Bicuspid aortic valve aortopathy: genetics, pathophysiology and medical therapy

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Abstract

The association between ascending aortic aneurysm (AA) and bicuspid aortic valve (BAV) has been well established. Different genetic, haemodynamic and cardiovascular risk factors have been implicated in the development and progression of AA. However, to date, definite conclusions cannot be drawn regarding the exact molecular, cellular and haemodynamic mechanisms causing BAV-associated aortopathy. For this study, we performed a thorough electronic systematic review of the literature using MEDLINE (1960–2012) and EMBASE databases. MeSH terms included: ‘bicuspid aortic valve and ascending aorta’, ‘bicommissural aortic valve and aneurysm’, ‘bicuspid aortopathy’, ‘bicuspid aortic valve pathophysiology’, ‘bicuspid aortic valve and genetics’ and ‘bicuspid aortic valve and treatment’. We aim in this review to discuss the mechanisms, pathophysiology, genetics and modern drug therapy in the context of BAV-associated aortopathy.

Keywords: Aortic aneurysm • Aortopathy • Bicuspid aortic valve • Genetics • Medical therapy

THE BICUSPID AORTIC VALVE

A congenital bicuspid aortic valve (BAV) is the commonest cardiac defect, occurring in 0.5–2% of the general population [1]. The precise aetiology of the BAV has not been clearly defined, and it is a precursor of complications occurring a decade earlier in life than in a tricuspid aortic valve (TAV). It can cause aortic valve disease (stenosis and/or regurgitation), infective endocarditis and thrombus formation and is associated with ascending aortic aneurysm (AA) and dissection [2]. The majority of the BAV occurs sporadically; however, familial BAV has been reported with prevalence in first-degree relatives of affected individuals being as high as 9%, suggesting an autosomal dominance pattern with reduced penetrance [3]. It has been shown to be more frequent in males than in females, with a ratio of 3:1 [4]. Furthermore, BAV is associated with other congenital heart defects in first-degree relatives of those with BAV [5]. BAV can also be part of other syndromes, e.g. Turner syndrome and Shone’s complex [6, 7], patent ductus arteriosus, ventricular septal defects [8] and coarctation of the aorta [9].

Animal studies suggest the involvement of neural crest cells in the development of both the aortic valve and the ascending aorta [10, 11]. Disruption of fibroblast growth factor 8 expression in the pharyngeal arch ectoderm leads to abnormalities in the great vessels and coronary arteries as well as BAV. Endothelial nitric oxide is important in vascular and valve formation, and knockout mice without endothelial nitric oxide synthase can develop the BAV. Recent studies have shown that different BAV morphologies may result from different aetiologies. Right and left BAVs result from the anomalous septation of the proximal portion of the outflow tract, likely caused by a distorted behaviour of neural crest cells. Right and non-coronary BAVs are the product of a morphogenetic defect that occurs before cardiac outflow tract septation and that probably relies on an exacerbated nitric-dependent epithelial-to-mesenchymal transformation. Thus, in accordance with these results, both morphologies might rely on different genotypes [12].

BICUSPID AORTIC VALVE-ASSOCIATED AORTOPATHY

The normal aortic wall consists of three layers: an inner intimal layer consisting of endothelial cells, a thicker medial layer consisting of smooth muscle cells (SMCs) embedded in an extracellular matrix (ECM), an average of 50 lamellae of elastic fibres accounting for aortic elasticity and of collagen fibres accounting for aortic tensile strength; and finally, a strong covering adventitial layer consisting of collagen fibres enwrapping the aorta [13].

An AA is an increase in aortic size above the normal threshold set for age, gender and body mass index. The annual growth rate of an ascending AA is between 0.1 and 1.0 cm/year [14]. Studies are varied in reporting the prevalence of ascending AA associated with BAV, starting from 35% till about 80% of BAV patients developing ascending AA, depending on the different study criteria [15, 16]. Both BAV and Marfan syndrome can carry devastating complications such as aortic rupture and dissection; however, Marfan syndrome still has a very low incidence (0.01–0.02%) compared with how common BAV is (0.5–1% of the population) [17]. As a result, BAV is a bigger liability by presenting a more common cause for AA than for Marfan syndrome in the community [2]. It is important to keep in mind that larger aortas have a substantial...
increase in their 5-year mortality risk, particularly when the aortic diameter reaches a hinge point of 6 cm [18]. Therefore, the cut-off point for replacing the dilated aorta is when the aneurysm is ≥ 5 cm or when there is a fast progression of aortic dilatation ≥0.5 cm/ year [14]. However, other criteria for intervention should also be considered based on the presence of symptoms and family history of AA and dissection.

