Bicuspid Aortic Valve Disease

Ify Mordi
Institute of Cardiovascular and Medical Sciences
University of Glasgow, United Kingdom

Nikolaos Tzemos
Institute of Cardiovascular and Medical Sciences
University of Glasgow, United Kingdom
1 Introduction

Bicuspid aortic valve (BAV) is the commonest congenital cardiac anomaly, with a prevalence thought to be between 1-2% in the general population (Mordi & Tzemos, 2012; Ward, 2000). It is 3 times more common in males, although gender is not a prognostic indicator in the natural history of BAV (Tutar, Ekici, Atalay, & Nacar, 2005). It is commonly an isolated finding; however it is also associated with other congenital cardiac disease. BAV is not just a valvular anomaly, but is also associated with aortic disease, commonly described as aortopathy, typically characterised by dilatation of the ascending aorta. While many people with BAV have aortic valves that function normally throughout life, complications are frequent in the BAV population. It is estimated that complications related to the aortic valve or ascending aorta requiring surgery occur in around a third of all patients with BA (Vallely, Semsarian, & Bannon, 2008). Because these complications are common in the BAV population, there is a large burden of morbidity and mortality in comparison to many other congenital diseases as a percentage of the general population. The main causes of adverse outcome in BAV patients are either related to the valve itself (stenosis, regurgitation or endocarditis) or to the aortopathy (leading to aneurysm and dissection). Given the high incidence of adverse events, routine screening is recommended for BAV patients to allow for timely intervention.

2 Embryology and Anatomy

The definitive fetal cardiac structure is developed by 8 weeks. The normal aortic valve consists of three valve cusps, sinuses, the aorto-ventricular junction and the sinotubular junction (Angelini et al., 1989). The semi-lunar valves form from the division of the truncus arteriosus into two separate channels which form the aortic and pulmonary trunks. The channels are created by the fusion of two truncal ridges across the lumen. Small swellings appear on the inferior margins of each of the truncal ridges forming the basis of the adult valve leaflets. In each channel a third swelling occurs opposite the first two which forms the 3rd leaflet. In the normal aortic valve the left and right leaflets of the adult valve are formed from the respective swellings while the posterior leaflet is formed from a swelling in the aortic trunk (Anderson, Webb, Brown, Lamers, & Moorman, 2003; Restivo, Piacentini, Placidi, Saffirio, & Marino, 2006). Simultaneously, the coronary arteries are formed from buds which arise from the coronary sinuses of the aorta. Usually however, only two buds establish a connection with the epicardial tree to form future coronary arteries. This associated timing explains the frequent association between the aortic valve and coronary artery abnormalities.

Despite our knowledge of the formation of normal aortic valves, the exact pathogenesis that leads to the formation BAV is not yet fully understood. It does however appear to be more complex than just a simple fusion of two valve cusps. The bicuspid valve is composed of two leaflets, of which one is usually larger, although the fused valve leaflet in BAV is actually smaller in area than the total area of two separate leaflets would be if the valve were tricuspid. (Roberts, 1970, 1992). Commonly the larger of the two cusps (the conjoined leaflet) has a ridge or “raphe” which is the site of the valve fusion. This can make the valve appear tricuspid on echocardiography, requiring optimal imaging to be certain of the diagnosis. A number of systems have been proposed to classify BAVs according to their orientation (Schaefer et al., 2008; Sievers & Schmidtke, 2007). The commonest method used is to classify the valvular anatomy into type 1, 2 and 3 (or A-C) according to the site of leaflet fusion (Schaefer et al., 2008) (figure 1). Type 1,
Figure 1: The anatomy of the bicuspid aortic valve (BAV). A – The normal tricuspid aortic valve; B – Type 1 (A) BAV with fusion of the right and left coronary cusps; C – Type 2 (B) BAV with fusion of the right and non-coronary cusps; D – Type 3 (C) BAV with fusion of the left and non-coronary cusps. The dotted line represents the fused cusps and signifies the potential presence of a raphe at the site of fusion. LC – left coronary cusp; LM – left main coronary artery; NC – non-coronary cusp; RC – right coronary cusp; RCA – right coronary artery.

