REVIEW

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Relationship between anatomical variations in the aortic arch and risk of aneurysm formation- a systematic review and meta-analysis

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SUMMARY

Anatomical variations in the arch of the aorta have been presumptively involved in aneurysm formation, because they lead to alterations in the vascular morphology and hemodynamics. This systematic review with meta-analysis evaluated the occurrence of bovine arch and aberrant subclavian artery variations of the aortic arch and aneurysm formation rate. The structured search was conducted across seven databases, namely PubMed, Embase, Web of Science, Scopus, Cochrane Library, CINAHL, and ClinicalTrials.gov, by using Boolean operators and MeSH terms. The review followed the guidelines of PRISMA and applied PECOS frameworks for individuals with aortic arch variations, quantifying the incidence or risk of aneurysm formation. The review utilized ROBINS-I and SYRCLE tools to assess the quality and bias, and a GRADE certainty assessment was used. A random-effects model was used for the meta-analysis, and sensitivity analyses were carried out to find out the robustness of the conclusion.

A total of seven studies were included, comprising both clinical cohort studies and animal research. The analysis indicated that individuals with anatomical variations such as the bovine arch had a higher mean difference (MD) of aneurysm risk compared to those without variations (MD 0.90 (0.63, 1.17); $p < 0.00001$). Vessel dimensions were significantly greater in those with anatomical variations associated with increased aneurysm risk (MD 9.00 (7.96, 10.04); $p < 0.00001$). Additionally, a comparison between patients with thoracic aortic aneurysms and healthy controls showed a notable increase in aortic arch dimensions in the aneurysm group (MD 11.46 (6.85, 16.08); $p < 0.00001$). The presence of specific anatomical variations in the aortic arch, particularly the bovine arch and aberrant subclavian artery, was associated with an increased risk of aneurysm formation. Variability in outcomes across age groups and study designs indicated that both anatomical and hemodynamic factors contribute to aneurysm formation risk. These findings emphasize the importance of individualized assessment of aortic arch anatomy in clinical practice for aneurysm risk stratification.

Key words: Aortic arch – Anatomical variations – Aneurysm formation – Bovine arch – Aberrant subclavian artery – Hemodynamics – Risk assessment

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INTRODUCTION

The aortic arch is an important anatomical structure acting as a pathway for blood flow from the heart to the large arteries that supply the head, neck, and upper body (Ehrlich et al, 2020). Variations in the branching patterns and morphology of the aortic arch are not uncommon and can manifest in several forms, including the "bovine arch" (a common origin of the brachiocephalic and left common carotid arteries), aberrant subclavian arteries, isolated left vertebral arteries, and other complex anatomical deviations (Aboulhoda et al., 2019). These variations are generally asymptomatic and often incidental findings during imaging; however, their clinical implications have garnered increasing attention in recent years, particularly in the context of vascular disease susceptibility (Kefalidi et al., 2022; Mazine et al., 2022).

Aortic thoracic aneurysms, particularly those involving the aortic arch, are serious conditions that incur significant morbidity and mortality. These are abnormal dilations of the aortic wall, which may cause catastrophes such as rupture or dissection (Taghizadeh et al., 2021). Thoracic aortic aneurysms have multifactorial etiology, including genetic predispositions, environmental factors, and, with growing evidence, particular anatomical configurations of the aortic arch. Different anatomical variations may have unequal mechanical stress applied to the aortic wall, and perhaps, there is a difference in the tendency for aneurysm formation as well (Rahimi et al., 2021). Variations that alter the hemodynamic forces in the aortic arch may be associated with predisposition to localized weakening of the wall, thus putting them at an increased risk for aneurysmal formation (Heber et al., 2021; Ben Ahmed et al., 2022; Sokolis et al., 2022; Bouaou et al., 2024).

The pathophysiological mechanisms that underlie the association of aortic arch anomalies with aneurysm formation are numerous and also pretty complex. The studies of hemodynamics indicated that anatomical variations may cause irregular flow velocities, wall shear stress, and oscillatory stress at the level of the aortic arch. Such changes in hemodynamics may cause local dysfunction of the endothelium, degradation of the extracellular matrix, and subsequently, aneurysm formation (Sokolis et al., 2022; Bouaou et al., 2024; Pidvalna et al., 2022). Such discoveries also indicate that there are specific pathways related both to aortic aneurysms and anatomical variations, giving the possibility of genetic predisposition to further modulate the impact of anatomical variants upon aneurysm risk. The relationship between genetic susceptibility, anatomical variation, and hemodynamic stress remains somewhat obscure at the moment (Mertens et al., 2019; Solano et al., 2023).

Some anatomic anomalies, including the bovine arch, have been hypothesized to influence hemodynamics, thereby creating greater mechanical stress on certain portions of the aorta (Ben Ahmed et al., 2022). Other abnormal patterns of subclavian artery branching and variations in branching might also generate turbulence-producing flow dynamics, which would initiate endothelial damage and chronic inflammation, the two identified risk factors for the formation of aneurysms (Sokolis et al., 2022). Although such conclusions do exist, the association of specific aortic arch abnormalities with aneurysm formation is incomplete because, although some studies directly correlate them, many others do not; hence a systematic review of the literature is required (Bouaou et al., 2024).

Given the potential clinical implications of anatomical variations in the aortic arch, understanding their role in the pathogenesis of aneurysms is crucial. Structural differences in the arch may influence hemodynamic stress distribution, vessel wall integrity, and susceptibility to pathological remodelling, thereby contributing to aneurysm formation. Identifying such associations could aid in refining risk stratification models, guiding targeted screening protocols, and informing preventive strategies to mitigate aneurysm-related complications. Hence, this systematic review and meta-analysis aims to comprehensively evaluate the relationship between anatomical variations of the aortic arch and the risk of aneurysm development by synthesizing evidence from diverse study designs addressing this topic.

MATERIALS AND METHODS

Study design

The PECOS protocol for this review was designed strictly according to the reporting guidelines of PRISMA (Page et al., 2023). Population (P) was defined as individuals or animal models with anatomical variations in the aortic arch, with the Exposure (E) being specific anatomical variations (such as a bovine arch, or an aberrant subclavian artery). The Comparator (C) was designated to be individuals without such variations; however, this group was not considered to be mandatory, considering the exploratory nature of the review. The Outcome (O) was ascertained to be the incidence or risk of aneurysm formation, with observational studies, cohort case-control and animal studies being the Study design (S) under consideration.

