

**RANGE AND FREQUENCY OF AORTIC ARCH VARIANTS IN A
SOUTH AFRICAN POPULATION.**

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3. Abstract

The purpose of this study was to describe the range and frequency of aortic arch (AA) branching patterns using multi-detector computed tomography (MDCT). MDCT images of 400 patients who attended Groote Schuur Hospital between January 2013 and December 2014 for CT Chest and CT Thoracic angiogram were assessed. Six different branching patterns were observed. A left-sided AA with three major branches was present in 67% of the patients. Bovine-type AA (26 %) and independent origin of the left vertebral artery (5%) were the next two most common patterns. The pattern and distribution of aortic arch branching patterns demonstrated in our study matches those found in studies conducted in other populations in South Africa, Kenya and other countries around the world. In addition, a link between gender and aortic arch branching patterns has been demonstrated in our study. Knowledge of the presence of variant aortic arch branching patterns will aid interventionists and surgeons to better plan procedures in order to avoid complications. Therefore, performing CT Angiograms of the chest in patients admitted for procedures involving the thorax would be beneficial.

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5. Introduction and Literature review

The “normal” aortic arch is left sided and has three branches; however, as many as 11 branches have been found. (Celikyay et al. 2013; Ergun et al. 2013; Natsis et al. 2009). The development of the aortic arch and the major vessels is a complex process that occurs during the embryonic period taking its definitive configuration by the eighth week of gestation (Celikyay et al. 2013; Jakanani & Adair 2010). Variant patterns result from differences in development (Vučurević et al. 2013).

5.1. Embryology

The “hypothetical double arch” model by Edwards which describes the process of development of the classical aortic arch accounts for anatomical variation (Edwards 1948; Edwards 1953; Celikyay et al. 2013)(Edwards 1948; Edwards 1953; Celikyay et al. 2013). Early in the embryonic period, the main branch of the heart, the truncus arteriosus, gives rise to multiple bilateral and symmetrical aortic arches, also referred to as branchial arch arteries, numbered according to their order of development (Celikyay et al. 2013; Jakanani & Adair 2010; Lale et al. 2014). These then merge on either side of the pharynx to form two dorsal aortae (Celikyay et al. 2013; Jakanani & Adair 2010; Lale et al. 2014). During the third week of gestation, the dorsal aortae join at the level of the fourth thoracic vertebra to form a single descending aorta (Jakanani & Adair 2010; Celikyay et al. 2013). The proposed double arch constitutes the paired branchial arch arteries ventrally and the dorsal aortae dorsally that form a vascular ring encircling the oesophagus and trachea (Celikyay et al. 2013). The branchial arteries that do not contribute to the final anatomy of the aortic arch regress, namely the first, second and fifth branchial arteries (Jakanani & Adair 2010; Celikyay et al. 2013). Most of the right sixth branchial artery regresses but a small portion remains as the right pulmonary artery (Rea et al. 2014). The left sixth branchial artery forms the ductus arteriosus (Rea et al. 2014). Failure of the embryological process of development characterised by fusion and regression results in anatomical variations (Jakanani & Adair 2010; Celikyay et al. 2013; Natsis et al. 2009; Nayak et al. 2006; Ogeng’o et al. 2010).

During the formation of the aortic arch, the right dorsal aorta distal to the origin of the ipsilateral seventh segmental artery regresses breaking the vascular ring and resulting in a solitary left sided aortic arch (Celikyay et al. 2013). The proximal right dorsal aorta and the right seventh intersegmental artery migrate cranially and remain connected to the aortic sac

by the right fourth branchial artery (Celikyay et al. 2013). These structures give rise to the right subclavian artery and brachiocephalic trunk respectively (Celikyay et al. 2013; Jakanani & Adair 2010).

The third branchial arteries give rise to the common carotid arteries bilaterally (Celikyay et al. 2013; Jakanani & Adair 2010). The left fourth branchial artery forms the left subclavian artery, the main aortic arch and continues inferiorly as the descending aorta (Jakanani & Adair 2010). The aortic sac develops into the ascending aorta (Celikyay et al. 2013).

The process of angiogenesis is related to the local release of certain growth factors by the developing tissues (Bhatia et al. 2005). Premature or delayed release as well as altered levels of these factors may result in variations in arterial morphology (Bhatia et al. 2005).

It is well documented that the arterial vasculature of the thorax, including the aortic arch, has anatomical variations (Nayak et al. 2006; Kumar & Mishra 2015). These variants have been studied and documented by various authors in different study populations and their frequency is said to have changed during the twentieth century (Bhatia et al. 2005; Nayak et al. 2006).

5.2. Introduction

Many studies directed at determining the frequency of aortic arch branching pattern have been conducted using cadaveric dissection and conventional digital subtraction angiography (DSA) whereas studies conducted using multi-detector CT are limited (Karacan et al. 2014; Ergun et al. 2013). A small sample population restricts the few studies that have been done to date (Rea et al. 2014). Of note, the documented frequencies of the various aortic arch branching patterns differ among the studies (Bhatia et al. 2005). This vast range is a result of differences in ethnicity, socio-economic factors and environmental factors, which influence angiogenesis (Rea et al. 2014; Jakanani & Adair 2010; Ergun et al. 2013; Vučurević et al. 2013). Chromosomal abnormalities also contribute to the presence of aortic arch variations (Kumar & Mishra 2015).

There are few studies investigating the link between gender and aortic arch branching patterns (Karacan et al. 2014). Ergun et al demonstrated that, overall, aortic arch variants were more common in females compared to males (Ergun et al. 2013). Although it has been said that there is no meaningful relationship between anatomical variants of the aortic arch and gender, studies by Moltz and Piyavisetpat et al. demonstrated that the aberrant right subclavian artery occurs more in females compared to males, which was in agreement with Karacan et al.(Molz 1976; Piyavisetpat et al. 2011; Karacan et al. 2014; Shakeri et al. 2013). Karacan et al. then demonstrated that the aberrant vertebral artery arising directly from the aortic arch was more common in males compared to females whereas the frequencies of other variant were comparable (Karacan et al. 2014). Natsis et al. demonstrated the “bovine arch” to occur more frequently in males than females (Natsis et al. 2009).

Previous studies, conducted using different modalities in various study populations, demonstrated a dominance of the normal branching pattern with a prevalence of 64% to 85% of patients (Natsis et al. 2009; Ergun et al. 2013; Celikyay et al. 2013; Jakanani & Adair 2010; Berko et al. 2009; Budhiraja et al. 2013). The “bovine” aortic arch, which bears no resemblance to the aortic arch present in cattle, is the most common anatomical variant of the aortic arch in a number of studies (Jakanani & Adair 2010; Berko et al. 2009; Natsis et al. 2009; Budhiraja et al. 2013; Vučurević et al. 2013; Rea et al. 2014). The Bovine arch is characterised by a two-branch pattern whereby the left common carotid artery shares either a common root or trunk with the brachiocephalic artery, followed by the left subclavian artery (Ergun et al. 2013; Rea et al. 2014). Delayed growth between the third and fourth aortic arches results in fusion of the left common carotid artery with the brachiocephalic trunk (Jakanani & Adair 2010). Studies conducted using different modalities have shown Bovine arch prevalence ranging from 20%-30% in various study populations (Celikyay et al. 2013; Berko et al. 2009; Budhiraja et al. 2013; Jakanani & Adair 2010; Ogeng'o et al. 2010; Makhanya et al. 2004).

