Pathogenesis of Calcific Aortic Valve Disease
A Disease Process Comes of Age (and a Good Deal More)

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Background—Over the past 10 to 15 years, calcific aortic valve disease, which includes aortic sclerosis and aortic stenosis, has come to be recognized as an active process, based on: (1) epidemiologic studies demonstrating associations of specific risk factors with increased prevalence or rate of progression of aortic valve disease; (2) identification, in valve lesions, of histopathologic features of chronic inflammation, lipoprotein deposition, renin–angiotensin system components, and molecular mediators of calcification; and (3) identification of cell-signaling pathways and genetic factors that may participate in valve disease pathogenesis. These studies will be reviewed and organized into a proposed global hypothesis for the pathogenesis of calcific aortic valve disease. (Arterioscler Thromb Vasc Biol. 2006;26:1721-1728.)

Key Words: aortic valve disease □ calcification □ lipoproteins □ matrix □ angiotensin II

Calcific aortic valve disease is identified by thickening and calcification of the aortic valve leaflets in the absence of rheumatic heart disease. It is divided, on a functional basis, into aortic sclerosis, in which the leaflets do not obstruct left ventricular outflow, and aortic stenosis, in which obstruction to left ventricular outflow is present. Aortic sclerosis is present in more than 25% of patients over age 651 and is associated with a 50% increase risk of cardiovascular events.2 Aortic stenosis is present in 2% to 5% of very elderly patients,1,3 is the second most common indication for cardiac surgery,4 and carries an 80% 5-year risk of progression to heart failure, valve replacement, or death.5 Though the disease is associated with substantial clinical consequences, there currently is no effective therapy for the disease other than surgical aortic valve replacement.

The lack of medical therapies for calcific aortic valve disease can be traced to at least two important issues, one intellectual, the other practical. The first was the long-held notion that calcific aortic valve disease was a “degenerative,” and therefore unmodifiable, condition.6 However, more recent studies have demonstrated convincingly that calcific aortic valve lesions have many features characteristic of an active pathobiological process, including chronic inflammation,7–9 lipoprotein deposition,10–12 active calcification,13–18 and renin–angiotensin system activation.19,20 These features are present in both trileaflet and bileaflet aortic valve lesions.21 Also, an emerging body of literature is investigating how genetic factors might influence disease development.22–25

The second issue is that, for many years, there were no animal models that faithfully replicated the key histological features of the disease. Recently, rabbit models had been developed,16,26,27 with that of Rajamannan and colleagues already providing a number of novel insights.16–18,28,29 In particular, these models have implicated the Wnt18 and Runx2/Cbfa116,17,27 signaling pathways in disease pathogenesis.

Nonetheless, through a combination of epidemiological studies, histopathologic evaluation of human lesions, and genetic epidemiology, the past several years have seen rapid advances in our understanding of calcific aortic valve disease pathogenesis. Some potential therapies have been evaluated in retrospective studies using echocardiography31–33 or computed tomography.34–36 Moreover, the era of randomized clinical trials in aortic valve disease has finally begun.37 This review will summarize our current understanding of the pathogenesis of calcific aortic valve disease, attempt to place what currently is known in the context of on-going or recently-completed clinical trials, and identify some areas for future investigation.

Epidemiology
Over the past several years, a number of risk factors for calcific aortic valve disease have been identified. One early study identified male gender, triglycerides, and smoking as independent risk factors for early aortic valve replacement in AS patients.38 In the Cardiovascular Health Study cohort, age, male gender, hypertension, and current smoking were correlated with the presence of echocardiographically-detected aortic sclerosis.1 Correlations also were found between elevated levels of lipoprotein(a) [Lp(a)] and low-density lipoprotein cholesterol (LDL) and increased risk of aortic sclerosis,1 though the relative risks appeared to be lower than those typically reported for atherosclerosis. Other studies
have identified high LDL, smoking, and hypertension, as well as diabetes and elevated body mass index, as risk factors for echocardiographic progression of aortic stenosis. However, a more recent study found no correlation between LDL or total cholesterol levels and risk of aortic stenosis progression. In addition, end-stage renal disease has long been known to be a risk factor for the presence and progression of aortic stenosis, though mild to moderate renal disease does not appear to be significantly associated with aortic valve calcification. One study recently has identified metabolic syndrome as an additional risk factor for valve calcification. The similarities between risk factors for atherosclerosis and calcific aortic valve disease have led to the hypothesis that calcific aortic valve disease is primarily a manifestation of atherosclerosis. However, there also are dissimilarities in these disease processes that may suggest a more complicated picture.

