RESEARCH

A retrospective analysis of mitral valve pathology in the setting of bicuspid aortic valves

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Abstract

The therapeutic implications of bicuspid aortic valve associations have come under scrutiny in the transcatheter aortic valve implantation era. We evaluate the spectrum of mitral valve disease in patients with bicuspid aortic valves to determine the need for closer echocardiographic scrutiny/follow-up of the mitral valve. A retrospective analysis of echocardiograms done at a referral hospital over five years was conducted in patients with bicuspid aortic valves with special attention to congenital abnormalities of the mitral valve. One hundred and forty patients with a bicuspid aortic valve were included. A congenital mitral valve abnormality was present in eight (5.7%, \(P=0.01\)) with a parachute mitral valve in four (2.8%), an accessory mitral valve leaflet in one (0.7%), mitral valve prolapse in one, a cleft in one and the novel finding of a trileaflet mitral valve in one. Minor abnormalities included an elongated anterior mitral valve leaflet \(P<0.001\), the increased incidence of physiological mitral regurgitation \(P<0.001\), abnormal papillary muscles \(P=0.002\) and an additional chord or tendon in the left ventricle cavity \(P=0.007\). Mitral valve abnormalities occur more commonly in patients with bicuspid aortic valves than matched healthy individuals. The study confirms that abnormalities in these patients extend beyond the aorta. These abnormalities did not have a significant functional effect.

Introduction

Bicuspid aortic valves (BAVs) are a common congenital cardiac abnormality occurring in 0.5–1.4% of the general population (1). The underlying pathophysiology remains unclear with abnormalities in cell migration, signalling pathways and genetic susceptibility postulated (2). While BAVs can occur in isolation, its presence should prompt a full evaluation for associated cardiovascular and congenital defects, including, but not restricted to an aortopathy with or without aortic root dilatation (3), aorta coarctation (4) and the rare, but interesting, Shone complex (5). The therapeutic implications of BAV associations have come under renewed scrutiny in the era of transcatheter aortic valve implantation.

The association between mitral valve dysfunction and BAVs has not been well defined yet. However, several studies have shown what appears to be more than a coincidental link between bicuspid aortic valve and mitral valve prolapse (6, 7, 8) with an incidence as high as 5% reported in this setting by Schaeffer and coworkers (9). An association with rare congenital abnormalities of the mitral valve has been suggested, including a case report of a double orifice mitral valve in the setting of a bicuspid aortic valve (10). Minor structural abnormalities of the
mitral valve in the setting of BAVs have also been reported with one small study showing an association with an abnormal anterior mitral valve leaflet (11). The association of BAV and Shone complex, a rare disease involving obstruction of the left ventricular outflow (valvular/subvalvular stenosis or coarctation) and inflow (parachute mitral valve or supravalvular mitral membrane) (5), is an uncommon yet interesting one as it serves to illustrate the range of congenital abnormalities, including those of the mitral valve, that can coexist in patients with BAV. The complex is also often present in a forme fruste, and based on first principles, it is possible that this syndrome is underreported in its milder forms.

Left ventricular outflow tract or aorta abnormalities that are commonly associated with BAVs include coarctation of the aorta (22–60%) (4), supravalvular stenosis (37%) (12) and subvalvular stenosis (23%) (13), sinus of valsalva aneurysm, ascending aortic aneurysm and aortic dissection (3). Other congenital abnormalities occurring in the setting of BAVs include ventricular septal defect, patent ductus arteriosus and atrial septal defect (2) as well as coronary artery abnormalities including reversal of coronary dominance, a short left main stem (<5 mm) and single coronary arteries (14, 15). The heterogeneity in the associated lesions could suggest a more global disorder of cardiac development as a basis for the disorder, while the association with left ventricular outflow tract obstruction not only suggests a possible shared pathophysiology but also fulfils two of the four components of the Shone complex in a large proportion of patients. Given these findings, it is possible that the incidence of congenital abnormalities of the mitral valve in the setting of BAVs is higher than originally thought. We therefore postulated that the morphology of the mitral valve might be abnormal in these patients even in the absence of a clearly identifiable congenital abnormality or functional impairment. This would warrant careful scrutiny for detection and follow-up of the mitral valve in these patients even if the bicuspid aortic valve was surgically corrected or replaced and could have treatment implications in the current transcatheter aortic valve implantation era.