Studies conducted in populations from Greece and Turkey using DSA and CT angiography respectively, found lower prevalence of the bovine arch of 15% in Greece and 7.8 % in Turkey (Natsis et al. 2009; Ergun et al. 2013). Although this pattern is often asymptomatic, it has been linked with cough, fever and dyspnoea associated with mediastinal enlargement (Celikyay et al. 2013). The bovine arch has also been linked to cardiac and coronary artery

anomalies (Ogeng'o et al. 2010). Importantly, higher failure rates due to technical difficulty during carotid artery stenting have been associated with the bovine arch (Berko et al. 2009). In addition, unintentional blockage of the common trunk can result in significant ischaemic complications as it supplies both the common carotid arteries, the right vertebral artery and the right subclavian artery (Ogeng'o et al. 2010; Nayak et al. 2006).

Normally, the vertebral arteries arise as the first branch arising from the posterior superior surface of the first part of the subclavian artery (Ergun et al. 2013; Budhiraja et al. 2013). There are various documented anomalous origins of the vertebral arteries including their origin from the aorta, common carotid, internal carotid and external carotid arteries (Ergun et al. 2013). More commonly, the left vertebral artery has an anomalous path compared to the right and previous studies have demonstrated that the most common of these variants is a left vertebral artery arising independently from the aortic arch (Ergun et al. 2013). The aberrant left vertebral artery may arise between the left common carotid artery and the left subclavian artery or distal to the subclavian artery (Ergun et al. 2013; Ogeng'o et al. 2010). Its position as the third branch, proximal to the left subclavian artery is more common (Ergun et al. 2013; Celikyay et al. 2013; Rea et al. 2014). In this case, the aberrant left vertebral artery enters the transverse foramen at the level of the fourth or fifth cervical vertebra rather than the sixth vertebral body (Rea et al. 2014). This pattern may result when the left vertebral artery arises from a persistent sixth cervical intersegmental artery as opposed to the seventh, and failed regression of a segment of the dorsal aorta allowing blood to flow through the patent routes (Rekha & Senthilkumar 2013; Lale et al. 2014). An alternative theory suggests that there is absorption of the tissue of the developing left subclavian artery between the vertebral artery and the aortic arch (Budhiraja et al. 2013). This correlates with the third most common aortic arch branching pattern present in between approximately 4% to 7% of patients as seen in previous studies (Jakanani & Adair 2010; Berko et al. 2009; Celikyay et al. 2013; Ergun et al. 2013). Budhiraja et al. utilised 52 cadavers from an Indian population to study this variant and noted a higher prevalence of 15.3% in comparison (Budhiraja et al. 2013). An Australian cadaveric study conducted by Bhatia et al., demonstrated that the prevalence of aberrant left vertebral arteries increased from 7% to 14% when only patients from a community with a lower socio-economic status, in Southern Australia, were considered (Bhatia et al. 2005; Jakanani & Adair 2010). The lowest prevalence rates of this variant were found in studies done by Natsis et al., (0.79%) and Makhanya et al. (0%), both of which used conventional DSA techniques (Natsis et al. 2009; Makhanya et al. 2004). At

DSA, failure to catheterise the aberrant vertebral artery arising directly from the aortic arch may result in the incorrect diagnosis of vertebral artery occlusion or absence (Ergun et al. 2013; Natsis et al. 2009). It is thought that the results achieved by Natsis et al. concerning the aberrant left vertebral artery may have underestimated the prevalence of this variant (Natsis et al. 2009; Ergun et al. 2013). Similarly, if the aberrant left vertebral artery lies outside the region of interest during non-invasive imaging like CTA, MRI or Doppler ultrasound, it may be considered absent or diseased (Natsis et al. 2009). In the absence of aneurysm formation, this variant is not associated with any specific clinical symptoms (Natsis et al. 2009). Although there is no irrefutable evidence associating the aberrant left vertebral artery with cerebrovascular disorders, it is hypothesized that altered haemodynamics increase the risk of intracranial aneurysm formation (Lale et al. 2014). The anomalous origin of the left vertebral artery from the aortic arch has been associated with an increased occurrence of spontaneous left vertebral artery dissection (Celikyay et al. 2013; Berko et al. 2009; Karacan et al. 2014; Nayak et al. 2006). This may be due to inherent defects in the arterial wall or differences in the forces controlling cerebral blood flow (Berko et al. 2009; Karacan et al. 2014). According to Budhiraja et al., the prevertebral segment of the aberrant LVA is often affected by atherosclerosis (Budhiraja et al. 2013). At endovascular repair of aneurysms, poor visualisation may result in endoleaks or ischemic complications in the brain and upper limbs (Celikyay et al. 2013). This variant is especially important for neurovascular interventionists and neurosurgeons as injury to the vertebral artery is a recognised complication of the extended lateral decompression during anterior cervical surgery and can result in heavy bleeding and ischaemic complications (Natsis et al. 2009). Generally, these patients do not develop subclavian steal syndrome, but they are prone to developing variants of this syndrome (Berko et al. 2009).

The occurrence of other aortic arch variations has been less frequent (Ergun et al. 2013; Natsis et al. 2009). A bicarotid trunk (i.e., both common carotid arteries arising from a common origin flanked by the subclavian arteries on either side) has been described and develops when the embryonic aortic sac fails to divide (Natsis et al. 2009). This variant was demonstrated in 4 studies: using conventional DSA techniques in Greece (Natsis et al.), Multi-detector Computed Tomography (MDCT) for thoracic imaging and carotid CT Angiography (CTA) in Turkey (Celikyay et al. and Ergun et al.), and a cadaveric study in India (Budhiraja et al.) (Natsis et al. 2009; Celikyay et al. 2013; Ergun et al. 2013; Budhiraja et al. 2013). The latter study conducted on the Indian population yielded a significantly

higher prevalence (19.2%) compared to studies in Greece and Turkey, which had a prevalence ranging between 0.2% and 0.5% (Natsis et al. 2009; Celikyay et al. 2013; Ergun et al. 2013; Budhiraja et al. 2013). Of the various aortic arch branching patterns, the bicarotid trunk is most commonly associated with an anomalous aberrant right subclavian artery (Ergun et al. 2013). This variant may occur with congenital cardiovascular abnormalities and chromosomal disorders like polyvalvular disease; Di-George syndrome; Trisomy 13, 18, 21; Tetralogy of Fallot and Noonan syndrome (Natsis et al. 2009; Celikyay et al. 2013; Ergun et al. 2013; Budhiraja et al. 2013; Karacan et al. 2014). It is documented that the bicarotid trunk is the most common cause for tracheobronchial compression due to congenital cardiovascular anomaly (Natsis et al. 2009). Other congenital abnormalities associated with the bicarotid trunk include oesophageal atresia, trachea-oesophageal fistula and origin of the left coronary artery from the pulmonary artery (Karacan et al. 2014). However, it has not been shown to influence the supply of oxygen to the brain (Natsis et al. 2009; Ergun et al. 2013).

