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Natural History Of Thoracic Aortic Aneurysm Associated With Bicuspid Aortic Valve

Thais Faggion Vinholo

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Natural History of Thoracic Aortic Aneurysm Associated with Bicuspid Aortic Valve

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

by
Thais Faggion Vinholo
2020
ABSTRACT

THE NATURAL HISTORY OF THORACIC AORTIC ANEURYSM ASSOCIATED WITH BICUSPID AORTIC VALVE

Thais Faggion Vinholo, Mohammad Zafar, Jinlin Wu, Dimitra Papanikolaou, Mohamed Abdelbaky, Mahnoor Imran, Hesham Ellauzi, Joelle Buntin, Bulat Ziganshin, Sandeep Mukherjee, John A. Elefteriades.

Aortic Institute, Yale University School of Medicine, New Haven, CT

Hypothesis: Thoracic aortic aneurysm (TAA) is a silent but virulent disease. Bicuspid aortic valve (BAV) is the most common congenital heart disease. The association between BAV and ascending TAA (ATAA) is well described. However, the guidelines for surgical management to treat patients with thoracic aortic aneurysms associated with bicuspid aortic valve (ATAA-BAV) remains controversial. We hypothesized that the surgical management of patients with ATAA-BAV should not differ from the management of those who have ATAA with a trileaflet aortic valve (TAV). Additionally, we suspected that BAVs that are free of stenosis and regurgitation can be spared in the setting of ATAA repair. In this study, we aimed to (1) characterize the natural behavior of BAV-ATAA, (2) define surgical guidelines for elective intervention in patients with ATAA-BAV, and (3) characterize the behavior of spared bicuspid aortic valves during ATAA resection.

Methods: A retrospective review of the Yale Aortic Institute database was done to identify patients with ATAA-BAV. We calculated rate of growth, yearly rate of complications, 5-year event-free survival through a Kaplan-Meier curve, as well as a logistic regression that looked into risk of complications as a function of aortic size. Of these patients, the ones
whose valve was spared at the time of surgery were further analyzed. Postoperative and preoperative echocardiograms were compared to determine changes in valve function of this smaller cohort.

**Results:** We identified 514 patients with ATAA-BAV through data collection. The mean growth rate of ATAA-BAV was 0.21 cm/year. The larger the aneurysm, the faster it grew. There was a 13% yearly rate of rupture, dissection, and death in patients with an ATAA diameter ≥ 6cm. These patients have a 13-fold increase risk of suffering an aortic complication compared to patients with an aortic size of 4-4.5 cm (p<0.05). There was a sharp increase in the probability of aortic complications including dissection, rupture, and death at ATAA diameters of 5.0, 5.5, and 6.0 cm. Out of the 514 patients, did not have their valve replaced. There was 100% echocardiogram follow-up for these 23 patients. The average time between preoperative and postoperative echocardiograms was 4.50±4.09 years (0.19-15.63). Aortic stenosis or regurgitation changed from none to mild in 21.7% of patients, with an average echocardiographic interval follow-up of 3.08 years, and from none to severe in 2 (8.7%), with an interval of 11.7 years. One patient required reoperation, including aortic valve replacement, during follow-up.

**Conclusion:** Prophylactic size-based surgery in BAV-ATAA patients can be considered at 5.0 cm at expert aortic centers as a means to afford protection from natural complication. Non-expert center may wait for 5.5 cm. BAV free of aortic stenosis or insufficiency before surgery and “healthy” appearing at surgery can safely be preserved.
Acknowledgements:

In memorium of my father, Flavio Bueno Vinholo, who was my first mentor and continues to be my role model. In dedication to my mother who has never measured her efforts for my career. To my brother who is one of the best friends a girl could have ever asked for and to my grandma who is my biggest supporter and prayer warrior.

I would not be where I am if it wasn’t for my mentors. To my mentor, Dr. John Elefteriades, who has led by example has made me fall in love with cardiac surgery and most importantly, the aorta. Thank you for instilling in me a curiosity and drive to understanding thoracic aortic disease and helping to prevent patients from dying from catastrophic events. Thank you, Dr. “E”, for showing me that it is possible to be an incredible clinician surgeon.

To my friends and mentors, Mohammad Zafar and Bulat Ziganshin, who have taught me how to appreciate the intricacies of aortic surgery research. Thank you for all you continue to teach me. Last but not least, Dr. Mukherjee. Thank you for all your advice and support during this journey.

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To my beloved and sweet “family from New Haven”, the Oliveiras. Thank you for making me feel like home away from home, for your love and support. To my dear friends Yejoo Jeon, Fan Zhang, Julie Chung, Liliya Benchetrit, Diana Yanez, thank you for your friendship, prayers, and unwavering support.

Lastly, and most importantly, all honor and glory to God, whom all blessings come from.
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GLOSSARY OF ABBREVIATIONS

AI – Aortic Insufficiency

AS – Aortic Stenosis

ATAA – Ascending Thoracic Aortic Aneurysm

ATAA-BAV – Ascending Thoracic Aortic Aneurysm associated with BAV

ATAA-TAV – Ascending Thoracic Aortic Aneurysm associated with TAV

AVR – Aortic Valve Replacement

BAV – Bicuspid Aortic Valve

TAA – Thoracic Aortic Aneurysm

TAV – Trileaflet Aortic Valve

TAVR – Transcatheter Aortic Valve Replacement
INTRODUCTION

Thoracic Aortic Aneurysm

Thoracic aortic aneurysm (TAA) is a silent but virulent disease. It affects roughly 1% of the general population, making aneurysm and dissection of the aorta a major cause of death, accounting for 1-2% of deaths in Western Countries\(^1\). Most patients are asymptomatic and incidentally diagnosed by chest x-ray, CT scan, or echocardiogram acquired for alternative reasons\(^2\). In the absence of surgical intervention, the natural behavior of TAA is progressive increase in size, often until a potentially-lethal complication occurs, such as aortic dissection or rupture\(^3\). According to the Centers for Disease Control and Prevention (CDC), aortic aneurysm is the 19\(^{th}\) leading cause of death overall and the 17\(^{th}\) leading cause of death in individuals over 65 years of age, ranking well above human immunodeficiency virus (HIV)\(^4\). Moreover, we suspect that even these alarming numbers may be an underestimation. A Japanese study of postmortem CT scans revealed that 7% of patients whose pre-hospital deaths were attributed to cardiopulmonary arrest had actually suffered an acute aortic event\(^5\). This supports our suspicion and highlights the need for further efforts to detect TAA prior to potentially lethal complications.

