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REVIEW

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Aortic arch variant with a common origin of the innominate and left carotid artery as a determinant of thoracic aortic disease: a systematic review and meta-analysis

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Key question

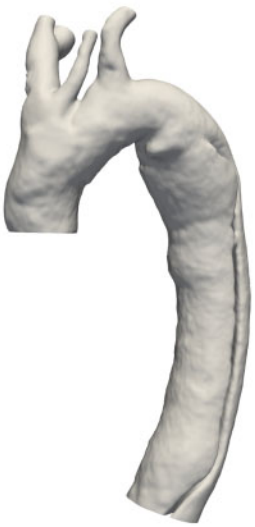
Is the 'bovine' arch variant associated with an increased risk for the development of thoracic aortic disease?

Key findings

This study indicates a correlation between the presence of 'bovine' arch and the onset of aortic disease.

Take-home message

The 'bovine' arch should be recognized as a risk factor for thoracic aortic disease and should be consistently cited in radiological reports.



Type B dissection in aortic arch variant with a common origin of the innominate and left carotid artery

Summary

The aim of this study was to investigate whether the 'bovine' arch [i.e. arch variant with a common origin of the innominate and left carotid artery (CILCA)] is associated with an increased risk of thoracic aortic disease (TAD). The study was conducted according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed, EMBASE and Cochrane databases were searched to identify all case series reporting about CILCA arch and TAD between January 2008 and December 2018. A total of 485 studies were screened. The prevalence of CILCA arch was assessed, and data analysis was performed considering the difference in the risk of TAD for presence versus absence of CILCA arch. Eight studies enrolling 11 381 subjects were retrieved for quantitative analysis. The proportion of TAD among CILCA arch patients was higher [41.5% (28.1–56.4)] than the proportion among patients with standard arch configuration 34.0% (20.1–51.4). The odds ratio of developing TAD was 1.4 times higher in subjects with CILCA arch (95% confidence interval 1.068–1.839). The test for an overall effect indicated a significant association between CILCA arch and TAD ($P < 0.015$). The I^2 was 78.1% with a value of $P < 0.001$ for heterogeneity. The Egger test did not show evidence of publication bias ($P = 0.317$). In conclusion, our meta-analysis supports the hypothesis of a correlation between the presence of CILCA arch and the onset of TAD. Our results warrant a specific and long-term surveillance for patients with this anatomical variant, and a thorough awareness of its potential clinical implications during image interpretation.

Keywords: Aortic arch • Common origin of the innominate and left carotid artery • Bovine arch • Thoracic aortic disease

ABBREVIATIONS

CI	Confidence interval
CILCA	Common origin of the innominate and left carotid artery
OR	Odds ratio
TAD	Thoracic aortic disease
TEVAR	Thoracic endovascular aortic repair

INTRODUCTION

The aortic arch with a common origin of the innominate and left carotid artery (CILCA) is commonly known, and thus far reported in the literature, as the misnomer 'bovine arch' [1]. It represents the second most common arch configuration in the population following the standard pattern that consists in a brachiocephalic trunk, a left common carotid and a left subclavian artery originating from the aortic arch [2]. A less common variant, defined as 'type 2 bovine arch' [3], occurs when the left common carotid artery originates directly from the innominate artery rather than as a common trunk (Fig. 1).

The prevalence of the CILCA arch in the general population is 13.6%, with relevant difference among ethnicities, being more frequent in African populations (i.e. 26.8%) and less frequent in Asiatic populations (i.e. 7.5%) [2]. The real prevalence of this configuration, however, is likely to be underestimated, being CILCA arch largely unreported in radiological studies [4, 5] because of the presumed negligible consequences of this finding.

The clinical relevance of the CILCA arch has become apparent in planning surgical and endovascular procedures involving the aortic arch [6, 7]. Its reputation as a benign anatomical variant has been ultimately shattered by further studies [3, 4, 8, 9] that identified the CILCA arch as a potential marker for thoracic aortic disease (TAD). In fact, controversial data are available regarding the association between a CILCA arch and a TAD [10, 11], and the prognostic value of this configuration remains to be established [10]. Also, the mechanisms potentially underlying the development of TAD in subjects with a CILCA arch represent a largely unaddressed issue [9].

