Circulus arteriosus cerebri: Anatomical variations and their correlation to cerebral aneurysms

By

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DECLARATION:

I, *Francesca du Toit*, hereby declare that the work on which this dissertation / thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of Abbreviations

Abbreviations of artery names used in the study:

A1 – A1 segment (precommunicating) of the anterior cerebral artery

A2 – A2 segment (postcommunicating) of the anterior cerebral artery

ACA – anterior cerebral artery

AComA – anterior communicating artery

CAC – circulus arteriosus cerebri

ICA – internal carotid artery

MCA – middle cerebral artery

P1 – P1 segment of the posterior cerebral artery

P2 – P2 segment of the posterior cerebral artery, distal to the posterior communicating artery

PCA – posterior cerebral artery

PComA – posterior communicating artery

Other abbreviations used in the study:

A – Anterior

L – Left

MRA – Magnetic Resonance Angiography

MRI – Magnetic Resonance Imaging/Image

P – Posterior

R – Right

TOF – Time of flight sequence

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Abstract

The anatomical structure of circulus arteriosus cerebri was first described by Thomas Willis in 1664. Many variations in the circulus arteriosus cerebri have since been reported. The extent to which anatomical variations within the circle influence aneurysm formation in a South African sample has not yet been established. The results of such a study would be of value to clinicians treating patients with vascular diseases. The aim of the study was to determine if there is a correlation between arterial variations in the circulus arteriosus cerebri and cerebral aneurysm formation.

The brains of 39 cadavers at the Faculty of Health Sciences were removed and the circulus arteriosus dissected. In addition, 113 patients who underwent a MRI or MRA of the circulus arteriosus cerebri at the Department of Radiology at the Groote Schuur Hospital, Cape Town were included. For both of these samples the anatomical variations and any aneurysms present were documented. The external diameters of the arteries forming the circulus arteriosus cerebri were also measured.

No aneurysms were found in the cadaver sample, thus the correlation could not be tested. In the sample of images from the 113 patients, 111 images showed one or more anatomical variation of the circulus arteriosus cerebri. Of these, 59 had one or more cerebral aneurysm and 52 had no aneurysms.

Statistical analysis showed no significant correlation between cerebral aneurysms and anatomical variations in the circulus arteriosus cerebri for a South African sample. This is contradictory to what is seen in the literature. Further investigation is required to establish the reason why the results from this South African sample differ from the results reported in the international literature.

Chapter 1 : Introduction

The circulus arteriosus cerebri (CAC) or the Circle of Willis was first described by Thomas Willis in 1664 (Figure 1.1) and is present in all people (Griffiths & Lee, 2008; Hartkamp & Van der Grond, 2000).

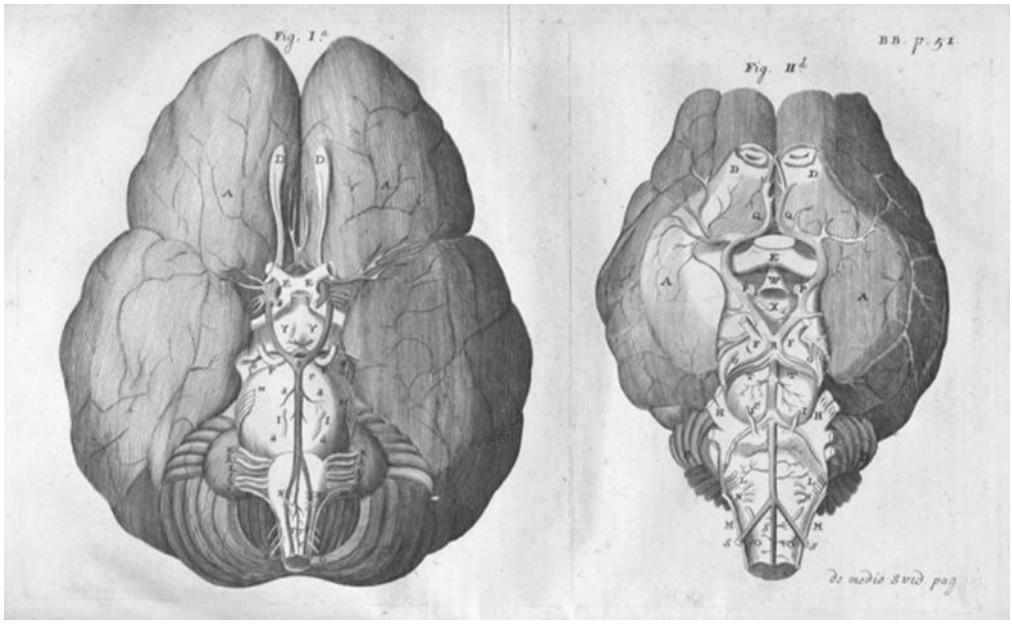


Figure 1.1: Original drawing by Christopher Wren and published in *Cerebri Anatome* by Thomas Willis in 1664. Human brain is on the left and that of a sheep on the right (MU Libraries 2011).

In a review of the literature and an anatomical study by Eftekhar *et al.* (2006), the majority of subjects studied had some form of variation from the original description by Willis (Willis, 1664). Lippert and Pabst (1985) estimated that 50% or more of the population had one or more arteries absent or hypoplastic. Kayembe *et al.* (1984) suggested that haemodynamic changes caused by variations in the CAC may have an influence on the formation of cerebral aneurysms. It has also been hypothesised that haemodynamic insults at the point of arterial bifurcation influence the formation of intracranial aneurysms (Mamatha *et al.,* 2012).

There are considerable variations in the CAC between individuals and these are said to be contributing risk factors in cerebral aneurysm formation (Padget, 1944; Alpers & Berry, 1963). Collection and analysis of data for a South African sample is required in order to describe variations in the CAC. The extent to which these variations influence or contribute to cerebral aneurysm formation in South Africans needs to be established and made available to doctors and surgeons wanting to treat patients with vascular disease. Knowledge of the CAC will enable doctors to better identify persons who are most likely to develop cerebral aneurysms and treat them preventatively and / or intervene operatively early on (Dimmick & Faulder, 2009).

The aim of the study was to determine if there is a correlation between arterial variations in the CAC and cerebral aneurysm formation. If there is such a correlation, it is aimed to establish which type of arterial variation has the greatest or least association with aneurysm formation.

To achieve these aims the following objectives for a South African sample were studied:

- Determine the number of circulus arteriosus cerebri found with a classic arterial arrangement as described in conventional literature on human anatomy

- Document the variations of the circulus arteriosus cerebri that are found on the patient images and cadaver samples

- Describe the types of aneurysms found on the patient images (if present)

- Identify the arterial variations in the circulus arteriosus cerebri, which are most likely to have a correlation with cerebral aneurysms

- List the factors that influence the formation of aneurysms, based on a study of the literature and thereafter apply the knowledge gained to the patient images

- Determine the risk of individuals developing aneurysms based on patient images and a study of the literature

- Estimate the predictive value that variations in the circulus arteriosus cerebri have in regard to aneurysm formation

- Compare variations in the circulus arteriosus cerebri and the occurrence of aneurysms found in the South African sample with international literature

Chapter 2 : Literature review

2.1 Background

Three concentric membranes, the meninges, enclose the brain and spinal cord. They provide support and protection for the brain and its associated structures. From external to internal are the dura mater, arachnoid mater and pia mater. The dura mater is a tough, fibrous sheath that incompletely divides the cranial cavity into compartments and forms the dural venous sinuses. The arachnoid mater is much thinner than the dura, and is almost transparent. It loosely surrounds the brain, spanning over the sulci and gyri but following the course of the great longitudinal fissure. The pia mater is a microscopically thin membrane, which follows the contours of the brain and closely adheres to its surface. The arachnoid can easily be separated from the dura revealing the subdural space, which is in fact a potential space. The subarachnoid space separates the arachnoid mater from the pia. This space varies greatly in depth (Standring, 2008). This space contains cerebrospinal fluid, trabecular cells and collagen fibrils, the roots of the cranial nerves, arteries and veins (Haines, 2013) as shown in Figure 2.1.

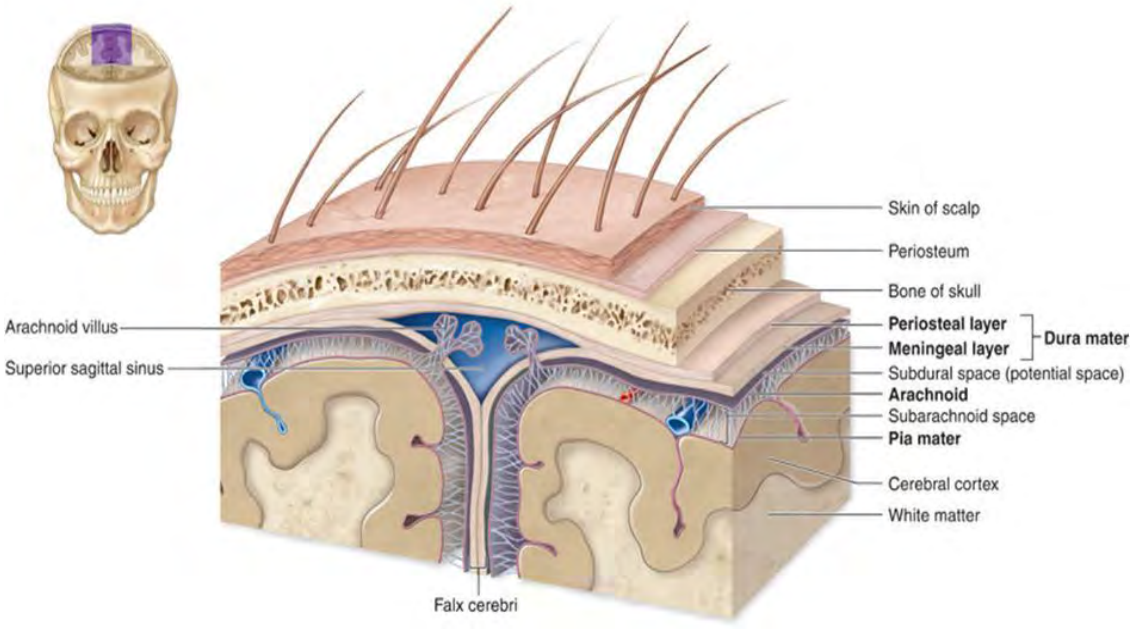


Figure 2.1: Section through the skull and meninges (Wheeler).

The brain receives its blood supply from the left and right vertebral arteries and the left and right internal carotid arteries. These arteries are found at the base of the brain within the subarachnoid space (Griffiths & Lee, 2008; Iqbal, 2013) as in Figure 2.2.

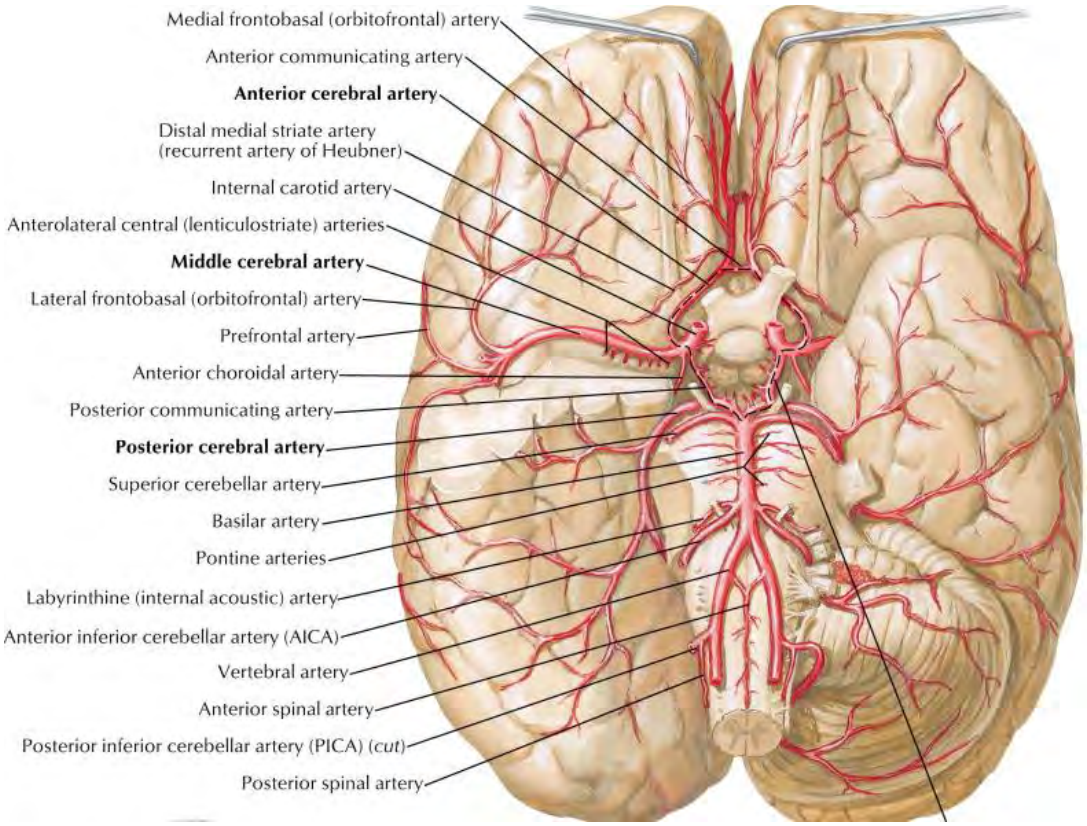


Figure 2.2: Circulus arteriosus cerebri at the base of the brain (Netter, 2014).

Being a highly vascularised organ, the brain receives about 15% of the cardiac output. The circulus arteriosus cerebri (CAC) is a ring-like structure at the base of the brain. The CAC distributes oxygenated blood throughout the cerebrum, and it is the only major arterial anastomosis of the brain (Mamatha *et al.,* 2012). The CAC is formed by the anterior communicating, the anterior cerebral (precommunicating / A1 segment), the posterior cerebral (precommunicating / P1 segment), the posterior communicating and the internal carotid arteries (Alawad *et al.,* 2009).

The brain is said to receive its blood supply either via the anterior or posterior circulation. Each internal carotid artery (ICA) bifurcates into the middle cerebral artery (MCA) and anterior cerebral artery (ACA) on each side, in order to supply the frontal, parietal and temporal regions of the brain; this comprises the anterior circulation of the brain. The posterior circulation of the brain includes the basilar artery, which is formed by the union of the two vertebral arteries. In turn the basilar artery divides into the right and left posterior cerebral arteries (PCA) to perfuse the occipital lobes, cerebellum and the brain stem. The anterior communicating artery connects the two ACA arteries, while the two posterior communicating arteries connect the posterior circulation to the anterior circulation, as shown in Figure 2.3 (Alastruey *et al.,* 2007; Alawad *et al.,* 2009).

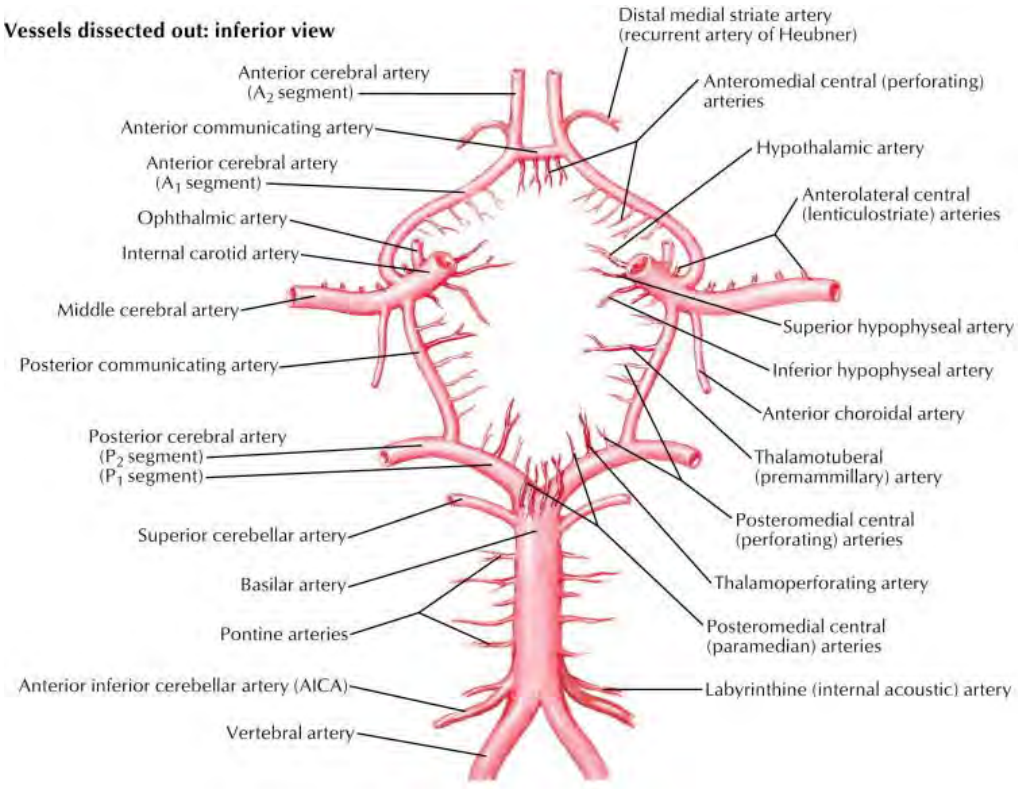


Figure 2.3: Arteries forming the circulus arteriosus cerebri (Netter, 2014).

2.2 Embryology

The major embryonic arteries may be classified as either pharyngeal arch arteries (or aortic arches) or arteries of the trunk or limbs. Six pharyngeal (branchial) arch arteries arise in the embryo, but not all persist throughout embryonic life. The pharyngeal arch arteries first start developing in the fourth week post-fertilisation (Moore *et al.,* 2015). The first pharyngeal arch artery, bilaterally, will largely disappear except for a small contribution to the maxillary artery. The second pharyngeal arch artery largely disappears leaving the stapedial artery, bilaterally. Bilaterally, the third pharyngeal arch artery will persist as the internal carotid artery. The common carotid artery on each side is formed from the part of the bilateral horns of the aortic sac, which is closely related to the third arch artery. The dilated distal region of the truncus arteriosus forms the aortic sac and with the lengthening of the embryonic neck the aortic sac becomes drawn out into two 'horns'. From either side of the root of the internal carotid artery an outgrowth forms, the external carotid artery. On the left side the fourth pharyngeal arch artery becomes the distal end of the arch of the aorta, the proximal end of the adult aortic arch is formed from the left horn of the aortic sac. On the right side the fourth pharyngeal arch artery forms the right proximal part of the subclavian artery; the left 7th intersegmental artery, that becomes continuous with the aortic arch, forms the distal part of that subclavian artery. Bilaterally, the fifth pharyngeal arch artery disappears completely. Bilaterally, the sixth pharyngeal arch artery becomes continuous with the pulmonary trunk from which further branches extend into the lungs as the pulmonary arteries. The more dorsal part of the left sixth pharyngeal arch artery remains connected to the dorsal aorta. This connection is referred to as the ductus arteriosus, which diverts much of the blood from the pulmonary trunk to the dorsal aorta in the embryo and fetus (Allan & Kramer, 2010) (Figure 2.4).

