JACC Vol. 30, No. 7
December 1997:1809–12

A Prospective Study to Assess the Frequency of Familial Clustering of Congenital Bicuspid Aortic Valve

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Objectives. **This study sought to determine the rate of familial occurrence of congenital bicuspid aortic valve (BAV) by using echocardiography to screen family members.**

Background. **Congenital BAV is a common anomaly that carries with it a significant risk of potential long-term cardiac complications. Despite several reports of the familial occurrence of BAV, the condition is not generally considered to be inherited.**

Methods. **Thirty consecutive patients with echocardiographically documented congenital BAV were interviewed to construct three-generation family pedigrees. All first-degree relatives were contacted to undergo echocardiography to specifically determine aortic valve morphology.**

Results. **Of the 210 first-degree relatives, 190 (90.5%) agreed to undergo echocardiography. Four members had technically difficult studies. Of the remaining 186 subjects, 17 (9.1%) were identified as having BAV; 11 (36.7%) of the 30 families had at least one additional member with the condition. The male/female ratio of affected members in the 11 families was 1. In one family, two instances of male-to-male transmission were observed. The distribution of BAV in the majority of multiplex families is compatible with autosomal dominant inheritance with reduced penetrance.**

Conclusions. **We demonstrated a high incidence of familial clustering in congenital BAV. We believe that the high rate of occurrence of the condition in immediate relatives justifies echocardiographic screening of first-degree relatives to anticipate and prevent future complications associated with this common cardiac malformation.**

(J Am Coll Cardiol 1997;30:1809–12)

Congenital bicuspid aortic valve (BAV) is the most common congenital valve abnormality, with an estimated incidence of ~1% (1,2). It is a clinically important condition because of its association with serious potential complications including aortic valve dysfunction, aortic dissection or rupture and infective endocarditis (3–9). Aortic valve stenosis or regurgitation can develop in patients with BAV. Regurgitation appears to be more common in younger patients, whereas stenosis becomes more frequent with age (1,4,10). Patients are also at risk for the development of endocarditis, which often leads to rapid deterioration of aortic valve function (1,4). Early recognition of this condition is therefore crucial to its proper management.

Congenital BAV is generally not considered a hereditary malformation, because its occurrence in more than one family member is thought to be uncommon despite the relatively high prevalence of the condition in the general population (11). However, some reports have suggested that familial clustering of bicuspid valve does occur, although most (12–18) have described only a single family. In this study we assessed prospectively the familial occurrence of congenital BAV by screening family members with the use of two-dimensional echocardiography.

Methods

Patients. The data base of the echocardiographic laboratory at the University of Ottawa Heart Institute was reviewed to identify 30 consecutive patients with echocardiographically documented congenital BAV. These patients were contacted by phone to request their participation in the study. Those agreeing were interviewed, and three-generation family pedigrees were constructed. Specific questions were asked to ascertain whether any relative was known to have cardiac abnormalities, and relevant information on more distant relatives was also recorded. All first-degree relatives were then contacted and, if willing to participate, were scheduled for an echocardiogram to assess the presence of BAV. The study was approved by the Ottawa Civic Hospital Research Ethics Committee.

Echocardiographic studies. Echocardiographic studies were performed by using commercially available systems (Hewlett-Packard 1500, 2000 and 2500) equipped with 2.5- and 3.5-MHz transducers. Multiple standard cardiac views were obtained with particular attention to the aortic valve (19). The morphologic features used to identify congenital BAV have been previously described, and particular attention was paid to the opening motion of the aortic cusps during systole, which

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Manuscript received March 10, 1997; revised manuscript received June 27, 1997, accepted September 2, 1997.

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Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00372-0

often has a fish-mouth appearance in the presence of BAV (19). Only valves that had clearly defined commissures and fulfilled the diagnostic criteria were accepted as definite congenital BAV. We have shown (unpublished data) that this technique has a sensitivity of 0.92 and specificity of 0.96 when compared with pathologic examination of the valve. When most of the diagnostic features were present but the commissure was not completely visualized, as in the presence of calcification, the diagnosis of BAV was considered probable.

Statistical analysis. Data were expressed as mean value ±SD. Intergroup comparison was performed by using the Student *t* test for continuous variables and chi-square analysis for discrete variables. A p value <0.05 was considered significant.

Results

The probands were 17 men and 13 women with a mean age of 45 years (range 20 to 75). Of the 210 first-degree relatives, 190 (90.5%) agreed to undergo echocardiography. Four relatives had technically difficult studies that were suboptimal for assessment of aortic valve morphology. Of the remaining 186 relatives, 17 (9.1%) were identified as having BAV (definite diagnosis in 15, probable diagnosis in 2). This is a highly significant increase over the 1% rate expected in the general population ($p < 0.001$).