The thoracic aorta resembles the shape of a candy cane. It is divided into ascending, arch, and descending portions. The ascending segment begins at the aortic annulus and ends at the brachiocephalic artery while the descending segment starts at the level of the left subclavian artery (Figure 1). The aortic arch is found in between. The focus of this thesis is on aneurysms involving the ascending portion of the aorta (ATAA).
Thoracic aortic aneurysm and dissection (TAAD) can be divided into two entities: syndromic and non-syndromic. Syndromic TAAD involves other organ systems in addition to the aorta, whereas non-syndromic TAAD is confined to the aorta. The involvement of other organ systems can provide overt clinical signs of disease to alert the physician. Syndromic patients suffer from systemic diseases such as Marfan syndrome, Loeyz-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome, aneurysm-osteoarthritis syndrome, and cutis laxa syndrome\textsuperscript{7}. However, these syndromes only account for approximately 5\% of all TAADs, whereas familial and sporadic non-syndromic TAAD account for 95\% of TAAD\textsuperscript{7,8}. Furthermore, the distinct cardiovascular, musculoskeletal, and ocular phenotypic manifestations of syndromic TAAD may bring these patients to medical attention earlier in their disease course, whereas the lack of overt clinical stigmata in non-syndromic TAAD patients delays diagnosis, underlining the importance of finding additional clues to detect TAA, especially in the non-syndromic category.
In the search for further clues to help on the detection of TAA throughout the years, TAA was proven to be associated with multiple comorbidities. A paradigm of “guilt by association” was presented by Homick et al\(^3\) where a number of “guilty associates” that are frequently accompanied by TAA were described including intracranial aneurysms, abdominal aortic aneurysms, aortic arch anomalies, simple renal cysts, positive family history of aortic disease, positive thumb-palm test, temporal arteritis, and bicuspid aortic valve (BAV)\(^3\) (Figure 2). The most common associated aortic arch anomaly is the bovine aortic arch, in which there is a common origin of the brachiocephalic and left common carotid artery from the aortic arch. Any of these findings warrants further investigation for the presence of TAA. Up to 84% of BAV patients are affected with ATAA\(^9\), 80-fold greater than the general population\(^10\). The high prevalence of ATAA-BAV has driven scientific efforts to understand the pathophysiology of this association.

Figure 2. Paradigm of “guilt by association” for detection of silent thoracic aortic aneurysms (reproduced with permission from ref\(^3\)).
Natural History of TAA

The Aortic Institute at Yale has been internationally recognized for its investigative efforts regarding the natural history of TAA since our original work on a cohort of 230 patients was published in 1997\textsuperscript{11}. Since then, we have been committed to describing the behavior of TAA during its natural course in hopes of using this information to predict risk of TAA complications, to guide surgical management, and ultimately to significantly decrease the burden of this deadly disease.

Previous Studies

*Height Index*

Historically, absolute aortic diameter was used to predict future TAA behavior and guide decision-making for surgical intervention. Subsequently, once patients body size was shown to be associated with differing normal aortic sizes\textsuperscript{12}, the aortic size index (ASI) was introduced. The ASI is the aortic diameter divided by the body surface area (BSA); thus both patient height and weight were incorporated into decision making\textsuperscript{13}. However, our group posited that height alone as an adjustment for normal aortic size and risk of TAA complications might suffice (instead of BSA), as a person’s weight may vary throughout an adult lifetime, but the aorta is unlikely to mirror that weight fluctuation. For instance, a 5 cm aneurysm may be tolerable for a 6’ tall person while it may present substantial danger for someone who is 5’ tall. In a retrospective cohort study of 780 patients with ATAA, we stratified annual risk of complications by a new measure, the aortic height index (AHI), and demonstrated that AHI is not only equivalent but mildly superior as a predictor of aortic complications compared to ASI\textsuperscript{14}. The AHI is calculated by dividing the aortic diameter by the patient’s height\textsuperscript{14}. With this data we were able then to construct a
nomogram to stratify patients as “low risk”, “moderate risk”, “high risk”, and “severe risk” as a function of aortic diameter in relation to their height (Figure 3)\textsuperscript{14}. Although this nomogram is a highly useful guide for clinical decision-making for prophylactic aortic aneurysm repair, it makes no distinction between patients with different aortic valve morphology (BAV vs. trileaflet aortic valve (TAV)).

Figure 3. Risk of aortic event (dissection, rupture, and death) in patients with ATAA as a function of aortic diameter and height\textsuperscript{14}

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<thead>
<tr>
<th>Height (inches)</th>
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<tr>
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**Bicuspid Aortic Valve**

The aortic valve is normally composed of three leaflets, making it a trileaflet valve. However, failure of leaflet separation during embryogenesis may lead to an aortic valve with only two distinct leaflets, rendering it a bicuspid aortic valve (BAV)\textsuperscript{15}. BAV was first described by Leonardo da Vinci over 400 years ago\textsuperscript{16}. Since that time, it has drawn significant attention for its major impact on society. For example, BAV is the most
common congenital cardiac disorder and afflicts 1-2% of the general population\textsuperscript{17} with a male/female ratio of 2:1\textsuperscript{18}.

