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A Case-Control Investigation of the Relationship Between Bicuspid Aortic Valve Disease and Coronary Heart Disease

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1. Introduction

Bicuspid aortic valve disease is the most common congenital heart defect, affecting 1% to 2% of the general population, with a higher prevalence in males (Hoffman & Kaplan, 2002; Movahed et al., 2006). Quite often, the diagnosis of bicuspid aortic valve disease is an incidental finding during an echocardiogram. However, the disease may be associated with significant valvular dysfunction and lead to aortic stenosis (Subramanian et al., 1984; Roberts & Ko, 2005) or aortic regurgitation (Roberts et al., 1981; Olson et al., 1984) and is a risk for infective endocarditis (Lamas & Eykyn, 2000; Fenoglio et al., 1977). Aortic regurgitation is probably more common in younger patients, and aortic stenosis becomes more frequent with age (Movahed et al., 2006). In this paper we reviewed the current literature on bicuspid aortic valve disease, particularly its etiopathogenesis, and report a case-control investigation of the relationship between this disease and coronary heart disease.

1.1 History

The earliest description of a bicuspid aortic valve has been attributed to Leonardo da Vinci, who over 400 years ago sketched the bicuspid variant of the aortic valve (Mills et al., 1978, as cited in Braverman et al., 2005). In 1844, Paget brought attention to the propensity of the bicuspid aortic valve to develop disease, and in 1858, Peacock reported the tendency of these valves to develop obstructive lesions initially, with subsequent incompetence (Roberts, 1970, as cited in Braverman et al., 2005). The clinical significance of the bicuspid aortic valve was also emphasized by Osler in 1886 when he described 18 cases of bicuspid aortic valve with the predilection of these valves to develop infective endocarditis (Wauchope, 1928, as cited in Braverman et al., 2005). In the 1950s, investigators observed that the propensity to develop isolated calcific aortic stenosis occurring in the setting of bicuspid aortic valve was the result of an intrinsic property of the bicuspid aortic valve rather than the result of rheumatic disease (Campbell et al., 1953, Smith & Matthews, 1955, and Bacon & Matthews, 1959, as cited in Braverman et al., 2005). Wauchhope's autopsy studies established that the bicuspid aortic valve is the commonest congenital anomaly of the heart (Mills et al., 1978 and Wauchope, 1928, as cited in Braverman et al., 2005). Furthermore, the association of bicuspid aortic valve with diseases of aorta was first commented on by Abbott in 1927 with the description of an association between congenital bicuspid aortic valve with aortic dissection (Acierno, 1994, as cited in Braverman et al., 2005).

1.2 Morphogenesis of bicuspid aortic valve

Bicuspid aortic valve likely results from a complex developmental process, not simply the fusion of two normal cusps (Sans-Coma et al., 1996). However, the exact mechanism remains unclear. Some researchers have implicated the anomalous behaviour of cells derived from the neural crest as a possible etiology (Kappetein et al., 1991; Fernández et al., 1998; Mancuso et al., 2002). The proponents of this theory note that bicuspid aortic valve is associated with congenital malformations of the aortic arch and other neural crest derived systems (Duran et al., 1995; Kappetein et al., 1991). In particular, some researchers suggest that a molecular abnormality in the extracellular matrix may lead to abnormal valvulogenesis, becouse matrix proteins help direct cell differentiation and cusp formation during valvulogenesis (Hinton et al., 2006; Eisenberg & Markwald, 1995; Fedak et al., 2002). This could also explain why bicuspid aortic valve is often linked to other cardiovascular anomalies, which will be mentioned below (Duran et al., 1995). In an another study Lee et al. (2000) reported that mice lacking endothelial nitric oxide synthase had a predisposition to forming bicuspid aortic valve, which suggests that abnormalities in this protein may lead to the disruption of intricate cell signals required for proper valvulogenesis in the mammalian heart. In human development, organogenesis is completed during the first trimester of pregnancy, after which further maturation and growth predominate. The first organ to form is the heart, with the earliest recognizable cardiac structure evident on day 15 of gestation, when the cardiac progenitor cells have been specified and are organized in a crescent shape. At three weeks of gestation, these bilaterally symmetric heart primordial cells migrate to the midline and fuse to form a single linear heart tube with an inner endothelial lining surrounded by an outer myocardial cell layer, which are separated by extracellular matrix. During the sixth and seventh weeks of gestation, the heart divides into four distinct chambers and an aorta and pulmonary artery, respectively, resulting in separated pulmonary and systemic circulations (Rabkin-Aikawa al., 2004; van den Hoff et al., 1999). The process of valvular morphogenesis begins from the time at which the heart is a simple tube. The initial endocardial cushions, which will contribute to all four cardiac valves, are formed by the thickening of the extracellular matrix in the region of the atrioventricular and outflow tract. Within the next day, there is a complex interplay of myocardial and endocardial signaling, which is necessary for proper endothelial-to-mesenchymal transformation. This process is initiated by the secretion of extracellular matrix proteins such as fibronectin and transferrin across the cardiac jelly to the adjacent endocardium. The endocardium then secretes transforming growth factor beta family members, which act synergistically with bone morphogenetic protein-2 secreted by the myocardium, to increase mesenchyme formation and proliferation, which results in the growth of the endothelial cushions. The myocardial cells then invade the margins of the cellular endothelial cushions. In the outflow tract, the truncal cushion swellings contribute to form three leaflet valves of the aorta and pulmonary artery. When this process is distrupted in the aorta, the primordial leaflets do not separate or remain fused, which results in bicuspid aortic valve (reviewed in De Mozzi et al., 2008).

