Calcific aortic valve disease: outflow obstruction is the end stage of a systemic disease process

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Over the past decade, a body of evidence has accumulated demonstrating that calcific aortic valve disease (CAVD) is prevalent in older adults and that the presence of calcific valve disease is associated with adverse clinical outcomes, even in the absence of left ventricular (LV) outflow tract obstruction. Stritzke et al. report for the KORA/MONICA study that degenerative (or calcific) aortic valve disease was present in 28% of a population-based sample of >900 adults with a mean age of ~50 years.1 This finding parallels previous population-based studies such as the Helsinki Aging Study with a prevalence of aortic sclerosis of 21% in adults aged 55–71 years and the Cardiovascular Health Study (CHS) with aortic sclerosis in 26% of adults age 65 years or older.3

Further, in the KORA/MONICA study, the presence of calcific valve disease was associated with age, active smoking, and elevated total cholesterol on a baseline evaluation carried out 10 years before the echocardiographic study.3 These findings support the concept that patients ‘at risk’ of CAVD can be identified based on these associated clinical factors. In addition to age, smoking, and hypercholesterolaemia, previous studies have convincingly shown that the presence of calcific valve disease is associated with hypertension, diabetes, and the metabolic syndrome.3,4 Recent data from the Multi-Ethnic Study of Atherosclerosis (MESA) study indicated that the total cholesterol to HDL ratio is associated with an increased risk of CAVD across the entire age range (45–84 years), whereas LDL is associated with increased risk only in those <65 years of age.5

‘At risk’ patients also include those with a congenitally bicuspid aortic valve, which accounts for >50% of aortic valve replacements, and may explain the male predominance of CAVD.6 Genetic factors may modulate the risk of calcific valve disease, with clustering of cases suggesting a familial component7 and case-control studies suggesting association with polymorphisms in the vitamin D receptor, oestrogen receptor, interleukin-10, and apolipoprotein E4 allele, among others.8

We also know that the presence of CAVD without obstruction to LV outflow, e.g. aortic sclerosis, is associated with adverse clinical outcomes. In the CHS study, aortic sclerosis was associated with an ~50% increased risk of cardiovascular death and myocardial infarction, even after correction for known coronary disease and associated clinical factors.9 In the LIFE hypertension study, the presence of aortic sclerosis was associated with a doubling of cardiovascular events, both in those with and without known coronary artery disease.10 In the ARIC study of 2279 African-American adults, the strongest multivariate predictor of myocardial infarction and cardiovascular death was aortic sclerosis, with less strong predictors including blood pressure, smoking, and markers of systemic inflammation.11 The consistent findings of these diverse studies suggest that CAVD is a marker of systemic disease and that these patients are at increased risk of adverse clinical events long before there is mechanical obstruction to ventricular ejection.

In that light, it is intriguing that the KORA/MONICA study found differences in LV geometry and diastolic function between subjects with and without calcific valve disease, even though these patients did not have significant outflow obstruction. Compared with subjects with a normal aortic valve, those with calcific valve disease had a higher relative wall thickness and LV mass index, as well as a higher ratio of early diastolic transmitral to tissue Doppler velocity, suggesting elevated LV filling pressures. Further, over the 10 year interval, relative wall thickness increased more in those with calcific valve disease than in those with a normal valve. The possibility of subtle changes in LV afterload related to early valve disease cannot be ignored, although the reported haemodynamics are consistent with aortic sclerosis, not valve obstruction. If these findings are confirmed in future studies, they suggest that adverse changes in LV geometry accompany CAVD, rather than simply reflecting the ventricular response to chronic pressure overload.12
Our understanding of the natural history of aortic stenosis has evolved from the view that valve calcification is an inevitable consequence of ageing that only has clinical significance once symptoms due to valve obstruction occur, to the view that CAVD is the result of an active, potentially modifiable pathological process, with a spectrum of disease ranging from aortic sclerosis to severe symptomatic aortic stenosis. We can further refine this conceptual framework (Figure 1) to include several progressive stages of disease.

The first stage is the patient ‘at risk’ of calcific valve disease. This stage includes all patients with a bicuspid aortic valve as well as those with clinical factors associated with calcific valve disease. We can all agree that patients at risk of calcific valve disease should receive appropriate preventative therapy for hypertension, hypercholesterolaemia, and diabetes, and should be encouraged to stop smoking, exercise regularly, and eat a healthy diet. Of course, these recommendations apply to all adults; whether more aggressive therapy of lipid levels or other clinical factors is justified in those recommendations apply to all adults; whether more aggressive therapy of lipid levels or other clinical factors is justified in those with clinical factors associated with calcific valve disease.

