

STATE-OF-THE-ART PAPER

Insights Into Degenerative Aortic Valve Disease

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Despite the dramatic decline of rheumatic heart disease over the past 5 decades, there has not been a concordant decline in the prevalence of valvular heart disease. Degenerative aortic valve disease (DAVD) has become the most common cause of valvular heart disease in the Western world, causing significant morbidity and mortality. No longer considered a benign consequence of aging, valve calcification is the result of an active process that, much like atherosclerotic vascular disease, is preceded by basement membrane disruption, inflammatory cell infiltration, and lipid deposition and is associated with diabetes, hypercholesterolemia, hypertension, and tobacco use. These realizations, in addition to pathological insights gained from emerging imaging modalities, have led to the exploration of a variety of therapeutic interventions to delay or prevent the progression of DAVD. Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, angiotensin-converting enzyme, and matrix metalloproteinase have all been studied as potential disease modifiers. Moreover, tissue engineering, aided by emerging stem cell technology, holds immense potential for the treatment of valvular heart disease as adjuncts to surgical interventions. Here we review the epidemiology and pathophysiology of DAVD, in addition to highlighting emerging therapeutic interventions for this growing problem. (J Am Coll Cardiol 2007;50:1205-13)

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The prevalence of valvular heart disease in the adult U. S. population at the beginning of the twenty-first century has been estimated at more than 5 million (1). Degenerative valve disease, now the most common etiology of valvular heart disease in industrialized nations (2,3), is an emerging health problem with broad consequences (Fig. 1). Aortic valve disease is the third most common cause of cardiovascular disease, and the prevalence of degenerative aortic valve disease (DAVD) rises as life expectancy increases. An estimated 95,000 valve procedures are performed each year in the U. S., and aortic valve disease is responsible for more than 25,000 annual deaths (4). In the Euro Heart Survey, aortic stenosis was the most frequent etiology of single native left-sided valve disease and was predominantly degenerative in origin (Fig. 2) (3,5).

Characterized by progressive dystrophic calcification of the valve cusps (6), the early stages of DAVD are similar to the active inflammatory process of atherosclerosis including basement membrane disruption, inflammatory cell infiltration, lipid deposition and calcification (7,8). The clinical risk factors associated with the genesis and progression of atherosclerosis, including age, gender, diabetes, low-density lipoprotein (LDL) cholesterol, hypertension, and smoking have been implicated in the development of DAVD (9,10). Despite multiple common risk factors, a discrepancy in

coexisting prevalence exists between calcific aortic stenosis and coronary artery disease. Only one-half of patients with severe calcific aortic stenosis have significant coronary artery disease, and most patients with coronary artery disease do not have aortic stenosis (11). This discrepancy highlights the fact that despite the shared risk factors between calcific aortic valve disease and coronary artery disease, additional factors contribute to the development of DAVD.

Pathophysiologic Insights on DAVD

Endothelial function. Unique structural and functional components of valvular endothelium contribute to the degenerative processes underlying valvular calcification (12). The aortic valve is chronically exposed to complex shear forces. Evidence has shown that directional shear stress is generally responsible for arterial endothelial alignment *in vivo* (13). Cultured aortic endothelial cells align perpendicular to flow direction, in contrast to the typical parallel alignment to flow seen in other endothelial culture studies (14). Calcification occurs primarily on the aortic side of the aortic valve leaflets, where flow is most turbulent, suggesting that shear stress and its interaction with valvular endothelium plays a role in calcification (Fig. 3).

Comparison to atherosclerotic disease. Degenerative aortic valve disease shares many characteristics with atherosclerotic disease. The early lesion of both vascular and calcific aortic disease involves basement membrane disruption; macrophage and T-lymphocyte migration; and lipid infiltration, notably apolipoprotein (apo) B, apo(a), and apoE (Fig. 4) (7,15-17). Ensuing inflammation causes activation

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Abbreviations and Acronyms

- ACE** = angiotensin-converting enzyme
- BMP** = bone morphogenic protein
- CMR** = cardiac magnetic resonance imaging
- DAVD** = degenerative aortic valve disease
- LDL** = low-density lipoprotein
- MMP** = matrix metalloproteinase
- MSR** = macrophage scavenger receptor
- RANK** = receptor activator of nuclear factor kappa B
- TGF** = transforming growth factor
- TNF** = tumor necrosis factor

of myofibroblasts, release of cytokines such as tumor necrosis factor (TNF)-alpha and transforming growth factor (TGF)-beta-1, and expression of matrix metalloproteinase (MMP). Cytokine release helps to initiate the calcification process in both valvular and vascular tissues by up-regulating MMP and bone morphogenic protein (BMP) expression, which in turn promote osteogenic phenotypes within both tissue types (Fig. 5) (18-28).