The clinical presentation of BAV is remarkably heterogenous\textsuperscript{10}. Age at diagnosis ranges from neonates\textsuperscript{19} to the elderly\textsuperscript{20}. BAV can be detected incidentally by auscultation during physical exam or by advanced imaging such as echocardiography. Alternatively, BAV may be detected in a symptomatic patient, as BAV is associated with early-onset aortic insufficiency (AI), early-onset aortic stenosis (AS), and higher rates of bacterial endocarditis\textsuperscript{18}. These findings can lead to a rapid decline in BAV function\textsuperscript{21}. BAV has been identified as an underlying factor for as many as 50% of isolated stenotic aortic valves meeting requirements for surgery\textsuperscript{22}. The high prevalence of this abnormal valve morphology, combined with its associated comorbidities, has driven an incredible effort from the scientific community to understand this phenomenon.

Familial occurrence of BAV is common. Approximately 9-15% of first-degree relatives of patients with BAV also have BAV\textsuperscript{21,23,24}. To date, no single gene has been unequivocally and generally associated with BAV. Still, the familial pattern observed likely suggests a multifactorial genetic mechanism\textsuperscript{9}. Secondly, it is noteworthy to recognize that BAV is not always an independent phenomenon. BAV is often seen in concurrence with other cardiovascular conditions including but not limited to coarctation of the aorta, Turner syndrome, and Loeys-Dietz syndrome\textsuperscript{9}.

BAV has been linked to aortic dissection and vasculopathies including ascending aortic dilation and aneurysm formation. As mentioned previously, 84% of BAV patients are affected with ATAA, 80-fold higher than the general population\textsuperscript{10}. While these numbers draw attention, they still may not fully capture the true number of affected
patients, given that we may miss individuals who remain asymptomatic for the majority of their lives.

ATAA Association with BAV

Historically, the association between ATAA and BAV has been explained by two different schools of thought: the hemodynamic and genetic theories. Understanding the root behind this association is important due to its important clinical implications.

Hemodynamic Theory

This theory alleges that the formation of aneurysms is due to the turbulent flow caused by the abnormal BAV morphology. According to Sievers and colleagues, there are three major types of BAV morphology: type 0, type 1, and type 2, with type 1 being the most common (75% of clinical cases). Although these are often grouped together, it has been demonstrated that the fusion pattern may determine the aortic wall shear stress distribution throughout the aorta and consequently determine aortopathy remodeling. The classification is determined by the pattern of commissural fusion (Figure 4).

Figure 4. BAV phenotype morphology schematic presentation.
**Genetic Theory**

This theory supports the notion that there is a strong genetic component in the development of ATAA in patients with BAV. The discovery of familial aggregation of AAA by Tilson at Yale in 1984\(^{26}\) ultimately triggered a search for genetic factors contributing to the development of TAA in the late 1990s\(^{27,28}\).

Our group publishes annual updates reviewing the genes that have been associated with TAA and dissection (TAAD) in the Yale journal AORTA. In a recent review, we specifically described genes that have been associated with both ATAA and BAV\(^{29}\). Our understanding of the genetics of ATAA-BAV continues to evolve every year. Recent significant findings have enhanced our understanding of the pathogenesis of ATAA-BAV. Gould *et al.*, with the intent of identifying genes playing a role in the pathogenesis of non-syndromic ATAA-BAV, performed whole-exome and targeted sequencing on 736 individuals with ATAA-BAV and 376 controls. In 1.77% of the affected individuals (13/736), a new heterozygous mutation in the *ROBO4* gene was identified, including 2 variants that segregated with disease among 2 affected families\(^{30}\). *ROBO4* is markedly expressed in endothelial cells and plays a role in endothelial barrier function. In this study, *ROBO4* expression was found to be diminished in the resected aorta of an affected individual with ATAA. To further test their hypothesis that *ROBO4* variants lead to disruption of endothelial performance at a cellular level, thus altering vascular permeability, the authors cultured human aortic endothelial cells and either silenced *ROBO4* or expressed *ROBO4* variants. They confirmed that *ROBO4* abnormalities did indeed induce endothelial barrier dysfunction. Lastly, the authors created homozygous *ROBO4* knockout mice and a knock-in mouse with a ROBO4 splice donor site mutation;
the affected mice presented with a mix of aortic valve dysfunction (BAV and/or aortic regurgitation or stenosis) and ATAA, confirming their suspicion that a heterozygous mutation in *ROBO4* can lead to a non-syndromic presentation of ATAA-BAV\(^{30}\).

It is well documented that there is an increased risk for TAA among individuals with Turner Syndrome (TS), although the precise etiology has thus far remained elusive. Corbitt and colleagues shed light on this subject by demonstrating that TS individuals with deleterious mutations in *TIMP3* are significantly more likely to suffer from BAV and TAA than TS patients without *TIMP3* variants. Furthermore, they found that having hemizygosity for *TIMP1*, which is functionally redundant to *TIMP3*, along with a *TIMP3* variant, synergistically increased the risk for BAV and TAA\(^ {31}\).

To date, 37 genes have been associated with TAAD. We estimated that at least 30% of patients with familial and sporadic non-syndromic TAAD harbor variations in these 37 genes. Variations in 13 of these 37 genes have also been associated with BAV (*ACTA2, FBN2, FLNA, LOX, MAT2A, NOTCH1, ROBO4, SMAD3, SMAD6, TIMP3, TIMP1, TGFB2, TGFBR1, TGFBR2*)\(^ {29}\). Most of these genes are involved in determining the structure and maintenance of the aortic wall and its contained vascular smooth muscle cells (VSMC)\(^ {32}\). The increasing number of genes discovered every year has led us to believe that ATAA is primarily a genetic disease, which suggests that ATAA-BAV may be no different.