<table>
<thead>
<tr>
<th>Type 1 BAV</th>
<th>Type 2 BAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>More likely to become stenotic in adulthood</td>
<td>Valvular complications at a younger age</td>
</tr>
<tr>
<td>More common in males</td>
<td>Equal sex distribution</td>
</tr>
<tr>
<td>More likely to have aortic dilation at the sinus of Valsalva</td>
<td>More likely to have aortic dilatation at ascending aorta and aortic arch</td>
</tr>
</tbody>
</table>

Table 1: Bicuspid aortic valve types and their associations

the commonest configuration of the bicuspid is fusion of the left and right coronary cusps. Type 2 BAVs are caused by fusion of the right and non-coronary cusps. Type 3 BAV, the most rare, occurring in less than 1% of patients is due to fusion of the left and non-coronary cusps. The relevance of classification of BAV has been demonstrated in studies looking at the natural history of the valve. A study by Calloway et al, examining 1,128 patients, suggested that, with the suggestion that type 1 BAVs are more likely to become stenotic as adults while patients with type 2 valves tended to have valve complications as children or adolescents (Calloway et al., 2011). Schaefer et al studied the link between the valve morphology and aortic disease in 191 patients (Schaefer et al., 2008). In this study, the authors found that type 1 BAVs were more common in males and aortic dilatation at the sinus of Valsalva, while type 2 BAVs were associated with ascending aortic dilatation, aortic arch disease and myxomatous mitral valve disease. This pattern was also seen in study by Khoo et al (Khoo, Cheung, & Jue, 2013). This certainly may have implications for monitoring of BAV aortopathy. Finally, a study by Fernandes et al suggested that type 1 BAV was associated with coarctation of the aorta, in contrast to type 2 valves which were associated with more significant valvular disease than type 1 (Fernandes et al., 2004).
Aortopathy is the commonest abnormality associated with BAV. While the altered aortic blood flow explains some of the dilatation of the aorta, there is evidence that there are other contributory mechanisms. Several studies have suggested that the pathogenesis of aortopathy is somewhat similar to that seen in Marfan syndrome, with the presence of cellular structural abnormalities including decreased fibrillin, causing smooth muscle cell detachment and cell death (de Sa, Moshkovitz, Butany, & David, 1999; Fedak et al., 2002; Parai, Masters, Walley, Stinson, & Veinot, 1999). What is clear is that the development of aortopathy in BAV is fairly heterogeneous throughout the population – many patients may not develop any aortic disease throughout their life, whereas a small subset of patients develop aortic complications at a very young age, suggesting that there is a genetic component to the development of BAV aortopathy (Nistri et al., 1999). Recently, Kang et al have also shown that the development and progression of BAV aortopathy differs in patients dependent on the orientation of the valves (i.e. which valves are fused) (Kang et al., 2013). The development of BAV aortopathy and the influence of genetic and hemodynamic factors in its progression are further discussed in section 5.3.

Another major abnormality associated with BAV disease is coarctation of the aorta. This occurs in at least 20% of cases and perhaps up to 85% (Bonderman et al., 1999; Presbitero et al., 1987; Stewart, Ahmed, Travill, & Newman, 1993). BAV is also associated with other congenital cardiac disease such as hypoplastic left heart syndrome, and BAV is also found in other developmental diseases, for example Turner and Williams’ syndrome (Siu & Silversides, 2010).

The final major association regards abnormalities of the coronary arterial circulation. Most patients with BAV disease have a left dominant coronary circulation (Roberts, 1970). The left main can also be up to 50% shorter than in normal in up to 90% of cases (Fedak et al., 2002). This is an important consideration for any aortic valve surgery to ensure that steps are taken to avoid coronary artery damage during any valvular operation.

3 Genetics

It is now generally accepted that there is a heritable component to BAV disease. Initially, it was postulated that abnormal blood flow across the embryonic aortic valve may lead to BAV, however there is no convincing evidence to support this hypothesis. Meanwhile, the connection of BAV and the association of BAV with other congenital abnormalities such as coarctation of the aorta and ventricular septal defect again suggests that there may be a developmental, and therefore genetic, link (Duran et al., 1995).

