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Mini Review

Family Screening in Patients with Bicuspid Aortic Valve

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ABSTRACT

Bicuspid Aortic Valve (BAV) is the most frequent congenital heart defect, with an incidence of 0.5%–1.4%. BAV may frequently lead to significant Valvular dysfunction and is associated with progressive aortic dilatation with risk of aortic dissection and sudden death. Familial clustering has been demonstrated. Based on this familial occurrence and the risk of dissection, Guidelines recommend considering cardiac screening of First-Degree Relatives (FDR). This mini-review summarizes the current knowledge on family screening in patients with BAV and discusses the feasibility and yield of screening FDRs.

Keywords: Congenital Heart Disease; First-degree relatives; Aortic valve replacement; Aortopathy; Pediatric cardiology

INTRODUCTION

Bicuspid Aortic Valve (BAV) is the most frequent Congenital Heart Defect (CHD), with an incidence of 0.5%–1.4% and a male predominance of approximately 3:1 [1]. BAV may lead to progressive aortic stenosis and/or aortic insufficiency. In cases of asymptomatic patients with no or minimal dysfunction at initial diagnosis, Aortic Valve Replacement (AVR) was needed in over 20% during 20 years follow-up and in cases with any dysfunction at initial diagnosis in over 50% during 25 years follow-up, respectively [2,3]. Furthermore BAV is also associated with progressive ascending aortic dilatation in up to 40%, which may lead to aortic dissection, aortic rupture and sudden death [2]. Because of this association, the BAV condition may be viewed as a valvulo-aortopathy for which the term 'bicuspid aortic disease' may be appropriate [4]. Concerning detection, symptoms are rare in ascending aortic aneurysms. Only 5% of patients are symptomatic before an acute event occurs [5].

REVIEW OF LITERATURE

In patients with BAV, familial clustering has been demonstrated [6,7] including also isolated ascending aortic dilatation in First-Degree Relatives (FDR) without BAV [8,9]. Based on this familial occurrence and the risk of aortic dissection, the 2014 European Society of Cardiology Aortic Guidelines recommend considering cardiac screening of FDRs (Class IIa-C) [10]. The 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on Valvular Heart Diseases recommend screening of FDRs only if the index patient has an associated aortopathy or a family history of Valvular heart diseases or aortopathy [11].

Most studies of family screening in patients with BAV were performed in tertiary centres comprising also patients with associated CHD. A recent study showed the yield of family screening in a general hospital in patients with isolated BAV, i.e. without associated CHD [12]. This mini-review summarizes the current knowledge on family screening in patients with BAV and discusses the feasibility and yield of family screening.

RESULTS

Bicuspid aortic valve in FDRs, initial studies

Initial reports about the familial occurrence of BAV were published by Emanuel et al in 1978 and Glick and Roberts in 1994 [13,14]. In the initial dedicated studies by Huntington et al. and Cripe et al., the prevalence of BAV in FDRs of patients with BAV was 9.1% and 9.3% and the occurrence of 'familial BAV', families with more than 1 affected member, was 37% and 32 % respectively (Table 1).

Later studies

Table 1 showed that in the later studies in adult patients by Robledo-Carmona et al., Cozijnsen et al. and Galian Gay et al, comprising more index patients, the prevalence of BAV in FDRs was lower, between 4.6% and 6.6% and the occurrence of 'familial BAV' between 15%-17%, respectively. In a recent large study in pediatric patients with BAV by Massardier et al., the prevalence of BAV in

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FDRs was 6.6%, similar to adult studies, and the occurrence of 'familial BAV' was 26%. Higher recurrence rates were observed in selected groups. In siblings of pediatric patients with isolated BAV, Hales et al. discovered a prevalence of 10.1%. In FDRs of adult patients who had undergone surgery for BAV, Panayotova et al. discovered a prevalence of 8%.

Isolated aortic dilatation in FDRs, initial studies

The occurrence of ascending aortic dilatation in FDRs without BAV was first reported by Huntington et al, who observed isolated aortic dilatation in 5 of 169 (3%) FDRs with TAV.(6) Table 2 showed that in initial studies, Loscalzo et al. and Biner et al. observed 22% and 32% prevalences of isolated ascending aortic dilatation in FDRs. Loscalzo et al. acknowledged that the 13 families were selectively referred with known aneurysm, dissection or rupture and that their data must be interpreted with care. Among the index patients in the study of Biner up to 50% also had a dilated aorta (Table 2).

Table 1: Screening FDRs of patients with BAV.