Certain genetic patients may develop acute aortic events at a smaller aortic diameter. Hence, supporters of this theory consider the risk of acute aortic complications to be higher in patients harboring these mutations and therefore apply more aggressive management.
Most authorities give credence to both hemodynamic and genetic contributions to ATAA-BAV patients.

**Imaging Modalities**

The biggest challenge in the realm of TAA remains unsolved: its diagnosis. Ideally, patients with ATAA-BAV must be captured while they are still asymptomatic - that is, before they develop an acute ATAA complication (rupture, dissection, or death).

TAA can be detected through the following imaging modalities: CXR, echocardiography (transthoracic and transesophageal), computed tomography (CT) scan, and magnetic resonance imaging (MRI). Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)/CT imaging, a vascular metabolic imaging technique pioneered by Sakalihasan and colleagues from Liege, is also emerging as a method to monitor aortic aneurysm disease progression and to predict the risk of adverse aortic events based on intensity of FDG uptake by inflammatory cells. Although screening programs and criteria are well established for other types of aneurysms, there are no clinical criteria in place for patients with ATAA.

There exists no ‘gold-standard’ imaging modality for screening and monitoring TAAs, with each method having its own limitations and advantages. Echocardiography is most useful for visualizing the aortic root, while CT and MRI are more crucial for the remaining segments of the aorta (mid ascending, arch, and descending aorta). The use of echocardiography supplemented by CT or MRI allows for a comprehensive assessment of the aorta. Despite certain inherent limitations, TTE is the recommended imaging modality for patients with ATAA-BAV.
Radiographic screening of aneurysms is extremely valuable and addresses the most important factor guiding the decision to intervene electively: TAA size. However, imaging alone does not suffice. We cannot image the entire general population, where detection of asymptomatic TAA is paramount. However, negative imaging may lead to missed aneurysms that are genetically programmed to occur but have not yet reached a detectable size. Moreover, there are times when negative events might occur without the aorta having achieved a significant enlargement, especially in the setting of pathogenic TAAD-causing genetic mutations. This emphasizes the urgent need for biomarkers for TAAs, and better screening tools for non-syndromic TAD such as in patients with ATAA-BAV. The purpose of this study is to understand the behavior of ATAA-BAV.

**Surgical Intervention Guidelines**

Although ATAA is a potentially deadly disease, surgical repair restores a patient’s life expectancy to normal\(^{35}\). The clinical decision in favor of surgery is made when the risk of an adverse event supersedes the risks imposed by ATAA repair surgery. Thus, one of the most important decisions for health care providers involving patients with ATAA-BAV is the timing of surgery. Given that open cardiac surgery does not come without risk, it is important to consider when the benefits of surgery outweigh its potential harm. We hope that a better understanding of the natural behavior of ATAA-BAV will inform us when to intervene surgically.

Most recent guidelines for prophylactic aortic repair surgery in patients with a TAV recommend intervention at an aortic diameter of 5.0 cm. However, surgical management for ATAA-BAV remains controversial. Multiple major international societies have created diverging guidelines for managing patients with ATAA-BAV. These recommendations
vary from aggressive approaches suggesting ATAA-BAV management be the same as for Marfan and other connective tissue disorders, to more conservative measures. Consequently, diverging guidelines have paradoxically raised more questions than answers.

The American College of Cardiology/American Heart Association (ACC/AHA) in 2010 recommended ATAA replacement at a 5.0 cm diameter cutoff for patients free of valve dysfunction\(^2\). Subsequently, the same group released revised guidelines in 2014 recommending intervention at ATAA size of 5.5 cm\(^3\). In 2016, a clarification statement was released by the ACC/AHA on the management of ATAA-BAV, recommending surgical intervention at a 5.0 cm aortic diameter\(^3\). The change in recommendation within a short period of time by the group sheds light on the fact that comprehensive knowledge and prediction of ATAA-BAV remains elusive and lacks clear supporting evidence.

Recently, our principal investigator (J.A.E.) and other experts in the field published a clarification statement regarding the ideal time for patients with ATAA-BAV to undergo operative intervention. However, the authors admit that literature describing the long-term events of patients with ATAA-BAV is lacking\(^9\). Guidelines have changed over recent years, reflecting the lack of consensus due to insufficient understanding of the natural history of ATAA-BAV.

**Sparing the bicuspid aortic valve during aneurysmectomy**

Similar to the management of ATAA-BAV, another controversy regarding the management of BAV still exists. While current literature has focused on the efficacy of BAV repair, valve replacement, or reimplantation of the BAV (the David procedure), we
decided to investigate the behavior of completely spared, untouched valves, during ATAA repair.

There is vast literature regarding the David operation, first described in 1989 by David et al., when this procedure was performed in patients with Marfan’s syndrome and a trileaflet aortic valve\(^3\). Since then, this procedure, involving aortic root replacement with reimplantation of the aortic valve, has been extended to patients with BAV\(^3\). It is important to highlight the distinction between the David operation, where the aortic root is replaced and native aortic valve is re-implanted, and our patient cohort in whom the ascending aorta was replaced but the aortic valve and aortic root were left untouched.
STATEMENT OF PURPOSE AND SPECIFIC AIMS

The purpose of the study at hand is to provide information on the long-term complications of ATAA-BAV and to inform future surgical recommendations for patients with BAV. There is significant heterogeneity in BAV associated aortopathy, often necessitating case-by-case decision-making regarding surgical intervention. The present study comprises a large cohort of patients who have been followed both clinically and radiographically until and after surgery.

Aim 1: To characterize the natural behavior of ascending thoracic aortic aneurysm associated with bicuspid aortic valve;

Aim 2: To define surgical guidelines for elective intervention in patients with ascending thoracic aortic aneurysm associated with bicuspid aortic valve;

Aim 3: To characterize the behavior of the spared bicuspid aortic valve during ascending thoracic aortic aneurysmectomy.
MATERIALS AND METHODS

This investigation was approved by the Human Investigation Committee of the Yale University School of Medicine.