There have been several studies that appear to show episodes of familial clustering of BAV, again supporting the genetic theory (Glick & Roberts, 1994; Huntington, Hunter, & Chan, 1997). Huntington et al screened 190 first-degree relatives of patients with congenital BAV and reported BAV prevalence in this group of 9.1% (Huntington et al., 1997). The high prevalence in this study suggests that BAV might be an autosomal dominant disorder with variable penetrance. It seems more likely however that BAV has polygenic inheritance, though few of these pathways have as yet been completely identified. A more recent study by Robledo-Carmona et al reported lower rates of BAV in people with affected first-degree relatives (Robledo-Carmona et al., 2013). The authors studied 553 patients from 100 families and only found a BAV rate of 4.6% in patients with affected first-degree relatives. This is certainly lower than reported in the Huntington study. The study by Robledo-Carmona et al was conducted within a Mediterranean population however, perhaps suggesting a variable world-wide distribution – this might add further support to a heritable component to BAV.
Despite the increasing observational evidence suggesting that there is a genetic link to the development of BAV, discovery of the majority of genetic pathways leading to BAV has been elusive. Mutations in a gene called \textit{NOTCH1}, a trans-membrane receptor that has a role in determining cell outcome in organogenesis, were noted in two families with BAV (Garg \textit{et al.}, 2005). This seems to be the strongest genetic link discovered yet with further discoveries of missense \textit{NOTCH1} mutations causing impaired Notch signalling (Foffa \textit{et al.}, 2013; McKellar \textit{et al.}, 2007; Mohamed \textit{et al.}, 2006). Several other genetic loci have been postulated including chromosomes 18q, 5q and 13q, though no specific causative genes have been found. Not only are mutations in \textit{NOTCH1} associated with abnormal valve morphology, but also they are also associated with accelerated calcium deposition within the valve, perhaps providing a mechanism for the advanced early calcific disease seen in the condition (Acharya \textit{et al.}, 2011; Garg \textit{et al.}, 2005). Work is being done to find other genes that might be associated with BAV. Recent data has linked the \textit{Gata5} gene with BAV and the development of aortopathy (Laforest, Andelfinger, & Nemer, 2011; Padang, Bagnall, Richmond, Bannon, & Semsarian, 2012).

Recent guidance from the American College of Cardiology/American Heart Association takes account of the evidence supporting a genetic component and recommend that all patients with a 1\textsuperscript{st} degree relative with BAV should be evaluated for BAV and aortopathy using echocardiography (Hiratzka \textit{et al.}, 2010). No studies have been done as yet however to prove an economic benefit to screening, however recent guidance suggests that first-degree relatives of BAV patients should be screened (Hiratzka \textit{et al.}, 2010).

### 4 Diagnosis

Non-invasive testing plays an important role in the diagnosis and management of BAV patients.

Clinical findings are usually limited to auscultation with most patients having an ejection systolic murmur heard loudest at the apex (Mills, Leech, Davies, & Leathan, 1978). There may also be clinical signs of aortic stenosis (or incompetence) and coarctation of the aorta if associated. The electrocardiogram is usually normal however there may be signs of left ventricular hypertrophy.

The mainstay of diagnosis is echocardiography (transthoracic or transesophageal) which can provide a definitive diagnosis in the majority of patients. Echocardiography is the current gold-standard for diagnosis (Warnes, Williams, Bashore, Child, Connolly, Dearani, del Nido, Fasules, Graham, Hijazi, Hunt, King, Landzberg, Miner, Radford, Walsh, & Webb, 2008). Figures of 92% sensitivity and 96% specificity have been reported when images are adequate, although due to the natural history of BAV to lead to heavily calcified stenotic valves, the accuracy of transthoracic echocardiography can be reduced (Chan, Stinson, & Veinot, 1999; Tanaka \textit{et al.}, 2010). Because of this, transesophageal echocardiography may be required. 3-dimensional transesophageal echocardiography is a newer technique which may add further detailed information, although this technique is not usually required (Koh, 2013).

Using transthoracic echocardiography, the parasternal short axis view allows for direct visualization of the valve cusps and allows diagnostic confirmation. In this view the normal triangular opening shape is lost, becoming more “fish mouth”-like in appearance, more akin to the mitral valve (figure 2). This is especially pronounced in systole, as in diastole the raphe can appear similar to a commissure of the third cusp. Other views (parasternal long axis and apical views) can show turbulent flow and eccentric lines of valve closure. If necessary, transesophageal echocardiography can be carried out to confirm the diagnosis. Because of the eccentricity of the valve jet in patients with aortic stenosis, it is recommended...
that aortic valve area is calculated using the continuity equation rather than by direct planimetry (Donal et al., 2005). Regurgitation can be measured using routine parameters such as pressure half time, regurgitant fraction and width of the vena contracta. 3-D echocardiography may also provide even more accurate diagnosis and characterization of the valve (figure 3) (Sadron Blaye-Felice et al., 2012). The severity of aortic valve disease as measured by echocardiography has been shown to be predictive of future valve repair in BAV patients (Ahmed et al., 2007).

It is also important to assess the aorta in BAV patients, given the prevalence of aortopathy. The proximal ascending aorta can usually be assessed satisfactorily using echocardiography, however, as described earlier, aortopathy can often affect the ascending aorta above the level of the root, and so complimentary imaging modalities are often needed for complete vascular assessment, especially if the suprasternal windows using transthoracic echocardiography are not satisfactory. This is most commonly conducted by computed tomography (CT) or cardiovascular magnetic resonance (CMR).

