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Thema:

The “Bovine Aortic Arch” in Stroke Patients: Prevalence, Embryological Development, and Hemodynamic Implications of a Common Aortic Arch Branching Variation

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Abbreviations

CT/CTA =	Computed Tomography / Computed Tomography Angiography
MRI/MRA =	Magnetic Resonance Imaging / Magnetic Resonance Angiography
DSA =	Digital Subtraction Angiography
BA =	Bovine Aortic Arch
BT =	Brachiocephalic Trunk
RCC =	Right Common Carotid Artery
LCC =	Left Common Carotid Artery
RSA =	Right Subclavian Artery
LSA =	Left Subclavian Artery
BCT =	Bicarotid Trunk
ARSA =	Aberrant Right Subclavian Artery
ESUS =	Embolic Stroke of Unknown Source
CI =	Confidence Interval
N/A =	Not Applicable or Not Available
y =	years
SD =	Standard Deviation

Figures

Figures 1 – 4 are illustrations created by the author, based on Rathke (1843)

Figures 7 – 11 are volume-rendered 3D reconstructions of CT scans created by the author using volume-rendering software

Tables

Introduction

Currently, biomarkers are isolated for a multitude of clinical situations. Traditionally, laboratory data like platelet counts or cytokine levels have been examined and transformed into predictive or prognostic biomarkers. However, with the evolution of medical imaging techniques, image parameters have emerged as possible biomarkers. One of the first steps in the development of an imaging biomarker is to investigate whether the chosen parameter qualifies as a marker for a specific outcome. An important part of the so-called qualification process is to demonstrate an association between a biomarker and a clinical endpoint in an ‘initial derivation cohort’. Thus, before large groups of patients are examined in a prospective setting, a connection should be established by retrospectively evaluating a small patient collective [1].

One example for a vascular structure that serves as an imaging biomarker is the aberrant right subclavian artery (ARSA), a variant branching pattern of the aortic arch in which the right subclavian artery originates from the aortic arch distal of the left subclavian artery (LSA). The ARSA has been recognized as a prenatal ultrasound marker for Down’s Syndrome and structural cardiac anomalies [2, 3].

Another proposed vascular biomarker, which has also been linked to congenital cardiovascular defects [4], is a branching variation of the supra-aortic vessels often referred to as the ‘bovine aortic arch’ (BA). The bovine aortic arch is characterized by a common origin of the brachiocephalic trunk and the left common carotid artery, and is reportedly the most common variant aortic arch branching variation found in human beings. It occurs quite frequently, with the reported percentages ranging widely from 6% to 31% [5–17]. In the past, the bovine arch has largely been regarded as a clinically insignificant incidental finding. It usually stays asymptomatic, and only becomes of interest when cardiothoracic surgery or endovascular procedures are planned. However, recent studies suggest an association of the bovine arch variant with the development of thoracic aortic disease, such as aortic arch dilation or aneurysm [18–21].

Due to the differing vascular anatomy, patients with bovine arches are also more likely to suffer from adverse neurological outcomes after carotid artery stenting [22–24] and thrombectomies [25] – two interventions that are frequently performed in stroke patients. The altered branching point and angling of the left common carotid artery may complicate the vascular access during endovascular interventions in these patients.

Furthermore, it is conceivable that an atypical branching pattern of the supra-aortic vessels such as the bovine arch might lead to a disturbance in hemodynamics, which in turn could influence embolus formation and their redirection towards the cranial vessels. As of yet, there is little information available on the hemodynamic properties of bovine arches and how often they occur in stroke patients. An association between the bovine arch and embolic strokes should be investigated.

Both CT and MR imaging are important and well-established methods in the acute diagnostics, treatment and etiological work up in stroke patients. Strokes are among the leading causes of death and disability in adults in industrialized states [26, 27]. In Europe and North America, the majority of strokes are ischemic in nature, and most can be attributed to either large vessel disease or cerebral embolism. In many cases, a source of embolism can be found and treated accordingly, for instance by administering anticoagulant medication to patients with atrial fibrillation.

However, there is a significant proportion of stroke patients whose stroke etiology remains cryptogenic after a complete diagnostic work-up - even in individuals who present with embolic lesion patterns in imaging. Due to these typical patterns pointing to an embolic etiology, those strokes are then classified as ‘Embolic Stroke of Unknown Source’, reflecting a most likely cardioembolic stroke origin which remains to be found. Common etiologies for cerebrovascular embolism include diseases that negatively influence hemodynamics and rheology, such as atrial fibrillation, congestive heart failure with a reduced ejection fraction, and mitral or aortic valve disease. Possibly the bovine arch could lead to altered hemodynamics, and may in turn influence embolus formation and/or their redirection towards the cranial vessels as well as hemispheric lateralization.

Whether the bovine arch has a clinical implication in the stroke setting remains largely unstudied so far. Thus, the aim of the presented study was to investigate an association of embolic brain infarctions, with the bovine aortic arch variant, and to evaluate whether it may be characterized as an imaging biomarker for stroke development.

2. Scientific Background

2.1 Branching Variations of the Aortic Arch

2.1.1 The Standard Aortic Arch Branching Pattern

In the majority of human beings, three large vessels arise from the aortic arch. Usually, the brachiocephalic trunk is the first branch of the aortic arch, followed by the left common carotid artery as the second and the left subclavian artery as the third branch. After giving off the left subclavian artery, the aortic arch continues into the descending aorta. The branches of the brachiocephalic trunk are the right common carotid artery, the right vertebral artery, and the right subclavian artery. The left vertebral artery usually originates from the left subclavian artery.
This aortic arch branching pattern is the one commonly shown in anatomy textbooks, and will hereafter be referred to as the 'Standard Aortic Arch'.

2.1.2 The 'Bovine' Aortic Arch

The so-called 'bovine' aortic arch is the second most common aortic arch branching pattern, and the most common branching variation. In this pattern, the aortic arch only gives off only two great vessels: the left common carotid artery and brachiocephalic trunk arise from a shared aortic origin. It is often reported to be found in around 20% of people [5, 8, 10, 12, 17], though it has been suggested that there is some variation depending on patient ethnicity [28]. The percentages found in previous studies vary greatly, from 6.0% in a Thai patient collective [13] up to 31.2% in a Jordanian cohort [14].

There are two subtypes of bovine aortic arches, herein referred to as 'Type A' and 'Type B'. With a prevalence of around 13% [5], the Type A bovine arch is the more common variety. It is characterized by a V-shaped common origin of the brachiocephalic trunk and the left common carotid artery. In Type B bovine arches, which are reportedly found in 8-9% of people [5, 6], the left carotid artery does not arise from the aortic arch, but as the first proper branch of the brachiocephalic trunk. Due to this morphological difference, the distance between the aortic origin of the brachiocephalic trunk and the separation point of the left carotid artery is generally longer in Type B arches than in the Type A counterpart. It may measure up to 2.5 cm [28].

A bovine arch is often considered a clinically insignificant incidental finding. Knowledge of a patient’s supra-aortic anatomy may however become relevant prior to cardiothoracic surgeries or endovascular interventions. It has been suggested that peri-interventional complications are more common in patients with alternative vascular patterns [22, 23, 29]. As mentioned in the introduction, the bovine aortic arch has also been linked to ascending aortic aneurysm in several studies. Histological examinations have revealed that the vascular tissues of patients with bovine arches and ascending aortic aneurysm had different histological properties than those of patients with ascending aortic aneurysm and standard anatomy [30].

It must be noted that even though the term “bovine arch” is widely used for this aortic arch branching variation, it has been considered a misnomer by some researchers, because this human anatomical variation does not resemble the actual aortic arch branching pattern found in cattle. The “true bovine arch” found in cows usually gives off a single large brachiocephalic trunk separating into the left and right subclavian arteries, with a bicarotid trunk arising in the middle [28]. Descriptive names, such as “common brachiocephalic trunk” [4] or “common origin of the innominate artery and left common carotid artery” (CILCA) [28], have been proposed.

2.1.3 Other Notable Branching Variations

In about 4% of people [5], the left vertebral artery originates directly from the aortic arch as a smaller fourth branch. This is generally referred to as an isolated left vertebral artery (iLVA). Most frequently it arises between the left carotid artery and the left subclavian artery; an iLVA originating distal of the left subclavian artery is much less common.

A rare but potentially clinically relevant variation is the aberrant right subclavian artery (ARSA). This pattern also shows four supra-aortic vessels: the right and left common carotid arteries arise from the aorta as the first and second branch, followed by the left subclavian artery and lastly, as the fourth and most distal branch, the aberrant right subclavian artery. Originating on the left side of the body, the ARSA passes towards the right side either behind the esophagus or between the esophagus and trachea [31], where it can lead to dysphagia or dyspnea. As mentioned in the introduction, it also serves as a prenatal biomarker for Down’s syndrome and cardiac defects.

There are many other, very rare branching patterns. More than twenty variant patterns have been described [5]. Occasionally, patients may show a combination of variations, such as a bovine arch with an isolated left vertebral artery, or an ARSA with a common origin of the carotid arteries (bicarotid trunk).

2.2 Embryological Development of the Aortic Arch

The aortic arch forms around the fourth to eighth weeks of gestation [32, 33]. The commonly accepted model describing the development of the aortic arch and supra-aortic vessels was first formulated by zoologist and embryologist Martin Rathke in 1843 [34].

The embryological development of the aortic arches of other mammals, such as horses [35], pigs [36], and mice [37] has been studied extensively in the beginning of the 20th century. Comparing specimen from various gestational ages allowed researchers to track the timeline of the development of these animals’ aortic systems. Due to the obvious ethical implications, studies examining human fetuses in the same manner are not easily conducted. Nevertheless, some information about the process of aortic arch development in humans has been gathered. In 2014, Rana et.al. [33] published a paper which gave some insight on the cardiovascular anatomy of human embryos during different stages of development. They created three-dimensional reconstructions of 19 human embryos collected from medically-induced abortions, showcasing the cardiovascular system during different stages of development.

The aortic arch and supra-aortic arteries develop from two ventral and two dorsal aortae, fetal vessels that are connected by six paired vessels which are referred to as “aortic arches”, gill arteries or pharyngeal arch arteries [31, 33, 38]. Initially, a common arterial trunk or “aortic sac” that arises from the heart can be observed, the cranial aspects of which are later drawn out into two separate ventral aortae as the embryo grows. At around six to seven weeks gestation, a membrane of pharyngeal mesenchyme has migrated into the common arterial outflow tract, forming a membrane that separates the lumen of the aortic sac [33]. The now separated large vessels arising from the heart later go on to form the ascending aorta and truncus pulmonalis.

The dorsal aortae arise from a large posterior arterial trunk, which later becomes the descending aorta.

2.2.1 Pharyngeal Arch Arteries

The ventral and dorsal aortae are connected by six successively forming and later partially regressing pairs of pharyngeal arch arteries, numbered I through VI. Even though illustrations typically show six paired pharyngeal arch arteries, there is no point in development where all six pairs can be observed at the same time. The first and second pair of vessels appear and almost completely regress early on. The fifth pair very briefly appears much later [35], after the third, fourth and sixth pharyngeal arch arteries have been formed, and then promptly regresses.

The third and fourth pharyngeal arch arteries go on to form part of the aortic arch and the craniocervical vessels. The sixth pair of arteries is not directly involved in the formation of the aortic arch; it is thought to develop into the truncus pulmonalis and ductus arteriosus Botalli on the left side, and to completely involute on the right side [39].

In the early stages of development, only pharyngeal arch arteries I and II originate from the ventral aortae (albeit briefly, as they regress soon after), while pharyngeal arch arteries III, IV and VI initially arise from the aortic sac (see Figure 1A). The fifth arch artery either involutes very rapidly or is never fully formed [33, 39].

As the embryo grows, its neck elongates, and with it the paired ventral aortae lengthen. Consecutively, the separation point of the ventral aortae from the common arterial trunk shifts downward, so that later on, pharyngeal arch arteries III and IV also arise from the newly elongated ventral aortae. The sixth pair of arteries still originates from the aortic sac (see Figure 1B).

