari *et al.*⁴⁴
- Unilateral, but not separated into sides: ranged from 6.4% according to Saikia *et al.*⁵ to 10.6% according to Kapoor *et al.*⁷
- Bilateral: ranged from 5.7% to 13.2% according to Kapoor *et al.*⁷

There is variation in the FTP as it can be full or partial. However, the literature does not currently agree on the definition of a full or partial embryonic configuration, and this has resulted in a large range being recorded for these variations.⁶⁸ This study agrees with the definitions proposed by van Raamt *et al.*⁶⁸, who defines a partial FTP (pFTP) as one where the P1 segment is hypoplastic and a full FTP (fFTP) as one having a non-patent hypoplastic or absent P1 segment. According to this definition, a fFTP will result in a P1 segment that is not visible on an MRI scan because it is non-patent. Therefore, the frequency of FTP may vary depending on the method used⁶⁹: angiographic or dissection. This definition agrees with the

studies conducted by Javed *et al.*¹ and Arjal *et al.*⁶⁹. With this definition, van Raamt *et al.*⁶⁸ determined the prevalence of FTP in the literature to be as follows:

- Unilateral pFTP: 11% to 29%
- Bilateral pFTP: 1% to 9%
- Unilateral fFTP 4% to 26%
- Bilateral fFTP 2% to 4%

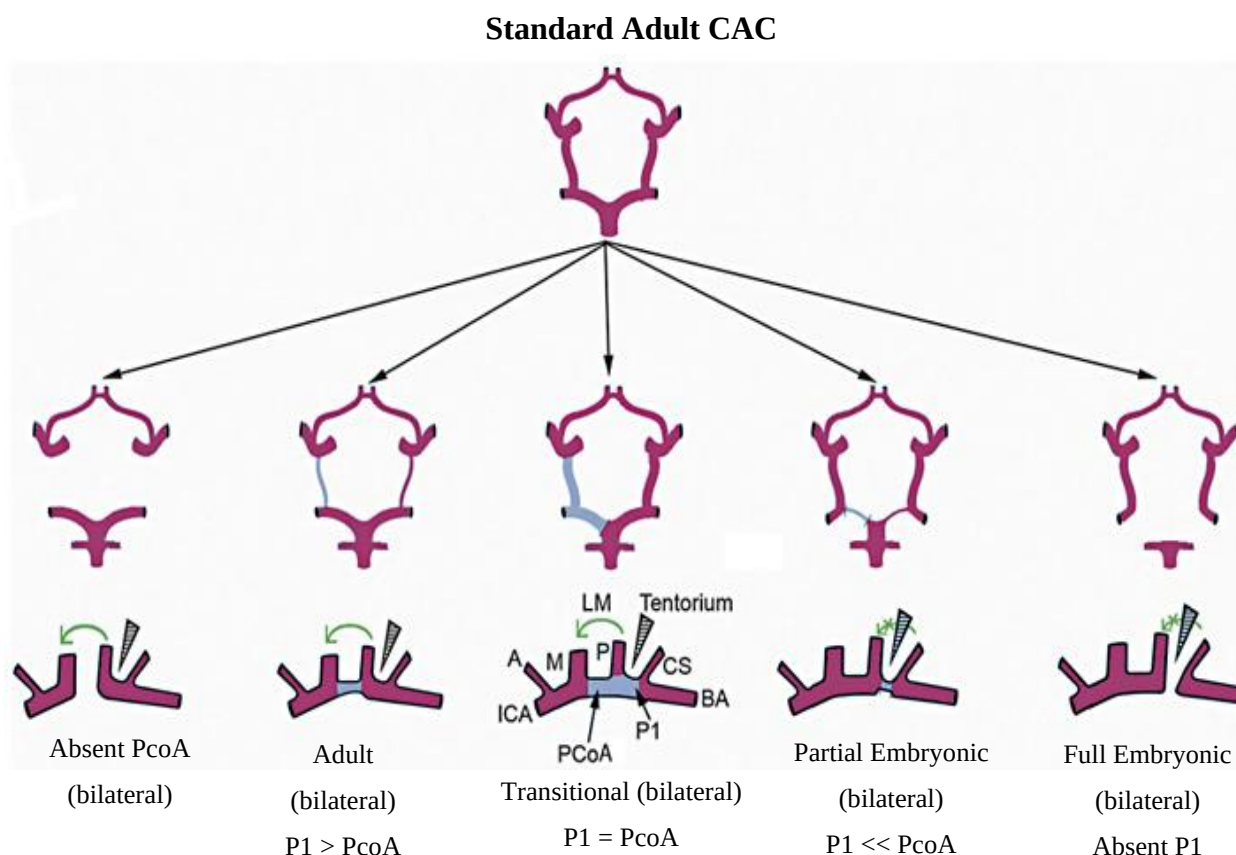


*Figure 2.12: A schematic diagram depicting several variations observed in the posterior circulation of the circulus arteriosus cerebri. The adult, transitional and embryonic (full and partial) configurations have been labelled. [ICA: internal carotid artery; PcoA: posterior communicating artery; A: anterior cerebral artery; M: middle cerebral artery; P: posterior cerebral artery; CS: superior cerebellar artery; BA: basilar artery; P1: pre-communicating segment of the PCA; LM: leptomeningeal vessels]. The image is modified from van Raamt *et al.*⁶⁸.*

Both FTP and adult configurations can be observed unilaterally¹¹ because of differential development of the left and right sides of the CAC. Therefore, it is possible for a single CAC to have both the adult and FTP configurations. These posterior CAC configurations are clinically significant since there are potential haemodynamic changes with each configuration.

2.3.4.1.1 Posterior communicating artery

The PcoA appears to be the most variable component of the CAC^{5,11,12} and variations include hypoplasia, aplasia, fenestration and varied location of termination. Various studies noted that the most common variation of the PcoA was hypoplasia and the incidence of both unilateral and bilateral PcoA hypoplasia has been recorded as ranging from 10%⁶² to 53%³, as reflected in *Table 2.4*.

Windle⁴⁹ reported that in 3.5% of his sample both PcoAs were ‘extremely small’ and in 14% there was a large size difference between the left and right PcoA. Furthermore, Windle⁴⁹ noted that the left side usually had the smaller or missing PcoA, which potentially explains why the left MCA tends to be obstructed by a blood clot more frequently than the right MCA. Therefore, the right PcoA is more likely to be dominant over the left PcoA.^{47,49}

Table 2.4: The frequency of unilateral and bilateral posterior communicating artery hypoplasia. The table has been divided into two sections, as follows: Studies that stated unilateral vs bilateral hypoplasia and studies that stated the overall hypoplasia observed, i.e. did not separate unilateral and bilateral hypoplasia.

Author, year	Sample size	Study type	Country	Unilateral hypoplasia	Bilateral hypoplasia
Windle, 1888⁴⁹	200	D	UK	14% (left); 7.5% (right)	3.5%
Fawcett & Blachford, 1905⁴⁷	700	D	UK	12.4% (left); 9.1% (right)	0.7%
Riggs & Rupp, 1963⁵¹	994	D	USA	8.9%	12.7%*
Fisher, 1965⁵²	414	D	USA	6%	32%*
Lazorthes et al., 1979⁴⁵	200	D	France	14%	22%*
Ozaki et al., 1977⁴¹	153	D(e)	China	6%	6%
El Khamlichi et al., 1985⁵⁵	100	D	Morocco	14%	24%*
Eftekhari et al., 2006⁴⁴	102	D	Iran	20%	27%*
Ghanbari et al., 2008¹⁰	100	D(e)	Iran	5% (left); 7% (right)	28%
Kapoor et al., 2008⁷	1000	D(e)	India	6.2% (left); 6.9% (right)*	3.6%
De Silva et al., 2011⁵⁶	225	D(e)	Sri Lanka	11.5%	23%*
Saikia et al., 2014⁵	140	D(e) TOF	India	19.28%*	12.8%
Cilliers et al., 2017⁴³	39	D(e)	South Africa	23.1%*	10.3%
Dhakal et al., 2020⁶³	95	CTA	Nepal	14.7%	20%*
Hindenes et al., 2020⁶²	1864	TOF	Norway	12.2% (left); 7.3% (right)	27.8%*
Alpers et al., 1959⁵⁰	350	D	USA	22%	
Kamath, 1981⁶⁷	100	D (e)	India	10%	
Papantchev et al., 2007⁶⁰	99	CTA	Bulgaria	27.3%*	
Iqbal, 2013³	50	D(e)	India	10%*	

The * indicates that the observed hypoplasia was the most common variation in the study. The grey areas represent studies that did not differentiate between aplastic and hypoplastic posterior communicating arteries.

The column labelled 'study type' refers to the methodology used: dissection of human remains or radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection of embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; UK: United Kingdom; USA: United States of America.

The PcoA can be aplastic unilaterally or bilaterally and the frequencies noted in the literature are in Table 2.5. According to the data in Table 2.5, the PcoAs are more commonly missing unilaterally than bilaterally. Bilateral PcoA aplasia would separate the anterior and posterior

circulations and is likely a less favourable configuration since collateral circulation would not be allowed and could be detrimental.

Table 2.5: The frequency of unilateral and bilateral aplastic posterior communicating arteries.

Author, year	Sample size	Study type	Country	Unilateral PcoA aplasia	Bilateral PcoA aplasia
Windle, 1888 ⁴⁹	200	D	UK	11% (left 6.5%; right 4.5%)	1.5%
Fawcett & Blachford, 1905 ⁴⁷	700	D	UK	3.2% (left 1.4%; right 1.8%)	0.4%
Ozaki <i>et al.</i> , 1977 ⁴¹	153	D(e)	China	14.7%	3.7%
Chen <i>et al.</i> , 2004 ⁵⁹	507	CTA	Taiwan	12%	42.8%
Eftekhari <i>et al.</i> , 2006 ⁴⁴	102	D	Iran	7%* (left 3%; right 4%)	3%
Kapoor <i>et al.</i> , 2008 ⁷	1000	D(e)	India	0.9% (left 0.4%; right 0.5%)	0.1%
Ghanbari <i>et al.</i> , 2008 ¹⁰	100	D(e)	Iran	11% (left 6%; right 5%)	-
Iqbal, 2013 ³	50	D(e)	India	6.00%	-
Saikia <i>et al.</i> , 2014 ⁵	140	D(e) TOF	India	1.4%	3.6%
Machasio <i>et al.</i> , 2019 ⁷⁰	2019	CTA	Kenya	4.3%	41.5%
Dhakal <i>et al.</i> , 2020 ⁶³	95	CTA	Nepal	3.2%	4.2%
Hindenes <i>et al.</i> , 2020 ⁶²	1864	TOF	Norway	19.3% (left 12.2%; right 7.3%)	27.8%*
Enyedi <i>et al.</i> , 2021 ⁷¹	50	TOF	Romania	22.2%*	15.9%

The * indicates that aplasia was the most common variation in the study and the '-' indicates that no value was provided by the study, or the variation did not occur. The grey areas represent studies that did not differentiate between aplastic and hypoplastic posterior communicating arteries.

The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; United Kingdom; USA: United States of America.

Different triggers during development could result in PcoA aplasia. For instance, if the anastomosis between the ICA and BA never develops in the embryo, then the PcoA will be absent in the mature CAC.^{7,49,53} Another possible cause of PcoA aplasia or hypoplasia is the persistence of the trigeminal artery that may hinder the development of the PcoA because the

PcoA is supposed to fully develop before the primitive/persistent trigeminal artery (PTA) disintegrates.⁵³

The current literature indicates that the origin of the PcoA from the ICA tends to be certain, however, the termination of the PcoA can vary with Lazzaro *et al.*⁷² recording five different sites of termination: types I – IV (Table 2.6).

Table 2.6: The description and frequency of the five types of posterior communicating artery terminations, as outlined by Lazzaro *et al.*⁷².

Termination Type	Termination Site	Frequency (%)
I	Anastomosis with the PCA	92.94%
II	Anastomosis with the last portion of the BA directly	1.17% (left only)
III	The PcoA terminates in a triangular fenestration at the junction of the PcoA and PCA	0.58%
IV	There is an extra loop in the CAC, where the PcoA terminates	0.58% (left only)
V	There is no terminating anastomosis: this is an incomplete CAC	1.17% (1 left; 1 right)

The CAC is incomplete in the fifth termination type (V), but the relevant PcoA still supplies the posterior portion of the cerebrum through the two P2 segments that are present,⁷² as seen in Figure 2.13.

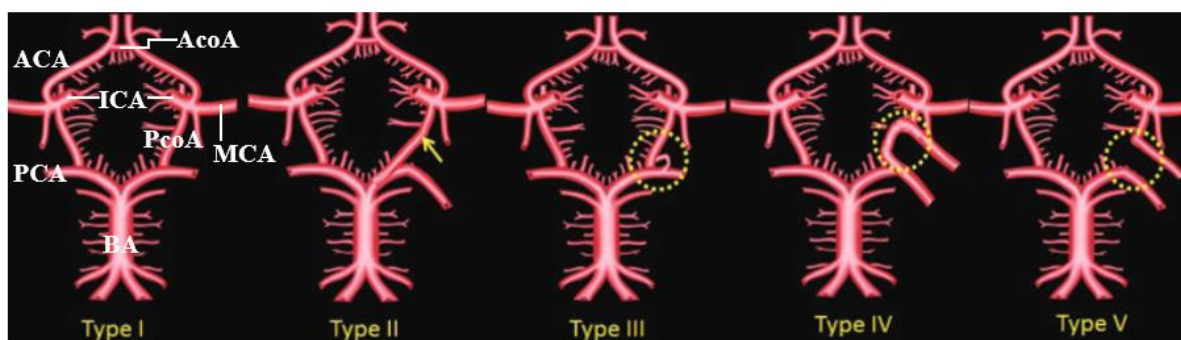


Figure 2.13: The five types of posterior communicating artery (PcoA) terminations described by Lazzaro *et al.*⁷². Type 1 is the conventional anatomical configuration of the PcoA termination. The yellow arrow indicates the position of the PcoA in type II termination and the dotted circles indicate the variation of the PcoA termination in types III – V. [ACA: anterior cerebral artery; AcoA: anterior communicating artery; ICA: internal carotid artery; PcoA: posterior communicating artery; PCA: posterior cerebral artery; BA: basilar artery; MCA: middle cerebral artery]. Image adapted from Lazzaro *et al.*⁷².

2.3.4.1.2 Posterior cerebral artery

The FTP is the most common variation associated with the PCA,⁵ but another possible variation is non-typical origin of the PCA (Table 2.7). It is common for one of the PCAs to arise from the ICA and not its embryonic origin: the BA.⁴⁹ The incidence of unusual origins of the PCA is lower on the left than on the right and least common bilaterally.^{47,49} An example of one of the PCA origins that is not typical is the PcoA.⁴⁸

Table 2.7: The frequency of the pre-communicating segment of the posterior cerebral artery (P1) arising from the internal carotid artery, a non-typical origin.

Author, year	Sample size	Study Type	Country	P1 originating from the internal carotid artery			
				Left	Right	Bilateral	Total
Windle, 1888 ⁴⁹	200	D	UK	4.5%	5.5%	2%	12%
Fawcett & Blachford, 1905 ⁴⁷	700	D	UK	0.57%	0.85%	-	1.44%
Alpers et al., 1959 ⁵⁰	350	D	USA	-	-	-	15%
Riggs & Rupp, 1963 ⁵¹	994	D	USA	18.68%	3.32%	22%	44%
Chen et al., 2004 ⁵⁹	507	TOF	Taiwan	5.13%	5.92%	11%	22.05%
Iqbal, 2013 ³	50	D(e)	India	6%	4%	10%	20%
Dhakal et al., 2020 ⁶³	95	CTA	Nepal	-	-	-	8.4%

The '-' indicates that no value was provided by the study.

The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography CTA: Computed Tomography Angiography; United Kingdom; USA: United States of America.

Kapoor *et al.*⁷ noted that the PCA was present in all their samples, but some had variations. In a duplicated PCA (Figure 2.14A) there are two branches, namely: caudal and rostral, that run nearly parallel to each other.⁷ These branches were equal in size in 52% of the duplicated samples, whereas one of the branches was larger in the remaining 48%.⁷ Often, one branch was from the PcoA while the other was given off by the BA and these were connected by a short, thin artery.⁷ Prior to this study, Windle⁴⁹ noticed that the smaller branch was often derived from the BA and the larger branch from the ICA. These two PCAs followed the same pathway as a standard PCA and were connected by a single or many tiny anastomosing branches,⁴⁹ which agrees with observations made by Kapoor *et al.*⁷.

In a triplicated PCA (*Figure 2.14B*) there are three branches given off by the P1 that run nearly parallel to each other and supply the occipital and temporal lobes.⁷ Triplicated PCAs had a frequency of 0.8% in the study conducted by Kapoor *et al.*⁷ and in half of these, the middle branch was non-patent due to its exceedingly small diameter.

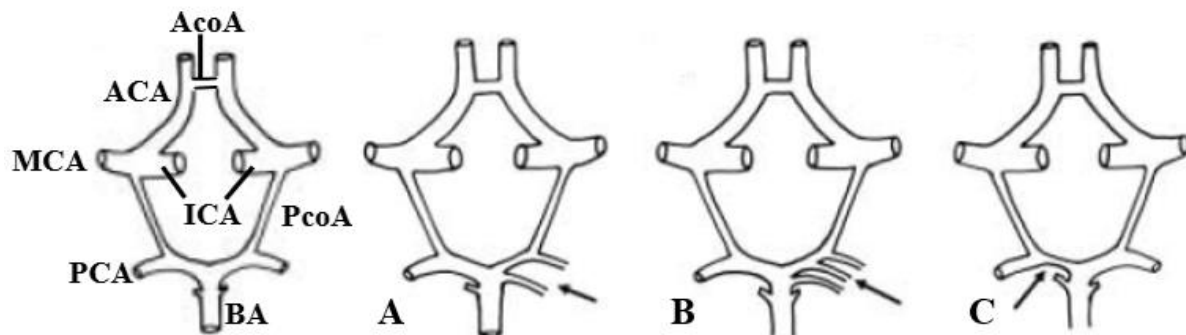


*Figure 2.14: Unilateral variations of the posterior cerebral arteries. A standard configuration is depicted in the first illustration and variations are depicted in A-C. Duplicated left PCA (A), triplicated left PCA (B) and hypoplastic right PCA (C). [AcoA: anterior communicating artery; ACA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery; PCA: posterior cerebral artery; BA: basilar artery; PcoA: posterior communicating artery]. Image modified from Kapoor *et al.*⁷.*

The P1 segment of the PCA has been reported to be unilaterally or bilaterally hypoplastic (*Figure 2.14C*), with an incidence of 6% to 17.7%,^{3,5,511} as summarised in *Table 2.8*. A hypoplastic P1 develops due to altered vasculogenesis that causes a small blood supply from the BA.⁷ The small supply from the BA results in a larger P2 to develop since it now receives a higher volume of blood from the PcoA.⁷ This variation is more frequently unilateral than bilateral.⁷

Table 2.8: The frequency of unilateral and bilateral hypoplasia and aplasia of the pre-communicating segments of the posterior cerebral artery (P1).

Author, year	Sample size	Study type	Country	Unilateral hypoplasia	Bilateral hypoplasia	Unilateral aplasia	Bilateral aplasia
Fisher <i>et al.</i>, 1905⁵²	414	D	USA	0.9%	4%	-	-
Riggs & Rupp, 1963⁵¹	994	D	USA	4.7%	3.3%	-	-
Puchades-Orts <i>et al.</i>, 1976⁵³	62	D	Spain	11.3%	-	-	-
Lazorthes <i>et al.</i>, 1979⁴⁵	200	D	France	2.5%	3%	-	-
El Khamlichi <i>et al.</i>, 1985⁵⁵	100	D	Morocco	3%	1%	-	-
Kapoor <i>et al.</i>, 2008⁷	1000	D(e)	India	4.3% (left); 4.9% (right)	1.4%	-	-
De Silva <i>et al.</i>, 2011⁵⁶	225	D(e)	Sri Lanka	0.8%	0.4%	-	-
Saikia <i>et al.</i>, 2014⁵	140	D(e) TOF	India	12.1%	4.3%	6.4%	5.7%
Machasio <i>et al.</i>, 2019⁷⁰	94	CTA	Kenya	-	7.4%	-	-
Hindenes <i>et al.</i>, 2020⁶²	1864	TOF	Norway	-	-	2.3% (left); 2.2% (right)	1.1%

The studies highlighted in grey did not differentiate between hypoplasia and aplasia. Instead, both were classified as hypoplasia. The ‘-’ indicates that no value was provided by the study, or the variation did not occur.

The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis.

D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; United Kingdom; USA: United States of America.

2.3.4.1.3 Basilar artery

Many variations in the BA are explained by the presence of a ‘persistent carotid-basilar artery anastomosis’ (PCBAA) caused by several embryonic arteries persisting during embryological development and remaining as a variation in the BA region.³⁴ Of these variations, a PTA is the most frequent followed by a persistent hypoglossal artery.³⁴ Hypoplastic BAs are uncommon but are often accompanied by a PCBAA when present.³⁴ Furthermore, fenestration of the BA has been reported with an incidence rate of 5% and increases the patient’s risk of developing a BA aneurysm.³⁴ Although the BA does not form part of the CAC, it is very closely related and certain variations of the BA may impact the PCAs. Therefore, the BA will be assessed for hypoplasia in the current study.

2.3.4.2 Anterior circulation

Usually, the frequency of variations in the anterior circulation is lower than in the posterior circulation and the AcoA appears to be the most variable artery of the anterior circulation. Some variations include alterations to both the AcoA and ACAs. For instance, in 1888, Windle⁴⁹ noted that 4.5% of the sample had triplicate ACAs: the ACA had 3 branches. More recently the third branch, which runs between the other 2 branches,⁴⁹ has been called the ‘artery of the corpus callosum’ or the ‘median artery of corpus callosum’ because of its pathway over the rostrum of the corpus callosum.⁷ The third vessel usually arises from the AcoA but can also arise from one of the ACAs⁷ and this variation is referred to as a median ACA (MedACA) or as an AcoA that gives rise to a median artery. In the literature MedACA has a prevalence of 0.7%⁵ to 22.7%⁵⁴.

2.3.4.2.1 Aplastic arteries in the anterior circulation

Windle⁴⁹ noted direct fusion of the left and right ACAs, which may or may not be accompanied by an AcoA. In 1% of samples where the AcoA was present, the ACAs had two connections: one by direct fusion and one via the AcoA. In the 3% of samples with no AcoA, there was direct fusion of the ACAs approximately 2 - 3.5cm after their origin to form a single ACA. This variation has also been noted in more recent studies.^{5,7} After 0.5 - 4cm, the unpaired ACA bifurcated to give rise to a left and right pericallosal artery.^{7,12} These branches follow the usual path of the ACAs.⁷ In this variation, the ACA is not accompanied by an AcoA since it merges approximately where this artery would lie.^{7,12} The AcoA was absent in 1.8% of the sample examined by Kapoor *et al.*⁷, however, in 27.7% of these cases, the ACAs were still connected.

Furthermore, there are two types of temporary direct fusion of the ACAs: one-point (short) fusion and long fusion.⁴¹ An example of short fusion (*Figure 2.15A*) is when the left and right ACAs are connected by a fistula owing to their proximity to each other and after this point of connection the arteries continue along their normal paths.⁷ In long fusion, there is no AcoA and no so-called true ACAs since there is only a single unpaired artery.⁴⁹ According to Riggs & Rupp⁵¹ direct fusion was common with those that had neurological conditions. The frequencies reported are in *Table 2.9*.

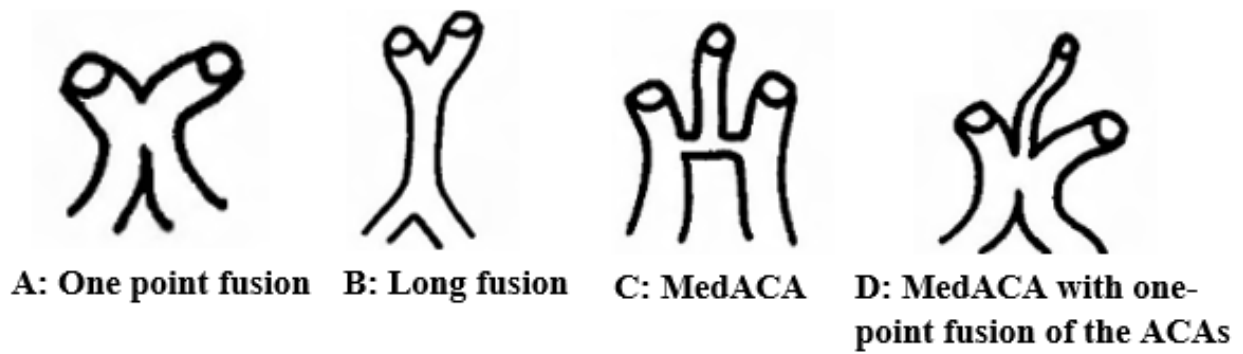


Figure 2.15: An illustration of variations of the anterior cerebral arteries (A-D). [MedACA: Median anterior cerebral artery]. Image reproduced from Ozaki et al.⁴¹.

Windle⁴⁹ also noted a unilateral absence of the ACA in 1% of the sample. The A1 segment may be unilaterally absent if the ICA continues as the MCA on either side.⁷ This variation seems to cause the ipsilateral ICA to have a reduced size and the contralateral A1 to be enlarged.⁷ Approximately 1cm from its origin, the A1 gives off a left and right A2 branch to compensate for the lack of an A1 segment on the contralateral side.^{5,7} The resulting branches are approximately equal in size and run almost parallel to one another.⁷ The frequency of unilateral ACA aplasia in the literature is reported in *Table 2.9*.

Table 2.9: The frequency of aplasia in the anterior circulation noted in the literature. The anterior communicating artery is reported as aplastic with no connection between the left and right anterior cerebral arteries and as being aplastic in a sample that has long or short fusion (one connection).

Author, year	Sample size	Study type	Country	AcoA			A1
				No connection	One connection		Unilateral
					Long fusion	Short fusion	
Windle, 1888⁴⁹	200	D	UK	-	0.5%	4%	1%
Fawcett & Blachford, 1905⁴⁷	700	D	UK	0.14%	-	-	0.14%
Alpers <i>et al.</i>, 1959⁵⁰	350	D	USA	2%	-	-	-
Puchades-Orts <i>et al.</i>, 1976⁵³	62	D	Spain	3.2%	-	-	0.8%
Ozaki <i>et al.</i>, 1977⁴¹	153	D(e)	China	0.7%	-	-	-
Chen <i>et al.</i>, 2004⁵⁹	507	TOF	Taiwan	11.4%	1.38%	5.92%	9.86%
Eftekhari <i>et al.</i>, 2006⁴⁴	102	D	Iran	1%	-	-	-
Kapoor <i>et al.</i>, 2008⁷	1000	D(e)	India	0.4%	0.9%	0.5%	0.4%
Saikia <i>et al.</i>, 2014⁵	140	D(e) TOF	India	5%	-	1.4%	2.1%
Machasio <i>et al.</i>, 2019⁷⁰	94	CTA	Kenya	4.3%	-	4.3%	11.7%
Hindenes <i>et al.</i>, 2020⁶²	1864	TOF	Norway	2.6%	-	-	0.7%
Enyedi <i>et al.</i>, 2023⁷¹	126	TOF	Romania	-	-	-	13.49%

Studies highlighted in grey indicate that the studies did not differentiate between aplastic and hypoplastic arteries. The ‘-’ indicates that the study did not provide a value, or the variation did not occur.

The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography. United Kingdom; USA: United States of America.

2.3.4.2.2 Hypoplasia in the anterior circulation

Hypoplasia and aplasia of the AcoA is uncommon⁶⁰ and Fawcett & Blachford⁴⁷ noted an aplastic AcoA in only 1 of 700 (0.14%) CACs. Hypoplastic AcoAs have been reported with a frequency of 1.05% to 14%,^{56,63} as summarised in Table 2.10. Moreover, Cilliers *et al.*⁴³ noted a higher prevalence (33.3%) of this variation in their South African sample. Saikai *et al.*⁵ noted that unilateral A1 hypoplasia was the most common variation in the anterior circulation in their study. Furthermore, hypoplastic A1 segments with an average sized A2 have been observed by various studies (Table 2.10).

Table 2.10: The frequency of hypoplasia in the anterior circulation. The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis of MRA/CT scans or a combination of both dissection and radiological analysis.

Author, year	Sample size	Study type	Country	AcoA	A1	
					Bilateral	Unilateral
Windle, 1888 ⁴⁹	200	D	UK	-	-	0.5%
Riggs & Rupp, 1963 ⁵¹	994	D	USA	9.2%	8.2%	3.8%
Fisher <i>et al.</i> , 1965 ⁵²	414	D	USA	3%	-	-
Lazorthes <i>et al.</i> , 1975 ⁴⁵	200	D	France	4.5%	-	1.5%
Ozaki <i>et al.</i> , 1977 ⁴¹	153	D(e)	China	-	-	11%
El Khamlich <i>et al.</i> , 1985 ⁵⁵	100	D	Morocco	11%	-	2%
Kapoor <i>et al.</i> , 2008 ⁷	1000	D(e)	India	2.1%	-	1.7%
De Silva <i>et al.</i> , 2011 ⁵⁶	225	D(e)	Sri Lanka	14%	-	3%
Saikia <i>et al.</i> , 2014 ⁵	140	D(e) TOF	India	7.8%	-	9.2%
Cilliers <i>et al.</i> , 2017 ⁴³	39	D(e)	South Africa	33.3%	-	2.6%
Cilliers & Page, 2018 ³⁸	10	D(e)	South Africa	5.1%	-	-
Dhakai <i>et al.</i> , 2020 ⁶³	95	CTA	Nepal	1.05%	-	4.2%
Alpers <i>et al.</i> , 1959 ⁵⁰	350	D	USA	3%	2%	
Puchades-Orts <i>et al.</i> , 1976 ⁵³	62	D	Spain	6.4%	6.4%	
Kamath, 1981 ⁶⁷	100	D (e)	India	2%	2%	
Iqbal, 2013 ³	50	D(e)	India	4%	4%	

The studies highlighted in grey did not differentiate between hypoplasia and aplasia in their study. The ‘-’ indicates that the study did not provide a value, or the variation did not occur. The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; United Kingdom; USA: United States of America.

2.3.4.2.3 Anterior communicating artery

AcoA variations may be observed frequently because the AcoA develops through the regression of the reticulated anastomosis between the ACAs. However, a trigger that alters regression allows for multiple or plexiform AcoAs to develop by the preservation of this plexus of smaller vessels.^{7,41,42} Plexiform AcoAs (Figure 2.16F), were observed with a frequency of 0.4% to 6.8% in the literature^{7,41} (Table 2.11).

AcoA duplication (double) and triplication was reported by Fawcett & Blachford⁴⁷ in 7.2% and 0.14% of their sample, respectively. Duplicated AcoAs tend to be more common and have been observed with an appearance of 5%⁷³ to 32%⁵ (*Table 2.11*) and there are typically three configurations duplicated AcoAs may have, as described below:

1. Parallel/double: The two branches run parallel to one another and approximately 0 - 0.5mm apart.⁷ One of the arteries may be hypoplastic.⁷
2. 'H'-shape (*Figure 2.16D*): Adding to the parallel configuration, the two branches are connected by a small anteroposterior vessel,⁷ which gives the AcoA a 'H'-shape.
3. Duplication in part of the AcoA where the branches are not parallel to each other, and the resulting apex is on either side.⁷ Two such configurations that exist are forked or 'Y'-shaped (*Figure 2.16C*) and 'V'-shaped (*Figure 2.16E*). Less commonly, 'O'-, 'N'- and 'X'- shapes have been observed.⁴³

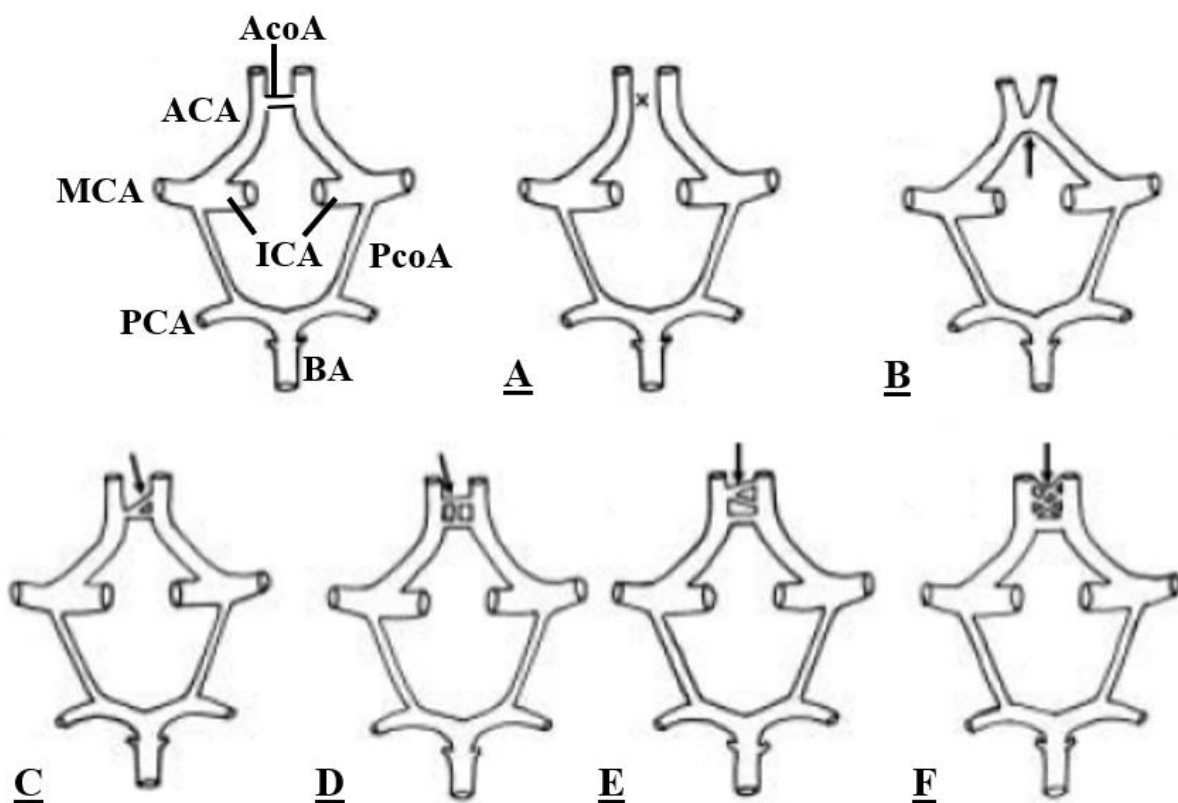


Figure 2.16: An illustration depicting several variations observed in the anterior communicating artery (AcoA). The first illustration (top left) depicts the conventional anatomy and A-F depict variations in the AcoA. These include: an absent AcoA (A); an absent AcoA resulting from the direct fusion of the left and right A1 segments -short fusion (B); the different AcoA duplications possible (C -E) where C is a forked or 'Y-shaped' configuration, D is a 'H-shaped' configuration and E is a 'V-shaped' configuration; a plexiform AcoA (F). [ACA: anterior cerebral artery; AcoA: anterior communicating artery; ICA: internal carotid artery; PcoA: posterior communicating artery; PCA: posterior cerebral artery; BA: basilar artery; MCA: middle cerebral artery]. The image is adapted from Kapoor et al.⁷.