A number of studies conducted in Turkish, Greek and American populations by Karacan et al., Natsis et al. and Berko et al., respectively, demonstrated unique variants whereby the thyroid artery arose independently from the aortic arch (0.1% to 0.2% prevalence) (Natsis et al. 2009; Berko et al. 2009; Karacan et al. 2014). They also demonstrated an aortic arch variant branching pattern with a left brachiocephalic trunk (0.1% prevalence) (Berko et al. 2009; Karacan et al. 2014; Natsis et al. 2009; Ergun et al. 2013). It is documented that the thyroid ima artery may arise from a number of places including the aortic arch, brachiocephalic trunk, the common carotid, internal thoracic, the pericardiophrenic, the subclavian, the thyrocervical trunk, the inferior thyroid or the transverse scapular artery (Natsis et al. 2009; Karacan et al. 2014). More often, it is right-sided (Natsis et al. 2009). The clinical importance of this variant is during surgical resection of the thyroid or laryngeal transplantation where it can be injured (Natsis et al. 2009; Karacan et al. 2014).

An absent brachiocephalic trunk with four vessels arising independently from the aortic arch is a rare and inconsequential variant that has been demonstrated in South African and Turkish populations with a prevalence between 0.2% and 0.7% (Ergun et al. 2013; Natsis et al. 2009; Satyapal et al. 2003).

A two-branch pattern with a common origin for the common carotid arteries and a common origin for the subclavian arteries is described as the avian form, occurring in birds, and is very rare (Natsis et al. 2009). Clinical significance is associated with the common trunk for the carotid arteries and the aberrant course of the right subclavian artery (Natsis et al. 2009).

The aberrant right subclavian artery is described interchangeably as an anomaly and a variant, and is often seen in conjunction with other aortic arch variants such as a bicarotid trunk and a four-branch aortic arch (Ergun et al. 2013; Karacan et al. 2014). It is the most frequently occurring vascular ring anomaly (Rea et al. 2014). Development of this anomaly occurs when there is premature obliteration of the right fourth aortic arch and the proximal part of the right dorsal aorta (Kumar & Mishra 2015). The right subclavian artery then develops from the right seventh intersegmental artery (Kumar & Mishra 2015). Differential growth in the aortic arch shifts the origin of the right subclavian artery towards the left subclavian artery (Kumar & Mishra 2015). This aberrant right subclavian artery courses from its position as the last branch of the aortic arch to supply the right upper limb (Ergun et al. 2013; Natsis et al. 2009). Most commonly, it passes posterior to the oesophagus in as many as 85% of cases (Ergun et al. 2013; Natsis et al. 2009; Rea et al. 2014). However, it can also pass between the oesophagus and trachea or anterior to the trachea (Ergun et al. 2013; Natsis et al. 2009; Rea et al. 2014). If pressure is exerted on the oesophagus, the patient may experience dysphagia and occasionally pain - so called “dysphagia lusoria”, which is more common in cases where there is aneurysmal dilation of the proximal subclavian artery (Kommeral diverticulum) (Jakanani & Adair 2010; Celikyay et al. 2013; Natsis et al. 2009). A Kommeral diverticulum is more commonly associated with a right-sided aortic arch and aberrant left-sided subclavian artery (Jakanani & Adair 2010). In cases where the aberrant right subclavian artery comes into contact with the trachea, it may cause dyspnoea (Natsis et al. 2009). Compared to DSA, multi-detector computer tomography (MDCT) is better at demonstrating the pressure effects of the artery lusoria on the oesophagus and trachea (Celikyay et al. 2013). Importantly, the aberrant right subclavian artery accompanies an anomalous course of the right laryngeal nerve, at times, where the nerve is unable to loop around the right subclavian artery. In this situation, it is a “non-recurrent” laryngeal nerve (Natsis et al. 2009). Occlusion of this vessel may perpetuate the “subclavian steal” syndrome or result in blood pressure differences between the right and left upper limbs (Natsis et al. 2009). The aberrant right subclavian artery can result in complications when performing a tracheostomy (Celikyay et al. 2013; Natsis et al. 2009). Salivary bypass tubes increase the

risk of creating a fistula between the aberrant right subclavian artery and the oesophagus (Celikyay et al. 2013).

5.3. Significance of the current study

Anatomical variations of the aortic arch are often ancillary findings, however, knowledge of their existence is important when they cause physical discomfort or result in complications during endovascular procedures (Natsis et al. 2009; Rea et al. 2014; Karacan et al. 2014). Patients with variants are more likely to suffer from iatrogenic vascular injury during interventional radiology and surgical procedures (Vučurević et al. 2013). Taking into account the increase in the number of radiological and surgical procedures involving the head, neck and chest, knowledge of the anatomical variation of the aortic arch is important because this can result in unexpected difficulties and fatal consequences if overlooked (Celikyay et al. 2013; Budhiraja et al. 2013; Ogeng'o et al. 2010).

We believe that the outcomes of this study will contribute towards comprehensive knowledge of variant anatomy, as well as better policies and guidelines concerning radiological intervention and surgical strategies involving the aorta and its major branches, particularly in this unique Western Cape population.

5.4. Reason for using Multi-detector Computer Tomography

MDCT is an effective tool and is the principal non-invasive diagnostic method for demonstrating variations of the aortic arch and evaluating their clinical outcomes (Celikyay et al. 2013; Shakeri et al. 2013; Rea et al. 2014). Its multi-planar capabilities are helpful in this regard (Celikyay et al. 2013). It has excellent spatial resolution and MDCT allows visualisation of the adjacent structures and their anatomical relationship with the vasculature (Celikyay et al. 2013; Karacan et al. 2014). Additional advantageous characteristics of CT are that it is non-invasive, it has a relatively fast acquisition time and is inexpensive compared to other digital angiographic methods (Shakeri et al. 2013). Disadvantages include patient exposure to ionising radiation and the use of iodinated contrast (Karacan et al. 2014). MRI is a radiation free alternative but lacks the spatial resolution offered by CT (Karacan et al. 2014). One significant disadvantage of DSA is that occluded vessels may be considered absent (Celikyay et al. 2013).

6. Methods

6.1. Research paradigm

The research paradigm of the study is retrospective and quantitative with a descriptive component. CT Angiograms of the thoracic aorta and contrasted CT chest studies done for any reason between January 2013 and December 2014 were analysed and used to assess the frequency of aortic arch variants in the study population. The anatomical variants were then categorised using a standardised classification system.

6.2. Sample

The study population includes adult South Africans (age 18 years and over), both male and female, living in the Western Cape and who attended Groote Schuur Hospital between January 2013 and December 2014 for Contrasted CT Chest and CT angiogram of the thoracic aorta. A total of 1930 patients were scanned at Groote Schuur Hospital during this period.

6.2.1 Inclusion criteria

Adult patients (male and female) who had a contrasted CT chest or CT angiogram of the thoracic aorta at Groote Schuur Hospital between January 2013 and December 2014.

6.2.2 Exclusion criteria

1. Patients presenting for Contrasted CT Chest or CTA post trauma – these were excluded as trauma to the aortic arch can potentially impair the ability to identify the anatomy.
2. Patients known with or newly diagnosed aortic aneurysms as presented in the referring history or the radiology report.
3. Patients with known or incidental finding of a right sided aortic arch – these were considered anomalies and not anatomic variants by the investigators.
4. CT studies without attached radiological reports - these were required for meeting the exclusion criteria.

