Bicuspid aortic valve: a literature review and its impact on sport activity

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The bicuspid aortic valve (BAV) is the most common congenital cardiac malformation. A literature search was performed using the key words ‘bicuspid aortic valve’, ‘pathophysiology’, ‘exercise’ and ‘training’. BAV is the result of a complex developmental process where several genes seem to lead to abnormal valvulogenesis. Complications associated with BAV include aortic stenosis (AS) and regurgitation, infective endocarditis and aortic dilation and dissection. Moreover, BAV may be associated with other cardiovascular anomalies, mainly aortic coarctation. There is greater awareness of BAV in the young population who practice sport, with an increasing interest on the impact of regular and competitive exercise on athletes with BAV. The early identification of BAV through pre-participation screening is of paramount importance, and the justification of the more appropriate diagnostic methods is still an area of debate. A normally functioning BAV usually does not represent a limit for practising sport. The stress of regular and intense exercise on an abnormal aortic valve may favour its early deterioration and accelerate the development of complications. Therefore, athletes with BAV warrant regular follow-up, which should include echocardiographic assessment at least every year. The eligibility for participation and ability to continue to practise competitive sports in athletes with BAV cannot be generalized, but needs to be individualized depending on age, severity of lesions and type of sport. Further studies are required to elucidate the impact of physical training and competitive sports on the natural course of the BAV.

Keywords: bicuspid aortic valve/pathophysiology/exercise/training
Introduction

Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, affecting 1–2% of the general population, with a higher prevalence in males. The fate of BAV includes aortic stenosis (AS) and aortic regurgitation. The latter is probably more common in younger patients, and the former becomes more frequent with age. Patients are also at risk to develop endocarditis, which often leads to rapid deterioration of aortic valve function. Aortic aneurysm, dissection and rupture are the other recognized serious complications associated with BAV. BAV may occur in association with other cardiovascular malformations (CVM), including coarctation of the aorta (50–80%), interruption of the aorta (36%) and ventricular septal defect (20%). Other associations include patent ductus arteriosus, coronary anatomic variants and other conditions such as Marfan’s and Turner’s syndromes. Quite often, the diagnosis of BAV is an incidental finding during an echocardiogram.

The distinction of a normal, tricuspid, aortic valve from a BAV has been easy since the advent of two-dimensional echocardiography (2DE). Recently, a greater attention to this cardiac anomaly has been paid in the young population, particularly in those who practise sport.

There is an increasing interest on the role of regular exercise on the natural course of BAV. Theoretically, the physiological stress of regular and intense exercise on an abnormal aortic valve would induce its early deterioration and dilatation of the ascending aorta. However, the impact of regular training on patients with BAV and its natural course is still not fully clarified.

Methods

We performed a search using the keywords ‘bicuspid aortic valve’ in combination with ‘pathophysiology’, ‘exercise’ and ‘training’, with no limit regarding the year of publication. The following databases were accessed on 6th September 2007: PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/); Ovid (http://www.ovid.com); Cochrane Reviews (http://www.cochrane.org/reviews/). Given the linguistic capabilities of the research team, we considered the publications in English, Spanish, and Italian. Two authors (P.D.M., U.G.L.) independently read the abstract of each publication identified (if an abstract was available). If no abstract was available, the publication was excluded. In addition, the references section of all the publications identified were studied to...
ascertain whether other relevant material could be found. The personal collection of scientific material of the two senior authors (G.G. and N.M.) was consulted for the same purpose. If deemed relevant, all relevant publications were retrieved.

The most relevant material was drawn between the years 1991 and 2007. The total number of publications studied was greater than 200. A large number of publications focusing on surgical techniques and outcomes were not included. The publications thus selected were examined by all authors. After this further selection, 101 publications relevant to the topic at hand were included.

**Morphogenesis of BAV**

BAV results likely from a complex developmental process, not simply the fusion of two normal cusps.\(^{15}\) However, the exact mechanism remains unclear. Some researchers have implicated anomalous behaviour of cells derived from the neural crest as a possible aetiology.\(^{16}\) In particular, some researchers suggest that a molecular abnormality in the extracellular matrix (ECM) may lead to abnormal valvulogenesis, as matrix proteins help to direct cell differentiation and cusp formation during valvulogenesis.\(^{17}\) This could also explain why BAV is often linked to other cardiovascular anomalies (i.e. coarctation of the aorta, patent ductus arteriosus, hypoplastic left ventricular outflow tract, etc.).\(^{5}\)

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 heart, with the earliest recognizable cardiac structure evident at day 15 of gestation, when the cardiac progenitor cells have been specified and are organized in a crescent shape.