In a triple AcoA, the middle branch is called the ‘corpus callosal branch’ and typically arises from the ACA.³ The middle branch can be patent or non-patent⁷ and has approximately the same diameter as the other two branches.³ This branch generally travels in an oblique direction.⁷

Table 2.11: The frequency of anterior communicating artery multiplications reported in the literature.

Author, year	Sample size	Study type	Country	Duplication (%)					Triplex (%)	Plexiform (%)
				Parallel	V-shaped	Y-shaped	N-shape	H-shaped		
Ozaki <i>et al.</i>, 1977⁴¹	153	D(e)	China	-	12.2	6.8	6.1	-	-	-
Kapoor <i>et al.</i>, 2008⁷	1000	D(e)	India	4.4	1.3	1.6	-	2.7	1.2	0.4
Cilliers <i>et al.</i>, 2017⁴³	39	D(e)	South Africa	-	-	5.1	2.6	5.1	-	-
Windle, 1888⁴⁹	200	D	UK	7.0					0.5	1.5
Fawcett & Blachford, 1905⁴⁷	700	D	UK	7.2					0.14	-
Puchades-Orts <i>et al.</i>, 1976⁵³	62	D	Spain	6.4					4.83	
Iqbal, 2013³	50	D(e)	India	6					2	-
Saikia <i>et al.</i>, 2014⁵	140	D(e) TOF	India	5.0					-	2.8
Alpers <i>et al.</i>, 1959⁵⁰	350	D	USA	9.0						

The ‘-’ indicates that the study did not provide a value, or the variation did not occur. The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; United Kingdom; USA: United States of America.

Saikia *et al.*⁵ described a fenestration of the AcoA as a ‘button-hole formation’, which was noticed in 4.3% of their samples and Charlick & Das²⁴ noted that fenestration of the AcoA was the most frequent variation in their study. However, it can be difficult to differentiate between a fenestrated AcoA and a duplicated AcoA with the ‘V’, ‘Y’, ‘H’ or ‘N’ configuration.⁴³ Therefore, fenestrated AcoAs are not reported often and may be mistaken for a duplicated AcoA.

2.3.4.2.4 Anterior cerebral artery

Fenestrated A1 segments were reported with a frequency of 6.4% by Saikia *et al.*⁵. According to Kwon *et al.*⁶⁶, a fenestrated A1 is usually seen in conjunction with other variations, including

a fused ACA and a hypoplastic A1. These researchers⁶⁶ noted that aneurysm development with a fenestrated A1 is ‘unique’ and their research revealed that there were only 18 other reports of a saccular aneurysm being associated with A1 fenestration from 1983 to 2011.

2.3.5 Combinations of variations

Variations of the CAC do not always occur in isolation, but combinations of variations are frequently reported. Reports of multiple variations are so common that they are noted in the classification systems outlined by Lazorthes *et al.*⁴⁵, Chen *et al.*⁵⁹ and Ayre *et al.*². For instance, studies by Kapoor *et al.*⁷ and Pascalau *et al.*¹² reported multiple variations in 7.4% and 40% of their samples, respectively. Kapoor *et al.*⁷ noted that these were usually two hypoplastic arteries and Pascalau *et al.*¹² noted that the majority of these occurred in the posterior circulation. Multiple variations should be reported together, as the overall haemodynamic effect of the combined variations could be more complicated than individual variations. Some of the possible combinations that may occur are in *Table 2.12*.

Table 2.12: The frequency of some commonly reported combinations of variations in the current literature. None of these studies differentiated between aplasia and hypoplasia.

Variations	Riggs & Rupp, 1963 ⁵¹	Fisher <i>et al.</i> , 1965 ⁵²	Lazorthes <i>et al.</i> , 1979 ⁴⁵	El Khamlichi <i>et al.</i> , 1985 ⁵⁵	Eftekhari <i>et al.</i> , 2006 ⁴⁴	De Silva <i>et al.</i> , 2011 ⁵⁶	Cilliers <i>et al.</i> , 2017 ⁴³	Hindenes <i>et al.</i> , 2020 ⁶²
Hypoplasia: unilateral PcoA, ipsilateral A1 and AcoA	1.6%	0.4%	1%	3%	-	-	2.6%	-
Hypoplasia: Unilateral PcoA and AcoA	4.1%	3%	5%	6%	4%	7%	5.1%	9.3%
Hypoplasia: Bilateral P1s and unilateral A1	0.5%	0.7%	0.5%	-	-	0.4%	-	-
Hypoplasia: A1 and contralateral PcoA	0.7%	0.2%	0.5%	-	-	-	-	0.8%
Hypoplasia: Bilateral PcoA and unilateral A1	5.8%	5%	3%	-	-	2%	-	1.5%
Hypoplasia: Unilateral P1 and contralateral A1	0.2%	2%	-	-	-	-	-	0.1%
Hypoplasia: PcoA and contralateral P1	2.6%	11%	1.5%	3%	2%	0.4%	-	6.2%
Hypoplasia: Bilateral PcoA and AcoA	6.7%	14%	17%	10%	4%	16%	5.1%	9.3%
Hypoplasia: P1, contralateral PcoA and ipsilateral A1	1%	1%	-	1%	-	-	2.6%	1.4%
Hypoplasia: P1 and ipsilateral A1	2%	0.2%	1.5%	1%	0.9%	2%	-	0.6%
Hypoplasia: AcoA and bilateral P1s	1.3%	2%	0.5%	-	-	0.4%	-	0.8%
Hypoplasia: AcoA, unilateral PcoA and contralateral P1	1.7%	7%	0.5%	1%	0.9%	-	-	0.9%
Hypoplasia: PcoA, ipsilateral A1 and contralateral P1	1.3%	3%	-	1%	-	-	-	0.3%
Hypoplasia: AcoA and unilateral P1	3.5%	-	2%	4%	0.9%	3%	-	1.9%

The '-' indicates that the study did not provide a value, or the variation did not occur.

2.3.6 Conclusion of variations

There are many variations that may be present in the CAC in either isolation or in combinations. The literature indicates that the PcoA is the most variable segment of the CAC^{5,11,12} and is more commonly hypoplastic than aplastic (Tables 2.5 and 2.6). The AcoA tends to be the most

variable segment in the anterior circulation. Variations that may occur in the current study include aplasia, hypoplasia, fenestrations, duplications, triplications, short fusion, long fusion, and a plexiform AcoA.

2.4 Clinical significance

2.4.1 Intracranial aneurysm development

Variations in the CAC have the potential to have adverse effects on the wellbeing of a patient if the collateral flow through the communicating arteries is affected by the configuration.⁵ Most intracranial aneurysms (IAs) are in the CAC or closely related arteries¹³ with some variations of the CAC being linked to IA location, development and subsequent rupture.^{11,12} Aneurysms are unusual dilations of arteries⁷⁴ that extend from the lumen through the wall of the artery.¹⁹ These dilations can develop rapidly and result from a structural weakening in the arterial wall, usually because of a reduction of the internal elastic lamina and altered media layers.⁷⁵ Structural deterioration of the arterial wall is prompted by adaptive responses, including inflammatory processes, that result in endothelial dysfunction. These responses are brought about by contributing factors, primarily haemodynamic stress,^{12,75,76} and increase the probability of IAs rupturing in a CAC with particular variations in pattern and dimension.¹² IAs develop in approximately 3 - 5% of people^{76,77} and are vital to understand, especially in the context of CAC variations.

Usually, unruptured cerebral aneurysms are asymptomatic, but this may depend on the size and location of the aneurysm.⁷⁴ For instance, an aneurysm that increases pressure on the optic nerve may result in visual disturbances as is the case with third nerve palsy (TNP).⁷⁸ TNP is the most frequent clinical presentation of an aneurysm on the PcoA because the IA applies significant pressure on the oculomotor nerve and some pressure on surrounding nerves.⁷⁸ Symptoms such as headaches, neck stiffness and vomiting usually appear if an IA ruptures and causes a subarachnoid haemorrhage (SAH),⁷⁴ also referred to as a haemorrhagic stroke, which could be fatal. Saccular aneurysms are the most common type of IA⁷⁷ and are described as an out-pouching of the arterial wall that usually forms at points of bifurcation^{19,77} or ‘abrupt vascular angles’⁷⁵ (*Figure 2.17*).

Other types of IAs include fusiform and dolichoectasia aneurysms (*Figure 2.17*). Fusiform aneurysms are dilations and elongations of an arterial segment^{19,77} instead of an out-pouching like that of the saccular aneurysms. These usually form in the arterial trunks.⁷⁷ Dolichoectasia

aneurysms are a form of fusiform aneurysm that are usually found in the vertebrobasilar system.⁷⁷

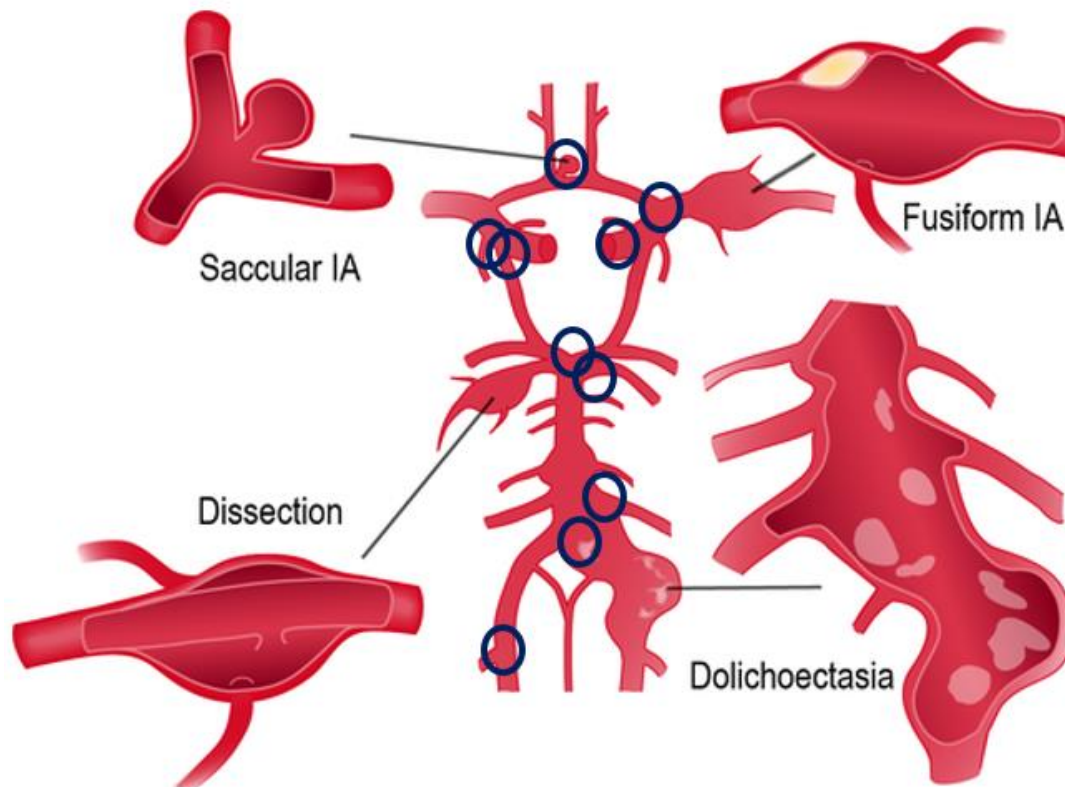


Figure 2.17: An illustration depicting the common types of intracranial aneurysms that can develop in the circulus arteriosus cerebri. The most common sites of intracranial aneurysms are indicated by the navy circles. [IA: intracranial aneurysm]. Image adapted from Kurtelius et al.⁷⁷.

In 2015, Nam *et al.*⁷⁴ conducted a haemodynamic experiment with a novel microfluid system to determine how blood flow affects the severity and location of aneurysm development. Their experiment demonstrated that in an occlusion-free, complete CAC there was bilateral symmetry in shear stress, which was greatest at points of bifurcation. While, areas that were further away from points of bifurcation, such as the centres of arteries, had low shear stress.⁷⁴ They noted that saccular aneurysms developed at points of high shear stress, especially at points of bifurcation, owing to greater frictional forces in the region.⁷⁴ This was especially evident in cases of hypertension which resulted in greater overall shear stress in the CAC.⁷⁴ Furthermore, Hong *et al.*⁶⁴ demonstrated that points of bifurcation have oscillatory wall shear stress (*Figure 2.18*), that is low at homeostasis to prevent the formation of blood clots.¹⁴ Therefore, there is a greater probability of IAs developing in regions with high shear wall stress, predominantly points of bifurcation. Furthermore, IAs can rupture if the shear wall stress is high and there is an increased risk of SAH.

If there is long term exposure to high shear wall stress, then adaptive responses are prompted in the endothelial cells of the arterial wall and increases the risk of atherosclerotic plaques developing.¹² This, in turn, increases the risk of ischaemic stroke. Atherosclerosis is one of the most common diseases that results in the deterioration of the arterial wall and eventual stroke.^{16,79} Atherosclerosis can result in haemodynamic instability and the development of a thromboembolism or a blood clot in circulation²; both of which can cause ischaemic stroke. Therefore, atherosclerosis is a factor that should be noted in studies investigating IA development and causes of ischaemic stroke.

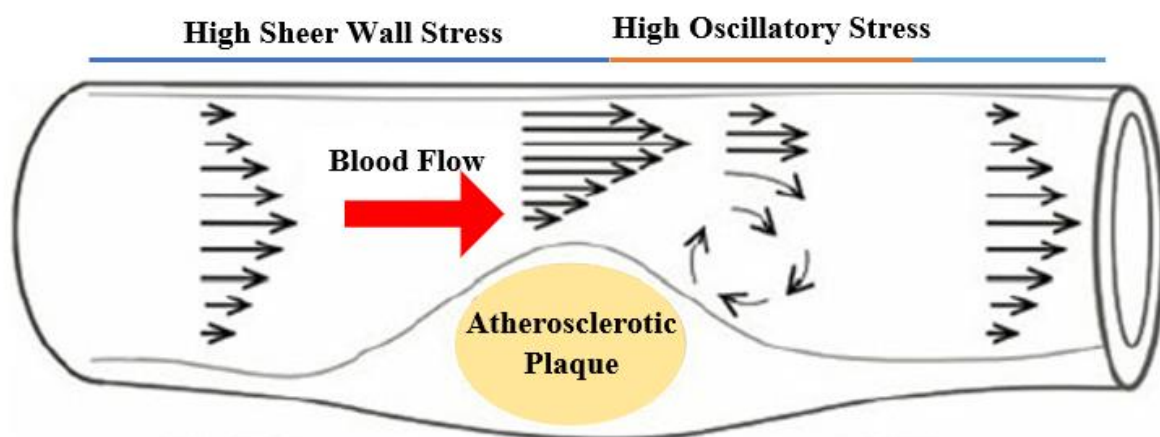


Figure 2.18: The types of stress exerted on the arterial wall by blood flow because of an atherosclerotic plaque. Schematic showing high shear stress (blue) and oscillatory shear stress (orange) in an artery containing an atherosclerotic plaque, indicated by the yellow-orange circle. The turbulence caused by the presence of the atherosclerotic plaque results in high oscillatory stress once the blood passes the plaque. The direction of blood flow is shown by the red arrow and the effects on blood flow are shown with the black arrows. Image adapted from Cho et al.⁸⁰.

The Hagen-Poiseuille equation, below, is used to evaluate shear wall stress by calculating the resistance to blood flow¹² and shows that a small decrease in the width of an artery results in a large increase in resistance to the flow of blood through that artery.⁶⁰ For instance, if atherosclerosis results in the radius of the artery decreasing by 75%, then the resistance rises by 256 times.⁶⁰ Therefore, it is evident that hypoplastic arteries would have higher resistance to blood flow than those that have an average or greater than average width. Hypoplastic arteries also change the standard geometry of the CAC by causing more imbalanced bifurcation geometry,¹² and altering the amount of friction at points of bifurcation. The increased pressure at the point of bifurcation in a hypoplastic artery is likely because blood flow would be slowed in this region. Furthermore, Nam *et al.*⁷⁴ reported that an aplastic PcoA or P1 resulted in approximately an 18% and 59% increase in shear stress, respectively. Thus, aplasia also has

the potential to increase sheer wall stress in the CAC. However, accessory or embryonic arteries were found not to disrupt the bifurcation geometry as significantly as hypoplastic arteries since the diameter of the main artery remained unchanged.¹²

$$R = \frac{8ln}{\pi r^2}$$

Where the variables are:

- R : Resistance to the flow of blood^{12,60}
- l : Length of the artery or arterial segment in question^{12,60}
- n : The viscosity of blood flowing through the artery^{12,60}
- $Pi (\pi)$: A mathematical constant, approximately equal to 3.14159, derived from the ratio of the circumference of a circle to the diameter of the circle.²²
- r : Radius of the artery in question^{12,60}

According to Kamath⁶⁷, the volume of blood that flows through a vessel is directly associated with the vessel diameter and has an inverse relationship with the vessel length. Thus, shorter and wider vessels tend to have more efficient or greater blood flow than longer and narrower vessels. The reason being shorter and wider vessels have less resistance because of a smaller endoluminal vessel wall area.^{18,60} Typically, Kamath⁶⁷ and Hoksbergen *et al.*¹⁸ found that arteries on the right side were longer and narrower. Furthermore, Lazorthes *et al.*⁴⁵ noted that the diameter of arteries in the CAC is the most frequent variation. Therefore, it is important that CAC studies consider both the length and diameter of arteries.

2.4.1.1 Associations of intracranial aneurysms and circulus arteriosus cerebri variations

In 1984, Kayembe *et al.*⁵⁴ compared CAC samples with and without IAs and noted that variations were more frequent in the IA group. The results of their study indicated that there was a higher incidence of asymmetric ACAs and PcoAs in the IA group. This agrees with a later study by Oberman *et al.*⁷⁶ who observed that the most common sites for IAs were on the PcoA and AcoA and that these were more likely to rupture than IAs in other locations. Furthermore, Oberman *et al.*⁷⁶ noted that A1 asymmetry and FTP often accompanied ruptured aneurysms and they concluded that CAC variations are significantly associated with the rupture of IAs; especially variations in the anterior circulation, where the A1 appeared to be a significant risk factor for rupture⁷⁶. FTP was noted by Oberman *et al.*⁷⁶ in 22.4% of the PcoA

aneurysm patients in their study, however, no association was found. In contrast, the PcoA aneurysms in the study conducted by Ozaki *et al.*⁴¹ were present with adult configuration (1.1%), transitional configuration (0.55%) and A1 and VA fenestrations (0.55%).⁴¹ Furthermore, Du Toit⁸¹ reported that there was no statistically significant difference between artery diameter and the location of IAs. In agreement with Kayembe *et al.*⁵⁴ and Oberman *et al.*⁷⁶, other researchers have also noted a high association of CAC variations and IAs.^{7,12,74} The association of CAC variations and IA development is likely explained by altered haemodynamic stress and the increased risk of rupture may be due to irregular artery wall morphology in the resulting IA.⁷² Moreover, the anatomical and haemodynamic characteristics of the communicating arteries increases the possibility of PcoA or AcoA IA rupture⁷⁶.

Additionally, AIs on the ACA-AcoA junction in the study conducted by Ozaki *et al.*⁴¹ were found with the following AcoA variations: one point fusion (0.54%), double AcoA with MedACA (0.54%), MedACA (0.54%) and 1.08% standard (single) AcoA. The PcoA aneurysms in the study conducted by Ozaki *et al.*⁴¹ were present with adult configuration (1.1%), transitional configuration (0.55%) and A1 and VA fenestrations (0.55%). There is currently debate in the literature about the relationship between fenestrations in the CAC and IA development with IAs being present with a fenestration with a frequency of 2.5% - 17%.⁶⁵ One study that found an association between duplication and fenestration with the development of IAs was Dimmick & Faulder⁸². In contrast to the aforementioned studies, Machasio *et al.*⁷⁰ found no association with the configuration of the CAC and IAs in their Kenyan cohort.

Many of the reported associations of CAC variations with the presence of IAs are vague in that the association could be for any variation in the CAC being present with an IA in any of the CAC arteries. For instance, Cohen-Gadol & Rhoton¹³ refer to aneurysms being present on the ICA-PcoA, ACA-AcoA, PCA-BA, ICA bifurcation, A1-A2 and PCA-PcoA but do not refer to what variations were associated with these.

2.4.2 Stroke

According to the World Health Organisation, 89% of deaths and disability caused by strokes are from low to middle income countries and this correlates to 66.7% of stroke patients residing in low to middle income countries,⁷⁹ like South Africa. In South Africa, stroke is reported as one of the top 10 causes of disability and approximately 20 000 deaths per year despite data being largely unavailable.⁸³ The permanent side-effects or disabilities experienced by the 15 - 35% of aneurysmal SAH survivors range from physical disability to cognitive deficits that

significantly decreases their quality of life.^{76,84} Of concern, aneurysmal SAH is one of the most frequent causes of disability and death in younger patients,⁷² with mortality rates of almost 50%.⁸⁴

The two types of strokes are ischaemic and haemorrhagic stroke: approximately 85% of strokes are ischaemic²¹ and are caused by a rapid reduction in blood flow to a region of the central nervous system by a blockage of an artery (*Figure 2.19*). This blockage can consist of groups of tumour cells, bacteria, a large air bubble, a thrombus or fragments of atherosclerotic plaques.¹⁹ Moreover, clots tend to form where there is ‘turbulent blood flow’,²¹ such as points of bifurcation. If the localised anaemia is long enough, the tissue usually supplied by the occluded artery becomes necrotic.¹⁹ The severity depends on the size of the blockage and the amount of time the designated areas do not receive blood flow¹⁹: transient (temporary) or permanent. If severe enough, ischaemic stroke is fatal.¹⁹ Whilst a haemorrhagic stroke or SAH (*Figure 2.19*), is less common and occurs in approximately 15% of reported stroke cases.²¹ SAH is caused by bleeding into the brain tissue or surrounding spaces and has several potential causes including infection, disease, trauma or developmental defects that results in a burst saccular aneurysm or leaking/rupture of a damaged blood vessel.¹⁹ Some risk factors for the development and rupture of IAs, include the morphology of the IA, hypertension, sex (females have a higher probability of rupture) and age.⁸⁴ Smoking is another risk factor because it has been associated with weakening arterial walls and increasing blood pressure.⁸⁴ When considering SAH in a South African sample, Swartbooi *et al.*⁸⁴ noted that IAs in the anterior circulation are at a higher risk of rupture than posterior circulation aneurysms.

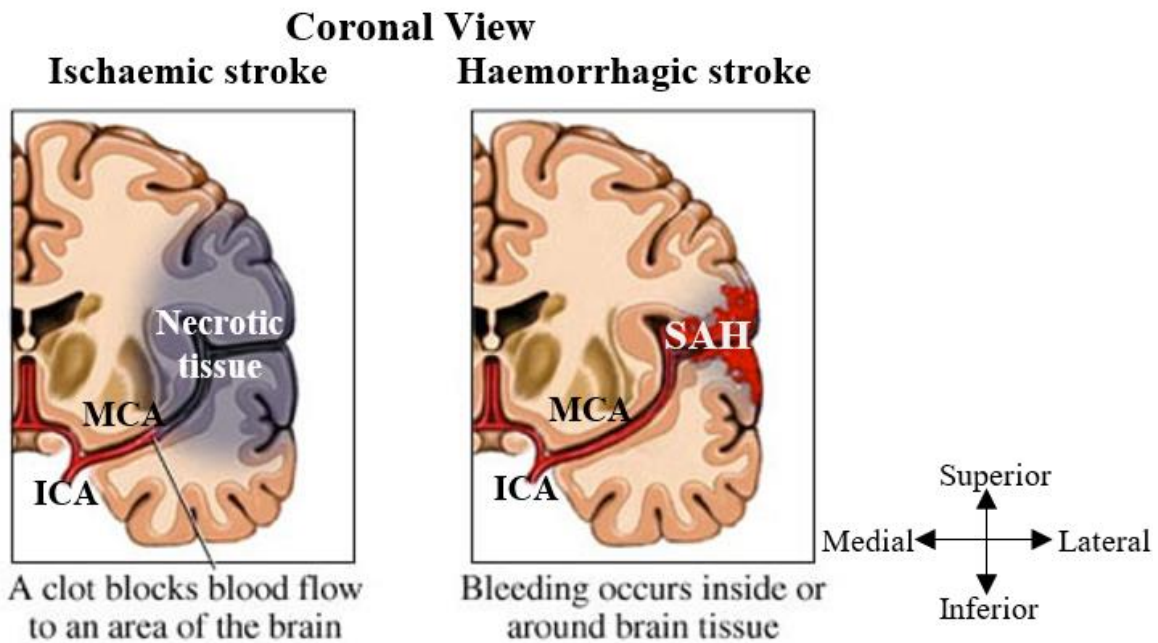


Figure 2.19: An illustration depicting the effects on blood supply to regions of the brain during an (A) ischaemic and (B) haemorrhagic stroke. The images merely provide an example of a cause for each type of stroke. [ICA: internal carotid artery; MCA: middle cerebral artery; SAH: subarachnoid haemorrhage]. Schematic adapted from the UCLA Interventional Neuroradiology website.⁸⁵

Stroke patients with the conventional CAC configuration tend to have lower stroke severity, lower probability of mortality, lower rate of recurrence and improved recovery over those with CAC variations.¹² Thus, implying the CAC can compensate for the alterations in blood flow more easily if it has the conventional configuration. The same observations have been made for ischaemic events: those who experienced ischaemic events had more variations than those who did not. A metanalysis conducted by Haghighimorad *et al.*⁸⁶ indicated that anatomical variations of the CAC resulted in patients being 1.38 times more likely to have an ischaemic stroke compared to those with the conventional anatomy. If the communicating arteries were hypoplastic or partially obstructed, then the patient had a higher risk of ischaemic stroke, especially if the patient had severe ICA occlusive disease,¹⁸ because collateral blood flow would have been hindered. Furthermore, the ICA has a predisposition to developing atherosclerosis and is vulnerable to stenosis and dislodging of the atherosclerotic plaque (embolism) which would move towards the brain owing to the direction of blood flow.²⁴ A large stenosis or occlusion of the ICA is a major contributor to stroke and transient ischaemic attacks and is a common cause of death and disability globally.²⁴ Likewise, BA occlusion that results in an ischaemic stroke is also usually owing to atherosclerosis.³⁴ Therefore, it is important to understand the CAC variations present in a population and the potential effects of these variations.

2.4.3 Other clinical significances

A CAC variation does not necessarily have a significant influence on blood flow. The only variation that is guaranteed to prevent the collateral function of the CAC would be the extremely rare occurrence of aplasia of both the PcoAs and the AcoA with no connection between the ACAs.⁸⁷ Moreover, variations in the CAC are not only associated with IAs and stroke, but with conditions such as migraines^{12,87} and psychiatric difficulties.¹² Kapoor *et al.*⁷ noted that patients with certain forms of pathology had more variations in the CAC and variations had a crucial role in the manifestation of clinical symptoms. Furthermore, Kamath⁶⁷ noted that patients with mental health challenges and a history of strokes had been reported to have a higher frequency of diameter variations.

2.4.4 Conclusion of clinical significance

A thorough understanding of CAC variations is accompanied by an array of benefits to clinicians, patients and researchers. Research into CAC variations could potentially improve clinical examination, diagnostics, patient selection for treatment³, treatment and cerebral operation outcomes through a better understanding of the symptoms presented by patients and their associations with CAC variations.¹¹ Knowledge of the CAC anatomy is vital for neurologists, neurosurgeons and neuroradiologists⁶ because variations could predispose patients to or result in complications during neurosurgery. For example, variations must be understood during aortic arch surgeries to ensure the brain is adequately perfused throughout the surgery.⁶⁰ Unilateral selective cerebral perfusion is one method of ensuring constant perfusion of the brain and relies on the collateral blood flow allowed by the CAC.⁶⁰ However, CAC variations may hinder collateral blood flow and result in complications during such surgeries.¹² Furthermore, knowing the average dimensions of cranial arteries may help surgeons determine if a shunt operation is appropriate.⁶⁷ Another example of when an intricate knowledge of CAC variations is required is during pathological lesion diagnosis and treatment. A better understanding may potentially allow for better treatment of stroke patients and Chuang *et al.*⁸⁸ believe that a CT scan conducted 24 hours after intravenous thrombolysis would allow predictions to be made about the estimated outcome of an ischaemic stroke patient. Their hypothesis is that a complete CAC would predict an improved functional outcome⁸⁸, meaning the recovery would result in improved behaviour or lessened physical limitations.

Additionally, this knowledge can aid anatomists, doctors, surgeons and radiologists when researching or investigating procedures, conditions or associations of variations to frequent

pathologies. Furthermore, this knowledge can be shared to improve teaching of the CAC to future researchers, doctors, surgeons and patients.³

2.4.5 Issues that arise when comparing studies

There are several factors that make direct comparisons of the current literature difficult and produce inconsistent results across studies. The current literature provides a wide range for many variations,⁸⁹ and this restricts the understanding of variations in the CAC. Additionally, the reliability of clinically significant diagnoses and procedures related to the CAC is decreased. The sources of inconsistency include differences in nomenclature,^{3,18} classification system used,⁶² sample size,^{43,62} cohort selection and study type.^{43,56,62,89}

2.5.1 Nomenclature

The nomenclature used to describe several variations of the CAC is inconsistent⁸⁹ and influences the perceived frequency of variations in the literature. One example of this is the definition of hypoplasia that differs among researchers. For instance, Kamath⁶⁷ and Iqbal³ state that hypoplastic arteries are either those with a diameter smaller than 0.5mm or 1mm, depending on the artery in question. However, others define hypoplasia as an artery with a diameter of less than 0.8mm.^{40,59,70} Lazzaro *et al.*⁷² and Zimelewicz Oberman *et al.*⁷⁶ indicate that an artery is hypoplastic if the diameter of the artery is less than 50% the diameter of the largest A1 segment of the CAC. In contrast, 56.25% of studies,⁸⁹ such as those conducted by Eftekhari *et al.*⁴⁴, Kapoor *et al.*⁷, Cilliers & Page³⁸ and Saikia *et al.*⁵, indicate that the diameter of hypoplastic arteries is smaller than 1mm, irrespective of the artery being analysed. This agrees with the current study. According to the meta-analysis conducted by Jones *et al.*⁸⁹, 18.75% of studies gave no definition of hypoplasia and this lack of a definition makes comparisons between studies very unreliable. Hoksbergen *et al.*¹⁸ states that the threshold diameter of the AcoAs and PcoAs ranges from 0.4mm to 0.6mm. Future studies should build on previous research, such as that conducted by Hoksbergen *et al.*¹⁸, to determine if the threshold diameter is the same for all arteries or if it is different for the communicating arteries. This could potentially allow for a consensus of hypoplasia to be developed.

Unfortunately, disparities in the use of nomenclature are not limited to hypoplasia and result in a wide range of measurements.^{3,18} For example, some studies may confuse an azygos ACA for a MedACA and vice versa.^{7,36} An azygos ACA occurs when the left and right A2 segments fuse to form a single A2 segment.^{41,73} This confusion potentially arose because both variations

develop from the persistence of the median artery of the corpus callosum.⁵⁷ However, definitions differ between studies and depending on the definition used, these terms could be confused or used interchangeably.

2.5.2 Classification system

There is no standardised classification system for the anatomical variations of the CAC, and this has resulted in researchers making use of different classification systems to define CAC variations. According to the metanalysis conducted by Jones *et al.*⁸⁹, 46.88% of studies use their own classification system. Others modify or use a pre-existing system such as the one developed by Lazorthes *et al.*⁴⁵ that classified variations into 22 types according to vessel diameter. The system developed by Chen *et al.*⁵⁹ divided variations into 15 anterior and 15 posterior circulation variations and Ayre *et al.*² separated variations into 82 variants (types) within five continuous groups. A comparison of these pre-existing classification systems is summarised in Table 2.13. Ayre *et al.*² states that their classification system enables the classification of both recorded and unrecorded variations and is beneficial for past and future studies. The classification systems by Lazorthes *et al.*⁴⁵ and Chen *et al.*⁵⁹ do not allow for this freedom.

Table 2.13: A comparison of three classification systems used for the circulus arteriosus cerebri: Lazorthes et al.⁴⁵, Chen et al.⁵⁹, and Ayre et al.².

	Lazorthes <i>et al.</i> , 1979 ⁴⁵	Chen <i>et al.</i> , 2004 ⁵⁹	Ayre <i>et al.</i> , 2021 ²
Standard Configuration	Type 1	-	-
Hypoplasia			
AcoA	Type 3	Anterior type G	Group 1: Type 1
Unilateral A1	Type 8	-	Group 1: Type 2
Unilateral PcoA	Type 4	-	Group 1: Type 3
Bilateral PcoA	Type 6	Posterior type E (non-patent)	Group 1: Type 11
Unilateral P1	Type 9	-	Group 1: Type 4
Bilateral P1	Type 10	Posterior type C (both patent) Posterior I (non-patent)	Group 1: Type 13
Aplasia			
AcoA (no connection)	-	Anterior type G	Group 2: Type 25
AcoA (long fusion)	-	Anterior type E	-
AcoA (short fusion)	-	Anterior type D	-
Unilateral A1	-	Anterior type H	Group 2: Type 26
Unilateral PcoA	-	Posterior type D	Group 2: Type 27
Bilateral PcoA	-	Posterior type E	Group 2: Type 31
Unilateral P1	-	-	Group 2: Type 28
Bilateral P1	-	Posterior type I	-

Multiplications			
Triple AcoA	-	Anterior type B	Group 4: Type 51
Duplicated AcoA (Parallel)	-	Anterior type B	Group 4: Type 42
Duplicated (H) AcoA	-	Anterior type B	-
Duplicated (V or Y) AcoA	-	Anterior type B	Group 5: Type 70
Plexiform AcoA	-	Anterior type B	-
MedACA	-	Anterior type C	Group 4: Type 52
Unilateral A1	-	-	Group 4: Type 59
Duplicated PCA	-	-	Group 4: Type 62 (unilateral)
Combined variations			
Unilateral hypoplasia of PcoA and AcoA	Type 5	-	Group 1: Type 5 Group 2: Type 29 (absent)
Bilateral hypoplasia of PcoAs and AcoA	Type 7	-	Group 1: Type 15 Group 2: Type 32 (absent)
Hypoplasia of the P1 and contralateral A1	Type 11	-	Group 1: Type 10
Hypoplasia of the P1 and ipsilateral A1	Type 12	-	Group 1: Type 9
Bilateral hypoplasia of P1s and A1s	Type 13	-	-
Hypoplasia of A1 and contralateral PcoA	Type 14	-	Group 1: Type 8
Hypoplasia of AcoA and P1	Type 15	-	Group 1: Type 6
Hypoplasia of the PcoA, ipsilateral A1 and AcoA	Type 16	-	-
Hypoplasia of the PcoA and contralateral P1	Type 17	Posterior type B (both patent) Posterior type F (P1 non-patent) Posterior type G (PcoA non-patent) Posterior type H (both non-patent)	Group 1: Type 12
Bilateral hypoplasia of the PcoAs and A1	Type 18	-	Group 1: Type 18 Group 2: Type 33 (absent)
Hypoplasia of the PcoA, AcoA and contralateral P1	Type 19	-	Group 1: Type 16
Hypoplasia of the P1, contralateral PcoA and ipsilateral A1	Type 20 (left PcoA) Type 22 (right PcoA)	-	Group 1: Type 19
Bilateral hypoplasia of the P1s and AcoA	Type 21	-	Group 1: Type 17

Not all the potential variations are included in the table. The ‘-’ indicates that there was no match for the variation in the classification system.