5. Patients with failed/suboptimal contrast injections on CT as evaluated by the primary investigator.
6. Cases where all four Radiologists involved in the study did not reach a consensus on the presence of a dominant aortic arch branching pattern.

6.3. Materials and Methods

CT images were obtained retrospectively from the Groote Schuur Hospital PACS along with diagnostic reports, dating from January 2013 to December 2014.

Finalised diagnostic reports for scans acquired during the study period were obtained from Phillips iSite Enterprise (Eindhoven, Netherlands) and were reviewed by the primary investigator to exclude patients according to set exclusion criteria.

CT scanners used to acquire the images at GSH hospital include:

- Siemens Somatom Emotion 16 (Erlangen, Germany), used in spiral mode. 16 slice multiple detector array.
- Toshiba Aquillion PRIME (Tochigi, Japan), used in spiral mode. 160 slice multiple detector array.

CT images are acquired routinely according to set Groote Schuur Hospital (GSH) Radiology protocols.

CT angiograms of the chest are routinely acquired following intravenous administration of 100 ml Jopamiron 370 water-soluble contrast (Bracco, Italy) by an automatic injector, at a flow rate of 4 ml/sec through right sided IV access. Images are acquired using the bolus tracking method. The region of interest is positioned in the ascending aorta and the threshold is set at HU 180. Scan parameters are pre-set at 100 to 120 kV and 380 mA. Slice thickness is approximately 3 to 5 mm.

Contrast enhanced CT chest studies are acquired in the arterial phase following intravenous administration of 100 ml Omnipaque 300 water soluble contrast (Little Chalfont, United Kingdom) by an automatic injector at a flow rate of 2.5ml/sec through IV access. Scanning is performed caudocranially with a field of view measuring 512 mm and set to include the liver inferiorly. On the Siemens Somatom Emotion 16 (Elargan, Germany), the delay is set to 25 seconds. On the Toshiba Aquilon PRIME (Tochigi, Japan), the delay is set to 35 seconds.

Three readers, all consultant radiologists, reviewed each study using Phillips Intellispace Portal (Eindhoven, Netherlands). Images were reviewed in axial, coronal and sagittal planes using 4 mm slice thickness and maximum intensity projection (MIP). The readers were blinded from each other and the history of the participants. Branching patterns were then classified according to set criteria provided on a tick sheet aided by diagrammatical representation of the variant patterns. The consultant reports were then compared with each other and majority opinion was used to determine the branching pattern in each case. In the case of three different opinions, a fourth radiology consultant was called upon to settle the dispute.

Figures 1 to 8 below summarise aortic arch branching patterns used on the study tick sheet according to criteria set by Natsis et al.:

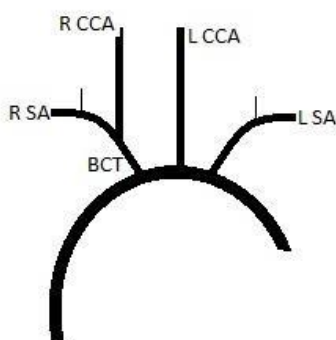


Figure 1: Type 1 aortic arch characterised by 3 aortic arch branches in the following order: (1) Brachiocephalic trunk , giving rise to the right subclavian and right common carotid arteries;(2) the left common carotid and (3) the left subclavian artery

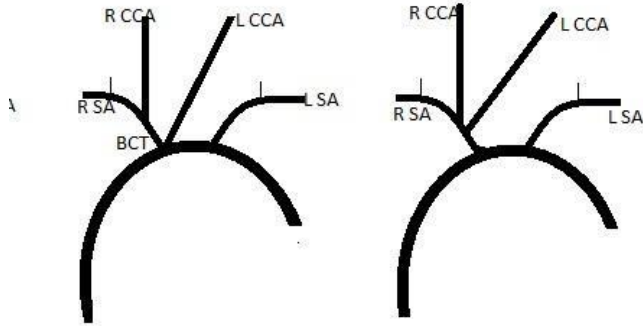


Figure 2: Type 2 (Bovine) Aortic Arch characterised by 2 aortic arch branches in the following order: (1) Common origin/trunk of the brachiocephalic artery and the left common carotid artery and (2) left subclavian artery

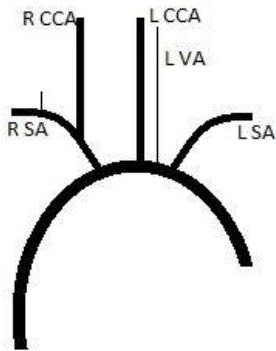


Figure 3: Type 3 Aortic Arch characterised by four branches in the following order: (1) Brachiocephalic artery; (2) Left common carotid artery; (3) Left vertebral artery; (4) Left subclavian artery

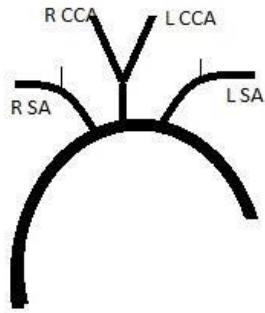


Figure 4: Type 4 Aortic Arch characterised by a common origin of the common carotid arteries and 3 branches in the following order: (1) Right subclavian artery; (2) Bicarotid trunk and (3) Left subclavian artery.

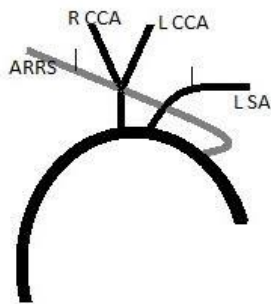


Figure 5: Type 5 Aortic Arch characterised by 3 branches in the following order: (1) Bicarotid trunk; (2) Left subclavian artery and (3) Aberrant right subclavian artery.

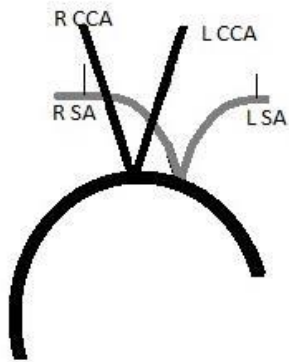


Figure 6: Type 6 Aortic Arch characterised by 2 branches in the following order: (1) Bicarotid trunk and (2) Common origin for the right and left subclavian arteries.

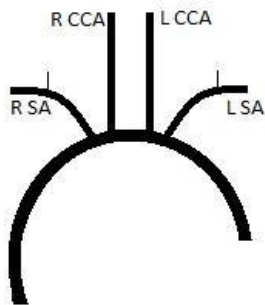


Figure 7: Type 7 Aortic Arch characterised by four aortic arch branches in the following order: (1) Right subclavian artery; (2) Right common carotid artery; (3) Left common carotid artery and (4) Left subclavian artery.

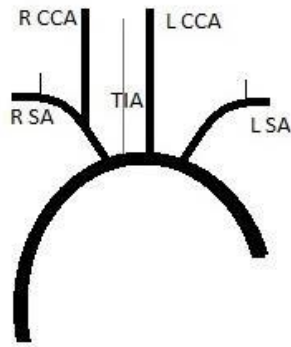


Figure 8: Type 8 Aortic Arch characterised by an aortic with four branches in the following order: (1) Brachiocephalic artery; (2) Thyroid ima artery; (3) Left common carotid artery and (4) Left subclavian artery.

6.4. Data collection

Data was classified according to a predefined range of anatomical variations which were considered present or not present under these categories in binary on an excel sheet.

