The elusive link between aortic wall histology and echocardiographic anatomy in bicuspid aortic valve: implications for prophylactic surgery

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Received 4 April 2011; received in revised form 17 May 2011; accepted 25 May 2011

Abstract

OBJECTIVE: Prediction of aortic dissection or rupture is extremely difficult in patients with bicuspid aortic valve. We aimed to identify clinical and echocardiography predictors of histological abnormalities of the aortic wall in patients with bicuspid aortic valve undergoing aortic surgery.

METHODS: We assessed the histology of the aortic wall and clinical and echocardiography variables in a cohort of patients with bicuspid aortic valve (n = 127) and a wide spectrum of valvar disease who underwent replacement of the ascending aorta (with or without aortic valve surgery). Histology was classified using a 5-grade system developed by Larson and Edward.

RESULTS: Histological alterations of the aortic wall were absent/mild (grade 0–1) in 77 patients (61%) and moderate/severe (grade 2–3) in 50 (39%). Patients with moderate/severe histological alterations were younger (47 ± 17 vs 53 ± 16; p = 0.042). Eighteen patients out of 48 (38%) with an ascending aorta diameter ≤ 4.5 cm had grade 2–3 aortic wall disease as did 8 out of 18 (44%) with a diameter ≤ 4 cm. Nineteen out of 46 (41%) patients with a maximal ascending aortic area/height ratio < 10 cm² m⁻¹ had moderate/severe histological alterations. Multivariate logistic regression analysis showed that the indexed diameter of the aortic annulus was significantly associated with grade 2–3 aortic wall disease (odds ratio (OR): 12.22, 95% confidence interval (CI): 1.65–90.38, p = 0.014).

CONCLUSIONS: A high proportion of patients with bicuspid aortic valve and mild to moderate aortic dilatation have severe histological abnormalities of the aortic wall that are not predictable by clinical and echocardiographic findings. These observations suggest that risk stratification for aortic dissection or rupture in patients with bicuspid aortic valve is so far quite suboptimal and future investigations are warranted.

Keywords: Bicuspid aortic valve • Histological abnormalities • Echocardiography

INTRODUCTION

Bicuspid aortic valve and the associated risk for aortic rupture or dissection are currently the focus of intense debate [1–4]. Patients with bicuspid aortic valve are at higher risk of ascending aortic dissection compared to age-matched patients with a normal trileaflet aortic valve [5–7], and the risk increases exponentially with increasing aortic size [8]. A jet lesion caused by asymmetric flow through a bicuspid (and frequently stenotic) valve has been proposed to mechanically cause aortic wall damage [9, 10]. More recently, the risk of aortic dilation and dissection appears to be genetically determined, at least in part, and possibly caused by histological abnormalities of the ascending aortic wall [11, 12]. However, the role of clinical and echocardiography variables in predicting the risk of aortic dissection is unclear, and current guidelines for prophylactic surgery are based mainly on the size of the ascending aorta [13–15].

The purpose of the present study was to evaluate the frequency of histologic abnormalities of the aortic wall and their association with clinical and echocardiography variables in patients undergoing prophylactic replacement of the ascending aorta with or without aortic valve surgery.

METHODS

Setting and study design

Consecutive patients (n = 254) with bicuspid aortic valve evaluated at the Institute of Cardiology of Bologna and undergoing
cardiac surgery from January 1998 to December 2009 were considered for the present study. Only patients with intraoperative confirmation of bicuspid aortic valve were selected for this study. Patients who underwent isolated aortic valve replacement were excluded from the study (n = 107).

A total of 147 patients underwent prophylactic replacement of the ascending aorta (with or without aortic valve surgery). A detailed echocardiographic examination was available for retrospective analysis in 136 out of 147; in 9 patients, intraoperative inspection did not confirm a previously bicuspid aortic valve diagnosis based on echocardiography and these patients were excluded. Thus, 127 patients were included in the final study cohort. The decision to replace the ascending aorta was based on preoperative measurements and/or intraoperative evaluation of the aortic wall.

Echocardiography

For each patient, the most recent transthoracic echocardiographic examination and/or intraoperative transesophageal echocardiography were reviewed by two expert investigators (S.Z. and M.F.) who were blinded to the clinical and histological data. All echocardiographic examinations were performed at the Cardiology Institute at the S. Orsola-Malpighi University Hospital, Bologna, using a Philips Sonos 5500 ultrasound system (Philips Ultrasound, Andover, MA, USA). The morphology of the bicuspid aortic valve was defined in the parasternal short-axis view, and bicuspid aortic valve anatomy was classified according to the cusp fusion pattern: left coronary–right coronary cusp fusion (type A), right coronary–non-coronary cusp fusion (type B), or left coronary–non-coronary cusp fusion (type C) [3]. Aortic dilation was evaluated in all patients by measuring aortic diameters in parasternal long-axis view, at the aortic annulus, sinuses of Valsalva, and sinutubular junction level. The ascending aorta was also measured 1 cm above the sinutubular junction or at its maximum diameter [3]. Values from three consecutive measurements were averaged.