For Ayre et al.² there may be two options for the combination variations since the researchers separated aplastic and hypoplastic arteries, whereas, the other two classification systems did not differentiate between hypoplastic and aplastic arteries.

Table 2.13 emphasises that different classification systems cannot always be compared fully,⁶² are often ambiguous^{1,2} and can create confusion during comparisons. Sometimes this confusion results in the classification system being used incorrectly.² Furthermore, some studies, like Papantchev *et al.*⁶⁰, required the side of unilateral variations to be stipulated, but others, such as Riggs *et al.*⁵¹, did not. This has the potential to affect the perceived haemodynamic flow in certain studies or result in fewer comparisons among studies. Additionally, the classification systems by Lazorthes *et al.*⁴⁵ and Chen *et al.*⁵⁹ do not differentiate between aplastic and hypoplastic segments. Other studies use the terms interchangeably and refer to an aplastic or hypoplastic vessel as having zero diameter, such as the study conducted by Hindenes *et al.*⁶². This cannot reliably be compared to studies that separate variations into hypoplastic or aplastic arteries. A consensus needs to be made among researchers to allow for easy comparison between studies. Jones *et al.*⁸⁹ suggests creating a database to assist with the creation of a universal classification of the CAC.

2.5.3 Sample size and cohort selection

The frequency of CAC variations observed may differ between similar studies if their sample sizes differ significantly.⁴³ Moreover, studies with a large sample size have a higher chance of recording so-called rare variations compared to studies with a small sample size.⁴³

In addition to nomenclature discrepancies, the use of pathological brains with neurovascular diseases or conditions could contribute to a wide range being reported. Pathological brains could have an altered CAC and the conclusions made from data collected from these brains may be affected.^{47,52,58,90} The use of pathological brains could also introduce selection bias to the study as stated by Arjal *et al.*⁶⁹ who used radiographic images of brains from patients with cerebrovascular system complaints.

2.5.4 Different study types employed by researchers

Study type or methodology also varies in the literature and includes dissection, radiographic imaging, and a combination of dissection and radiographic imaging. These approaches may have different degrees of reliability and limitations should be stated in the study.

There are also differences between studies within the same study types. For instance, dissection studies have used embalmed and un-embalmed brains. Different techniques and solutions may be used for embalment, and this could result in varied presentation of the arteries. It is debated whether embalming processes cause vessel diameters to increase or decrease.

Balta *et al.*⁹¹ took CT scans of blood vessels before and after the embalming process and noted that injection of the embalming fluids caused the diameter of arteries to increase in highly vascularised structures (heart, lungs and liver) because of the pressure of the liquid. The vasculature was fixed in the enlarged state in samples that were embalmed using a strong fixing agent,⁹¹ like a formaldehyde solution. Therefore, the diameter of arteries may increase with formaldehyde fixation. This agrees with a statement made by Saikia *et al.*⁵ that the diameter of small arteries may increase with time. As such hypoplastic arteries may be mistaken for average diameter arteries.^{5,43} In contrast, some studies argue that the diameter of arteries may decrease after death and embalmment. A decrease in diameter could be attributed to the absence of blood pressure and muscle cell decay in the arterial wall.^{18,43} Further embalmment with formaldehyde may cause artery wall rigidity and shrinkage.⁹⁰ Therefore, arteries with the average diameter may be mistaken for hypoplastic arteries. For these reasons, some researchers, such as Van Eijk *et al.*⁹⁰, prefer to use un-embalmed brains because changes that may occur during embalming are eliminated. Un-embalmed samples are refrigerated, and this should slow decomposition. However, the extent of preservation of each sample in both embalmed and un-embalmed brains may vary and lead to discrepancies.⁵ Embalmed brains are used more frequently because they are more easily available for use at medical schools and universities as embalmed bodies are used in educational dissections in Health Science Faculties. Furthermore, embalmed structures are less prone to breakage and the brains are firmer in embalmed samples than in un-embalmed samples.¹⁰ Therefore, it is easier to dissect embalmed samples and some studies that receive un-embalmed brains from pathology services embalm the samples prior to dissection.^{7,10,56}

Moreover, the method used to determine the external diameter of arteries in dissection studies is not uniform⁵⁶ with different methods having varied limitations and levels of accuracy and precision. All the listed limitations to dissection studies must be considered when extracting from the literature, comparing results and making conclusions.

The different radiographic techniques used have some benefits over dissection, such as being *in vivo* and allowing for the analysis of variations in a sample of the living population.^{5,12,92} If no contrast materials are used, then some of these methods are non-invasive.⁹² Three common radiographic techniques include multi-slice computed tomography angiography (CTA) used by Arjal *et al.*⁶⁹, digital subtraction angiography used by Dhakal *et al.*⁶³ and 3D-TOF-MRA used by some other researchers.^{5,59} Each imaging technique has different levels of sensitivity, spatial resolution, specificity and accuracy in diagnosing different conditions. Therefore, they

may not yield the same results. Furthermore, some of these methods, such as 3D-TOF-MRA and CTA, rely on the volume and direction of blood flow.⁵ Consequently, arteries with a very small diameter and slow or turbulent flow may be misinterpreted as being aplastic.⁵ Thus, a complete CAC may be under-estimated and an incomplete CAC over-estimated.⁵ Therefore, some hypoplastic arteries may be observed in cadaveric study, but not in the imaging studies because these arteries could be non-patent, but still present.^{12,76} This would be an example of arteries being anatomically complete, but not physiologically complete⁷ and is the reason patency tests were conducted in the current study.

Dissection and radiographic studies cannot be reliably compared to each other since dissection studies measure the external diameter of arteries with zero luminal pressure,⁵⁶ whereas radiographic studies measure the internal diameter with blood pressure.^{43,44,56} However, according to the metanalysis conducted by Jones *et al.*⁸⁹, no statistically significant difference was found between the results provided by dissection and radiological studies. In fact, there was an overlap, but Jones *et al.*⁸⁹ found no pattern or correlation between the types of studies. This is despite the limitations provided in the current literature for comparing the results of different study types because of the limitations of dissection studies, discussed previously, and dissection studies allow for visualisation of the arteries in situ, which is not possible in radiological studies.⁸⁹

2.5.5 Demographic information and *circulus arteriosus cerebri* variations

In addition to age and sex, some studies have investigated associations between CAC variations with geographic location. Population differences in CAC configuration is supported by Jones *et al.*⁸⁹, De Silva *et al.*⁵⁶ and Kornieieva *et al.*⁹³. Eftekhari *et al.*⁴⁴ highlights that variation studies of the CAC have the potential to explain the frequency of cerebrovascular diseases in patients of different ancestry or geographic location. However, Eftekhari *et al.*⁴⁴ found no statistically significant difference between the populations compared in their study, but this could have been owing to the classification system used. Furthermore, De Silva *et al.*⁵⁶ indicated that the geographical variations in the CAC show both intra- and inter-population differences. These variations could be due to genetic influences, environmental factors or a combination of these.^{3,56} Therefore, the proportion of variations may be due to anatomical variations that are population-specific⁸⁹ and this has the potential to cause discrepancies between studies.^{44,56,89} As such, more research in each region, including South Africa, needs to be done with a standardised classification system. However, since there is also intra-population variation,⁵⁶

each province or region within a country should be analysed. This study will be the second study to observe the entire CAC in the context of the area surrounding Groote Schuur Hospital in Cape Town.

Chapter 3: Materials and methodology

3.1 Study design

This was a retrospective, cross-sectional and quantitative study.

3.2 Macroscopic dissection

To analyse the variations present in a sample of the deceased South African population, the brains of 94 bodies in the Department of Human Biology (HUB) at UCT were analysed. Bodies from two cohorts were used: 2022 and 2023 cohorts. Of the 94 brains available, 64 were suitable for this study. Age (years) and sex (male or female) of each body was recorded in accordance with the HUB register of human remains. An employee of HUB recorded this information from the death certificates of the incoming bodies prior to the embalming process. During data collection, the spreadsheets had a column labelled 'Body ID', referring to the record-keeping number given to each body by HUB. The Body ID was on the identification tag of each body and was only used for record keeping. The Body ID number will not be revealed at any stage and solely allowed for proper record keeping being maintained. The tables in *Appendix B* (spreadsheet templates) and *Appendix C* (data) have a column including the unique 'reference number' given to each body for this study. The reference number will always be published without the Body ID. The reference number consisted of a number, given to the bodies in numerical order, followed by 'M' or 'F' to allow for easy separation of males and females during data analysis. A summary of the methodology used is seen in *Figure 3.1* and will be elaborated on in this chapter.

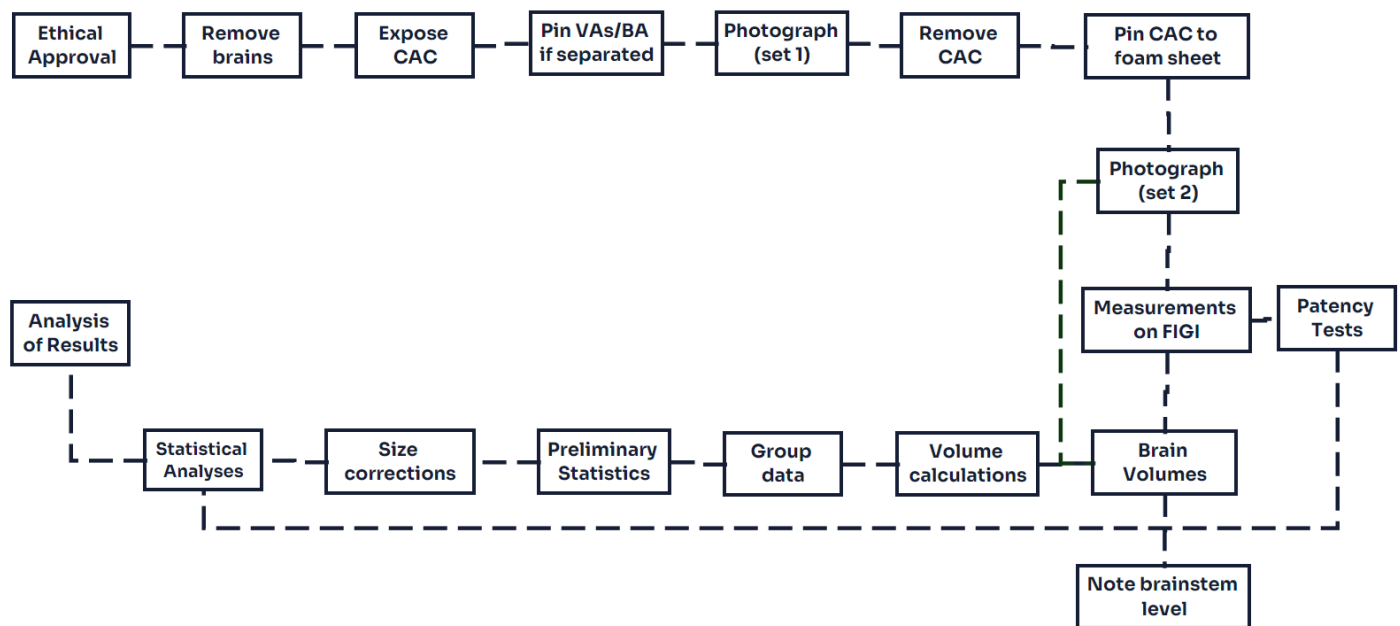


Figure 3.1: An overview of the methodology used for the macroscopic dissection component of the study.

3.2.1 Inclusion and exclusion criteria

All brains that were fully intact and had CACs that were intact were included. However, brains with extensive damage to the arteries were excluded since accurate measurements could not be obtained. The BA was excluded when a portion of the artery was missing, and the pieces found on the clivus and brainstem did not align. If the BA did not align with its bifurcation on the brain, then the posterior circulation was excluded from the study.

3.2.2 Removal of the brain

To study the CAC, the brain was exposed by removing the cranial vault of the skull using an oscillating saw. The oscillating saw was operated by trained technicians from HUB for both cohorts. A technician removed the brains for the 2022 cohort, however, to preserve the CAC in the 2023 cohort, the researcher and trained technicians removed the brains with more emphasis on preservation of the arteries. The technique used to remove the brain was as follows: The falx cerebri was separated from the crista galli with a scalpel and the dura was removed gently while trying to minimise damage to the delicate brain tissue beneath. Thereafter, any attachments from the base of the skull were severed using a scalpel. These included the cranial nerves entering/leaving the skull through their foramina and the stalk of the pituitary gland. The attachments of the tentorium cerebelli to the petrous temporal and occipital bones were cut and the spinal cord was separated from the medulla oblongata. The ICA was cut as close to its foramen as possible. Once the brain had no attachments to the base

of the skull it was gently removed. Care was taken to try keep the cerebellum attached to the cerebral hemispheres.

The CAC was exposed by placing the brain on its dorsal surface and removing the arachnoid mater and connective tissue coverings. The tiny penetrating arteries were removed if they obstructed the view of the CAC. The brains were stored in buckets filled with embalming fluid (80% ethanol, 3.3% thymol, 3.3% formaldehyde, 0.1% phenol and 13.3% water). Each body had its own bucket labelled with the Body ID.

3.2.3 *Circulus arteriosus cerebri* reconstruction

During the initial analysis of the CAC samples, it was noted that complete or partial absence of the posterior circulation was common. In some samples, the missing arteries were found on the brainstem accompanying the cerebellum that had become separated from the cerebral hemispheres. For other samples, the VA anastomosis and BA had to be removed from the clivus of the bodies. Thereafter, the arteries were pinned to the pons with a black map pin to reconstruct the CAC. The BA and/or VA anastomosis were aligned with the remaining arteries and placed in an anatomically correct position. The arteries were not stretched or forced into a particular position, but placed as they would naturally lie. Therefore, any curving of the arteries was not altered.

Once reconstruction was complete, the CAC of suitable brains were photographed using a Nikon DX camera with a resolution of 24.2 megapixels. An 18-55mm lens was used. In cases where the cerebellum and accompanying brainstem were separated from the cerebral hemispheres, the cerebellum was held in an anatomically correct position. For consistency, a tripod and ruler were used to ensure brains were photographed at the same height each time (31cm). A photograph of the Body ID on top of the brain was taken followed by a photograph of the brain angled anteriorly and a third photograph of the brain angled posteriorly. The brain was tilted to compensate for the 3D nature of the CAC and to allow for a clear view of both the anterior and posterior circulations. The brain was tilted posteriorly to make the posterior circulation more visible and tilted anteriorly to make the anterior circulation more visible. These photographs were used as a reference later in the study.

3.2.4 *Circulus arteriosus cerebri* removal

During the initial analysis of the CAC, it was determined that the curvature of the arteries, most notably the posterior circulation, hindered accurate measurements being taken with Fiji[®], a

form of ImageJ software.⁹⁴ Therefore, the CAC was removed from the base of the brain and photographed in isolation. The CAC was removed from the ventral surface of the brain in a similar manner to Hur *et al.*⁹⁵, who made use of rat brains. Arteries are larger in humans and more force was required to separate the arteries from the underlying soft tissue. Therefore, a scalpel was used, not just forceps. The ACAs, MCAs and PCAs were released from the underlying tissue and lifted slightly. Once the anterior circulation was free to be manoeuvred over the optic chiasm, the arteries were removed by lifting the ACAs and MCAs in an anterior-dorsal direction.⁹⁵ Thereafter, the BA and cerebellar arteries were separated from the underlying soft tissue and manoeuvred in a dorsal-anterior direction.⁹⁵ Any resistance caused by small projecting arteries was released by cutting these arteries. Since the BA needed to be preserved, an incision after the VA anastomosis was made (*Figure 3.2*). The CAC was freed from the underlying soft tissue and pinned to a black foam sheet. The method was altered for absent segments of the CAC and arteries that had previously been pinned in place were pinned to the foam sheet accordingly. Sewing pins were used instead of map pins to prevent obstruction of the arteries. If the arteries could not be aligned suitably on the foam sheet, then a space was left between the pieces. When taking measurements, the two smaller measurements were added together. Therefore, the risk of an overlap of the arteries causing an inaccurate length measurement was reduced.

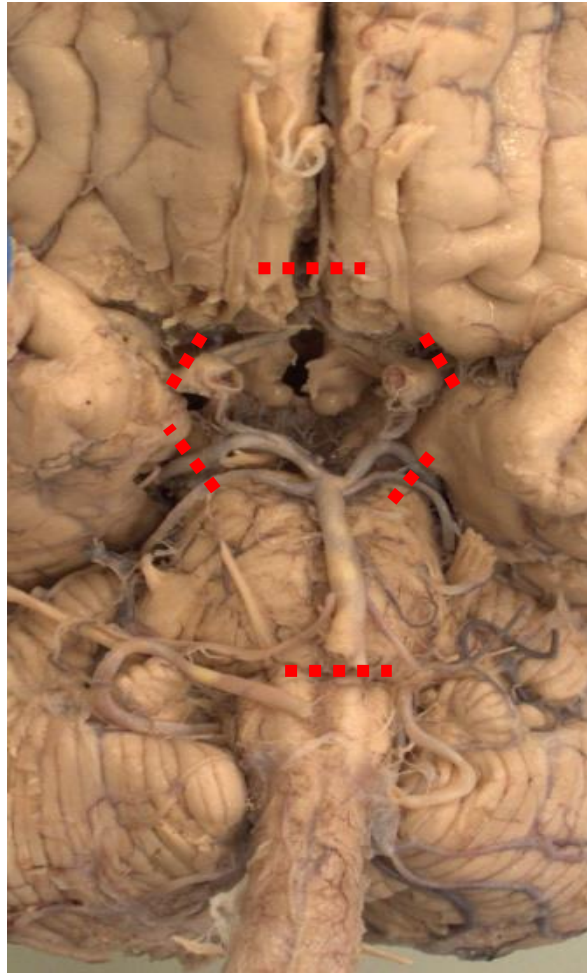


Figure 3.2: The position of potential incisions to remove the circulus arteriosus cerebri from the ventral surface of the brain. The points of incision are marked by red dashed lines. In this sample, the vertebral arteries had already been cut close to their anastomosis during removal of the brain from the skull, determining the position of the most posterior incision. Photograph obtained from the current study.

3.2.5 Photographing the *circulus arteriosus cerebri*

Suitable photographs were required to use Fiji® software to measure the dimensions of the arteries. The photographs were taken as follows: The removed CAC was pinned to a foam sheet and photographed with the same Nikon camera. The camera was maintained perpendicular to the CAC to avoid errors that may have arisen because of different viewpoints.⁴⁴ A tripod was used to ensure the camera was directly above the CAC when the photograph was taken and not at an angle. The distance between the CAC and the lens of the camera was measured using a 31cm ruler before each photograph was taken. If there was a change in distance between the lens and the CAC, then the position of the foam sheet was adjusted to ensure the correct distance was maintained. A ruler was included in each photograph to allow for calibration of the software.

3.2.6 Measurements

Before measurements were made on each photograph, the software was manually calibrated by setting a scale using the ruler in the photograph. Following this, three measurements were conducted for each of the length and diameter measurements. If the measurements differed by more than 0.2mm, then the measurements were redone. For the artery length, measurements were taken for both the inner and outer edge of the artery. To ensure accuracy of the data, the average of the six measurements was calculated and reported as the length of the artery. If an artery was broken along its length, then the edges of the pieces were measured and added together. If a PcoA was broken and it was not clear in the original photograph where the PcoA would have inserted into the P1, then a new photograph was taken to be able to measure the length of the P1 segment. A circular sticker was cut into quarters and one quarter was placed on the foam sheet to ‘point’ at the point of anastomosis. Thereby, acting as a marker for the measurement in Fiji[®]. However, if the PcoA was aplastic, then the ipsilateral P1 was excluded from the length measurements since the PcoA was the landmark being used for the P1 length. A reliable length measurement would not have been obtained. The data used for statistical analyses is in *Table a and b (Appendix C)*.

The inner and outer edge of the AcoA, A1, PcoA, P1 and BA arteries were measured using the multipoint option in Fiji[®], as follows (*Figure 3.3A*):

- AcoA: From ACA to ACA
- A1: From the ICA to the point where it joins the AcoA
- PcoA: From the ICA to PCA
- P1: From the PCA to the point where it meets the PcoA
- BA: From the centre of the inverted ‘V’ created by the fusion of the two VAs to the centre of the ‘V’ created by the bifurcation of the BA into left and right PCA

The external diameter of the AcoA, A1, PcoA, P1 and BA were measured using the straight option in Fiji[®]. The diameter measurements were taken as close to the centre of the vessel as possible (*Figure 3.3B*) depending on if and where the vessel was broken.

Since variations can be unilateral or bilateral,^{44,60} both the left and right arteries were measured for paired arteries: A1, PcoA and P1. Other variations, such as fenestrations or duplications were noted. A sample was said to have short fusion if the ACAs were directly fused or a

compressed 'x' shape was noted, indicating a fistula-style connection. The length and diameter of significant accessory vessels were also recorded where possible.

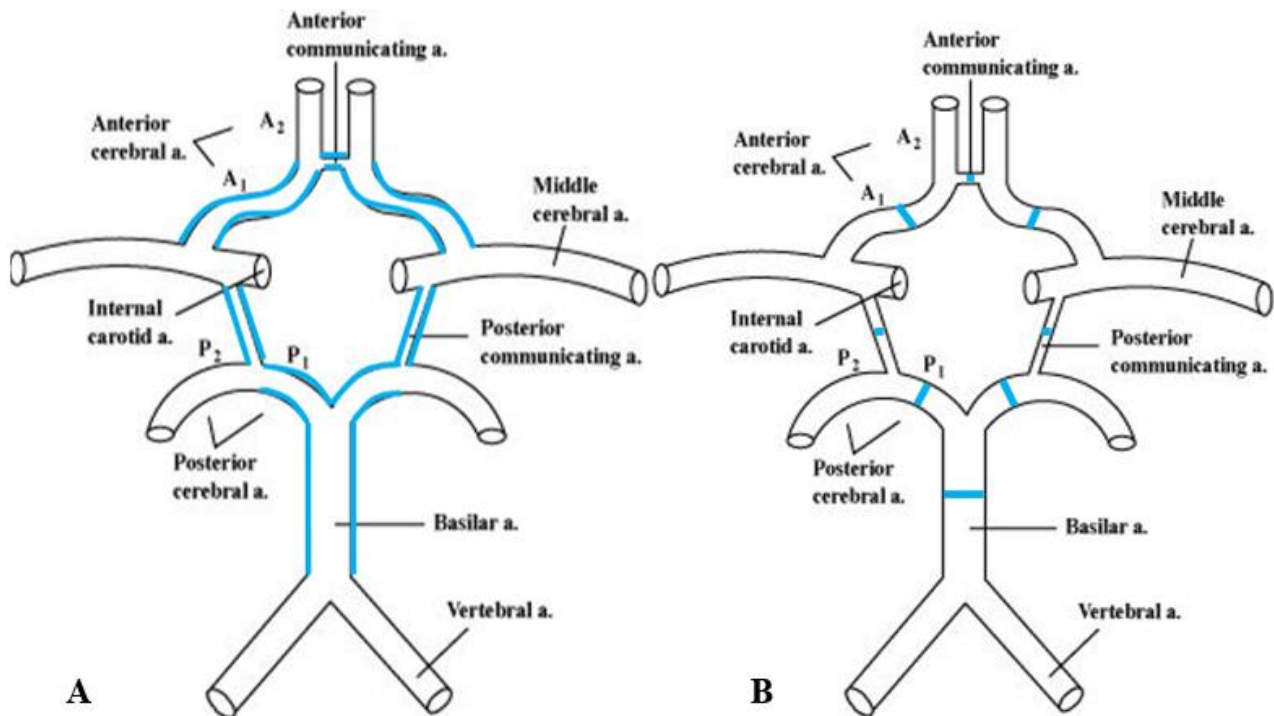


Figure 3.3: Illustrations depicting the approximate locations of the length (A) and diameter (B) measurements. To determine the length of the artery, both the outer and inner edges of each vessel were measured. For the basilar artery, the left and right edges were measured. The image is adapted from Gaigalaite et al.⁴⁰.

3.2.7 Patency test

The patency of arteries with a diameter smaller than 1.5mm and those with unusual branching patterns, that may have resulted in the arteries being non-patent, were analysed to determine if the vessel was patent or not. To do this, suitable arteries were cut in cross-section in multiple places along their length and placed under an Olympus dissection microscope to determine if the vessel had an open lumen. A cross-section close to the point of anastomosis was analysed for each side of the artery to ensure the point of anastomosis allowed for blood flow. Patency data is in *Table c (Appendix C)*.

In samples where the lumen appeared closed or flattened, a syringe with a thin 27G needle was used to determine if water could pass through the vessel. If water could pass through, then the vessel was patent. If water could not pass through, then the vessel was non-patent.

If an artery was believed to be aplastic, then the arteries that the aplastic vessel would usually anastomose with were analysed under the same dissecting microscope to ensure the vessel was

not removed from the CAC. The other arteries were analysed for any indication of anastomosis: a hole in the wall that would have indicated a lumen of the missing artery. If no indication of anastomosis was found, then the absent artery was declared aplastic.

3.2.8 Brain volumes

It was hypothesised that there would be a statistically significant difference in brain size within the sample, as such it was a consideration that the size of the brain could influence the dimensions of the CAC arteries. Therefore, a correction factor may be needed when comparing artery dimensions across the sample. For this reason, the volumes of all suitable brains were measured and compared to investigate whether correction factors were needed.

A water displacement method was used to measure the volume of each brain. It was determined that the following formula would be used to calculate the volume of the brain:

$$\text{brain volume } (V_t) = V_f - V_i$$

Total brain volume (V_t) was determined by subtracting the initial volume (V_i) from the final volume (V_f). The final volume was calculated as the mean of the three displaced volumes obtained from the water displacement method. The calculations for each brain are in *Table e (Appendix C)*.

To obtain each volume required for the calculations, a 5000ml (5L) beaker was filled to the 3000ml (3L) mark: the initial volume (V_i). The brain was drained of excess embalming fluid by holding it above a bucket until dripping ceased. The brain was then placed in the beaker and the change in volume was read and recorded after bubbles stopped appearing and the water was still. If the brain floated (occurred 10 times), then a dissection probe was used to hold the brain underwater or to manoeuvre the brain into a position where the whole brain was submerged without the use of the probe. This process was repeated three times to obtain three volume measurements for each brain (V_{1-3}). The mean of V_{1-3} was calculated for the volumes (V_f).

The CAC supplies the cerebellum and as such, volume measurements were done with the cerebellum. If the cerebellum had detached from the cerebral hemispheres, the volumes with and without the cerebellum were taken. While taking the measurements, the observer ensured that their eyes were horizontally in-line with the beaker markings to ensure the level was read correctly. The level read was at the bottom of the meniscus (*Figure 3.4*).

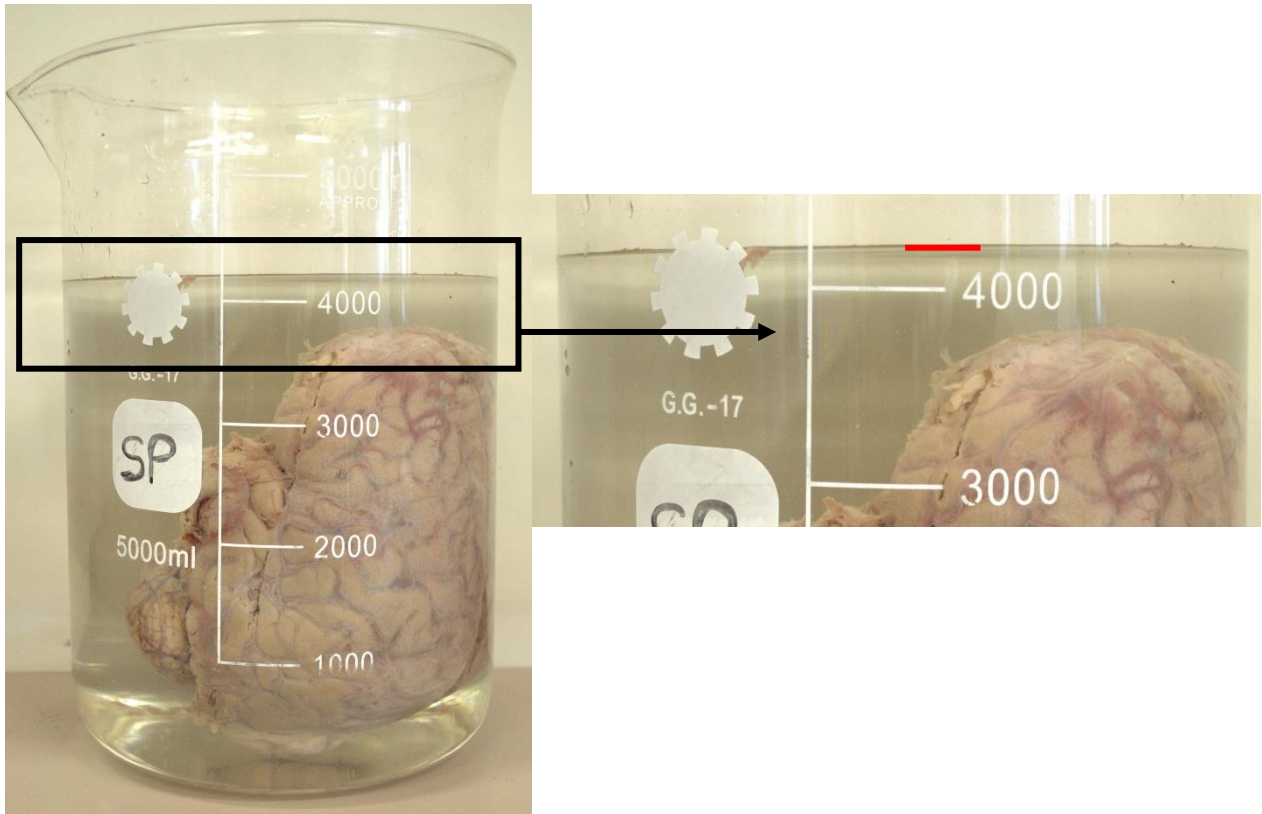


Figure 3.4: A photograph demonstrating the water displacement method for calculating the brain volume. The volume measurements were read in-line with the meniscus and the red line marks the bottom of the meniscus. The photograph is from the current study.

As seen in *Figure 3.4*, the beaker used only had demarcations at each 1000ml (1L) point. Therefore, to obtain the volumes for each repeat (V_{1-3}), water was removed from the beaker using a measuring cup until the bottom of the meniscus was in line with the white 4000ml (4L) demarcation. The volume of removed water was measured using a 5ml syringe and the appropriately sized measuring cylinder. This volume was added to 1000ml to complete the volume measurement. This was done to prevent using smaller glassware to measure the 1000ml displacement up to the 4000ml demarcation. Thereafter, the brain was removed from the beaker and water was removed until the bottom of the meniscus aligned with the 3000ml demarcation. The volume of the next brain was then measured.

The level at which the brainstem was cut was observed and noted (*Table e; Appendix C*) to determine if the remaining tissue significantly altered the volume reading. The brainstem was marked as A-D depending on the segments that remained, and segments B and D were measured (in mm) if the brainstem ended in those regions (*Figure 3.5*). This was done in case further statistical analyses were required at a later stage.

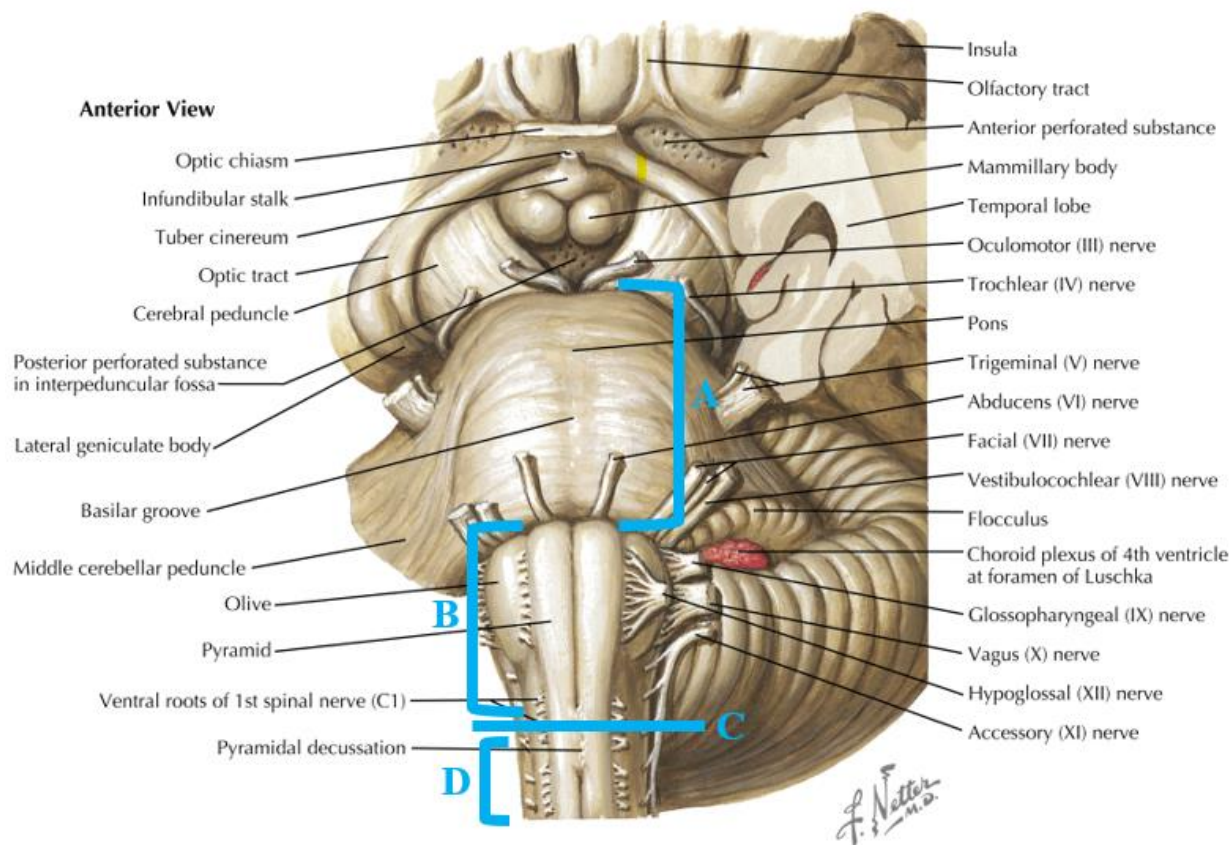


Figure 3.5: Illustration showing the demarcations of the brainstem. The brainstem was divided into four segments to record what remained of the brainstem and spinal cord once the brain was removed from the skull. A: The pons; B: Medulla oblongata; C: Decussation of pyramids and D: Spinal cord. The image is adapted from Felton et al.⁹⁶.