Patient Selection

The investigative efforts of the Aortic Institute at Yale-New Haven Hospital have accrued 3,914 current or former patients with thoracic aortic disease (ascending and descending) as part of our database. This database was queried to find patients with an ascending aortic dimension of ≥ 3.5 cm during their first encounter at the Institute, and the concomitant presence of a BAV. The morphology of the aortic valve was confirmed either through echocardiographic imaging preoperatively or through direct observation intraoperatively or both. 514 patients met our inclusion criteria, forming our study group of ATAA-BAV. Patients who had undergone prior aortic valve replacement (AVR) or ATAA surgical repair were excluded from the study. Although the threshold of 3.5 cm approached the lower normal limit of an aneurysmal dimension, the intent of this study was to capture ATAA at its early stage in order to observe growth in a comprehensive manner over time. For the purpose of this study, the “ascending” aorta is defined as the segment from the sinotubular junction aortic annulus to the innominate artery. We call the portion between the aortic annulus and the sinotubular junction as the “aortic root”.

Of the patients fulfilling the criteria for the overarching natural history study (N=514), a subset of patients had their BAV spared during the ATAA repair, forming another separate study group. Our policy was to replace all BAVs with any significant abnormality (aortic stenosis or insufficiency) observed through TEE or by direct visual inspection that suggested that the BAV would not function adequately for many years we
replaced any BAV that was significantly abnormal during TEE or direct inspection during ATAA repair. ATAA-BAV patients that were found intraoperatively to have a functional BAV had their valve spared, forming a subset of patients. From among the initial 514 patients, 491 had their aortic valve replaced or repaired, leaving 23 patients with preserved BAVs who form the subgroup for this part of the study.

**Data collection and processing**

A thorough hospital chart review, including both paper and electronic records, was done for the study group. During this review, clinical, surgical, radiologic, demographic, and risk factor data were collected. Marfan syndrome and other connective tissue diagnoses were applied when either proven through genetic testing or by convincing clinical stigmata as evaluated by the senior author and primary investigator (J.A.E.). A positive family history of TAA was indicated when a patient’s relative was diagnosed with TAA or aortic dissection through an imaging study, intraoperative observation, or autopsy. When patients reported sudden death in a family member, they were identified under the “possible” family history category.

Long-term survival follow-up was done in accordance with the previously described Yale Aortic Institute method - including online database interrogation, hospital EMR interrogation (clinical and mortality), referring doctor follow-up, as well as online obituary search. The last date of proven clinical interaction was considered the end of the follow-up period. Through this method, we were also able to determine whether or not the patients had a TAA associated complication. The list of complications included type A dissection, rupture, or death. A TAA associated complication and surgical intervention were considered an end point follow up in our study.
In order to assess and follow up on the BAV performance of the patients with BAV spared, we measured function before, during, and after surgery via echocardiography for these 23 patients. The severity of AS and/or AI were classified as either non/trace, mild, moderate, or severe.

**ATAA Measurement**

Aortic dimensions were manually measured by our primary investigator (J.A.E.) using one or more of the following imaging modalities: computed tomography (CT) scan, transthoracic echocardiogram (TTE), or magnetic resonance imaging (MRI). Radiologic reports from the Yale Radiology Department were also taken into consideration. When there was a major discrepancy between the two reads, we would decide on the final dimension through consensus during a group lab meeting with the participation of multiple investigators including T.F.V. When faced with a measurement discrepancy between different imaging modalities, the highest measurement was chosen. Serial aortic measurements were carefully made in the same plane and anatomical level in sequential scans. The maximal ATAA-BAV dimension was the largest measurement made prior to the study end point (ATAA-BAV complication, operation, or end of follow-up).

We defined a patient as having a bovine aortic arch when the union of the innominate and left common carotid arteries was observed above the aortic arch\(^{41}\) through preoperative imaging or through direct observation intraoperatively.

**Statistical analysis**

Statistical analysis was performed using R 3.5.2 (R foundation for Statistical Computing, Vienna, Austria) and Excel (Windows Excel 2016, Microsoft, Redmond, WA,
Means and standard deviations (SDs) were reported for continuous variables and frequencies with percentages for categorical variables. Student t-test and Wilcoxon rank sum test were done for continuous and categorical variables, respectively. Multivariable logistic regression was performed to evaluate the association of aortic size with overall risk for ATAA-BAV complication (aortic dissection, aortic rupture, and death), adjusting for sex and age. These variables were chosen through a univariable analysis. Aortic size was stratified into 6 different groups: 3.5-3.9, 4.0-4.4, 4.5-4.9, 5.0-5.4, 5.5-5.9, ≥6 cm. This stratification was done based on the measurement distribution to permit meaningful interpretation with an adequate number of observations within each group. Evaluation of 5-year event-free survival was done via Kaplan-Meier analysis.

We used an instrumental variable approach that was previously validated by our group to estimate growth rates\(^{42}\). In essence, this approach was designed to diminish inherent errors associated with measuring and comparing TAA dimensions\(^{42}\). Patient characteristics including age, gender, Marfan syndrome/connective tissue disorder, presence of family history, and bovine aortic arch configuration were considered in the analysis to assess their impact on the growth rate.

Statistical significance was determined at a p-value of <0.05. (Statistics for the natural history of ATAA-BAV were done by the author J.W.).