Histology

An aortic specimen (not oriented) was examined for each patient. The dimensions ranged from 2 to 12.5 cm. Six samples were obtained from different sites on each explanted aorta, fixed in 10% buffered formalin, and embedded in paraffin. Sections (2 mm) were stained with hematoxylin–eosin, Azan–Mallory’s trichrome, and Weigert’s elastic stain–Van Gieson stain. Histological analysis was performed in a blinded manner by a single investigator (O.L.). Aortic medial disease was evaluated histologically as follows: (a) elastic fiber fragmentation, (b) smooth muscle cell loss, and (c) basophilic material (mucopolysaccharide) accumulation. These alterations, formerly referred to as cystic medial necrosis, were graded according to the 5-grade scale proposed by Larson and Edwards [16] as follows: grade 0, no lesions; grade 1, lesions involved 1–10% of the medial tissue; grade 2, 11–25%; grade 3, 26–50%; and grade 4, 51–100% (Fig. 1). Patients were divided into two groups, namely patients with grade 0–1 disease in whom histological alterations of the aortic wall were absent or mild and patients with grade 2–3 disease who showed moderate/severe alterations. No medial laminar necrosis or inflammatory infiltrates were seen in any of the aortic specimens.

Statistical analysis

Categoric variables were expressed as total number and percentages. Continuous variables are expressed as means ± standard deviation. Comparison of categoric variables was performed with the chi-square test and continuous variables were analyzed with the Student’s t-test as appropriate. Univariate and multivariate logistic regression were used to identify independent predictors of advanced histological abnormalities (grade 2–3).
A two-tailed p value 0.05 was considered statistically significant. Data processing and statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 statistical program (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline clinical, echocardiography, and histological characteristics of the study population are listed in Table 1. The clinical and echocardiography findings according to the severity of histological abnormalities are summarized in Table 2. Patients with grade 2–3 aortic wall disease were younger (47 ± 17 years vs 53 ± 16 years, p = 0.042) and had a greater mean indexed annulus diameter than patients with grade 0–1 (1.45 ± 0.21 cm m⁻² vs 1.36 ± 0.20 cm m⁻², p = 0.015). There were no other clinical or echocardiographic differences between the two groups; in particular, no differences were found between bicuspid aortic valve morphology and grade of histological abnormalities.

In terms of the grades of histological abnormalities, the prevalence was comparable in patients with either absent-to-moderate or severe aortic valve stenosis and in patients with either absent-to-moderate or severe aortic regurgitation (data not shown). Grade 2–3 aortic wall disease was present in 18 patients out of 48 (38%) with an ascending aorta/aortic root diameter ≤4.5 cm and in eight out of 18 (44%) of those with a diameter ≤4 cm (Fig. 2A). Nineteen out of 46 (41%) patients with a maximal ascending aorta/aortic root area/height ratio <10 cm² m⁻¹ had moderate/severe histological alterations (Fig. 2B). The age distributions within the two histological groups (grade 0–1 vs grade 2–3) differed: while the frequency of grade 0–1 increased in patients up to their seventh decade (i.e., in patients aged 60–69), the highest prevalence of grade 2–3 disease occurred in the sixth decade (i.e., in patients aged 50–59) and decreased thereafter (Fig. 3).

The results of univariate and multivariate analysis of clinical/echocardiographic correlates of grade 2–3 histological lesions are shown in Table 3. Tertiles of age (by univariate analysis) and aortic annulus diameter (by both univariate and multivariate analyses) were significantly associated with grade 2–3 aortic wall disease. The same analyses were performed with height-indexed aortic measurements and the results did not differ (data not shown).

**DISCUSSION**

This study was unique due to the availability of both clinical/echocardiographic data and aortic wall histological data from a large number of patients with bicuspid aortic valve undergoing prophylactic replacement of the ascending aorta with or without aortic valve surgery. All the patients underwent cardiac surgery on the basis of the current guidelines. The decision of proceeding to a prophylactic replacement of ascending aorta was based either on the finding of aortic dimensions exceeding the limit suggested by the guidelines or, in selected cases, on intraoperative inspection of the aortic wall even if the ascending aorta/
The aortic root diameter was <5 cm or even <4.5 cm [20]. Within this context, the present study found a high frequency of advanced histological abnormalities in patients with nonsevere aortic dilatation as well as an independent association between advanced histological abnormalities and aortic annulus size. The age distribution of mild versus advanced histological abnormalities differed, and there was no association between histological abnormalities and aortic valve morphology.

