Variations in arterial supply via the external and internal carotid arteries to the bony orbit and eyeball in full-term fetuses, infants, children, adolescents, and adults – A South African perspective.

By

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Declaration

I, *Kentse Sana Mpolokeng*, hereby declare that the work on which this 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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Abstract

The anatomy of the orbital region is of great importance for many highly specialised clinical disciplines such as ophthalmology, maxillofacial surgery, and neurosurgery. The main source of arterial blood supply to the orbital region is by the ophthalmic artery, a branch of the internal carotid artery, and to a lesser extent by the anastomotic patterns which are formed through the external carotid artery. A range of arterial variations which may be developmental in origin, or which may develop due to pathologies later in life, may affect the ophthalmic artery in terms of its origin, course, and branching. If clinicians are not aware of the variations occurring in this region, the eye of the patient may be at risk of injury during invasive procedures, which may lead to partial or complete visual loss.

Up until the present time, there have been only a few cadaveric studies that revealed some of the variant patterns and the overall frequencies of the recorded anastomotic patterns for the orbital blood supply. Whilst the anatomical variations are known, the frequencies of variations in the population are not. Furthermore, no published data exists regarding the variations in the orbital blood supply in a South African population. Therefore, the aim of this study was to investigate the orbital vascular supply within the South Africans of different age groups, to document and describe any variations in anastomotic patterns and record their frequencies.

The current study was conducted through dissections of bodies in the Department of Human Biology, University of Cape Town, and patients' angiograms from Groote Schuur Hospital. The angiograms included data obtained from other hospitals within the Cape Town area and were reviewed retrospectively. The dissection sample included six full term fetuses and 63 adults, and the angiograms accounted for 870 individuals.

The ophthalmic artery was studied from the point of origin from the internal carotid artery and its course in relation to the optic nerve, and both sides were compared to note any similarities or differences. Statistical analyses were performed to record the frequencies of the patterns of variations and to note whether there were any associations between sex, age, sidedness, and these variations. The results revealed statistically significant associations between age and sex for the patterns of variation.

Several variations were noted in the current study. Among the novel findings were those in the origin of the ophthalmic artery from the internal carotid artery, whereby a lateral and inferior origin were recorded in both samples (dissected bodies and angiograms). In addition, it was noted that the ophthalmic artery may take origin from the A2 segment of the anterior cerebral artery, which is also a novel finding. This study, therefore, adds significantly to the current body of knowledge regarding the patterns of arterial supply to the ophthalmic region in a South African sample.

List of Abbreviations

A - anterior

a. - artery

ACAs – anterior cerebral arteries

AChA – anterior choroidal artery

AComA - anterior communicating artery

AEA - Anterior ethmoidal artery

Anat. F. - anatomic frequency

Ang. F. - angiographic frequency

AMA - accessory meningeal artery

Ant.S. - anterosuperior

BA - basilar artery,

CNS - central nervous system

CRA - central retinal artery

CRV - central retinal vein

COF - cranio-orbital foramen

CRL - crown rump length

CTA - computed tomography angiography

DICOM - digital imaging and communications in medicine

dIMA - distal branch of the internal maxillary artery

DNA - Dorsal nasal artery

DSA - digital subtraction angiography

ECA - external carotid artery

FA – facial artery

FPA - frontopolar artery

GSH - Groote Schuur Hospital

OA - ophthalmic artery

ON - optic nerve

MRA - magnetic resonance angiography

I - inferior

IAC - intra-arterial chemotherapy

ICA - internal carotid artery

ICA-O - internal carotid artery occlusion

ICS - intracranial space

IFA - infraorbital artery

ILT - inferolateral trunk
IMA - inferior maxillary artery
Inf. L. - inferolateral
inf. M. - inferomedial
IOS - intra-orbital space
IOV – inferior ophthalmic vein
L - left
LPCA - Long posterior ciliary artery
LS - lenticulostriate arteries
MCA - middle cerebral artery
MMA - middle meningeal artery
MPA - Medial palpebral artery
MRI - magnetic resonance imaging
MTF - modulation transfer function
N - nasal
OAC - ophthalmic artery chemosurgery
OC - optic canal
Occ.A - occipital artery
OFA - orbitofrontal artery
OlfA - olfactory artery
P - posterior
PA - pericallosal artery
PAA - posterior auricular artery
PACS - picture archiving and communication system
PCA - posterior cerebral artery
PComA - posterior communicating artery
PDOA - primitive dorsal ophthalmic artery
PEA - Posterior ethmoidal artery
Pit. Gland - pituitary gland,
PTA - polar temporal artery
PVOA - primitive ventral OA
R - right
RF - radiofrequency
S - superior
SOA - Supra-orbital artery
SOF - superior orbital fissure
SOV - superior ophthalmic vein

SPCA - Short posterior ciliary artery

Sup.Tr.A - Supratrochlear artery

StA - stapedial artery

Sup.TA - superficial temporal artery

Sup. L. - superolateral

Sup. M. - superomedial

T - temporal

TOF - time-of-flight

T1 - tesla 1

T2 - tesla 2

VA - vertebral artery

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CHAPTER 1: INTRODUCTION

The arterial supply to the peri-orbital region is complex with a range of variations. Some of these may be congenital, while others may develop later in life due to pathologies that may arise from certain disease conditions (Hayreh, 2006; Edizer *et al.,* 2009; Greene, 2011). The main contribution of the orbital blood supply is through the ophthalmic artery (OA), a branch of the internal carotid artery (ICA) and not so much through the patterns of anastomosis formed by the infra-orbital branch of the maxillary artery emerging from the external carotid artery (ECA) (Whitnall, 1923; Lemp and Snell, 1998; Hayreh, 2006; Bertelli, 2016). Hayreh (2006) stated that the abnormal origin of the OA from the ECA may also be explained by the comparative anatomy of the orbital arteries. For example, in lower animals, the OA is derived from the ECA and with increasing complexity across the animal kingdom, the OA tends to arise from the ICA instead of the ECA. In the intermediate species, both the external and internal OAs arise from the external and internal carotid arteries, respectively. According to Collin's dictionary, lower animals are defined as "relatively simple or primitive animals and not mammals or vertebrates" and the amphibians and reptiles are considered intermediate species (Collins, 2021).The external OA supplies the orbit and the internal OA supplies the eyeball with the anastomotic connection between the two maintaining circulation from either source (Hayreh, 2006).

Sometimes these orbital blood vessels present with pathologies that may lead to conditions that require interventions. The periorbital region may be affected by trauma, malignancies and ophthalmic pathologies which may lead to difficulties in treatment (Hayreh, 2006; Edizer *et al.,* 2009). Whilst anatomical variations are known, the frequency of variations in the population is not known and requires further studies to determine this, and the potential risk to the orbit/eye if this is not taken into account by clinicians (Bertelli *et al.,* 2017).

It would be important to further build on the body of knowledge as this may be useful to determine possible connections between the internal and external carotid systems contributing towards the intra-orbital circulation for application in surgical procedures. This knowledge may be helpful in procedures dealing with severe facial trauma affecting the orbital region where there is a need for emergency repair where a scan cannot be done prior to the surgical procedure. Additionally, it is helpful in cases where there is an ischaemic infarct in certain portions of the blood vessels of the eye aiding to prevent access to an area targeted for treatment. Lastly, infarction may also lead to impaired vision where certain portions of the retina receive an inadequate blood supply (Edizer *et al.,* 2009).

After a literature search was performed using various research platforms (EBSCOhost research database) of the general anatomical studies on intra-orbital blood supply, it became evident that no such study has been done in a South African sample. Most available published reports of the orbital vascular supply are from other regions of the world such as Italy (Edizer *et al.,* 2009), Asia (Bertelli *et al.,* 2016 and 2017) and North America (Bertelli *et al.,* 2016 and 2017). These studies were based on case reports describing some of the pathologies that were identified mainly during surgery. Meyerson and Lazar, (1971) state that retrospective studies of angiographic records for pathologies of patients who are undergoing treatment for intra-arterial diseases within the orbital region and several other pathologies that can be noted in post-mortem procedures should be studied. However, it is not yet known whether these findings are applicable to the South African population, therefore, prompting further investigation.

1.1 Background to the current study

Up until the present time, there have been only a few cadaveric studies that revealed some of the variant patterns and the overall frequencies of the recorded anastomotic patterns. According to Bertelli *et al.* (2016 and 2017), through their systematic review of the overall published studies globally including full-term fetuses, children and adults, no single study recorded the overall frequencies of the anastomotic patterns or provided population specific data. They were also limited to the geographical regions listed earlier. In the present study, the anastomotic patterns of the orbital vascular anatomy were investigated in full-term fetuses, infants, children, adolescents and adults in order to document the prevalence of variation in anastomotic patterns in a local sample across all listed age groups. Furthermore, knowing the specific individual pattern in a particular patient could improve outcomes in treatment, for example, in chemotherapy for retinoblastoma and for interventions treating intracranial aneurysms.

1.2 Age categories

The following are categories of age groups in life stages that were used in this study and assisted in the grouping of the sample:

i) full-term fetuses (deliveries between 37 and 41 weeks) (Spong, 2013),
ii) infants (0-3 years),
iii) children (4-12 years),

iv) adolescents (13-18 years) and
v) adults (19+ years) as categorised by Sacco, (2013).

1.3 Problem statement

The following gaps in the literature were identified:

- If clinicians are not aware of the possible variations at the site of origin of the OA, some magnetic resonance angiography (MRA), digital subtraction angiography (DSA) and the computed tomography angiography (CTA) endovascular or surgical interventions may put the arterial supply to the eye of the patient at risk of injury, which may lead to partial or complete blindness. The frequency of variations within the local sample (South African) needs to be documented and compared to published studies in other parts of the world.
- The anastomoses that may occur between the OA and the ECA represent a collateral pathway that may provide alternative routes for the blood supply of the orbit, but also for the passage of material during embolisation procedures of ECA branches.
- Information needs to be recorded about the frequency of variations in anastomotic patterns in the South African sample which will be compared with the international studies. This information will be useful for clinicians in South Africa and other anatomical studies on South African samples.
- Variations need to be recorded at the area of the anterior wall of the OA. There is an increased risk of aneurysms of the anterior wall of the ICA in the presence of an anomalous origin of the OA.

1.4 Aim

The aim of this study was to investigate the orbital vascular supply within South Africans of different ages, to document and describe any variations in anastomotic patterns. This would also determine whether there are any patterns of variation within the sample and whether the data obtained would be useful to clinicians.

1.5 Objectives

The following are the objectives of this study:

- To describe the anastomotic patterns between the ECA and ICA in both the left and right eyes and record the frequencies of variations in these patterns.

- To determine the observed patterns of anastomosis for the branches other than the ICA in both the left and right eyes and record the frequencies of variations in these patterns.
- To determine whether the variant anastomotic patterns occur either unilaterally or bilaterally. If the pattern is unilateral, determine whether it is more common in the left or right orbit.
- To determine if there is an association between age and the frequency of anastomotic patterns. This would help clinicians to be aware of the variations in certain age groups before performing any procedures.
- To determine whether there are differences in frequency of anastomotic patterns between males and females.
- To compare the findings of the current study with other published studies to add to the body of knowledge with respect to human variation.

Orbital lesions necessitating surgical intervention can be challenging in view of the restricted space available to the surgeon, and many of these are referred to the neurosurgeons for surgical management. In order for the surgical specialist to successfully work on the orbital region, they need to have thorough knowledge about the area and the possible variations that may be found in the region.

1.6 The importance of knowledge of the orbital anatomy

It is imperative that the surgeon is intimately familiar with the microsurgical anatomy of the area (in this case the orbital anatomy), before venturing into this complex region as an understanding of the local anatomical details is necessary to ensure optimal surgical results and minimising the risks of injuring the related anatomical structures (Govsa *et al.,* 2014). Dissections of the orbital region in cadavers would add to the existing knowledge of the morphological anatomy of the OA and related structures. This information would aid in building a database for the South African sample. Findings in the local sample were compared with studies in other parts of the world to establish whether there were any variations found in the present study that has not been reported elsewhere. Furthermore, it would be used to determine whether any variations reported by other authors are not present in the South African sample.

As the orbital region may present with several pathologies, Pai and Nagarjun, (2017) describe the spaces within the orbit (Figure 1.1) which are common sites of occurrence of orbital pathologies as follows:

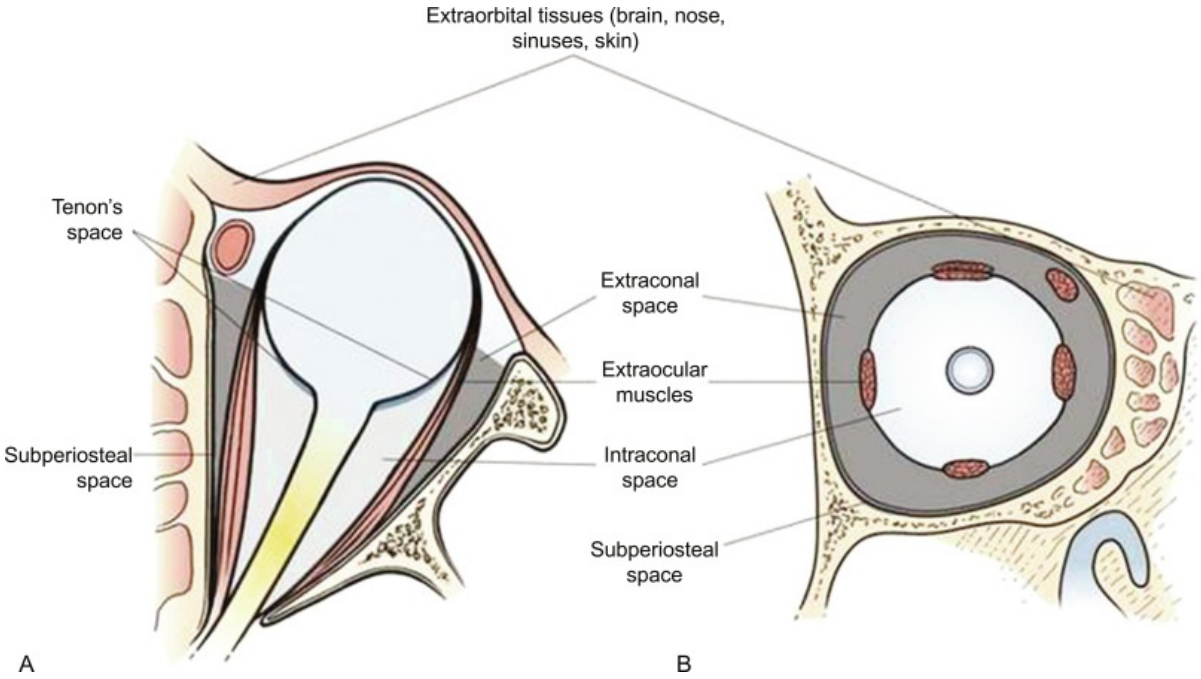

Figure 1.1: *Anatomy of the orbital surgical spaces.*

By permission from Elsevier. Piniara and Geogalas, (2021). A) Axial view and B) Coronal view of the orbit.

i) The subperiosteal space:
   - the space between the orbital bony wall and the underlying periorbita,
   - harbours bony tumours and dermoid cysts

ii) The peripheral surgical (extraconal) space:
   - space between periorbita and the muscular cone,
   - is the site of occurrence of cavernous angiomas, fibrocystic histiocytomas and lacrimal gland tumours

iii) The central surgical (intraconal) space:
   - the space inside the muscular cone,
   - harbours optic nerve tumours (glioma and meningioma), cavernous angiomas and neurilemmomas

iv) Tenon's space (intra-ocular space):
   - space separating the capsule from the outer surface of the sclera
   - harbours intra-ocular tumours

These spaces are filled with neurovascular bundles and, therefore, when working on these regions, one needs to have an extensive knowledge of the anatomical structures of the area. It is, however, beyond the scope of this dissertation to discuss all the orbital pathologies in detail. The only orbital pathology that will be discussed is retinoblastoma as the subjects

represented in the group of children during data collection represented those undergoing the intra-arterial chemotherapy treatment.

1.7 Retinoblastoma

Retinoblastoma is one of the commonest paediatric intra-ocular malignant tumours worldwide which accounts for up to 1% of all infancy tumours . This tumour often presents in the first two to three years of life and may occasionally present later. In Africa, retinoblastoma is the one of the common and life-threatening childhood cancers, accounting for 10-15% of childhood cancers overall (Parulekar, 2010; Meel *et al.,*2012 and Goolam *et al., 2018*). Although the survival rate of retinoblastoma cases in the high income countries is at 95%, the survival rate at 50% worldwide (Leal-Leal *et al.,* 2004). Early diagnosis and prompt treatment is crucial in saving both vision and the life of the patient. Leukocoria followed by strabismus (squint) is the most common presenting sign for retinoblastoma (Ibrahim *et al.,* 2019). Most cases are detected in advanced stages in developing countries, with those diagnosed at early stages being able to still achieve a prolonged period time free of pathology (Leal-Leal *et al.,* 2004). Meek *et al. (*2014) further states that a combination of factors such as poverty, low levels of literacy, alternate medical systems and lack of access to healthcare facilities and resources explains the high rate of progressed disease stages in low income countries.

James Wardrop was a surgeon who described retinoblastoma as an entity for the first time in 1809. He further demonstrated the extension of the tumours to the optic nerves and brain, and described metastases to different parts of the body (Albert, 1987).

1.7.1 The classification of intra-ocular retinoblastoma

An international classification for intra-ocular retinoblastoma has been developed, taking in consideration number of factors which may have effect on the treatment outcome (Table 1.1). Grading of the patient and the a description of the size of the tumour and degree of spread are recorded. Murphree (2005) used foveola instead of fovea centralis.

Table 1.1: The international classification of intra-ocular retinoblastoma (Murphree, 2005).

Group	Sub-group	Quick reference	Specific features
A	Very low risk	Small tumours	Retinoblastoma below 3mm in size and located 1.5mm from the optic nerve and 3mm from the foveola
B	Low risk	Larger tumours Macula Juxtapupillary Subretinal fluid	Retinoblastoma above 3mm in size Macula retinoblastoma location (below 3mm to foveola) Juxtapupillary retinoblastoma location (below 1.5mm to disc) Clear subretinal fluid below 3mm from margin
C	Moderate risk C2 C2 C3	Focal seeds	Discreet retinoblastoma with or without subretinal fluid less than 1 quadrant and, Subretinal seeds below 3mm from retinoblastoma Vitreous seeds below 3mm from retinoblastoma Both subretinal and vitreous seeds below 3mm from retinoblastoma
D	High risk D1 D2 D3	Diffuse seeds	Retinoblastoma with or without subretinal fluid greater than 1 quadrant and, Subretinal seeds greater than 3mm from retinoblastoma Vitreous seeds greater than 3mm from retinoblastoma Both subretinal and vitreous seeds greater than 3mm from retinoblastoma
E	Very high risk	Extensive retinoblastoma	Extensive retinoblastoma occupying over 50% of globe or Tumours touching lens. Diffuse infiltrating tumours, tumours involving anterior segment, neovascular glaucoma, tumours necrosis with aseptic orbital cellulitis, pthisis bulbi or opaque media from haemorrhage

In addition to the classification of the intra-ocular retinoblastoma is the staging of retinoblastoma.

1.7.2. The five stages of retinoblastoma

Retinoblastoma has five stages of disease and the timing of presentation for treatment will determine the survival rate (Goolam *et al.,* 2018). Meel *et al. (*2012) state that if the retinoblastoma is not treated in a timely fashion, it has a potential to spread to others sites such as the central nervous system (CNS) along the optic nerve (ON), bone marrow through blood, and lymph nodes via the lymphatics. The stages of retinoblastoma are based on the systemic extent of the tumours and thus foretells survival (Meel *et al.,* 2012). Staging is based on the changes in tissue structure and results from scans, taking in consideration the observation that extra-ocular retinoblastoma with spread to regional lymph nodes has an overall survival rate that is similar to non-metastatic extra-ocular retinoblastoma (Chantada *et al.,* 2006 and Meel *et al.,* 2012).

Table 1.2 is a summary of the stages of retinoblastoma. This summary gives an extension of the stage and how the eye is treated.

Table 1.2: The international retinoblastoma staging system (Murphree, 2005).

Stage	**Description**
Stage 0	Patient is treated conservatively. No enucleation (one or both eyes may have intra-ocular disease)
Stage I	Enucleation, tumours completely resected
Stage II	Enucleation with microscopic residual tumours
Stage III	Regional extension Overt orbital disease Preauricular or cervical lymph node extension
Stage IV	Metastatic disease Heamatogenous metastasis • Single lesion • Multiple lesion CNS extension • Perichiasmatic lesion • Leptomeningeal disease

1.7.3 Genetics of retinoblastoma

Knudson (1971) states that retinoblastoma to sometimes has a genetic basis with a classic Mendelian autosomal dominant pattern. Furthermore, the loss of the RB1 gene that normally

materialise leads to this autosomal dominant pattern. The RB1 gene was believed to be significant in retinal cancers only, and it is now recognised that the loss of this gene is an important step in the development of most adult non-ocular cancers (Knudson, 1971). The RB1 gene which is found on chromosome 13q14 consist of 27 exons. This gene is a tumour suppressor and its absence leads to an aberration of chromosomes which increase, and leads to the start, development and finally metastasis of the tumour (Ibrahim *et al.,* 2019). The retinoblastoma tumours is caused by an RB1 constitutional mutation (M1) on one allele followed by a somatic RB1 mutation on the other allele (M2), leading to loss of function of the retinoblastoma protein and initiation of the tumour (Ibrahim *et al.,* 2019).

About one third of retinoblastoma tumours occur bilaterally with a median age of one year at the time of diagnosis and carry a germ line RB1 mutation. The other two thirds of the tumours occur unilaterally, have some somatic inactivation of both RB1 alleles, occurring with a median age of two years at the time of diagnosis. Furthermore, 14% of the retinoblastoma tumours are hereditary, whereas mostly 86% are non-hereditary (Ibrahim *et al.,* 2019). The retinoblastoma heredity role was however not appreciated until the 19th century because of imprecise definition of the disease and non-survivors (Albert, 1987). It was illustrated that patients with heritable retinoblastoma are extremely prone the develop other non-ocular cancers. The heritable retinoblastoma is explained as heterozygous at the retinoblastoma locus and having one chromosome containing the tumours-predisposing allele and the other one with the normal allele (Abramson *et al.*,1976). Friend *et al. (*1986) and Francis *et al. (*2012) noted that patients with the RB1 germ line are able to pass on the mutations to their descendants with a great prospect of developing secondary tumours.
Therefore to enhance the clinical standard of managing the affected patient and members of their family at risk, a complete identification of the RB1 mutations in each family with retinoblastoma is crucial (Friend *et al.,* 1986 and Francis *et al.,* 2012). Thus, genetic counselling and prenatal testing for pregnancies that are at risk is important (Ibrahim *et al.,* 2019).

1.7.4 Diagnosis of retinoblastoma

As Meel *et al. (*2012) stated, the retinoblastoma is generally diagnosed on indirect ophthalmoscopy. Furthermore, clinical analysis in the form of imaging is performed in the following:

- when cases are complex and to be diagnosed accurately
- if an opaque media preventing indirect ophthalmoscopy

- evaluation of the presence of extra-ocular extension or associated cerebral lesions in trilateral cases. James *et al. (*2010) explains trilateral cases as primary midline intracranial tumour in the presences of a unilateral or bilateral retinoblastoma

The imaging diagnosis of retinoblastoma is based on documentation of an intra-ocular mass with calcification through an ultrasound. However if calcification is not detected on ultrasound, a recommendation for a CT scan is made (Meel *et al.,* 2012). The CT scan is used more extensively in the low income countries because of their access. Moreover, because CT scan may pick up an extra-ocular extension in a greater number of the cases. MRI is deemed to be highly reactive in detecting an extra-ocular extension and some cases are more likely to go undetected if an MRI is not done routinely (Meel *et al.,* 2012). An MRI has advantage of revealing a tumour with secondary retinal detachment such as Coat's disease, primary hyperplastic vitreous and retinopathy of prematurity. An increased risk of survivors developing secondary malignancies later is observed in cases where a CT scan is carried out in patients with bilateral retinoblastoma. This comes as a result of exposure to the ionising radiation, whereas MRI does not carry such risk and is currently used as the standard imaging modality to rule out an extra-ocular extension (Murphree *et al.*, 2006). The disease is staged based on the findings of the clinical and imaging procedures once a diagnosis is confirmed, and intra-ocular retinoblastoma is categorised in order to decide on suitable treatment (Meel *et al.,* 2012).

1.7.5 Incidence of retinoblastoma cases

The worldwide incidence is 1 in 15 000 to 20 000 live births per annum without taking sex or ancestry into consideration (Goolam *et al.,* 2017). Several reports show that in Africa, many studies have been performed on factors such as incidence, inheritance pattern, treatment outcomes and secondary cancers as a result of metastases of the retinoblastoma (Stiller *et al.,* 1996; Bowman *et al.,* 2008; El Kettani *et al.,* 2014; He *et al.,* 2014; Kruger *et al.,* 2014; Hill *et al.,* 2016; Goolam *et al.,* 2017; Parkin and Stefan 2017).

A study by Goolam *et al. (*2017), in Pretoria South Africa, reported a recording of 282 retinoblastoma cases over a 20-year period. About 40% of cases are bilateral and 60% are unilateral. A haematogenous spread to bones, lungs and abdominal solid organs comes as a result of the tumour extending along the ON to involve the central nervous system (CNS) or through the choroid in advanced cases (Goolam *et al.,* 2017). Investigations can be done by means of computer tomography (CT), digital subtraction angiography (DSA) or magnetic

resonance (MR) scans (Goolam *et al.,* 2017). Within the last 40 years, retinoblastoma evolved from being fatal cancer to a mostly treatable cancer. The current procedures aim to salvage the eye and provide the best visible results as possible (Parulekar, 2010). There are various modalities of treatment available such as laser therapy, cryotherapy, radiotherapy, chemotherapy and lastly enucleation.

1.7.6 Treatment of retinoblastoma

In 1809, James Wardrop proposed a novel treatment in that early enucleation of the involved eye might save the life of the patient. However, this did not resolve the problem as the disease returned and the patient died (Albert, 1987). Following this type of treatment was first attempt to treat the retinoblastoma by radiation with x-rays, carried out by H.L. Hilgartner in 1903 (Albert, 1987). After treatments with 84 x-rays, the patient was unfortunately lost in follow-up (Albert, 1987).

In 1919, Schoenberg described the use of radiation therapy with bilateral retinoblastoma in which one eye with a large tumour was enucleated and the other with a smaller tumour was treated by radium therapy after which the tumour regressed. Three years after treatment the child had good vision. The patient had a cataract removal performed 10 years after initial therapy and in 1944, a “scar tissue sarcoma” *(sic)* evolved over the temporal portal being used during the radium therapy which led to the death of a patient due to metastatic disease (Albert, 1987, Verhoeff, 1921 and Reese, 1951).

In 1921, Verhoeff reported on a patient who had been treated with x-irradiation. In this case, the right eye was enucleated and the patient received sub-erythema dosage exposure in the left eye and was reported to have maintained good visual acuity in the years between 1921 and 1977. The tumour recurred in 1980 and immediate enucleation was performed (Albert, 1987).

In 1930, Moore and colleagues developed a pioneering work to make use of radioactive isotopes to destroy the retinoblastoma by means of implantation of a radon seed through the sclera puncture (Moore *et al.,* 1931). Followed by this was a development by Carl Kupfer in 1953, the first ophthalmologist to combine chemotherapy through the use of a nitrogen mustard agent intravenously with radiation therapy (Kupfer, 1953). The technique was then abandoned as patients developed immediate side effects including even death. Eventually he recognised that the externally administered radiotherapy dose could be reduced safely and effectively with no chemotherapy use (Abramson, 2005).

In the 1990s, clinicians throughout the world began using systemic chemotherapy for treatment of intra-ocular disease (Abramson, 2005). This technique is used in patients with bilateral retinoblastoma and those of unilateral retinoblastoma in stages I,II or III with hope of shrinking the tumour and treating focally. In the stages IV and V tumours, it is used with the aim to avoid enucleation or external beam radiation. The main focus of treatment is to preserve the life of the patient and the secondary aim is to salvage the eyeball and vision in the affected eye (Meel *et al.,* 2012). A plan of treatment is designed in a joint effort with the ophthalmologist, paediatric oncologist and paediatric radiation oncologist using three modalities of treatment: surgery, chemotherapy and radiotherapy.

Intra-arterial chemotherapy (IAC) has become the most significant advancement in the interventional radiological technique. This procedure involves the delivery of a high dose of the chemotherapy agent into the OA by means of a cannulated transfemoral artery (Parulekar, 2010).

1.8 Knowledge of the blood supply to the head and neck regions

An extensive understanding of the arterial supply to the head and neck is important when treating cases related to the orbital region. This will likely limit injury to the blood vessels which could lead to acute haemodynamic and airway compromise from bleeding, as well as compromised flow of blood or embolism leading to visual deficit (Taylor *et al.,* 2015). The origin of the OA is sometimes closely related to the sphenoid bone. That being the case, it must be taken into account that it poses a chance of the OA and ON being involved in sphenoid sinus disease (Hayreh, 2006). Furthermore, knowledge of the detailed anatomy of the region will speed up the process of making a precise prognosis and angiographic analysis in what can be a critical time if a patient is actively bleeding (Taylor *et al.,* 2015). Injury to blood vessels would also present with a laceration leading to contrast medium leakage from a vessel, and preventing the vessel from revealing the desired route of treatment.

A single artery provides blood to the orbit, eyeballs and all surrounding orbital contents, but it must always be taken into account that there may also be further anastomotic patterns in this region. These arteries are at risk of being damaged because they may be hidden from view during surgery (Govsa *et al.,* 2014). Therefore, an investigation of the anastomotic arteries, their course in the orbital wall and the branching pattern and frequency of their existence should also be considered.

1.9 The importance of anastomotic patterns

The OA has a substantial anastomotic network that reacts protectively in the case of occlusion. These anastomotic networks divide into both deep and superficial branches (Kotsiomitis *et al.,* 2015). Several authors have described the OA as having anastomoses with branches of the ECA, e.g. the middle meningeal with the recurrent meningeal, the facial with the frontal or dorsal nasal, and the superficial temporal with the supraorbital artery (Hayreh, 2006; Bertelli *et al.,* 2016 and 2017). Further details about these anastomoses are covered in Chapter 2. These anastomotic patterns, therefore, need to be remembered while doing embolisation procedures to help avoid any possible complications. Typically, the anastomotic patterns are not visualised on the cerebral angiograms but may be discovered during embolisation (Govsa *et al.,* 2014). In cases of the cranio-orbital foramen (COF), there may be unexpected bleeding during surgical interventions to the lateral wall of the orbit due to rupture of or damage to an anastomotic artery (Govsa *et al.,* 2014). Embolisation of the orbital region is risky as in other cases where there may be a central retinal artery occlusion (CRA) which could result in the patient losing their eyesight (Kotsiomitis *et al.,* 2015).

The concept of functional vascular anatomy was initiated by Lasjaunias and Berenstein in the 1980s in order to analyse the arterial anatomy of the head and neck by their territories. The three regions within these territories that serve as the major extracranial and intracranial anastomotic patterns are as follows:

i) The orbital region through the OA is the interface between the internal maxillary and the internal carotid territories.
ii) The petrous-cavernous region through the inferolateral trunk (ILT), the petrous branches of the ICA and the meningohypophyseal trunk to the ICA (Figure 1.2).
iii) The upper cervical regions through the ascending pharyngeal, the occipital and the ascending and deep cervical arteries to the vertebral artery.

Several imaging diagnostic modalities such as MRA, DSA and CTA have been of great value in the investigation, diagnosis and management of cerebrovascular disease (Winn, 2017).

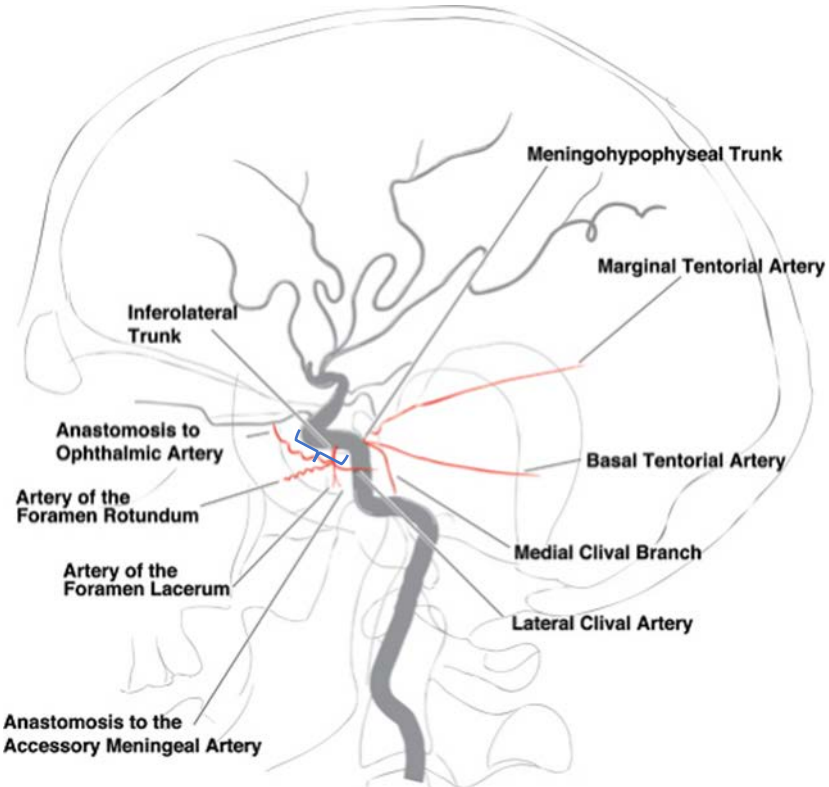

Figure 1.2: *Angiographically visible branches of the cavernous internal carotid artery.*

Modified from Lasjaunias and Berenstein, (1982). Cavernous internal carotid artery indicated by blue bracket.

1.10 A brief history on angiography and imaging

Angiography use for study of the vascular system by means of the radiopaque contract media in the clinical setting dates to the 1920s (Hurst, 2003). The novel work in angiography was done by Egaz Moniz in 1927 where he reported the first angiogram of the cerebral circulation for clinical imaging in cerebrovascular disease. Furthermore, Egaz Moniz first described the angiographic appearance of the OA in 1934 (Di Chiro, 1961; Hurst, 2003). Curtis (1949), Schurr, (1951) and Toti (1956) have additionally reported the angiographic observations on the normal OA and its branches.

Since then, several methods were used until the development of non-ionic contrast materials became available. These materials led to more high-level angiographic imaging techniques which have made cerebral angiography a safe and routinely performed procedure that provides precise information on the cerebral vasculature (Hurst, 2003). Cerebral angiography is a technique that was developed by Seldinger in 1953. The procedure is commonly carried out through the femoral artery by means of a puncture (Hurst, 2003).

1.11 The importance of neuroradiological imaging

Cerebrovascular diseases and lesions result in the disruption to the intracranial blood vessels and affect their capacity to deliver oxygenated blood to the brain (Winn, 2017). Treatment of cerebrovascular diseases and lesions requires a precise pre-operative anatomic evaluation to determine the appropriate surgical or endovascular treatment procedure. Advances in all facets of neurosurgery have improved the surgical results and lowered the morbidity and mortality rates (Katterner *et al.,* 2004). Various available diagnostic modalities allow for the evaluation of patients with neurological diseases and enable non-invasive visualisation of the inside of the body. Detection of such diseases, abnormalities, the diagnosis management and treatment of patients all over the world is thus possible (Winn, 2017). The very small anatomical structures, in this case, the OA, can better be visualised by neuroradiological imaging as this helps with precision in identification close to that obtained by the anatomical dissections (Viorel *et al.,* 2018).

1.12 The benefits of working on computed tomography angiography, digital subtraction angiography and magnetic resonance angiography

Three types of imaging modalities were used to gather patient data for this study and are discussed below.

1.12.1 Computed tomography angiography (CTA)

The most widely used imaging modality is CTA, which is a quick, non-invasive imaging modality with excellent spatial and temporal resolution. Modern computed tomography (CT) scanners can provide sub-millimetre isotropic three-dimensional datasets within a single breath-hold during the first intravenous infusion of the iodinated contrast medium (Murphy *et al.* 2018).

The earliest CT scanner was developed by Sir Godfrey Hounsfield in 1967. Independently of this, Allen Cormark developed a CT scanner for brain imaging in 1972 (Dolmatch, 2005). Many hours were required for scan time and days of computation in order to supply the complete image of skull, brain and the cerebrospinal fluid by means of tomographic slices (Dolmatch, 2005). Distinctive images were produced and for the first time enabled visualisation of the soft tissues within the skull, with both the contrast medium and spatial resolution which could not be achieved with other tomographic techniques (Dolmatch, 2005).

In the mid-1980's, the CT scanners still worked in the same way as previous scanners by obtaining images slice by slice, with incremental table movement followed by one circular revolution of the x-ray/detector array gantry around the patient for each image. The provided series of relatively thick and discontinuous slices were produced through the slow body scanning (Dolmatch, 2005).

In the early 1990's, the first helical CT scanners were first introduced in the clinical practice using the slip-ring mechanism that allowed the x-ray tube/detector array gantry to rotate continuously while the patient was moved through the scanner. The continuous scanning shortened the study times compared with nonhelical scanners. The applications used by the early helical scanners were relatively slow when producing the image (Dolmatch, 2005).

In the mid-1990's, the advancement of computers could provide large image data sets of which may be constructed into a CTA image using a dedicated workstation. However, only one image could be acquired during gantry rotation as the scanners were still too slow. Most gantry spin times had reached a lower threshold of 0.5 seconds to one second (Dolmatch, 2005).

In the late 1990's the arrival of multiple rows of detectors were introduced which could produce many images through a single helical revolution. The improved Z-axis resolution and decreased scan time came as a result of multiple slices acquisition. This enabled scanning via the lengthy body compartments by means of acceptable volumes of rapidly delivered intravenous contrast medium (Dolmatch, 2005). In the 2000's, most single-detector array helical CT scanners were replaced with the multirow detector units (Dolmatch, 2005).

In recent years, the scanners have progressed from 64- row detector scanners up to 256-slicer scanners which are now widely used to perform CTA of the coronary and peripheral arteries (Dolmatch, 2005; Mishra *et al.,* 2017). Scanning time has also been rapidly reduced. Scanning the peripheral arteries from the skull base to the common femoral arteries with collimation of 0.5mm to 1mm takes no longer than 12 seconds. The images are typically superior to those obtained using invasive angiography (Dolmatch, 2005; Uricchio *et al.,* 2019). Among the commonly described disadvantages of CTA in the literature is the suboptimal evaluation of severely calcified arteries, as this will lead to inaccurate grading of the stenosis (Ota *et al.,* 2004). However, with recent developments in technology, images obtained on a 256-slicer scanner are of high resolution and thin, and it is possible to obtain a scan in true arterial phase which can improve the assessment of calcified vessels (Mishra *et al.,* 2017).
Additionally, in the last decade, the important advances in the CTA have resulted in it becoming the first line method for neurovascular imaging and is the highly utilised imaging

modality for the evaluation of most orbital pathologies (Figure 1.3) (Wells, 1989; Zhang *et al.,* 2015). Added advantages include assessing arteries as small as 1mm in diameter, showing the lumen of an artery and is a fast, low-cost tool that is generally accessible for intracranial aneurysm detection (Kumamaru *et al.,* 2010; Kuruoglu *et al.,* 2016).

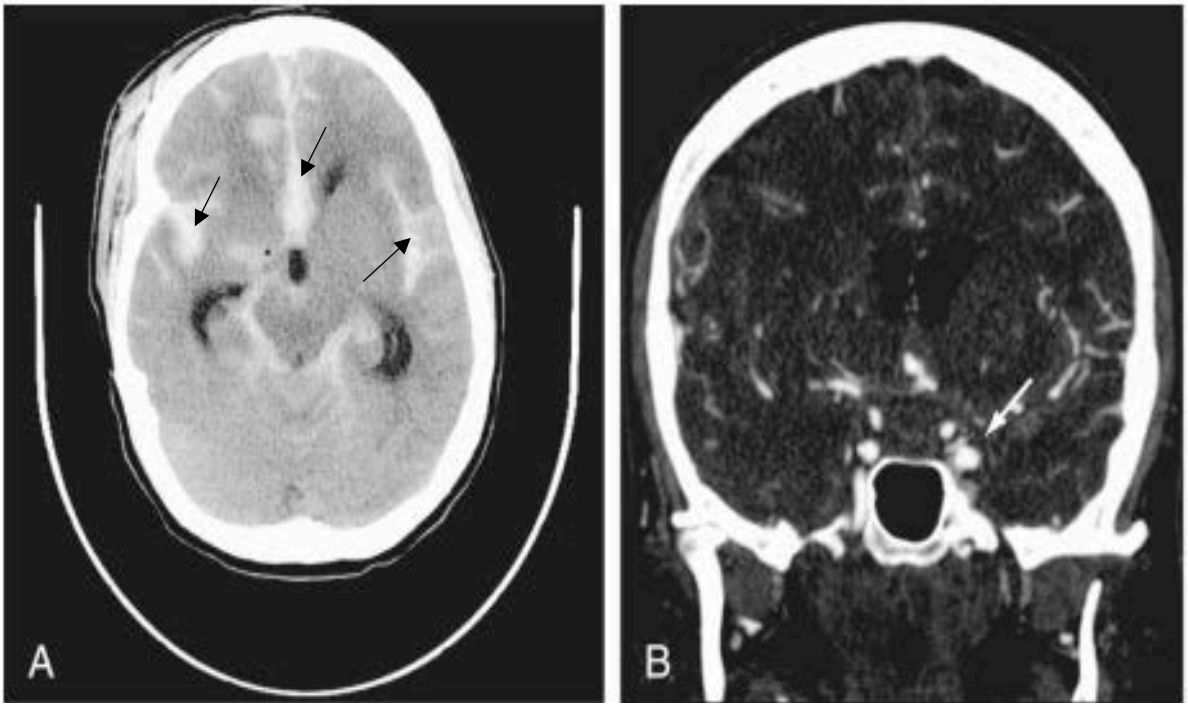

Figure 1.3: *Non-contrast enhanced computed tomography images of the head.*
By permission from Elsevier. Winn, (2017). A) An illustration of subarachnoid haemorrhage (black arrows), B) Coronal 2-dimensional image of the brain with an aneurysm in the artery (white arrow).

CTA is a less harmful method that is used more progressively in establishing the obliteration of aneurysms post-clipping. With its nature of being minimally invasive, CTA carries a reduced danger for patients developing neurologic difficulties and exposes patients to less ionising radiation (Uricchio *et al.,* 2019).

The metrics of CT image quality focuses on the ability to work out and illustrate tissue differences. These three common and functional metrics as stated by Murphy *et al. (*2018) are:

i) **Spatial resolution** measures the smallest high-contrast object illustrated by the CT system and it largely depends on the detector collimation and reconstruction kernel. Spatial resolution can also be described in terms of the modulation transfer function (MTF) of the system. The MTF describes how well the CT scanner can separate objects with different spatial frequencies. Larger objects with poorly defined edges have predominantly low spatial frequencies; small objects with sharp edges have higher spatial frequencies,

ii) **Temporal resolution** is used particularly for cardiac imaging. Dual-source CT provides the best temporal resolution available by using two radiation sources to simultaneously acquire different data projections and volume coverage. Multi segment reconstruction increases the patient radiation dose compared with single-segment reconstruction and is prone to artefacts from beat to beat variation. Adaptive segmented reconstruction can compensate for some cardiac irregularity artefacts and improve sensitivity, specificity, and accuracy in the detection of significant stenoses when compared with the half-scan reconstruction of the same data and
iii) **Volume coverage** is the z-axis coverage per gantry rotation which plays a large role in obtaining the CTA.

