January 2011

Bovine Aortic Arch: A Marker For The Development And Progression Of Thoracic Aortic Disease

Matthew Alan Hornick
Yale School of Medicine, hornick.m@gmail.com

Bovine Aortic Arch: A Marker for the Development and Progression of Thoracic Aortic Disease

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor in Medicine

by

Matthew Alan Hornick

2011

BOVINE AORTIC ARCH: A MARKER FOR THE DEVELOPMENT AND PROGRESSION OF THORACIC AORTIC DISEASE. Matthew Hornick, Remo Moomiaie, Hamid Mojibian, Esther. S. Lee, John A. Rizzo, Maryann Tranquilli, and John A. Elefteriades. Section of Cardiac Surgery, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

This study investigated the relationship between congenital bovine arch (BA) variant and thoracic aortic aneurysm (TAA), thoracic aortic expansion rate, bicuspid aortic valve (BAV), and aortic complications. We hypothesized that BA would be significantly associated with the presence and progression of thoracic aortic disease.

To determine prevalence of BA, we retrospectively reviewed thoracic CT and/or MRI scans of 616 patients with thoracic aortic disease and 844 patients without thoracic aortic disease (all from Yale-New Haven Hospital). In patients with thoracic aortic disease, we assessed accuracy of official radiology reports in citing BA, and reviewed all available hospital records to determine disease location, thoracic aortic growth rate, presence of bicuspid aortic valve (BAV), and prevalence of thoracic aortic dissection and rupture in patients with and without BA.

BA was observed in 26.1% of patients with thoracic aortic disease and 16.4% of patients without thoracic aortic disease ($P<0.001$). Radiology reports cited BA in only 16.1% of patients with aortic disease and concomitant BA. There was no association between BA and location of aortic disease, prevalence of dissection ($P=0.39$), or presence of BAV ($P=0.68$). Rate of aortic expansion was 0.29 cm/year in the BA group and 0.09 cm/year in the non-BA group ($P=0.003$). Mean age at initial aortic repair was 56.2 years in BA patients and 61.4 years in non-BA patients ($P=0.0004$).

Our findings suggest that BA is indeed associated with both the development and progression of thoracic aortic disease, and support the following conclusions: 1) BA is significantly more common in patients with thoracic aortic disease than in the general population. 2) Radiologists often overlook BA. 3) BA is not significantly associated with BAV, aortic dissection, or disease at any particular location within the thoracic aorta. 4) BA is associated with elevated TAA growth rate and earlier repair.

Acknowledgements:

I owe several toasts to the many fantastic people who have contributed to this thesis, and without whom this project would not have been possible. To Dr. Remo Moomiaie, for recruiting me when this study was still in its infancy. To Dr. Mojibian, for generously spending countless hours reviewing hundreds upon hundreds of aortic arches. To Esther Lee, for providing all of the raw control data, and for carrying out the necessary randomization procedure. To Dr. Rizzo, for providing unmatched statistical expertise. To Abdullah Zafar for helping review echocardiography reports. To Alex Baker for your elegant illustrations of the bovine arch. To everyone in the Section of Cardiac Surgery, and especially to Maryann Babcock, Marianne McCarthy, and Lorena Capone, for your incredible kindness and patience. To Dr. Griepp for your input regarding the bovine arch misnomer and your encouragement to re-name the variant. And to Dr. Geibel and the Yale Department of Surgery for your consistent support.

To Dr. E – you are a fantastic surgeon and researcher, a dedicated caregiver, and a true role model in every sense of the word. You have been and you always will be a tremendous inspiration behind my own pursuit of a career in surgery, and I cannot thank you enough for your mentorship.

And of course, to Terri – forever the arch to my aorta.

Table of Contents

INTRODUCTION

Bovine Aortic Arch

"Bovine arch" (BA) refers to a group of congenital variants of the great vessels of the aorta in which there is aberrant origin of the left common carotid artery. In the most frequently observed bovine arch variant in humans, there is a common origin of the left common carotid and innominate arteries, such that the left common carotid and innominate branches arise from the same trunk (Fig. 1). In a less frequent variant, the left common carotid artery originates from the innominate artery proper, such that there is distance along the innominate artery between the aorta and the origin of the left common carotid (Fig. 1) [1,2]. For purposes of this study, we will refer to the former configuration as type 1 BA, and the latter configuration as type 2 BA. Both configurations are typically classified under the general heading "bovine arch" [1].

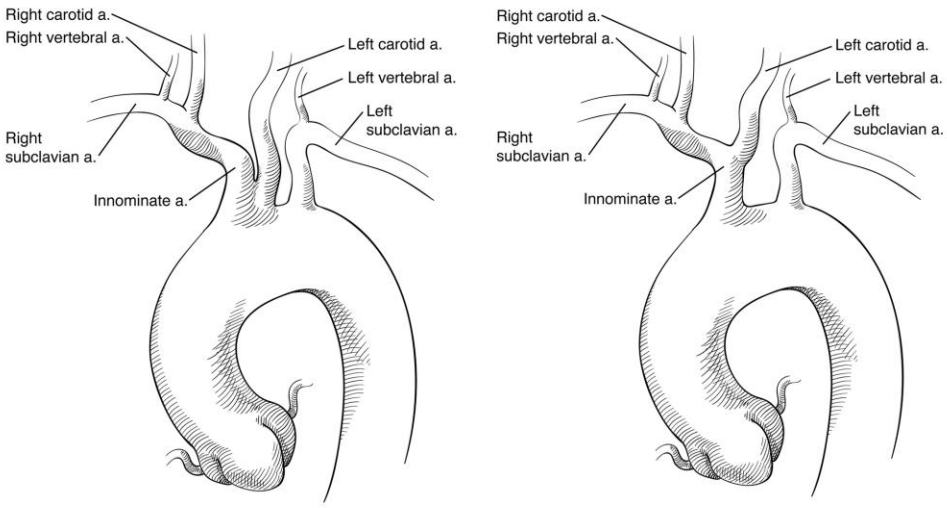


Figure 1. Anatomic configurations of "bovine arch" in humans (type 1 BA on L, type 2 BA on R)

Nomenclature

There is much speculation as to the origin of the "bovine" designation, since it is, in fact, a misnomer – a true BA, that is, what is observed in bovine species, consists of a single root branching from the aortic arch from which all four great vessels (right subclavian, right common carotid, left common carotid, left subclavian) originate [1]. Some have postulated that this anatomically incorrect designation stems from the resemblance of the human variant branching pattern to the appearance of cattle horns [3]. Others have proposed re-naming the variant altogether – Elster suggests "canine, feline, or lapine arch" in light of the similarity of the human branching pattern to the aortic arch of dog, cat, and rabbit species [4]. Berko proposes "simian arch" due to the biologic similarities between humans and monkeys, and the frequent use of simian models when studying human physiology [5,6]. Despite considerable controversy, the misnomer "bovine arch" has endured to this point.

BA Prevalence in the General Population

Dating back to the mid-1800s, several autopsy studies and thoracic imaging reviews have sought to determine the prevalence of BA (and other variant branching patterns) in the general population, with great variability in sample size and results. Estimates of BA prevalence have ranged from 1% to 27.4% over the last century [7-20], and from 8.7% to 27.4% in two large computed tomographic angiography (CTA) series published during the last two years alone [17,20]. Type 1 BA is generally regarded as the more common anatomic sub-variant, with reported prevalence typically about twice as high as type 2 BA (average estimates hover around 10% and 5%, respectively, in the general population) [2]. As mentioned, however, extremely disparate findings have been published in studies of different types and sizes.

Clinical Significance of BA

While the true prevalence of BA in humans has been a topic of interest and speculation, to date there is a paucity of literature specifically addressing clinical implications of the presence of BA in patients. Historically, BA has been regarded as a "normal," clinically insignificant anatomic variant, often incidentally discovered on thoracic imaging studies or during thoracic surgery. BA has been a particularly frequent finding in patients undergoing aortic and aortic arch vessel interventions, but few authors have gone so far as to suggest an association between BA and thoracic aortic disease [21-32].

BA and Aortic Catheterization

BA seems to be associated with technical failure and neurological complications in carotid stenting procedures, but this reflects the challenge of traversing variant anatomy with a catheter rather than the natural history of the BA aorta itself [21-24]. Although percutaneous carotid revascularization is typically performed via the femoral approach, the presence of BA increases the technical complexity of this technique. Accessing the left common carotid from the femoral vessels in the context of BA requires increased catheter flexibility, and risks perforating the common trunk [21,22]. Several reports recommend an alternative approach, either via the right radial or brachial artery, to safely stent the left common carotid in patients with BA anatomy [21-24].

BA in Blunt Chest Trauma

Multiple case reports highlight a potential association between BA and traumatic vascular injury [25-30]. Innominate artery rupture (at its takeoff from the aortic arch) is the most common traumatic injury involving the aorta and great vessels, and BA seems to be associated with an increased likelihood of innominate transection [25]. One retrospective study of patients who experienced blunt chest trauma found that 29% of patients with bovine arch sustained injury to

the common trunk, compared to 11% of patients without bovine arch [25]. In the context of chest trauma, BA – with two great vessels stabilizing the aorta instead of three – may predispose to increased motion of the aortic arch at the time of sudden deceleration, with consequent sternal compression of arch vessels contributing to "traumatic avulsion" [25]. Others have noted how physical principles of arch anatomy dovetail these clinical findings. Specifically, the common trunk is essentially a fixation point that is nearly perpendicular to the aortic arch, origin of left common carotid, and left subclavian artery. This orientation of attachments maximizes tension at the common trunk, thereby predisposing to injury at this site when these attachments are in motion (as in acute deceleration) [26]. The observed association between BA and traumatic injury of the aorta and great vessels is thought to be purely mechanical in nature, and specific to the setting of trauma, rather than a reflection of the natural history of these vessels in the presence of the variant.

BA in Aortic Arch Procedures

BA has also been reported as an incidental finding in patients with atraumatic aortic disease. Type 2 BA variant appears to facilitate bilateral selective antegrade cerebral perfusion, a technique employed in aortic arch operations requiring deep hypothermic circulatory arrest [31,32]. Typically this mode of cerebral perfusion involves right axillary artery cannulation to perfuse the right common carotid artery (with proximal clamping of the innominate) and direct cannulation of the left common carotid to ensure bilateral cerebral blood supply. Several reports suggest the relative ease of bilateral cerebral perfusion when the left common carotid artery arises directly from the innominate artery (type 2 BA). Provided that there is adequate distance along the common trunk between the aorta and the takeoff of the left common carotid to clamp proximally on the common trunk, perfusion through a right axillary cannula then perfuses both common carotid arteries without the need for left carotid cannulation (which is a risk factor for dissection and rupture) [31,32]. All such reports attesting to the utility of BA in aortic arch

procedures imply an association between BA and aortic disease, but this possibility has yet to be explored in depth.

BA Prevalence in Turner's Syndrome

BA has been reported with increased frequency in studies investigating anatomic correlates of Turner's syndrome, an inherited condition resulting from X monosomy or XX mosaicism (45,X or 45,X/46,XX, respectively) that predisposes to aortopathy. Abnormalities of the heart and great vessels are detected in nearly 50% of all women with Turner's, with BAV, aortic coarctation, and elongated transverse arch particularly common in this population [33]. A prospective MRI study comparing prevalence of arterial anomalies in women with and without Turner's syndrome found a 28.6% BA prevalence in the Turner's group (98 patients) compared to a 12.1% BA prevalence in the control group (33 patients). Although BA was not significantly associated with ascending aortic aneurysm, the study did not account for longitudinal aortic growth, and the control group was far too young to accurately represent prevalence of aortic disease (mean age 37) [34]. Nonetheless, BA certainly seems to be associated with Turner syndrome, and coexists with BAV and ascending aortic disease in many of these patients.