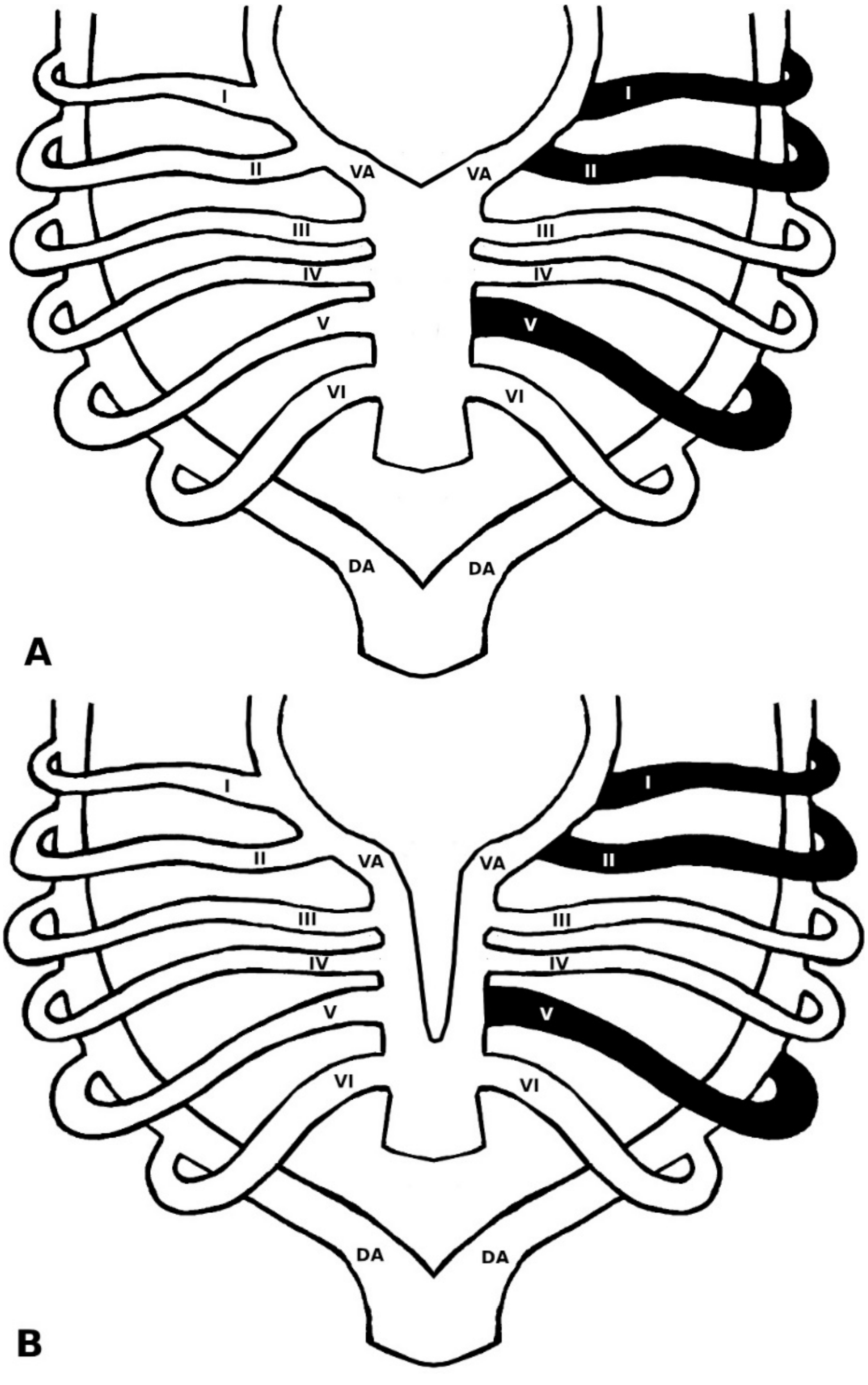

Figure 1: Hypothetical development of the aortic arch.

Two paired ventral aortae (VA) and dorsal aortae (DA) are each connected by six pharyngeal arch arteries (labeled I through VI). During development, pharyngeal arch arteries number one, two and five involute (visualized by black coloration on the right sight of the image).

- ***A)*** *Initially, the ventral and dorsal aortae are connected by pharyngeal arch arteries I and II, while arteries III through VI originate from a common arterial trunk.*
- ***B)*** *As the fetus grows, the ventral aortae are drawn out further and their separation point shifts downward, so that pharyngeal arch arteries I through V arise from the ventral aortae.*

2.2.2 Development of the Supra-aortic Vessels from the Fetal Vessels

The cranial and caudal portions of the dorsal aortae eventually separate as the so-called carotid duct [33], i.e. the portion of dorsal aorta connecting the third and fourth pharyngeal arch artery, disappears. The caudal portion of the left dorsal aorta forms the distal part of the aortic arch and the descending aorta (see Figures 2, 3). The caudal portion of the right dorsal aorta involutes completely below the third arch artery.

On both sides, the cranial segments of the dorsal aortae and the third pair of pharyngeal arch arteries develop into the internal carotid arteries. The ventral aortae develop into the common and external carotid arteries. The fourth pharyngeal arch artery on the right forms part of the right subclavian artery, while the aortic arch itself and the left subclavian artery are derived from the left fourth pharyngeal arch artery.

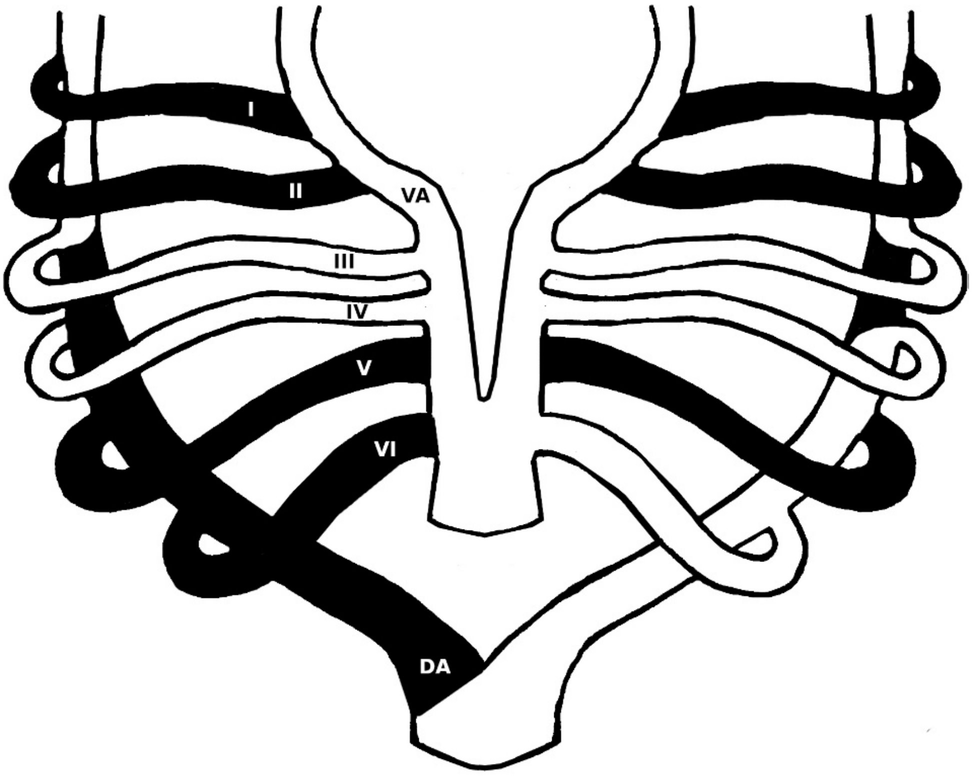

Figure 2: Partial regression of vascular structures.

Regressing vessels are shaded in black. Pharyngeal arch arteries one, two and five on both sides disappear during embryological development. The cranial and caudal portions of the left dorsal aorta separate between the third and fourth pharyngeal arch artery. The caudal portion of the right dorsal aorta regresses completely. The sixth arch artery on the right regresses, as well, while the one on the left forms the Ductus arteriosus botalli. I – VI = pharyngeal arch arteries one through six, VA = ventral aorta, DA = dorsal aorta.

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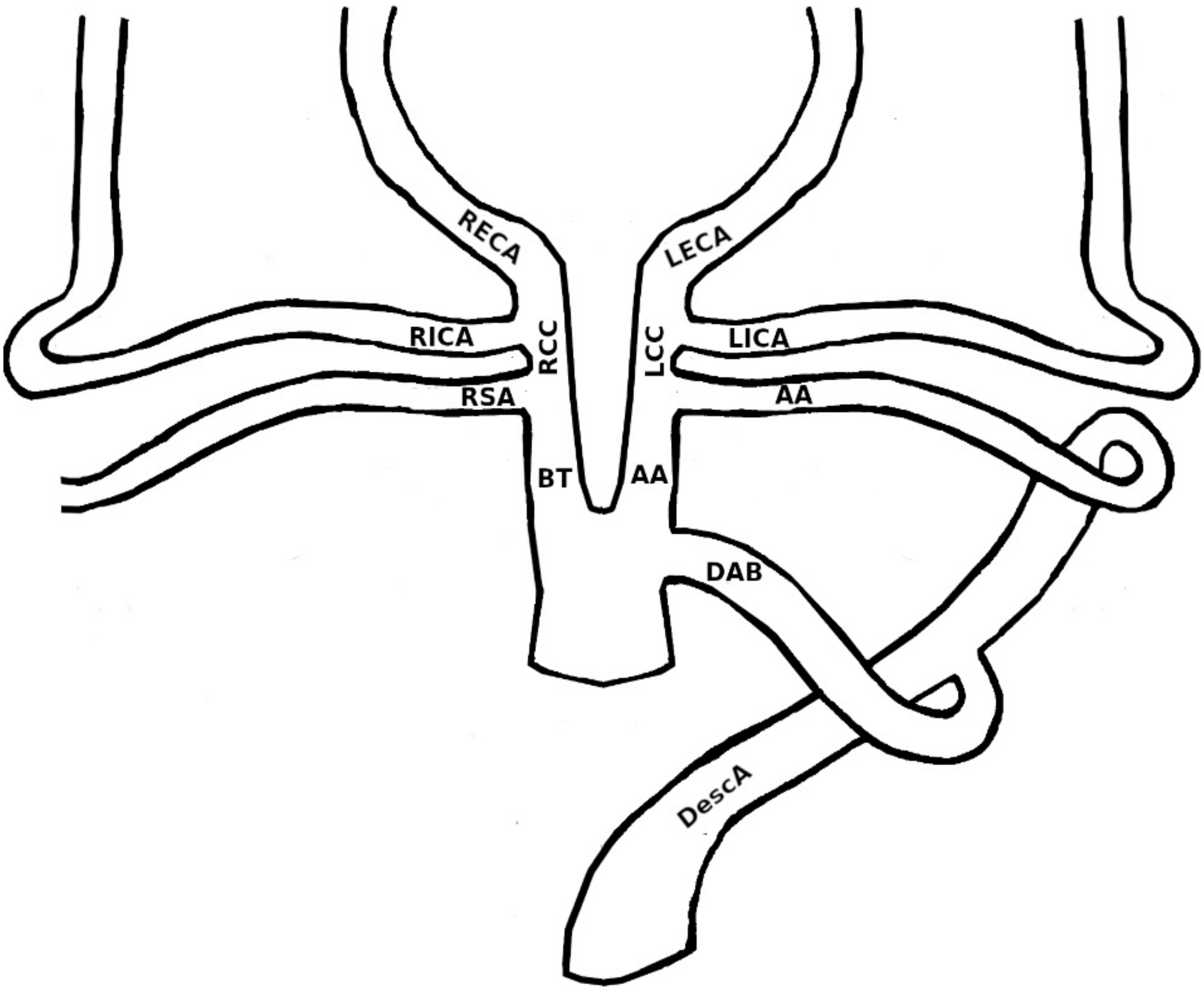

Figure 3: The remaining vessels go on to form the aortic arch and supra-aortic vessels.

BT = Brachiocephalic Trunk, RSA = Right Subclavian Artery, RCC = Right Common Carotid Artery, RICA = Right Internal Carotid Artery, RECA = Right External Carotid Artery, AA = Aortic Arch, LCC = Left Common Carotid Artery, LICA = Left Internal Carotid Artery, LECA = Left External Carotid Artery, DAB = Ductus arteriosus Botalli, DescA = Descending Aorta.

2.2.3 Explanations for the Development of Variant Anatomy

Thus far, it is not entirely clear why some people develop variant vascular anatomy, and at what exact developmental stage a bovine arch is formed.

Assuming the aortic arch develops in the described fashion, a possible explanation for the formation of a bovine arch could be an altered separation point of the ventral aortae from the truncus arteriosus. Normally, the truncus arteriosus separates into the two ventral aortae between the origins of the fourth and sixth pharyngeal arch arteries (see Figures 2, 3). However, in patients with a bovine arch, the separation possibly happens between the origins of the third and fourth arch arteries instead, creating an area that goes on to form a "common origin" of both ventral aortae (which go on to form the carotid arteries) and the right fourth pharyngeal arch artery (which develops into the right subclavian artery) (see grey area shaded in Figure 4).

Nelson et. al. attribute this to a comparatively slower growth of the ventral aortae [40]. Meyer et. al. [41] have described the mechanism as an "underdevelopment" of the aortic sac or the right ventral aorta, i.e. fetal vessels that go on to form the brachiocephalic trunk, and suggest a concurrent "overdevelopment" of the left fourth pharyngeal arch artery (which forms the distal part of the aortic arch). Their research showed that in children with bovine arches, the distance between the origins of the bovine arch and the LSA was significantly greater than the distance between the brachiocephalic trunk and LSA in children with standard anatomy. Because of this finding, they hypothesize that a bovine arch might result from a proximal movement of the LCC during development, furthering the distance between the origins of the LCC and the LSA.

Rana et. al. argue that the left common carotid artery usually arises from the aortic arch because the right lateral part of the aortic sac (i.e. the right ventral aorta) undergoes a more pronounced elongation than its left-sided counterpart [33], resulting in the formation of the brachiocephalic trunk. Conversely, this statement suggests that a bovine arch might result from either an underdevelopment of the right ventral aorta, as described by Meyer et.al., or a relative "overdevelopment" of the left ventral aorta.