1.3 Genetics

Although most cases of bicuspid aortic valve disease are sporadic, familial clusters have been identified (Emmanuel et al., 1978; Glick & Roberts, 1994; Hungtington et al., 1997). The earliest studies suggesting that bicuspid aortic valve disease was the consequence of an underlying genetic abnormality were case reports describing familial clustering of bicuspid

aortic valve disease and reports of bicuspid aortic valve disease in monozygotic twins (McKusick, 1972; Gale et al., 1977; Godden et al., 1987; McDonald & Maureer, 1989; Brown et al., 2003). Subsequently, other authors sought to evaluate the relatives of patients with bicuspid aortic valve disease to investigate the prevalence of bicuspid aortic valve disease in the family members of affected patients. Emmanuel et al. (1978) studied 41 families with a member having surgically proven bicuspid aortic valve disease. Six of the families had more than one affected member. Of note, the diagnosis of bicuspid aortic valve disease in this study was based largely on the findings of the clinical examination, chest radiograph, and electrocardiogram; only a limited number were examined using M-mode echocardiography (Emmanuel et al., 1978). In contrast, Glick and Roberts (1994) studied the genetics of six families in whom greater than one member had aortic valve disease; 11 members had bicuspid aortic valve disease confirmed during surgery. They noted that of the 71 family members investigated, 17 (24%) had evidence of aortic valve disease likely secondary to a bicuspid aortic valve. In a prospective study, Hungtington et al (1997) assessed the frequency of familial clustering of congenital bicuspid aortic valve using two-dimensional echocardiography. They identified 39 consecutive patients with bicuspid aortic valve disease in their database and attempted to enroll 210 first-degree relatives. They were able to obtain echocardiographic evaluations in 89% of the first-degree relatives and reported that 9% of the relatives had a definitive diagnosis of bicuspid aortic valve. This was a significantly higher prevalence than the 1% prevalence that has generally been described in the literature for the general population. However, given the asymmetric clustering of a number of cases in some of the families, the inheritance pattern in those families was felt to be more compatible with an autosomal-dominant inheritance pattern with reduced penetrance (Hungtington et al., 1997).

Other studies have suggested multiple complex modes of inheritance for bicuspid aortic valve disease. Statistical genetic models have been tested to demonstrate that the regions of the genome are responsible for the phenotype of bicuspid aortic valve. However, to date, only a few studies have identified responsible genomic regions. Interestingly, some of the genes identified appear to account for inheritance in only a small proportion of the familial cases of bicuspid aortic valve disease reported. One of these genes identified is *NOTCH1*. Analyses of mouse and zebrafish Notch mutants revealed an essential role for NOTCH1 in promoting the epithelial-to-mesenchymal transition process (Timmerman et al., 2004). During the development of aortic valve in mice, *NOTCH1*, is highly expressed and represses the activity of a central transcriptional regulator of osteoblast cell fate (reviewed in Artavanis-Tsakonas et al., 1999). In 2005, Garg et al. (2005) identified a five-generation European-American family showing linkage for bicuspid aortic valve to a single locus on chromosome 9q34-35. Direct sequencing of all coding exons of the *NOTCH1* gene revealed a heterozygous C-to-T transition of nucleotide 3322 leading to a premature stop codon at position 1108 (p.R1108X). Additionally, in a second and smaller Hispanic family, a second mutation (p.H1505del) in *NOTCH1* co-segregated with the disease in three affected family members. None of these mutations could be found in the 1138 controls. The authors suggested that mutations of the *NOTCH1* gene may have caused an early developmental defect in the aortic valve and later led to a de-repression of calcium deposition and an aortic valve disease.

Other genes identified in bicuspid aortic valve disease are the potassium channel gene *KCNJ2* (chromosome 17q24.3) (Andelfinger et al., 2002) and the ubiquitin fusion degradation 1–like gene *UFD1L* (chromosome 22q11.2) (Mohamed et al., 2005). The *UFD1L* gene encodes

a component of a multi-enzyme complex involved in the degradation of ubiquitin fusion proteins, and is highly expressed during embryogenesis in certain tissues. It seems to play a key role in the development of ectoderm-derived structures, including neural crest cells. Downregulation of the *UFD1L* gene, hypothetically resulting from an anomalous behavior of neural crest cells, may lead to reduced degradation activities, and may finally lead to fusion of valve cushions, a key factor in the development of congenital bicuspid aortic valve (Yamagishi et al., 2003). The presence of multiple genomic regions associated with bicuspid aortic valve disease demonstrates genetic heterogeneity and further supports complex inheritance. Given that a large proportion of bicuspid aortic valve disease familial cases are of unknown etiology, it is expected that other regions of the genome also predispose individuals to develop bicuspid aortic valve or associated cardiovascular malformations. Martin et al. (2007) have recently identified some regions of the human genome that harbor genes influencing the inheritance of bicuspid aortic valve disease or associated cardiovascular malformations. In particular, three novel loci for bicuspid aortic valve and associated cardiovascular malformations were identified on chromosomes 18, 5, and 13.

1.4 Bicuspid aortic valve anatomy, variants, and pathologic features

An intraoperative appearance of bicuspid aortic valve is shown in Figure 1. The anatomy of the bicuspid aortic valve usually includes unequal cusp size (due to fusion of two cusps leading to one larger cusp), the presence of a central raphe (usually in the center of the larger of the two cusps), and smooth cusp margins. The leaflets are usually oriented right to left, with the true commissures oriented anterior and posterior. Three morphologies are identified: type 1, fusion of right coronary cusp and left coronary cusp; type 2, fusion of

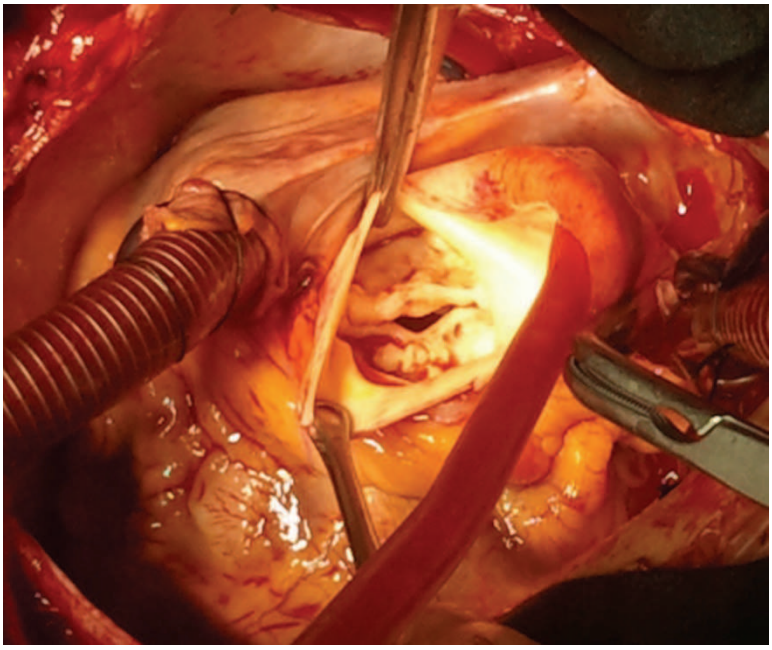

Fig. 1. An intraoperative appearance of bicuspid aortic valve

right coronary cusp and noncoronary cusp; and type 3, fusion of left coronary cusp and noncoronary cusp (Schaefer, 2008; Sievers & Schmidtke, 2007). The most common is type 1 (70% to 86%), followed by type 2 (12% to 28%) and type 3 (1% to 3%) (Fernandes et al., 2004; Sabet et al., 1999). The raphe or fibrous ridge is the site of congenital fusion of the two components of the conjoined cusps and is identifiable in most bicuspid aortic valve patients (Sabet et al., 1999). Of interest, pathologic examination of the raphe has shown that it does not contain valve tissue (Pomerance, 1972). Sometimes it shows a deep indentation, which gives a false image of a tricuspid valve on two-dimensional echocardiography. Valvular incompetence is usually caused by the redundancy of one cusp, since the two cusps usually have different dimensions (reviewed in De Mozzi et al., 2008). Few cases of congenital bicuspid aortic valve are accompanied by an abnormal fibrous band stretched from the center of the conjoined cusp to the aortic wall, and they appear to be associated with valve insufficiency (Nakamura et al., 1999).