Inclusion and exclusion criteria

Human Studies

Human studies meeting the inclusion criteria consisted of anatomical variations in the aortic arch and their relation to the risk of aneurysm. There were cohort, case-control, and cross-sectional study designs that qualified. These should have reported quantitative data indicating a relationship between aneurysm formation or progression and such aortic arch variations, such as the bovine arch or aberrant subclavian artery. Excluded human studies were case reports, reviews, editorials, and studies on congenital heart diseases not related to aortic arch variations. Studies that did not clearly report their findings concerning the outcome of aneurysms with regard to anatomical variations were also excluded.

Animal Studies

For studies in animals, the inclusion criterion was experimental models investigating anatomical variations of the aortic arch and the implications for aneurysm formation or risk. Research on reproducible models with measurable outcomes, such as morphological changes or volume assessments or wall characteristics, was included. Excluded animal studies were those that focused on congenital anomalies unrelated to aortic arch variations, did not have quantifiable data linking anatomical variation to aneurysm outcome, or did zznot give findings relevant to the research aims.

Database search strategy

The database search strategy comprised of seven databases: PubMed, Embase, Web of Science, Scopus, Cochrane Library, CINAHL, and ClinicalTrials.gov. Boolean operators combined with MeSH terms maximized the number of relevant studies available for retrieval. Boolean operators like "AND," "OR," and "NOT" are used in formulating the question to narrow its focus further (Table 1). No limitations were placed on the timeframe of the searched articles. The search was conducted keeping in mind the indexing and abilities of each database to ensure an adequate scope.

Data extraction process

Systematic extraction of data was performed to collect all relevant information comprehensively and accurately. Key data items extracted were the author, year of publication, type of study design, population demographics, for example, age, sex, and sample size, and specific aortic arch anomalies under investigation, such as the bovine arch or aberrant subclavian artery. The diagnostic modalities applied in the studies, such as CT angiography, MRI, or other imaging techniques, were also recorded. Besides, the prevalence of aneurysms related to these anomalies was extracted, along with summary statistics such as odds ratios, relative risks, and confidence intervals to quantify the relationship between aortic arch variations and aneurysm risk. In addition, details regarding confounders controlled in the studies, including age, comorbidities, or lifestyle factors, were also carefully documented to assess the robustness of the findings. Data extraction was performed by two independent reviewers to minimize bias and ensure accuracy. Any disagreement over the extracted data was resolved by a third reviewer through discussion and consensus.

Quality assessment and certainty bias assessment strategy

Bias was systematically assessed across multiple domains to ensure the validity and reliability of the included studies. For observational studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Igelström et al., 2021) was used. This tool assesses potential biases in domains such as selection, confounding, measurement, and reporting. Selection bias was evaluated to check whether participants were selected without systematic differences between groups, thus ensuring comparability. Bias due to confounding was checked to ensure that the studies controlled for age, sex, or comorbid conditions that could affect the outcomes. Measurement bias dealt with the precision of the techniques used to measure exposures and outcomes, including standardization of imaging modalities like CT angiography or MRI. Reporting bias was assessed to check that all the pre-specified outcomes were reported and that there was no selective reporting of results. Each study was rated to have a "low," "moderate," "serious," or "critical" risk of bias based on these domains, which led to an overall risk assessment.

For animal studies, the SYRCLE tool (Hooijmans et al., 2014) was adapted from Cochrane Risk of Bias tool for particular use in animal experiments. Selection bias was controlled by assessment of randomization and allocation concealment to achieve comparable groups. Performance bias was performed to verify blinding of researchers and caregivers to prevent differential treatment of the animals. Detection bias had to be oriented towards blinding outcome assessors to ensure an unbiased evaluation of results. Attrition bias had to be considered for any exclusions or dropouts, making sure that data are complete. Other types of bias such as housing conditions and conflicts of interest were also evaluated under the domain of "other bias." Every domain was scored, resulting in an overall bias risk assessment for every animal study.

To further add robustness to the assessment, the GRADE assessment (Bezerra et al., 2024) was employed to rate the certainty of evidence as high, moderate, low, or very low together with bias assessment tools.

Statistical analysis strategy

Meta-analysis was done with RevMan 5 (v 5.4.1). The review and forest plots for three comparisons were shown as mean differences (MD). The first one was the risk of aneurysm compared to non-anatomical variations, which anatomical variations possess against non-anatomical variations. The second one was the correlation between the aortic arch vessel dimensions in individuals with anatomical variations that have risks compared to those without anatomical variations with an increased chance of aneurysm occurrence. The third being the comparison of the aortic arch

Table 1. Search strings utilised across the assessed databases.

Database	Search String	Time Period
PubMed	("Aortic Arch"[MeSH] OR "Aortic Arch Variation"[MeSH] OR "Aortic Arch Anomalies"[MeSH]) AND ("Anatomical Variation"[MeSH] OR "Bovine Arch" OR "Aberrant Subclavian Artery" OR "Aortic Arch Anomaly") AND ("Aneurysm"[MeSH] OR "Aortic Aneurysm") AND ("Risk Factors"[MeSH] OR "Risk")	Studies selected irrespective of time period.
Embase	("Aortic Arch" AND "Anatomical Variation") OR ("Bovine Arch" OR "Aberrant Subclavian Artery" OR "Left Vertebral Artery") AND ("Aortic Aneurysm" OR "Aneurysm Formation") AND ("Risk Factors" OR "Incidence") NOT ("Congenital Heart Disease")	Studies selected irrespective of time period.
Web of Science	TS=("Aortic Arch Variation" OR "Aortic Arch Anomaly" OR "Bovine Arch") AND TS=("Aneurysm Formation" OR "Thoracic Aortic Aneurysm") AND TS=("Risk Factors" OR "Incidence" OR "Prevalence")	Studies selected irrespective of time period.
Scopus	TITLE-ABS-KEY(("Aortic Arch Anatomical Variation" OR "Aortic Arch Abnormality") AND ("Aneurysm Risk" OR "Aneurysm Incidence") AND ("Bovine Arch" OR "Aberrant Subclavian Artery" OR "Left Vertebral Artery"))	Studies selected irrespective of time period.
Cochrane Library	((Aortic Arch Variation OR "Bovine Arch" OR "Aberrant Subclavian Artery") AND (Aneurysm OR "Aneurysm Risk" OR "Aneurysm Formation") AND ("Anatomical Variation" OR "Vascular Abnormality")) in Title Abstract Keyword	Studies selected irrespective of time period.
CINAHL	(MH "Aortic Arch") AND (MH "Aortic Aneurysm") AND (("Bovine Arch" OR "Aberrant Subclavian Artery" OR "Isolated Left Vertebral Artery") AND ("Risk Factors" OR "Prevalence" OR "Incidence" OR "Case-Control"))	Studies selected irrespective of time period.
ClinicalTrials.gov	"Aortic Arch Anomalies" AND "Aneurysm Risk" AND ("Bovine Arch" OR "Subclavian Artery Anomaly" OR "Isolated Vertebral Artery") AND ("Case-Control Study" OR "Prospective Cohort" OR "Retrospective Cohort")	Studies selected irrespective of time period.