6.5. Reliability and validity

CT is a valid modality for the evaluation of the aortic arch given its multiplanar capabilities and excellent spatial resolution. It is non-invasive, delivers high resolution images in a short period and can assess the anatomy of the aortic arch and its branches as demonstrated by multiple previous studies. For the aforementioned reasons, CT angiography is currently the gold standard for assessment of vascular structures.

To counter any possibility regarding the reliability of interpretation, each contrasted CT chest and CT angiogram included in this study was interpreted by three consultant radiologists, who classified the arch configuration into set criteria provided on a tick sheet. The readers were blinded from each other and from the participant's history. In the case of a dispute, a majority decision on the branching pattern was accepted. In the case of a three way split, the decision of a fourth radiology consultant was accepted.

6.6. Bias

This was a hospital-based population. If the presence of an aortic arch variant predisposed individuals to certain pathology, the incidence of aortic arch variants is likely to be higher in this population. However, with the exception of the pre-set exclusion criteria, patients were included in the study irrespective of the reason for CT chest and CT angiogram referral. Indications for CT chest are vast, and this variability is hoped to reduce statistical bias towards a particular pattern. The study population was of mixed gender and ethnicity.

6.7. Data analysis and statistics

Data was collected as frequencies and percentages, and subcategorised according to gender. Comparative statistics for prevalence of each type of anomalous branching pattern and gender distribution was performed using the Chi-squared and Fisher Exact tests.

7. Results

A total of 400 CT scans were reviewed by three Radiologists. Consensus regarding a dominant pattern was not reached on seven CT scans. The seven CT scans were then reviewed by a fourth Radiologist. Of the seven CT scans a dominant pattern was found in two subjects. The remaining five CT scans were excluded. Two more CT scans were excluded due to inadequate contrast opacification. The results of 393 CT studies were analysed further.

Six different aortic arch branching patterns were recognised in our study. They were classified according to criteria previously described in a study by Natsis et al. (Natsis et al. 2009). The classical aortic arch branching pattern (Type 1) was found in 265 (67%; CI 62.6 – 72.0 %) of the study population (Figure 9). 128 (33 %) patients had a variant branching pattern.



Figure 9: Coronal maximum-intensity projection (A) and 3D Reconstruction (B) images demonstrate a Type 1 Aortic Arch with a three-vessel branching pattern.

(A) A 40-year-old female, known with lung necrosis. Contrast CT performed for evaluation of the lungs prior to surgical resection.

(B) A 46-year-old female who presented with a history of angina. Incidental para-tracheal mass identified on chest x-ray. Contrast CT performed for further evaluation

BC= Brachiocephalic Artery. LCC = Left Common Carotid Artery. LS = Left Subclavian Artery. RCC = Right Subclavian Artery. RS = Right Subclavian Artery.

In those patients with variant aortic arch branching patterns, 103 (26 %; CI 21.9 – 30.9%) had a type 2 (Bovine) pattern (Figure 10), 20 (5%; CI 3.1 – 7.8%) had a type 3 pattern (Figure 11) and 3 (1 %; CI 0.2 – 2.2%) had a type 5 pattern (Figure 12). 2 (1 %; CI 0.1 – 1.8%) had branching patterns not described on the study tick sheet (Figures 13 and 14). However, both branching patterns had been recognised in previous studies in other population groups (Celikyay et al. 2013; Ergun et al. 2013; Karacan et al. 2014; Kumar & Mishra 2015; Lale et al. 2014; Nayak et al. 2006).



Figure 10: Coronal maximum-intensity projection (A) and 3D Reconstruction (B) images demonstrate a Type 2 (Bovine) Aortic Arch with a common origin for the BC and LCC.

(A) An HIV-positive patient, known with Kaposi Sarcoma. Lung mass on Chest x-ray.

Contrasted CT performed for further evaluation.

(B) A 49-year-old female who presented with haemoptysis and an abnormal chest x-ray. Contrast CT was performed for further evaluation.

BC= Brachiocephalic Artery. LCC = Left Common Carotid Artery. LS = Left Subclavian Artery

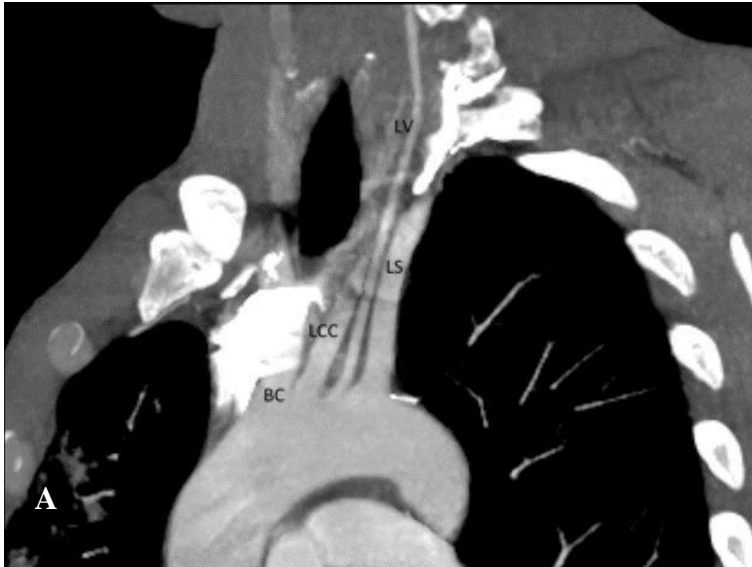


Figure 11: Coronal maximum-intensity projection (A) and 3D Reconstruction (B) images demonstrate a Type 3 Aortic Arch with an Aberrant Left Vertebral Artery (LV).

(A) A 41-year-old HIV-positive male patient known with fibrocystic lung disease who presented with haemoptysis. Contrast CT performed for further evaluation.

(B) A 70-year-old male with lower respiratory tract infection and poor response to anti-biotic treatment. Contrast CT performed for further evaluation.

BC = Brachiocephalic Artery. LCC = Left Common Carotid Artery. LV = Left Vertebral Artery. LS = Left Subclavian Artery.

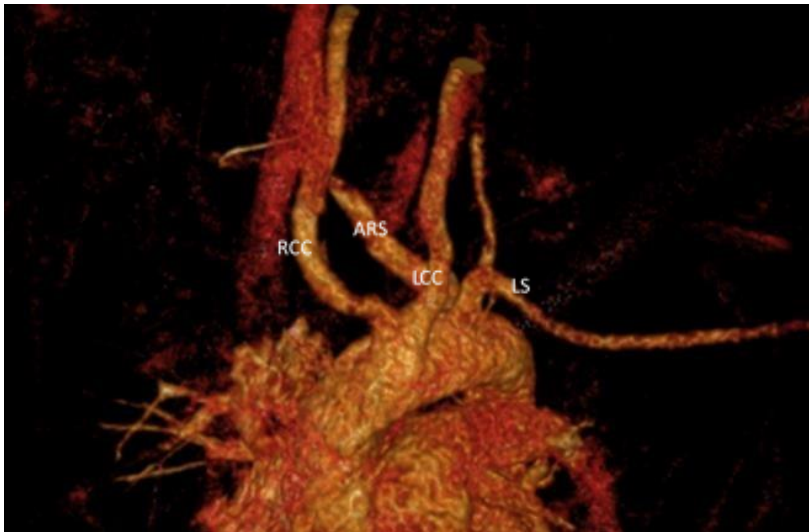


Figure 12: CT 3D Reconstruction image in a 36-year-old HIV-positive female known with pulmonary tuberculosis and no improvement on treatment, demonstrates a Type 5 Aortic Arch with a 3-vessel branching pattern characterised by a common trunk for BC and LCC and an ARS.