The diagnostic sensitivity of CTA was reported to be between 70 and 96% depending on the size and location of the pathology (Kuruoglu *et al.,* 2016). The CTA data sets can be used to treat an aneurysm and thus avoid only performing diagnostic DSA (Kuruoglu *et al.,* 2016). Furthermore, CTA has a high utility and some abnormalities determined by CTA have a strong prognostic value (Kuruoglu *et al.,* 2016; Uricchio *et al.,* 2019). Nevertheless, CTA still has a reduced reactivity to detect aneurysms less than 3mm in size despite the mentioned technical advances. CTA may also be lacking in detection of arterial branches incorporated into the aneurysmal sac, and as a result, this affects surgical decision making (Kuruoglu *et al.,* 2016; Uricchio *et al.,* 2019).

Lastly, the connection of suitable clinical data with the results from relevant imaging studies allows for a specific diagnosis to be ruled out in most of the paediatric orbital pathology cases (Wells *et al.,* 1989).

1.12.2 Digital subtraction angiography (DSA)

DSA is another diagnostic technique that provides superior quality in interventional radiology for visualising smaller blood vessels (Zhang *et al.,* 2015). DSA eliminates radiopaque structures such as bone by digitally subtracting the pre-contrast mask image from angiographic images acquired following injection of contrast medium into vessels through catheterisation and offers critical information particularly by improving the delineation of small and peripheral vessels. When appropriate, these blood vessels are critical anatomical landmarks during interventional procedures on the body under radiographic guidance (Tateishi *et al.,* 2020). DSA is an emerging technology that has many characteristics in common with the development of the CT scanner during the 1970's (Harrington and Murray, 1982). DSA integrates the digital data collection and computer processing to produce an

image. In the DSA imaging interpretation, the x-ray signals are detected electronically rather than on film and are converted to a digital form to be processed by a computer before being displayed (Pelz, 1985).

DSA units became available in the 1980's which makes obtaining of angiographic images much faster when compared with standard film-screen technique. DSA marked the new era in both the diagnostic utility of x-ray angiography and the ability to perform minimally invasive endovascular procedures in the angiography suite (Teitelbaum, 2000). This technique furthermore made the storage of the large number of angiographic images generated during a single case far more efficient.

DSA is the most sensitive imaging modality in the evaluation of extra- and intracranial vascular lesions such as aneurysms and arteriovenous malformations (Zhang *et al.,* 2015; Kuruoglu *et al.,* 2016). DSA is part of a larger phenomenon known as digital radiology computer assisted technique for its function of integrating digital data collection and computer processing for image production (Figure 1.4) (Harrington and Murray, 1982).

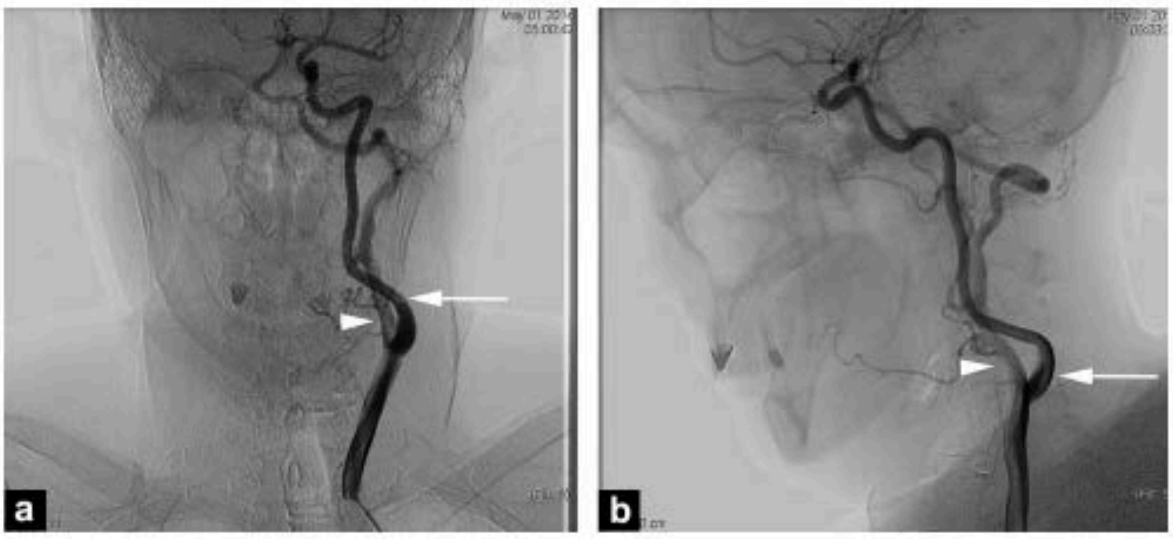

Figure 1.4: *A digital subtraction angiograph of the head and neck showing the internal carotid artery.* **By permission from Elsevier. Iana *et al. (*2016).** a) Anteroposterior projection, b) lateral projection. white arrow and arrowhead = the intersegmental artery.

In cerebral angiography, DSA is advantageous in separately evaluating all three phase of injection i.e. arterial, venous and capillary (Bashir *et al.,* 2018).
The first step is the process of image subtraction (also known as time or temporal subtraction). In this step, an image has to be obtained before the arrival of contrast material at the area of investigation, then one or several images are acquired after the arrival of a contrast bolus and

are placed into a second digital memory. The second operation occurs after subtraction and is an expansion of the dynamic range of the subtracted image which results in the enhancement of the final image. Subtraction and enhancement are performed in real-time, which means that the processing of data is sufficiently rapid so that the results are available in time to influence the clinical examination. DSA may be performed in several different modes and serial imaging is the most common mode used where image acquisition rates can be relatively low (from one to eight images per second) (Harrington and Murray, 1982). One of the advantages of using DSA is that smaller volumes of dilute contrast material can be channelled through smaller and softer catheters as a result of the delicate contrast resolution provided by the computer enhancement (Pelz, 1985).

Some of the limitations of using DSA are that is expensive, requires invasive arterial access and brings an associated risk of between 0.1% and 2.6% morbidity and mortality in healthy patients but increases 2.5-fold in patients above 60 years of age with occlusive cerebrovascular disease (Zhang *et al.,* 2015; Kuruoglu *et al.,* 2016). Sedation is administered to patients undergoing DSA, which then exposes them to the risks associated with use of anesthetics. Additionally, direct consequences of the DSA procedure is that it can cause neurological complications lasting only for a short time or permanently (Uricchio *et al.,* 2019).

1.12.3 Magnetic resonance angiography (MRA)

MRA is a magnetic resonance imaging (MRI) non-invasive technique that has become essential in the visualisation of structural and functional information involving the human body. An MRI further allows for evaluation of many types of cerebrovascular diseases and can also distinguish vascular flow from the surrounding tissues (Ai *et al.,* 2012; Fink and Fink, 2018). MRA is currently routinely used as a non-invasive imaging tool in the cerebral vasculature (Figure 1.5).

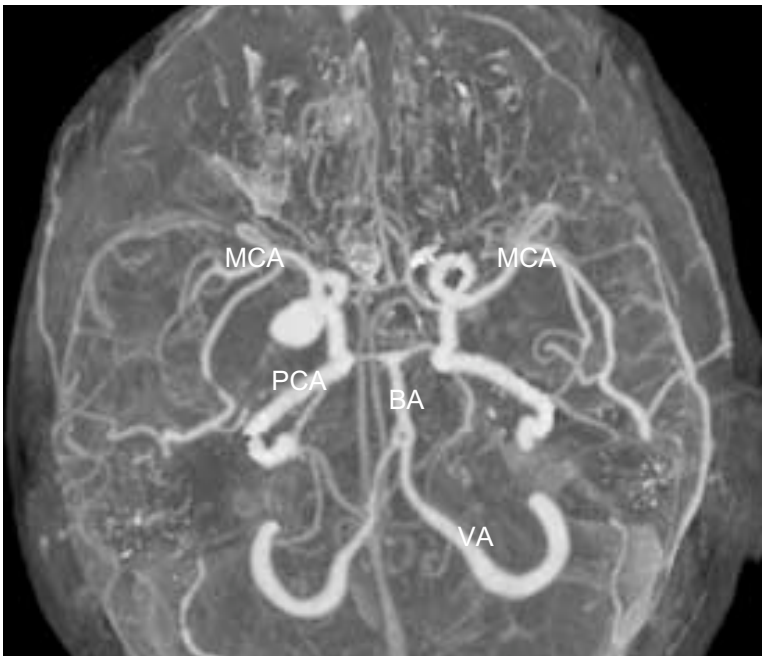

Figure 1.5: *A magnetic resonance angiogram demonstrating the posterior circulation contributing to the arterial circle of the cerebrum.*

Modified from Jones *et al.* (2021). MCA = middle cerebral artery, PCA = posterior cerebral artery, BA = basilar artery, VA = vertebral artery

MRA arrived relatively late to the diagnostic radiology world. Paul Lauterbur first demonstrated the use of nuclear MR to create images in 1973 (Edelman, 2014). In the 1980's, the MR angiographic technique came into use following the pioneering work by Paul Lauterbur and MRA has subsequently grown to become more accurate, thereby increasing its role in non-invasive vascular imaging (Teitelbaum, 2000 and Edelman, 2014). Since the initial use of MRI in the early 1980's, this has undergone marked development in the diagnosis and treatment of a wide variety of medical conditions (Ai, *et al.,* 2012). By the year 2010, there were thousands of MRI scanners (mostly with high to very high field strength) used to perform approximately 30 million MRI examinations worldwide (Edelman, 2014). Engineers, physicists and radiologists have further invented different techniques, pulse sequence strategies and hardware components that aided in reducing the times for obtaining the images. These techniques also aided in enhancing image quality and facilitated the advanced functional and anatomic imaging (Ai *et al.,* 2021).

MRI often provides further characterisation of space occupying lesions. Routine cerebral MRA does not require the use of intravenous or intra-arterial contrast agents (Wells, 1989) as non-contrast MRA depends on tagging moving protons and relies on inherent inflow for visualising vessels (Fink and Fink, 2018). Figure 1.6 shows an example of the MRI in axial view.

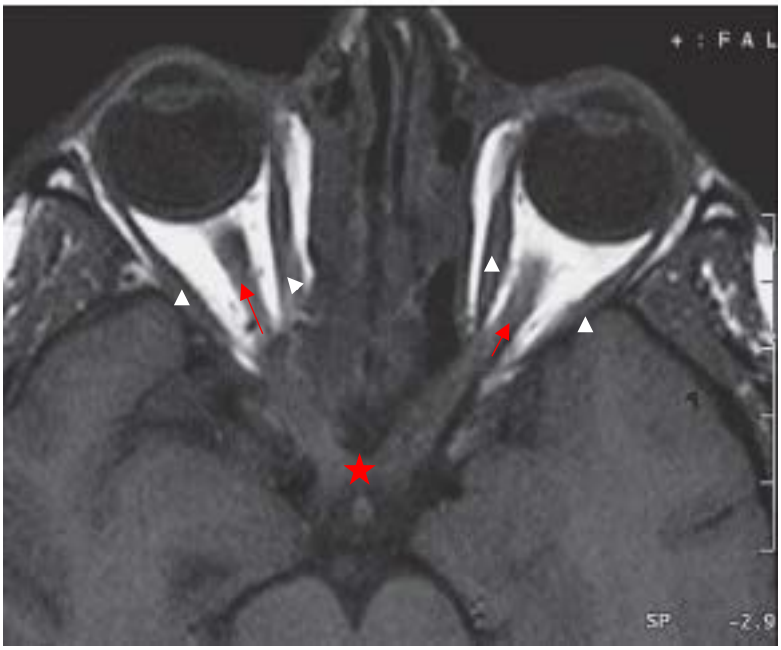

Figure 1.6: *An example of a magnetic resonance angiogram showing an axial view of the anatomy of the orbits.*

Modified from Grant (2021). white arrowheads = extra-ocular muscles, red arrows = optic nerve, red star = optic chiasm.

Contrast-enhanced MRA is similar to CTA in that vascular visualisation relies on contrast opacification, thus the contrast-enhanced MRA is dependent on accurate contrast bolus timing for the acquisition of high quality imaging (Fink and Fink, 2018). Thulborn (2008) states that the capability of MRI to diagnose an acute stroke is not in debate, even though its function in the acute stroke management of is still minimal. Furthermore, MRA is a visualisation of the haemodynamic flow using imaging techniques that discriminate flowing spins in blood from those in stationary tissue. Spins are the fundamental property of particles that make up the nucleus of an atom (Kiruluta and Gonzalez, 2016). The nucleus of an atom contains protons which are positively charged particles and neutrons which neutrally charged particles. A spin (Figure 1.7) is a rotation of the nucleus around its axis which in combination with the charge of the nucleus gives that proton a magnetic property (Pooley, 2005).

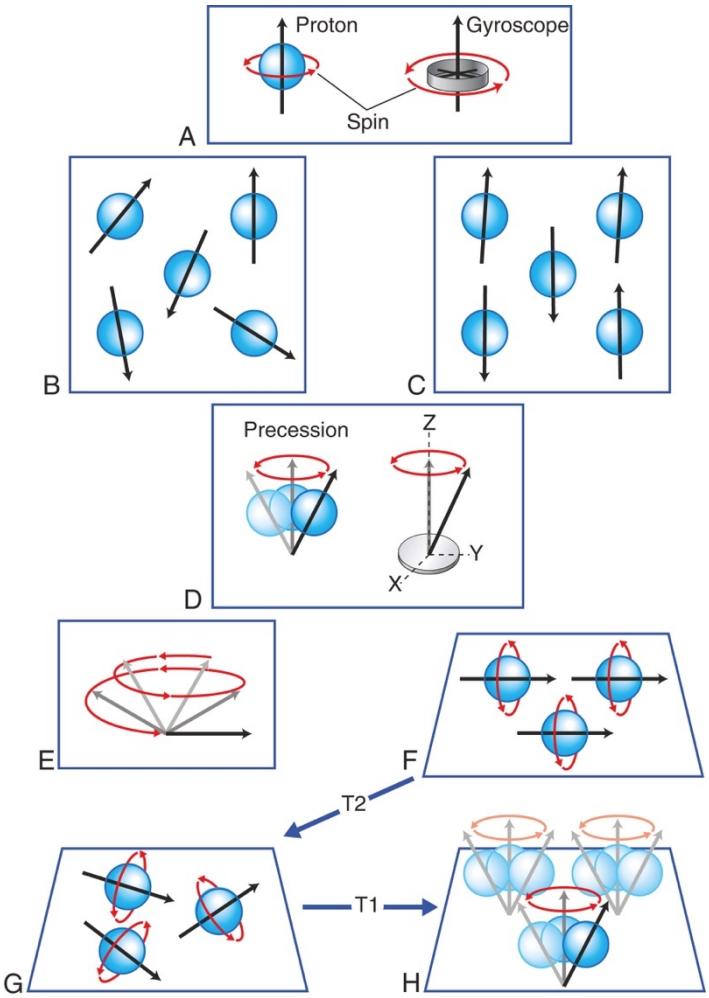

Figure 1.7: *An illustration of nuclear spins in the magnetic field showing proton orientations indicated by arrows and its manipulation by radiowaves.*

By permission from Elsevier. Mtui *et al.* (2021). A) The hydrogen nucleus proton is in a constant state of spin, analogous to that of a gyroscope B) the orientation of the axes of the spinning protons is random (at rest) C) all the axes become oriented along its longitudinal, z axis the moment an external magnet is switched on. Most are parallel with a small antiparallel, as indicated D) The magnetic moments precess around the axis like a wobbling gyroscope immediately, being oriented in an intermediate state between the z axis of the magnetic field and the x–y axis at right angles to it E) An excitatory radiofrequency pulse at right angles to the axis of the external magnetic field tips the net magnetic moment along a 'snail shell' spiral into the x–y plane F) While the radiofrequency transceiver pulse is 'on', the nuclei are precessing in phase G) When the radio frequency is switched off, it allows the nuclei to dephase immediately, with a brief T2 time constant H) Conical precession is resumed under the influence of the external magnet with a longer T1 time constant.

MR images are based on the time-of-flight (TOF) (gradient-echo sequence) which is based on the idea of tesla. There are two types of tesla, namely, T1 and T2. T1 refers to the rate of longitudinal relaxation recovery and T2 refers to the rate of transverse relaxation. Both T1 and T2 measure the magnetic strength and determine the tissue contrast (Winn, 2017). T1 works together with T2 for image acquisition as protons return to equilibrium while energy is released simultaneously (Choy and Hayano, 2017). T1 is used for MR images where flowing water is

effectively shorter than that of stationary water (Kiruluta and Gonzalez, 2016). The difference can be attributed to the fact that when stationary the spins would be saturated by the radio frequency excitation, but when flowing fresh, spins with full magnetisation would replace the stationary spins thereby increasing the signal (Kiruluta and Gonzalez, 2016). Blood flowing through the vessel is not refocused, since, by the time 180˚ pulse is applied, the segment of blood for a given slice has moved onto a subsequent slice segment (Kiruluta and Gonzalez, 2016).

TOF-MRA, on the other hand, is non-invasive, non-contrast-enhanced MRA technique which provides contrast between blood vessels and stationary tissues by inducing blood inflow effects (Yamamoto *et al.,* 2016). Laub and Kaiser first introduced the TOF-MRA in 1988 (Ai *et al.,* 2012). Since the cerebral arterial blood flows in the following directions: anteroposterior, supero-inferior and transverse directions, three directions are also used in performing the TOF-MRA of the intracranial blood supply (Fink and Fink, 2018).

All MRI systems use the resonance of the hydrogen nucleus because it is easy to detect the MR signal. Constant magnetic fields such as the electromagnet, a permanent magnet assembled from ferromagnetic material, and a superconducting magnet are used for creating signals (Winn, 2017). The hydrogen nucleus has the largest magnetic moment of any nucleus and is therefore the most detectable. The hydrogen natural abundance is also high at 99.99%. Lastly, water is a molecule made up of hydrogen and oxygen, which is high in concentration in the body; in the brain, the concentration of water is approximately 67% by weight (Winn, 2017). According to Hall and Hall (2021), the body fluid is distributed mainly between two compartments: the extra- and intracellular fluid. The interstitial fluid and blood plasma forms the divisions of the extracellular fluid. About 28 to 48 litres of fluid in the body are inside the trillions of cells and is collectively called the intracellular fluid, which constitutes about 40% of the total body weight in an average person (70 kg) (Hall and Hall, 2021). Furthermore, all the fluids outside the cells are collectively called the extracellular cells which account for about 20% (14 litres) of body weight in an average person (Hall and Hall, 2021).

An MRI has three gradients namely x, y and z (Figure 1.8) which serve two purposes. Firstly, it limits the excitation to one plane or slab if a radiofrequency (RF) pulse is transmitted during the time that a gradient is applied. Excitation will affect only one slice of the slab, the thickness of which depends on the amplitude of the gradient and the bandwidth of the RF pulse (Winn, 2017).

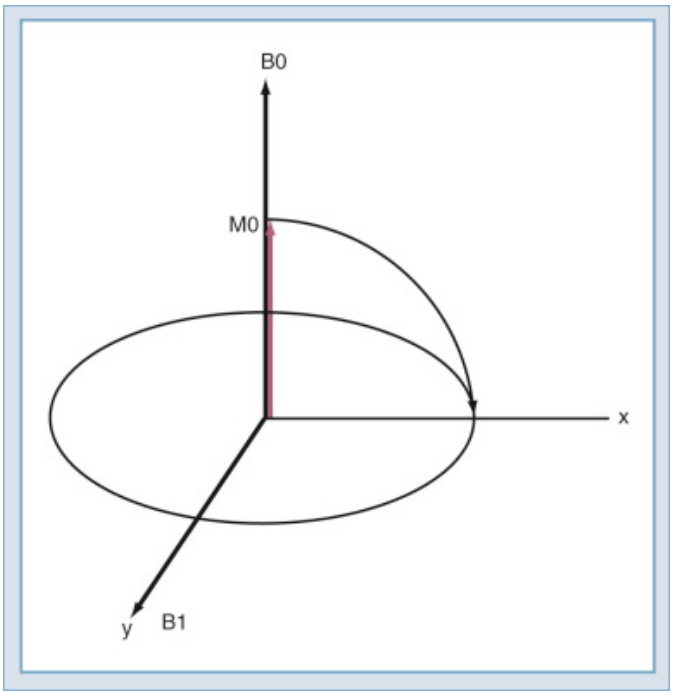

Figure 1.8: *An illustration of the radiofrequency magnetic field.*

By permission from Elsevier. Winn, (2017). B0= constant homogenous magnetic field; B1= energy field applied; M0= transverse magnetic field.

Secondly, the MR gradient serves the purpose of encoding the spatial location of spins to form the MRI (Winn, 2017). In a slice, the two directions of encoding required are frequency and phase. To establish location along the frequency-encoding axis, a gradient is applied during the signal readout time. To encode the orthogonal axis, a gradient is applied somewhere between the time of excitation and reception and is called phase encoding. One unique value of phase encoding is applied each time that the readout gradient is applied. The excitation and readout must be repeated to make an image (Winn, 2017).

1.13 Summary

A thorough knowledge of the orbital vascular anatomy is essential when working in the area, together with the pathologies which may affect the orbit. In assessing the orbital vascular supply, the orbital pathology that affects mainly children was explained in detail and different imaging modalities which were used for data collection from the images of patients from different age groups. A combination of data gathered in the form of patient angiograms and human dissections were used in this study. The results that were obtained in this study are intended to be used as a guide for neurosurgeons and intervention radiologists and will also add to the body of knowledge about anatomical variations.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy of the orbital cavity

In order to address the question regarding the orbital blood supply, one needs to be aware of the orbital structure and all its contents.

The bony orbit forms the surrounding structure for the eyeball and orbital contents, including the arterial supply and the venous drainage. Assessing orbital osteology will help define relationships of different anatomical landmarks forming points of entry and exit of blood vessels and nerves, i.e. foramina. Knowledge of the osteology may increase the technical safety, predictability of results and overall success rate as surgeons from various specialities perform procedures involving the intra-orbital region (Cheng *et al.,* 2008; Remington, 2012). Blood vessels and nerves pass through several major orbital foramina (Figure 2.1). The OA usually enters the orbit through the optic canal (OC) and can cross either inferior or superior to the ON (Hayreh, 2006). In variant cases where the OC is not the point of entry for the OA, other vessels from different foramina may contribute to the main source of blood supply to the orbit. Several anastomotic patterns between the OA and ECA are thus formed (Gailloud *et al.,* 2009).

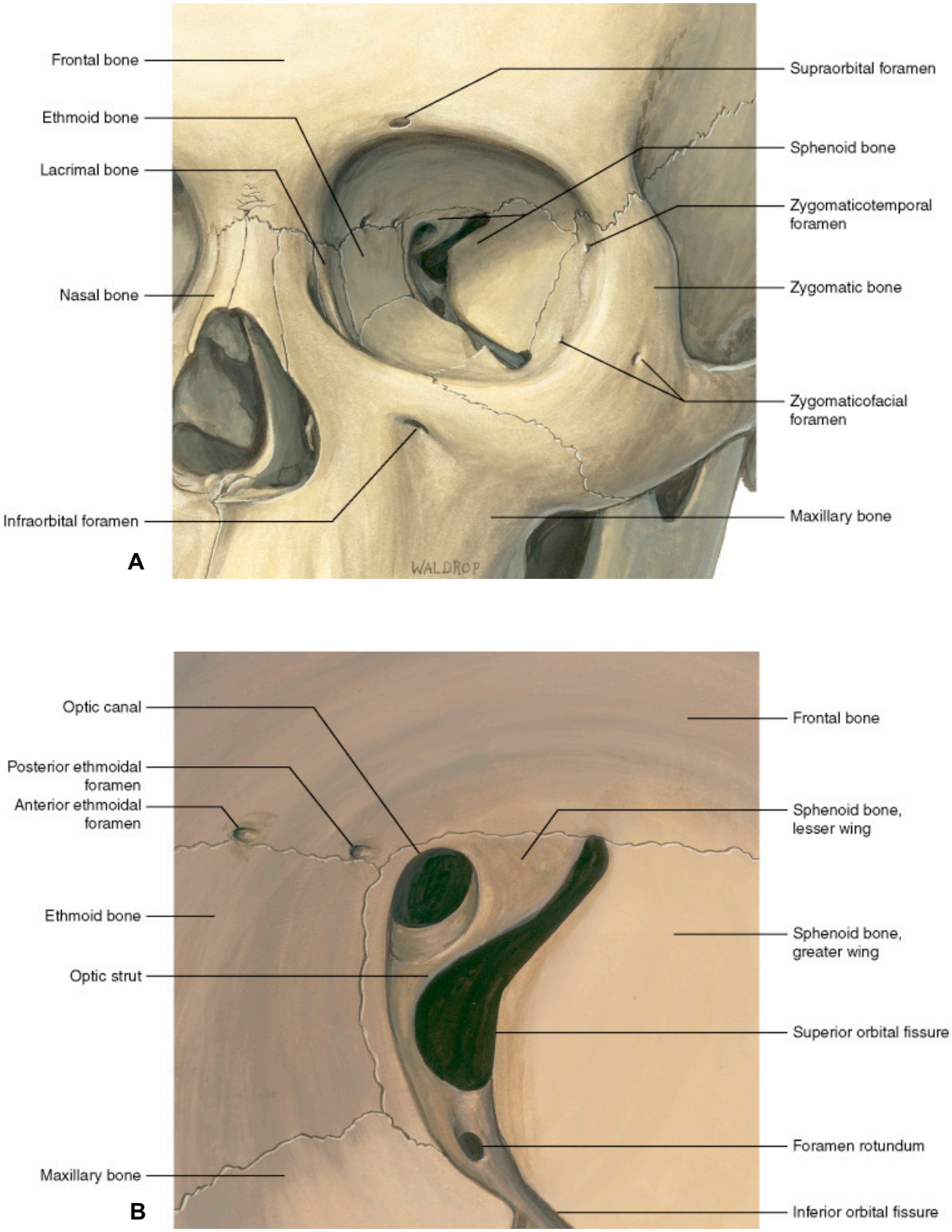

Figure 2.1: *The anterior view showing A. the bones contributing to the orbit, B. as well as the associated foramina.*

By permission from Elsevier. Dutton, (2011).

The superior, lateral and inferior walls of the orbit project anteriorly to fit the equator of the globe, the eyeball. The thin medial walls of the orbit are parallel to each other, while the thicker

lateral wall of the orbit is at 45° to the medial wall. The two lateral walls are, therefore, at right angles to each other (Figure 2.2). The ON and the eyeball are positioned centrally on the orbital axis which is 22,5° lateral to the sagittal axis. The visual axis is about 23° to the orbital axis (Vanderah, 2019).

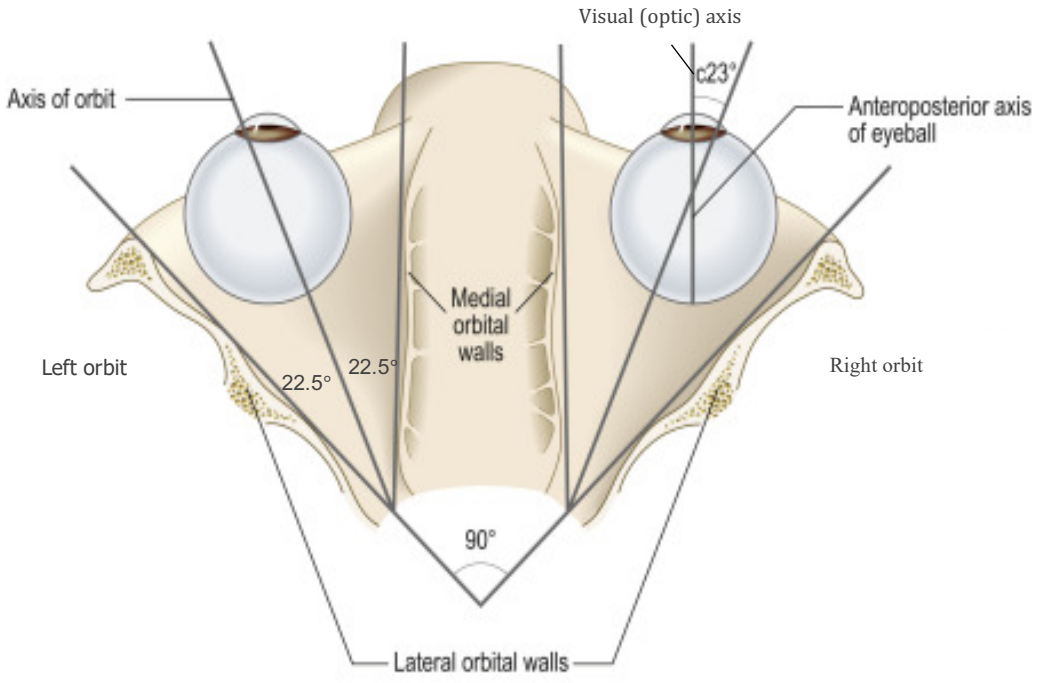

Figure 2.2: *The superior view showing the orbital and visual axes formed by the medial and lateral walls of the orbit.*

Modified from Standring, (2021).

2.2 Variant orbital foramen providing an alternative route for the vascular supply

One of the common orbital foramen that provides an alternative route for the vascular supply is the cranio-orbital foramen (COF) (Govsa *et al.,* 2014). According to other authors, the COF is also known as the meningo-orbital foramen, sinus canal foramen, spheno-frontal foramen, foramen of Hrytl and lacrimal foramen (Georgiou and Cassell, 1992; Stanley *et al.,* 1998; Chauhan and Khanna 2013; Uchino *et al.,* 2013). For the purpose of this study, the term cranio-orbital foramen will be used.

The COF is a small opening usually located on the roof of the lateral wall of the orbit. It is considered a cause of haemorrhage during deep lateral orbital dissection as it functions as an anastomosis between the lacrimal artery (LA) and the middle meningeal artery (MMA) (Govsa *et al.,* 2014)**.** Multiple COF may be found conveying the orbital branch of the MMA and forming a secondary link between the orbit and the middle cranial fossa. The COF incidence is

reported to range between 29% and 82,6% (Beden *et al.,* 2007; Govsa *et al.,* 2014). In addition, published literature in anatomical studies shows that the COF and its contents are associated with the embryological development of the orbital vascular supply (Georgiou and Cassell, 1992; Govsa *et al.,* 2014). It is therefore assumed that the COF represents a point at which the supraorbital division of the stapedial artery enters the orbit through the greater wing of the sphenoid bone that has not ossified yet (Govsa *et al.,* 2014).

2.3. The embryological development of the orbital vascular system

The complexity of embryological development of the OA describes the several variations of this artery not only in its origin but also in its course and branching (Robert *et al.,* 2020). The vascular system is affected by embryological development throughout all the stages of gestation (Lasjaunias *et al.,*1990). The OA variants originate through a diversity in the development of anastomotic networks. In the literature, certain variations in the patterns of the orbital blood supply are explained through embryological development, whereas in other cases the embryological link could not be found. Clear embryological explanations for variants exist, although certain discrepancies exist, and some explanations are speculative (Louw, 2014). Louw (2014) furthermore states that developmental variations of the OA can be explained in the following manner. An early diffuse capillary plexus forms a definitive arterial stem, marked by the disappearance of certain vessels and the appearance of other vessels, and disturbances in these patterns result in a range of variable patterns. Moreover, most OA variations can be satisfactorily explained based on migration, partial or complete regression, and persistence of primitive vessels and/ or remaining anastomotic loops (Louw, 2014). Therefore, the crossing of the OA superior or inferior to the ON depends upon which segment disappears or appears (Hayreh, 2006).

Bhogal *et al. (*2020) states that the OA represents the result of a complex series of anastomoses between a variety of vessels during embryogenesis that begin at the 4-5mm stage (at approximately three weeks post fertilisation) of the embryo. During early embryologic development of the CNS, the posterior circulation of the brain forms primitive anastomoses with the left and right ICAs. These anastomoses will ultimately disappear, excluding the posterior communicating arteries (PComAs) which persist in adults. The OA develops from primitive arteries that may be annexed by either the internal or external carotid systems, and contributions from either system may provide the dominant orbital blood supply as both the orbital- or extra-orbital branches of these two arterial systems exist in a haemodynamic balance (Osborn, 1999; Mitsos, 2014). Formation of the definitive OA is complex and to a

certain extent late in the embryonic period**.** Figure 2.3 shows the OA at different embryological stages from 4-5mm up to 40mm crown rump length (CRL) based on Padget's observations highlighting the arterial changes that occur intra-orbitally (Padget, 1948; Hayreh, 2006).

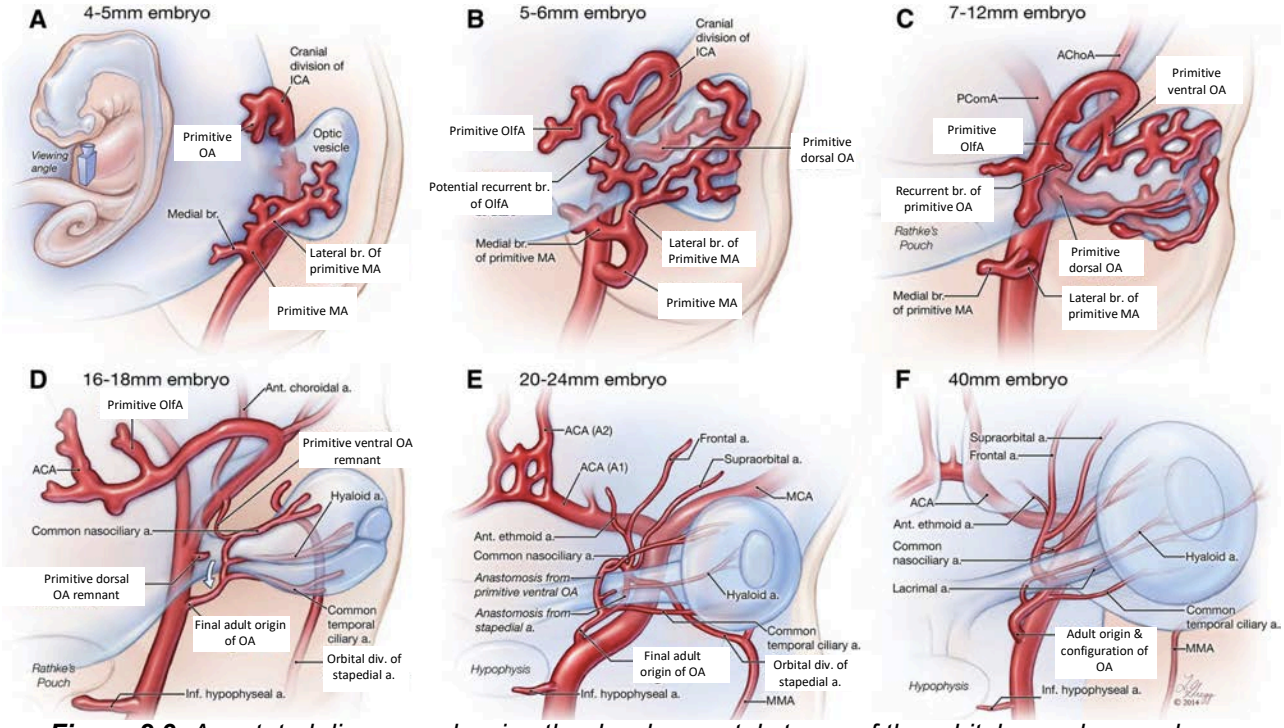

Figure 2.3: *Annotated diagrams showing the developmental stages of the orbital vascular supply.*

Modified from Gailloud *et al. (*2016). A: 4-5mm stage (at approximately three weeks post fertilisation): the primitive maxillary artery (MA) arises from the future cavernous segment of the ICA, providing a lateral branch to the optic vesicle and a medial branch to the Rathke's pouch. **B: 5-6mm stage (at approximately five weeks):** the primitive olfactory artery (OlfA) and primitive dorsal ophthalmic artery (PDOA) arise from the ICA distal to the origin of the primitive MA. The PDOA takes origin at the level of PCA origin and courses the optic vesicle superiorly to the site of the future lens. **C: 7-12mm stage (at approximately seven weeks):** the primitive ventral OA (PVOA) emerges from the ICA (at the level of the developing anterior choroidal artery) to supply cranial and ventral portions of the optic cup. The primitive OlfA branches off a small twig that will later become the adult anterior cerebral artery (ACA). **D: 16-18 mm stage (at approximately nine weeks):** the final origin of OA can now be seen lying proximal to both the PVOA and PDOA and distal to the remnants of the primitive MA. The stem of the final OA joins the temporociliary artery and the hyaloid branch from the PDOA. The ACA has become the dominant continuation of the ICA, the primitive OlfA now appearing as an ACA side branch. **E: 20-24mm stage (at approximately 11 weeks):** the medial branch of the primitive MA has become the inferior hypophyseal artery. The primitive OlfA regress further, whereas the primitive orbital artery (continuation of the stapedial artery) establishes an intra-orbital anastomosis with the OA creating an arterial loop around the ON, formed in part by the previous acquisitions of the PDOA and the PVOA, and **F: 40mm stage (at approximately 12 weeks)**: the advanced stage where the primitive structures have involuted - the OA joins the primitive orbital artery from the stapedial artery (Gailloud *et al.,* 2016). a. = artery, MCA = middle cerebral artery, inf. Hypophyseal a. = inferior hypophyseal artery, lateral br. = lateral branch, medial br. = medial branch, orbital div. of stapedial a. = orbital division of stapedial artery, A1 – A2 = divisions of the anterior cerebral artery, AChoA = anterior choroidal artery, ICA = internal carotid artery.

Hayreh and Dass (1962b) reported three stages of influence in the developmental history of the vascular system as postulated by Roux in 1878, namely:

i) Entirely dependent on genetic factors initially,

ii) A transitional stage in which hereditary formation is gradually supplemented by adaptational factors, and

iii) Influences of the haemodynamic factors.

2.4 The orbital blood supply

2.4.1 The origin of the ophthalmic artery

The OA is the first major branch of the ICA and is bordered by a network of sympathetic nerves. The OA leaves the ICA as it exits the cavernous sinus medial to the anterior clinoid process (Figure 2.4.) (Hayreh, 2006; Standring, 2021; Dutton, 2011). At its origin from the ICA, the OA lies within the subarachnoid space as it runs anteriorly on its way to the OC. The OA usually arises from the ICA at its anteromedial or superomedial aspects (Hayreh, 2006). In a study by Hayreh (1962a), the additional positions of the OA origin from the ICA were noted to be medial in 7% of the subjects and antero-superior in 1% of the subjects in their study. In addition, a superolateral origin was recently reported by N'da *et al.,* in 2013.

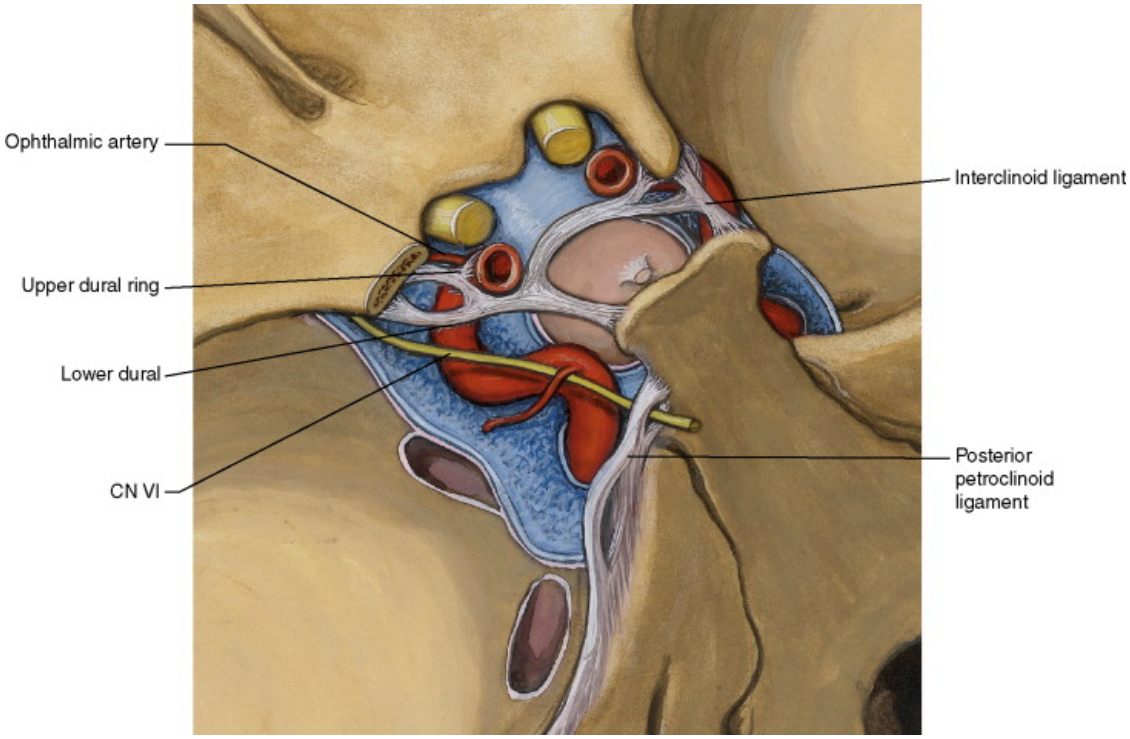

Figure 2.4: *The relationships of the ophthalmic artery within the cavernous sinus.*

By permission from Elsevier. Dutton, (2011).

As the OA usually emerges from the ophthalmic segment of the ICA in the majority of individuals, in 10% of individuals it may also emerge from the clinoid segment, the cavernous segments, or more rarely from the inferolateral trunk of the cavernous segment of the ICA. In such cases, the OA may gain access the orbit through the superior orbital fissure (SOF) instead of the OC (Dutton, 2011). Knowledge of the origin of the OA will determine an effective approach for selective procedures such as the catheterisation in treatment of the CRA occlusion or retinoblastoma chemotherapy (Kotsiomitis *et al.,* 2015).

2.5. Anatomy of the intracranial arterial supply

The anatomical and imaging studies provide details of the structure and makeup of the arterial supply and surrounding structures. The intracranial vasculature (veins and arteries) provides the necessary nutrients for the well-functioning of the CNS (Konan *et al.,* 2020). The scope of the study, covers only the arterial supply.

The blood supply to the brain is by the two pairs of main arteries on the left and right sides (the ICAs and the vertebral arteries) which form an anastomosis by means of an arterial circle on the base of the skull (Chandra *et al.,* 2017; Konan *et al.,* 2020). Two systems that form from the arterial circle are the vertebrobasilar (for posterior circulation) and the internal carotid (for anterior circulation) systems (Goldman and Schafer, 2020; Standring, 2021). This arterial anastomosis shown in Figure 2.5 is called the cerebral arterial circulation, also known as the Circle of Willis, originally described by Thomas Willis in 1664 (Chandra *et al.,* 2017; Goldman and Schafer, 2020; Standring, 2021).