Eleven (36.7%) of the 30 families had at least one additional family member with bicuspid aortic valve (Fig. 1). In these 11 families the male/female ratio of those with the condition was 1. Among the 19 subjects with nonfamilial BAV, the ratio was 1.8:1. Affected members were found in two generations in six families (pedigrees 2, 9, 23, 26, 28 and 29) and in three generations in two families (pedigrees 10 and 27).

Associated cardiac abnormalities were detected in patients with both familial and nonfamilial BAV (Table 1). Dilated ascending aorta was the most common finding, although its prevalence was higher in those with the nonfamilial form ($p = 0.009$). In the 11 families with familial BAV, dilated ascending aorta was detected in four family members who did not have BAV but in only one relative of subjects with nonfamilial BAV ($p = 0.14$).

Among the 28 subjects with familial BAV, only 3 had significant aortic valve dysfunction; 2 of the 3 had severe aortic stenosis and 1 had moderate aortic regurgitation. Similarly, only 2 of the 19 subjects with nonfamilial BAV had significant aortic valve dysfunction, and both had moderate aortic regurgitation.

Discussion

Familial clustering of BAV has been previously reported, although many of the reports (12–18) described a single family. The two larger series were by Emanuel et al. (16), and Glick and Roberts (17). Glick and Roberts (17) retrospectively examined their surgical pathologic data over 27 years and identified six families (17 family members) in which >1 family member had aortic valve disease. BAV was confirmed at operation in 11 of the 17 cases, but the frequency with which it occurred in additional family members cannot be determined from their data because only cases with evidence of familial clustering were selected for analysis. Emanuel et al. (16)

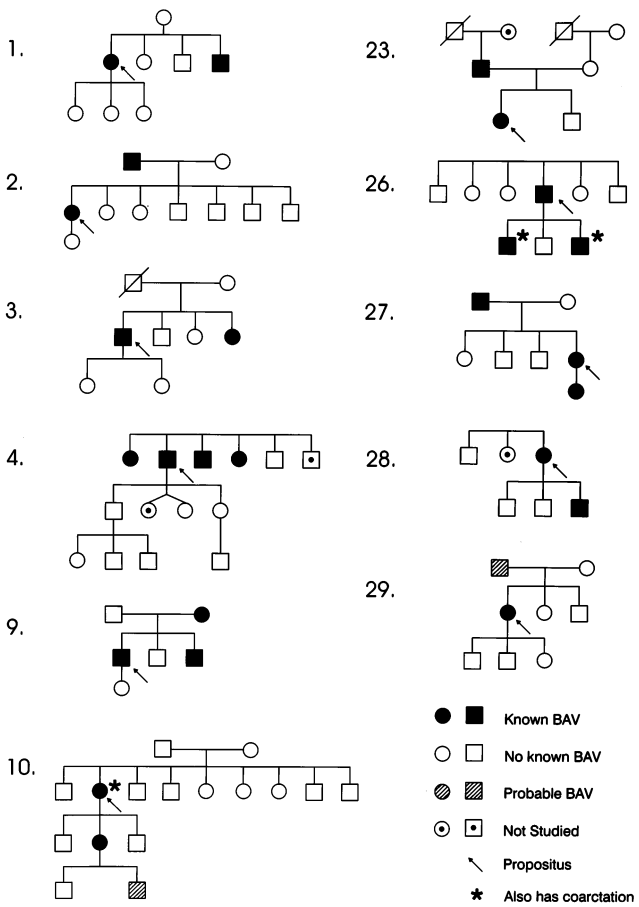

Figure 1. Pedigrees of 11 families with more than one member with echocardiographic evidence of bicuspid aortic valve (BAV).

Table 1. Associated Cardiac Abnormalities in Propositi and Relatives of Subjects With Familial Versus Nonfamilial Bicuspid Aortic Valve

	Familial BAV (11 families)	Nonfamilial BAV (19 families)
Patients with BAV	28	19
Coarctation of aorta	3	2
Dilated AA	7	13
MV prolapse	1	1
ASD and abnormal PM*	1	0
Pulmonary stenosis	0	1
Relatives without BAV	65	104
Dilated AA	4	1
MV prolapse	2	3

*This patient had a secundum atrial septum defect, and the two papillary muscles in the left ventricle were close together, although there was no mitral stenosis. AA = ascending aorta; ASD = atrial septal defect; BAV = bicuspid aortic valve; MV = mitral valve; PM = papillary muscle.