Sex (M/F)	Probands n	Characteristics	FDR n	Male n(%)	BAV n(%)	Male n(%)	Fam>1 n(%)
Huntington 1997 [6]	30	adults, mixed	186	ND	17 (9.1)	11 (65)	11 (36.7)
Cripe 2004 [7]	50	pediatric, mixed range 1 day-78 yr	259	117 (45)	24 (9.3)	11 (46)	16 (32)
Panayotova 2013 [18]	24	adult, post AVR	52	19 (37)	4[a] (8)	2 (50)	4 (16.7)
Robledo-Carmona 2013 [24]	100	adults, mixed	348	156 (45)	16[a] (4.6)	11 (69)	15 (15)
Hales 2014 [25]	181	pediatric, isolated median 7-11yr,	207[b]	ND	21 (10.1)	15 (71)	ND
Cozijnsen 2017 [12]	54	adults, mixed isolated	134	55 (41)	8[a] (6)	5 (63)	9 (17)
Galian-Gay 2018 [26]	256	adults, mixed	724	356 (49)	46 (6.4)	33 (72)	38 (15)
Massardier 2020 [22]	213	pediatric, mixed median 11 yr	482[c]	244 (51)	32 (6.6)	ND	30 (16)

Note: FDR: First-Degree Relative; BAV: Bicuspid Aortic Valve; Fam>1: Family with more than 1 individual with BAV; AVR: Aortic Valve Replacement; ND: No Data; Yr: Years of age; [a]: newly diagnosed; [b]: only siblings; [c]: 32% siblings

Table 2: FDRs with TAV and aortic dilatation.

Study	Probands	Characteristics	FDR	Imaging	BAV n (%)	TAV n	Isolated aortic dilatation, n(%)
Loscalzo 2007 [8]	13	BAV with AAD	110	TTE	15 (13.6)	80	24/80[a] (22)
Biner 2009 [9]	49	BAV, 50% with AAD	53	2D-guided TTE	5 (9.4)	48	14/44[b] (32)
Robledo-Carmona 2013 [24]	100	BAV ± AAD	283	2D-TTE (II-diastolic)	13 (4.6)	270	9/270[b] (3.3)
Cozijnsen 2017 [12]	54	BAV ± AAD	134	2D-TTE (LL-diastolic)	8 (6)	126	10/134[c] (7.5)
Galian-Gay 2018 [26]	256	BAV ± AAD	724	2D-TTE (LL-diastolic)	46 (6.4)	678	65/678[c] (9.6)
Dayan 2019 [21]	49	BAV with AAD	74	2D-TTE (diastolic)	16 (11.4)	124	13/69[d] (18.8)
	31	BAV without AAD	66				2/56[d] (3.6)
Massardier 2020 [22]	213	pediatric BAV ± AAD	482	2D-TTE (II-systolic)	32 (6.6)	450	4/450[e] (0.9)

Note: FDR: First-Degree Relative; BAV: Bicuspid Aortic Valve; TAV: Tricuspid Aortic Valve; AAD: Ascending Aortic Dilatation; II: Inner edge to Inner edge; LL: Leading edge-Leading edge. [a]: sinus of Valsalva, sinotubular junction, tubular ascending; [b]: annulus, sinus of Valsalva, sinotubular junction, tubular ascending; [c]: sinus of Valsalva, tubular ascending aorta; [d]: aortic root; [e]: ascending aorta

Later studies

Table 2 Showed that in later studies, by Robledo-Carmona et al., Cozijnsen et al. and Galian Gay et al. the reported prevalence of isolated aortic dilatation was lower: 3.3%, 7.5%, and 9.6%, respectively. Dayan et al demonstrated that TAV-FDRs of probands with ascending aortic aortopathy had a higher incidence of aortic root aortopathy than those of probands without ascending aorta aortopathy (18,8 vs 3.6%, p=0.012). In comparison with the three aforementioned studies, a higher prevalence of 18% isolated aortic dilatation was observed selected FDRs of probands with ascending aortic dilatation; a lower prevalence of 0.9% was observed in FDRs of pediatric patients, respectively.

Several differences between these studies must be noted. Table 2 indicated: i) at what level the investigators made their aortic measurements, ii) if they were performed end-diastolic or end-systolic, and iii) whether they used the leading-edge-to-leading-edge or the inner-edge-to-inner-edge method. Furthermore, Loscalzo et al., Biner et al., Robledo-Carmona et al., Galian Gay et al., and Dayan et al. related their aortic measurements to body surface area and derived their upper level of normal from published reference populations [15]. Cozijnsen et al. defined the ascending aorta dilated if the diameter was >40 mm, following ESC Guidelines [10]. Massadier et al. defined the ascending aorta dilated if the diameter was >40 mm for adults and if the Z-score ≥ 2 SD for the pediatric population [16].