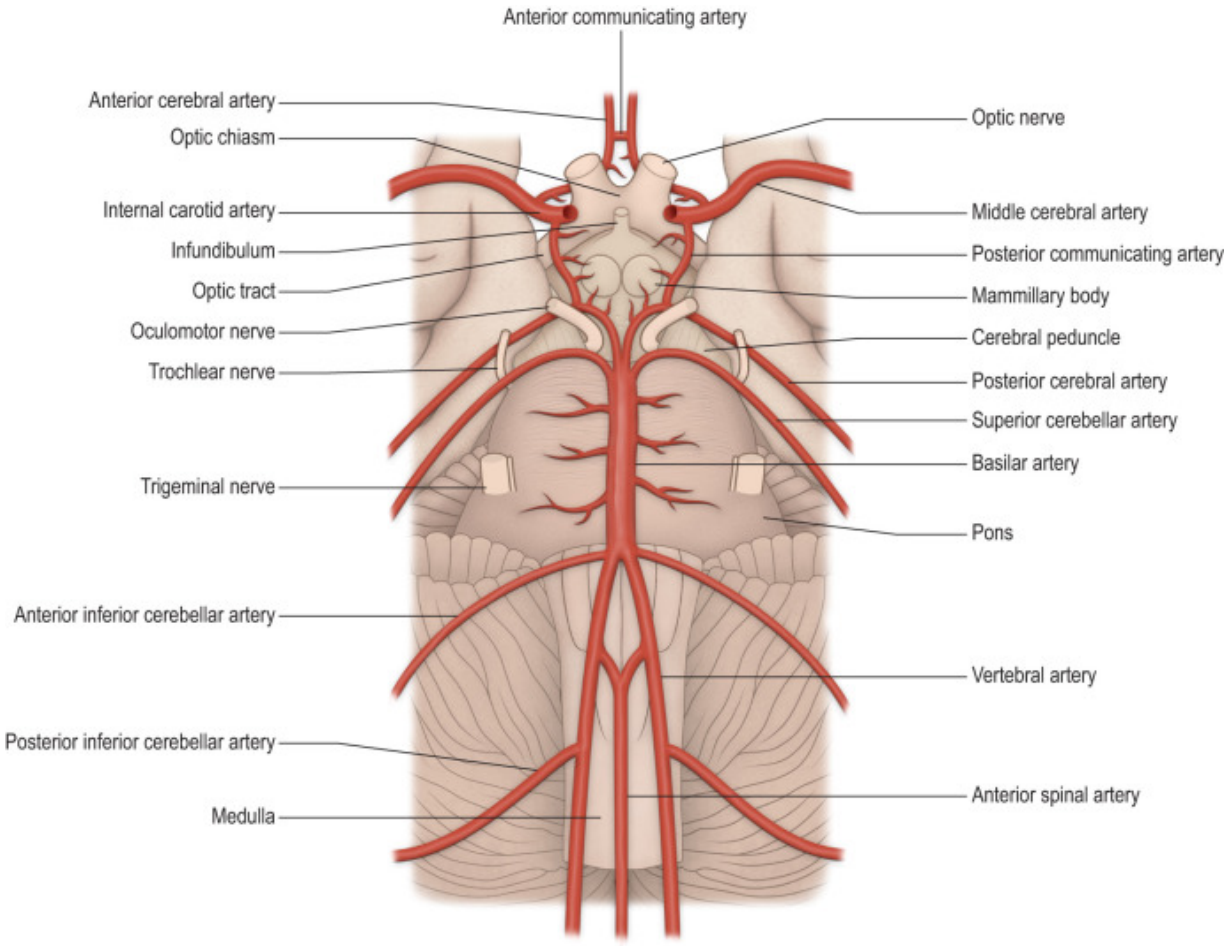

Figure 2.5: *Anatomy of the cerebral arterial circulation and its branches.*

By permission from Elsevier. Crossman and Neary, (2020).

The anterior circulation originates from the ICAs and supplies a large portion of the overall brain (70%) including the forebrain (frontal, temporal, parietal lobes, diencephalon and the internal capsule) (Chandra *et al.,* 2017). The arteries that form the anterior circulation together with the ICAs are the anterior cerebral arteries (ACAs), anterior communicating artery (AComA), middle cerebral artery (MCA) and the anterior choroidal artery (AChA) (Standring, 2021).

The two ACAs are joined by the AComA (Goldman and Schafer, 2020). The MCAs are found on each side lateral to the ICA and AChA typically arises from the supraclinoid portion just before the bifurcation of the MCA and ACA. The posterior communicating arteries (PComAs) connect the ICAs in the proximal posterior cerebral arteries (PCAs) (Goldman and Schafer, 2020). The origin of the posterior circulation is from the two vertebral arteries which unite to form a basilar artery (BA). The posterior circulation provides only about a third (30%) of the total flow perfusing the posterior portion of the brain (occipital lobe, most of the anterior and posterior portions of the brainstem and the cerebellum). A PComA runs from the PCA to the

ICA on each side (Chandra *et al.,* 2017). The PComA and PCA supply blood to the deep and superficial regions of the brain.

The supply of the midbrain and the diencephalon is shared by the two systems with the vertebrobasilar system supplying most of the thalamus and the internal carotid system supplying most of the hypothalamus (Vanderah, 2019). The arteries of the brain from the ICA (showing all parts of the ICA), the ACA, MCA and PCA are shown in Figure 2.6. For the scope of this study, the focus is on the anterior circulation as it provides the orbital blood supply, usually from the ICA.

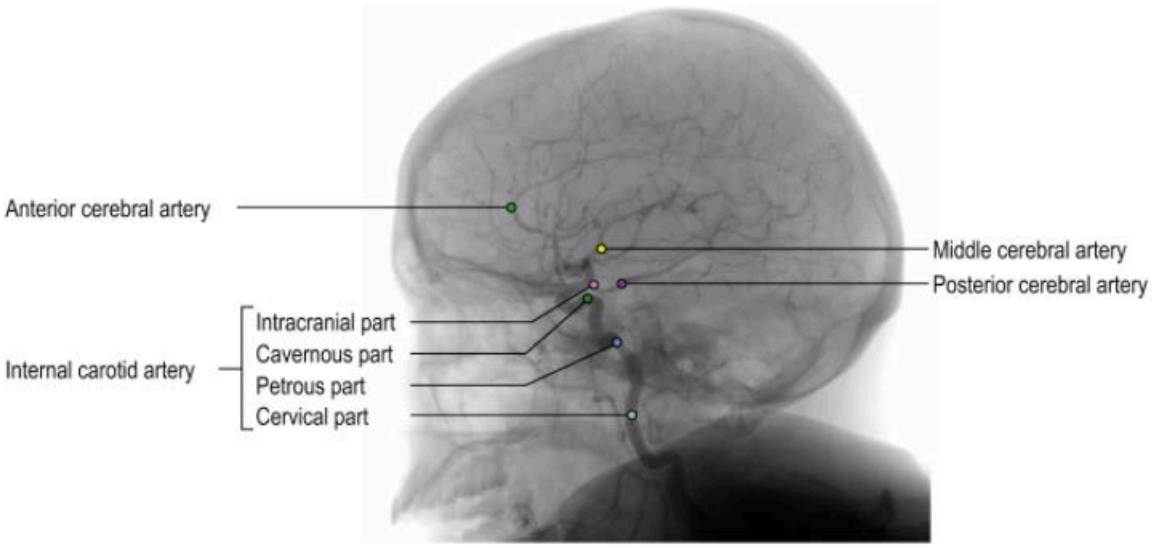

Figure 2.6: *A lateral projection angiogram showing the arterial supply to the brain.*
By permission from Elsevier. Standring, (2021).

2.5.1 The internal carotid artery

The ICA runs in a cranial direction through the neck and gains its entrance to the skull through the carotid canal, which is positioned in the petrous portion of the temporal bone just superior to the jugular fossa (Remington, 2012). The jugular fossa forms a depression on the inferior surface of the petrous temporal bone posterior to the inferior opening of the carotid canal (Flint *et al.,* 2021). The ICA then exits the carotid canal and immediately enters the cavernous sinus, where it travels anteriorly along the medial wall beside the sphenoid bone (Remington, 2012). Figure 2.7 is a depiction of how the ICA is divided into seven segments as was described by Bouthillier *et al. (*1996). The OA emerges from the sixth segment of the ICA at the distal dural ring and ends just proximal to the origin of the PComA. The proximal segment is the intradural portion of the anterior loop of the ICA (Bouthillier *et al.,* 1996). The OA and its branches

represent a bridge of anastomotic connections between the internal and external carotid arteries (Di Chiro, 1961).

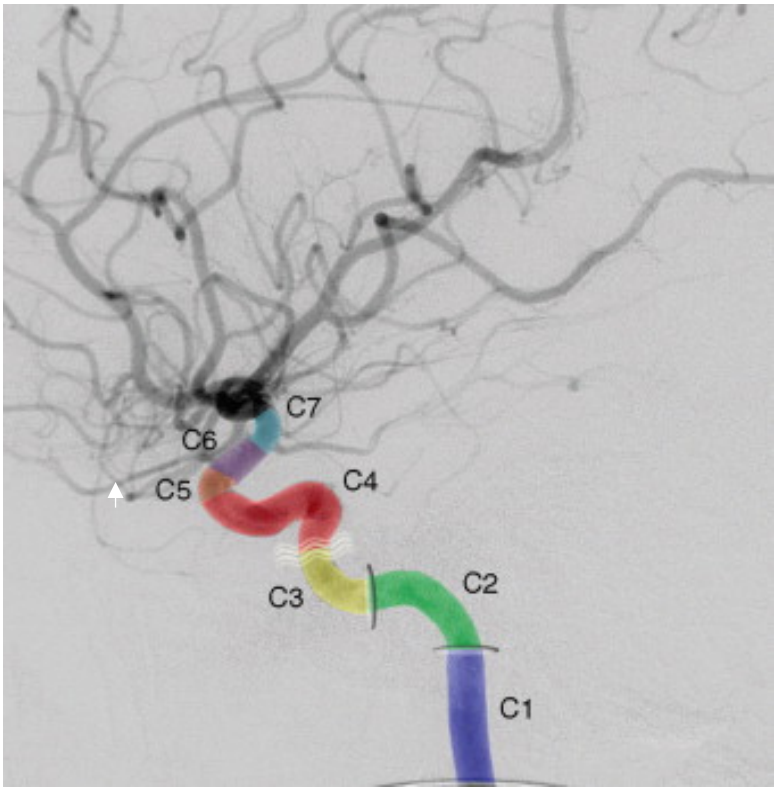

Figure 2.7: *The lateral view angiogram showing the seven divisions of the internal carotid artery.*

By permission by Elsevier. Doshi *et al.* (2013): Labels associated with the segments reflected on the diagram above: C1 = cervical segment, C2 = petrous segment, C3 = lacerum segment, C4 = cavernous segment, C5 = clinoid segment, C6 = ophthalmic segment, C7 = Communicating segment, white arrow = ophthalmic artery.

2.6 The course of ophthalmic artery

The entire course of the OA can be divided into three parts being the intracranial, intracanalicular and intra-orbital course (Hayreh, 2006). The OA travels through the OC into the orbit. The OA proceeds further anteriorly within the arachnoid sheath of the ON and eventually pierces the meningeal sheath. The OA then comes to lie on the outside of the ON and courses inferolateral to the ON for a short distance, before crossing either superior or inferior to the ON (Lemp and Snell, 1998; Remington, 2012).

2.6.1 The intracranial course of the ophthalmic artery

During the intracranial part, the OA is closely related to the proximal part of the ICA to which it frequently adheres to for some distance (Hayreh, 2006). The OA lies in the subdural space

and is attached to the inferior of the ON by a loose network of fibrovascular connective tissue. In the area of the OC, the two layers of the dura mater are fused, but they subdivide in the cranial cavity to form the cavernous sinus, while in the orbit the inner layer forms the dural sheath of the ON and the outer layer forms the orbital periosteum (Hayreh and Dass, 1962b; Hayreh, 2006). The OA mostly lies in the subdural space intracranially, but it always lies between the two layers intra-orbitally. Thus, it has to pierce the inner dural layer on route from the cranial cavity to the orbit. The OA pierces the inner dural layer usually at the OC (Hayreh and Dass, 1962b; Hayreh, 2006). Hayreh (2006) further states that the intracranial course may not be present in some cases.

2.6.2 The intracanalicular course of the ophthalmic artery

This is the section of the OA that lies within the OC, usually inferolateral to the ON. The OA usually lies partially in both the subdural space and also within the substance of the dural sheath. It lies minimally within the dural sheath with no subdural course. During its course within the subdural sheath, OA is disconnected from the surrounding dura by areolar tissue, except for where it makes penetration through the dural sheath proximally (Hayreh and Dass, 1962b; Hayreh, 2006).

2.6.3 The intra-orbital part of the ophthalmic artery

The entrance of the OA into the orbit is by means of the orbital apex, via the OC which may be duplicated, or rarely, through the SOF (Hayreh, 2006). The intra-orbital course has three segments. The first segment goes alongside the inferolateral aspect of the OA and extends from the point where the OA enters the orbit to point where it takes a different direction and thus becoming the second segment. The second segment takes on a lateral to medial direction (superior or inferior to the ON) from the inferolateral to the superomedial aspect of the nerve. The third segment of the OA extends from the angle where the second segment bends at the medial aspect on the ON to its termination at the superomedial angle of the orbital opening (Hayreh, 2006; Perrini *et al.,* 2007). Furthermore, the branching pattern of the OA is very complex and is unique not only to individuals but also to each orbit in the same person (Kotisomitis *et al.,* 2015).

2.6.3.1 The intra-orbital blood supply through the OA and its branches

The OA enters the orbit through the OC inferior to the ON, coursing for a short distance before giving off various branches which supply the orbital contents (Figure 2.8) (Hayreh 2006; Gailloud *et al.,* 2016; Standring 2015). Below is an example of the course of the OA in relation to the ON from its point of emergence for the ICA as was demonstrated by Naudy *et al.* (2018). A similar schematic representation will be drawn later on in this study in order to show the interpretation of the orientation of the OA from point of emergence from the ICA and its course.

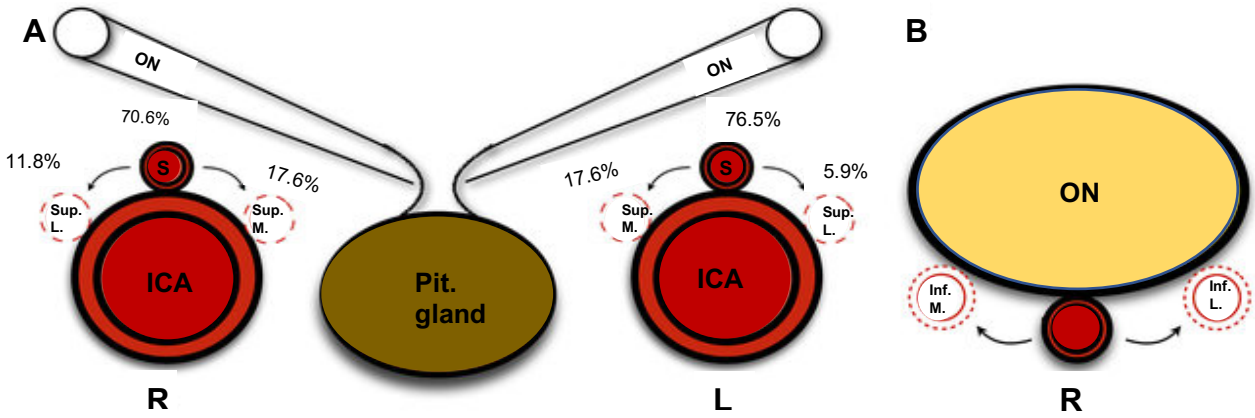

Figure 2.8*: A schematic illustration of variations in the position of the ophthalmic artery in relation to the optic nerve and the internal carotid artery.*

Modified from Naudy *et al.* (2018). A) The origin of the OA from the ICA, B) its position relative to the intracranial ON segment. The percentages for each position of origin from the ICA are shown. ON = optic nerve, ICA = internal carotid artery, Pit. Gland = pituitary gland, S = superior, Sup. L. = superolateral, Inf. L. = inferolateral, Sup. M. = superomedial, inf. M. = inferomedial, L = left, R = right.

Consequently, the various deviations in the course of the OA are of embryological origin and the disticntion of the vascular pattern from the diffuse capillaries may be due to morphogenetic or mechanical influences (Hayreh and Dass, 1962b). The branches of the intra-orbital part run within the adipose compartments of the orbit and pierce the orbital septa from one compartment to the other (Figure 2.9). The course of the arteries predominantly radiates from the centre of the orbital apex (Hayreh, 2006).

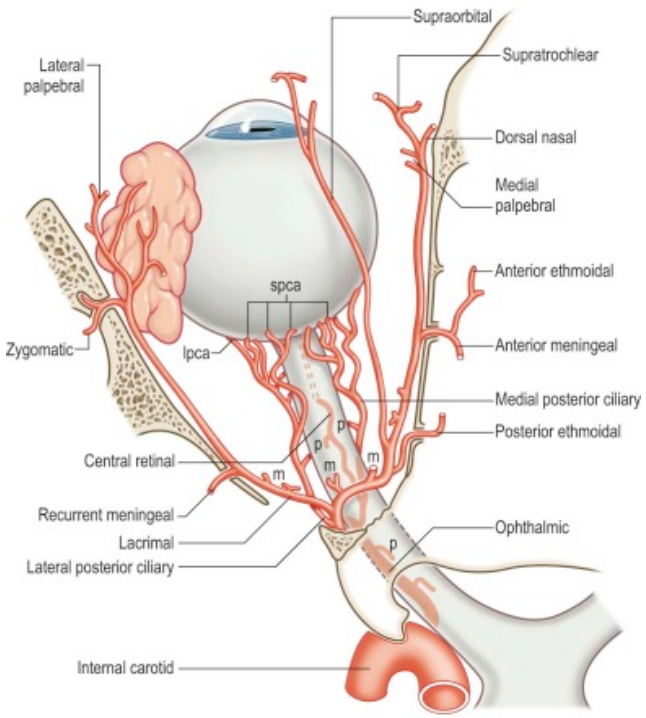

Figure 2.9: *The vascular supply to the eyeball and surrounding structures within the orbit.*
By permission from Elsevier. Standring, (2021). p = collateral branch, m = muscular branch, lpca = long posterior ciliary artery**,** spca = short posterior ciliary artery.

The intra-orbital part of the OA gives off branches, the order and appearance of which depend on the course of the artery in relation to the ON. The branches of the OA are usually divided into three groups:

- the branches supplying and penetrating the eyeball (ocular),
- supplying the intra-orbital structures such as the muscles and the lacrimal gland (orbital)
- and the branches that exit the orbit through various orbital foramina and pierce certain orbital septae to supply the extra-orbital structures (extra-orbital).

These three groups of branches are shown in Table 2.1 (Whitnall, 1932; Mokin and Siddiqui, 2016).

Table 2.1: The arrangement of the ophthalmic artery branches according to different groups.

Orbital group	**Ocular group**	**Extra-orbital group**
Lacrimal artery (LA)	Central retinal artery (CRA)	Posterior ethmoidal artery (PEA)
Small branches to the periosteum	Long posterior ciliary artery (LPCA)	Anterior ethmoidal artery (AEA)
Small branches to the areolar connective tissue	Short posterior ciliary artery (SPCA)	Supra-orbital artery (SOA)
Muscular arteries	Anterior ciliary artery (ACA)	Medial palpebral artery (MPA)
		Dorsal nasal artery (DNA)
		Supratrochlear artery (Sup.Tr.A)
		Branches of the lacrimal artery: Zygomatic and lateral palpebral

Figure 2.10 further shows the orbital arterial supply and the extra-ocular branches emerging from the OA as shown in Table 2.1.

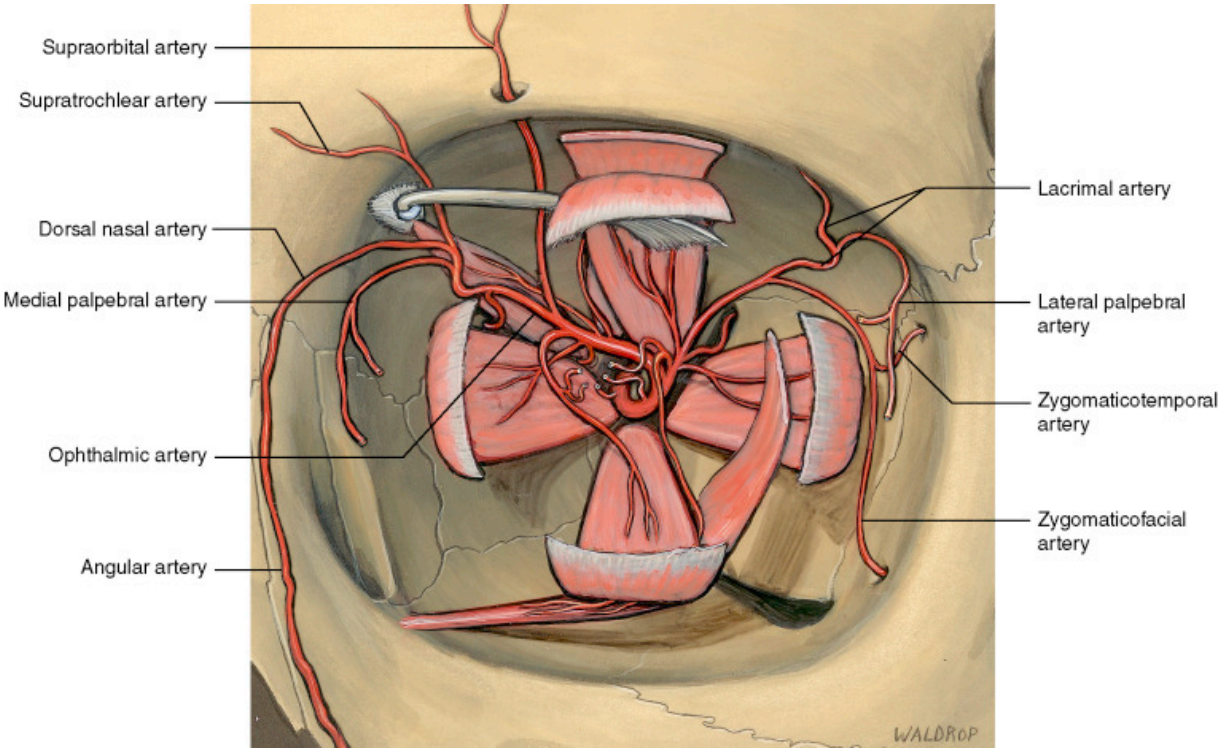

Figure 2.10: *The frontal orbital view showing the ophthalmic artery and its branches.*

By permission from Elsevier. Dutton, (2011).

2.7 The orbital venous drainage

The venous system of the orbit is complicated and greatly variable. No other parts of the body have directly corresponding veins and arteries except for the superior ophthalmic vein (SOV) that corresponds with the OA in the orbit. The SOV passes through the SOF to the cavernous sinus. The inferior ophthalmic vein (IOV) which originates in the orbital floor and the medial wall of the orbit may join the SOV or empty directly into the cavernous sinus through the inferior orbital sinus (Figure 2.11). The central retinal vein (CRV) stretches across the ON to end in either the SOV or the cavernous sinus (Hayreh, 2006;). The orbital veins have inconsistent pattern and form venous networks in several places, which result in considerable uncertainty regarding their number, nomenclature, and pattern unlike the orbital arteries (Hayreh, 2006).

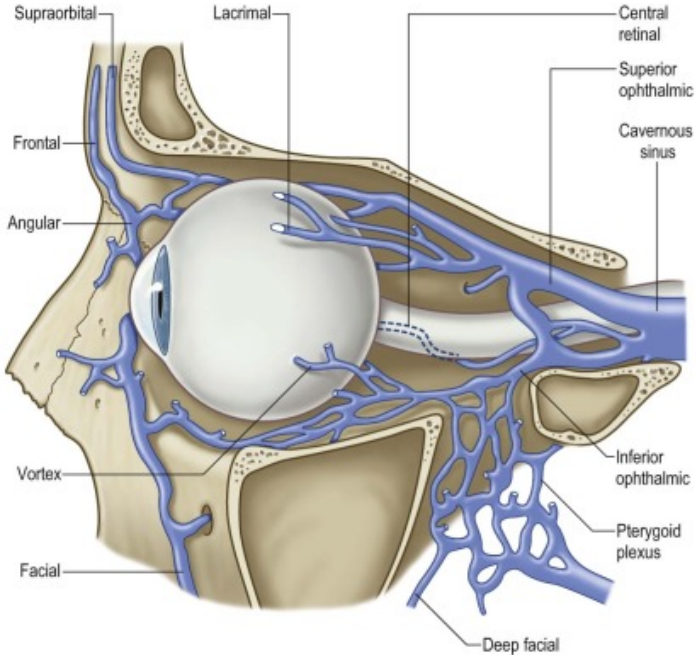

Figure 2.11: *The orbital venous drainage.*

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2.8 The arterial anastomotic patterns within the orbital region

Anastomotic patterns between branches of the OA and the ECA are variable. Many are clinically relevant, although published records on their frequency and patterns are limited (Bertelli *et al.,* 2017). The ECA system is substantial in that it forms an anastomotic network around the orbital region which can offer collateral supply to intracranial blood flow in the event of severe ICA occlusion or stenosis (Perrini *et al.,* 2007). Krause's Law states that the varieties originate through deviations from the normal pattern of anastomoses, as quoted by Hayreh (2006). This is illustrated in Figure 2.12. The ICA gives blood supply the intracranial structures,

the eye and its surrounding structures, while the ECA supplies the superficial areas of the head and neck including a small portion of the circulation to accessory structures of the eye (Remington, 2012).

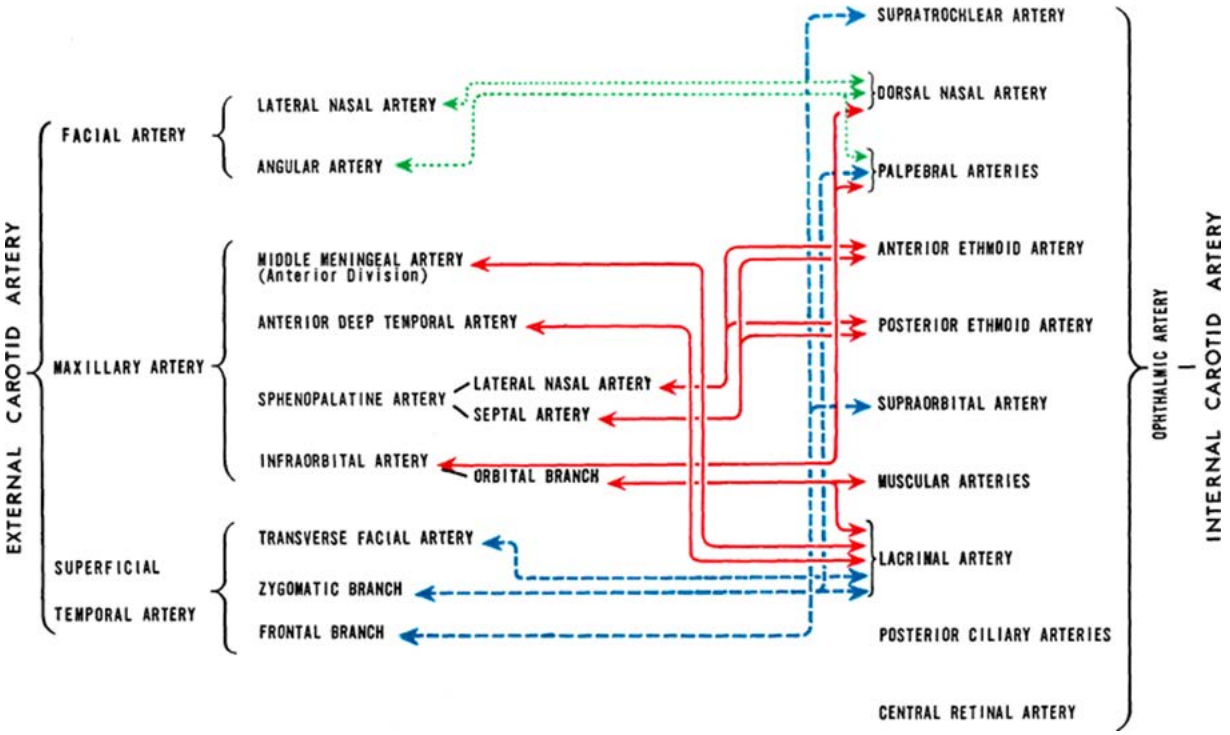

Figure 2.12: *A diagrammatic representation of the anastomoses between the external and internal carotid arteries in the head and neck.*

Hayreh (2006). red solid lines = maxillary branches; blue dotted lines = superficial temporal branches; green dotted lines = superficial facial branches.

After careful consultation the original article including the diagram above, it can be concluded that the red solid lines show the most common anastomosis, blue broken showing less common anastomosis and small broken green lines showing least anastomosis. This information is not provided by the original author.

Knowledge of multiple arterial networks between branches of the ICA and ECA is crucial for the prognosis and treatment of the orbital vascular diseases (Mokin and Siddiqui, 2016). The application of this knowledge may be valid for effective and safe infusion of therapeutic agents intra-arterially. For example, for the treatment of retinoblastoma, where it may also reduce the risk to other procedural interventions. It is known that the anastomosis between the branches taking origin from the third part of the OA and of the ECA is one of the major collateral channels between the ICA and ECA. This collateral circulation is sufficient to prevent blindness after occlusion of the ICA or OA in 90% of patients (Ogawa *et al.,* 1990) (Table 2.2).

Table 2.2: Branches of the ophthalmic artery and their anastomoses with the external carotid artery.

	OA artery branch	**Origin of the OA branch**	**ECA branch**
Type 1	Proximal lacrimal artery (main branch)	Second portion of the OA	MMA (through the superior orbital fissure) (Geibprasert *et al.,* 2009)
Type 2	Distal lacrimal artery (inferior branch)	Second portion of the OA	Anterior deep temporal artery and infraorbital artery (Geibprasert *et al.,* 2009; Kotsiomitis *et al.,* 2015)
Type 3	Anterior ethmoidal artery	Third portion of the OA	Septal arteries: sphenopalatine artery, (IMA), MMA (Lasjaunias *et al.,* 1975; Geibprasert *et al.,* 2009; Kotsiomitis *et al.,* 2015)
Type 4	Posterior ethmoidal artery	Second and third portion of OA	Sphenopalatine artery, greater palatine artery (IMA), MMA (Geibprasert *et al.,* 2009)
Type 5	Supraorbital artery	Third portion of OA	Supratrochlear artery (STA) (Geibprasert *et al.,* 2009)
Type 6	Dorsal nasal artery	Terminal branch of OA	Angular termination of facial artery (FA), infraorbital artery (Geibprasert *et al.,* 2009)

The patterns of orbital blood supply contribution between the ICA and ECA or blood vessels other than the ECA contributing to the orbital blood supply may be categorised into further relationships as was documented by Bertelli *et al. (*2016) (Table 2.3).

Table 2.3: The relationships of the anastomotic contribution between the external and internal carotid arteries.

Vessels of the ECA and ICA commonly forming anastomotic relationships	**Anastomotic patterns of other vessels**
Lacrimal artery & middle meningeal artery	Meningolacrimal artery & deep temporal artery
Lacrimal artery & anterior deep temporal artery	
Lacrimal artery & zygomatico-orbital artery	
Ophthalmic artery & middle meningeal artery	
Ophthalmic artery & facial artery	
Supra-orbital artery & superficial temporal artery	
Supra-orbital artery & middle meningeal artery	
Dorsal nasal artery & infra-orbital artery	
Supra-orbital artery & zygomatico-orbital artery	
Supratrochlear artery & superficial artery	

2.9 Anatomical variations of the arterial blood supply and clinical applications

Increasing interest in the OA started from the 1880's and its various anastomoses with branches of the ECA by the pioneer work of Meyer (Meyer, 1887). Kyoshima *et al. (*2000) reported that in 90% of the cases in their study, the OA is the first branch of the intradural segment (C6) of the ICA. Hayreh and Dass (1962 a, b and c) in their dissection study of 170 human orbits noted the different origins of the OA other than the ICA.

The intradural origin of the OA was confirmed by Erdogmus and Govsa (2006) to be the most common origin and found an extradural origin of the OA in 5% of the orbits in the eyes they dissected in their study.The presence of these variation in the OA taking origin from the ACA and the double OAs taking origin from the ICA can be described by early the embryonic development (4-18 mm stages), before the formation of the primitive OA (Louw, 2014). The stapedial artery and its modifications during fetal life (18-40 mm stages) played an important role in vascular variations during fetal development such as OA origin from the BA, MMA or a persistent loop of the ICA, OA and MMA (Lasjaunias *et al.,* 1977; Tanaka 2009; and Louw, 2014).

The anatomy of the OA is complex with various anomalous origins, variations and anastomoses between the ICA and ECA systems (Toma, 2016). In several clinical settings, variations of the vascular supply can be tricky, specifically for neurovascular interventionists, neuroradiologists and orbital surgeons. Possible variations occurring in the site of origin of the OA unbeknown to the clinician while performing certain endovascular or surgical interventions

involving the orbital arterial supply may pose a great risk of injury to the eye of the patient or result in unsuccessful treatment (Bertelli *et al.,* 2016 & 2017).

After the ICA emerges from the carotid canal of the temporal bone, the origin of the OA varies in relation the course of the ICA penetrating the cavernous sinus. The ICA courses within the cavity of the cavernous sinus and penetrates the dura mater to enter the subarachnoid space allowing the branching of OA from any portion along the ICA (Matsumura and Nagashima, 1999). In 2 to 8% of cases, the OA can originate extradurally from the clinoid segment or the intracavernous portion of the ICA (Hayreh, 2006; Perrini, 2007). In such cases, instead of the OA gaining access to the orbit via the OC, the OA travels via the SOF or by means of an anomalous foramen in the optic strut. Rarely, a duplicate origin of the OA from the ICA can be encountered (Lasjaunias *et al.,* 1974).

The most common variations of the orbital vascular supply are in its course and branches (Hayreh, 2006; Bracco *et al.,* 2015). These variations are found at the orbital apex as they form through various deviations from the usual development, regression of the stapedial artery (StA) and its anastomosis with the OA (Diamond, 1991; Bracco *et al.,* 2016). Furthermore, the postnatal pattern of arterial blood supply of the orbit is derived during the fetal development of anastomoses forming these arteries and their partial or total regression (Bracco *et al.,* 2016).

The variations around the blood supply of the orbit are formed due to the complicated OA development with involvement of these arteries: the StA, PVOA and the PDOA (Hayreh, 2006; Bracco *et al.,* 2016). The postnatal pattern of the arterial blood supply of the orbit is derived by means of fetal development of anastomoses among these arteries and by their successive partial or total regression, (Komiyama, 2009). Although these variations are rare, they have critical implications in the pre-operative and operative treatment of various diseases (Belotti *et al.,* 2016). Majority of the variations of the OA can be suitably described based on migration, partial or complete regression, and persistence of primitive vessels and/or remaining or additional anastomotic loops (Louw, 2014).

A detailed understanding of the OA microsurgical anatomy, the form of its branches on the angiograms, anastomoses of the OA with the ECA system, variations in origin and course of the OA, and its relationship to the ON are clinically important. All of this information is used when making an accurate diagnosis and when performing endovascular treatment and other surgical procedures which involve this vascular area and also when dealing with various orbital disorders (Lang and Kageyama, 1990; Perrini *et al.,* 2007). For the scope of this study, the

variations from anywhere in the anterior circulation of the cerebral arterial circle were investigated and recorded.

Variations in the origin of the OA are observed in 3.1% of MRA studies done by Balci and Arat, (2019). These include the OA taking origin from the intracavernous part of the ICA, a double OA origin from the ICA and the OA taking origin elsewhere than from the ICA.

2.10 The variant ophthalmic artery taking origin from the internal carotid artery

2.10.1 Intracavernous origin of the ophthalmic artery

This is a rare type of the OA origin with an occurrence rate of 0.4% (Bertelli *et al.,* 2017). Dilenge first reported this type of variation in 1965. The intracavernous origin of the OA can be explained as an anatomical variation which occurs by the regression of the PVOA instead of the PDOA through embryology (Lasjaunias *et al.,* 1977). In addition, other authors support the explanation of this anatomical variation put forward by Padget, namely the persistence of an anastomosis between the first segment of the OA and the ILT with stems from both PDOA and PVOA forming a subsequent regression of (Gailloud *et al.,* 2009; Parlato *et al.,* 2011; Toma, 2016; Bertelli *et al.,* 2017).

The cavernous variant origin of the OA is divided into three types.

- Type I: the OA takes origin from the ICA close to the dural ring. It then takes an upward curve in order to gain access to the OC. Following that, this OA variant has the course and distribution of a usual OA (Gailloud *et al.,* 2009).

- Type II: the OA originates from the segment of cavernous ICA horizontally. It corresponds to a branch of the ILT - the deep recurrent OA. The OA, thus, enters the orbit through the medial aspect of the SOF and progresses as the first part of the OA. This proximal connection suggests that this variant type supplies the entire ophthalmic distribution, including the optic apparatus (Gailloud *et al.,* 2009).

- Type III: also originates from the horizontal segment of the ICA, but in this case, the connection is established with the StA (or with the MMA at the adult stage). This variant type has the course and distribution of the anterior ramus of the StA. The artery enters the orbit through the COF if it involves the meningolacrimal artery or via the lateral aspect of the SOF if it involves the sphenoidal artery.

Figure 2.13 illustrates the three types of intracavernous origin of the OA from the ICA as prepared Lydia Gregg. This shows the embryonic precursors of the OA and their role in several variants of the OA origin (Gailloud *et al.,* 2009).

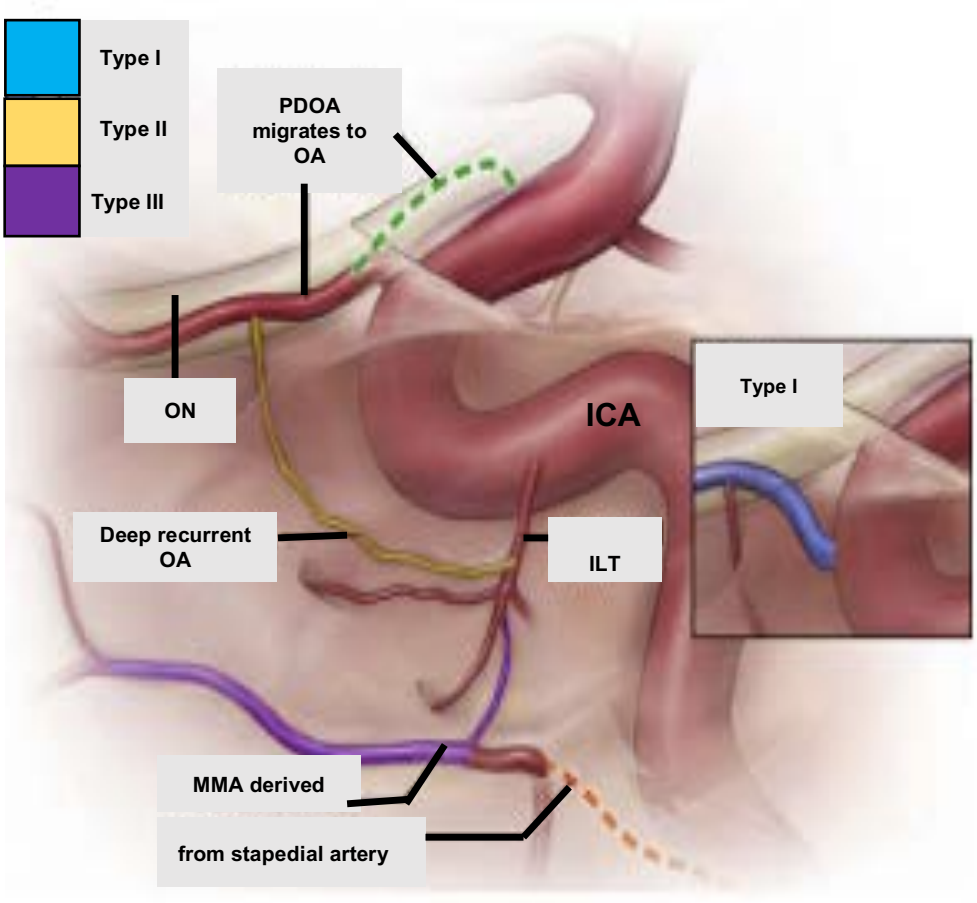

Figure 2.13: *The three types of intracavernous origin of the ophthalmic artery.*

Used with permission and modified from Gailloud *et al. (*2009). green dotted line = the primary origin of the PDOA; yellow= the deep recurrent OA; purple= the StA and a persistent connection with the inferior lateral trunk of the ICA; orange= involuted origin of the StA from the petrous ICA. PDOA = primitive dorsal ophthalmic artery, OA = ophthalmic artery, ON = optic nerve, ILT = inferolateral trunk, MMA = middle meningeal artery, ICA = internal carotid artery.

2.10.2 A rare double ophthalmic artery origin from the internal carotid artery

On rare occasions a double OA arising from the ICA, also known as a duplicate OA can be encountered. The first case was reported by Lasjaunias *et al. (*1977). This can present in two ways, namely the upper duplicate artery which arises from the supraclinoid (supracavernous) portion of the ICA and passes through the OC, and the lower duplicate artery which arises from the ICA in its intracavernous portion and passes through the SOF (Perrini *et al.,* 2007;

Nemoto and Namba, 2013). This variant type of origin has an estimated incidence of around 0.2% (Bertelli *et al.,* 2017).

The ventral OA (VOA) originates from the supracavernous ICA siphon and is known as the primitive OA. The VOA then forms an anastomotic ring with the dorsal OA (DOA) inside the orbit around the ON (Kam *et al.,* 2003). The anatomical variation of a double OA can be explained by the absence of the anastomotic ring between the PDOA and the PVOA around the ON. As a result, the PDOA does not regress.

Figure 2.14 shows an example from the current study showing the double origin of the OA from the ICA.

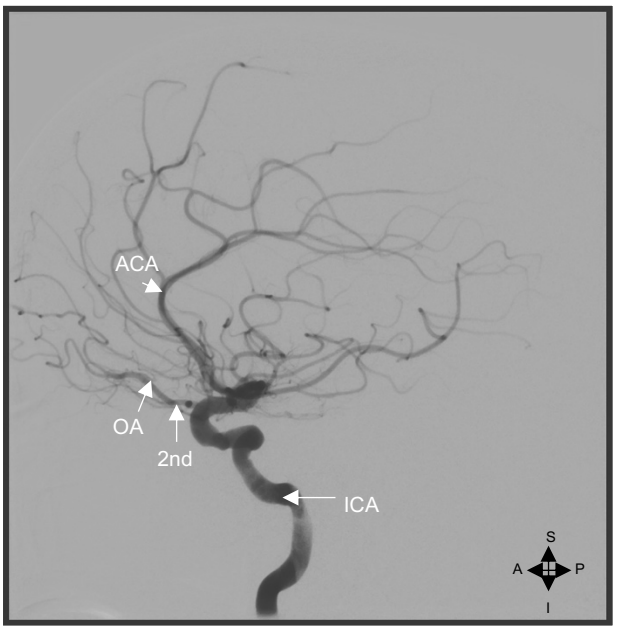

Figure 2.14: *The internal carotid artery giving off two branches that gives blood supply to the orbit (current study).*

ACA = anterior cerebral artery; OA = ophthalmic artery; ICA = internal carotid artery; 2nd = additional branch from the ICA; S = superior, I = inferior; A = anterior, P = posterior.

2.11 The ophthalmic artery taking origin from elsewhere than the internal carotid artery

When the OA takes origin from elsewhere than the ICA, it will provide the full blood supply to the orbit (Uchino *et al.,* 2013).

2.11.1 The ophthalmic artery taking origin from the middle meningeal artery (MMA)

The MMA is a branch of the maxillary artery which is one of the largest branches of the ECA. It is one of the most important dural arteries because it supplies more than two-thirds of the cranial dura (Robert *et al.,* 2020; Standing, 2021). The MMA is the branch of the ECA and it gains access to the orbit by means of the foramen spinosum and continues in the groove of the squamous part of the temporal bone (Figure 2.15). Whilst Figure 2.16 shows the anatomy of the MMA with its anterior and posterior branches.

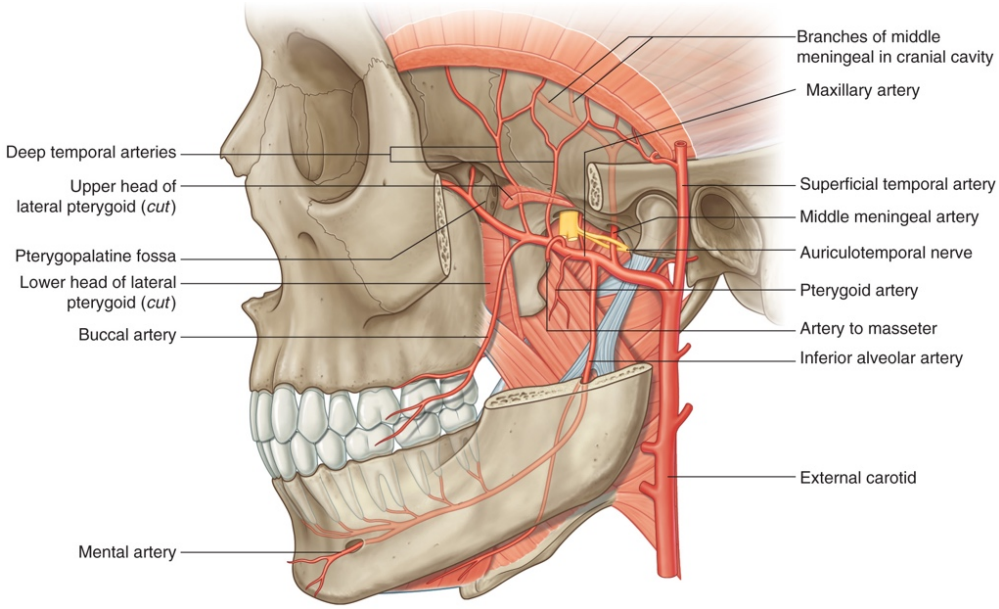

Figure 2.15: *The middle meningeal artery and its branches within the cranial cavity.*
By permission from Elsevier. Drake *et al.* (2020).