The aim of this work was to perform a systematic review of the literature on the association between CILCA arch and TAD, and assess the value of this anatomical variant as a determinant of pathological derangements of the aortic wall.

METHODS

Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] (Fig. 2). The Medline, EMBASE and the Cochrane medical literature databases were searched to identify observational studies in which the outcomes 'bovine aortic arch' (solely or within a group of other arch variants) and 'thoracic aortic disease' (represented by thoracic aortic aneurysms and/or thoracic aortic dissections) were assessed. Studies investigating the association between TAD and CILCA arch were eligible for inclusion.

The review included manuscripts published between January 2008 and December 2018, and was performed using the following search string: ('Bovine Aortic Arch' OR 'Bovine Arch' OR 'Arch Anomaly' OR 'Arch Variant' OR 'Arch Anatomy') AND ('Thoracic Aortic Disease' OR 'Aneurysm' OR 'Dissection'). The reference lists of reviews, meta-analysis and thesis statements were searched manually to retrieve additional publications.

Study selection

Two authors independently screened titles and abstracts of all publications (485 manuscripts), and performed the selection of studies and data extraction. In the case of disagreements, the final decision was reached by consensus meetings. All eligible studies were included regardless of geographical and racial background of the study population. The exclusion criteria of the study included language other than English, reviews, letters,

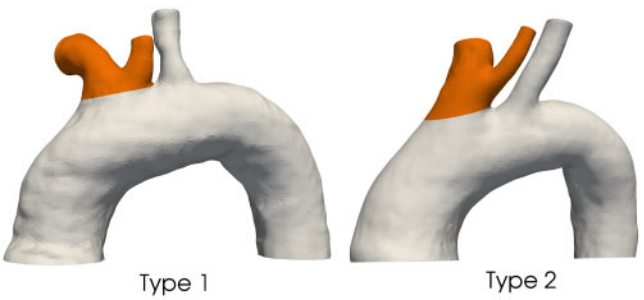


Figure 1: Anatomical configurations of the common origin of the innominate and left carotid artery arch: type 1 and type 2.

