Calcific Aortic Stenosis
A Disease Ready for Prime Time

Nalini M. Rajamannan, MD

Calcific aortic stenosis is the number 1 cause for surgical valve replacement in the United States and Europe. In 2006, surgical valve replacement still remains the number 1 indication for the treatment of this disease process, as defined by the American College of Cardiology/American Heart Association guidelines for valvular heart disease by Bonow et al. This standard of care for patients with severe symptomatic aortic stenosis requiring surgical valve replacement was defined in 1968 by Ross and Braunwald as the main therapy for this disease. For years, this disease has been described as a passive process that develops secondary to serum calcium attaching to the valve leaflet surface to cause nodule formation. Therefore, surgical replacement of the valve is the obvious approach toward relieving outflow obstruction in these patients. Until recently, the lack of experimental models in this field has limited our understanding of the disease.

In the middle of the last century, the field of cardiology was in a similar position with our understanding of coronary vascular atherosclerosis. This was summarized in 1942 by Dr James B. Herrick, who wrote a short history of cardiology. In the chapter on coronary atherosclerosis, he predicted the future of therapeutic approaches for vascular atherosclerosis. In this textbook, he wrote of heart disease: “This is the story of a bad disease....The outlook for dread angina it thought to be more favorable than it was first thought...though the cause...has not been discovered, and vascular disease may never be warded off or cured, research may unearth secrets by which premature or old age may be post-poned.” In 2006, we are in a unique position to predict that therapeutic approaches for calcific aortic stenosis will be possible with the emergence of models that recapitulate this disease process.

After the study by Ross and Braunwald and the surgical advances in the field of aortic valve surgery, the next landmark study in the field of valvular heart disease was by Stewart et al, which defined the independent risk factors for calcific aortic stenosis, including hypertension, elevated low-density lipoprotein (LDL), male gender, smoking, and diabetes. These findings have been confirmed in many other retrospective databases across the country. These studies provide the basis that atherosclerotic risk factors play a role in the development of this disease process.

The study by Weiss et al in this issue of Circulation demonstrates the first experimental evidence that elevated cholesterol in a genetic mouse model causes severe aortic stenosis by echocardiographic measurements and hemodynamic catheterization studies. The study tested the genetic knockout mouse, which lacks the gene for the LDL receptor and expresses only the receptor for the human apolipoprotein B-100 (LDLR-ApoB<sup>−/−</sup>) in an aging genetic mouse model. This genotype is known to be associated with a human atherogenic lipoprotein profile and with the development of atherosclerotic lesions involving 15% to 20% of the aortic intimal surface in the absence of any specific diet. This model induces mineralization, as confirmed by Von Kossa staining, which stains for calcium and phosphate mineral. The investigators also measured evidence of oxidative stress by measuring superoxide (oxymethidium fluorescence) and found an increase in superoxide activity 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.

The concept that degenerative aortic valve disease has an active biology has been challenged by a growing number of investigators. There are a number of experimental models testing the effects of a cholesterol diet on the aortic valve. Sarphie demonstrated the first histochemical effects of cholesterol on the development of valvular heart disease. Drolet et al have also shown that a high cholesterol diet and vitamin D treatment can induce an aortic valve that is stenotic and atherosclerotic. Experimentally, our group has also shown in an in vivo model of hypercholesterolemia that the aortic valve develops atherosclerosis, which calcifies over time secondary to the expression of specific bone matrix markers including osteopontin and Cbfal, the key transcriptional regulator of bone formation. O’Brien et al and Olsson et al have confirmed the presence of lipoproteins in human diseased aortic valves. These animal models, the confirmation of lipids in human valves, and the study by Weiss et al are the first to show that hyperlipidemia by means of a diet or a genetic mouse approach will induce an atherosclerotic valve that mineralizes and stenosis over time.

If cholesterol is important in the initiating step in the development of valvular heart disease, then the presence of superoxide as described by Weiss et al provides evidence that endothelial dysfunction is important in the initiation of this disease process. Studies by our group and Charest et al 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 mineralization in the aortic valve. Therefore, these early studies provide the evidence that aortic valve disease has similar initiating mechanism of oxidative stress that is found in vascular atherosclerosis.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Cardiology and Department of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, Ill.