At 3 weeks of gestation, these bilaterally symmetric heart primordial cells migrate to the midline and fuse to form a single linear heart tube which has an inner endothelial lining surrounded by an outer myocardial cell layer which are separated by ECM. 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.\(^{18,19}\)

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 ECM in the region of the atrioventricular and outflow tract.\(^{20}\) Within the next day, there is a complex interplay of myocardial and endocardial signalling which is necessary for proper
endothelial to mesenchymal transformation. This process is initiated by secretion of ECM 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 BMP2 secreted by the myocardium to enhance mesenchyme formation and proliferation, resulting in the growth of the endocardial cushions. The myocardial cells then invade the margins of the cellular endocardial 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 disrupted in the aorta, most commonly the right and non-coronary cusps, the leaflet primordia do not separate or remain fused, resulting in BAV. The molecular pathways governing the later morphogenetic events of leaflet formation remain to be elucidated, but recent reports from human genetic studies have implicated several molecular cascades including NOTCH1 signalling.

Anatomy of BAV

A BAV 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 centre of the larger of the two cusps) and smooth cusp margins (Fig. 1). The direction of the two cusps is in most patients latero-lateral, and rarely antero-posterior. The raphe or fibrous ridge is usually present in the middle of the greater cusp, the site of congenital fusion of the two components of the conjoined cusps, and is identifiable in most BAV patients (Fig. 2). Sometimes it shows a deep indentation, which gives a false image of a tricuspid valve on 2DE. Valvular incompetence is usually caused by the redundance of one cusp, since the two cusps have usually different dimensions. Few cases of congenital BAV are accompanied by an abnormal fibrous band stretched from the centre of the conjoined cusp to the aortic wall, and they appear to be associated with valve insufficiency. An anomalous origin and course of the coronary artery is rarely seen in subjects with BAV. This depends on the spatial orientation of the two cusps. When it is latero-lateral, the right coronary artery takes origin from the right Valsalva’s sinus and the common trunk from the left; when the orientation is antero-posterior, both coronary arteries originate from the anterior sinus. The importance of an anomalous origin of the coronary arteries associated with BAV, although rare, lies in an increased risk of sudden cardiac death (SCD) during exercise.
Heredity

Although most cases of BAV are sporadic, familial clusters have been identified, with incidence as high as 10–17% in first-degree relatives of probands. Chan and co-workers determined the rate of familial occurrence of BAV with the use of echocardiography to screen family members of affected individuals. Of the 30 families screened, 11 families (36.7%) had more than one first-degree relative with BAV.

Fig. 1 Anatomy of bicuspid and tricuspid aortic valves.

Fig. 2 Direction of the two cusps.
The high incidence of familial clustering is compatible with autosomal dominant inheritance with reduced penetrance. Further studies have suggested multiple complex modes of inheritance for BAV. Statistical genetic models have been tested to demonstrate that the regions of the genome are responsible for the phenotype of BAV and/or associated CVM. 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 BAV reported to date.

One of these genes identified is NOTCH1. In a study of a large pedigree with autosomal-dominant BAV with early calcification of the valve, as well as other forms of congenital heart disease, NOTCH1 gene mutations appeared causative. Mutations found in two unrelated families were nonsense and frameshift defects, respectively, suggesting haploinsufficiency. NOTCH1 haploinsufficiency seemed to play a role also in premature aortic valve calcification.

NOTCH1 encodes a single-pass transmembrane receptor, functions in a highly conserved pathway, and may play critical roles in cell fate determination during organogenesis.

In mammals, there are four members of the NOTCH family, NOTCH1–4. Each NOTCH family member has a distinct expression pattern. During embryogenesis, NOTCH1 is expressed in the endocardium and in the outflow tract cushion mesenchyme. Finally, NOTCH1 signalling seems to play a pivotal role in later stages of aortic valve formation.

Other genes identified in BAV are KCNJ2 (chromosome 17q24.3) and UFD1L (chromosome 22q11.2). A number of studies have shown that 22q11.2 deletions cause a variety of cardiac outflow tract defects, not only AS associated with BAV. These cardiac defects are also seen after neural crest ablation, suggesting that certain genes controlling neural crest cells may be involved in the development of cardiac outflow tract malformations and may map to chromosome 22.

