The natural history of the bicuspid aortic valve and bicuspid aortopathy

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No Disclosures
Clinical Problem

- Burden of surgery for BAV patients in the USA exceeds 1 billion dollars per year.
- Frequency of aortic interventions has doubled over the past decade.
- There is limited scientific evidence for the timing and extent of these prophylactic interventions.
Uncertainty of Clinical Guidelines for BAV Aortopathy

Surgical approaches are aggressive for genetic aortopathy
Inherited Aortopathy?

- Common in young asymptomatic patients
- Seen with “normal” BAV function (No AS/AR)
- Progression of dilatation after AVR
- Some similarities to known genetic aortopathies
Aortic Dilation: BAV versus TAV in Children

Beroukhim ... Yetman, AJC 2006
Vascular Matrix Disruption in BAV Disease

AORTIC MEDIA

Tricuspid AV (TAV)  Bicuspid AV (BAV)
Fibrillin-1 Deficient Mouse: Matrix Disruption in Aortic Media

Normal Mouse
Normal Matrix
No Aortic Dilation

Fbn-1 Deficient Mouse
Disrupted Matrix
Aortic Aneurysm

Circ Res 2001; 88(1): 37
SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

HISTOLOGIC ABNORMALITIES OF THE ASCENDING AORTA AND PULMONARY TRUNK IN PATIENTS WITH BICUSPID AORTIC VALVE DISEASE: CLINICAL RELEVANCE TO THE ROSS PROCEDURE

Mauro de Sa, MD
Yaron Moshkovitz, MD
Jagdish Butany, MD
Tirone E. David, MD

JTCVS 1999; 118: 588
Molecular Mechanisms of BAV Aortopathy

Normal aorta: Elastin & collagen, Smooth Muscle Cells

BAV aortopathy: disrupted elastin and collagen, smooth muscle cell loss, MMP release

BAV aortopathy - disease of the extracellular matrix (ECM)

Fedak et al. Circulation 2002
Knowledge, attitudes, and practice patterns in surgical management of bicuspid aortopathy: A survey of 100 cardiac surgeons

Subodh Verma, MD, PhD, FRCSC, a Bobby Yanagawa, MD, PhD, a Sameer Kalra, a Marc Ruel, MD, PhD, FRCSC, b Mark D. Peterson, MD, PhD, FRCSC, a Michael H. Yamashita, MDCM, MPH, CPH, c Andrew Fagan, MD, d Maria E. Currie, MD, e Christopher W. White, MD, f Stephane Leung Wai Sang, MD, MSc, g Cristian Rosu, MD, h Steve Singh, MD, PhD, FRCSC, i Holly Mewhort, MD, j Nandini Gupta, MD, b and Paul W. M. Fedak, MD, PhD, FRCSC j,k

- 52% believed **genetics**, 2% believed valve **hemodynamics**
- 61% believed in resection at **45mm at time of AVR**
- 33% performed resection at **<45mm at time of AVR**
Perspectives and attitudes on the etiology (inherited aortopathy versus acquired from hemodynamic stress) rather than validated scientific and clinical evidence appeared to influence the surgical treatment of BAV aortopathy
Is progression of BAV aortopathy predictable for individual patients?

Bicuspid aortic valve syndrome: heterogeneous but predictable?

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This editorial refers to ‘Aortic elasticity and size in bicuspid aortic valve syndrome’ by S. Nistri et al.,† on page 472

Bicuspid aortic valve (BAV) has long been associated with a spectrum of vascular complications such as ascending aortic dilatation, aortic aneurysms, and catastrophic aortic root dissection. The mechanism responsible for the associated vascular complications in this seemingly benign and common congenital lesion of aortic valve morphology remains controversial. Some argue that flow dynamics from the mis-shapen outflow valve result in aberrant post-valvular haemodynamics that trigger progressive aortic dilatation. In many patients with advanced valve dysfunction, this mechanism probably contributes to aortic valve pathology.

The implications of this heterogeneity are numerous. The candidate genes and molecular markers that mediate the valve and aortic complications remain elusive. It is tempting to speculate that BAVS is a final common pathway for a wide variety of altered molecular events and genetic defects. Perhaps similar to left ventricular dilatation in the failing heart, BAV and associated aortic dilatation result from different aetiologies but manifest similarly on a clinical basis. Because the lesion may have diverse molecular triggers, it may be difficult to characterize the inciting events that result in a BAV and its associated aortopathy. Currently, extracellular matrix dysregulation and cell death pathways show promise as important molecular mechanisms of the aortopathy, while candidate genes such as NOTCH may reflect important genetic influences. An improved understanding of the cellular and molecular pathways that lead to BAVS may provide new insights into the development of novel therapeutic strategies to prevent aortic complications.
Variable Patterns of BAV Aortopathy

- ROOT
- MID ASC
- PROX ARCH
Variable BAV Cusp Morphology

Valve Fusion and Flow Pattern

A  Right–left fusion pattern

B  Right–noncoronary fusion pattern

RL fusion

RN fusion

BACKGROUND  Bicuspid aortic valves are associated with valve dysfunction, ascending aortic aneurysm and dissection. Management of the ascending aorta at the time of aortic valve replacement (AVR) in these patients is controversial and has been extrapolated from experience with Marfan syndrome, despite the absence of comparative long-term outcome data.

OBJECTIVES  This study sought to assess whether the natural history of thoracic aortopathy after AVR in patients with bicuspid aortic valve disease is substantially different from that seen in patients with Marfan syndrome.