However, specific cellular and genetic mechanisms of degeneration affect the aortic valve substrate. In addition to the unique milieu created by shear forces at the valvular level (13), the molecular mechanisms responsible for valve and vascular calcification

are associated with differential cellular expression. Valves lack smooth muscle cells, which are an important feature of atherosclerotic lesions in the vasculature (18). In contrast, valves contain myofibroblasts that proliferate in response to decreased nitric oxide levels; angiotensin II; and local hormones, including tissue growth factor and platelet-derived growth factor (15).

Calcification and bone formation. Calcification is a distinguishing feature of DAVD that relies on bone-regulatory protein expression. In a study of explanted valve allografts, Shetty et al. (19) found that heavy calcification was prom-

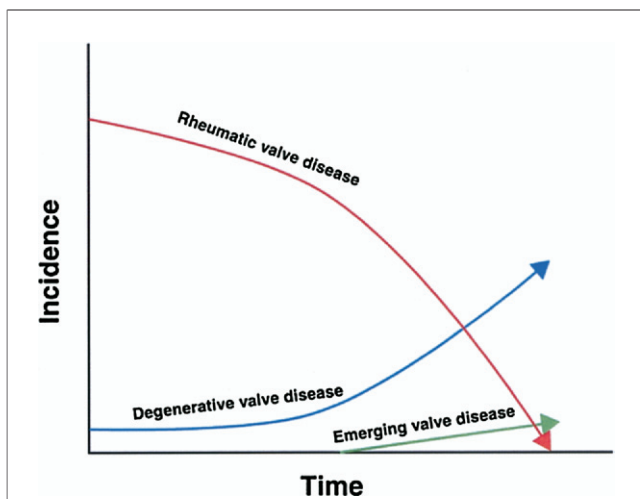


Figure 1 Evolution of Valve Disease in Industrialized Nations

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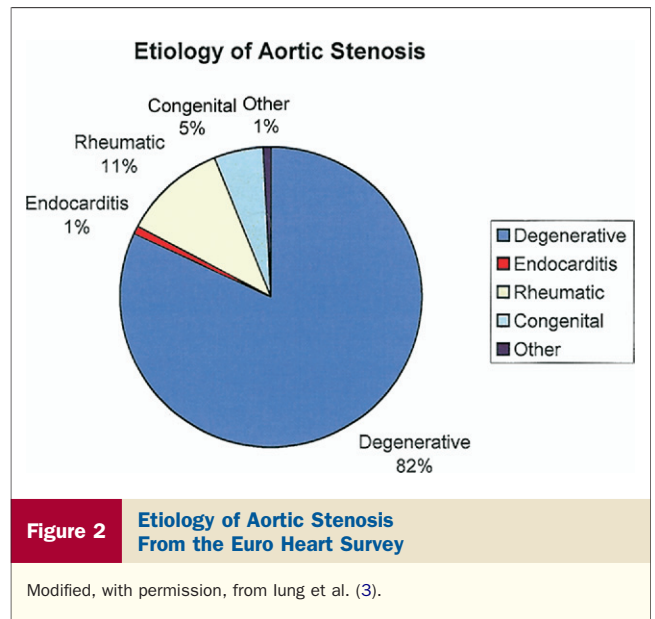


Figure 2 Etiology of Aortic Stenosis From the Euro Heart Survey

Modified, with permission, from lung et al. (3).

inent in stenotic valves and that calcified regions were associated with osteocalcin and increased bone alkaline phosphatase expression. The authors examined calcified valve allografts and found that they expressed the bone-specific transcription factor Cbfa-1, osteopontin, and osteonectin, which were not present in normal valves (19). They went on to show that receptor activator of nuclear factor kappa B (RANK) ligand, which is expressed by osteoblasts and T-cells in areas of active bone remodeling, was present in calcified valve allograft leaflets. Colocalization of the RANK ligand binding site and osteoprotegerin (a protein that binds to RANK ligand and regulates osteoclast activity) confirmed that expression pattern of the RANK ligand/RANK/osteoprotegerin system may have a regulatory role in osteoclastogenesis and calcification of human valve allografts (Fig. 5) (19,20).