UFD1L gene encodes a component of a multienzyme 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. A downregulation of the UFD1L gene, hypothetically resulting from an anomalous behaviour 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 BAV.

The presence of multiple genomic regions associated with BAV demonstrates genetic heterogeneity and further supports complex inheritance. Given the strong genetic basis and the large proportion of BAV familial cases of unknown genetic aetiology, we expect that other
regions of the genome also predispose individuals to develop BAV and/or associated CVM. Martin et al. have recently identified some regions of the human genome, which harbour genes influencing inheritance of BAV and/or associated CVM. In particular, three novel loci for BAV and associated CVM were identified on chromosomes 18, 5 and 13. A sizable proportion of families contributes to each of these loci, suggesting that they may account for a substantial number of BAV. These regions likely contain genes, whose mutation results in BAV and/or associated CVM indicating their important role in valvulogenesis and cardiac development. No X-linked loci were identified. Although specific genes remain to be identified, all these results are an important first step in understanding the complex aetiology of valve development and disease.

**Complications**

BAV occurs in 1–2% of the population, compared with 0.8% for all other forms of congenital cardiac diseases combined. Serious complications will develop in at least one-third of patients with BAV. Indeed, the bicuspid valve may be responsible for more deaths and morbidity than the combined effects of all the other congenital heart defects. The important clinical consequences of BAV disease are valvular stenosis, regurgitation, infective endocarditis and aortic complications such as dilation, dissection and rupture. The incidence of fatal complications in cohorts of patients with BAV has been published (although many of these patients would nowadays survive following surgery): AS, 15–71%; aortic regurgitation, 1.5–3%; infective endocarditis, 9.5–40%; and aortic dissection, 5%. The wide ranges reported for each complication reflect their link with age. AS occurs predominantly in middle age, and the lower figure is derived from a young population. Infective endocarditis is a complication of the young, and the upper figure is from this age group.

**Aortic stenosis**

AS is the most common complication of BAV, occurring in about 50% of subjects. It becomes more rapidly progressive in the fourth decade and beyond. BAV is a leading cause of AS requiring aortic valve replacement. Furthermore, these patients are generally one decade younger than those with tricuspid AS requiring aortic valve replacement. The progression of AS parallels the development and progression of sclerotic changes in the aortic valve, which share histological and
immunochemical similarities with the process of atherosclerosis.\textsuperscript{40} Those changes are mainly represented by fibrosis and superimposed cusp calcification, which occur in an accelerated fashion with respect to the normal tricuspid valve. Stenosis progresses more rapidly if the cusps are asymmetrical and antero-posterior. High serum low-density lipoprotein cholesterol, high serum lipoprotein (a) and smoking are independent risk factors for AS, and presumably contribute to the age-related deterioration.\textsuperscript{41} Surgery is required when the AS becomes severe and symptoms intolerable.\textsuperscript{4,42}

**Aortic insufficiency**

Aortic regurgitation in BAV appears to be more common in younger patients compared with AS. Its aetiology is more complex than that of AS. It may occur in isolation, frequently caused by redundancy and prolapse of the greater cusp or in association with dilation of the aortic root and/or the sino-tubular junction, aortic coarctation and endocarditis.\textsuperscript{43} Aortic regurgitation in BAV in young subject carries an increased risk of endocarditis. Probably because of its association with coarctation of the aorta, and especially with infective endocarditis, patients with aortic regurgitation die or undergo surgery at an earlier age than those with AS.\textsuperscript{44}

Aortic valve replacement is indicated for severe valvular dysfunction, symptomatic patients and/or those patients with evidence of abnormal left ventricle (LV) dimensions and function. Patients with isolated aortic regurgitation may be candidates for aortic valve repair, an intervention that obviates the need for long-term anticoagulation.\textsuperscript{45}

**Endocarditis**

Endocarditis is potentially a devastating complication that occurs in up to 30\% of patients with BAV, particularly with regurgitant valves. BAV as a substrate for infective endocarditis is predominantly a complication in children and young adults. The most frequent microorganisms involved are Staphylococcus spp. and *Streptococcus viridans*.\textsuperscript{46} Maintaining adequate oral hygiene and prophylactic antibiotic therapy is essential in subjects with BAV.