**AETIOLOGY OF BICUSPID AORTIC VALVE AORTOPATHY**

Different aetiological factors contributing to the development and progression of BAV-associated AA are shown in Fig. 1.

**Cardiovascular risk factors**

Epidemiological studies have been undertaken as an attempt to pinpoint the predictors for AA in BAV patients [15, 19]. High-risk groups in these studies were those of increased age, those suffering from diabetes and hypercholesterolaemia and those with aortic regurgitation and smokers.

Several factors contribute to the development and progression of AA (Fig. 1), but it is difficult to predict the phenotypic specifics of patients who will develop AA and the exact rate of progression of the aneurysm.

**Genetics**

Many genes have been implicated in the aetiology of non-syndromic AA such as ACTA2, MYH11, FLNA and SMAD3 [20–26]. Similarly, other genes such as FBN1 and transforming growth factor beta receptor (TGFBR)1/2 have been implicated in the development of syndromic AA [27], but none of them have been proven to be conclusive in causing BAV aortopathy. Similarly, linkage studies have demonstrated novel associations between BAV and non-syndromic familial AA with chromosomal regions 5q, 13q and 18q [28, 29]. More recent studies have shown an association between BAV patients with GATA5 and NOTCH1 mutations [30, 31]. However, only a small proportion of BAV patients with AA carried these mutations; therefore, it is apparent that BAV-associated aortopathy is a polygenic disease, and further detailed genetic studies are crucial to elucidate its cause (s). Genes associated with the presence of BAV are listed in Table 1.

**Altered haemodynamics**

Three morphologies have been identified as demonstrated in Fig. 2. Type 1 is where there is fusion of right and left coronary cusps (the most abundant), Type 2 is fusion of the right and non-coronary cusps and Type 3 is fusion of the left and non-coronary. Aortic dilatation in the BAV usually occurs at the level of the aortic root and arch much more often than in the descending or abdominal aorta. Doming, wrinkling and folding of the BAV during the cardiac cycle can cause an abnormality in the blood jet generated when compared with the TAV [32]. Furthermore, magnetic resonance imaging (MRI) studies demonstrated the presence of turbulent flow through the BAV and ascending aorta despite a functionally normal valve [33]. Various studies have implicated valve orientation in the development aortic valve disease and AA (Table 2). However, Jackson et al. [16] found no pattern in aortic dilatation in 300 BAV patients undergoing open-heart surgery related to leaflet morphology. In contrast, the latest study by Barker et al. [34] demonstrated an increase in wall shear stress on BAV aortas, particularly right-to-left valve orientation, using four-dimensional MRI.

The discovery of true detrimental flow patterns and pathologic gene(s) in association with aortic dilatation in BAV patients may aid us to identify high-risk geno-phenotypes, which will in turn help in risk stratification, creation of guidelines and tailoring optimal treatment to individual patients’ needs.

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**Figure 1:** Showing different tributaries to the development and progression of aneurysm in BAV disease. Genetic [30, 31] and haemodynamic factors [34] contributing to the weakness of the aortic wall and trigger the increase in MMP release leading to the TGFBR pathway activation and further dilatation [46, 47]. The presence of cardiovascular risk factors may also contribute to the progressive dilatation of the aorta [15, 19]. All the above interact with and are influenced by epigenetic control [50].
It has been shown that BAV is associated with aortic wall intrinsic disease, exhibiting premature cystic medial degeneration in around half of BAV aortas [35] and reduced fibrillin-1 content independent of valve function [36]. It has also been shown that ascending aortas continue to expand despite aortic valve replacement at a rate of 1.9 vs 1.3 mm per year when compared with TAV [37]. Furthermore, BAV patients are significantly younger and have considerably larger aortas than TAV [35]. It has been observed that the degree of stenosis was not always proportional to that of turbulence [38]. Therefore, AA appears to be independent of the presence of valvular disease. A study by Pees and Michel-Behnke [39] demonstrated a decrease in aortic wall elasticity in BAV patients, particularly right-to-left valve orientation, a finding persisting even after valve surgery, hence supporting the defective aortic wall theory.

An ECM plays an important role in regulating cellular events, binding and storing secreted proteins and in maintaining the structural integrity of the vascular wall [40]. The degradation of ECM is under the balanced control of matrix metalloproteinases (MMPs) and their specific tissue inhibitors (TIMPs), which are secreted by vascular SMCs, fibroblasts and endothelial cells [41].