1.5 The bicuspid aortic valve and associated congenital or acquired cardiovascular lesions

Despite its importance, our understanding of bicuspid aortic valve disease is incomplete, and questions remain unanswered about this common condition. Although much of the original focus centered on the abnormal bileaflet valve, the disease is significantly more complex. Bicuspid aortic valve disease is not only a disorder of valvulogenesis, but also represents the coexistent aspect of a genetic disorder of aorta or cardiac development. Accordingly, associated congenital cardiovascular anomalies have been reported in as many as 25% of patients. Patent ductus arteriosus and ventricular septal defect are the most frequent heart defects associated with bicuspid aortic valve disease (Deshpande & Kinare, 1991; Suzuki et al., 1994). Hypoplastic left heart syndrome, complete atrioventricular canal defect, Ebstein's anomaly, and partial or total anomalous pulmonary venous return. Tetralogy of Fallot, double-outlet right ventricle (Fernandes, et al., 2004), Williams syndrome (Lopez-Rangel et al., 1992), and Down syndrome (Weinhouse et al., 1995) are occasionally associated with bicuspid aortic valve disease. Shone's complex, which is defined by four cardiovascular defects (supravalvular mitral membrane, valvular mitral stenosis with a parachute mitral valve, subaortic stenosis, and aortic coarctation), is rare and forms another association in bicuspid aortic valve disease cases (Popescu et al., 2008).

Moreover, many vascular abnormalities, such as aortic dilatation (Sabet et al., 1999; Ward, 2000; Fedak et al., 2002; Bauer et al., 2002; Alegret et al., 2003), aortic aneurysm (Sabet et al., 1999; Ward, 2000; Fedak et al., 2002; Bauer et al., 2002; Alegret et al., 2003), aortic dissection (Larson & Edwards, 1984; Ward, 2000; Fedak et al., 2002), coarctation of the aorta (Ward, 2000; Lindsay, 1988; Warnes, 2003), interrupted aortic arch (Roberts et al., 1962), cervicocephalic arterial dissection (Schievink & Mokri, 1995), ductus diverticulum aneurysm (Sagic et al., 1997), and annuloaortic ectasia (Oyonarte et al., 1992) have been described in association with bicuspid aortic valve disease. Aortic dilatation, with an estimated prevalence of approximately 50%, is the most common abnormality among these vascular abnormalities that have been reported in association with bicuspid aortic valve disease (Pachulski et al., 1991 Hahn et al., 1992; Fedak et al., 2002; Alegret et al., 2003).

1.6 The bicuspid aortic valve and associated disorders in coronary arteries

Besides these abnormalities involving different arteries, some reports have also suggested the involvement of coronary arteries, including congenital coronary artery anomalies

(Rashid et al., 2005; Palomo et al., 1985; Doty, 2001), coronary artery fistulas (Oomman & Mao, 2000), spontaneous coronary artery dissection (Labombarda et al., 2009), reversal of coronary dominance (Hutchins et al., 1978; Higgins & Wexler, 1975), and immediate bifurcation and a shorter length of the left main coronary artery (Hutchins et al., 1978; Higgins & Wexler, 1975; Yuan et al., 2010).

There have also been some case reports describing patients with bicuspid aortic valve disease associated with coronary heart disease (Shimuzu et al., 1984; Bensaid et al., 1978; Yokoyama et al., 2002; Theleman et al., 2006) and even with acute myocardial infarction (Demir, 2009). There are also some studies in which the prevalence rate of angiographic coronary heart disease among the patients with bicuspid aortic valve disease has been given (Yuan et al., 2010; Goland et al., 2007). However, to the best of our knowledge, there is only one study in the current literature comparing the prevalence rate of angiographic coronary heart disease between patients with and without bicuspid aortic valve disease (Yuan et al., 2010). However, that study was retrospective in nature and was not designed primarily to compare the prevalence rate of angiographic coronary heart disease in bicuspid aortic valve disease patients with the rate in an age- and gender-matched control group.

On the other hand, it has been suggested that from 15% to 50% of patients with coronary heart disease lack any of the four conventional risk factors for this disease (i.e., hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking) (Hennekens, 1998; Futterman & Lemberg, 1998; Khot et al., 2003; Greenland et al., 2003). Atherosclerosis is a complex disease process resulting from the interaction of a number of environmental and genetic factors. Evidence from epidemiologic studies has consistently demonstrated that there is a substantial heritable component to atherosclerosis susceptibility (Hunt et al., 2002; Fox et al., 2003).

1.7 Aim of the study

Based on the above-mentioned knowledge, in the present study, we aimed to determine whether or not there is a relationship between the presence of bicuspid aortic valve disease and the occurrence, severity, and extent of angiographic coronary heart disease. We also sought to determine whether the relationship, if any, between bicuspid aortic valve disease and coronary heart disease is due to the changes in flow dynamics secondary to stenosis or regurgitation in the aortic valve. We also sought to determine any possible relationship between the type of bicuspid aortic valve and occurrence of coronary heart disease.

2. Material and methods

2.1 Study design

Over a 9-year period, 11,702 consecutive patients who underwent coronary angiography at our institution for the first time for suspected coronary heart disease (mainly for the evaluation of typical, atypical, or non-anginal chest pain or electrocardiogram findings suggesting the disease) were subjected to routine transthoracic Doppler echocardiography to detect bicuspid aortic valve disease. Based on echocardiographic examinations, a diagnosis of bicuspid aortic valve disease was made in 115 (0.98%) of the patients (bicuspid aortic valve disease group). From the same population and during the same period, for each case patient, we randomly selected a control from the patients who had no bicuspid aortic valve disease, age- (within 1 year) and gender-matched to the case patient (control group, n = 115). For the purposes of the study, from the coronary angiograms, we determined the

prevalence rate of coronary heart disease and the scores derived using three different scoring systems, which reflect severity and extent of the disease, in the bicuspid aortic valve disease group and control group, and we compared these variables between these two groups.