3.3 Radiology

Unfortunately, the radiological component of the study was not successfully pursued for a variety of reasons, including difficulties with the identification of the necessary arteries in the images and the subsequent progression of the cadaveric portion of the study. However, the proposed methodology, as laid out in the thesis proposal, is still included.

Angiographs were analysed to determine the variations present with aneurysms in a sample of the South African population. The MRA/I images were obtained from the Radiology Department of Groote Schuur Hospital (GSH), Cape Town. These were from patients who underwent an MRA/I of the brain. A summary of the methodology used is in *Figure 3.6*.

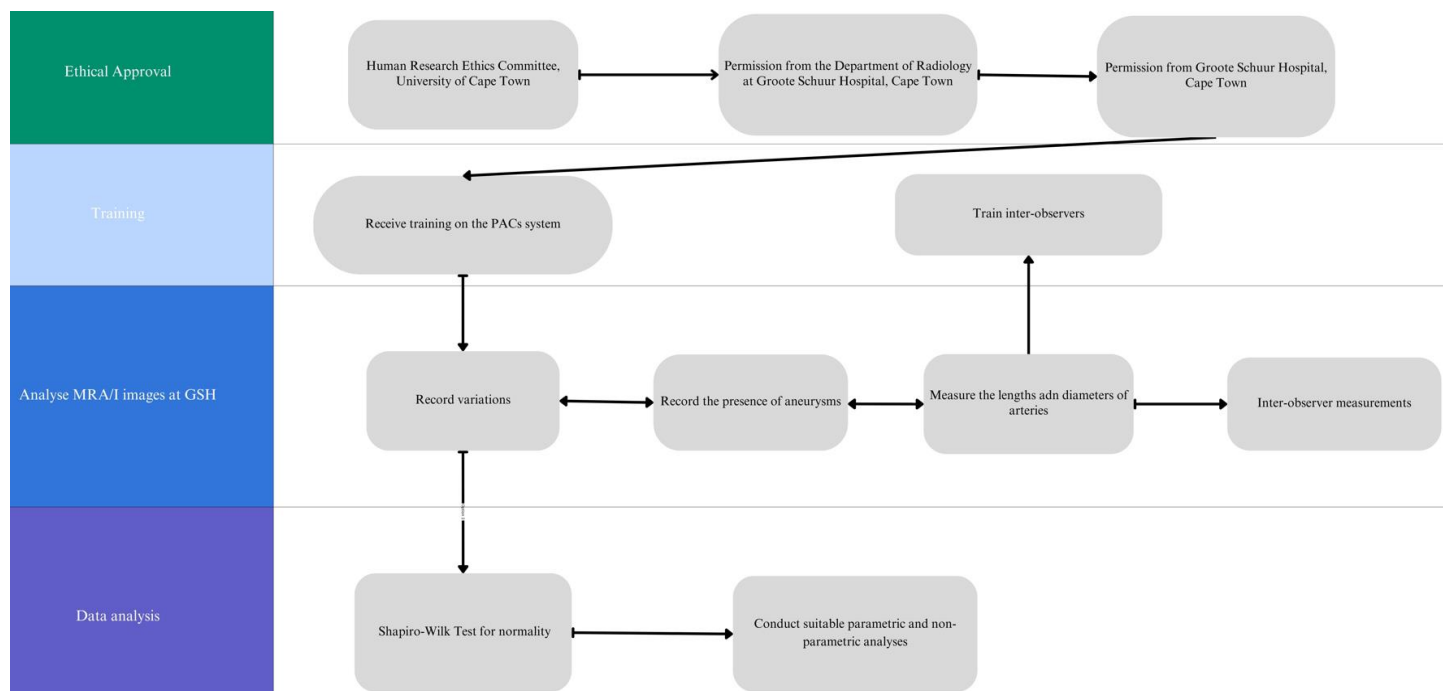


Figure 3.6: Overview of the methodology for the radiographic dissection component of the study.

3.3.1 Sample size

The number of images that were required was calculated using the following formula:

$$n = \frac{[(z - score)^2 \times (sd)(1 - sd)]}{(margin\ of\ error)^2}$$

Where, n was the sample size that was required. The z-score was consistent with the confidence level and was a constant.⁹⁷ The most common confidence intervals, or z-scores, were 90%, 95% and 99%.⁹⁷ This study made use of the most accepted confidence level in variation studies: 95%, which corresponded to a z-value of 1.96. The standard deviation (sd) was 0.5 as this ensured the sample size would be sufficient.⁹⁷ Lastly, the most common margin of error of $\pm 5\%$ or 0.05 was used.⁹⁷ From the above formula, it was estimated that 384 MRA/I images had to be analysed for this study.

3.3.2 Inclusion and exclusion criteria

All images with well visualised CACs and a time-of-flight (TOF) sequence were included in the study. Images were excluded if they aligned with one or more of the exclusion criteria. Exclusion criteria included patients with significant alterations to the CAC or the base of the brain and included those with trauma to the head, surgery or pathological lesions⁴⁴ that had the potential to alter the CAC. The image was excluded if the MRA/I was unreliable owing to pathologies, such as severe haemorrhagic stroke or infection.⁴⁴ Furthermore, blurry or distorted

MRA/I images were excluded. Images with IAs were only included if the aneurysm did not obstruct the MRA/I image. Images had to have a TOF sequence and were excluded if this was not present.

3.3.3 Analysis of the MRA/I images

To analyse the images, Philips Intellispace[®] software on the Picture Archiving and Communication system (PACs) was used. Philips Intellispace[®] software allowed for analysis of the 3D images,⁹⁸ while the PACs system allowed for the safe and secure storage of the images.⁹⁹

Only magnetic resonance perfusion (MRP) images were used for measurement. Measurements were taken at the same locations as those for the macroscopic dissection component of the study (*Figure 3.3*). Each measurement was conducted three times and the average of the three measurements was used in statistical analyses. These measurements were recorded in a Microsoft Excel spreadsheet like that in *Tables a-b, Appendix B*. Each patient was given a unique reference number that replaced the patient number to maintain anonymity of the results. Thereby, protecting the patients' identities.

3.4 Intra-observer and inter-observer analyses

3.4.1 Intra-observer analyses

To ensure accuracy, each measurement was conducted three times, and the average was calculated. The repeat measurements were not conducted immediately and were either separated by other measurements or were conducted on different days. The values were compared and if the measurements were not within 0.2mm of each other, then the cause of this difference was determined, corrected and the measurements conducted again. The corrected measurements were used in this study.

3.4.2 Inter-observer analyses

Inter-observer measurements were conducted with both supervisors of this study. Selected data where some difficulties were experienced when taking measurements were checked by the same three people. Both supervisors confirmed that the location of each measurement was correct and that the repeat measurements were within 0.2mm of each other.

3.5 Statistical analysis of macroscopic data

The data was statistically analysed using STATA 17.0[®] software accessed through the UCT computer labs. All values were rounded after calculations and analyses were conducted.

3.5.1 Grouping of data

Before statistical tests were conducted, the data from the intact samples was grouped according to the classification system developed by Ayre *et al.*². This system consists of 82 different CAC variations (types) organized into five main groups, as follows:

- Group 1: CACs with one or more hypoplastic segments (24 types)
- Group 2: CACs with one or more aplastic segments (11 types)
- Group 3: CACs with hypoplastic and aplastic segments (6 types)
- Group 4: CACs with one or more accessory segments/ vessels (26 types)
- Group 5: Other types of variations (15 types)

This classification system was used because it differentiated between aplastic and hypoplastic segments and was thorough in its description of the anatomical variants of the CAC. Furthermore, if a variation was not already categorised in the system, it was relatively easy to group the sample based on other variations in the group. A summary of this classification system is in *Table a, Appendix A*. Any variations that were not noted by Ayre *et al.*² were placed in the group that best described the variations noted. In addition to the five variant groups, CACs with the conventional configuration were classed into group 6.

The CAC was defined as having the conventional anatomical configuration if the following criteria were met:

1. The CAC was complete: All the component arteries were present^{7,56}
2. All the arterial origins were from their typical source^{1,7}
3. There were no additional arteries present^{1,7,56}
4. There were no hypoplastic arteries present^{1,7,56}
5. There were no enlarged arteries present: no dominance where neither vessel is hypoplastic⁷

In accordance with various studies,^{3,5,7,67,72} an artery was defined as hypoplastic if it had a diameter of less than 1mm. Accessory vessels were not classed as hypoplastic since the standard diameter of such arteries had not been described. Instead, their sizes were noted.

CACs that were incomplete owing to broken arteries or were too segmented could not be reliably categorised into groups 1-6. Instead, this data was used in conjunction with the intact samples to assess the individual variations present. The frequency of individual variations was analysed for all CACs that were not excluded. Therefore, in CACs with multiple variations, each variation was recorded separately.

Furthermore, the sample was divided into three age groups and two sex groups, as shown in *Table 3.1*. The upper and lower limits for the age groups were set in a manner to try establishing an appropriate number of samples in each group for comparative purposes.

Table 3.1: A contingency table depicting the forty intact samples divided into two sex and three age groups.

Age group (years)	Number of samples		
	Male	Female	Total
30-59	4	1	5
60-75	6	7	13
76-100	10	12	22
Total	20	20	40

3.5.2 Statistical tests

3.5.2.1 Demographic information, variations and artery dimensions

Summary statistics were calculated for the artery dimensions and brain volumes to ensure the data was fully understood. Summary statistics included: maximum, minimum, mean, median, range and standard deviation for each variable.

Shapiro-Wilk tests were conducted to determine if the data was normally distributed. The D'Agostino-Pearson Omnibus test was used to confirm the result from the Shapiro-Wilk test if the p-value was equal to or slightly greater than 0.05.

If data was found to be not normally distributed, then more robust, non-parametric tests were conducted. These tests included Kruskal-Wallis H tests and Chi-squared tests for independence.

Kruskal-Wallis H tests were conducted to determine:

- If the frequency of individual variations was statistically significant.
- If age and the frequency of variations was statistically significant.
- If sex was associated with differences in both diameter and length for each artery.

- If age was associated with differences in both diameter and length for each artery.

Chi-square tests for independence were conducted to determine:

- If the frequency of symmetry and asymmetry was significant.
- If the difference in frequency of variations between males and females was significant.

However, if data was normally distributed for any of the variables, then a two-way independent sample t-test was conducted instead of a Kruskal-Wallis test.

One-way ANOVA was conducted to determine if the difference in variations between the age groups was statistically significant.

3.5.2.2 Brain volume and correction factors

The brains were grouped according to the level of the remaining brainstem: groups A to D. If the brainstem data was not normally distributed, a Kruskal-Wallis H test was used to determine if there was a statistically significant difference between the groups. If there was no difference between groups A-D, then all the volumes were grouped together for further analysis.

To determine if a correction factor should be used in variation studies of the CAC, the samples were grouped into small, medium and large groups based on the brain volumes. The groups were decided upon by assessing a bar graph of the volumes and visually assessing the data.

After the volume data summary statistics were analysed, the volume data was tested for outliers using the interquartile range (IQR) method. The IQR method uses the IQR (75th percentile - 25th percentile) to determine the upper and lower bounds of the data with the following formulas:

$$\text{Lower bound} = 25\text{th percentile} - 1.5(\text{IQR})$$

$$\text{Upper bound} = 75\text{th percentile} + 1.5(\text{IQR})$$

Any outliers were removed before the volume data was analysed further. One-way ANOVA tests were conducted:

- To determine if there was a statistically significant difference between the means of the three groups (small, medium and large).
- On the length to volume ratio to determine if there was a statistically significant difference between at least two group means.

- On the diameter to volume ratio to determine if there was a statistically significant difference between at least two group means.

If there was a difference between at least two groups, then correction factors were calculated by determining the average for each of the three groups and creating ratios. For the small volume brains, the mean of the small volume brains was divided by the mean of the medium volume brains. Thereafter, the ratio was multiplied by 100 to get a percentage. This percentage was the correction factor that needed to be added to the vessel dimensions of the small volume brains group. The formula to calculate the correction factor for the small volume brains was:

$$\text{Correction factor} = \frac{\text{Mean volume for small volume brain group}}{\text{Mean volume for the medium volume brain group}} \times 100$$

For the correction factor required to reduce the large volume brain group towards the sample mean, the following equation was used:

$$\text{Correction factor} = \frac{\text{Mean volume for medium volume brain group}}{\text{Mean volume for the large volume brain group}} \times 100$$

These calculations provided the two correction factors required. The small volume brain group would have the correction factor added to the length and diameter measurements. The large volume brain group would have the correction factor subtracted from the length and diameter measurements. All zero values (aplastic or missing arteries) were excluded from these calculations.

Thereafter, Wilcoxon signed-rank tests were conducted on the lengths and diameters of the small and large volumed samples combined before and after the correction factor was applied to determine if there was a statistically significant difference between the pairs of results (before and after).

3.6 Ethical approval

Approval to use the bodies in the Department of Human Biology at the University of Cape Town was granted by the Departmental Research Committee (DRC) and Cadaver Research Governance Committee (CRGC) with reference number: CRGC 2022/009. Thereafter, ethical approval was obtained from the Human Research Ethics Committee (HREC) for dissection of the bodies and the analysis of MRI/A images (ref: 645/2022). Further permission was obtained from Groote Schuur Hospital and the Head of Radiology at Groote Schuur Hospital, to gain access to the required images (*Appendix E*).

Once data collection was completed, the brains remained in the Department of Human Biology to be used for other research and educational purposes. Use of the brains and CAC samples was and will continue to be done at the discretion of the Department.

Chapter 4: Results

A total of 30 samples were excluded from the study for both the 2022 and 2023 cohorts, 22 and 8 samples respectively (*Table 4.1*). Therefore, the sample size for this study was 64 brains. The reasons for exclusion included: the samples were too segmented/damaged, not available for the study since they were being used for educational purposes, cut in multiple planes prior to analysis as part of the postgraduate teaching programme, and samples had no *circulus arteriosus cerebri* present because the arteries were cut too close to the soft tissue of the brain. Damage and segmentation were attributed to the difficulties in fixation of the brain during the embalming process and extensive damage to the arteries during removal of the brain from the skull.

Table 4.1: A summary of the excluded samples. The reason and number of excluded brains are recorded.

Reason for exclusion	Frequency
Too segmented	20
Cut in multiple planes prior to analysis	4
Used for educational purposes	2
No <i>circulus arteriosus cerebri</i> present	4

4.1 Intact sample variations

Of the 64 samples suitable for the study, only 40 samples were fully intact. Of the 40 fully intact samples, 9 (22.5%) had the conventional anatomical configuration and 31 (77.5%) displayed variations. The intact samples were categorised according to the classification system developed by Ayre *et al.*², as seen in *Figure 4.1*.

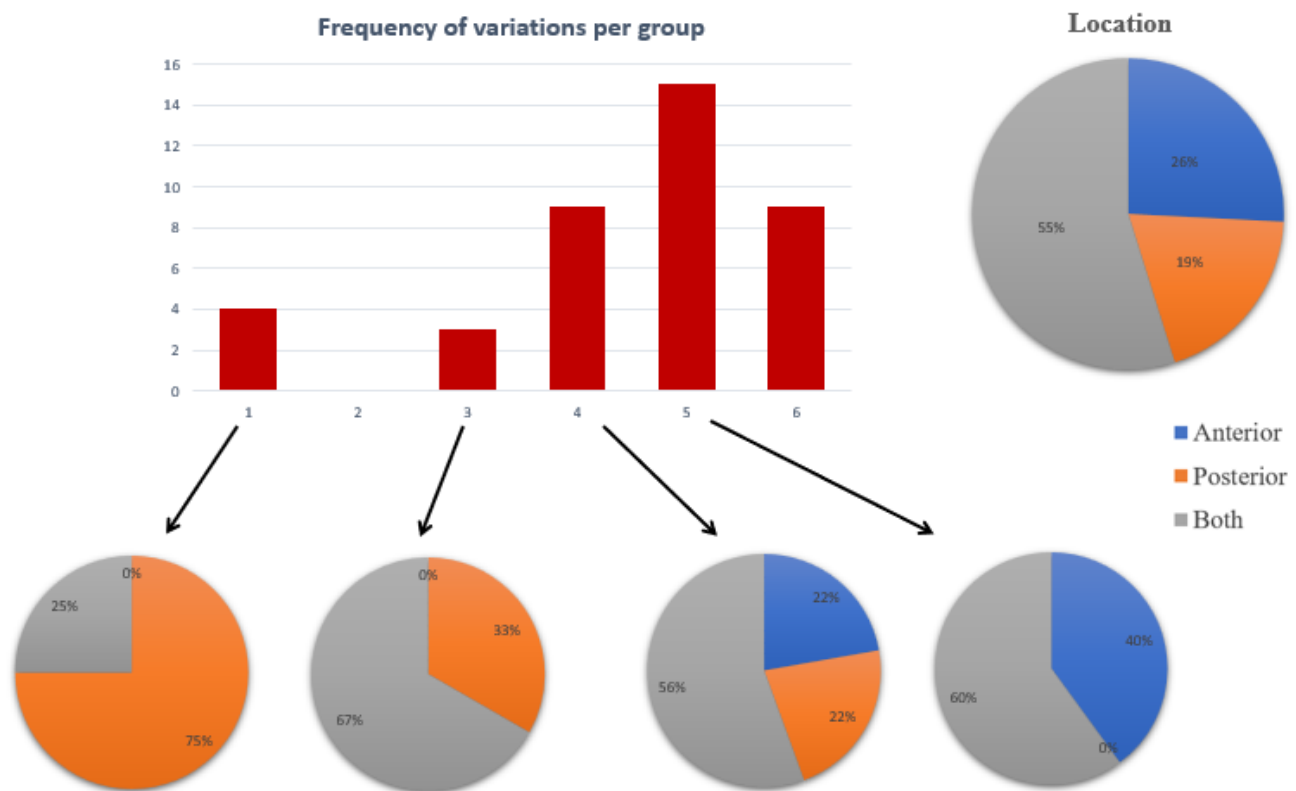


Figure 4.1: The results for the 40 intact *circulus arteriosus cerebri* samples. The samples were grouped according to the classification system developed by Ayre et al.² (groups 1-5) with the addition of a group 6 for samples that displayed the conventional anatomical pattern. The Ayre et al.² groups are: (1) hypoplastic arteries only, (2) aplastic arteries only, (3) hypoplastic and aplastic arteries only, (4) one or more accessory vessels and (5) other types of variations. The bar graph illustrates the frequency of variations per group. Each group is further divided into whether the variations are in the anterior (blue), posterior (orange) or both the anterior and posterior circulations (grey), as seen in the pie charts linked by the arrows to groups 1-5. The pie chart labelled 'location' indicates where the variations are found for the intact sample (n=31): a culmination of the smaller pie charts.

Figure 4.1 indicates that group 5 (other variations) had the highest frequency of variations (n=15; 37.5%)[‡] followed by group 4 (accessory vessels) and group 6 (conventional anatomical pattern) with 9 samples each (22.5%). Group 2 had no samples (n=0). The frequency of the different variation types within each group can be seen in *Table 4.2*. The most common location for variations in this study was in both the anterior and posterior circulations combined (55%). Followed by variations in the anterior circulation only (26%) and the lowest number of variations occurred in the posterior circulation only (19%).

[‡] The raw statistical outputs can be viewed in Appendix D.

Table 4.2: The types of variations observed within each group of the intact sample and their frequency. A description for each has been provided. Group 6 is excluded since no variations occurred in the conventional anatomical configuration group.

Type	Description	Frequency
Group 1		
3	Hypoplastic: one PcoA	1
4	Hypoplastic: one P1 segment	1
7	Hypoplastic: one A1 segment and ipsilateral PcoA	1
-	Hypoplastic PcoA and ipsilateral hypoplastic P1	1
Group 2		
	No samples	
Group 3		
37	One hypoplastic PcoA and aplastic contralateral PcoA	1
-	Unilateral hypoplastic A1, unilateral PcoA aplasia and unilateral PcoA hypoplasia	1
-	Unilateral PcoA aplasia and hypoplastic A1	1
Group 4		
42	Duplicated AcoA	1
43	Duplicated AcoA and one hypoplastic PcoA	1
44	Duplicated AcoA and both PcoAs hypoplastic	1
52	MedACA	1
54	MedACA and one hypoplastic PcoA	1
-	bilateral accessory PCA	1
-	Duplicated AcoA, with one hypoplastic AcoA, and bilateral PcoA hypoplasia	1
-	MedACA and bilateral P1 hypoplasia	1
-	Double P2 and bilateral PcoA aplasia	1
Group 5		
69	Duplicated AcoA ('V'-shaped) and both PcoAs hypoplastic	1
77	One fenestrated A1 segment and ipsilateral aplastic P1 segment	1
-	Short fusion of ACAs and unilateral hypoplastic P1	1
-	Short fusion and unilateral PcoA hypoplasia	2
-	Short fusion only	3
-	'H' AcoA	2
-	Double AcoA and 2 accessory vessels (left and right) A1-AcoA junction	1
-	A1 fenestration and unilateral PcoA hypoplasia	1
-	Plexiform AcoA, unilateral PcoA aplasia and PcoA hypoplasia	1
-	MedACA, 'Y' AcoA, unilateral PcoA hypoplasia and unilateral P2 duplication.	1
-	AcoA accessory vessel and bilateral PcoA hypoplasia	1
		n=31

- No type: The sample did not match any of the descriptions provided in the classification system of Ayre *et al.*². In circumstances where a sample did not match a type described by Ayre *et al.*², the sample was placed in the group that was the closest match to the observed variations.

The most common variation types in the intact sample were all uncategorised by Ayre *et al.*² but were categorized into group 5 for this study. These were short fusion only (n=3) followed

by 'H' AcoA only (n=2), and short fusion with unilateral PcoA hypoplasia (n=2). Furthermore, multiple variations were present in 55% (n=22) of the intact sample. All other types (categorised and uncategorized) represented in the sample only appeared once (n=1).

Group one was the third most common variant group and consisted of 24 pre-described types and three of these types occurred in the current study. This group only had one previously uncategorised type: Hypoplastic PcoA and ipsilateral hypoplastic P1. Group two was the least common group with no samples being categorised into this group. Therefore, aplasia did not occur as the only type of variation in the CAC. It was always in combination with other variations. Group three was the second least common group and contained six pre-described types, only one of which was found in the current study. An additional two previously uncategorised types were observed in the current study. Group four had 26 pre-described types and the current study categorised an additional four undescribed types into this group. Of the pre-described types, only five were found in this study.

4.2. Individual variations

However, when considering individual variations, samples that were not intact could be included. In samples with multiple variations present in combination, each variation was recorded separately. Therefore, the frequency of variations was recorded for both the intact and broken samples combined (*Figure 4.2*), where the total number of variations is 81. This was higher than the number of samples in the study because variant arteries were considered separately.

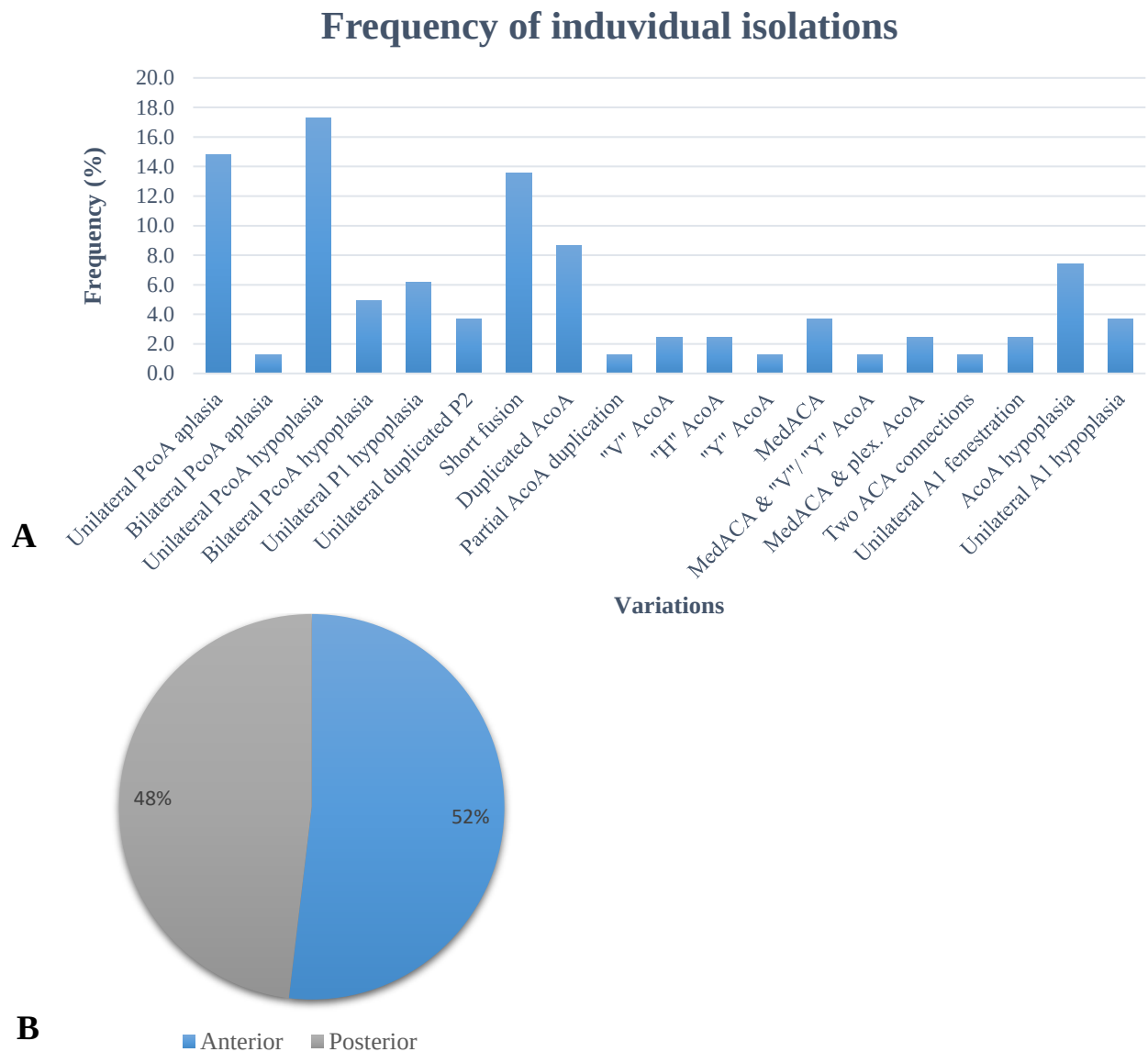


Figure 4.2: A: The frequency (%) of individual variations for both the intact and broken samples (total =81). B: The frequency (%) of anterior and posterior circulation variations for individual variations.

The most common individual variations were unilateral hypoplasia and unilateral aplasia of the PcoA with an occurrence of 17.3% (n=14) and 14.8% (n=12), respectively. The most variable artery in the posterior circulation and the second most variable artery in this study was the PcoA with variations in the PcoA accounting for 42% (n=34) of variations in the CAC. This includes P2 duplication since the PcoA is altered in this variation. The remaining 7.4% (n=5) of posterior circulation variations is attributed to unilateral P1 hypoplasia.

The most common variation in the anterior circulation was short fusion with a frequency of 13.6% (n=11) and this was the third most common variation. The most variable artery in the study was the AcoA, accounting for 44.4% (n=36) of variations in the CAC. MedACA and

short fusion were included since the morphology of the AcoA is affected. The remaining 7.4% of anterior circulation variations were due to unilateral A1 hypoplasia (3.7%; n=3), two ACA connections with long fusion of the A2s (1.2%; n=1) and unilateral A1 fenestration (2.5%; n=2).

Moreover, in the current study 51.9% of individual variations occurred in the anterior circulation, while 48.1% occurred in the posterior circulation. The data were not normally distributed according to a Shapiro-Wilk test ($p=0.00311$) at the 0.3% level. Therefore, there was only a 0.3% chance that the data were normally distributed. Consequently, a Kruskal-Wallis H test was conducted to determine if the different frequencies were statistically different for the individual variations. The analysis showed that there was not a statistically significant difference between the frequencies of the variations, $\chi^2(17)$ with ties= 17.00; $p = 0.4544$. The ‘with ties’ output was used since multiple variations had the same frequency.

A selection of these variations can be seen in *Figures 4.3, 4.4 and 4.5*.

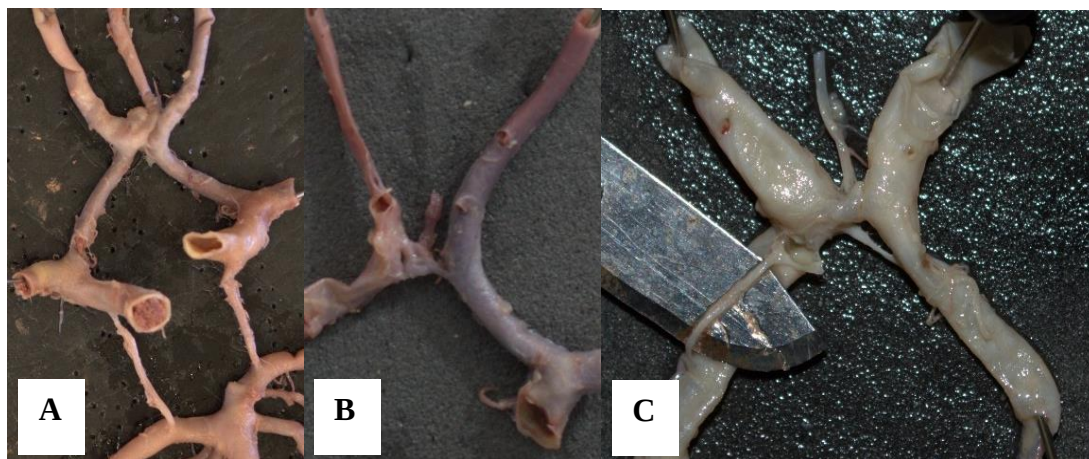


Figure 4.3: Three anterior circulation variations that were classified as a median anterior cerebral artery (MedACA). A: MedACA with an aneurysm on the junction of the right anterior cerebral artery and anterior communicating artery (AcoA). B: MedACA with a plexiform AcoA. C: MedACA with a ‘V’ AcoA and an accessory vessel on the right A1.

The third branch of the MedACA variations usually had a smaller diameter than the A2 segments (71.4%). However, in 28.6%, the three arteries were approximately equal in diameter.

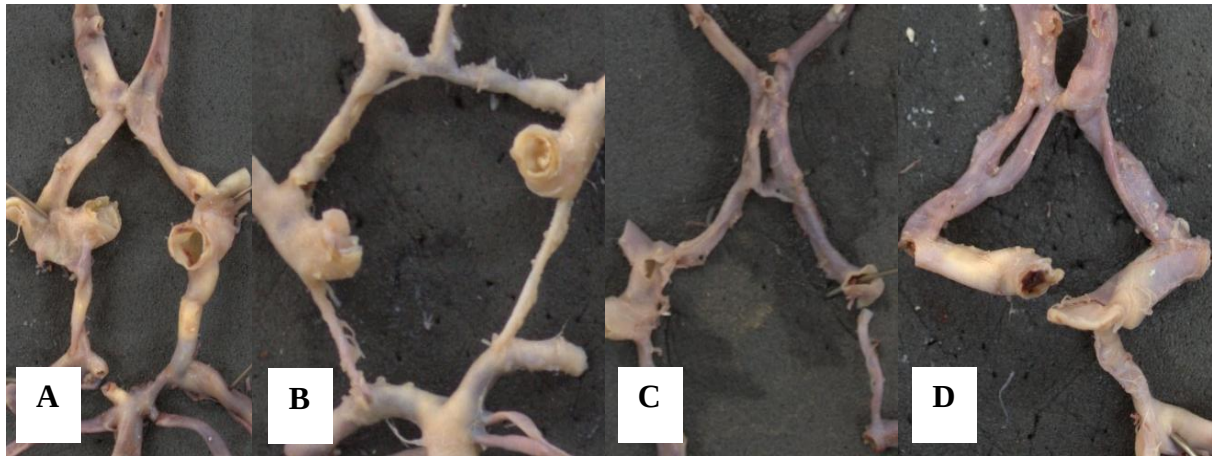


Figure 4.4: Several variations observed in the anterior circulation. A: Short fusion of the anterior cerebral arteries and an aplastic anterior communicating artery (one connection only). B: 'Y' anterior communicating artery (AcoA). C: Two anterior cerebral artery connections – 'Y' AcoA and long fusion of the post-communicating segments of the anterior cerebral artery (A2) more anteriorly. D: Fenestration of the right pre-communicating segment of the anterior cerebral artery (A1).

In *Figure 4.4C*, the lumen of a cut artery is visible on the long fusion between the ACAs, however, the artery could not be followed because it was cut prior to analysis. There were no other signs of a lumen on the long fusion, therefore, it is likely that the branch perfused brain tissue.

In *Figure 4.4D*, the two branches of the fenestration were patent and approximately equal in diameter and length.



Figure 4.5: A partial anterior communicating artery (AcoA) duplication with an accessory vessel on the left pre-communicating segment of the anterior cerebral artery (A1). The partially duplicated artery originated from the left A1, moved posteriorly and inserted into the posterior aspect of the AcoA.