All patient characteristics whose BAV were spared were tested for statistically significant association with change in BAV function. Fisher’s exact probability test was used for binary variables and two-sample \( t \) test was used for continuous variables (these statistics were performed by the author T.F.V.).
RESULTS

ATAA-BAV Natural History

This section focuses on the natural behavior of ATAA-BAV over a period of time. Patient characteristics are outlined in Table 1. The majority of patients were men (n=395, 76.7%). Median age was 55.1±13.7 years. Only 2.3% of patients had Marfan’s or another connective tissue disorder and 78/514 (15.2%) had proven positive family history of aortic disease.

Table 1. Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number (%)/Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>394 (76.7)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>55.1±13.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.6±10.4</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>88.4±24.7</td>
</tr>
<tr>
<td>Marfan/CT (%)</td>
<td>12 (2.3)</td>
</tr>
<tr>
<td>Family History (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>278 (54.1)</td>
</tr>
<tr>
<td>Proven</td>
<td>78 (15.2)</td>
</tr>
<tr>
<td>Likely</td>
<td>27 (5.3)</td>
</tr>
<tr>
<td>Possible</td>
<td>47 (9.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>84 (16.3)</td>
</tr>
<tr>
<td>Hx of cardiac surgery (%)</td>
<td>67 (13.0)</td>
</tr>
<tr>
<td>Bovine Arch (%)</td>
<td>79 (15.4)</td>
</tr>
<tr>
<td>AAA (%)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>131 (51.2)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>68 (26.6)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>99 (38.7)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>66 (25.8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>23 (9.0)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>98 (38.3)</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>MI (%)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>42 (16.4)</td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>6 (2.6)</td>
</tr>
</tbody>
</table>
The ATAA-BAV maximal size distribution is shown in Figure 5. The majority of patients (34.82%) had a maximal aortic size ranging between 5.0 to 5.4 cm and only 7.19% of patients had an aortic size ≥6 cm.

Figure 5. Maximal ascending aortic dimension distribution before a study endpoint (aortic complication – dissection, rupture, or death – or surgical intervention).

As depicted in Figure 6, the mean growth rate of ATAA-BAV was estimated to be 0.21±0.04 cm/year. There was a positive correlation between increasing aneurysm size and speed of growth: the larger the aneurysm, the faster it grew. In approximation, while a 4 cm aortic aneurysm grew at a rate of 0.16 cm/year, a 7 cm aortic aneurysm grew at a rate of 0.28 cm/year.

Figure 6. Average annual growth rate of the ATAA-BAV based on initial aneurysm size.
The average yearly risk of ATAA-BAV complications (dissection, rupture, and death) for the 6 stratified aortic size groups (3.5-3.9, 4-4.4, 4.5-4.9, 5-5.4, 5.5-5.9, ≥6cm) is depicted in Figure 7. The number above each histogram portrays the percentage of patients at risk of each complication per year. Patients with larger aortic aneurysms were subject to consistently higher yearly complication risks. An ATAA diameter ≥ 6cm was associated with a 13% yearly risk of rupture, dissection, and death compared with 4.9% in a 5-5.4 cm aortic size.

Figure 7. Yearly risk of ATAA-BAV complications (dissection, rupture, death, dissection/rupture, dissection/rupture/death) at different aortic dimensions.

![Histogram of ATAA-BAV complications](image)

The probability of complications (rupture, dissection, and death) increased abruptly at 3 hinge points: 5.0, 5.5, and 6.0 cm (Figure 8).

Multivariable regression analysis showed that patients with aneurysms ≥ 6cm have a 13-fold increased risk of suffering an aortic complication (dissection or rupture) compared to patients with an aortic size of 4.0-4.5 cm (p<0.05) (Table 2). Surgical mortality in operated BAV-AATA patients was 4/425 (0.9%).
Figure 8. Estimated probability of ATAA-BAV complications (dissection/rupture/death) by aneurysm size.

Table 2. Multivariable logistic regression of ATAA-BAV complication.
**Figure 9** illustrates the 5-year complication-free survival for ATAA-BAV as a function of aortic size. Higher ATAA size was associated with decreased survival.

Figure 9. Kaplan-Meier curves for free of Event Free Survival (including dissection, rupture, death).
Spared BAV

This section focuses on the patients who had their BAV spared during aneurysmectomy surgery. These results have been published in the Journal of Cardiac Surgery\textsuperscript{43}. Patient characteristics are described in Table 3. Of the patient population (n=23), 12 were male and 11 were female. The mean age was 62.0±11.8 years (39.0 – 81.2). No patients had Marfan or Ehlers Danlos syndrome. Both preoperative and postoperative echocardiogram evaluations regarding BAV function were retrieved for all patients. The mean aortic root dimensions were 3.52 cm pre-operatively and 3.67 cm post-operatively.

Table 3. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Average age, mean ± SD</td>
<td>62 ± 11.8</td>
</tr>
<tr>
<td>Max age</td>
<td>81.1</td>
</tr>
<tr>
<td>Min age</td>
<td>38.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>Family history</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Reoperations</td>
<td>1</td>
</tr>
<tr>
<td>AVR in reoperation</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: AVR, aortic valve replacement; Max, maximum; Min, minimum.

BAV Function

Pre-operatively, 22 patients had none or trace AS while 1 had mild. 15 patients had none or trace AI, 7 had mild, and 1 had moderate. Post-operatively, 7 patients had an increase in severity of either AS (Figure 10) and AI (Figure 11), or both. The overall mean duration of echocardiography follow-up was 4.50±4.09 years (0.19-15.63). The mean
number of years between pre-operative and post-operative echocardiograms for patients who had an increase in AS or AI from none to mild and none to moderate/severe were 3.08±1.52 years (1.26 – 4.96) and 11.70±1.78 years (10.45 – 12.96), respectively, and for those whose BAV function was unchanged were 3.85±4.10 (0.19-15.63). Additionally, there were three patients whose AI went from mild pre-operatively to none post operatively with an echo interval time average of 4.86±4.07 (0.47 – 8.53).