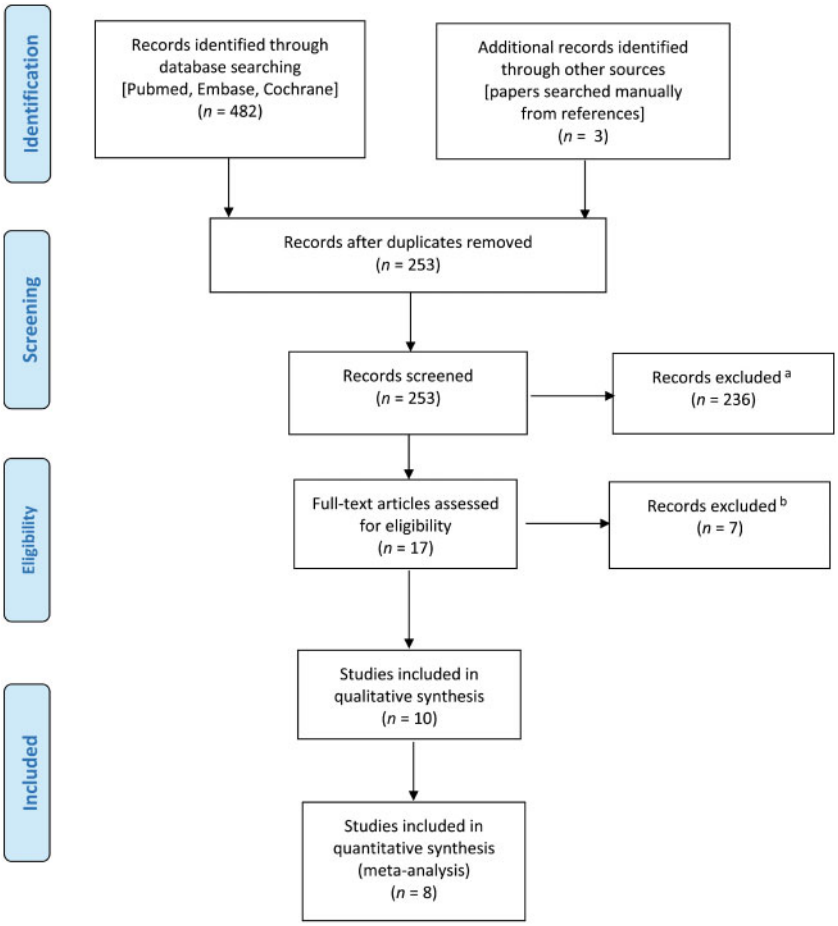


Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) chart. [a]Text not in English, reviews, commentaries, case reports, studies exclusively reporting other arch anomalies, studies exclusively reporting interventional and surgical implications of common origin of the innominate and left carotid artery. [b]Common origin of the innominate and left carotid artery prevalence in thoracic aortic disease was not analysed, lacking outcome of interest, insufficient or unextractable data.

commentaries, case reports and non-original articles, duplicates, reports on bovine arch merely focusing on other outcomes, insufficient or unextractable data.

Statistical analysis

The Comprehensive Meta-Analysis statistical software version 3.3 (Biostat Inc., Englewood, NJ, USA) was used to explore the association of CILCA arch (i.e. presence/absence) with the development of TAD using odds ratios (ORs).

The heterogeneity of the included studies was evaluated by the χ^2 test on Cochrane's Q statistic and quantified by the I^2 statistic. I^2 values of 25%, 50% and 75% were considered as representing low, medium and high heterogeneity, respectively [13].

Considering the heterogeneity in patient populations of the different studies, the random-effects model was used as the model of choice. The combined ORs and the corresponding 95% confidence intervals (CIs) were calculated and reported in the Forest plot. The risk of potential publication bias was evaluated by visually inspecting the Funnel plot and performing the Egger test [14].

The pooled proportion of TAD among patients with and without CILCA arch with the respective 95% CIs was calculated using a proportion meta-analysis random-effects model.

Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Ten manuscripts [3, 4, 8–11, 15–18] were retrieved for qualitative analysis. Three studies reported on the same case series from the Yale University [4, 16, 18], and therefore only one of these [16] was included in the meta-analysis.

Among the type of aortic disease, 1 study included only aortic aneurysm [8], 4 studies [3, 4, 16, 17] reported both on aneurysm and dissections, and 2 of them included also aortic rupture and intramural haematoma [4, 16], and 5 focused only on dissections [9–11, 15, 18].

Anatomical subvariants type 1 and type 2 CILCA were considered only in 2 studies [3, 10], and one of them reported a prevalence of type 2 CILCA in patients with TAD [3].

Two manuscripts from the same group [4, 16] reported an earlier onset of TAD in CILCA arch patients, who also underwent initial aortic operation at a younger age, compared to patients without CILCA, and were less frequently affected with cardiovascular risk factors, like hypertension. Also, the presence of a bicuspid valve, which is well-established to be associated with ascending aortopathy and often coexists with the CILCA arch,

Table 1: Eligible studies and their descriptive characteristics

Authors	Country	Patients with CILCA/TAD (%)	Age	Gender M/F (%)	Type of TAD	Type I/type II CILCA in TAD (%)
Malone *et al.* [8]	USA	50/191 (26.2)	69 ± 13	129/62 (67.5)	Aneurysm	NA
Wanamaker *et al.* [15]	USA	54/176 (31)	68 ± 14	104/72 (41)	Type A (66) and type B (110) dissections	NA
Dumfarth *et al.* [16]	USA	137/556 (24.6)	59 ± 14	86/51 (62.7)	Aneurysm (432) Type A (96) and B (23) dissections IMH (2) Aortic rupture (3)	NA
Tapia *et al.* [11]	China	62/525 (11.8)	52 ± 14	374/151 (71.2)	Type A (174) and type B (351) dissections	NA
Moorehead *et al.* [3]	USA	55/156 (35.3)	69 ± 1	97/59 (62.6)	Aneurysm (130) Type A and B dissections (26)	18 (11.5) 37 (23.7)
Ikeno *et al.* [17]	Japan	82/815 (10)	72 ± 11	529/286 (65)	Aneurysm (416) Type A (321) and type B (90) dissections[a]	NA
Mylonas *et al.* [10]	Germany	57/322 (17.8)	59 ± 13	99/55 (64.3)	Type A (154) and type B (168) dissections	NA
Shalhub *et al.* [9]	USA and Ireland	62/185 (33.5)	58 ± 12.4	134/51 (72.4)	Type B dissection	NA

[a]Twelve cases with both aneurysm and dissection.