Methods

A retrospective echocardiographic analysis was conducted at Tygerberg hospital, a 1300-bed academic hospital in South Africa serving a population of 3.6 million people of predominantly mixed racial descent. All echocardiograms done at this institution are saved on a central EchoPAC database with the complete echocardiogram video clips available for review. In selected cases with clear pathology, 3D echocardiograms were available for review. Information on the age and gender of the patients were also obtained from this database.

All reports of echocardiograms done between January 2011 and December 2015 were screened for evidence of confirmed or suspected bicuspid aortic valve disease or bicuspid aortic valve disease spectrum (unicuspid and quadricuspid valves). These echocardiograms were then reviewed by the principal investigator to confirm the presence of bicuspid spectrum aortic valve disease. Uncertain cases were reviewed by the principle investigator and co-investigator (PG Herbst), and a joint decision was made. All patients with bicuspid spectrum aortic valve disease were included regardless of whether an intervention was done on the aortic valve, provided that there was adequate documentation to support the diagnosis of the congenital abnormality. Cases where an intervention on the mitral valve had already been done and no echocardiogram prior to the intervention was available for review were excluded. Studies were then evaluated with special attention to the presence of any congenital abnormalities of the mitral valve.

First, BAVs were classified according to whether or not a raphe was present. If a raphe was present, they were further subdivided into type 1 (right-left coronary cusp fusion), type 2 (right-noncoronary cusp fusion) and type 3 (left-noncoronary cusp fusion) (16). Functional evaluation of the aortic valve using standard European Association of Echocardiography guidelines (17, 18) was then performed.

Cases were then evaluated for obvious congenital abnormalities of the mitral valve. Abnormalities were classified, according to the part of the mitral valve complex involved, into leaflet abnormalities (mitral valve prolapse, cleft anterior mitral valve leaflet, mitral ring and Ebstein’s malformation), abnormalities of the tensor apparatus (arcade/hammock mitral valve, straddling mitral valve) and abnormalities of the papillary muscles (parachute mitral valve). Subsequently, studies were evaluated for more subtle morphological abnormalities, which included measuring the mitral valve annulus diameter, the anterior mitral valve leaflet length and papillary muscle number and position. Mitral valve annulus diameter was measured in the parasternal long axis just before mitral valve opening at end-systole. In cases where the parasternal long axis was unavailable or of poor image quality, the apical 3-chamber view was used.
The anterior mitral valve leaflet length was measured in the same view from the base of the anterior mitral valve leaflet where it joins the aortic leaflet hinge point (annulus) to the tip of the anterior mitral valve leaflet in a frame with the full length of the leaflet visible. Care was taken not to measure chordal structures. The assessment of the papillary muscles included noting the number as well as the shape and size of the papillary muscles. Papillary muscles are usually defined not only as muscles located in the ventricles but also as attaching to the cusps of the atroventricular valves via the chordae tendineae. For the purpose of this study, we included all additional muscles that had the appearance of a papillary muscles regardless of whether chordal attachments were demonstrated. The papillary muscle position was then measured on the parasternal short axis view according to the method defined by Stanley and coworkers (19). A fixed reference point (0°) was defined at the medial junction of the right ventricular free wall with the posteroinferior ventricular septum. A point was then placed into the centre of the left ventricle, and the position of both papillary muscles in degrees of arc was then measured around the point representing the centre of the left ventricle from 0° to the middle of the base of the anterolateral and posteromedial papillary muscles (Fig. 1). The presence of anomalous chordae or false tendons within the left ventricle as well as the insertion points of these structures were noted if present. This was followed by a functional evaluation of mitral valve using standard European Association of Echocardiography guidelines (20).

The presence of subvalvular/supravalvular obstruction was noted as well as the presence of an aortopathy which was classified into three types based on the pattern of aortic involvement described by Verma and coworkers (21). Aortic diameters were measured on 2D imaging (inner edge to inner edge) with all measurements taken at end-diastole.

One hundred and forty-six controls were obtained from both normal volunteers and patients not known with any cardiac disease requiring pre-chemotherapy screening echocardiograms. Patients with complex congenital heart disease causing marked distortion of the normal cardiac anatomy were not matched, but were included for other parameters. Children younger than 16 years were also not matched, and their linear measurements were not included in the overall assessment given the marked difference in the age-related normal range.

This study complies with the Declaration of Helsinki. Ethics approval was obtained from the local ethics committee who waived informed consent given the retrospective nature of this study.