Figure 10. Change in aortic stenosis from preoperative (Pre-Op) echocardiogram to postoperative (Post-Op).

Figure 11. Change in aortic valve insufficiency from preoperative (Pre-Op) echocardiogram to postoperative (Post-Op).
Reason for no AVR

One patient out of the studied cohort was adamant about having his valve spared. Three patients had coronary artery bypass graft (CABG) done concurrently with the ascending aortic aneurysm repair and the intention was to avoid adding to the complexity of the surgery with superfluous AVR. Regardless of these factors, all patients did not undergo AVR because their BAV was found to be in good condition, with no or almost no calcification, and overall normal function on echo, with the senior author (J.A.E) judging that the valve would last many years. Direct visual inspection and supplementary intraoperative TEE evaluation of the aortic valve were used to make this determination. We did not preserve valves that manifested thickening, fenestrations, or calcifications. Of note, the one patient who had moderate AI pre-operatively presented with only minimal AI when evaluated through transesophageal echocardiography intraoperatively.

Reoperation

One patient underwent a reoperation, which was accomplished safely. This patient had an increase in AI severity (from none to severe) and underwent AVR. This patient had undergone CABGx3, performed concurrently during the first surgery with the ascending aortic aneurysm repair.

Change in BAV Function and Patient Characteristics

Associations between relevant risk factors and change in BAV function were tested for statistical significance. No statistically significant association was demonstrated (Table 4).
Table 4. Risk factors and change in bicuspid aortic valve function association.

<table>
<thead>
<tr>
<th></th>
<th>Total N</th>
<th>Increased AS and/or AI N</th>
<th>No change or decrease in AS and/or AI N</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y. mean ± SD</td>
<td>62.0 ± 11.8</td>
<td>62.0 ± 6.3</td>
<td>62.0 ± 13.7</td>
<td>1.000</td>
</tr>
<tr>
<td>Male sex</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>0.667</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>0.405</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0.626</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>History of smoking</td>
<td>11</td>
<td>3</td>
<td>8</td>
<td>1.000</td>
</tr>
<tr>
<td>Family History</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0.142</td>
</tr>
<tr>
<td>Echo interval, y. mean ± SD</td>
<td>4.5 ± 4.09</td>
<td>5.5 ± 4.5</td>
<td>4.0 ± 3.98</td>
<td>0.490</td>
</tr>
</tbody>
</table>

Abbreviations: AI, aortic insufficiency; AS, aortic stenosis.
DISCUSSION

TAAs are known to be silent (most commonly causing no symptoms) and continually grow toward the point at which dissection or rupture can occur. Rupture and dissection, when they occur, can be lethal. However, if patients are identified, followed, and treated with appropriate prophylactic surgical intervention, life expectancy can essentially be restored to normal once the operation is complete. ATAA-BAV has a high prevalence and continues to present a burden to the general population. Although this association has been long established, the guidelines for surgical intervention are not clear and supporting evidence remains elusive. In the present study, we report the natural history data from a group of 514 patients with ATAA-BAV. We found that the ATAA in this group of patients grows at 0.21 cm/year. Despite the growth rate being almost twice as fast as our previous findings for all-inclusive ATAA (0.14cm/year)\textsuperscript{14}, the risk of complications adjusted for aortic size was comparable between both groups. In other words, although ATAA-BAV may grow faster they do not seem to be more virulent than ATAA-TAV.

Hinge points

Figure 8 illustrates the increasing probability of ATAA-BAV complications (dissection, rupture, and death) with increasing aortic size. There are three points where the risk of complications increases significantly: 5, 5.5, and 6cm – the “hinge points”. These were similar to the ones identified for all-inclusive patients with ATAA (5.25 and 5.75 cm)\textsuperscript{14}. The comparable probability of aortic events between overall TAA and ATAA-BAV may suggest that the threshold for surgical repair of ATAA-BAV should not differ from that of TAV-ATAA. Prophylactic size-based surgery in ATAA-BAV patients can be
considered at 5.0 cm at expert aortic centers as a means to afford protection from natural complications. Non-expert centers may wait for 5.5 cm.

*Sparing BAV valve during ATAA surgical repair*

The present study also supports applying surgical judgment regarding potential concomitant replacement of a BAV at the time of ATAA replacement. Valves with good function, free of significant AS or AI, and free of calcification at surgical inspection, can safely be spared with expectation of continued good, long-term function.

*Risk of AS or AI*

Less than half of the patients experienced an increase in AS or AI over time (7/23, 30.4%). Of those patients, 2 had an increase in severity of AS only, 4 of AI only, and 1 of both (Figure 10, 11). Three patients had a decrease in severity of AI from mild to none (Figure 11).

*Patients with increase in Aortic Stenosis or Aortic Insufficiency*

Of the cohort of patients who had post-operative echos (n=23), 10 had changes in their BAV function. However, of this group, only 7 had an increase in aortic stenosis or aortic insufficiency. Most of them, 5 out of 7, had an increase in aortic stenosis or regurgitation from none to mild. The remaining 2 patients had an increase from none to moderate or severe.

Patient 1 did not have aortic stenosis or insufficiency pre-operatively. However, 12.96 years later, his echo revealed moderate aortic stenosis, while insufficiency progressed from none to mild during the interval.
Although patient 2’s echo showed continued freedom from stenosis, a worsening degree of regurgitation, from none to severe, was observed. However, this patient’s surgery was for a concomitant CABGx3. The complexity of the surgery, above and beyond a straightforward ascending aneurysm repair played a role in deciding whether the valve should or should not be spared. This is the only patient who required reoperation.

Thus, the only advent of severe bicuspid aortic valve disease in long-term follow-up in this study (one patient) occurred under special circumstances: a patient undergoing extensive associated CABG.