The median number of diseased vessels, the distribution of the coronary arteries disease, and conventional risk factors for coronary heart disease (hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, and family history for premature coronary heart disease), the frequency of patients with an associated congenital coronary artery anomaly and with a comorbid condition, median of length of the left main coronary artery, and the frequency of coronary artery dominance patterns were also determined and compared between the groups.

To determine whether bicuspid aortic valve disease is an independent risk factor for coronary heart disease, we also conducted a multivariate logistic regression analysis with coronary heart disease as the dependent variable, and with age, gender, hypercholesterolemia, diabetes, smoking, family history for premature coronary heart disease, and bicuspid aortic valve disease as independent variables. We also compared the prevalence rates of the four conventional risk factors for coronary heart disease and the prevalence rate of the patients without any of these risk factors between patient groups, which consisted of patients in the total study population with and without angiographic coronary heart disease.

Furthermore, to determine whether the association, if any, between bicuspid aortic valve disease and coronary heart disease was due to functional alterations in the aortic valve, we first determined the presence and severity of aortic stenosis and aortic regurgitation and the presence of aortic dilatation in the bicuspid aortic valve disease group, and then compared the frequency of patients with moderate or severe aortic stenosis, moderate or severe aortic regurgitation, moderate or severe aortic stenosis or regurgitation, and aortic dilatation between coronary heart disease-present and coronary heart disease-absent subgroups of this group.

Finally, to determine whether there is a relationship between the type of the bicuspid aortic valve and occurrence of coronary heart disease, we compared the prevalence rates of coronary heart disease within each of the three subgroups, which were divided according to the type of the bicuspid aortic valve in the bicuspid aortic valve disease group.

2.2 Angiographic measurements

All patients underwent coronary angiography, using standard techniques. Angiograms were assessed independently by two experienced interventional cardiologists (M.N.A., A.C.) who were blinded to the patients' clinical parameters. Coronary heart disease was defined as the presence of angiographic coronary stenosis greater than or equal to 50% of the luminal diameter in at least one of the three major epicardial arteries or in a major branch on quantitative coronary analysis. The patients with no irregularities or with minor irregularities of the coronary vasculature, or with a moderate diameter reduction less than 50%, were classified as without coronary heart disease.

All coronary angiographies classified as coronary heart disease were assessed using the modified Gensini index as previously described (Gensini, 1983; Ringqvist et al., 1983). Briefly, location, degree of stenosis (severity), and number of occluded segments (extent) were evaluated. Coronary vasculature was divided into 27 coronary segments, and each involved segment was weighted by a value from 0.5 (least important) to 5.0 (critical location), reflecting the location of coronary artery lesions. The severity (percentage of

stenosis) was weighted as follows: < 25%, 2; 26–50%, 4; 51–75%, 8; 76–90%, 16; 91–99%, 32; 100%, 64. Extent was determined by the number of occluded segments (from 1 to 27) and constitutes score III. Score II is the sum of the weighted severity for all involved segments. The product of the weights for location and severity is the total weight for each arterial segment, and the sum of all segments involved constitutes score I (the modified Gensini index), reflecting location, severity and extent (Ringqvist et al., 1983). The length of the left main coronary artery was measured on the right anterior oblique view of the archived coronary angiography images.

2.3 Echocardiographic measurements

Comprehensive two-dimensional and Doppler echocardiographic examinations were performed in a systemic manner by experienced cardiologists who were blinded to the study. In addition to the other routine examinations, aortic valve morphology and function, as well as aortic arterial dimensions were determined. Aortic valve morphology was assessed in the parasternal long- as well as short-axis views. The diagnosis of bicuspid aortic valve was based on previously defined criteria (Brandenburg et al., 1983) as the presence of only two cusps was clearly identified in systole and diastole in the short-axis view. Patients with fusion of the commissures attributable to rheumatic disease (Rose, 1986; Passik et al., 1987) were not included as having bicuspid aortic valve. An example for the echocardiograms of our patients with bicuspid aortic valve is shown in Figure 2. In this transthoracic two-dimensional echocardiogram in parasternal short-axis view at the aortic valve level, a clear systolic ''fish-mouth'' appearance of the aortic valve in mid-systole (arrow) is seen. The type of bicuspid aortic valve was determined from the short-axis view of transthoracic echocardiograms as previously described (Schaefer et al., 2008). Three morphologies, namely, type 1 (fusion of right and left coronary cusps), type 2 (fusion of right and noncoronary cusps), and type 3 (fusion of left and noncoronary cusps), were identified based on orientation of the valve cusps.

Aortic regurgitation was evaluated by color Doppler in the parasternal long-axis and short-axis views, and in the apical long-axis and five-chamber views. The severity of aortic regurgitation was assessed by the ratio of proximal jet area to left ventricular outflow tract area in combination with the ratio of jet height to left ventricular outflow tract height. In addition, the rate of deceleration of the velocity signal of aortic regurgitation and the presence of retrograde flow in the abdominal aorta on continuous-wave Doppler echocardiography were also considered in our assessment. These combined indices were analyzed to grade aortic regurgitation as mild, moderate, or severe, according to the American Society of Echocardiography criteria (Zoghbi et al., 2003).

Aortic stenosis was evaluated by both pulsed-wave and continuous-wave Doppler. Aortic stenosis was defined as present when the aortic peak velocity obtained by continuous-wave Doppler was > 2.5 m/s, and was classified as mild (valve area > 1.5 cm^2; mean pressure gradient < 25 mmHg), moderate (valve area, 1.0-1.5 cm^2; mean pressure gradient = 25-40 mmHg), or severe (valve area < 1.0 cm^2; mean pressure gradient > 40 mmHg) (Bonow et al., 2006). Figure 3 shows an example of the continuous wave Doppler images of severe aortic stenosis and mild aortic regurgitation in a patient with bicuspid aortic valve disease.

Thoracic aortic diameter measurements were taken in the parasternal long-axis view at the end of diastole at the level of the aortic annulus, sinus of Valsalva, sinotubular junction, and proximal ascending aorta (measured 1 cm from the sinotubular junction), as previously described (Roman et al., 1989). Measurements were made perpendicular to the long axis of

the aorta using the leading-edge-to-edge method in views showing the largest aortic dimensions. The average of two measurements taken at every level was recorded. A dilated aorta was defined as an ascending aorta with a diameter greater than 37 mm, which is near the 95th percentile for this region for gender and body surface area (Roman et al., 1989; Vasan et al., 1995).