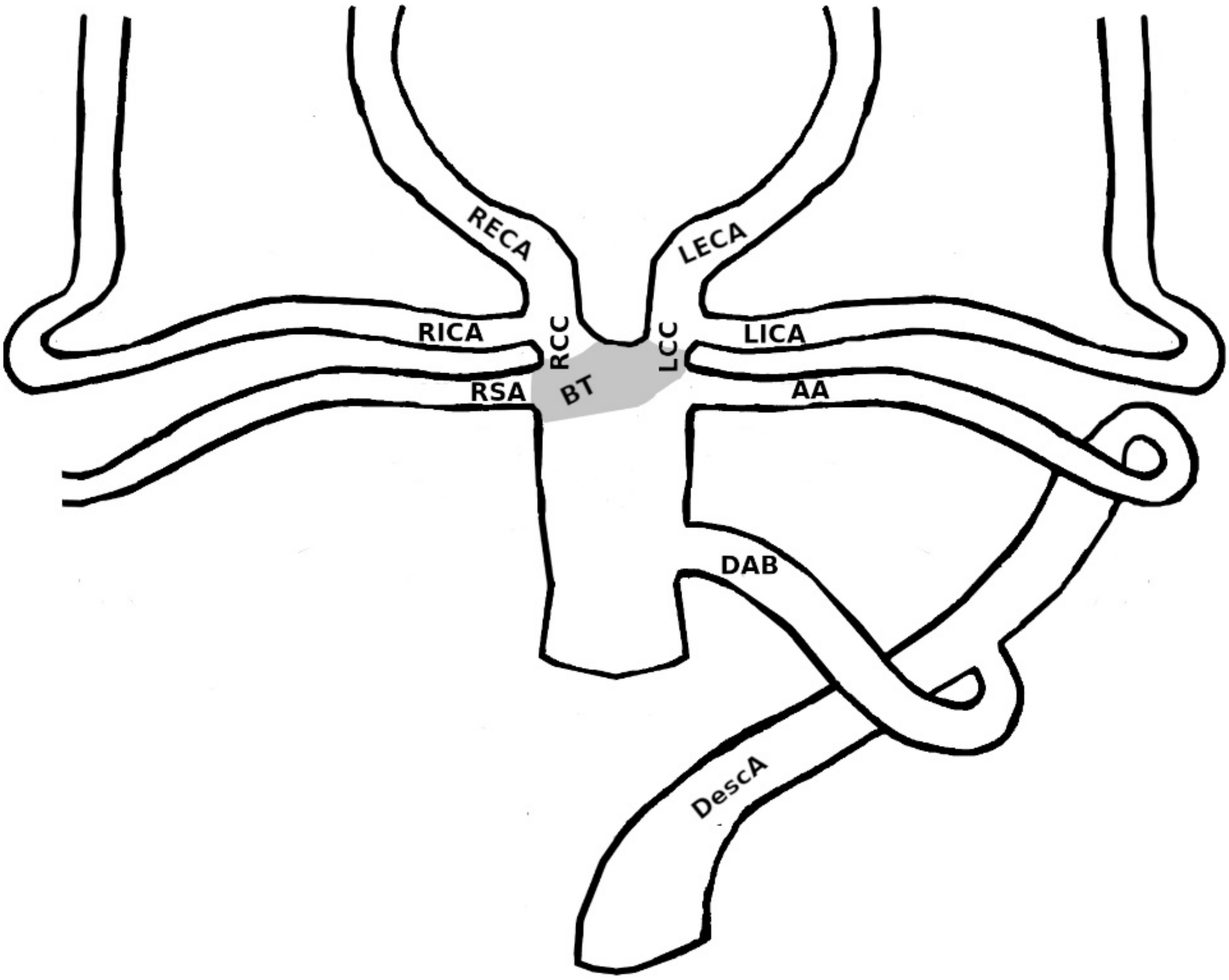

Figure 4: Proposed reason for the formation of a bovine arch.

Marked in grey is the area that could go on to form the common origin of the brachiocephalic trunk and left common carotid artery (the so-called "bovine arch"). Possibly, in patients with a bovine arch, the ventral aortae separate from the common arterial trunk between the origin of the third and fourth pharyngeal arch arteries rather than between the fourth and sixth pair.

BT = Brachiocephalic Trunk, RSA = Right Subclavian Artery, RCC = Right Common Carotid Artery, RICA = Right Internal Carotid Artery, RECA = Right External Carotid Artery, AA = Aortic Arch, LCC = Left Common Carotid Artery, LICA = Left Internal Carotid Artery, LECA = Left External Carotid Artery, DAB = Ductus arteriosus Botalli, DescA = Descending Aorta.

2.3 Stroke

In many developed countries, strokes are among the leading causes of death and disability in adults [26, 27]. The majority of strokes are ischemic in nature, leading to cerebral tissue necrosis through hypoxia induced by restricted blood flow. Hemorrhagic strokes, i.e. brain ischemia due to intracerebral or subarachnoid hemorrhage, are rather rare in Western European and Northern American populations, but more common among Asian ones [42].

There are two major causes of ischemic strokes [26]. The first is large vessel disease, in which atherosclerotic lesions in the carotids or large cerebral arteries either lead to a hemodynamically relevant stenosis of the vessel, or in the case of atherosclerotic plaque rupture, to the formation of a local arterial thrombus. In these strokes, the blood clot forms within the diseased vessel, at the site of the occlusion.

In contrast to that, in embolic strokes, a blood clot is formed in a more central part of the vascular system (most likely the heart or the aortic arch) and travels towards the cerebral arteries, where it becomes stuck and cuts off the blood flow to brain areas supplied by the occluded vessel.

Other causes of focal brain ischemia include microangiopathy (small vessel disease), and rare diseases such as cerebral vasculitis, Moyamoya disease or CADASIL.

2.3.1 Causes of Embolic Strokes

A stroke may be considered of cardioembolic or aortogenic origin if the cerebral ischemia is a result of embolic obstruction of one or more cerebral arteries by a blood clot or parts of a ruptured plaque, with the embolus arising from the heart or ascending aorta.

Aortogenic emboli generally originate from complex atheromas of the ascending aorta. Complex atheromas are defined by a plaque thickness of more than 4 millimeters, plaque ulceration, or visualization of mobile debris in echocardiography [43].

There are several mechanisms of cardiogenic embolism, the most important being arrhythmic disorders, especially atrial fibrillation [44]. Others include blood stasis in the heart due to congestive heart failure, the formation of thrombi due to wall motion abnormalities post myocardial infarction or due to valvular pathologies such as endocarditis, or paradoxical embolism in patients with a patent foramen ovale [45].
Cardioembolic strokes are often very clinically severe, with high NIHSS-Scores upon presentation, a high prevalence of lasting disability in 6-month follow-ups [46, 47], higher likelihood of recurrence and lower survival rates [48, 49].

2.3.2 Embolic Strokes of Undetermined Source

Different stroke types require different aftercare and medication. For example, patients with ischemic strokes are usually prescribed platelet inhibitors like acetylsalicylic acid and/or P2Y12-inhibitors for secondary stroke prevention, unless an accompanying disease indicating anticoagulation therapy, such as atrial fibrillation [50], is present.

To determine the specific aftercare regime best suited to the patient, it is important to investigate possible causes of an ischemic stroke. If no immediate stroke etiology is apparent, several tests need to be performed after a stroke to determine its source. Typical tests include 24-hour ECG monitoring, transesophageal echocardiography, and doppler/duplex ultrasound of the carotid arteries, as well as testing for hyperlipidemia, hypertonia, diabetes mellitus, and in some cases rare diseases like vasculitis or coagulopathies [51].

In some patients however, even an extensive post-stroke work-up may not lead to a conclusive stroke etiology. If no source of embolism can be found, but imaging characteristics point to an embolic etiology, these strokes may be classified as ESUS, embolic strokes of undetermined source. Imaging characteristics of embolic stroke include the presence of several small lesions in multiple territories, a large, isolated cortical and subcortical lesion, abrupt cutoffs in vessels that exhibit no other signs of atherosclerosis, or evidence of spontaneous recanalization in follow-up (CT) angiography [43, 52].

ESUS are often thought to be caused by subclinical atrial fibrillation or low-risk cardiac sources of embolism [53–55]. Histopathologically, the cerebral thrombi extracted from ESUS patients closely resemble thrombi of cardioembolic origin [56] . However, even after long-term rhythm monitoring, episodes of atrial fibrillation can only be proven in a minority of patients [57] . In many cases, the stroke etiology remains undetermined.

3. Material and Methods

3.1 Patient Collective

This study was reviewed and approved by the Greifswald University Hospital ethics committee. Informed consent was waived due to the retrospective study design, the long study period of almost ten years, and the high rates of death and lasting disability associated with embolic strokes. It was expected that a majority of the included patients would either not be able to give informed consent, or already be deceased.

Aortic arch branching patterns were retrospectively evaluated in 474 individuals. The study included 152 patients suffering from acute embolic strokes of the anterior circulation. All these patients had undergone diffusion weighted cerebral MRI, and had also received a contrast enhanced CT scan of the chest or neck from which oblique parasagittal planes could be reconstructed to evaluate aortic arch branching patterns.

Included in the study were stroke patients with cardiogenic or aortogenic embolic stroke etiology or ESUS admitted to Greifswald University hospital. All patients who were diagnosed with an acute stroke in our institution via MR imaging between August 2008 and February 2018 were reviewed. Since a bovine arch would be unlikely to influence embolus lateralization in the vertebrobasilar circulation, only patients suffering from strokes in the anterior circulation, i.e. brain areas supplied with blood by the internal carotid arteries, were included. Additional to diffusion weighted cerebral MRI, appropriate CT imaging of the aortic arch had to be available. Contrast enhanced CT scans were required to enable a reliable de novo reconstruction of the aortic arch.

Patients were sought out via a keyword search of all diffusion-weighted cerebral MRI reports created between August 2008 and February 2018, including the keywords ‘embolisch’ (embolic), ‘Ischämie’ (ischemia) and ‘Infarkt’ (infarction). This search yielded 1471 eligible stroke patients. After the initial MRI databank search, the availability of appropriate CT scans was confirmed manually in PACS (Picture Archiving and Communications system), while an embolic stroke etiology was confirmed using medical records provided by the Department of Neurology. Appropriate imaging of both the brain and the aortic arch was available in 152 eligible stroke patients. The majority of patients had received CT angiographies of the cervical and cranial vessels prior to thrombectomy. For individuals who had not been eligible for thrombectomy, and thus had not received such imaging, CT scans acquired for reasons unrelated to the stroke were used to evaluate the aortic arch.

In order to compare the prevalence of aortic arch branching variations among stroke patients to the general population, a control group was examined.
For this control group, we retrospectively examined 350 randomly selected patients who had received contrast enhanced CT scans of the chest (arterial contrast phase, slice thickness 1-2 mm) in the Institute for Diagnostic Radiology and Neuroradiology Greifswald within the same time period (2008 – 2018). The majority of scans were acquired due to suspected pulmonary embolism, in the setting of a CT pulmonary angiography or triple rule out. Other indications included cancer stagings and trauma scans. 28 of 350 studies were excluded due to the following reasons: poor contrasting of the thoracic aorta or imaging artifacts (n=18), extensive previous aortic arch stenting or surgery (n=3), acute dissection or aortic trauma (n=4), two patients were already included in the stroke group (n=2), and one was a minor (n=1). Thus, 322 of 350 patients could be included in the control group.

Age matching was not deemed necessary, since vascular variations are innate.
Ethnic differences in the frequency of the bovine arch pattern have been proposed [28]. The patient collective was ethnically homogenous. All patients were of Caucasian descent.

3.2 Classification of Stroke Etiologies

Information on etiologies was extracted from medical records using Lorenzo patient record systems (DXC Technology; Tyson's Corner, Va., USA). Stroke etiologies were classified by neurologists in charge of the stroke treatment, using the SSS-TOAST criteria for cardioembolic stroke [43].

Etiologies included atrial fibrillation (n=69), patent foramen ovale with atrial septum aneurysm (n=15), congestive heart failure with massively reduced ejection fraction resulting in the formation of cardiac thrombi (n=5), mitral/aortic valve endocarditis with mobile plaques (n=4), complex atheromatosis of the ascending aorta with atheroma

thickness > 4 mm (n=8), and peri-interventional embolism after percutaneous transluminal coronary angioplasty (n=2). Additionally, 49 patients with undetermined embolic stroke etiology (ESUS) were included.
Cervical vessel stenosis > 50% (NASCET) ipsilateral to the stroke lesion, autoimmune diseases, vasculitis and coagulopathies were reasons for exclusion.

3.3 Determining Strokes on Diffusion Weighted MRI

Patients were considered to suffer from a brain infarction if their cerebral MRI showed hyperintense lesions in diffusion weighted sequences corresponding to a drop in ADC (Apparent Diffusion Coefficient) values [52]. Patients presenting with lesions atypical for embolic strokes, such as lacunar or watershed lesions, were excluded.

3.4 MRI Acquisition and Evaluation

Brain MRI were acquired over a ten-year timespan, on two different Siemens MAGNETOM MRI scanners (SIEMENS Healthineers; Erlangen, Germany), a 1.5T-system and a 3T-system, using diffusion weighted sequences.
In the initial clinical process of stroke treatment, brain images were read by attending radiologists (1st reader) for the presence of lesions indicating acute stroke, as well as imaging signs pointing to possible stroke etiologies. For this study, the images were re-evaluated by a neuroradiologist (2nd reader) blinded to the original findings. In case of disagreements, the 2nd reader's report was considered 'gold standard'.

3.5 Aortic Arch Imaging Acquisition and Evaluation

Imaging of the aortic arch was obtained from contrast enhanced CT scans of the chest and neck (slab thickness 1 – 2 mm). Images were acquired on two different multi-slice CT scanners: a 16-slice system, and a 256-slice system (SOMATOM Sensation 16 / SOMATOM Definition Flash; SIEMENS Healthineers).

For aortic arch evaluation, left oblique parasagittal planes were reconstructed de novo using IMPAX Volume Viewing MIP/MPR with the following settings: 2 mm slab thickness, 1 mm slab distance, and Average Intensity Projection. This was necessary to enable a truly perpendicular view of the aortic arch, since it arises on the right and ventral side of the body and travels towards the left and dorsal side, continuing into the descending aorta below the fourth thoracic vertebra. A patient was considered to have a bovine arch if a common trunk could be identified in both the axial plane (see Figure 5) as well as the reconstructed oblique parasagittal plane (see Figure 6). If necessary, three-dimensional volume rendered reconstructions were generated to further visualize the supra-aortic vessels using IMPAX Volume Viewing 3D/Plus/Vessel Viewing.