BA, Valvular Pathology, and Aortic Disease

A small number of reports have hinted at a possible association between BA, bicuspid aortic valve (BAV), and ascending aortic disease in non-Turner's patients, but the literature to support this claim is scant at best. In one of the aforementioned case reports discussing bilateral selective cerebral antegrade perfusion, the authors present a series of three consecutive patients undergoing repair for bicuspid valve and ascending aortic aneurysm who were found to have concomitant BA. They briefly touch upon two possible explanations for this observed overlap between BAV and BA: (1) an "incidental correlation" between bovine arch, bicuspid valve, and ascending aortopathy, or (2) an "anatomic predisposition to a syndrome involving the left

ventricular outflow tract" [31]. While the link between BAV and ascending aortic disease is well-established, the proposed connection between BA and either BAV or ascending disease has yet to be investigated.

Embryology of BA

The precise embryologic events underlying the development of common origin of the innominate and left common carotid arteries remain incompletely understood. However, several studies suggest that the aortic cusps, left ventricular outflow tract, and the arterial media of ascending aorta, aortic arch, and arch vessels (including the innominate and left common carotid) originate from the neural crest, and are thus embryologically linked [35-37]. Given this potential association, it seems entirely plausible that BA (a variant of great vessel morphology) might be associated with both BAV (a disorder of the aortic cusps) and ascending aortopathy (a disorder of the aortic media).

In summary, a small number of case reports and a few studies of aortic anatomy in patients with Turner's syndrome hint at a possible link between congenital BA variant and later development of aortopathy. Clinicians within our own group have noted in general terms that BA is relatively common in patients with thoracic aortic aneurysm (TAA)—BA is frequently observed intraoperatively in patients undergoing TAA repair or replacement. To date, however, no large study has thoroughly investigated the potential association between BA and thoracic aortic disease.

Clinical Aspects of Thoracic Aortic Disease

Aortic Anatomy

The human aorta consists of three layers: intima on the luminal aspect, media internally, and adventitia externally. The media consists of elastin and collagen fibers, smooth muscle cells,

and an amorphous ground substance rich in polysaccharides, and is particularly relevant to aortic disease since it confers elasticity and hence resistance to dilatation [38]. Medial components are organized in discrete units called lamellae, with a relatively fixed distribution of lamellae in particular portions of the aorta. Specifically, the ascending aorta (35-46 lamellae) contains a higher number and a higher density of lamellae than the descending aorta (25-28 lamellae) [39].

Physics of the Aorta

From a mechanical perspective, the aorta is a tubular vessel through which pressurized pulsatile blood flows, and hence is subject to basic physical principles. Laplace's law states that wall tension within such a vessel is directly proportional to both the pressure of fluid within the vessel and the diameter of the vessel, while wall thickness and elasticity absorb radial force and effectively temper wall tension [40]. To validate the clinical relevance of Laplace's law, Okamoto et al. used aortic tissue models to demonstrate that aortic wall stress increases linearly with diameter and systolic blood pressure [41].

Definition, Classification, and Demographics of TAA

While the precise size criterion for defining aortic aneurysm remains a topic of debate, a thoracic aorta with a diameter greater than 4.0 cm is typically recognized as abnormal. Aneurysms come in two distinct morphologic varieties – fusiform, which is a dilatation of the entire circumference of the aorta, and saccular, which is an abnormal outpouching of only a portion of the vessel's circumference. Aneurysms occur in all regions of the thoracic aorta, and may be classified on this basis as well – aneurysms of the descending thoracic and thoracoabdominal aorta, for example, are more prevalent than aneurysms of the ascending aorta and aortic arch [39]. The incidence of thoracic aortic aneurysm is thought to be 6 per 100,000 people per year [42], affecting men and women roughly equally but presenting earlier in men (on average, men present in their early 60s, while women present in their mid- to late-70s) [43]. Most

TAAs are asymptomatic, and are discovered incidentally on thoracic imaging obtained for other reasons.

Because many diseased aortas escape detection until after catastrophic complications take place, thoracic aortic disease is frequently lethal. A recent CDC estimate cites aortic disease as the 17th most common cause of death in all individuals and the 15th most common cause of death in individuals over age 65 [44], despite improved methods of detection and treatment. Deaths most often occur secondary to aortic dissection or rupture, acute events that typically arise in the setting of progressive aortic dilatation. Patients with untreated TAAs demonstrate an extremely high risk of eventual complication, with aortic rupture causing death approximately 50% of the time [45].

Aortic Dissection: Definition

In "classic" aortic dissection, an intimal tear allows pressurized blood to enter the aortic wall, which then propagates through a split, or "dissected," medial layer. This splitting of layers establishes two distinct lumens for blood flow, denoted true (referring to the vessel's original lumen) and false (referring to the lumen created by the intimal tear). The Stanford system classifies thoracic aortic dissection according to the location of intimal disruption: type A dissection originates in the ascending aorta or arch, and type B dissection originates in the descending aorta. Type A frequently arises just distal to the sinotubular junction, whereas type B classically originates just distal to the takeoff of the L subclavian artery. Both type A and type B dissections very frequently propagate through the full extent of the thoracic (and abdominal) aorta distal to their point of origin [39].

Acute Dissection: Indications for Emergent Repair

Aortic dissection is potentially life-threatening. Splitting renders the aortic wall inherently weaker, since the outer medial and adventitial layers of the dissected aorta, normally

shielded by the full thickness media, are exposed to luminal pressures. In an early natural history study, 77% of patients with untreated dissection ultimately ruptured, presumably owing to compromised aortic wall integrity [45]. Moreover, blood flow may be impaired through one or both lumens in a dissected vessel, which can disrupt perfusion to any of the numerous critical branches originating from the aorta. Dissection may ultimately cause death via four distinct mechanisms: (1) intrapericardial rupture leading to cardiac tamponade; (2) free rupture of descending dissection leading to pleural hemorrhage; (3) acute aortic insufficiency (secondary to dissection through the aortic valve orifice); (4) occlusion of any branch of the aorta, from the coronary arteries to the iliac bifurcation, with distal end-organ malperfusion [39]. It is now common practice to urgently repair all acute type A dissections to prevent devastating valvular complications and/or cardiac tamponade. Operation typically involves completely replacing the intimal flap and dissected ascending aorta with a Dacron graft. Conversely, most uncomplicated type B dissections are managed medically (with anti-hypertensive medications), given the high risk of spinal cord injury and paraplegia in descending aortic operations. Urgent intervention remains warranted if type B dissection leads to acute rupture or branch occlusion with end-organ damage. Patients with type A dissections that extend through the arch and descending aorta typically undergo initial repair or replacement of the ascending segment, with subsequent monitoring of the dissected descending segment [39].

Chronic Dissection and Variants

Not all dissections are lethal, and many patients with subacute type A dissections and uncomplicated type B dissections are managed with anti-hypertensive medications in lieu of immediate surgical repair. Patients who survive acute events develop chronic dissections, in which flow may either persist through both the true and false lumens, or the false lumen may partially or completely thrombose [46]. Variant presentations of dissection include intramural hematoma and penetrating aortic ulcer, both of which tend to be chronic in nature. Intramural

hematoma refers to a circumferential medial hematoma in absence of a detectable intimal flap; its origin is controversial, and may result from classic dissection or from rupture of the vasa vasorum supplying the aortic wall. Penetrating aortic ulcers, which are typically encountered in the setting of severe aortic atherosclerosis, result from erosions into atherosclerotic plaque that ultimately perforate the aortic intima and allow blood to enter the media. Like acute dissection, all variants of chronic dissection weaken the aortic wall, predisposing to accelerated aortic dilatation and ultimately rupture, and thereby require regular imaging follow-up [39].

Indications for TAA Repair

Although acute events do occasionally occur in smaller aortas, the risks of dissection and/or rupture generally rise with increasing aortic diameter. Several database studies by the Yale group and others have delineated the median size at which aneurysmal thoracic aortas dissect or rupture in order to empirically establish criteria for surgical intervention [48-51]. Coady et al. found that dissection and/or rupture strikes at a median diameter of 6.0 cm in ascending aortas and 7.2 cm in descending aortas, and identified these dimensions as specific anatomic "hinge points" beyond which the risk of complication increased sharply – in the ascending aorta, the prevalence of dissection rose by 32.1% at 6.0 cm, and in the descending aorta, the prevalence of dissection rose by 43.0% at 7.0 cm. In order for operation to preempt the vast majority of these complications, the authors recommended a 5.5 cm threshold for repairing ascending aneurysms, and a 6.5 cm threshold for repairing descending aneurysms [48]. To further illustrate this "hinge," a more recent study by the Yale group reported annual risk of dissection or rupture as a function of ascending aortic diameter: 2% per year risk for TAAs < 5.0 cm, 3% per year risk for aneurysms 5.0-5.9 cm, and 7% per year risk for aneurysms ≥ 6.0 cm [51]. The specific size criteria outlined here remain the current standard for operative repair in the majority of patients with thoracic aortic disease. Exceptions do exist – for patients with a concomitant connective tissue disorder (such as Marfan's or Ehlers-Danlos, both of which affect extracellular matrix

proteins in the aortic wall), congenital BAV, or family history of aortic disease, ascending aortic operation is indicated at diameter ≥ 5.0 cm. Other risk factors that may prompt semi-urgent intervention at even smaller diameters include the presence of otherwise unexplained symptoms and/or rapid aneurysm expansion [52,53]. Chronic dissection typically does not influence size criteria for operative repair, although one study found that descending aortic rupture occurred at smaller diameters in patients with chronic type B dissection [54].

Growth Rate in Thoracic Aortic Disease

Previous studies by the Yale group and others have sought to better define the natural history of the pathologic aorta, particularly with respect to rate of diametric growth. Despite significant variation between individual aortas [50], aortic disease is now widely recognized as an indolent process, with aneurysmal aortas growing 0.1 cm/year on average. Several factors have been shown to influence rate of diametric expansion. Location of aneurysm is a particularly important determinant of mean growth rate, with aneurysmal descending thoracic segments expanding 0.1 - 0.2 cm/year more rapidly than ascending segments in most studies [48-51]. Although the precise explanation for this discrepancy is unclear, Elefteriades has postulated that perhaps the higher growth rate reported in descending thoracic aneurysms is attributable to the comparatively lower density of elastic lamellae in this segment of the aorta [48]. The presence of chronic dissection is also associated with increased aortic growth rate, expanding approximately 0.2 cm/year faster than non-dissected segments, and presumably for similar reasons – the adventitial layer contains far fewer elastic lamellae than the medial layer, and in absence of a full thickness media, the aorta tends to dilate rather than recoil [48-51]. Recent studies have illustrated a significant association between growth rate and false lumen patency in the context of chronic dissection, with accelerated aortic expansion observed in descending aortas with patent false lumens [46,47,55]. Diameter of the aorta at any given point in time is another influential variable, since, in accordance with Laplace's law, circumferential wall tension is directly proportional to

the diameter of the vessel [48,50]. Coady et al. found that average annual growth rate varied from 0.10 cm/year in 4.0 cm ascending aneurysms to 0.19 cm/year in 8.0 cm ascending aneurysms, and from 0.28 cm/year in 4.0 cm descending aneurysms to 0.56 cm/year in 8.0 cm descending aneurysms [48]. Bicuspid valve is also known to affect growth rate, as will be discussed.

Growth Rate Measurement

Calculating aortic growth rate presents several technical challenges. Serial aortic imaging is fraught with inconsistencies, owing to the complex shape of the vessel itself, the multitude of imaging modalities used to visualize the aorta, and the inevitable variance between different institutions and different interpreting radiologists. While axial CT and MRI imaging is often used to size the aorta, the image seen in the axial plane is not necessarily perpendicular to the plane of the vessel, and thus does not necessarily represent its true diameter. Given the typical curvature of the ascending aorta, the vast majority of axial slices depict an orthogonal view of much of the ascending segment. Moreover, different scans may portray the same segment from somewhat different perspectives, thereby falsely representing changes in the size of the vessel. Growth rate calculations also assume that interpreting radiologists measure the aorta at exactly the same location over time, which is extremely unlikely in practice. This inter-observer measurement variability only compounds the technical challenges inherent to growth rate calculations [56].