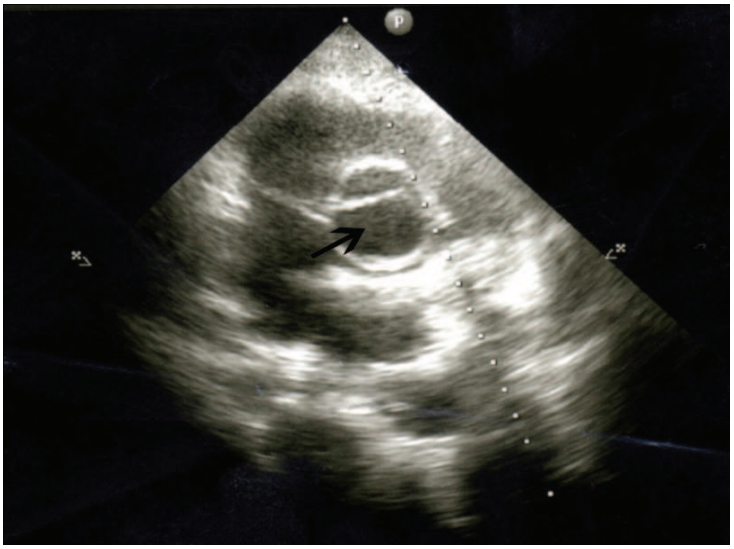

Fig. 2. Transthoracic two-dimensional echocardiogram in parasternal short-axis view of the aortic valve in mid-systole showing a clear systolic ''fish-mouth'' appearance of the bicuspid aortic valve orifice (arrow)

2.4 Other definitions

The five conventional risk factors for coronary heart disease were defined as follows: hypercholesterolemia: having a serum total cholesterol level of greater than or equal to 200 mg/dL, or an LDL-cholesterol level of greater than or equal to 130 mg/dL, or current treatment with lipid-lowering agents; hypertension: having an average blood pressure of greater than or equal to 140 mmHg systolic or 90 mmHg diastolic on three different occasions, or using antihypertensive medication; diabetes mellitus: having a fasting serum glucose of greater than or equal to 126 mg/dL (if confirmed on a subsequent day) or a 2-hour post load glucose of greater than or equal to 200 mg/dL, or using antidiabetic medication; family history of premature coronary heart disease: having a history of coronary heart disease in a first-degree male relative less than 55 years old or in a female first-degree relative less than 65 years old; and cigarette smoking: smoking more than or equal to 5 cigarettes per day for at least one year.

2.5 Exclusion criteria

Patients with a history or evidence of current or previous acute coronary syndrome, or with a history of percutaneous coronary intervention or coronary artery bypass grafting were excluded from the study.

The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all study participants.

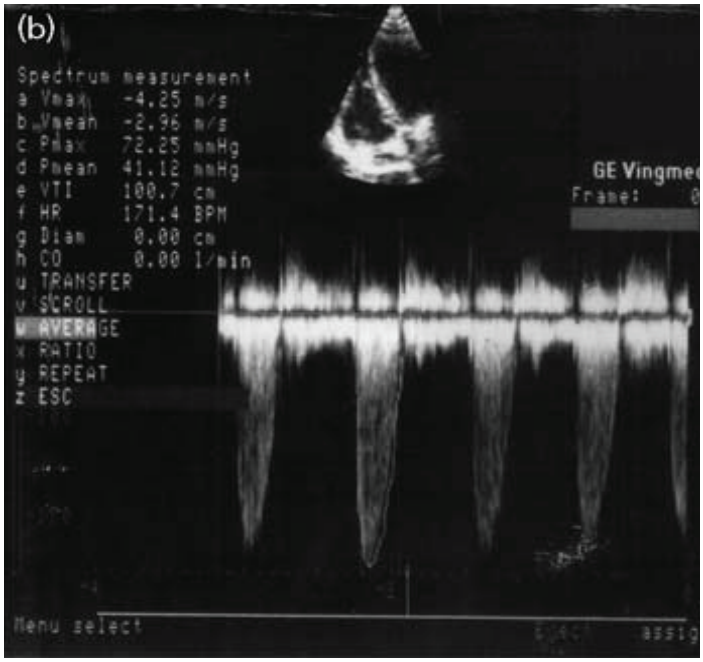

Fig. 3. Continuous wave Doppler recording of a bicuspid aortic valve (from apical five-chamber approach) showing severe stenosis across the valve and mild regurgitation

2.6 Statistical analyses

Statistical calculations were done using SPSS 17 (SPSS Inc., Chicago, IL, USA). Before the comparisons between the groups, the continuous variables were tested for normality using the Kolmogorov-Smirnov test. Data are expressed as mean ± standard deviation for normally distributed continuous variables, as median (25th, 75th percentile) for non-normally distributed continuous variables, and as numbers and percentages [n (%)] for categorical variables. All tests were two-sided, and alpha was set at = 0.05. For comparisons, Student's *t*-test was used for normally distributed data, and the Mann–Whitney U-test was used for data that was non-normally distributed. A $\chi 2$ test with Yates's correction or Fisher's exact test was used for categorical data.

3. Results

3.1 Study population

As seen in Table 1, the bicuspid aortic valve disease group and control group were not significantly different in age, gender, the frequency of the indications for coronary angiography (i.e., presence or absence of typical, atypical, or non-anginal chest pain), conventional risk factors for coronary heart disease, the presence of an associated congenital cardiovascular anomaly, or comorbidity status.

	Bicuspid Aortic Valve Disease Group (n = 115)	Control Group (n = 115)	p
Age (years)	56.4 ± 13.8	56.4 ± 13.6	N.S.
Gender (male)	96 (83.5)	96 (83.5)	N.S.
Indications for angiography			
Typical chest pain	71 (61.7)	67 (58.3)	N.S.
Atypical or non-anginal chest pain	34 (29.6)	36 (31.3)	N.S.
No chest pain	10 (8.7)	12 (10.4)	N.S.
Conventional risk factors for coronary heart disease			
Hypertension	25 (21.7)	20 (17.4)	N.S.
Diabetes	7 (6.1)	8 (7.0)	N.S.
Ever smoker	27 (23.5)	30 (26.3)	N.S.
Hypercholesterolemia	20 (17.4)	15 (13.0)	N.S.
Family history of premature coronary heart disease	6 (5.2)	7 (6.1)	N.S.
Associated congenital cardiovascular anomaly present	3[1] (2.6)	0 (0.0)	N.S.
Comorbidity			
Atrial fibrillation	5 (3.8)	2 (1.7)	N.S.
Renal failure	2 (1.7)	1 (0.9)	N.S.
Hypothyroidism	1 (0.9)	1 (0.9)	N.S.
Hyperthyroidism	0 (0.0)	1 (0.0)	N.S.
Marfan's syndrome	1 (0.9)	0 (0.0)	N.S.
Iron deficiency anaemia	1 (0.9)	1 (0.9)	N.S.