METHODS  In this retrospective comparison, outcomes of 13,205 adults (2,079 with bicuspid aortic valves, 73 with Marfan syndrome, and 11,053 control patients with acquired aortic valve disease) who underwent primary AVR without replacement of the ascending aorta in New York State between 1995 and 2010 were compared. The median follow-up time was 6.6 years.

RESULTS  The long-term incidence of thoracic aortic dissection was significantly higher in patients with Marfan syndrome (5.5 ± 2.7%) compared with those with bicuspid valves (0.55 ± 0.21%) and control group patients (0.41 ± 0.08%, p < 0.001). Thoracic aortic aneurysms were significantly more likely to be diagnosed in late follow-up in patients with Marfan syndrome (10.8 ± 4.4%) compared with those with bicuspid valves (4.8 ± 0.8%) and control group patients (1.4 ± 0.2%) (p < 0.001). Patients with Marfan syndrome were significantly more likely to undergo thoracic aortic surgery in late follow-up (10.4 ± 4.3%) compared with those with bicuspid valves (2.5 ± 0.6%) and control group patients (0.50 ± 0.09%) (p < 0.001).

CONCLUSIONS  The much higher long-term rates of aortic complications after AVR observed in patients with Marfan syndrome compared with those with bicuspid aortic valves confirm that operative management of patients with bicuspid aortic valves should not be extrapolated from Marfan syndrome and support discrete treatment algorithms for these different clinical entities.  (J Am Coll Cardiol 2015;65:2363-9) © 2015 by the American College of Cardiology Foundation.)
Risk of Aneurysm Formation and Aortic Dissection After Definite Bicuspid Aortic Valve Diagnosis

Michelena, H. I. et al. JAMA 2011;306:1104-1112

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Can valve-mediated hemodynamic stress be assessed in the ascending aorta of patients with BAV disease?
4D Flow MRI

4D (3D volume + time); flow (3-dir. velocity encoding) MRI

- Res. ~ 2mm isotropic, $T_{Res} \sim 40\text{ms}$
- $T_{Acq} \sim 8 - 15\text{min}$

BAV without dysfunction has significant flow eccentricity

Tricuspid AV (TAV) (No valve dysfunction)

Bicuspid AV (BAV) (No valve dysfunction)
Flow eccentricity creates “shear” on inner surface of aortic wall

Wall Shear Stress (WSS)

- **Hemodynamic WSS** is the tangential force exerted on the endothelium due to a **blood velocity gradient** \( (dV/dr) \) and **blood viscosity** \( (\mu) \)

- The drag force exerted on a vessel wall

\[
WSS_{rz} = \mu \left. \frac{dV_z}{dr} \right|_{r=R}
\]
**WSS Atlases and Heatmaps**

*Individual Patient:* Detect regions with abnormal WSS

- **3D WSS**
- **3D Ao geometry**
- **Normal WSS**
- **WSS heat map**

Registration & interpolation

Valvular Heart Disease

Bicuspid Aortic Cusp Fusion Morphology Alters Aortic Three-Dimensional Outflow Patterns, Wall Shear Stress, and Expression of Aortopathy

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Background—Aortic 3-dimensional blood flow was analyzed to investigate altered ascending aorta (AAo) hemodynamics in bicuspid aortic valve (BAV) patients and its association with differences in cusp fusion patterns (right-left, RL versus right-noncoronary, RN) and expression of aortopathy.

Methods and Results—Four-dimensional flow MRI measured in vivo 3-dimensional blood flow in the aorta of 75 subjects: BAV patients with aortic dilatation stratified by leaflet fusion pattern (n=15 RL-BAV, mid AAo diameter=39.9±4.4 mm; n=15 RN-BAV, 39.6±7.2 mm); aorta size controls with tricuspid aortic valves (n=30, 41.0±4.4 mm); healthy volunteers (n=15, 24.9±3.0 mm). Aortopathy type (0–3), systolic flow angle, flow displacement, and regional wall shear stress were determined for all subjects. Eccentric outflow jet patterns in BAV patients resulted in elevated regional wall shear stress (P<0.0125) at the right-anterior walls for RL-BAV and right-posterior walls for RN-BAV in comparison with aorta size controls. Dilatation of the aortic root only (type 1) or involving the entire AAo and arch (type 3) was found in the majority of RN-BAV patients (87%) but was mostly absent for RL-BAV patients (87% type 2). Differences in aortopathy type between RL-BAV and RN-BAV patients were associated with altered flow displacement in the proximal and mid AAo for type 1 (42%–81% decrease versus type 2) and distal AAo for type 3 (33%–39% increase versus type 2).

Conclusions—The presence and type of BAV fusion was associated with changes in regional wall shear stress distribution, systolic flow eccentricity, and expression of BAV aortopathy. Hemodynamic markers suggest a physiological mechanism by which the valve morphology phenotype can influence phenotypes of BAV aortopathy. (Circulation. 2014;129:673-682.)

Key words: aortic diseases ■ bicuspid aortic valve ■ hemodynamics ■ magnetic resonance imaging
Does local tissue tissue remodeling follow patterns of valve-mediated hemodynamics?

Valve-mediated hemodynamics predict local tissue remodeling

Guzzardi, Barker, Fedak et al, JACC 2015
Key Points

• BAV aortopathy with progressive dilation of ascending aorta is common
• Patterns and rates of progression are highly variable between patients
• Risk of fatal aortic events is low
• Valve-mediated hemodynamics may play an important role in progression
• Patient-specific resection strategies are needed to avoid unnecessary surgery