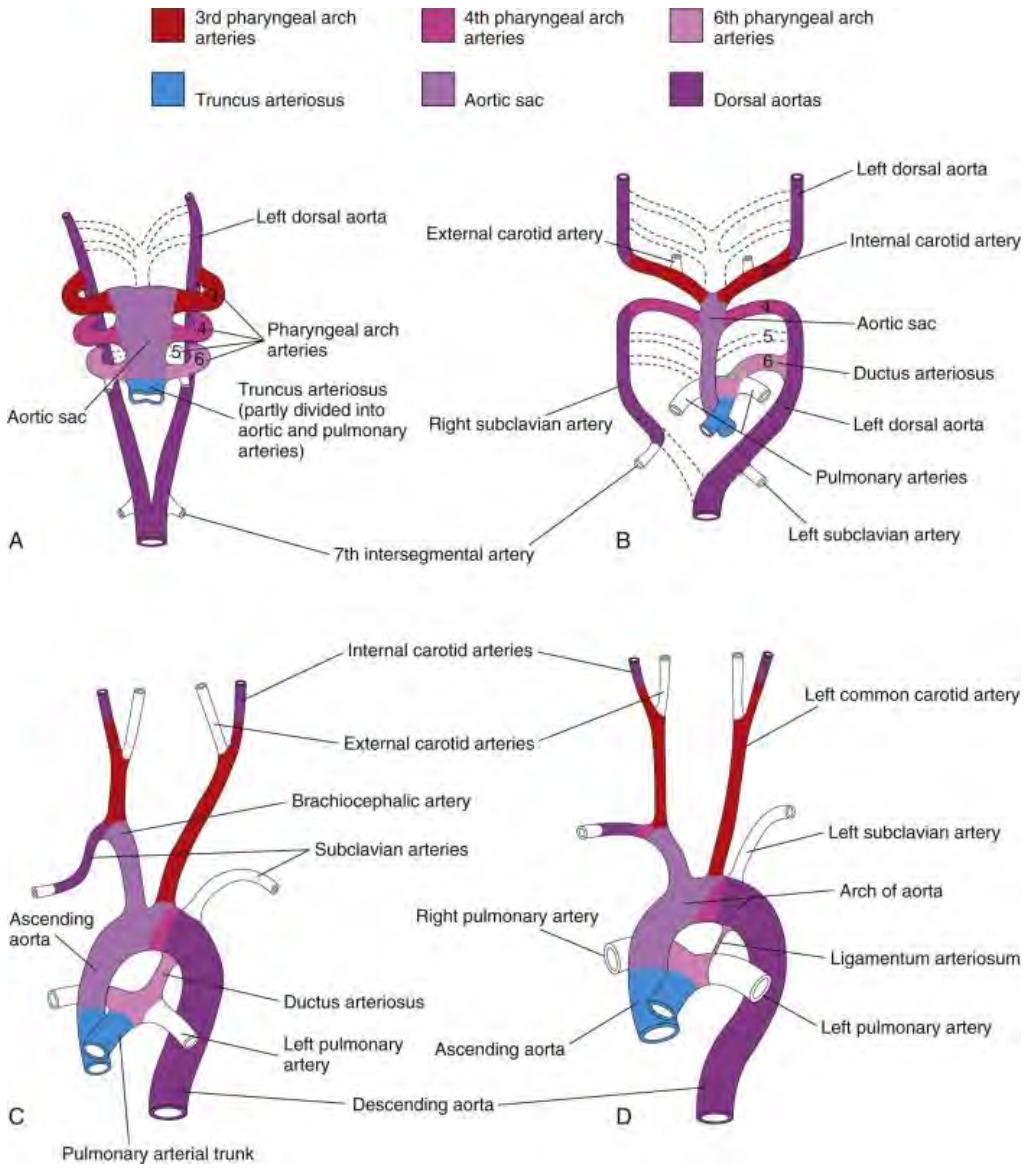


Figure 2.4: Pharyngeal arch arteries (Moore *et al.*, 2013).

The process of neurulation is completed during the sixth week post-fertilisation (gestational age) and a plexus of cranial vessels first appears in embryos at approximately 3 – 5mm crown-rump length (CRL) (age 5 weeks post-fertilisation). The primitive carotid system supplies the entire developing brain. The vertebral arteries take over the supply to the vertebrobasilar territory at the 7 - 12mm stage (age 6 weeks post-fertilisation). During this 7 – 10 day period, certain primitive anastomotic arteries will act as a supplementary blood supply. In a cranial-to-caudal sequence these primitive arteries are: the cranial extension of the ICA, the otic, pro-atlantal intersegmental, trigeminal, and hypoglossal arteries (Vasovic' *et al.*, 2002).

Embryogenesis of the cerebral arteries begins at approximately five weeks post-fertilisation. At this stage two groups of principal arteries are present in the embryo, namely the bilateral longitudinal neural and the internal carotid arteries. The anterior CAC originates from the ICA's, while the bilateral longitudinal neural arteries give rise to the vertebrobasilar system (Niederberger *et al.*, 2010; Dimmick & Faulder, 2009).

A carotid-vertebrobasilar anastomosis may be present when the vertebrobasilar system fails to regress during embryonic development (Dimmick & Faulder, 2009).

2.3 Normal anatomy

Kayembe and colleagues (1984) defined a "typical" circulus arteriosus cerebri with respect to its components as a closed circuit in which blood may flow from any entry point back to the same point, with all cerebral vessels more than 1mm in external diameter, and if the pattern of formation is as originally described by Thomas Willis (Figure 2.5). Iqbal (2013) described a classical arterial circle as being bilaterally symmetrical and forming a complete ring of vessels. Hartkamp and Van der Grond (2000) further illustrated a symmetrical arterial circle, with a single AComA, and bilateral PComA's that typically has smaller external diameters than the precommunicating segments (P1 segments) of the PCA on the corresponding side. Siddiqi *et al.* (2013) further added that there should be no duplications or triplications present in the typical circulus arteriosus cerebri.

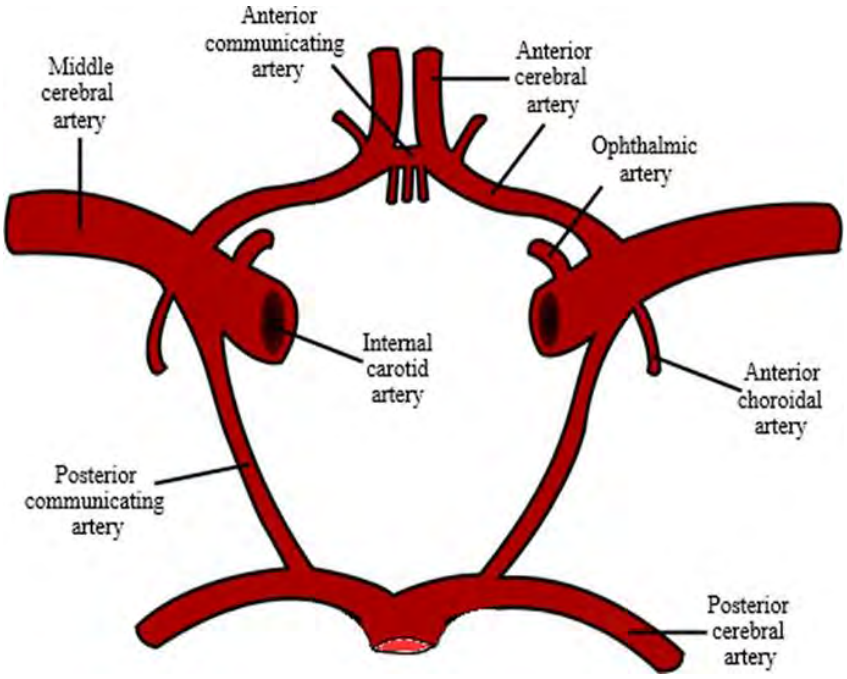


Figure 2.5: Basic anatomy of the circulus arteriosus cerebri (Heimlich, 2013).

With respect to the external diameter of these blood vessels, some authors differ as to what criteria should be used to define "hypoplasia", i.e. less than 0.5mm (Hoksbergen *et al.,* 2000), less than 0.8mm (Hartkamp, 1999), less than or equal to 1mm (Alpers & Berry, 1963; Riggs & Rupp, 1963; Fisher 1965; Lazorthes *et al.,* 1979; El Khamlichi *et al.,* 1985; Eftekhar *et al.,* 2006; Tanaka *et al*., 2006; Kapoor *et al.,* 2008; De Silva *et al*., 2011; Li *et al.,* 2011; Mamatha *et al*., 2012; Siddiqi *et al*., 2013). Some authors differentiate between the communicating arteries and the cerebral arteries, where the communicating arteries are less than 0.5mm and the cerebral arteries are less than 1mm (Kamath, 1980; Dimmick & Faulder, 2009; Iqbal, 2013) or even using a formula comparing relative sizes of vessels in the same individual (Lazzaro *et al.,* 2014).

2.4 Internal carotid arteries

The common carotid artery bifurcates into the internal carotid artery (ICA) and the external carotid artery. The ICA runs in the neck, entering the carotid canal within the temporal bone. Subsequently the ICA is said to have cervical (C1), petrous (C2–

C3), cavernous (C4) and intracranial / cerebral parts (C5-C7), as seen in Figure 2.6 (Griffiths & Lee, 2008).

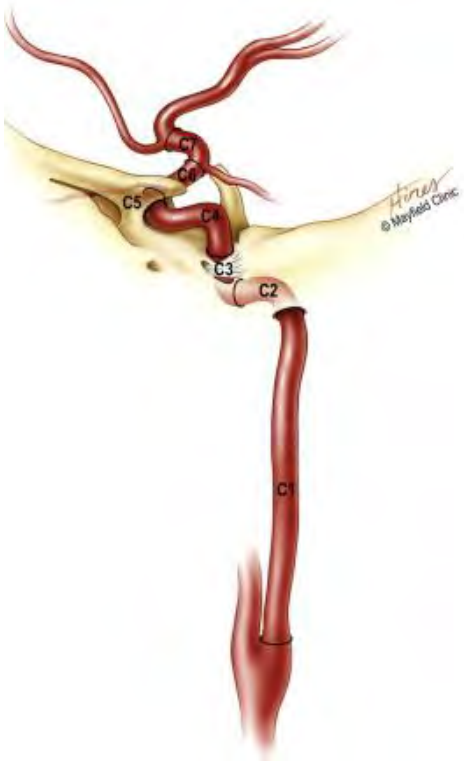


Figure 2.6: Course of the internal carotid artery (DePowell *et al.*, 2014).

The cervical part ascends up the neck and enters the carotid canal to form the petrous part, giving rise to several small peripheral branches (Haines & Lancon, 2013). Ascending in the carotid canal, the petrous part of the ICA curves anteromedially and then superomedially to enter the cranial cavity. The cavernous part of the ICA is a continuation of the petrous part within the cavernous sinus. As it ascends to the posterior clinoid process, the cavernous part turns anteriorly (Figure 2.7). It then deviates medially towards the anterior clinoid process emerging through the roof of the cavernous sinus. Upon reaching the anterior perforated substance of the lateral fissure, the ICA branches into the anterior and middle cerebral arteries (Griffiths & Lee, 2008). The inferior hypophysial and meningeal arteries arise from the cavernous part of the ICA. After leaving the venous sinus, the cavernous part of the ICA continues in the cerebrum as the cerebral part. The cerebral part gives off the anterior

choroidal, ophthalmic, superior hypophysial and posterior communicating arteries (Haines & Lancon, 2013).

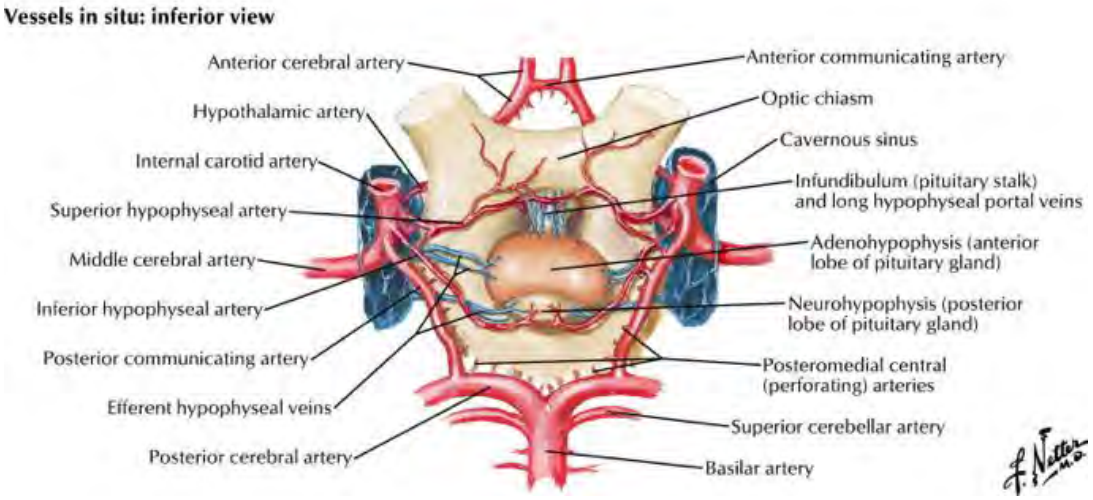


Figure 2.7: The internal carotid artery within the cavernous sinus (Netter, 2014).

2.5 The anterior cerebral arteries

The ACA is the smallest of the terminal branches of the ICA. The ACA runs superior to the optic nerve towards the longitudinal fissure. Here it will connect with the ACA from the opposite side via the anterior communicating artery (Griffiths & Lee, 2008).

The ACA on each side may be divided into different segments (Figure 2.8). The A1 or precommunicating segment runs anteriorly and medially towards the longitudinal fissure, giving rise to the anteromedial central arteries (Li *et al.,* 2011). The A2 or postcommunicating segment runs anteriorly to the rostrum and genu of the corpus callosum. Three main branches arise from the A2 segment, the recurrent artery of Heubner or medial striate artery, the orbitofrontal artery and the polar frontal artery (Li *et al.,* 2011). The A3 to A5 segments surround the corpus callosum. Two main divisions arise from the A3 segment namely the pericallosal artery and the callosomarginal artery (Li *et al.,* 2011).

Both anterior cerebral arteries pass within the great longitudinal fissure. They curve around the corpus callosum; they run along its upper surface to the posterior end where they then anastomose with the posterior cerebral arteries. The ACA's give off both central and cerebral branches (Griffiths & Lee, 2008).

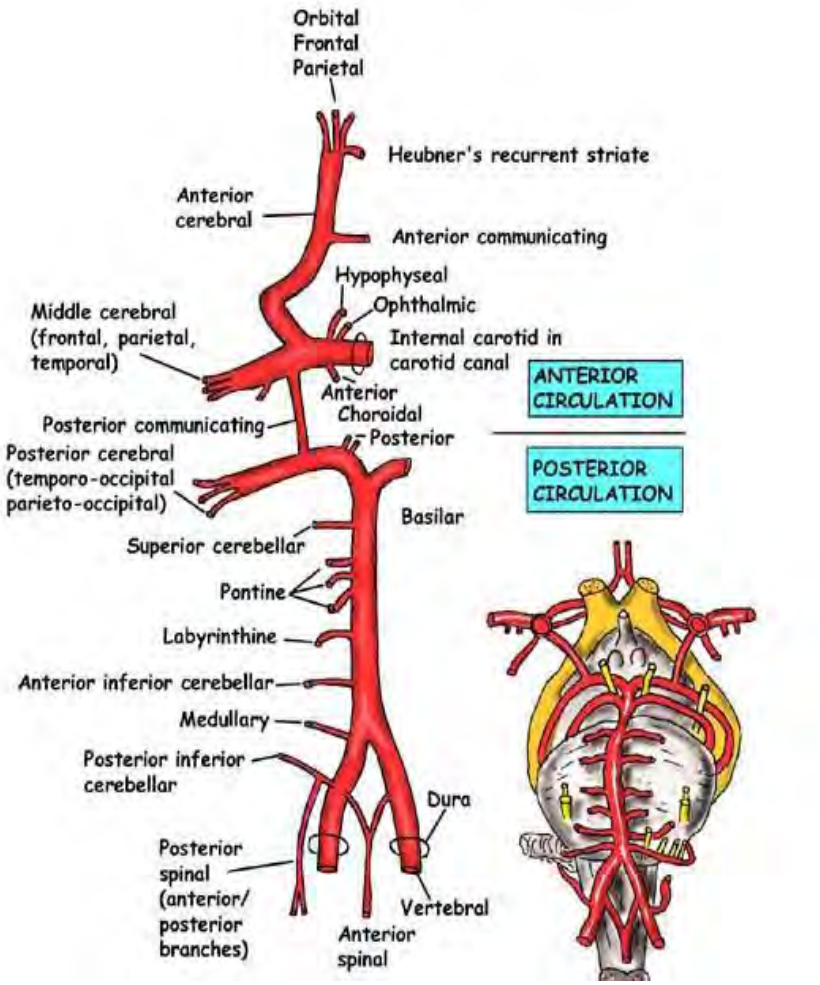


Figure 2.8: Arterial branches from the circulus arteriosus cerebri (Cadogan, 2008).

2.6 The anterior communicating artery

The anterior communicating artery (AComA) is a single artery connecting the anterior cerebral arteries from either side. It is located superiorly and anteriorly to the optic chiasm (Li *et al.*, 2011). The AComA is about 4mm in length and may be

duplicated. The AComA has numerous branches supplying different areas including: the hypothalamus, optic chiasm, cingulate gyrus, para-olfactory areas, and the lamina terminalis (Griffiths & Lee, 2008) (Figure 2.8).

2.7 Basilar artery

The right and left vertebral arteries ascend in the neck though the foramina in the transverse processes of the cervical vertebrae, pass through the foramen magnum in order to enter the cranial cavity (Figure 2.9). The basilar artery is a large vessel formed by the joining of the two vertebral arteries at the pontomedullary junction. It lies in the pontine cistern. It follows a shallow groove on the ventral surface of the pons, extending to the upper pontine border (Griffiths & Lee, 2008).

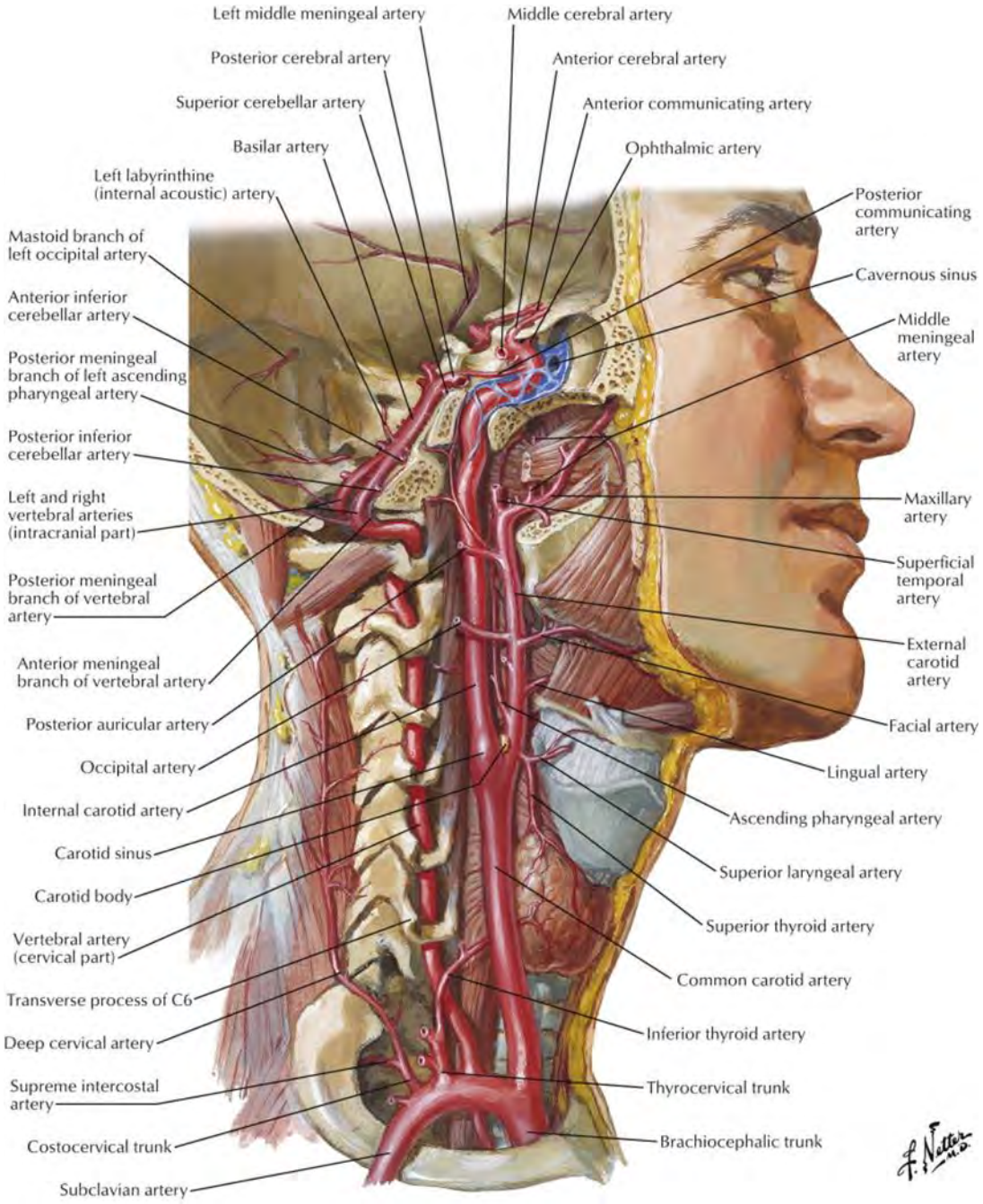


Figure 2.9: Course of the vertebral and basilar arteries in the head and neck (Netter, 2014).