**Aortic dilatation and dissection**

BAV is associated with dilatation of the aortic root and ascending aorta, usually disproportionate to the associated valvular lesions.\textsuperscript{47}
This finding is present on echocardiography in more than 50% of subjects with normally functioning BAV. In the past, the aortic root disease associated with BAV was termed poststenotic dilation. However, the severity of BAV stenosis does not correlate with aortic root dimensions, and functionally normal valves may be associated with large aortic root aneurysms. The most severe aortic root dilation usually occurs when there is a severe aortic valve regurgitation (Fig. 3).

Aortic dilatation has been explained by intrinsic histological abnormalities of the ascending aorta, including cystic medial necrosis, thinner elastic lamellae and elastic fragmentation. Recent experimental evidence suggests that the expression of endothelial nitric oxide synthase may have an influence on the anatomy of the aortic valve and aneurysmal dilatation of the aorta.

The presence of a BAV increases the risk of dissection 9-fold, and this rises to 18-fold if there is a unicommissural aortic valve. Aortic dissection usually occurs at a younger age and in previously asymptomatic patients with BAV.

The risk of aortic dissection is highest when the aortic diameter is more than 5 cm and with concomitant systemic hypertension. Therefore, operative repair of the AA is generally recommended when the diameter increases to 5 cm. Evaluation of aortic root anatomy and dimensions should be standard in all patients with aortic valve disease. In some patients, the timing of surgery will be dictated by progressive root dilation, even when valve dysfunction is not severe. When valve disease is the primary indication for surgical intervention,
concurrent aortic root replacement should be considered if significant aortic dilation is present.

**Diagnosis and classification**

A clinical diagnosis of BAV based purely on the presence of an aortic ejection click, with or without an ejection systolic murmur, lacks predictive accuracy, as the aortic ejection click may be heard in tricuspid aortic valve stenosis, or in aortic dilatation from any cause, and is absent when the valve cusps are rigid.\(^{53,54}\) The ECG in subjects with BAV may show non-specific changes such as left ventricular hypertrophy, atrial enlargement and arrhythmias. The reliability of diagnosis has been significantly improved by the introduction of cross sectional and Doppler echocardiography; a specificity of 96\%, a sensitivity of 78\% and a predictive accuracy 93\% have been reported.\(^{55}\) Diagnosis is based on the demonstration of two cusps and two commissures during short axis visualization. Supportive features include cusp redundancy and eccentric valve closure, and a single coaption line between the cusps during diastole. However, the usually bicuspid nature of a valve may be obscured by severe fibrosis or calcification, and false-negative results may be produced by a prominent raphe, which can give the appearance of a third coaption line. A false-positive diagnosis may occur when one coaption line of a tricuspid valve is unclear. Colour-Doppler analysis is essential to identify the presence and the extent of valvular obstruction or regurgitation and possible cardiovascular abnormalities such as aortic coarctation or complications associated with BAV such as endocarditis or aortic dissection. As part of echocardiographic assessment, it is important to quantify the dilatation of the aorta, measuring aortic diameters at different levels, in particular valvular insertion; Valsalva’s sinuses; sino-tubular junction, 1–2 cm from the sino-tubular junction in the ascending aorta; and aortic arch. Transoesophageal echocardiography is an excellent tool for the evaluation of the aortic valve and proximal thoracic aorta morphology, but it is not indicated for serial imaging.\(^{56}\) Cardiovascular magnetic resonance imaging (MRI) is emerging as a noninvasive modality that likely provides both high diagnostic sensitivity and specificity. The high spatial resolution and reproducibility of MRI angiography make this technique especially useful for the serial assessment and surveillance of the aorta. In addition, velocity-encoded MRI also appears to be useful for the evaluation of stenotic and regurgitant valvular lesions, although data are limited in this field.\(^{57,58}\)

The new American College of Cardiology/American Heart Association recommendations highlight the role of MRI and computed tomography (CT) as complementary tools to echocardiography for the
diagnosis and surveillance of the morphology of the aortic valve and ascending aorta in subjects with BAV.\textsuperscript{59,60}