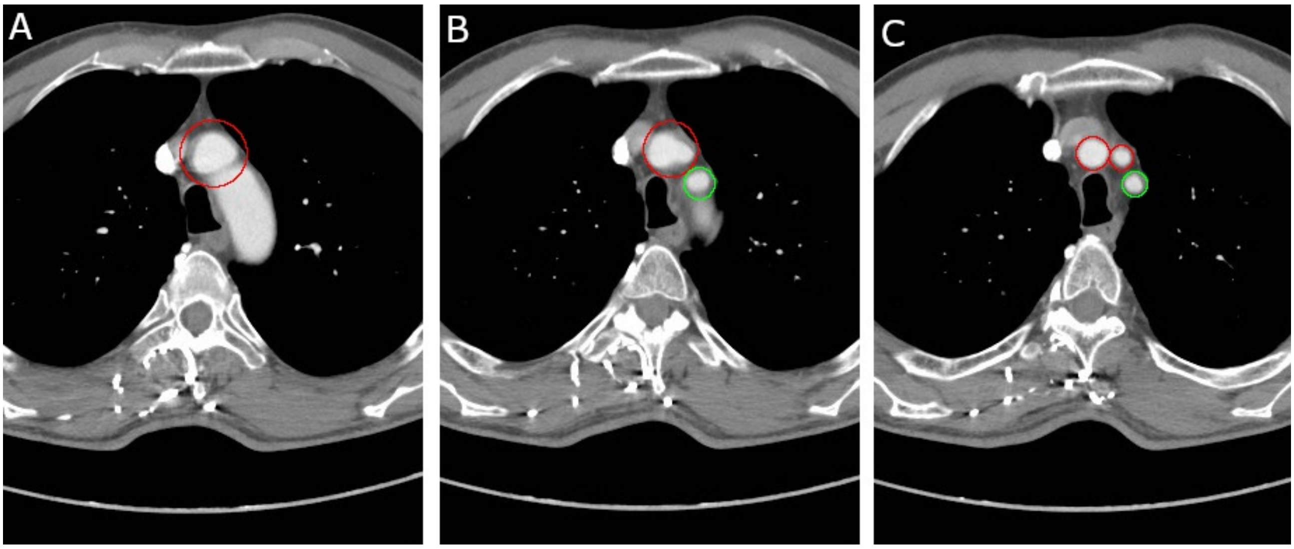

Figure 5: Identifying a Common Origin of Brachiocephalic Trunk and Left Common Carotid Artery.

Three consecutive axial slices spaced 5 millimeters apart, taken from a contrast-enhanced chest study, show two large vessels originating from the aortic arch.

A) The common trunk (circled in red) arises as the first supra-aortic vessel.

B) Two large vessels can be identified – the common trunk (circled in red) and the left subclavian artery (circled in green).

C) The common trunk has separated into the brachiocephalic trunk and the left common carotid artery (two red circles).

Figure 6: Bovine Arch Reconstruction. *CT-Angiography, 1mm slab thickness. Two-dimensional reconstruction of an oblique parasagittal plane, slab thickness set to 20mm, slab distance set to 2 mm for visualization purposes.*

A) Baseline drawn through the common aortic origin of the BT and LCC

B) A measurement from the upper separation point of the LCC to the baseline, parallel to the course of the common trunk, demonstrates the common arterial trunk.

3.6 Statistical Analyses

Statistical analyses were performed using Microsoft Excel (2010; Microsoft, Redmond, Wa., USA) and SPSS (Version 25; IBM, Chicago, Ill., USA. A biostatistician was consulted during the process of data analysis and interpretation.

Categorical variables are reported as number and percentage of patients, continuous variables as mean ± standard deviation. For categorical data (patient sex, aortic arch branching patterns), Pearson's χ^2-test with a Yates correction and Fisher's Exact test were used to evaluate statistical independence. Continuous variables (patient age) were tested for normal distribution using the Shapiro-Wilk test. Levene's test was used to test for homogeneity of variance. Even though patient ages were not normally distributed, a two-sided Student's t-test was used to further evaluate them, since the t-test has been shown to be very robust despite a non-normal distribution of data if the sample size is greater than 25, and more powerful than non-parametric tests which would otherwise be applied in this situation [58].

A significance level of $p < 0.05$ was considered significant.

4. Results

4.1 Patient Characteristics

The ratio of male to female patients was nearly equal in both groups, with 55.3% male patients in the stroke group (n=84), compared to 53.4% in the control group (n=172) (p=.781) (see Table 1).

With a mean age of 72±10.2 years (min: 40 years, max: 88 years, median: 74 years), stroke patients were on average around six years older (p<.001) than those in the control group, who had a mean age of 65.8±14.0 years (min: 29 years, max: 94 years, median: 67 years).

Characteristic	Stroke Group	Control Group	p
Male sex [n(%)]	84 (55.3)	172 (53.4)	.781
Mean age [years]	72±10,2	65.8±14.0	<.001**

***Table 1:* Comparison of Age and Sex between Control Group vs. Stroke Group**
*** indicates a statistically highly significant finding*

4.2 Observed Aortic Arch Variations

Four major aortic arch branching patterns were identified (for distribution among stroke group and control group, see Table 2). In some cases, more than one branching variation could be observed in the same patient. All patterns showing a common origin of the carotid arteries were expected to have a similar effect hemodynamics, and thus were classified in the bovine arch category for statistical analyses. This includes bovine arches coinciding with iLVA, and ARSA with bicarotid trunk (see 4.2.2).

Aortic Arch Branching Pattern	Stroke Group n (%)	Control Group n (%)	p-value	OR [95%CI]
Standard Pattern	105 (69.1)	251 (78.0)	.048*	.63 [0.41 - 0.97]
iLVA	6 (3.9)	15 (4.7)	.911	.84 [0.32 – 2.66]
ARSA	2 (1.3)	0 (0.0)	.102	-
Right Aortic Arch with ALSA	0 (0.0)	1 (0.3)	1	-
Bovine Arch total	39 (25.7)	55 (17.1)	.039*	1.67 [1.05 – 1.97]
‘Classic’ Bovine Arch	35 (23.0)	53 (16.5)	-	-
Bovine Arch + iLVA	2 (1.3)	2 (0.6)	-	-
Bicarotid Trunk + ARSA	2 (1.3)	0 (0.0)	-	-
Bovine Arch Type A	23 (15.1)	39 (12.1)	.444	1.29 [0.74 – 2.26]
Bovine Arch Type B	16 (10.5)	16 (5.0)	.039*	2.25 [1.09 – 4.63]

Table 2: ***Aortic Arch Branching Variations in Control vs. Stroke Group***

“total” indicates the sum of all patients showcasing a ‘bovine-type’ pattern with a common origin of the carotid arteries

** indicates a statistically significant finding*

4.2.1 Standard Aortic Arch

In 75.1% of all observed imaging studies (n=356), the standard aortic arch branching pattern with separate origins of the brachiocephalic trunk, left common carotid artery and left subclavian artery was seen. Standard anatomy was observed in 69.1% of stroke patients (n=105) and 78.0% of controls (n=251). Stroke patients were significantly less likely to show standard anatomy than controls (p=.048).

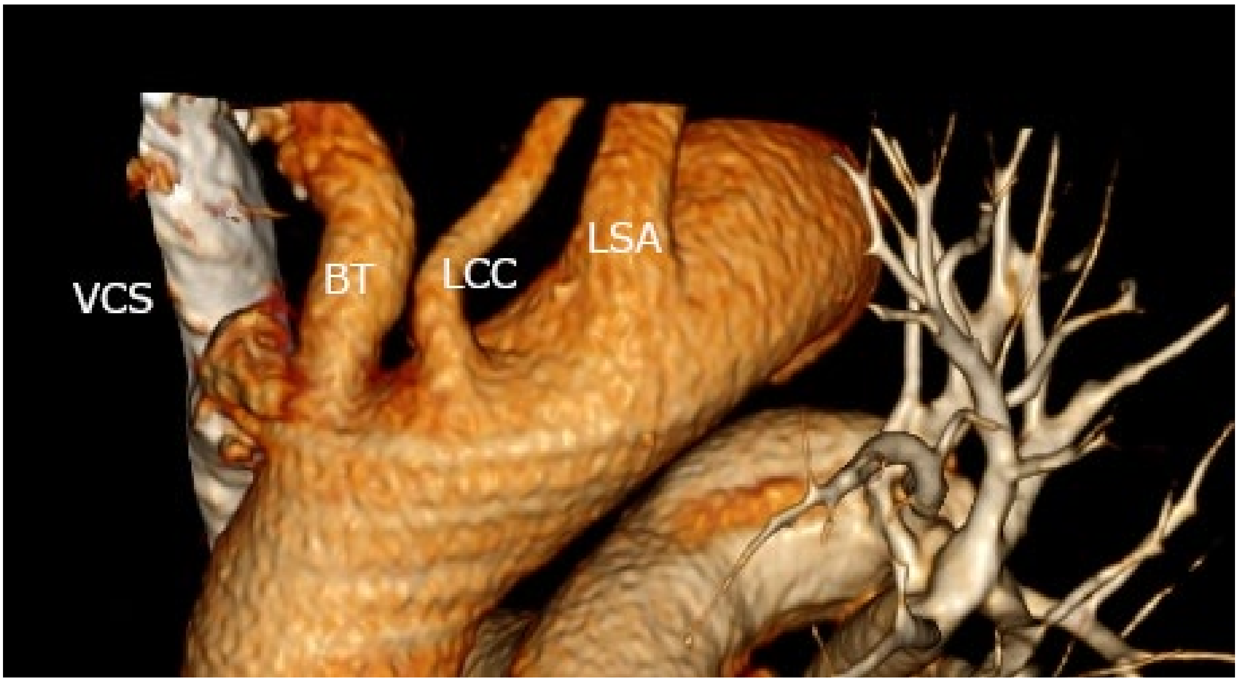

Figure 7: Standard Aortic Arch.

VCS = Superior Vena Cava. BT = Brachiocephalic Trunk. LCC = Left Common Carotid Artery. LSA = Left Subclavian Artery.

4.2.2 Bovine Aortic Arch

Overall, 88 of 474 patients (18.6%) showed the 'classic' bovine arch pattern, with only two large supra-aortic vessels arising from the aortic arch. Additional to these 88 cases, four patients simultaneously had an isolated left vertebral artery and a bovine arch, while two patients shared a common origin of both carotid arteries (bicarotid trunk) with an ARSA. They are listed as separate branching patterns in Table 2, but were included in the 'bovine arch' category for statistical analyses. Since these 'bovine-type' variations all share a common vascular origin of the carotid arteries, they are expected to have similar hemodynamic properties.

For the same reason, patients with iLVA or ARSA, but standard branching anatomy of the BT and LCC, were included in the 'Non-Bovine' category for statistical purposes. Including the aforementioned six patients with additional anomalies, 94 of 474 patients showed a bovine-type pattern (19.8%).

Bovine arches were found significantly more often in stroke patients, occurring in 25.7% of cases, compared to only 17.1% of controls (p=.039, OR=1.67). The higher frequency of bovine arches was mostly due to a surplus of bovine arches Type B within the stroke group. While Type A bovine arches occurred similarly often in both populations (15.1% vs. 12.1%, p=.444, OR=1.29), the percentage of bovine arches Type B was significantly larger among stroke patients (10.5% vs. 5.0%, p=.039, OR=2.25). No significant differences were observed concerning the prevalence of the isolated left vertebral artery and ARSA. For details, see Table 2 and Figure 6.

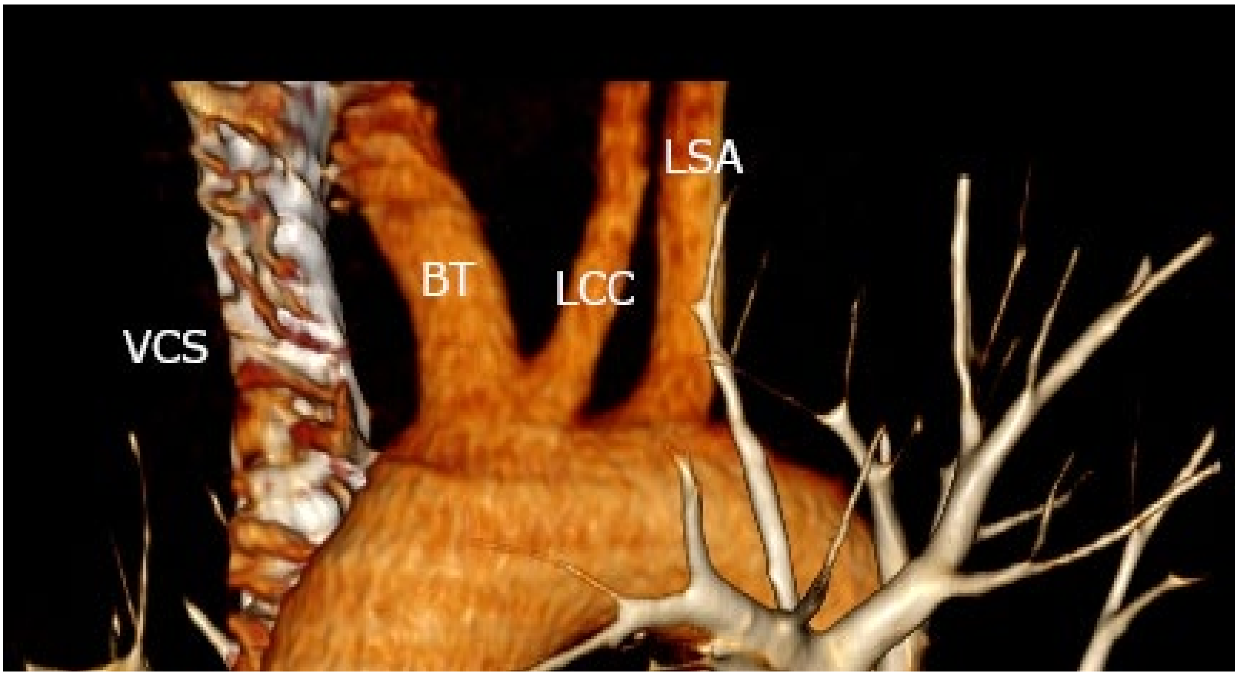

Figure 8: Bovine Aortic Arch Type A. A V-shaped common trunk separating into the brachiocephalic trunk and the left carotid artery can be observed.