Statistical analysis
IBM SPSS version 22 was used to analyse the data. A P value <0.05 was considered statistically significant. All morphological data are presented as mean±1 s.d. Pearson’s chi-square tests, Student’s t-test as well as ANOVA methods were employed to explore and compare differences in variables between the groups, allowing for multiple testing corrections. Linear regression analyses were also performed to explore the relations between measurements as well as to identify group effects.

Results
Baseline characteristics
A total of 23,784 echocardiography reports were screened, and 210 patients were identified of which 140 patients
fulfilled criteria for inclusion (Fig. 2). The median age was 44 years (range 1–90), and 60% were male.

**Aortic valve morphology and function**

A raphe was present in 82 patients (59%), which included 42 patients with type 1, 31 patients with type 2 and 9 patients with type 3 bicuspid aortic valve morphology. Fifty patients (36%) had BAVs without raphes. In one patient with previous surgery to his aortic valve, the type of bicuspid aortic valve was unknown. The remaining 7 patients (5%) had quadricuspid aortic valves.

Aortic stenosis was present in 82 patients (58.6%) with severe aortic stenosis present in 40 patients (48.7%) with 5 (6%) of these patients having low-gradient severe aortic stenosis. Aortic regurgitation was present in 103 patients (73.6%), but it was mild or trivial in 54 patients (52.4%) and severe in only 12 patients (11.6%).

**Mitral valve morphology and function**

A clear congenital abnormality of the mitral valve was present in 8 patients (5.7%; Table 1). This was statistically significant compared to the control group ($P=0.01$; LR 9.4). The most common abnormality was a parachute mitral valve, which was present in four patients (2.8%). Of these patients, one had the complete Shone complex, two had three of the four components, and the remaining patient had only two components. One patient (0.7%) had an accessory mitral valve leaflet, one patient had mitral valve prolapse, one patient had a cleft in the anterior mitral valve leaflet, and one patient a novel echocardiographic finding of a trileaflet mitral valve with three commissures and three associated papillary muscles supplying chords to the mitral valve (Fig. 3).

The entire bicuspid aortic valve spectrum found in our cohort was represented in the group with mitral valve disease. There was no clear pattern or association with the type of bicuspid aortic valve and the presence of mitral valve disease.

Mitral regurgitation was present in 75 patients (53.6%). It was mild or trivial in 68 patients (90.7%), moderate in six patients (8%) and severe in one patient (1.3%). In the majority of cases, the mitral regurgitation was considered to be physiological, either often due to a prominent interscallop separation in the posterior mitral valve leaflet or due to tethering of an otherwise normal valve. However, mitral regurgitation from any cause was statistically significantly associated with the presence of a bicuspid aortic valve ($P<0.001$; LR 28.9), and this difference persisted if mitral regurgitation due to congenital mitral valve disease ($P<0.001$) or congenital mitral valve disease and/or tethering was excluded ($P=0.02$). Mitral stenosis was present in only one patient.
Mitral valve disease and bicuspid aortic valve

with a parachute mitral valve and a mitral valve area of 1.6 cm$^2$.

The anterior mitral valve leaflet was significantly longer in all of the patients ($P<0.001$) even if corrected for left ventricular end diastolic diameter (Table 2).

Abnormalities of the papillary muscles were frequently present ($P=0.002$) with the most common abnormality, an additional papillary muscle ($P<0.001$) typically positioned more anteriorly in degrees of arc than the anterolateral papillary muscle. More than 1 additional papillary muscle was frequently present with up to 7 papillary muscles seen in one patient. A papillary muscle complex or single papillary muscle was seen in the patients with parachute mitral valve. Both papillary muscles were also found to be positioned more anteriorly in degrees of arc in patients with BAVs ($P<0.001$).

A false tendon or chord was seen in the left ventricle in 27 patients (19.3%). The majority of these were in the mid-ventricle or apex, but in four patients, a thick, prominent chord/tendon extended to the base of the anterior septum giving a very abnormal appearance, but no functional effect.

Aortopathy, subvalvular and supravalvular obstruction

An associated aortopathy was present in 49 patients (35%) with type 1 aortopathy present in 29 patients, type 2 in 14 patients and type 3 in 6 patients. Subvalvular obstruction was present in 8 (5.7%). This was due to a subvalvular ridge in four patients, a subvalvular membrane in three patients with one patient having an accessory mitral valve leaflet causing left ventricular outflow tract obstruction. Supravalvular obstruction was present in 11 patients (7.9%) with 10 patients having aorta coarctation and 1 patient an interrupted aortic arch.