identified 41 patients who had surgically proved BAV. They evaluated prospectively 188 of 220 living first-degree relatives; however, only 53 relatives (29%) underwent M-mode echocardiography. Four clinical diagnostic criteria were used: an ejection sound, an ejection murmur, dilated ascending aorta on chest radiography and abnormal eccentricity index of the aortic valve on the echocardiogram. The presence of three of the four criteria was considered adequate for the diagnosis of BAV. The diagnosis was considered doubtful if two of the four criteria were present. On the basis of these criteria, 7 first-degree relatives (3.7%) were found to have aortic valve disease, and an additional 11 had doubtful evidence of BAV. Thus, six families (14.6%) had more than one member with aortic valve disease, and this proportion increased to 31.7% if doubtful cases were included. The study's major weakness was its use of nonspecific variables that can be present in several other conditions as diagnostic criteria. Our study used only echocardiographic findings based on current two-dimensional echocardiography to make the diagnosis, and the diagnosis was considered definite only when the commissure could be visualized in its entirety. Both the percent of multiplex families (36.7%) and the incidence of BAV in first-degree relatives (9.1%) were higher in our study than in that of Emanuel et al. (16), likely reflecting the high sensitivity of two-dimensional echocardiography in detecting these cases.

Dilated ascending aorta. Recent studies (20,21) have shown that dilated ascending aorta is common in patients with BAV and that it can occur in the absence of significant aortic valve dysfunction. Similar observations were made in this study. The higher rate of dilated aorta in the nonfamilial group does not appear to be related to aortic valve dysfunction, which was similar in both groups, and may have arisen as a result of the small sample size. In addition, four family members in the familial group had a dilated ascending aorta but did not have BAV. If a dilated aorta is considered a manifestation of BAV, as suggested in recent studies (22,23), the prevalence of the condition among first-degree relatives will then be as high as 11.8%.

Inheritance pattern. The rate of occurrence of BAV among the first-degree relatives in our 30 families (9.1%) is close to the rate that would be expected if BAV were a multifactorial condition with an incidence of 1% and high heritability (Edward's approximation 10%). However, the distribution of cases among our families is very asymmetric, with all 17 cases limited to 11 of the 30 families, most of which had several affected members. The pattern in most of these 11 families is most compatible with autosomal dominant inheritance with reduced penetrance.

The etiology of BAV is likely diverse. In the 11 families with more than one affected member, both genders were equally affected. This finding is in contrast to the reported male preponderance in this condition (1,2) and with the 1.8:1 distribution in our subjects with nonfamilial BAV. In the autopsy series of Roberts (1), 61 (72%) of the 85 patients were male. This observation may support the hypothesis that the cause of BAV is multifactorial but that a single major gene is operative in a subset of these patients. It is also possible that men are overrepresented in surgical and autopsy studies because they have a higher propensity for complications, and more women may remain undetected (24,25).

A high incidence of BAV was reported (26) in a single family of Syrian hamsters subjected to high endogamous pressure. The estimated frequency of BAV in these animals was 30.5%, and the male/female ratio was 1.1:1. Although the relative contributions of genotype and environment to the phenotypic variation were uncertain, the investigators suggested that the phenotypic spectrum might represent a quantitative inheritance pattern resulting from the interaction of genetic and environmental factors.

Associated cardiac anomalies. Of the several associated cardiac anomalies detected, most affected the left side of the heart. The association between left-sided anomalies and BAV has been previously reported, and it has been suggested (27,28) that abnormal hemodynamics of the left side is responsible for both the aortic valve malformation and other left-sided anomalies. Left-sided lesions due to altered hemodynamics include coarctation, aortic stenosis, hypoplastic left heart, secundum atrial septal defect and ventricular septal defect (28).

Implications. Patients with BAV have an increased lifetime risk of developing complications, some of which can be prevented by appropriate intervention such as antibiotic prophylaxis. Proper follow-up is also important to monitor valve function so that valve surgery can be performed at the optimal time to prevent endocarditis and to avoid the development of ventricular and aortic dysfunction. Early detection of this condition is therefore crucial to the management of these patients. In view of the high incidence of familial clustering, it is prudent to perform echocardiographic screening in all first-degree relatives of affected persons. A genetic linkage analysis is now in progress to attempt to identify the gene or genes responsible for this condition. Localization of the responsible genes will provide a better understanding of the inheritance pattern and be a crucial step in deciphering factors, genetic or otherwise, that are responsible for the observed uneven distribution of cases and apparent lack of penetrance among families.

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