VCS = Superior Vena Cava. CT = Common Trunk of BT and LCC. BT = Brachiocephalic Trunk. LCC = Left Common Carotid Artery. LSA = Left Subclavian Artery.

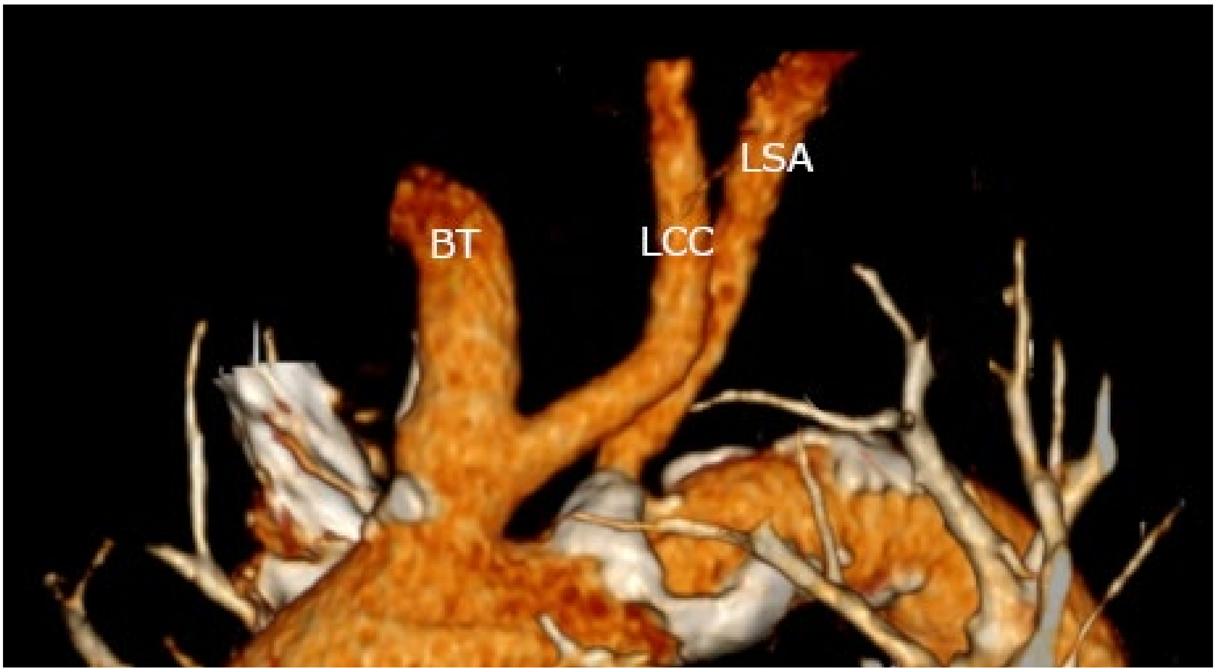

Figure 9: Bovine Arch Type B. The left carotid artery originates from the brachiocephalic artery as a proper branch.

BT = Brachiocephalic Trunk. LCC = Left Common Carotid Artery. LSA = Left Subclavian Artery.

4.2.3 Isolated Left Vertebral Artery

In 21 cases (4.4%), four branches of the aortic arch where seen. In these individuals, the left vertebral artery arose directly from the aortic arch rather than from the left subclavian artery, but the brachiocephalic trunk and left carotid artery had separate origins. This pattern occurred in 4.7% of controls and 3.9% of stroke patients (p=.911).

4.2.4 Bovine Arch with Isolated Left Vertebral Artery

Four patients (0.8%) showed an alternative three-branch pattern, with a common origin of brachiocephalic trunk and left carotid artery, the left vertebral artery originating directly from the aortic arch, and the left subclavian artery. It was seen in 0.6% of controls and 1.3% of stroke patients.

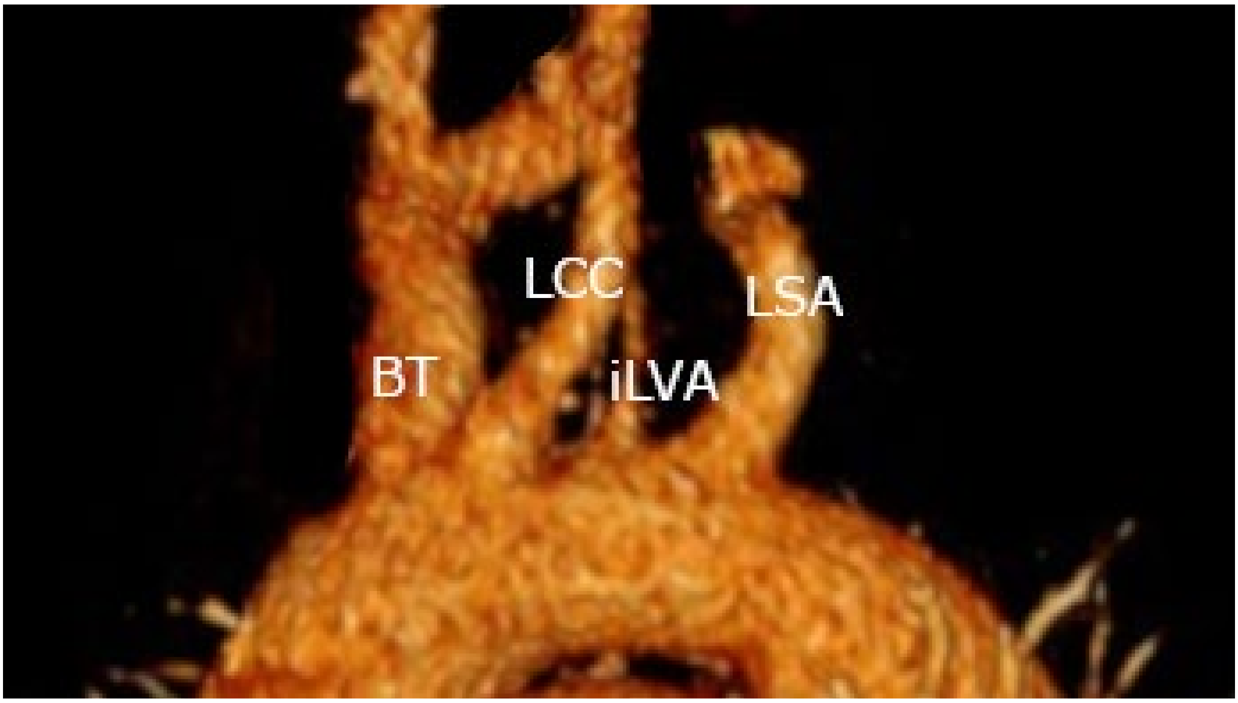

Figure 10: Bovine Aortic Arch with isolated Left Vertebral Artery.

BT = Brachiocephalic Trunk. LCC = Left Common Carotid Artery. iLVA = isolated Left Vertebral Artery. LSA = Left Subclavian Artery.

4.2.5 Aberrant Right Subclavian Artery

A right subclavian artery originating from the aortic arch as a fourth branch distal of the left subclavian artery was observed in 2 patients (both in the stroke group). In this pattern, the right common carotid artery is the first branch off the aortic arch, followed by a separately arising left common carotid, the left subclavian and lastly the right subclavian artery.

4.2.6 Bicarotid Trunk with Aberrant Right Subclavian Artery

In this rare branching variation, three great vessels arise from the aortic arch: the first of them is a bicarotid trunk, i.e. a common origin of both carotid arteries, followed by the left subclavian artery, and lastly the aberrant right subclavian artery. It was observed in 2 individuals (both in the stroke group).

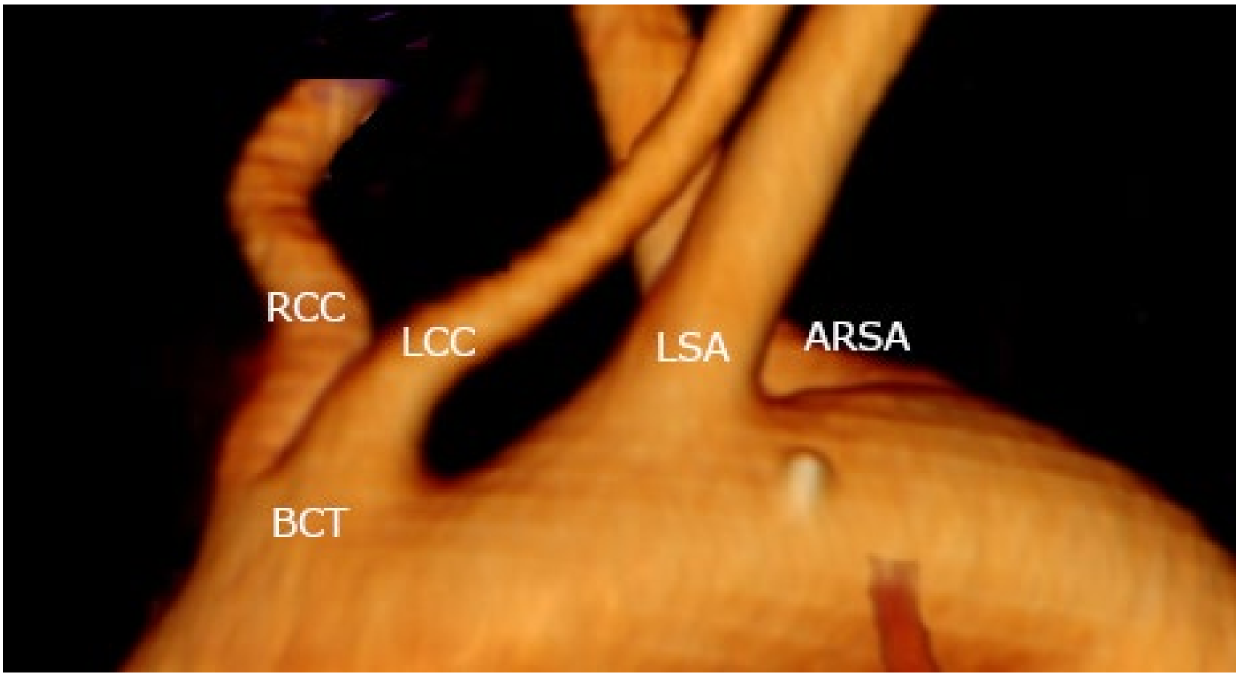

Figure 11: Bicarotid Trunk with Aberrant Right Subclavian Artery.

BCT = Bicarotid Trunk. RCC = Right Common Carotid Artery. LCC = Left Common Carotid Artery. LSA = Left Subclavian Artery. ARSA = Aberrant Right Subclavian Artery.

4.2.7 Right Aortic Arch with Aberrant Left Subclavian Artery

The right aortic arch is a rare developmental variation in which the aorta courses down the right side of the body, passing over the right main bronchus instead of the left. It develops when instead the right dorsal aorta persists during development, while the left one regresses. Analogue to the ARSA in regular aortic arches, patients with right aortic arches can show an aberrant left subclavian artery, which arises as the fourth branch of the aortic arch and courses to the left side of the body between the trachea and esophagus. This extremely rare variant pattern was seen in one patient in the control group.

4.3 Bovine Arch Frequency in Stroke vs. Control Patients

Bovine arches were found significantly more often in stroke patients, occurring in 25.7% of cases, compared to only 17.1% of controls (p=.039, OR=1.67). The higher frequency of bovine arches was mostly due to a surplus of bovine arches Type B within the stroke group.

While Type A bovine arches occurred similarly often in both populations (15.1% vs. 12.1%, p=.444, OR=1.29), the percentage of bovine arches Type B was significantly larger among stroke patients (10.5% vs. 5.0%, p=.039, OR=2.25). No significant differences were observed concerning the prevalence of the isolated left vertebral artery and ARSA. For further details, see Table 2 and Figure 12.

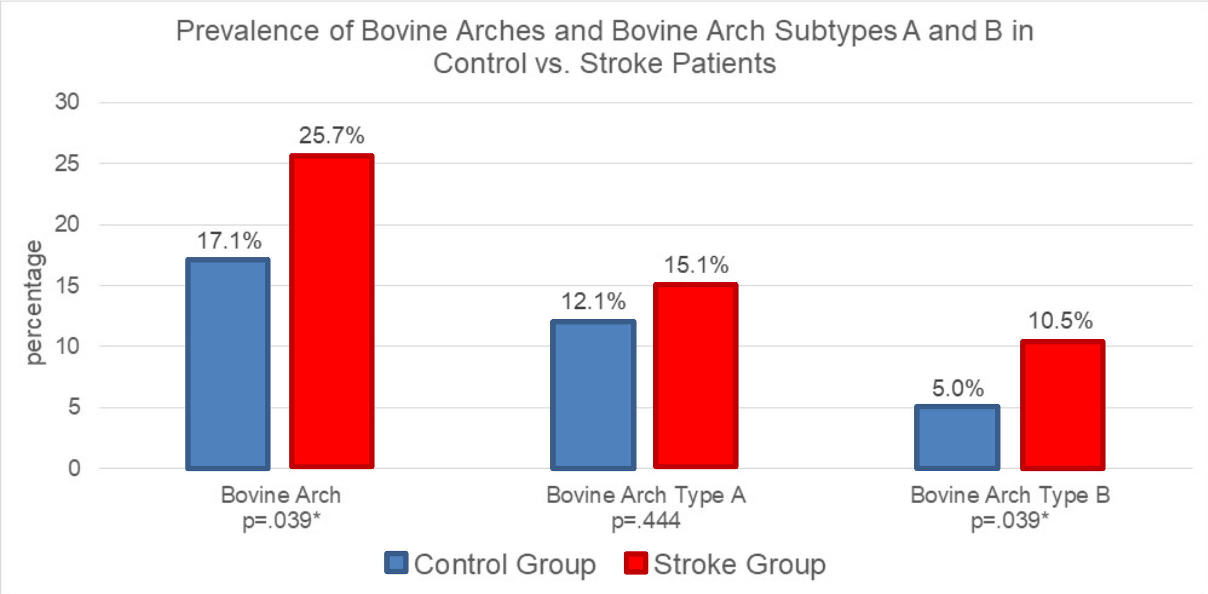

Figure 12: Relative frequencies of Bovine Aortic Arches in Control Group vs. Stroke Group.