[1]Coarctation of the aorta in 1, secundum type atrial septal defect in 1, and operated patent ductus arteriosus in 1 case.

Table 1. Baseline characteristics of the groups. N.S.: Not significant

	Number and percentage of patients
a) Functional alterations of the aortic valve	
Aortic regurgitation	**38 (33.0)**
Severe	10 (8.7)
Moderate	15 (13.0)
Mild	13 (11.3)
Aortic stenosis	**32 (27.8)**
Severe	9 (7.8)
Moderate	13 (11.3)
Mild	10 (8.7)
Combined aortic stenosis and regurgitation	**28 (24.4)**
Severe or moderate stenosis	10 (8.7)
Severe or moderate regurgitation	10 (8.7)
Severe or moderate stenosis and regurgitation	4 (3.5)
Mild stenosis and regurgitation	4 (3.5)
No functional abnormalities	17 (14.8)
b) Aortic dilatation	**47 (40.9)**

Table 2. Functional alterations of the aortic valve and prevalence of aortic dilatation in 115 patients with bicuspid aortic valve disease

In the bicuspid aortic valve disease group, data on the type of the bicuspid aortic valve were not available in 25 (21.7%) patients. Among the remaining 90 patients, the most common morphology of the bicuspid aortic valve was type 1 (n = 70 [77.8%]), followed by type 2 (n = 18 [%20.0]) and type 3 (2 [2.2%]). Among the 115 patients with bicuspid aortic valve disease, the bicuspid aortic valve was regurgitant in 38 (33.0%) patients, stenotic in 32 (27.8%) patients, combined regurgitant and stenotic in 28 (24.4%) patients, and functionally normal in 17 (14.8%) patients, and aortic dilatation was present in 47 (40.9%) patients (Table 2).

3.2 Angiographic results

Coronary angiography revealed a significantly higher incidence of coronary heart disease in the bicuspid aortic valve disease group than in the control group (73.9% vs. 60.0%; p = 0.035). The median (25th; 75th percentile) number of diseased vessels (2.0 [2.0; 2.0] vs. 2.0 [1.0; 2.0]; p = 0.021) and indices of severity (score II, 99.0 [77.0; 122.0] vs. 88 [77.0; 111.0]; p = 0.029) and extent (score III, 10.9 [7.8; 12.55] vs. 8.9 [6.7; 11.65]; p = 0.026), and the modified Gensini index (score I, 106.0 [84.0; 129.0] vs. 95.0 [84.0; 118.0]; p = 0.016), which reflects location, severity, and extent, were also significantly higher in the bicuspid aortic valve disease group than in the control group (Table 3). Additionally, the median (25th; 75th percentile) length of

	Bicuspid Aortic Valve Disease Group (n = 115)	Control Group (n = 115)	p
Coronary heart disease on angiogram	85 (73.9)	69 (60.0)	0.035
No of diseased vessels	2.0 (2.0; 2.0)	2.0 (1.0; 2.0)	0.021
Indexes of severity and extent of coronary heart disease			
Score I (location/severity/extent)	106.0 (84.0;129.0)	95.0 (84.0;118.0)	0.016
Score II (severity)	99.0 (77.0;122.0)	88.0 (77.0;111.0)	0.029
Score III (extent)	10.9 (7.8;12.55)	8.9 (6.7;11.65)	0.026
1-vessel disease	11 (12.9)	18 (26.1)	0.062
Multi-vessels disease	74 (87.1)	51 (73.9)	0.062
Left main coronary artery	3 (1.7)	1 (0.8)	0.641
Left anterior descending artery	81 (46.8)	61 (48.4)	0.877
Circumflex artery	31 (17.9)	32 (25.4)	0.155
Right coronary artery	58 (33.5)	32 (25.4)	0.166
Length of the left main coronary artery, mm	7.7 (6.0;9.0)	8.9 (4.7;9.7)	0.019
Coronary artery anomaly	2[1]2.4)	1[2] (1.5)	1.000
Coronary dominance patterns			
Dominant right coronary artery	90 (78.3)	103 (89,6)	0.031
Dominant circumflex artery	22 (19.1)	10 (8.7)	0.036
Co-dominant arteries (right coronary artery, circumflex artery)	3 (2.6)	2 (1.7)	0.645

[1]Split right coronary artery in one patient and a fistula from the right coronary artery to the right ventricle in the other one patient.
[2]Circumflex artery arising from the proximal right coronary artery.

Table 3. Coronary angiographic findings in the groups

the left main coronary artery was significantly shorter (7.7 [6.0; 9.0] vs. 8.9 [4.7; 9.7]; p = 0.019) and the prevalence of left dominance (19.1% vs. 8.7%, p = 0.036) was significantly higher in the bicuspid aortic valve disease group than in the control group than in the control group (Table 3). Furthermore, although the difference was not significant, the test showed a higher frequency of multi-vessel disease in the bicuspid aortic valve disease group than in the control group (87.1% vs. 73.9%; p = 0.062). There were no significant differences between the two groups with regard to the distribution of the diseased coronary arteries (Table 3).

3.3 Results of the logistic regression analysis

The results of the logistic regression analysis are presented in Table 4. This analysis revealed that together with age (Odds ratio: 1.03; 95% confidence interval: 1.002-.048; p = 0.031), the presence of bicuspid aortic valve disease (Odds ratio: 1.90; 95% confidence interval: 1.070-3.357; p = 0.028) was an independent risk factor for coronary heart disease. In this analysis, none of the other independent variables, namely, gender, hypercholesterolemia, diabetes, smoking, and family history for premature coronary heart disease, was significant.

