Calcification of bicuspid aortic valves

C M Otto

Calcific valve disease represents a disease spectrum that ranges from mild irregular valve thickening (or sclerosis) to severe valve obstruction

Over the past decade, our concept of the pathogenesis of calcific aortic valve disease has undergone a major transformation. We now recognise that calcific valve disease is the end stage of an active disease process and is not caused by “wear and tear” of the valve tissue. Immunohistochemical studies of trileaflet aortic valves with varying degrees of valve stenosis have demonstrated the presence of inflammation, lipid infiltration, and production of proteins that mediate tissue calcification. These studies have established the presence of T lymphocytes and macrophages both in the early stages of this disease process and in valves with severe stenosis removed at surgery. The inflammatory cell infiltrate is located in areas of subendothelial lipid infiltration on the aortic side of the valve leaflet with extension into the adjacent fibrosa, the dense collagenous layer of the leaflet that provides tensile strength. The focal presence of neutral lipid can be demonstrated with oil-red-O staining with specific immunohistochemical markers being consistent with infiltration of low density lipoprotein and lipoprotein Lp(a). In addition, there is evidence of lipid oxidation, as is seen in atherosclerotic lesions. The interrelations between lipid infiltration, oxidation, and inflammation appear to be similar to the process of atherosclerosis. In addition, several proteins associated with tissue calcification have been localised in sclerotic and stenotic trileaflet aortic valves. In vitro hybridisation has shown that osteopontin is produced by a subset of lesion macrophages, while bone morphogenetic proteins 2 and 4 are expressed by myofibroblasts, in areas adjacent to lymphocyte infiltration. Other evidence of an active disease process in calcific aortic valve disease includes up-regulation of adhesion molecules, expression of matrix metalloproteinase, and production of the large extracellular matrix glycoprotein, tenasin-C.

AORTIC STENOSIS

This disease process eventually leads to increased leaflet thickness and stiffness, resulting in left ventricular outflow obstruction and the clinical presentation of the patient with valvar aortic stenosis. In patients with an anatomically normal trileaflet aortic valve, this process occurs in only a subset of patients with symptoms typically occurring at age 70–80 years. Clinical factors associated with atherosclerosis are also associated with calcific aortic valve disease, including age, sex, hypertension, raised serum cholesterol concentration, smoking, and diabetes. However, the specific factors that initiate this disease process have not been well defined. By analogy with atherosclerosis, our underlying assumption is that endothelial disruption occurs, possibly caused by low shear stress on the aortic side of the valve. Low shear stress might explain why the calcific process often is seen first and most severely on the non-coronary cusp. Mechanical or tensile stress on the valve leaflets also has been proposed as an important factor in initiation of the disease process. The major evidence for this hypothesis is that calcific disease occurs at an earlier age in patients with a bicuspid valve, typically with symptoms occurring at 50–60 years of age. Also, in contrast to the small number of patients with a trileaflet valve that develop severe stenosis, nearly all patients with a bicuspid valve will develop significant outflow tract obstruction. Because the stress–strain relations of a bicuspid valve are abnormal, this higher tensile stress may contribute to earlier initiation and more rapid progression of disease. However, the disease process at the tissue level in bicuspid aortic valves has not been specifically examined, until now.

In this issue of Heart, the study by Wallby and colleagues is the first to compare the disease process at the tissue level in bicuspid and in trileaflet valves in patients with severe stenosis undergoing aortic valve replacement. They observed that T lymphocyte infiltration was present in both bicuspid and trileaflet aortic valves, with a similar pattern and extent of T lymphocytes in the stenotic valve leaflets. Their observations confirm the hypothesis that the disease process is the same in trileaflet and bicuspid valves, again suggesting the differences in clinical presentation are related to the mechanical characteristics of the valve. Although this study examined only valves removed at surgery, extrapolating from previous studies on trileaflet valves, severe calcific valve disease represents the extreme end of a disease spectrum that ranges from mild irregular valve thickening (or sclerosis) to severe valve obstruction.

CLINICAL IMPLICATIONS

These findings have important clinical implications. A bicuspid aortic valve is present in 1–2% of the population and most of these patients will eventually develop stenosis, requiring valve surgery. A minority of patients develop aortic regurgitation as a young adult but the majority have progressive valve stenosis, with only about 1% maintaining normal valve function over their
Anomalous origin of left anterior descending and circumflex coronary artery from two separate ostia in the right aortic sinus

A 63-year-old woman presented with atypical chest pain. A 12-lead ECG showed a complete left bundle branch block; the echocardiogram was not diagnostic. At coronary angiography the left coronary ostium was not observed. Aortography showed the left anterior descending (LAD) artery and the circumflex (CX) artery each originating from a separate ostium in the right aortic sinus. The right coronary artery (RCA) had a normal independent origin. The three vessels were then selectively engaged (the LAD with an internal mammary catheter, the CX with a multipurpose catheter, the RCA with a right Judkins catheter), resulting in the patient being free from atherosclerotic disease. Subsequent stress myocardial perfusion imaging was negative for inducible ischaemia. The patient had an uneventful two-year follow-up.

The independent origin of both the LAD and CX from two separate ostia in the right aortic sinus is an exceedingly rare anomaly. The hazard of this coronary anomaly depends on the LAD course. An LAD course between the aorta and the pulmonary artery is potentially responsible for myocardial ischaemia and sudden death, while an LAD course anterior to the right ventricle (like the present case), or behind the aorta, is at low risk of adverse events. In this regard, the scintigraphic findings obtained in our patient confirmed the benign prognosis associated with an anterior free wall course of the LAD.

REFERENCES

Calcification of bicuspid aortic valves

C M Otto

Heart 2002 88: 321-322
doi: 10.1136/heart.88.4.321

Updated information and services can be found at:
http://heart.bmj.com/content/88/4/321

These include:

References
This article cites 16 articles, 7 of which you can access for free at:
http://heart.bmj.com/content/88/4/321#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Drugs: cardiovascular system (8842)
Aortic valve disease (415)
Hypertension (3006)
Diabetes (842)
Tobacco use (635)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/