4.4 Bovine Arch Frequency in Male vs. Female Patients

Bovine arches were evenly distributed among both sexes. In the control group, bovine arches were found in 15.3% of female patients and 18.6% of males (p=.396, OR=1.26). 27.9% of female stroke patients had bovine arch anatomy, compared to 23.8% of their male counterparts (p=.154, OR=.81).

Patient Group	**Bovine Arch n(%) Male**	**Bovine Arch n(%) Female**	**p**	**OR [95%CI]**
Control	32 (18.6)	23 (15.3)	.396	1.26 [0.70 – 2.27]
Stroke	20 (23.8)	19 (27.9)	.154	.81 [0.39 - 1.67]

Table 3: Bovine arch frequencies in male and female patients.

4.5 Age of Patients with Bovine vs. Non-Bovine Aortic Arch Anatomy

Stroke patients with a bovine arch were on average around two years younger than those with other aortic arch branching patterns (70,7±14,3 vs. 72,9±13,9 years, p=.426). The mean age of control patients with bovine arches was around 1.5 years older than that of their counterparts with non-bovine anatomy (67,2±11,3 vs. 65,6±9,7 years, p=.250). These differences were not statistically significant.

Patient Group	Bovine Arch (mean age in y ± SD)	Non-Bovine Arch (mean age in y ± SD)	P
Control	67,2 ± 11,3	65,6 ± 9,7	.250
Stroke	70,7 ± 14,3	72,9 ± 13,9	.426

Table 4: Mean ages of patients with bovine vs. non-bovine aortic arch anatomy in the stroke and control groups.

A logistic regression analysis and Hayes's moderation analysis was performed to determine whether age serves as a moderator variable in the relationship between bovine arches and embolic strokes. We found a significant association between bovine arch anatomy and embolic strokes (r=.516, p=.030, OR=1,675, 95%CI=1.05-2.67) However, patient age did not affect this association in any way (r = .005, p = .545, OR = 1.005, 95%-CI: .99 – 1.02). For this reason, no further age adjustment was deemed necessary.

4.6 Characteristics of Stroke Patients with ESUS vs. those with defined Stroke Etiology

ESUS patients were on average 4.5 years younger than those with a defined stroke etiology (69.3 ± 11.4 vs. 73.8 ± 9.2 years, p=.018). With frequencies of 32.7% vs. 22.3%, there was a trend towards more bovine arches in ESUS patients compared to those with strokes of aortogenic or cardiogenic origin. This difference did not prove to be statistically significant (p=.173). Bovine arches type B occurred in similar percentages in both groups (12.2% vs. 9.7%, p=.846)

Characteristic	**ESUS** n(%)	**Cardio-/Aortogenic Etiologies** n(%)	**p**
Mean age (y ± SD)	69.3 ± 11.4	73.8 ± 9.2	.018*
Bovine Arch	16 (32.7)	23 (22.3)	.173
Bovine Arch Type B	6 (12.2)	10 (9.7)	.846

Table 5: Comparison of mean age and bovine arch frequency in stroke patients with ESUS vs. those with cardio-/aortogenic stroke etiology.

** Indicates a statistically significant finding.*

5. Discussion

The bovine arch, though previously thought to be a clinically insignificant incidental finding, has been characterized as a possible biomarker for thoracic aortic disease by several authors [19–21, 59].

In these studies, authors suggest “fundamental alterations in the aortic wall from the time of embryogenesis” [19], a focal fragility of the aortic arch and an altered blood flow within it [20] as possible reasons for the association between bovine arches and thoracic aortic disease. Whether the bovine arch also has an influence on the formation and lateralization of cerebral emboli, however, remains largely unstudied so far.

CT and MRI scans of 474 patients, divided into stroke and control cohorts, were retrospectively evaluated for the presence of aortic arch branching variations. It was investigated whether the bovine aortic arch variation is found more often among stroke patients than in a randomly selected control group.

Results showed that bovine arches were significantly more common in stroke patients, in particular the Bovine Arch Subtype B, which is characterized by a left common carotid artery that arises for the brachiocephalic trunk instead of the aortic arch.

5.1 Frequency of Bovine Aortic Arches in the General Population

The bovine aortic arch variation was found in 17.1% of control cases (55 of 322 patients) and 25.7% of stroke patients (39 of 152 patients).

These percentages are in line with the findings of other researchers, who reported bovine arch frequencies ranging from 15% to 23.5% in European populations [8–12, 17, 60], and 15% and 27.4% in US-American ones [7, 18, 20, 21].

Concerning subtypes of bovine arches, Wacker, Lippert and Pabst [5] describe frequencies of 13% and 9% for Type A and Type B, respectively, resulting in a total of 22%. We found a similar proportion of 12.1% and 15.1% Type A bovine arches in the control and stroke groups, respectively. There was some discrepancy in the prevalence of Type B bovine arches, however. While only 5.0% of control patients showed this pattern, it could be observed in 10.5% of stroke patients.

While most research groups report percentages ranging from around 15 – 25%, some studies found bovine arches to be much less common. For example, Müller et.al. [6], who examined a large cohort of 2033 patients, reported bovine arches in only 8.0% of cases. However, this smaller proportion is explained by the group's definition of bovine arches. Unlike many other researchers, they only considered the Type B bovine arch to be a true aortic arch branching variation. Type A bovine arches were counted as standard arches in their study.

Similarly, Piyavisetpat et.al. [13] found the bovine arch variation in only 41 of 687 patients (6.0%). Their research, however, was conducted in Thailand, presumably featuring patients of mostly Southeast-Asian origin, and ethnic differences regarding the frequency of the bovine arch have been suggested [28]. Smaller studies based on cadaveric dissection also point to lower percentages of aortic arch branching variations in Southeast- and East-Asian populations. An Indian study featuring 66 cadaveric dissections revealed a percentage of 4.8% bovine arches [61]. Only one of 42 Nepali bodies (2.4%) examined by Kumar et. al. [62] showed the bovine pattern. After dissecting 193 Japanese-American men on Hawaii, Nelson et.al. reportedly [40] only found two cases of bovine arches (1.0%).

As mentioned before, studies conducted in European countries and North America show much higher bovine arch percentages, which are very similar to our findings (see Table 6). The discrepancies between the reported percentages support the hypothesis that there are ethnic differences, pointing to a lower frequency of branching variations in (South-)East-Asian cohorts compared to ones of European, Middle-Eastern or African descent.

Author	Number of Patients	Method	Country of Origin	Bovine Aortic Arch+
This Study (Control Group)	322	CT	Germany	17.1%
Piyavisetpat et al [13]	687	CT	Thailand	6.2%
Lale et. al. [16]	881	CT	Turkey	7.3%
Wanamaker et. al. [18]	179	CT	USA	15.1%
Reinshagen et. al. [60]	2033	DSA	Germany	15.2%
Natsis et. al. [9]	633	DSA	Greece	15.4%
Vucurevic et. al. [11]	1266	CT	Serbia	15.6%
Hornick et. al. [21]	844	CT, MRA	USA	16.4%
Malone et. al. [20]	391	CT	USA	20.5%
Ruken et. al. [10]	1136	CT	Turkey	22.1%
Jakanani et. al. [8]	861	CT	UK	22.9%
Ergun et. al. [12]	270	DSA	Turkey	23.7%
Rea et. al. [17]	1359	CT	Italy	23.7%
Berko et. al. [7]	1000	CT	USA	29.4%
Mustafa et. al. [14]	500	CT	Jordan	33.2%

Table 6: Frequency of the bovine arch as reported in comparable imaging studies

CT = contrast enhanced thoracic CT/CT angiography, MRA = magnetic resonance angiography, DSA = digital subtraction angiography.

+ the percentages are a sum of classic bovine arch patterns plus bovine arches combined with iLVA plus bicarotid trunks combined with ARSA.

5.2 Frequency of Bovine Arches in Stroke Patients

Unfortunately, not much information is available on bovine arch prevalence in stroke cohorts. Feiz et.al.[63] found 8.9% Type B arches in a group of stroke patients, which is similar to the 11.3% found in our own patient collective. This group worked with the same definition for bovine arch as Müller et. al. (see 5.1) did, only counting Type B bovine arches as branching variations. Since the bovine arch Type A was not considered to be an aortic arch branching variation in this study, no information on the frequency of bovine arches Type A in their patient collective is available.

5.3 Clinical Significance of the Bovine Arch

For a long time, the bovine arch was assumed to be a clinically insignificant incidental finding, which presumably goes unreported in many cases. However, in recent years it has become apparent that the shared origin of the carotid arteries found in bovine arches presents certain risks and possibilities. For instance, there have been case reports of bilateral carotid artery dissections originating from a single entry site in bovine arches [64, 65].

As mentioned before, several studies have linked the bovine arch to thoracic aortic disease, including aneurysms, dissection, aortic rupture and intramural hematoma. A meta-analysis which included 11,381 patients from eight separate studies further supports this hypothesis. In it, the authors found the Odds Ratio of developing thoracic aortic disease to be 1.4 times higher in patients with bovine arch anatomy. They also argue that due to this connection, radiologists should be encouraged to report bovine arches as a finding [59].

According to Moorehead et.al. [66] the bovine arch Type B in particular seems to be more common among patients with thoracic aortic disease. Due to the altered anatomy, patients with bovine arches will sometimes require specific fenestrated stent grafts to treat aortic arch aneurysms through endovascular intervention [67].

In a case report by Kaul et. al., the authors elaborate on how a common origin of both carotid arteries could be beneficial in the setting of thoracic vascular surgery. When performing surgery on the aortic root, ascending aorta and proximal arch of a bovine arch patient, both sides of the anterior circulation could be perfused antegradely via cannulation of the right axillary artery, without needing to rely on the patency of the circle of Willis [68].

On the other hand, the differing vascular anatomy of bovine arches can lead to longer duration and a higher rate of complications of endovascular interventions. This might be one of the reasons why bovine arch patients are more likely to suffer from adverse neurological outcomes after carotid artery stenting [22–24] and intracranial thrombectomies [25].

5.4 Hemodynamics in the Bovine Arch

The high proportion of bovine arches in the embolic stroke cohort suggests that the bovine arch may be a risk factor for embolus formation.
According to Pham et. al. [30], there are histological differences between the vascular tissue of ascending aortic aneurysms in patients with a bovine arch compared to those with standard anatomy. Aneurysmatic bovine arches showed higher intimal and adventitial thicknesses, and lower medial thicknesses compared to aneurysmatic arches with standard anatomy. Literature research did not reveal any studies on non-aneurysmatic bovine arch tissues.
In a prenatal ultrasound evaluation of 39 fetuses, Clerici et.al. [69] showed significant differences in hemodynamics of fetuses with bovine aortic arch anatomy.

Not much is known about flow patterns in adult bovine arches yet. In a small, preliminary examination using 4D Flow MRI, Shalhub et.al. [70] compared flow patterns in the aortic arches of three healthy patients: one with standard aortic arch anatomy, one with a bovine arch, and one with an aberrant right subclavian artery. Hemodynamic measurements revealed higher regional shear stress in the bovine aortic arch, and flow alterations which are typically associated with endothelial injury and vascular stiffness. An increased shear rate plays a role in thrombus formation [71], and has been shown to depend on the curvature of the aortic arch [72].

It is conceivable that the higher shear stress observed in the bovine arch might be caused by an altered branching angle of the supra-aortic vessels. This could be especially important for Type B arches, which were found significantly more often in stroke patients, while Type A arches were not.

Prospectively, if Shalhub et.al.'s observations can be reproduced and confirmed in a larger cohort, hemodynamic differences might also help to explain embolus formation in the case of ESUS patients, when no apparent sources of embolism can be found in the standard post-stroke workup. Another possibility, concerning patients with defined cardioembolic stroke etiologies, may be that the proposed altered hemodynamics influence embolus redirection towards the carotid arteries rather than more distal vessels, thus leading to more cerebral infarctions.

The investigation of these hypotheses, however, will require further evaluation of the hemodynamic properties of bovine aortic arches.

5.5 Conclusion

A correlation between embolic brain infarctions and the bovine aortic arch variation was retrospectively shown in a small group of patients. The presented study was conceived as a retrospective explorational trial, examining whether there is a correlation between branching anomalies of the supra-aortic vessels and embolic stroke frequency and laterality. The next step in the process of biomarker development would be to confirm this relationship in a larger study population, ideally in a prospective setting, using standardized imaging modalities for all patients.

With the use of 4D post-processing programs, phase contrast MR angiographies of the aortic arch could be utilized to evaluate flow patterns, velocities and wall shear stress [73] in bovine aortic arches. This could reveal whether there are truly hemodynamic differences, and how they might influence embolus formation and redirection.

6. References

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DIAGNOSTIC NEURORADIOLOGY

The so-called "bovine aortic arch": a possible biomarker for embolic strokes?