**Biological Processes Implicated In Aortic Valve Lesion Pathogenesis**

**Chronic Inflammation**

In 1994, a series of 3 studies reported that aortic valve lesions contained the cell types characteristic of chronic inflammation: macrophages and T lymphocytes. One also found expression of important chronic inflammation effector molecules, including interleukin (IL)-2 and the Class II human leukocyte antigen, HLA-DR. More recently, mast cells and the proinflammatory cytokines, IL-1β and tumor necrosis factor (TNF)-α, also have been identified in stenotic aortic valves. In addition, aortic valve lesions contain a number of matrix-metalloproteinases (MMPs), which degrade various components of the extracellular matrix. Results differ as to whether levels of the natural inhibitors of MMPs, tissue inhibitors of matrix metalloproteinases (TIMPs), are increased or unchanged in valve lesions. These molecules typically are expressed in inflammatory and fibrosing illnesses. In the case of atherosclerosis, MMPs appear to play important roles in the regulation of vascular calcification, but also are thought to play a key role in the extracellular matrix degradation and subsequent plaque instability that leads to plaque rupture and clinical cardiovascular events. It is not clear why MMPs and TIMPs may contribute to the extracellular matrix degradation and plaque instability that lead to clinical cardiovascular events in some individuals but participate in the progressive fibrosis and leaflet rigidity that result in aortic stenosis in others.

**Lipoprotein Deposition**

Another hallmark of atherosclerosis is deposition of plasma lipoproteins in plaques. Similarly, the “atherogenic” lipoproteins, LDL and Lp(a), are deposited in human aortic valve lesions, and aortic valve cholesterol content is increased in a hypercholesterolemic rabbit model of aortic valve disease. Similar to atherosclerosis, aortic lesion lipoprotein deposition likely is mediated, at least in part, by accumulated extracellular matrix proteoglycans, including biglycan and decorin. Proteoglycans consist of a core protein to which is attached one or more glycosaminoglycan (GAG) side chains. In general, lipoproteins bind to proteoglycans via charge–charge interactions between positively-charged basic amino acids on apolipoproteins and negatively-charged glycosaminoglycan side chains of proteoglycans. Interestingly, a mutation of the single basic amino acid in apoB that mediates LDL binding to proteoglycans markedly decreases atherosclerosis in a murine model. Therefore, lipoprotein–proteoglycan interactions may not only link elevated plasma LDL and Lp(a) levels with increased aortic valve disease risk, but also may represent a therapeutic target.

Oxidized lipids also have been detected in human aortic valve lesions, particularly in areas of developing calcification. In vitro studies have shown that oxidized cholesterol stimulates calcified nodule formation by valve fibroblasts, and that calcified nodule formation by these cells is inhibited by simvastatin. Together, these observations provide a potential link between accumulated lesion lipoproteins and calcification and also suggest that statins might have therapeutic benefit. Other potential mechanisms mediating lesion calcification will be discussed subsequently.

Consistent with a role for lipoproteins in valve calcification, retrospective studies have demonstrated strong associations between statin use and decreased risk of progression of aortic valve calcification and stenosis. However, a recent small prospective randomized trial showed no benefit of high-dose statin therapy over an average of 3 years. This highlights the concern that more advanced AS may be less amenable to statin therapy. It also is possible that effective statin therapy may require longer treatment periods and/or targeting of earlier disease stages.

**Renin–Angiotensin System Activation**

Recent studies also have implicated the renin–angiotensin system, particularly angiotensin converting enzyme (ACE), angiotensin II (Ang II), and the angiotensin II Type 1 (AT1) receptor in aortic valve lesion pathogenesis. Ang II, which is generated from angiotensin I by ACE, has a number of potential, AT-1 receptor–mediated, lesion-promoting effects. These include stimulating inflammation and macrophage cholesterol accumulation, impairing fibroinolysis, increasing oxidant stress (summarized in reference), and stimulating fibroblast expression of the lipoprotein-retaining proteoglycan, biglycan.

A subset of aortic valve lesion macrophages express ACE. Surprisingly, a large proportion of valve lesion ACE colocalizes with LDL in the extracellular matrix. Ang II also is localized to these regions, suggesting that the LDL-associated ACE is enzymatically active. In addition, AT1 receptor is expressed by fibroblasts only in lesions. Degranulated mast cells also are present in lesions. This latter observation is important, because mast cell granules contain chymase, a non-ACE enzyme that also can generate Ang II.