**Treatment**

The treatment of BAV is primarily surgical. Several aspects have to be taken into account when evaluating the most appropriate surgical option in patients with BAV. Most patients are young at the time of surgery and therefore the longer life expectancy will lead to an increased cumulative risk of valve-related morbidity, including valve thrombosis, thromboembolism and haemorrhage after mechanical valve implantation. An accurate assessment of the morphology of the BAV, the size of ascending aorta and the extent and rate of progression of aortic dilatation may be important to determine an individualized surgical approach. Finally, an adequate risk assessment of the difficulty of the surgical procedure and associated comorbidities needs to be incorporated into the decision-making process. With the exception of paediatric patients in whom aortic valvuloplasty for AS is preferred, replacement of the AV is indicated in symptomatic patients with severe stenotic or regurgitant BAV.\textsuperscript{61} Although combined valve and ascending aorta replacement has been the most common surgical approach, several valve-sparing approaches with comparable mid-term results to the classic procedures have recently been reported.\textsuperscript{62,63} However, longer follow-up studies will be helpful to better define the advantages of these new surgical options. BAV replacement using the Ross procedure (an autograft of the patient’s own pulmonary valve in aortic position and a pulmonary allograft replacement) has been used for many years with the advantage of avoiding anticoagulation.\textsuperscript{64,65} Surgeons should adopt appropriate techniques to avoid late dilatation when performing a Ross procedure.\textsuperscript{66} Although surgery remains the mainstay of treatment for BAV, it is important to consider also lifestyle recommendations and pharmacological options. Valve calcification is an active process preceded by inflammation, lipid deposition and accumulation of extracellular bone matrix proteins. Several retrospective studies have suggested a potential role for statin therapy in inhibiting aortic valve calcification.\textsuperscript{67,68} Modification of risk factors, including smoking cessation and management of hyperlipidemia, remains essential. In asymptomatic patients with mild to moderate aortic dilatation, blood pressure should be aggressively controlled. Beta-blocker therapy may be of particular benefit to prevent slow disease progression, especially in patients with Marfan’s syndrome.\textsuperscript{69} However, there are no available data showing the benefit of prophylactic beta-blocker therapy to prevent aortic dilatation in patients with
Physiological changes of the heart in sporting activity

Physical activity is needed by healthy adults to improve and maintain health. It has a beneficial impact on personal fitness, reduces the risk for chronic diseases and disabilities and prevents unhealthy weight gain. In 1995, the American College of Sports Medicine and the Centres for Disease Control and Prevention published national guidelines on Physical Activity and Public Health which were recently updated. All healthy adults aged 18–65 years need moderate-intensity aerobic (endurance) physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on 3 days each week. Combinations of moderate- and vigorous-intensity activity can be performed. It is interesting to see how the new recommendation emphasizes that physical activity above the recommended minimum amount provides even greater health benefits. It is important to highlight the difference between recreational sports activity and competitive activity in which athletes undertake a hard training programme. A competitive athlete is one who participates in an organized team or individual sport, which requires systematic training and regular competition against others and places a high premium on athletic excellence and achievement. Competitive athletes have typically a strong inclination to push themselves to extremely high levels of exertion, often exceeding their native physical limits, sometimes for prolonged periods of time, regardless of other considerations. On the other hand, individuals participating in recreational sports engage in a range of exercise levels from modest to vigorous on either a regular or an inconsistent basis, which do not require systematic training or the pursuit of excellence, and are without the same pressure to excel against others that characterizes competitive sports. The lack of systematic athletic conditioning in the definition of recreational sports is expected to decrease the risk of cardiovascular events. In competitive athletes, physiological changes of the heart occur. Long-term athletic training is associated with cardiac morphologic changes, including increased left ventricular cavity dimension, wall thickness and mass, that are commonly described as ‘athlete’s heart’. Those changes represent a physiological adaptation to increase the efficiency of the heart and vascular system, in part in response to increases in volume and peripheral resistance with intense athletic
training. The duration and type of exercise appear to affect the degree and type of cardiac changes that an athlete may experience.

Two main types of sports can be differentiated: endurance or dynamic training (such as long-distance running and swimming) and strength and power training (such as sprinting or weightlifting). In athletes, long-term cardiovascular adaptation to dynamic training produces volume load on the LV through increased cardiac output and increased maximal oxygen uptake. Dynamic exercise (e.g. endurance running) is more likely to finally result in a predominantly increased LV chamber size with a proportional increase in wall mass.

Conversely, strength exercise causes largely a pressure load with little or no increase in oxygen uptake with the result of an increase in LV mass without increasing chamber size.73

A marked increase in aortic root size is recognized in elite strength-trained athletes,74 in all segments (the annulus, sinuses of Valsalva, supra-aortic ridge and ascending aorta), and is most evident when the duration of the training is taken into account.