Genetic factors. Genetic factors play a definitive role in the risk of DAVD and provide a link to the pathobiology

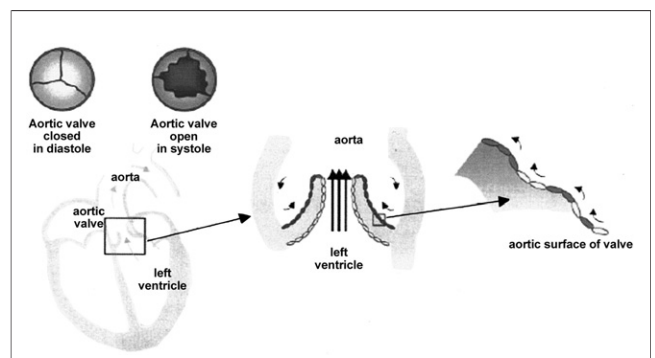


Figure 3 Aortic Valve Endothelial Heterogeneity

Regional and local forces affect endothelial alignment. Reprinted, with permission, from Davies et al. (12).

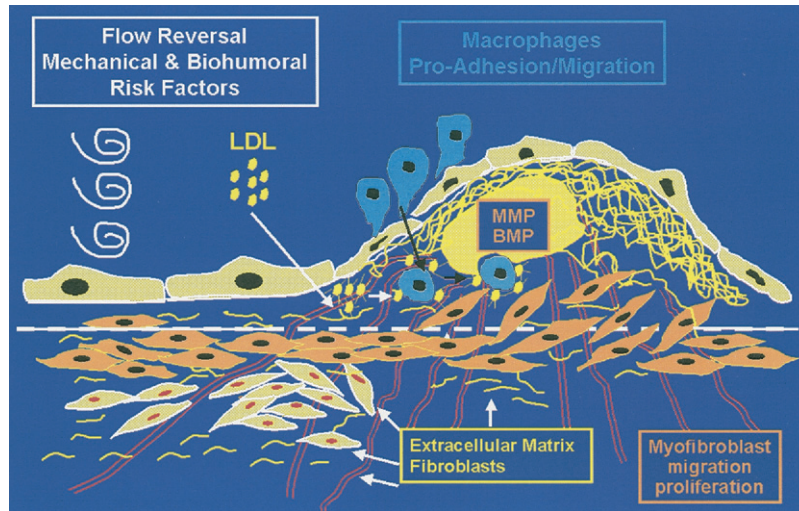


Figure 4 Diseased Valvular Endothelium

Diseased endothelium exhibits nonlaminar flow, low-density lipoprotein (LDL) deposition, macrophage infiltration, and matrix metalloproteinase (MMP) expression. Differential expression of cytoskeletal elements promotes a valvular phenotype. BMP = bone morphogenic protein. Modified, with permission, from Fuster et al. (18).

of valve calcification. The NOTCH1 transcriptional factor regulates osteogenic differentiation as well as valve development. Functional mutations in the gene may increase osteoblast formation and calcification and alter the structural development of the valve (Fig. 5) (21). In fact, gene mutations in NOTCH1 were found in 2 cohorts of patients with valvular anomalies and severe valvular calcification (22).

Somatic cells reaching a certain age enter into replicative senescence, a nondividing state associated with

certain morphologic and cellular changes (23). For example, telomeres shorten as cells replicate (24). Kurz et al. (25) recently hypothesized that aortic valve cusps, which are under constant mechanical stress and thus in need of constant cell turnover, may contain senescent cells with decreased telomere length. After examining 193 older patients with and without aortic stenosis, the researchers found that shorter leukocyte telomere length was in fact associated with the presence of calcific aortic disease (Fig. 5).

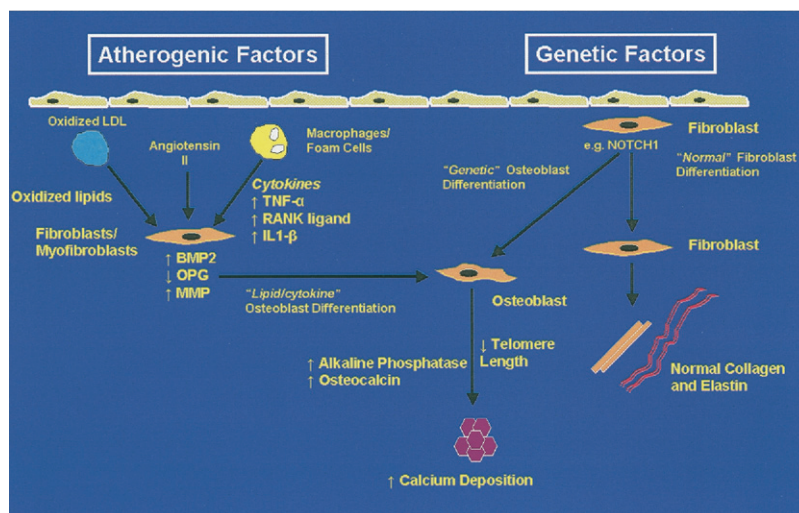


Figure 5 Interplay of Lipids and Inflammation With Genetics on Degenerative Aortic Valve Disease

IL = interleukin; OPG = osteoprotegerin; RANK = receptor activator of nuclear factor kappa B; TNF = tumor necrosis factor; other abbreviations as in Figure 4. Modified, with permission, from O'Brien (21).