Discussion

A clear congenital abnormality of the mitral valve was statistically significantly ($P=0.01$) associated with a bicuspid aortic valve when compared to the control group. Mitral valve abnormalities in this cohort were equally divided between leaflet abnormalities and abnormalities of the papillary muscles rather than a single associated lesion. This suggests a spectrum of mitral valve disease in the setting of a bicuspid aortic valve rather than a single associated lesion.

Interestingly, congenital abnormalities of the mitral valve leaflets predominantly involved the anterior leaflet.

### Table 1
Clinical and echocardiographic findings of patients with clear congenital mitral valve disease.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>BAV</th>
<th>LVOTo</th>
<th>AoC</th>
<th>Type MV abnormality</th>
<th>Associated congenital abnormalities</th>
<th>Severity of obstruction</th>
<th>Type BAV</th>
<th>Severity of obstruction</th>
<th>Associated congenital abnormalities</th>
<th>MR</th>
<th>Associated congenital abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>parachute MV</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild-moderate</td>
<td>None</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>parachute MV</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild-moderate</td>
<td>None</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Trileaflet MV</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Mild-moderate</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>MVP (A2)</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Parachute MV</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>39</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Cleft MV</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>54</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Parachute MV</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
<tr>
<td>71</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Accessory MV</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>Trace</td>
<td>None</td>
<td>Trace</td>
<td>None</td>
</tr>
</tbody>
</table>

AoC, aorta coarctation; AR, aortic regurgitation; BAV, bicuspid aortic valve; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; MV, mitral valve; VSD, ventricular septal defect.
with prolapse of the A2 segment, an accessory mitral valve leaflet attached to the anterior mitral valve leaflet as well as a cleft in the anterior mitral valve leaflet. More subtle abnormalities of the anterior mitral valve leaflet were also found, which could suggest that a structurally abnormal anterior mitral valve leaflet may be present in patients with BAVs and play an important role in the spectrum of congenital mitral valve disease in these patients. The anterior mitral valve leaflet in our bicuspid aortic valve cohort measured statistically significantly longer when compared with the control group ($P < 0.001$). This was in keeping with our visual impression as well as supporting the findings of a previous smaller study (10).

In our cohort, none of the patients had systolic anterior motion of this abnormally long anterior mitral valve leaflet, and therefore no functional implications of this abnormality were noted. However, this could become clinically relevant in the post-operative setting where systolic anterior motion of the mitral valve is more likely to occur. The incidence of mitral valve prolapse in our cohort was much lower than the 5% incidence reported by Schaeffer and coworkers (9). Since both studies were done retrospectively with reasonably similar cohort sizes, this finding was unexpected. It may be an illustration of the known marked variation in the phenotypic presentation of bicuspid aortic valve disease, but subtle bias in the way retrospective cohorts are constructed cannot be excluded.

The most common abnormality congenital abnormality of the mitral valve in our cohort was a parachute mitral valve. More subtle abnormalities of the papillary muscles were also frequently noted. Additional papillary muscles were found in 37 of the matched patients with many patients having multiple additional papillary muscles. These papillary muscles were typically anteriorly positioned, just above the anterolateral papillary muscles.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls ($N=146$)</th>
<th>BAV ($N=125$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao annulus (cm)</td>
<td>$2.1 \pm 0.21$</td>
<td>$2.2 \pm 0.34$</td>
<td>0.065</td>
</tr>
<tr>
<td>Ao sinus (cm)</td>
<td>$2.9 \pm 0.37$</td>
<td>$3.1 \pm 0.67$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Ao STJ (cm)</td>
<td>$2.4 \pm 0.34$</td>
<td>$2.7 \pm 0.7$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Ao Asc (cm)</td>
<td>$2.4 \pm 0.38$</td>
<td>$2.9 \pm 0.84$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>MV annulus (cm)</td>
<td>$2.8 \pm 0.29$</td>
<td>$2.9 \pm 0.48$</td>
<td>0.07</td>
</tr>
<tr>
<td>AMVL length (cm)</td>
<td>$2.6 \pm 0.35$</td>
<td>$3.0 \pm 0.46$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>PM position (PM) (°) ($N=133$)</td>
<td>$309 \pm 19$</td>
<td>$300.8 \pm 19.7$</td>
<td>0.001</td>
</tr>
<tr>
<td>PM position (AL) (°)</td>
<td>$189 \pm 19.7$</td>
<td>$178.7 \pm 22.7$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Abnormal PM ($N=134$)</td>
<td>21</td>
<td>37</td>
<td>0.002</td>
</tr>
<tr>
<td>Additional PM</td>
<td>21</td>
<td>35</td>
<td>0.004</td>
</tr>
<tr>
<td>False tendon/chord</td>
<td>14</td>
<td>27</td>
<td>0.007</td>
</tr>
</tbody>
</table>