CT is widely available, fast and non-invasive. It offers excellent spatial resolution and allows 3-D evaluation of the whole aorta (figure 4). Retrospective ECG-gated CT study acquisition allows visualization of the valve is both systole and diastole, allowing clear diagnosis of the valve. CT has been shown to have diagnostic accuracy for differentiation of BAV and tricuspid aortic valves with both sensitivity and specificity ranging from 94-100% in recent studies (Alkadhi et al., 2010; Lee et al., 2012; Tanaka et al., 2010). CT can offer coronary artery evaluation, which could aid surgical planning in the case of anomalous coronary arteries, which as described earlier are common in BAV patients. Also, in older patients evaluation of the coronary arteries is mandatory prior to cardiac surgery. Finally, the use of retrospective gating also enables calculation of left ventricular volumes and ejection fraction. The main drawback of CT is its use of ionizing radiation, which means that it may not be practical to use it for serial assessment of the aorta, although scanners continue to improve and radiation doses continue to decline.

CMR is increasingly used in the assessment of BAV and enables views of the valve to be obtained without interference from calcification. It also allows for excellent assessment of the aorta. A recent study of 123 patients with confirmed BAV found that 10% of the patients were misidentified as having a tricuspid valve using transthoracic echo and 28% had a non-diagnostic study, in comparison to 4% being misidentified as having a tricuspid valve by magnetic resonance imaging and 2% having a non-diagnostic study (Malaisrie et al., 2012). Using cine imaging and phase-contrast imaging, the severity of any valvular disease can also be assessed with reasonable accuracy, although echocardiography remains...
**Figure 3:** Bicuspid aortic valve seen using 3-dimensional echocardiography. The aortic valve is severely stenosed with area measured by direct planimetry of 0.9cm$^2$ (arrow).

**Figure 4:** Computed tomography in the assessment of bicuspid aortic valve. A heavily calcified aortic valve is seen (A, arrow), as well as ascending aortopathy (AA, panels A and B). CT allows complete 3-dimensional reconstruction of the whole aorta allowing evaluation of the extent of aortopathy and assessment of any coarctation (C).
the mainstay for diagnosis. There are limitations however – not least its limited availability and higher technical requirements (both for the technician and the reporting cardiologist/radiologist). The limited temporal resolution of CMR also means that measurements of peak velocity can be inaccurate, although there is reasonable correlation with echocardiographic values (Caruthers et al., 2003; Cawley, Maki, & Otto, 2009).

The main advantage of CMR lie in its accurate assessment of ventricular volumes and function, for which it is the non-invasive gold-standard, and, perhaps more importantly, its ability to completely characterise the extent and nature of any aortopathy (Tsai, Trivedi, & Daniels, 2012) (figure 5). Furthermore, its lack of ionizing radiation confers an advantage over CT, particularly for surveillance, although certainly CT can also accurately image both the valve and the aorta (Joo et al., 2012).

In summary, all 3 non-invasive techniques have advantages and disadvantages. A recent study evaluated 262 patients undergoing aortic valve surgery and found all 3 non-invasive techniques to have high diagnostic accuracy (>95%) for assessment of valve morphology (Lee et al., 2012). Echocardiography remains the mainstay for diagnosis and surveillance, however both CT and CMR can provide clearer images and are also able to provide complete aortic evaluation.

Figure 5: Type 1 bicuspid aortic valve seen in diastole (A) and systole (B) using cardiovascular magnetic resonance imaging allowing excellent visualization of proximal aortopathy (C and D). AA – ascending aorta; DA – descending aorta; LA – left atrium; LC – left coronary cusp; NC – non-coronary cusp; RA – right atrium; RC – right coronary cusp; RVOT – right ventricular outflow tract.
5 Clinical Progression

The natural history of BAV has been evaluated a several cohort studies. It is known to be variable and of course somewhat dependent on associated abnormalities. In some patients there is the appearance of severe aortic stenosis in childhood, however many patients (forming the majority) are asymptomatic until adulthood. Indeed, there have been reports of incidental findings of a minimally calcified BAV in patients in their 70s (Fenoglio, McAllister, DeCastro, Davia, & Cheitlin, 1977). More commonly however (in around 75% of patients) there is progressive fibro-calcific stenosis of the valve eventually requiring surgery. This usually leads to presentation in middle age – only around 2% of children have clinically significant BAV disease (Bonow et al., 2006).

Until recently, there had been few recent studies investigating the natural clinical course of the BAV. The first large cohort study was by Michelena et al (Michelena et al., 2008). In this study, the authors examined a cohort of 212 asymptomatic patients with BAV (age 32+/20 years) and followed them up for a mean of 15 years. The authors found that the BAV group had the same 20 year survival rate as the normal population (around 90%) but also an increased frequency of cardiac events including aortic valve surgery, ascending aorta surgery and any other cardiovascular surgery. Predictive factors for cardiovascular events were found to be age ≥50 years and valve degeneration at diagnosis while an ascending aorta ≥40 mm at baseline independently predicted surgery for aorta dilatation.