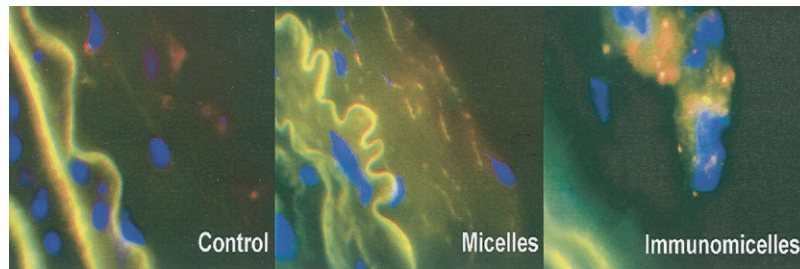


Figure 6 Ex Vivo Confocal Microscopy Performed at 100× Magnification of Apo-E Knockout Murine Aortas

The aortas were incubated with control, nitro-2-1,3-benzoxadiazol-4-yl (NBD)-labeled micelles (green), and NBD-labeled immunomicelles (green) and stained with 4',6-diamidino-2-phenylindole (blue) and R-phycoerythrin-labeled anti-CD68 (red) that stains for macrophages. Reprinted, with permission, from Lipinski et al. (27).

Role of New Imaging Technologies

In addition to the ability to diagnose and quantify aortic stenosis, new imaging modalities may better define the pathologic pathways involved in DAVD. Contrast-enhanced molecular imaging techniques are rapidly emerging as powerful adjuncts to traditional contrast cardiac magnetic resonance imaging (CMR). Lipid-based gadolinium-complexed nanoparticles can penetrate atherosclerotic plaque, enhancing the ability of CMR to detect and characterize atheromatous plaque (26). High-density lipoprotein gadolinium-nanoparticles that have high affinity and greater specificity for atherosclerotic lesions have recently been developed. Studies with these nanoparticles showed both early enhancement in macrophage-rich plaques and late enhancement of advanced lesions in vivo (27). Labeling gadolinium-containing micelles with specific antibodies may increase the specificity of molecular imaging techniques by targeting areas of atherosclerosis that contain certain surface markers. Lipinski et al. (27) used immunomicelles linked with a monoclonal antibody for macrophage scavenger receptor (MSR)-A, a receptor implicated in atherosclerosis progression, to enhance ex vivo imaging of atherosclerotic plaque (Fig. 6). They found that both micelles and immunomicelles were superior to standard-contrast agents in vitro and that immunomicelles targeting the MSR-A receptor in murine apoE knockout aortas enhanced ex vivo imaging over standard micelles.

Micro-computerized tomography has been utilized to assess mineral levels in explanted human heart valves (28). Rajamannan et al. (28) report a characteristic pattern of calcification in a series of 22 explanted aortic valves, with the heaviest mineralization occurring near the outer edges of each calcified nodule. Micro-computerized tomography revealed the depth and extent of calcification and suggested that valve calcification is an active process of bone formation associated with an osteoblast phenotype (Fig. 7). Novel imaging techniques hold significant promise for further pathologic characterization and potential clinical application that may bear directly on treatment and outcomes of DAVD.

Therapeutic Insights for DAVD

Risk factor modification. Given the clear relationship between systemic atherosclerosis and DAVD (29,30) and the predilection for patients with cardiovascular risk factors to develop DAVD (9,31), modification of these risk factors appears the most obvious method for preventing or treating valvular calcification. However, with the exception of lipid management, no clinical trials have addressed whether interventions aimed at altering cardiovascular risk factors such as hypertension, diabetes, and tobacco use have any effect on the progression of DAVD.

HMG-CoA reductase inhibitors. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG-CoA), known as statins, inhibit the rate-limiting step in cholesterol biosynthesis. Statins have aggressively been studied as a therapeutic option for DAVD. In addition to lowering lipid levels, statins also possess pleiotropic mechanisms that may hinder the progression of DAVD.