The transient hypertension due to increased heart rate and cardiac output has been well documented in strength training and is exaggerated during the Valsalva manoeuvre. The blood pressure and cardiac output response during weightlifting can explain an increase in aortic root diameter through a structural reorganization of the aortic wall and consequent morphologic alteration of the aortic root. Aortic regurgitation represents the result of increased aortic root diameter when aortic valve cusps are unable to expand in area, and the degree of cusp overlap is reduced.75,76

An increased left and right ventricular (RV) and left atrial cavity size (and volume), associated with normal systolic and diastolic function, are well recognized in about 50% of trained athletes. Only limited data are available about the RV morphology and function in competitive sporting activity, because its complex shape makes it less suitable to the echocardiographic technique. However, recent studies show that the RV mass is increased in both dynamic and strength exercise, in similarity to the changes of the LV mass. In contrast with the parameter of ventricular mass, the parameters of RV volume seem to be increased in the anaerobic power athletes (strength training) but not in dynamic training (e.g. marathon runners).77,78 However, its significance remains to be determined and needs further clarification, and longitudinal studies on the morphological changes of the RV in professional athletes during training and during deconditioning later in their life need to be performed.

Left atrial remodelling is an additional physiological adaptation frequently present in highly trained athletes, especially in endurance sport, and is largely explained by associated LV cavity enlargement and
volume overload. There is no evidence showing that athlete’s heart
remodelling leads to a long-term disease progression, cardiovascular
disability or SCD.\textsuperscript{79,80} The cardiac remodelling in competitive athletes
is reversible with cessation of training.\textsuperscript{81,82}

Athletes usually have a normal cardiovascular examination. The
finding of pulse rates as low as 30–40 beats per minute is common,
and usually reflects increased vagal tone. Other distinctive findings,
such as a slightly displaced apical impulse, an atrial or ventricular
gallop and a systolic regurgitant murmur may also be noted.

Electrocardiographic abnormalities such as sinus bradycardia, sinus
arrhythmia, atrial or ventricular premature beats, AV blocks, voltage
criteria of right/left ventricular hypertrophy, ST elevations or T-wave
changes may be seen in up to 40\% of competitive athletes. They rep-
resent the result of electrophysiological remodelling associated with
physical training.\textsuperscript{83}

Because of the electrocardiographic and echocardiographic changes
seen in athlete’s heart, differentiating these physiological changes from
pathological conditions can be relatively difficult. For example, an
abnormal ECG or echocardiogram in an athlete may be difficult to dis-
tinguish from one seen in hypertrophic cardiomyopathy, dilated cardio-
myopathy and myocarditis. Although in most athletes the increase in
wall thickness or cavity size remains within normal limits, diagnostic
dilemmas arise when the remodelling adaptations mimic pathological
conditions. The differential diagnosis between physiological and patho-
logical heart adaptations to exercise has critical implications for dedi-
cated athletes (and their physicians) because cardiovascular disease
may represent the basis for disqualification from competitive sports to
reduce the risk of sudden death. Furthermore, some athletes with
cardiac disease judged to be at high risk may subsequently become can-
didates for an implantable defibrillator and prophylactic prevention of
sudden death.\textsuperscript{84}

**Effect of sport activity on BAV**

BAV does not normally represent an obstacle to obtain clearance to
practise sport after preparticipation screening. However, the impact of
regular training on patients with BAV and its natural course is not fully
clarified.\textsuperscript{71,85} Theoretically, the physiological stress of regular and
intense exercise on an abnormal aortic valve would favour its early
deterioration and dilatation of the ascending aorta. BAV accounts for
up to 50\% of cases of SCD in patients younger than 70.\textsuperscript{86,87}

Presenting symptoms of BAV may include fatigue, light-headedness,
dizziness, syncope and chest pain, especially if associated with
significant AS. On examination, a constant apical ejection click and systolic ejection murmur can be found.

Physiological adaptations of the heart have to be differentiated from pathological adaptations, and it is important to take into account the adverse consequences that regular training can have on subjects with BAV through different mechanisms. In athletes with BAV and associated aortic regurgitation, for example, a pre-existing pathological adaptation caused from a slightly elevated volume load due to the aortic regurgitation has to be taken into account, and can have negative effect when the athlete is engaged in regular training. In endurance exercise, for example, the development of eccentric hypertrophy and ventricular dilatation may have disastrous consequences on this pre-existing pathological adaptation. In athletes involved in mainly static or isometric exercise, the pressure overloads from/to the high systemic arterial pressure found in this type of exercise will cause a chronically elevated aortic wall tension, and consequently aortic dilatation and regurgitation. In the case of BAV with a pre-existing aortic dilation, intensive and competitive exercise carries high risk for aortic dissection or rupture, which is even higher in isometric exercise. In fact, during competition, often phases of high intensities occur, inducing relevant increases in arterial blood pressure which would facilitate an aortic rupture.