The largest study in BAV patients was conducted by Tzemos et al (Tzemos et al., 2008). The authors examined outcomes in 642 patients with both symptomatic and asymptomatic BAV (mean age 35+/16 years) and followed them up for a mean of 9 years, again with a 10-year survival rate similar to the normal population (96%). One or more primary cardiac events occurred in 25% including cardiac death in 3%, intervention on the aortic valve or ascending aorta in 22%, aortic dissection or aneurysm in 2% and congestive heart failure requiring hospital admission in 2%. Independent predictors of primary cardiac events were age older than 30 years, moderate or severe aortic stenosis and moderate or severe aortic regurgitation (figure 6).

![Figure 6: Outcomes in Bicuspid Aortic Valve Patients (from Tzemos et al.)](image-url)
A more recent study has looked at the incidence of aortic complications in 416 BAV patients (mean age 35 years) (Michelena et al., 2011). Incidence of aortic dissection was found to be 1.5% in all patients regardless of the progression of BAV; however this increased markedly in patients aged 50 or older at baseline to 17.4% and even more in those found to have aneurysm formation at baseline (44.9%). 25 year rate for aortic surgery was 25% and there was a significant burden of progression of disease to cause aortic dissection with 49 of the 384 patients without baseline aneurysms developing them during follow-up, giving an age-adjusted relative risk of 86.2 and an incidence of 84.9 cases per 10000 patient-years.

The common denominator in all three of these large outcome studies is the independent prognostic significance of age, suggesting that over time, many patients will require some sort of intervention. This has lead to the increased drive towards surveillance of BAV patients.

All in all, life expectancy in patients with BAV is not significantly different from the general population – Tzemos et al reported a 10-year survival of 96% in patients with a spectrum of valve dysfunction (Tzemos et al., 2008). Despite this, there are several complications which have been identified in BAV patients. These can be divided into two groups: valvular complications (aortic stenosis, aortic incompetence and endocarditis) and vascular complications i.e. aortopathy.

5.1 Aortic Stenosis

The symptoms of the BAV tend to worsen with increasing stenosis severity and measurements of the valve orifice. The main symptoms are (exertional) dyspnea, syncope and chest pain. These patients should be evaluated and managed similarly to patients with tricuspid aortic valve stenosis, but of course the patients will generally present much earlier as described previously.

The fetus can generally survive with severe aortic stenosis due to blood flow through the right side of the heart, however in infancy there is usually a sudden decline in cardiovascular status. One study indicated that children with a valve gradient greater or equal to 50mmHg had a risk of adverse cardiovascular events of 1.2% per year (J. F. Keane et al., 1993). In infants, due to the lack of valvular calcification, balloon valvuloplasty is the chosen treatment rather than valve replacement (Tworetzky et al., 2004). Re-operation is common however, with one study reporting further intervention in 26% of patients within 10 years (Janatuinen, Vanttinen, Saraste, & Ingberg, 1989).

In adults with BAV, stenosis occurs by similar methods to the process in patients with tricuspid aortic valves i.e. leaflet calcification (Subramanian, Olson, & Edwards, 1984). Similarly to tricuspid aortic valve stenosis, it is felt to be an active process with inflammation and endothelial dysfunction (Wallby, Janerot-Sjoberg, Steffensen, & Broqvist, 2002). Indeed, it has been suggested that up to 50% of adults with aortic stenosis have a congenitally BAV and that it is the commonest cause of aortic stenosis in patients under 70 (Pomerance, 1972; Ward, 2000). Echocardiographic data has suggested that sclerosis of the valve begins to occur at the age of 20, with calcification prominent at age 40. The valve gradient is estimated to increase by an average of 18mmHg per decade (Beppu et al., 1993). Some studies have also suggested that leaflet orientation may be a predictive factor in the rate of valve stenosis, although this was not replicated in the larger studies by Tzemos and Michelena (Beppu et al., 1993; Fernandes, Khairy, Sanders, & Colan, 2007). A further recent study in 167 patients using CT and echocardiography found that patients with type 1 BAV were more likely to have stenotic valves than those with type 2 (Kang et al., 2013). The variability of stenotic valves with BAV orientation was also found in another study by Huang et al (Huang & Le Tan, 2013).
5.2 Aortic Incompetence