The first branch from the basilar artery is the anterior inferior cerebellar artery (AICA); it generally originates from the lower third of the basilar artery and passes through the cerebellopontine cistern. The labyrinthine (internal acoustic) artery is usually a branch from the AICA. The labyrinthine artery enters the internal acoustic meatus along with the facial and vestibulocochlear nerves. The basilar artery gives of

numerous pontine arteries, which penetrate the pons immediately as paramedian branches, travel a short distance as short circumferential branches or pass for a longer distance as long circumferential branches. The superior cerebellar artery is the last major branch of the basilar artery (Haines & Lancon, 2013).

The hypophysis (pituitary gland) lies within the hypophyseal fossa of the sella turcica, as shown in Figure 2.10. The edges of the sella turcica are made of the anterior and posterior clinoid processes and the dorsum sellae. The basilar artery terminates by dividing into the two posterior cerebral arteries, at a variable level, usually behind the dorsum sellae, in the interpeduncular cistern (Griffiths & Lee, 2008).

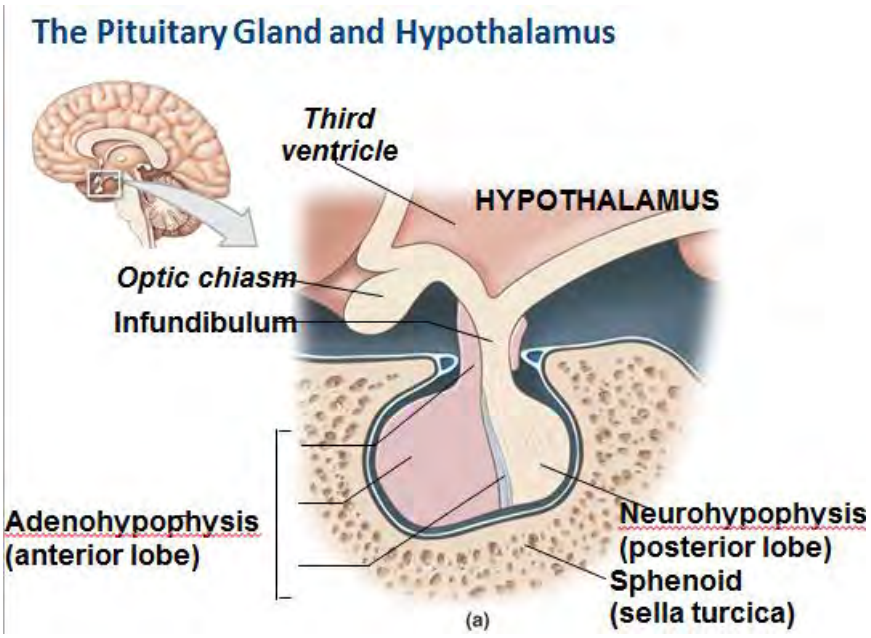


Figure 2.10: The sella turcica containg the anterior and posterior lobes of the hypophysis (Martini *et al.*, 2011).

2.8 The posterior cerebral arteries

The posterior cerebral arteries (PCA) are the terminal branches of the basilar artery. The PCA can be divided into three segments, namely: P1: bifurcation of the basilar artery to the junction of the P1 segment with the PComA, P2: from the PComA to the

perimesencephalic (ambient) cistern, and P3: the part of the PCA that runs within the calcarine fissure, as shown in Figure 2.11.

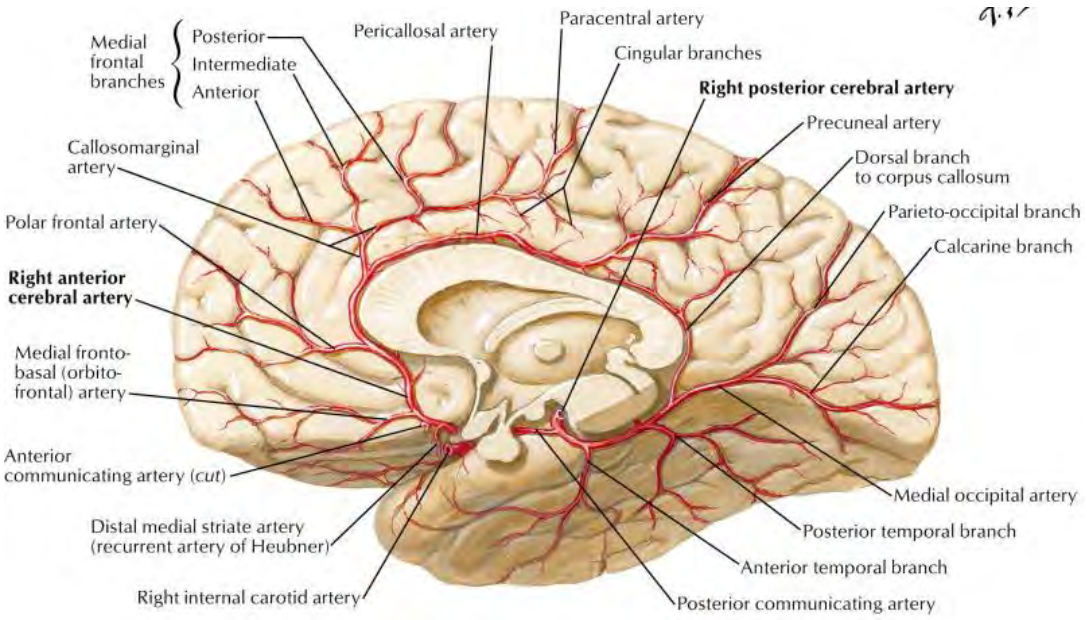


Figure 2.11: Calcarine fissure containing the P3 segment of the posterior cerebral artery (Netter, 2014).

The superior cerebellar artery is normally smaller than the PCA. The oculomotor and trigeminal nerves separate these two arteries from one another. The PCA runs parallel with the superior cerebellar artery. The PCA curves around the cerebral peduncle after receiving the PComA. It supplies the occipital and temporal (except the temporal poles) lobes of the brain (Griffiths & Lee, 2008).

2.9 Posterior communicating arteries

The posterior communicating arteries (PComA) join the PCA with the ipsilateral ICA (Griffiths & Lee, 2008) (See Figure 2.8).

2.10 Anatomical variations of the circulus arteriosus cerebri

In order to obtain a better understanding of arterial variations, some terminology needs to be defined.

- Duplication: two distinct arteries having origins that are separate and no distal convergence (Dimmick & Faulder, 2009).
- Fenestration: a division of the arterial lumen into separate channels, including separate muscularis and endothelial layers, but the adventitia layer might be shared (Dimmick & Faulder, 2009).
- According to various authors, arteries and communicating arteries are said to be hypoplastic when one of the following criteria is applied:
    - < 0.5mm (Hoksbergen *et al.,* 2000)
    - < 0.8mm (Hartkamp *et al.,* 1999)
    - < 1mm (Alpers & Berry, 1963; Riggs and Rupp, 1963; Lazorthes *et al.,* 1979; El Khamlichi *et al.,* 1985; Eftekhar *et al.,* 2006; Tanaka *et al.,* 2006; Kapoor *et al.,* 2008; De Silva *et al.,* 2011; Li *et al.,* 2011; Mamatha *et al*., 2012; Siddiqi *et al.,* 2013)
    - ≤ 1mm (Fisher, 1965)
    - External diameter of the artery being ≤ 50% of the dominant A1 segment as used by Lazzaro *et al.,* 2014

For the purpose of this study the circulus arteriosus cerebri was defined as consisting of one anterior communicating artery, bilateral posterior communicating arteries and the bilateral A1 and P1 segments of the ACA and PCA respectively. The definition was further expanded to include the feeding arteries to the circulus arteriosus cerebri, namely the basilar artery and the bilateral internal carotid arteries; as well as the A2 and P2 segments of the ACA and PCA respectively. Hypoplasia was defined as any vessel being less than 1mm in external diameter, in keeping with the majority of previous authors (above) and the most recently published articles on this subject.

Various authors have described normal / common variations of the CAC, but there have only been a few sets of authors who have described these for the entire CAC, as seen in Table 2.1.

Table 2.1: Summary of studies on the entire circulus arteriosus cerebri

Author:	Date:	Country of sample:
Riggs and Rupp	1963	USA
Fisher	1965	USA
Lazorthes *et al.*	1979	France
El Khamlichi *et al.*	1985	Morocco
Eftekhar *et al.*	2006	Iran
Dimmick and Faulder	2009	Australia
De Silva *et al.*	2011	Sri Lanka

All except Dimmick and Faulder (2009), Riggs and Rupp (1963) and Fisher (1965) used the same 22 types of variations of the CAC as reference when describing their findings.

The 22 types of variations was originally described by Lazorthes *et al.,* in 1979, and used by El Khamlichi *et al.,* (1985), Eftekhar *et al.,* (2006), and De Silva *et al.,* (2011) were:

- Typical
- All segments hypoplastic
- Hypoplasia of the AComA
- Unilateral hypoplasia of the PComA
- Unilateral hypoplasia of the PComA & AComA
- Bilateral hypoplasia of the PComA's

- Bilateral hypoplasia of the PComA's & hypoplastic AComA
- Hypoplasia of the A1 segment
- Unilateral hypoplasia of the P1 segment
- Bilateral hypoplasia of the P1 segments
- Hypoplasia of the P1 & contralateral A1
- Hypoplasia of the P1 & ipsilateral A1
- Bilateral hypoplasia of the P1's & A1's
- Hypoplasia of the A1 & contralateral PComA
- Hypoplasia of the AComA & P1
- Hypoplasia of the PComA, ipsilateral A1 & AComA
- Hypoplasia of the PComA & contralateral P1
- Bilateral hypoplasia of the PComA's & A1
- Hypoplasia of the PComA, AComA & contralateral P1
- Hypoplasia of the P1, contralateral PComA & ipsilateral A1
- Bilateral hypoplasia of the P1's & AComA
- Hypoplasia of the PComA, ipsilateral A1 & contralateral P1

Dimmick and Faulder (2009):

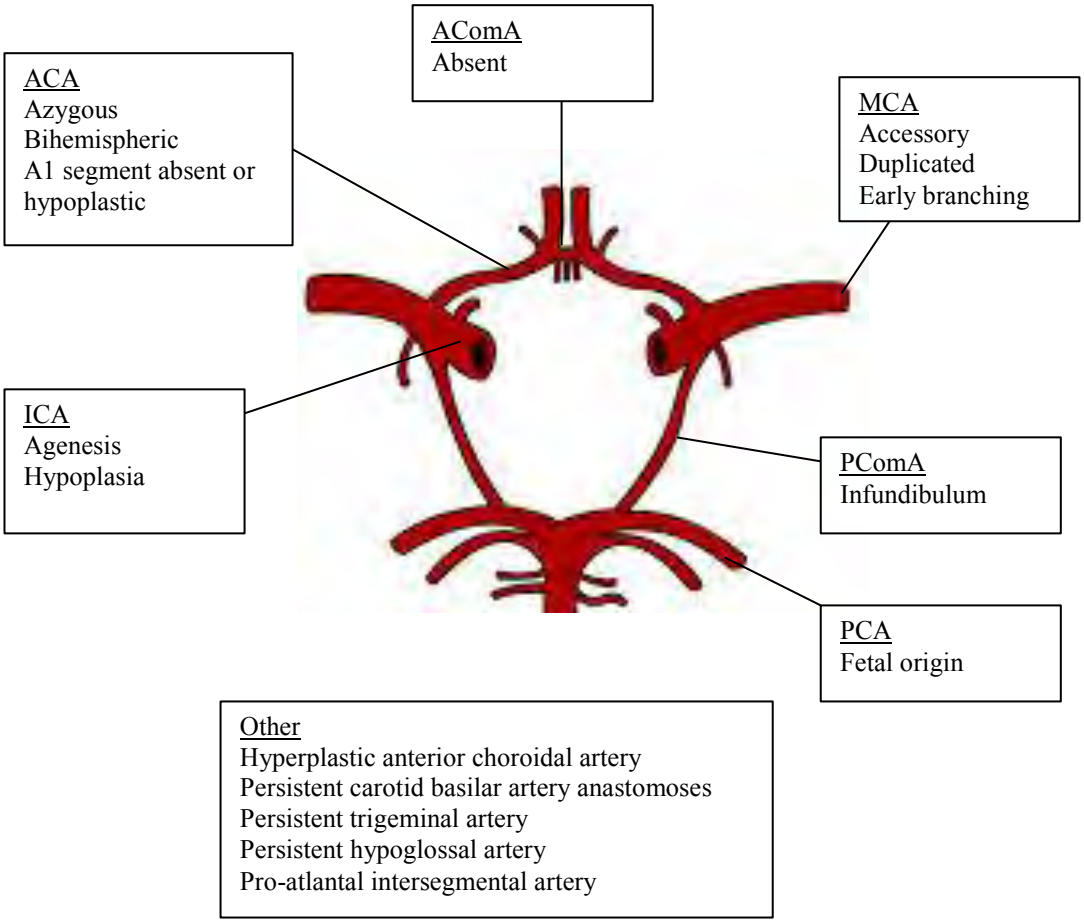


Figure 2.12: Summary of the findings of the study by Dimmick and Faulder, figure modified from Rhcastilhos, 2007.

Variations as described by Dimmick and Faulder (2009)

The embryonic median artery of the corpus callosum may persist as an azygos anterior cerebral artery. Thus, both the ACA territories are supplied by a single midline A2 trunk. An azygos anterior cerebral artery is clinically relevant in the event of an anterior cerebral artery occlusion secondary to surgical error or thrombo-embolic disease; both hemispheres will therefore be affected by the resultant ischaemia (Dimmick & Faulder, 2009).

Trifurcation of the ACA is the occurrence of three A2 segments. This could be due to the persistence of the median callosal artery (Dimmick & Faulder, 2009).

A bihemispheric ACA occurs when one of the A2 segments is hypoplastic. The contralateral A2 segment will provide the majority of the arterial supply bilaterally. In the event of occlusion of the dominant A2 segment, ischaemia of both hemispheres will occur (Dimmick & Faulder, 2009).

In the event of A1 segment aplasia or hypoplasia, the contralateral ACA may supply part or all of the ACA territories by way of a large AComA. In the event of thrombo-embolic disease, a reduced collateral supply may result in an increased risk of infarction (Dimmick & Faulder, 2009).

The anterior communicating artery may be absent or hypoplastic (Dimmick & Faulder, 2009).

Arising from the ACA, an accessory MCA will course parallel to the M1 segment of the MCA. The accessory MCA supplies the anterior-inferior region of the frontal lobe. A distinction must be made between an accessory MCA and a duplicated MCA. A smaller MCA branch arising from the ACA is designated as an accessory MCA. Duplication of the MCA occurs when a branch from this artery arises superior to the

bifurcation of the internal carotid artery. This duplicate artery runs parallel to the main MCA. The accessory MCA, in the presence of an occlusion, may supply collateral blood supply to the distal MCA territory. Because an aneurysm may occur at the origin of an accessory MCA, this variant is clinically much more significant than a duplicate MCA (Dimmick & Faulder, 2009).

In cases where the temporo-occipital branches of the posterior cerebral artery arise from the anterior choroidal artery, the anterior choroidal artery is said to be hyperplastic. The anterior choroidal artery arises from the internal carotid artery, distal to the posterior communicating artery (Dimmick & Faulder, 2009).

The PCA is said to have a fetal origin when the external diameter of the PComA is equal to or greater than that of the ipsilateral P1 segment. The embryonic PComA failed to regress (Dimmick & Faulder, 2009).

In the event of a PComA infundibulum, a dilatation is found where the PComA originates from the ICA. The infundibulum can be conical or round with a diameter of <2mm and it is symmetric. The ICA is at its base and the PComA arises from its apex. It is important to distinguish an infundibulum from aneurysms of the PComA and ICA (Dimmick & Faulder, 2009).

The PComA may be aplastic or hypoplastic. In the case of a hypoplastic PComA, the external diameter of the artery is less than 0.5mm (Dimmick & Faulder, 2009).

A persistent carotid basilar anastomosis is formed when any of the following arteries fails to regress during embryonic development: trigeminal, otic, hypoglossal and/or pro-atlantal intersegmental artery. Each of these arterial variations is described below (Dimmick & Faulder, 2009).

The most common and most cephalic variation is a persistent trigeminal artery. This artery arises from the ICA after its exit from the carotid canal. Two types of the persistent trigeminal artery can be defined:

- Lateral type: coursing with the trigeminal nerve
- Medial type: having a transhypophyseal course

Anomalies associated with this variation include intracranial aneurysms. In patients whom are to undergo transsphenoidal surgery for pituitary adenoma, it is essential to note the presence of a persistent trigeminal artery, because transection of this artery may result in a life-threatening haemorrhage (Dimmick & Faulder, 2009).

A primitive hypoglossal artery originates from the ICA at the vertebral level of C1-C3. The primitive hypoglossal artery passes through the hypoglossal canal and anastomoses with the basilar artery. Hypoglossal nerve paralysis and glossopharyngeal neuralgia can be caused by this type variation (Dimmick & Faulder, 2009).

A pro-atlantal intersegmental artery originates from the common carotid artery bifurcation or from the external or internal carotid arteries at the level of the C2-C4 vertebral bodies. In the suboccipital region, the pro-atlantal intersegmental artery joins the vertebral artery. Two variants can be defined, in type one the artery arises from the dorsal aspect of the ICA. In type two the artery arises from the external carotid artery. Hypoplasia or aplasia of one or both vertebral arteries may be identified. Abnormalities include intracranial aneurysms (Dimmick & Faulder, 2009).

A less common variation is agenesis of the internal carotid artery. This is a congenital absence of the ICA; it can be unilateral or bilateral. There exists an association between the development of intracranial aneurysms and the agenesis of the ICA (Dimmick & Faulder, 2009).

The ICA may also be hypoplastic; this variation is associated with a small carotid canal. Congenital hypoplasia of the ICA may be associated with anencephaly and basal telangiectasia (Dimmick & Faulder, 2009).

