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Low-density lipoprotein and aortic stenosis

Nalini M Rajamannan

With the decline of acute rheumatic fever, calcific aortic stenosis has become the most common indication for surgical valve replacement in the USA. In the past decade, Stewart and Otto[12] have described the risk factors for calcific aortic stenosis, including lipids, hypertension, male gender, renal failure, and diabetes. Furthermore, these risk factors are parallel to those described for vascular atherosclerosis. For years this disease process was thought to be due to a degenerative phenomenon by which calcium attaches to the surface of the aortic valve leaflet. Initial models of experimental hypercholesterolaemia have demonstrated that initiating events in aortic valve disease are similar to those of vascular atherosclerosis. Over the past decade, there have been a growing number of studies evaluating human aortic valve specimens defining the cellular pathways important in this disease process. Studies from two independent laboratories, Mohler *et al*[3] and Rajamannan *et al*,[4] have shown that the presence of calcification in the aortic valve is secondary to a bone formation process present in the aortic valve. The clinical importance of calcification was first described by Rosenhek *et al*,[5] who defined a poor prognostic implication for patients who had heavily calcified aortic valves.

The study by Côté *et al*[6] in this issue ***(see article on page 1175)*** demonstrates an association between circulating oxidised low-density lipoprotein (LDL) and fibrocalcific remodelling of the aortic valve in aortic stenosis. The investigators performed an extensive and sophisticated analysis of the development of fibrocalcific aortic stenosis and the correlation of the level of elevated circulating ox-LDL with the valves that had a high remodelling score. The higher valve remodelling scores were also associated with higher valve calcium content. Circulating ox-LDL level also correlated significantly with the following proteins including apoB, LDL-C, triglyceride and apoA-1.

The importance of lipids in the development of vascular atherosclerosis has been studied in experimental models for over 100 years. Cholesterol-rich LDL also has a critical role in the onset and further progression of the atherosclerotic lesion via an inactivation of endothelial nitric oxide synthase (eNOS),[7–10] contributing to an abnormal oxidation state within the vessel. If cholesterol is important in the initiating step in the development of valvular heart disease, this provides evidence that endothelial dysfunction is important in the initiation of this disease process. Studies by our group[11] and Charest *et al*[12] have also shown that endothelial nitric oxide enzyme activity plays a role in the early valve lesions. Elevated cholesterol decreases the enzyme expression and induces early mineralisation in the aortic valve.[11] Therefore, these early studies provide the evidence that aortic valve disease has a similar initiating mechanism of oxidative stress to that found in vascular atherosclerosis. The study by Weis *et al*[13] demonstrates the first evidence that elevated cholesterol in a genetic mouse model induces severe aortic stenosis by echocardiographic measurements and haemodynamic catheterisation confirmation. These investigators tested a genetic knockout mouse which lacks the receptor for the low-density lipoprotein receptor and expresses only

Correspondence to: Nalini M Rajamannan, MD, Northwestern University Feinberg School of Medicine, 300 E Chicago, Tarry 12-717, Chicago, Illinois 60611, USA; n-rajamannan@northwestern.edu.

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the receptor for the human apoB100 ($LDLr^{-/-}apoB^{100/100}$) in an ageing genetic mouse model. This study also confirmed mineralisation and abnormal oxidative stress in the calcified stenotic valves as compared with controls. This study provides further evidence to the growing field of valvular biology that lipids play a critical role in the development of valvular heart disease as well as vascular heart disease.

Surgical pathological studies in humans have also demonstrated the presence of LDL and atherosclerosis in calcified valves, demonstrating similarities between the genesis of valvular and vascular disease and suggesting a common cellular mechanism.[1415] Patients who have the diagnosis of familial hypercholesterolaemia develop aggressive peripheral vascular disease and coronary artery disease, as well as aortic valve lesions which calcify with age. The first index case of atherosclerotic aortic valve disease in this patient population demonstrated that the development of early atherosclerosis occurs in the aortic valve. This was shown in a patient with familial hypercholesterolaemia with the low density lipoprotein receptor mutation.[16] The atherosclerotic lesion develops along the aortic surface of the aortic valve and in the lumen of the left circumflex artery.[16] This background has provided the experimental evidence that developing models of experimental atherosclerosis provide the premise to identify the cellular pathways important in the development of aortic stenosis.

This study by Côté *et al* provides the first quantitative evidence correlating oxidised LDL and the level of calcification in human aortic valves removed at the time of surgical valve replacement. If aortic valve disease has an active biology is there medical therapy for calcific aortic stenosis? The first landmark randomised prospective trial published in this field, SALTIRE,[17] demonstrated that high-dose atorvastatin does not slow the progression of this disease. SALTIRE initiated atorvastatin in patients who had more advanced aortic stenosis as defined by the mean aortic valve area 1.03 cm^2, with heavy burden of calcification as measured by aortic valve calcium scores. The investigators in this study acknowledged [18] that the timing of therapy for aortic valve stenosis may play the key role in the future treatment of this disease. The important issue may be treating this disease earlier in the disease process to slow the progression of bone formation in the aortic valve. In the future, randomised trials for this disease will provide important information similar to the discoveries regarding vascular atherosclerosis in terms of medications and timing of the disease. The more recent study by Moura *et al*,[19] RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium), demonstrated, in a trial designed to test the hypothesis that statin therapy slows the progression in moderate to severe aortic stenosis in patients with high LDL levels, that statins can slow the progression of aortic stenosis. In the 21st century, there have been a growing number of epidemiological and experimental studies which have confirmed that this disease has an actual biology which is similar to the initiating events found in vascular atherosclerosis. Furthermore, this disease process is ready for an aggressive change in the paradigm towards considering this disease as an active biological process. Côté *et al* have provided further confirmatory evidence that medical therapy for aortic stenosis will be a feasible approach for this disease process.

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