The variation labelled as a double P2 segment could also be categorised according to the five different PcoA termination types described by Lazzaro *et al.*⁷². The variation in *Figure 4.6A* was a termination type 4, while the variation in *Figure 4.6B* was a type 5 termination.

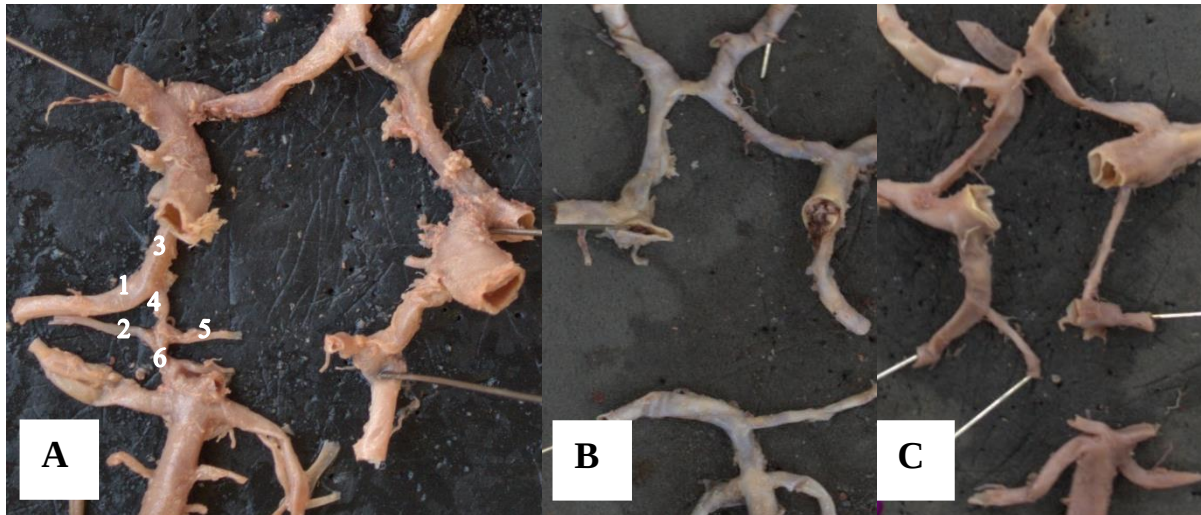


Figure 4.6: Several variations observed in the posterior circulation. A: Unilateral double post-communicating segment of the posterior cerebral artery (P2) on the right side of the circulus arteriosus cerebri (CAC). The numbers 1-6 indicate the arteries that are part of the variation – (1) Anterior P2, (2) posterior P2, (3) PcoA, (4 and 6) segments of the P1 and (5) large perforating branch. B: Unilateral double P2 segment on the left of the CAC with bilateral posterior cerebral artery aplasia. C: Unilateral P1 hypoplasia on the right side of the CAC and Unilateral PcoA hypoplasia on the left side of the CAC.

The A1 fenestration depicted in *Figure 4.4D* and the variations depicted in *Figure 4.6A-C* were examples of asymmetry within the CAC. Other causes of asymmetry are expanded upon in *Figure 4.7*, where the total number of arteries that were involved in asymmetry was 78. This was higher than the number of samples in the study because arteries were considered separately.

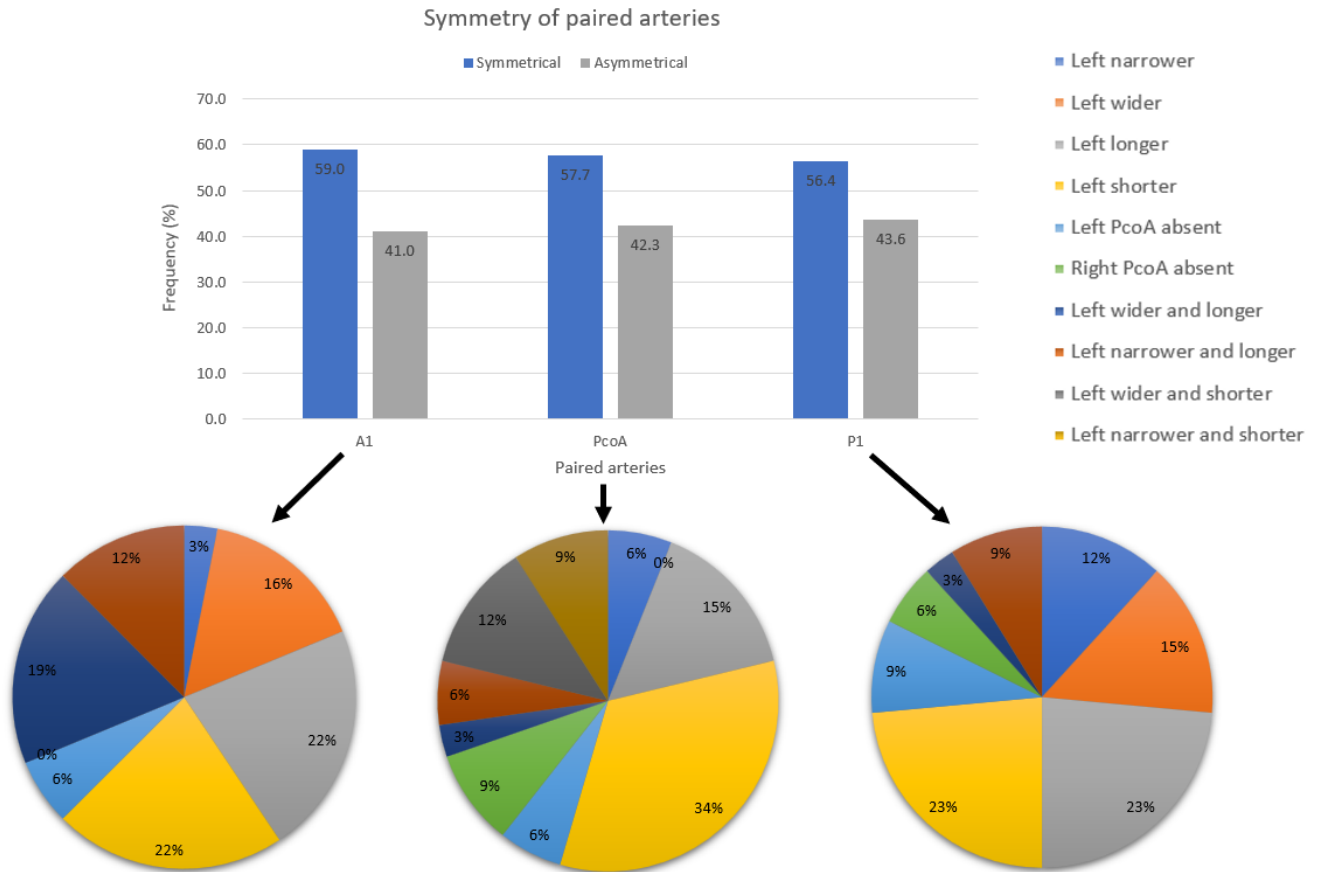


Figure 4.7: A summary of the symmetry of paired arteries (total=78) of the circulus arteriosus cerebri for the intact group. The pie charts indicate the percentage of each characteristic that resulted in asymmetry between left and right sides. These are: the left artery is narrower than the right artery, the left artery is wider than the right artery, the left artery is longer than the right artery, the left artery is shorter than the right artery, the left artery is both wider and longer than the right artery, the left artery is both narrower and longer than the right artery, the left artery is both wider and shorter than the right artery or the left artery is both narrower and shorter than the right artery. The posterior communicating artery (PcoA) has an additional characteristic: the left or right artery may be absent/aplastic. [A1: Proximal pre-communicating segment of the anterior cerebral artery; P1: Pre-communicating segment of the posterior cerebral artery].

The P1 presented as the most asymmetrical artery (43.6%) with the most common asymmetry as the left P1 being shorter than the right P1 (23%). However, a chi-square test for independence was conducted and determined that there was insufficient evidence to claim the frequency of symmetry and asymmetry was different for the paired arteries ($\chi^2(4) = 6.0000$; $Pr = 0.199$). Therefore, the differences observed were not statistically significant. However, the results indicated that asymmetry was more common on the left than the right.

4.3 Patency of small diameter arteries

Ninety-two small diameter arteries (1.5mm>) of both the broken and intact CAC groups were tested to determine if the arteries were patent or not (Table 4.3).

Table 4.3: The number of small diameter arteries (1.5mm>) that were tested for patency among the intact and broken samples combined. The frequency (%) of hypoplastic arteries (1mm>) among this group was identified and displayed as a proportion of the small diameter artery group. The results of the patency tests were indicated as patent and non-patent. The percentages of patent and non-patent are as a proportion of the 92 small diameter arteries.

Artery	Small diameter arteries n	Hypoplastic arteries n (%)	Patent n (%)	Non-patent n (%)
AcoA	17	6 (6.5%)	16 (17.4%)	1 (1.1%)
A1 (Right)	6	2 (2.2%)	6 (6.5%)	0 (%)
A1 (Left)	12	1 (1.1%)	12 (13%)	0 (%)
PcoA (Right)	20	9 (9.8%)	20 (21.7%)	0 (%)
PcoA (Left)	24	12 (13%)	24 (26.1%)	0 (%)
P1 (Right)	7	3 (3.3%)	7 (7.6%)	0 (%)
P1 (Left)	6	2 (2.2%)	6 (6.5%)	0 (%)
BA	0	0 (0%)	0 (0%)	0 (%)
Total	92	35 (38%)	91 (98.9%)	1 (1.1%)

n: number of observations.

There were 92 arteries with a diameter of less than 1.5mm and 38% (n= 35) of these were hypoplastic with a diameter of less than 1mm. Of the small diameter arteries, only one AcoA was not patent (1.1%). The PcoA was the most common hypoplastic artery (22.8%) and was more common on the left (13%) than on the right (9.8%).

4.4 Association of variations with demographic data

To assess the associations between the demographic data and frequency of variations, only the 40 intact samples were used. The samples were categorized into the five Ayre *et al.*² groups and group 6 (conventional anatomical pattern). The sample was further divided into the two sex groups (male and female), as seen in Table 4.4.

Table 4.4: The incidence of intact samples in each classification group (1-6) for males and females.

Group	Male	Female	Total
1	1	3	4
2	0	0	0
3	1	2	3
4	5	3	8
5	6	10	16
6	7	2	9
Total	20	20	40

In males, the most common group was group 6 (conventional anatomical pattern), followed by the variant group 5 (other variations). In women, the most common group was the variant group 5, with 50% (n=10) of females displaying variations that were categorised as group 5. Therefore, group 5 was the most common variant group for both sexes. However, females were observed to have a higher frequency of variations compared to males, 18 (90%) and 13 (65%) respectively. According to a chi-square test of independence ($\chi^2(20) = 24.5000$; $Pr=0.221$), these differences were not significant.

The samples that were categorized into the six groups were also divided into three age groups, as seen in Table 4.5.

Table 4.5: The incidence of variations with age of intact samples.

Group	30-59 years	60-79 years	80-100 years	Total
1	0	1	3	4
2	0	0	0	0
3	0	2	1	3
4	2	1	5	8
5	1	6	9	16
6	3	2	4	9
Total	6	12	22	40

Age was skewed with a higher number of samples in the 80-100 years age range. However, for age groups 60-79 years and 80-100 years, the most common group was the variant group 5 (other variations), whereas the most common group for the youngest age group (30-59 years) was group 6 (conventional anatomical pattern). According to a one-way ANOVA test ($p=0.1518$) there was no statistically significant difference in variations between the age groups.

4.5 Length and diameter of arteries

Where possible, the diameter and length of each artery for both the intact and broken CACs was recorded (*Tables 4.6 and 4.7*). The lengths of the arteries, excluding the AcoA, were not normally distributed according to a Shapiro-Wilk test ($p=0.05580$). Therefore, the distribution of the AcoA lengths was confirmed with a D'Agostino-Pearson Omnibus test. The results of the D'Agostino-Pearson Omnibus test also concluded that the data was approximately normally distributed ($p=0.54863$).

Table 4.6: Summary statistics for the diameter of arteries in both the intact and broken samples combined.

Vessel	Frequency n	Min mm	Max mm	Range mm	Median mm	Mean mm	Standard deviation mm
AcoA	51	0.823	0.833	2.423	1.563	1.699	0.5488
A1 (Right)	57	0.857	3.663	2.807	2.180	2.225	0.6922
A1 (Left)	60	0.750	3.257	2.507	2.198	2.124	0.5975
PcoA (Right)	41	0.540	3.237	2.697	1.300	1.476	0.5773
PcoA (Left)	43	0.667	3.890	3.223	1.400	1.572	0.7162
P1 (Left)	58	0.740	3.390	2.650	2.468	2.308	0.6256
P1 (Right)	57	0.833	3.740	2.907	2.317	2.285	0.6963
BA	54	2.000	5.730	3.730	4.410	4.357	0.7135

Absent and aplastic arteries (0mm) were excluded for more reliable summary statistic calculations. n: number of observations.

By looking at the means and medians, it was determined that the widest vessel was the BA (mean 4.357mm; median 4.410mm) and the narrowest vessel tended to be the right PcoA (mean 1.476mm; median 1.300mm). When comparing the means and medians across the arteries, it was observed that the communicating arteries tended to be the narrowest arteries of the CAC. Furthermore, when comparing the range (maximum-minimum) across the arteries, it was observed that the BA had the largest range (3.730mm) and the left PcoA has the second largest range (3.223mm). The AcoA had the smallest range (2.423mm) followed by the left A1 (2.507mm). However, the vessel with the highest degree of variation was the left PcoA with a standard deviation of 0.7162mm.

Table 4.7: Summary statistics for the length of arteries in both the intact and broken samples combined.

Vessel	Frequency n	Min mm	Max mm	Range mm	Median mm	Mean mm	Standard deviation mm
AcoA	50	0.968	7.773	6.805	3.049	3.037	1.3470
A1 (Right)	49	1.086	18.080	16.994	13.737	13.418	3.1335
A1 (Left)	57	1.035	17.692	16.657	12.807	11.962	3.4782
PcoA (Right)	43	4.878	22.580	17.702	14.000	13.540	3.0211
PcoA (Left)	44	1.227	29.237	28.010	12.911	12.712	3.9679
P1 (Left)	50	1.668	23.718	22.050	5.618	7.046	4.5443
P1 (Right)	50	1.973	18.075	16.102	6.350	7.212	3.6417
BA	54	18.162	41.575	23.413	29.004	29.257	5.0246

*Absent and aplastic arteries (0mm) were excluded for more reliable summary statistic calculations.
n: number of observations.*

By looking at the means and medians, it was observed that the longest vessel was the BA (mean 29.257mm; median 29.004mm) and the shortest vessel was the AcoA (mean 3.037mm; median 3.049mm). When comparing the range (maximum-minimum) across the arteries, it was observed that the left PcoA had the largest range (28.010mm) and the BA had the second largest range (23.413mm). The AcoA had the smallest range (6.805mm) followed by the right P1 (16.102mm). The vessel with the highest degree of variation in length was the BA with a standard deviation of 5.0246mm.

4.5.1 Associations of artery dimensions with age and sex

4.5.1.1 Age

The diameter (*Table 4.8*) and length measurements (*Table 4.9*) for each artery of the CAC were recorded according to the three age groups to help determine if the difference in mean artery dimensions between the age groups were statistically significant or not.

Table 4.8: The mean diameter measurements, for both the intact and broken samples, for each artery according to the three age groups: 30-59 years, 60-79 years and 80-100 years.

	30-59 years	60-79 years	80-100 years	Distribution	P-value	Statistical Significance
AcoA (mm)	1.960	1.398	1.754	Normal	0.0366	Yes
Left A1 (mm)	2.331	2.162	2.030	Normal	0.3682	No
Right A1 (mm)	1.909	2.397	2.210	Normal	0.2179	No
Left PcoA (mm)	1.639	1.790	1.429	Not normal	0.3382	No
Right PcoA (mm)	1.754	1.374	1.432	Not normal	0.1613	No
Left P1 (mm)	2.340	2.486	2.165	Not normal	0.4335	No
Right P1 (mm)	2.149	2.438	2.220	Normal	0.4660	No
BA (mm)	4.418	4.347	4.346	Normal	0.9676	No
n	10	19	29			

n: number of observations.

The AcoA and right PcoA were widest in the 30-59 year age group followed by the 80-100 year age group. While, the left A1 was widest in the 30–59 year age group followed by the 60-79 year age group. The 60-79 year age group tended to have the widest diameter with the right A1, left PcoA, left P1 and right P1. However, only the difference in diameter of the AcoA was statistically significant.

Table 4.9: The mean length measurements, for both the intact and broken samples, for each artery according to the three age groups: 30-59 years, 60-79 years and 80-100 years.

	30-59 years	60-79 years	80-100 years	Distribution	P- value	Statistically significant
AcoA (mm)	2.888	2.818	2.929	Normal	0.9564	No
Left A1 (mm)	11.634	13.416	12.423	Normal	0.1932	No
Right A1 (mm)	14.136	13.803	13.041	Normal	0.5435	No
Left PcoA (mm)	11.931	13.076	12.189	Not normal	0.8879	No
Right PcoA (mm)	12.013	14.022	13.701	Not normal	0.4877	No
Left P1 (mm)	5.787	7.935	6.328	Not normal	0.4137	No
Right P1 (mm)	5.741	5.891	6.874	Normal	0.4955	No
BA (mm)	24.498	29.279	29.762	Normal	0.0874	No (5% level) Yes (10% level)
n	10	19	29			

n: number of observations.

The left A1, left and right PcoA, left P1 right P1 and BA were generally shorter in the 30-59 year age group when compared to the other two age groups. Therefore, the observed mean lengths indicate that the 30-59 year age group generally had the shortest arteries. The 80-100 year age group generally had the longest AcoA and BA when compared to the other groups. However, the 60-79 year age group tended to have the longest arteries, with the left A1, left and right PcoA and the left and right P1 being longest in the 60-79 year age group. The difference in mean artery length and age was statistically significant at the 10% level for the BA according to a one-way ANOVA ($p=0.0874$), but not at the 5% level. The difference in length between the age groups for the other arteries was not significant.

4.5.1.2 Sex

The mean diameter (*Table 4.10*) and length measurements (*Table 4.11*) for each artery of the CAC were recorded according to the two sex groups to help determine if the difference in mean artery dimensions between males and females was statistically significant or not.

Table 4.10: The mean diameter measurements for each artery according to the two sex groups (male and female).

	Male	Female	Distribution	P-value	Statistical Significance
AcoA (mm)	1.799	1.561	Normal	0.1511	No
Left A1 (mm)	2.240	2.023	Normal	0.1622	No
Right A1 (mm)	2.279	2.176	Normal	0.7099	No
Left PcoA (mm)	1.626	1.526	Not normal	0.3612	No
Right PcoA (mm)	1.586	1.350	Not normal	0.2095	No
Left P1 (mm)	2.433	2.200	Not normal	0.1984	No
Right P1 (mm)	2.291	2.279	Normal	0.9498	No
BA (mm)	4.368	4.349	Normal	0.9205	No
n	28	33			

n: number of observations.

For all the component arteries of the CAC, males had wider arteries than females. However, Kruskal-Wallis and independent sample t-tests were conducted to determine if there was an association between sex and diameter. The results indicated that there were no associations

between sex and the difference in diameter was not statistically significant for all the arteries assessed.

Table 4.11: The mean length measurements for each artery according to the two sex groups (male and female).

	Male	Female	Distribution	p-value	Statistically Significant
AcoA (mm)	2.922	2.848	Normal	0.8221	No
Left A1 (mm)	12.939	12.313	Not normal	0.4047	No
Right A1 (mm)	14.642	12.363	Not normal	0.0012	Yes
Left PcoA (mm)	13.034	11.877	Not normal	0.2895	No
Right PcoA (mm)	13.228	13.757	Not normal	0.7241	No
Left P1 (mm)	7.443	6.264	Not normal	0.9761	No
Right P1 (mm)	6.380	6.309	Not normal	0.8181	No
BA (mm)	28.947	28.541	Not normal	0.5944	No
n	28	33			

n: number of observations.

For the component arteries of the CAC, males tended to have longer arteries than females, except for the right PcoA, which was longer in females than males. However, Kruskal Wallis and independent sample t-tests were conducted to determine if there was an association between sex and length. The results indicated that there were no associations between sex and the difference in length is not statistically significant, except for the right A1. Therefore, males had longer right A1s than females and this was statistically significant.

4.6 Aneurysms

Aneurysms are outpouchings of the arterial wall that may be visible in dissection studies. Several saccular aneurysms were noted during analysis of the CAC samples of the study, as shown in *Figure 4.8*.

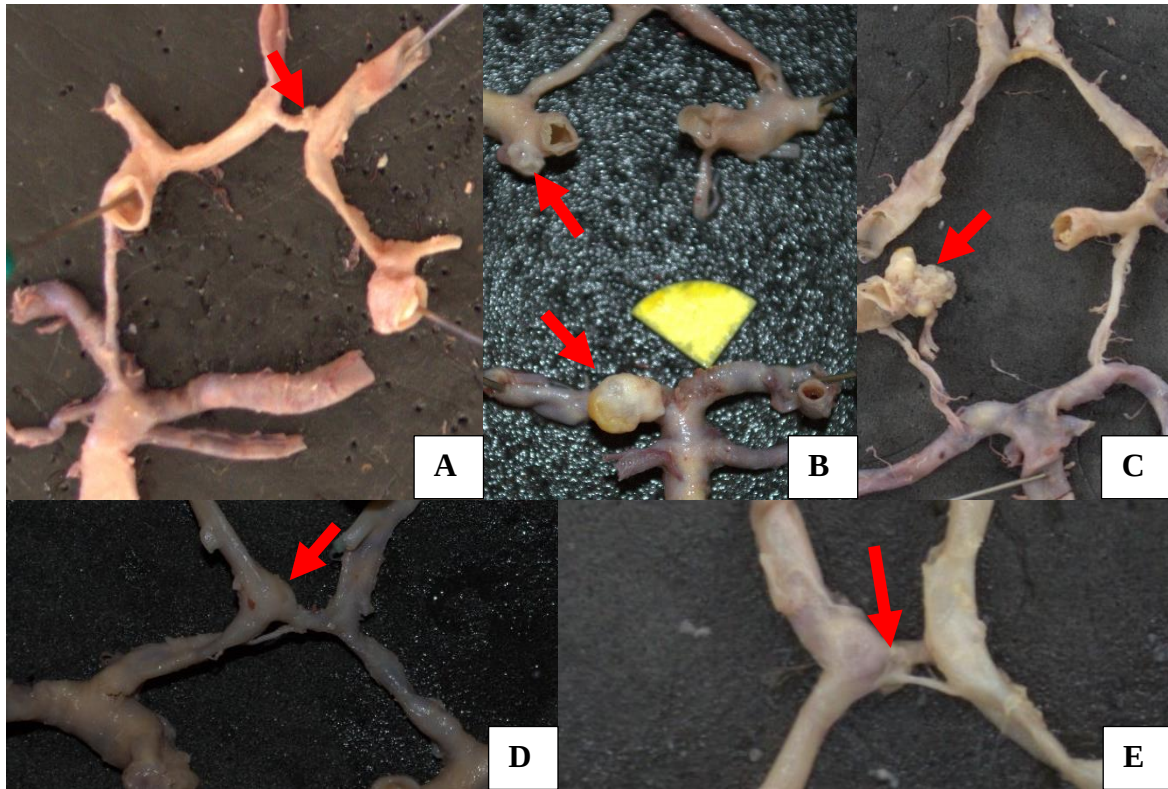


Figure 4.8: Six of the seven aneurysms observed in the current study. A: A small aneurysm on the junction of the left anterior cerebral artery and anterior communicating artery (ACA-AcoA). B: Two aneurysms with an aplastic PcoA on the ipsilateral side. There are aneurysms where the right internal carotid artery and posterior communicating artery junction (ICA-PcoA) and the right posterior cerebral artery and posterior communicating artery junction (PcoA-P1) should be. C: An aneurysm on the internal carotid artery. D: A small aneurysm on the right ACA-AcoA junction. E: A small aneurysm on the right ACA-AcoA junction.

Only six samples had aneurysms, therefore, the sample size was too small to conduct statistical analyses. However, the positions of the aneurysms are shown in *Figure 4.8*. The most common site of aneurysms in the sample was the AcoA-A1 junction with four (57.1%) aneurysms appearing here. The sixth sample with an aneurysm was seen in *Figure 4.3A*.

4.7 Brain volume and correction factors

Brain volume was not significantly affected by the level at which the brainstem was cut in this study, according to a one-way ANOVA ($p=0.1264$). Therefore, brain volumes were analysed as one large group. While analysing the brain volume summary statistics it was noticed that the maximum and minimum are potential outliers. Using the IQR method, three volumes were identified and removed as outliers. These were the brains with volumes 516ml, 1568ml and 1630ml. The set of summary statistics before and after the outliers were removed is shown in Table 4.12 and shows the effects of removing the outliers on the data.

Table 4.12: Summary statistics for brain volume both before and after the removal of the three outliers identified by the interquartile range (IQR) method.

	Sample size	Minimum ml	Maximum ml	Range ml	Mean ml	Median ml	Standard deviation ml	IQR ml
Before removing outliers	72	516	1630	1114	1181.6	1188	152.23	169
After removing outliers	69	903	1388	485	1179.2	1186	111.9	156

The post-outlier removal data was used to calculate the correction factors. The mean was 1179.2ml and data closer to the maximum and minimum values required correction factors to cluster the ‘outer’ data more closely to the mean. Therefore, the correction factors should decrease the range even further.

According to a Shapiro-Wilk test, the brain volume data was normally distributed with the three outliers removed from the sample. By visually interpreting a histogram of the brain volumes, the sample was divided into three groups based on the volume of the brains: small (903ml<1050ml), medium (1094ml<1264ml) and large (1266ml<1361ml). The one-way ANOVA showed that at least one group mean was statistically different to the other two size group means ($21.8>19.48$ meaning $F\text{-stat}>F\text{-crit}$). Furthermore, a one-way ANOVA on the length to volume ratio showed that there was a statistically significant difference between at least two groups ($12.24>9.47$ meaning $F\text{stat}>F\text{crit}$). However, there was no statistical difference between group means for the diameter to volume ratio according to the one-way ANOVA ($4.747<9.47$ meaning $F\text{stat}<F\text{crit}$) conducted.

The correction factor calculations yielded correction factors of +15% for the small volume brains group and -11% for the large volume brains group. These were applied to the data since the one-way ANOVA for length to volume ratios showed a statistical difference between groups. Thereafter, Wilcoxon signed-rank tests were conducted on the lengths and diameters of the small and large volume samples collectively before and after the correction factor was applied, as seen in *Tables 4.13 to 4.15*.

Table 4.13: The length and diameter measurements before and after a correction factor was applied (+15% on small volume brains and -11% on large volume brains) for the basilar artery (BA). The results of the Wilcoxon signed-rank tests are included at the end of the table.

BA length (mm)		BA diameter (mm)	
Before CF	After CF	Before CF	After CF
32.8717	37.8024	4.9267	5.6657
29.8417	34.3179	3.6500	4.1975
35.6817	41.0339	3.7633	4.3278
26.0817	29.9939	4.0700	4.6805
29.2500	33.6375	3.5033	4.0288
28.9667	33.3117	4.7233	5.4318
25.1950	28.9743	4.8167	5.5392
28.5767	32.8632	4.1000	4.7150
28.6783	32.9801	3.8500	4.4275
22.9033	26.3388	4.8567	5.5852
22.3000	25.6450	3.5133	4.0403
27.5650	24.5329	5.3267	4.7407
27.8900	24.8221	3.8067	3.3879
22.0767	19.6482	4.1700	3.7113
31.2783	27.8377	3.0033	2.6730
29.1533	25.9465	3.7333	3.3227
32.2917	28.7396	3.1200	2.7768
31.2333	27.7977	5.2600	4.6814
32.6200	29.0318	4.8833	4.3462
34.6917	30.8756	4.7300	4.2097
27.3233	24.3178	4.2133	3.7499
36.9083	32.8484	4.1200	3.6668
26.4100	23.5049	4.8067	4.2779
31.1400	27.7146	4.8267	4.2957
41.5750	37.0018	4.7733	4.2483
Prob > z = 0.3819		Prob > z = 0.2641	
Exact prob = 0.3957		Exact prob = 0.2752	

CF: correction factor.

The results indicate that there were no statistical differences between the before and after correction factor application for the BA length and diameter, as both the Prob>|z| and exact prob were greater than 0.05 for both length and diameter.

Table 4.14: The length and diameter measurements before and after a correction factor was applied (+15% on small volume brains and -11% on large volume brains) for the left posterior communicating artery (PcoA). The results of the Wilcoxon signed-rank tests are included at the end of the table.

Left PcoA length (mm)		Left PcoA diameter (mm)	
Before CF	After CF	Before CF	After CF
1.7098	1.9663	1.1167	1.2842
1.2270	1.4111	1.1467	1.3187
1.4650	1.6848	2.1067	2.4227
1.0138	1.1659	1.3167	1.5142
1.4877	1.7108	2.3033	2.6488
1.3845	1.5922	3.8900	4.4735
0.9100	1.0465	0.9967	1.1462
1.3953	1.3952	1.5900	1.8285
2.9237	2.9234	0.8500	0.7565
1.5045	1.5043	2.5000	2.2250
0.7862	0.7861	1.4100	1.2549
1.4035	1.4034	0.8533	0.7594
1.4150	1.4149	2.3100	2.0559
1.3620	1.3619	2.3900	2.1271
1.1895	1.1894	1.6100	1.4329
0.9902	0.9901	1.4700	1.3083
1.2255	1.2254	2.1433	1.9076
		2.9100	2.5899
Prob > z = 0.2416		Prob > z = 0.9826	
Exact prob = 0.2698		Exact prob = 1.0000	

CF: correction factor.

The Prob>|z| and exact prob indicate that there were no statistical differences between the before and after correction factor application for the left PcoA length and the left PcoA diameter.

Table 4.15: The length and diameter measurements before and after a correction factor was applied (+15% on small volume brains and -11% on large volume brains) for the right proximal pre-communicating segment of the anterior cerebral artery (A1). The results of the Wilcoxon signed-rank tests are included at the end of the table.

Right A1 length (mm)		Right A1 diameter (mm)	
Before CF	After CF	Before CF	After CF
1.2743	1.4655	3.6633	4.2128
1.4673	1.6874	1.8833	2.1658
1.4203	1.6334	2.2200	2.5530
1.7773	2.0439	3.0400	3.4960
1.3128	1.5098	1.5367	1.7672
1.2188	1.4017	2.1733	2.4993
1.2907	1.4843	2.9767	3.4232
1.6285	1.8728	2.5633	2.9478
1.0597	1.2186	1.1667	1.3417
1.4382	1.6539	1.8500	2.1275
1.2470	1.4341	2.6500	3.0475
1.2047	1.0722	2.6900	2.3941
1.3382	1.1910	1.7133	1.5249
1.5392	1.3699	1.8433	1.6406
1.6218	1.4434	0.9400	0.8366
1.6365	1.4565	2.4800	2.2072
1.3737	1.2226	3.4567	3.0764
1.6258	1.4470	3.5000	3.1150
1.4360	1.2780	2.3567	2.0974
1.3232	1.1776	1.4533	1.2935
1.5983	1.4225	2.3900	2.1271
1.3452	1.1972	2.7567	2.4534
Prob > z = 0.0716		Prob > z = 0.3065	
Exact prob = 0.0738		Exact prob = 0.3209	

CF: correction factor.

The Prob>|z| and exact prob indicate that there were statistical differences between the before and after correction factor application for the right A1 length at the 10% significance level, but not the 5% level. There were no statistical differences for the right A1 diameter.

Therefore, there were no statistical differences for the mean vessel diameters before and after the correction factors were applied for the three arteries. This was expected because of the results of the one-way ANOVA. However, two of the three arteries had statistical differences for the mean artery length at the 5% and 10% level. These were the left PcoA and right A1 respectively.

Chapter 5: Discussion

In the current study, the intact sample was grouped according to the classification system developed by Ayre *et al.*² and 22.5% of samples had the conventional anatomical configuration. This fell into the wide range of 5%⁵² to 72.8%⁴⁷ recorded in the current literature (*Table 2.3*). If radiographic studies were excluded and only dissection studies were considered, then this range remained unchanged since both the lower and upper bounds were from dissection studies. The metanalysis conducted by Jones *et al.*⁸⁹ observed that the average mean prevalence of a variant CAC in a healthy sample was $68.22\% \pm 14.32$. In the current study, variations were found in 77.5% of the intact group and this fell into the reported standard deviation of average means determined by Jones *et al.*⁸⁹. The most common location for 55% of these variations was in both the anterior and posterior circulations combined and 55% of the current sample had multiple variations. Furthermore, individual variations in the intact sample were found in the anterior circulation (26%) more frequently than the posterior circulation only (19%). This differs from studies that observed posterior circulation variations more frequently. However, many of these studies did not allow for the analysis of variations being in both the anterior and posterior circulation in a single sample. Whether variations are in the anterior circulation, posterior circulation or in both circulations concurrently influences the changes in haemodynamic flow through the CAC. This altered haemodynamic flow may influence the type and risks of stroke owing to the brain territory that would be affected. Furthermore, the variations may influence the site of aneurysm formation at areas of high sheer wall stress, especially points of bifurcation.

In the current study, the most common variant types for the intact sample were in group 5 (37.5%), consisting of 15 other variation types, and group four (22.5%), consisting of 26 accessory vessel types only. However, the Lazorthes *et al.*⁴⁵ classification system only had types that fell into groups 1 and 2 of the Ayre *et al.*² classification system and the Chen *et al.*⁵⁹ classification system, only had three types that fell into group 4 and one type fell into group 5 of the Ayre *et al.*² classification system. Therefore, comparison with the most common groups of the Ayre *et al.*² classification system was not fully possible with these classification systems. When comparing with the Chen *et al.*⁵⁹ classification system, the anterior type B was comparable to types 42 and 70 in the Ayre *et al.*² classification system. However, since this was for duplicated AcoA, this was discussed in the individual variations section to ensure reliable comparisons. The same applied to the anterior type C and type 52 (MedACA).

The classification system developed by Ayre *et al.*² was still considered new since it was published in 2021. To the researcher's knowledge, other studies have not yet published their results with this classification system, and it was difficult to compare studies using the Lazorthes *et al.*⁴⁵ and Chen *et al.*⁵⁹ classifications to the Ayre *et al.*² classification system. This was predominantly owing to the types in the other two systems usually corresponded to group 1 of the Ayre *et al.*² system (Table 2.13). Therefore, comparisons of groups 2-5 in the current study may not be as reliable as comparisons with studies using the same classification system. Furthermore, it was difficult to compare the results to studies that did not report multiple variations together. For these reasons, comparisons of the current study with other studies were primarily done with the individual variations.