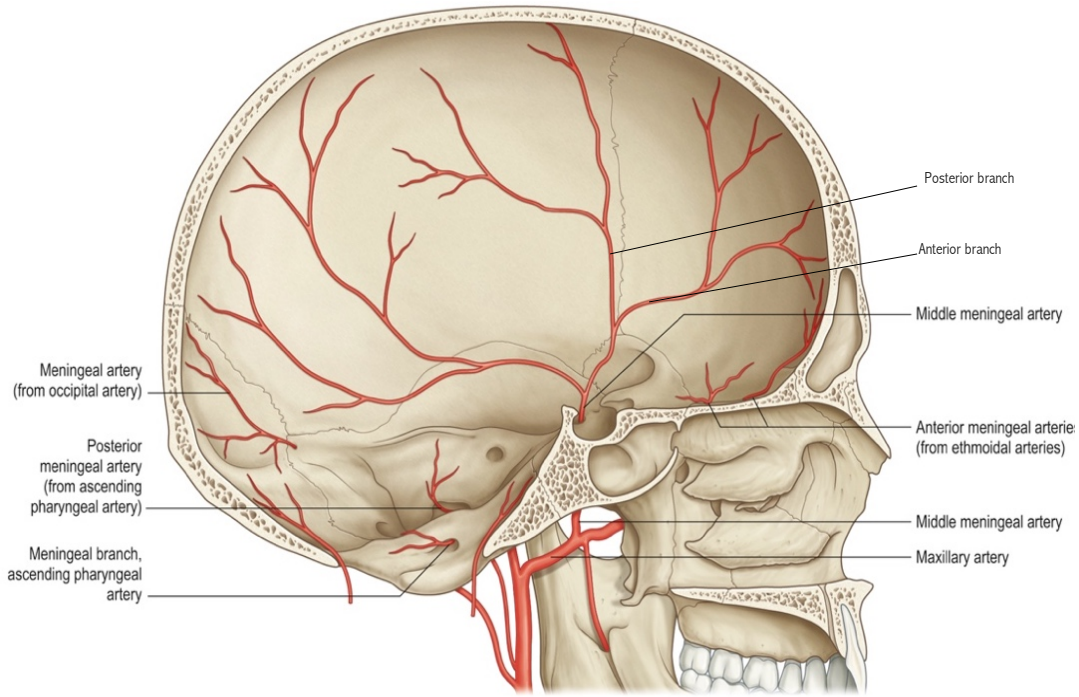

Figure 2.16: *The anatomy of the middle meningeal artery within the skull.*

Modified from Elsevier. Standring, (2021).

The middle meningeal artery (MMA) then divides into an anterior branch contributing to the orbital blood supply via the SOF or the cranio-orbital foramen (Hyrtl canal) and posterior branches on the greater wing of the sphenoid bone (Aktas *et al.,* 2020). Therefore, the most vital collateral blood supply to the orbital region is the MMA (Kotsiomitis *et al.,* 2015; Aktas *et al.,* 2020). In addition, the OA origin from the MMA is the most commonly unusual origin that has been reported in the literature (Hayreh, 2006). An OA origin from the MMA has crucial clinical implications and this was noted in several surgical procedures performed in this area (Perrini *et al.,* 2007). When an OA origin is confirmed angiographically to be from the MMA, an endovascular embolisation procedure will carry the risk of visual impairment due to embolic occlusion of the CRA (Perrini *et al.,* 2007).

The initial explanation of the orbital branches taking origin from the MMA was by Curnow in 1872 (Robert, 2020). The branch of anastomosis with MMA is either that of the LA or the OA, and the branch anastomoses with the anterior division of the MMA through the cranio-orbital foramen. Furthermore, an anastomoses of the anterior branch of the MMA and the recurrent meningeal branch (a branch of the LA) through the SOF. The MMA is quite thin, tortuous and rarely visible angiographically however, in some instances the anastomosis is very large and becomes the main source of blood supply to the orbit. The anterior branch of the MMA anastomoses with the anterior falx artery (a branch of the AEA) within the falx cerebri (Perrini

et al., 2007 & Aktas, 2020). The anastomoses between the OA and MMA are also clinically important (Aktas *et al.,* 2020).

The formation of this variation is a consequence of two different embryological processes. The first being failure of the regression of the supra-orbital branch at the level of the SOF, and the second being the absence of anastomosis between the maxillomandibular branch of the supra-orbital branch and the IMA (Lasjaunias and Moret, 1977&1978). As a result, the MMA originates from the OA passing through the lateral part of the SOF and in this case the foramen spinosum is usually absent (Robert *et al.,* 2020). The division of the orbital ramus occurs within the cranial cavity in other cases where one branch enters the orbit through the orbitomeningeal foramen and becomes the meningolacrimal artery. The other branch passes through the SOF and is attached to the OA. If the ethmoidonasal artery fails to regress entirely at the level of the SOF, a direct anastomosis between the MMA and the OA is found in the adult and is referred to as the meningo-ophthalmic artery (Bertelli *et al.,* 2017).

2.11.2 The ophthalmic artery taking origin from the anterior cerebral artery

The ACA and its branches contain both clinically significant and incidental variations (Tahir *et al.,* 2019). The ACA is the smaller artery of the two terminal branches of the ICA (Standring, 2021), and supplies the developing telencephalon in both amphibians and mammals (Tahir *et al.,* 2019). The ACA starts at the medial end of the stem of the lateral fissure and then passes anteromedially superior to the ON to the great longitudinal fissure where it connects with the other ACA on the contralateral side by a short transverse communicating artery (Standring, 2021). The two ACAs travel together in a great longitudinal fissure. Together, the two ACAs pass around the curve and along the upper surface of the genu of the corpus callosum and then to the posterior end where these ACAs will anastomose with the PCAs (Standring, 2021). Surgical nomenclature divides the ACA into three parts:

- A1: from termination of the ICA to the junction with the ACoA,
- A2: from the junction of the ACoA to the origin of the callosomarginal artery
- A3: distal to the origin of the callosomarginal artery. This segment is also known as the pericallosal artery.

Figure 2.17 shows these three segments of the ACA from the medial aspect of the brain. Mancall (2011) has labelled the orbital artery, whereas other authors (Winn, 2017; Zammit and Whitfield, 2020) refer to the artery as the orbitofrontal artery.

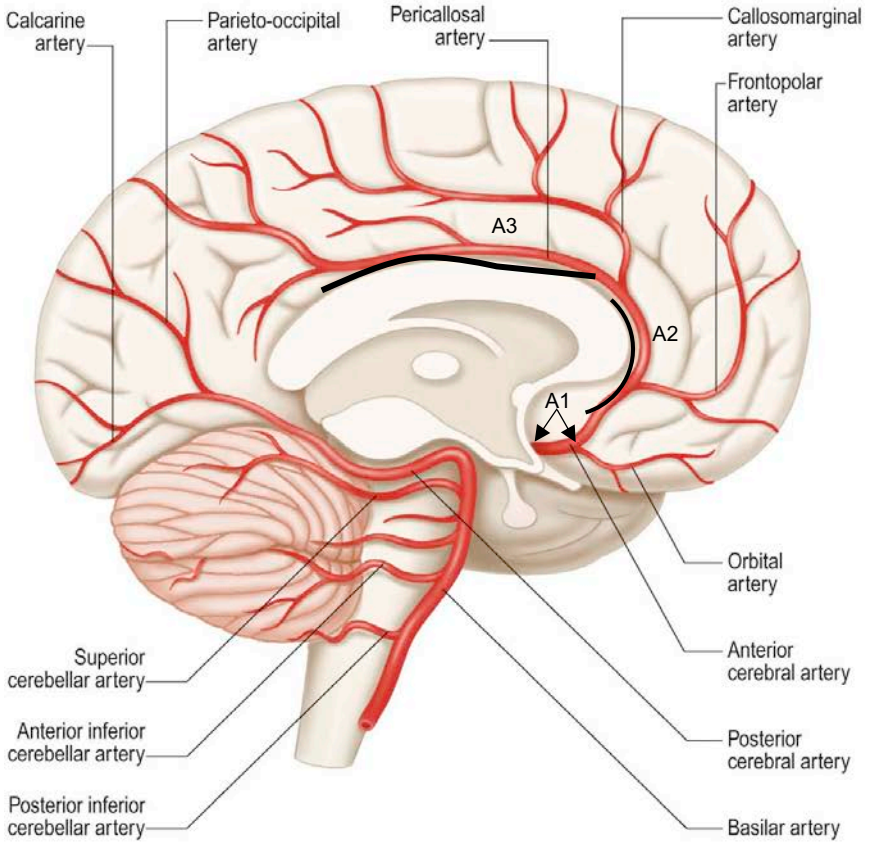

Figure 2.17: *The medial aspect of the brain showing major arteries with the anterior cerebral artery.*

Modified from Mancall, (2011).

A representation showing the ACA segments: A1, A2 and A3.

The unusual origin of the OA from the ACA can be described as the origin of the OA from the ACA which resulted from the persistence of the PVOA and atrophy of the DOA (Li *et al.,* 2011). Furthermore, the presence of an infra-optic course of the A1 tract could also represent maldevelopment in the cerebral arterial circle embryogenesis, resulting from the persistence of the primitive prechiasmal arterial anastomosis or an error in the development of the definitive OA.

In addition, according to Watanabe, (1996) and Li *et al. (*2011) the following features also forms the characteristic of this unusual origin:

- the anomalous artery branches off from the ICA at the level of the OA (just as it becomes intradural) or above,
- the anomalous artery passes beneath the ON, and
- the anomalous vessel is frequently associated with other vascular anomalies secondary to embryogenic variations such as cerebral aneurysms.

The ACA forms key anastomoses with the OA, AChA and the ECA. Therefore, knowledge of the ACA anatomy is imperative for surgeons and angiographers in diagnosing and treating pathological lesions while preventing complications (Tahir *et al.,* 2019).

2.11.3 The ophthalmic artery taking origin from the middle cerebral artery

MCA is a large terminal branch of the ICA. MCA runs at first in the lateral fissure, then posterosuperiorly on the insula and divides into branches distributed to the insula and the adjacent lateral cerebral surface. MCA supplies the bulk of the frontal, parietal and lateral portions of the temporal lobes (Goldstein, 2020). MCA has both the central and cortical branches. The cortical branches send orbital vessels to the inferior frontal gyrus and the lateral orbital surface of the frontal lobe (Standring, 2021). The frontal branches supply the precentral, middle and inferior frontal gyri. Surgical nomenclature divides the vessel into four parts:

- M1 (sphenoidal) from the termination of the ICA to the bi/trifurcation
- M2 (insular) running in the lateral (Sylvian) fissure
- M3 (opercular) coming out of the lateral fissure and,
- M4 cortical portions.

Figure 2.18 shows the four segments of the MCA in the coronal view.

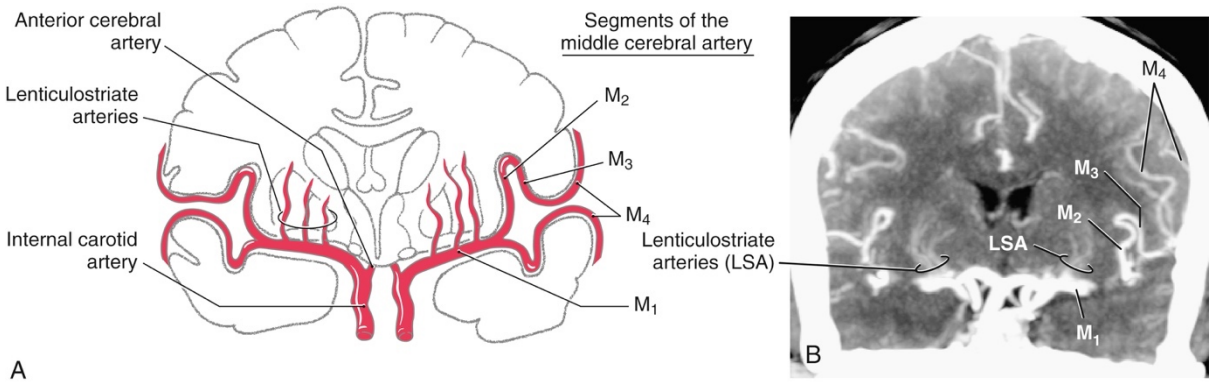

Figure 2.18: *The cerebral hemispheres showing the middle cerebral artery segments in the coronal section.*

By permission from Elsevier. Haines, (2018).

A) A representation showing the MCA segments: M1, M2, M3 and M4, B) A CTA showing the blood vessels in segments (M1 – M4) in a patient. LSA = lenticulostriate arteries.

Whilst Figure 2.19 represents an angiogram showing both the MCA and ACA with their segments in the anterior view. The rare variation of the OA taking origin from the MCA can be explained by the non-migration of the PVOA taking into consideration that the MCA is

embryologically a branch of the anterior division of the primitive ICA which appears later than the usual migration of the PVOA (Robert *et al.,* 2020).

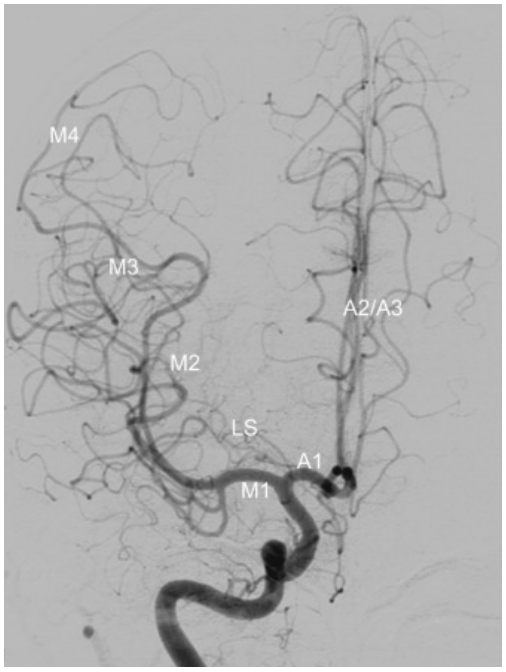

Figure 2.19: *A digital subtraction angiogram of the internal carotid artery with segments of the middle and anterior cerebral arteries.*

By permission from Elsevier. Barras and Bhattacharya, (2021).

Segments of the middle cerebral arteries (M1 - M4), and anterior cerebral artery (A1 - A3) are visible. LS = lenticulostriate arteries.

2.11.4 The ophthalmic artery taking origin from the posterior communicating artery

Studies by (Fisher 1913; Keen 1946; Hills and Sament 1968; Nakata and Iwata 1987; Naeini *et al.,* 2005) so far that reported of the cases where the OA was seen taking origin from the PComA. The study by Nakata and Iwata (1987) was however published in non-English literature although the abstract was written in English. The findings from these studies are summarised in Table 2.4.

Table 2.4: Summary of studies showing the ophthalmic artery taking origin from the posterior communicating artery

Author, year	**Additional findings**
Fisher (1913)	Absence of both ICA. On the right side, the OA was seen emerging on the common trunk for the anterior and middle cerebral arteries. On the left side, the OA emerged on the trunk close to the PCA.
Hills and Sament (1968)	Bilateral absence of the ICA, with the OA taking origin from the PComA.
Keen (1946)	
Nakata and Iwata (1987)	Complete absence of the left ICA, OA arose from the PComA.
Naeini *et al. (*2005)	Unilateral absence of the right ICA, origin of OA from the ipsilateral PComA.

No informative embryological explanations were given in the development of this OA variant. In Figure 2.20 is an example showing the rare type of OA origin from the PComA.

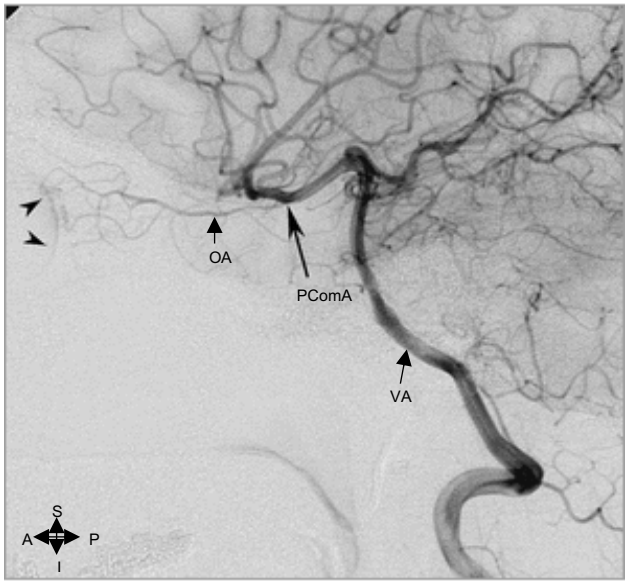

Figure 2.20: *An anteroposterior view of angiogram showing the origin of the ophthalmic artery from the posterior communicating artery.*

(Modified from Naeini *et al. (*2005). OA = ophthalmic artery, PComA = posterior communicating artery, VA = vertebral artery, arrowheads = indicate choroidal blush within the orbit.

2.11.5 The ophthalmic artery taking origin from the basilar artery

The basilar artery (BA) origin of the OA is exceptionally rare, and the current developmental theories do not provide a satisfactory explanation for this occurrence. Schumacher and Wakhloo (1994) state that the primordium of the OA appears significantly later than the regression of the primitive carotidobasilar anastomotic arteries, and that it is formed from several vessels instead of one primitive trunk. For this variation the authors noted that the ICA was not involved in providing the origin of the OA. Mohr *et al. (*2004) further state that the origin of this variation type can be explained by the primitive trigeminal artery (PTA) which connects the proximal intracavernous portion of ICA and distal third of BA. Therefore, anastomosis between the stapedial artery and the vertebrobasilar system or the PTA appears to be a more probable explanation of this unusual variation (Schumacher and Wakhloo, 1994; Mohr *et al.,* 2004). In Figure 2.21 is an example showing the OA taking origin from the BA.

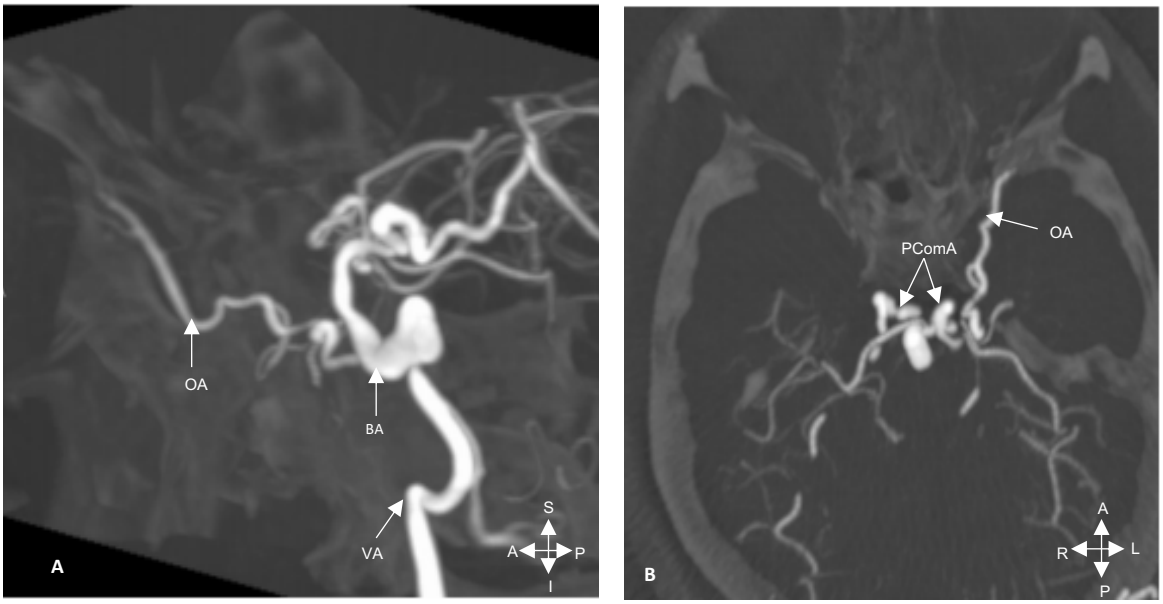

Figure 2.21: *An ophthalmic artery taking origin from the basilar artery.*

Modified from Rivera *et al. (*2015).

A) a lateral view showing the OA arising from the basilar trunk and coursing toward the orbit, B) an axial view showing the OA arising from the basilar trunk and coursing towards the orbit.

A high risk of ICA anterior wall aneurysms is associated with anomalous origins of the OA (Bertelli *et al.,* 2017). Intra-orbital OA aneurysms appear to occur in the first or second part of the OA (Bertelli *et al.,* 2017). Clinical features of the intra-orbital ophthalmic aneurysms are not fully understood as there are few published descriptive reports (Ezura *et al.,* 1997; Bertelli *et al.,* 2016). Rupture of the intra-orbital ophthalmic aneurysm is an extremely rare occurrence which has an associated high risk of affecting vision. Surgery should therefore be performed

to prevent rupture of the aneurysm. Large OA aneurysms frequently result in a gradual loss of the visual field (Bertelli *et al.,* 2017).

In addition to the formation of the OA aneurysms, there are several arterial diseases and pathologies that may develop intra-orbitally, altering the arterial and haemodynamic patterns (Bertelli *et al.,* 2016). Among those diseases and pathologies are: rubeosis iridis (also called neovascularisation of the iris), neurovascular glaucoma and retinoblastoma. Rubeosis iridis and neurovascular glaucoma develops through a gradual chronic ocular ischaemia in patients with the complete internal carotid artery occlusion (ICA-O) and are mostly seen in adults (Bertelli *et al.,* 2016). In cases where the OA does not originate from the ICA, the intra-orbital blood supply in a patient with ICA-O will become limited (Ogawa *et al.,* 1990).

The close anatomical relation of the OA with the ON, dural margin of optic canal (OC) and anterior clinoid process pose a difficulty in accessing the ophthalmic segment for surgical procedures. This may lead to several surgical operations such as extensive removal of the anterior clinoid process, unroofing of the OC, mobilisation of the OA and complete circumferential dissection around the ICA at the level of the dural ring (Kotsiomitis *et al.,* 2015).

2.12 Retinoblastoma treatment in Groote Schuur Hospital

Children who are receiving intra-arterial chemotherapy (IAC) treatment for retinoblastoma may present with different anastomotic arterial patterns caused by late stage pathology (Bertelli *et al.,* 2016). The treatment for intra-ocular retinoblastoma is intra-arterial chemotherapy and, therefore, it is imperative that the clinician identifies the correct vessel to administer the treatment (Bertelli *et al.,* 2016). In 2006, another method of treatment, the ophthalmic artery chemosurgery (OAC) was introduced with the hope of saving eyes with extensive intra-ocular retinoblastoma in order to avoid enucleation (Abramson *et al.,* 2012). This method has successfully been performed in over 26 countries worldwide (Abrahamson *et al.,* 2012). The OAC treatment at the Groote Schuur Hospital (GSH) in South Africa was first done in 2009, and to date, the number of successful cases is continuously increasing, according to Dr Karin Lecuona (personal communication on 30 May 2017), an ophthalmologist who dealt with retinoblastoma cases during her tenure.

2.13 Summary

After having done an extensive literature review of the anatomy of the orbital blood supply, it became evident that a range of variations in both the origin and course of the OA are well documented. The anastomotic patterns between the ECA and ICA and their role in the orbital blood supply are also well documented. The anastomotic patterns between the ECA and OA are quite numerous, some were seen to be more common and some rare. This study presented an opportunity to explore more on this topic.
Thorough embryological studies in the past offer explanations for the formation of variations and anastomotic patterns.

Different imaging modalities are also used, highlighting the benefits and disadvantages which were of great value in the approach to reviewing the patients' images. It was noted that some variations will be clearly seen only in certain haemodynamic circumstances. Therefore, it was important to select the best imaging modality to generate a hight quality image in order to visualise the orbital anastomoses and variations. Images of patients receiving treatment for retinoblastoma in its early stages were also included in the current study to see the patterns of blood supply.

Studies done on this topic are however in regions of the world elsewhere than South Africa up until the present time. The current study presented an opportunity for exploration of variations and their frequencies in a South African sample and to compare these findings with published studies from other parts of the world.

No single published study was seen conducting this research across all age groups. The current study was an investigation into variations in the arterial supply via the external and internal carotid arteries to the bony orbit and eyeball in full-term fetuses, infants, children, adolescents and adults.

Lastly, through a combination of the gathering data by dissection and use of patients' images, it was possible to record and describe the anastomotic patterns between the ICA and ECA in both the left and right orbits of the subjects. All variations in patterns were observed and documented, also noting the laterality, sex, age and the side most commonly showing the variations.

The findings from this study may help surgeons and interventional radiologists when performing procedures in this area as a useful reference when looking for connections

between the ECA and ICA. Several other variations found to be unique to this study will add to the existing body of applied anatomical knowledge.

The chapters that follow will give an overview of how the study was conducted, highlight the findings and discuss the results in comparison to published studies from elsewhere in the world.

CHAPTER 3: MATERIALS AND METHODS

3.1 Study design

This was a descriptive, observational study which focused on identifying the variation patterns of the orbital blood supply and their frequencies.

3.2 Ethical considerations

The ethical approval to use samples for the current research was sought in two ways for the dissections and access of patient files:

i) The use of human remains for this project was approved by the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences, University of Cape Town with ethics number: 469/2018 (refer to appendix A). Bodies were acquired by the Department of Human Biology through the Body Donation programme in the form of consenting donations and bodies of indigent people by strictly adhering to the South African National Health Act, 61 of 2003, sections 62-64. No additional ethical approval was required for research on the bodies donated to the Department of Human Biology, as consent for teaching and research activities is included in the documentation under the Body Donation programme. The indigent people did not give consent for use of their bodies; therefore, permission was granted by the Department of Health.

ii) Permission to access and use the patient files was granted by the Groote Schuur Hospital Ethics committee (refer to appendix A) and the head of Radiology Department in Groote Schuur Hospital granted permission by email communication to access and use the patient records within the Department. No informed consent by the patient was required as the study on the patient's records was done retrospectively.

3.3 Description of the population forming the sample size

The sample for this study consisted of two components:

i) Dissections done bilaterally on human bodies (full-term fetuses and adults) in the Department of Human Biology. The full-term fetuses are obtained in a form of donations from the New Somerset Hospital in Cape Town. The Department of Human Biology, University of Cape Town receives approximately 120 adult bodies per year used for both teaching and research purposes. Traditionally the term cadaver has been used to describe

bodies available to undergraduate and postgraduate students at institutions such as this one. In recent times with a more humanistic approach to human remains being used for the training of health care professionals the term body is being used more frequently.

ii) Reviewing of patient files from Groote Schuur Hospital in the form of angiograms of children and adults who had come in for clinical interventions of the cerebrovascular region.

3.4 Orbital dissection on human bodies in the dissection hall

3.4.1 Sample size

A total of 63 adults and six full-term fetuses were dissected.

3.4.2 Sample selection

All bodies received in the Department of Human Biology between the years 2017 and 2019 were used for the study. The sample consisted of individuals from 22 to 100 years old and comprised both male and female sex. The bodies consisted of both unembalmed full-term fetuses (five males and one female) and adults (embalmed and unembalmed). Table 3.1 shows the total number of adults in terms of age groups.

Table 3.1: The number of adults in the total sample in terms of age groups.

Age group (yrs.)	**Males (n)**	**Females (n)**
20 - 30	4	1
31 - 40	5	4
41 - 50	7	2
51 - 60	4	2
61 - 70	7	3
71 - 80	5	3
81 - 90	7	4
91 - 100	1	2
Unknown age	2	0
Total	**42**	**21**

Table 3.2 displays the adults dissected through the orbital roof and Table 3.3 shows adults dissected through exenteration.

Table 3.2: The adult bodies dissected through the orbital roof in terms of age.

Age group (yrs.)	Males (n)	Females (n)
20 - 30	2	1
31 - 40	1	1
41 - 50	3	1
51 - 60	2	0
61 - 70	6	0
71 - 80	3	1
81 - 90	3	1
91 - 100	1	1
Unknown age	2	0
Total	**23**	**6**

Table 3.3: The adult bodies dissected through exenteration in terms of age.

Age group (yrs.)	Males (n)	Females (n)
20 - 30	2	0
31 - 40	4	3
41 - 50	4	1
51 - 60	2	2
61 - 70	1	3
71 - 80	2	2
81 - 90	4	3
91 - 100	0	1
Unknown age	0	0
Total	**19**	**15**

3.4.3 Inclusion and exclusion criteria

i) Inclusion criteria

- All bodies in the dissection hall where the orbital blood supply was able to be examined.

ii) Exclusion criteria

- All heads with pathologies in the relevant area of the skull and haemorrhage of orbital blood vessels.
- Eyes previously dissected by students during their dissection sessions, because the blood vessels were damaged.

3.4.4 Research methods

All dissections were done on bodies within the Department of Human Biology in the dissection hall and were photographed at an appropriate distance to obtain the best view of the image. An illuminating magnifying lamp (RS PRO LED with Table Clamp Mount, 3dioptre, 125mm Lens Dia., 125mm Lens) was used for dissections to show the arteries being dissected more clearly. Two dissection methods were performed for the embalmed and unembalmed bodies which are detailed below.

3.4.4.1 Dissection of embalmed adult bodies

Embalmed bodies consisted of those used for teaching purposes in the dissection halls. The endocranial cavities were pre-opened by the anatomical technicians in preparation for the practical sessions for the medical and postgraduate students working on the bodies. Dissection on 34 embalmed bodies was done through exenteration. The orbital rim was identified by palpation and the orbital content was removed using a scalpel along that orbital rim from below the level of the eyebrows all the way around through the orbicularis oculi muscle. The incisions were extended deeper towards the bony orbital rim; the periosteum was elevated first to the anterior lacrimal crest and then back to the anterior ethmoidal foramen as described by Campbell *et al.* (1995). The eyeballs were then removed from the orbits by cutting through the ON proximal to the eyeball leaving just the blood supply and orbital extrinsic muscles still intact. Further dissection was performed to remove any excess tissue from around the arteries and extrinsic eye muscles. All the branches of the OA that were visible were analysed and the order of the OA origin and course in relation to the ON was recorded. The orbital walls were examined to see if there were any additional foramina and structures running within them in order to determine whether there were any additional arteries other than the OA supplying blood to the orbit. Figure 3.1 is an example of the dissection performed through exenteration.

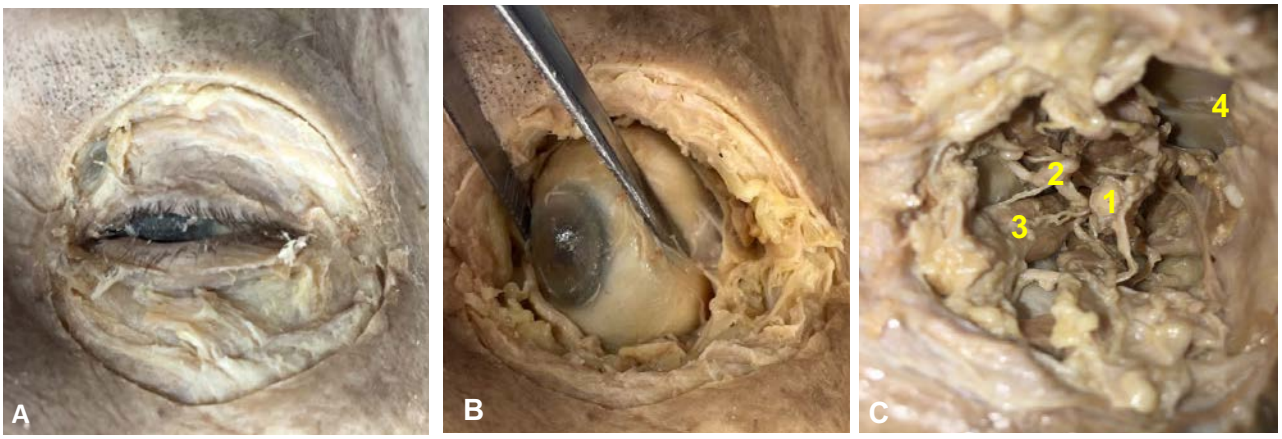

Figure 3.1: *The successive steps showing dissection of the orbit through exenteration.*

A) The skin around the orbital rim was removed to expose the eyeball with eyelids B) The eyeball was retracted and loosened from the surrounding fat pad in preparation for removal and leaving just the muscle cone and the optic nerve intact posteriorly. C) The eyeball and orbital fat was removed from the orbit exposing the extra-ocular muscles and the blood vessels within the orbit. 1 = optic nerve, 2 = ophthalmic artery, 3 = extra-ocular muscle, 4 = orbital roof, S = superior, N = nasal, I = inferior, T = temporal.

3.4.4.2 Dissection of unembalmed bodies

Silicone was injected into the ICA on the neck on one side of the head until a sufficient amount had filled the arterial system, which was achieved by observing the silicone emerging from the opposite ICA. Silicone was injected intra-arterially to identify the arterial supply to the orbit more clearly.

Figure 3.2 is an example showing the injected silicone into the internal carotid arteries on both sides of the heads.

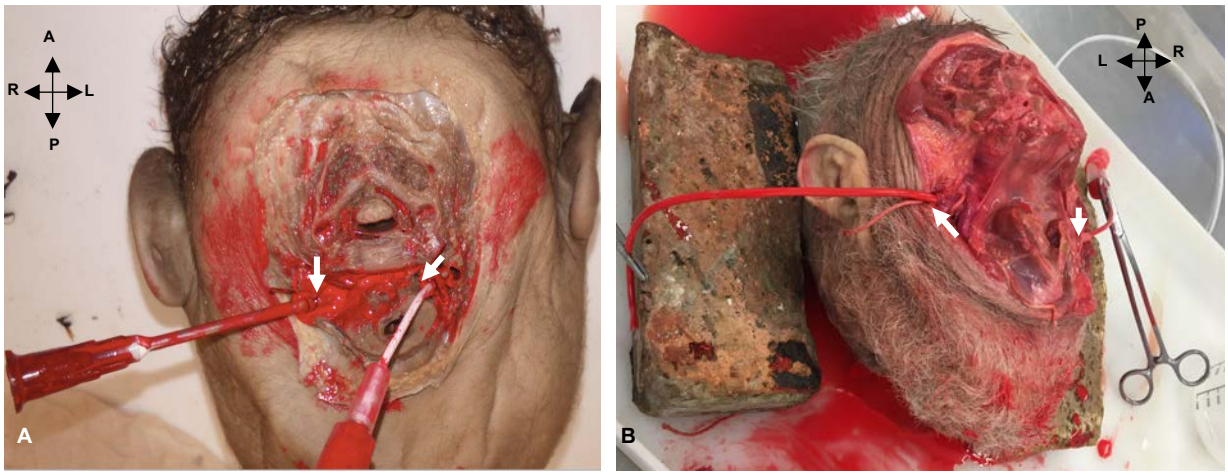

Figure 3.2: *Injection of silicone into the internal carotid arteries in both sides of the neck using the canula.*

A) a full-term fetus head B) an adult head. White arrows = indicate the point where canula enters the ICAs on both sides of the neck.

Table 3.4 shows the silicone solution ingredients preparation processes.

Table 3.4: Silicone ingredients.

Measurements	Reagents
5mL	S1 thermoplastic silicone elastomer
25mL	S14 Ti-acetyl acetonate silicone pressure-sensitive adhesive

3.4.4.3 Preparation of silicone injection procedure

The liquid ingredients listed above were mixed in a glass bowl (Arcoroc with dimensions: 270mm(L) x 195mm(W) x 95mm(H)) and stirred with a wooden paint stick (15cm) until slightly thick and ready to be injected into the heads. The heads from bodies that were used in surgical workshops that were kept in a freezer post-workshop after they were stored at -20 ^{o}C were injected with silicone. For the purpose of the present study, these heads were thawed overnight and checked that they were completely thawed the following day before silicone was injected through the internal carotid system. A cannulated tube was inserted in the ICA on one side of the neck and ligated with string. This was done to help prevent backflow of the silicone during the injection.

Water was injected through the cannula prior to injection with silicone using a 50mL syringe until it was seen escaping from the ICA on the contralateral side. This was done to wash away any particles/blood clots that might have been lodged within the arterial system. If leakage of the internal vessels occurred, the volume of the water outlet would be notably reduced. Silicone was injected through the same cannula into the ICA and the pressure maintained until the solution appeared through the opposite ICA. Hand pressure was applied to the syringe to inject both the water and silicone. Subsequently, the head was placed in a freezer at a temperature of -22^{o}C for 2 days to allow the intra-arterial silicone to solidify before dissection commenced.

A highspeed bone drill was used to open the intracranial cavity in order to gain access to the orbital roof of both orbits. The orbital roof was removed, the orbital contents were exposed, and dissections of the orbits were done through a superior approach. The superior approached allowed access to the structures within the orbit. The orbital roof was removed from a total of 29 skulls. The optic sheath below the bone (periorbita) was incised using a scalpel elevating it with tweezers to expose the OA and related structures. This type of dissection method allowed for the OA to be exposed and observed from its entry point through the OC at the orbital apex after branching off from the ICA. The origin and course of the OA

were described as either superolateral, superior, superomedial, inferior, inferolateral or inferomedial from the ICA. A similar method was used to describe the position of the OA origin relative to the ON. Figure 3.3 is an example of the dissection through the orbital roof.

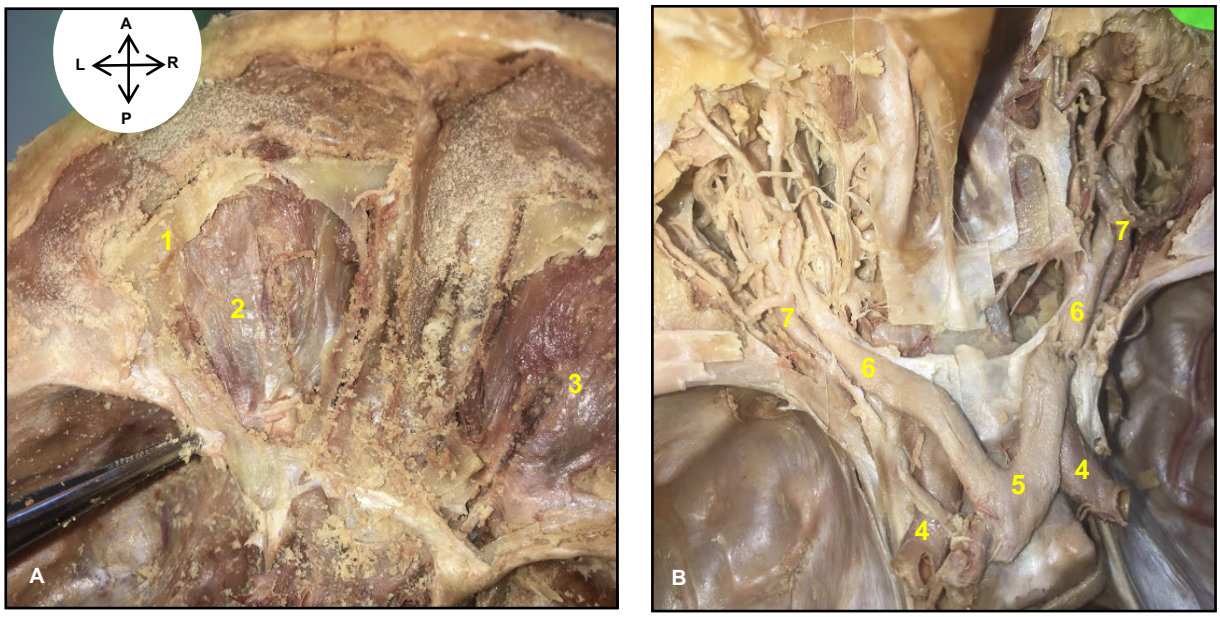

Figure 3.3: *A superior view showing dissections through the orbital roof.*

A) the anterior cranial fossa showing the opened orbital roof B) the orbital roof is removed exposing the orbital contents. 1 = remnants of the bone forming the orbital roof, 2 = periorbital sheath over the extra-ocular muscles, 3 = superior extra-orbital muscles exposed,4 = internal carotid artery, 5 = optic chiasma, 6 = optic nerve, 7 = ophthalmic artery.

The relationships between the proximal course of OA, ON, OC and ICA were identified and recorded using digital photography by means of a cellphone rear camera (iPhone 6s Plus, 12 megapixels). The frontal nerve was reflected anteriorly together with the superior group of extrinsic orbital muscles namely, superior oblique, superior rectus, levator palpebral superioris. This was done to help visualise the orbital blood supply patterns in relation to the ON and the extra-ocular muscles. The orbits were examined after these dissections had been performed in order to determine whether there were any other foramina that could provide points of entry for certain blood vessels other than the OA.

3.4.4.4 Dissection on full-term fetuses

Dissections of full-term fetuses were performed in the same manner as in the unembalmed adult bodies (Section **3.4.5.2)**. This was done to establish whether there were any changes in the patterns of blood supply in the full-term fetus life stage in comparison to the adults. Digital

photographs were taken at an appropriate distance for each eye to display all the dissected blood vessels.

3.4.5 Data gathering and analysis

Dissected specimens were given reference numbers for identification purposes. In order to protect the right to anonymity of all subjects in this study, both bodies in the dissection hall and patients who have undergone angiograms, a reference number was assigned to each individual which was known only to the principal researcher. These dissected specimens were recorded in the report sheet with additional notes. The notes were used to record the results and the discussion of the findings. Digital photographs that were taken were transferred to a computer. The images were studied, and the orbital vascular anatomy was analysed. The Microsoft PowerPoint tools (Microsoft Office 2019) were used to highlight and trace the OA and its branches from the point of emergence at the ICA. Further schematic representations were produced in consultation with a professional artist.

3.4.6 Inter- and intra - observer error

i) Intra-observer error

The first ten dissections were performed and data was collected. Before moving on to the next set of dissections the following day, data recording on the first ten dissections was repeated and results were compared. If the results were similar, the researcher continued with dissections. If the results were different, the researcher examined the dissected specimen again and recorded the findings for a third time. The three reports were then compared to determine which two were most similar and the results were then recorded.

ii) Inter-observer error

A colleague was trained to observe and record findings in the area while working independently. After collecting data from the first ten dissections, the dataset of the researcher and that of the colleague were then compared to see if there were any discrepancies. If the results were similar, then the researcher moved to the next set of dissections. If the results were different both the researcher and this colleague sat together and went through the dissected specimens again to identify the structures more accurately and thereby resolved

these differences. Based on the discussion with the colleague involved, the researcher then proceeded with accurate data collection.

The illustrations shown in Figures 3.1 and 3.2 are based on studies by Hayreh (1962a, 1962b and 2006) and Naudy *et al. (*2018) reporting alternative OA course orientations. The following illustrations were designed for this study to assist with categorising the OA orientations revealed in the sample population. These were used to identify and record all the observations in the study for the dissections and angiograms. Figure 3.4 shows the different OA course orientations in relation to the ON from the point of emergence at the ICA. These orientations were noted and recorded similar to that of the dissections done through the orbital roof.