To summarise these findings by Dimmick and Faulder (2009), the variations can be grouped as:

- An azygos ACA
- Trifurcation of the ACA
- Bihemispheric ACA
- A1 segment absent or hypoplasia
- Absent AComA
- Accessory MCA
- Early branching of the MCA
- Duplicated MCA
- Hyperplastic anterior choroidal artery
- Fetal origin of the PCA
- PComA infundibulum
- Persistent Carotid Basilar artery anastomoses
- Persistent Trigeminal artery
- Primitive Hypoglossal artery
- Pro-atlantal intersegmental artery
- ICA agenesis
- Hypoplasia of the ICA

Various other authors, such as Niederberger *et al.,* (2010) have described variations in only a portion of the CAC.

According to Niederberger *et al.,* (2010) anatomical variations of the CAC are common, especially in the anterior region. They also stated that multiple anterior communicating arteries are the most common variant, followed by hypoplasia of the artery. These variations do not appear to be significantly associated with aneurysms.

Swetha and Dakshayani (2011) investigated the variability of the anterior cerebral artery in human cadavers and found that hypoplasia of the A1 segment of the ACA may facilitate the occurrence of embolism in the ACA distribution, leading to infarction in the respective areas.

In a study done by De Silva *et al.* (2009) they found that 85.5 % of the arterial circles they included in their study showed hypoplasia. They determined that the most common site for abnormal external diameters was in the posterior part of the CAC. This might be due to the basilar and internal carotid arteries forming anastomoses during embryological development of the posterior half of the CAC. See Appendix A on page 81, for a Table summarising the findings by various authors.

By combining the findings of Dimmick and Faulder (2009), and those of the other authors who focused on whole or part of the CAC, a Table of variations was constructed for use in this study, as can be seen Appendix B on page 82.

2.11 Clinical significance

The circulus arteriosus cerebri has an important influence on cerebral haemodynamics through collateral anastomoses. The presence of a complete CAC should be more effective in facilitating blood flow compared to situations where there are deficiencies in the CAC (De Silva *et al.,* 2009).

In the study done by Iqbal (2013), he stated that cerebrovascular diseases such as stroke, aneurysms, and ICA occlusion, unilateral flow restrictive external carotid

artery disease, together with their signs and symptoms, grossly depend upon the variations of the CAC.

Knowledge of variations such as duplications, fenestrations and persistent fetal arteries has an impact on the diagnosis and management of subarachnoid haemorrhage and acute stroke (Dimmick & Faulder, 2009; Iqbal, 2013).

The CAC provides collateral blood supply for the cerebral circulation when a vessel is absent or obstructed (Alastruey *et al.,* 2007). This collateral pathway will maintain adequate cerebral perfusion in the event of diminished afferent (inflow) blood supply through the ICA's or basilar artery (Hartkamp & Van der Grond, 2000). The CAC is not an equalizer and does not distribute blood from different sources; there is no mixing of blood from different sources in the CAC under normal circumstances. The CAC also offers a potential shunt under abnormal conditions such as might occur during an occlusion or vasospasm (Iqbal, 2013).

The CAC has a compensatory capacity which is important for vascular surgeons and neurosurgeons, when a procedure involving the cerebral arteries is to be attempted (Alastruey *et al.,* 2007; Kedia *et al.,* 2013).

Knowledge of anatomical variations of the CAC is important for the safe performance of radiologic or neurosurgical procedures within the brain (Alawad *et al.,* 2009; Swetha & Dakshayani, 2011).

2.12 The circulus arteriosus cerebri and aneurysm formation

Cerebral aneurysms can be defined as defects in the vessel wall causing balloon-like swellings on arteries, usually at points of bifurcation (Griffiths & Lee, 2008). Cerebral aneurysms are located within the skull and can range from small (berry or saccular aneurysms) to very large (giant aneurysms), or they may involve an elongated portion of the vessel (fusiform aneurysm) as shown in Figure 2.13 (Haines & Lancon, 2013).

Iqbal (2013) concluded that arterial aneurysms and arterial variations are interconnected; he further stated that aneurysms usually occur at branches or at the bifurcations of cerebral arteries.

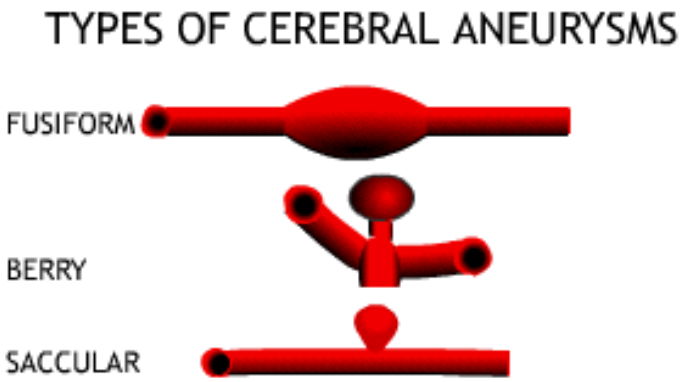


Figure 2.13: Different types of cerebral aneurysms (RnCeus, 2007).

In a study done by Songsaeng *et al.,* (2010), the authors report on the impact variations in the CAC had on the incidence and recurrence of aneurysms following endovascular treatment. The study found that an underdeveloped vascular system could explain some of the variations seen in the CAC. In some instances, the selection of vessels and their process of maturation had stopped before development was completed, leading to a “less mature” anatomical deposition. They hypothesised that the less mature vessel may lead to a “weaker” vessel wall that may be prone to developing aneurysms.

Certain of the variations in the CAC may play a role in the development of aneurysms by producing haemodynamic changes in blood flow and inducing strain on the weak points of arteries at bifurcation (Alawad *et al.,* 2009) (Figure 2.14).

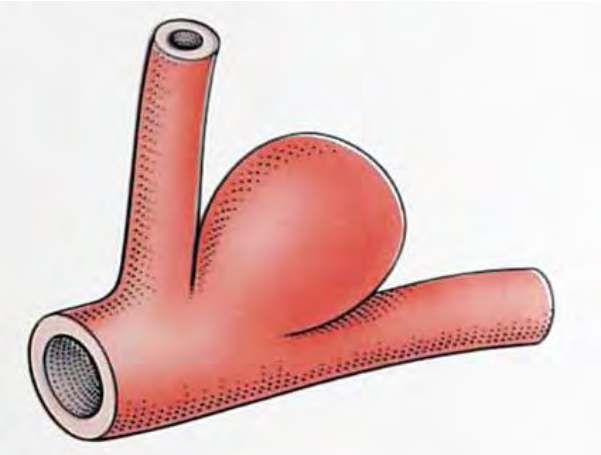


Figure 2.14: Aneurysm at the point of arterial bifurcation (NHLBI, 2011).

In the study done by Kayembe *et al.,* (1984) it was found that the incidence of a typical CAC was significantly higher in their control group (no evidence of aneurysms). The aneurysm group, however, showed a significantly higher incidence of variation in the CAC. They concluded that variations are a factor in aneurysm formation.

In a study done by Lv *et al.,* (2011) it was found that aneurysms associated with the CAC have a greater rate of subarachnoid haemorrhage.

According to Dimmick and Faulder (2009), an association has been found between the presence of fenestrations and aneurysm formation in the arteries of the CAC. They also concluded that arterial fenestrations are more common in the vertebrobasilar arteries than in the anterior circulation, i.e. the MCA, ACA and ICA.

In a study done by Sun *et al.,* (2012) fenestrations of intracranial arteries were found to be rare variants resulting from the incomplete fusion of primitive vessels. The

incidence of an aneurysm associated with a fenestration is reported to be 7%, increasing to 35.5% when associated with an aneurysm at the vertebrobasilar junction.

Lazzaro *et al.,* (2012) compared ruptured and unruptured cerebral aneurysm to variations in the CAC. They hypothesized that CAC variations were more common in ruptured versus unruptured cerebral aneurysms of the AComA and PComA's. Multivariate regression analysis revealed a higher risk of aneurysm rupture when a CAC variation was present.

Thus, the association between variations and the incidence of aneurysms can be interpreted in terms of the haemodynamic stress caused by variation (Kapoor *et al.,* 2008).

Chapter 3 : Methodology

3.1 Materials

3.1.1 Study design

The study was a cross-sectional study using analytical and observational techniques.

3.1.2 Sample population

The sample population included cadavers from the Department of Human Biology at the University of Cape Town. The cadaver brains were dissected and photographed, and the variations found in the circulus arteriosus cerebri were documented.

The sample population also included all patients that underwent a MRI or angiogram of the CAC. This allowed the researcher to gather data at the Department of Radiology at the Groote Schuur Hospital. Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town.

Sex and ancestry were recorded as a reflection of what appeared in the register of cadavers in the Department of Biology. This information would have been obtained from the death certificate of each cadaver. For the images from patients, the information appeared on the specialist's report on the patient.

Statistics South Africa classifies people by population group; however, an individual's population group is not based on a legal definition, but rather on self-perception and self-classification (Patterson, et al., 2009). South Africa is a nation of over 51 million people, who are broadly classified as Black (79.2%), Coloured

(8.9%), Indian/Asian (2.5%), White (8.9%) and other (0.5%) (Statistics South Africa Census 2011, 2011).

In an anthropological context, the South African population can be socially classified into four groups, namely White, Black, Coloured and Indian/Asian (L'Abbé *et al.,* 2011).

Indigenous Africans (Blacks) may be placed into two main groups, namely Sotho-Tswana and Nguni. White South Africans largely descend from colonial immigrants of the late 17th, 18th and 19th centuries, including European groups such as the Dutch, German, British and French Huguenots. The term Coloured is used to define, both culturally and socially, people with an origin from Central African, Malaysia, the indigenous Khoisan from the Cape, as well as modern white and black people. South African Coloureds are considered a distinct population group, despite their various origins (L'Abbé *et al.,* 2011).

For the purposes of this study the term ancestry is used in accordance with the anthropological study done by L'Abbé *et al.,* in 2011 as well as what was documented for each person (cadaver or patient) according to the cadaver register kept in the Department of Human Biology at the University of Cape Town as reflected on the certificate of death, or as reflected on the patients' report kept at the Department of Radiology at the Groote Schuur Hospital, Cape Town.

3.1.3 Sample size

All the cadavers in the Department of Human Biology at the University of Cape Town as dissected by students in the third year of their medical degree (MBChB 3) and postgraduate students during 2014 were included in the sample size.

The sample size for the patient images needed was calculated with the assistance of a biostatician at the Faculty of Health Sciences at the University of Cape Town. Using the formula: $n = \frac{[(z-score)^2 x\ (std.dev)(1-std.dev)]}{(margin\ of\ error)^2}$ where,

n = sample size

Z-score = 1.96 (the accepted value for a confidence level of 95%)

Std.dev = standard deviation of 10% or 0.1 (in order to keep the sample size manageable)

Margin of error / confidence interval = ± 5% or 0.05 (most commonly used)

By using the above mentioned formula a sample size of 138 is calculated. Thus, 138 patients' images were included in the study.

3.1.4 Sample selection

The blood supply of the brain was studied on the cadavers dissected during 2014. The cadavers were part of the Department of Human Biology at the University of Cape Town. The MBChB 3 students removed the cadaver brains from the skulls during their practical sessions. The information obtained from the cadaver brains served as a baseline for variations in the CAC. Any aneurysms found in the cadaver brains were documented and included in the study. All results were compared with those of the patient records of the persons who underwent a MRI or angiogram of the CAC (see below).

The arterial configuration of the CAC was studied in patients who underwent a MRI or angiogram at the Department of Radiology at the Groote Schuur Hospital in Cape Town, and the patients included in the sample were selected non-randomly. The exclusion criteria for this sample are listed below.

3.1.5 Exclusion criteria

For the cadavers, if the arteries were too damaged for accurate measurements to be taken, the brains were excluded from the sample.

In order to eliminate any errors in the descriptions of variations in the CAC, images of patients with head trauma that affected the CAC, previous head surgery to that region, or a stroke leading to the obscuring of the CAC were excluded from the sample. An image (MRI or angiogram) was also excluded if it did not clearly show the CAC, if the view was obstructed (for example by an aneurysm), and if obscured or distorted (for example due to the patient moving or because of the presence of a metal artefact). Only patient images that include a time of flight (TOF) sequence were included in the sample. The TOF sequence is necessary for the analysis of the data as will be explained below.

3.2 Methods

To study the Circle of Willis of the cadavers, it was first necessary to remove the brain from the skull. Firstly, the vault of the skull was removed. The dura mater was removed taking care not to damage the underlying brain tissue. The falx cerebri was detached from the crista galli anteriorly. The optic nerves were cut anterior to the optic chiasm as they emerge from the optic canals. The infundibulum or stalk of the pituitary gland was severed. The oculomotor, trochlear, trigeminal and abducent nerves were cut through. The tentorium cerebelli, which forms a roof over the posterior cranial fossa, was incised along its attachments to the petrous temporal bone and to the occipital bone posteriorly. Finally, a cut was made just inferior to the medulla to free the brain from the spinal cord. The brain could then be removed from the skull.

The bases of the brains were photographed once the arachnoid mater was removed and the CAC was dissected. All variations and anomalies were photographed and

documented on the standardised data sheet. Each cadaver brain was assigned a code for identification purposes. The unique code was assigned in numerical order to each cadaver brain enabling an external observer to check if all brains, documentation and photographs are accounted for.

3.2.1 Measurements on the cadaver brains

The external diameter of the ICA, ACA, AComA, PCA, PComA and basilar arteries were measured and documented. Measurements were taken where these arteries formed part of the CAC. The P1 segment of the PCA was measured between the PComA and the basilar artery; it was measured as close to its origin from the basilar artery as possible. The P2 segment of the PCA was measured after the attachment of the PComA to the PCA. The PComA's were measured between their attachment to the ICA and the ipsilateral PCA. The A1 segment of the ACA was measured between the ICA and the AComA. The A2 segment of the ACA was measured after the AComA. The AComA was measured between the two ACA's. The ICA was measured before its bifurcation into the MCA and ACA, as close to the bifurcation as possible. The basilar artery was measured before the superior cerebellar arteries branched off, but if the superior cerebellar arteries were absent or they branched off early, the measurement was taken as close to the termination of the basilar artery into the PCA's as possible, as shown in Figure 3.1.

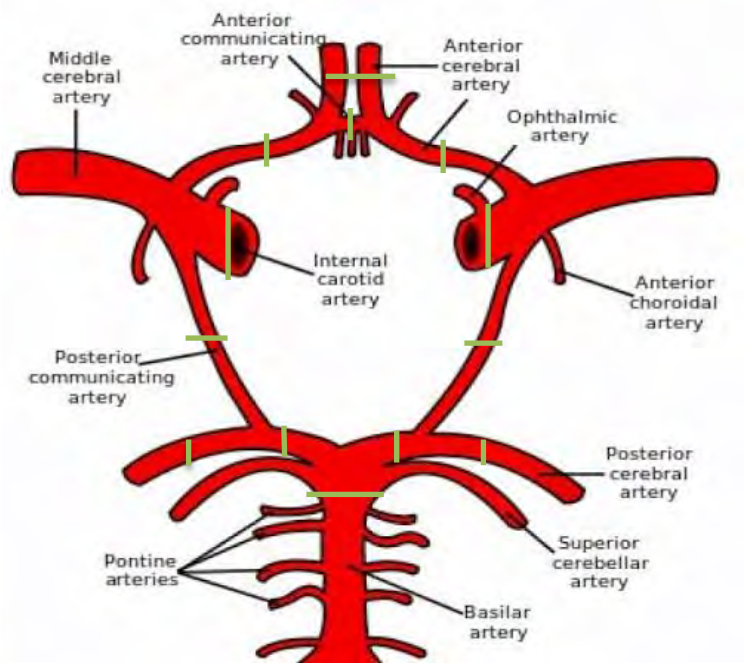


Figure 3.1: Diagram indicating where the measurements of the external diameters for the arteries of the cadaver brains were taken (Rhcastilhos, 2007).

Three measurements of each artery were taken and an average was obtained. The averages were used in the statistical analyses of the data. Measurements were taken in millimetres to a hundredth of a millimetre.

The external diameters were measured using a digital Vernier calliper with precision to 0.01mm or 0.0005 inches. The calliper was zeroed between the measurements of each CAC. Photographs of the base of each brain were taken from above, perpendicular to the brain (Ansari *et al.,* 2009; Siddiqi *et al.,* 2013).

For the study of the blood supply of the brain of patients, magnetic resonance imaging (MRI) was the preferred way of imaging the brain. Human body tissue, including brain tissue, is made up of a large proportion of protons (hydrogen). These hydrogen atoms consist of a nucleus, a shell of electrons and a north and a south pole, as they spin around an angulated axis. As the electrons move with the spinning atom, they induce an electrical current that creates a magnetic field. They are aligned randomly because of the changing magnetic effects on each other. When the protons

are exposed to a powerful magnet, they stop pointing randomly and align themselves parallel to the external magnetic field, but at different energy fields. Thus, the stronger the external magnetic field, the faster the frequency of the spin at that angle. When undergoing an MRI examination, the patient becomes the magnet, with all the protons aligning along the external magnetic field and spinning at an angle with a certain frequency (Haines *et al.,* 2013).

A radio wave is an electromagnetic wave. When a radio wave is sent as a short burst into the magnet containing the patient, it is known as a radiofrequency (RF) pulse. Only when the frequency strength of the RF pulse matches the frequency strength of the angulated spinning protons will the protons absorb energy from the radio wave. This is called resonance, and is the "resonance" in "magnetic resonance imaging". This results in a twofold effect: pulse cancels out the magnetic effects of certain protons and it raises the energy levels and magnetic effects of others. When the radio wave is turned off, the cancelled-out protons gradually return to their original state and strength of magnetization, called relaxation, and is described as a time constant, T1. The protons that aligned themselves at a higher energy and magnetization also start to lose their energy, this is the time constant T2. A receiver coil (antenna) absorbs this information and a computer determines the characteristics of the emitted radio waves from all the specific points in that section of the body. The MR image is then constructed and transferred to a computer monitor or recorded on film (Haines *et al.,* 2013).

The most widely used MR angiography imaging techniques (used to visualize arteries and or veins) can be characterized as phase-contrast, time of flight or contrast enhanced methods. For the purpose of this study the time of flight method is described below.

Time of flight (TOF) techniques differentiate between stationary tissue and flowing blood by manipulating the magnitude of the magnetization. This measurement is manipulated in such a way that the magnitude of the magnetization from the moving spins (spin of the atom around its angulated axis) is large and that of the stationary

spins is small. This will lead to a large signal from the moving spins (blood) and a reduced signal from the stationary spins (tissues) (Korosec, 1999).

To study the CAC on the patients' images the computer software iSite and OsiriX was used, as described below. Data was collected at the Department of Radiology at the Groote Schuur Hospital in Cape Town. The Department of Radiology uses the iSite software to capture and store all their imaging, including MRI and MRA. By applying the inclusion and exclusion criteria, the images were sorted and a sample population selected. The images from the sample population were then exported from iSite and imported into the OsiriX software.

OsiriX is image processing software dedicated to DICOM images; thus images with a ".dcm"/".DCM" extension. These images are produced by imaging equipment; MRI, CT; PET, PET-CT, SPECT-CT or ultrasounds. OsiriX can receive DICOM images from any PACS or imaging modality. OsiriX has been designed to navigate and visualise multimodality and multidimensional images; 2D, 3D, 4D and 5D (3D series with temporal and functional dimensions; e.g. Cardiac-PET-CT). OsiriX is also processing software for medical research, 3D and functional imaging, confocal microscopy and molecular imaging.

The OsiriX software was used to calculate a 3D image of the arteries supplying the brain for each patient using the TOF sequences. Measurements for the external diameter of the arteries were taken either on the TOF sequence of images, as explained below. The compiled 3D image was used to easily identify any of the arterial variations, for example duplications and aplasia.