5.1 Individual variations

When variations of the CAC were considered as individual variations, instead of being categorized into a type where combinations were observed, then it was suitable for broken samples to be included. In this study, 51.9% of variations were found in the anterior circulation and 48.1% were observed in the posterior circulation. There were wide ranges reported in the literature and the range of anterior circulation variations (Table 2.3) was 7.37%⁶³ to 47.86%.⁵ Therefore, the frequency of individual anterior circulation variations in the current study was higher than what was reported in the current literature. The range of variations that occurred in the posterior circulation was 32%³ to 85.6%.⁵⁹ The range of posterior circulation variations observed in the current study fell within the range in the literature and the average determined by Jones *et al.*⁸⁹. The higher frequency of anterior circulation variations may have been caused by more posterior circulations being broken in the current sample than anterior circulations. However, both Saikia *et al.*⁵ and He *et al.*⁶¹ found that anterior circulation variations were more common in their studies conducted in India and China respectively. In contrast, a South African study conducted by Cilliers *et al.*⁴³ found an equal proportion of variations in the anterior and posterior circulations. The current study was the first South African study to report a higher frequency of anterior variations than posterior variations and more South African studies are required to determine which circulation is more variable. It may be found that the difference in frequency of anterior and posterior variations is lower than in international studies that dominate the CAC variation literature.

Furthermore, analysing individual variations allowed for individual arteries to be assessed. For instance, the second most variable artery in the current study was the PcoA that accounted for

42% of the individual variations observed. The most common variations were unilateral PcoA hypoplasia and aplasia with a frequency of 17.3% and 14.8% respectively. PcoA hypoplasia was frequently reported in the literature and as the most common variation in other CAC variation studies (*Table 2.4*), such as Saikia *et al.*⁵ who reported that unilateral PcoA hypoplasia was the most common variation in their study. However, hypoplasia was not always separated into unilateral and bilateral variations, such was the case with Iqbal³ and Papantchev⁶⁰, who both reported PcoA hypoplasia as the most common variation: 10% and 27.3% respectively. Other studies that reported PcoA hypoplasia as the most common variation separated the variation into unilateral and bilateral hypoplasia, as in the current study. The studies that reported unilateral PcoA hypoplasia as the most common variation include Saikia *et al.*⁵, Kapoor *et al.*⁷ and Cilliers *et al.*⁴³ with frequencies of 19.28%, 13.1% and 23.1% respectively. In the current study, only 4.9% of the sample displayed bilateral PcoA hypoplasia. This falls into the lower portion of the range reported in the literature (*Table 2.4*): 0.7%⁴⁷ to 32%.⁵² This could partly be because of the 24 broken CAC samples used in the current study as some hypoplastic PcoAs may have been missing.

Moreover, the different definitions of hypoplasia may have contributed to the wide ranges of unilateral and bilateral PcoA hypoplasia observed. In addition, the current study measured the diameter of arteries and confirmed whether small diameter arteries were hypoplastic or not. Morphological studies have not always measured small diameter arteries to confirm hypoplasia. If small diameter arteries were assumed to be hypoplastic without measurements being conducted, then the reported ranges could be including small diameter arteries that are not hypoplastic. Furthermore, some studies did not differentiate between aplastic and hypoplastic arteries. Therefore, their reported hypoplasia included aplastic arteries. As such, the reported ranges in the literature may not be a true reflection of the prevalence of hypoplasia.

In the current study hypoplastic PcoAs accounted for 22.8% of small diameter arteries and were more common on the left (13%) than the right (9.8%). This agreed with the current literature (*Table 2.4*), as other studies that separated unilateral PcoA hypoplasia into sides also reported the left PcoA being hypoplastic more frequently than the right PcoA.^{10,49,63} All the hypoplastic PcoAs in the current study were patent. Therefore, hypoplastic and aplastic arteries should not be assumed to have the same haemodynamic effects and should not be grouped together as some studies and classification systems have done.

PcoA aplasia was noted as unilateral (14.8%) or bilateral (1.2%) in the current study. The frequency of both variations fell into the ranges noted in the literature (*Table 2.5*). The range for unilateral PcoA aplasia was 0.9%⁷ to 14.7%.⁴¹ However, Enyedi *et al.*⁷¹ had an unusually high frequency of unilateral PcoA aplasia at 22.7%. This could have been a result of a population specific difference, the classification of hypoplasia as an artery smaller than 0.8mm or the use of patients experiencing potential side effects of neurological conditions (nausea, dizziness and headaches). Unilateral PcoA aplasia was on the high end of the reported range. The range of bilateral PcoA aplasia reported in the literature was 0.1%⁷ to 42.8%⁵⁹ and the frequency in the current study fell into the lower portion of the range. Therefore, the frequencies of both unilateral and bilateral PcoA hypoplasia observed in the current study aligned with those observed in both local and international studies. The haemodynamic effects resulting from hypoplasia and aplasia of the PcoA were not investigated in the current study, but these variations may alter the haemodynamic blood flow of the CAC and its ability to provide collateral circulation for the brain. These variations may increase both the risk and severity of a stroke, especially in cases of ICA or BA occlusion²⁴. Furthermore, the changes in blood flow may influence the formation of IAs at areas of high shear wall stress, especially at points of arterial bifurcation.

Figure 4.2 illustrates that PcoA variations were more commonly unilateral than bilateral in the current study. However, this contradicted some of the literature with bilateral PcoA hypoplasia being reported as more frequent than unilateral hypoplasia by studies conducted by Saikia *et al.*⁵ and Hindenes *et al.*⁶², among others.^{59,63,70} These differences could have been owing to different definitions of hypoplasia being used, the use of broken samples in the current study or population specific differences since Cilliers & Page³⁸ also reported unilateral hypoplasia (23.1%) more frequently than bilateral hypoplasia (10.3%). Bilateral hypoplasia of the PcoAs may diminish the protective effects of the CAC with fluctuations of blood because the collateral flow of blood would be hindered as the connection between the anterior and posterior circulations may be decreased. Furthermore, there may be neurosurgical implications where the collateral blood flow of the CAC is imperative to ensure cerebral perfusion, for example endovascular coiling⁷⁸.

Three type four and five PcoA terminations (3.7%) were observed in the current study as P2 duplications (*Figure 4.6A-B*). These variations are uncommon and were reported with a frequency of 0.58% and 1.17% in the study by Lazzaro *et al.*⁷². In *Figure 4.6A*, there was a unilateral double P2 on the right and was an example of a type four PcoA termination, as

described by Lazzaro *et al.*⁷². The anterior P2 (closer to the ICA) was large and the posterior P2 (closer to the BA) was hypoplastic. There was also a large perforating artery that originated near the posterior P2 on the contralateral side of the artery. This perforating artery may have assisted with compensation of blood flow to the required regions. It was also noted that the two ICA bifurcations in the sample were unusual. This may have contributed to the development of the variation. However, unusual ICAs were noted with other variations during data collection but was outside the scope of this study. The association of unusual ICA bifurcations with CAC variations should be investigated in future studies. In *Figure 4.6B*, there was a unilateral P2 duplication on the left side accompanied by bilateral PcoA aplasia. Therefore, this was a type five PcoA termination, as described by Lazzaro *et al.*⁷². PcoA terminations were not commonly assessed in previous CAC variation studies. However, variations in PcoA termination have the potential to alter haemodynamics in the CAC and should be considered in future studies.

It was suggested that variations in the posterior circulation were more common because of the fast growth of the occipital lobe during embryonic development.⁴ However, variations in the anterior circulation were common and accounted for 52% of individual variations in the current study. Moreover, the AcoA was the most variable artery in the current study and accounted for 44.4% of the individual variations observed. Short fusion (*Figure 4.4A*) was the most common variation in the anterior circulation and the third most common variation in the study (13.6%), after unilateral PcoA hypoplasia and aplasia. Short fusion was frequently reported and had a range of 0.5%⁷ to 5.92%⁵⁹. Therefore, the current study had a higher occurrence of short fusion than reported in the literature. This could have been owing to the small sample size in the current study or population specific differences. The way in which researchers define short fusion during data collection was not usually addressed and could have influenced the results of the current study, as well as previously published studies. Moreover, not all studies reported short fusion and some studies, such as De Silva *et al.*⁵⁶, did not distinguish between long and short fusion. More research in South African samples is required to confirm the prevalence of short fusion as Cilliers *et al.*⁴³ reported one point fusion in 15.4% and 5% in their study and pilot study respectively. However, these researchers reported no occurrence in two other published papers^{38,57} and Du Toit⁸¹ did not report the occurrence of short fusion either. Both long and short fusion may interfere with the planning and execution of various neurosurgical procedures, such as endovascular clipping or thrombolysis. This is because of the altered shape of the CAC because of the absence of the AcoA landmark and related potential angle changes between the ACAs.

Multiplications of the AcoA were observed in the current study and included duplicated AcoA (8.6%), partial AcoA duplication (1.2%), 'V' AcoA (2.5%), 'H' AcoA (2.5%) and 'Y' AcoA (1.2%). It was difficult to compare AcoA multiplications because it can be difficult to determine the shape of the duplication in this small artery. For instance, the difference between an 'H' or 'N' or a 'V' and 'Y'. Furthermore, AcoA fenestrations may have been classed as an 'H', 'N', 'V' or 'Y' AcoA instead of a fenestration.⁴³ Some studies, like that conducted by Ozaki *et al.*⁴¹, grouped AcoA multiplications as 'V' and 'Y' or 'N' and 'H' and triple AcoAs and plexiform AcoAs were grouped together. Of the AcoA multiplications, 'Y' AcoA was the most frequently reported with a range of 1.6%⁷ to 7.2%⁴⁷ and Milenkovic *et al.*⁷³ reported a frequency of 32% in fetal brains. Therefore, the range of 1.2% in the current study falls into the range reported in the literature.

Duplications were not always complete and Windle⁴⁹ noted a variation in which there was an incomplete duplication of the AcoA. In this variation, the second branch was posterior to the 'true' AcoA and merged into the 'true' AcoA at some point along its path. An intervacular space resulted and was in the shape of a triangle.⁴⁹ A partial AcoA was observed in the current study (*Figure 4.5*) and seemed to be a rare variation. In the sample observed in this study, there was a very thin, non-patent artery projecting from the partially duplicated vessel to the contralateral ACA. However, since this artery was non-patent, this was not considered a full duplication. The partially duplicated artery was patent. To the researcher's knowledge, this variation has not been reported in a South African sample before and has been rarely reported in international data⁴⁹.

Furthermore, the accessory arteries in *Figures 5.3C and 5.5* had the potential to be A1 fenestrations. However, the current study did not include histological testing of small accessory arteries and these accessory arteries were not assumed to be fenestrations. Other researchers did not state how they determined if a small accessory vessel was or was not a fenestration. The current study recognised that the channels of a fenestrated artery share the adventitia layer but have separate endothelial and muscular layers,⁶⁵ as defined in chapter 2 (section 2.3.3). Since it was not known whether these small diameter arteries shared an adventitia layer or not, these were classified as small diameter accessory vessels on the A1.

Previously, MedACA was reported with a prevalence of 0.7%⁵ to 14.2%,⁴¹ whereas Kayembe *et al.*⁵⁴ reported an unusually high frequency of MedACA at 22.7% in their aneurysm group (*Table 5.1*). However, their control group had a prevalence of 14.6%, which was close to the

upper range reported by Ozaki *et al.*⁴¹. In the current study MedACA accounted for 7.4% (n=6) of variations but was observed in several combinations: MedACA only (3.7%), MedACA with a plexiform AcoA (2.5%) and MedACA with 'V'/'Y' AcoA (1.2%). This fell into the range observed in *Table 5.1*. These variations are seen in *Figure 4.3A-C* and *4.4B* and in addition to the AcoA variation in *Figure 4.3C*, there was a patent accessory vessel on the right A1 that could have further altered haemodynamics in the CAC sample. In the South African study conducted by Cilliers *et al.*⁴³, the prevalence of MedACA was 12.8%. This 12.8% consisted of five MedACA, three MedACA with a duplicated AcoA and one MedACA with a 'Y' AcoA. Furthermore, Cilliers & Page⁵⁷ noted that the MedACA artery did not always arise from the AcoA but could also arise from the A2 segment (14.3%). However, the MedACA predominantly arose from the AcoA (85.7%). The current study only observed MedACAs that originated from the AcoA.

Table 5.1: The frequency of median anterior cerebral arteries (MedACAs) reported in the current study and literature.

Author, year	Sample size	Study type	Country	Frequency
Current study, 2023	64	D(e)	South Africa	7.4%
Windle, 1888⁴⁹	200	D	UK	4.5%
Fawcett & Blachford, 1905⁴⁷	700	D	UK	3.3%
Baptista <i>et al.</i>, 1963¹⁰⁰	504	D(e)	Brazil	13.1%
Ozaki <i>et al.</i>, 1977⁴¹	153	D(e)	China	14.2%
Kayembe <i>et al.</i>, 1984⁵⁴	148	D(e)	Japan	22.7%
Macchi <i>et al.</i>, 1996⁵⁸	118	TOF	Italy	9%
Chen <i>et al.</i>, 2004⁵⁹	507	TOF	Taiwan	2.96%
Kapoor <i>et al.</i>, 2008⁷	1000	D(e)	India	2.3%
Uchino <i>et al.</i>, 2010¹⁰¹	3491	TOF	Japan	3%
De Silva <i>et al.</i>, 2011⁵⁶	225	D(e)	Sri Lanka	2%
Iqbal, 2013³	50	D(e)	India	4%
Saikia <i>et al.</i>, 2014⁵	140	D(e) TOF	India	0.7%
Gunnal <i>et al.</i>, 2015³⁶	170	D(e)	India	0.9%
Cilliers <i>et al.</i>, 2017⁴³	39	D(e)	South Africa	12.8%
Machasio <i>et al.</i>, 2019⁷⁰	94	CTA	Kenya	1%

The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography CTA: Computed Tomography Angiography; United Kingdom.

Windle⁴⁹ considered a direct fusion of the two ACAs with an AcoA present as a rare variation since less than 1% of CACs analysed had this variation. In the current study, two ACA connections in the form of an AcoA and long fusion of the A2 segments more anteriorly was observed in one sample (1.2%), as seen in *Figure 4.4C*. To the researcher's knowledge, this variation has not been reported in a South African population. Furthermore, unilateral A1 fenestration (*Figure 4.4D*) was observed in 2.5% of the sample and fell into the range observed in the literature (*Table 5.2*).

Table 5.2: The frequency of A1 fenestrations reported in the current literature and study.

Author, year	Sample size	Study Type	Country	Unilateral		Bilateral	Total
				Left	Right		
Current study	64	D(e)	South Africa	1.25%	1.25%	-	2.5%
Fawcett & Blachford, 1905⁴⁷	700	D	UK	0.57%	0.85%	0%	1.42%
Ozaki <i>et al.</i>, 1977⁴¹	153	D(e)	China	-	-	-	2.1%
Kapoor <i>et al.</i>, 2008⁷	1000	D(e)	India	1.2%	1.3%	0.1%	2.6%
Saikia <i>et al.</i>, 2014⁵	140	D (e) TOF	India	-	-	-	6.4%

The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography; United Kingdom. The '-' indicates that the study did not provide a value for the variation, or the variation did not occur.

Hypoplasia in the anterior circulation was less common than in the posterior circulation with AcoA hypoplasia and unilateral A1 hypoplasia occurring with a frequency of 7.4% and 3.7% respectively. However, both fell into the range observed in the literature according to *Table 2.10*.

The proportion of variations differ to those observed by the study conducted by Du Toit⁸¹ in the same region of South Africa. Du Toit⁸¹ observed AcoA and PcoA variations in 7.7% and 15.4% of variations in the sample analysed. This was lower than observed in the current study. Furthermore, P1 variations were observed in 15.4% of the sample analysed by Du Toit⁸¹, which was higher than the current study. These differences could be attributed to the different methodologies used and the different sample sizes. However, the differences between the frequencies of the individual variations were found to not be significant ($p=0.4544$) in the current study and should be studied further in future studies.

5.2 Asymmetry

Unilateral variations were the causes of asymmetry and the current study examined asymmetry of paired arteries (*Figure 4.7*). In the current study, asymmetries were more common in the posterior circulation than in the anterior circulation and the P1 showed the most asymmetry (43.6%). For this reason, it may be useful to look at the different BA bifurcation patterns in future studies. In contrast, both Windle⁴⁹ and Fawcett & Blachford⁴⁷ observed the PcoA to be

the most common cause of asymmetry with Fawcett & Blachford⁴⁷ reporting unilateral PcoA hypoplasia in 21.5% of their sample. Windle⁴⁹, Fawcett & Blachford⁴⁷ and the current study all agreed that asymmetries were more common in the posterior circulation than in the anterior circulation. However, the current study disagreed with the other two since the P1 was the cause of asymmetry more often than the PcoA. This difference could be owing to the current study not only viewing hypoplasia as a size difference, but also small diameter arteries (<1.5mm). Therefore, the difference in size of the P1 segments was not restricted to arteries smaller than 1mm but encompassed a larger range of size differences between the arteries. Furthermore, the technique used to measure artery dimensions differed with the current study making use of software that was not available in 1888 or 1905, when Windle⁴⁹ and Fawcett & Blachford⁴⁷ conducted their dissection studies. Furthermore, the differences in length of paired arteries were considered in the current study, unlike in the other two studies. However, in the current study asymmetries were not statistically significant ($p=0.199$). Cilliers *et al.*⁴³ reported no statistical significance with asymmetry, but they noted that more variations appeared on the right than on the left. This agreed with the current study. More research with a focus on CAC asymmetry is required in a South African context because of the implications of the altered haemodynamic blood flow: increased risk of stroke, IA formation and potential rupture and surgical implications where collateral blood flow is important for a successful surgical outcome.

5.3 Patency

Patency of arteries was investigated in the current study to determine the prevalence of patent and non-patent hypoplastic arteries. In dissection studies, patency is not usually assessed and only a few dissection studies have considered patency of hypoplastic arteries. The patency of the 92 small diameter arteries in the current study were analysed and it was determined that 38% ($n=35$) of these small diameter arteries were hypoplastic. All the hypoplastic arteries were patent and only a small diameter AcoA that was greater than 1mm (not hypoplastic) was non-patent. However, the patency results of the current study differ from Kapoor *et al.*⁷, as they observed that although hypoplastic PcoAs are usually patent, they are not always patent. For instance, of the 69 right PcoAs analysed, 55 (79.7%) were patent and 14 (20.3%) were non-patent in the study conducted by Kapoor *et al.*⁷. Furthermore, Iqbal³ reported that most of the hypoplastic vessels in their sample were patent, however, no percentage was provided. Therefore, patency should be analysed in future studies to confirm if the assumption of hypoplastic arteries being non-patent should be addressed, as the current study, and those

conducted by Iqbal³ and Kapoor⁷, indicated. Ideally, future studies should have a larger sample of small diameter arteries.

5.4 Demographic data and variations

Associations of CAC variations with age and sex was assessed because both of these variables were identified as risk factors for aneurysm formation⁷⁴ and stroke.⁸⁶ The literature was conflicted as to whether there was an association with variations and age or sex with some studies stating that there was an association, while others state there was not. For instance, Hindenes *et al.*⁶² found that variations were associated with age but not with sex. Whilst Machasio *et al.*⁷⁰ found that females had a higher proportion of CACs with a complete anterior circulation than males, 97.2% and 77.4% respectively. However, males had a higher proportion of complete CACs than females, 37.7% and 36.6% respectively.⁷⁰ Horikoshi *et al.*¹⁰² and Chen *et al.*⁵⁹ also observed differences in variations with sex and these were statistically significant. In contrast, Kapoor *et al.*⁷ concluded that there was not a significant correlation between the frequency of CAC variations with sex. Similarly, Du Toit⁸¹ found no statistical association with sex in the South African sample analysed and this agreed with the current study. The intact sample in the current study had no statistically significant difference between age or sex and the occurrence of variations ($p = 0.1518$ and 0.2210 respectively). However, in agreement with Machasio *et al.*⁷⁰, males had a higher proportion of CACs with the conventional anatomical configuration than females (35% vs 10%).

Differences in variations according to age may be caused by decreased elasticity of the arterial walls with ageing and a decreased ability to compensate for haemodynamic changes.¹⁰ Chen *et al.*⁵⁹ noted that their younger cohort had a higher prevalence of complete CACs. This agreed with the current study, although no statistical significance was found, the most common group in the younger cohort was group six, the conventional anatomical pattern. This could have been caused by the small sample of 30-59 year-olds in the current study ($n=6$), as was the nature of dissection samples. Therefore, there could be potential for variations to form after embryonic development and in adults. However, a South African study conducted by Cilliers *et al.*⁴³ indicated that the age group 40-59 years had the most variations. In contrast, Kapoor *et al.*⁷ concluded that there was not a significant correlation between the frequency of CAC variations with age. More research should be conducted to determine if age does influence the variations observed.

5.5 Length and diameter

Both length and diameter were important artery characteristics to be considered when the variations of the CAC were analysed because both influence haemodynamics according to the Hagen-Poiseuille equation. Therefore, both length and diameter have the potential to alter blood flow through the CAC and may impact on the risk of having a stroke and IA formation. The greatest disparity in diameter in the current study was in the left PcoA with a standard deviation (sd) of 0.7162mm. The greatest disparity in length was for the BA (sd = 5.0246mm), followed by the left P1 (sd= 4.5443mm). The artery with the least disparity in diameter and length was the AcoA with a sd of 0.5488mm and 1.3470mm respectively. This contradicts the data from a study conducted by Kamath⁶⁷ who indicated that the AcoA had the greatest disparity in length. However, the results of Kamath⁶⁷ and the current study do agree that the PcoA had the greatest disparity in diameter with the left tending to have more discrepancy than the right. In contrast, Chen *et al.*⁵⁹ found that there was no statistically significant difference in artery diameter, except in older subjects with a small diameter A1 segment. *Table 5.3* shows a comparison of the diameters in the current study with the diameters reported in the current literature. All the average diameters in the current study are larger than that observed by Jeton *et al.*⁴, however no standard deviation was provided for the diameters reported by those researchers.

Table 5.3: The average diameters of the arteries of the circulus arteriosus cerebri for the current literature and study.

Author, year	Sample size	Study Type	Country	Average mean diameter (mm $\pm$ sd)							
				AcoA	Left A1	Right A1	Left PcoA	Right PcoA	Left P1	Right P1	BA
Current study	64	D(e)	South Africa	1.699 $\pm$ 0.549	2.124 $\pm$ 0.598	2.225 $\pm$ 0.692	1.572 $\pm$ 0.716	1.476 $\pm$ 0.577	2.308 $\pm$ 0.626	2.285 $\pm$ 0.696	4.357 $\pm$ 0.714
Kamath, 1981⁶⁷	100	D(e)	India	1.90 $\pm$ 0.90	2.40 $\pm$ 0.50	2.2 $\pm$ 0.60	1.40 $\pm$ 0.70	1.50 $\pm$ 0.70	2.20 $\pm$ 0.60	2.10 $\pm$ 0.70	-
Hoksbergen et al., 2000¹⁸	12	D(u)	Hungary	0.10 $\pm$ 0.61	1.80 $\pm$ 0.39	1.65 $\pm$ 0.25	0.75 $\pm$ 0.32	0.94 $\pm$ 0.61	1.83 $\pm$ 0.28	1.61 $\pm$ 0.68	-
Gunnal et al., 2014¹⁰³	150	D(e)	India	1.70 $\pm$ 0.08	2.80 $\pm$ 0.09	2.80 $\pm$ 0.09	2.10 $\pm$ 0.12	2.10 $\pm$ 0.12	2.80 $\pm$ 0.08	2.80 $\pm$ 0.08	4.90 $\pm$ 0.07
Gunnal et al., 2015³⁶	170	D(e)	India	-	-	-	-	-	-	-	4.80 $\pm$ 0.7
Jeton et al., 2018⁴	513	TOF	Kosovo	1.16	2.06	2.04	1.15	1.17	2.03	2.0	3.37

The results of Jeton et al.⁴ were not reported with a standard deviation (sd) for the average diameters of each artery. Therefore, the results are present as reported by the researchers. The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis of MRA/I or CT scans or a combination of both dissection and radiological analysis. D(e): Dissection using; embalmed samples; TOF: 3D Time of Flight Magnetic Resonance Angiography. The '-' indicates that no value was provided by the study for the variation, or the variation did not occur.

The mean length of the PcoA, P1 and BA in the current study were within the ranges stipulated by Mahakul & Agarwel²² and Gunnal et al.³⁶, respectively. The average length of the A1 in the current study and the study conducted by Mahakul & Agarwel²² were recorded as the same value of 12.7mm. However, the average length of the AcoA was on the upper bound of the range recorded by Mahakul & Agarwel²². The data from the current study fell within the reported values and indicates that the length measurements of the current study agreed with international and local data (Table 5.4). The present study also found no statistically significant association between sex and mean artery length.

Table 5.4: The mean lengths of arteries of the circulus arteriosus cerebri for the current study and literature.

Author, year	Sample size	Study type	Country	Mean Length (mm $\pm$ sd)							
				AcoA	Left A1	Right A1	Left PcoA	Right PcoA	Left P1	Right P1	BA
Current study	64	D(e)	South Africa	3.037 $\pm$ 1.35	11.96 $\pm$ 3.48	13.42 $\pm$ 3.13	12.71 $\pm$ 3.97	13.54 $\pm$ 3.02	7.046 $\pm$ 4.54	7.212 $\pm$ 3.64	29.26 $\pm$ 5.02
Kamath, 1981⁶⁷	100	D(e)	India	2.50 $\pm$ 1.80	13.80 $\pm$ 2.70	14.70 $\pm$ 3.00	13.30 $\pm$ 3.30	13.50 $\pm$ 3.40	6.90 $\pm$ 3.10	6.80 $\pm$ 2.70	-
Hoksbergen et al., 2000¹⁸	12	D(u)	Hungary	2.28 $\pm$ 1.27	13.25 $\pm$ 1.66	14.25 $\pm$ 1.71	12.92 $\pm$ 3.70	15.67 $\pm$ 3.63	7.38 $\pm$ 1.96	7.45 $\pm$ 2.73	-
Gunnal et al., 2014¹⁰³	150	D(e)	India	2.60 $\pm$ 0.21	17.4 $\pm$ 0.33	17.8 $\pm$ 0.34	15.4 $\pm$ 0.43	15.9 $\pm$ 0.46	7.6 $\pm$ 0.28	7.5 $\pm$ 0.30	-
Gunnal et al., 2015³⁶	170	D(e)	India	-	-	-	-	-	-	-	30.2 $\pm$ 3.5
Cilliers et al., 2017⁴³	39	D(e)	South Africa	3.00 $\pm$ 1.33	13.45 $\pm$ 2.09	14.11 $\pm$ 2.40	12.44 $\pm$ 2.86	12.43 $\pm$ 2.78	6.30 $\pm$ 1.41	5.99 $\pm$ 2.14	-
Cilliers et al., 2017⁴³ pilot study	20	D(e)	South Africa	2.65 $\pm$ 1.08	14.42 $\pm$ 2.13	15.06 $\pm$ 1.78	12.54 $\pm$ 1.77	13.02 $\pm$ 2.15	6.56 $\pm$ 1.86	5.97 $\pm$ 1.47	-
Pascalau et al., 2019¹²	10	D(e)	Romania	2.31	14.63		12.98		5.89		26.48

The data from Pascalau et al.¹² is reported without a standard deviation (sd) because this is how their data was reported. The ‘-’ indicates that the study did not provide a value for the mean length of the artery.

The column labelled ‘study type’ refers to the methodology used in the study: dissection of human remains or radiological analysis of MRA/I or CT scans or a combination of both dissection and radiological analysis. D: Dissection – not specified if embalmed or un-embalmed samples were used; D(e): Dissection using; embalmed samples; D(u): Dissection using un-embalmed samples.

The results of this study were similar to those of Du Toit⁸¹ from South Africa because both studies found that there was no statistically significant association between sex and mean artery diameter. However, this contrasted with Jeton et al.⁴ from Egypt. These researchers reported a significant difference in mean diameter between the sexes, with females generally having wider ACAs and AcoAs than males.⁴ Whilst males had wider P1 and VAs than females.⁴ In contrast, Chen et al.⁵⁹ indicated that males tended to have greater or equal vessel diameters to females, but this was not significant.

In the current study, age and mean artery diameter were statistically significant at the 5% level for the AcoA, whereas age and mean artery length were significant at the 10% level for the

BA. The mean artery length and diameter were not statistically significant for the other arteries of the CAC. Therefore, both the length and diameter of arteries could potentially be altered throughout adulthood. The differences observed between the age groups could be owing to physiological compensation of the brain and the arteries supplying the brain throughout life. In agreement, Jeton *et al.*⁴ reported a significant difference in artery diameter between age groups. They reported that the A1, AcoA and ICA were wider in their younger cohort (younger than 40years), whereas the PcoA, P1 and BA were wider in their older cohort (over 40years).⁴ The current study had a middle age group (60-79 years) that had the widest right A1, left PcoA, left P1 and right P1. Therefore, the current study agreed that the P1 is wider in older samples, however, the AcoA was widest in the youngest cohort (30-59 years) in the current study, which disagreed with Jeton *et al.*⁴. The differences in results between the two studies could be owing to the larger sample size (n=513) in the study conducted by Jeton *et al.*⁴, as well as the study types. Jeton *et al.*⁴ was a radiological study and used 3D-TOF-MRA, while the current study was a dissection study. In addition, there could be population-specific differences between the samples: South Africa and Kosovo.

5.6 Aneurysms

In the current study, seven saccular IAs were observed across six CACs and the most common location for the presence of IAs in the sample was the AcoA-ACA junction (57.1%). In half of these samples, there was a 'V' or 'Y' AcoA (*Figure 4.8D-E*) and one with a MedACA (*Figure 4.3A*). The one sample with an IA at the AcoA-ACA junction had a standard AcoA (*Figure 4.8A*), but the posterior circulation had variations including unilateral PcoA hypoplasia and aplasia. The sample with two IAs (*Figure 4.8B*) had an aplastic PcoA on the ipsilateral side as the IAs. These IAs were located approximately where the PcoA would have anastomosed with the ICA and PCA. Therefore, aplasia could have had a high enough effect on haemodynamics within the CAC that aneurysms developed. Moreover, the trigger that resulted in the variation forming during embryological development could have caused a weakening of the epithelial cell layer to develop. Thereby, predisposing the CAC to aneurysm development in the location of the weakened epithelial layer. However, more research needs to be conducted to determine the effects of variations, such as aplasia and 'V' or 'Y' AcoA, on haemodynamics in the CAC. The current study had too few aneurysms to run statistical analyses, but Kayembe⁵⁴ concluded that anatomical variations in the CAC do have an impact on IA development.

Haines & Mihailoff¹⁹ identified that approximately 85% of IAs were found in the anterior circulation, which agrees with an earlier study conducted by Niederberger *et al.*³⁰. Of the 85%, approximately 35% were on the AcoA or the ACA-AcoA junction; approximately 30% on the ICA or the ICA-PCA junction; and the remaining 25% were on the first segment of the MCA.¹⁹ The current study agrees that IAs on the AcoA or ACA-AcoA junction is the most common location for IAs as this was the most common location in the current study. The remaining 15% of IAs were in the posterior circulation and most of these were at the BA bifurcation.¹⁹ Other common sites in the posterior circulation were on the BA and the posterior inferior cerebellar artery-VA junction or on the posterior inferior cerebellar artery itself.¹⁹ Additionally, Kapoor *et al.*⁷ noted that there were saccular aneurysms in 1% of their sample and these were all in the anterior portion of the CAC and two CACs had multiple IAs on the AcoA. In six CACs, IAs were accompanied by a duplicated AcoA or a hypoplastic ACA.⁷ A South African study conducted by Swartbooi *et al.*⁸⁴ agrees that IAs are more common in the anterior circulation as 72% of the IAs in their sample were in the anterior circulation. Therefore, according to the current literature (*Table 5.5*), the predominant locations for IAs are on the AcoA and the PcoA.⁸⁴ This agrees with the current study since 85.7% of the IAs were in the anterior circulation and predominantly on the ACA-AcoA junction. In contrast, Du Toit⁸¹ observed IAs in 54% of the radiological sample analysed and these were more commonly in the posterior circulation with 64% on the PcoA. Furthermore, Du Toit⁸¹ reported that there was no statistically significant difference between artery diameter and the location of IAs. Therefore, more research in a South African context needs to be conducted.

Table 5.5: Table indicating the location and incidence of aneurysms in the circulus arteriosus cerebri.

Author, year	Sample size	Study type	Country	Total	Location of aneurysms (%)						
					AcoA	MCA	MCAB	PcoA	ICA	ACAB	Other
Current study	64	D(e)	South Africa	7 cases	57.1	-	-	-	28.6	-	14.3
Ozaki <i>et al.</i>, 1977⁴¹	153	D(e)	China	5.9%	2.7	-	-	2.2	-	-	-
Kayemba <i>et al.</i>, 1984⁵⁴	148	D(e)	Japan	-	40.3	22.4	-	11.9	-	-	-
Machasio <i>et al.</i>, 2019⁷⁰	94	CTA	Kenya	24.5%	43.6	21.7	-	-	-	-	13.0
Dhakai <i>et al.</i>, 2020⁶³	95	CTA	Nepal	22 cases	22.73	-	22.73	9.09	31.82	4.55	9.10

The '-' indicates that the study did not provide a value for the variation, or the variation did not occur. The column labelled 'study type' refers to the methodology used in the study: dissection of human remains or radiological analysis of MRA/I or CT scans or a combination of both dissection and radiological analysis. D(e): Dissection using; embalmed samples; CTA: Computed Tomography Angiography; MCAB: bifurcation of the MCA; ACAB: bifurcation of the ACA.

5.7 Volume and correction factors

There were no statistical differences for the average artery diameters before and after the correction factors were applied for the tested arteries. The lack of a statistically significant difference for the mean artery diameters in the before and after groups implies that artery diameter is not affected by the size (volume) of the brain. The artery diameters of small, medium and large volumed brains are approximately the same. Therefore, it is likely that correction factors for artery diameter are not required in future studies. However, the left PcoA and right A1 had statistical differences for the average artery length at the 5% and 10% level, respectively. The statistically significant differences for the mean artery lengths in the before and after groups for these two arteries implies that the artery length is affected by the size (volume) of the brain. The artery length of small, medium and large volumed brains is different. Consequently, correction factors for artery length may be required for future studies evaluating CAC variations. To our knowledge, this is the first study investigating CAC variations that has investigated the use of correction factors for the dimensions of the arteries. Consequently, it is recommended that more research into correction factors for the component arteries of the CAC is conducted.