	Odds ratio	95% Confidence intervals	p
Age	1.03	1.00-1.05	0.019
Male gender	0.81	0.37-1.75	N.S.
Hypercholesterolemia	1.24	0.54-2.83	N.S.
Hypertension	1.42	0.63-3.18	N.S.
Diabetes	1.94	0.57-6.59	N.S.
Smoking	1.02	0.508-2.029	N.S.
Family history for premature coronary heart disease	0.92	0.27-3.09	N.S.
Bicuspid aortic valve disease	1.90	1.07-3.37	0.028

Table 4. Results of the multivariable logistic regression for the presence of angiographically proven coronary heart disease. N.S.: Not significant

3.4 Comparison of the demographic data and the frequency of patients with a risk factor for coronary heart disease and those without any of these factors between the coronary heart disease-present and -absent groups in the total study population

The mean age was significantly higher and the prevalence of patients without any of the four risk factors for coronary heart disease were significantly lower the coronary heart disease-present group than in the coronary heart disease-absent group. However, none of the four risk factors for coronary heart disease were significantly different between the groups, although there was a trend toward a higher prevalence of hypertension, diabetes, and hypercholesterolemia in the coronary heart disease-present group (Table 5).

3.5 Relationship between the functional alterations in aortic valve and aortic dilatation and the presence of coronary heart disease in the bicuspid aortic valve disease group

No significant changes were detected between the coronary heart disease-present and coronary heart disease-absent subgroups of the bicuspid aortic valve disease group with respect to the frequency of patients with moderate or severe aortic stenosis, moderate or severe aortic regurgitation, moderate or severe aortic stenosis or aortic regurgitation, and aortic dilatation, although all of these variables tended to be higher in the former than the latter subgroup (Table 6).

	Coronary Heart Disease		
	Present (n = 154)	Absent (n = 76)	p
Age	57.9 ± 13.7	53.2 ± 13.2	0.014
Gender (male)	128 (83.1)	64 (84.2)	0.983
Hypertension	34 (22.1)	11 (14.5)	0.234
Diabetes	11 (7.1)	4 (5.3)	0.795
Ever smoker	38 (24.7)	19 (25.0)	1.000
Hypercholesterolemia	25 (16.2)	10 (13.2)	0.678
Family history for premature coronary heart disease	8 (5.2)	5 (6.6)	0.901
Absence of these risk factors	50 (32.5)	37 (48.7)	0.025

Table 5. Comparison of the demographic data and the prevalence of the coronary heart disease risk factors and of absence of any of these risk factors between the coronary heart disease-present and -absent groups in the total study population

	Coronary Heart Disease Present (n = 85)	Coronary Heart Disease Absent (n = 30)	p
Moderate or severe aortic stenosis	26 (30.6)	6 (17.0)	0.381
Moderate or severe aortic regurgitation	28 (32.9)	7 (23.3)	0.452
Moderate or severe aortic stenosis or regurgitation	57 (67.1)	14 (46.7)	0.079
Aortic dilatation	37 (43.5)	10 (33.3)	0.447

Table 6. Comparison of coronary heart disease-present and -absent subgroups of the bicuspid aortic valve disease group by the presence of moderate or severe aortic stenosis, moderate or severe aortic regurgitation, moderate or severe aortic stenosis or aortic regurgitation, and aortic dilatation

3.6 Comparison of the prevalence rates of coronary heart disease within subgroups which were divided according to the type of bicuspid aortic valve

None of the comparisons of the prevalence rates of coronary heart disease within subgroups which were divided according to the type of bicuspid aortic valve among 90 bicuspid aortic valve disease patients showed a significant difference (Table 7).

	Coronary Heart Disease-Present (n = 66)	Coronary Heart Disease-Absent (n = 24)	p
Type 1	54 (81.8)	16 (66.7)	N.S.
Type 2	12 (18.2)	6 (25.0)	N.S.
Type 3	0 (0.0)	2 (8.3)	N.S.

Table 7. Comparison of the prevalence rates of coronary heart disease within subgroups which were divided according to the type of bicuspid aortic valve. N.S.: Not significant

4. Discussion

In the present study, in a specific population consisting of patients who underwent coronary angiography for suspected coronary heart disease (i.e., a population in which the incidence of coronary heart disease is expected to be high), we found a significantly higher prevalence of coronary heart disease in those patients with bicuspid aortic valve disease than in their age- and gender-matched counterparts without bicuspid aortic valve disease (73.9% vs. 60.0%). The indices of angiographic severity and extent of coronary heart disease were also significantly higher in the bicuspid aortic valve disease group than in the control group.

As mentioned earlier, there have been some case reports describing patients with bicuspid aortic valve disease associated with coronary atherosclerosis (Shimuzu et al., 1984; Bensaid et al., 1978; Yokoyama et al., 2002; Theleman et al., 2006) and even with acute myocardial infarction (Demir, 2009). However, to the best of our knowledge, there are only two studies in which the frequency of angiographic coronary heart disease has been given for patients with bicuspid aortic valve disease (Yuan et al., 2010; Goland et al., 2007). In one of these studies (Goland et al., 2007), which included 252 bicuspid aortic valve disease patients (mean age: 61 ± 15, 66.3% male) undergoing aortic valve replacement, the prevalence of coronary heart disease was 40.5%. In the other study (Yuan et al., 2010), the prevalence of angiographic coronary heart disease was not significantly different between the group consisting of the patients with bicuspid aortic valve disease who underwent cardiac surgery (n = 241), and the control group consisting 225 patients without bicuspid aortic valve disease who underwent an operation for an isolated aortic dilation, a combined aortic dilation and aortic valve abnormality, coarctation of the aorta, Marfan's syndrome, aortic dissection, infective endocarditis, or aortic valve disorders (22.82% vs. 28.9%; p = not significant). However, that study was not designed primarily to compare the frequency of coronary heart disease in bicuspid aortic valve disease patients with that in an age- and gender-matched control group. Accordingly, there were significant differences between these two groups, mainly with regard to mean age (56.1 ± 15.1 vs. 62.8 ± 14.7; $p < 0.0001$) and gender distribution (male/female: 3.38/1 vs. 1.78/1). To our knowledge, the present study is unique in prospectively examining the relationship between the presence of bicuspid aortic valve disease and the occurrence, severity, and extent of angiographic coronary heart disease. According to our knowledge, neither the above-mentioned two studies (Yuan et al., 2010; Goland et al., 2007) nor the five case reports (Shimuzu et al., 1984; Bensaid et al., 1978; Yokoyama et al., 2002; Theleman et al., 2006; Demir, 2009) nor any other publication in the literature have suggested any explanation for a possible association between bicuspid aortic valve disease and coronary heart disease.

First, it must be emphasized that since both of these diseases have high prevalences, there is a great possibility that their coexistence is not uncommon. Moreover, in some of the above-mentioned reported cases, in addition to bicuspid aortic valve disease and coronary heart disease, a third disorder, which may be relevant to coronary heart disease, namely rheumatoid arthritis in one case (Shimuzu et al., 1984) and mitral annular calcification in an another case (Theleman et al., 2006), was also present.