3.2.2 Measurements performed on the images

BA: measurements were taken after the vertebral arteries formed the basilar artery, but before the superior cerebellar artery branched off.

PCA (P1 segment): measurements were taken after the basilar artery bifurcated into the P1 segments of the PCA on the left and right.

PCA (P2 segment): measurements were taken after the PComA joined the PCA on the left and right.

PComA: measurements were taken between the origin from the PCA and where it joined the ICA.

ICA: measurements were taken before it bifurcated into the ACA and the MCA.

ACA (A1 segment): measurements were taken between its origin from ICA and AComA.

ACA (A2 segment): measurements were taken after the AComA joins the ACA on the left and right.

AComA: measurements were taken between the left and right ACA. If more than one anterior communicating artery was found, measurements were taken for all the anterior communicating arteries present.

3.3 Statistical analyses

Information obtained from the cadaver brains and the patient images was statistically analysed using the software program STATA 13 (StataCorp, 2013).

Shapiro-Wilk tests were used to analyse the numerical data, to determine normality. Data found to be normally distributed were further analysed using the Student's t-test

as well as one-way analysis of variance (ANOVA). Data found not to be distributed normally was analysed using the Wilcoxon Rank sum test as well as the Kruskal Wallis test. Categorical data was analysed to determine whether there was an association between any categorical variable and the presence of aneurysms and of variations, including the locations of both of these. For the analyses of the categorical data chi-square tests were used.

Logistic regression and multinomial regression tests were done on the data to compute models, allowing the estimation of which anatomical variations or combinations of variations are the best predictors for cerebral aneurysms in the sample. These tests did not yield any models that could serve as a good predictor for the presence of aneurysms in the sample. The models also showed a high rate of false positives, thus predicting the presence of an aneurysm when it is not. Therefore, the details of the findings of the regression analyses were not included in the results and discussion sections.

For all statistical analyses, significance was determined by using a p-value of 0.05. All numerical results were reported to a maximum of three decimal places. This was done to assure that statistically significant results were accurately represented, as well as ensuring that they remained significant by not rounding up to fewer decimal places.

Individuals were grouped according to the type of variation present. This led to some groups having no or very few persons (<5). For the purpose of performing statistical analyses the group sizes needed to be increased. Thus 8 main groups were formed, as listed below; the relevant details for these groups are covered in the Chapters dealing with the results and discussion.

Group 1: Typical (Type 1)

Group 2: Variations of the A2 segment of the ACA, including trifurcations, bihemispheric ACA and an azygos ACA. (Types 2-4)

Group 3: Variations of the A1 segment of the ACA, including hypoplasia, aplasia and loop formation or fenestrations. (Types 5-9)

Group 4: Variations of the AComA, including hypoplasia, aplasia and fenestrations. (Types 10-13)

Group 5: Variations of the P1 segment of the PCA, including hypoplasia, aplasia, fenestrations and fetal origin. (Types 14-18)

Group 6: Variations of the PComA, including hypoplasia, aplasia, fenestrations and PComA infundibulum. (Types 19-26)

Group 7: Other. (Types 27-28)

Group 8: Multiple variations.

Furthermore, for the purpose of statistical analyses individuals were grouped according to the absence or presence and locations of aneurysms. Thus, eight groups were formed, as listed below.

Group 1: No aneurysm

Group 2: Middle cerebral artery aneurysm

Group 3: Anterior communicating artery aneurysm

Group 4: Posterior communicating artery aneurysm

Group 5: Basilar artery tip aneurysm

Group 6: Location not specified

Group 7: Multiple aneurysms

Group 8: Other

Group 8 refers to aneurysms outside the circulus arteriosus and its immediate branches, for example aneurysms of the ophthalmic and internal carotid arteries.

Chapter 4 : Results

4.1 The cadaver sample

The total number of cadavers available for the study was 41. Two brains were excluded from the sample due to being too damaged to obtain accurate measurements. The number of brains dissected for the study was 39, of these 29 (74%) was male and 10 (26%) were female.

4.1.1 Variations seen in the cadaver sample

Figure 4.1 shows a circulus arteriosus cerebri of typical configuration, type 1. All segments of the circle are present and none are hypoplastic. There are no duplications or triplications.

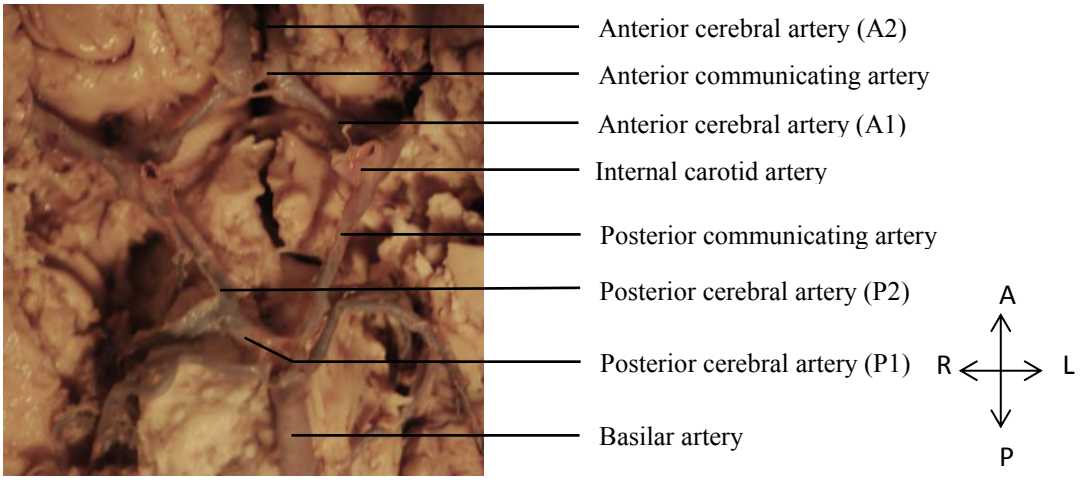


Figure 4.1: Cadaver sample - Typical arrangement of the arteries forming the circulus arteriosus cerebri.

Variations of the anterior circulation of the circulus arteriosus cerebri

Common variations found in the anterior circulation of the circulus arteriosus cerebri are grouped below.

Figure 4.2 below shows a type 3 variation. Trifurcation of the A2 segment of the anterior cerebral arteries are clearly present. This variation was found in three of the cadaver brains.

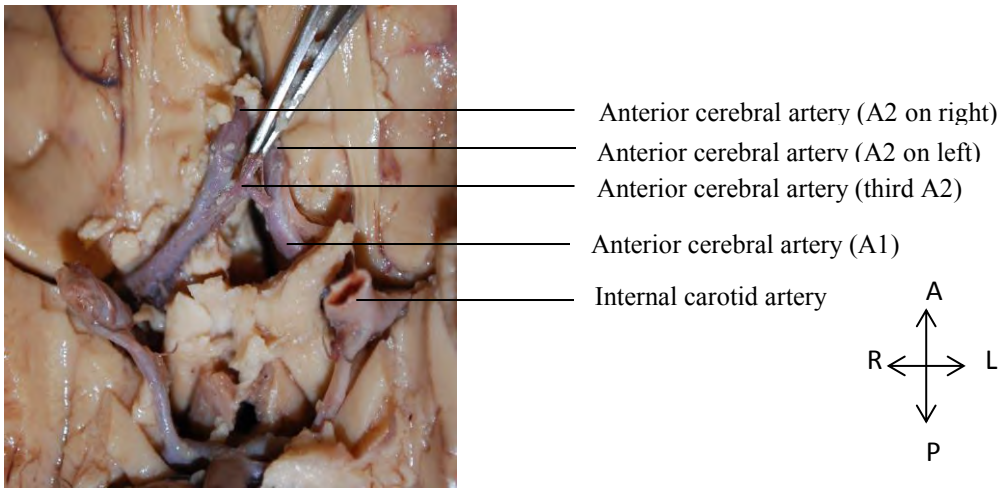


Figure 4.2: Cadaver sample - Trifurcation of the A2 segment of the anterior cerebral artery.

A duplication of the anterior communicating artery (type 11) can be seen in Figure 4.3.

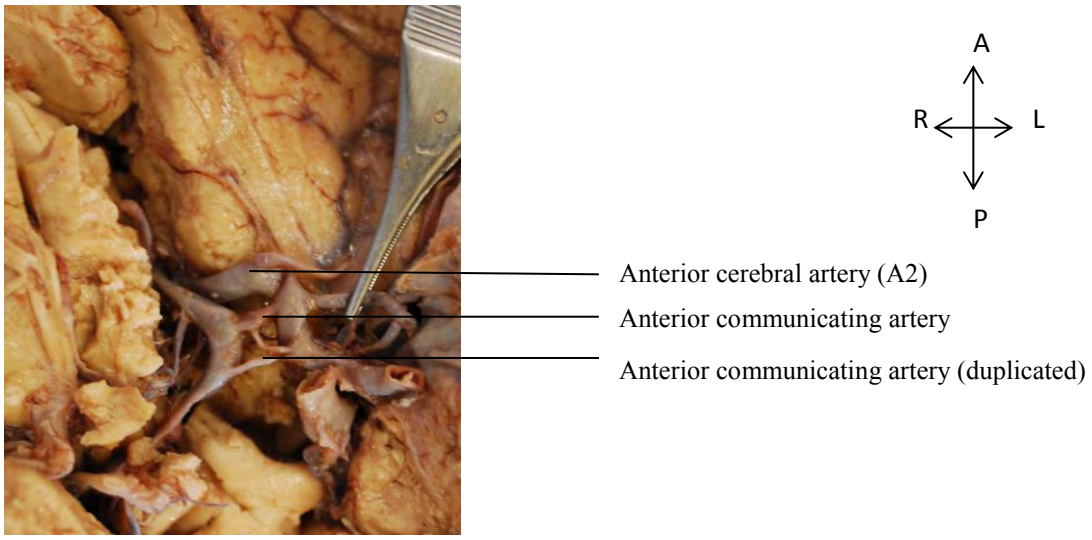


Figure 4.3: Cadaver sample - Duplicated anterior communicating artery.

Fenestrations differ from duplications in that only part of the artery is duplicated and not the artery as a whole, as was seen in Figure 4.3.

Loop formation or fenestration of the anterior cerebral artery is seen in Figure 4.4. As can be seen in Figure 4.4, part of the A1 segment of the right anterior cerebral artery is duplicated (type 9).

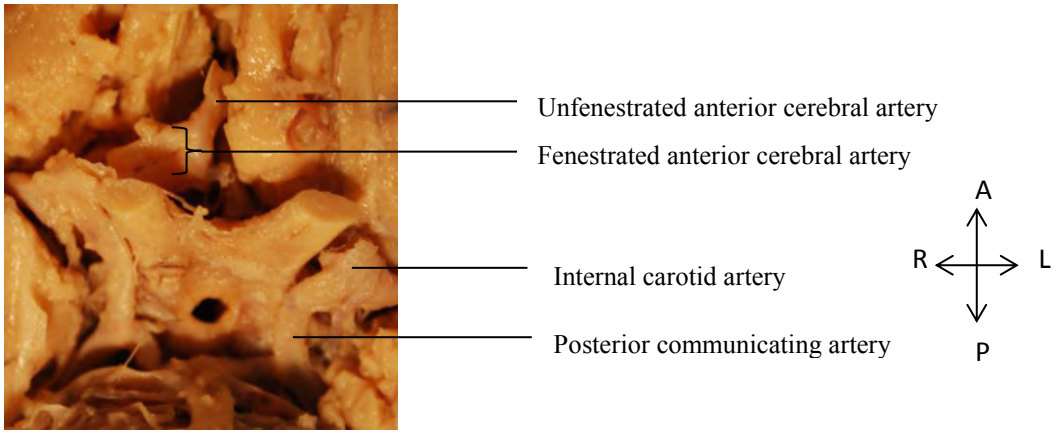


Figure 4.4: Cadaver sample - Example of loop formation in the anterior cerebral artery.

Figure 4.5 shows fenestration of the anterior communicating artery (type 12); this differs from the complete duplication seen in Figure 4.3.

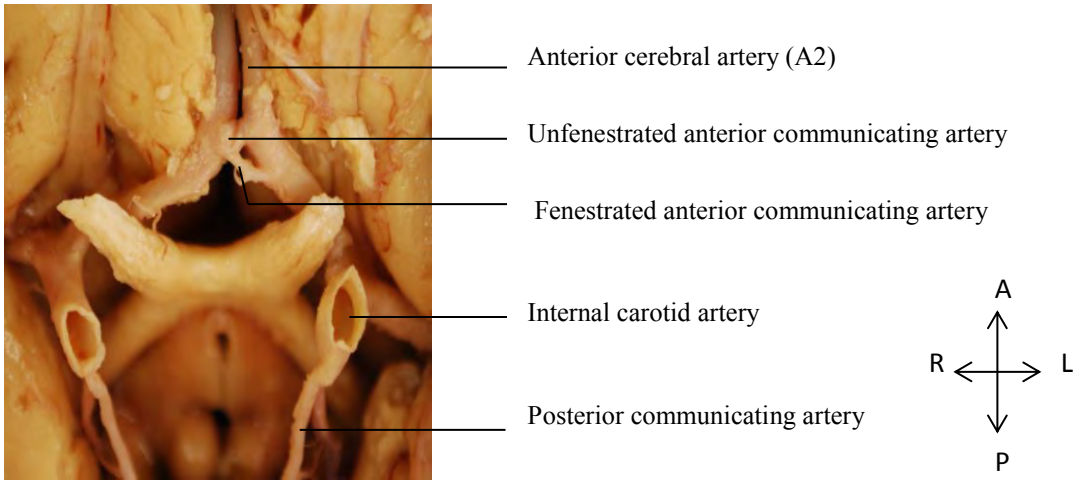


Figure 4.5: Cadaver sample - Fenestration of the anterior communicating artery.

Variations of the posterior circulation of the circulus arteriosus cerebri

Fetal origin of the posterior communicating artery is a type of variation where the external diameter of the posterior communicating artery is equal to or greater than the external diameter of the ipsilateral P1 segment of the posterior cerebral artery (type 14). This variation was determined from the measurements taken and is very difficult to see with the naked eye.

Figure 4.6 shows a cadaver sample with multiple variations of the posterior circulation. Hypoplasia of the P1 segment of the posterior cerebral artery (type 15) on the left and hypoplasia of the posterior communicating artery on the right is indicated (type 20). Although the segments appear smaller visually, hypoplasia can only be established by determining the external diameters of the arteries involved.

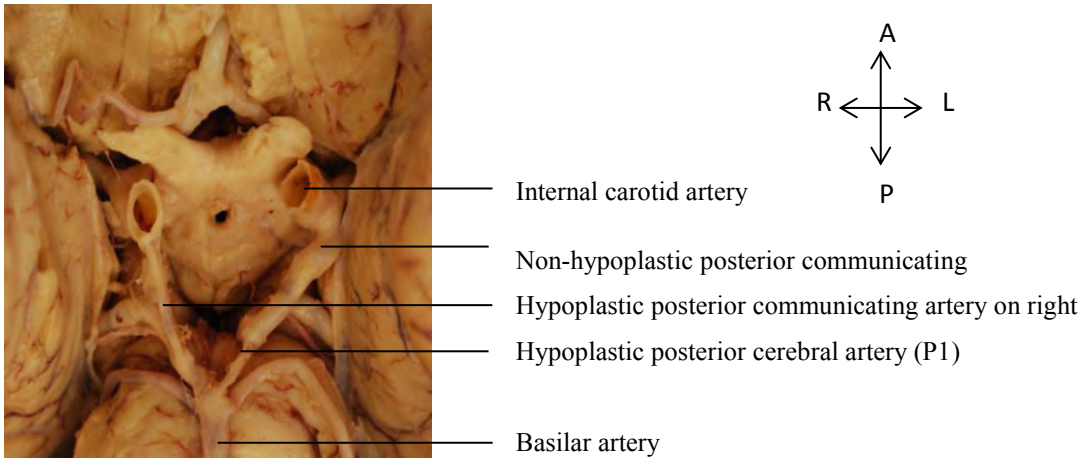


Figure 4.6: Cadaver sample - Unilateral hypoplasia of the P1 segment of the left PCA and unilateral hypoplasia of the right PComA.

Absence of an artery was established after careful examination of all the segments to determine that the artery was not accidently removed or damaged during dissection or removal of the brain from the skull. If no evidence of the artery or remnants of the artery was found, it was said to be absent or aplastic, as shown in Figure 4.7. Figure 4.7 also shows an absent PComA on the left.

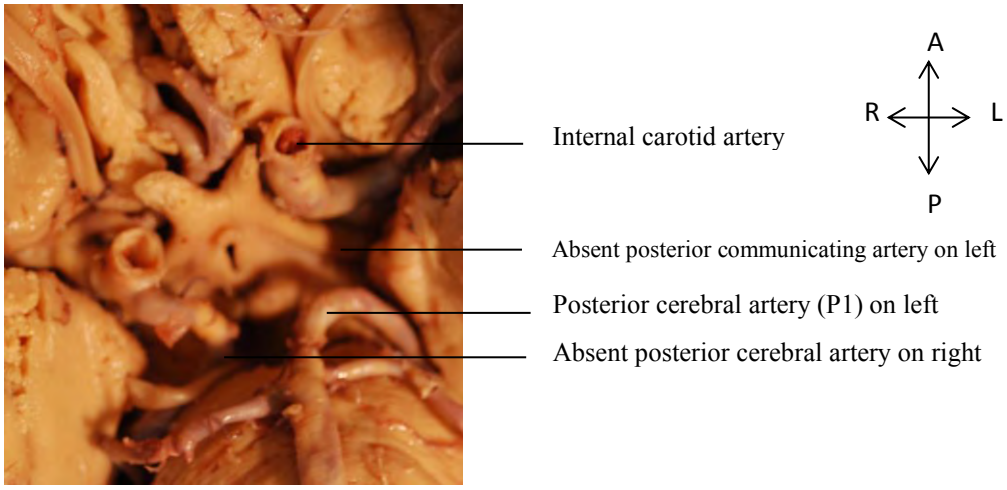


Figure 4.7: Cadaver sample - Aplasia of the posterior cerebral artery on the right.

Figures 4.8 and 4.9 show hypoplasia as found within the posterior circulation of the CAC. Figure 4.9 also shows a bilateral fetal configuration, where the external diameters of the posterior communicating arteries are equal to or greater than the ipsilateral P1 segment of the posterior cerebral artery.

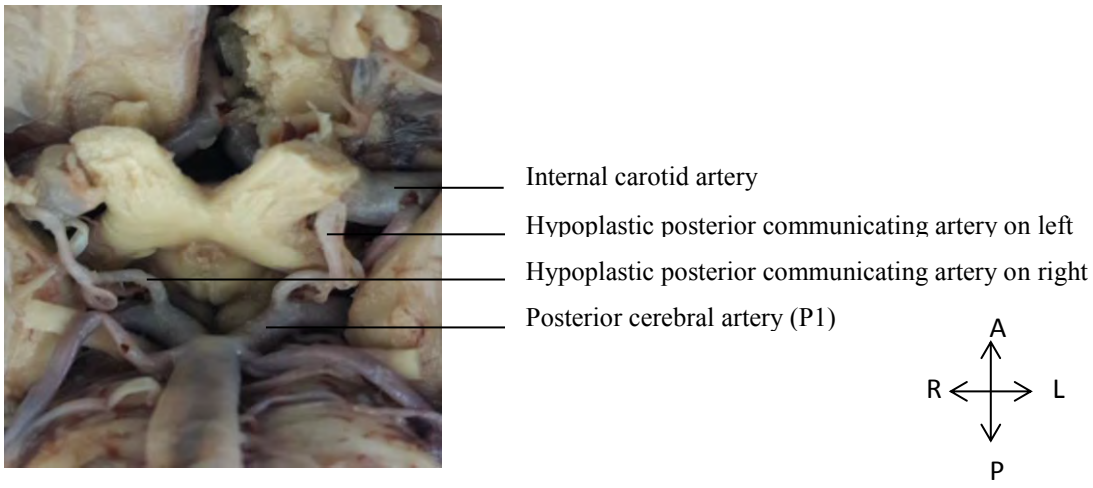


Figure 4.8: Cadaver sample - Bilateral hypoplasia of the posterior communicating artery.