Not surprisingly, estimates of aortic growth rate have varied considerably between studies. Hirose et al. initially utilized an arithmetic calculation – final aortic diameter minus initial diameter, divided by duration between measurements – to determine growth rate of thoracic aortic aneurysms [57]. Their first estimate was relatively high (0.42 cm/year), owing at least in part to their truncation of negative growth rates. Inclusion of negative values is crucial in any aortic growth rate estimation because these serial measurements accurately reflect inter-scan and inter-observer variability. Masuda et al., who found a mean annual growth rate of 0.13 cm/yr, showed that inclusion of negative growth rate values eliminates much of the error associated with

the arithmetic method [58]. Rizzo developed a novel method for calculating growth rate via multivariate regression analysis, based on the premise that aortic growth follows an exponential distribution as a function of aortic size at any particular instant (consistent with Laplace's law and clinical data previously discussed) [59,60]. This approach has generated growth rate estimates that remain widely accepted today—approximately 0.10 cm/year in ascending aneurysms and 0.30 cm/year in descending aneurysms [48].

Mechanisms of Thoracic Aortic Disease

Precise causes of aortic disease are multifold and not yet fully elucidated. The natural history of the aorta is subject to several variables, including gross anatomic structure, progressive tissue remodeling and related congenital predispositions, and mechanical influences affecting circumferential wall stress. Aortic disease reflects a complex interaction of these various contributing factors.

Mechanical Influences

Laplace's law explains several basic principles of aortic expansion. First, hypertension predisposes to aortic dilatation. This has been borne out in the literature, as 60-70% of patients with aneurysm are hypertensive; moreover, studies investigating the precise timing of thoracic aortic dissection identify hypertension in times of physical or emotional stress as an important inciting factor [61-63]. Laplace's law also predicts that aneurysmal disease begets aneurysmal disease, since a larger aorta will be subject to greater wall tension, which will, in turn, predispose to further dilatation (and ultimately dissection or rupture). Several studies have confirmed that aortic expansion follows an exponential distribution [50,51], and this principle now forms the basis of regression analyses used to calculate aortic growth rate [60]. In vivo calculations of ascending aortic wall stress demonstrate how the variables in Laplace's law, namely aortic

diameter and blood pressure, contribute concomitantly to the etiology of aortic complications. Specifically, Koullias et al. showed that when systolic pressure within a 6.0 cm aorta nears 200 mm Hg, aortic wall stress approaches 860 kPa, which exceeds the maximal tensile strength of the vessel and thereby predisposes to dissection or rupture [64]. Hypertension within a "hinge point"-sized aorta is thus potentially catastrophic.

Changes in the constitution of the aortic wall itself render the pathologic aorta all the more vulnerable to mechanical influences. These constitutional changes will be considered at length in the proceeding sections.

Effects of Aging

Aging inevitably results in some degree of aortic dilatation. With chronic exposure to high-pressure luminal blood flow, the constitution of the aortic wall evolves over the lifetime, and progressive remodeling reduces the vessel's inherent distensibility. Several histologic changes are observed in the media of the "normal" aging aorta, including: (1) cystic medial necrosis, characterized by the degradation of elastin and collagen with subsequent pooling of mucoid material; (2) elastin fragmentation, referring to disruption of lamellar units; and (3) fibrosis, which is an increase in collagen at the expense of smooth muscle cells [65,66]. As elastin in the media is degraded and disorganized, the relatively collagenous aorta becomes prone to dilatation with repeat exposure to luminal blood. Age-related structural changes alone, however, cannot ultimately account for the full spectrum of aortic disease, since many individuals never develop clinically significant dilatation or worrisome aneurysms [66].

Ascending Aortopathy

As is the case in aging aortas, tissue specimens from diseased ascending aortas typically exhibit some form of medial degeneration. In pathologic aortas, however, these degenerative medial changes occur earlier and to a greater extent than in normal aging, predisposing to more

radical dilatation (that often presents in younger age groups). Much of our understanding of the pathophysiology of aortic wall degeneration stems from studies of Marfan's syndrome and bicuspid aortic valve (BAV), two conditions that predispose to premature ascending aortic disease [67].

Marfan's-associated ascending aneurysms are related to a congenital deficiency in fibrillin-1, a component of the aortic media that contributes to tissue elasticity by linking vascular smooth muscle cells to adjacent elastin fibrils. In addition, matrix metalloproteinases, which function primarily in the degradation of extracellular matrix, are upregulated in ascending aortas of Marfan's patients (relative to healthy controls), and have subsequently been implicated in the etiology of ascending aortic dilation in non-syndromic patients as well [67-69].

Bicuspid aortic valve (BAV) will be considered in greater detail in this study because of its extremely high prevalence in ascending aortic disease and its potential association with BA (as discussed previously). BAV is a congenital anomaly present in 1-2% of the general population that is frequently associated with early aortic stenosis and ascending aortopathy; prevalence of ascending aortic dilatation in BAV patients has ranged from 40-70% in several natural history studies [70-73]. This association between BAV and ascending aneurysm is well-established, but the underlying mechanism has been a point of controversy. Ascending disease in the setting of BAV was initially thought to be hemodynamic in nature, with post-stenotic dilatation presumably resulting from turbulent flow through the deformed valve [35,74]. A significant body of evidence, however, suggests that ascending aortopathy in BAV disease is a consequence of progressive tissue abnormalities rather than post-stenotic hemodynamic effects. Several studies have shown that proximal aortic enlargement in BAV patients occurs irrespective of the type or degree of valvular dysfunction [71,73,75,76], and one group demonstrated that valve replacement in BAV patients does not affect subsequent progression of aortic dilatation [77]. Tissue analyses have further substantiated the notion of intrinsic aortic wall abnormalities associated with BAV. In

aortic specimens from patients who underwent ascending aortic replacement, several pathologic findings were more pronounced in patients with BAV than in patients with tricuspid aortic valve (TAV), including cystic medial necrosis, elastin fragmentation, and changes in smooth muscle orientation [78]. Moreover, patients with BAV appear to have thinner and more sparsely distributed elastic lamellae in their ascending aortic media [79].

Many of the tissue abnormalities seen in aortas of Marfan's patients, such as fibrillin-1 deficiency and MMP overexpression, have been encountered in BAV patients as well. Fedak et al. suggested that deficient fibrillin-1 in BAV ascending aortas might prompt MMP-mediated matrix remodeling and ultimately aortic dilatation, and went on to postulate that congenital BAV results from inherited defects in genes regulating fibrillin-1 integration into ECM (there is no evidence yet to support this particular claim) [80]. Recent molecular analyses of aortic tissue in BAV patients have indicated that imbalanced expression of MMPs and their endogenous inhibitors (TIMPs) might underlie ascending aortic disease in this group. Koullias et al. found that MMP-2 and MMP-9 levels were elevated in BAV relative to TAV aortas, whereas TIMP-1 was lower in BAV tissue [81]. Several studies affirm the primary role of MMP-2 and MMP-9 in the etiology of ascending disease [80,82], while others suggest that TIMP downregulation is the primary intrinsic wall abnormality underlying ascending dilatation [83]. Moreover, not only do expression profiles of MMPs and TIMPs differ in BAV and TAV patients, but MMP expression appears to depend in part on TAA size, perhaps suggesting that MMP and TIMP levels fluctuate throughout the natural history of each individual aorta [84,85]. Further investigation is necessary to determine if MMP is inherently overexpressed in diseased aortas, or if underlying mechanical triggers ultimately promote MMP upregulation [86].

Natural history studies suggest that BAV is associated with both the presence and expansion of ascending aortic aneurysms. As mentioned, approximately 50% of BAV patients ultimately develop clinically significant ascending aortic dilatation [73]. Davies et al. reported in

a Yale database review that BAV patients presented with ascending aneurysm far earlier than patients in the TAV group (49.0 years versus 64.2 years), and also exhibited significantly higher ascending aortic growth rates (0.19 cm/year, versus 0.13 cm/year in TAV patients) [87]. Ferencik reported slightly lower aortic growth rates in the setting of BAV, with highest mean expansion rate 0.09 cm/year in the proximal ascending aorta [75].

Recently, several genetic mutations have been implicated in the pathogenesis of BAV and concomitant ascending aortopathy, but most remain speculative. There is at the very least strong evidence that the association between BAV and ascending aortic disease is largely a consequence of progressive congenital tissue abnormalities in the aortic wall.

Descending Aortopathy

Ascending and descending aortic disease exhibit markedly different characteristics, and in fact appear to be distinctly different pathologic processes. While ascending disease is typically associated with medial degeneration, descending disease is most frequently characterized by aortic arteriosclerosis [39]. One thought is that intimal plaque deposition triggers inflammatory changes that increase proteinase activity in the media, ultimately weakening the descending aortic wall [88]. This theory, however, fails to account for the large percentage of patients with aortic atherosclerosis who never develop aneurysmal disease [89]. Agmon et al. suggest that atherosclerosis has a limited role in aneurysm formation, citing a weak relationship between atherosclerosis and distal thoracic aortic diameter [90]. Scherer hypothesized that descending aortic dilatation may actually predispose to atherosclerosis, suggesting that as the aorta dilates, hemodynamic forces cause subintimal proliferative changes resulting in plaque formation [91]. All such theories are controversial, and many have postulated that the link between atherosclerosis and descending aortic disease is associative rather than causative. Molecular analyses of pathologic descending aortic tissue have demonstrated the importance of MMPs in the etiology of dilatation, as has been observed in ascending aortic disease. Specifically, MMP-9

expression predominates in the anterior wall of descending aortic aneurysms, where diameter is most volatile [86]. Ascending TAAs and infrarenal abdominal aortic aneurysms (AAAs) are characterized by distinct gene expression patterns, and it seems likely that descending TAAs exhibit a distinct molecular profile as well [92].

Natural history studies indicate that acute aortic complications are a significant risk in descending TAAs, with descending rupture occurring in approximately 20% of untreated patients. Risk factors for descending aortic rupture and/or dissection parallel what has been observed in ascending aortopathy—while size appears to be the most important single criterion for operative intervention, growth rate and symptoms are also significant indications [93]. Descending and thoracoabdominal aneurysms tend to grow more rapidly than ascending aneurysms, likely due to regional differences in elastin content of the aortic wall (as already discussed). That being said, dissection and rupture in descending disease generally occurs at larger aortic diameters [48,54].

Heritability of Thoracic Aortic Disease

Ascending aortopathy is frequently encountered in association with specific genetic syndromes affecting connective tissues, including Marfan's syndrome, Ehlers-Danlos syndrome, and Turner's syndrome, among others [67]. Non-syndromic ascending aortic disease appears to be heritable as well, with several studies demonstrating a significant predisposition to thoracic aortic disease in first-degree relatives of thoracic aortic disease patients [94,95]. Albornoz et al. found that 21% of non-syndromic thoracic aortic disease patients have first-degree relatives also affected by the disease, with the majority of these patients exhibiting an autosomal dominant inheritance pattern. Moreover, "familial" TAAs presented earlier (58.2 years) and expanded more rapidly (0.21 cm/year) than "sporadic" TAAs (65.7 years and 0.16 cm/year, respectively), leading the authors to postulate that familial aortic disease constitutes a more aggressive clinical entity [96]. Multiple gene loci predisposing to non-syndromic ascending aortopathy have now been identified, suggesting that ascending disease in families is subject to significant genetic

heterogeneity [97-100]. Descending aortic disease also appears to harbor a genetic component, with a possible association between descending TAAs and AAAs in first-degree relatives [96].