This is relatively common in BAV and is often independent of aortic stenosis (M. G. Keane et al., 2000; Sadee, Becker, Verheul, Bouma, & Hoedemaker, 1992). One cohort of 118 BAV patients found that of 70 patients without aortic stenosis, 28 (40%) had moderate to severe aortic regurgitation. The mechanisms of aortic incompetence in children are usually due to prolapsing cusps, post-valve surgery or endocarditis, while as the patients age dilatation of the ascending aorta can lead to a functionally regurgitant valve. Tzemos et al (Tzemos et al., 2008) however suggested that rates of intervention in BAV patients with solitary aortic incompetence tended to be low. Another important cause of aortic incompetence is myxoid degeneration of the valve. This is where the connective tissue of the valve is replaced by acid mucopolysaccharides disrupting the structural integrity of the valve. One case series included 27 patients with BAV who had pure aortic incompetence – 16 of these had severe myxoid degeneration and required earlier intervention than the other 11 (average 40 years v 52) (Yotsumoto et al., 1998).

The prevalence of aortic regurgitation in adults with BAV has varied – one study reported rates of 13% (Sabet, Edwards, Tazelaar, & Daly, 1999) whereas the large study by Michelena et al reported almost half of their cohort to have some aortic regurgitation. Intervention rates for pure aortic incompetence were low in both this study and that conducted by Tzemos et al. Patients who undergo intervention for this indication tend to be younger however, perhaps due to the association of aortic incompetence with infective endocarditis and aortic coarctation (Ward, 2000).

5.3 Aortopathy/Aortic Dissection

BAV is often associated with dilatation of the aortic root and the ascending aorta (Nistri et al., 1999). This is otherwise known as aortopathy. This can lead to aneurysm and dissection. In BAV patients, the risk of aortic dissection is 8-fold. Furthermore, the risk of aortic aneurysm is 26% over 25 years and around a quarter of patients will require aortic surgery over this same time frame (Michelena et al., 2011). The dilatation has been reported during childhood, and it has also been suggested that increased aortic size at baseline is predictive for earlier dilatation and worse outcomes (Dore, Brochu, Baril, Guertin, & Mercier, 2003; Holmes et al., 2007). The aorta is generally larger in patients with BAV compared to those with tricuspid aortic valves (Morgan-Hughes, Roobottom, Owens, & Marshall, 2004). The most likely risk factor for progression of aortopathy is felt to be age. Aortic root size itself is related to valve morphology and the presence of significant disease (Schaefer, Lewin, Stout, Byers, & Otto, 2007; Thanassoulis et al., 2008) however, a recent study did suggest that while most patients with BAV and ascending aortic aneurysm had severe valve dysfunction, there was a small proportion of patients (5%) who did have aneurysm formation without any aortic valve dysfunction (Aydin et al., 2013).

Many theories have been postulated for the mechanism of BAV aortopathy. For a long time it has been thought to be predominantly genetic in origin, however there is increasing evidence for the contribution of a hemodynamic mechanism (Padang et al., 2013). Recent work using CMR has shown abnormal flow in the proximal ascending aorta in BAV patients which may lead to shear stress and promotion of aortic dilatation, with variable patterns of aortic dilation seen with different valve orientations (Hope et al., 2011). It is felt that it is due to defects in the aortic media, such as elastin fragmentation, loss of smooth muscle cells, and an increase in collagen (Bonderman et al., 1999; Fedak et al., 2003; Michelena et al., 2011; Niwa et al., 2001). Systemic features have also been noted in BAV patients that may predispose to aneurysm formation including systemic endothelial dysfunction and higher plasma levels of
matrix metalloproteinases (Tzemos et al., 2010). Also noted has been an increased amount of wall stress in the ascending aorta (Nathan et al., 2011).

Aortic dissection is a devastating concern in these patients however reported incidence of this in the literature has been variable, from no events and 0.1% in the larger studies, up to 4% in pooled earlier studies (Guntheroth, 2008; Michelena et al., 2008; Tzemos et al., 2008). Risk stratification for BAV and development of aortopathy still has a long way to go as there has so far appeared to be little correlation between echocardiographic and histologic findings and development of aortic disease (Leone et al., 2012). Recent advances in echocardiography may help to identify at-risk patients in future (Santarpia et al., 2012). The incidence of aortic dissection is actually much higher in patients with Marfan syndrome, however due to the increased prevalence of BAV in comparison it is by far the commoner etiology (Larson & Edwards, 1984).

There is still a lot of evidence pointing towards a genetic origin. 4 “important lines of evidence” have been identified for the genetic theory (Bonow, 2008): 1. Greater aortic size in patients with BAVs and aortic stenosis compared with those with tricuspid valves and aortic stenosis who are matched for hemodynamic severity (Novaro et al., 2003); 2. Enlarged aortas are found in patients (including children) with BAVs but without any aortic stenosis or aortic regurgitation, compared with age-matched normal controls (Cecconi et al., 2005; Pachulski, Weinberg, & Chan, 1991); 3. Studies have demonstrated progressive enlargement of the aorta after aortic valve replacement (AVR) in patients with BAVs (Borger et al., 2004; Russo et al., 2002) and 4. Studies have demonstrated degeneration of the extracellular matrix of the aorta in patients with BAVs, including elastic fiber fragmentation, increased metalloproteinase expression, decreased expression of tissue inhibitors of metalloproteinases, and smooth muscle cell apoptosis as mentioned previously.