DISCUSSION

Prevalence of bicuspid aortic valve in FDRs

In the later and larger studies, BAV prevalence in FDRs was lower than in the initial studies by Huntington et al. and Cripe et al. (4.6%-6.6% vs 9.1%-9.3%. The initial investigators contacted FDRs directly, resulting in high numbers of FDRs per index patient (mean 5.2 and 6.3) and in this initial period of family screening, native valve anatomy will be more often not known than nowadays. In patients with left ventricular outflow tract obstruction, a study indicated that 39% of cardiac abnormalities in their screening of FDRs were already known [17]; however, most studies did not clearly mention if they included also patients with already known phenotype. For starting a screening program, one need to know what will be the yield of new cases in screening FDR's. The recurrence rate in probands with BAV and associated CHD or in probands with isolated BAV did not seem to differ. This is important information for general hospitals; they will have more patients with isolated BAV under follow-up whereas patients with associated CHD usually will have their follow-up in tertiary centres.

Recurrence rate after surgery for bicuspid aortic valve

When the proband had undergone surgery for BAV, the recurrence rate in FDRs was somewhat higher in comparison with the aforementioned later and larger studies (8% vs 4.6%-6.6%) [18]. A similar observation was made by the author of this review in a not yet published study. It may urge to have special attention for patients under follow-up after AVR with respect to family screening. Among these patients, up to one-third may have had a BAV preoperatively and native valve anatomy may be often not known in average patients for various reasons [19]. For these cases, clinicians may need access to the surgical report, especially for the description of the valve inspection.

Prevalence of isolated aortic dilatation in FDRs

In the later and larger studies, the prevalence of isolated aortic dilatation in FDRs was lower than in the initial studies by Loscalzo et al. and Biner et al. (3.6%-9.6%. vs. 22%-32%). In the initial studies, probands had associated aortic dilatation in 100% and 50% of cases, where there must have been some form of selection which may have increased the prevalence of isolated aortic dilatation in FDRs. Dayan et al. demonstrated that the presence or absence of ascending aortic dilatation in probands considerably influenced the prevalence of isolated aortic dilatation in FDRs [20,21]. This explains the wide range in prevalences to which can be added the differences in aortic measurements and normal values. In pediatric FDRs and in young adults a lower prevalence of isolated aortic dilatation may be expected, as showed by Massardier et al. [22].

Uptake of family screening

In the later and larger studies much lower numbers of FDRs per index patients were screened than in initial studies by Huntington et al. and Cripe et al. (mostly <3 FDRs per index patient vs mean 5.2 and 6.3 FDRs per index patient). The uptake in daily practice may considerably differ from that in a research setting. A recent study on the uptake of genetic counselling for inherited cardiac conditions observed that among 717 eligible relatives, 60% attended genetic counselling, 41% in the first year [23]. Concerning the male-female ratio in the reviewed studies, in the newly diagnosed BAV patients, this ratio was lower than the expected 3:1 in the general population. This may well be related to the lower percentage of men among screened FDRs which was in line observations in the previously mentioned study about the uptake of genetic counselling. They discovered a small but significant difference in uptake between men and woman: 59% for males and 62% for females [23].

The feasibility of family screening

Panayotoya et al., Cozijnsen et al., and Massardier et al. investigated and discussed the feasibility of family screening. Considering the expected increase in workload of familial screening of a condition with such a high prevalence, Panayotova et al. routinely offered familial screening to surgical patients only, as a pilot project. The referral and response rate (70%) was lower than initially anticipated and hence also the additional workload for the echocardiography department and clinical follow-up service [18].

Cozijnsen et al. performed familial screening in a general hospital during daily clinical practice. During follow-up at the outpatient clinic, BAV patients received a letter for their FDRs that cardiac screening was advised. This method promoted the spread of the extra workload over several years. Furthermore, only a median of 2 FDRs per index patient was referred by the general practitioner for screening, which was in line with the aforementioned reduced and delayed uptake of counselling [12,23]. For this cardiac screening, performing echocardiography is usually sufficient to exclude BAV and aortic dilatation. In The Netherlands almost everyone is ensured against medical expenses and the insurer reimburses the costs of cardiac screening. This may be different in other countries.

Massardier et al. studied the yield and feasibility of family screening in pediatric cardiology daily practice. One-third of FDRs didn't perform the screening. A mean number of 2.3 FDRs per index patient was tested and they reported the same yield of screening as in adult studies. Their findings support the implementation of actual guidelines in pediatric cardiology practice. They concluded that exhaustiveness of family screening and additional burden to implement the guidelines remain a challenge in daily practice [22,24-26].

CONCLUSION

Based on recent studies, screening FDRs in non-selected adult patients with BAV resulted in 4.6%-6.6% new cases with BAV and 3.6%-9.6% new cases with isolated aortic dilatation. Also in a general hospital, family screening was feasible during daily cardiology practice and resulted in a substantial yield of new cases with BAV or isolated ascending aortic dilatation. The yield of screening in pediatric cardiology was similar as in adult studies.

CONFLICTS OF INTERESTS

None

FINANCIAL DISCLOSURES

None

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