Study Rationale and Aims

The BA literature, as well as our own clinical experience, point toward a potential association between BA and thoracic aortic disease. Like bicuspid aortic valve (BAV), BA is a congenital abnormality that may predispose to progressive tissue abnormalities in the aortic wall. Moreover, given the variant's deviance from standard arch anatomy, its potential to alter flow mechanics through the aorta must not be overlooked.

TAA is a lethal condition that is nearly always asymptomatic until rupture or dissection; thus, it is critical to identify markers associated with the development of aortic disease. Moreover, since diseased aortas demonstrate a highly variable natural history, it is important to define markers for disease progression in patients with known aortopathy. BA is a congenital variant, and so is present throughout life, both before aortic disease develops and during the course of the disease itself.

This retrospective study aims to better define the association between BA and the prevalence and progression of thoracic aortic disease. We intend to explore potential relationships between BA and TAA, BAV, aortic growth rate, dissection, and rupture. If a true association exists between BA and thoracic aortic disease, it is our hope that the presence of BA on thoracic scan may be used as a marker for increased risk of TAA development, progression and complications.

METHODS

Patient Population, Definitions, and Demographics

The present study is part of a broad, on-going investigation of TAA approved by the Yale Human Investigation Committee. We retrospectively recruited patients for this study from a population of 947 consecutive patients seen at the Yale Center for Thoracic Aortic Disease between June 2003 and June 2010.

For purposes of this study, "thoracic aortic disease" was defined as any one of the following: (a) TAA (thoracic aortic diameter ≥ 4.0 cm per at least one imaging report), (b) thoracic aortic dissection (intramural hematoma and/or classic dissection with a visible intimal flap) or thoracic aortic rupture, or (c) history of thoracic aortic surgical repair for symptomatic dilatation. Only patients with thoracic aortic disease (by these criteria) and at least one thoracic computed tomography (CT) scan or magnetic resonance imaging (MRI) scan on record at Yale-New Haven Hospital (with adequate visualization of the aortic arch vessels) were included. Of the 947 eligible patients, 26 were excluded because they did not meet criteria for thoracic aortic disease, 301 were excluded because they had no thoracic images available for review at Yale-New Haven Hospital, and 4 were excluded due to inadequate visualization of arch vessels on thoracic scan. The remaining 616 patients (416 male, 200 female) comprised our study population. Of these 616 patients, 450 had TAA and no thoracic aortic dissection, 149 had thoracic aortic dissection (76 type A, 73 type B), 16 had thoracic aortic rupture, and 1 patient underwent operative repair for symptomatic dilatation at aortic diameter < 4.0 cm.

Control Group

A control group of 844 patients (396 male, 448 female) without thoracic aortic disease was randomly selected from Yale-New Haven Hospital imaging records. A random number generator was used to designate specific dates between May 2006 and May 2008, and then used

again to randomly select 25% of the patients who underwent thoracic CT scans at Yale-New Haven Hospital on each of those specific dates. Patients made eligible in this fashion were included in the control group only if (a) they were at least 18 years old at the time of the scan, (b) the scan clearly demonstrated aortic arch anatomy, and (c) there was no evidence of thoracic aortic disease by the aforementioned criteria on the scan of interest or on subsequent scans, which were also reviewed for each eligible patient. Mean age at time of thoracic CT scan was 55.7 years.

Prevalence of BA Variant

To determine the presence or absence of BA variant in the 616 patients with thoracic aortic disease and the 859 patients without thoracic aortic disease, their thoracic CT and/or MRI scans were retrospectively reviewed by our team and then confirmed by a cardiac imaging specialist in the Department of Radiology. All scans were reviewed in all available planes, including axial, coronal, and sagittal images, as well as multi-planar reconstructions. Patients were deemed BA+ if the point of separation of the innominate and left common carotid arteries was visualized cephalad to the plane of greater curvature of the arch in all available views.

BA Type (see Fig. 1)

BA+ patients were classified as "type 1" if the innominate artery and left common carotid artery shared a common trunk – that is, if the left common carotid artery originated partially from the aorta rather than entirely from the innominate artery. BA+ patients were classified as "type 2" if the left common carotid artery branched directly and exclusively from the innominate artery proper, such that there was distance (along the innominate artery) between the origin of the left common carotid artery and the aorta itself.

Citation of BA Variant

For patients with thoracic aortic disease, all imaging reports accompanying CT or MRI scans were screened for radiologists' citation of the presence of BA variant. Imaging reports were compared with our own findings to assess the accuracy and completeness of standard radiology reports in documenting arch anatomy.

Demographics

Information regarding gender, presence or absence of hypertension, family history of aortic disease (defined as any relative with thoracic aortic disease and/or AAA), age at presentation (age at which TAA, dissection, or rupture was initially discovered), and dates of operative repair was obtained from scans, imaging reports, and Yale Center for Thoracic Aortic Disease chart records.

Location of Thoracic Aortic Disease

For each of the 616 patients with thoracic aortic disease, location of disease was defined as (a) ascending (including aortic root), (b) aortic arch, or (c) descending (including thoracoabdominal). Patients with a history of TAA were classified according to aortic region with greatest absolute diameter prior to operation. In patients with a history of operative aortic repair and no record of aortic diameter prior to operation, the region initially repaired was considered the affected location, regardless of subsequent dilatation or repair in other regions. Patients with thoracic aortic dissection who did not meet criteria for TAA (diameter < 4.0 cm) and did not undergo operative aortic repair were classified according to region of initial intimal disruption. We calculated the proportion of patients in the BA and non-BA groups with disease at each location.

Prevalence of Dissection and Rupture

Information regarding presence of dissection and/or rupture was obtained from thoracic scans, imaging reports, and Yale Center for Thoracic Aortic Disease chart records. Dissection was classified as type A or type B, according to the Stanford classification system. We calculated prevalence of overall dissection, type A and type B dissection, and aortic rupture in all BA and non-BA patients with thoracic aortic disease. We also compared prevalence of dissection and rupture in BA and non-BA patients with concomitant BAV, and in patients with type 1 and type 2 BA.

Aortic Growth Rate

For all patients with thoracic aortic disease, serial measurements of aortic diameter were obtained from imaging reports associated with thoracic CT and MRI scans from Yale-New Haven Hospital, as well as records of imaging reports from CT and MRI scans performed at outside hospitals. Echocardiographic findings were not included. For patients whose measurements prior to initial surgical repair could not be obtained, but who later developed TAAs in other locations, these post-repair measurements were used to determine growth rate. Serial aortic measurements were available for 217 patients. Patients with serial follow-up were excluded from the growth rate calculation if duration of radiographic follow-up did not exceed three months. 8 patients in the BA group and 10 patients in the non-BA group were excluded by these criteria. For patients in whom acute dissection occurred after initial scan, we included in the growth rate analysis only serial aortic measurements that either preceded the dissection event or followed the dissection event. We deliberately excluded changes in aortic size associated with the dissection event itself, since acute dissection independently inflates aortic growth rate.

Growth rate was defined as the difference between last and first aortic diameter, divided by the duration between tests. We calculated mean growth rate in the setting of chronic dissection, no dissection, ascending/arch disease, and descending disease in all BA and non-BA

patients. We also compared growth rate in type 1 versus type 2 BA, and in BA and non-BA patients with concomitant BAV.

Bicuspid Aortic Valve

Patients in the thoracic aortic disease group were screened for presence of BAV by reviewing operative notes and/or echocardiography reports. In patients who underwent ascending aortic replacement, operative notes provided the most reliable source of information about aortic valve morphology since they documented direct visual observation of the valve apparatus. For patients who did not undergo operative intervention or in whom the nature of the aortic procedure did not directly visualize the aortic valve, information about aortic valve morphology was obtained from digital echocardiography reports (if performed at Yale-New Haven Hospital) or reports on file at Yale Center for Thoracic Aortic Disease (if performed at outside institutions). We then compared demographics, prevalence of complications, and aortic growth rate in BA and non-BA patients with BAV.

Statistics

The two-tailed, unpaired t-test was used to evaluate the difference in aortic growth rates and the difference in age at presentation between BA and non-BA groups and between type 1 and type 2 BA groups. Pearson chi-square test and Fisher exact test were used to compare proportions, including the difference in BA prevalence between aortic disease and control groups, the difference in prevalence of ascending, arch, and descending disease in BA and non-BA groups, and the difference in dissection rate between BA and non-BA groups and between type 1 and type 2 BA groups. Statistical significance was defined as $P < 0.05$.

Author Contributions

The primary author (Matthew Hornick) was involved in several aspects of this study, including experimental design, screening for BA in scans of disease group and control group

patients, reviewing all disease group imaging reports and chart records for radiologists' citation of BA, location of aortic disease, serial TAA diameter, presence of BAV, and demographic data, and organization of results and statistical calculations. Dr. John Elefteriades conceived of this experiment and advised the primary author (MH) during each phase. Maryann Tranquilli provided records of consecutive aortic disease patients treated and/or seen in consultation at Yale Center for Thoracic Aortic Disease. Dr. Remo Moomiaie was involved in study design and assisted with screening for BA in disease group patients. Esther S. Lee generated a randomized group of thoracic CT scans in patients without thoracic aortic disease, and assisted in screening these control group scans for BA. Dr. Hamid Mojibian confirmed interpretations of imaging scans (BA+/BA- and type 1/type 2) for all disease group and control group patients. Dr. John Rizzo advised statistical methodology and confirmed all statistical calculations.

RESULTS

Table 1. Prevalence of BA in Thoracic Aortic (TA) Disease Group and Control Group

Variable	TA Disease Group	Control Group	P value
Total number	616	844	
Total BA+ (% of total)	161 (26.1%)	138 (16.4%)	<0.001
No. male	416	396	
BA+ (% of male)	109 (26.2%)	64 (16.2%)	<0.001
No. female	200	448	
BA+ (% of female)	52 (26.0%)	74 (16.5%)	0.005

Prevalence of BA Variant (see Table 1)

Of 616 patients with known thoracic aortic disease, 161 patients (109 male, 52 female) were found to have concomitant BA (26.1% prevalence). Upon reviewing all imaging reports, the presence of BA was cited by a radiologist in only 26 (16.1%) of the 161 BA patients with aortic disease. Of 844 control group patients without TAA or dissection, 138 patients (64 male, 74 female) were found to have BA (16.4% prevalence). BA prevalence was significantly greater in

the thoracic aortic disease group than in the control group of patients without aortic disease (P<0.001), and this held true for both male and female patients when considering each gender independently (P<0.001 for males and P=0.004 for females).

Table 2. Demographics, Location, and Complications in Thoracic Aortic Disease, by BA Group

Variable	BA+	BA-	P value
Thoracic Aortic Disease (no.)	161	455	
Sex (male)	109 (67.7%)	307 (67.5%)	1
Age at presentation (mean, yrs)	56.8	61.3	0.002
Operative repair	122 (75.8%)	339 (74.5%)	0.82
Age at repair (mean, yrs)	56.2	61.4	0.0004
Bicuspid aortic valve	43 (26.7%)	114 (25.1%)	0.68
Family history of TAA/AAA	34 (21.1%)	97 (21.3%)	1
Hypertension	101 (62.7%)	317 (69.7%)	0.11
Location of Disease			
Ascending (incl. Root)	130 (80.7%)	369 (81.1%)	0.92
Arch	5 (3.1%)	12 (2.6%)	0.78
Descending	26 (16.2%)	74 (16.3%)	1
Thoracic aortic dissection	43 (26.7%)	106 (23.3%)	0.39
Type A	19 (11.8%)	57 (12.5%)	0.81
Type B	24 (14.9%)	49 (10.8%)	0.16
Thoracic aortic rupture	5 (3.1%)	11 (2.4%)	0.77

Demographics (see Table 2)

Among patients with thoracic aortic disease, patients with BA were 67.7% male and patients without BA were 67.5% male; there was no association between BA and gender (P=1). Relative to patients without BA, patients with BA were significantly younger at initial discovery of thoracic aortic disease and initial operative repair. Mean age at presentation with TAA or dissection was 56.8 years (median 58.4 years) in the BA group and 61.3 years (median 62.0 years) in the non-BA group (P=0.002). Mean age at initial operative aortic repair was 56.2 years (median 57.8 years) in the BA group and 61.4 years (median 62.7 years) in the non-BA group (P=0.0004). 75.8% of BA patients and 74.5% of non-BA patients underwent surgical aortic repair

or replacement. Bicuspid aortic valve (BAV) was present in 26.7% of BA patients and 25.1% of non-BA patients with thoracic aortic disease (P=0.68). With respect to family history, 21.1% of BA patients and 21.3% of non-BA patients had at least one relative with thoracic or abdominal aortic disease (P=1). Hypertension was documented in 62.7% of BA patients and 69.7% of non-BA patients, which was not a statistically significant difference (P=0.11).