measurements of patients with thoracic aortic aneurysm versus healthy controls. The random effects (RE) model with 95% confidence intervals was applied to account for heterogeneity across the selected studies.

RESULTS

Study selection process

Following the PRISMA guidelines (Fig. 1) records were identified in the databases containing PubMed (49), Embase (51), Web of Science (46), Scopus (45), Cochrane Library (43), CINAHL (50), and ClinicalTrials.gov (80). After excluding 39 duplicate records, 325 unique records remained for screening. All 325 were screened with no excluded at this point. Of those, a total of 325 reports were sought for retrieval, while 41 reports were not retrieved because these were locked behind paywalls and lacked full-text access in the databases. A total of 284 reports were found eligible to be assessed. Reasons for exclusion were studies failing PECOS criteria where the studies were relevant to the general topic but did not meet specific inclusion criteria defined by the PECOS framework (72), literature reviews (62), these articles (49), case reports (65), and off-topic articles which were unrelated to the primary research question of the review (29). Ultimately, seven studies (18-24) entered the review.

Demographic variables assessed

Table 2 summarizes demographic characteristics from the included studies (Boillat et al., 2023; Bonser et al., 2000; Eleshra et al., 2021;

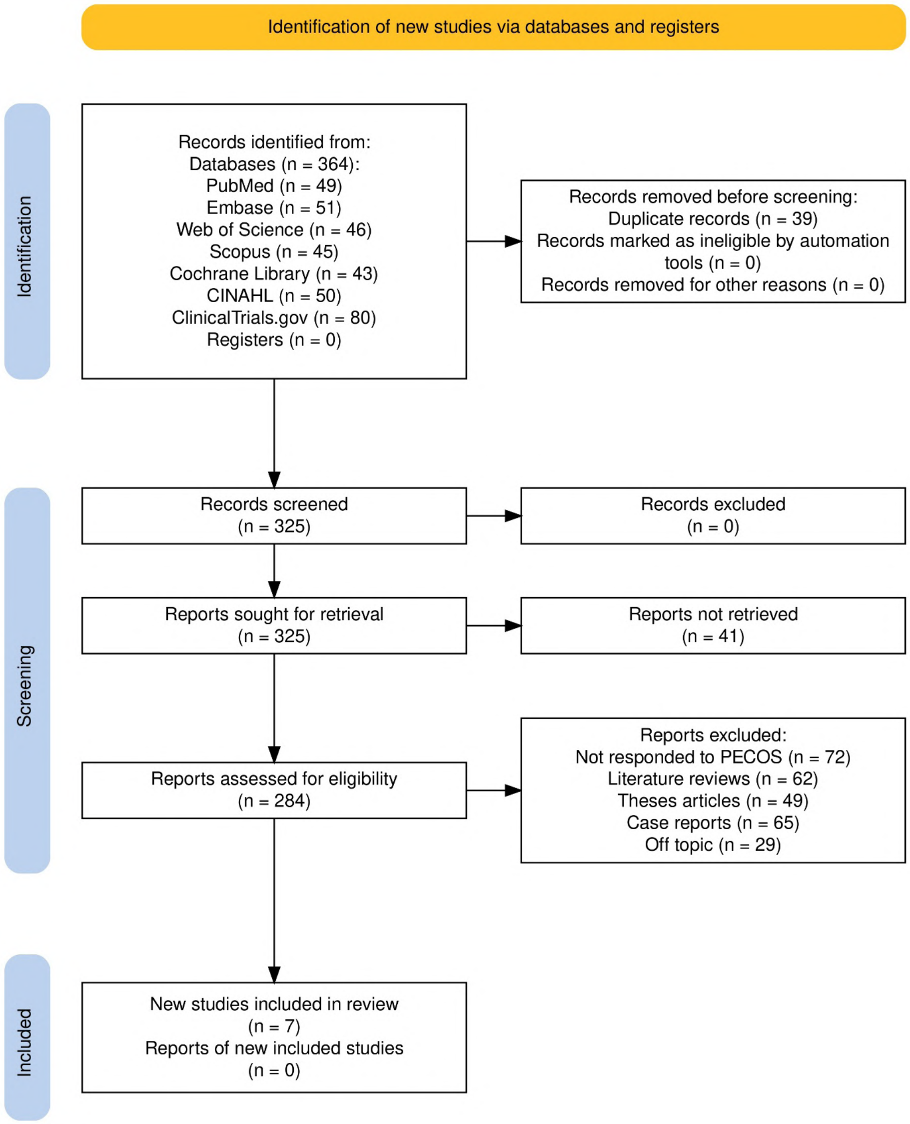


Fig. 1.- PRISMA flow diagram illustrating the study selection process, including identification, screening, eligibility, and inclusion criteria.

Table 2. Demographic variables assessed across the included studies (AngII: Angiotensin II; ePPE: Elastase Porcine Pancreatic Elastase; BAPN: Beta-Aminopropionitrile).