CILCA: common origin of the innominate and left carotid artery; F: female; IMH: intramural haematoma; M: male; NA: not available; TAD: thoracic aortic disease.

Table 2: Events considered for risk of developing thoracic aortic disease in CILCA versus non-CILCA arch

	CILCA aortic arch		Non-CILCA aortic arch	
Authors	Events	Total	Events	Total
Malone *et al.* [8]	50	130	141	452
Wanamaker *et al.* [15]	54	81	122	274
Dumfarth *et al.* [16]	137	783	419	4390
Tapia *et al.* [11]	62	139	463	911
Moorehead *et al.* [3]	55	288	101	625
Ikeno *et al.* [17]	82	217	733	2107
Mylonas *et al.* [10]	57	76	265	356
Shalhub *et al.* [9]	62	138	123	414
Total	559	1852	2367	9529

CILCA: common origin of the innominate and left carotid artery.

was not found to be a confounding factor for the association between CILCA arch and TAD in the same studies ($P = 0.72$ and $P = 0.119$, respectively) [4, 16].

Regarding the location of the aortic disease, the arch was found to be the most common site for both aneurysm development ($P = 0.003$) [8], and entry tears formation in dissections [18, 19] ($P = 0.043$ and $P < 0.001$, respectively).

Finally, from a prognostic point of view, CILCA arch was found to be associated with an increased risk of mortality [10], and adverse neurological events in patients with aortic dissections [18, 19].

Eight studies [3, 8–11, 15–17] reported adequate information for the quantitative analysis, and their characteristics are reported in Table 1. The number of events considered for evaluating the risk difference of developing TAD in CILCA versus non-CILCA arches is reported in Table 2.

The proportion of TAD among patients with CILCA arch was higher [41.5% (28.1–56.4)] than the proportion in subjects with standard arch configuration [34.0% (20.1–51.4)].

The Forest plot is reported in Fig. 3. The I^2 was 78.1% with P-value <0.001 for heterogeneity.

The OR of developing TAD was 1.4 times higher in subjects with a CILCA arch (OR 1.40, 95% CI 1.068–1.839; $P < 0.015$).

The Egger test did not show evidence of publication bias ($P = 0.317$). The Funnel plot of the included studies is reported in Fig. 4.

DISCUSSION

Our work provides evidence to identify the CILCA arch variant as a risk factor for the development of TAD. Hence, our findings warrant a heightened awareness of the predictive relevance of this anatomical variant, which mandates a consistent citation of the presence of a CILCA arch in diagnostic imaging reports [4]. Also, a specific surveillance protocol should be established for patients presenting with a CILCA arch, in order to possibly prevent the development of TAD complications in a timely manner [16]. In this respect, the suggested prognostic value of this anatomical configuration [10, 18, 19] may dictate a specific treatment algorithm in patients with aortic dissections [9], and an early treatment in patients with aortic aneurysm [8], as for subjects with connective tissue disorders.

The predisposing mechanism by which a CILCA arch is prone to TAD development remains to be identified, and deserves further studies. Current pathophysiological hypotheses include genetical defects (i.e. deletion in chromosome 22q11) [20], embryological derangements [21] and ill-defined haemodynamic mechanisms [9, 15, 22].

Specifically, it was proposed that the aortic wall may be weaken as a result of congenital structural defects [20] or altered neural cell migration [21], but more recent histological studies failed to find any relevant mechanical and failure properties that may entail an increased risk of aortic rupture in CILCA arch [23, 24].

According to another hypothesis, the relatively greater diameter of the arch vessels may alter the local flow haemodynamics, leading to an increased wall shear stress, with the inherent detrimental effects on the aortic wall [9, 15]. In fact, it is likely that other peculiar geometric features of the CILCA arch, consistent with other anatomical configurations particularly prevalent in patients with TAD [25], entail a local biomechanical environment that adversely affects the aortic wall properties and its integrity. Yet, the pathophysiological mechanisms underlying the onset of aneurysm and dissections are different, and the proposed