Statin therapy disrupts many of the inflammatory pathways critical for the development of DAVD. Statins significantly down-regulate the expression of numerous inflammatory cytokines, including TGF-beta-1 and TNF-alpha in

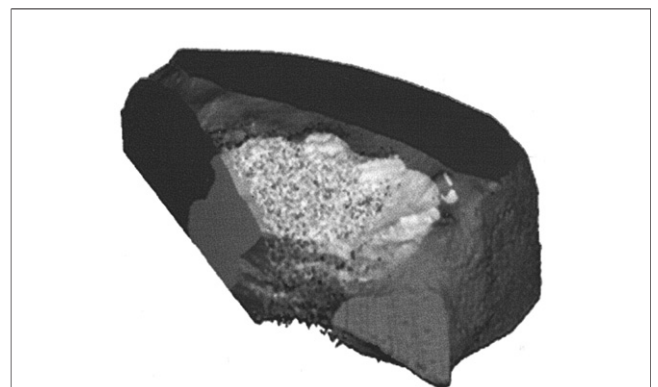


Figure 7 Micro-Computerized 3-Dimensional Reconstruction of the Calcified Aortic Valve

Reprinted, with permission, from Rajamannan et al. (28).

Table 1 Summary of Retrospective Studies of Medical Therapy in the Prevention of Calcific Aortic Stenosis

Study	n	Patient Characteristics	Study Groups	Parameter Reported	Findings
Retrospective studies					
Pohle et al. (37)	104	Patients with coronary and AV calcification	LDL <130 mg/dl vs. LDL >130 mg/dl	AV calcium on electron beam tomography	Lower LDL associated with slower progression of AV calcification
Aronow et al. (42)	180	Patients with mild AS and 2 echocardiograms >2 yrs apart	LDL >125 mg/dl without statin vs. LDL >125 mg/dl with statin vs. LDL <125 mg/dl without statin	Peak transvalvular gradient on echocardiogram	Lower LDL and statin use associated with slower progression of AS
Novaro et al. (38)	174	Patients with mild-to-moderate calcific AS and 2 echocardiograms >12 months apart	Statin therapy vs. no statin therapy	AV area and peak gradient on echocardiogram	Statin use associated with slower progression of AS
Shavelle et al. (39)	65	Patients with 2 electron beam tomography scans >6 months apart	Statin therapy vs. no statin therapy	AV calcium on electron beam tomography	Statin use associated with slower progression of AV calcification
Bellamy et al. (40)	156	Patients with AS, mean transvalvular gradient 10 mm Hg and aortic valve area 2.0 cm ²	Statin therapy vs. no statin therapy	AV area and mean gradient on echocardiogram	Statin use associated with slower progression of AS
Rosenhek et al. (41)	211	Patients with aortic jet velocity >2.5 m/s, normal LVEF, no other valvular lesion with 2 echocardiograms >6 months apart	Statin therapy vs. no statin therapy; ACE inhibitor therapy vs. no ACE inhibitor	Aortic-jet velocity and peak transvalvular gradient on echocardiogram	Statins, but not ACE inhibitors, associated with slower AS progression, independent of LDL levels
Prospective studies					
Cowell et al. (SALTIRE) (43)	155	Calcific AS with aortic jet velocity >2.5 m/s with no statin indication	Randomized to atorvastatin (80 mg) vs. placebo	Aortic-jet velocity on echocardiogram and AV calcification on computed tomography	No difference between groups
Moura et al. (RAAVE) (44)	121	Moderate to severe AS with AV area 1.0 cm ²	Rosuvastatin (20 mg) vs. placebo based on baseline LDL	Progression of AS on echocardiogram and improvement in serum LDL	Rosuvastatin associated with slower progression of AS and lower serum LDL

Modified, with permission, from Rajamannan and Otto (15).

ACE = angiotensin-converting enzyme; AS = aortic stenosis; AV = aortic valve; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction.

valve interstitial cells (32) and the expression of TNF-alpha in macrophages (33) and endothelial cells (33). Numerous statins inhibit the secretion of MMPs from rabbit vascular smooth muscle cells and macrophages (34). In addition to altering the inflammatory milieu in degenerative heart valves, statins specifically inhibit the calcification process in vitro. Statins were found to down-regulate the expression of BMP-2 and -6 in human aortic valve interstitial cells (32) and to inhibit alkaline phosphatase activity, a marker of osteoblastic differentiation, in cell culture models of valve calcification (32,35). Data suggest that statin effects on valve calcification are independent of the pleiotropic effects caused by inhibition of protein prenylation (35) and that they may in part be due to attenuation of LDL receptor-related protein-5/beta-catenin protein levels (36) and up-regulation of endothelial nitric oxide synthase (15).