Study ID	Year	Location	Study Design	Sample Size	Mean Age (Years)	Male Ratio	Follow-up Period
Boillat et al [2023]	2023	Switzerland	Experimental (Animal Study)	9	0.48 (approx. 25 weeks)	Not specified	Not specified
Bonser et al [2000]	2000	United Kingdom	Observational Cohort	87	63.6	52:35	6-month intervals
Eleshra et al [2021]	2021	Germany	Retrospective Cohort Study	12	70 ± 10	9:3	13 ± 4.3 months
Ibrahim et al [2022]	2022	Austria	Experimental (Animal Study)	38 (AngII), 20 (ePPE), 8 (ePPE + BAPN), 17 (PPE)	11–15 weeks (AngII), 8–12 weeks (other models)	Not specified	Variable based on model (27 days for AngII, 13-21 days for others)
Ikeno et al [2019]	2018	Japan	Retrospective Cohort Study	815 (aortic arch disease), 1506 (control	70.4 ± 11.0 (aortic arch disease), 49.9 ± 19.8 (control)	65% male in aortic arch disease group, 74.2% male in control group	Not specified
Salmasi et al [2022]	2022	United Kingdom	Prospective cohort study	34	Not specified	Not specified	Not specified
Suh et al [2014]	2014	USA	Prospective Study	15	64 ± 14	9:6	Not specified

Ibrahim et al., 2022; Ikeno et al., 2019; Salmasi et al., 2022; Suh et al., 2014). The majority of the studies were conducted in geographically distant locations, namely Switzerland (Boillat et al., 2023), the United Kingdom (Bonser et al., 2000; Salmasi et al., 2022), Germany (Eleshra et al., 2021), Austria (Ibrahim et al., 2022), Japan (Ikeno et al., 2019), and the USA (Suh et al., 2014). The sample sizes ranged from a minimum of 12 participants in a human study (Eleshra et al., 2021) to more than 1500 in a human study (Ikeno et al., 2019), or from a minimum 9 in an animal study (Boillat et al., 2023) to 83 in another animal study (Ibrahim et al., 2022). The age range was from as young as 49.9 years in controls to as old as 70.4 years among those having aortic arch disease, the age range most commonly affected by aneurysms (Bonser et al., 2000; Eleshra et al., 2021; Ikeno et al., 2019; Suh et al., 2014). Animal models were also carried out in corresponding ages modelled in weeks to equate with the human conditions (Boillat et al., 2023; Ibrahim et al., 2022). In the human studies, male predominance was seen with ratios of 65% of patients suffering from aortic arch disease and 74.2% controls (Ikeno et al., 2019). This is congruent to higher incidence rates of aneurysms in males (Bonser et al., 2000; Eleshra et al., 2021). The periods of follow-up were also variable: as many as 13 months among the human studies, whereas animal studies contain a model-specific duration much shorter than this (Ibrahim et al., 2022).

Anatomical variations of the aortic arch

There were a range of these anatomical variations, including the bovine arch, an aberrant subclavian artery, and renovisceral arterial anomalies (Table 3). The incidence of these were described in particular cohorts. The bovine arch, for instance, had an incidence of 10.1% in patients affected by aortic arch disease but only 9% in controls, suggesting an association with the presence of disease (Ikeno Y et al., 2019). The bovine arch was linked with aneurysms that developed proximally, whereas the aberrant subclavian artery was more commonly associated with distal aneurysms that pointed toward a spatial heterogeneity in aneurysm risk based on the variations themselves (Ikeno Y et al., 2019). In thoracoabdominal aortic aneurysms (TAAAs), accessory renal arteries and celiac artery anomalies were also found, which helped in the successful endovascular repair with low morbidity and mortality results (Eleshra A et al., 2021).

Diagnostic modalities and aneurysm locations

Table 3: Aneurysm-associated outcomes and their correlation observed with anatomical variations of the aortic arch across the selected studies (AngII: Angiotensin II; ePPE: Elastase Porcine Pancreatic Elastase; BAPN: Beta-Aminopropionitrile; CKD: Chronic Kidney Disease; F/B-EVAR: Fenestrated/Branched Endovascular Aneurysm Repair; PWV: Pulse Wave Velocity).

Study ID	Groups Assessed	Aortic Arch Variations (Type & Prevalence)	Diagnostic Modality & Aneurysm Location	Confounding Factors	Aneurysm Morphology & Wall Characteristics	Anomalies & Hemodynamic Factors	Key Conclusion
Boillat et al [2023]	Common Carotid Arteries	Type 1 variation (lCCA bifurcation from BCT and aortic arch)	Necropsy & dissection; Not applicable	Not specified	Not applicable	No anomalies in subclavian artery anatomy	Established anatomical landmarks for future rabbit model surgery
Bonser et al [2000]	Thoracic aortic aneurysms, dissections	Not specified	CT, MRI; ascending aorta, aortic arch, descending aorta	Age, thrombus presence	Thrombus linked to accelerated expansion	Dissection, calcification not growth-linked	Exponential aneurysm growth influenced by thrombus; prior surgery reduced growth rate
Eleshra et al [2021]	TAAAs with renovisceral variations	Accessory renal arteries, celiac artery variant	CT angiography; thoracoabdominal aorta	Age, CKD, hypertension	Not specified	Anomalies in renovisceral arteries	Demonstrated success of F/B-EVAR in TAAAs with low morbidity and mortality
Ibrahim et al [2021]	AngII, ePPE, PPE Models	Not specified	3D Ultrasound; abdominal aorta)	Age, strain	Fusiform with thrombi	Volume & diameter reproducible across models	Early detection and volume assessment; model suitability for treatment testing
Ikeno et al [2019]	Aortic arch aneurysm, aortic dissection	Bovine arch (10.1% in disease, 9% control); aberrant subclavian artery (1.7% disease, 0.5% control)	CT angiography; proximal & distal aortic arch	Age, comorbidities	Not specified	Bovine arch with proximal aneurysms; aberrant subclavian with distal aneurysms	Bovine arch and aberrant subclavian artery associated with increased risk of aortic arch disease
Salmasi et al [2022]	Ascending thoracic aneurysms	Not specified	Uniaxial testing; ascending aorta	Age, PWV	Fusiform; wall thinner on outer curve	Circumferential stiffness	Outer curve more prone to dissection; variable biomechanics suggest surgery implications
Suh et al [2014]	Thoracic aortic aneurysms, dissections	Not specified	CT Angiography; ascending aorta, aortic arch, descending aorta	Age, respiratory influences	Not specified	Increased wall shear stress during respiration	Respiratory translation affects aortic arch geometry, impacting endovascular repair designs

Various diagnostic modalities were employed such as CT angiography, MRI, 3D ultrasound, and necropsy in animal models for varied objectives. CT and MRI were widely used for high-resolution imaging to identify aneurysms in different segments of the aorta, such as the ascending aorta, aortic arch, and the descending thoracic aorta (Bonser et al., 2000; Ikeno et al., 2019). In the animal models, 3D ultrasound revealed repeatable volume and diameter measurements crucial for the early detection and evaluation of aneurysm enlargement (Ibrahim et al., 2022). In some of the animal models, necropsy and anatomical dissection were conducted with direct visualization of arterial structures, which was very significant in ascertaining the anatomical landmarks for further research and potential surgical applications (Boillat et al., 2023).