Once CAVD (e.g. aortic sclerosis) is detectable by echocardiography, or other imaging procedures, the patient does have an increased risk of adverse cardiovascular events. Again, appropriate risk factor evaluation and reduction is essential in these patients.

Obviously, removing a sclerotic valve would not decrease the risk of adverse cardiovascular events. Although aortic sclerosis is prevalent in older adults, only a small subset (<10%) of these patients appear to develop aortic stenosis with obstruction to LV outflow. Factors predicting a transition from aortic sclerosis to stenosis have not yet been fully elucidated; in the CHS study, progression was predicted by age and male gender, but not by C-reactive protein levels.

In those patients who convert from aortic sclerosis to aortic stenosis, progressive valve obstruction is typical, with a gradual increase in transaortic velocity and gradient and progressive decrease in valve area. As disease severity increases from mild to moderate to severe, most patients remain asymptomatic, despite ‘severe’ obstruction, for a variable period of time. However, even mild symptoms, most often dyspnoea on exertion or decreased exercise tolerance, herald a marked change in the disease course with a high risk of heart failure, angina, and sudden death. Aortic valve replacement at the onset of early symptoms prevents these outcomes, with the risk of surgery almost always far less than the risk of medical therapy alone. Patients who initially present with severe symptomatic aortic stenosis have a very poor prognosis; prompt aortic valve replacement is recommended in this situation.

The challenge now is to identify factors that predict transition from an ‘at risk’ patient to a patient with aortic sclerosis and to identify which aortic sclerosis patients will go on to progressive aortic stenosis. Hopefully, these data will provide insights into potential approaches to prevention of CAVD, early in the disease course.

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References
An unusual presentation of a tumour of the heart

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A 62-year-old woman with a long-standing history of dyspnoea on exertion (NYHA class II) presented with worsening dyspnoea (NYHA class III) since 2 weeks. Clinical examination revealed a right parasternal heave, an elevated jugular venous pulse, bilateral ankle oedema, and a systolic ejection murmur, most pronounced at the upper left sternal edge, consistent with cor pulmonale. Electrocardiogram showed sinus rhythm with left posterior fascicular block, inverted T waves over the anterior and inferior wall and a rightward shift of the QRS axis. Cardiac enzymes and D-dimers were normal. Transthoracic and transoesophageal revealed a normal left ventricular function, a moderately dilated right ventricle, a maximal pressure gradient between the right atrium and right ventricle of 65 mmHg, and a gradient over the right ventricular outflow tract (RVOT) of 50 mmHg. Cardiac CT and MRI revealed a mass (14 x 14 x 16 mm) in the RVOT, attached to the interventricular septum. Cardiac surgery showed a sessile structure in the RVOT prolapsing through the thickened and retracted pulmonary valve. The tumour and pulmonary valve were resected, the defect was closed with a pericardial patch, and the valve replaced with a stentless bioprosthesis. Histologically, the lesion was characterized by spindle cell proliferation with a high mitotic and apoptotic index and marked MDM2 (murine double minute-2) immunoreactivity, whereas epithelial, muscle, endothelial, and melanocytic markers were negative. Dual-colour FISH analysis, using loci-specific probes, confirmed high-level expression of PDGFRA (platelet-derived growth factor receptor alpha) and MDM2 genes in tumour cells, a cytogenetic hallmark of intimal sarcoma.

Panel A. Computed tomography showing the tumour in the right ventricular outflow tract (arrow).
Panel B. Peri-operative image revealing the tumour after incision of the pulmonary artery.
Panel C. Double-colour, interphase FISH analysis on paraffin sections from tumour tissue using a co-hybridization of digoxigenin- or biotin-differentially labelled BAC’s DNA RP11-231C18 (hybridizing to PDGFRA/4q12) and RP11-1064P9 (hybridizing to MDM2/12q15) probes (both from Research Genetics, Huntsville, AL, USA). The presence of multiple red and green hybridization signals indicates PDGFRA and MDM2 amplification.
Panel D. Atypical spindle cell proliferation with high mitotic activity (arrows). Haematoxylin and eosin stain, × 400.