Location of Disease (see Table 2)

Of the 161 thoracic aortic disease patients with BA, 130 (80.7%) had ascending disease, 26 (16.2%) had descending disease, and 5 (3.1%) had aortic arch disease. Of the 455 thoracic aortic disease patients without BA, 369 (81.1%) had ascending disease, 74 (16.3%) had descending disease, and 12 (2.6%) had arch disease. BA was not significantly associated with thoracic aortic disease at any particular location (Table 2).

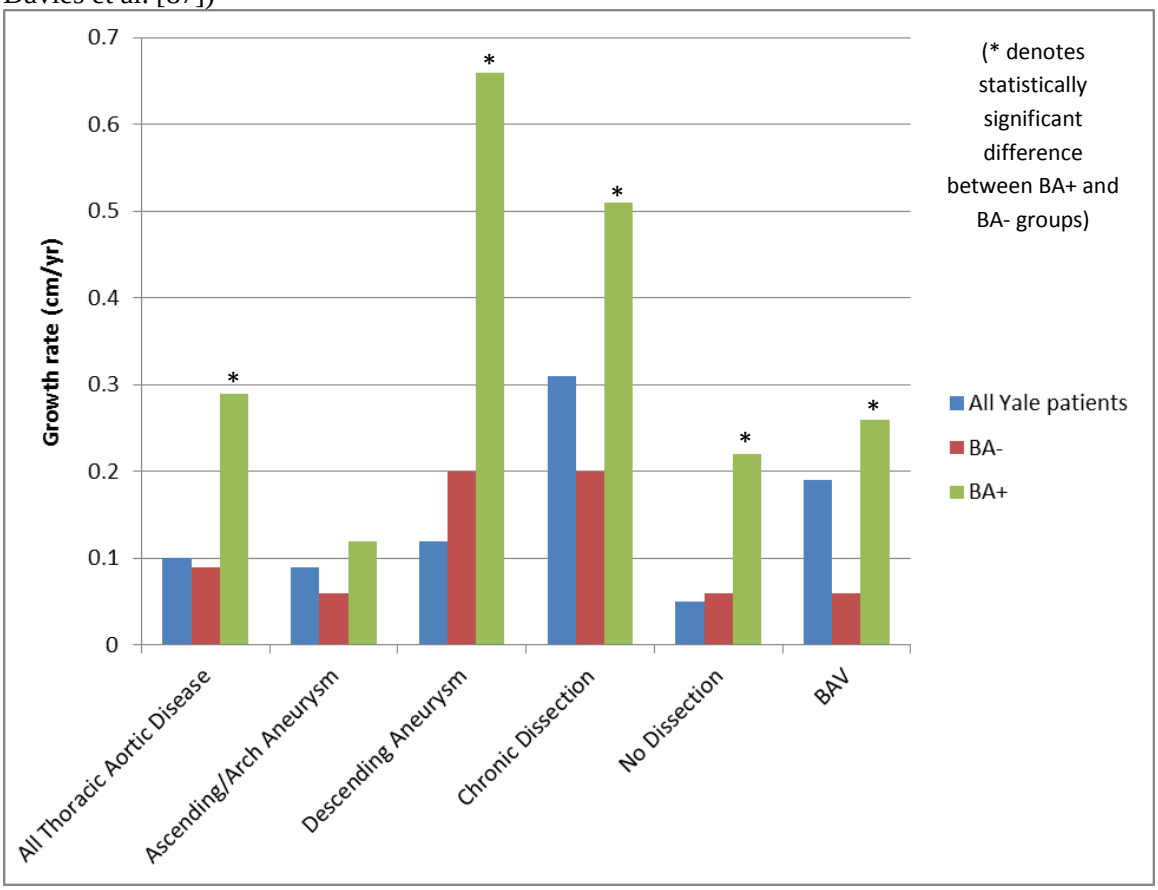
Prevalence of Dissection and Rupture (see Table 2)

Overall prevalence of dissection was 26.7% in BA patients (43 of 161), including 24 with type B and 19 with type A, and 23.3% (106 of 455) in non-BA patients, including 49 with type B and 57 with type A. There was no significant association between BA and type A (P=0.81), type B (P=0.16), or overall dissection (P=0.39). There were 5 instances of thoracic aortic rupture in the BA group (3.1%), and 11 instances of rupture in the non-BA group (2.4%). Difference in prevalence of rupture between BA and non-BA groups was not statistically significant (P=0.77).

Table 3. Aortic Growth Rate (cm/yr), by BA Group (*comparison data from Coady et al. [48])

Variable	**All Yale patients***	**BA- (n)**	**BA+ (n)**	**P value (BA- vs. BA+)**
All Thoracic Aortic Disease	0.10	0.09 (164)	0.29 (54)	0.003
Chronic Dissection	0.31	0.20 (33)	0.51 (13)	0.01
No Dissection	0.05	0.06 (131)	0.22 (41)	0.04
Ascending/Arch	0.09	0.06 (130)	0.12 (37)	0.44
Descending	0.12	0.20 (34)	0.66 (17)	0.001

Figure 2. Aortic Growth Rate (cm/yr), by BA Group ("Yale" data from Coady et al. [48] and Davies et al. [87])



Aortic Growth Rate (see Table 3 and Figure 2)

Follow-up ranged from 3.1 to 184.7 months. Mean aortic growth rate was 0.29 cm/year in all BA patients (mean follow-up 32.8 months), compared to 0.09 cm/year in all non-BA patients (mean follow-up 31.7 months). This difference in overall growth rate between BA and non-BA patients was statistically significant (P=0.003). Furthermore, subgroup analysis revealed a significant association between BA and elevated aortic growth rate in patients with descending aortic disease, as well as in patients both with and without chronic dissection (P=0.01 and P=0.04, respectively). In ascending aortic disease, BA patients also demonstrated a faster rate of aortic growth, but this association between BA and ascending aortic expansion was not statistically significant.

Table 4. Demographics, Location, Dissection, and Rupture in BA Patients, by BA Type

Variable	Type 1 BA	Type 2 BA	P value
No.	108	53	
No male (%)	76 (70.4%)	33 (62.3%)	0.30
Age at presentation (mean, yrs)	55.7	58.9	0.17
Operative repair	83 (76.9%)	39 (73.6%)	0.65
Age at repair (mean, yrs)	55.7	57.4	0.55
Bicuspid aortic valve	29 (26.8%)	14 (26.4%)	1
Family history of TAA/AAA	23 (21.3%)	11 (20.8%)	0.92
Hypertension	68 (63.0%)	33 (62.3%)	0.92
Location of Disease			
Ascending (incl. Root)	87 (80.6%)	43 (81.1%)	0.92
Arch	3 (2.8%)	2 (3.8%)	1
Descending	18 (16.7%)	8 (15.1%)	1
Thoracic aortic dissection	26 (24.1%)	17 (32.1%)	0.28
Type A	10 (9.3%)	9 (17.0%)	0.15
Type B	16 (14.8%)	8 (15.1%)	1
Thoracic aortic rupture	2 (1.9%)	3 (5.7%)	0.33
Growth rate (cm/yr)	0.31 (n=37)	0.25 (n=17)	0.61

BA Type (see Table 4)

Of 161 BA patients, there were 108 patients with type 1 BA and 53 patients with type 2 BA. Patients with type 1 BA presented 3.2 years earlier and demonstrated a slightly higher mean growth rate than patients with type 2 BA, but these differences were not statistically significant (P=0.17 and P=0.61, respectively). Furthermore, there were no significant differences in operative aortic repair, age at operation, prevalence of bicuspid aortic valve, family history of aortic disease, or presence of hypertension between type 1 and type 2 BA groups. There were also no significant differences in prevalence of dissection or rupture between groups (Table 4).

Table 5. Bicuspid Aortic Valve (BAV) Patients, by BA group

Variable	BA+	BA-	P value
No. BAV	43	114	
Hypertension	19 (44.2%)	68 (59.6%)	0.08
Age at presentation (mean, yrs)	48.3	53.8	0.040
Operative repair	39 (90.7%)	102 (89.5%)	1
Age at repair (mean, yrs)	49.2	57.0	0.002
Growth rate (cm/yr)	0.26 (n=14)	0.06 (n=31)	0.018

BA in Patients with BAV (see Table 5)

Among patients with BAV and thoracic aortic disease, hypertension was present in 44% of BA patients and 59.6% of non-BA patients, which was not a statistically significant difference (P=0.08). Mean age at presentation with aortic disease was 48.3 years in BA patients with BAV and 53.8 years in non-BA patients with BAV, which was a significant difference (P=0.040). Mean age at operative repair was 49.2 years in the BA group and 57.0 years in the non-BA group, which was also a significant difference (P=0.002). BA patients with BAV demonstrated higher mean aortic growth rate than non-BA patients with BAV (P=0.018). There was no association between BA and prevalence of operative repair in BAV patients.

Table 6. Ascending Aortic Disease, by BA group

Variable	BA+	BA-	P value
No. with ascending disease	130	369	
Age at presentation (mean, yrs)	55.4	59.8	0.002
Operative repair	105 (80.8%)	287 (77.8%)	0.48
Age at repair (mean, yrs)	55.9	60.7	0.002
No. BAV (%)	42 (32.3%)	112 (30.4%)	0.68

BA in Ascending Aortic Disease (see Table 6)

BA patients with ascending aortic disease presented at a significantly younger age than non-BA patients with ascending disease (P=0.002). BA patients also underwent ascending aortic operation at a significantly younger age than non-BA patients with ascending disease (P=0.002).

There was no significant difference in prevalence of operative repair between BA and non-BA patients with ascending disease. 32.3% of BA patients with ascending disease and 30.5% of non-BA patients with ascending disease had concomitant BAV (P=0.68)

Table 7. Descending Aortic Disease, by BA group

Variable	BA+	BA-	P value
No. with descending disease	26	74	
Age at presentation (mean, yrs)	63.5	67.3	0.25
Operative repair	14 (53.8%)	44 (59.5%)	0.62
Age at repair (mean, yrs)	59.5	64.4	0.26
No. BAV (%)	1 (3.8%)	2 (2.7%)	1

BA in Descending Aortic Disease (see Table 7)

BA patients with descending aortic disease presented at a younger age than non-BA patients with descending disease (63.5 years versus 67.3 years), but this difference was not statistically significant (P=0.25). Mean age at initial aortic operation was lower in the BA group as well, but this trend did not reach statistical significance (P=0.26). There was no association between BA and prevalence of operative repair in patients with descending aortic disease.

DISCUSSION

Historically, BA has been considered a clinically insignificant variant of aortic arch anatomy. Isolated reports of complex aortic arch operations and a few studies of aortic anatomy in women with Turner's syndrome have hinted at a potential association between BA, BAV, and thoracic aortic disease, but with very little substantial evidence [25-37]. To our knowledge, this study is the first to document a statistically significant association between congenital BA variant and thoracic aortic disease.