Retrospective clinical trials have shown significant reductions in the progression of DAVD with statin therapy (37–42). Using echocardiographic measures of aortic stenosis (38,40–42) and aortic valve calcium scores as determined by electron-beam computed tomography (37,39), statin therapy appeared to reduce the progression of aortic stenosis

by approximately 50% (Table 1). With some exceptions (37), data suggest that the ability of statins to slow the progression of aortic stenosis is likely secondary to pleiotropic effects of statin therapy and not on the lipid-lowering effects (38–42).

Data from prospective clinical trials are not as clear (43,44). In the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Therapy) trial, patients with severe aortic stenosis (mean valve area = 1.03 cm²) were randomized to atorvastatin or placebo; statin therapy failed to halt or reverse the progression of calcific aortic stenosis (43). However, the RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium) study, a prospective, nonrandomized trial, demonstrated that in patients with moderate to severe aortic stenosis (mean valve area = 1.23 cm²), treatment with rosuvastatin for elevated serum LDL slowed the progression of aortic stenosis as compared to patients with normal LDL levels not needing statin therapy (44). Numerous features of these 2 trials may explain the discrepancies between them. First, patients with an indication for statin therapy were excluded from the SALTIRE trial, whereas in previous studies and in the RAAVE study, statin therapy was

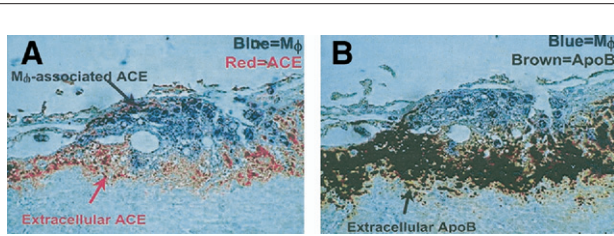


Figure 8 ACE in a Human Aortic Valve Lesion

(A) Double immunostaining for macrophages (blue stain) and angiotensin-converting enzyme (ACE) (red stain) demonstrate that the majority of macrophages lack ACE protein (blue stain); most staining is extracellular. A minority of macrophages contain ACE protein (purple stain). (B) Double immunostaining for macrophages (blue stain) and apolipoprotein B (apoB), the primary protein of low-density lipoprotein cholesterol particles (brown stain), demonstrates the presence of extensive extracellular apoB staining, which colocalizes with extracellular ACE. Original magnification $\times 400$. Reprinted, with permission, from O'Brien et al. (46).

prescribed specifically for the management of hyperlipidemia (38–45). Given this difference in the risk factor profile of studied patients, it is conceivable that calcific valve disease may behave differently in these patient populations (33). The SALTIRE trial patients had heavily calcified aortic valves before study enrollment (43). Valve calcification was not quantified in the RAAVE study; nevertheless, the authors suggest that the burden of valve calcification in RAAVE study patients was likely less than in the SALTIRE trial (44). Consequently, although statins failed to halt or reverse the progression of calcific aortic stenosis, they may still be able to prevent its development. As shown by Wu et al. (35), statin therapy inhibits valve calcification in vitro but stimulates calcification of osteoblasts. As 15% of patients with end-stage calcific aortic valve disease have mature lamellar bone with active osteoblasts within their valve leaflets, it is possible that statins could actually accelerate valve calcification in this subset of patients (23). Thus, the stage at which statin therapy is initiated may significantly alter the noted effects. The ongoing prospective clinical trials SEAS (Simvastatin and Ezetimibe in Aortic Stenosis), ASTRONOMER (Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin), and STOP-AS (Stop Aortic Stenosis) will help delineate the patient populations with aortic stenosis that might benefit from statin therapy.

Angiotensin-converting enzyme (ACE) inhibitors. The presence of ACE in diseased calcific valves is a hallmark of these lesions. O'Brien et al. (46) found that ACE was present in diseased, but not normal aortic valves and that it was predominantly associated with extracellular apolipoprotein B (Fig. 8). Western blotting confirmed that ACE was present on normal plasma LDL, suggesting that LDL may have been the mechanism of entry of ACE into the endothelium. Advanced valve lesions also contain both angiotensin II and the angiotensin II receptor AT-1, indicating that the renin-angiotensin system plays a signif-

icant role in calcific valvular disease (46,47). Retrospective data suggests that ACE inhibitor use is associated with slowed aortic valve calcium accumulation (48), although they were not found to inhibit the progression of aortic stenosis (41). Rosenhek et al. (41) failed to show a beneficial effect of ACE inhibitors on progression of aortic stenosis, in part because of the hemodynamic effects of ACE inhibitors, which may obscure the effects on valve stenosis by altering flow conditions across the valve (15,49). Although the role of ACE inhibition on the progression of DAVD remains to be clarified, ACE inhibitors have favorable effects on cardiac remodeling in aortic stenosis (50).