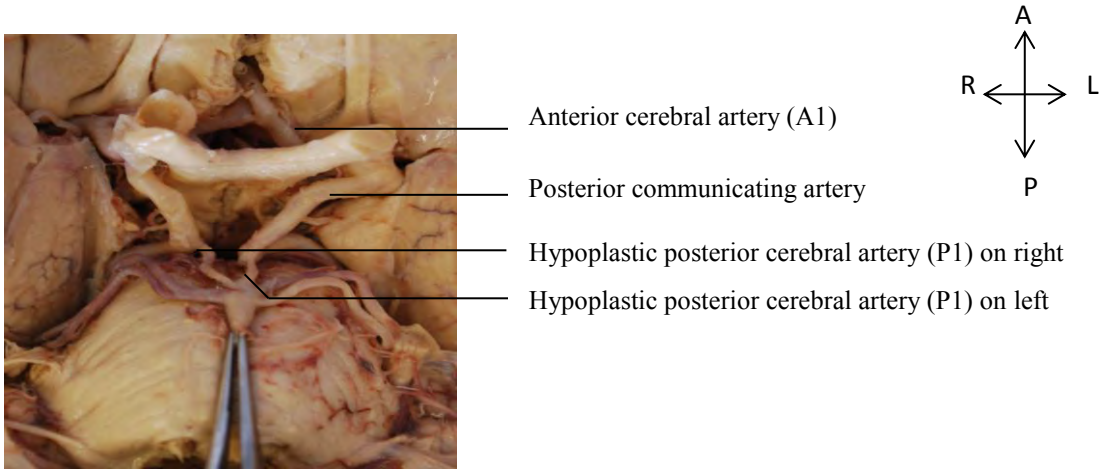


Figure 4.9: Cadaver sample - Bilateral hypoplasia of the P1 segment of the posterior cerebral artery.

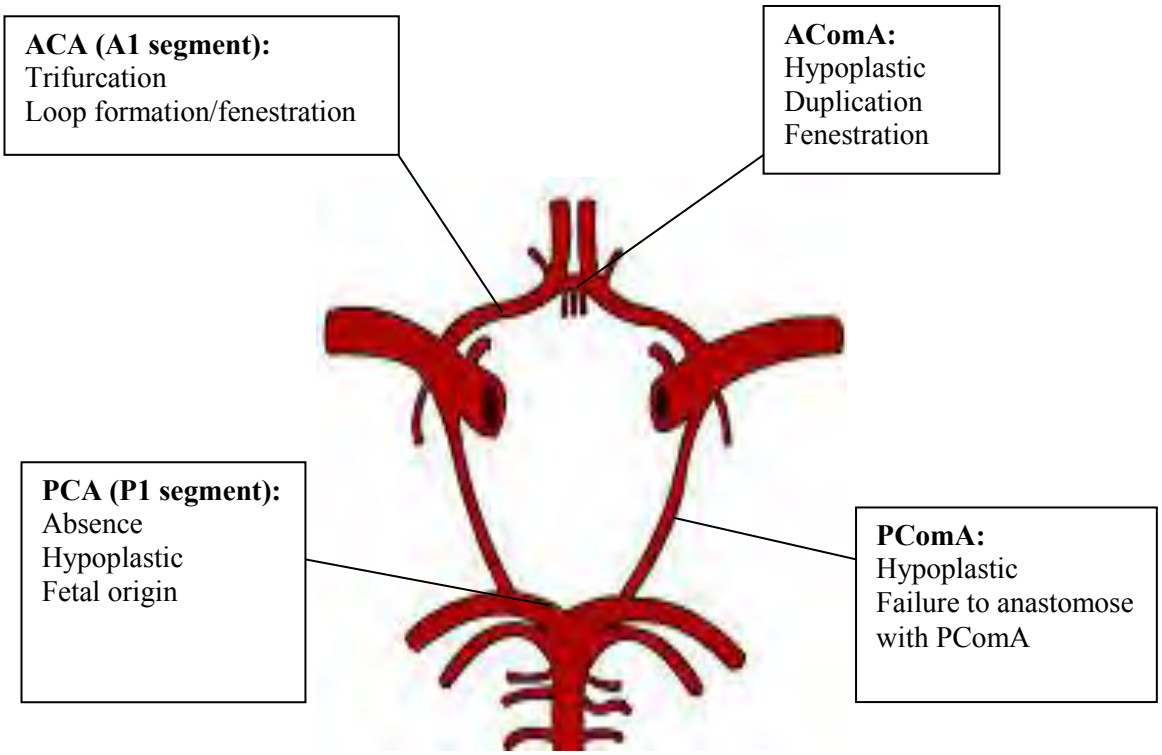


Figure 4.10: Summary of the variations found in the cadaver sample, figure modified from Heimlich, 2013.

4.2 Statistical analyses of the cadaver sample:

Statistical analyses were done on the cadaver sample using the statistical software STATA 13 (StataCorp, 2013). In reporting of the results of the analyses a maximum of three decimal places were retained. This was to accurately reflect if a statistically significant difference or association was found.

Furthermore, for statistical analyses, the entire cadaver sample was divided into two groups, based on whether or not the individuals had one or more variations in the CAC, or no variations. Those that had variations in the CAC were then further subdivided according to the number (single versus multiple) and location of the variations (see above, groups 1-8). Individuals were recorded as having a variation (single or multiple) in the anterior circulation, posterior circulation or in both

circulations. All numerical and categorical data was tested against the above-mentioned subgroups. As will be explained below, this was done in order to test whether there was a significant difference between vessel size and the absence / presence of vessels for the following variables: the presence of a variation and location of variation. The only statistical analyses that could be performed on the group of individuals without any variations were the Shapiro-Wilk test for normality. Statistical analyses could not be done with regards to the presence of aneurysms or the location of aneurysms, since none were documented for the cadaver sample.

Cadavers B024 and B026 were excluded from the statistical analysis, because of damage to their brains during the removal from the skull, and therefore accurate measurements could not be obtained. The total cadaver sample included in the study was 39.

Groups 3 and 7 were excluded from statistical analyses, because none of the sample fell within these two groupings of variation. Statistical analyses were done on the remaining 6 groups. Table 4.1 shows the number of persons (and therefore the frequency of occurrence of a cluster of variations within the overall sample) in each group 1 through 8, but excluding 3 and 7. It also indicates the percentage of persons with a particular variation or set of variations.

Table 4.1: Cadaver sample - Number of individuals as per variation group

Group	Frequency	Percentage
1	10	25.6
2	1	2.6
4	3	7.7
5	8	20.5
6	6	15.4
8	11	28.2
Total	39	100.0

4.2.1 Test 1: Shapiro-Wilk test for normality

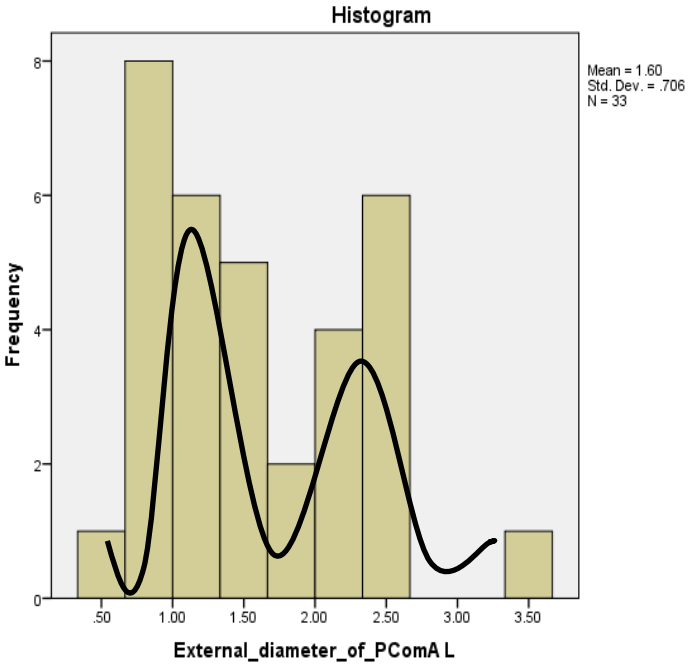
Table 4.2 (below) shows the result of the Shapiro-Wilk test of normality. It should be noted that all the data are normally distributed ($p > 0.05$) except the data for the posterior communicating arteries on the left and right, highlighted in yellow.

The data for the posterior communicating arteries was analysed by studying the histograms, Q-Q plots and the box plots. The relevant graphs clearly show the data as being bimodal, see Graphs 4.1 and 4.2 below. This is due to the high number of individuals with hypoplasia of the posterior communicating arteries. Two peaks can clearly be seen on the graphs; the one peak indicates the individuals with hypoplasia and the other peak individuals with a larger, normal external diameter of the posterior communicating arteries. Thus, there are two subgroups within the data for the posterior communicating arteries.

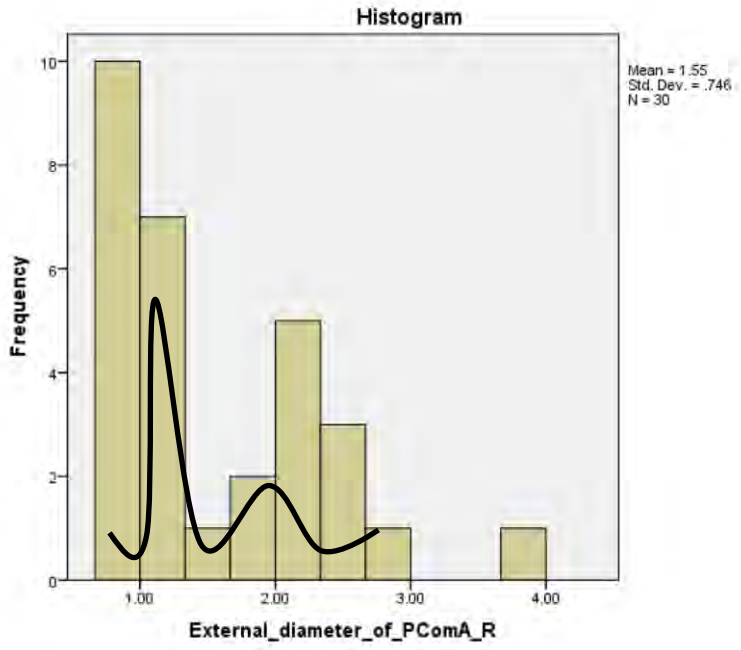
Table 4.2: Shapiro-Wilk test for normality for the cadaver sample, non-normal data highlighted in yellow

Tests of Normality

	Shapiro-Wilk	
	Frequency	Sig.
External diameter of ACA (A1) on Left	39	0.629
External diameter of ACA (A2) on Left	38	0.229
External diameter of ACA (A1) on Right	38	0.271
External diameter of ACA (A2) on Right	37	0.172
External diameter of AComA	37	0.190
External diameter of PCA (P1) on Left	38	0.414
External diameter of PCA (P2) on Left	29	0.928
External diameter of PCA (P1) on Right	38	0.142
External diameter of PCA (P2) on Right	30	0.868
External diameter of PComA on Left	33	0.045
External diameter of PComA on Right	30	0.001
External diameter of BA	39	0.866
External diameter of ICA on Left	36	0.115
External diameter of ICA on Right	36	0.462
Age	39	0.155



Graph 4.1: Cadaver sample - Bimodal data, black line, for the posterior communicating artery on the left



Graph 4.2: Bimodal data, black line, for the posterior communicating artery on the right

Furthermore, the Shapiro-Wilk test for normality was also done on the data by subgroup, i.e. having a variation and the location of variation within the CAC. By sorting the data into variation present or absent, against which all vessels were tested. It was found that the data for the A1 segment of the anterior cerebral artery on the left and right (p=0.041), A2 segment of the anterior cerebral artery on the right (p=0.041), the anterior communicating artery (p=0.045) and the posterior communicating artery on the right (p=0.002) were non-normally distributed.

By sorting the data by the location of the variation in the CAC it was found that the data for the A1 segment of the anterior cerebral artery on the left and right (p=0.041), A2 segment of the anterior cerebral artery on the right (p=0.041), the anterior communicating artery (p=0.045) and posterior communicating artery on the left (p=0.036) and right (p=0.006) were non-normally distributed.

The demographics of the sample were tabulated as seen in Table 4.3 below. This was done for comparison reasons, to establish what part of the sample was representative of females and males and how many individuals were in each of the ancestry groups.

Table 4.3: Demographics for the cadaver sample

	Ancestry			**Total**
	Black	White	Coloured	
Male	5	15	9	29
Female	0	4	6	10
Total	5	19	15	39

4.2.2 Test 2: Comparison of means

For the normally distributed data, the Student's t-test was used to determine if there was a statistically significant difference for the size of the external diameter of each of the vessels between individuals with and those without a variation in their CAC.

A significant difference was found in the size of the external diameter of the P1 segment of the posterior cerebral artery between individuals with and those without variation in the CAC (p=0.047).

No statistically significant difference was found between:

- size of the external diameter of the vessel and age of the individual, and
- age of an individual and having a variation in the CAC

The Wilcoxon rank sum test was done on the non-normally distributed data. No statistically significant difference was found in the size of the external diameter of the vessel between individuals with and those without variation in the CAC.

4.2.3 Test 3: One way analysis of variance (ANOVA) and Kruskal Wallis test

No statistically significant difference was found for the size of the external diameter of the vessels between the locations of variations within the CAC.

4.2.4 Test 4: Chi-squared test

No statistically significant association was found between the following:

- presence of a variation in the CAC and the vessel being present or absent,
- presence of a variation in the CAC and hypoplasia of the vessel,
- presence of a variation and the sex of the individual,
- location of variation and the categorical variables (presence of vessels and hypoplasia of vessels),
- presence of a variation and the ancestry of the individual,
- size of the external diameter of the vessels and the sex of the individual, and

- size of the external diameter of the vessel and the ancestry of the individual

4.3 The patient sample

A total of 113 patient images were included in this sample. It consisted of 28 males (25%) and 85 females (75%). The demographics of the sample were tabulated in Table 4.4 as seen below.

Table 4.4: Demographics for the patient image sample

	Ancestry			**Total**
	Black	White	Coloured	
Male	7	0	21	28
Female	15	10	59	84
Total	22	10	80	112

The ancestry of one female could not be determined, thus she was excluded for the composition of the demographics of the sample.

4.3.1 Variations seen in the patient image sample

4.3.1.1 Typical arrangement of the circulus arteriosus cerebri

Figure 4.11 shows the typical arrangement of the CAC as seen in the patient image sample. Only two individuals had a complete CAC without hypoplasia and no extra vessels.

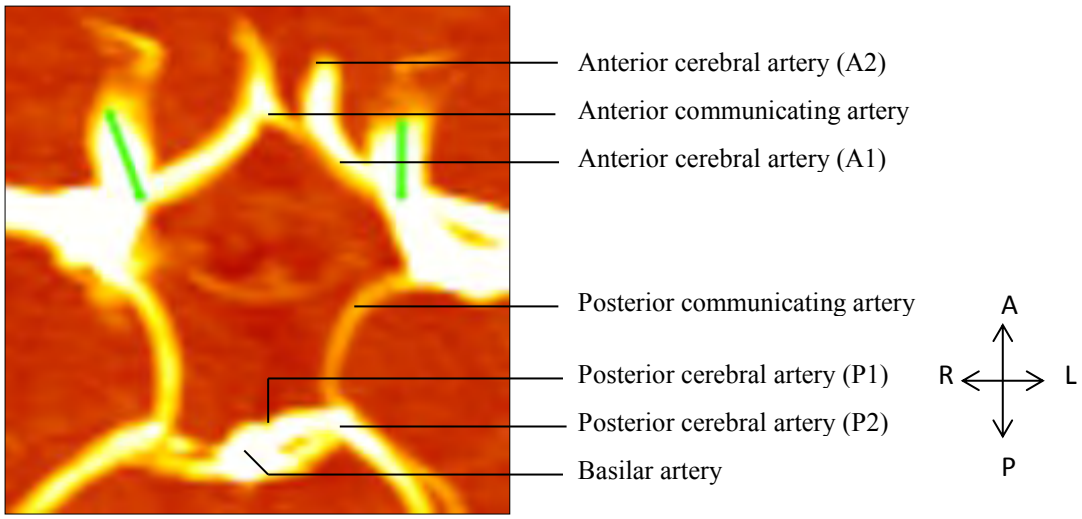


Figure 4.11: Patient sample - Typical arrangement of the CAC, green lines indicate the internal carotid arteries.

4.3.1.2.Variations in the anterior circulation of the circulus arteriosus cerebri

Figures 4.12 and 4.13 show variations most commonly seen in the anterior circulation of the circulus arteriosus cerebri.

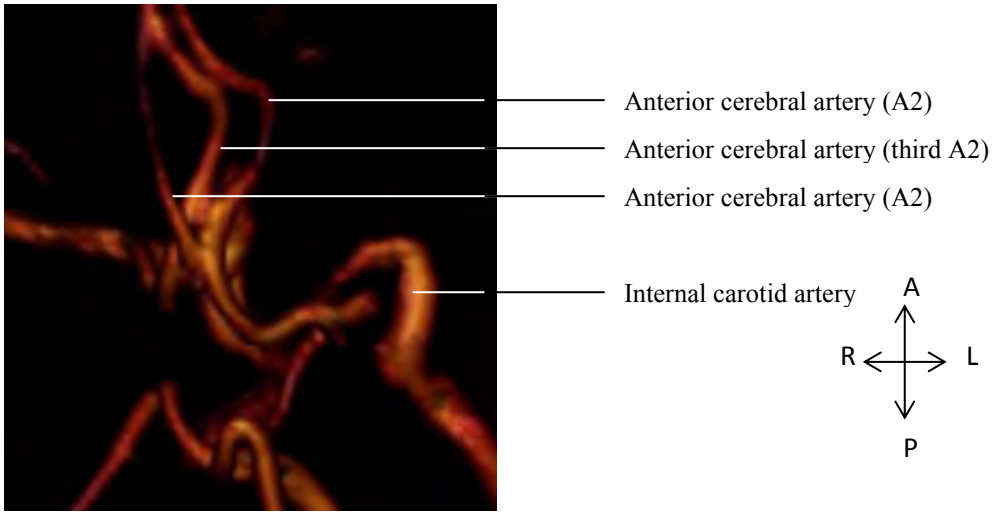


Figure 4.12: Patient sample - Trifurcation of the A2 segment of the ACA.