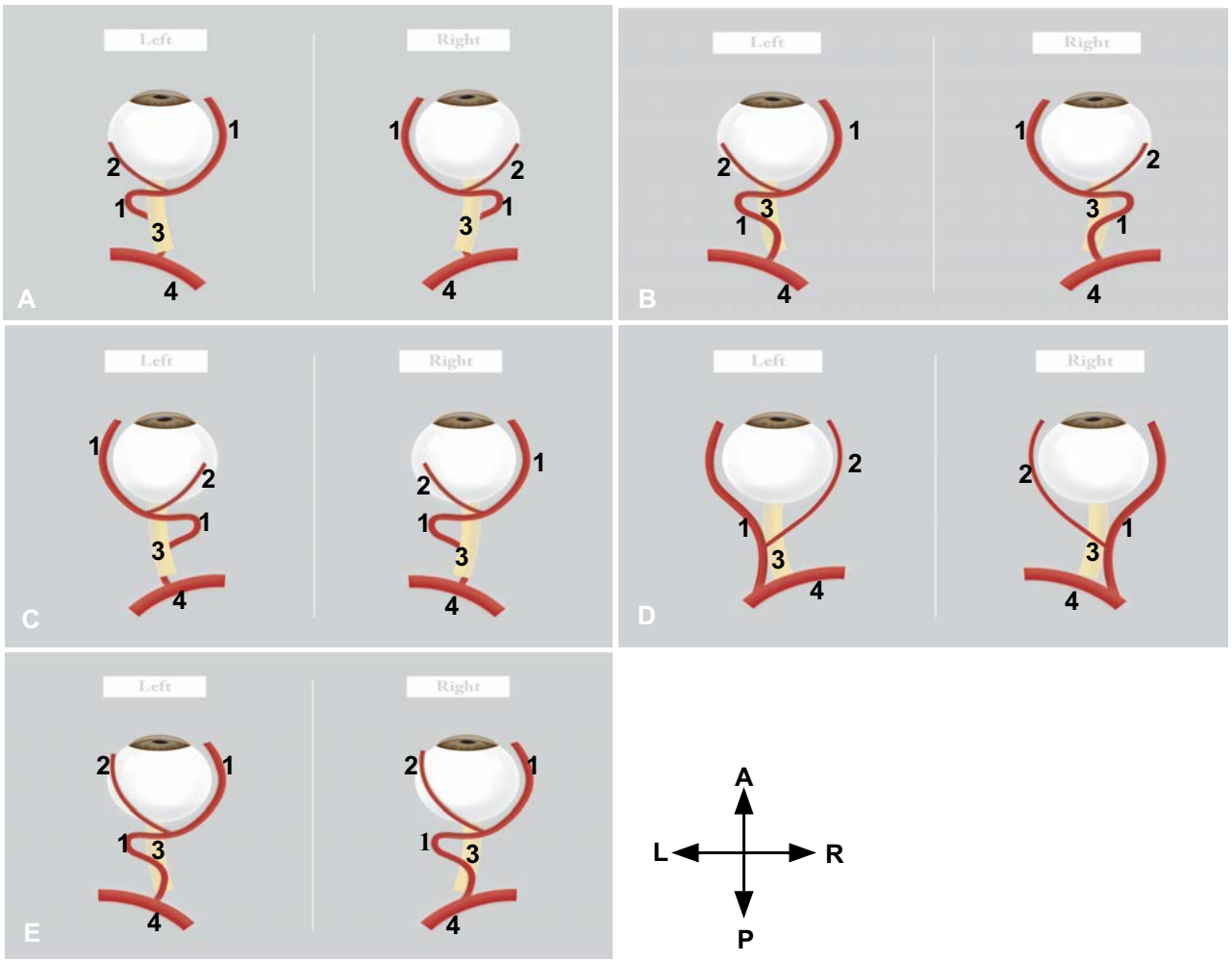

Figure 3.4: *Schematic representations showing different ophthalmic artery orientations in relation to the optic nerve from the point of emergence at the internal carotid artery.*

A) OA originates from the ICA and courses inferior to the ON and laterally in both the left and right orbits. OA then crosses superior to the ON towards the medial side and gives off branches. B) OA originates from the ICA and courses superior to the optic nerve in both the left and right orbits crossing toward the medial side. C) OA originates from the ICA and courses inferior to the optic nerve towards the medial side in both the left and right orbits. OA then crosses superior to the ON towards the lateral side and gives off branches. D) OA originates from the ICA and courses laterally without crossing the optic nerve. It then gives off branches. E) OA originates from the ICA and courses superior to the optic nerve in both the left and right orbits. In the left orbit it crosses towards the medial side, whereas in the right orbit it crosses towards the lateral side. 1 = ophthalmic artery (OA); 2 = branch from the OA (contralateral side); 3 = optic nerve (ON); 4 = internal carotid artery (ICA).

The positions of the OA in relation to the ON when the OA was dissected through exenteration are shown in the illustration in Figure 3.5.

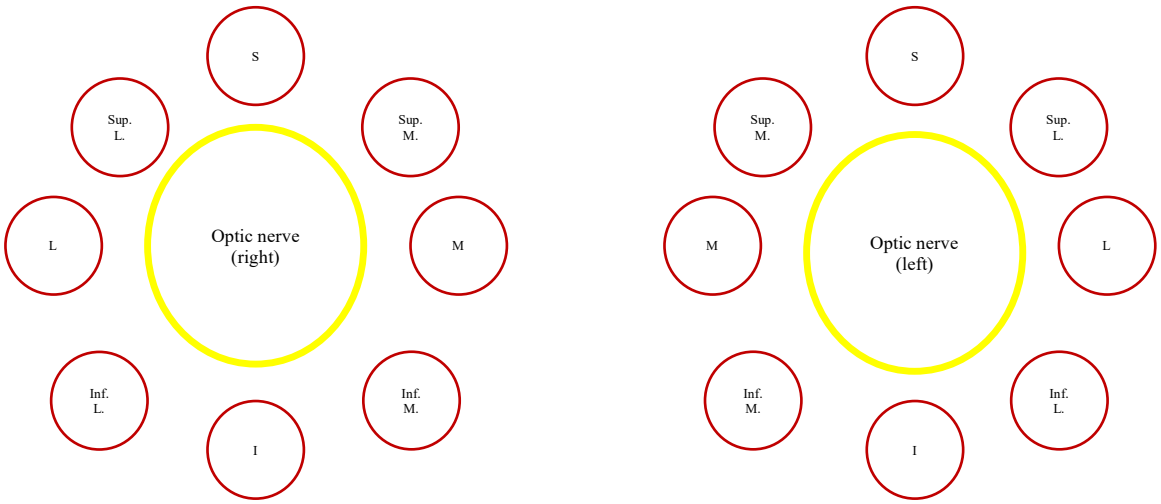

Figure 3.5: *Positions of the ophthalmic artery in relation to the optic nerve.*

S = superior, Sup.M. = superomedial, M. = medial, Inf.M. = inferomedial, I = inferior, Inf. L = inferolateral, L = lateral, Sup.L = superolateral

3.5 Methodology for angiograms of the orbital blood supply

3.5.1 Analysis of angiograms - a retrospective study

In order to complement the cadaveric data and to source information for age groups missing from the cadaver orbital dissections, a retrospective study was done using angiograms. All patient data were accessed retrospectively within the Groote Schuur Hospital premises through the hospital database known as the picture archiving and communication system (PACS). The PACS system database is a software that keeps files of all clinical images within the hospital and has a search portal that requires a unique password and username for the user to gain access to the records. Data images in the PACS system are stored in the digital imaging and communications in medicine (DICOM) system. These records consist of several angiograms and written reports with all the clinician's notes showing the diagnosis of patients and procedures performed. These records also have demographic data which was helpful to evaluate the images.

Images reviewed were of patients who were admitted to the hospital for interventions for the treatment of intracranial aneurysms, thrombolysis, trauma, and retinoblastoma. To maintain confidentiality, each patient was given a specific identification number by the researcher in order to hide their identity which was only known to the researcher.

3.5.2 Sample size

A total of 923 patients of both the male and female sex going through intracranial interventions at the Groote Schuur Hospital were analysed. Of the analysed cases, only 870 (519 females and 351 males) cases were included in the study.

3.5.3 Sample selection

Data was collected from all contrast injected angiograms that were available between January 2015 to August 2020. The files were opened to see all those that showed folders marked DSA and Intracranial vascular intervention. Within each of these two folders, separate folders for CT and MRA scans had mostly been prepared. In a small number of instances, the images were not divided into separate folders for the scans.

All selected cases were then analysed from the first case available on the list and following the sequence in which they appeared according to data availability. All these data were stored on a computer in a separate folder with reference numbers created by the researcher and these data were later used for compiling the research report. Demographic data such as age and sex and anatomical features of the OA from the point of emergence from the ICA and the course of OA in relation to the ON were recorded.

Guidance and supervision were provided by the supervisor and by a neurosurgeon in reviewing the first few images to ensure accuracy (Further details have been outlined in the intra- and inter- observer error section 3.4.5.). Among the reviewed images were also those of children who underwent retinoblastoma treatment. These children were referred from three hospitals in Cape Town namely, Groote Schuur Hospital, Tygerberg Hospital and Red Cross War Memorial Children's Hospital where they were admitted presenting retinoblastoma for treatment. The available data for treatment is of children ranging between the ages 1 – 8 years old. The sample for reviewed patients was made up of those in the early stages of treatment. In other cases reviewed, the arterial system could be visualised only in the eye receiving treatment as the contrast medium was injected into that eye only resulting in the arterial pattern of the other eye not being able to be visualised.

3.5.4 Inclusion and exclusion criteria

In order to eliminate any form of errors in the descriptions of variations in the OA and its branches, the following criteria were used:

i) Inclusion criteria:

- All images that showed contrast medium within the intracranial arterial system through to the orbital blood vessels.
- All the MRA and/ MRI (axial) view images which revealed the OA origin from the ICA and its course orientation.
- All the MRA and/ MRI (axial) view images which revealed the orbital blood supply even if it was not taking origin from the ICA.
- All files with all demographic data included sex and date of birth.

ii) Exclusion criteria:

- Subjects where intervention was performed through the posterior circulation with entrance through the vertebral arteries. The intervention in the posterior circulation did not allow the contrast medium to fill the anterior circulation.
- Subjects where the intra-orbital region was not shown.
- Images of patients with late stages of tumours for the treatment of retinoblastoma. The late stages of tumours can alter the patterns of blood supply, therefore give false results for our study.
- Files with incomplete demographic data sex and date of birth.

3.5.5 Research methods

The programmes that were used for analysis of the data were CTA, DSA and MRA. According to Wells *et al. (*2009), CT represents the most relevant form of imaging for the evaluation of the eye and orbit. Orbital fat provides excellent contrast for the demonstration of soft tissue structures with CT. Furthermore, the cross-sectional imaging provided by CT is well suited for the depiction of the complex anatomic relationships of the orbital structures. This advantage is shared by MRI, which has the additional capability of direct sagittal imaging. The MRI is particularly well suited to imaging the intracranial and intracanalicular portions of the optic nerves and the optic tracts (Wells *et al.,* 2009).

The arterial system was clearly shown through the highlights formed from the injection of radio-opaque contrast agent intra-arterially by means of a catheter and imaging was done through the X-ray based techniques. The radio-opaque dye allows for a detailed study of small blood vessels (Hanania *et al.,* 2002). The reviewed images were displayed in two views - the superior (axial) and lateral views. The most widely used MR imaging techniques for visualisation of the arterial system can be categorised as phase-contrast, time of flight or contrast enhanced methods.

The non-contrast MR- time of flight (TOF) and MRA scans were analysed in the axial view. Multiple planes were performed in order to achieve the correct plane for the demonstration of the OA as it emerged from the ICA coursing into the orbit. Images were evaluated in terms of the origin of the ICA and course through the optic canal to the orbit. The order of the OA crossing was also recorded, noting whether the OA crossed superior or inferior to the ON. The point of OA emergence from the ICA was also recorded noting whether it was superolateral or superomedial.

The OA was analysed both through the lateral and frontal views. Both the left and right sides of the patients were studied, and results were recorded for the available sides. If both sides of the patients were given a contrast medium, these were compared to note any differences and similarities. If only one side was available, the results were recorded.

The following types were developed for the current study to aid in identifying the varying patterns and positions of the ophthalmic artery taking origin from the ACA. These identification types were not mentioned in the literature.

- Type 1: the orbital blood supply taking origin from the ACA through the orbitofrontal artery, also known as the orbital artery, (no OA contribution).
- Type 2: the orbital blood supply taking origin from the ACA through the frontopolar branch (with OA contribution).
- Type 3: the orbital blood supply taking origin from the ACA through the orbitofrontal branch (with OA contribution).
- Type 4: the orbital blood supply taking origin from the ACA - A1 segment (no OA contribution). Type 5: the orbital blood supply taking origin from the ACA through the frontopolar branch (no OA contribution).

3.5.6 Inter- and intra-observer error

To measure the accuracy of observation and identification, the following criteria were used:

i) Intra-observer error

To limit the inter observer error, scans of 15 patients were reviewed in a day. Data collection was repeated on these scans the following day before moving on to the next set. This was done to establish whether the results from the previous day were identical. If results were not identical, the researcher made a third recording. The three sets of recordings were then compared and the two sets of the three that showed the most similar results were recorded. If results were identical then data collection continued and was paused at 30 patients and rechecked to confirm whether they results similar or different.

ii) Inter-observer error

The scans of first 15 patients were reviewed under the guidance of the supervisor with some input from the radiology registrar as they are knowledgeable in the imaging anatomy. All the images were then transferred to the PowerPoint presentation file. Relevant blood vessels were labelled, and the file was sent to a neuroradiologist who then confirmed the accuracy of identified structures. If the neuroradiologist was not in agreement with the findings, both he and the researcher sat together and went through the images again to identify the structures more accurately, reach agreement and then proceed.

3.5.7 Data recording

The raw data of the DSA, CTA and MRA/I were imported into a Microsoft Excel (Microsoft Office 2019) spreadsheet. This data was used for the analysis of the extra- and intra- orbital anastomoses between the ECA and ICA branches and also recorded any anatomical variations present.

3.6 Statistical analyses

Statistical analyses were accomplished with assistance after consultation with the statistician.

All data that were collected and recorded on the Microsoft Excel spreadsheets were sent to the statistician for statistical analysis and interpretation. All analysis was conducted using Stata Ver. 13 (StataCor, TX USA). Significance was taken as $\alpha < 0.05$.

The following values were tested: the mean frequencies and the standard deviation which was evaluated for all parameters. The differences between the eyes (left and right) were analysed using the student t-test. The following statistical tests were performed, namely the Shapiro Wilk, the Kruskal Wallis and Pearson's Chi-square tests.

i) The Shapiro-Wilk test is used to determine whether a random sample comes from a normal distribution (complete sample normality) (Shapiro and Wilk, 1965)

In this study, the test was used to determine if numerical variables (age) were normally distributed.

ii) The Kruskal Wallis tests are used commonly to determine whether the two or more groups are the same or different on same variable of interest when an ordinal level of data, or an interval or ratio level of data is available (Kruskall and Wallis, 1952).

In this study, the test was used to assess differences in age associated with the variations.

iii) The Pearson's Chi square test is a non-parametric test which is used in discrete data in the form of frequency. It is an independence test and is used to estimate the probability of some non-random factors to take account of the observed correlation (Turhan, 2020).

Categorical variables were analysed using the Pearson's Chi-squared test. The distribution by sex, age groups and presence of variations were reviewed.

Descriptive statistics were also used to describe distributions of the variables in the sample. The variables were measured by distribution by age, sex and presence of variations. The age categories were used to group the individuals for statistical analysis. To determine the age of the individual, the researcher used the provided demographic data on both the Departmental cadaver register and the PACS system. The ages of the bodies received in the Department of Human Biology were already recorded in the Departmental register and these were, therefore, transferred to the Microsoft Excel spreadsheet.

On the PACS system, the age was determined from the date of birth listed on the system and that of the clinical intervention. The age of the patient was calculated by subtracting the year of the clinical intervention from the year of birth and the ages were recorded in the Excel spreadsheet. The age categories were divided according to following the life stages: full-term fetuses, infants, children, adolescents, and adults as explained in Chapter 1.

When conducting data analysis on the cadavers, it became evident that most of the cadavers fell under the adults (19+ years) category, with a few full-term fetuses. It was, therefore, decided that in addition to the mentioned life stages, data needed to be presented in groups of decades from 20 to 90+ years in order to distribute the frequencies evenly e.g., 20 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69, 70 – 79, 80 – 89 and 90+ years. By dividing the age into decade categories, one could, therefore, make comparisons between the age groups and explore the non-linear relationships.

CHAPTER 4: RESULTS

Data were collected in two parts as described in Chapter 3, namely through orbital dissections and by reviewing angiograms. This chapter will provide detailed results from the research study. The results are presented in the form of photographs, figures, graphs and tables.

4.1 Orbital dissections

4.1.1 Adult cadavers

A total of 63 adult bodies were dissected. The dissections were performed in the from two orientational views, namely the orbital roof in 29 (46%) and by exenteration in 34 (54%) bodies. The sample consisted of individuals from 22 to 100 years old, with a mean (± SD) age of 60 years (± 21 years). All 63 bodies were included in the sample and of the 63, the age was known in 61 bodies and two bodies were of unknown ages and thus were listed as unknown in the data collection sheets and later in graphs showing results.

The sample consisted of both male and female sex. The majority of cadavers were male (n= 42; 66.7%). No statistically significant differences were noted in the mean age (p= 0.6813) between dissection techniques. The Pearson chi-squared test was used to determine if there was a significant difference between the two methods of dissection used in the study. There was no statistically significant difference between the males and females by the method of dissection (p = 0.049) (Table 4.1). Unless otherwise specified, all tables and graphs were copied from the statistical report.

Table 4.1: Distribution of sex between two dissection methods

Method of dissection	**Sex**		**Total**
	Female	**Male**	
Exenteration	15	19	34
Orbital roof	6	23	29
Total	21	42	63

Pearson chi-squared (1) = 3.8656, p-value = 0.049

The results of this study show both the usual and unusual course of the OA from its point of origin from the ICA and the relationship of its course in relation to the ON. The 'usual course' is an anatomical term that is used to refer to the normal (showing no variations) course of OA and the 'unusual course' refers to showing variations as used by Hayreh (2006) and Bertelli *et al. (*2016) in their reports on the OA.

4.1.1.1 Origin of the ophthalmic artery (OA) in terms of the internal carotid artery (ICA)

In the majority of cases, the OA originated from the ICA in both the left (n=61; 96.8%) and right (n=62, 98.4%) sides (Figure 4.1). Data stated as a percentage relates to the total sample size. In a total of three cases, the OA did not take origin from the ICA. In two cases, the origin of the OA was from the MMA on the left and from the ICA in the right eye. In one case the origin of the OA was from the MMA on the right, and from the ICA on the left. The OA in both the left and right orbits took origin from the ICA.

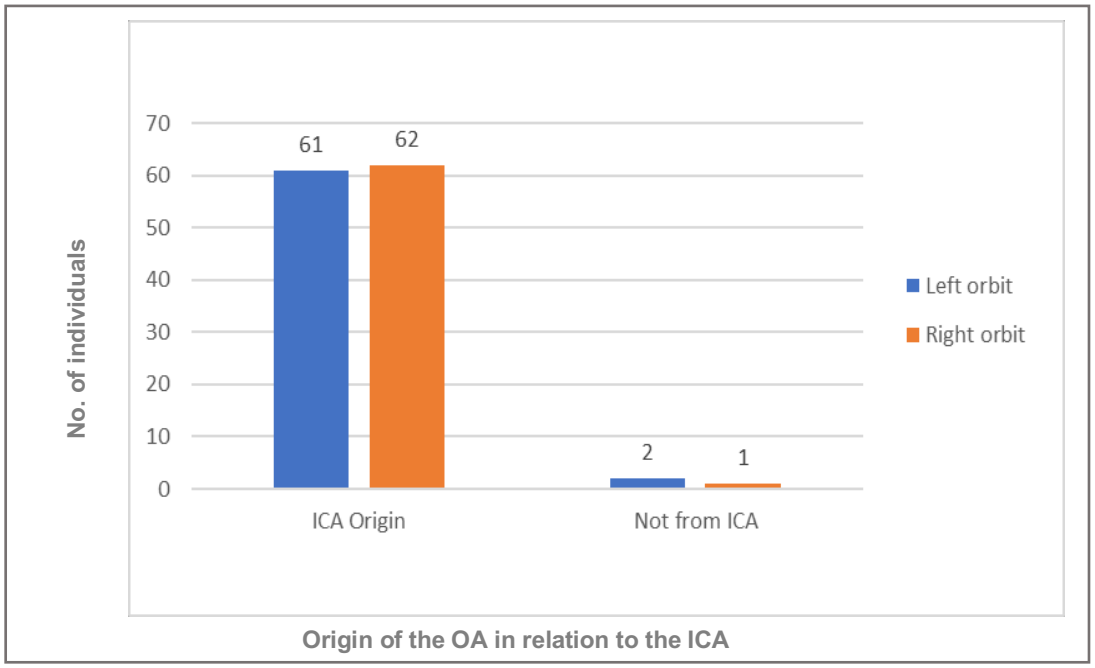

Figure 4.1: *Origin of the ophthalmic artery in the left and right orbits.*

The two cases (3.14%) of which the OA originated from the MMA in the left orbit are those of a 39-year old female and a 63-year old male, these showed the lowest percentage in the left orbit (Figure 4.2). The eleven individuals (17.46% of the total sample) in the 80-89 age category showed the highest percentage in OA taking origin from the ICA. This was because there were more individuals in this age group compared to the other age group categories. All of the individuals in each category showed the origin of the OA from the ICA with an exception

to the two with the origin of the OA from the MMA. Figures 4.2 and 4.3 below show the cases of the OA taking origin from the ICA and those not taking origin from the ICA.

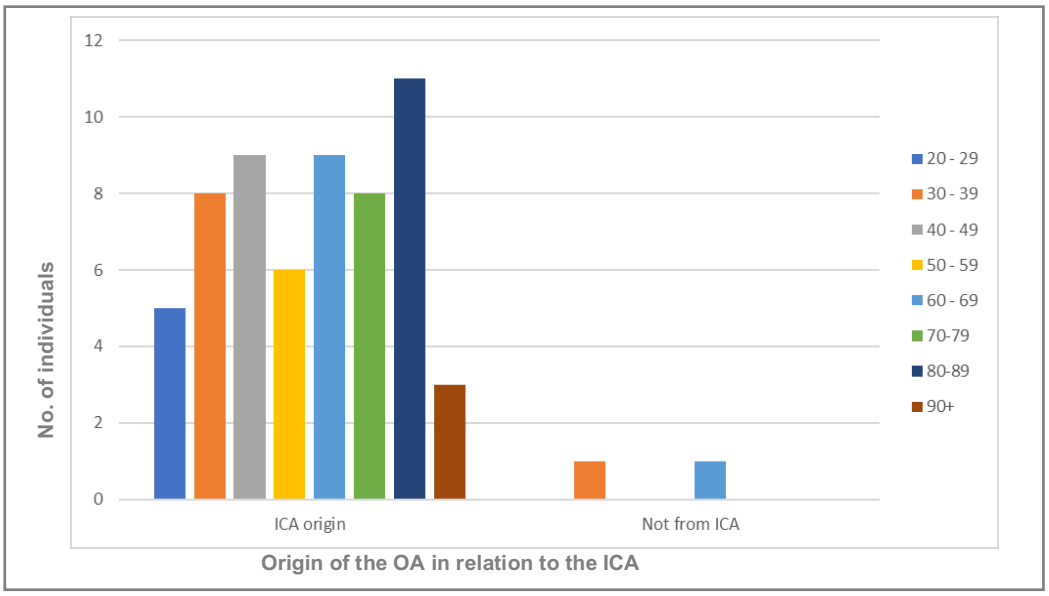

Figure 4.2: *Distribution of age groups by origin of the ophthalmic artery in the left orbit.*

The one case where the OA did not originate from the ICA in the right orbit was from a male of unknown age (Figure 4.3). A comparison was done in all cases in both the left and right eyes.

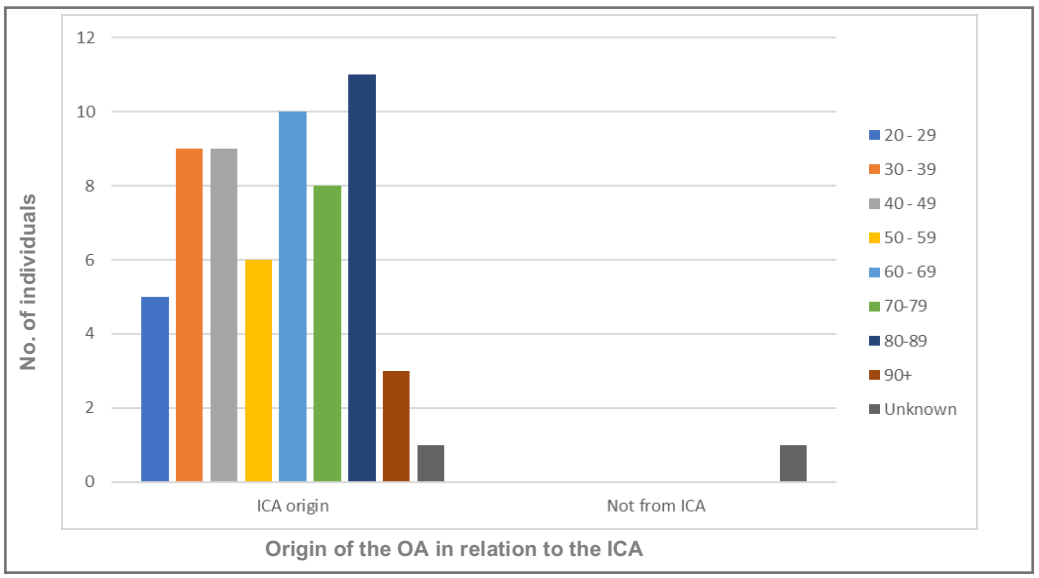

Figure 4.3: *Distribution of the age groups by origin of the ophthalmic artery in the right orbit.*

4.1.1.2 The intracranial and intra-orbital course of the ophthalmic artery in relation to the optic nerve

Figure 4.4 is an example of the latex filled left orbit of a 76-year old male which was dissected through the orbital roof. The usual course of the OA emerging from the ICA intracranially and coursed to emerge through the OC to reach the intra-orbital space in the left orbit is shown. Two regions are indicated in the figure as the OA emerged from the ICA, namely, the intracranial space (ICS) and as it coursed intra-orbitally and the intra-orbital space (IOS).

The OA then continued to travel laterally and changing direction just before it reached the posterior part of the eyeball and crossed superior to the ON towards the medial side of the orbit. The OA then gave off several branches to supply the different orbital contents, including the eyeball and extra-ocular muscles.

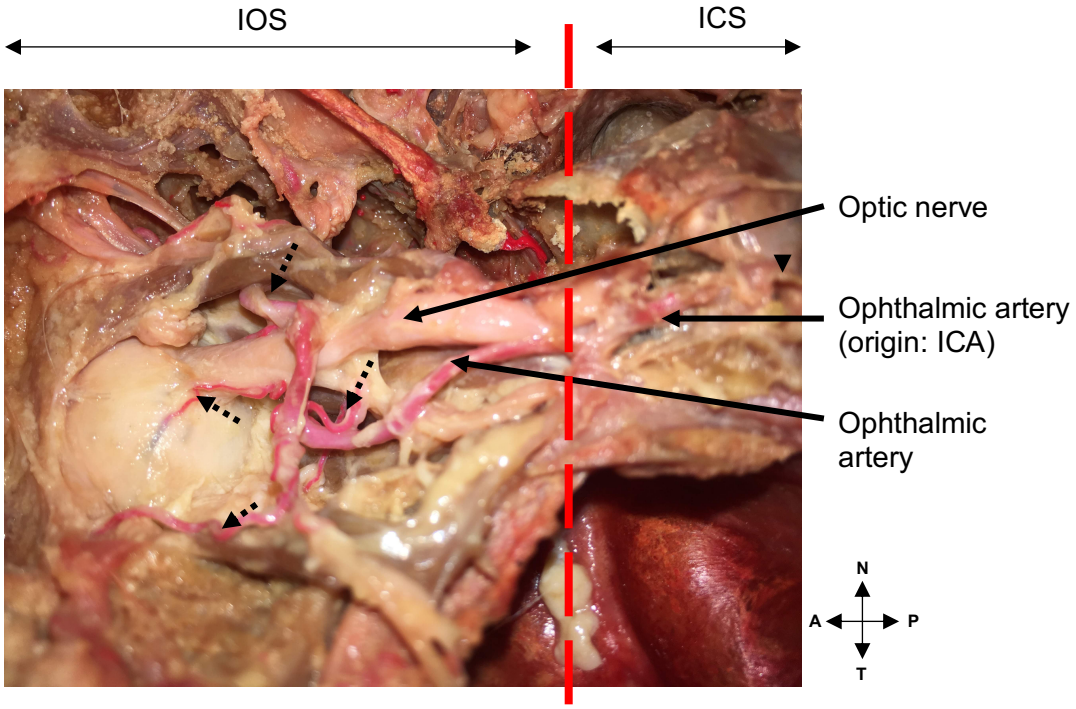

Figure 4.4: *The ophthalmic artery emerging from the internal carotid artery intracranially and coursing towards the intra-orbital region.*

ICA = internal carotid artery, IOS = intra-orbital space, ICS = intracranial space. black arrowheads with dotted lines show branches of the OA, black arrowhead points to the ICA. A = anterior, P = posterior, N = nasal, T = temporal.

4.1.1.3 The orientation of the origin of the ophthalmic artery with respect to the internal carotid artery and the optic nerve

The point at which the OA emerged from the ICA was observed and recorded in 126 orbits (63 bodies). In the bodies that were dissected through the orbital roof, the point of origin of the OA from its intracranial segment, OA origin from the ICA and the course of OA intra-orbitally in relation to the ON was recorded. Significant differences were noted in the patterns of the OA and ON relationship (Figure 4.5) when comparing individuals using both dissection methods ($p<0.001$ on the left and right sides).

The OA emerged from the ICA and coursed in relation to the ON in all of the orientation directions with respect to the ON upon leaving from the ICA as shown in Figure 4.5. A total of eight different orientations were noted in both the left and right orbits.

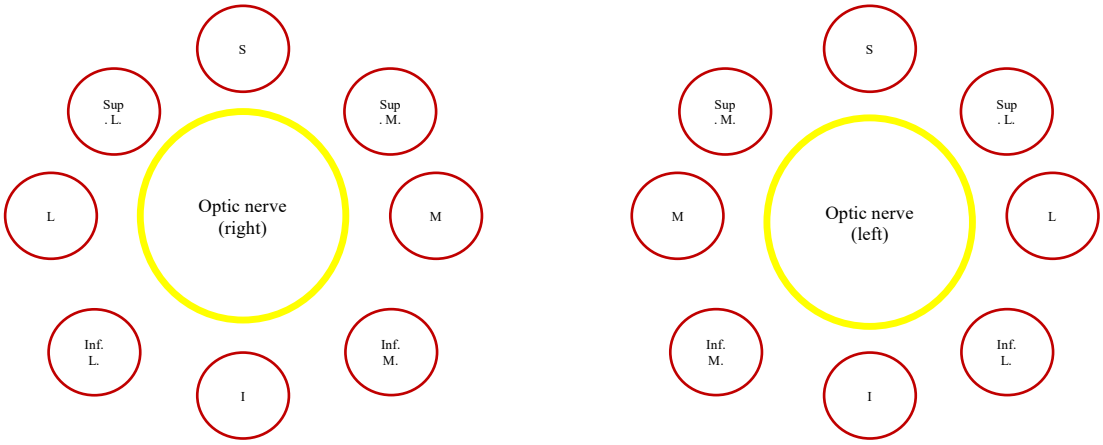

Figure 4.5: *A schematic representation of the ophthalmic artery orientation with respect to the optic nerve.*

I = inferior, Inf. M. = inferomedial, Inf. L = inferolateral, L = lateral, Sup.L = superolateral, S = superior, Sup.M. = superomedial, M. = medial.

As the OA emerged from the ICA at a certain orientation with respect to the ON, the OA maintained the original orientation in its course along the nerve. For example, when the OA origin from the ICA was inferior, the course of the OA in relation to the ON was also inferior. Therefore, the OA did not cross the ON but maintained the original orientation in its course.

In other cases, the OA emerged from the ICA in one orientation and then followed a different orientation in course. For example, the OA emerged from the ICA inferiorly, and then progressed medially until crossing the ON superiorly on the medial side. Therefore, the OA origin from the ICA was inferior, and its course in relation to the ON was superomedial. Tables 4.2 and 4.3 shows the frequencies of the OA orientation by age groups in terms of origin from

the ICA and course in relation to the ON in both the left and right orbits. In the left orbit, the origin of the OA was inferolateral and coursed medially in all individuals across all age groups except for one individual in the 30-39 age category. The individual in the 30-39 age category showed an inferolateral origin and inferior course (Table 4.2).

Table 4.2: The orientation of the ophthalmic artery by age group in bodies dissected through the orbital roof (left orbit) in ten-year intervals.

OA Orientation	**20-29 yrs.** **n (%)**	**30-39 yrs.** **n (%)**	**40-49 yrs.** **n (%)**	**50-59 yrs.** **n (%)**	**60-69 yrs.** **n (%)**	**70-79 yrs.** **n (%)**	**80-89 yrs.** **n (%)**	**90+ yrs.** **n (%)**
Inferior (origin and course)	-	-	-	-	-	1 (25%)	-	-
Inferior origin, superomedial course	-	-	-	-	2 (40%)	-	-	-
Inferolateral (origin and course)	-	-	-	-	1 (20%)	-	-	-
Inferolateral origin, inferior course	-	1 (100%)	-	1 (50%)	-	-	-	-
Inferolateral origin, medial course	2 (66.67%)	-	1 (25%)	1 (50%)	2 (40%)	2 (50%)	3 (75%)	1 (50%)
Inferolateral origin, superior course	1 (33.33%)	-	-	-	-	-	-	-
Inferolateral origin, superomedial course	-	-	2 (50%)	-	-	-	1 (25%)	-
Inferomedial (origin and course)	-	-	-	-	-	1 (25%)	-	-
Inferomedial origin, inferior course	-	-	1 (25%)	-	-	-	-	1 (50%)
Superolateral origin, medial course	-	-	-	-	-	-	-	-

- indicates no individuals showed this orientation

In the right orbit (Table 4.3), all individuals had an inferolateral OA origin orientation and medial course except for the one individual in the 20-29 age category. None of the individuals showed an inferior origin and course; inferior origin, and superomedial course; and the inferolateral origin and course in all age groups.

Table 4.3: The orientation of the ophthalmic artery by age group in bodies dissected through the orbital roof (right orbit) in ten-year intervals.

OA Orientation	20-29 yrs. n (%)	30-39 yrs. n (%)	40-49 yrs. n (%)	50-59 yrs. n (%)	60-69 yrs. n (%)	70-79 yrs. n (%)	80-89 yrs. n (%)	90+ yrs. n (%)
Inferior (origin and course)	-	-	-	-	-	-	-	-
Inferior origin, superomedial course	-	-	-	-	-	-	-	-
Inferolateral (origin and course)	-	-	-	-	-	-	-	-
Inferolateral origin, inferior course	-	1 (50%)	-	-	-	1 (25%)	-	-
Inferolateral origin, medial course	-	1 (50%)	1 (25%)	1 (50%)	3 (50%)	2 (50%)	3 (75%)	1 (50%)
Inferolateral origin, superior	-	-	-	1 (50%)	-	-	-	-
Inferolateral origin, superomedial course	2 (66.67%)	-	2 (50%)	-	1 (16.67%)	-	1 (25%)	-
Inferomedial (origin and course)	1 (33.33%)	-	-	-	1 (16.67%)	1 (25%)	-	-
Inferomedial origin, inferior course	-	-	1 (25%)	-	-	-	-	1 (50%)
Superolateral origin, medial course	-	-	-	-	1 (16.67%)	-	-	-

- indicates no individuals showed this orientation

When comparing the left and right orbits, a superolateral origin and medial course orientation were not seen in the left orbit, but this was seen in one individual in the 60-69 age category in the right orbit. The most common trend seen in the left and right orbit was an inferolateral origin and a medial course (n=12; 41.38%).

Overall, a Kruskal-Wallis test shows that there were no significant differences noted in the mean age of cadavers between different orientations (left orbit: p=0.6602; right orbit: p=0.7918) (Table 4.4). No significant association was noted between age groups and orientations (left orbit: p=0.393; right orbit: p=0.857).

Table 4.4: Mean age by orientation of the ophthalmic artery in bodies dissected through the orbital roof.

	Left Orbit		Right Orbit	
OA Orientation	**n**	**Mean (yrs.)**	**n**	**Mean (yrs.)**
Inferior (origin and course)	1	79	-	-
Inferior origin, superomedial course	2	61.5	-	-
Inferolateral (origin and course)	1	65	-	-
Inferolateral origin, inferior course	2	42.5	2	55
Inferolateral origin, medial course	12	65.3	14	63.3
Inferolateral origin, superior course	1	23	2	38.5
Inferolateral origin, superomedial course	3	59.3	4	59.5
Inferomedial	1	76	2	70.5
Inferomedial origin, inferior course	2	67.5	2	67.5
Superolateral origin, medial course	-	-	1	63

- indicates no individuals showed this orientation

4.1.1.4 The ophthalmic artery not taking origin from the internal carotid artery and its subsequent course

There were several cases where the OA did not originate from the ICA in individuals throughout the sample. Figure 4.6 is an example showing the intra-orbital vascular pattern from a superior view in both orbits of a 23-year old female dissected through the orbital roof without the use of latex infusion. In this individual, the pattern seen in the left orbit was different to that seen in the right orbit. In the left orbit, the OA coursed inferolateral to the ON and then gave off a common trunk that crossed superior to the ON after giving off several branches to supply the eyeball and surrounding structures within the orbit. In the right orbit, the OA coursed inferomedial to the ON and then gave off a branch before giving a common trunk that crossed superior to the ON.

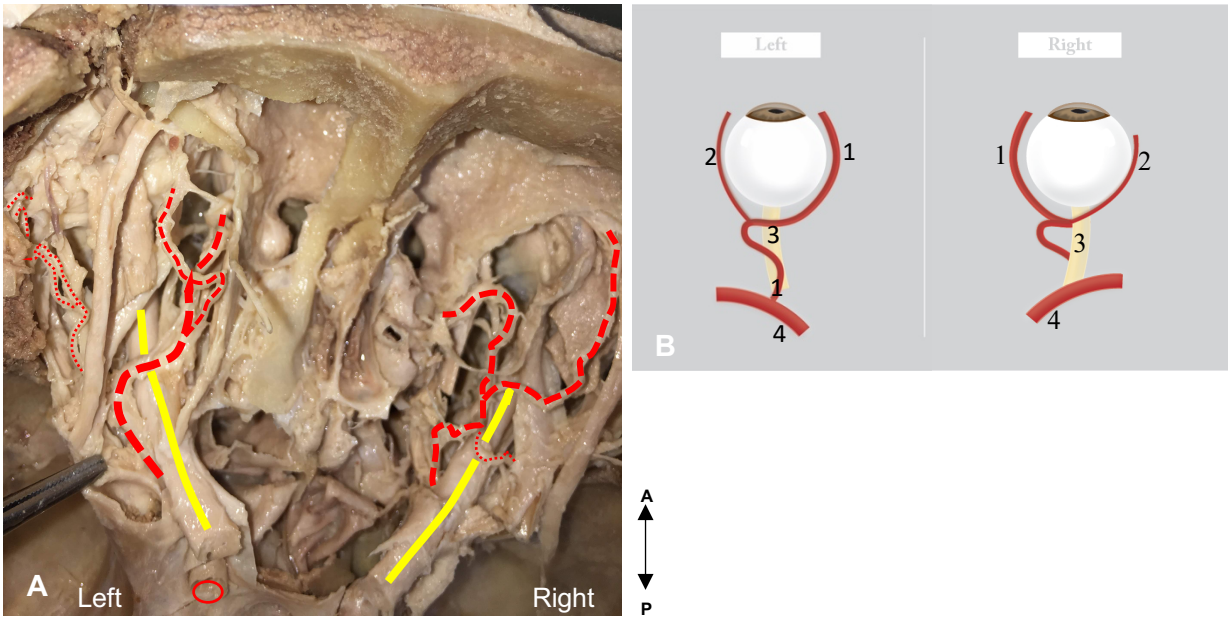

Figure 4.6: *Superior view of the orbital vascular supply in relation to the optic nerve of the left and right orbits illustrating the differences in orientation.*

A) Orbital dissection red ICA; thick red dotted lines = OA; small red dotted lines = several branches from the OA; yellow solid line = optic nerve and B) a schematic representation. 1 = ophthalmic artery; 2 = branch from the OA; 3 = optic nerve; 4 = internal carotid artery. A = anterior, P = posterior.

4.1.1.5 The orbital dissection through exenteration

Exenteration allows for a frontal view of the orbit and its contents. A total of eight different orientations of the OA in relation to the ON were observed in both the left and right orbits as previously shown in Figure 4.4.

Data was analysed in a form that could also show numbers according to age groups. The age groups were categorised in ten-year intervals starting from age 20 to 90+. No significant differences were noted in the mean age of bodies based on the Kruskal-Willis test displaying these orientations (left orbit: p=0.3642; right orbit: p=0.7229). No significant association was noted between age groups displaying mentioned orientations of the ophthalmic artery in relation to the ON (left orbit: p=0.522; right orbit: p=0.892).

Table 4.5 shows observations that were recorded within the left orbit. The majority of individuals displayed superolateral origin and superior course orientation of the OA in relation to the ON. The second highest frequency of orientation of the OA in relation to the ON was in a superolateral origin and course. Only one individual showed each of the following orientations: a medial origin and course, and also the superior origin and course (both in 30-39 age category), and an Inferomedial origin and inferior course (in the 80-89 age category).

Table 4.5: The orientation of the ophthalmic artery by age group for dissections through exenteration in ten-year intervals (left orbit).

OA Orientation	20-29 yrs. n (%)	30-39 yrs. n (%)	40-49 yrs. n (%)	50-59 yrs. n (%)	60-69 yrs. n (%)	70-79 yrs. n (%)	80-89 yrs. n (%)	90+ yrs. n (%)
Inferior (origin and course)	-	1 (14.29%)	-	1 (25%)	-	-	1 (14.29%)	-
Inferolateral (origin and course)	-	-	-	-	-	-	-	-
Inferolateral origin, inferior course	-	-	-	-	-	-	-	-
Inferolateral origin, medial course	-	-	-	-	-	-	-	-
Inferomedial (origin and course)	-	1 (14.29%)	1 (20%)	-	-	1 (25%)	1 (14.29%)	-
Inferomedial origin, inferior course	-	-	-	-	-	-	1 (14.29%)	-
Inferomedial origin, superior course	-	-	-	-	-	-	2 (28.57%)	-
Lateral (origin and course)	-	-	-	-	-	-	-	-
Lateral origin, superior course	-	-	-	-	-	-	-	-
Medial (origin and course)	-	1 (14.29%)	-	-	-	-	-	-
Medial origin, superior course	-	-	-	-	1 (25%)	1 (25%)	-	-
Superior (origin and course)	-	1 (14.29%)	-	-	-	-	-	-
Superolateral	2 (100%)	-	-	2 (50%)	1 (25%)	1 (25%)	1 (14.29%)	-
Superolateral origin, superior course	-	3 (42.86%)	3 (60%)	1 (25%)	2 (50%)	-	-	1 (100%)
Superomedial (origin and course)	-	-	1 (20%)	-	-	1 (25%)	1 (14.29%)	-
Superomedial origin, inferior course	-	-	-	-	-	-	-	-
Superomedial origin, superior course	-	-	-	-	-	-	-	-

- indicates no individuals showed this orientation

In the right orbit, the majority of individuals displayed superolateral origin and superior course of the OA in relation to the ON, closely followed by the medial origin and course (Table 4.6). The second highest was seen in each of the following orientations: inferior origin and course; medial origin and course, superior origin and course. The least frequency was seen in only one individual in each of the following: in the superomedial origin and superior course; inferolateral origin and inferior course; inferolateral origin and course; and superomedial origin and inferior course.

Table 4.6: The orientation of the ophthalmic artery by age group in bodies dissected through exenteration in ten-year intervals (right orbit).