On the other hand, two possible explanations for the coexistence of the aforementioned congenital vascular abnormalities with bicuspid aortic valve disease or for long-term complications of bicuspid aortic valve disease have been proposed: (1) they may be secondary to flow dynamics (e.g., post-stenotic dilatation), and (2) there may be a common underlying developmental defect involving the aortic valve and the arterial wall (Niwa et

al., 2001; Bonderman et al., 1999; Hahn et al., 1992; Pachulski et al., 1991). In favor of the latter mechanism, the ascending aorta above a bicuspid aortic valve was reported to be dilated, irrespective of the presence or absence of aortic stenosis or regurgitation (Hahn et al., 1992; Pachulski et al., 1991). Moreover, the study by Niwa et al. (2001) reported that light and electron microscopic abnormalities in the tunica media of the ascending aorta above a bicuspid aortic valve were also identical irrespective of the functional state of the valve. The authors concluded that this observation was in favor of the view that there is an inherent fault in the ascending aortic media. Accordingly, we believe that similar mechanisms may also have been involved in our finding that the presence of bicuspid aortic valve disease is associated with the occurrence, severity, and extent of coronary heart disease. In favor of the former of the above two mechanisms, we observed trends toward an increased frequency of patients with moderate or severe aortic stenosis, aortic regurgitation, aortic stenosis or aortic regurgitation, and aortic dilatation in the coronary heart disease-present subgroup of the bicuspid aortic valve disease group. However, none of these differences were significant, perhaps because of the limited size of the study population.

Of interest is that in some earlier papers it was suggested that more than 50% of patients with coronary heart disease lacked any of the aforementioned four conventional risk factors for atherosclerosis (Futterman & Lemberg, 1998; Hennekens, 1998). However, in some more recent studies, this percentage was reported to be between 15 and 20 **(**Khot et al., 2003; Greenland et al., 2003). In the present study, the percentage of patients without any of these risk factors was 27.1% in the coronary heart disease-present subgroup of the bicuspid aortic valve disease group and 39.1% in the coronary heart disease-present subgroup of control group (data not shown). Atherosclerosis, the major underlying cause of coronary heart disease, is present in all humans at an advanced age, and it progresses over a lifetime, but its extent and progression is dependent on its risk factors (Berenson et al., 1998). In addition, genetic factors are important. Twin studies indicate that the heritability of coronary heart disease, defined as the proportion of the interindividual differences resulting from genetic factors, is 30% to 60% (Marenberg et al., 1994). Existing research into the genetic basis of coronary heart disease falls into two categories. Firstly, earlier studies investigated candidate genes on which suspicion fell as result of evidence that the gene influenced one of the mechanisms by which coronary heart disease arose, such as lipoprotein metabolism or inflammation. More recently, genome-wide association studies have investigated many variants across the genome, without any underlying hypotheses. With the availability of high-density genome-wide association studies, and as studies become larger and more numerous, significant positive findings are emerging. These studies have resulted in the identification of 17 loci associated with coronary heart disease (reviewed in Sivapalaratnam et al., 2011). Still, only part of the heritability of coronary heart disease is currently explained. Accordingly, it can be also stated that there is a possibility for a common genetic basis for the association between bicuspid aortic valve disease and coronary heart disease.

It is interesting that degenerative-calcific aortic stenosis, which predominantly affects older people, is a presentation of atherosclerosis (Faggiano et al., 2011; Otto et al., 1999; Branch et al., 2002). However, according to our knowledge, there are no studies in the literature reporting such an association for aortic stenosis of rheumatic origin or due to bicuspid valves and for aortic regurgitation or aortic dilatation of any origin.

Among the findings of this study was the lack of independent predictiveness of the five conventional risk factors for coronary heart disease, namely hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, and a family history of premature

coronary heart disease. Accordingly, none of these five risk factors was significantly different between the coronary heart disease-present and -absent groups in the total study population, although a trend toward a higher prevalence of hypertension, diabetes, and hypercholesterolemia in the former group was observed. We believe that these findings may probably be partly due to the relatively high prevalence of patients who were using medications against these risk factors (i.e., antihypertensive, antidiabetic, and lipid-lowering drugs).

Finally, it should be also stated that, our findings that the increased prevalence of left dominance (Hutchins et al., 1975; Higgins & Wexler, 1975) and significantly shorter left main coronary artery length (Hutchins et al., 1975; Higgins & Wexler, 1975; Yuan et al., 2010) in patients with bicuspid aortic valve disease are in general in accord with the studies in the literature.

5. Limitations of the study

Because it is unethical to do coronary angiography on every patient with bicuspid aortic valve disease, the study was done on patients who underwent coronary angiography for suspected coronary heart disease (i.e., on patients in whom the probability of coronary heart disease was high). It is clear that this is not an ideal design to investigate a probable relationship between bicuspid aortic valve disease and coronary heart disease.

6. Conclusion

In conclusion, there may be an association between bicuspid aortic valve disease and coronary heart disease. It is both possible that this association is due to structural changes in the walls of the coronary arteries secondary to flow dynamics in bicuspid aortic valve disease or to a common underlying congenital cause involving both the aortic valve and coronary arteries. It is also possible that both of these factors may make the coronary arteries prone to atherosclerosis. More studies are needed to confirm our findings and to study the potential mechanisms of this association.

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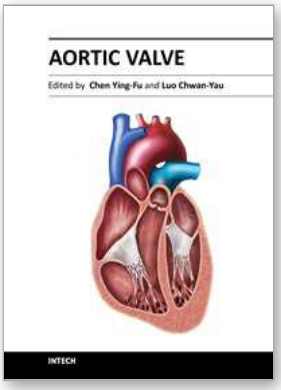

Aortic Valve

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Much has evolved in the field of aortic valve disease because of the increase in knowledge in the last decade, especially in the area of its management. This book "Aortic Valve" is comprised of 18 chapters covering basic science, general consideration of aortic valve disease, infective endocarditis, aortic sclerosis and aortic stenosis, bioprosthetic valve, transcatheter aortic valve implantation and a special section on congenital anomalies of the aortic valve. We hope this book will be particularly useful to cardiologists and cardiovascular surgeons and trainees. We also believe that this book will be a valuable resource for radiologists, pathologists, cardiovascular anesthesiologists, and other healthcare professionals who have a special interest in treating patients with aortic valve disease. We are certain that information in this book will help to provide virtually most new areas of aortic valve disease that will be employed in the current era.

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