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Abstract

Purpose To examine the prevalence of the so-called bovine aortic arch variation (common origin of the brachiocephalic trunk and the left common carotid artery) in embolic stroke patients, compared with a control group.

Methods Aortic arch branching patterns were retrospectively evaluated in 474 individuals with ($n = 152$) and without ($n = 322$) acute embolic stroke of the anterior circulation. Contrast-enhanced CT scans of the chest and neck (arterial contrast phase, 1–2-mm slice thickness) were used to evaluate aortic arch anatomy. The stroke cohort included 152 patients who were treated for embolic strokes of the anterior circulation between 2008 and 2018. A total of 322 randomly selected patients who had received thoracic CT angiographies within the same time frame were included as a control group.

Results With a prevalence of 25.7%, the bovine aortic arch variant was significantly more common among patients suffering from embolic strokes, compared with 17.1% of control patients ($p = 0.039$, OR = 1.67, 95%CI = 1.05–1.97). Stroke patients were more likely to show the bovine arch subtype B (left common carotid artery originating from the brachiocephalic trunk instead of the aortic arch) (10.5% vs. 5.0%, $p = 0.039$, OR = 2.25, 95%CI = 1.09–4.63), while subtype A (V-shaped common aortic origin of the brachiocephalic trunk and the left carotid) was similarly common in both groups. There was no significant difference regarding the frequency of other commonly observed variant branching patterns of the aortic arch.

Conclusion The bovine aortic arch, particularly the bovine arch subtype B, was significantly more common among embolic stroke patients. This might be due to altered hemodynamic properties within the bovine arch.

Keywords Bovine arch · Vascular anatomy · Aortic arch branching variation · Embolic stroke · CT angiography

Introduction

Currently, biomarkers are isolated for a multitude of clinical situations. With the evolution of imaging techniques, image parameters have emerged as possible biomarkers. One of the first steps in the development of an imaging biomarker is to demonstrate an association between the chosen parameter and a clinical endpoint in an "initial derivation cohort." Before large groups of patients are examined in a prospective setting, a connection should be established by retrospectively evaluating a small patient collective [1].

An example for an imaging biomarker is the aberrant right subclavian artery (ARSA), a variant branching pattern of the aortic arch in which the right subclavian artery originates from the aortic arch distal of the left subclavian artery. The ARSA has been recognized as a prenatal ultrasound marker for Down syndrome and structural cardiac anomalies [2, 3]. Another proposed vascular imaging biomarker, which has also been linked to congenital cardiovascular defects [4], is a branching variation of the supra-aortic vessels referred to as the "bovine aortic arch" (BA). The bovine aortic arch is characterized by a common origin of the brachiocephalic trunk and the left common carotid artery and is reportedly the most common variant aortic arch branching pattern found in human beings. It occurs quite frequently, with percentages found in previous studies ranging from 6 to 31% [5–17]. This variant usually stays

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asymptomatic and only becomes of interest when cardiothoracic surgery or endovascular procedures are planned. However, recent studies associate the bovine arch with the development of thoracic aortic disease, such as aortic arch dilation or aneurysm [18–21]. Due to the differing vascular anatomy, patients with bovine arches are also more likely to suffer from adverse neurological outcomes after carotid artery stenting [22–24] and thrombectomies [25]—two interventions that are frequently performed on stroke patients.

Furthermore, it is conceivable that an atypical branching pattern of the supra-aortic vessels such as the bovine arch might lead to a disturbance in hemodynamics, which may influence embolus formation and their redirection towards the cranial vessels.

Whether the bovine arch has a clinical implication in the stroke setting remains largely unstudied so far. Thus, the aim of this study was to investigate an association between embolic brain infarctions and the bovine aortic arch variant, to find out if in the future it may serve as a possible biomarker for stroke development.

Methods and material

Patient collective

This study was reviewed and approved by the local ethics committee. Informed consent was waived due to the retrospective study design.

Aortic arch branching patterns were retrospectively evaluated in 474 individuals with ($n = 152$) and without ($n = 322$) acute embolic strokes.

The study included 152 patients who were treated for acute embolic strokes of the anterior circulation in our Department of Neurology between August 2008 and February 2018.

Stroke patients with embolic stroke etiology (ICD-10 I63.4) admitted to our university hospital were selected via a local databank search. Since a bovine arch would be unlikely to have an influence on the hemodynamics in the vertebrobasilar circulation, only strokes of the anterior circulation were included.

The initial databank search yielded 1471 eligible stroke patients. The next step was to manually confirm the availability of contrast-enhanced CT scans of the chest or neck (arterial contrast phase, slice thickness 1–2 mm), from which oblique parasagittal planes could be reconstructed to evaluate the aortic arch branching pattern. Appropriate CT images were available for 152 of 1471 patients. Most of these patients had received CT angiographies of the neck and head prior to thrombectomy. For individuals who had not been eligible for thrombectomy, and thus had not received such imaging, CT scans acquired for reasons unrelated to the stroke were used to evaluate the aortic arch.

For the control group, 350 randomly selected CT scans of the chest (arterial contrast phase, slice thick- ness 1–2 mm) from the same time period (2008–2018) were chosen for evaluation of the aortic arch branching pattern. The patients underwent imaging for various indications. The majority of scans were acquired due to suspected pulmonary embolism, in the setting of a CT pulmonary angiography or triple rule out. Other indications included cancer staging and trauma scans.

Twenty-eight studies were excluded due to the following reasons: poor contrasting of the thoracic aorta or imaging artifacts ($n = 18$), extensive previous aortic arch stenting or surgery ($n = 3$), acute dissection or aor- tic trauma ($n = 4$), two patients who were already in- cluded in the stroke group ($n = 2$), and one who was a minor ($n = 1$). Thus, 322 of the initially chosen 350 patients could be included in the control group.

Stroke imaging and etiology

Information on etiologies was extracted from medical records using Lorenzo patient record systems (DXC Technology; Tyson's Corner, VA, USA). Stroke etiolo- gies were classified by the neurologists in charge of the clinical stroke treatment using SSS-TOAST criteria for cardioembolic stroke [26].

Etiologies included atrial fibrillation ($n = 69$), patent foramen ovale with atrial septum aneurysm ($n = 15$), congestive heart failure with massively reduced ejection fraction resulting in the formation of cardiac thrombi ($n = 5$), mitral/aortic valve endocarditis with mobile plaques ($n = 4$), complex atheromatosis of the ascending aorta with atheroma thickness > 4 mm ($n = 8$), and peri-interventional embolism after percutaneous transluminal coronary angioplasty ($n = 2$).

Additionally, 49 patients suffering from embolic strokes of undetermined source (ESUS) were included. ESUS are often thought to be caused by subclinical atrial fibrillation or low-risk cardiac sources of embo- lism [27–29]. Histopathologically, the cerebral thrombi extracted from ESUS patients closely resemble thrombi of cardioembolic origin [30]. However, even after long- term rhythm monitoring, episodes of atrial fibrillation can only be proven in a minority of patients [31]. In many cases, the stroke etiology remains undetermined even after extensive diagnostic workup.

Individuals with cervical vessel stenosis > 50% (NASCET) ipsilateral to the stroke lesion, autoimmune diseases, vasculitis, and coagulopathies were excluded.

Patients were considered to suffer from an acute stroke if their cerebral MRI showed hyperintense lesions in diffusion-weighted sequences corresponding to a drop in apparent diffusion coefficient values [32]. Patients presenting with lesions atypical for embolic strokes, such as lacunar or watershed lesions, were excluded.

Aortic arch imaging acquisition and evaluation

Imaging of the aortic arch was obtained from contrast-enhanced CT scans of the chest and neck (slab thick- ness 1–2 mm). Images were acquired on two CT scan- ners: either a 16-slice system, or a 2 × 64-slice dual energy system (SOMATOM Sensation 16/SOMATOM Definition Flash; SIEMENS Healthineers, Erlangen, Germany).

For aortic arch evaluation, left oblique parasagittal planes were reconstructed de novo using IMPAX Volume Viewing MIP/MPR with the following settings: 2-mm slab thickness, 1-mm slab distance, and average intensity projection. This was necessary to enable a tru- ly perpendicular view of the aortic arch. A patient was considered to have a bovine arch if a common trunk could be identified in both the axial plane as well as the reconstructed oblique parasagittal plane. The scans were read by two attending radiologists (M.K., N.H.).

Statistical analysis

Statistical analyses were performed using Microsoft Excel (2019; Microsoft, Redmond, WA, USA) and SPSS (version 25; IBM, Chicago, IL, USA). A biostatistician was consulted. Categorical variables are reported as number and percentage of patients, and continuous variables as mean ± standard deviation.

For categorical data (patient sex, aortic arch branching patterns), Pearson's χ^2 test with a Yates cor- rection and Fisher's exact test were used to evaluate statistical independence. Continuous variables (patient age) were tested for normal distribution using the Shapiro-Wilk test. Levene's test was used to test for homogeneity of variance. Even though patient ages were not normally distributed, a two-sided Student's *t* test was used to further evaluate them, since the *t* test has been shown to be very robust despite a non-normal distribution of data if the sample size is greater than 25 and more powerful than non-parametric tests which would otherwise be applied in this situation [33]. A logistic regression analysis and Hayes's moderation analysis [34] were performed to evaluate whether pa- tient age serves as a moderator variable in the relation- ship between bovine arches and the occurrence of strokes. PROCESS Procedure for SPSS (version 3.3) was used for Hayes's moderation analysis.

A significance level of $p < 0.05$ was considered significant.

Results

Overall patient characteristics

The ratio of male to female patients was nearly equal in both groups, with 55.3% male patients in the stroke group (n = 84), compared with 53.4% in the control group (n = 172) (p = 0.781) (see Table 1). With a mean age of 72 ± 10.2 years (min 40 years, max 88 years, median 74 years), stroke patients were on average around 6 years older ($p <$ 0.001) than those included in the control group, who had a mean age of 65.8 ± 14.0 years (min 29 years, max 94 years, median 67 years).

Aortic arch branching patterns in the stroke group

In the stroke group, the standard aortic arch branching pattern was seen in 69.1% of cases (n = 105) (see Fig. 1, Table 2). A total of 1.3% showed an ARSA with separate origins of the carotid arteries (n = 2), and 3.9% showed an isolated left vertebral artery (iLVA), a varia- tion in which the left vertebral artery arises directly from the aortic arch rather than from the left subclavian artery (n = 6).

A total of 23.0% of stroke patients had a classic bovine aortic arch pattern (see Figs. 2 and 3) (n = 35). A bovine arch combined with an isolated left vertebral artery (see Fig. 4) was seen in 1.3% of patients (n = 2), as was a bicarotid trunk with an aberrant right subclavian artery (n = 2) (see Fig. 5). Thus, 39 patients showed a pattern featuring a common origin of the carotid arteries, resulting in an overall prevalence of 25.7% of "bovine-type" aortic arches.

Of these, 23 were type A bovine arches, while 16 were type B bovine arches, frequencies of 15.1% and 10.5%, respectively.

Aortic arch branching patterns in the control group

In the control group, there were 78.0% standard arches (n = 251). A total of 4.7% of patients showed an iLVA (n = 15).

Table 1 Age and sex characteristics of the stroke and control groups

Characteristic	Stroke group	Control group	p
Male sex (*n* (percentage))	84 (55.3)	172 (53.4)	0.781
Mean age (years)	72 ± 10.2	65.8 ± 14.0	<0.001**

Male to female ratios were very similar in both groups. Control patients were, on average, around 6 years younger than those in the stroke group

**Marks a statistically highly significant finding

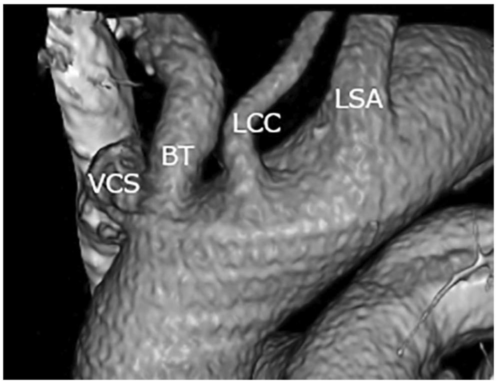


Fig. 1 Standard aortic arch branching pattern. The BT and LCC originate from the aortic arch as two separate branches. VCS = superior vena cava, BT = brachiocephalic trunk, LCC = left common carotid artery, LSA = left subclavian artery

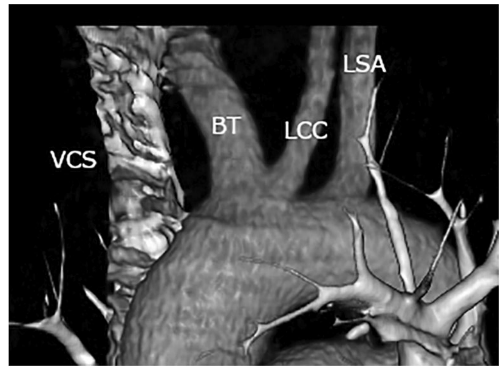


Fig. 2 Bovine aortic arch type A. The BT and LCC share a V-shaped common aortic origin. VCS = superior vena cava, BT = brachiocephalic trunk, LCC = left common carotid artery, LSA = left subclavian artery

The ARSA variant was not observed in the control group. One case of a right aortic arch with an aberrant left subclavian artery (ALSA) was identified.

A total of 16.5% of control patients showed a classic bovine arch ($n = 53$), while 0.6% showed a bovine arch with an iLVA ($n = 2$), resulting in an overall prevalence of 17.1% bovine-type arches. Of these, 12.1% were type A bovine arches ($n = 39$), and 5.0% type B bovine arches ($n = 16$).