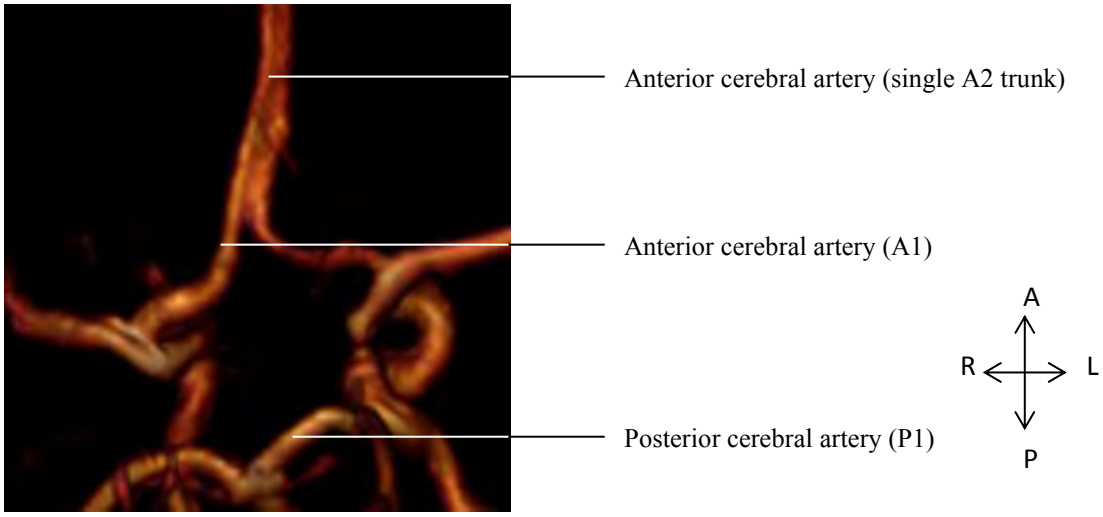


Figure 4.13: Patient sample - Single A2 trunk of the ACA.

4.3.1.3 Variations in the posterior circulation of the circulus arteriosus cerebri

Absence or aplasia of a vessel was commonly seen in the patient image sample, especially in the posterior circulation of the CAC. Most commonly the posterior communicating artery was aplastic, either unilaterally of bilaterally, as seen in Figure 4.14.

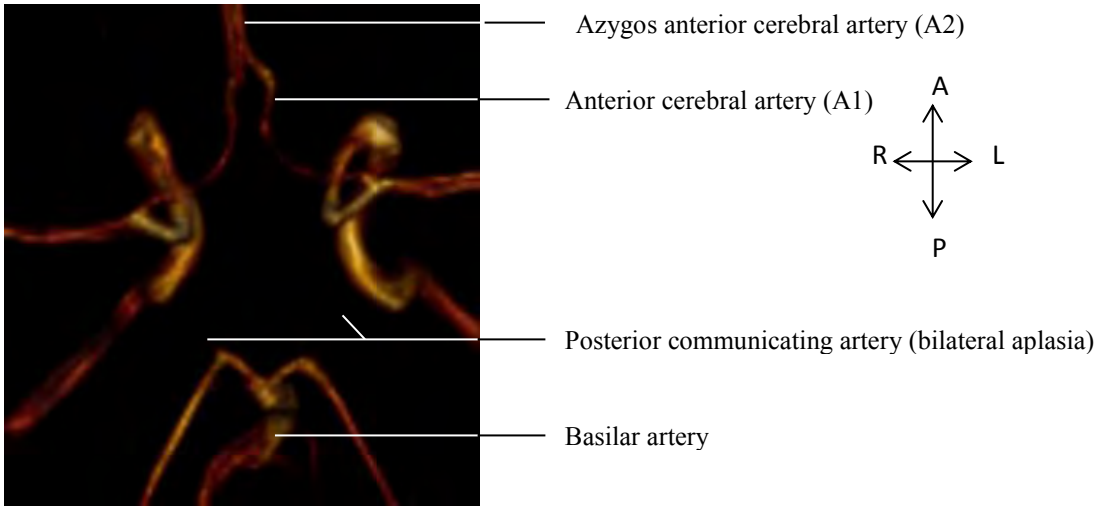


Figure 4.14: Patient sample - Bilateral aplasia of the posterior communicating arteries.

4.3.2 Aneurysms seen in the patient sample

Sixty-one aneurysms were documented for the patient sample. Thirteen images showed aneurysms in the anterior communicating artery, of which a typical example is shown in Figure 4.15.

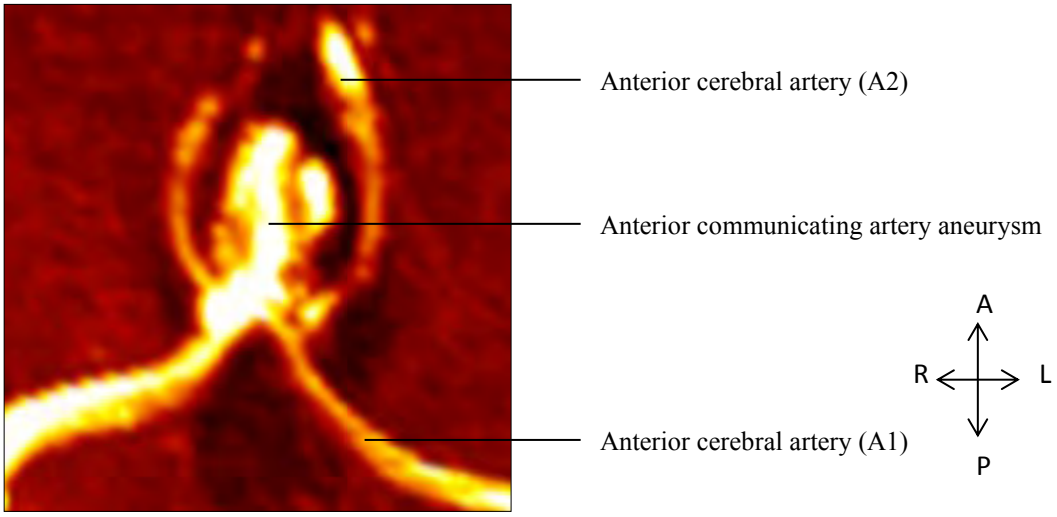


Figure 4.15: Patient sample - Aneurysm of the anterior communicating artery.

4.4 Statistical analyses of the patient image sample

Statistical analyses were done on the patient image sample using the statistical software STATA 13 (StataCorp, 2013). In reporting of the results of the analyses a maximum of three decimal places were retained. This was to accurately reflect if a statistically significant difference or association was found.

All information obtained from the patient image sample was statistically analysed for the presence or absence of a variation and for the location of a variation within the circulus arteriosus cerebri. For the patient image sample, the information was furthermore analysed for the presence or absence of aneurysms and the location of aneurysms in the circulus arteriosus cerebri.

Because it was not possible to obtain accurate measurements of the arteries on certain of the images, these were excluded from the statistical analyses. In addition, more of the images were excluded from the analysis because of the presence of extreme outliers in order to obtain meaningful results. Therefore 26 images were excluded and 113 images were included in the sample that was analysed.

Furthermore, for statistical analyses, the entire sample of images was divided into two groups, based on the individuals having either no variations, or one or more variations in the CAC. Those that had variations in the CAC were then further subdivided according to the number (single versus multiple) and location of the variations (see above, groups 1-8). Individuals were noted as having a variation (single or multiple) in the anterior circulation, posterior circulation or in both circulations. All numerical and categorical data was tested against the above-mentioned subgroups. As will be explained below, this was done in order to test whether there was a significant difference between vessel size and the absence / presence of vessels for the following variables: the presence of a variation and location of variation, presence / absence of aneurysms and location of aneurysm.

In the image sample, only two individuals were found to have a typical arrangement of the CAC. A sample of two is not large enough to allow statistical analyses, and therefore only the individuals with variations could be tested against the other variables listed in the preceding paragraph (n = 111).

4.4.1 Test 1: Shapiro-Wilk test for normality

The Shapiro-Wilk test for normality was done on the data by subgroup: having a variation and the location of variation within the CAC. Furthermore, for the information obtained from the images, data was also analysed with regards to the subgroups having an aneurysm and the location of aneurysms within the CAC.

In sorting by variation, it was found that the variables of the anterior communicating artery, the posterior communicating arteries and the P2 segment of the posterior cerebral artery were non-normally distributed.

In sorting by aneurysm, it was found that the variables of the posterior communicating artery on the left and right were non-normally distributed.

4.4.2 Test 2: Comparison of means

The size of the external diameter of the A1 segment of the ACA on the left was statistically significantly different between individuals with aneurysms and those without ($p=0.0374$). For the normally distributed data, no other significant difference was found for the size of the external diameter of a vessel and the presence of aneurysms.

The Wilcoxon rank sum test showed no significant difference in the size of the external diameter of the vessels and the presence of aneurysms for the non-parametric data.

4.4.3 Test 3: One way analysis of variance (ANOVA) and Kruskal Wallis test

The ANOVA showed no statistically significant difference for the size of the external diameters and the location of the aneurysm within the CAC.

The ANOVA showed a statistically significant difference for the external diameters of the A1 segment of the ACA on the left, the A1 and A2 segment of the ACA on the right and the P1 segment of the PCA on the right, and the location of variation.

The Kruskal Wallis test showed no significant difference in the size of the external diameters of the vessels and the location of aneurysms for the non-normally distributed data.

However, the Kruskal Wallis test did find a significant difference between the median size of the external diameter of the AComA and the locations of variations in the CAC ($p=0.021$). Thus, the median size of the external diameter of the AComA was significantly different between the locations of variation within the CAC.

4.4.4 Test 4: Chi-square test

The Chi-square test showed two associations between the following:

- location of the variation (in general) and the presence of an aneurysm ($p=0.026$), and
- presence or absence of the P1 segment of the PCA and the presence of an aneurysm ($p=0.003$)

No association was found between the following:

- any categorical variable and the presence of variations due to the high rate of variation within the sample. Only two of the patient images showed a CAC with a typical arrangement, and therefore the occurrence of variations in the sample was too common to test whether there was an association between the categorical variables (as listed in Appendix C on page 84) and the presence of a variation within the CAC. The image sample is biased in the sense that all the patients who underwent a MRI or angiogram may have had some form of an underlying pathology; therefore one could possibly expect a high occurrence of variation within this sample,
- categorical variables and the location of aneurysms, and
- any categorical variable and the location of variations

Chapter 5 : Discussion

5.1 The cadaver sample

For data to be normally distributed it should follow a characteristic bell shaped curve when plotted on a graph. A bell curve has one mode or peak, which will coincide with the mean and median of the data set; this is the centre of the curve where it is at its highest. A bell curve is symmetrical, thus, if folded along a vertical line at the mean, both halves would match perfectly.

The data for the posterior communicating arteries did not follow this shape, rather it is said to be bimodal, having two peaks and not the traditional one. The data for the posterior communicating arteries was analysed by studying the histograms, Q-Q plots and the box plots. These graphs clearly showed the data as being bimodal, as seen in Graphs 4.1 and 4.2 on page 53. This was due to the high number of individuals with hypoplasia of the posterior communicating arteries. Two peaks can clearly be seen on the histograms, the one peak indicating the individuals with hypoplasia and the other peak individuals with a larger, normal external diameter of the posterior communicating arteries. Thus there are two subgroups within the data for the posterior communicating arteries.

It was found that there is no significant association between the sexes and ancestry for the data. Thus, a white male has the same probability to have a variation in his arterial supply than a white female. The same could be said for the ancestry: a black female has the same probability to have a variation in her arterial supply than a coloured female.

For the statistical analysis of the cadaver sample groups 3 and 7 were excluded, because none of the individuals were found to have variations of these groups. Thus, this sample does not include any person with variations of the A1 segment of the anterior cerebral artery or variations of the internal carotid artery.

There was found to be a significant difference in the size of the external diameter of the P1 segment of the posterior cerebral artery between individuals with and those without variation in the CAC (p=0.047).

No significant difference was found between the variation groups and age or ancestry. It should be noted that age might play a role in the diameter of arteries, especially the luminal diameter. Older persons tend to have a smaller lumen in most of their arteries due to disease of the wall of the vessel e.g. atherosclerosis (Mathur *et al.,* 1963). None of the cadaver sample was noted to have any disease that had an impact on the diameter, either external or internal, of their arteries.

No aneurysms of the vessels studied were observed in the cadaver sample, thus the hypothesis that there is a correlation between arterial variation in the circulus arteriosus cerebri and cerebral aneurysms could not be tested. It has been estimated that intracranial aneurysms occur in 1-6% of the general population (as found by studies done in the USA and Kenya) (Ogeng'o *et al*., 2009; Keedy, 2006; Vega *et al.,* 2002). Thus, it was not expected (unlikely) to find an aneurysm in the cadaver sample of only 39. The cadaver sample has established a baseline of data, without aneurysms or pathologies, against which the clinical data, the image sample could be compared.

5.2 The patient sample

Most of the data for the patient image sample was distributed normally, following the characteristic bell shaped curve. In sorting by variation, it was found that the variables anterior communicating artery, the posterior communicating arteries and the P2 segment of the posterior cerebral artery on the left were non-normally distributed. Variations were present for all of the above-mentioned variables. The non-normal distribution of the data could be due to the small number of individuals within these variables, as seen in Table 5.1 below. Individuals with hypoplasia of the communicating arteries could be grouped together and individuals without

hypoplasia of the vessel could be grouped together. Furthermore, the high incidence of absence of the communicating arteries and the P2 segment of the posterior cerebral artery could also contribute to the non-normal distribution.

Table 5.1: Patient sample - Non-normal distribution of variables by presence of variation in the circulus arteriosus cerebri

Variable	p-value	Frequency
Anterior communicating artery	0.028	51
Posterior communicating artery on left	0.032	28
Posterior communicating artery on right	0.000	42
P2 of posterior cerebral artery on left	0.035	19

In sorting by aneurysm, variations in the diameters of the posterior communicating artery on the left and right were non-normally distributed. The non-normal distribution could be due to the small number of individuals grouped for these variables, see Table 5.2. Furthermore, the majority of aneurysms were found to be on the posterior communicating arteries.

Table 5.2: Patient sample - Non-normal distribution of variables by presence of aneurysms in the circulus arteriosus cerebri

Variable	p-value	Frequency
Posterior communicating artery on left	0.021	17
Posterior communicating artery on right	0.001	22

The size of the external diameter of the A1 segment of the ACA on the left was significantly different between individuals with aneurysms and those without (p=0.0374). The mean external diameter of the A1 segment of the ACA on the left in individuals with aneurysms was 1.299mm; which is larger than the mean external diameter of 1.155mm in individuals without aneurysms. The mean external diameter for the A1 segment of the ACA is not necessarily a true reflection of the internal diameter of the vessel (McGregor, 1987). Even though the individuals with

aneurysms had a larger mean external diameter, this does not necessarily imply they had a larger internal diameter. It could be that the individuals with aneurysms had narrower luminal diameters resulting in a higher pressure within the vessel and leading to formation of the aneurysm. What has been described for the common carotid artery (Polak *et al.,* 1996) is that atherosclerosis results in a narrowing of the lumen and therefore a compensatory increase in the mean external diameter of the blood vessels in order to compensate for the higher pressure, and this pathophysiology could be relevant here. The simplest explanation could also be that an individual in the sample simply had an extremely large external diameter of the vessel, thus increasing the mean vessel size for the entire group of individuals with aneurysms.

One way analysis of variance (ANOVA) showed a statistically significant difference for the external diameters of the A1 segment of the ACA on the left, the A1 and A2 segment of the ACA on the right and the P1 segment of the PCA on the right, and the location of variation. Thus, there was a significant difference in the size of the vessels and the location of variation within the circulus arteriosus cerebri for the above named vessels.

Based on these findings, it appears that the external diameter of vessels predisposes one to having an aneurysm. This being said, the external diameter of a vessel is not necessarily a true reflection of the internal diameter of the vessel (McGregor, 1987). An individual could have a large external diameter, but a narrowed internal diameter due to pathology, e.g. atherosclerosis. A similar set of explanations of the pathophysiological process as described in the paragraph above applies here as well (Polak *et al.,* 1996).

Variations were grouped as being in the anterior circulation, posterior circulation or in both. For the variables (i.e. external diameters of the A1 segment of the ACA on the left and right, A2 segment of the ACA on the right and P1 segment of the PCA on the right) the majority of the variations were within the anterior circulation of the circulus arteriosus cerebri, as shown in Table 5.3 below. The number of individuals

with variations in the posterior circulation was about equal to the number of individuals with variations in both circulations, as shown in Table 5.3. The significant change in the external diameters for the above mentioned segments compared to the different locations could be due to the majority of the variations being in the anterior circulation as compared to the posterior circulation or both circulations. The reason for the variations occurring more frequently in the anterior circulation is an area for further research.

Table 5.3: Patient sample - Number of individuals for each variable as per location of variation

Variable	Location of variation		
	Anterior circulation	**Posterior circulation**	**Both circulations**
A1 of anterior cerebral artery on left	96	7	8
A1 of anterior cerebral artery on right	92	7	9
A2 of anterior cerebral artery on right	47	4	7
P1 of posterior cerebral artery on left	89	7	9

The Kruskal Wallis test found a significant difference between the median size of the external diameter of the AComA and the locations of variations in the CAC ($p=0.021$). Thus, the median size of the external diameter of the AComA was significantly different between the locations of variations within the CAC. The majority of the variation was found in the anterior circulation of the CAC, as seen in Table 5.4. The significant difference could be due to the high number of hypoplastic vessels found in the anterior communication artery, which would contribute to the increase number of variation in the anterior circulation.

Table 5.4: Patient sample - Number of individuals for the different locations of variations in the circulus arteriosus cerebri

Location of variation	Frequency
Anterior circulation	41
Posterior circulation	4
Both circulations	6

The Chi-square test showed an association between the location of the variation and the presence of an aneurysm (p=0.026). Interestingly no significant association was found between having a variation of the CAC and the presence of aneurysms. It would seem that the location of variations plays a greater role in the development of an aneurysm, than the presence of the variation *per se*.

An association was also found between the presence or absence of the P1 segment of the PCA and the occurrence of an aneurysm (p=0.003). The only statistically significant association between variation of a vessel and the presence of aneurysms was found for the P1 segment of the posterior cerebral artery.

It would appear that the presence of an aneurysm is more likely in people who have only one P1 segment (103) as opposed to having none (8) or both (2), as shown in Table 5.5. A possible explanation for this is that the anterior circulation compensates for the reduced blood flow in individuals where there are no P1's. Having no P1 segment changes the direction of the blood flow within the circle. This change in haemodynamics could account for the greater association between aneurysms and absence of the vessels, putting greater pressure on the remaining blood vessels, causing them to balloon out quicker thus forming aneurysms.

Table 5.5: Patient sample - Number of individuals grouped as per the presence of the P1 segment of the posterior cerebral artery

P1 segment presence	Frequencey
Bilaterally present	2
Unilaterally presnt	103
Bilateral aplasia	8

In the typical arrangement of the CAC, blood flows from the basilar artery into the P1 segment of the posterior cerebral arteries and then either continues into the P2 segments or flows into the posterior communicating arteries. In cases where the P1 segment of the PCA is absent, blood cannot flow from the BA through the PCA to the PComA. The anterior circulation is able to compensate for this, via a process through which blood flows from the internal carotid arteries into the PComA's, as shown by the black arrows in Figure 5.1, to supply the P2 segments of the posterior cerebral artery if present. Alternatively, the PComA can continue to supply the area of the PCA, if the entire PCA is absent.