Thus, aortic valve lesions contain a number of potential sources of Ang II: (1) LDL-associated ACE, (2) macrophage-associated ACE, and (3) mast cell chymase. Moreover, the major pathogenic receptor for Ang II is present in valve lesion...
fibroblasts. However, whereas smooth muscle cells constitutively express AT-1 receptor, this receptor is only expressed by valve fibroblasts of lesions. Thus, unlike atherosclerosis, where Ang II may affect normal non-plaque smooth muscle cells, valve fibroblasts may be protected from the adverse effects of Ang II until they begin to express AT-1 receptor in early-stage lesions, thereby blunting any potential effects of Ang II on valve lesion pathogenesis. This also may account for the mixed results of retrospective studies, with one showing a strong association between ACE inhibitor use and decreased rate of valve calcification and another finding no effect on progression of AS. However, in the latter study, AS was severe in nearly half of all subjects and mean follow-up was only 24 months. It therefore may be that, if ACE inhibitors or angiotensin receptor antagonists are to have any benefit, treatment will need to be extended over longer periods of time and/or targeted to either aortic sclerosis or earlier-stage AS.

A proposed scheme for the roles of lipoprotein retention and oxidative modification and renin–angiotensin system activation in disease pathogenesis is shown in Figure 1.

Calcification

In addition to fibrosis, calcification is a defining feature of aortic valve lesions. Calcification may contribute to lesion rigidity, thereby worsening obstruction to left ventricular outflow. Moreover, the extent of lesion calcification correlates both with more rapid disease progression and worse clinical outcomes.

Aortic valve calcification now has been shown unequivocally to be an active, rather than a passive, process. Valvular calcium deposits contain both calcium and phosphate as hydroxyapatite, the form of calcium-phosphate mineral present in both calcified arterial tissue and bone. Proteins involved in regulation of tissue calcification have been detected in calcified valvular tissue, including osteopontin, bone morphogenic proteins (BMPs) 2 and 4, and receptor activator of nuclear factor NF-κB ligand (RANKL). Osteoprotegrin (OPG), which prevents mineral resorption in bone tissue, is a soluble decoy receptor that resembles RANK and acts as a competitive inhibitor of RANK binding to RANKL. RANK is expressed in normal valve leaflets, but is downregulated in aortic valve lesions. The osteoblast-specific transcription factor, Runx2/Cbfa1, has been detected in rabbit models of experimental aortic valve disease, human aortic valve lesions contain heterotopic bone, and osteoblast-like cells have been identified both in a rabbit model and in calcified human valves. Finally, a subset of end-stage human aortic valve lesions contain heterotopic bone, further confirming the dysregulated nature of aortic valvular calcification.

In aortic valve lesions, calcified nodules appear to first form in regions of lipid deposition, particularly those with oxidized lipids. They also contain tenasin C, an extracellular matrix glycoprotein found in developing bones. Recently, groups have isolated a subset of valvular fibroblasts that express osteoblast markers and spontaneously form hydroxyapatite-containing calcified nodules in vitro. In response to oxidized cholesterol, transforming growth factor (TGF) β1, BMP2, and RANKL, these cells increase their expression of osteoblast markers and increase their rate of calcified nodule formation. In addition, tenasin C upregulates matrix metalloproteinase (MMP)-2 expression in these cells. Importantly, it recently has been shown that statins inhibit calcified nodule formation in these cells, at least in part through inhibition of protein prenylation.

Figure 1. Potential roles of lipoprotein retention, oxidative modification, and renin–angiotensin system activation in the pathogenesis of calcific aortic valve disease. Low density lipoprotein (LDL) is trapped on lesion proteoglycans. After oxidative modification, oxidized LDL (OxLDL): (1) induces endothelial cell expression of adhesion molecules (VCAM-1, ICAM-1) and chemoattractants (MCP-1), leading to monocyte/macrophage infiltration, and (2) is taken up by macrophages, leading to macrophage foam cell formation and activation. Activated macrophages produce multiple cytokines (including RANKL, IL-1β, and TNF-α) and also express enzymes generating oxidants (O2·−) that further promote LDL oxidation. Retained LDL also contains angiotensin converting enzyme (ACE) which, along with mast cell-produced chymase, generates Ang II from Ang I. Ang II then activates the Ang II Type 1 receptor (AT1-R), leading to increased production of both oxidants and proteoglycans.
a rat model of aortic medial elastocalcinosis. Interestingly, osteopontin is expressed by infiltrating macrophages in both atherosclerotic and aortic valve lesions. However, whereas atherosclerotic plaque smooth muscle cells also express osteopontin, valve lesion fibroblasts do not. Thus, as a result of differences in osteopontin expression by the dominant mesenchymal cell type, the relative efficacy of osteopontin as a calcification inhibitor may differ in atherosclerosis and aortic valve disease.