OA Orientation	20-29 yrs. n (%)	30-39 yrs. n (%)	40-49 yrs. n (%)	50-59 yrs. n (%)	60-69 yrs. n (%)	70-79 yrs. n (%)	80-89 yrs. n (%)	90+ yrs. n (%)
Inferior (origin and course)	-	1 (14.29%)	-	-	1 (25%)	-	2 (28.57%)	-
Inferolateral (origin and course)	-	-	1 (20%)	-	-	-	-	-
Inferolateral origin, inferior course	-	-	1 (20%)	-	-	-	-	-
Inferolateral origin, medial course	-	-	-	-	-	-	1 (14.29%)	-
Inferomedial (origin and course)	-	1 (14.29%)	-	1 (25%)	-	-	1 (14.29%)	-
Inferomedial origin, inferior course	-	-	-	-	-	-	-	-
Inferomedial, superior course	-	-	-	-	-	-	-	-
Lateral (origin and course)	-	1 (14.29%)	-	-	1 (25%)	-	-	-
Lateral origin, superior	-	-	-	-	1 (25%)	-	-	-
Medial (origin and course)	-	1 (14.29%)	-	-	-	2 (50%)	1 (14.29%)	-
Medial origin, superior course	-	-	-	-	-	-	-	-
Superior (origin and course)	-	1 (14.29%)	1 (20%)	1 (25%)	-	1 (25%)	-	-
Superolateral (origin and course)	2 (100%)	-	-	1 (25%)	-	-	-	-
Superolateral origin, superior course	-	1 (14.29%)	1 (20%)	1 (25%)	1 (25%)	-	-	1 (100%)
Superomedial (origin and course)	-	1 (14.29%)	1 (20%)	-	-	-	1 (14.29%)	-
Superomedial origin, inferior course	-	-	-	-	-	1 (25%)	-	-
Superomedial origin, superior course	-	-	-	-	-	-	1 (14.29%)	-

- indicates no individuals showed this orientation

The following results seen when comparing the left and right orbits. The orientations that were found in the left orbit and not in the right orbit were as follows: when comparing the left and

right orbits: the inferomedial origin and inferior course orientation (one individual in the 80-89 age category); inferomedial origin and superior course (two individuals in the 80-89 age category) and the medial origin and superior course in (two individuals in the 60-69 and 70-79 age categories). Similarly, the following orientations were found in the right orbit and not in the left orbit: inferolateral origin and course (one individual in the 40-49 age category); inferolateral origin and inferior course (one individual in the 40-49 age category); inferolateral origin and medial course (one individual in the 80-89 age category); lateral origin and course (two individuals, one in the 30-39 age category and another one in the 60-69 age category); lateral origin and superior course (one individual in the 60-69 age category); superomedial origin and inferior course (one individual in the 70-79 age category) and lastly in the superomedial origin and superior course (one individual in the 80-89 age category).

The most common trend seen was a superolateral origin and superior course in both the left (n=10) and right (n=5) orbits.

4.1.1.6 The intra-orbital course of the ophthalmic artery from the point of origin at the internal carotid artery and its relationship with the optic nerve

An example of the two orbits from a 32-year old male that was dissected through exenteration is shown in Figure 4.7. A dissection without the use of latex infusion was performed in the right orbit. The OA emerged superolateral to the ON and crossed superior to the ON towards the medial side. In the left orbit, the OA emerged medial to the ON and continued to course medially. A schematic representation is included to show the OA emergence and its relationship with the ON in both the left and right orbits (Figure 4.7).

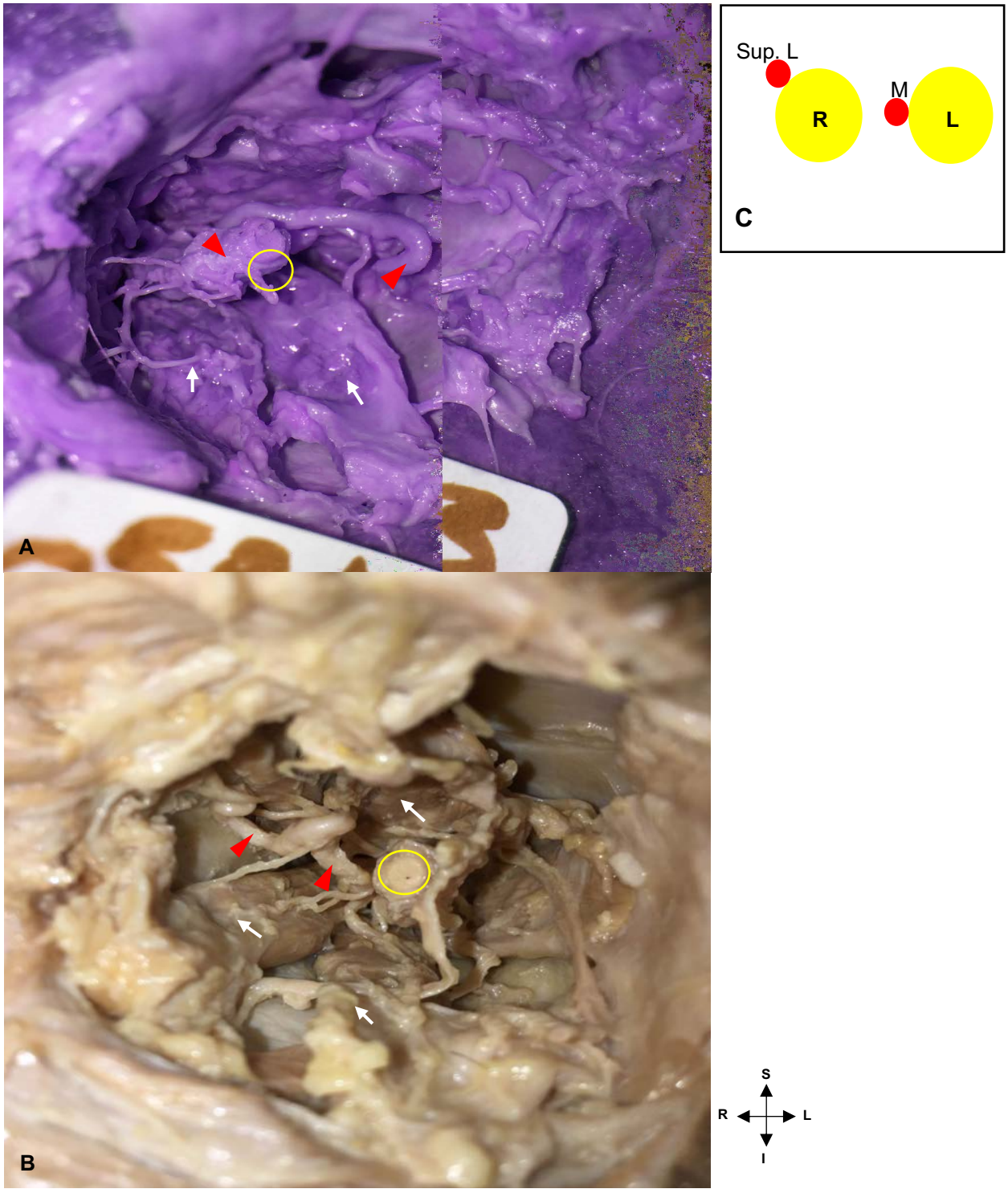

Figure 4.7: *The ophthalmic artery position from point of emergence and its course orientation in relation to the optic nerve.*

A) right orbit and B) left orbit C) a schematic representation. white arrows = extra-ocular muscles; red arrowheads = ophthalmic artery; yellow circle = optic nerve; red circle = position of the ophthalmic artery in relation to the optic nerve; L = left; I = inferior; S = superior, Sup.L = superolateral, M = medial, R = right.

4.1.2 Dissection of the full-term fetuses

A total of 10 full-term fetuses were dissected through the orbital roof and only six were included in the study as the latex solution did not move throughout the arterial system of the other four. Figure 4.8 shows the results of the OA position of emergence from the ICA origin and the orientation in its course in relation to the ON intra-orbitally in both the left and right orbits.

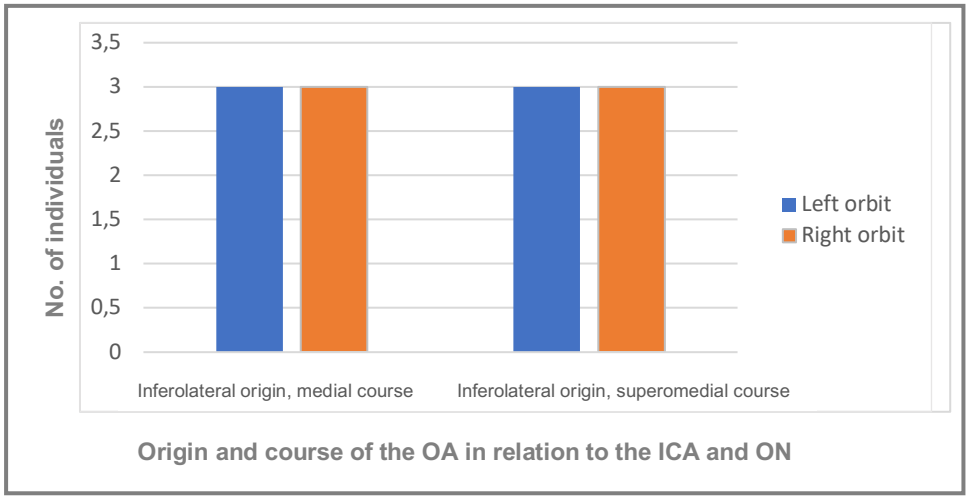

Figure 4.8: *Orientation of the ophthalmic artery from its point of emergence from the internal carotid artery and its relation to the optic nerve.*

The OA emerged inferolaterally from the ICA in both the left and right orbits. However, the course of OA in relation to the ON in the left orbit was medial, whereas in the right orbit was superomedial. No variations were noted in all six dissected full-term fetuses. Figure 4.9 shows an example of the latex filled left orbit of a full-term fetus that was dissected through the orbital roof. The OA emerges from the ICA and continues to course lateral to the ON intra-orbitally. After travelling for a short distance, the OA was seen crossing superior to the ON towards the medial side.

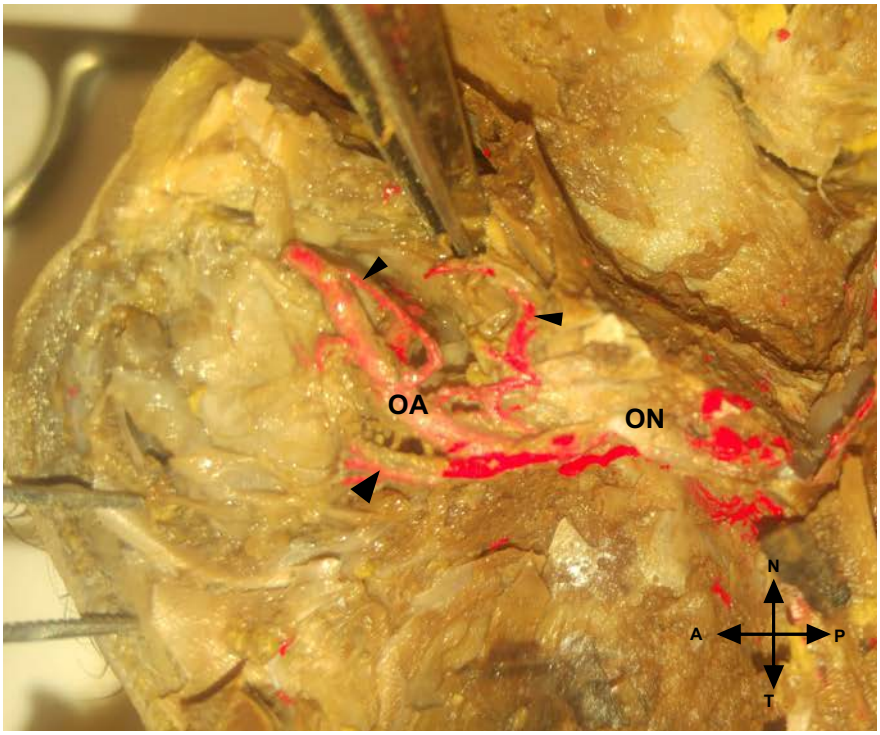

Figure 4.9: *The ophthalmic artery origin and course in relation to the optic nerve.*

OA = ophthalmic artery; ON = Optic nerve; A = anterior; P = posterior; N = nasal, T = temporal. black arrowheads= branches of the ophthalmic artery.

4.2 Observations on patient angiograms

In order to complement the cadaveric dissection study, the origin and course of the OA were reviewed in a total of 870 patients through the use of angiographic images obtained from the Groote Schuur Hospital PACS database. Analysing the images of patients who received treatment for several cerebrovascular pathologies was useful to further illustrate the surgical relevance of the findings.

The age of the patients ranged from one to 91 years old with a mean (± SD) age of 44 years (± 17yrs). The patients were of both the female (n=519;59.6%) and male (n=351;40.4%) sex. A significant difference was seen in the mean age between males and females ($p<0.001$).

Table 4.7 shows the total sample of the patients in age and sex presented in life stages.

A significant difference exists in the distribution of males and females across age groups ($p<0.001$). This was most notable in the 13-18 age category which had a higher proportion of males and the 0-3 age category which had a greater proportion of females.

Table 4.7: The total sample of patients by age and sex (in life stages).

	0-3 yrs.	**4-12 yrs.**	**13-18 yrs.**	**19+ yrs.**	**Total**
Female	18	6	8	487	**519**
Male	2	10	19	320	**351**
Total	**20**	**16**	**27**	**807**	**870**

Table 4.8 shows the total sample of the patients in age and sex presented in life groups.

Table 4.8: The total sample of patients by age and sex (age groups).

	0-9 yrs.	**10-19 yrs.**	**20-29 yrs.**	**30-39 yrs.**	**40-49 yrs.**	**50-59 yrs.**	**60-69 yrs.**	**70-79 yrs.**	**80-89 yrs.**	**90+ yrs.**	**Total**
Female	24	13	33	84	115	113	100	29	7	1	**519**
Male	6	31	56	67	88	65	27	10	1	-	**351**
Total	**30**	**44**	**89**	**151**	**203**	**178**	**127**	**39**	**8**	**1**	**870**

- *indicates unknown age*

One male was of an unknown age. A significant difference exists in the distribution of males and females across age groups ($p<0.001$). This was most notable in the 10-19 and 20-29 age category which had a higher proportion of males and the 60-69 age category which had a higher proportion of females.

4.2.1 The orientation of the ophthalmic artery with respect to the optic nerve

Four different orientations were observed on angiograms and are shown in Table 4.9. Most cases displayed a superomedial orientation, namely 91.6% and 92.1% in the left and right orbits respectively. No significant difference was seen in the orientation of the OA between the left and the right orbits ($p= 0.95$). No significant differences were also noted in the mean age of patients displaying any one particular orientation (left orbit: $p= 0.5913$; right orbit: $p= 0.1117$).

Table 4.9: The orientation of the ophthalmic artery in relation to the optic nerve in both the left and right orbits.

OA orientation	Left orbit n (%)	Right orbit n(%)
Medial	7 (3.7%)	6 (3.2%)
Superior	6 (3.1%)	7 (3.7%)
Superolateral	3 (1.6%)	2 (1.1%)
Superomedial	175 (91.6%)	175 (92.1%)

Data were analysed according to life stages: 0-3, 4-12, 13-18 and 19+ years of age in Table 4.10, separated in to left and right orbits. There were no significant associations seen between the age groups and OA orientation in both the left (p= 0.308) or right (p= 0.443) orbits. There were no images for individuals in the 0-3 and 4-12 age groups.

Table 4.10: The orientation of the ophthalmic artery in relation to the optic nerve in both the left and right orbits (by life stages).

OA orientation	Left orbit				Right orbit			
	0-3 yrs. n (%)	4-12 yrs. n (%)	13-18 yrs. n (%)	19+ yrs. n (%)	0-3 yrs. n (%)	4-12 yrs. n (%)	13-18 yrs. n (%)	19+ yrs. n (%)
medial	-	-	-	7 (3.8%)	-	-	-	6 (3.28%)
superior	-	-	1 (14.29%)	5 (2.72%)	-	-	1 (14.29%)	6 (3.28%)
superolateral	-	-	-	3 (1.63%)	-	-	-	2 (1.09%)
superomedial	-	-	6 (85.71%)	169 (91.85%)	-	-	6 (85.71%)	169 (92.34%)

- indicates no individuals showed this orientation

Within both orbits, the majority of males (left orbit: 87.8% and right orbit: 87.7%, respectively) displayed superomedial orientation of the OA. Similarly, the majority of females (left orbit: 93.6%; right orbit: 94.4%) also displayed superomedial orientation of the OA. However, no statistically significant differences were noted in the orientations between males and females in the left orbit (p=0.221) or right orbit (p=0.281) (Table 4.11).

Table 4.11: The orientation of the ophthalmic artery in relation to the optic nerve in both the left and right orbits (by sex).

OA orientation	Left orbit		Right orbit	
	Female n (%)	**Male n (%)**	**Female n (%)**	**Male n (%)**
medial	2 (1.6%)	5 (7.6%)	2 (1.6%)	4 (6.2%)
superior	4 (3.2%)	2 (3.0%)	4 (3.2%)	3 (4.6%)
superolateral	2 (1.6%)	1 (1.5%)	1 (0.8%)	1 (1.5%)
superomedial	117 (93.6%)	58 (87.8%)	118 (94.4%)	57 (87.7%)

4.2.2 The emergence and course of the ophthalmic artery in the angiograms

The results were recorded using non-contrast MRA, CT and DSA scans, showing axial, lateral and anterior views, as described below.

4.2.2.1 The order of the ophthalmic artery crossing the optic nerve in MRA scans

According to Hayreh (2006), the OA usually emerges from the ICA along the medial side of the anterior clinoid process and runs anteriorly to pass through the OC with the ON. Furthermore, Hayreh (2006) states that the OA then usually crosses the ON superiorly from lateral to the medial side in both the left and right orbits. A similar observation was made in some of the findings of the current study as shown in Figure 4.10, an example of a 44-year old male.

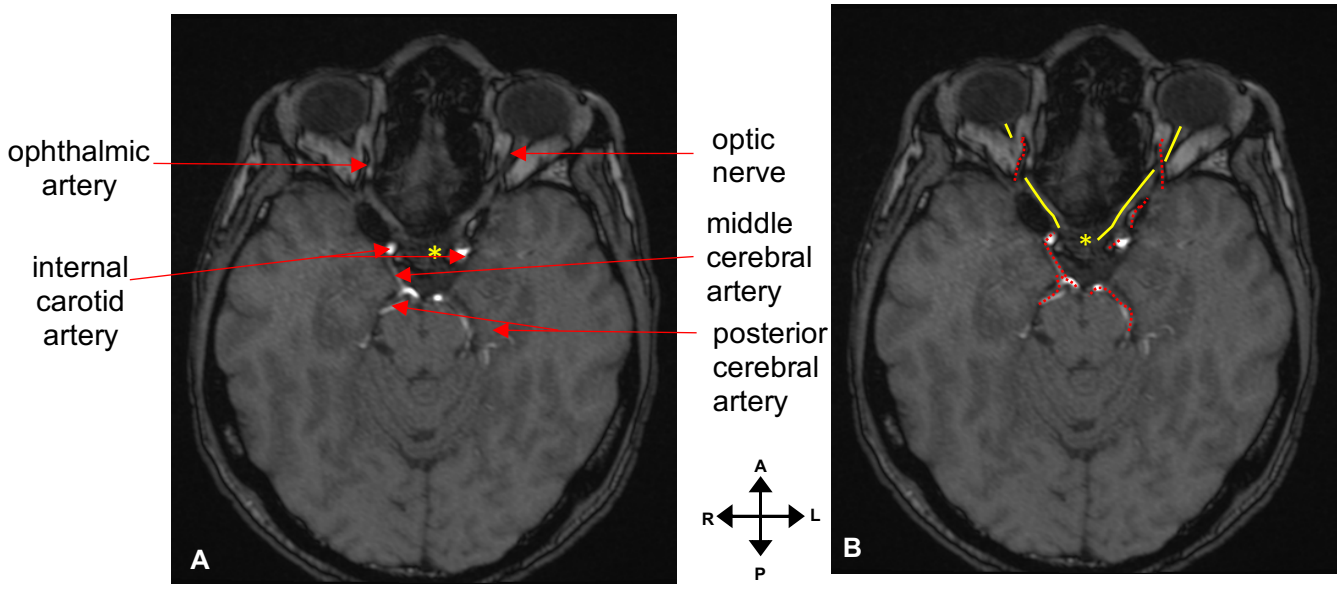

***Figure 4.10**: An example of a slice of non-contrast MRA scan showing the intracranial blood supply.*

A) Intracranial orbital contents B) An illustration of the arterial system. red dotted lines = arteries, yellow solid line = optic nerve, yellow asterix = optic chiasm

A total of eight different OA crossing orientations were recorded for the OA crossing the ON. These orientations were visible in 720 (82.6%) cases. In most cases (n=709; 98.61%) the OA was seen crossing superior to the ON from medial to lateral in both the left and right orbits. No significant difference was noted in the mean age of patients displaying certain OA crossing orientations (p= 0.1893). Table 4.12 shows the different orientation types of the OA crossing the ON in the total sample axial MRA scans.

Table 4.12: Descriptions and orientations of the ophthalmic artery in relation to the optic nerve in the MRA scan.

Type	Description
1	OA emerged from the ICA laterally, crossed superior to the ON, travelled superolateral toward the medial side and progresses medially
2	OA emerged from the ICA medially, crossed superior to ON from medial to lateral in the right orbit, and medial to lateral in the left side
3	OA emerged from the ICA medially, crossed superior to ON from medial to lateral in the left orbit; course medially on the right side without crossing the ON
4	OA emerged from the ICA medially, crossed superior to the ON from medial to lateral in the left orbit, no OA seen in the right orbit
5	OA emerged from ICA medially, did not cross the ON in both orbits but continued medially
6	OA emerged from the ICA laterally, crossed the ON superolaterally toward the medial side in the right orbit, no OA seen in the left orbit
7	OA emerged from the ICA medially, crossed superior to the ON from medial to lateral in the right orbit, but in the left orbit travels medially without crossing
8	OA emerged from the ICA medially, crossed superior to the ON from medial to lateral in both orbits

Table 4.13 shows the total frequencies of the OA orientations in relation to the ON. Types 1, 3, 4, 5, 6 and 7 only appeared once (0.14% in each type), type 2 in four cases (0.56%) and type 8 was found to be the most frequent (n=709; 98.61% of cases).

Table 4.13: The frequency of OA orientation in terms number and mean age.

Type	n (%)	mean age (yrs.)
1	1 (0.14%)	67
2	4 (0.56%)	46.5
3	1 (0.14%)	61
4	1 (0.14%)	57
5	1 (0.14%)	69
6	1 (0.14%)	18
7	1 (0.14%)	35
8	709 (98.61%)	46.23

The distribution of the OA crossing the ON was recorded in age groups (Table 4.14). None of the OA crossing category types was seen in the infants (0-3 age group), however, most

orientations of types 8 were seen in the adults (19+ age group). All children (4-12 age group) showed the type 8 orientation (n=5; 100%) and adolescents (13-18 age group) showed (n=22; 95.65%) of this orientation.

Table 4.14: Distribution of the ophthalmic artery crossing the optic nerve (by age groups)

Type	0-3 yrs. n (%)	4-12 yrs. n (%)	13-18 yrs. n (%)	19+ yrs. n (%)
1	-	-	-	1 (0.14%)
2	-	-	-	4 (0.58%)
3	-	-	-	1 (0.14%)
4	-	-	-	1 (0.14%)
5	-	-	-	1 (0.14%)
6	-	-	1 (4.35%)	-
7	-	-	-	1 (0.14%)
8	-	5 (100%)	22 (95.65%)	681 (98.7%)

- indicates no individuals showed this orientation

With regards to the OA crossing orientation according to the sex of the sampled individuals, no statistically significant differences were noted in the distribution of the orientations in OA crossing between males and females (p= 0.270). In most cases, the OA was seen crossing superior to the ON from the medial to the lateral side in both the left and right orbits (variation type 8) (Table 4.15).

Table 4.15: Distribution of orientation in the ophthalmic artery crossing (by sex).

Type	Female n (%)	Male n (%)
1	-	1 (0.35%)
2	2 (0.46%)	2 (0.69%)
3	-	1 (0.35%)
4	1 (0.23%)	-
5	1 (0.23%)	-
6	-	1 (0.35%)
7	-	1 (0.35%)
8	427 (99.07%)	282 (97.92%)

- indicates no individuals showed this orientation

4.2.2.2 The emergence of the ophthalmic artery from the internal carotid artery and its course as demonstrated in the lateral and anterior views of the DSA imaging.

The standard explanation in anatomy textbooks is that the OA commonly arises from the ICA as described by Dutton (2011) and Standring (2021).

Figure 4.11 shows an example of the most commonly described origin from the ICA indicated by the white arrows and its course. This was seen in the left side of a 56-year old female. The white arrows show the OA emerging from the ICA and coursing anteriorly towards the intra-orbital space. Of the 15 types of variations, this was described as type 3.

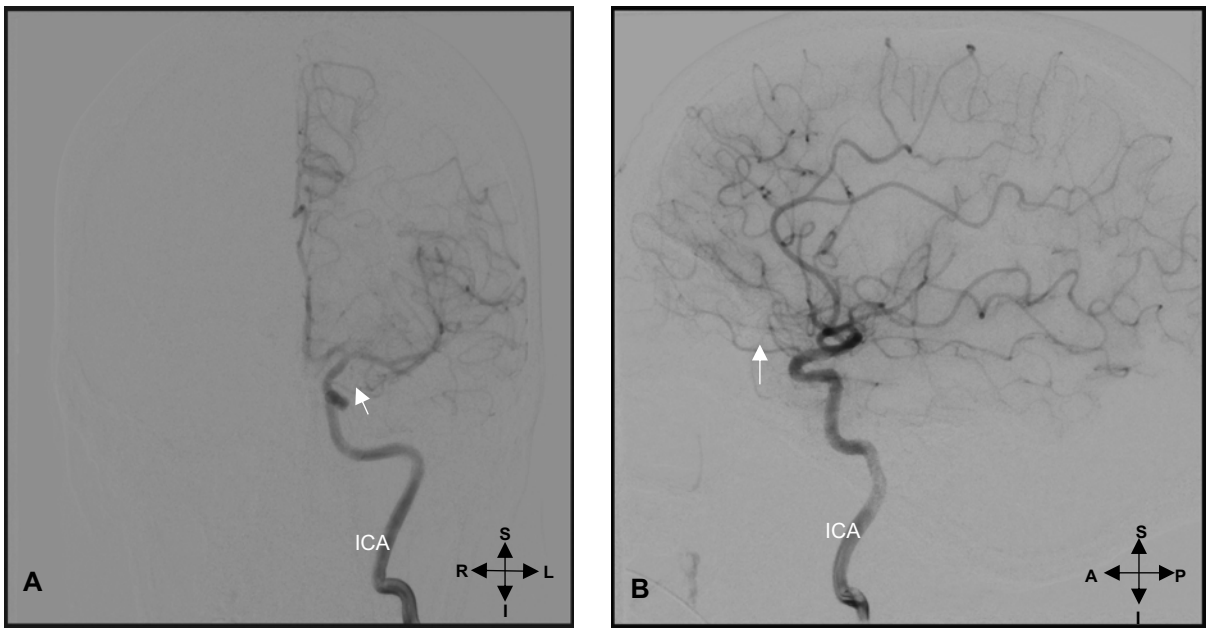

Figure 4.11: *The cerebrovascular and orbital supply with contrast injection through the internal carotid artery.*

A) anterior view, B) lateral view. ICA = internal carotid artery; white arrows = ophthalmic artery; S = superior, L = left, R = right, I = Inferior; A = anterior, P = posterior

4.2.2.3 The lateral and anterior views of DSA showing the variation in the intra-orbital blood supply

A total of 15 different variations in the pattern of the blood supply were recorded (Table 4.16). These variations were visible in 541 (62.1%) cases in the left orbit and 579 (70.78%) cases in the right orbit. No significant difference was seen in the blood supply patterns between the left and right orbits (p= 0.797).

Table 4.16: The full range variations of the blood supply in the current study.

Variation type	Description
1	The Blood supply was only by the meningo-lacrimal branch
2	The blood supply was through the branches of the OA anastomosing with the superficial branches of the ECA
3	The most frequently occurring pattern of blood supply whereby the OA was seen emerging from the ICA
4	The OA gave the main blood supply to the orbit, with contribution from the 2nd additional branch also emerging from the ICA (double ophthalmic artery)
5	No OA was seen branching off from the ICA, a branch from the ACA (orbitofrontal artery) was seen giving blood supply to the orbit
6	The OA gave the main blood supply to the orbit, with contribution from the 2nd additional branch also emerging from ACA (A1 segment)
7	The OA gave the main blood supply to the orbit, with contribution from the 2nd additional branch from ACA (orbitofrontal artery)
8	No OA was seen branching off from the ICA. The main blood supply was seen mainly by the contributions through the first segment of the MCA (first segment)
9	No OA was seen branching off from the ICA. The main blood supply was seen mainly by the contributions through a branch from ACA supplying the orbit (frontopolar)
10	No OA was seen branching off from the ICA. The main blood supply was seen mainly by the contributions through the ECA anastomosis, lacrimal through the deep temporal artery
11	The OA gave the main blood supply to the orbit, with a contribution through the ECA anastomosis by accessory meningeal artery
12	The OA gave the main blood supply to the orbit, with a contribution through the ECA anastomosis by (sphenoid meningeal)
13	The OA gave the main blood supply to the orbit, with a contribution through the ECA anastomosis by (sphenoid meningeal + small distal inferior maxillary)
14	No OA was seen branching off from the ICA. The main blood supply was seen mainly by the contributions through the ECA anastomosis (lacrimal artery)
15	The OA was seen branching off from the ICA. The main blood supply was seen mainly by the contributions through a branch from ACA (frontopolar)

Table 4.17 shows the total frequencies of variations in origin of the OA. The variation types with the low frequencies were 4, 9, 12, 13, 14 and 15 in the left orbit, with variations occurring only once in each type, whereas the types 8, 9, 10, 11 and 15 in the right orbit showed the low

frequencies. The type 3 variation showed the highest frequency in both the left and right orbits. In some cases, these variations were unilateral, whereas some were bilateral within the same individual.

Table 4.17: Total frequencies of variations seen in angiography.

Type	Left orbit n (%)	Right orbit n (%)
1	3 (0.55%)	2 (0.35%)
2	6 (1.11%)	5 (0.86%)
3	518 (95.75%)	563 (97.23%)
4	1 (0.18%)	2 (0.35%)
5	2 (0.37%)	2 (0.35%)
6	2 (0.37%)	-
7	2 (0.37%)	-
8	-	1 (0.17%)
9	1 (0.18%)	1 (0.17%)
10	-	1 (0.17%)
11	-	1 (0.17%)
12	1 (0.18%)	-
13	1 (0.18%)	-
14	1 (0.18%)	-
15	1 (0.18%)	1 (0.17%)

- indicates no individuals showed this orientation

Examples of all variations described in Table 4.16 are shown in the following section. Presented below are all the 14 types that were. The type 3 variation is presented in section 4.2.2.2. In cases where there was no contribution to the orbital blood supply by the OA arising from the ICA, the ECA was seen to be the main source of the blood supply through anastomotic branches.

Figure 4.12 is an example of a type 1 variation. The OA and MMA were seen giving blood supply to the orbit in the right side of an 8-year old female. This variation type was seen in three individuals in the left orbit and two in the right orbit.

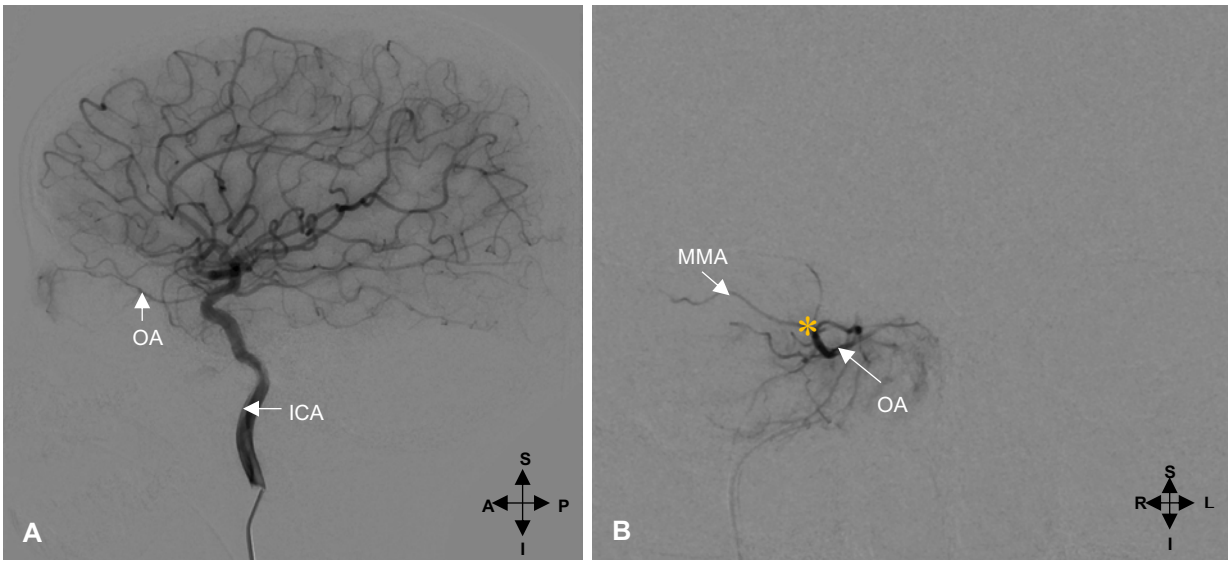

Figure 4.12: *Type 1 variation: the ophthalmic artery with contribution from the middle meningeal artery as the blood supply to the orbit.*

A) Lateral view showing the ICA – OA contribution, B) Anterior view showing the OA and MMA contribution. OA = ophthalmic artery; ICA = internal carotid artery; MMA = middle meningeal artery; S = superior, I = inferior; A = anterior, P = posterior; L = left, R = right.

Figure 4.13 is an example of a type 2 variation. The OA and the branches of the through anastomosis ECA were seen giving blood supply to both the left and right orbits of a 42-year old male. Contributing branches from ECA were from the supraorbital artery (12 orbits on the left and 20 orbits on the right) and the supratrochlear artery (12 orbits on the left and 16 orbits on the right).

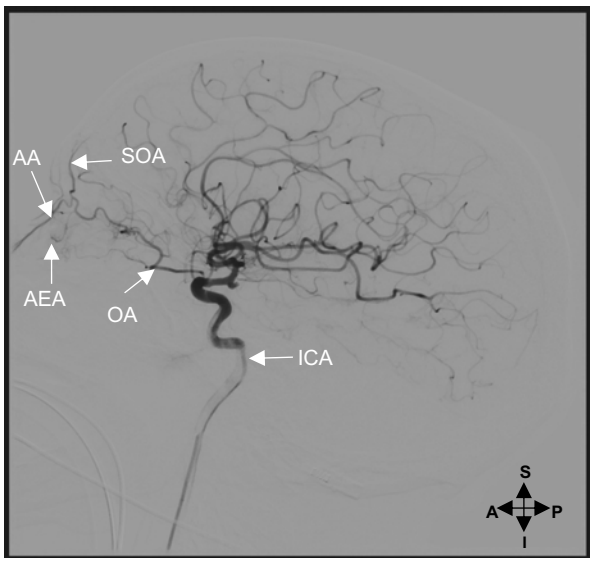

Figure 4.13: *Type 2 variations: the orbital blood supply through anastomosis of the ophthalmic artery and the branches of the external carotid artery.*

ACA = anterior cerebral artery, OA = ophthalmic artery, ICA = internal carotid artery, AA = angular artery, SOA = supra orbital artery, AEA = anterior ethmoidal artery.

Figures 4.14, 4.15 and 4.16 show examples of the type 4 variation where the OA emerged from the ICA and a second additional branch originated from the ICA and travelled together with the OA to the intra-orbital space. This observation was seen in three cases, one in the left orbit and one in the right orbit. This variation is known as the double ophthalmic artery and was seen in a 52-year old female in the left orbit and two individuals in the right orbit.

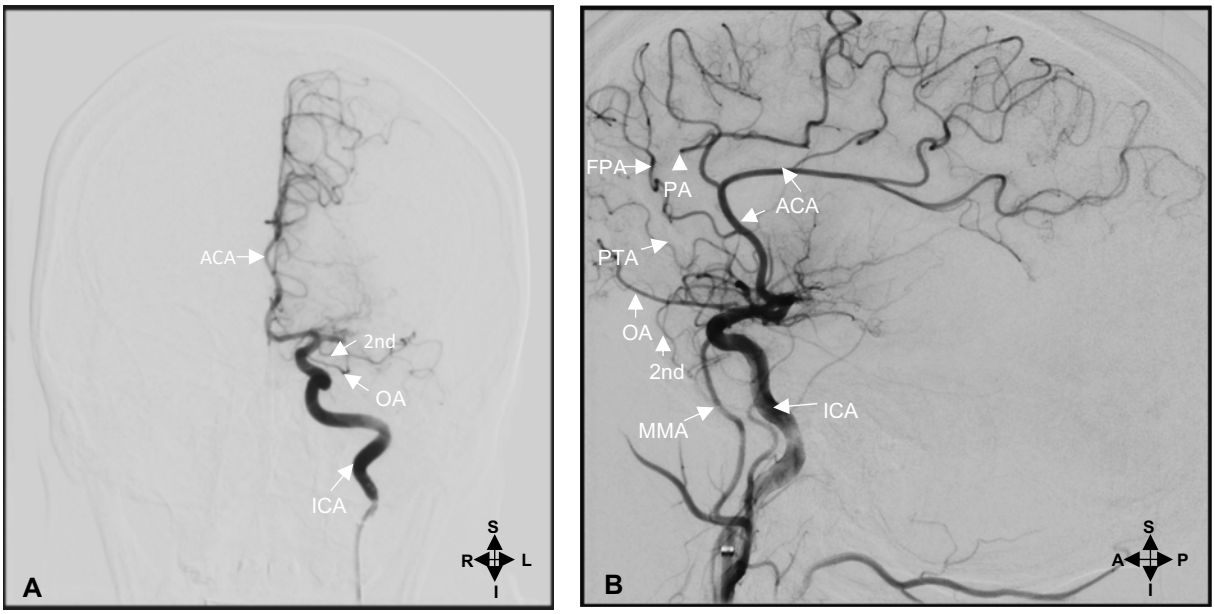

Figure 4.14: *Type 4 variation: the ophthalmic artery joined by an additional branch emerging from the internal carotid artery.*

A) Anterior view, B) Lateral view. ACA = anterior cerebral artery; 2nd = second branch from the ICA; OA = ophthalmic artery; FPA = frontopolar artery; MMA = middle meningeal artery; PA = pericallosal artery; PTA = polar temporal artery; S = superior, L = left, R = right, I = inferior; A = anterior, P = posterior

Figure 4.15 is another example of type 4 variation. The OA was seen emerging from the ICA and a second branch was seen emerging from the OA coursing through intra-orbitally to supply the orbit in a 24-year old male.

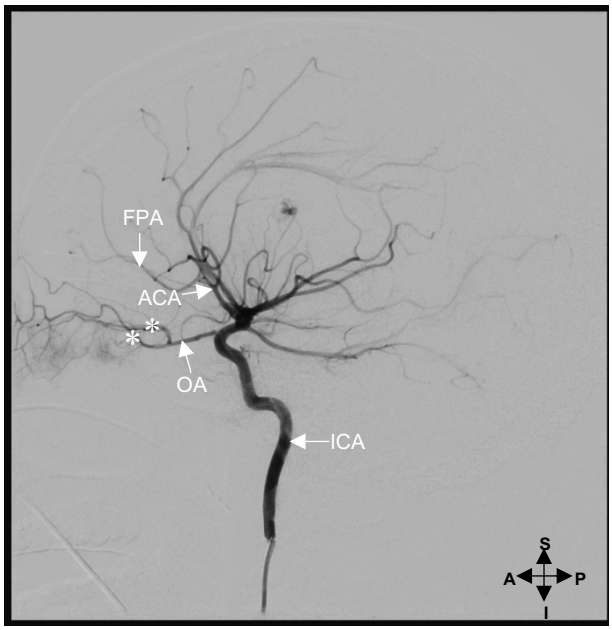

Figure 4.15: *Type 4 variation: the ophthalmic artery giving off two main branches to supply the orbit.*

ACA = anterior cerebral artery; OA = ophthalmic artery; ICA = internal carotid artery; FPA = frontopolar artery; asterisks the two branches of the OA; S = superior, I = inferior; A = anterior, P = posterior. white asterisks = two blood vessels giving blood to the orbit.

Figure 4.16 is a third example of a type 4 variation. The OA was seen emerging from the ICA with a second additional branch and both coursing through to the orbit. This variation was seen in one individual in the right orbit of a 51-year old female.

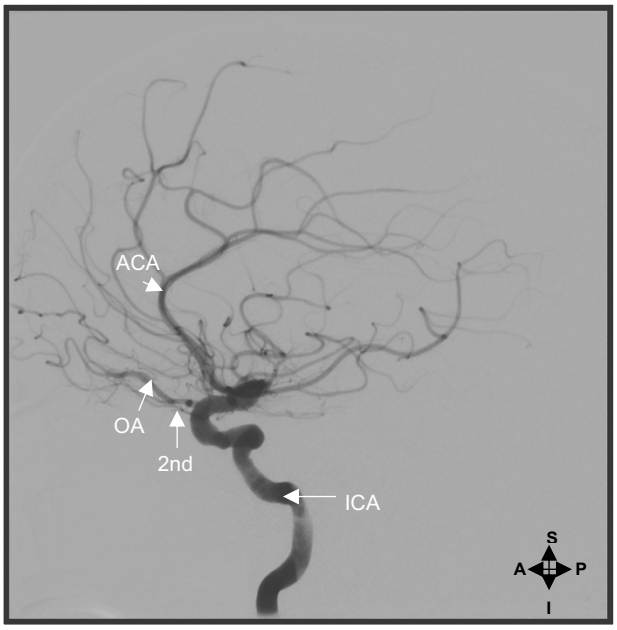

Figure 4.16: *Type 4 variation: the internal carotid artery giving off two branches to supply orbit.*

ACA = anterior cerebral artery; OA = ophthalmic artery; ICA = internal carotid artery; 2nd = duplicated OA from the internal carotid artery; S = superior, I = inferior; A = anterior, P = posterior

Figure 4.17 is an example of a type 5 variation. The OA was absent altogether as shown. In this case, the orbit received its blood supply from a branch of the ACA. This variation type was seen in both the left and right orbits of a 63-year old female.

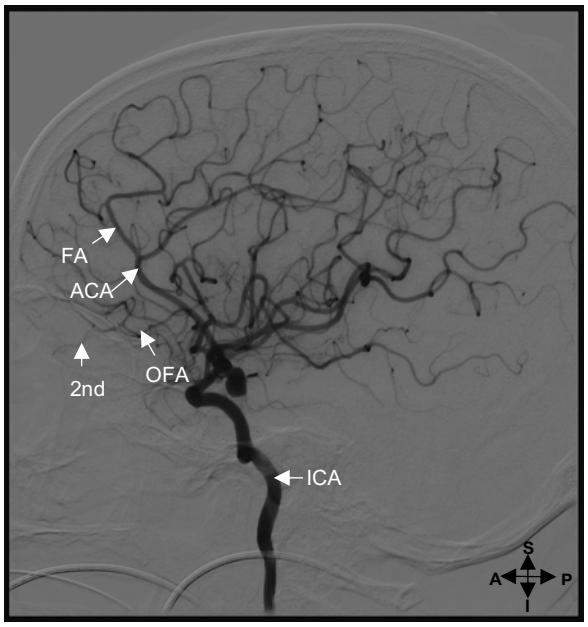

Figure 4.17: *Type 5 variation: a lateral view scan showing the orbit receiving its blood supply from the anterior cerebral artery in the absence of the ophthalmic artery.*

ACA = anterior cerebral artery; 2nd branch = unnamed; ICA = internal carotid artery; FPA = frontopolar artery; OFA = orbitofrontal artery; S = superior, I = inferior; A = anterior, P = posterior.