### Table 1: Genes associated with bicuspid aortic valve (human and animal models)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene name</th>
<th>Chromosome</th>
<th>Human disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>45, X</td>
<td>Unidentified</td>
<td>XO</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>5q, 9q34, 13q, 15q25.1-26, 18q</td>
<td>Unidentified</td>
<td>5, 9, 13, 15, 18</td>
<td>BAV</td>
</tr>
<tr>
<td>ACTA2</td>
<td>α-smooth muscle actin</td>
<td>10</td>
<td>Familial aortic aneurysm, Type 6</td>
</tr>
<tr>
<td>AXIN1</td>
<td>Axin-1</td>
<td>16</td>
<td>BAV</td>
</tr>
<tr>
<td>ELN</td>
<td>Elastin</td>
<td>7</td>
<td>Cutis laxa/BAV</td>
</tr>
<tr>
<td>ENG</td>
<td>Endoglin</td>
<td>9</td>
<td>Hereditary haemorrhagic telangiectasia</td>
</tr>
<tr>
<td>FBN1</td>
<td>Fibrillin-1</td>
<td>15</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>FGF8</td>
<td>Fibroblast growth factor 8</td>
<td>10</td>
<td>BAV</td>
</tr>
<tr>
<td>FN1</td>
<td>Fibronectin-1</td>
<td>2</td>
<td>BAV</td>
</tr>
<tr>
<td>GATA5</td>
<td>GATA binding protein 5</td>
<td>20</td>
<td>BAV</td>
</tr>
<tr>
<td>HOXa1</td>
<td>Homeobox A1</td>
<td>7</td>
<td>BAV</td>
</tr>
<tr>
<td>JAG1</td>
<td>JAGGED1</td>
<td>20</td>
<td>Alagille syndrome; tetralogy of Fallot</td>
</tr>
<tr>
<td>KCNJ2</td>
<td>Potassium inwardly rectifying channel J2</td>
<td>17</td>
<td>Andersen syndrome</td>
</tr>
<tr>
<td>NKX2.5</td>
<td>NKX2-5</td>
<td>5</td>
<td>Hypoplastic left heart syndrome 2</td>
</tr>
<tr>
<td>NOS3</td>
<td>Endothelial nitric oxide synthase</td>
<td>7</td>
<td>BAV</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>NOTCH1</td>
<td>9</td>
<td>BAV</td>
</tr>
<tr>
<td>PDIA2</td>
<td>Protein disulphide isomerase A2</td>
<td>16</td>
<td>BAV</td>
</tr>
</tbody>
</table>

### Table 2: Pathologies associated with bicuspid aortic valve morphology

<table>
<thead>
<tr>
<th>Valve orientation</th>
<th>Associated pathology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-left</td>
<td>Aortic stenosis</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>Coarctation of aorta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase aortic wall shear stress</td>
<td>[31]</td>
</tr>
<tr>
<td>Right-non-coronary</td>
<td>Aortic stenosis</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>Aortic regurgitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic aneurysm</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>Larger aortic arch dimensions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myxomatous mitral valve disease</td>
<td>[62]</td>
</tr>
<tr>
<td>Left-non-coronary</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 2:

Demonstrating different bicuspid aortic valve (BAV) phenotypes. RCC: right coronary cusp; LCC: left coronary cusp; NCC: non-coronary cusp. Showing in (A) normal TAV, (B) Type I BAV phenotype, (C) Type II BAV phenotype and (D) Type III BAV phenotype.
MMPs play an important role in connective tissue homeostasis, and after production, they are stored in their inactive form until needed [42]. All these various functions of the ECM render it an important player in normal development and disease processes. It has been argued that the intrinsic pathology of the ascending aortic wall, involving an abnormality in the process of ECM remodelling, may be the underlying mechanism of this dilatation. Their inhibition is regulated by TIMPs, which are produced by vascular SMC and fibroblast present in the aortic wall [43]. Like MMPs, the expression of TIMPs is controlled during tissue remodelling and physiological conditions to maintain a balance in the metabolism of the ECM [44]. The balance between MMPs and TIMPs regulates the degradation of the ECM both in normal and pathological states and can lead to aneurysm formation when the balance is tipped towards increased MMP activity [36, 45]. Various studies have shown a disturbance in the ECM of AA in the BAV with an increased activity of MMPs [46, 47]. This increase in MMP activity leads to apoptosis and degeneration of the aortic wall with the eventual progression of AA. However, it is unknown if this rearrangement in MMP/TIMP activity is genetically pre-programmed or whether it is due to the effect of increased transforming growth factor (TGF)-β signalling contributing to the progression of AA [48].