RCC = Right Common Carotid Artery. LCC = Left Common Carotid Artery. LS = Left Subclavian Artery ARS = Aberrant Right Subclavian Artery. BC = Brachiocephalic Artery.

Additional variant branching patterns identified in our population that were not described on the study tick sheet were as follows:

1. Four branches arising from the aortic arch in order - Right common carotid artery (RCC), Left Common carotid artery (LCC), Left subclavian artery (LSC) and Aberrant right subclavian artery (ARS) (Figure 13).

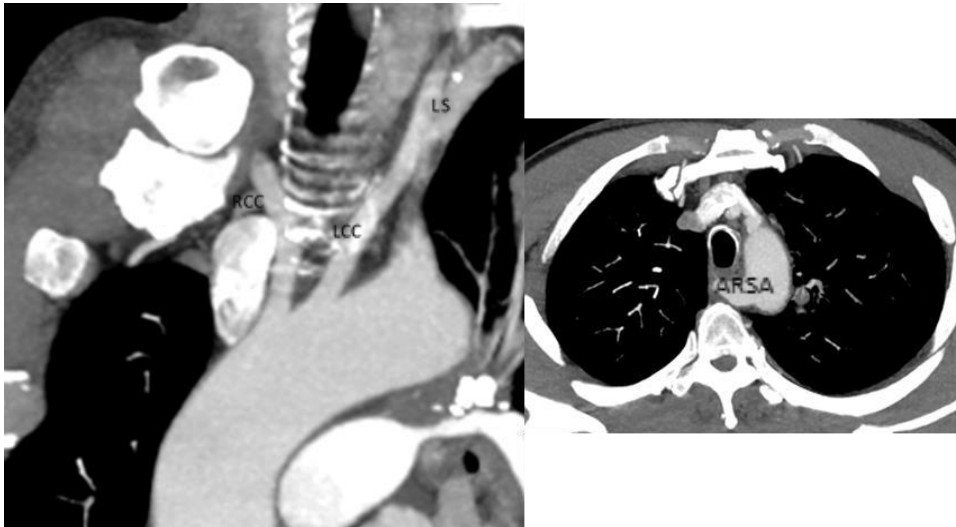


Figure 13: Coronal and axial maximum-intensity projection images demonstrate 4-vessel Aortic Arch branching pattern not described on our study tick sheet in a 59-year-old male with a suspicious left upper lobe lung mass.

RCC = Right Common Carotid Artery. LCC = Left Common Carotid Artery. LS = Left Subclavian Artery. ARS = Aberrant Right Subclavian artery.

2. Bovine pattern with a separate origin for the left vertebral artery in the following order- Common trunk for the brachiocephalic artery and left common carotid artery (CT BC&LCC), left vertebral artery (LV) and left subclavian artery (LS). (Figure 14).

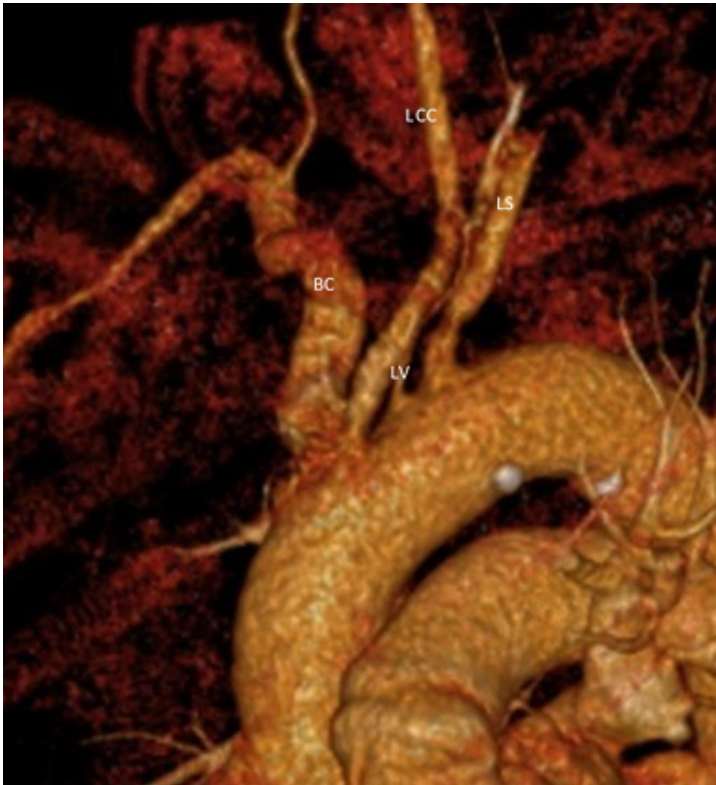


Figure 14: 3D Reconstruction demonstrates a 3-vessel Aortic Arch branching pattern characterised by a common trunk for the BC and LCC, and an aberrant LV in a 35-year-old female with previous pulmonary Tuberculosis infection and suspicious nodules on Chest x-ray.

BC = Brachiocephalic Artery. LCC = Left Common Carotid Artery. LV = Left Vertebral Artery. LS = Left Subclavian Artery.

The frequency and proportional distribution of the branching patterns is demonstrated in Figure 15 below. Patterns 4, 6, 7 and 8 were not present in our population.

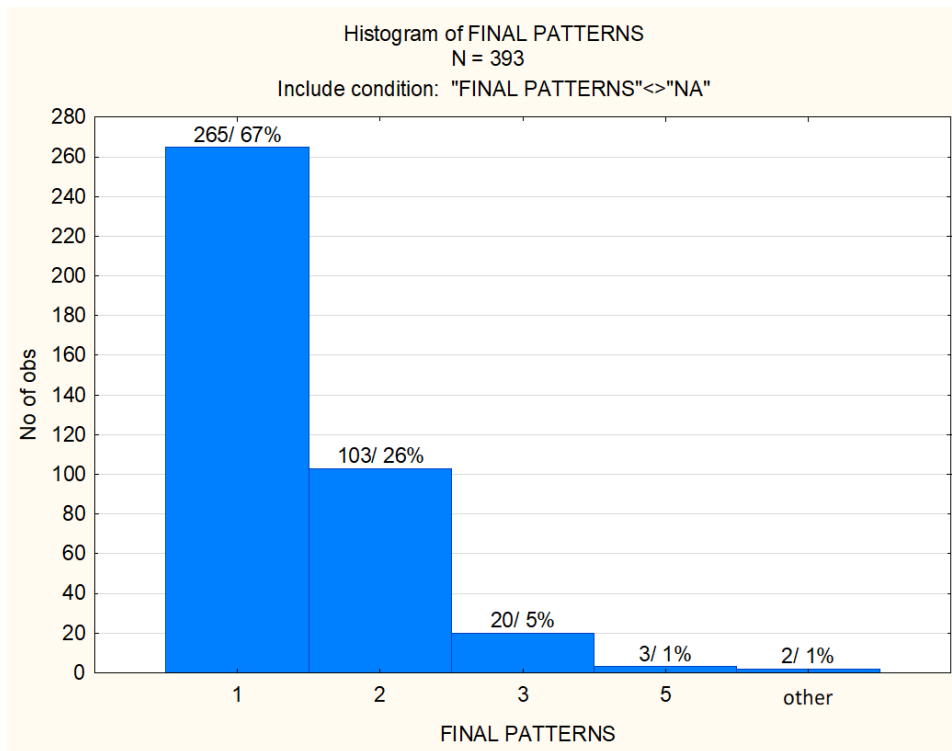


Figure 15: Prevalence of aortic arch branching patterns in a Western Cape population attending Groote Schuur Hospital (n = 393; percentages to the nearest integer).