5.4 Infective Endocarditis

Endocarditis is more common in BAV. The estimated incidence is 0.16% per year in unoperated children and adolescents (Gersony et al., 1993). In adults the two large case series by Tzemos and Michelena give an incidence of 0.3% and 2% per year respectively.

Outcomes in BAV patients with infective endocarditis tend to be worse than in those with normal valves. A recent observational study of 310 patients with infective endocarditis found that the 50 patients with BAV were younger at presentation and had a higher incidence of aortic perivalvular abscess (Bonow et al., 2008). Early surgery was also performed in most of the BAV patients (72%) with similar perioperative mortality to those with tricuspid aortic valves. In-hospital mortality and 5 year survival was also comparable to patients with normal valves. Infective endocarditis associated with BAV is more common in children, and indeed in one cohort was the cause of death in over half the patients under 30, whereas it was the cause of death in only 13% of over 70s (Ward, 2000).

6 Management

The only treatments to offer any sort of curative option are surgical. Medical therapies are to try and alleviate symptoms and slow progression.
6.1 Screening and Surveillance

Given the possible genetic link we described earlier, and the clearer evidence of increased familial clustering, there has been increased interest in screening for the condition (Kerstjens-Frederikse et al., 2011). As an asymptomatic disease with a relatively easy non-invasive method of diagnosis and defined treatments it is a disease that certainly meets WHO criteria for adoption of screening. Recent guidance from the ACC/AHA have recommended screening first degree family members of patients with BAV, however this has not been adopted in European guidelines as yet (Warnes, Williams, Bashore, Child, Connolly, Dearani, del Nido, Fasules, Graham, Hijazi, Hunt, King, Landzberg, Miner, Radford, Walsh, et al., 2008).

Once diagnosed, patients with BAV should undergo yearly transthoracic echocardiograms if aortic root diameter is >40mm or there is significant valve disease, or every 2 years if less than 40mm (Warnes, Williams, Bashore, Child, Connolly, Dearani, del Nido, Fasules, Graham, Hijazi, Hunt, King, Landzberg, Miner, Radford, Walsh, & Webb, 2008).

6.2 Medical

It is generally felt that blood pressure should be aggressively controlled to try and slow the progression of aortopathy. Small studies in patients with Marfan syndrome and ascending aortic dilatation have shown some benefit in reduction of cardiac events in the use of beta-blockers (Ladouceur et al., 2007; Shores, Berger, Murphy, & Pyeritz, 1994). Nevertheless, the role of beta-blockers in BAV aortopathy is as yet unproven. The joint ACC/AHA guidelines have however suggested use of beta-blockers as first-line therapy in BAV patients with dilated aortic roots (>4.0cm) who are not candidates for surgery and have no more than mild aortic regurgitation (Bonow et al., 2008).

Extrapolating from patients with aortopathy in Marfan syndrome there is also a suggestion that ACE inhibitors and angiotensin receptor blockers may have a role to play, however the evidence in BAV is still lacking (Ahimastos et al., 2007; Brooke et al., 2008; Yetman, Bornemeier, & McCrindle, 2005). There is interest in the use of angiotensin receptor blockers in patients with aortopathy based on positive results in mouse models of aortopathy (Habashi et al., 2006) – there are two trials presently being conducted in patients with Marfan syndrome which may provide insight into the mechanisms behind BAV aortopathy also (Detaint et al., 2010; Radonic et al., 2010).

Of course, concomitant conditions and risk factors should be treated as in the normal population.

6.3 Surgical

Indications for valve surgery in patients with BAV are similar to those with tricuspid aortic valves and are summarized in table 2. Due to the variation in patient characteristics and pathology an individual approach must be taken to all surgical decisions. In children it is usually not practical to do AVR as they outgrow the prosthetic valve. Due to the lack of valve calcification in children balloon valvuloplasty is possible and is the management strategy of choice. Studies have shown good follow-up in both the immediate and medium-terms, with 50% of patients in one series (the majority of whom had BAV) requiring no intervention at 38 months (Rosenfeld et al., 1994).