Confounding factors

Confounding factors present in all studies included age and the existence of thrombus, co-variety that includes hypertension, chronic kidney disease, and respiratory influences, which are all documented to have huge impacts on the formation and progression of aneurysms themselves (Boillat et al., 2023; Bonser et al., 2000; Eleshra et al., 2021; Ibrahim et al., 2022; Ikeno et al., 2019; Salmasi et al., 2022; Suh et al., 2014). This was exemplified by the fact that thrombus presence was particularly implicated, as studies showed that aneurysm expansion was accelerated without any corresponding increase in calcification, indicating a distinct pathophysiological mechanism in aneurysmal growth (Bonser et al., 2000). Inclusion of respiratory influences in some studies dynamically applied to the risk assessment of aneurysms, suggesting that physiological conditions can intrude and modify the behaviour of the aneurysm and its consequences on treatment modalities (Suh et al., 2014).

Morphology and wall characteristics of aneurysms

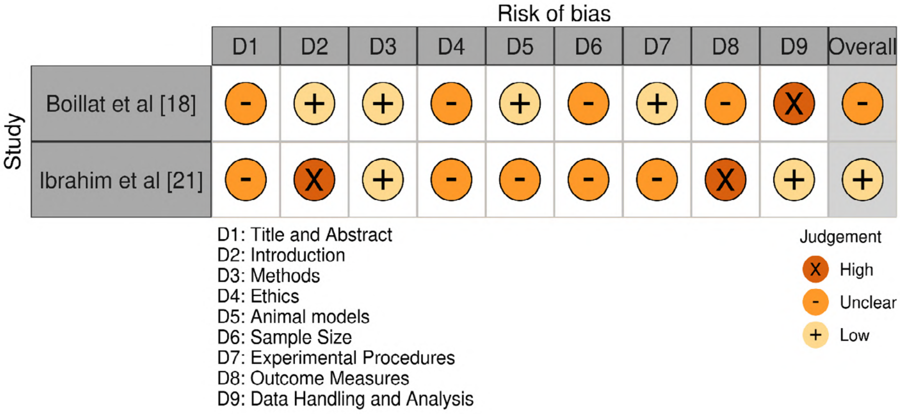
Morphologically, aneurysm was largely fusiform in all the studies. Wall characteristics varied according to location. Specific studies outlined thinner walls on the outer curve of the ascending aorta and increased circumferential stiffness, which affected the stability of aneurysms (Ibrahim et al., 2022; Salmasi et al., 2022). These findings indicated that dissection was more likely along the outer curve of the aorta, and that localized biomechanical factors played a role in progression of aneurysms. Wall features, such as thrombus presence and circumferential stiffness, were also predictive of greater probability of aneurysm dilation, mainly in the ascending thoracic aorta but mostly suggesting that the type of surgical strategy applied to the individual anatomical setting may carry some significance (Salmasi et al., 2022).

Haemodynamic factors and anomalies

Haemodynamic factors such as wall shear stress and also the respiratory-induced wall translation were found to significantly impact the geometry, as well as growth of aneurysms. Increased wall shear stress during phases of respiration and the consequent translocation of the aortic arch were found to cause alterations in geometry at the level of the arch and were thought to have major design and performance implications for the size and configuration of endovascular repair devices (Suh et al., 2014). Such studies thereby also shown that anatomical anomalies will increase hemodynamic forces and thus also increase the mechanical wall strain that occurs within the aortic wall, which may accelerate the progression of aneurysms and impact clinical decision-making for endovascular interventions.

Quality assessment and bias levels observed

For Boillat et al. (2023), and Ibrahim et al. (2022), the SYRCLE tool (Fig. 2) observed low to moderate scores in many domains, with the former showing moderate bias in "Title and Abstract," "Ethics," and "Outcome Measures" but high ratings in "Data Handling and Analysis." Ibrahim et al. (2022) had moderate bias in "Introduction," with high ratings in various domains, showing that study designs and methodological rigors do vary. The ROBINS-I tool (Fig. 3) indicated overall low risk of bias in Bonser et al. (2000), Eleshra et al. (2021), Ikeno et al. (2019), Salmasi et al. (2022) and Suh et al. (2014). Bonser et al. (2000) and Suh et al. (2014) displayed universally low scores through all items, except some areas showing moderate risk. Eleshra et al. (2021) exhibited low risk in most domains but with a high bias in "D4" (confounding factors). Ikeno et al. 2019) and Salmasi et al. (2022) showed moderate bias generally, but with high risks in "D2" (selection of participants) for Ikeno et al. (2019), and in "D1" and "D3" for Salmasi et al. (2022), reflecting shortcomings in participant selection and control of the experiment.