Furthermore, three outliers were removed before conducting statistical analyses on the volumes of the brains. The removal of the outliers had an impact on the summary statistics, as seen in *Table 4.12*. Therefore, it is recommended that future variation studies consider the effects of outliers and exclude them.

5.8 Issues that arose while comparing studies

As previously mentioned, there are several complications that need to be considered when comparing data from CAC variation studies. These included differences in nomenclature,^{3,18} classification system,⁶² sample size,^{43,62} cohort selection and study type.^{43, 56, 62, 89}

5.8.1 Nomenclature

The current study agreed with 56.25% of studies investigated in the metanalysis conducted by Jones *et al.*⁸⁹ that a hypoplastic artery is one with a diameter of less than 1mm, irrespective of the artery being analysed. Another issue that arose with hypoplasia was some studies did not differentiate between aplasia and hypoplasia. The current study did differentiate between the two types of variations. However, comparisons with studies that did not differentiate are less reliable than if the variations had been separated.

There are other variations that had differences in nomenclature in the literature and researchers should report the definition used in their study to allow for more reliable comparisons to be made.

5.8.2 Classification system

This study made use of the classification system developed by Ayre *et al.*² since this system separated hypoplastic and aplastic arteries. Furthermore, it allowed for combinations of variations to be recorded even if these variations were in both the anterior and posterior circulations, as was the case in 55% of the intact sample in the current study. The arrangement of variation types classified into groups enabled the addition of variations that were not recorded in the pre-existing types described by Ayre *et al.*². For instance, the current study categorised nine undescribed types into group five, as the variations noted in the undescribed types either closely resembled one of the pre-described types in the group or did not fit the requirements of groups one to four. More specifically, types 71 through to 74 were CACs displaying short fusion with another variation. However, three CACs in the current study only displayed short fusion. As short fusion was only represented in group five and did not meet the

requirements of groups one to four, CACs with short fusion only were categorised into group five. The same logic was applied for other uncategorised variations.

While this may have been useful for the current study and future studies, a reliable and full comparison to data classified according to other classification types was not easy. There was not always a corresponding type in different classification systems. This was especially evident with the comparison of hypoplastic and aplastic arteries since the classification systems developed by Lazorthes *et al.*⁴⁵ and Chen *et al.*⁵⁹ did not separate hypoplastic and aplastic arteries. However, the classification system developed by Ayre *et al.*² was new, and comparisons will potentially become easier as more studies adopt this approach.

5.8.3 Sample size and cohort selection

The sample size used by researchers may distort the resulting data and small samples cannot reliably reflect a population as the data may be skewed. Moreover, studies with large samples were more likely to observe uncommon variations than studies with small sample sizes. However, a larger sample was still more representative of a population if the samples were collected at random. Sample sizes for dissection studies in the literature, excluding case studies, ranged from 10 samples¹² to 1000 samples.⁷ Therefore, the sample size of the current study was appropriate despite it being relatively small. A limitation to dissection studies was that the sample size was generally smaller than in radiological studies due to the availability of samples. Furthermore, only obvious signs of pathology could be excluded in many dissection studies, especially where patient records were not available for body donors, such was the situation for the current study.

5.8.4 Different study types employed by researchers

The current study used embalmed brains and the researcher and supervisors hypothesised that the acidic pH of embalming fluid used at UCT may have caused arterial walls to constrict. This agreed with studies conducted by Hoksbergen *et al.*¹⁸ and Van Eijk *et al.*⁹⁰. If the arterial walls constrict, then the diameters in the current study may be smaller than in a living subject. However, it is recommended that this should be tested in future studies by comparing un-embalmed arteries to arteries that have undergone an embalming processes.

5.8.5 Demographic information and *circulus arteriosus cerebri* variations

South Africa has a rich social history and a population that is often referred to as the ‘Rainbow Nation’ because of the high variation in ancestral diversity present in the country. Race, commonly referred to as ancestry, is a social construct which is self-perceived.¹⁰⁴ Consequently, there is no legal definition to separate people into population groups.¹⁰⁴ For these reasons, the current study did not seek to assess associations between ancestry and CAC variations. However, the researcher agrees with and supports comparisons between studies in the same country versus international studies.

5.9 Reflections on the current study

The current study had some limitations and there were some aspects that could be improved in future research. The age range was skewed towards the older age groups owing to the use of a cadaveric sample. Skewed age is considered normal for a cadaveric sample because of the correlation between age and mortality due to associated biological factors outside the scope of this study. If a dissection method is being used, then this must either be stated as a limitation or a wider age range could be used with the addition of a radiological component. Initially, the current study had aimed to have a radiological component, however, this was removed as the study progressed. Reasons for this included difficulties in measuring the AcoA and the PcoAs because these arteries were not well visualised in the TOF-MRA/I images analysed during data collection. According to the clinicians and radiologists whom the student consulted, these arteries are often not well defined in images with no contrast medium. The dissection component of the study became more complex and demanded more time. The researcher and supervisors felt that inclusion of the radiological sample would take the project beyond the requirements for a MSc study.

Unfortunately, in dissection studies there is always a risk of damaging some samples, especially fragile structures, such as small accessory or hypoplastic arteries of the CAC. This resulted in a lower sample size in the current study and could also have caused some samples to be incorrectly categorized.⁴³ For instance, bilateral PcoA hypoplasia could have been categorized as unilateral PcoA hypoplasia because one PcoA had been excluded from the study because of the CAC being broken: the contralateral PcoA could have been missing. Some of the CAC samples were broken because of removal of the brain from the skull. This was especially apparent in the 2022 cohort. However, precautions were in place to minimize damage to the arteries in the 2023 cohort. The methodology laid out should be adhered to closely to prevent

damage during removal of the brain and further removal of the arteries from the brain. However, the sample was being shared by two researchers that were analysing different aspects of the CAC. Therefore, the cleaning methods and knowledge of the CAC may have varied slightly, despite continuous communication.

For the current study, the equipment used was a limitation. The 5L beaker available for the study only had litre demarcations. Therefore, smaller measuring cylinders, a measuring jug and a 5ml syringe were used to conduct smaller measurements, as described in the methods. However, despite the researcher taking precautions to minimise water loss, there were always a few drops of liquid that were not accounted for as there would be water on the outside of the measuring cup and drip off the bottom as the water was being poured into measuring cylinders. The researcher tried to ensure as much water from the outside of the measuring jug was directed to the beaker or measuring cylinder as possible. In future studies recording the volume of brains using a water displacement method, a beaker with smaller measurement demarcations should be used. Alternatively, the water could be collected using a large syringe or siphon, instead of using a small measuring jug. This will make data collection easier, faster and more reliable. Other factors, that were not addressed by the current methodology, which could have affected the volumes, included the amount of embalming fluid that remained in the brain (even with draining) and the amount of pia mater attached to the brain may not have been uniform across the specimens. However, this structure was important to maintain, where it was present since the brains will be used for educational purposes after the study. Nevertheless, the researcher and supervisors believe that the water displacement method was the most appropriate method for determining the volume of brains for this type of study. It is their recommend method to determine the volume of a cadaveric brain.

In the current study, photographs of the isolated CAC were taken and Fiji[®] was used to make the measurements. This was owing to the issues that arose while photographing the arteries while the CAC was still on the ventral surface of the brain. Initially, the 2D photograph obtained was too unreliable because of the curvature of the BA on the brainstem towards the soft tissue of the brain and the resulting position of the PCAs caused an angle. Therefore, the CAC was removed and photographed. Prior to photographing the CAC, the researcher attempted to get a 3D image of the CAC using a handheld 3D scanner. However, the scanner was unable to detect the CAC and only detected the foam sheet beneath it. Alternative methods were attempted to have the CAC recognised. However, none of these worked with the handheld 3D scanner that was available for the study. MRI reconstruction of the samples was considered,

but this would have increased the timeline of the study and fees would have been applied for the use of necessary machinery. Both of which were out of the budget for this study, which was funded for the initially proposed timeline of two years. Conducting measurements on a 3D image would have allowed for more accurate measurements, would have made the methodology more reproducible and should be considered by future studies.

While using Fiji® software, it was noticed that measurements could vary according to the distance, height and angle of the observer to the screen. Therefore, the observer should try to have their eyeline horizontal to the screen (as with volume measurements with a meniscus) to prevent the measurements being altered by the view of the observer (error of parallax). The observer should try to be in approximately the same position to the screen for each repeat measurement conducted. Furthermore, three measurements should be conducted to reduce this type of human error. Moreover, the AcoA sometimes had a cone-like shape and the measurement conducted in the middle of the vessel should suffice. Alternatively, three measurements could be taken: one in the middle of the AcoA and two on either side of the AcoA, as it joins with the left and right A1 respectively. However, this should be analysed in future studies.

5.10 Future research

In addition to future research suggestions previously mentioned, below are alternative research avenues:

Many research studies have investigated aspects of the CAC, such as variations in one artery, but few have looked at how variations affect the entire CAC. It is not seen how a variation in one artery affects the other CAC arteries.⁶⁰ Furthermore, more studies based on quantitative measurements of both internal (luminal)⁵ and external diameters should be conducted. Moreover, the closely related arteries of the CAC should also be analysed for variations, especially the VAs and ICAs since variations in these arteries could have an influence on the configuration of the CAC. Future research should expand upon this and analyse variations in the ICA and VA with the prevalence of CAC variations. During analysis of the arteries in the current study, it was noted that the BA bifurcation was very variable in the sample, in agreement with Gunnell *et al.*³⁶. Therefore, future research should analyse BA bifurcation patterns alongside other CAC variations. Furthermore, the differences in nomenclature should be explored and attempts at creating a consensus should be made. The same applies to classification systems used.

Additionally, more haemodynamic studies are required to analyse the effects of variations and IAs. Degeneration of vascular endothelium has a significant role in IA development⁷⁴ and studies that investigate this are needed. Furthermore, sheer wall stress in the formation of IAs⁷⁴ and the divergence in angles of arteries at points of anastomosis need to be investigated further when considering IA development.

To further the understanding of the variables associated with IA rupture, more research into CAC variations as a risk factor for IA rupture should be conducted. The risk of rupture owing to haemodynamic forces on IAs are currently not well studied.⁷⁶ For instance, comparing CAC variations in ruptured vs unruptured IAs has not been studied extensively⁷² and may assist with identifying the risks associated with IA rupture. One risk factor is the size of the IA¹⁹ and another risk factor is infection⁶¹. For example, human immunodeficiency virus (HIV) infection as a comorbid condition should be analysed to determine the effects of infection on IA morphology.⁶¹

Lastly, the association between the incidence of both ischaemic and haemorrhagic stroke with CAC variations needs to be researched further as the association is unclear.⁸⁶ Some CAC variations, such as PcoA hypoplasia, have been suggested to be associated with stroke, but more research is required to confirm this.

Chapter 6: Conclusions

In international literature, the CAC is relatively well described, and studies have reported associations of CAC variations with the presence of IAs, age and sex. However, only a handful of studies have been conducted in a South African context. Du Toit⁸¹, those by Cilliers^{38,43,57} and the current study were all conducted in the Western Cape and variations in the CAC in the Western Cape are currently the most well studied in South Africa. There were similarities and differences between the five studies, and this implies that more research is still required in the Western Cape. Furthermore, it would be valuable to expand such studies into the rest of the country.

In the current study, an intact sample was categorised according to the classification system developed by Ayre *et al.*². The most common group was group 5 (other variations; 37.5%) followed by group 4 (accessory vessels; 22.5%) and group 6 (the conventional anatomical configuration; 22.5%). Classification of the samples in this manner also highlighted that variations were mostly found in the anterior and posterior circulations combined (55%) and were found least commonly in the posterior circulation only (19%). To the researcher's knowledge, this is the first study to use this classification system since its development in 2021. This slightly hindered the comparison of the intact sample results to other studies. However, it is the researcher's belief that this is the most encompassing classification system to date and should be used in future studies.

An analysis of variations for the entire sample was conducted and indicated that there was no statistically significant difference between the frequencies of individual variations. The most common individual variations were unilateral PcoA hypoplasia (17.3%), unilateral PcoA aplasia (14.8%) and short fusion (13.6%). Unlike some previous studies, the PcoA was not the most variable artery, but the second most variable and accounted for 42% of individual variations. All hypoplastic arteries were patent and only a small diameter AcoA was non-patent. This indicates that hypoplastic arteries and aplastic arteries should be considered separately. Furthermore, the AcoA was the most variable artery in the sample (44.4%) and individual variations were found in the anterior circulation (51.9%) more frequently than in the posterior circulation (48.1%). The current study was the first South African study to report a higher frequency of anterior variations than posterior variations.

Moreover, some uncommon variations were noted in the current sample, including type four and five PcoA termination types (3.7%). In the current study, these were classed as a double P2 segments and have not been reported by other South African studies.

In addition, the dimensions of arteries were assessed in the current study and the communicating arteries tended to be the narrowest arteries of the CAC with the narrowest artery generally being the right PcoA (1.476mm). The difference in mean vessel diameter and length with age was statistically significant. In the youngest cohort (30-59 years), the AcoA and right PcoA had the greatest diameters, and this cohort had the shortest arteries forming the CAC among the three age groups. Generally, the middle cohort (60-79 years) had the longest arteries forming the CAC, excluding the AcoA and BA. The oldest cohort (80-100 years) generally had the longest AcoA and BA. In contrast to age, the differences in mean arterial diameter and length between male and female groups were not statistically significant, except for the length of the right A1, where there was a statistically significant difference. Males appeared to have arteries with a greater length and diameter overall, which may be a reflection of sexual dimorphism.

Further associations that were tested included the frequency of variations with age and the frequency of variations with sex. Neither of these associations were statistically significant, although females displayed a higher frequency of variations when compared to males. It was the intention of the researchers to test whether there was an association between variations and the presence of IAs. More IAs were expected to be observed in the radiological portion of the study, however, this portion of the study was not pursued owing to time restraints and the researcher was unable to identify the structures necessary for the radiological component to be pursued, even with the assistance of radiologists. As a result, the number of IAs observed in the cadaveric sample was too low to conduct statistical analyses and the most frequent location was the AcoA-ACA junction (57.1%).

Correction factors were calculated and applied to the lengths and diameters for the small (903ml<1050ml; CF: +15%), and large (1266ml<1361ml; CF: -11%) brains. The results of Wilcoxon-rank tests indicated that there were no statistical differences for the mean artery diameters before and after the correction factors were applied. However, only the A1 had statistically significant differences for the mean artery length before and after correction factors were applied. The conclusion was that brain size potentially affects the lengths of some arteries, but not the diameters of any of the arteries forming the CAC. Despite human variation being

an important factor that should be considered in CAC studies, to the researcher's knowledge this is the first study to test whether correction factors are required for CAC variation studies. These results indicate that correction factors should be used in future studies of the CAC in order to address human variation and the water displacement method is recommended to determine differences in brain volume in a cadaveric sample.

In conclusion, more individual variations were found in the anterior circulation than in the posterior circulation. This may influence the territory affected by a stroke and the location of IA formation. Furthermore, PcoA hypoplasia and aplasia were the most common variations in the current study. These variations may alter the haemodynamics in the CAC and may increase the risk and severity of stroke as well as the development and rupture of IAs. The third most common variation was short fusion of the ACAs, which potentially alters the shape of the CAC sufficiently to affect the planning and execution of various neurosurgeries. As such, it is important for local neurosurgeons to know the prevalent CAC patterns in the local population when planning and executing surgeries. All these variations have the potential to affect the collateral perfusion enabled by the CAC and as such neurosurgeons may have to alter surgeries that impact brain perfusion in general. Furthermore, age appears to be an important factor to consider with CAC variations since this study indicates that there are associations between age and arterial lengths and diameters. The investigation of CACs with the conventional pattern and variations in the cadaveric sample at University of Cape Town yielded results that mostly agree with international data, however, there are some differences with local data and more research in a South African setting is needed.

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Appendix A: Summary of the classification system by Ayre et al.²

The classification system created by Ayre *et al.*² consists of 82 anatomical variations, as seen in *Table a* (Appendix A). These variations are separated into five main groups, as follows:

Group 1: Hypoplastic segments only

Group 2: Aplastic segments only

Group 3: Combination of hypoplastic and aplastic segments

Group 4: Accessory segments in combination with hypoplastic or aplastic segments

Group 5: Other variations

Table a: Summary of the classification system created by Ayre et al.².

Variation	Classification Number
Group 1	
Hypoplastic: one AcoA	1
Hypoplastic: one A1 segment	2
Hypoplastic: one PcoA	3
Hypoplastic: one P1 segment	4
Hypoplastic: AcoA and one PcoA	5
Hypoplastic: AcoA and one P1 segment	6
Hypoplastic: one A1 segment and ipsilateral PcoA	7
Hypoplastic: one A1 segment and contralateral PcoA	8
Hypoplastic: one A1 segment and ipsilateral P1 segment	9
Hypoplastic: one A1 segment and contralateral P1 segment	10
Hypoplastic: both PcoAs	11
Hypoplastic: one PcoA and contralateral P1 segment	12
Hypoplastic: both P1 segments	13
Hypoplastic: one P1 segment and one P2 segment	14
Hypoplastic: AcoA and both PcoAs	15
Hypoplastic: AcoA, one PcoA and contralateral P1 segment	16
Hypoplastic: AcoA and both P1 segments	17
Hypoplastic: both PcoAs and one A1 segment	18
Hypoplastic: A1 segment, ipsilateral PcoA and contralateral P1 segment	19
Hypoplastic: A1 segment, contralateral PcoA and ipsilateral P1 segment	20
Hypoplastic: both P1 segments and one A1 segment	21
Hypoplastic: both PcoAs and one P1 segment	22
Hypoplastic: AcoA, both PcoA, one P1 segment and one P2 segment	23
Hypoplastic: AcoA, both A1 segments, one A2 segment and PcoA	24
Group 2	
Aplastic: AcoA	25
Aplastic: one A1 segment	26
Aplastic: one PcoA	27

Aplastic: one P1 segment	28
Aplastic: AcoA and one PcoA	29
Aplastic: A1 segment and ipsilateral PcoA	30
Aplastic: both PcoAs	31
Aplastic: AcoA and both PcoAs	32
Aplastic: one A1 segment and both PcoAs	33
Aplastic: one A1 segment and both P1 segments	34
Aplastic: both PcoAs, one P1 segment and one P2 segment	35
Group 3	
One aplastic A1 segment and hypoplastic contralateral P1 segment	36
One hypoplastic PcoA and aplastic contralateral PcoA	37
One plastic PcoA and hypoplastic contralateral P1 segment	38
One hypoplastic AcoA and both PcoAs aplastic	39
Both PcoAs hypoplastic and absent AcoA	40
One aplastic A1 segment and both P1 segments hypoplastic	41
Group 4	
Duplicated AcoA	42
Duplicated AcoA and one hypoplastic PcoA	43
Duplicated AcoA and both PcoAs hypoplastic	44
Duplicated AcoA, one hypoplastic PcoA and aplastic contralateral PcoA	45
Duplicated AcoA and one aplastic PcoA	46
Duplicated AcoA and both PcoAs aplastic	47
Duplicated AcoA with one hypoplastic AcoA	48
Duplicated AcoA with one hypoplastic AcoA and one hypoplastic PcoA	49
Plexiform AcoA and one hypoplastic PcoA	50
Tripllicated AcoA	51
MedACA	52
MedACA and one hypoplastic A1 segment	53
MedACA and one hypoplastic PcoA	54
MedACA both PcoAs hypoplastic	55
MedACA and one aplastic PcoA	56
Lateral triplicated ACA	57
Lateral triplicated ACA, hypoplastic AcoA and hypoplastic ipsilateral PcoA	58
One duplicated A1 segment	59
One duplicated A1 segment and hypoplastic ipsilateral P1 segment	60
Tripllicated PcoA with one hypoplastic PcoA, hypoplastic contralateral PcoA and hypoplastic ipsilateral P1 segment	61
One duplicated P1 segment	62
One P1segment duplicated from the origin and one aplastic A1 segment	63
One duplicated PCA with an intermediate communicating artery	64

One duplicated PCA with an intermediate communicating artery and one hypoplastic P1 segment with carotid origins	65
Lateral triplicated ACA and duplicated AcoA	66
One duplicated A1 segment and ipsilateral duplicated P1 segment	67
Group 5	
Duplicated AcoA ('V'-shaped) and one hypoplastic PcoA	68
Duplicated AcoA ('V'-shaped) and both PcoAs hypoplastic	69
Duplicated AcoA ('trident'-shaped)	70
Azygous ACA and one aplastic P1 segment	71
Azygous ACA and both P1 segments aplastic	72
Short fusion of ACAs and both PcoAs hypoplastic	73
Short fusion of ACAs and one hypoplastic A1 segment, ipsilateral aplastic PcoA and contralateral hypoplastic P1 segment	74
Duplicated AcoA ('V'-shaped) and fenestrated A1-A2 junction	75
Aplastic AcoA, one aplastic A1 segment, aplastic ipsilateral A2 segment, contralateral fenestrated A1-A2 junction, contralateral aplastic PcoA and aplastic ipsilateral PcoA	76
One fenestrated A1 segment and ipsilateral aplastic P1 segment	77
One fenestrated PcoA	78
One fenestrated P1 segment	79
One fenestrated A1 segment and ipsilateral fenestrated A2 segment	80
Elongated PcoA and aplastic contralateral PcoA	81
One hypoplastic A1 segment, aplastic ipsilateral PcoA and contralateral elongated PcoA	82

Appendix B: Spreadsheet Templates

This appendix contains the spreadsheet templates used during data collection. Both the macroscopic dissection and radiological components of the study used the same template, but in different Microsoft Excel spreadsheets.

Table a: Template for the length measurement data. Separate tables were used for internal and external measurements. The average from both sets were used to calculate the overall length of the arteries. Sex was recorded as male (M) or female (F).

Reference Number	Age (Years)	Location of aneurysms	BA (mm)				P1 (mm)				PcoA (mm)				ICA (mm)				A1 (mm)				AcoA (mm)			
			1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A
1M																										
2M																										
1F																										
2F																										

Table b: Template for the diameter measurement data. Sex was recorded as male (M) or female (F).

Reference Number	Age (Years)	Location of aneurysms	BA (mm)				P1 (mm)				PcoA (mm)				ICA (mm)				A1 (mm)				AcoA (mm)			
			1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A	1	2	3	A
1M																										
2M																										
1F																										
2F																										

Appendix C: Data from macroscopic dissection

This appendix contains the raw data used in the statistical analyses.

Table a: Data for the length measurements from the macroscopic dissection. The average measurement is reported for each artery.

Reference number	Age (years)	BA (mm)	Left P1 (mm)	Left PcoA (mm)	Left A1 (mm)	AcoA (mm)	Right P1 (mm)	Right PcoA (mm)	Right A1 (mm)
1M	80	27.323	5.345	13.620	14.195	3.950	3.997	14.503	14.360
2M	90	37.133	13.998	9.842	8.040	3.493	12.755	0.000	16.362
1F	94	34.168	0.000	0.000	0.000	1.445	0.000	0.000	13.193
2F	86	31.507	7.818	8.010	13.493	0.000	11.787	7.935	12.857
3M	38	26.410	8.018	9.902	10.902	2.845	5.070	11.358	15.983
3F	92	31.278	13.177	7.862	13.632	3.382	8.487	15.545	15.392
4F	84	22.300	2.125	9.100	1.215	3.072	15.927	22.580	12.470
5F	87	22.123	4.225	11.213	12.807	0.000	4.970	14.178	13.877
6F	32	29.250	8.822	14.650	12.745	2.345	8.413	9.733	13.128
7F	89	29.717	7.680	15.340	13.733	2.545	7.118	17.355	10.645
8F	72	28.577	13.165	14.877	13.280	0.968	3.983	0.000	16.285
9F	82	0.000	0.000	0.000	10.037	1.837	0.000	0.000	11.058
10F	79	29.598	3.938	1.227	10.623	2.577	3.852	0.000	0.000
4M	48	0.000	4.623	8.323	12.143	4.560	3.487	4.878	16.483
5M	78	33.057	8.498	13.023	17.692	3.412	8.383	16.962	18.080
6M	63	28.160	17.338	11.625	14.030	0.000	7.198	14.900	12.448
7M	97	24.675	6.330	11.763	15.890	2.007	6.393	13.815	15.692
11F	91	40.858	5.750	13.127	11.370	3.353	6.663	15.693	15.077
12F	91	35.682	5.352	12.270	12.058	0.000	6.307	14.853	14.203
8M	75	0.000	5.333	10.833	10.080	5.917	4.055	14.053	16.113

13F	84	23.985	3.807	10.397	12.298	3.752	3.292	0.000	8.487
14F	87	0.000	0.000	0.000	12.453	1.785	0.000	0.000	11.800
9M	73	34.692	23.718	0.000	13.827	1.908	10.703	11.017	16.258
10M	59	27.565	4.248	13.953	14.270	1.523	1.973	12.905	12.047
11M	65	26.082	0.000	0.000	0.000	3.257	7.773	15.105	17.773
15F	68	25.757	4.163	8.842	13.642	1.035	0.000	0.000	15.567
16F	77	28.678	2.412	0.000	13.382	0.000	0.000	0.000	10.597
17F	63	32.872	4.975	17.098	14.118	3.640	4.727	10.138	12.743
12M	86	27.182	4.497	18.303	13.452	2.353	5.780	13.670	11.363
13M	76	36.908	8.112	11.895	13.324	2.413	4.748	12.982	13.232
14M	74	28.655	5.798	0.000	0.000	0.000	0.000	0.000	0.000
18F	87	31.233	0.000	0.000	15.060	0.000	0.000	0.000	0.000
19F	75	30.160	0.000	0.000	17.642	2.328	6.630	15.137	14.952
15M	60	32.292	7.072	14.150	11.517	3.105	5.210	18.075	16.365
20F	83	28.967	5.738	10.138	13.673	0.000	2.680	14.000	12.188
21F	78	26.328	5.497	10.535	10.545	3.045	4.187	15.075	13.453
16M	81	27.855	18.608	16.982	13.903	1.485	4.208	0.000	15.080
22F	90	18.162	1.668	0.000	8.348	2.220	1.233	0.000	7.383
23F	86	36.362	7.467	14.817	15.400	2.217	5.448	14.002	12.280
17M	81	41.575	3.550	12.255	12.952	0.000	5.152	11.600	13.452
24F	78	29.842	0.000	0.000	15.098	3.092	0.000	0.000	14.673
25F	90	25.195	9.743	0.000	10.737	5.058	7.607	9.458	12.907
26F	74	21.802	5.485	12.798	12.130	1.673	5.083	0.000	1.086
27F	58	31.140	0.000	0.000	9.273	4.353	8.088	0.000	0.000
18M	86	0.000	2.917	10.753	11.612	1.607	4.530	12.535	14.663
19M	80	36.747	0.000	0.000	14.268	3.133	5.708	17.475	6.862
28F	77	27.890	5.850	29.237	13.092	0.000	0.000	0.000	0.000
20M	86	0.000	0.000	0.000	10.038	1.650	0.000	0.000	9.947

21M	58	32.873	5.793	0.000	13.623	2.593	11.037	9.803	17.755
29F	74	22.903	6.935	13.845	14.403	3.153	6.473	13.652	14.382
22M	85	27.640	5.243	15.162	16.148	3.350	15.018	9.130	15.877
23M	70	32.620	4.978	0.000	13.072	3.357	5.930	14.147	13.737
30F	75	28.717	9.568	0.000	0.000	3.027	5.320	11.045	10.710
24M	50	29.042	0.000	0.000	8.133	3.907	5.865	0.000	13.873
25M	47	22.077	4.780	15.045	11.993	1.177	2.768	16.843	13.382
26M	30	22.123	4.225	11.213	12.807	0.000	4.970	14.178	13.877
31F	92	31.567	5.318	13.718	13.073	5.747	6.408	11.190	13.433
27M	86	31.835	2.780	18.010	15.687	0.000	6.788	11.087	18.045
28M	88	29.153	2.818	14.035	12.807	4.208	0.000	0.000	16.218
32F	55	0.000	0.000	10.433	10.447	2.690	0.000	16.402	10.697
33F	80	19.600	5.920	13.630	11.890	3.708	6.722	13.407	13.013

Sex was recorded as male (M) or female (F) in the reference number.

Table b: Data for the diameter measurements from the macroscopic dissection. The average measurement is reported for each artery.

Reference number	Age (years)	BA (mm)	Left P1 (mm)	Left PcoA (mm)	Left A1 (mm)	AcoA (mm)	Right P1 (mm)	Right PcoA (mm)	Right A1 (mm)
1M	80	4.213	2.747	1.610	1.650	1.307	2.457	2.380	2.357
2M	90	4.363	2.870	1.400	2.473	2.247	3.127	0.000	3.503
1F	94	4.897	2.770	0.000	1.990	1.343	3.153	0.000	1.990
2F	86	5.300	2.803	1.433	2.883	2.793	0.853	1.747	1.553
3M	38	4.807	2.777	2.143	2.307	2.257	2.143	1.853	2.390
3F	92	3.003	0.863	0.853	1.207	1.527	2.197	2.183	1.843
9M	73	4.730	2.717	0.000	1.877	1.873	1.243	1.243	3.500
4F	84	3.513	0.837	1.590	2.213	1.267	1.853	1.257	2.650
5F	87	4.457	2.467	0.883	2.383	0.000	2.730	1.297	2.220
6F	32	3.503	2.037	2.107	2.747	2.263	1.513	1.037	1.537

7F	89	3.860	1.430	2.473	2.530	2.447	2.307	1.710	2.907
8F	72	4.100	2.500	3.890	1.443	1.137	2.073	0.000	2.563
9F	82	0.000	2.573	0.000	1.830	1.500	2.130	0.000	1.667
10F	79	4.230	2.310	1.307	1.703	0.883	2.730	0.000	2.360
4M	48	0.000	2.090	2.297	2.390	1.570	1.510	2.363	1.837
5M	78	4.523	3.390	2.143	1.450	1.520	1.907	2.437	1.857
6M	63	5.247	2.977	2.320	3.110	0.000	3.267	1.433	3.143
7M	97	3.440	2.130	0.913	1.430	1.530	1.250	0.953	2.180
11F	91	4.513	2.133	2.790	2.523	1.413	2.963	1.487	2.090
12F	91	3.763	3.207	1.147	2.190	0.000	2.827	0.877	2.220
8M	75	0.000	3.213	1.580	1.780	2.243	2.813	0.830	0.857
13F	84	5.533	2.797	0.860	1.387	1.283	2.487	0.000	2.183
14F	87	0.000	0.000	0.000	1.863	1.823	0.000	0.000	2.047
10M	59	5.327	3.097	0.850	2.407	0.847	1.327	1.993	2.690
11M	65	4.070	2.723	0.000	2.873	0.933	3.343	0.993	3.040
15F	68	5.730	2.187	1.800	3.053	1.633	3.433	0.000	2.720
16F	77	3.850	2.550	0.000	1.880	1.850	0.000	0.000	1.167
17F	63	4.927	2.627	1.117	1.433	1.520	2.267	0.870	3.663
12M	86	5.040	2.263	0.903	2.843	1.690	2.657	0.780	3.187
13M	76	4.120	2.470	1.470	1.900	0.913	2.930	1.517	1.453
14M	74	3.940	2.440	0.000	2.767	0.000	2.800	0.000	0.000
18F	87	5.260	2.870	0.000	1.597	0.000	1.253	0.000	0.000
19F	75	4.633	2.723	0.000	0.750	1.880	2.397	0.857	3.307
15M	60	3.120	2.133	2.390	2.230	1.217	1.880	1.967	2.480
20F	83	4.723	2.670	1.317	2.663	0.000	2.307	1.147	2.173
21F	78	3.690	2.190	1.087	1.570	0.823	2.163	1.073	1.513
16M	81	4.200	2.497	1.133	2.580	2.270	1.550	0.000	3.163

22F	90	2.000	1.123	0.000	1.253	1.410	1.103	0.000	1.217
23F	86	5.160	2.570	0.943	2.190	1.563	3.740	0.973	1.510
17M	81	4.773	1.410	2.910	1.393	0.000	1.667	1.977	2.757
24F	78	3.650	1.310	0.000	1.787	1.533	2.743	0.000	1.883
25F	90	4.817	2.263	2.303	1.290	2.610	1.830	1.950	2.977
26F	74	5.023	2.837	0.667	2.717	1.393	2.953	0.000	2.027
27F	58	4.827	1.157	0.000	2.297	1.983	2.743	0.000	0.000
18M	86	0.000	1.950	1.087	2.923	2.207	1.920	1.077	2.220
19M	80	5.157	2.727	0.000	1.197	1.890	2.947	0.540	2.283
28F	77	3.807	1.460	2.500	3.257	0.000	1.550	0.000	0.000
20M	86	0.000	0.000	0.000	2.570	1.117	0.000	0.000	1.340
21M	58	4.003	2.923	0.000	2.300	3.247	2.707	1.770	1.997
29F	74	4.857	2.537	0.997	3.023	1.280	2.317	2.160	1.850
22M	85	4.810	0.740	1.047	1.327	2.503	0.833	3.237	2.207
23M	70	4.883	2.723	0.000	2.633	1.443	2.957	1.300	3.457
30F	75	3.817	2.180	0.000	0.000	1.093	0.997	1.180	2.710
24M	50	4.490	2.263	0.000	2.403	2.273	2.780	0.000	1.377
25M	47	4.170	2.740	1.410	2.463	1.597	1.890	1.543	1.713
26M	30	4.217	1.980	1.647	2.153	0.000	2.723	1.533	2.037
31F	92	4.350	2.407	0.830	1.470	1.510	2.573	0.970	1.937
27M	86	3.463	2.320	0.950	2.207	0.000	2.483	1.173	1.573
28M	88	3.733	1.370	2.310	3.077	2.693	2.753	0.000	0.940
32F	55	0.000	0.000	1.020	1.847	1.603	0.000	1.940	1.600
33F	80	4.663	1.807	1.183	1.757	1.900	2.197	0.930	3.207

Sex was recorded as male (M) or female (F) in the reference number.

Table c: Data obtained from the patency tests of the small diameter arteries (<1.5mm), including hypoplastic arteries (<1mm).