The Ross procedure can be used in BAV patients with very good outcome. In this operation first described in 1962, the patient’s aortic valve is replaced with their own pulmonary valve (“autograft”), while the pulmonary graft valve is replaced by a cadaveric pulmonary valve (“allograft”) (Ross, 1962). This is the operation of choice in children. The main advantages of this procedure are thought to be an
Indication for Surgery

| Aortic Stenosis (AS) | Surgery is indicated in symptomatic patients with severe AS, patients with severe AS undergoing CABG, other valvular or aortic surgery, asymptomatic patients with LV ejection fraction ≤50% not due to any other cause and asymptomatic patients with severe AS and exercise related symptoms (on exercise testing)*.
Echocardiographic criteria:
- Valve area <1cm²
- Mean gradient >40cm²
- Maximum jet velocity >4m/s |
| Aortic Incompetence (AI) | Surgery is indicated in symptomatic patients with severe AI, asymptomatic patients with resting LV ejection fraction ≤50% or patients undergoing CABG, other valvular surgery or aortic surgery.
Echocardiographic criteria:
- Effective Regurgitant Orifice Area ≥30mm²
- Regurgitant Volume ≥60ml
- Pressure half time <200ms
- Vena Contracta width >6mm |
| Aortopathy | Aortic root repair or replacement if >5cm or rate of increase in diameter ≥0.5cm/year.
Aortic root repair or replacement if >4.5cm and undergoing AVR for severe AS or AI.
Yearly screening (by echocardiography, CT or CMR) if aortic root diameter >4cm. |

* Class 2b in ACC/AHA guidelines, Class I in ESC guidelines.

Table 2: Class I indications for surgery in patients with BAV (adapted from ACC/AHA 2008 guidelines (Bonow et al., 2008) and the ESC guidelines (Vahanian et al., 2012) for valvular heart disease).

...improvement in hemodynamics, the growth of the valve with the patient (allowing the use of the procedure in children) and the use of tissue for the valve. The major disadvantage is that the patient has to undergo double valve operation despite the fact that only one valve is diseased. Despite this, the operation is associated with low mortality and morbidity (David, Woo, Armstrong, & Maganti, 2010; El-Hamamsy et al., 2010). There are some concerns regarding long-term outcome however (David et al., 2000; Mokhles et al., 2012).

In adults, the favoured operations are AVR and aortic valve repair. Although AVR is associated with excellent outcomes, because BAV patients tend to be younger, valve sparing repair surgery tends to be favoured so as to avoid complications of prosthetic valves. Patients with 180° orientated valves with minimal calcification/stenosis are ideal candidates for aortic valve repair. Aortic root surgery can also be carried with excellent results (Boodhwani et al., 2009; Schafers, Kunihara, Fries, Brittner, & Aicher, 2010). Prior to any surgery in adults coronary angiography (either invasive or by CT) is mandatory.

The 2008 AHA/ACC guidelines recommend aortic root repair or replacement if the root is greater than 50mm or the rate of increase in diameter is 5mm or more per year. The guidelines also suggest that patients with BAV undergoing aortic valve surgery should also have concomitant replacement of the ascending aorta if it is greater than 45mm in diameter (Bonow et al., 2008). This has been supported by evidence looking at outcomes in over 200 patients with varying aortic diameters (Borger et al., 2004). Estimated 15 year freedom from complications was 86% in patients with an aortic diameter less than 40mm, dropping down to 81% in those with diameter 40-44 and 43% in patients with a diameter 45mm or great-
er. Once the ascending aorta reaches 50mm or greater, it is also appropriate to carry out aortic root replacement with a tube graft.

New techniques of repair such as transcatheter aortic valve implantation (TAVI) have also been reported in BAV with promising results (Kochman, Huczek, Koltowski, & Michalak, 2012). Recently, Hayashida et al evaluated a cohort of 229 patients undergoing TAVI, of which 21 had BAV and found that there was no appreciable difference in outcome between the BAV group and those with tricuspid valves with similar device success, rate of annulus rupture, mean post-operative gradient and 30-day mortality in both groups (Hayashida et al., 2013).

7 Conclusion

BAV is the commonest congenital cardiac abnormality, and presents a significant burden on cardiac services. Recent cohort studies have given us knowledge of the clinical progression of the disease and when to operate, however there is still a need for further evidence for screening and for medical therapies to be evaluated. Surgical techniques will also continue to be refined, with the advent of transcatheter aortic valve implantation holding significant promise in this group of patients. The roles of CT and CMR as imaging tools will continue to enlarge. Much remains to be discovered about the genetics behind BAV, and as we discover more about this area we may be able to identify which patients are more likely to require early intervention and perhaps pick them up earlier. As our understanding of the pathogenesis of valve degeneration and aortopathy improves, this will allow us to identify new targets for treatment such as angiotensin receptor blockers which hold some promise in slowing the progression of aortopathy.

References