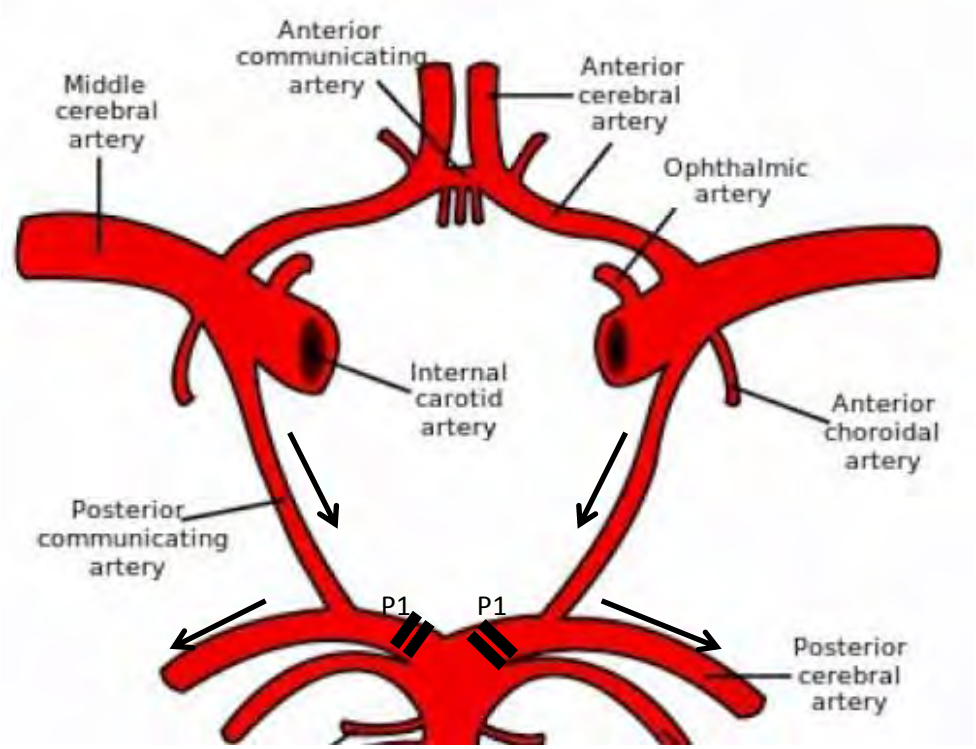


Figure 5.1: Anterior circulation compensating for absent P1 segment of the posterior cerebral artery, the black arrows represent blood flow from the ICA's into the posterior cerebral artery/-ies via the PComA's (Heimlich, 2013).

The Black population were under-represented in the cadaver sample, namely only five individuals, all of whom were male. These were the only cadavers in the Department of Human Biology available for dissection at the time of the study.

The White population was under represented in the image sample, with only 10 individuals, all of whom were female. Males were under-represented in the patient sample, comprising 28 males and 84 females. This could be due to different forms of health-seeking behaviour amongst males, such as a tendency to wait longer before seeking health care or go to the hospital for check-ups and medical tests (Harvard Health Publications, 2010).

5.3 Strengths, weaknesses and recommendations of project

The data obtained in this study is novel as it provides details specifically for a South African population, within the constraints of the varying sample sizes of the subdivisions into various groups based on ancestry.

This study is an expansion on the existing literature. Padget (1944) and other authors who preceded him described only the aneurysms that they could dissect at autopsy. Subsequent studies described aneurysms only when researchers happened to come upon them by chance through imaging or dissection. This study investigated aneurysms as an integral part of the CAC and provided detailed correlations between variations in the entire CAC and aneurysms found.

This study evaluated a large sample size, which included a basic anatomical description in a cadaver population and a clinical aspect through the study of images from patients that underwent a MRI or MRA at the Groote Schuur Hospital. The study also included descriptions of the entire CAC and its associated branches.

All available literature was either on patient or on cadaver brains. This study aimed to consolidate these two samples and report on similarities, differences and shortcomings.

Challenges in collecting data for this study included the difficulty in taking measurements of the arteries while the CAC was still attached to the base of the brain in the cadaver. Furthermore, a judgement call had to be made when a blood vessel was absent, i.e. was it removed during dissection or was it missing antemortem. For future studies it is advised that the CAC be removed from the base of the brain, cleaned and then be measured *ex situ*.

For analysis of the patient images, the measurements were taken on the TOF sequence of the MRI's and for future studies it is recommended that post contrast T1 sequences be used. The post contrast sequences more clearly show the vessel lumen, with minimal disturbance around it. Unfortunately, T1 post contrast sequences were not readily available at the time of the study, thus TOF sequences were used to visualize vessel diameter.

Under representation of the White population and overall under representation of males in the patient sample, made comparison for sex and ancestry more challenging. The Black population was also under represented in the cadaver sample, with only five males in the group. A more inclusive sample representative of the South African population is recommended for future studies.

Chapter 6 : Conclusion

To date, no accurate depictions of the circulus arteriosus cerebri in a South African sample have been available for use as a reference by health care professionals. This research project is the first to describe the different types of variations in the circulus arteriosus cerebri for such a sample. The variations that were found within the CAC were studied in detail and a list of 28 types was compiled in order to represent the complete range seen in this sample. Furthermore, there is no data on the incidence of cerebral aneurysms in a South African sample. This study documented the number of cerebral aneurysms and their location for this sample. In addition, the study documented the sex and ancestry of the individuals which are not consistently reported in the literature covering other studies of the CAC. Finally, based on the literature that was available for review in preparation for this project, this is the first study to incorporate information obtained both from cadavers and from images of patients for data collection and full analysis.

The aim of the study was twofold. Firstly, to determine if there was a correlation between arterial variations in the circulus arteriosus cerebri and the formation of cerebral aneurysms. If such a correlation was found, then to establish which type of variation had the greatest or least association with the formation and location of aneurysms in the circulus arteriosus cerebri.

The number of individuals with a typical arrangement of the circulus arteriosus cerebri was determined for the sample. The classic arrangement as described by Thomas Willis has always been accepted as the norm for humans. However, the results of this study shows that in the majority of cases there is at least some deviation from the classical description; with 111 of the 113 individuals in the image sample having one or more variation within the CAC. One could consider using the classical arrangement of the CAC as a framework for learning and teaching students the blood supply to the brain. Students should, however, be made aware of the fact that it is far more common to encounter variations in the classical pattern of the CAC, particularly in patients who present for imaging of the cerebral blood vessels.

The study found a significant difference in the size of the external diameter of the P1 segment of the posterior cerebral artery when comparing individuals with and without variations in the CAC. An association was also found between the unilateral presence of the P1 segment and the occurrence of aneurysms within the sample. It is speculated that the haemodynamic changes caused by the variation of the P1 segment may be responsible for the presence of aneurysms in this sample. In an individual undergoing a MRI or angiogram it is important to establish whether the P1 segment is absent on one or both sides, since this could be an indication of aneurysms within the CAC developing sometime in the future.

No association was found between the presence of variations (except for the variation in the P1 segment of the PCA) in the CAC and the occurrence of aneurysms. However, an association was established between the varying locations of variations and the occurrence of aneurysms. For example, variations of the A1 segment of the ACA on the left, the ACA on the right and the P1 segment of the PCA on the left. Health care professionals should ideally take note of the location of the variations within the CAC rather than merely establishing that the patient does have a variation because the location of a variation is thought to be a better indication of the occurrence of aneurysms than just the presence of a variation.

The location of variations within the CAC was found to have a significant association with the size of the external diameter of the anterior communicating artery. The size of the external diameter is important when determining whether a vessel can be classified as hypoplastic or not, based on the use of the term “hypoplasia” in this study, when referring to a decreased external diameter.

The luminal diameters of the various vessels of the CAC were not measured and therefore it was not possible to establish whether the internal diameter was a factor in the formation of aneurysms in this sample. Some international studies have reported that a decrease in luminal size is a factor in the formation of aneurysms. The association between the luminal diameters of vessels in the CAC for a local sample is therefore research work that could be pursued in another project.

In the current study, it was not possible to calculate the risk of individuals developing aneurysms due to the small sample size. In order to determine the risk of individuals developing cerebral aneurysms data should be collected on a larger sample, which is more representative of the South African population. Another research project could focus specifically on increasing the sample size to obtain an appropriate number of individuals to determine risk for the South African population.

For this study, regression analyses were used to determine whether variations in the CAC could be used as predictors for the presence of aneurysms. The resulting mathematical models were not fit for this purpose - the models showed false positives, thus predicting the presence of aneurysms when, in fact, there were none. Further analyses by a biostatician with expertise in the field of regression analyses are necessary to refine the models for better fit of the data.

The South African sample showed no significant association between variations in the circulus arteriosus cerebri and the occurrence of cerebral aneurysms. This finding differs from those in the literature on this topic. International studies have usually been performed on samples based in the northern hemisphere, except for the study by Baptista (1964) (Appendix A – in Brazil) and the study by Dimmick and Faulder (2009) (Appendix A – in Australia). Baptista did not report on aneurysms within the CAC, but only described variations of the anterior cerebral artery. Dimmick and Faulder (2009) performed a retrospective study on the literature and did not obtain their own measurements for statistical analyses. Therefore it is speculated that there could be one or more confounding factors when comparing the results from the studies seen in Appendix A with the results of the current study. This confounding factor(s) could be explored in a future study by doing analyses on two samples, one from each hemisphere, and comparing the results.

To determine whether there was an overall correlation between anatomical variations in the circulus arteriosus cerebri and cerebral aneurysms, all the above-mentioned associations were taken into account, i.e. both those found to be significant and those which were non-significant. No significant overall correlation was found between

variations in the CAC and the presence of cerebral aneurysms. A confounding factor may be present for the South African sample leading to the presence of variations and the formation of aneurysms. Further investigations are recommended in order to determine what these factors could be in a sample such as the present one.

Future research questions that arose from the study include:

- The relationship between sex and anatomical variation in the CAC
- Some ancestral groups in South Africa are more likely to have variation in their CAC that predisposes them to aneurysm formation
- The significance of the contribution of variation in the CAC to other cerebral pathologies, e.g. stroke, vascular dementias or psychological conditions

Chapter 7 : References

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APPENDIX A: Summary of findings by main international authors

Authors	Country of sample	Sample size	Individuals with variation (%)
Alawad *et al* (2009)	Sudan	143	28
Alpers and Berry (1963)	USA	350	48
Baptista (1964)	Brazil	381	25
De Silva *et al* (2009)	Sri Lanka	225	86
Dimmick and Faulder (2009)	Australia	300	Not available for this study
Eftekhar *et al* (2006)	Iran	102	63
Fisher (1965)	USA	414	70
Kamath (1980)	India	100	25
Kayembe *et al* (1984)	USA	44	88.7
Riggs and Rupp (1963)	USA	994	79
Swetha and Dakshayani (2011)	India	70	21

APPENDIX B: List of variations used in the current study

	Type of Variation:	**Definition:**
1	Typical	The configuration of the CAC is as originally described by Thomas Willis.
2	Azygous ACA/Median artery of the corpus callosum	The persistence of the embryonic median artery of the corpus callosum. Bilaterally, the anterior cerebral artery territories are supplied by a single midline A2 trunk.
3	Trifurcation of the ACA	Occurrence of three A2 segments of the ACA.
4	Bihemispheric ACA	Hypoplasia of one A2 segment with the contralateral A2 segment providing the major arterial supply bilaterally to the ACA territory.
5	Aplasia of A1 segment of ACA	Complete absence of the A1 segment of the ACA can be uni- or bilaterally.
6	Unilateral hypoplasia of A1 segment of ACA	The external diameter of the A1 segment of the ACA is less than 1mm, on one side.
7	Bilateral hypoplasia of A1 segment of ACA	The external diameter of both A1 segments of ACA is less than 1mm.
8	Unilateral duplication of A1 segment	Presence of two A1 segments of the ACA on one side.
9	Loop formation/fenestration of ACA	Part of the A1 segment of ACA is duplicated/ loop if formed in part of the A1 segment.
10	Hypoplasia of the AComA	The external diameter of the AComA is less than 1mm.
11	Duplication of AComA	Presence of two distinct AComA's.
12	Fenestration of the AComA	Duplication in part of the AComA.
13	Aplasia of the AComA	Absence of the AComA
14	Fetal origin of the PCA	The external diameter of the PComA is the same or greater than the ipsilateral P1 segment.
15	Unilateral hypoplasia of the P1 segment	The external diameter of P1 segment is less than 1mm, on one side.
16	Bilateral hypoplasia of P1 segment	The external diameter of both P1 segments are less than 1mm.
17	Aplasia of P1 segment	Absence of the P1 segment can be uni- or bilateral.
18	Fenestration of the PCA	Duplication in part of the P1 segment of the PCA.
19	PComA infundibulum	A funnel shaped region of dilatation is found at the origin of the PComA from the ICA.
20	Unilateral hypoplasia of the PComA	The external diameter of PComA is less than 1mm on one side.
21	Bilateral hypoplasia of the PComA	The external diameter of both PComA's are less than 1mm.
22	Unilateral aplasia of the PComA	Absence of one PComA
23	Bilateral aplasia of the PComA	Absence of both PComA's
24	Unilateral duplication of PComA	Presence of two PComA's on one side
25	Bilateral duplication of PComA	Presence of two PComA's on both sides

26	Fenestration of the PComA	Duplication in part of the PComA.
27	ICA agenesis	Congenital absence of the ICA can be uni-or bilateral.
28	Hypoplasia of the ICA	The external diameter of the ICA is less than 1mm.

APPENDIX C: List of categorical variables

Sex		**Race**		**Aneurysm/ Variation**	
1 =	Male	1 =	Black	1 =	Yes
2=	Female	2 =	White	2 =	No
		3 =	Coloured		

Location of aneurysm		**Presence of arteries**		**Hypoplastic**	
1 =	No aneurysm	1 =	Bilaterally present	1 =	Yes
2 =	MCA	2 =	Unilaterally present	2 =	No
3 =	AComA	3 =	Absent		
4 =	PComA			**Location of variation**	
5 =	BA tip			1 =	Anterior circulation
6 =	unknown			2 =	Posterior circulation
7 =	multiple			3 =	Both circulations
8 =	other				

APPENDIX D: Summary of information obtained from sample

Code	Age	Sex	Ancestry	Variation
A002	70	Male	Coloured	Yes
A008	42	Male	Coloured	Yes
A010	56	Female	Coloured	Yes
A011	63	Female	Coloured	Yes
A013	50	Male	Coloured	Yes
A016	51	Female	Coloured	Yes
A017	51	Female	Coloured	Yes
A018	43	Female	Coloured	Yes
A019	47	Female	Black	Yes
A020	58	Female	Coloured	Yes
A021	53	Female	Coloured	Yes
A022	58	Female	White	Yes
A023	51	Female	Coloured	Yes
A024	40	Female	Coloured	Yes
A026	30	Female	Black	Yes
A028	60	Female	Coloured	Yes
A029	44	Male	Black	Yes
A030	33	Female	White	Yes
A031	43	Female	Coloured	Yes
A032	46	Female	Coloured	Yes
A033	42	Female	Coloured	Yes
A037	18	Female	Black	Yes
A038	54	Female	Coloured	Yes
A039	58	Female	White	Yes
A040	69	Female	Coloured	Yes
A041	64	Male	Coloured	Yes
A042	78	Female	Black	Yes
A043	51	Female	Coloured	Yes
A044	30	Male	Coloured	Yes
A045	45	Female	Coloured	Yes
A047	62	Female	White	Yes
A048	60	Female	Coloured	Yes
A049	43	Male	Coloured	Yes
A050	40	Female	Coloured	Yes
A053	48	Male	Coloured	Yes
A054	72	Female	Coloured	Yes
A056	63	Female	Coloured	Yes
A057	38	Male	Coloured	Yes
A058	56	Male	Black	Yes
A059	66	Female		Yes

A060	46	Female	Coloured	Yes
A061	51	Female	Coloured	No
A062	60	Female	Coloured	Yes
A063	57	Female	Coloured	No
A064	32	Female	Coloured	Yes
A065	44	Male	Coloured	Yes
A066	44	Female	Coloured	Yes
A067	60	Female	Coloured	Yes
A068	60	Female	Coloured	Yes
A069	52	Female	Coloured	Yes
A070	43	Male	Coloured	Yes
A071	50	Female	Coloured	Yes
A072	46	Female	Coloured	Yes
A073	34	Male	Black	Yes
A075	44	Female	Coloured	Yes
A076	68	Female	Black	Yes
A077	55	Male	Coloured	Yes
A078	44	Female	Coloured	Yes
A080	58	Male	Coloured	Yes
A081	23	Female	Black	Yes
A082	22	Male	Black	Yes
A083	69	Female	White	Yes
A084	50	Female	Black	Yes
A085	54	Male	Black	Yes
A086	75	Female	Black	Yes
A087	48	Female	Coloured	Yes
A088	49	Male	Coloured	Yes
A089	69	Male	Coloured	Yes
A090	51	Female	Coloured	Yes
A091	54	Female	Coloured	Yes
A093	57	Female	Black	Yes
A094	37	Male	Black	Yes
A095	73	Female	Coloured	Yes
A096	50	Female	Black	Yes
A097	32	Female	Black	Yes
A099	56	Female	White	Yes
A100	55	Female	Coloured	Yes
A101	71	Male	Coloured	Yes
A102	46	Female	Coloured	Yes
A103	43	Male	Coloured	Yes
A104	73	Female	Coloured	Yes
A105	61	Female	Coloured	Yes
A106	48	Female	Coloured	Yes
A107	60	Female	Coloured	Yes
A108	44	Female	Coloured	Yes

A109	54	Female	Coloured	Yes
A110	50	Male	Coloured	Yes
A111	25	Female	Black	Yes
A112	44	Female	Black	Yes
A113	48	Female	Coloured	Yes
A114	16	Female	White	Yes
A115	51	Female	Coloured	Yes
A116	57	Female	White	Yes
A117	50	Female	Coloured	Yes
A118	56	Female	Coloured	Yes
A119	37	Male	Coloured	Yes
A120	70	Male	Coloured	Yes
A123	59	Male	Coloured	Yes
A124	21	Female	Black	Yes
A125	51	Female	Coloured	Yes
A126	42	Female	Coloured	Yes
A127	46	Female	Coloured	Yes
A128	69	Female	Coloured	Yes
A129	49	Male	Black	Yes
A130	43	Male	Coloured	Yes
A132	46	Female	Coloured	Yes
A133	46	Female	Coloured	Yes
A134	66	Female	Coloured	Yes
A135	49	Female	Coloured	Yes
A136	53	Female	White	Yes
A137	55	Female	White	Yes
A138	68	Female	Coloured	Yes
A139	72	Female	Black	Yes
Cadaver sample:				
B001	30	Male	Black	No
B002	30	Female	Coloured	No
B003	82	Male	White	No
B004	98	Female	White	Yes
B005	43	Male	Coloured	Yes
B006	70	Male	White	Yes
B007	37	Female	Coloured	Yes
B008	90	Male	White	Yes
B009	43	Female	Coloured	Yes
B010	78	Male	White	Yes
B011	33	Male	Coloured	Yes
B012	40	Male	Coloured	Yes
B013	27	Female	Coloured	Yes
B014	27	Male	Coloured	Yes
B015	57	Female	White	Yes

B016	66	Male	Black	No
B017	65	Male	White	Yes
B018	83	Male	White	Yes
B019	61	Male	Coloured	Yes
B020	66	Male	Coloured	Yes
B021	78	Male	White	No
B022	62	Male	White	Yes
B023	81	Male	White	No
B025	83	Male	White	Yes
B027	66	Male	White	No
B028	37	Male	Coloured	No
B029	45	Male	Black	No
B030	45	Male	Black	Yes
B031	90	Male	White	Yes
B032	69	Female	Coloured	Yes
B033	50	Male	Black	Yes
B034	56	Female	Coloured	Yes
B035	73	Male	White	Yes
B036	71	Female	White	No
B037	76	Male	White	Yes
B038	92	Female	White	Yes
B039	48	Male	Coloured	Yes
B040	82	Male	White	Yes
B041	57	Male	Coloured	Yes

APPENDIX E: Ethical clearance certificate

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsana@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 August 2014

HREC REF: 530/2014

Prof G Louw
Human Biology
Anatomy Building

Dear Prof Louw

PROJECT TITLE: CIRCULUS ARTERIOSUS CEREBRI: ANATOMICAL VARIATIONS AND THEIR CORRELATION TO CEREBRAL ANEURYSMS- MSc candidate Francesca Du Toit

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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 30th August 2015

Please submit a progress form, using the standardised Annual Report Form 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)

We also acknowledge the MSc student Francesca du Toit is also involved in this study.

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

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938