A number of studies have reported a higher prevalence of advanced histological abnormalities of the aortic wall in patients with bicuspid aortic valve compared to patients with tricuspid aortic valve [17,18]. These abnormalities include the following: extracellular matrix degeneration, elastic fiber fragmentation, increased metalloproteinase expression, decreased expression of tissue inhibitors of metallo-proteinases, and smooth muscle cell apoptosis. These findings are generally associated with aortic dilation and are considered risk factors for aortic dissection or rupture. The present study confirmed and extended these observations by showing that advanced histological abnormalities might be present before severe aortic dilatation occurs, independent of the presence and the degree of valve dysfunction. In contrast to other studies [19], this study excluded atherosclerotic parietal changes when histological abnormality grading was performed; we considered such changes to be more age- and comorbidity-related and less specific to aortic wall disease. Indeed, around 45% of our bicuspid aortic valve patients with an aortic diameter <4.5 cm showed advanced medial degenerative lesions of the aortic wall; according to the current guidelines, a surgical substitution of the ascending aorta would not be recommended for these patients.

Interestingly, advanced histological aortic abnormalities were associated with a larger annulus diameter and a different age distribution compared to absent/mild aortic wall abnormalities, supporting the hypothesis of a genetic substrate for advanced histological abnormalities. Indeed, while the dilatation of the ascending aorta could be influenced by factors such as the hemodynamic effect of a jet lesion, the annular diameter is a constitutional parameter and reflects an intrinsic aortic wall abnormality. Furthermore, the prevalence of absent/mild histological abnormalities was age dependent, increasing up to the eighth decade, whereas the highest prevalence of advanced histological abnormalities occurred in the sixth decade, in agreement with the concept of penetrance of a genetically determined disease.

Unfortunately, apart from their pathogenetic significance, these observations do not provide useful indications toward risk stratification for aortic dissection in patients with bicuspid aortic valve. Indeed, the difference in annular size between the two groups, although statistically significant, approximates...
the inter-observer variability threshold and is therefore of limited clinical use. Nevertheless, the identification of an enlarged annulus in an otherwise low-risk patient according to the classic ascending aorta/aortic root echocardiographic criteria could help guide the surgical decision. This observation should be confirmed by further studies and interpreted in the context of the ongoing scientific debate [21]. Indeed, it must be noted that the exact frequency of parietal complications in bicuspid aortic valve and the real prognostic significance of any type of histological aortic wall abnormalities remain to be determined. For example, Michelsen et al. reported as in 212 patients with asymptomatic bicuspid aortic valve followed for 15 years no aortic dissections occurred [4]. In addition, despite the fact that Marfan syndrome and bicuspid aortic valve share common histopathological findings [22], only in Marfan syndrome histological alterations are an established marker for dissection, whereas the level of evidence in bicuspid aortic valve is clearly inferior [23].

Finally, we did not confirm the single previous observation regarding an association between bicuspid aortic valve morphology and high-grade histological abnormalities. In the study by Russo et al. [19], type A bicuspid aortic valve (fusion of the two coronary cusps) was found to be associated with a more severe degree of both aortic root dilatation and histopathological abnormalities. In our study, bicuspid aortic valve morphology was not associated with either aortic size or histological alterations severity. This difference may be due in part to the histological scoring system [12] used by Russo et al., which also included nonspecific changes such as atherosclerotic and inflammatory abnormalities.

**Study limitations**

The retrospective nature and small sample size represent the major limitations of this study. In fact, the number of enrolled patients may be too small to detect a significant association of clinical and echocardiographic findings with advanced aortic wall abnormalities. Moreover, some analytical techniques were not used in this study; specifically, the following were not performed: genetic tests; immunohistochemistry and quantitative fluorescence microscopy for evaluating microfibrillar proteins (fibrillin-I, collagen, and elastin); and gelatinezymography for measuring matrix metalloproteinase activity. However, this study is one of only two published studies to evaluate the association between clinical and echocardiographic variables and histological abnormalities of the aortic wall in patients with bicuspid aortic valve undergoing replacement of ascending aorta.

**CONCLUSIONS**

Patients with bicuspid aortic valve frequently had advanced histological abnormalities of the ascending aortic wall that were independent of the severity of aortic valve dysfunction and that were associated with increased aortic annulus diameter. The correlation between the severity of aortic wall disease and the annulus or aortic root diameter, although significant, approximated the inter-observer variability threshold and is therefore of limited clinical use. A high proportion of patients with bicuspid aortic valve and mild to moderate aortic dilatation showed advanced histological abnormalities of the aortic wall that could not be predicted by clinical and echocardiographic findings. These observations suggest that risk stratification for aortic dissection or rupture in patients with bicuspid aortic valve is far quite suboptimal. There is no simple ‘receipt’ to overcome these limitations. Any surgical decision should not simply be based on numbers but should take into consideration the overall evaluation of the patient, including personal and familial data. Future studies are warranted to clarify this topic and to identify new risk factors; noninvasive evaluation of aortic compliance [24,25] could probably contribute to increase the predictive role of preoperative echocardiogram.

**Conflict of interest: none declared.**

**REFERENCES**