Together, these findings implicate oxidized lipids and macrophage- and T-lymphocyte–produced cytokines in valvular calcification. They also suggest that specific signaling mechanisms are involved in valvular calcification. For example, the presence of chronic inflammation, inflammatory cytokines, oxidized lipids, and RANKL in lesions suggests that NF-κB activation is a crucial step in the vascular calcification process. NF-κB is upregulated by inflammatory cytokines, oxidant stress, and Ang II, and it signals through the mitogen-activated protein (MAP) kinase pathway.

Atherogenic factors, including oxidized lipids, TNF-α, and hyperglycemia, all might mediate valvular calcification, at least in part, through pathways activated by BMP2. BMP2 is present in human aortic valve lesions and stimulates calcified nodule formation by valvar fibroblasts in vitro. BMP2 can upregulate both an “osteogenic” pathway involving the transcription factor Msx2 (which activates Wnt signaling), and a chondro-osteogenic pathway involving the transcription factor Runx2/Cbfa1. Shao and colleagues have demonstrated that Msx2-overexpressing mice have increased vascular calcification. That this effect was mediated through Wnt activation was supported by additional evidence by Msx2 overexpression experiments in TOPGAL+ (Wnt reporter) mice. Rajamannan and colleagues have directly implicated the Wnt/LDL receptor–related protein 5 (Lrp5)/β-catenin pathway in valvular calcification by demonstrating upregulation of Lrp5 and β-catenin in hypercholesterolemic rabbit aortic valve lesions. In addition, they have shown that atorvastatin decreases aortic valve lesion levels of Lrp5 and β-catenin and that LDL exposure upregulates Lrp5 and β-catenin expression in myofibroblasts in vitro. More recently, that group has published immunohistochemical results suggesting that the canonical osteogenic Wnt ligand, Wnt3, is detectable in calcified human aortic valves, though results suggesting that the canonical Wnt ligand, Wnt3, is detectable in calcified human aortic valves, though this observation was not confirmed by Western blot analysis or by reverse transcriptase-polymerase chain reaction (PCR) analyses of Wnt3 mRNA levels.

However, atherogenic factor–mediated upregulation of valve lesion BMP2 could also activate a chondro-osteogenic pathway involving Runx2/Cbfa1. Indeed, a recent in vitro study has demonstrated that BMP signaling is required for activation of the Runx2/Cbfa1 pathway in both a mesenchymal cell line as well as in primary cultures of marrow stromal cells. The Runx/Cbfa1 transcription factor is increased in aortic valves of 2 hypercholesterolemic rabbit models. Interestingl, treatment with an angiotensin receptor antagonist, olmesartan, inhibited aortic valve leaflet Runx2/Cbfa1 upregulation and macrophage accumulation in the latter study. As noted previously, phosphate induces vesicle formation in myofibroblasts. In vascular smooth muscle cells, this effect of phosphate is mediated by its binding to the sodium-dependent phosphate cotransporter Pit1, which upregulates Runx2/Cbfa1. It is possible that phosphate binding to Pit1 has a similar effect on valve fibroblasts. In addition, a recent article (discussed below) has implicated mutations in NOTCH1, a transcription factor that normally represses Runx2/Cbfa1, in valvular calcification in two families. Thus, the chondro-osteogenic Runx2/Cbfa1 pathway may be activated not only by BMP2, but also by chronic kidney disease–associated hyperphosphatemia and by specific genetic abnormalities.

Together, these studies have demonstrated that calcific aortic valve disease is an actively-regulated process and have identified several potential therapeutic targets, including lipid-lowering, lipoprotein/proteoglycan retention, inflammatory and fibrosing cytokines, the renin-angiotensin system, and specific cell-signaling pathways regulating vascular calcification. Recent studies also have begun to investigate how genetic factors may influence valve disease pathogenesis.