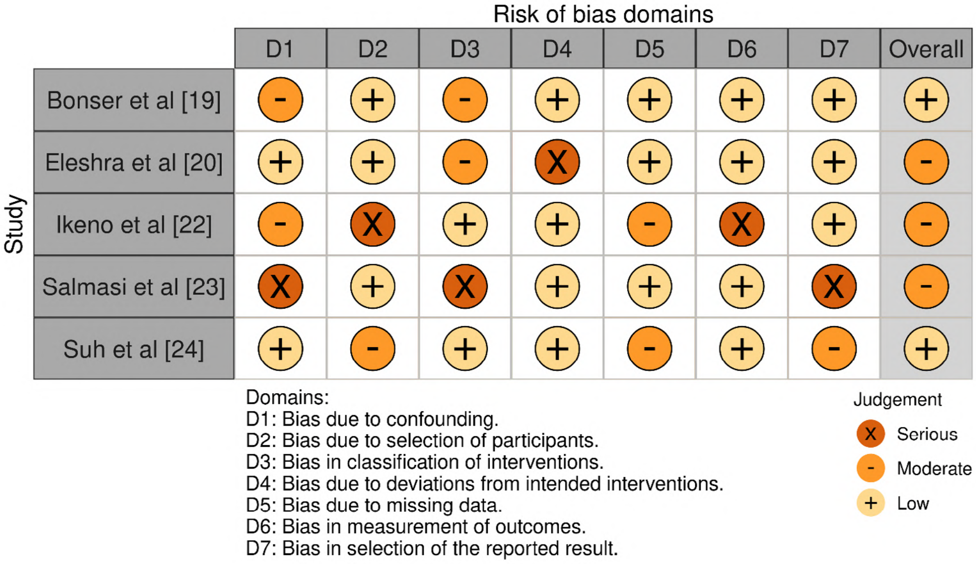
Risk of bias

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	Overall
Boillat et al [18]	-	+	+	-	+	-	+	-	X	-
Ibrahim et al [21]	-	X	+	-	-	-	-	X	+	+

D1: Title and Abstract
D2: Introduction
D3: Methods
D4: Ethics
D5: Animal models
D6: Sample Size
D7: Experimental Procedures
D8: Outcome Measures
D9: Data Handling and Analysis

Judgement
X High
- Unclear
\+ Low

Fig. 2.- Quality assessment of experimental animal studies using the SYRCLE tool, evaluating study design, randomization, allocation concealment, and blinding.



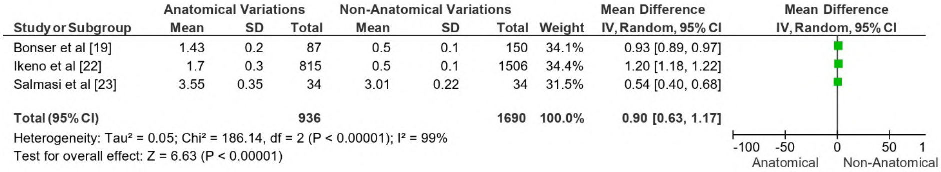
Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Bonser et al [19]	-	+	-	+	+	+	+	+
Eleshra et al [20]	+	+	-	X	+	+	+	-
Ikeno et al [22]	-	X	+	+	-	X	+	-
Salmasi et al [23]	X	+	X	+	+	+	X	-
Suh et al [24]	+	-	+	+	-	+	-	+

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
\+ Low

Fig. 3.- Quality assessment of non-randomized studies using the ROBINS-I tool, assessing potential biases in confounding, selection, classification, and outcome measurement.



Study or Subgroup	Anatomical Variations Mean	Anatomical Variations SD	Anatomical Variations Total	Non-Anatomical Variations Mean	Non-Anatomical Variations SD	Non-Anatomical Variations Total	Weight	Mean Difference IV, Random, 95% CI
Bonser et al [19]	1.43	0.2	87	0.5	0.1	150	34.1%	0.93 [0.89, 0.97]
Ikeno et al [22]	1.7	0.3	815	0.5	0.1	1506	34.4%	1.20 [1.18, 1.22]
Salmasi et al [23]	3.55	0.35	34	3.01	0.22	34	31.5%	0.54 [0.40, 0.68]
Total (95% CI)			**936**			**1690**	**100.0%**	**0.90 [0.63, 1.17]**

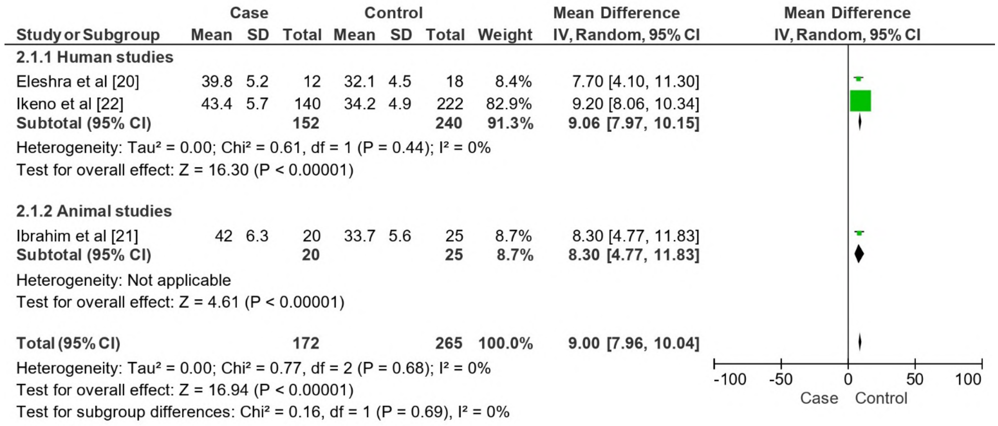
Heterogeneity: Tau² = 0.05; Chi² = 186.14, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 6.63 (P < 0.00001)

Fig. 4.- Comparative analysis of aneurysm risk in patients with anatomical variations versus those without variations, highlighting key statistical findings.

Meta-analytical observations

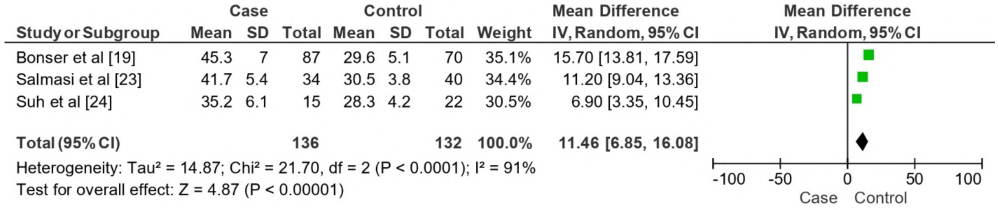
Figure 4 summarises the risk of aneurysm in cases with anatomical variations compared to those who do not show anatomical variations. The MD in aggregate was at 0.90 (0.63, 1.17), showing a greater risk in cases with anatomical variations. Strong heterogeneity was established (Tau^2 = 0.05, Chi^2 = 186.14, df = 2, $P < 0.00001$; I^2 = 99%); thus there is heterogeneity between studies. The effect size was statically significant (Z = 6.63, $P < 0.00001$), which supported increased aneurysm risk associated with anatomical variations.