A total of 211 males and 182 females were analysed (n= 393). The normal (Type 1) pattern was found in 155 (73.46%) of the total males in our study, compared to 110 (60.44%) of the total females. Variant aortic arch branching patterns were found in 56 (26 %) of the male subjects, compared to 72 (39.56 %) of the female subjects. A statistically significant difference was noted between male and females, with males more frequently having a normal (Type 1) arch while females were more likely to have to variant aortic arch branching pattern (p= 0.02). The most common variant pattern in both genders is the Type 2 (Bovine). The results are summarised in Tables 1 and 2.

Table 1 Prevalence of variant aortic arch patterns in males and females as a proportion of the whole study population (n=393).

Branching Pattern	Total (n; %)	Male (n; %)	Female (n; %)
Type 1 (Normal arch)	265 (67.4%)	155 (39.4%)	110 (28%)
Variant aortic arch branching patterns	128 (32.6 %)	56 (14.3 %)	72 (18.3%)
Totals	393 (100%)	211 (54.7%)	182 (46.3%)

Table 2: Summary of the prevalence of each aortic arch branching pattern according to gender. (n=393)

Marked cells have counts > 10. Chi-square(df=4)=11.34, p=.02299 Fisher Exact(r x c) p=0.02						
Gender	FINAL PATTERNS 1	FINAL PATTERNS 2	FINAL PATTERNS 3	FINAL PATTERNS 5	FINAL PATTERNS other	Row Totals
F	110	58	10	3	1	182
Row %	60.44%	31.87%	5.49%	1.65%	0.55%	
M	155	45	10	0	1	211
Row %	73.46%	21.33%	4.74%	0.00%	0.47%	
Totals	265	103	20	3	2	393

8. Discussion

Our study demonstrated a normal aortic arch branching pattern (Type 1) in 67% of the study population, which as with other studies, is the most common aortic arch branching pattern in humans. The prevalence of the Type 1 pattern in our study closely matched the results achieved by other studies conducted in African populations in South Africa and Kenya, as well as study populations in the USA and India (Makhanya et al. 2004; Ogeng'o et al. 2010; Budhiraja et al. 2013; Berko et al. 2009).

This is in contrast to studies conducted on populations in Turkey and Greece which demonstrated a higher prevalence of the normal aortic arch branching pattern, ranging between 74 and 83 % (Karacan et al. 2014; Celikyay et al. 2013; Natsis et al. 2009; Ergun et al. 2013).

The Bovine arch, Type 2 pattern, is documented as the most common anatomical variant of the aortic arch in a number of study populations in Africa, Asia, America and Europe. (Jakanani & Adair 2010; Berko et al. 2009; Natsis et al. 2009; Budhiraja et al. 2013; Vučurević et al. 2013; Rea et al. 2014; Ergun et al. 2013). Previous studies demonstrated prevalence of the Bovine arch ranging from 8 to 28 % in various populations (Celikyay et al. 2013; Berko et al. 2009; Budhiraja et al. 2013; Jakanani & Adair 2010; Ogeng'o et al. 2010; Makhanya et al. 2004; Natsis et al. 2009; Ergun et al. 2013). Our study mirrored these findings and the Bovine Arch (Type 2 pattern) was the most common variant aortic arch branching pattern, present in 26 % of our study population. This frequency is similar to results attained from other studies done in South Africa, Kenya and the USA (Makhanya et al. 2004; Ogeng'o et al. 2010; Berko et al. 2009).

The Type 3 pattern, is the third most common aortic arch branching pattern in multiple previous studies (Ogeng'o et al. 2010; Natsis et al. 2009; Berko et al. 2009; Celikyay et al. 2013; Ergun et al. 2013; Budhiraja et al. 2013; Karacan et al. 2014). This correlates with our study, which demonstrated a prevalence of the Type 3 pattern of 5%. More patients in our study population had this variant compared to patients from other South African and Kenyan populations. Studies conducted in the USA and Turkey, also using MDCT also had a similar proportion of patients with the Type 3 variant (Berko et al. 2009; Ergun et al. 2013; Karacan et al. 2014).

As in previous studies, the Type 5 pattern and the two other patterns were few. In our study population, 1% of patients had the Type 5 pattern. The Type 5 pattern was also present in studies conducted in Greece in Turkey with a prevalence of 0.16% and 0.6%, respectively (Natsis et al. 2009; Karacan et al. 2014).

The aortic arch pattern characterised by four branches arising from the aortic arch as follows- Right common carotid artery (RCC), Left Common carotid artery (LCC), Left subclavian artery (LSC) and Aberrant right subclavian artery (ARS) (Figure 13), was identified in our study population. It was not part of our study tick sheet but has been recognised in multiple

previous studies conducted in Europe and Asia (Celikyay et al. 2013; Ergun et al. 2013; Karacan et al. 2014; Kumar & Mishra 2015; Lale et al. 2014; Nayak et al. 2006).

The bovine pattern with a separate origin for the left vertebral artery in the following order-Common trunk for the brachiocephalic artery and left common carotid artery (CT BC&LCC), left vertebral artery (LV) and left subclavian artery (LS) (Figure 14) was identified in our study population. It was not part of our study tick sheet but has been previously recognised in multiple other studies conducted in Europe and Asia (Budhiraja et al. 2013; Celikyay et al. 2013; Karacan et al. 2014; Rea et al. 2014; Rekha & Senthilkumar 2013).

Table 3: Comparison of the prevalence of aortic arch branching patterns in different study populations.

AUTHOR	STUDY POPULATION	MODALITY	N	MALE (%)	FEMALE (%)	BRANCHING PATTERN TYPES (%)								
						TYPE 1	TYPE 2	TYPE 3	TYPE 4	TYPE 5	TYPE 6	TYPE 7	TYPE 8	OTHER
Budhiraja et al 2013	India	Cadaveric dissection	52	Not specified		63.5	19.2	15.3	0	0	0	0	0	2
Makhanya et al 2004	South Africa	DSA	60	Not specified		65	28	0	0	0	0	0	0	7
Berko et al 2009	USA	MDCT	1000	65.8	34.2	65.9	27.4	6.1	0	0	0	0	0	0.6
Kasirye et al 2019	South Africa	MDCT	393	54	46	67	26	5	0	1	0	0	0	1
Ogeng'o et al 2010	Kenya	Cadaveric dissection	113	Not specified		67.3	25.7	0.9	0	0	0	0	0	6.1
Jakanani et al 2010	UK	MDCT	861	Not specified		74	20	5	0	0	0	0	0	1
Celikyay et al 2013	Turkey	MDCT	845	Not specified		74.4	21.1	2.9	0	0	0	0	0.1	1.5
Karacan et al 2014	Turkey	MDCT	1000	61	39	79.2	14.1	4.1	1.2	0.6	0.7	0.1	0	0
Natsis et al 2009	Greece	DSA	633	71	29	83	15	0.79	0.16	0.16	0.16	0.16	0	0.57
Kumar et al 2015	Nepal	Cadaveric dissection	42	71	29	83	2.4	11.9	0	0	0	2.4	0	0
Ergun et al 2013	Turkey	MDCT	1001	51.8	48.4	85.2	7.8	5.1	0.2	0	0	0.7	0	1.2
Lale et al 2014	Turkey	MDCT	881	59.8	40.2	87.4	7.2	2.8	0	0	0	0	0	2.6