We found that BA was significantly more common in patients with thoracic aortic disease (26.1% prevalence in patients with TAA, thoracic aortic dissection, or rupture) than in the general population of patients without thoracic aortic disease (16.4% prevalence in control group patients without TAA, dissection, or rupture). The presence of BA was cited by radiologists in only 26 (16.1%) of the 161 BA patients in the thoracic aortic disease group, suggesting that radiologists overlook or underreport this anatomic variant, even when specifically monitoring the aorta. This trend likely reflects the popular sentiment that BA is a "normal" variant that does not warrant reporting.

In our series, BA was not significantly associated with location of thoracic aortic disease, with prevalence of aortic disease at any given location virtually equivalent across BA and non-BA groups. Thoracic aortic dissection was slightly more prevalent in patients with BA (26.7%) than in patients without BA (23.3%), but this difference was not statistically significant. Since the vast majority of dissections occurred prior to the initial scan, we were unable to determine the mean aortic diameter at which BA patients initially dissected. Further investigation will be required to establish whether the presence of BA should impact surgical intervention criteria for TAA.

With respect to growth rate, our results indicate that BA is associated with a significantly higher rate of aortic expansion – 0.29 cm/year in the BA group, compared to 0.09 cm/year in the non-BA group. This association between BA and growth rate was particularly pronounced in descending aortic disease and in the setting of chronic dissection, with mean growth rate 0.66 cm/year and 0.51 cm/year, respectively, in these two subgroups of BA patients. Thus, although BA does not appear to be associated with location of disease, the variant may differentially influence growth rate in different regions of the aorta. Similarly, while BA may not be directly associated with a higher prevalence of dissection, it may very well contribute to the progression of aortic dilatation once dissection occurs. Among patients with ascending aortic disease, BA

patients trended towards a higher growth rate as well (0.12 cm/year, compared to 0.06 cm/year in non-BA patients), but this difference was not statistically significant.

BA patients also presented with aortic disease approximately 4.5 years earlier than non-BA patients, and underwent initial aortic operation over 5 years earlier, on average. The younger presentation and repair observed in BA patients dovetails to our findings with respect to accelerated aortic growth in this group. Interestingly, despite a statistically insignificant relationship with growth rate in ascending aortic disease, BA was nonetheless associated with significantly earlier presentation and repair in patients with ascending aortic disease. By the same token, despite a statistically significant association with growth rate in descending aortic disease, BA was not significantly associated with earlier presentation and repair in patients with descending aortic disease. That being said, results trend toward accelerated growth rate, earlier presentation, and earlier repair in both ascending and descending aortic disease patients with BA, and greater statistical power would likely resolve these inconsistencies.

We used an arithmetic method to calculate mean growth rate (defined as last diameter minus first diameter, divided by duration between measurements), which has been criticized in the past for inflating growth rate estimates [57,60]. In prior studies, however, much of the error attributed to this technique has been related to the deliberate truncation of negative and null growth rates; to minimize this source of growth rate inflation, negative and null growth rates were included in this analysis. It is worth noting that the mean arithmetic growth rate that we observed in non-BA patients (0.09 cm/year) nearly matched the mean growth rate calculated via regression analysis (0.10 cm/year) in a previous study of Yale Center for Thoracic Aortic Disease patients [48]. Therefore, despite the host of inconsistencies and technical challenges inherent to serial aortic size measurements and growth rate calculations [56], there does appear to be some consistency between studies and between methods of calculation. Moreover, any effects related to methodology would be expected to distribute evenly across BA and non-BA groups, which lends

further credence to the relatively higher growth rate observed in the BA group. Our findings demonstrate that while aortic disease in non-BA patients is indeed an indolent process, BA seems to be associated with a markedly elevated and far less indolent rate of aortic expansion.

There was no significant association between BA and BAV in this study, which challenges vague suggestions in the literature as to a possible relationship between these two congenital anatomic variants [34-37]. This is a relevant finding because it indicates that BAV is not a confounding variable in the observed association between BA and thoracic aortic disease, despite the already well-established association between BAV and ascending aortopathy. However, our results do suggest that in patients with BAV, the concomitant presence of BA is associated with even earlier presentation and operative repair, and more rapid aortic growth rate. These results imply that the presence of BA (or some unidentified associated factor) may essentially exacerbate an already accelerated aortopathy in BAV patients.

There were few clinical differences observed between patients with type 1 and type 2 BA. Patients with type 1 BA presented with aortic disease 3.2 years earlier than patients with type 2 BA and demonstrated a slightly higher overall growth rate (0.31 cm/year, compared to 0.25 cm/year in type 2 BA). Given the relatively low number of patients in each group, however, none of these differences reached statistical significance. Both variants represent a fairly radical departure from typical aortic arch anatomy, and it is difficult to intuit which variant is intrinsically more "abnormal" – in type 1 BA, there is a large common trunk branching from the proximal arch, and in type 2 BA, the takeoff of the L common carotid is displaced far from its typical origin. Further studies with larger patient populations will be required to better distinguish between the clinical significance of these two BA configurations.

One important limitation of this study was our failure to address the specific pathophysiologic mechanisms by which a congenital BA contributes or relates to the later development of thoracic aortic disease. We have identified an association, but we have no

definitive explanation as to why this association exists. Clinical aortopathy is an extremely complex process, and it seems likely that several variables contribute to aortic disease in BA patients.

On the one hand, BA may predispose to aortic dilatation through altered flow dynamics within the walled area of the variant. As already mentioned, BA represents a fairly striking deviation from normal aortic arch anatomy, and a mechanical explanation for this association seems entirely plausible. One thought is that the common trunk in type 1 BA creates, at its origin, a point of functionally increased aortic diameter, thereby increasing circumferential wall tension in this region by extension of Laplace's law [40]. If this were indeed the case, however, we would expect a disproportionately high number of arch and proximal descending aortic disease in BA, which is not what we observed in this study. Another possibility is that the altered branching pattern in BA predisposes to abnormal flow patterns in the aorta, which exert increased stress on particular regions of the aortic wall and ultimately accelerate dilatation. Magnetic resonance velocity mapping studies have demonstrated that both the caliber of the aorta and the configuration of the arch vessels impact aortic flow dynamics [101,102], so it seems likely that BA may exert at least some influence in this regard. We suspect that aortic modeling, dynamic flow studies, and a better understanding of the hemodynamics of type 1 and type 2 BA will shed light on the mechanical consequences of BA.

Alternatively, BA may be associated with TAA due to concomitant congenital abnormalities in the structure of the aortic wall, as is well-established in patients with BAV [70-84]. We demonstrated in this study that the presence of BA seems to further exacerbate the clinical picture characteristic of BAV, but it is unclear if BA represents an exaggeration of BAV-associated pathology or a distinct pathologic process altogether. Since BA, like BAV, is a congenital variant of outflow tract anatomy, the notion of an associated predisposition to pathologic aortic tissue remodeling is certainly compelling. Further study, presumably

investigating the molecular properties of aortic tissue in the setting of BA (with and without BAV) is necessary to investigate this possibility. Given the particularly strong association between BA and growth rate in descending thoracic aortic disease, it will be equally as important to study characteristics of descending aortic tissue in patients with BA. And lastly, despite the observed non-association between BA and family history of aortic disease in this study, the potential heritability of BA and its role in the later development of aortic disease cannot be ruled out and certainly deserves future consideration.

A second limitation of this study was our strategy for classifying disease location, which confined patients to one specific group rather than accounting for dilatation in multiple regions of the aorta. Many patients ultimately developed TAAs in a second or even a third location, but only the initial region of maximal dilatation factored into our classification scheme.

A third limitation was our failure to age-match the control group to the thoracic aortic disease group. Mean age of patients in the control group (55.7 years) was younger than the mean age at which patients in the disease group presented with TAA or dissection (56.8 years in patients with BA and 61.3 years in patients without BA). This discrepancy is relevant because certain patients in the control group may develop TAA or dissection as they approach the age at which aortic disease is typically detected, which would exclude these patients from the control group altogether. However, since thoracic aortic disease is relatively rare in the general population [43], we would expect this age-related cross-over number to be vanishingly small. Moreover, age has no bearing on the absolute number of patients with BA, since BA is a congenital variant that is present, and apparent, from birth.

A fourth limitation pertains to the selection bias inherent to this study's retrospective case-control design. We have determined prevalence of BA in (1) a population of patients referred to the Yale Center for Thoracic Aortic Disease and (2) a population of patients without thoracic aortic disease who underwent thoracic imaging at Yale-New Haven Hospital for various

reasons, including lung cancer, breast cancer, lymphoma, chest pain, and other indications. Although the Yale Center for Thoracic Aortic Disease provides both medical and surgical care to a broad catchment area, the group of patients referred to Yale may be biased toward relatively complex cases; therefore, we acknowledge that all findings pertaining to the prevalence of aneurysm, dissection, and rupture do not necessarily reflect the general population of patients with thoracic aortic disease. Similarly, the control group of patients is not truly representative of the general population of patients without aortic disease, since these control patients were referred for thoracic imaging, which is certainly not a common or "general" occurrence. It is possible, though presumably unlikely, that certain pathologies for which control group patients were referred are positively or negatively associated with BA, and thus confounded our results. What we can say for certain is that none of the patients in the control group, at time of thoracic imaging or subsequently, have developed thoracic aortic disease by our definitions.

We are unable to address true incidence of aortic disease in patients with congenital BA variant, because this would require decades of prospective monitoring for the development and progression of dilatation in BA and control groups. We did follow aortic size longitudinally, but the retrospective nature of this study biases these findings because certain patients were monitored at more regular intervals and/or for longer periods of time. Most patients referred to Yale Center for Thoracic Aortic Disease undergo periodic imaging to monitor aortic size at least once every two years until operation; however, because aortic disease is often detected late in its course, many patients in this study had only a brief interval of serial follow-up prior to repair. Our growth rate data thus represent a fairly limited snapshot of what is in truth an extremely dynamic disease process.

Our rigid definition of thoracic aortic aneurysm fails to account for the aorta's inherent gradual dilatation over the course of the lifetime. The aorta naturally expands due to loss of vessel elasticity with aging [65,66], and yet we labeled any thoracic aorta with diameter greater than 4.0

cm as aneurysmal, regardless of patient age. How to precisely distinguish a patient with clinically relevant "aortic disease" remains a point of contention, since the boundaries are somewhat blurry. A 3.7 cm ascending aorta in a 25-year old patient, although not "aneurysmal" by our strict size criterion, certainly seems far more predisposed to dissection or rupture than an "aneurysmal" 4.1 cm ascending aorta in an 80 year-old patient. This quandary, once again, underscores the need for prospective longitudinal studies that will facilitate our understanding of the heterogeneous natural history of aortic dilatation.

As previously discussed, several autopsy studies and imaging reviews have measured prevalence of BA in the general population, with great variability in results. Much of this variability may be attributed to the somewhat ambiguous definition of BA, technical limitations in imaging the takeoff points of the great vessels, inconsistent interpretations of arch anatomy by radiologists, and differences in study populations [1,56]. We defined BA as "a point of separation of the innominate and left common carotid arteries cephalad to the plane of greater curvature of the arch." Unfortunately, as implied by this definition, identification of BA requires a partially subjective assumption about where the plane of greater aortic curvature *would* be if not for the takeoff of the innominate artery, which in itself explains a great deal of inter-observer variation. Berko et al. recently reported a 27.4% BA prevalence in a large review of consecutive CTA scans [17], which is the highest estimate (in non-syndromic patients) in the literature. Many of these CTA scans were performed in patients with suspected aortic dissection [17], which may have skewed the observed BA frequency in light of the potential relationship between BA and aortic disease. Here we report a relatively lower prevalence of BA – 26.1% in the thoracic aortic disease group and 16.4% in the control group. For purposes of this study, which seeks to define the clinical associations of BA, the differences observed between the aortic disease group and control group are more relevant than the precise prevalence of BA per se. In our series, the same radiologist, using consistent criteria for identifying BA in both groups and sophisticated imaging

at an Aortic Center, found a significant difference in BA prevalence between patients with and without thoracic aortic disease.