Those rare patients with BAVs associated with an anomalous origin of the coronary arteries have an increased risk of SCD during exercise. Although seldom recognized and often unappreciated, coronary artery aberrancies and anomalies (CAAA) account for up to 20% of cases of SCD in young athletes. Most types produce few, if any, symptoms, but some pose a much more substantial risk. Anatomical coronary abnormalities can imply a potential risk of coronary artery compression, especially following exercise. These consequences predispose to myocardial ischaemia, syncope or decompensated heart failure, and likely to account for most cases of SCD. Since CAAA are often asymptomatic and most patients have an unrevealing physical examination, their detection can be quite difficult. Although echocardiography, angiography, CT and MRI have all been used to visualize CAAA, their routine use for screening is not indicated. In patients in whom a CAAA has been identified, however, further participation in competitive sports should be prohibited, and a prompt evaluation and intervention by a cardiothoracic surgeon should be performed to reduce the risk of SCD.

Unlike acquired AS, congenital AS (seen frequently in BAV) is divided into mild (<20 mm Hg), moderate (21–49 mm Hg) and severe (>50 mm Hg), based on the peak instantaneous systolic pressure gradient measured by Doppler echocardiography. Current guidelines suggest
that patients with asymptomatic mild AS can participate in all competitive sports. Athletes with moderate AS can participate in low to moderate static or dynamic exercises if they: (1) have no LV strain and minimal LVH on ECG, (2) lack ischaemia or arrhythmias on exercise stress testing and (3) are asymptomatic. Athletes with AS and a history of syncope or severe disease should be prohibited from participation in competitive sports.88,89

Syncope can appear in a young athlete with a mild degree of AS. Nevertheless, symptoms such as angina and dyspnoea usually appear in a late stage of the disease. Occurrence of SCD is far more probable if one of these symptoms is present.90

Since there is a broad spectrum of phenotypic and genetic expression of BAV, patient subsets have varying levels of risk related to sport activity, and therefore a general judgement in athletes with BAVs on their ability for competitive sports is not possible; each subject should have a dedicated and accurate assessment.

**Recommendation in athletes and in subjects with BAV**

The importance attributed to preparticipation screening in athletes is predicated on the likelihood that intense athletic training and competition act as a trigger to increase the risk for SCD or disease progression in susceptible athletes with underlying heart disease.91 Sudden death in athletes shows a clear gender predilection with striking male predominance (male-to-female ratio up to 10:1).92 The higher participation rate of male compared with female athletes in competitive sports, and the more intensive training load and level of athletic achievement of males, contribute significantly to the predominance of fatal events in male athletes. More recently, male gender was reported to be, in itself, a risk factor for sports-related sudden death, most likely as a consequence of the greater prevalence and/or phenotypic expression in young males of cardiac diseases at risk of arrhythmic cardiac arrest, such as cardiomyopathies and premature coronary artery disease.93 In about 8% of athletes up to the age of 40 years, SCD during sports is caused by AS and ruptured aortic aneurysms,94 conditions commonly associated with BAV.