Bovine arch frequency in stroke vs. control patients

Bovine arches were found significantly more often in stroke patients, occurring in 25.7% of cases, compared with only 17.1% of controls ($p = 0.039$, OR = 1.67). The higher frequency of bovine arches was mostly due to a surplus of type B bovine arches within the stroke group. While type A bovine arches occurred similarly often in both populations (15.1% vs. 12.1%, $p = 0.444$, OR = 1.29), the percentage of type B bovine arches was significantly larger among stroke patients (10.5% vs. 5.0%, $p = 0.039$, OR = 2.25). No significant differences were observed concerning the prevalence of the isolated left vertebral artery and ARSA. For details, see Table 2 and Fig. 6.

Bovine arch frequency in male vs. female patients

Bovine arches were evenly distributed among both sexes. In the control group, bovine arches were found in 15.3% of female patients and 18.6% of males ($p = 0.396$, OR = 1.26). A total of 27.9% of female stroke patients had bovine arch anatomy, compared with 23.8% of their male counterparts ($p = 0.154$, OR = 0.81).

Age of patients with bovine vs. non-bovine aortic arch anatomy

Stroke patients with a bovine arch were on average around 2 years younger than those with other aortic arch branching

Table 2 Prevalence of aortic arch branching patterns in the stroke and control group

Aortic arch branching pattern	Stroke group n (percentage)	Control group n (percentage)	p	OR (95%CI)
Standard pattern	105 (69.1)	251 (78.0)	0.048*	0.63 (0.41–0.97)
iLVA	6 (3.9)	15 (4.7)	0.911	0.84 (0.32–2.66)
ARSA	2 (1.3)	0 (0.0)	0.102	–
Right aortic arch with ALSA	0 (0.0)	1 (0.3)	1	–
Bovine arch total	39 (25.7)	55 (17.1)	0.039*	1.67 (1.05–1.97)
"Classic" bovine arch	35 (23.0)	53 (16.5)	–	–
Bovine arch + iLVA	2 (1.3)	2 (0.6)	–	–
Bicarotid trunk + ARSA	2 (1.3)	0 (0.0)	–	–
Bovine arch type A	23 (15.1)	39 (12.1)	0.444	1.29 (0.74–2.26)
Bovine arch type B	16 (10.5)	16 (5.0)	0.039*	2.25 (1.09–4.63)

Stroke patients were significantly more likely to have a bovine aortic arch than control patients. There was a surplus of type B bovine arches within the stroke group, while type A arches occurred similarly often in both groups. There were no significant differences concerning other common aortic arch branching variations

*Marks a statistically significant finding

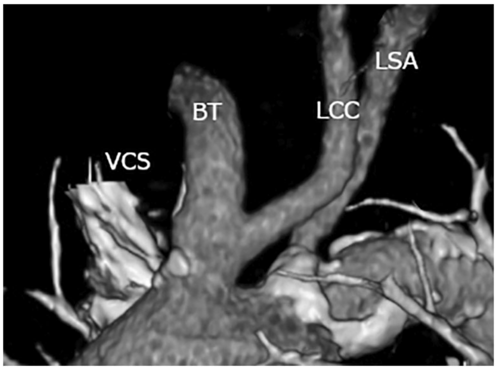


Fig. 3 Bovine aortic arch type B. The LCC arises from the BT as its first proper branch. BT = brachiocephalic trunk, LCC = left common carotid artery, LSA = left subclavian artery

patterns (70.7 ± 14.3 vs. 72.9 ± 13.9 years, p = 0.426). The mean age of control patients with bovine arches was around 1.5 years older than that of their counterparts with non-bovine anatomy (67.2 ± 11.3 vs. 65.6 ± 9.7 years, p =0.250). These differences were not statistically significant.

A logistic regression analysis and Hayes's moderation analysis were performed to determine whether age serves as a moderator variable in the relationship between bovine arches and embolic strokes. We found a significant association between bovine arch anatomy and embolic strokes (r = 0.516, p = 0.030, OR = 1.675, 95%CI = 1.05–2.67). However, patient age did not affect this association in any way (r = 0.005, p = 0.545, OR = 1.005, 95%CI = 0.99–1.02). For this reason, no further age adjustment was deemed necessary.

Characteristics of stroke patients with ESUS vs. those with defined stroke etiology

ESUS patients were on average 4.5 years younger than those with a defined stroke etiology (69.3 ± 11.4 vs. 73.8 ± 9.2 years, p = 0.018). With frequencies of 32.7%

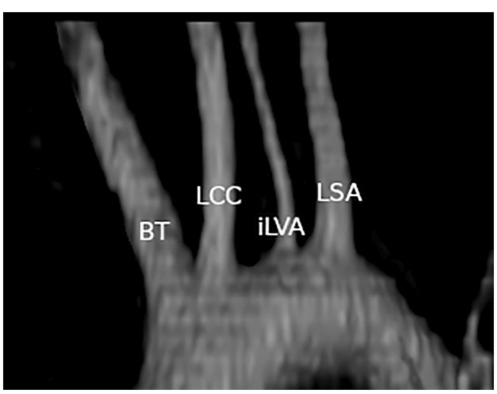


Fig. 4 Bovine aortic arch with an isolated left vertebral artery. BT and LCC share a common aortic origin. The LVA arises directly from the aortic arch proximal to the LSA. BT = brachiocephalic trunk, LCC = left common carotid artery, iLVA = isolated left vertebral artery, LSA = left subclavian artery

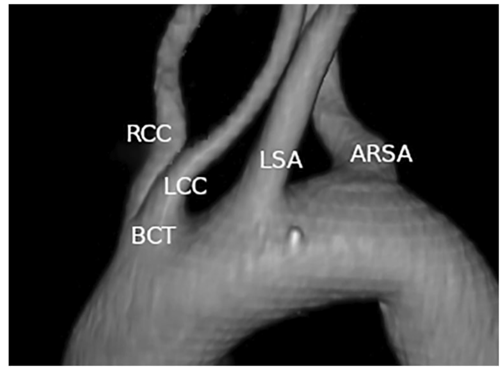


Fig. 5 Bicarotid trunk with an aberrant right subclavian artery. A common aortic origin of the carotid arteries can be seen, while the right subclavian artery arises as the fourth, most distal branch of the aortic arch. BCT = bicarotid trunk, RCC = right common carotid artery, LCC = left common carotid artery, LSA = left subclavian artery, ARSA = aberrant right subclavian artery

vs. 22.3%, there was a trend towards more bovine arches in ESUS patients compared with those with strokes of aortogenic or cardiogenic origin. This differ- ence did not prove to be statistically significant (p = 0.173). Type B bovine arches occurred in similar per- centages in both groups (12.2% vs. 9.7%, p = 0.846).

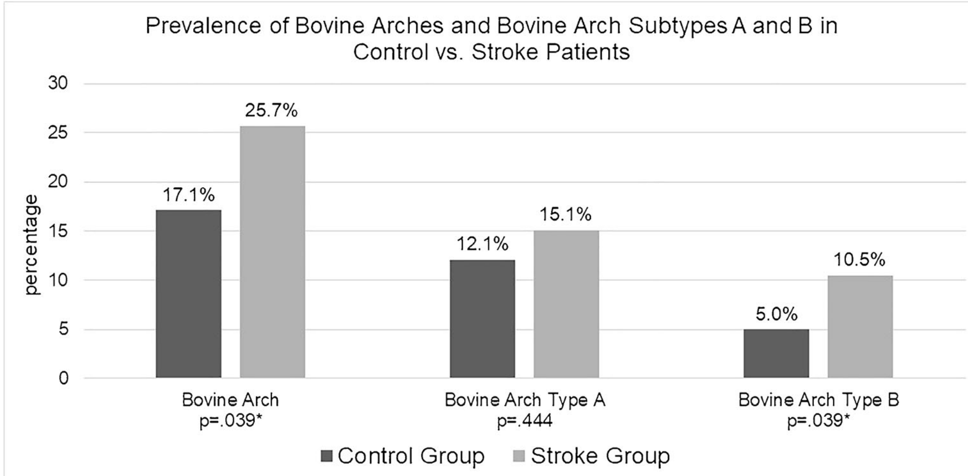
Discussion

Clinical significance of the bovine arch

The bovine arch, though previously thought to be a clinically insignificant incidental finding, has been mentioned as a possible biomarker for the development of thoracic aortic disease in several papers [18–21]. According to Moorehead et al., particularly type B bovine arches might be more common among patients with aortic arch dilation and aneurysm [35]. Additionally, being familiar with a patient's supra-aortic anatomy could help prevent complications of endovascular interventions. As mentioned before, bo- vine arches have been shown to be associated with adverse neurological outcomes after carotid artery stenting procedures [22–24] and thrombectomies [25], both of which are often performed in the treatment of stroke patients. For this reason, one could argue that a detailed knowledge of a patient's vascular anatomy does have a certain clinical significance in the stroke setting.

Lastly, varying vascular branching patterns might lead to altered hemodynamics within the affected vessels. Whether the bovine arch variation also has an influence on the formation of cerebral emboli, however, remains largely unstudied so far.

Fig. 6 Prevalence of bovine arches and bovine arch subtypes A and B in control vs. stroke patients. Bovine arches in general, and type B bovine arches in particular, are significantly more common among stroke patients, while type A bovine arches are not. * marks a statistically significant finding



Bovine arch prevalence among stroke patients

As of yet, not much information is available on the prevalence of bovine arches within stroke cohorts. In our control group, 17.1% of patients showed a bovine arch pattern. Several large CT-based studies have de- scribed similar frequencies of 15–25% bovine arches among European and North American populations [8, 10–12, 17, 20, 21, 36, 37]. However, there is much less information available on the prevalence of bovine arches among stroke patients.

Feiz et al. [38] report 8.9% type B bovine arches in a group of stroke patients, which is similar to the 10.5% found in our own patient collective. However, since this group did not consider the bovine arch type A to be an aortic arch branching variation and thus included them in the "standard pattern" category, no information on the frequency of type A bovine arches is given in this study.

Hemodynamics in the bovine arch

According to Pham et al. [39], histological differences between the vascular tissue of ascending aortic aneu- rysms in patients with a bovine arch and those with standard anatomy can be observed. Aneurysmatic bo- vine arches showed higher intimal and adventitial thick- nesses and lower medial thicknesses when compared with aneurysmatic arches with standard anatomy. Literature research did not reveal any comparable stud- ies on non-aneurysmatic bovine arch tissues.

In a prenatal ultrasound evaluation of 39 fetuses, Clerici et al. [40] showed significant differences in hemodynamics of fetuses with bovine aortic arch anatomy.

Not much is known about flow patterns in adult bovine arches yet. In a small, preliminary examination using 4D MRI, Shalhub et al. [41] compared flow patterns in the aortic arches of three healthy patients: one with standard aortic arch anatomy, one with a bovine arch, and one with an aberrant right subclavian artery. Hemodynamic measurements revealed higher regional shear stress in the bovine aortic arch and flow alterations which are typically associated with endothelial in- jury and vascular stiffness. An increased shear rate plays a role in thrombus formation [42] and has been shown to depend on the curvature of the aortic arch [43].

It is conceivable that the higher shear stress observed in the bovine arch might be caused by an altered branching angle of the supra-aortic vessels. This could be especially important for type B arches, which we found significantly more often in stroke patients, while type A arches occurred at similar rates in both stroke and control patients.

Prospectively, if Shalhub et al.'s observations can be reproduced and confirmed in a larger cohort, hemodynamic differences might also help to explain embolus formation in the case of patients suffering from embolic strokes of undeter- mined source, for whom no apparent sources of embolism can be identified in the standard post-stroke workup. Another pos- sibility, concerning patients with defined cardioembolic stroke etiologies, may be that the proposed altered hemodynamics influence embolus redirection towards the carotid arteries rather than more distal vessels, thus leading to more cerebral infarctions.

The investigation of these hypotheses, however, will re- quire further evaluation of the hemodynamic properties of bovine aortic arches.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived by the local ethics committee due to the retrospective study design.

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8. Statutory Declaration (Eidesstattliche Erklärung)

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät, keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Datum Unterschrift

9. Appendix

Ethikvotum

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BEARBEITER
Frau Dr. K. Saljé

DATUM
18.10.2018

Studientitel:	Die Prävalenz von Aortenbogenvarianten bei Schlaganfall-patienten und deren Einfluss des gemeinsamen Gefäßsprungs von Truncus brachiocephalicus und Arteria carotis communis sinistra auf die Lateralisation kardiogener zerebraler Emboli
Antrag vom:	21.06.2018
Eingegangen am:	22.06.2018
Interne Reg.Nr.:	BB 109/18

Stellungnahme der Ethikkommission

Sehr geehrter Herr Prof. Dr. Hosten,

die Ethikkommission der Universitätsmedizin Greifswald hat die zum o.g. Versuchsplan eingereichten Unterlagen in ihrer Sitzung am 31.07.2018 geprüft. Die in der Sitzung nachgeforderten Unterlagen sind am 08.08.2018 bzw. 11.10.2018 in der Geschäftsstelle der Ethikkommission eingegangen.

Die Kommission stellte mehrheitlich fest, dass gegen die Durchführung der Studie keine ethischen und rechtlichen Bedenken bestehen, und befürwortet deshalb das Vorhaben.

Die Ethikkommission erlaubt sich aber weiterhin den Hinweis, dass nur der verantwortliche Studienleiter, als gleichzeitig die für die Datenverarbeitung verantwortliche Person, Zugang zu den personen-bezogenen Daten der Studienteilnehmer haben sollte. Zudem sollten die Auswertung aller Patientendaten in anonymisierter Form erfolgen.

Die Ethik-Kommission macht darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens beim Studienleiter und allen beteiligten Ärzten/Mitarbeitern liegt.

Die Mitglieder der Kommission wünschen Ihnen viel Erfolg bei der Durchführung des Vorhabens.

Mit freundlichen Grüßen

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