**Limitations**

The retrospective and single center nature of this study is a limitation. We recognize that the cohort of patients for the assessment of the natural history of ATAA-BAV is from a referral aortic center. This introduces a possible selection bias and may not precisely reflect ATAA-BAV natural behavior in the general population. The group of patients who had their valve spared during aneurysm repair is small. However, we are looking at a specific subgroup among a very active aneurysm and bicuspid valve team’s cases.
FUTURE DIRECTIONS

BAV Morphology

ATAA-BAV has been described with three different morphologies: supracoronary, tubular, and marfanoid (Figure 12)\(^9\). The supracoronary type is the most common and has been addressed as more “malignant” and to have a quicker progression of aortopathy. Unfortunately, we did not differentiate the patients in this study into subgroups according to their aortopathy morphology. We plan to categorize each patient in our larger cohort in order to potentially guide management to each individual adjusting for ATAA morphology. Further research on aortopathy phenotype can possibly increase the understanding of ATAA-BAV pathophysiology.

Figure 12. ATAA-BAV morphology distribution (Yale Aortic Institute unpublished data).
Our understanding of the pathogenesis of TAAD is in constant evolution. The advancement of genetic analysis techniques enables rapid progress in the genetic and molecular understanding of TAA. As genome sequencing costs decrease, we anticipate accelerating progress. With our greater understanding of the genetics of individuals affected with TAAD and their specific genetic mutations, we can provide personalized aortic care, tailoring surgical recommendations for each patient depending on the individual mutation. Because most families, despite having multiple affected members with TAAD, do not have any of the known aortopathy genes, we expect to discover many new genes in the foreseeable future and thereby enhance our genetic dictionary. Furthermore, it is important to remind ourselves that every disease-causing mutation starts out as a variant of unknown significance (VUS). Only later does more data accumulate to secure the status as a disease-causing mutation.

Although we value our clinical and surgical efforts to understand ATAA-BAV behavior, we still believe that it is genetics that will enable individualized care for these patients. Since 2012, we have been ordering genetic screening by way of Whole Exome Sequencing (WES) on nearly all patients presenting to the Yale Aortic Institute. WES encompasses DNA sequencing of all coding regions (exons) of a genome and provides the following benefits: (1) it is comprehensive, including (but not limited to) testing all the 30-plus TAAD genes that have been identified to date (all in a single test done in one laboratory); (2) data can be reanalyzed retrospectively because the entire exome is sequenced, permitting testing of new disease-causing genes as they are discovered; (3) it is usually more affordable and efficient than testing individually for specific genes and
syndromes in various laboratories; and (4) it provides genome-wide data that can be ‘mined’ for new mutations\textsuperscript{44}. The fact that the genes identified to date only account for approximately 30% of aortic diseases in non-syndromic TAAD patients leads us to believe that there are many more genes yet to be discovered\textsuperscript{45}.

The information gleaned from WES becomes very valuable for family members of the proband. Once an individual is found to have a specific mutation, we look for that specific mutation using the less complex and cheaper ‘single-site’ Sanger Sequencing method in their family members\textsuperscript{46}. In this technique, sequencing is targeted to the gene already shown to harbor an anomalous variant in the proband genome\textsuperscript{46}. This way, instead of going through the “whole genetic alphabet” we can focus on the more likely culprit “letter” found in the proband.

\textit{RNA Signature}

In addition to looking at the genetic profile of our patients (DNA), we are currently working on identifying RNA expression patterns in peripheral blood that could be diagnostic for TAA, including ATAA-BAV. Success in such work would constitute a major advancement in the clinical care of the general population. Our previous study identified a distinct gene expression, ‘RNA Signature’, in peripheral blood that was able successfully to identify whether a patient had an aneurysm, with over 80% overall accuracy\textsuperscript{47}. Furthermore, this RNA Signature test was able to differentiate very accurately between ascending vs. descending aortic aneurysm, and between familial or sporadic TAA\textsuperscript{47}. We are currently completing a follow-up study aimed at validating our previous findings and developing a clinically useful simple blood test that can not only detect and
monitor aneurysm disease, but also biologically predict the risk of catastrophic aortic events based on the differential expression of aneurysm related RNAs.

**Transcatheter Aortic Valve Replacement**

In an era where endovascular approaches are taking center stage, we must consider the role transcatheter aortic valve replacement (TAVR) will play for BAV patients. The Placement of Aortic Transcatheter Valves PARTNER 3 Clinical trial showed that patients at low surgical risk undergoing a TAVR had non-inferior outcomes compared to surgical aortic valve replacement (SAVR)\(^48\). Patients with BAV morphology were excluded from the study group due to concern for the valve anatomy (i.e. non-circular annulus)\(^49\). However, since then, multiple centers representing the cardiovascular community have enrolled in an ongoing clinical trial to evaluate clinical outcomes of patients undergoing TAVR-BAV\(^50\). Although this is not yet approved by the FDA, it is important for us to consider what this will mean for patients with ATAA-BAV. This trial has focused on patients affected by BAV but has not considered patients that also suffer from vasculopathy linked to its valve morphology. Although endovascular techniques are already extant for the descending portion of TAA, we suspect that repair for ATAA will not be readily available in the near future, thus posing an even more challenging question of whether patients with stenotic BAV in conjunction with ATAA should be considered for TAVR.
CONCLUSION

This body of work allows us to arrive at the following conclusions:

1. ATAA-BAV grows at 0.21cm/year.
2. The natural risk of aortic complications (rupture and/or dissection) rises with increase in aortic size with three discriminative hinge points: 5, 5.5, and 6 cm.
3. Prophylactic size-based surgery in ATAA-BAV patients, just like TAV-ATAA, can be considered at 5.0 cm at expert aortic centers in order to avoid adverse aortic events.
4. BAV with good function, free of significant AS or AI, and free of calcification at surgical inspection, can safely be spared with the expectation of continued good long-term function.
REFERENCES


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