Correspondence to Nalini M. Rajamannan, MD, Valve Director, Bluhm Cardiovascular Institute, Northwestern University, Feinberg School of Medicine, 300 East Chicago Ave, Tower 12–717, Chicago, IL 60611. E-mail n-rajamannan@northwestern.edu

© 2006 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.106.657759

2007
The next critical step toward understanding of aortic valve calcification is to determine the signaling mechanisms involved in the development of this disease. The studies from Mohler et al\textsuperscript{20} and our group\textsuperscript{21} have shown that the aortic valve calcifies secondary to a bone phenotype. Recent studies from our group\textsuperscript{22} and Shao et al\textsuperscript{23} have demonstrated that the mechanism by which calcification develops is activation of the LDL receptor 5 (Lrp5)/Wnt pathway in the vascular and valvular interstitial cells. Our group has also confirmed the upregulation of the Lrp5 receptor in human disease valves from surgical valve repair and replacement. This study demonstrated an incremental increase in the Lrp5 receptor expression in the degenerative mitral valves as compared with the calcified aortic valves.\textsuperscript{23a} Therefore, these studies provide further evidence that the underlying mechanism of degenerative mitral regurgitation and aortic valve stenosis in humans is secondary to the activation of the Lrp5 receptor in the mesenchymal myofibroblast cells present in the cardiac valves and that elevated cholesterol induces the valve to undergo a phenotypic switch to bone-forming cells within the valve leaflets. These studies confirm that the presence of bone formation is the phenotypic expression of calcification in the aortic valve.\textsuperscript{21} Rosenhek et al\textsuperscript{24} have shown clinically that an increased burden of calcification is a marker of poor prognosis in the outcome of patients with severe asymptomatic aortic stenosis. Therefore, more calcification correlates with an increase in bone formation in these valves and a worse outcome for these patients. The Figure demonstrates the mechanism for the development of this disease as derived from the findings of all of these cumulative studies. In the presence of risk factors such as elevated cholesterol, the cells in the valve leaflet initiate the osteogenic gene program. Over time, the valve leaflet synthesizes bone matrix, which eventually calcifies and forms bone. Clinically, progressive stenosis develops in the valve leaflet, and the patient has eventual symptoms of shortness of breath, lightheadedness, and chest pain. If the aortic valve has an actual biology that is initiated by elevated cholesterol, then in the future, medical therapy such as statins or angiotensin-converting enzyme inhibitors may slow the progression of this disease.

If aortic valve disease has an active biology, is there medical therapy for calcific aortic stenosis? The first landmark randomized, prospective trial published in this field, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE),\textsuperscript{25} 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 of 1.03 cm², with heavy burden of calcification as measured by aortic valve calcium scores. Newby et al. recently acknowledged 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 its process to slow the progression of bone formation in the aortic valve. In the future, randomized trials for this disease will provide important information similar to the discoveries of vascular atherosclerosis in terms of medications and timing of the disease. There are currently a growing number of trials in progress to test the effects of statins in aortic valve disease, including RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium [Porto, Portugal]), ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin [Canada]), SEAS (Simvastatin and the Ezetimibe in Aortic Stenosis) [Europe], and STOP-AS (Stop Aortic Stenosis [Cleveland Clinic, Cleveland, Ohio]). In 2006, a growing number of epidemiological and experimental studies have confirmed that this disease has an actual biology that is similar to that of vascular atherosclerosis. Furthermore, this disease process is ready for an aggressive change from the paradigm of considering this disease as an atherosclerotic process. Early detection of this sclerotic lesion may provide an inexpensive method of detecting atherosclerosis with a stethoscope. Early detection of this sclerotic lesion may provide an inexpensive method of detecting atherosclerosis with a stethoscope and opens another avenue for the possibility of treating the atherosclerotic process earlier and slowing the progression of aortic stenosis.

Disclosures
Dr. Rajamannan is an inventor on a patent owned by the Mayo Clinic entitled: “Method for Slowing Heart Valve Degeneration.” Dr. Rajamannan does not receive any royalties from this patent.

References

Key Words: Editorials • aging • atherosclerosis • cholesterol • pathology • stenosis • valves
Calcific Aortic Stenosis: A Disease Ready for Prime Time
Nalini M. Rajamannan

doi: 10.1161/CIRCULATIONAHA.106.657759
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/19/2007

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/