MMP inhibitors. Matrix metalloproteinases are known to play a significant role in the vascular remodeling through their ability to degrade the extracellular matrix within vessel walls (Fig. 4) (51). Matrix metalloproteinase-mediated elastin degradation has been associated with aortic calcification (52). In cardiac valves, MMPs are thought to help maintain the integrity and pliability of valve tissue (16); however, abnormal expression of MMPs, as is caused by inflammation, subsequently plays a role in abnormal valve remodeling and calcification. Emerging data may determine whether inhibition of MMP activity decreases calcification within valve tissue as it does within the vasculature.

Emerging Interventional Therapies

Tissue engineering. Surgical repair or replacement with mechanical or bioprosthetic valves serves as the therapeutic end point in the management of DAVD. Despite improvements in both surgical technique and the design of mechanical valves, the risks of thromboembolism, prosthetic valve endocarditis, chronic anticoagulation, and poor hemodynamic performance remain high in patients receiving valve prostheses (53). Moreover, bioprosthetic valves, which are associated with less risk of thromboembolism, possess lim-

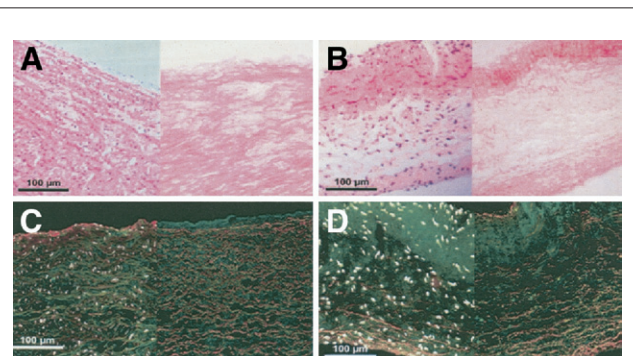


Figure 9 HE Staining of Native and Decellularized Porcine Pulmonary Heart Valves

Shown are conduit wall (A) and leaflet (B). Original magnification $\times 400$. (C, D) Native (left) and decellularized (right) porcine pulmonary heart valves, staining for collagen I and III (green), elastin (red), and deoxyribonucleic acid (white). Confocal laser scanning microscopy, original magnification $\times 400$. Shown are conduit wall (C) and leaflet (D). Reprinted, with permission, from Rieder et al. (56). HE = hematoxylin and eosin.

ited longevity and suffer from many of the same degenerative processes that afflict native valves (54).

Tissue engineering has been exploited in an effort to create a durable physiologic valve. The oldest approach relies on the use of acellular matrix xenografts as scaffolds that would ultimately become repopulated with cells from the patient (55). This technique has been hindered by failure to decellularize valves without harming the mechanics and cellular responses of the valve matrix, by an inability to repopulate matrix xenografts in vivo (55), and by retained immunologic activity of decellularized xenografts (Fig. 9) (56). In vitro repopulation of matrix xenografts is thought to hold greater potential for success (55). Steinhoff et al. (57) demonstrated in a sheep model that in vitro seeding of acellular allogenic heart valve conduits resulted in in vivo reconstitution of viable heart valve tissue. A second tissue-engineering approach involves the use of bioabsorbable scaffolds to regenerate valve tissue. After resorption of the scaffold, a valve composed only of the recipient's tissues would remain (55). The technique has seen some success in animal models. Hoerstrup et al. (58) demonstrated that rapidly bioabsorbable scaffolds seeded with myofibroblasts and endothelial cells implanted in the pulmonic position in

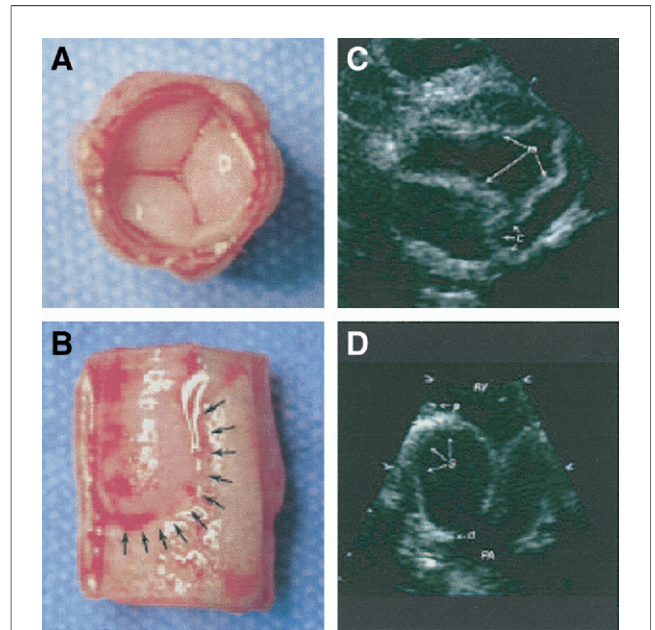


Figure 11 Macroscopic Appearance of Tissue-Engineered Semilunar Heart Valve Before Implantation