Figure 5 examined the aortic arch vessel dimensions in individuals with anatomical variations



Study or Subgroup	Case Mean	Case SD	Case Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Human studies								
Eleshra et al [20]	39.8	5.2	12	32.1	4.5	18	8.4%	7.70 [4.10, 11.30]
Ikeno et al [22]	43.4	5.7	140	34.2	4.9	222	82.9%	9.20 [8.06, 10.34]
Subtotal (95% CI)			**152**			**240**	**91.3%**	**9.06 [7.97, 10.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%								
Test for overall effect: Z = 16.30 (P < 0.00001)								
2.1.2 Animal studies								
Ibrahim et al [21]	42	6.3	20	33.7	5.6	25	8.7%	8.30 [4.77, 11.83]
Subtotal (95% CI)			**20**			**25**	**8.7%**	**8.30 [4.77, 11.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.61 (P < 0.00001)								
Total (95% CI)			**172**			**265**	**100.0%**	**9.00 [7.96, 10.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 2 (P = 0.68); I² = 0%								
Test for overall effect: Z = 16.94 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%								

Fig. 5.- Correlation between aortic arch vessel dimensions and aneurysm risk in patients with anatomical variations, visualizing potential hemodynamic implications.



Study or Subgroup	Case Mean	Case SD	Case Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bonser et al [19]	45.3	7	87	29.6	5.1	70	35.1%	15.70 [13.81, 17.59]
Salmasi et al [23]	41.7	5.4	34	30.5	3.8	40	34.4%	11.20 [9.04, 13.36]
Suh et al [24]	35.2	6.1	15	28.3	4.2	22	30.5%	6.90 [3.35, 10.45]
Total (95% CI)			**136**			**132**	**100.0%**	**11.46 [6.85, 16.08]**
Heterogeneity: Tau² = 14.87; Chi² = 21.70, df = 2 (P < 0.0001); I² = 91%								
Test for overall effect: Z = 4.87 (P < 0.00001)								

Fig. 6.- Comparison of aortic arch measurements between patients with thoracic aortic aneurysms and control groups, demonstrating structural differences and potential risk factors.

compared to those without, referencing its association to aneurysm risk. MD was generally 9.00 (7.96, 10.04), indicating that the vessel dimensions were significantly more pronounced in the individuals with anatomical variations associated with aneurysm risk. Heterogeneity was very low ($Tau^2 = 0.00$, $Chi^2 = 0.77$, df = 2, P = 0.68; $I^2 = 0\%$), and the overall effect was extremely strong (Z = 16.94, P < 0.00001). This indicates that there is a strong and consistent association of at risk for aneurysm with increased dimensions in anatomical variations of the aortic arch.

Figure 6 elucidates the MD of aortic arch measurements in patients with thoracic aortic aneurysms compared to healthy controls. MD = -11.46 (6.85, 16.08); significantly larger aortic arch measurements in aneurysm patients. $Tau^2 = 14.87$, $Chi^2 = 21.70$, df = 2, P < 0.0001; $I^2 = 91\%$. However, the overall effect was significant (Z = 4.87, P < 0.00001), so patients with thoracic aortic aneurysm had significantly larger aortic arch dimensions than controls.

GRADE assessment observations

The GRADE certainty assessment across studies suggested moderate to high certainty based on study design, findings, and influencing factors (Table 4). An anatomical landmark-based knowledge foundation drawn from experimental animal research in Switzerland (Boillat et al., 2023) and Austria (Ibrahim et al., 2022) focused less on the directness of findings and model-specific constraints led to a moderate certainty rating. There was moderate consistency in both observational cohort studies from United Kingdom (Bonser et al., 2000; Salmasi et al., 2022) and Germany (Eleshra et al., 2021), although the strength of their findings was compromised due to the presence of thrombus in aneurysm growth and outcomes related to morbidity.

Retrospective cohort studies (Ikeno et al., 2019) had moderate to high certainty, especially for findings that linked certain aortic arch abnormalities, like the bovine arch, with an increased risk of aneurysm. The evidence was based on large sample sizes and low-to-moderate bias ratings. Prospective studies (Suh et al., 2014) had more modest certainty, but were heterogeneously reported, largely due to biomechanical factors like circumferential stiffness and respiratory influences on aortic arch geometry.

Table 4. GRADE assessment observations.

Study Format	Total Studies	Observed Key Finding	Bias Risk	Result Inconsistency	Indirectness	Result Imprecision	Additional Factors	Overall Certainty
Experimental (Animal Study)	1	Established anatomical landmarks for future rabbit model surgery	Low	Moderate	Moderate	Low	None	Moderate
Observational Cohort	1	Exponential aneurysm growth influenced by thrombus; prior surgery reduced growth rate	Low	Moderate	Low	Moderate	Thrombus influence	Moderate
Retrospective Cohort Study	1	Demonstrated success of F/B-EVAR in TAAAs with low morbidity and mortality	Low to Moderate	Low	Moderate	Low	Morbidity and mortality outcomes	Moderate
Experimental (Animal Study)	1	Early detection and volume assessment; model suitability for treatment testing	Low	Low	Moderate	Low	Experimental model reliability	Moderate
Retrospective Cohort Study	1	Bovine arch and aberrant subclavian artery associated with increased risk of aortic arch disease	Low to Moderate	Low	Low	Low	Risk differences by variation type	High
Prospective Cohort Study	1	Outer curve more prone to dissection; variable biomechanics suggest surgery implications	Low	Moderate	Low	Moderate	Biomechanical variations	Moderate
Prospective Study	1	Respiratory translation affects aortic arch geometry, impacting endovascular repair designs	Low	Moderate	Low	Moderate	Respiratory influences	Moderate

DISCUSSION

This study synthesizes findings from a wide range of perspectives to provide a comprehensive understanding of how anatomical variations in the aortic arch influence aneurysm formation. By bridging clinical, biomechanical, and experimental insights, it underscores the importance of these variations in risk assessment, surgical planning, and treatment strategies, ultimately contributing to improved outcomes in managing thoracic aortic aneurysms.