To this point, BA has been regarded as a relatively insignificant variant of aortic arch anatomy. General apathy towards BA is manifest in its frequent omission from imaging reports, with only 16.1% of radiologists citing BA in scans specifically monitoring patients with aortic disease. This study demonstrates a strong association between BA and the presence and natural history of thoracic aortic disease, which we hope will encourage radiologists to consistently report BA anatomy. Moreover, BA is present in approximately one-quarter of all patients with thoracic aortic disease, rendering its detection all the more important. We recognize that a substantial number of patients with congenital BA may never go on to develop aortic disease, and for this reason we do not advise serial aortic screening in every person with BA. However, aortic disease patients with concomitant BA demonstrate a substantially elevated aortic growth rate and an earlier age at repair, which seems to warrant more careful follow-up in this particular population. In patients with thoracic aortic disease and BA, therefore, we suggest serial imaging at more frequent intervals to monitor for changes in aortic caliber. Aortic disease patients with BA and BAV appear to be at particular risk for an accelerated disease course, and deserve especially meticulous attention. As mentioned, further study is necessary to determine if the presence of BA should impact criteria for surgical intervention.

Parenthetically, as we have mentioned and Griepp has pointed out (personal communication), the name “bovine aortic arch” is not anatomically correct. The cow's aorta does not have either of the configurations typically subsumed under the heading “bovine arch,” namely a common origin of the innominate and left common carotid arteries or a left common carotid artery originating directly from the innominate artery [1]. We suggest the new name “*common origin* aortic arch” for the anatomic patterns classically described as “bovine aortic arch”; this alternate designation is succinct and accurately descriptive.

CONCLUSIONS

(1) There has been a paucity of literature addressing the clinical significance of BA, and consequently BA has been considered a "normal" variant of aortic arch anatomy that is typically not cited in radiology reports. (2) Our data demonstrate a significant association between the presence of congenital BA variant and the development of thoracic aortic disease. The mechanism underlying this association is unknown. (3) We found a significant association between presence of BA and increased rate of aortic expansion, particularly in descending aortic disease and in chronic dissection. BA was also associated with earlier age at presentation and initial operative repair. (4) There was no association between BA and bicuspid aortic valve (BAV). In patients with BAV and thoracic aortic disease, concomitant BA was associated with more rapid growth rates, earlier presentation, and earlier repair. (5) In light of these findings, BA should not be considered a clinically insignificant anatomic variant. BA is a marker for potential development and progression of thoracic aortic disease, and warrants more frequent serial imaging follow-up if present in patients with thoracic aortic disease. We encourage radiologists to take note of aortic arch anatomy on any thoracic scan in any age group (even those obtained for non-cardiac purposes), and consistently report BA if incidentally discovered. (6) Since "bovine aortic arch" is a misnomer, we propose the name "*common origin* aortic arch" to describe this group of variant configurations.

REFERENCES

1. Layton KF, Kallmes DF, Cloft HJ, Lindell EP, Cox VS. 2006. Bovine aortic arch variant in humans: clarification of a common misnomer. *AJNR Am J Neuroradiol.* 27(7):1541-1542.

2. Lippert H, Pabst R. 1985. *Arterial Variations in Man: Classification and Frequency*. München: J.F. Bergmann Verlag. 35 pp.

3. Vitek JJ. 2007. Bovine aortic arch. *AJNR Am J Neuroradiol.* 28(7):1205 (letter).

4. Elster AD. 2008. "Bovine" aortic arch. *AJNR Am J Neuroradiol.* 29(3):E2.

5. Kumar N, Lee JJ, Perlmutter JS, Derdeyn CP. 2009. Cervical carotid and circle of Willis arterial anatomy of Macaque monkeys: a comparative anatomy study. *Anat Rec (Hoboken).* 292(7):976-984.

6. Berko NS. 2009. Bovine aortic arch: in search of a more appropriate name. *Anat Rec (Hoboken).* 292(11):1699.

7. De Garis CF, Black IH, Riemenschneider EA. 1933. Patterns of the aortic arch in American white and Negro stocks, with comparative notes on certain other mammals. *J Anat.* 67(4):599-618.

8. Thomson A. 1893. Third annual report of committee of collective investigation of anatomical society of Great Britain and Ireland for the year 1891-92. *J Anat.* 27(2):183-194.

9. Keith A. 1895. The modes of origin of the carotid and subclavian arteries from the arch of the aorta in some of the higher primates. *J Anat*. 29(3):453-458.

10. Liechty JD, Shields TW, Anson BJ. 1957. Variations pertaining to the aortic arches and their branches; with comments on surgically important types. *Q Bull Northwest Univ Med Sch*. 31(2):136-143.

11. Nizankowski C, Rajchel Z, Ziolkowski M. 1975. Abnormal origin of arteries from the aortic arch in man. *Folia Morphol (Warsz).* 34(2):109-116.

12. Grande NR, Costa e Silva A, Pereira AS, Aguas AP. 1995. Variations in the anatomical organizations of the human aortic arch: a study in a Portuguese population. *Bull Assoc Anat (Nancy).* 79:19-22.

13. Nelson ML, Sparks CD. 2001. Unusual aortic arch variations: distal origin of common carotid arteries. *Clin Anat*. 14(1):62-65.

14. Gupta M, Sodhi L. 2005. Variations in branching pattern, shape, size, and relative distances of arteries arising from arch of aorta. *Nepal Med Coll J*. 7(1):13-17.

15. Bhatia K, Ghabriel MN, Henneberg M. 2005. Anatomical variations in the branches of the human aortic arch: a recent study of a south Australian population. *Folia Morphol (Warsz).* 64(3):217-223.

16. Natsis KI, Tsitouridis IA, Didagelos MV, Fillipidis AA, Vlasis KG, et al. 2009. Anatomical variations in the branches of the human aortic arch in 633 angiographies: clinical significance and literature review. *Surg Radiol Anat*. 31(5):319-323.

17. Berko NS, Jain VR, Godelman A, Stein EG, Ghosh S, et al. 2009 Variants and anomalies of thoracic vasculature on computed tomographic angiography in adults. *J Comput Assist Tomogr*. 33(4):523-528.

18. Demertzis S, Hurni S, Stalder M, Gahl B, Herrmann G, et al. 2010. Aortic arch morphometry in living humans. *J Anat.* 217(5):588-596.

19. Nayak SR, Pai MM, Prabhu LV, D'Costa S, Shetty P. 2006. Anatomical organization of aortic arch variations in the India: Embryological basis and review. *Jornal Vascular Brasileiro* 5(2):95-100.

20. Jakanani GC, Adair W. 2010 Frequency of variations in aortic arch anatomy depicted on multidetector CT. *Clin Radiol.* 65(6):481-487.

21. Shaw JA, Gravereaux EC, Eisenhauer AC. 2003. Carotid stenting in the bovine arch. *Catheterization Cardiovasc Interv*. 60(4):566-569.

22. Faggioli GL, Ferri M, Freyrie A, Gargiulo M, Fratesi F, et al. 2007. Aortic arch anomalies are associated with increased risk of neurological events in carotid stent procedures. *Eur J Vasc Endovasc Surg*. 33(4):436-441.

23. Montorsi P, Galli S, Ravagnani P, Ali SG, Trabattoni D, et al. 2009. Carotid stenting through the right brachial approach for left internal carotid artery stenosis and bovine aortic arch configuration. *Eur Radiol*. 19(8):2009-2015.

24. Gan HW, Bhasin A, Wu CJ. 2010. Transradial carotid stenting in a patient with bovine arch anatomy. *Catheterization Cardiovasc Interv.* 75(4):540-543.

25. Graham JM, Feliciano DV, Mattox KL, Beall Jr. AC. 1982. Innominate vascular injury. *J Trauma* 22(8):647-655.

26. Jweied E, Fogelson B, Fishman D, Merlotti G. 2002. Blunt injury of the innominate artery associated with a bovine arch. *J Trauma*. 52(5):1002–1004.

27. Roberts CS, Sadoff JD, White DR. 2000. Innominate arterial rupture distal to anomalous origin of left carotid artery. *Ann Thorac Surg*. 69(4):1263–1264.

28. Mauney MM, Cassada DC, Kaza AK, Long SM, Kern JA. 2001. Management of innominate artery injury in the setting of bovine arch anomaly. *Ann Thorac Surg*. 72(6):2134–2136.

29. Moise MA, Hsu V, Braslow B, Woo Y. 2004. Innominate artery transection in the setting of a bovine arch. *J Thorac Cardiovasc Surg*. 128(4):632–634.

30. Al-khaldi A, Robbins RC. 2006. Successful repair of blunt injury of aortic arch branches in the setting of bovine arch. *J Vasc Surg*. 43(2):396-398.

31. Bizzarri F, Mattia C, Di Nardo M, Di Marzio E, Ricci M, et al. 2008. Antegrade selective cerebral perfusion in patients with "bovine aortic arch": is it easier? *J Thorac Cardiovasc Surg.* 3(1), art. no. 60.

32. Kaul P, Javangula K, Ganti S, Balaji S, Sivananthan M, et al. 2009. Continuous selective bilateral antegrade cerebral perfusion through anomalous innominate artery for repair of root, ascending aortic, and arch aneurysm – challenges, vagaries, and opportunities of bovine arch variant anatomy and review of literature. *Perfusion*. 24(2):121-133.

33. Ho VB, Bakalov VK, Cooley M, Van PL, Hood MN, et al. 2004. Major vascular abnormalities in Turner syndrome: prevalence and magnetic resonance angiographic features. *Circulation*. 110(12):1694-1700.

34. Mortensen KH, Hjerrild BE, Anderson NH, Sorensen KE, Horlyck A, et al. 2010. Abnormalities of the major intrathoracic arteries in Turner syndrome as revealed by magnetic resonance imaging. *Cardiol Young*. 20(2):191-200.

35. Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton III LJ, Bailey KR, et al. 2003. Bicuspid aortic valve associated with aortic dilatation: a community-based study. *Arterioscler Thromb Vasc Biol.* 23(2):351-356.

36. Rosenquist TH, Beall AC, Modis L, Fishman R. 1990. Impaired elastic matrix development in the great arteries after ablation of the cardiac neural crest. *Anat Rec.* 226(3):347-359.

37. Kappetein AP, Gittenberger-de Groot AC, Zwinderman AH, Rohmer J, Poelmann RE, et al. 1991. The neural crest as a possible pathogenetic factor in coarctation of the aorta and bicuspid aortic valve. *J Thorac Cardiovasc Surg*. 102(6):830-836.

38. Schlatmann TJ, Becker AE. 1977. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. *Am J Cardiol.* 39: 13-20.

39. Elefteriades JA. 2008. Thoracic aortic aneurysm: reading the enemy's playbook. *Curr Probl Cardiol.* 33(5):203-277.

40. Folkow B. 1987. Structure and function of the arteries in hypertension. *Am Heart J.* 114(4):938-948.

41. Okamoto RJ, Xu H, Kouchoukos NT, Moon MR, Sundt III TM. 2003. The influence of mechanical properties on wall stress and distensibility of the dilated ascending aorta. *J Thorac Cardiovasc Surg*. 126(3):842-850.

42. Ince H, Nienaber CA. 2007. Etiology, pathogenesis and management of thoracic aortic aneurysm. *Nat Clin Pract Cardiovasc Med.* 4(8):418-427.

43. Clouse WD, Hallett Jr JW, Schaff HV, Gayari MM, Ilstrup DM, et al. 1998. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA.* 280(22):1926-1929.