Epigenetic control

The role of epigenetics is essential in regulating gene expression in BAV, leading to a change in the heritable genetic information without altering the DNA sequence [49]. This includes the study of histone modification and methylation of promoter regions of genes under different stimuli, which can lead to silencing certain genetic information leading to a change in the biological function without altering the DNA sequence. So far, the decreases in miR-29, miR-26A, miR-30b and miR-195 have been shown to be associated with BAV disease and AA [50, 51]. The role of microRNAs as governors of gene expression that modify the regulatory biological networks in the development of BAV and its associated complications needs to be further elucidated. Despite all the above studies carried out, there is still a need to establish a connection between unbalanced gene and protein expressions and wall shear stress in BAV aortas.

MEDICAL THERAPY

AA in BAV can be completely silent for many years and only discovered during imaging studies done for other reasons. Symptoms can vary from mild, such as fatigue, dyspnoea and palpitation, to more devastating complications such as aortic rupture [52]. Clinically viable, sensitive and specific early detection systems for AA presence, progression or rupture that have been attempted are still modest, and none of them are used in BAV clinical settings [44, 53].

The usefulness of medical treatment for AA in BAV is controversial. However, Slowing the progression of BAV-associated AA by the employment of different modality treatments is advocated. Such treatments are not specific to BAV, but due to histological
similarities of medial cystic degeneration exhibited by both BAV and Marfan syndrome aortas, similar medical regimens have been recommended for the treatment of AA in both [35]. Therapies include β-blockers, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers. Statins, however, were shown to decrease long-term mortality with abdominal AA, but not in ascending AA [54]. Fewer studies implicated the use of doxycycline as an MMP inhibitor, but human trials have not yielded reliable results [55]. Medical therapy to decrease the load on the aortic wall and hence to slow the progression of AA by using β-adrenergic receptor antagonist has been indicated [56, 57]. The most recent guidelines for the management of AA in non-Marfan patients recommend the use of β-blockers to decrease the blood pressure as low as the patient can tolerate [57, 58].

Angiotensin II (ANG II) exerts its action via the activation of two different receptors: Type 1 (AT1) and Type 2 (AT2; Fig. 3). AT1 mediates the TGF-β signalling pathway possessing profibrotic properties leading to an increase in MMP2, 9 and apoptosis. Therefore, ANG II induces fibrosis through the activation of the TGF-β pathway via the activation of AT1 [59]. TGF-β in vascular smooth muscle cells activates Smads, which upregulate fibronectin and collagen, eventually destroying elastic fibres. This complex process starts damaging the aorta, and in an attempt to repair it, remodelling is initiated, leading to fibrosis. Therefore, the development and progression of AA can potentially be slowed or even halted by utilizing AT1 blocking agents such as losartan. This will have a downstream effect on the TGF-β pathway, causing a decrease in MMP2, 9 and apoptosis. Losartan was found to specifically inhibit the TGF-β-mediated activation pathway, therefore blocking AT1 and ameliorating the severity of AA [60]. This encouraged the initiation of the multicentre losartan therapy trial that is underway at the moment with results expected in the coming few years [60]. On the other hand, using ACEi in mouse models was shown to be less effective in slowing the progression of AA than losartan (Fig. 3) [59]. This was due to the inherent property of ACEi in simultaneously blocking both AT1 and AT2. AT2 activation cascade possesses a protective effect by decreasing MMP levels, proliferation and hence fibrosis. Therefore, blocking this pathway using ACEi would lead to an imbalance between the protective AT2 effect and the proremodelling AT1 effect.

**FUTURE DIRECTIONS**

The BAV is a multifaceted heterogeneous disease with many cofactors contributing to its associated complications. Therefore, more vigorous attempts need to be taken to decipher the biological complexity and to explain the different mechanisms, genetic and molecular, causing aortic dilatation. More extensive haemodynamic stretch studies, in vitro and in vivo, need to be undertaken on cells and animal models, to determine the effect of shearing forces on the structure of the aorta [44]. Using next-generation exome sequencing in analysing BAV cohorts is important and timely [61]. On similar grounds, further genome-wide association studies are needed to propose novel genetic contributors in the development of AA [62]. Only by using a holistic, clinical and scientific approach incorporating clinical phenotypes, epigenetic control, genomics, transcriptomics, proteomics and metabolomics to solve the problems of BAV can a more complete understanding of the underlying pathology be identified that can lead to the discovery of novel therapeutic interventions and optimum treatments.

**Conflict of interest:** none declared.

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