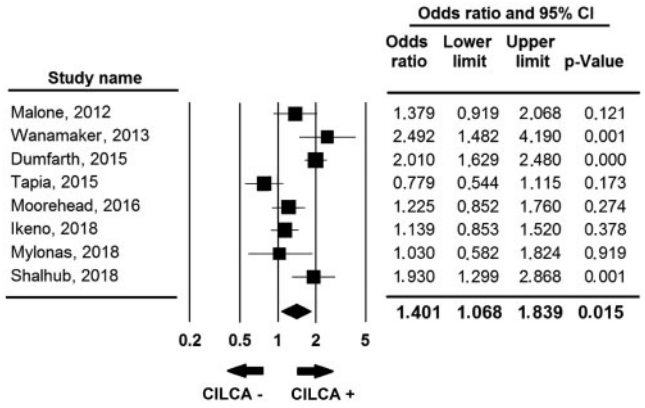


Figure 3: Forest plots of odds ratios for the association between the presence of the CILCA arch and the risk of developing thoracic aortic disease. The box size, which is proportional to study sample size, shows the point estimate; diamond, summary estimate; the horizontal lines indicate the 95% CI. CI: confidence interval; CILCA: common origin of the innominate and left carotid artery.

hypotheses do not account for the development of either one or the other.

The high prevalence of CILCA arch in subjects with TAD also implies that a considerable number of patients requiring thoracic endovascular aortic repair (TEVAR) present with this peculiar anatomical configuration. Notably, different studies reported a trend towards an increased risk of post-TEVAR mortality [9, 10] and complications, namely retrograde dissection [9, 26], in patients with CILCA arch. Hence, specific studies on the impact of the CICLA configuration on TEVAR planning appear warranted.

Finally, the matter of the nomenclature of the CILCA arch remains, in our opinion, an incompletely resolved issue. The recent STORAGE guidelines [1] recommend abandoning the term 'bovine', and suggest the use of a descriptive terminology. This approach, however, on one hand appears unpractical in scientific reports, considering the word count restraints adopted by peer-reviewed journals, and particularly for titles and abstracts. On the other hand, it may hamper the establishment of the CILCA arch as a specific anatomical configuration with a peculiar prognostic relevance, and jeopardize the desired consistency in scientific citation.

Limitations

We recognized some limitations of our study, including those inherent to the retrospective fashion of the retrieved studies. Also, TADs were considered altogether, reflecting the approach of the majority of the included series, even though aneurysms and dissections have different pathophysiological mechanisms. Finally, the diverse racial background of the considered cohorts of subjects may have led to estimation bias, considering the different prevalence of CILCA among ethnicities [2].

CONCLUSIONS

The CILCA arch should be regarded as an anatomical marker for the risk of developing TAD. Further studies are warranted to investigate the peculiar biomechanical patterns associated with this arch variant, which may represent the pathophysiological link to clinical sequelae.

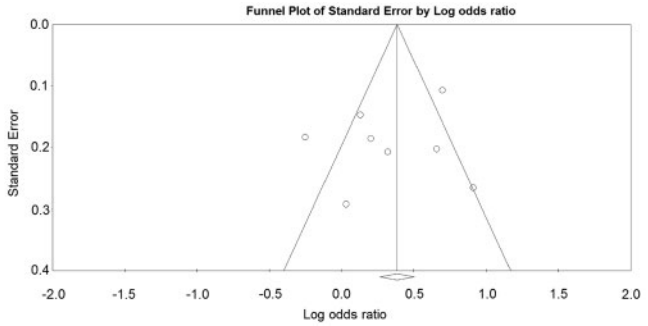


Figure 4: Funnel plot of standard error of risk difference of developing thoracic aortic disease for presence versus absence of common origin of the innominate and left carotid artery arch.

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Conflict of interest: none declared.

Author contributions

Massimiliano M. Marrocco-Trischitta: conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; writing—original draft. **Moad Alaidroos:** data curation; formal analysis; investigation; writing—original draft. **Rodrigo M. Romarowski:** data curation; formal analysis; investigation; writing—original draft. **Valentina Milani:** data curation; formal analysis; methodology; writing—original draft. **Federico Ambrogi:** data curation; formal analysis; methodology; writing—review & editing. **Francesco Secchi:** data curation; formal analysis; investigation; supervision; writing—review & editing. **Mattia Glauber:** data curation; formal analysis; supervision; writing—review & editing. **Giovanni Nano:** data curation; formal analysis; supervision; writing—review & editing.

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