In 2004–2005, the European Society of Cardiology (ESC) and the International Olympic Committee (IOC) presented initiatives addressing the methods for cardiovascular screening in large populations of young, trained athletes. These proposals advocate combining noninvasive testing (i.e. a 12-lead ECG) with standard history taking and physical examination.95,96 The European proposal is based on the unique 25-year Italian experience with a state-subsidized national programme.
in which all individuals 12–35 years of age participating in organized team or individual sports are mandated to obtain annual medical clearance based on history, physical examination and ECG by accredited sports medicine physicians. In fact, Italian investigators attribute a decline in the rate of SCD during sports to their long-standing systematic national preparticipation screening programme, which routinely includes a 12-lead ECG. They report an almost 90% decline in the annual incidence of SCD in competitive athletes (largely owing to reduced mortality from cardiomyopathy) from the Veneto region of north-eastern Italy. However, the recommendations of the ESC and IOC have triggered a new and complex debate related to justification of methods for preparticipation screening, including use of noninvasive tests such as the ECG. Although the ESC proposal is innovative and based on the generally favourable long-term experience in Italy, it cannot easily be translated into the other medical systems and environments due to practical, economical and legal issues. In particular, the absolute cost for a national preparticipation screening programme carried out on an annual basis with routine ECG would be enormous. For example, the present American Heart Association recommendations do not include the 12-lead ECG as part of routine preparticipation screening. The future for the prevention of sports-related fatalities related to congenital cardiac disease including BAV lies in the continuing efforts to better understand the substrates and mechanisms underlying sudden death in athletes, and to design more specific and efficient screening strategies. An international registry collecting all fatal events in young competitive athletes is warranted to evaluate how genetic and environmental factors interplay and influence the distribution of cardiovascular causes of sudden death in different countries. Echocardiography is a noninvasive and widely available tool with the potential to increase the screening accuracy for the detection of diseases carrying a risk of sudden death in an athlete. Cost-effectiveness of screening modalities based on systematic echocardiographic examination, either complete or limited, remains to be prospectively assessed by studies on large athletic populations.

The presence of BAV usually is not a limit to the eligibility to practise sport, especially in young athletes with an isolated, ‘near-normal’ BAV. However, the early identification of BAV will help in following up the modifications and perhaps preventing the potential adverse consequences of training. Echocardiography is sensitive and reliable for detecting aortic lesions and congenital cardiac conditions such as BAV. Even though currently not part of preparticipation screening, it should be performed at least once during an athlete’s sporting life. In particular, in athletes with BAV, since rapid valve deterioration and progressive, severe aortic dilation have been documented also in some subjects...
with a ‘near-normal’ valve, full cardiological examinations (comprising at least 2DE, ECG stress test, and, in selected subjects, blood pressure monitoring and 24-h Holter ECG monitoring) are required every year to continue sports. In those athletes who have developed valvular stenosis and/or incompetence, the eligibility for participation in sports must be individualized, depending on age, severity of lesions and on the type of sport.

Scharhag et al. reported an example of evaluation of the ability to participate in competitive sports of two soccer players with BAV.98 One of them presented with left ventricular eccentric hypertrophy and mild aortic regurgitation with good systolic and diastolic function and was allowed to participate in competitive soccer. Conversely, the other soccer player had moderate regurgitation and a significant dilation of the ascending aorta; he was disqualified from competitive sports due to the elevated risk of rupture and allowed only to exercise in recreational sports with low intensities.

When a definitive diagnosis of heart disease such as BAV is made, the consensus panel guidelines of Bethesda Conference No. 36 may be considered to formulate recommendations for either continued participation or disqualification (temporary or permanent) from competitive sports. For those young athletes with genetic heart disease who are disqualified from competitive sports, recommendations for recreational athletic activities and normal lifestyle are available.96,97

**Conclusion**

BAV affects 1–2% of the population. Subjects with normally functioning BAVs (i.e. no stenosis or insufficiency) do not require activity restrictions. They may participate in organized competitive sports activities. It is however important to identify early athletes with BAV to help in following up the modifications and perhaps preventing the potential adverse consequences of training through complete cardiological examinations, which should include echocardiography at least every year. Athletes with BAV who develop valve insufficiency or stenosis may require restrictions from strenuous competitive sports. In particular, subjects with aortic valve insufficiency and aortic dilatation should avoid strenuous sporting activity, given the increased risk of aortic rupture. A general judgement in athletes with BAV on their ability for competitive sports is not possible, and therefore the eligibility for participation and the ability to continue to practise competitive sports must be individualized, depending on age, severity of lesions and on type of sport though accurate assessment and regular follow-up. The Guidelines of Bethesda Conference No. 36 offer recommendations...
for either continued participation or disqualification (temporary or permanent) and recommendations for recreational athletic activities and normal lifestyle for those athletes who are disqualified from competitive sports. Finally, further studies are needed to better understand the genetics of BAV\textsuperscript{99,100} and the impact of regular training in patients with BAV and its natural course,\textsuperscript{99,101} in particular in competitive athletes.

References


96 Maron BJ, Thompson PD, Puffer JC et al. (1996) Cardiovascular preparticipation screening of competitive athletes: a statement for Health Professionals from the Sudden Death Committee (Clinical Cardiology) and Congenital Cardiac Defects Committee (Cardiovascular Disease in the Young), American Heart Association. *Circulation*, 94, 850–856.