AMVL, anterior mitral valve leaflet; Ao, aorta; BAV, bicuspid aortic valve; MV, mitral valve; PM, papillary muscle; STJ, sinotubular junction.
These papillary muscles had a typical appearance, but chords to the mitral valve leaflets were not seen except in the patient with a trileaflet mitral valve. When measured in degrees of arc, both papillary muscles were positioned more anteriorly than expected. Even though the absolute difference was small, this again suggests that abnormalities of the papillary muscles extend beyond just a parachute mitral valve.

While abnormalities of the tensor apparatus of the mitral valve were not found in our cohort, an interesting finding was the frequent observation of a chord or tendon extending across the left ventricular cavity ($P=0.009$). These were typically thin structures with no functional effect, but in four patients, these chords extended to the base of the anterior septum creating a very abnormal appearance.

Functionally, mitral regurgitation was a common finding present in more than half of patients. Even if congenital mitral valve disease or tethering due to ventricular dilatation or impaired systolic function related to the bicuspid aortic valve was excluded, mitral regurgitation was still a much more frequent finding in the study population than in the controls ($P=0.02$). Mitral stenosis was an uncommon finding only present in one of the patients and was due to a parachute mitral valve. None of the congenital abnormalities had a functionally significant effect with only one patient with a congenital mitral valve abnormality having more than mild mitral regurgitation and no patients having severe mitral regurgitation.

The prevalence of bicuspid aortic valve in screening studies among the general population is reported as 0.5–1.4%, while the frequency of BAVs in our screened cohort was 0.6%. Of course this is a study using a very different cohort of patients that have already preselected themselves for an echocardiogram, and therefore this figure is not necessarily generalizable to the prevalence in our population. Patients at our institution tend to present late in the disease course when it might not be possible to accurately differentiate a trileaflet aortic valve from a bicuspid aortic valve if significant calcification is already present. It is therefore possible that the true incidence in our population of predominantly mixed race could be substantially higher. Interestingly, a screening study currently underway at our institution to detect subclinical rheumatic heart disease did not record a single bicuspid aortic valve in the more than 2000 participants already screened, an observation which is as yet unexplained.

The bicuspid aortic valve morphology in our population differed from what is commonly reported. Type 1 bicuspid morphology was present in 30% of our cohort which, although still the most common type, is much less than the approximately 60% reported in other cohorts. Less common types like type 2 bicuspid morphology (22.1%) and quadricuspid valves (5%) occurred with a higher than expected frequency.

An aortopathy was present in 35% of cases, which is lower than the expected incidence of around 50% reported in other studies (21). This may reflect the fact that cases were selected for the presence of BAV rather than aortic dilatation primarily. The differences in the size of the aortic valve, aortic root and ascending aorta, while statistically significant, were also relatively modest given the mean age of 44 years in the cohort.

The main limitation of this study is the retrospective nature, which might impact on both the number of patients included and the accuracy and repeatability of the measurements obtained. However, images were re-analysed carefully, and multiple studies on the same patient were often available for analysis providing multiple images to ensure accurate measurements. 3D Echocardiography is not performed routinely in all cases in our practice, and 3D images were therefore not available for inclusion in the retrospective analysis for the majority of cases. Although 3D imaging adds useful information to the assessment of the mitral valve in selected pathologies such as for more complex cases of MVP, we felt that 2D imaging answered the specific questions asked in this study adequately.

## Conclusion

Mitral valve abnormalities occurs more commonly in patients with BAVs with a wide spectrum of disease ranging from subtle functional changes with an increased incidence of physiological mitral regurgitation, morphological abnormalities including an increased anterior mitral valve leaflet length or additional papillary muscles to clear congenital abnormalities including parachute mitral valve. While supporting the hypothesis that abnormalities in these patients extends beyond the aorta, none of these abnormalities had a significant functional effect.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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