Valve viewed from below with leaflet free margins apposed in closed position (A) and viewed in profile (B) with arrows outlining 1 sinus of Valsalva. Echocardiograms of implanted valve in short (C) and long (D) axes, in same approximate orientation as macroscopic images (A, B). Reprinted, with permission, from Sutherland et al. (63).

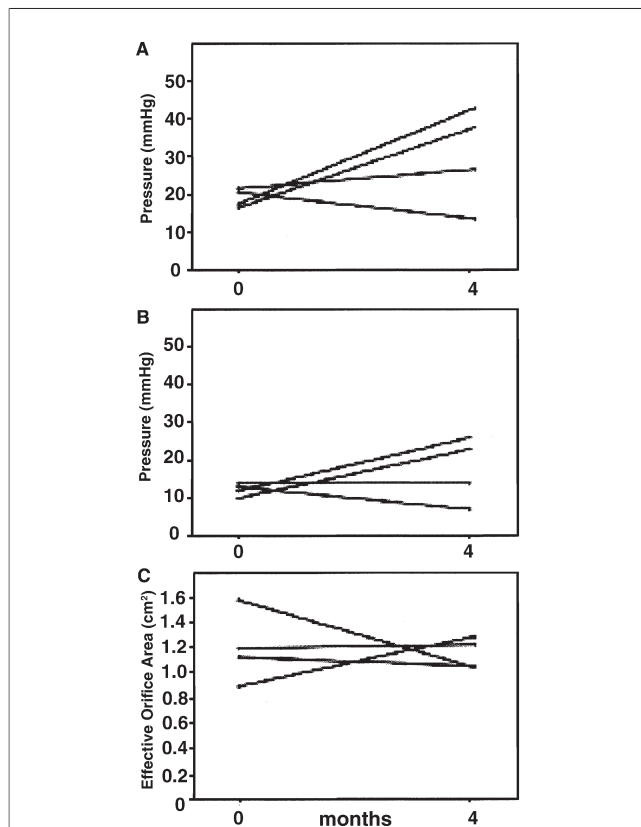


Figure 10 Changes in Hemodynamic Function Over 4 Months

Maximum systolic gradient (A), mean gradient (B), and effective orifice area (C) at time of implantation (t = 0) and after 4 months (t = 4) in vivo. Reprinted, with permission, from Sutherland et al. (63).

lambs functioned for up to 5 months with microstructure, mechanical properties, and extracellular matrix formation that resembled normal valves.

Percutaneous valve replacement. Percutaneous aortic valve replacement is emerging as a viable technique in patients with severe aortic stenosis and multiple comorbidities that might preclude open valve replacement. Andersen et al. (59) carried out feasibility studies using transcatheter expandable aortic valves in an animal model; in 2002, Cribier et al. (60) reported the first successful human implantation using an antegrade approach. Both retrograde arterial and transapical approaches have since been carried out in small groups. Reported procedural success rates are at least 75%, with immediate improvement in valve area and hemodynamic parameters. Short term (2- to 6-month) follow-up studies have suggested that after-procedural cardiac event rates are low (61,62). Improving techniques will likely broaden the patient population eligible for percutaneous valve replacement.

Stem cells. Stem cells are increasingly being evaluated as the source of cells for tissue-engineered heart valves due to their ability to differentiate into various cell types (55,63). Sutherland et al. (63) used a biodegradable scaffold seeded with mesenchymal stem cells derived from sheep bone marrow to create an autologous semilunar heart valve that functioned satisfactorily for more than 4 months (Fig. 10). The valves were found to remodel in vivo, creating

cellular phenotypes and structural organization that strongly mirrored those of native valves (Fig. 11) (63). Tissue engineering, aided by emerging stem cell technology, holds immense potential for the treatment of valvular heart disease.

Conclusions

Degenerative aortic valve disease is a highly prevalent disease associated with significant morbidity and mortality. Though it displays a similar risk factor profile and histopathology as atherosclerosis, DAVD is increasingly being recognized as a unique process. Elucidation of the cellular and molecular pathogenesis of degenerative valve disease has provided a basis for future therapeutic interventions to delay or prevent its progression.

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