Sample	Patency of small diameter vessels (Yes/No)						
	Left PcoA	Right PcoA	Left P1	Right P1	AcoA	Left A1	Right A1
6M	Yes	Yes					
7M	Yes*	Yes*		Yes		Yes	
17M			Yes			Yes	
7F			Yes				
3F	Yes*		Yes*			Yes	
2M	Yes						
2F	Yes			Yes*			
5F	Yes*	Yes					
10F	Yes				Yes*		
12F	Yes	Yes*					
10M	Yes*			Yes	Yes*		
17F	Yes*					Yes	
13M	Yes				Yes*		Yes
20F	Yes	Yes					
21F	Yes	Yes			Yes*		
16M	Yes						
23F	Yes*	Yes*					
18M	Yes	Yes					
29M	Yes*				No		
22M	Yes			Yes*		Yes	
31F	Yes*	Yes*		Yes		Yes	
27M	Yes*	Yes					
33F	Yes	Yes*					
8F					Yes	Yes	
5M						Yes	
13F	Yes*				Yes	Yes	
19F		Yes*				Yes*	

25F						Yes	
4F		Yes	Yes*		Yes		
11F		Yes			Yes		
15M					Yes		
9M		Yes		Yes			
6F		Yes					
16F							Yes
11M		Yes			Yes*		
8M		Yes*					Yes*
30F				Yes*	Yes		
19M		Yes*				Yes	
23M		Yes			Yes		
20M					Yes		Yes
1F					Yes		
12M	Yes*	Yes*					
1M					Yes		
25M	Yes						
28F			Yes				
32F	Yes						
24M							Yes
28M			Yes				Yes* **
9F					Yes		
34F					Yes*		
26F	Yes*						

*The vessel was hypoplastic.

**A very small lumen in relation to the vessel diameter was present.

Table d: Patency of accessory vessels.

Sample	Vessel	Patent (Yes/No)
1M	The slight triangular BA bifurcation	Yes
1F	The second branch of the duplicated AcoA	No
3F	AcoA-A1 accessory vessel	Yes
5M	Accessory vessel that comes off another accessory vessel of the AcoA posteriorly and goes into the AcoA anteriorly	Yes
5M	Accessory vessel A1 to AcoA-A1 junction on the lateral aspect	Yes*
23M	Second vessel of the duplicated AcoA	No
31F	AcoA-A1 accessory vessel	Yes*
9M	The triangular BA bifurcation	Yes
9M	‘V’ AcoA vessel	Yes
9M	Accessory vessel on the A1	Yes
10M	Second vessel of the duplicated AcoA	No

*A very small lumen in relation to the vessel diameter was present.

Table e: Raw data obtained from the water displacement method for volume calculations. The initial volume was subtracted from the final volume (average of V_{1-3}) to determine the volume of each brain.

Sample	Age	Brainstem Level	Brain volume: including cerebellum (ml)					
			V_i	V_1	V_2	V_3	$V_f = (V_{sum}/3)$	Volume (V_{f-i})
1M	80	A	3000	4325	4335	4335	4331.7	1332
2M	90	D	3000	4245	4250	4268	4254.3	1254
1F	94	B	3000	4253	4235	4223	4237.0	1237
2F	86	B	3000	4201	4175	4183	4186.3	1186
3M	38	-	3000	4319.5	4355	4363	4345.8	1346

3F	92	B	3000	4253	4275	4284	4270.7	1271
9M	73	D	3000	4338	4332	4324	4331.3	1331
4F	84	D	3000	4050	4052	4048	4050.0	1050
5F	87	B	3000	4188	4190	4191	4189.7	1190
6F	32	D	3000	4000	4000	4041	4013.7	1014
7F	89	D	3000	4170	4169	4163	4167.3	1167
8F	72	D	3000	4040	4035	4053	4042.7	1043
9F	82	D	3000	4152	4131	4130	4137.7	1138
10F	79	D	3000	4164	4126	4120	4136.7	1137
34F	79	D	3000	4221	4232	4188	4213.7	1214
4M	48	D	3000	4210	4228	4222	4220.0	1220
5M	78	A	3000	4230	4230	4240	4233.3	1233
6M	63	D	3000	4182	4178	4191	4183.7	1184
7M	97	D	3000	4150	4159	4162	4157.0	1157
11F	91	D	3000	4201	4210	4206	4205.7	1206
09/21	82	D	3000	3922	3965	3950	3945.7	946
12F	91	A	3000	4000	4000	4000	4000.0	1000
8M	75	A	3000	4081	4109	4070	4086.7	1087
12F	84	C	3000	4127	4180	4177	4161.3	1161
8M	37	C	3000	4572	4199	4189	4320.0	1320
13F	87	A	3000	4050	4073	4049	4057.3	1057
10M	59	D	3000	4255	4277.5	4265	4265.8	1266
11M	65	B	3000	4010	3990	4000	4000.0	1000
15F	68	A	3000	4262.5	4260	4270	4264.2	1264
16F	77	C	3000	4060	4050	4060	4056.7	1043
17F	63	D	3000	3910	3882.5	3917.5	3903.3	903
12M	86	C	3000	4115	4085	4095	4098.3	1098
13M	76	-	3000	4357.5	4332.5	4345	4345.0	1345

14M	74	B	3000	4180	4150	4167.5	4165.8	1166
18F	87	D	3000	4315	4295	4310	4306.7	1307
19F	75	D	3000	4240	4245	4252.5	4245.8	1246
15M	60	D	3000	4297.5	4315	4297.5	4303.3	1303
20F	83	D	3000	4000	4028	4027	4018.3	1018
21F	78	-	3000	4087	4097	4099	4094.3	1094
16M	81	D	3000	4225	4232.5	4225	4227.5	1228
22F	90	B	3000	4202.5	4185	4187.5	4191.7	1192
23F	86	A	3000	4210	4185	4180	4191.7	1192
17M	81	B	3000	4340	4370	4372.5	4360.8	1361
24F	78	B	3000	3920	3940	3930	3930.0	955
25F	90	B	3000	3940	3964.5	3960	3954.8	1027
26F	74	B	3000	3315	3222.5	3010	3182.5	516
27F	58	D	3000	4357.5	4375	4365	4365.8	1357
18M	86	D	3000	4235	4230	4220	4228.3	1228
19M	80	D	3000	4242.5	4235	4235	4237.5	1238
28F	77	D	3000	4292.5	4255	4262.5	4270.0	1270
20M	86	D	3000	4240	4250	4265	4251.7	1252
21M	58	D	3000	4202.5	4152.5	4167.5	4174.2	1174
29F	74	B	3000	4028	4050	4050	4042.7	1043
22M	85	D	3000	4245	4240	4257.5	4247.5	1248
23M	70	D	3000	4330	4310	4315	4318.3	1318
30F	75	D	3000	4180	4160	4147.5	4162.5	1163
24M	50	D	3000	4170	4165	4185	4173.3	1173
25M	47	D	3000	4287.5	4285	4277.5	4283.3	1270
26M	30	D	3000	3985	3935	4970	4296.7	1630
31F	92	D	3000	4240	4230	4225	4231.7	1232
27M	86	D	3000	4305	4310	4235	4283.3	1182

28M	88	D	3000	4320	4335	4307.5	4320.8	1277
33F	80	A	3000	4150	4160	4152.5	4154.2	1154

Sex was recorded as male (M) or female (F) in the reference number.

- Indicates that the brainstem was too damaged to group it according to the A-D system.

V_i : Initial volume; V_{1-3} : volumes 1 to 3 obtained from the displacement of water; V_f : final volume; V_{sum} : the sum of V_{1-3} .

Appendix D: Raw statistical outputs

This appendix contains the raw outputs of the statistical analyses conducted. The p-values were provided in the relevant sections of the dissertation and a brief interpretation is given for each test in this appendix. The names of variables are as recorded by STATA.

Tests for Normality

Individual variations: Shapiro–Wilk test

Variable	Obs	W	V	z	Prob>z
R	17	0.81332	3.944	2.736	0.00311

Interpretation: Prob>z is smaller than 0.05, therefore, the individual variation data is not normally distributed.

Age: Shapiro-Wilk test

Variable	Obs	W	V	z	Prob>z
Ageyears	40	0.84465	6.141	3.819	0.00007

Interpretation: Age is not normally distributed because Prob>z is smaller than 0.05.

Artery length: Shapiro–Wilk test

Variable	Obs	W	V	z	Prob>z
BA	61	0.81120	10.400	5.052	0.00000
LeftP1	61	0.87021	7.149	4.244	0.00001
LeftPcoA	61	0.89495	5.786	3.788	0.00008
AcoA	61	0.96205	2.091	1.591	0.05580
RightP1	61	0.94173	3.209	2.516	0.00594
RightPcoA	61	0.87071	7.122	4.236	0.00001
RightA1	61	0.81477	10.203	5.011	0.00000

Interpretation: Only the AcoA data is normally distributed since Prob>z is greater than 0.05. The rest of the artery length data is not normally distributed since Prob>z is smaller than 0.05.

AcoA length normality: D'Agostino-Pearson test

This test was conducted to confirm if the AcoA data is normally distributed or not since the Prob>z value obtained from the Shapiro-Wilk test was marginally greater than 0.05.

Variable	Obs	W'	V'	z	Prob>z
AcoA	61	0.98461	0.938	-0.122	0.54863

Interpretation: The AcoA length data is normally distributed because the Prob>z from the D-Agostino-Pearson test is also greater than 0.05.

Skewness and kurtosis tests for normality

This analysis was conducted to ensure the AcoA met the assumptions of normality.

Variable	Obs	Pr(skewness)	Pr(kurtosis)	Adj chi2(2)	Prob>chi2
AcoA	61	0.9425	0.3877	0.77	0.6795

Artery diameters: Shapiro–Wilk test

Variable	Obs	W	V	z	Prob>z
BA	54	0.97077	1.461	0.812	0.20839
LeftP1	58	0.92238	4.106	3.039	0.00119
LeftPcoA	43	0.88972	4.609	3.230	0.00062
LeftA1	60	0.97321	1.456	0.810	0.20902
AcoA	51	0.95798	2.007	1.487	0.06844
RightP1	57	0.97238	1.441	0.785	0.21617
RightPcoA	41	0.93977	2.426	1.868	0.03087
RightA1	57	0.97623	1.240	0.463	0.32178

Interpretation: Arteries with a Prob>z is smaller than 0.05 are not normally distributed.

These are the left P1 and left and right PcoA. The other arteries have a Prob>z value greater than 0.05 and are normally distributed.

Individual variations: Kruskal-Wallis H test

H0: There is no significant difference in the frequency of individual variations.

H1: There is a significant difference in the frequency of individual variations.

Allvariations	Obs	Rank sum
'H' AcoA	1	6.50
'V' AcoA	1	6.50
'Y' AcoA	1	2.50
AcoA hypoplasia	1	14.00
Bilateral PcoA aplasia	1	2.50
Bilateral PcoA hypoplasia	1	12.00
Duplicated AcoA	1	15.00
MedACA	1	10.00
MedACA & 'V' / 'Y' AcoA	1	2.50
MedACA & plex. AcoA	1	6.50
Short fusion	1	16.00
Two ACA connections	1	2.50

Unilateral A1 fenestration	1	6.50
Unilateral A1 hypoplasia	1	10.00
Unilateral P1 hypoplasia	1	13.00
Unilateral PcoA aplasia	1	17.00
Unilateral PcoA hypoplasia	1	18.00
Unilateral duplicated P2	1	10.00
chi2(17) = 16.579 Prob = 0.4832		
chi2(17) with ties = 17.000 Prob = 0.4544		

The 'with ties' values were used because there were variations with the same number of observations. The frequency of observations is not significant because the p-value ('Prob') is greater than 0.05. There is not enough evidence to reject H_0 .

Symmetry: Chi-square test for independence

H_0 : There is no association between the frequency of symmetry and asymmetry.

H_1 : There is an association between the frequency of symmetry and asymmetry.

Symmetrical n	Asymmetrical n			Total
	32	33	34	
44	0	0	1	1
45	0	1	0	1
46	1	0	0	1
Total	1	1	1	3

Pearson chi2(4) = 6.0000 Pr = 0.199

Interpretation: The chi-square statistic is 6.0000 with 4 degrees of freedom and the p-value is 0.199. The chi-square statistic is large, and this means that the observed frequencies are less likely due to chance. However, the p-value is greater than 0.05 and suggests that we cannot reject H_0 . Therefore, there is likely no association between the two variables and the difference is not statistically significant. There is insufficient evidence to claim the frequency of symmetry and asymmetry is significantly different for the paired arteries.

Associations of variations with demographic information

Sex and variations: Chi-square test of independence

H_0 : There is no association between the frequency of variations and sex.

H_1 : There is an association between the frequency of variations and sex.

	Female					
Male	0	2	3	10	20	Total
0	1	0	0	0	0	1
1	0	1	1	0	0	2
5	0	0	1	0	0	1
6	0	0	0	1	0	1
7	0	1	0	0	0	1
20	0	0	0	0	1	1
Total	1	2	2	1	1	7

Pearson $\chi^2(20) = 24.5000$ Pr = 0.221

Interpretation: The chi-square statistic is 24.5000 with 20 degrees of freedom and the p-value is 0.221. The chi-square statistic is large, and this means that the observed frequencies are less likely due to chance. However, the p-value is greater than 0.05 and suggests that we cannot reject H_0 . Therefore, there is likely no association between the two variables and the difference is not statistically significant. There is insufficient evidence to claim the frequency of variations with sex is significant.

Age and variations: One-way ANOVA

H_0 : There is no significant difference between the means of variations among the age groups.

H_1 : There is a significant difference between the means of variations among the age groups.

SUMMARY				
Groups	Count	Sum	Average	Variance
Ayer Group	6	21	3.5	3.5
Age 30-59	6	6	1	1.6
Age 60-79	6	12	2	4.4
Age 80-100	6	22	3.666667	10.26667

ANOVA						
Source of Variation	SS	df	MS	F	p-value	F crit
Between Groups	29.125	3	9.708333	1.964587	0.151809	3.098391
Within Groups	98.83333	20	4.941667			
Total	127.9583	23				

Interpretation: The p-value is 0.151809 and this is greater than 0.05. Additionally, $F\text{-stat} < F\text{-crit}$. Therefore, we fail to reject H_0 .

Association of artery dimensions with demographic information:

Age and diameter: Kruskal-Wallis test

Left PcoA

AgeGroup	Obs	Rank sum
1	7	164.50
2	13	334.00
3	23	447.50
chi2(2) = 2.168 Prob = 0.3383		
chi2(2) with ties = 2.168 Prob = 0.3382		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and age is not significant for this artery.

Right PcoA

AgeGroup	Obs	Rank sum
1	8	226.00
2	13	247.00
3	20	388.00
chi2(2) = 3.649 Prob = 0.1613		
chi2(2) with ties = 3.649 Prob = 0.1613		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and age is not significant for this artery.

Left P1

AgeGroup	Obs	Rank sum
1	9	269.00
2	21	693.50
3	28	748.50
chi2(2) = 1.671 Prob = 0.4336		

chi2(2) with ties = 1.672 Prob = 0.4335
--

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and age is not significant for this artery.

Age and diameter: ANOVA per artery

Basilar artery

H₀: There is no significant difference between the means of diameters among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 54		R-squared = 0.0013			
Root MSE = .726889		Adj R-squared = -0.0379			
Source	Partial SS	df	MS	F	Prob>F
Model	.03446487	2	.01723243	0.03	0.9679
AgeGroup	.03446487	2	.01723243	0.03	0.9679
Residual	26.946766	51	.52836796		
Total	26.981231	53	.50907982		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean diameters between the three age groups is not statistically significant.

Right P1

H₀: There is no significant difference between the means of diameters among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 57		R-squared = 0.0279			
Root MSE = .699094		Adj R-squared = -0.0081			
Source	Partial SS	df	MS	F	Prob>F
Model	.75692861	2	.37846431	0.77	0.4660
AgeGroup	.75692861	2	.37846431	0.77	0.4660
Residual	26.391531	54	.48873205		
Total	27.14846	56	.48479392		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean diameters between the three age groups is not statistically significant.

Right A1

H₀: There is no significant difference between the means of diameters among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 57		R-squared = 0.0549			
Root MSE = .685253		Adj R-squared = 0.0199			
Source	Partial SS	df	MS	F	Prob>F
Model	1.4721797	2	.73608987	1.57	0.2179
AgeGroup	1.4721797	2	.73608987	1.57	0.2179
Residual	25.35689	54	.46957203		
Total	26.829069	56	.47909052		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean diameters between the three age groups is not statistically significant.

Left A1

H₀: There is no significant difference between the means of diameters among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 60		R-squared = 0.0344			
Root MSE = .597282		Adj R-squared = 0.0006			
Source	Partial SS	df	MS	F	Prob>F
Model	.72546167	2	.36273083	1.02	0.3682
AgeGroup	.72546167	2	.36273083	1.02	0.3682
Residual	20.334512	57	.35674582		
Total	21.059973	59	.3569487		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean diameters between the three age groups is not statistically significant.

AcoA

H₀: There is no significant difference between the means of diameters among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 52		R-squared = 0.1263			
Root MSE = .564746		Adj R-squared = 0.0907			
Source	Partial SS	df	MS	F	Prob>F
Model	2.2599617	2	1.1299808	3.54	0.0366
AgeGroup	2.2599617	2	1.1299808	3.54	0.0366
Residual	15.627968	49	.31893813		
Total	17.88793	51	.35074372		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean diameters between the three age groups is not statistically significant.

Age and length: Kruskal-Wallis test

Left PcoA

AgeGroup	Obs	Rank sum
1	7	141.50
2	13	300.00
3	23	504.50
chi2(2) = 0.238 Prob = 0.8879		
chi2(2) with ties = 0.238 Prob = 0.8879		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and age is not significant for this artery.

Right PcoA

AgeGroup	Obs	Rank sum
1	8	135.50
2	13	304.00
3	20	421.50
chi2(2) = 1.436 Prob = 0.4877		
chi2(2) with ties = 1.436 Prob = 0.4877		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and age is not significant for this artery.

Left P1

AgeGroup	Obs	Rank sum
1	7	162.50
2	18	514.00
3	24	548.50
chi2(2) = 1.765 Prob = 0.4137		
chi2(2) with ties = 1.765 Prob = 0.4137		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and age is not significant for this artery.

Age and length: ANOVA per artery

AcoA

H₀: There is no significant difference between the means of lengths among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 49		R-squared = 0.0019			
Root MSE = 1.15875		Adj R-squared = -0.0415			
Source	Partial SS	df	MS	F	Prob>F
Model	.11969669	2	.05984834	0.04	0.9564
AgeGro	.11969669	2	.05984834	0.04	0.9564
Residual	61.764022	46	1.3426961		
Total	61.883719	48	1.2892441		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean lengths between the three age groups is not statistically significant.

Left A1

H₀: There is no significant difference between the means of lengths among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 57		R-squared = 0.0591			
Root MSE = 2.56145		Adj R-squared = 0.0242			
Source	Partial SS	df	MS	F	Prob>F
Model	22.242964	2	11.121482	1.70	0.1932
AgeGroup	22.242964	2	11.121482	1.70	0.1932
Residual	354.29647	54	6.5610457		
Total	376.53943	56	6.7239184		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean lengths between the three age groups is not statistically significant.

Right A1

H₀: There is no significant difference between the means of lengths among the age groups.

H₁: There is a significant difference between the means of diameters among the age groups.

Number of obs = 56		R-squared = 0.0227			
Root MSE = 3.03013		Adj R-squared = -0.0141			
Source	Partial SS	df	MS	F	Prob>F
Model	11.327764	2	5.6638818	0.62	0.5435
AgeGroup	11.327764	2	5.6638818	0.62	0.5435
Residual	486.62924	53	9.1816837		
Total	497.9 ⁵⁷	55	9.0537637		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean lengths between the three age groups is not statistically significant.

Right P1

H0: There is no significant difference between the means of lengths among the age groups.

H1: There is a significant difference between the means of diameters among the age groups.

Number of obs = 49		R-squared = 0.0301			
Root MSE = 3.0535		Adj R-squared = -0.0121			
Source	Partial SS	df	MS	F	Prob>F
Model	13.296027	2	6.6480135	0.71	0.4955
AgeGroup	13.296027	2	6.6480135	0.71	0.4955
Residual	428.89818	46	9.3238735		
Total	442.19421	48	9.2123793		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean lengths between the three age groups is not statistically significant.

Basilar artery

H0: There is no significant difference between the means of lengths among the age groups.

H1: There is a significant difference between the means of diameters among the age groups.

Number of obs = 55		R-squared = 0.0895			
Root MSE = 6.17619		Adj R-squared = 0.0545			
Source	Partial SS	df	MS	F	Prob>F
Model	194.95187	2	97.475934	2.56	0.0874
AgeGroup	194.95187	2	97.475934	2.56	0.0874
Residual	1983.5537	52	38.145263		
Total	2178.5056	54	40.342695		

Interpretation: The p-value (Prob>F) is greater than 0.05. Therefore, the difference in mean lengths between the three age groups is not statistically significant at the 5% level. However, it is significant at the 10% level as the p-value is less than 0.1.

Sex and artery length: Kruskal-Wallis tests per artery

Basilar artery

Sex	Obs	Rank sum
F	30	808.50
M	25	731.50
chi2(1) = 0.284 Prob = 0.5944		
chi2(1) with ties = 0.284 Prob = 0.5944		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Left P1

Sex	Obs	Rank sum
F	25	623.50
M	24	601.50
chi2(1) = 0.001 Prob = 0.9761		
chi2(1) with ties = 0.001 Prob = 0.9761		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Left PcoA

Sex	Obs	Rank sum
F	23	462.50
M	20	483.50
chi2(1) = 1.122 Prob = 0.2895		
chi2(1) with ties = 1.122 Prob = 0.2895		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Right P1

Sex	Obs	Rank sum
F	24	611.50
M	25	613.50
chi2(1) = 0.053 Prob = 0.8181		
chi2(1) with ties = 0.053 Prob = 0.8181		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Right PcoA

Sex	Obs	Rank sum
F	19	412.50
M	22	448.50
chi2(1) = 0.125 Prob = 0.7241		
chi2(1) with ties = 0.125 Prob = 0.7241		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Right A1

Sex	Obs	Rank sum
F	29	628.50
M	27	967.50
chi2(1) = 10.541 Prob = 0.0012		
chi2(1) with ties = 10.541 Prob = 0.0012		

Interpretation: The p-value (Prob) is less than 0.05. Therefore, the association between length and sex is significant for this artery.

Left A1

Sex	Obs	Rank sum
F	31	847.00
M	26	806.00
chi2(1) = 0.694 Prob = 0.4048		
chi2(1) with ties = 0.694 Prob = 0.4047		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between length and sex is not significant for this artery.

Sex and artery length: Independent t-tests per artery length

AcoA

H_0 : There is no significant difference between the means of length between males and females.

H_1 : There is a significant difference between the means of length between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	26	2.847949	.2231901	1.138051	2.38828	3.307617
M	23	2.922174	.2411988	1.156749	2.421958	3.42239
Combined	49	2.882789	.162207	1.135449	2.55665	3.208928
Diff	-.0742252	.3282847	-.7346489 .5861985			

diff = mean(F) - mean(M)

t = -0.2261

H_0 : diff = 0

Degrees of freedom = 47

H_a : diff < 0

H_a : diff != 0

H_a : diff > 0

Pr(T < t) = 0.4111

Pr(|T| > |t|) = 0.8221

Pr(T > t) = 0.5889

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of length between males and females at the 5% level.

Sex and artery diameter: Kruskal-Wallis tests per artery

Right PcoA

Sex	Obs	Rank sum
F	19	351.00
M	22	510.00
chi2(1) = 1.57 Prob = 0.2095		
chi2(1) with ties = 1.575 Prob = 0.2095		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and sex is not significant for this artery.

Left PcoA

Sex	Obs	Rank sum
F	23	468.50
M	20	477.50
chi2(1) = 0.834 Prob = 0.3612		
chi2(1) with ties = 0.834 Prob = 0.3612		

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and sex is not significant for this artery.

Left P1

Sex	Obs	Rank sum
F	31	832.00
M	27	879.00
chi2(1) = 1.654 Prob = 0.1984		

chi2(1) with ties = 1.654 Prob = 0.1984
--

Interpretation: The p-value (Prob) is greater than 0.05. Therefore, the association between diameter and sex is not significant for this artery.

Sex and artery diameter: Independent t-tests per artery

AcoA

H_0 : There is no significant difference between the means of diameter between males and females.

H_1 : There is a significant difference between the means of diameter between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	29	1.56092	.103288	.556223	1.349344	1.772495
M	23	1.79942	.1295748	.6214188	1.530699	2.068142
Combined	52	1.66641	.0821284	.5922362	1.501531	1.83129
Diff	-.2385007	.1635652	-.5670311	.0900296		
diff = mean(F) - mean(M)			t = -1.4581			

H_0 : diff = 0

Degrees of freedom = 50

H_a : diff < 0

H_a : diff != 0

H_a : diff > 0

$\Pr(T < t) = 0.0755$

$\Pr(|T| > |t|) = 0.1511$

$\Pr(T > t) = 0.9245$

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of diameter between males and females.

Basilar artery

H_0 : There is no significant difference between the means of diameter between males and females.

H_1 : There is a significant difference between the means of diameter between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	30	4.348556	.1477921	.8094905	4.046287	4.650824
M	24	4.368333	.1201829	.5887734	4.119716	4.616951
Combined	54	4.357346	.0970948	.7134983	4.162598	4.552093
Diff	-.0197778	.1972504	-.4155896	.3760341		

diff = mean(F) - mean(M)

t = -0.1003

H_0 : diff = 0

Degrees of freedom = 52

H_a : diff < 0

H_a : diff != 0

H_a : diff > 0

Pr(T < t) = 0.4603

Pr(|T| > |t|) = 0.9205

Pr(T > t) = 0.5397

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of diameter between males and females.

Right P1

H_0 : There is no significant difference between the means of diameter between males and females.

H_1 : There is a significant difference between the means of diameter between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	30	2.279444	.1274965	.698327	2.018685	2.540204
M	27	2.291222	.1361054	.7072246	2.011454	2.570991
Combined	57	2.285023	.0922234	.6962714	2.100278	2.469769
Diff	-.0117778	.1863676	-.3852668	.3617112		

diff = mean(F) - mean(M)

t = -0.0632

Degrees of freedom = 55

$$H_a: \text{diff} < 0$$

Ha: diff $\neq 0$

Ha: $\text{diff} > 0$

$$\Pr(T < t) = 0.4749$$
$$\Pr(|T| > |t|) = 0.9498$$
$$\Pr(T > t) = 0.5251$$

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of diameter between males and females.

Left A1

H_0 : There is no significant difference between the means of diameter between males and females.

H_1 : There is a significant difference between the means of diameter between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	32	2.022708	.1103776	.6243898	1.797592	2.247825
M	28	2.239762	.1045948	.5534634	2.025151	2.454373
Combined	60	2.124	.0771307	.5974518	1.969662	2.278338
Diff	-.2170536	.1533057	-.5239284	.0898212		
diff = mean(F) - mean(M)			t = -1.4158			

$$H_0: \text{diff} = 0$$

Degrees of freedom = 58

Ha: $\text{diff} < 0$

Ha: diff $\neq$ 0

Ha: $\text{diff} > 0$

$$\Pr(T < t) = 0.0811$$
$$\Pr(|T| > |t|) = 0.1622$$
$$\Pr(T > t) = 0.9189$$

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of diameter between males and females.

Right A1

H_0 : There is no significant difference between the means of diameter between males and females.

H_1 : There is a significant difference between the means of diameter between males and females.

Two-sample t test with equal variances

Group	Obs	Mean	St. err.	Std. dev.	[95% conf. interval]	
F	30	2.176333	.114328	.6262002	1.942506	2.41016
M	27	2.279136	.1476657	.7672933	1.975605	2.582667
Combined	57	2.225029	.0916793	.6921637	2.041374	2.408685
Diff	-.1028025	.1847555	-.4730608	.2674559		
diff = mean(F) - mean(M)			t = -0.5564			

H_0 : diff = 0 Degrees of freedom = 55

Ha: diff < 0

Ha: diff != 0

Ha: diff > 0

$\Pr(T < t) = 0.2901$

$\Pr(|T| > |t|) = 0.5802$

$\Pr(T > t) = 0.7099$

Interpretation: The p-value (highlighted in grey) is greater than 0.05. Therefore, we reject H_0 and there is a significant difference between the means of diameter between males and females.

Volume and correction factors:

Volume: Shapiro-Wilk

Variable	Obs	W	V	z	Prob>z
VolumeWith~n	69	0.97679	1. .412	0.750	0.22669

Interpretation: Volume is normally distributed with the exclusion of the three outliers.

Brainstem level and volume: One-way ANOVA

H_0 : There is no significant difference among the means of the four groups.

H_1 : There is a significant difference among the means of the four groups.

Analysis of variance

Source	SS	df	MS	F	Prob > F
Between groups	138855.95	3	46285.3166	2.00	0.1264
Within groups	1158791.09	50	23175.8217		
Total	1297647.04	53	24483.9064		

Bartlett's equal-variances test: $\chi^2(3) = 5.6905$ Prob> $\chi^2 = 0.128$

Interpretation: The p-value is 0.1264 and this is greater than 0.05. Therefore, we fail to reject H_0 , and the difference is not significant.

Correction factors (before and after): Wilcoxon signed rank tests

Basilar artery: length

H_0 : There is no significant difference between the before and after measurements.

H_1 : There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
Positive	14	130	162.5
Negative	11	195	162.5
Zero	0	0	0
All	25	325	325
Unadjusted variance			
		1381.25	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance			
		1381.25	
H_0 : BAlengthbefore = BAlengthafter $z = -0.874$ Prob > $ z = 0.3819$ Exact prob = 0.3957			

Interpretation: The p-value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups.

Basilar artery: diameter

H_0 : There is no significant difference between the before and after measurements.

H_1 : There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
Positive	14	121	162.5

Negative	11	204	162.5
Zero	0	0	0
All	25	325	325
Unadjusted variance		1381.25	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance		1381.25	
H0: BAdiameterbefore = BAdiameterafter z = -1.117 Prob > z = 0.2641 Exact prob = 0.2752			

Interpretation: The p-value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups.

Left PcoA: length

H0: There is no significant difference between the before and after measurements.

H1: There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
1	7	75	63
2	10	78	90
Zero	0	0	0
Combined	17	153	153
Unadjusted variance		105.00	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance		105.00	
H0: PcoALlengthbefore = PcoALlengthafter z = 1.171 Prob > z = 0.2416 Exact prob = 0.2698			

Interpretation: The p-value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups.

Left PcoA: diameter

H0: There is no significant difference between the before and after measurements.

H_1 : There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
Positive	10	85	85.5
Negative	8	86	85.5
Zero	0	0	0
All	18	171	171
Unadjusted variance		527.25	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance		527.25	
H0: PcoALdiameterbefore = PcoALdiameterafter			
z = -0.022			
Prob > z = 0.9826			
Exact prob = 1.0000			

Interpretation: The p-value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups.

Right A1: length

H_0 : There is no significant difference between the before and after measurements.

H_1 : There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
Positive	11	71	126.5
Negative	11	182	126.5
Zero	0	0	0
All	22	253	253
Unadjusted variance		948.75	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance		948.75	
H0: A1Rlengthbefore = A1Rlengthafter			
z = -1.802			
Prob > z = 0.0716			
Exact prob = 0.0738			

Interpretation: The p-value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups at the 5%

level. However, the p -value is less than 0.1 and there are significant differences at the 10% level.

Right A1: diameter

H_0 : There is no significant difference between the before and after measurements.

H_1 : There is a significant difference between the before and after measurements.

Sign	Obs	Sum ranks	Expected
Positive	11	95	126.5
Negative	11	158	126.5
Zero	0	0	0
All	22	253	253
Unadjusted variance		948.75	
Adjustment for ties		0.00	
Adjustment for zeros		0.00	
Adjusted variance		948.75	
H0: A1diameterbefore = A1diameterafter z = -1.023 Prob > z = 0.3065 Exact prob = 0.3209			

Interpretation: The p -value ('Exact prob') is greater than 0.05. Therefore, we fail to reject H_0 , and there are no statistical differences between the before and after groups.

Appendix E: Letters of Ethical Authorization

This appendix contains the ethical authorisation letters that were obtained before the commencement of the study. These are from the Cadaver Research Governance Committee, Human Research Ethics Committee and Groote Schuur Hospital. HREC approval needed to be renewed for the conclusion of this study and the first portion of the extension approval form is included.



University of Cape Town

CADAVER RESEARCH GOVERNANCE COMMITTEE

12/10/2022

Refs Number: CRCG 2022/009

Dear Dr Mpolokeng

Re: Variations in the circulus arteriosus cerebri and their potential to result in aneurysm development in a South African sample.

Thank you for your application. I am pleased to inform you that permission for this study to proceed has been granted on the following conditions:

1. Please remove the collection of ancestry data as this has no relevance to the study.
2. Please add a statement that no digital images will be placed on any form of social media.
3. Cadaver numbers will be assigned a study number. The master list linking the study number to the cadaver number will be released to Mr Michael Cassar.
4. Any publication must contain the following statement:

Permission for this study was granted by the Cadaver Research Governance Committee, Department of Human Biology, Faculty of Health Sciences, University of Cape Town.



Signed by candidate

CHAIR

A/Prof Delva Shamley



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

06 December 2022

HREC REF: 645/2022

Dr K Mpolokeng

Department of Human Biology

FHS

Email: Kentse.mpolokeng@uct.ac.za

Student: GRJES001myuct.ac.za

Dear Dr Mpolokeng

PROJECT TITLE: VARIATIONS IN THE CIRCULUS ARTERIOSUS CEREBRI AND THEIR POTENTIAL TO RESULT IN ANEURYSM DEVELOPMENT IN A SOUTH AFRICAN SAMPLE- (MSC CANDIDATE-MISS JESSICA GARLICK)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 December 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Miss Jessica Garlick will also be involved in this study.

Please quote the HREC REF 645/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN

CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC/ref 645.2022



FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	30.12.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Signed by candidate	Date Signed	14/1/2024

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
<http://www.health.uct.ac.za/fhs/research/humanethics/forms>

Comments to PI from the HREC	HUMAN RESEARCH ETHICS COMMITTEE 11 JAN 2024 HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN
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Western Cape
Government



GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick

e-mail: GSHResearchRequest@westerncape.gov.za

Dr Kentse Mpolokeng

Department of Human Biology

E-mail: kentse.mpolokeng@uct.ac.za

Dear Dr Mpolokeng

RESEARCH PROJECT: Variations in the circulus arteriosus cerebri and their potential to result in aneurysm development in a South African sample

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 December 2023**

Please note the following:

- a) Your research may not interfere with normal patient care.
- b) Hospital staff may not be asked to assist with the research.
- c) Confidentiality must always be maintained.**
- d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
- e) **No patient folders may be removed from the premises or be inaccessible.**
- f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
- g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
- h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
- i) Please discuss the study with the HOD before commencing.
- j) Please introduce yourself to the person in charge of an area before commencing.
- k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
- l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
- m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
- n) **Kindly submit a copy of the publication or report to this office on completion of the research.**
- o) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
- p) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER

Date: 19 January 2023

C.C. Mr. L. Naidoo, Mr. A. Mohamed, Dr H. Aziz, Professor S. Moosa

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