Figure 4.18 is an example of a type 6 variation. Both the ACA via the OFA and the ICA supplied the orbit was noted in four individuals in both the left and right orbits. This variation type was seen in two individuals in the left orbit (23-year old male, 47-year old male) and there were none in the right orbit.

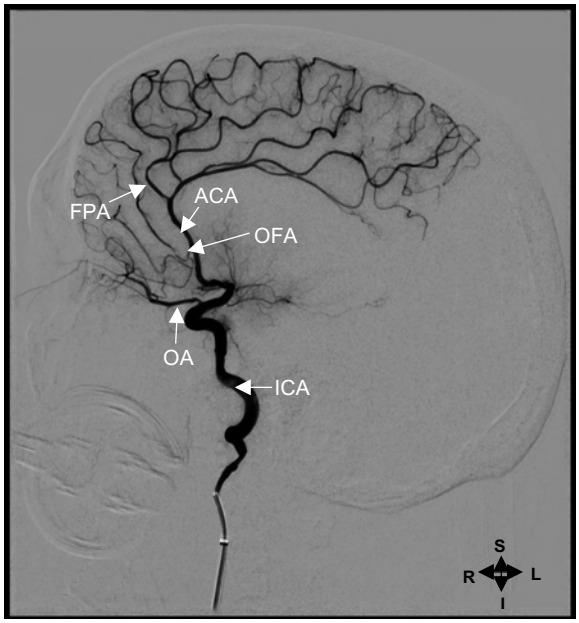

Figure 4.18: *Type 6 variation: a lateral view scan showing the ophthalmic artery being joined by the orbitofrontal artery from the anterior cerebral artery.*

ACA = anterior cerebral artery; OA = ophthalmic artery; ICA = internal carotid artery; FPA = frontopolar artery; OFA = orbitofrontal artery; S = superior, L = left, R = right, I = inferior.

Figure 4.19 is an example of a type 7 variation. The OA gave the main blood supply to the orbit, with second additional branch from the ACA also giving blood supply to the orbit. This additional branch is the OFA. This variation was seen in the right orbit of a 50-year old female.

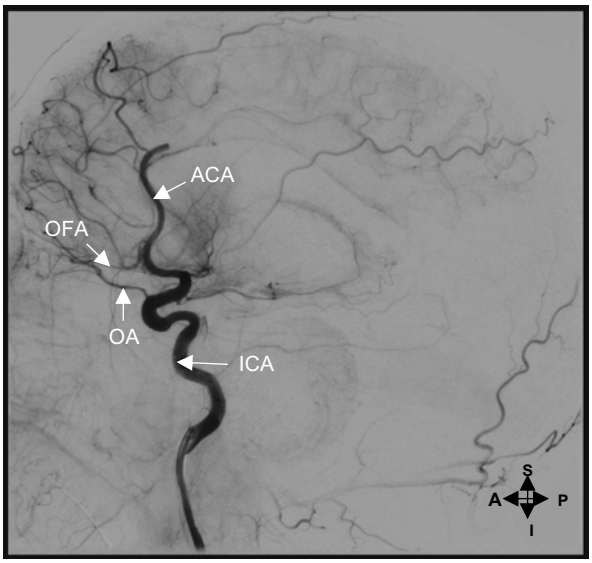

Figure 4.19: *Type 7 variation: an ophthalmic artery giving blood supply to the orbit, with the orbitofrontal artery also giving contribution.*

ACA = anterior cerebral artery; OA = ophthalmic artery; ICA = internal carotid artery; OFA = orbitofrontal artery; S = superior, L = left, R = right, I = inferior.

Figure 4.20 is an example of a type 8 variation where the OA was also absent. The intra-orbital blood supply was provided by the branches of the MCA. This variation was seen in one case in the right orbit of a 19-year old male and is shown on the lateral projection DSA image below.

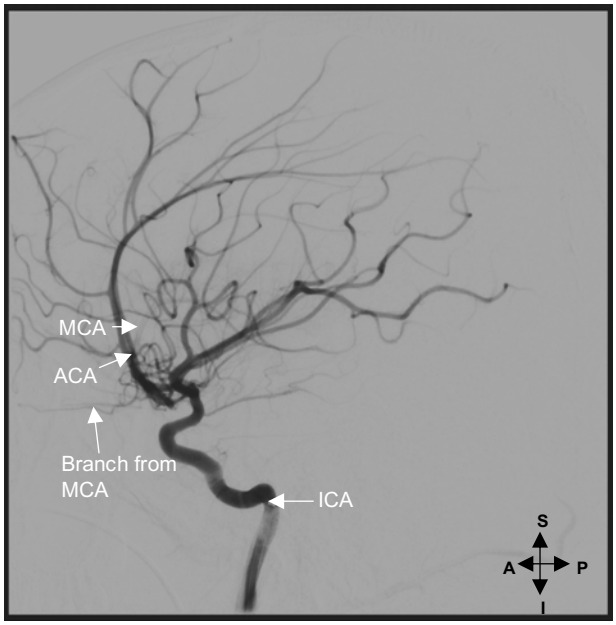

Figure 4.20: *Type 8 variation: an absent ophthalmic artery with blood supply coming from the branch of the middle cerebral artery.*

ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; Branch from middle cerebral artery (M1)

Figure 4.21 is an example of a type 9 variation where the OA was absent. No orbital blood supply taking origin from the ICA was revealed by the selective angiography. The orbital blood supply was seen coming from the orbitofrontal artery. This variation type was seen in one individual in the left orbit of a 61-year old female.

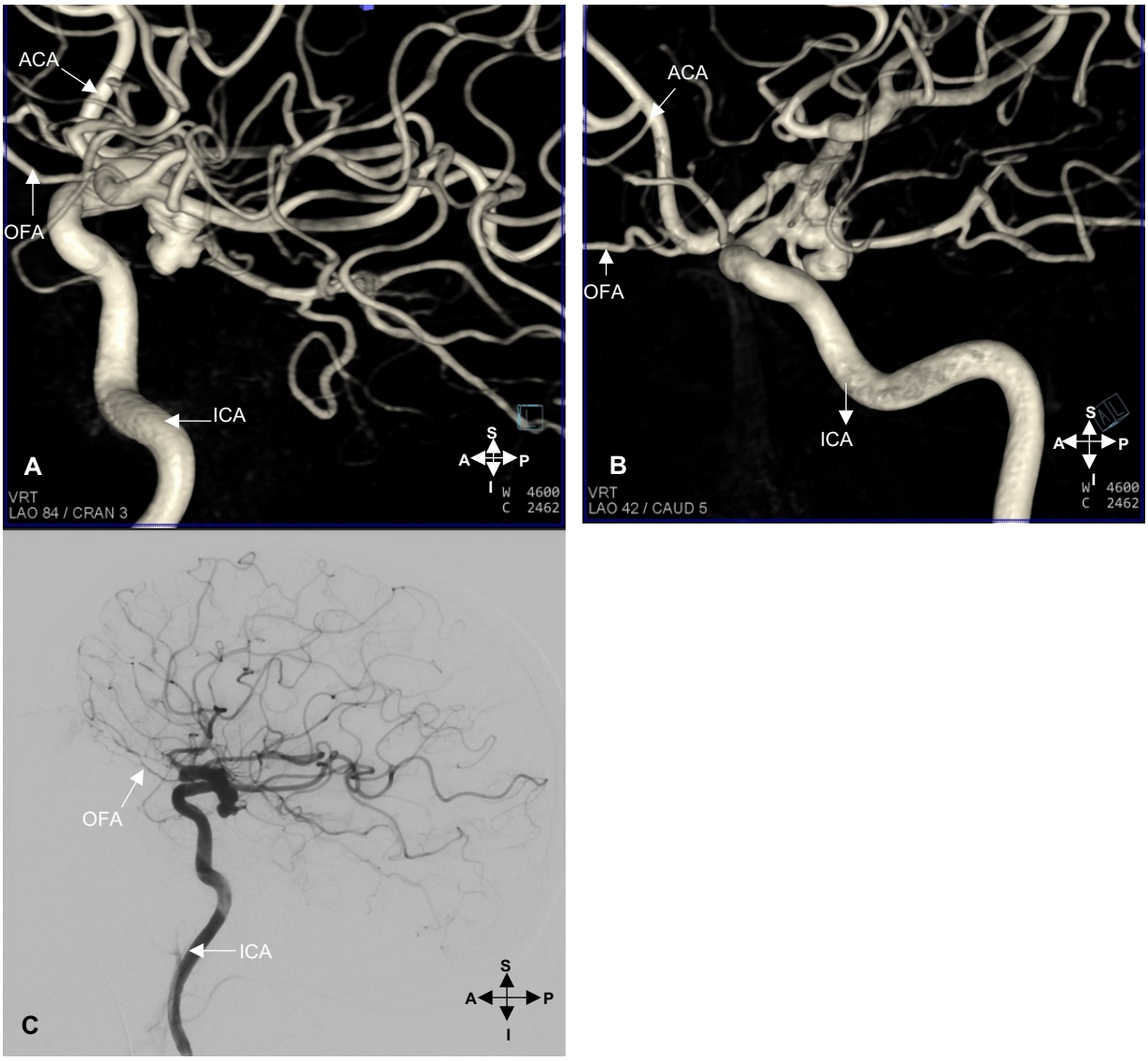

Figure 4.21: *Type 7 variation: a selective angiography of the internal carotid artery showing the absence of the ophthalmic artery with orbital blood supply by the orbitofrontal artery.*

A) and B) a 3-D view of the lateral projection, C) a DSA scan showing the lateral view. ACA = anterior cerebral artery; ICA = internal carotid artery; OFA = orbitofrontal artery; S = superior, I = inferior; A = anterior, P = posterior

Figure 4.22 is an example of a type 10 variation where the OA was absent. The main supply to the orbit was mainly by the contributions through the deep temporal artery (DTA) via the LA through ECA anastomosis. This variation type was seen in one individual in the right orbit of a 1-year old female.

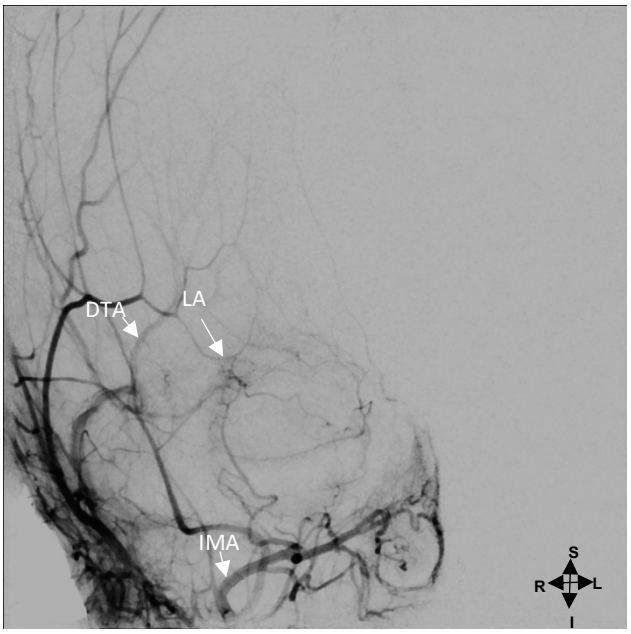

Figure 4.22: *Type 10 variation: mainly by the contributions through the deep temporal artery via the lacrimal artery through the external carotid artery anastomosis*

DTA = deep temporal artery; IMA = inferior maxillary artery; LA = lacrimal artery

Figures 4.23 and 4.24 are both examples of a type 11 variation. The OA emerged from the ICA forming an anastomosis with the MMA in the right orbit. The lacrimal and sphenoidal branches were seen providing the blood supply to the orbit This variation was seen in one individual in the right orbit of an 8-year old female.

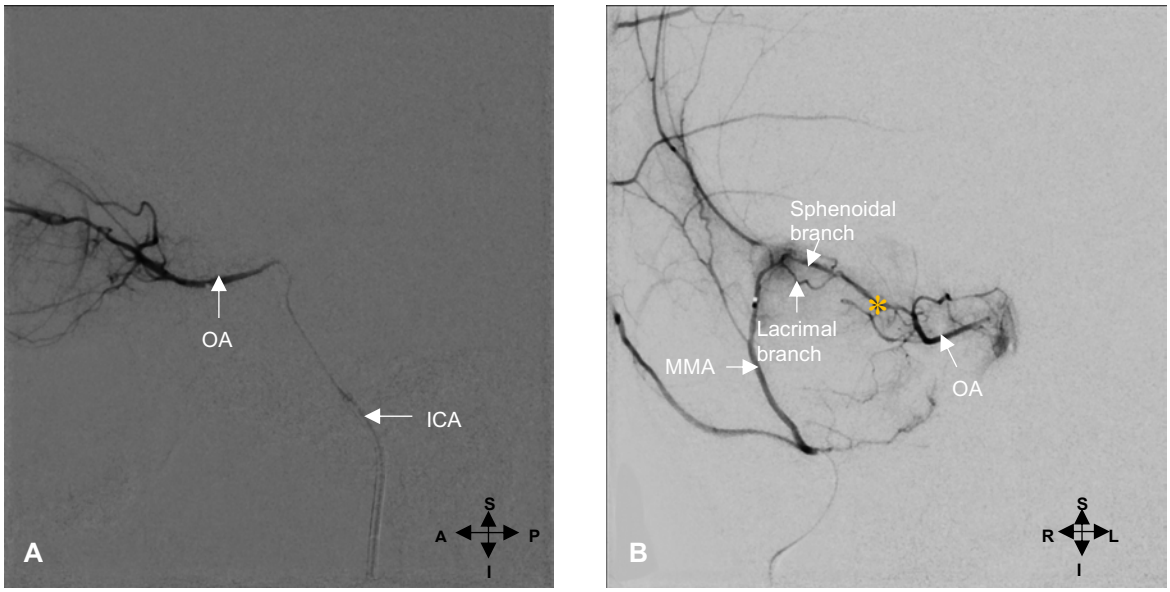

Figure 4.23: *Type 11 variation: anastomosis of the internal carotid artery and external carotid artery seen with the sphenoidal and lacrimal branches of the middle meningeal artery.*

A) lateral view showing the ICA and OA orbital blood supply. B) Anterior view showing the ECA branches giving orbital blood supply. OA = ophthalmic artery; ICA = internal carotid artery; MMA = middle meningeal artery; S = superior, I = inferior; A = anterior, P = posterior; L = left, R = right. Asterix = anastomosis between ECA and ICA.

Figure 4.24 is another example of a type 11 variation. The main source of orbital supply was via the ECA contribution from the branches of the in the right orbit of a 3-year old male.

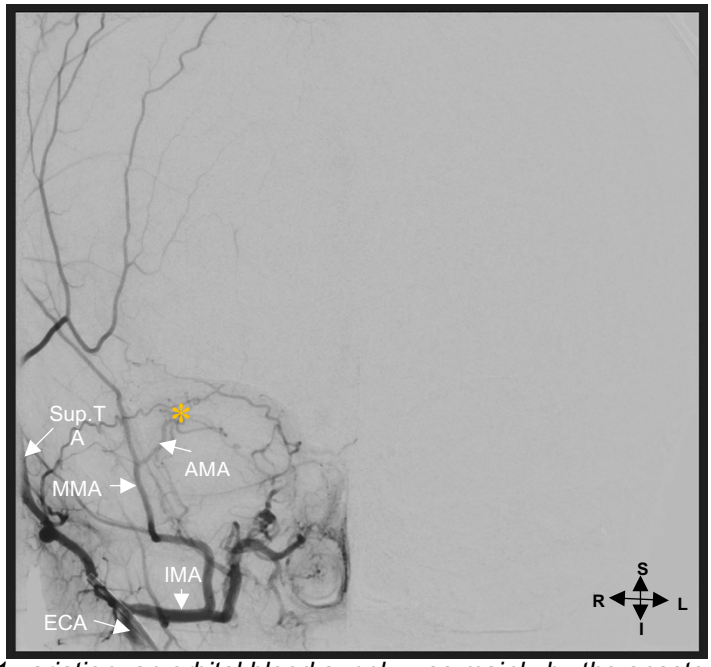

Figure 4.24: *Type 11 variation: an orbital blood supply was mainly by the anastomotic branches of the external carotid artery.*

ECA = external carotid artery; MMA = middle meningeal artery; IMA = inferior maxillary artery; AMA = accessory meningeal artery; Sup.TA = superficial temporal artery; S = superior, I = inferior; L = left, R = right. (asterix= anastomosis between ECA and ICA). (asterix= anastomosis between ECA and ICA).

Figure 4.25 is an example of a type 12 variation. The OA gave blood supply to the orbit with some contribution via the ECA through an anastomotic branch from the sphenoid artery, a branch of the MMA which arises from the ECA. This variation type was seen in one individual in the right orbit of a 38-year old female.

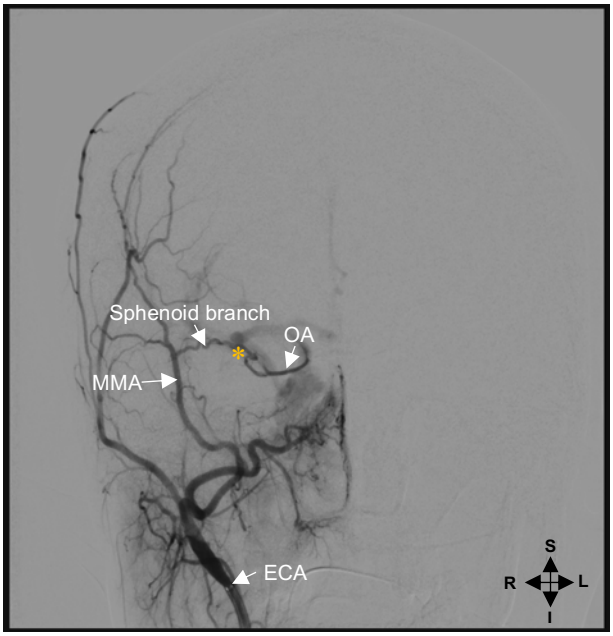

Figure 4.25: *Type 12 variation: the blood supply is through the ophthalmic artery with an anastomotic contribution from the sphenoid branch.*

OA = ophthalmic artery; MMA = middle meningeal artery; ECA = external carotid artery; S = superior, I = inferior; A = anterior, P = posterior (asterix = anastomosis between ECA and ICA). (asterix= anastomosis between ECA and ICA). (asterix= anastomosis between ECA and ICA).

Figures 4.26 and 2.27 are both examples of a type 13 variation. This is a lateral view scan showing the absence of the OA was through the contrast medium which was injected via the ECA. In this image, the branches of the ECA are seen providing contributions to the orbital blood supply through the IMA. This was seen in one case in the left orbit of a 30-year old male.

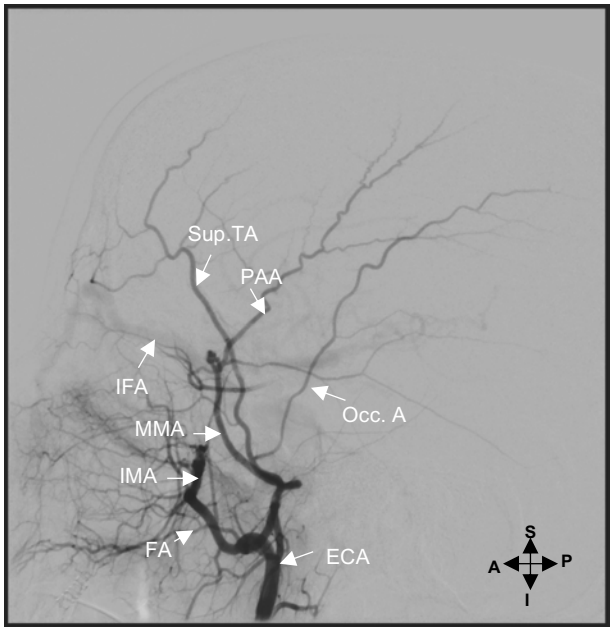

Figure 4.26: *Type 13 variation: an orbital blood supply from branches of the external carotid artery in absence of the ophthalmic artery.*

IMA = inferior maxillary artery (seen giving blood supply to the orbit); ECA = external carotid artery; PAA = posterior auricular artery; Sup.TA = superficial temporal artery; IFA = infraorbital artery Occ.A = occipital artery; FA = facial artery; MMA = middle meningeal artery; S = superior, I = inferior; A = anterior, P = posterior. asterix= anastomosis between ECA and ICA.

Figure 4.27 is another example of a type 13 variation. The was OA absent and the ECA contribution was the main source of the orbital blood supply through the sphenoid branch of the meningeal artery and the distal (IMA) branch. This variation type was seen on the left side of a 3-year old female.

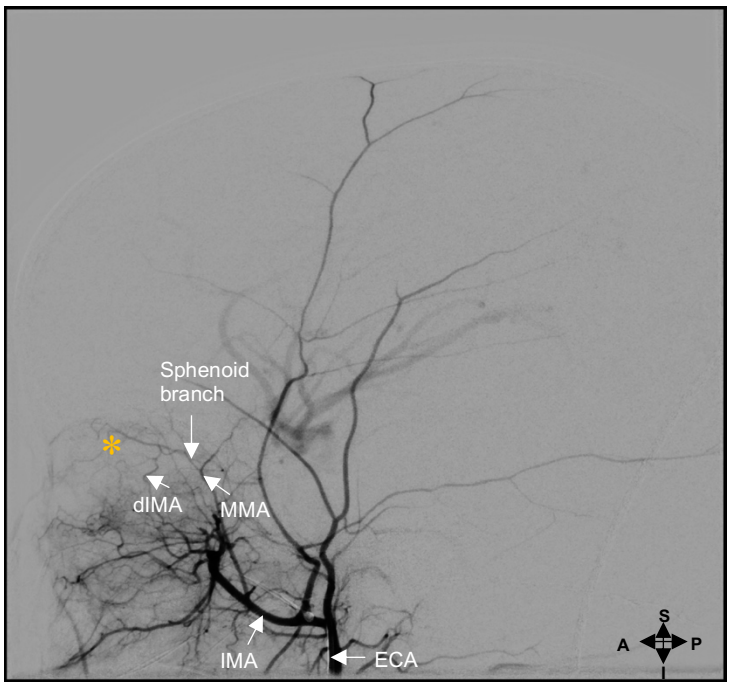

Figure 4.27: *Type 13 variation: the external carotid artery contribution to the orbit through the branches of the meningeal artery.*

ECA = external carotid artery; MMA = middle meningeal artery; IMA = inferior maxillary artery; dIMA = distal branch of the internal maxillary artery; S = superior, I = inferior; A = anterior, P = posterior. asterix= anastomosis between ECA and ICA. asterix= anastomosis between ECA and ICA.

Figure 4.28 is an example of a type 14 variation. The OA is occluded and the ECA contributes to the orbit through the inferior maxillary artery (IMA) and lacrimal artery (LA) in the left orbit of a 2-year old female.

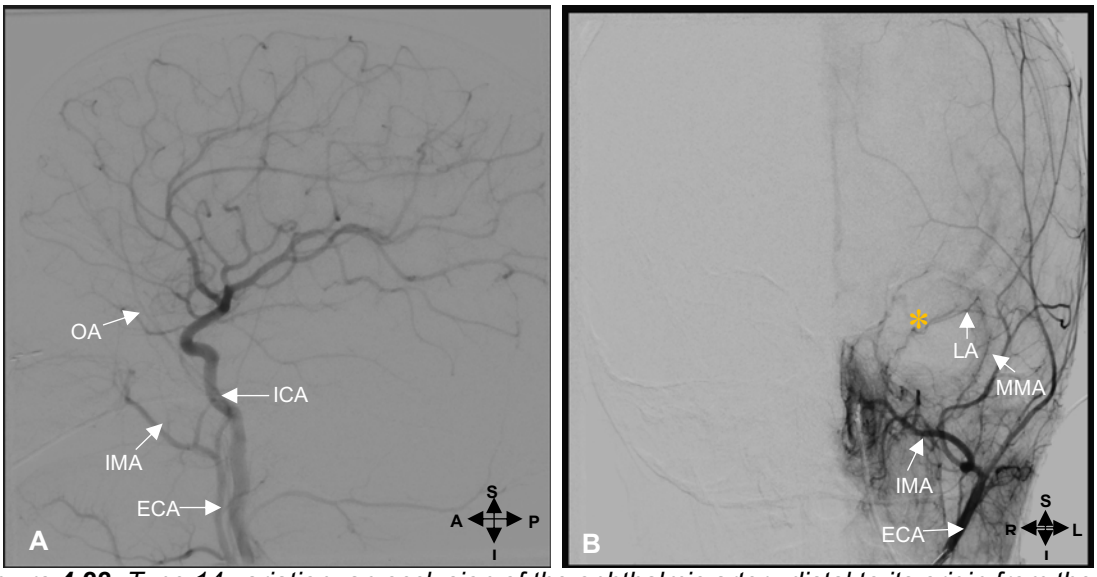

Figure 4.28: *Type 14 variation: an occlusion of the ophthalmic artery distal to its origin from the internal carotid artery and anastomoses through branches of the external carotid artery.*

A) Lateral view showing the ICA contribution, B) Anterior view showing the ECA contribution. OA = ophthalmic artery; ICA = internal carotid artery; ECA = external carotid artery; MMA = middle meningeal artery; LA = lacrimal artery; IMA = inferior maxillary artery; S = superior, I = inferior; A = anterior, P = posterior; L = left, R = right. asterix= anastomosis between ECA and ICA.

Figure 4.29 is an example of a type 15 variation. The orbital blood supply is by the ophthalmic artery and a contribution from the frontopolar artery, a branch of the anterior cerebral artery. This variation type was seen in the right orbit of a 20-year old male.

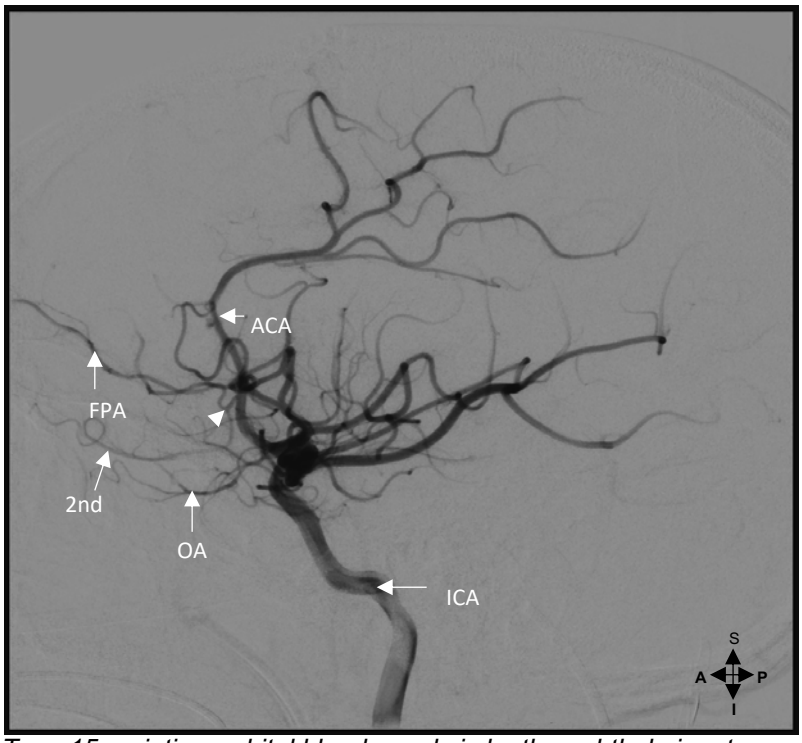

Figure 4.29: *Type 15 variation: orbital blood supply is by the ophthalmic artery and a contribution from the frontopolar artery.*

ACA = anterior cerebral artery; OA = ophthalmic artery; FPA = frontopolar artery; ICA = internal carotid artery; OFA = orbitofrontal artery. arrowhead = frontopolar artery giving off a branch that goes to the orbit. 2nd= unnamed.

4.3 Combined data

The following section describes the overall results for the combined data obtained from the full-term fetus, adult dissected bodies and patient data (angiograms). The orientation of the OA in relation to the ON could be assessed in 256 (28.8%) cases in the left orbit and 257 (28.9%) in the right orbit. A total of eight different orientations were observed in the left and right orbits. It was not possible to calculate the association with the 10-year age group interval due to many groups with no observations in certain categories of variations. Table 4.18 shows the mean age by the OA orientation in the overall study sample.

Table 4.18: Sample size showing the ophthalmic artery orientation in combined data.

OA Orientation	Left Orbit (n)	Right Orbit (n)
Inferior (origin and course)	5	5
Inferior origin, superomedial course	2	0
Inferolateral (origin and course)	1	1
Inferolateral origin, inferior course	2	3
Inferolateral origin, medial course	15	19
Inferolateral origin, superior course	2	2
Inferolateral origin, superomedial course	6	7
Inferomedial (origin and course)	5	5
Inferomedial origin, inferior course	3	2
Inferomedial origin, superior course	2	0
Lateral (origin and course)	0	2
Lateral origin, superior course	0	1
Medial (origin and course)	8	10
Medial origin, superior course	2	0
Superior (origin and course)	7	11
Superolateral (origin and course)	10	5
Superolateral origin, medial course	0	1
Superolateral origin, superior course	10	5
Superomedial (origin and course)	178	178
Superomedial origin, inferior course	0	1
Superomedial origin, superior course	0	1

A significant association was seen between the age groups and the orientation of the OA in relation to the ON in the left orbit (p= 0.012) (Table 4.19). This appeared to be due to the absence of the superomedial orientation in full-term fetuses compared to all other age groups displaying this type of orientation, and the greater proportion of fetuses displaying the inferolateral origin, and medial course; inferolateral origin and course; superomedial origin and course orientations.

A significant association was seen between age groups and the OA in the right orbit (p=0.031) (Table 4.20). This appeared to be due to the absence of the superomedial orientation in the full-term fetuses compared to all other age groups displaying this type of orientation, and the presence of the inferolateral, medial; inferolateral and superomedial orientations.

Table 4.21 shows the combined data of the age groups according to life stages. There were no individuals in the age categories 0-3 and 4-12 in both the left and right orbits.

The frequency of the superomedial OA orientation was calculated and seen to be the most prevalent in the left orbit (70.78%) and in the right orbit (70.49%).

Table 4.19: Ophthalmic artery orientation by age group for the combined data (left orbit).

OA Orientation	<0 yrs. n (%)	0 – 9 yrs. n (%)	10 – 19 yrs. n (%)	20 – 29 yrs. n (%)	30 – 39 yrs. n (%)	40 – 49 yrs. n (%)	50 – 59 yrs. n (%)	60 – 69 yrs. n (%)	70-79 yrs. n (%)	80-89 yrs. n (%)	90+ yrs. n (%)
Inferior (origin and course)	-	-	-	-	1 (2.70%)	-	1 (1.92%)	-	1 (4.55%)	1 (7.14%)	-
Inferior origin, superomedial course	-	-	-	-	-	-	-	2 (4.55%)	-	-	-
Inferolateral(origin and course)	-	-	-	-	-	-	-	1 (2.27%)	-	-	-
Inferolateral origin, inferior course	-	-	-	-	1 (2.70%)	-	1 (1.92%)	-	-	-	-
Inferolateral origin, medial course	3 (50%)	-	-	2 (11.11%)	-	1 (2.04%)	1 (1.92%)	2 (4.55%)	2 (9.09%)	3 (21.43%)	1 (25%)
Inferolateral origin, superior	-	-	-	1 (5.56%)	-	-	-	-	-	-	-
Inferolateral origin, superomedial course	3 (50%)	-	-	-	-	2 (4.08%)	-	-	-	1 (7.14%)	-
Inferomedial (origin and course)	-	-	-	-	1 (2.70%)	1 (2.04%)	-	-	2 (9.09%)	1 (7.14%)	-
Inferomedial origin, inferior course	-	-	-	-	-	1 (2.04%)	-	-	-	1 (7.14%)	1 (25%)
Inferomedial origin, superior course	-	-	-	-	-	-	-	-	-	2 (14.29%)	-
Lateral (origin and course)	-	-	-	-	-	-	-	-	-	-	-
Lateral origin, superior course	-	-	-	-	-	-	-	-	-	-	-
Medial(origin and course)	-	-	-	-	1 (2.70%)	2 (4.08%)	2 (3.85%)	3 (6.82%)	-	-	-
Medial origin, Superior course	-	-	-	-	-	-	-	1 (2.27%)	1 (4.55%)	-	-
Superior (origin and course)	-	-	1 (10%)	-	2 (5.41%)	1 (2.04%)	1 (1.92%)	(%)	(%)	1 (7.14%)	1 (25%)
Superolateral (origin and course)	-	-	-	2 (11.11%)	2 (5.41%)	-	3 (5.77%)	1 (2.27%)	1 (4.55%)	1 (7.14%)	-
Superolateral origin, medial course	-	-	-	-	-	-	-	-	-	-	-
Superolateral, superior course	-	-	-	-	3 (8.12%)	3 (6.12%)	1 (1.92%)	2 (4.55%)	-	-	1 (25%)
Superomedial (origin and course)	-	-	9 (90%)	13 (72.22%)	26 (70.27%)	38 (77.55%)	42 (80.77%)	32 (72.73%)	15 (68.18%)	3 (21.43%)	-
Superomedial origin, inferior course	-	-	-	-	-	-	-	-	-	-	-
Superomedial origin, superior course	-	-	-	-	-	-	-	-	-	-	-

- indicates no individuals showed this orientation

Table 4.20: Ophthalmic artery orientation by age group for the combined data (right orbit).

OA Orientation	<0 yrs. n (%)	0 – 9 yrs. n (%)	10 – 19 yrs. n (%)	20 – 29 yrs. n (%)	30 – 39 yrs. n (%)	40 – 49 yrs. n (%)	50 – 59 yrs. n (%)	60 – 69 yrs. n (%)	70-79 yrs. n (%)	80-89 yrs. n (%)	90+ yrs. n (%)
Inferior (origin and course)	-	-	-	-	1 (2.63%)	-	-	1 (2.22%)	-	2 (14.29%)	-
Inferior origin, superomedial course	-	-	-	-	-	-	-	-	-	-	-
Inferolateral (origin and course)	-	-	-	-	-	1 (2.04%)	-	-	-	-	-
Inferolateral origin, inferior course	-	-	-	-	1 (2.63%)	1 (2.04%)	-	-	1 (4.76%)	-	-
Inferolateral origin, medial course	3 (50%)	-	-	2(11.11%)	1 (2.63%)-	1 (2.04%)	1 (1.92%)	3 (6.67%)	2 (9.52%)	4(28.57 %)	1 (25%)
Inferolateral origin, superior course	-	-	-	1 (5.56%)	-	-	1 (1.92%)	-	-	-	-
Inferolateral origin, superomedial course	3 (50%)	-	-	-	-	2 (4.08%)	-	1 (2.22%)	-	1 (7.14%)	-
Inferomedial (origin and course)	-	-	-	-	1 (2.63%)	-	1 (1.92%)	1 (2.22%)	1 (4.76%)	1 (7.14%)	-
Inferomedial origin, inferior course	-	-	-	-	-	1 (2.04%)	-	-	-	-	1 (25%)
Inferomedial origin, superior course	-	-	-	-	-	-	-	-	-	-	-
Lateral (origin and course)	-	-	-	-	1 (2.63%)	-	-	1 (2.22%)	-	-	-
Lateral origin, superior course	-	-	-	-	-	-	-	1 (2.22%)	-	-	-
Medial (origin and course)	-	-	-	-	1 (2.63%)	2 (4.08%)	1 (1.92%)	3 (6.67%)	2 (9.52%)	1 (7.14%)	-
Medial origin, Superior course	-	-	-	-	-	-	-	-	-	-	-
Superior (origin and course)	-	-	1 (10%)	2(11.11%)	3 (7.89%)	1 (2.04%)	2 (3.85%)	-	1 (4.76%)	-	1 (25%)
Superolateral (origin and course)	-	-	-	2(11.11%)	2 (5.26%)	-	1 (1.92%)	-	-	-	-
Superolateral origin, medial course	-	-	-	-	-	-	-	1 (2.22%)	-	-	-
Superolateral origin, superior course	-	-	-	-	1 (2.63%)	1 (2.04%)	1 (1.92%)	1 (2.22%)	-	-	1 (25%)
Superomedial (origin and course)	-	-	9 (90%)	11(61.11%)	26 (68.42%)	39 (79.59%)	44 (84.62%)	32 (71.11%)	13 (61.90%)	4 (28.57%)	-
Superomedial origin, inferior course	-	-	-	-	-	-	-	-	1 (4.76%)	-	-
Superomedial origin, superior course	-	-	-	-	-	-	-	-	-	1 (7.14%)	-

- indicates no individuals showed this orientation

Table 4.21: Ophthalmic artery orientation in both the left and right orbits by life stages in combined data.

OA Orientation	Left Orbit					Right orbit				
	<0 yrs. n (%)	0-3 yrs. n (%)	4-12 yrs. n (%)	13-18 yrs. n (%)	19+ yrs. n (%)	<0 yrs. n (%)	0-3 yrs. n (%)	4-12 yrs. n (%)	13-18 yrs. n (%)	19+ yrs. n (%)
Inferior (origin and course)	-	-	-	-	4 (0.49%)	-	-	-	-	4 (1.64%)
Inferior origin , superomedial course	-	-	-	-	2 (0.25%)	-	-	-	-	-
Inferolateral (origin and course)	-	-	-	-	1 (0.12%)	-	-	-	-	1 (0.41%)
Inferolateral origin, inferior course	-	-	-	-	2 (0.25%)	-	-	-	-	3 (1.23%)
Inferolateral origin, medial course	3 (50%)	-	-	-	12 (1.48%)	3 (50%)	-	-	-	15 (6.15%)
Inferolateral origin, superior course	-	-	-	-	1 (0.12%)	-	-	-	-	2 (0.82%)
Inferolateral origin, superomedial course	3 (50%)	-	-	-	3 (0.367%)	3 (50%)	-	-	-	4 (1.64%)
Inferomedial (origin and course)	-	-	-	-	5 (0.62%)	-	-	-	-	5 (2.05%)
Inferomedial origin, inferior course	-	-	-	-	3 (0.37%)	-	-	-	-	2 (0.82%)
Inferomedial origin, superior course	-	-	-	-	2 (0.25 %)	-	-	-	-	-
Lateral (origin and course)	-	-	-	-	-	-	-	-	-	2 (0.82%)
Lateral origin, superior course	-	-	-	-	-	-	-	-	-	1 (0.41%)
Medial (origin and course)	-	-	-	-	8 (0.99%)	-	-	-	-	10 (4.10%)
Medial origin, Superior course	-	-	-	-	2 (0.25%)	-	-	-	-	-
Superior (origin and course)	-	-	-	1 (14%)	6 (2.47%)	-	-	-	1 (14.29%)	10 (4.10%
Superolateral (origin and course)	-	-	-	-	10 (4.12%)	-	-	-	-	5 (2.05%)
Superolateral origin, medial course	-	-	-	-		-	-	-	-	1 (0.41%)
Superolateral origin, superior course	-	-	-	-	10 (4.12%)	-	-	-	-	5 (2.05%)
Superomedial (origin and course)	-	-	-	6 (86%)	172 (70.78%)	-	-	-	6 (85.71%)	172 (70.49%)
Superomedial origin, inferior course	-	-	-	-	-	-	-	-	-	1 (0.41%)
Superomedial origin, superior course	-	-	-	-	-	-	-	-	-	1 (0.41%)

- indicates no individuals showed this orientation

CHAPTER 5: DISCUSSION

The overall results of this study will be discussed and compared with the findings of other authors in the published literature. Similarities in these findings will be noted in section 5.1.6 and possible reasons why differences were found will be explored.

An extensive systematic review was done by Bertelli *et al. (*2017) looking at the orbital blood supply with the main focus on the ophthalmic artery. They stated that anatomical variations are known, but the frequencies of variations in various populations are not. Therefore, this aspect requires further study in order to determine these variations in different populations as well as potential risks to the orbit if these are not taken into account by clinicians.

5.1 Findings from the current study

5.1.1 Demographics of the sample according to sex and age

The current study was performed to determine the variations and their frequencies in a South African sample of both cadavers and patients' angiograms. The sample consisted of individuals from full-term fetuses, infants, children, adolescents and adults which were grouped according to age groups (as reflected in Chapter 1, section 1.2). No other published studies grouped the results in age categories as in the current study.

The total cadaver sample in the study consisted of 42 (66.7%) males and 21 (33.3%) females of which some bodies were bequeathed and some were unclaimed.

Kramer *et al. (*2018) performed a retrospective study in which they examined the cadaver records within their institution (University of Witwatersrand, Johannesburg, South Africa) between the years 1921 and 2013, and found that the males accounted for 69.7% of the total sample, while females accounted for the remaining 30.3%. Similarly, at another local institution (University of Stellenbosch, Cape Town, South Africa) Labuschagne and Mathey (2000) also performed a retrospective study and looked at the records between the years 1956 and 1996. They also found more males (68.4%) than females (31.6%) in their cadavers.

More males tend to be migrant workers than females, therefore, in a South African context, unclaimed bodies were available often because the family of the deceased could not be traced, as little or no information on the individual or next of kin was available at the time of

death (Kramer and Hutchinson, 2014). In recent years, more bodies are being accepted in academic institutions of which most come as bequests (Kramer *et al.,* 2018) and few or none come as unclaimed bodies.

When looking at the patient angiograms, there were more females (n=519; 59.6%) than males (n=351; 40.3%) in the total sample. Having more females in the sample could be because women consult health care services more frequently on average than men do (Courtenay, 2000; Hunt *et al.,* 2011). Qualitative studies report a widespread reluctance on the part of men to consult such services (Hunt *et al.,* 2011). Courtenay (2000) has further drawn a direct link between denial of weakness and rejecting help as key practices of masculinity and help-seeking behaviour.

5.1.2 The ophthalmic artery taking origin from the internal carotid artery

As previously stated, the OA leaves the ICA as it exits the cavernous sinus, medial to the anterior clinoid process (Standring, 2021). It is, therefore, crucial that a surgeon working in this area first confirms the precise location of the OA origin. By confirming this location, specifically the carotid-ophthalmic junction, surgeons can more easily decide which blood vessel is affected by an aneurysm in this region, such as carotid-ophthalmic aneurysms and paraclinoid aneurysms, and also define infundibular dilatations at the site of the OA origin (Kim *et al.,* 2014). Being able to define such pathologies at unusual sites of origin of the OA will aid in improved diagnostic certainty where these variations are important in clinical presentations (Kim *et al.,* 2014).

Furthermore, Kotisomitis *et al. (*2015) stated that the OA origin defines an appropriate approach for the selective catheterisation of the OA or superselective catheterisation of the CRA for treatment of CRA occlusion or retinoblastoma chemo-embolisation.

According to Hayreh and Dass (1962a), the OA originated from the superomedial wall of the ICA in 40%, anteromedial wall in 51%, medial wall in 6% and superior wall in only 3% of the cases in their studies. These percentages, however, are not represented universally as other authors (Nishio *et al.,* 1985; Perrini *et al.,* 2007 & Kim *et al.,* 2014) have recorded different findings in their studies as reflected in Table 5.1. The absolute number (n) appears in the table only when it was available in the publication. This table also includes data from the current study as shown in the last row.

Table 5.1: A summary of the frequency of the ophthalmic artery origin from the internal carotid artery.