44. *National Center for Injury Prevention and Control*. Centers for Disease Control. http://webapp.cdc.gov/cgi-bin/broker.exe.

45. Pressler V, McNamara JJ. 1980. Thoracic aortic aneurysm: natural history and treatment. *J Thorac Cardiovasc Surg*. 79(4):489-498.

46. Sueyoshi E, Sakamoto I, Hayashi K, Yamaguchi T, Imada T. 2004. Growth rate of aortic diameter in patients with type B aortic dissection during the chronic phase. *Circulation.* 110(11 Suppl 1):II256-II261.

47. Sueyoshi E, Sakamoto I, Uetani M. 2009. Growth rate of affected aorta in patients with type B partially closed aortic dissection. *Ann Thorac Surg.* 88(4):1251-1257.

48. Coady MA, Rizzo JA, Hammond GL, Mandapati D, Darr U, et al. 1997. What is the appropriate size criterion for resection of thoracic aortic aneurysms? J *Thorac Cardiovasc Surg*. 113(3):496-491.

49. Coady MA, Rizzo JA, Elefteriades JA. 1999. Developing surgical intervention criteria for thoracic aortic aneurysms. *Cardiol Clin*. 17(4):827-839.

50. Dapunt OE, Galla JD, Sedighi AM, Lansman SL, Mezrow CK, et al. 1994. The natural history of thoracic aortic aneurysms. *J Thorac Cardiovasc Surg*. 107(5):1323-1333.

51. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, et al. 2002. Yearly rupture or dissection rate for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg.* 73(1):17-28.

52. Davies JE, Sundt TM. 2007. Surgery insight: the dilated ascending aorta – indications for surgical intervention. *Nat Clin Pract Cardiovasc Med.* 4(6):330-339.

53. Lobato AC, Puech-Leao P. 1998. Predictive factors for rupture of thoracoabdominal aortic aneurysm. *J Vasc Surg.* 27(3):446-453.

54. Juvonen T, Ergin MA, Galla JD, Lansman SL, McCullough JN, et al. 1999. Risk factors for rupture of chronic type B dissections. *J Thorac Cardiovasc Surg*. 117(4):776-786.

55. Bernard Y, Zimmerman H, Chocron S, Litzler JF, Kastler B, et al. 2001. False lumen patency as a predictor of late outcome in aortic dissection. *Am J Cardiol.* 87(12):1378-1382.

56. Elefteriades JA, Farkas EA. 2010. Thoracic aortic aneurysm: clinically pertinent controversies and uncertainties. *J Am Coll Cardiol.* 55(9):841-857.

57. Hirose Y, Hamada S, Takamiya M, Imakita S, Naito H. 1993. Growth rates of aortic aneurysms as a risk factor in rupture: an evaluation with CT. *Nippon Igaku Hoshasen Gakkai Zasshi.* 53(6):635-640.

58. Masuda Y, Takanashi K, Takasu J, Morooka N, Inagaki Y. 1992. Expansion rate of thoracic aortic aneurysms and influencing factors. *Chest*. 102(2):461-466.

59. Hirose Y, Hamada S, Takamiya M. 1995. Predicting the growth of aortic aneurysms: a comparison of linear vs exponential models. *Angiology*. 46(5):413-419.

60. Rizzo JA, Coady MA, Elefteriades JA. 1998. Procedures for estimating growth rates in thoracic aortic aneurysms. *J Clin Epidemiol*. 51(9):747-754.

61. Elefteriades JA, Hatzaras I, Tranquilli MA, Elefteriades AJ, Stout R, et al. 2003. Weight lifting and rupture of silent aortic aneurysms. *JAMA*. 290(21):2803.

62. Hatzaras I, Tranquilli M, Coady M, Barrett PM, Bible J, et al. 2007. Weight lifting and aortic dissection: more evidence for a connection. *Cardiology*. 107(2):103-106.

63. Hatzaras IS, Bible JE, Koullias GJ, Tranquilli M, Singh M, et al. 2007. Role of exertion or emotion as inciting events for acute aortic dissection. *Am J Cardiol.* 100(9):1470-1472.

64. Koullias G, Modak R, Tranquilli M, Korkolis DP, Barash P, et al. 2005. Mechanical deterioration underlies malignant behavior of aneurysmal human ascending aorta. *J Thorac Cardiovasc Surg*. 130(3):677.e1-677.e9.

65. Carlson RG, Lillehei CW, Edwards JE. 1970. Cystic medial necrosis of the ascending aorta in relation to age and hypertension. *Am J Cardiol.* 25(4):411-415.

66. Schlatmann TJ, Becker AE. 1977. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. *Am J Cardiol.* 39(1):13-20.

67. Hasham SN, Guo D, Milewicz DM. 2002. Genetic basis of thoracic aortic aneurysms and dissections. *Curr Opin Cardiol.* 17(6):677-683.

68. Ikonomidis JS, Jones JA, Barbour JR, Stroud RE, Clark LL, et al. 2006. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with Marfan syndrome. *Circulation.* 114(1 Suppl):I365-I370.

69. Milewicz DM, Michael K, Fisher N, Coselli JS, Markello T, et al. 1996. Fibrillin-1 mutations in patients with thoracic aortic aneurysms. *Circulation.* 94(11):2708-2711.

70. Pachulski RT, Weinberg AL, Chan KL. 1991. Aortic aneurysm in patients with functionally normal or minimally stenotic bicuspid aortic valve. *Am J Cardiol.* 67(8):781-782.

71. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. 1992. Association of aortic dilation with regurgitant , stenotic, and functionally normal bicuspid aortic valves. *J Am Coll Cardiol.* 19(2):283-288.

72. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, et al. 1999. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart.* 82(1):19-22.

73. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, et al. 2008. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation.* 117(21):2776-2784.

74. Jarchow BH, Kincaid OW. 1961. Poststenotic dilatation of the ascending aorta: its occurrence and significance as a roentgenologic sign of aortic stenosis. *Proc Staff Meet Mayo Clin.* 36:23-33.

75. Ferencik M, Pape LA. 2003. Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. *Am J Cardiol.* 92(1):43-46.

76. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, et al. 2000. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. *Circulation.* 102(19 Suppl 3):III35-III39.

77. Yasuda H, Nakatani S, Stugaard M, Tsujita-Kuroda Y, Bando K, et al. 2003. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve: comparison with tricuspid aortic valve. *Circulation.* 108 Suppl 1:II291-II294.

78. De Sa M, Moshkovitz Y, Butany J, David TE, Robicsek F, et al. 1999. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the Ross procedure. *J Thorac Cardiovasc Surg*. 118(4):588-596.

79. Bauer M, Pasic M, Meyer R, Goetze N, Bauer U, et al. 2002. Morphometric analysis of aortic media in patients with bicuspid and tricuspid aortic valve. *Ann Thorac Surg*. 74(1):58-62.

80. Fedak PWM, De Sa MPL, Verma S, Nili N, Kazemian P, et al. 2003. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. *J Thorac Cardiovasc Surg*.126(3):797-806.

81. Koullias GJ, Korkolis DP, Ravichandran P, Psyrri A, Hatzaras I, et al. 2004. Tissue microarray detection of matrix metalloproteinases, in diseased tricuspid and bicuspid aortic valves with or without pathology of the ascending aorta. *Eur J Cardiothorac Surg.* 26(6):1098-1103.

82. Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, et al. 2002. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Invest.* 110(5):625-632.

83. Tsarouhas K, Soufla G, Apostolakis S, Zaravinos A, Panagiotou M, et al. 2010. Transcriptional regulation of TIMPs in ascending aorta aneurysms. *Thromb Res.* 126(5):399-405.

84. Ikonomidis JS, Jones JA, Barbour JR, Stroud RE, Clark LL, et al. 2007. Expression of matrix metalloproteinases and endogenous inhibitors within ascending aortic aneurysms of patients with bicuspid or tricuspid aortic valves. *J Thorac Cardiovasc Surg*. 133:1028-1036.

85. McMillan WD, Tamarina NA, Cipollone M, Johnson DA, Parker MA, et al. 1997. Size matters: the relationship between MMP-9 expression and aortic diameter. *Circulation*. 96(7):2228-2232.

86. Sinha I, Behti S, Cronin P, Williams DM, Roelofs K, et al. 2006. A biologic basis for asymmetric growth in descending thoracic aortic aneurysms: a role for matrix metalloproteinase 9 and 2. *J Vasc Surg.* 43(2):342-348.

87. Davies RR, Kaple RK, Mandapati D, Gallo A, Botta DM, et al. 2007. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. *Ann Thorac Surg.* 83(4):1338-1344.

88. Michel JB. 2001. Contrasting outcomes of atheroma evolution: intimal accumulation versus medial destruction. *Arterioscler Thromb Vasc Biol.* 21(9):1389-1392.

89. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, et al. 2000. Independent association of high blood pressure and aortic atherosclerosis: a population-based study. *Circulation.* 102(17):2087-2093.

90. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Sicks JD, et al. 2003. Is aortic dilatation an atherosclerosis-related process? Clinical, laboratory, and transesophageal echocardiographic correlates of thoracic aortic dimensions in the population with implications for thoracic aortic aneurysm formation. *J Am Coll Cardiol.* 42(6):1076-1083.

91. Scherer PW. 1973. Flow in axisymmetrical glass model aneurysms. *J Biomech.* 6(6):695-700.

92. Absi TS, Sundt TM, Tung WS, Moon M, Lee JK, et al. 2003. Altered patterns of gene expression distinguishing ascending aortic aneurysms from abdominal aortic aneurysms: complementary DNA expression profiling in the molecular characterization of aortic disease. *J Thorac Cardiovasc Surg*. 126(2):344-357.

93. Griepp RB, Ergin MA, Galla JD, Lansman SL, McCullough JN, et al. 1999. Natural history of descending thoracic and thoracoabdominal aneurysms. *Ann Thorac Surg.* 67(6):1927-1930.

94. Biddinger A, Rocklin M, Coselli J, Milewicz DM. 1997. Familial thoracic aortic dilatations and dissections: a case-control study. *J Vasc Surg*. 25(3):506-511.

95. Coady MA, Davies RR, Roberts M, Goldstein LJ, Rogalski MJ, et al. 1999. Familial patterns of thoracic aortic aneurysms. *Arch Surg.* 134(4):361-367.

96. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, et al. 2006. Familial thoracic aortic aneurysms and dissections – incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg.* 82(4):1400-1405.

97. Guo D, Hasham S, Kuang S-Q, Vaughan CJ, Boerwinkle E, et al. 2001. Familial thoracic aortic aneurysms and dissections: genetic heterogeneity with a major locus mapping to 5q13-14. *Circulation.* 103(20):2461-2468.

98. Vaughan CJ, Casey M, He J, Veugelers M, Henderson K, et al. 2001. Identification of a chromosome 11q23.2-q24 locus for familial aortic aneurysm disease, a genetically heterogenous disorder. *Circulation.* 103(20):2469-2475.

99. Hasham SN, Willing MC, Guo DC, Muilenburg A, He R, et al. 2003. Mapping a locus for familial thoracic aortic aneurysms and dissections (TAAD2) to 3p24-25. *Circulation.* 107(25):3184-3190.

100. Guo DC, Pannu H, Tran-Fadulu V, Papke CL, Yu RK, et al. 2007. Mutations in smooth muscle alpha-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. *Nat Genet.* 39(12):1488-1493.

101. Hope TA, Markl M, Wigstrom L, Alley MT, Miller DC, et al. 2007. Comparison of flow patterns in ascending aortic aneurysms and volunteers using four-dimensional magnetic resonance velocity mapping. *J Magn Reson Imaging.* 26(6):1471-1479.

102. Fogel MA, Weinberg PM, Haselgrove J. 2006. The impact of aortic arch geometry on flow dynamics using a simplified approach with magnetic resonance velocity mapping. *Congenit Heart Dis.* 1(6):300-308.