Boillat et al. (2023) and Ibrahim et al. (2022) made anatomical assessments and worked on measurement reproducibility. Although Boillat et al., 2023 stressed anatomical modelling and validations, the extension by Ibrahim et al. (2022) was more relevant for the validation of measurement reproducibility. Yet again, these studies did not have direct applications to the clinical arena.

Bonser et al. (2000) and Suh et al. (2014) investigated biomechanical determinants of aneurysm formation. Bonser et al. (2000) focused on the thrombus's role in increasing the size of an aneurysm, whereas Suh et al. (2014) looked into the impact of respiratory wall shear stress on aortic geometry. The two studies investigated two different mechanisms, so their contributions were complementary rather than duplicative.

Eleshra et al. (2021) and Salmasi et al. (2022) discussed clinical and surgical implications of variations of the aortic arch. Eleshra et al. (2021) proved that F/B-EVAR in TAAAs with renovisceral variations is feasible with low morbidity rates. Salmasi et al. (2021) discussed structural vulnerabilities such as the risks of aortic dissection along the outer curve of the aorta and provided distinct surgical and structural points of view.

Ikeno et al. (2019) investigated the association between anatomical variations, like the bovine arch, and aneurysm risk. Their clinical population-based study supplemented Bonser et al.'s (2000) mechanistic approach with risk quantification related to certain anatomical variations.

Imaging modalities available for aortic arch anomalies include barium oesophagrams, echocardiography, CT angiography, MRI, and catheter angiography (Stojanovska et al., 2012). Although older techniques like barium oesophagrams and catheter angiography have limited utility due to 2D imaging and complexity in paediatric settings (Leonardi et al., 2015; Mądry et al., 2019), advanced modalities like CT angiography and MRI provide detailed anatomical evaluation. CT angiography is especially useful because it provides 3D reconstructions that improve spatial understanding and enables assessments of tracheal and oesophageal integrity (Lee et al., 2004; Türkvatan et al., 2009). Recent advancements have reduced radiation exposure and acquisition time, making these methods safer for paediatric patients, though concerns about radiation and contrast agents remain (Lim et al 2016; Ramos-Duran et al., 2012).

Our review reveals findings both in concurrence and conflict with the those reported by other reviews (Mantri et al., 2022; Bae et al., 2022; Açar, et al., 2022; Ahmad et al., 2023). In terms of similarities, both our review and the studies by Mantri et al. (2022) and Bae et al. (2022) emphasized the clinical importance of recognizing aortic arch anomalies, particularly in procedural contexts such as endovascular and neurointerventional approaches. Mantri et al. (2022) presented these differences and the complications they may present during neurointerventional procedures, aneurysm formation included, which aligns with our results wherein such differences as the bovine arch may be linked to a higher chance of proximal aneurysms. Bae et al. (2022) also found it helpful for the use of multidetector CT in determining an accurate diagnosis and classification of this variation, which is consistent with our conclusion that both CT and MRI were needed in order to achieve high-resolution imaging and risk assessment.

For instance, anatomical variations were much more qualitatively represented in the scope and implications derived from the variations. In fact, as opposed to this, while Açar et al. (2022) were concerned with the prevalence and classification of the variants of aortic arches in a large sample, as they uncovered the wide range of variation, including left-sided aortic arches with multiple subtypes, they did not strictly correlate these with aneurysm risk as we have done in our analysis. Our review provided more detailed information for specific types, like the bovine arch and aberrant subclavian artery, associated with aneurysm rupture locations, while Açar et al. (2022) relied on morphological classification primarily to justify surgical interventions instead of risk outcome evaluation.

Ahmad et al. (2023) found that their results partially agreed with the conclusion made by our endovascular repair methods. According to the meta-analysis by Ahmad et al. (2023), endovascular repair approaches to treat complex aortic arch pathologies have yielded high technical success rates and low early endoleak rates. This is compared to our findings on the successful use of F/B-EVAR in cases involving renovisceral arterial variations, showing low morbidity and mortality though our review did not focus much on endovascular techniques as the primary treatment outcome. Furthermore, whereas Ahmad et al. (2023) reported among others stroke rates and mortality, our systematic review was more concerned with implications to anatomical variation than with the outcomes of the specific procedure.

Limitations

Several limitations in this study are recognized that may influence interpretation and generalizability. For many of the reviewed studies, there was substantial heterogeneity in terms of the study design, sample size, and diagnostic modalities, and possibly affected the consistency of associations observed. Other variability was in the anatomical variations assessed, and differences in the follow-up periods that may have contributed to inconsistencies in the findings. Mechanisms about animal studies are thus rich, but their use directly as findings in human clinical cases cannot readily be translated. Additionally, the exclusion of articles due to restricted access, language barriers, or lack of availability of full texts is a notable limitation, as these studies might have provided relevant data that could influence the overall findings. Publication bias is another potential limitation, as studies with negative or non-significant results may have been less likely to be published or included, potentially skewing the results towards positive associations. Together, these factors emphasize the need for cautious interpretation of the results and underline the inherent challenges in conducting systematic reviews in this specialized area.

Clinical recommendations

The risk for aneurysm has been established with anatomical variations in the aortic arch recently across a number of investigations. With such findings, clinicians are thus motivated to include previous evaluations with high-resolution imaging when assessing patients predisposed to complications through vascular paths to identify any at-risk anatomical pattern. Future studies should try to standardize the diagnostic criteria, the methods of imaging, as well as confounding variables for improvements in between study comparability. That would then enable validation of larger cohort longitudinal studies for the predictive value of these anatomical variations for aneurysm risk. In addition, biomechanical studies in terms of wall stress and flow dynamics may ultimately improve understanding and underpinning and guide personalized intervention strategy in those individuals with at-risk aortic arch morphologies.

CONCLUSION

With the anatomical variations of the aortic arch, in the forms of bovine arch and aberrant subclavian artery, the risk of aneurysm formation increased as per our findings. As seen in this current review, other hemodynamic and morphological differences were found within the aortic arch due to these variations, thereby predisposing the individual to aneurysm formation and progress. Although such associations found were consistent, anatomical variability and differences in methodology among the studies point to a need for further work to determine whether such associations could be taken to the higher level of clinical relevance.

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