There are few studies investigating the link between gender and aortic arch branching patterns (Karacan et al. 2014). Unfortunately, many of the recent studies quoted above report on rates of branching patterns without gender analyses. Of the few studies that do, most are biased by utilisation of male-dominated cohorts. For instance, two studies reported that 71% of the study cohort were male (Natsis et al. 2009; Karacan et al. 2014). Our study was only comparable to Ergun et al. in terms of population gender balance, with near equal male and female study participant numbers (Ergun et al. 2013).

In our study, the two most common aortic arch branching pattern frequencies (Type 1 and 2) were not the same for both genders. In our study population, females had a lower proportion

of Type 1 pattern and a higher proportion of the Type 2 pattern ($p = 0.02$). There was no difference in the prevalence of the Type 3 pattern between male and female. Few patients had the Type 5 pattern and the patterns not present on the study tick sheet. In our study, all three patients who had the type 5 branching pattern were female. In each gender, one patient had a branching pattern that was not present on the study tick sheet.

Therefore, in our population, the variant branching patterns of the aortic arch are more common in females compared to males. This was in agreement with studies by Ergun et al and Karacan et al. who studied Turkish populations (Ergun et al. 2013; Karacan et al. 2014). In their study, Karacan et al. analysed the aortic arch branching patterns with respect to gender and they found no difference in the proportion of males and females with the Type 2 and Type 3 patterns (Karacan et al. 2014). Types 4, 5 and 6 were more common in females. Type 7 was only present in males (Karacan et al. 2014).

Table 4: Comparison of the distribution of aortic arch branching pattern variants according to gender in two study populations.

		Type 1 (%)	Type 2 (%)	Type 3 (%)	Type 4 (%)	Type 5 (%)	Type 6 (%)	Type 7 (%)	Type 8 (%)	Other (%)
Karacan et al	Male	80	14.1	4.1	1	0.3	0.2	0.2	0	0
(Turkey)	Female	77.9	14.1	4.1	1.3	1	1.5	0	0	0
Kasirye et al	Male	73	21	4.7	0	0	0	0	0	0.5
(South Africa)	Female	60	32	5.5	0	1.7	0	0	0	0.6

8.1. Results in context

The range and frequency of aortic arch branching patterns demonstrated in our study matches those found in studies conducted in other African populations in South Africa and Kenya, as well as other non-African populations around the world. The Type 2 branching pattern is the most common variant pattern present in our study population. Of note, the Type 2 branching pattern was significantly more common in female patients. Although the Type 2 branching pattern is often asymptomatic, it can be associated with adverse outcomes during angiography and interventional procedures. Knowledge of the presence of a Type 2 branching pattern is important, specifically in our population.

8.2. Current applications

The findings of this study are immediately applicable to clinical practice. Recommendations will be made to include imaging into the planning of interventional procedures with a view to mapping out variant aortic arch branching patterns. The proportionally more frequent findings of bovine type 2, type 3 and type 5 aortic branching patterns in females will impact work flow as more precautions are required to avoid procedural complications.

8.3. Limitations of the current study

Information regarding the ethnicity of patients was not obtained.

A small patient population was examined due to time constraints and work force.

8.4. Future applications

Performing contrasted CT studies of the chest in patients admitted for procedures involving the thorax and neck will aid interventionists and surgeons to better plan procedures and avoid complications.

Concerning further research, the following can be considered:

1. Utilising larger patient populations.
2. Multiple centres can be assessed for population group differences within South Africa, including gender and ethnicity.
3. The assessment of pulmonary arterial variants occurring in patients with aortic arch variants.
4. Other anatomical areas can be studied for the presence of variant arterial vasculature.
5. A larger field of view can be assessed for the simultaneous presence of variant arterial vasculature elsewhere in the body e.g. at carotid and renal arteries.

9. Conclusion

We were able to assess the frequency and gender distribution of aortic arch branching patterns present in an adult South African population in the Western Cape who underwent CT scanning of the chest at Groote Schuur Hospital. The range and frequency of aortic arch branching patterns demonstrated in our study matches those found in studies conducted in other African populations in South Africa and Kenya, as well as other populations in India

and the USA. The most common aortic arch branching pattern was the classical three-branch aortic arch that was present in 67 % of our study population. In our study population, 33% had variant anatomy of the aortic arch branching pattern and the bovine branching pattern was significantly more frequent in females than males. Given the prevalence of aortic arch branching pattern variants and their ability to result in surgical complications, we believe that it is worthwhile to perform a contrasted CT study of the chest for planning in patients admitted for interventional and surgical procedures involving the vasculature of the thorax and neck.

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Appendices

10.1. Ethics Clearance Certificate

	<p style="text-align: center;">UNIVERSITY OF CAPE TOWN Faculty of Health Sciences Human Research Ethics Committee</p>	
<p>Room E52-24 Old Main Building Groote Schuur Hospital Observatory 7925 Telephone (021) 404 7600 • Facsimile (021) 406 6411 Email: hos.ksame@uct.ac.za Website: www.health.uct.ac.za/fhs/research/humanethics/forms</p>		
<hr/>		
<p>08 July 2016</p>		
<p>HREC REF: 414/2016</p>		
<p>Prof S Andronikou Division of Radiology C16, NGSF</p>		
<p>Dear Prof Andronikou</p>		
<p>PROJECT TITLE: RANGE AND FREQUENCY OF AORTIC ARCH VARIANTS IN A SOUTH AFRICAN POPULATION (MMed-candidate-N Kasirye)</p>		
<p>Thank you for submitting your response letter to the Faculty of Health Sciences Human Research Ethics Committee dated 06th July 2016.</p>		
<p>It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.</p>		
<p>Approval is granted for one year until the 30th July 2017.</p>		
<p>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)</p>		
<p><i>We acknowledge that the student Napo Kasirye will also be involved in this study.</i></p>		
<p>Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.</p>		
<p>Please quote the HREC REF in all your correspondence.</p>		
<p>Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.</p>		
<p>Yours sincerely</p>		
<p>signature removed to avoid exposure online</p>		
<p>PROFESSOR M BLOCKMAN CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938</p>		
<p>HREC 414/2016</p>		

10.2. Data collection sheet

	CONSULTANT #	PATIENT #	AORTIC ARCH BRANCHING PATTERNS TYPES								PULMONARY ARTERY VARIANT			COMMENTS	
			1	2	3	4	5	6	7	8	OTHER	yes	no		Description of PA variant
0	<i>Example: NK</i>	<i>1234</i>			X								X		<i>Optional</i>
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