Author, (year)	Region	Study type	Sample size (n)	Findings (%)										
				Sup.M.	S.	Sup.L.	Post.M.	Ant.M.	L.	M.	Inf.M.	Inf.L.	Ant.S.	I.
Nishio *et al.*, (1985)	Japan	cadaver	25 bodies	71	29	-	-	-	-	-	-	-	-	-
Hayreh *and Dass* (1962a)	India	cadaver	58 bodies	37.5	-	-	-	53.6	-	7.1	-	-	-	-
Huynh-Le (2005)	Japan	cadaver	35 bodies	-	-	-	-	37	-	-	8	4	-	-
Perrini *et al.*, (2007)	Italy	cadaver	7 bodies	7.1	-	-	-	14.3	-	7.1	-	-	-	-
N'da et al., (2013)	France	case report	1 patient	-	-	100 (n=1)	-	-	-	-	-	-	-	-
Kim *et al.*, (2014)	Korea	case report	2 patients	-	-	-	50 (n=1)	-	-	50 (n=1)	-	-	-	-
Current study	South Africa	cadaver	69 bodies	5.8 (n=4)	3.6 (n=2)	18.8 (n=13)	-	-	2.2 (n=1)	5.1 (n=4)	16.7 (n=12)	34.8 (n=24)	-	7.3 (n=5)
		angiograms	870	29.3 (n=255)	1.6 (n=14)	2.5 (n=22)	-	-	0.2 (n=2)	1.6 (n=14)	1.4 (n=12)	3.9 (n=34)	-	0.9 (n=8)

- *indicates no data available.* Sup.M = superomedial, S. = superior, Sup.L. = superolateral, Post. M. = posteromedial, Ant.M. = anteromedial, L. = lateral, M. = Medial, Inf.M. = inferomedial, Ant.S. = anterosuperior, I. = inferior.

As noted in Table 5.1, the results from previous studies are quite variable. In the current study, the OA origin was investigated in two different samples, namely, the cadavers and patients' angiograms. The most common type of OA origin was found to be inferolateral (34.8%) in the cadaver sample. This type of origin was recorded by Huynh-Le *et al. (*2005) in 8% of their overall sample which was half the size of the current study and, therefore, the frequency reported by them may differ due to the smaller sample size. Similarly, the angiographic sample in the current study revealed a frequency of 3.9% in this type of OA origin, which was half of the findings by Huynh-Le *et al. (*2005) who worked with a cadaver sample.

In the cadaver sample of the current study, the point of the OA origin from the ICA was superomedial in 5.8%, which was the lowest frequency. This similar type of OA origin from the ICA was seen in a study by Nishio *et al. (*1985) to be 71% in their study which was double the findings of Hayreh and Dass (1962a) (37.5%). The sample size of Nishio *et al. (*1985) was half that of Hayreh and Dass (1962a), and the sample size in the current study was close to that of Hayreh and Dass (1962a). Therefore, this type of OA origin is rare in this South African cadaver sample and common in the Indian and Japanese samples. This could be because of differences in sample sizes.

When looking at the angiographic sample of the current study, the superomedial point of the OA origin from the ICA was in 29.3% of the sample. This frequency was close to that of Hayreh and Dass (1962a) and half that by Nishio *et al. (*1985).
Kim *et al. (*2014) published a case report of two patients, one (50%) showing the posteromedial origin of OA and the other one (50%) showing the medial origin of OA. The posteromedial type of OA origin was not found in other studies (Nishio *et al.,* 1985; Hayreh and Dass 1962a; Huynh-Le *et al.,* 2005; Perrini *et al.,* 2007 and N'da *et al.,* 2013), as well as in the current study. Due to the unusual nature of this variation, the other authors could not find it.

The medial type of OA origin was found by Kim *et al. (*2014) in one patient (50%) of the two patients in their case study. Hayreh and Dass (1962a) saw this type of variation in 7.1% of their study, which is similar to the findings by Perrini *et al. (*2007). However, the sample size in a study by Hayreh and Dass (1962a) was three times that of Perrini *et al. (*2007). Therefore, in the cadaver sample of the current study, the frequency of this origin type was 5.1%, which is very close to the findings by Hayreh and Dass (1962a) and Perrini *et al. (*2007), and the sample size in the current study was also very close to that of Hayreh and Dass (1962a). The low number of frequencies in this type of OA origin across all studies confirm that this type of variation was rare.

In their study, N'da *et al. (*2013) found a rare case in one patient showing the superolateral origin of OA from the ICA. The same type of OA origin was found in 2.53% (n=22) in angiogram sample and in the cadaver sample which was 18.84% (n=13) in the current study. The differences in frequencies between the angiogram sample and the cadaver sample in this type of OA origin in the current study could be explained by the sample size. The cadaver sample size was small compared to the angiogram sample. A smaller sample size could provide a higher frequency, whereas if the cadaver sample size was higher, it could have also shown a lesser frequency. This type of OA origin was not seen in any of the studies by previous authors (Nishio *et al.,* 1985; Hayreh and Dass 1962a; Huynh-Le *et al.,* 2005; Perrini *et al.,* 2007; Kim *et al.,* 2014) in other parts of the world except by N'da *et al. (*2013) who found this in one patient in their case study.

Three types of the OA origin from the ICA, namely, posteromedial, anteromedial and anterosuperior points of OA origin were not found in the current study. The posteromedial was found by Kim *et al. (*2014) in one patient of their case study, and this was not found in any other studies. The anteromedial type of OA origin from the ICA was found in studies by Hayreh and Dass (1962a) (53.6%), Huynh-Le *et al. (*2005) (37%) and Perrini *et al. (*2007) (14.3%) and no other studies showed this type of OA origin. The differences in frequencies are because of the overall sample sizes. Lastly, no studies were found which showed the anterosuperior origin of the OA. Similarly, the lateral and inferior types of OA origin were found in the current study and not in other regions of the world. This novel finding showed the OA taking origin on the inferior and lateral surface of the ICA. On the inferior surface it was recorded in 0.9% (n= 8) of the angiogram sample and in 7.3% (n=5) of the cadaver sample. On the lateral surface it was recorded in 0.23% (n=2) in the angiogram sample whilst in 2.2% (n=1) of the cadaver sample.

In the current study, the differences in the frequencies of origins of the OA found in the bodies (n=69) and the angiograms (n=870) may be due to the different sample sizes. If the sample size of bodies could have been increased to the same number as the angiograms, the results may have been different.

Nishio *et al. (*1985), Perrini *et al. (*2007) and Kim *et al. (*2014) state that the percentages mentioned earlier are not global figures. The findings showing the varying points of OA origin in Table 5.1 confirm the statement above that the differences in frequencies may be due to the different populations studied. The difference in frequencies of various patterns of the origin and course of the OA across all studies can also be explained according to the Bradford Hill criteria as set out in section 5.1.6. These differences also point to genetic variations and the

influence of epigenetic factors such as geographic location and diet. In addition, differences in the points of origin the orbital blood supply can be explained by variations in the embryological development of the vascular system. The human genome is predicted to contain between 20 000 and 25 000 genes of which a large number of their roles remain unclear. Lissauer and Carroll (2022) state that a remarkable level of diversity and complexity at the protein level is brought about by alternative messenger RNA splicing as well as by post translational modification of gene products. Furthermore, these authors explain that "Epigenetics describes the biological processes that connect the genotype of a cell or multicellular organism with the phenotype: the mechanisms or switches capable of turning genes on and off, or altering their expression. The result is functionally relevant changes that are not caused by alterations in the DNA sequence. The prenatal, neonatal and early childhood periods are when epigenetic DNA imprinting is most active" (Lissauer and Carroll, 2022, Illustrated textbook of paediatrics, ebook).

5.1.3 The course of the ophthalmic artery in relation to the optic nerve

The course of the OA in relation to the ON can be described by the three parts of the OA (Hayreh, 2006). The OA exits the OC inferiorly and courses laterally in relation to the ON and continues in close relationship and parallel to the ON (the first part of the OA) (Hayreh and Dass, 1962a). Hayreh and Dass (1960a) recorded this finding in n=36 (21%) of the 170 overall sample size in their study. The OA then courses medially passing superior to the ON (83%) or inferr to the ON (17%) (second part of the OA) and finally divides into branches medial to the ON (the third part) (Hayreh and Dass, 1960a; Hayreh, 2006). Variations of this course and branching patterns of the OA are quite common (Bracco *et al.,* 2016).

The following results discuss the course OA after exiting the OC. In the current study, it was not possible to determine whether the OA entered the orbit through the SOF or the OC in the angiographic sample, therefore only the cadaver sample was studied. The most common site of origin of the OA from the ICA was inferior in all full-term fetuses. The OA continued in this direction until entering the OC and the course of the OA in relation to the ON was lateral. This type of OA origin and course was recorded in all six of the full-term fetuses and it was similar to findings by Hayreh and Dass (1962a). In the adult cadavers, the OA originated superolaterally from the ICA and followed a superior course (22.1%; n=15) in relation to the ON in the orbits that were dissected through exenteration (n=58). In the orbits that were dissected through the orbital roof (n=68), the OA originated inferolaterally and coursed medially in relation to the ON in 41.4% (n=24) samples. No other studies recorded the

combination of the OA origin and course as reported by Hayreh and Dass (1962) in their study. Furthermore, a superolateral origin was found in one patient in a study by N'da *et al. (*2013) and they did not record the course. An inferolateral origin was found in 4% in a study by Huyn-Le (2015) and they too did not record the course.

5.1.4 Origins of the ophthalmic artery other than from the internal carotid artery

Several anatomical variants of the OA origin have been reported (Perrini *et al.,* 2007; Kotsiomitis, 2015). Unusual origins of the OA depend upon the anastomoses established by the OA with the adjacent vessels (Hayreh and Dass, 1962a). Multiple anastomoses between branches of the ECA and OA exist (Mokin and Siddiqui, 2016). Other rare variations of the orbital blood supply can be the result of the postnatal persistence of the primitive OAs (Bracco *et al.,* 2016). According to Weinberg *et al. (*1982), all anastomotic branches are considered potential contributors to the origin of variants in OAs. Bracco *et al. (*2016) state that some of these variations may go unnoticed at the time of angiographic examination because in some views the OA may be hidden by neighbouring structures. In other cases, only a portion of the OA may be visible.

Reports were conducted by several authors from the pioneering work of Meyer (1887) up to the present time (Hayreh, 2006, Robert *et al.,* 2020 and several other authors as reflected below in sections 5.1.41 to 5.1.4.5. In most cases, the varying pattern of origin of the OA is detected by angiography or during surgery. A few of these reports highlight the variant OAs of which some were also seen in the current study. These are discussed below.

5.1.4.1 The ophthalmic artery taking origin from the middle meningeal artery

The most key and common collateral blood supply to the orbit is the MMA (Kotsiomitis *et al.,* 2015; Aktas *et al.,* 2020). The first description the of orbital branches arising from the MMA was done by Curnow in 1872 (Robert, 2020). The OA origin from the MMA is the most common unusual origin that has been reported in the literature (Hayreh, 2006). This type of OA variant has important microsurgical and endovascular implications and this was noted in several surgical procedures performed in this area (Perrini *et al.,* 2007). When an OA origin is confirmed angiographically to be from the MMA, an endovascular embolisation procedure will carry the risk of visual impairment due to embolic occlusion of the CRA (Perrini *et al.,* 2007).

The anastomotic branch with MMA is either a branch of the LA or the OA, and the branch anastomoses with the anterior division of the MMA through the cranio-orbital foramen (Hyrtl

canal). Furthermore, the recurrent meningeal branch is a branch of the LA and it anastomoses with the anterior branch of the MMA through the SOF. The MMA is quite thin, tortuous and rarely visible angiographically, but in some cases, the anastomosis is very large and becomes the main supply of the orbital region. The anterior falx artery is a branch of the AEA and anastomoses with the anterior branch of the MMA within the falx cerebri (Perrini *et al.,* 2007; Aktas, 2020).

The anastomoses between the OA and MMA are clinically important (Aktas *et al.,* 2020). A summary of the orbital supply taking origin from the MMA is shown in Table 5.2.

Table 5.2: A summary showing the orbital blood supply taking origin from the middle meningeal artery.

Author (year)	**Region**	**Study type**	**Sample size** (n)	**Findings**
Whitnall, (1932)	Oxford museum	cadaver	1	Bilateral origin of MMA
Hayreh and Dass (1962a)	India	cadaver	170	1.18% dual origin of MMA and ICA contribution, 1.18% MMA completely (no ICA contribution)
Dilenge and Ascherl (1980)	Canada	MRA	3500	0.085%
Watanabe *et al.*, (1996)	Japan	case report	1	Bilateral origin of MMA
Liu and Rhoton (2001)	Florida	cadaver	10	In all 10 the LA gave rise to the recurrent branch, Fine anastomotic connections between the recurrent branch of LA and frontal branches of the MMA in 9 (90%)
Perrini *et al.*, (2007)	Italy	cadaver	7	29% - lacrimal branch (though the frontal branch) 25% - recurrent meningeal 78% - recurrent branch of the MMA
Uchino *et al.*, (2013)	Japan	MRA	1655	1.45%
Current study	South Africa	cadaver	69	2.89% (n=2)
		angiograms	870	0.57% (n=5) - meningo-lacrimal branch 0.11% (n=1) - accessory meningeal branch 0.11% (n=1) - sphenoid meningeal 0.11% (n=1) - sphenoid meningeal and small distal inferior maxillary 0.23% (n=2) - dual origin of MMA and ICA contribution

In studies by Whitnall (1932), Hayreh and Dass (1960), Hayreh and Dass (1962a), Dilenge and Ascherl (1980), Watanabe (1996), Liu and Rhoton (2001), Perrini (2007) and Uchino *et al. (*2013), the MMA provided a blood supply to the orbit independently with no OA contribution. The exception was 1.18% of cases in a study by Hayreh and Dass (1962a) where the OA taking origin from the ICA also contributed to the orbital blood supply which is a rare case. In the current study, the blood supply was mainly from the MMA with no ICA contribution in both the cadaver (n=2, 2.89%) and angiogram (n=8, 0.92%) samples. A rare occurrence of was seen in two cases (0.23%) where the orbital blood supply had a dual origin, both from the MMA and with contribution from the ICA, which is a similar finding like that oh Hayreh and Dass (1962a) in 1.18% cases of their sample.

In the current study, the cadaver sample with a sample size of 69 bodies, only 2.89% (n=2) of cases showed the orbital blood supply of MMA origin. This type of variation in the overall sample of the current study was seen mostly unilaterally with one individual showing a bilateral origin. In a study by Uchino *et al. (*2013), a right side and male predominance were found, whilst in other studies (Table 5.2) there was no record of the sides and sex predominance. In the current study, the left side was predominant and the male sex.

5.1.4.2 The ophthalmic artery taking origin from the anterior cerebral artery

The ACA and its branches contain both clinically significant and incidental variations (Tahir *et al.,* 2019). As reported in chapter 2, the surgical nomenclature divides the ACA into three segments: A1, A2 and A3. These regions will be referred to in Table 5.3. A few authors (Picard *et al.,* 1975; Hassler *et al.,* 1989; Islak *et al.,* 1994; Hannequin *et al.,* 2013) have reported the variant origin of the OA from ACA. The OA may rarely branch from the ACA (Li *et al.,* 2011). Table 5.3 shows the variations of the OA taking origin from the ACA by authors in different regions.

Table 5.3: A summary of the ophthalmic artery taking origin from the anterior cerebral artery.

Author (year)	Region	Study sample	Sample size	Findings
Honma *et al.*, (1997)	Japan	Case report	1	1 OA from ACA (A1)
Li *et al.*, (2011)	Tokyo	Case report	1	Origin of the OA from the anterior aspect of the ipsilateral ACA (A1) in the left side
Indo *et al.*, (2014)	Japan	MRA study	855	2 OAs from the ACA (A1)
Uchino *et al.*, (2015)	Japan	Case report	1	Origin of the OA from the anterior aspect of the ipsilateral ACA (A1) in the left side
Current study	South Africa	Cadaver	69	none
		Angiograms	870	2.13% (n= 12) A1 = 0.14% (n= 8) A2 = 0.72% (n= 4)

These variations were recorded from the angiograms only as it was not possible to investigate the cadaver sample because of the nature of dissections performed in the current study. This type of variation is quite rare as evident by Indo *et al. (*2014) where they looked at n=855 patients and could only find two patients presenting this variation type. In the current study with n=870 angiograms, n=12 patients (2.13%) presented with this type of variation. The variations recorded by Honma *et al. (*1997), Li *et al. (*2011), Indo *et al. (*2014) and Uchino *et al. (*2015) all show the OA taking origin from the A1 segment of the ACA. In the current study, the branches of the orbital blood supply originated from either the A1 and A2 segments of the ACA and none from the A3 segment. No studies were recorded showing the OA taking origin from the A3 segment. A novel finding from our study was when the OA was seen taking origin from the A2 segment of the ACA in n=4 (0.72%) cases where none of the other published studies showed this type of variation. The reason this rare finding in the A2 segment of the ACA was not found in other studies by Honma *et al. (*1997), Li *et al. (*2011) and Uchino *et al. (*2015) can be explained by the fact that they were reporting this type of variation from case reports involving one individual. In the study by Indo *et al. (*2014), as part of their methodology they have excluded patients with certain pathologies and by this might have missed on the ones with this type of variation.

Besides mentioning that the OA was seen taking origin from the A1 segment, no further details were given by the authors in terms of the exact point from the A1 segment where the OA was emerging (Honma *et al.,* 1997, Li *et al.,* 2011; Indo *et al.,* 2014), except in a study by Uchino *et al. (*2015) where the origin of the OA was recorded to be from the anterior aspect of the ipsilateral ACA (A1) in the left side. Furthermore, Indo *et al. (*2014) and Honma *et al. (*1997) did not report on the side and sex. Li *et al. (*2011) and Uchino *et al. (*2015) recorded and reported they found it on the left and the did not record the sex of the individuals. In the current study, the most prevalent side was left with the female predominance.

In the current study, certain cases showed the OA taking origin from the ICA contributing blood to the orbit with an additional branch taking origin from the ACA. In other cases, the OA taking origin from the ACA was the main contributor to the orbital blood supply. The five types of the ACA variations were found and recorded under section 3.5.5 in Chapter 3. These types were developed in the current study to describe the origin of the orbital supply and were not mentioned by other authors.

- Type 1: the orbital blood supply taking origin from the ACA through the orbitofrontal artery, also known as the orbital artery, (no OA contribution).
- Type 2: the orbital blood supply taking origin from the ACA through the frontopolar branch (with OA contribution).
- Type 3: the orbital blood supply taking origin from the ACA through the orbitofrontal branch (with OA contribution).
- Type 4: the orbital blood supply taking origin from the ACA - A1 segment (no OA contribution).
- Type 5: the orbital blood supply taking origin from the ACA through the frontopolar branch (no OA contribution).

In the current study, type 1 was seen in 0.72% (n= 4) of the sample. These were seen on the left and right sides (one male and one female). Type 2 was seen in 0.37% (n= 2) of the sample and these were seen on two left sides (one male and one female). The type 3 variation was seen in 0.37% (n= 2) of the sample on the left sides in two females. Type 4 was seen in 0.37% (n= 2) of the sample on the left and right sides in one male and one female. Lastly, type 5 was seen in 0.37% (n= 2) of the sample. These were seen bilaterally in one female.

Although other authors (Honma *et al.,* 1997, Li *et al.,* 2011; Indo *et al.,* 2014) have recorded these types of OA origin in their studies, details of the exact point of emergence from the ACA

were not recorded. Uchino *et al. (*2015) through their interpretation of the image of the orbital blood supply taking origin from the ACA, it was confirmed to be originating from the orbitofrontal branch of the ACA. All the variations were unilateral, except in one individual where it was bilateral. The variations were found predominantly in females.

5.1.4.3 The ophthalmic artery taking origin from the middle cerebral artery

On rare occasions, the ophthalmic artery can be seen taking origin from the MCA. As reported in chapter 2, the surgical nomenclature divides the vessel into four parts: M1, M2, M3 and M4.

Fisher (1913) reported that the OA might arise from the MCA when the ipsilateral ICA is absent. In his study, he examined one case of a male at postmortem and found the OA arising from the MCA in both the left and right orbits. The ICAs were absent on both sides. In the current study, the OA was seen taking origin from the MCA unilaterally on the right side of a female despite the presence of the ICA on that side. This is different from the findings in the study by Fisher (1913) where the variant was seen bilaterally in a male and the ICA was absent on both sides. Rare findings can be considered to be individual differences that reflect the full scale of human variation.

5.1.4.4 A rare double ophthalmic artery origin from the internal carotid artery

On rare occasions, a double ophthalmic artery also known as the duplicate OA from the ICA can be encountered. Table 5.4 shows some of the previously published studies that highlight this rare variation in different regions of the world.

Table 5.4: A summary of the studies that show the double origin of the ophthalmic artery from the internal carotid artery.

Author (year)	Region	Study sample	Sample size	Findings
Hamada *et al.*, (1991)	Japan	Case report	1	Bilateral bifurcation of the OAs from both ICAs
Kam *et al.*, (2003)	China	Case report	1	2 OAs from the ICA (cavernous and posterolateral aspect of the intracavernous ICA)
Nemoto and Namba (2013)	Tokyo	Case report	1	2 OAs from the ICA (supracavernous and cavernous portions)
Bracco *et al.*, (2016)	France	Case report	1	Bilateral bifurcation of the OAs from both ICAs
Current study	South Africa	Cadaver	69	none
		Angiograms	870	3 cases Bilateral bifurcation of the OAs from both ICAs

Angiograms from case reports by Hamada *et al. (*1991), Kam *et al. (*2003), Namba and Nemoto (2013) and Bracco *et al. (*2016) showed a double OA originating from the ICA on both the left and right sides. In the current study, the double OAs were seen from the ICA on the right side in two individuals and in one individual on the left side. Bracco *et al. (*2016) state that the second OA may lie hidden and reveal itself only under particular haemodynamic levels. This highlights the important point that is a series of angiograms does not include an image showing a double OA then this will not be detected (Bracco *et al.,* 2016).

5.1.4.5 The primary variations of the OA origin

Other rare types of OA variation in origin include the basilar artery, the PCoA and the PCA. None of these was part of this current study as the focus was on the anterior circulation of the cerebral arterial circulation.

Figure 5.1 shows a summary of all variations encountered. This is presented in a way that the bony orbit shows the orbital foramina for the entrance of blood vessels into the orbit and the

primary variations in Figure 5.1B showing how the vessels course to give the orbital blood supply.

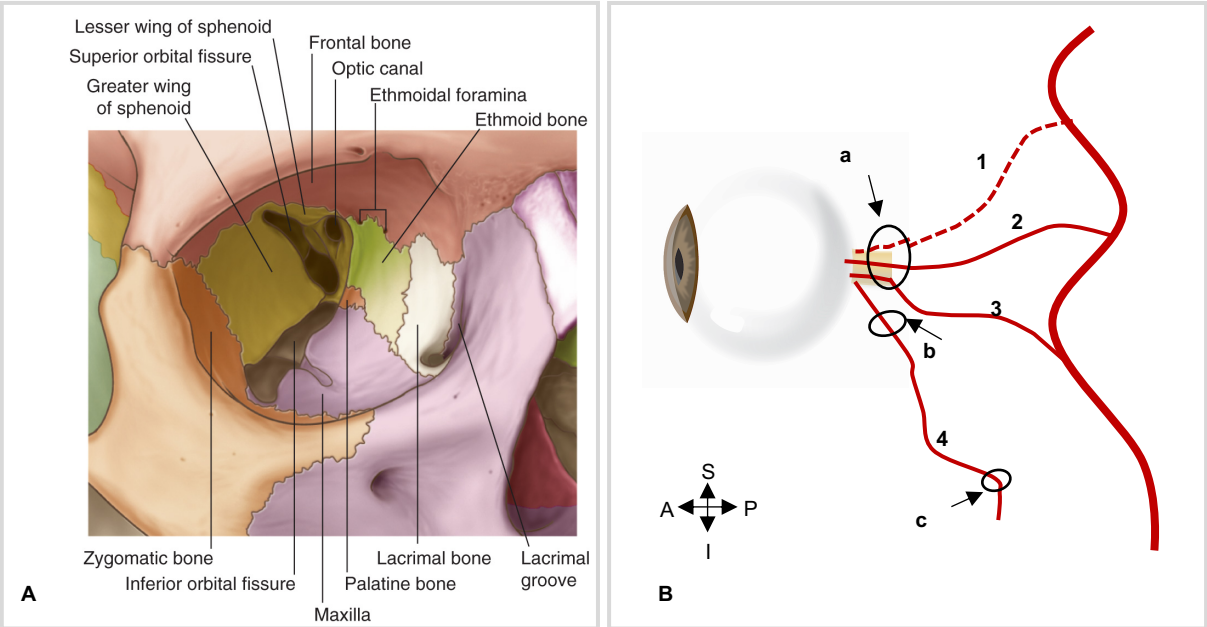

Figure 5.1: *A schematic representation showing the lateral view of the primary variations of the ophthalmic artery.*

By permission from Elsevier. Drake *et al. (*2020) A) An anterior view showing anatomy of the bony orbit, B) A schematic representation showing an illustration of the primary variations of the origin of the OA. Redrawn from Uchino *et al. (*2015). 1 = the OA arising from the ACA, 2 = normal OA from ICA, 3 = OA from the cavernous segment of the ICA, 4 = OA from the MMA, a = OC, b = SOF, c = foramen spinosum, S = superior, P = posterior, I = inferior, A = anterior.

5.1.5 Additional sources of the orbital blood supply from the external carotid artery

All the extra-ocular branches of the OA can have connections with the branches of the ECA. In several circumstances, some of these connections represent the major alternative pathways for the blood to the orbit (Macchi *et al.,* 2016). Furthermore, Bertelli *et al. (*2017) state that a few branches of the ECA can also supply part of the orbit without making meaningful anastomoses with the OA. The anastomoses between the OA and the ECA are numerous, with some being quite common and others being rare.

Table 5.5 shows the main anastomoses between branches of the ECA and the OA as investigated in previous studies and those of the current study appears at the bottom.

Table 5.5: The anastomoses between the branches of the external carotid artery and the ophthalmic artery.

Author (year)	Region	Study sample	Sample size	Findings			
				OA branch	**ECA branch**	**Cad. F.**	**Ang F.**
Berthelot and Hureau, (1982)	France	cadaver	60	Dorsal nasal a.	Facial a.	60%	-
				Dorsal nasal a.	Orbital branch of the infraorbital a.	27%	-
				Supraorbital a.	Superficial temporal a.	33%	-
Kiyosue *et al.*, (2015)	Japan	angiograms	54	Deep recurrent OA	Maxillary a.	-	3%
Bracco *et al.*, (2016)	France	angiograms	443	Dorsal nasal a.	Facial a.	-	8.9%
				Dorsal nasal a.	Orbital branch of the infraorbital a.	-	6.6%
				Supraorbital a.	Superficial temporal a.	-	2.22%
				Lacrimal a.	Anterior deep temporal artery	-	33.3%
				Lacrimal a.	Zygomatico-orbital a.	-	2.22%
				Supraorbital a.	Zygomatico-orbital a.	-	2.22%
				Supratrochlear a.	Superficial temporal a.	-	2.22%
Current study	South Africa	cadaver	69	none	-	-	-
		angiograms	870	Lacrimal a.	Anterior deep temporal artery	-	0.11%
				Dorsal nasal a.	Facial a.	-	1.84% (L)
							0.92% (R)
				Supraorbital a.	Superficial temporal a.	-	6.21% (L)
					Zygomatico-orbital a.	-	9.43% (R)
				Supratrochlear a.	Superficial temporal a.	-	5.29% (L)
							4.48% (R)

- indicates no data available. Cad. F. = anatomic frequency, Ang. F. = angiographic frequency; a. = artery, R =right, L= left (L., R. provided when known)

The anastomoses between ECA and branches of the OA that were seen in the current study were in angiograms and not in the dissected specimens. Various anastomotic patterns have been reported and are presented and discussed below.

Bracco *et al. (*2016) stated that the supraorbital artery can also make connections with the frontal branch of the superficial temporal artery or the zygomatico-orbital artery. In their study, Bracco *et al. (*2016) found anastomosis between the supraorbital artery and the supratrochlear artery in 2.22% of samples, also between the supraorbital artery and the zygomatico-orbital artery in 2.22% of the samples. In the current study, the anastomosis between the supraorbital artery and the supratrochlear artery was found in 6.21% of the total sample on the left side and between the supraorbital artery and the zygomatico-orbital artery in 9.43% of the total samples on the right side. Bracco *et al. (*2016) further found an anastomosis in 33.3% of samples between the lacrimal artery and the anterior deep temporal artery which was the highest number of the cases in their study. A similar observation was found in the current study in one case (0.11%) which was the lowest of the overall findings and was present unilaterally on the right side. Kiyosue *et al. (*2015) found an anastomosis between the deep recurrent OA and the maxillary artery in 3% of the cases in their study, which was an anastomosis that was not found in the current study. Kiyosue *et al. (*2015) and Bracco *et al. (*2016) did not record their findings according to the left or right sides. Berthelot and Hureau (1982) found in their study that the anastomoses between the branches of the OA and those of the ECA were more frequent on the right side than on the left. In the current study, anastomotic frequencies occurred at a level of 13.34% on the left and 14.83% the right, indicating a similar occurrence of such anastomoses.

The last type of anastomosis documented in the literature is between the palpebral arteries or the muscular branches of the OA. Bertelli *et al. (*2017) stated that this type of variation is rare and of less clinical importance. This variation was not recorded in the current study and no further types of anastomoses were found in the current study.

5.1.6 Differences between the current study and other published studies

When comparing the findings from studies by other authors with those from the current study, several differences emerge. The difference in frequencies of various patterns of the origin and course of the OA across all studies can be explained according to the Bradford Hill criteria. The Bradford Hill criteria were published in 1965 proposing nine aspects of association for evaluating traditional epidemiologic data as summarised in Table 5.6 (Hill, 1965).

Table 5.6: The nine aspects of the Bradford Hill criteria of causality and association (Hill, 1965).

Criteria	Description
Strength of association	Strength of association and imprecision in the effect estimate. A strong association supports causality. e.g. Strong association between an intervention or exposure and an outcome can lead to upgrading the quality of evidence.
Consistency	Consistency across studies, i.e., across different situations (different researchers). Causation is more likely if the results from various studies are consistent.
Specificity	Causation is more likely if there is a specific outcome related to a specific exposure in that altering the cause alters the disease.
Temporality	Study design, specific study limitations, randomised controlled trail fulfil this criterion better than observational studies, properly designed and conducted observational studies. There must be a temporal relation between the exposure and outcome.
Biological gradient	A biological gradient between exposure and the magnitude of an effect increases the confidence in causality.
Biological plausibility	Whether the association is plausible or not, it influences the causality.
Coherence	Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease.
Experiment	Study design, randomisation, properly designed and conducted observational studies
Analogy	Existing association for critical outcomes will lead to not downgrading the quality, indirectedness

When reflecting at all the aspects of the Bradford Hill criteria, the aspect that is important for the current study is consistency. From this aspect, it is explained that studies using a variety of populations, locations and methods may not produce results which can be linked to a specific region (Hill, 1965; Fedak *et al.,* 2015). Furthermore, the current study included people from all age groups, namely full-term fetuses, infants, children, adolescents, and adults, whereas other authors looked at adults only. In addition, it is well known that there are anatomical and physiological differences between children and adults (Figaji, 2017) which need to be taken into account when considering the outcomes of research projects that include subjects from a wide variety of age groups. The different sample sizes across the studies could have also contributed to the differences in frequencies of various patterns of the origin and course of the OA because some authors have found these variations in only one or two

individuals during surgical interventions, whereas in the current study 69 cadavers and 870 angiograms were studied.

5.2 Strengths and limitations

5.2.1 Methodology used in the dissection sample

5.2.1.1 Silicone injection on defrosted heads

The unembalmed heads were dissected and formed part of the sample. These were injected with silicon prior to dissection being performed as stated in Chapter 3 (see paragraph 3.4.4.2.). At the first attempt, the procedure worked well, and the orbital arterial system could be well visualised as the arterial system was highlighted. Some of the heads that formed part of the surgical workshops had small cuts around the neck and the temporal area. All the silicone in one syringe was injected and the was no evidence of any leaks from the cut areas. When the skulls were opened and blood vessels examined from the cranial fossae to the orbital blood vessels, there was no evidence of injected silicone intra-arterially. An explanation of this is that the silicone may have been absorbed into other soft tissues. It was, therefore, concluded that all heads displaying any cuts anywhere on the face or around the neck area should be excluded from the study as the latex could not be traced in the arterial system.

The process of preserving these heads for surgical workshops involves freezing at -22^{O}C. The heads are taken out of the freezer and left to thaw overnight in a bucket filled water prior to dissection being performed. One head at a time was taken for the silicone injection process. Upon filling the arterial system with water in order to flush out the blood clots and any material that might have clotted in the arterial system, the process was seen to be working well as the water with blood was seen coming out of the opposite carotid artery side (ICA). When the last injection was done, the brain tissue was seen escaping through the foramen magnum. It was then concluded that the blood vessels may have ruptured because of the freezing and thawing processes. The increased intracranial pressure when trying to wash out the arterial system with water also led to the rupture of the arterial wall. As a result, the silicone injection was never done. When working on the frozen and thawed material, it is necessary to take into consideration the days of freezing and temperature level. The freezing and temperature level play a role in the weakening of the arterial walls and thus leads to rupture as the tissue gets degraded and influences the degree of arterial wall injury (Muller-Shweinitzer, 2009). Freezing and thawing of blood vessels can cause substantial injury to cells and tissues.

Cryopreservation, a process used to preserve organelles, cells, tissues, or any other biological materials by cooling the samples to very low temperatures (Jang *et al.,* 2017), has been described as leading to a certain loss of both smooth muscle contractility and endothelial function in vascular tissues (Muller-Shweinitzer, 2009). These mechanical stresses are likely to damage the arteries.

5.2.1.2 Tagging (labelling) of specimens for identification purposes

It is essential to have all specimens tagged or labelled. This helps with identification as all demographic information would be easily drawn from the departmental register. The tags assisted in the data recording as bodies could be traced and be placed in certain age group categories using information in the departmental register.

5.2.1.3 Dissection on embalmed adult cadavers

A certain number of skulls could not be damaged by opening the orbital roofs as they needed to be kept for teaching and other research purposes. For this reason, in these skulls, the best method of dissection was opted for, which was exenteration. Although this method was good to show the intra-orbital anatomy and the OA orientation in relation to the ON, this method also limited the researcher to exploring and studying the intracranial origin and course of the OA.

5.2.2 Methodology used in the angiographic sample

5.2.2.1 Course of the ophthalmic artery in relation to the optic nerves retrospectively

The OA usually enters the orbit through the OC and in rare cases it may be seen entering through the SOF or other foramina. In the angiographic sample in the current study, it was not possible to determine whether the OA entered the orbit through the SOF or the OC because these could not be visualised in the scanned plane, therefore, the cadaveric sample was used to investigate the point of OA entrance into the orbit.

5.2.2.2 Children undergoing retinoblastoma intra-arterial chemotherapy treatment

Repeated sessions (three sessions) of intra-arterial chemotherapy were performed, and this offered the clinicians a chance to explore the haemodynamic changes and keep a record of

scans from the three sessions. Although angiograms from all sessions of treatment were available, only those taken during the first session were used in this study.

The second and third sessions were not added because of the changes to the blood supply. All the angiograms as they would add additional variables creating bias to the findings. In some of the cases where the OA was not the main source of the orbital arterial supply, a different route was considered for the procedure of chemotherapy treatment, and this, therefore, enabled the study of any variations.

The orbital branching pattern can only be seen in the eye receiving treatment as the contrast medium is injected intra-arterially to highlight the route taken by this medium towards the diseased eye. Only the diseased eyes were visualised and angiographs were taken. This, however, was not advantageous for the current study in cases where retinoblastoma was unilateral and treated unilaterally. The arterial supply of the eye not receiving treatment was not visualised and this made it impossible to compare the arterial pattern in both eyes of the same person. The variations that were present were recorded and reported on one side only.

5.2.2.3 Adults and children

Some of the patients included in our study was not all healthy as they came presenting with pathologies. These could have created biased results as some of the variations might have formed from the diseased patterns.

5.3 Reflections

Human dissection remains the gold standard for the visualisation of the anatomical structures. Together with the angiographic study, this current research could give an overview of the orbital vascular anatomy following the route of the OA from the point of origin from the ICA or elsewhere and its course to enter the orbit. Some of the views that could not be visualised from the anatomical dissections could be seen on angiography and those that could not be seen using angiography were studied on the anatomical dissections. The dissections consisted of two methods. These methods allowed the researcher to investigate the OA from different angles and record the variation, however, one of the methods was limiting in terms of visualising certain structures.

Working with both the human dissections and patient angiograms for the study allowed for a valuable balance of people from different age groups as the cadaver sample provided limited

number of ages and therefore could not be make up the all the age categories in the study objectives. The frequencies of variations were recorded across all age groups according to the sampled participants. However, the full-term fetuses were of a small number and increasing the number in the future could yield different frequencies. The different types of variations that were found in the current study were linked to human developmental stages. Some of those found in the current study could not be found in populations in other parts of the world and some variations in other parts of the world could also not be found in the current study. This could be influenced by epigenetic factors, genetic differences and the Bradford Hill criteria. The current study consisted of a small group of individuals from the region of South Africa (Cape Town). Therefore, a multicentre study will need to be done in the future adding all parts of South Africa to contribute to the current findings and yield results that could be representative of the total population of the country.

Many of the angiograms that were used in the current study were those of unhealthy individuals who went to the hospital to be treated for different intracranial vascular conditions. Most infants and children were also in the early stages of being treated for retinoblastoma. The presence of various pathologies in patients other than those being treated for the retinoblastoma could have also, in some way, contributed to different variations, although this was not tested in the current study.

People from all ancestral groups in South Africa were represented in this study. During the analysis of the patient angiograms it was noted that individuals from certain ancestral groups were represented in larger numbers than in other groups. A similar trend was noted in the bodies in the dissection hall. Ancestry was not used as one of the variables in the current study. Future studies can be conducted by adding the different ancestral groups to the list of variables investigated and recording the frequencies in variations of the orbital blood supply for these groups.

5.4 Future studies

The current study established a basis for similar studies in the future. These could focus on the same area with the aim of recording the overall frequency of variations in the orbital vascular supply which will be representative of the overall South African population. The current study was conducted using a portion of the South African population by means of human dissections in the University of Cape Town and patient angiograms accessed through Groote Schuur Hospital. A multi-centre study is required to provide a larger, overall frequency of variations that would be representative of the general South African population. The

representation in the age categories below 19 years old was small or in some instances absent altogether. This aspect can be addressed in future studies by adding and analysing an equal number of patients in certain age categories in order to verify the findings for these age groups from the current study. Lastly, ideally, look at patients who have an angiogram performed in order to investigate intracranial vascular pathologies that are not affecting the orbital blood supply.

CHAPTER 6: CONCLUSION

Up until the present time, there were no published data showing the frequencies in the origin, course and variations of the ophthalmic artery in a South African sample. The findings from the current study are novel because this is the first to describe the different variations found around the area of the orbital vascular supply within a South African sample.

Knowledge of anatomy in the study population is highly relevant for clinicians. This is important for the diagnosis of vascular-related pathologies within and around the orbit. The results of this study may assist surgeons and neuroradiologists in understanding the frequencies of variations in the vasculature of the orbital region when planning for endovascular interventions. This also adds to the current body of knowledge in human anatomy.

All the original objectives of the current study were achieved. The anastomotic patterns between the ECA and ICA in both the left and right eyes were described and the frequencies of observed variations were recorded. Anastomotic patterns for branches other than those from the ICA in both the left and right eyes were described and the frequencies of these variations were recorded. Where variant anastomotic patterns were observed, the study described whether they occurred either unilaterally or bilaterally. If the pattern was found to be unilateral, the most common side was determined. The study furthermore determined whether there was an association between age and the frequency of anastomotic patterns. Lastly, differences in frequency of anastomotic patterns between males and females were determined. These outcomes will aid clinicians in their awareness of these vascular variations in certain age groups and between the two sexes before performing any interventions.

The findings were recorded in all the categories presented and mentioned in the list of objectives. The frequencies in each category were compared with those in the published international studies.

The data in this study were documented in both the males and females and were obtained through the investigation of human cadavers and patient angiograms to provide frequencies across all the following variables: sex, age, laterality and patterns of variations. The frequency of each category was then compared with published international studies.

It became evident through the findings that variations predominated in male subjects. The frequencies of variations in terms of laterality were also recorded and most were found to be unilateral and most commonly on the left side.

In the current study, most classic variations described in previous studies were observed and some additional variations were recorded. The observed patterns of the anastomotic branches supplying the orbit taking origin from arteries other than the ICA on both the left and right sides were carefully described and noted as further variations.

The novel findings in the current study were as follows. The points of OA origin from the ICA were noted and recorded. The superolateral origin of the OA from the ICA was documented in 2.53% (n=22) of the angiograms and in 18.84% (n=13) of the cadavers. The difference in these two percentages is most probably due to the considerably different sample sizes of the angiograms (n=870) and the cadavers (n=69). These findings were not recorded in studies published by other authors except for one study (N'da *et al.,* 2013) where they found this type of OA origin in one patient in their case study. The lateral origin of the OA from the ICA was noticed in 0.23% (n=2) of the angiogram sample and in 2.2% (n=1) of the cadaveric sample. This type of OA origin was not found in previous studies and is, therefore, unique to the current study. In addition, the inferior origin of the OA from the ICA was documented in 0.92% (n=8) of the angiogram sample and in 7.25% (n=5) of the cadaveric sample. This type of OA origin was never found in previous studies and is once again unique.

Rare variations were also noted in the origin of the OA other than from the ICA. When looking at the OA taking origin from the ACA, it became evident that several authors did not record the specific points on the ACA segment from where the OA took origin except in one study by Uchino *et al. (*1985) confirming the OA taking origin from the orbitofrontal branch from the A1 segment of the ACA. All the points of the OA origin in the current study were recorded and, therefore, included the specific segment of the ACA. The OA was noted to be taking origin in the A2 segment (OA taking origin from the frontopolar artery) of the ACA in 0.37% (n=2) of the samples. This type of origin was found to be novel as it has not been found in studies by other authors.

The anastomotic patterns between the ECA and ICA in both the left and right sides were recorded and their frequencies were determined. The right side was noted to have 14.83% recorded variations and the left side was 13.34%. The right side, however, showed a marginal difference. A significant association was also found between the age groups. Therefore, this supports the concept that the anastomotic patterns do not change as individuals grow older.

From the findings of the current study, it was concluded that the OA origin and its course is complicated and essentially unique not only between individuals but also between the eyes of the same individual. A comparison was also made between the findings in the current study on the SA sample with previous studies from other parts of the world and differences in frequencies were observed and recorded. These differences were explained using the Bradford Hill criteria as a guideline.

It became evident that several traits observed in the South African sample could not be found in studies in other parts of the world, and some traits found in studies in other parts of the world were not found in the South African sample. Therefore, the investigation in the current study achieved the aim of recording the frequencies in variations of the orbital vascular supply within a large South African sample.

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APPENDICES:

Appendix A: Ethics approval (University of Cape Town)

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 July 2018

HREC REF: 469/2018

Prof G Louw
Human Biology
Anatomy Building

Dear Prof Louw

PROJECT TITLE: VARIATIONS IN ARTERIAL SUPPLY VIA THE EXTERNAL AND INTERNAL CAROTID ARTERIES TO THE BONY ORBIT AND EYEBALL IN FULL-TERM FETUSES, INFANTS, CHILDREN AND ADULTS - A SOUTH AFRICAN CONTEXT (PHD CANDIDATE - MS K MPOLOKENG)

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

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

Approval is granted for one year until the 30 July 2019.

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)

Please quote the HREC REF in all your correspondence.

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

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

The HREC acknowledge that the student, Kentse Mpolokeng will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 469/2018

Appendix B: Ethics approval (Groote Schuur Hospital)

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Dr G. Louw
Human Biology

E-mail: Graham.Louw@uct.ac.za / Kentse.mpolokeng@uct.ac.za

Dear Dr Louw,

RESEARCH PROJECT: Variations In Arterial Supply Via The External And Internal Carotid Arteries To The Bony Orbit And Eyeball In Full-Term Fetuses, Infants, Children and Adults – A South African Context (PhD Ms. Kentse Mpolokeng

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2019, subject to the approval of Professor Beningfield** (Steve.Beningfield@uct.ac.za)

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

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

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 17 October 2018

C.C. Mr L. Naidoo, Dr B. Jacobs, Professor S. Beningfield

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