**Genetic Factors**

Studies now have begun to emerge that have correlated specific genetic polymorphisms with increased risk of aortic valve disease. A specific Vitamin D receptor allele has been found with increased frequency in AS patients as compared with controls. Also, the apolipoprotein E4 allele, which has been associated with increased risks for atherosclerosis and Alzheimer disease, is significantly increased in frequency in AS patients, an association that persists after adjustment for age, gender, and coronary artery disease. More recently, combinations of specific estrogen receptor and TGF-β1 polymorphisms have been associated with increased risk of AS in postmenopausal women. Although intriguing, particularly because each of these polymorphisms has potential functional consequences that lend biological plausibility to their apparent associations with AS, these are all small single center reports. Therefore, these apparent associations must also be tested prospectively in larger and more ethnically-diverse cohorts.

Importantly, recent studies have emphasized not only the importance of bicuspid aortic valves as a risk factor for aortic stenosis but also demonstrated one specific genetic defect that can contribute to bicuspid valve morphogenesis. A recent, single center, consecutive series of 932 surgically-excised nonrheumatic AS valves found 49% of these valves to be congenitally bicuspid. This would represent a substantial enrichment of the proportion of congenitally abnormal valves in nonrheumatic AS compared with the overall population and suggests that the bicuspid valve has a much more powerful and widespread influence on progression to severe disease than recognized previously. Interestingly, a small, earlier study found a similar 42% prevalence of bicuspid valves in 43 consecutive patients referred for aortic valve replacement surgery.

Another recent study has identified that mutations in a specific transcription factor can link congenital valve abnormalities and valvular calcification. Mutations in the gene for...
the NOTCH1 transcriptional factor were identified in two families with an autosomal dominant pattern of inheritance of cardiac valvular and aortic wall abnormalities.25 The murine homolog Notch1 is highly expressed in developing aortic valves and acts through the hairy-related family of transcriptional proteins (Hrt) to repress Runx2/Cbfa1. Runx2/Cbfa1 appears to play central roles both in early valve development and in a chondro-osteogenic differentiation pathway. Thus, functional mutations in the NOTCH1 gene derepress Hrt and Runx2/Cbfa1, thereby leading to increased osteoblast differentiation. This latter effect could, in part, mediate an increased propensity to valvular calcification in patients with bicuspid aortic valves. However, what then explains the structural abnormalities, ie, the failure of normal leaflet formation and increased risk of aortic dissection seen in patients with bicuspid aortic valves? This may be in part attributable to an adverse effect of NOTCH1 mutations on valve morphogenesis. However, it also is possible that the Runx2/Cbfa1 activation resulting from mutations in NOTCH1 (or other proteins involved in this transcriptional pathway, including hrt or Runx2/Cbfa1 itself) may direct adult valve cells along an osteoblast differentiation pathway. Thus, valve cells could be directed away from the normal differentiation pathway that results in mature, collagen- and elastin-expressing adult valve fibroblasts. In this way, genetic defects in this key cell-signaling pathway could help to explain both the structural abnormalities that manifest in bicuspid aortic valves as well as the increased propensity to valve calcification. It also calls into question the common assumption that abnormal valve flow dynamics alone account for the increased risk of calcification in patients with congenital bicuspid valves. One important caveat is that, to date, NOTCH1 mutations have been associated with the bicuspid aortic valve phenotype in just 2 families.25 It is unlikely that NOTCH1 mutations account for a majority, or even a significant minority, of cases of congenital bicuspid aortic valves. Moreover, a potential role for NOTCH1, or other downstream proteins involved in this transcriptional pathway, needs to be replicated by others. Nonetheless, the study by Garg et al25 does serve as an important proof-of-principle that specific genetic defects might both mediate morphological defects and promote a calcifying cell phenotype in aortic valves.

Together, these sets of observations may have significant implications for relative benefit and timing of potential pharmacological therapies for calcific aortic valve disease.

Figure 2. Potential interplay of lipids and inflammation with genetics in the pathogenesis of valve calcification. Lipids, especially oxidized lipids, may induce osteoblastic differentiation of fibroblasts by upregulating expression of BMP2, which activates the Wnt/Lrp5/β-catenin pathway through upregulation of the transcription factor, Msx2. In addition, multiple cytokines, including TNF-α, IL-1β, and RANKL, may also promote calcification by activation of this pathway. However, a recent preliminary report has suggested that hypercholesterolemia is also associated with activation of the Runx2/Cbfa1 pathway in aortic valve disease. In addition, increased phosphate (PO4) levels, as are seen in chronic kidney disease, might promote valve calcification through upregulation of Runx2/Cbfa1. Genetic factors may interact to further promote osteoblastic differentiation. NOTCH1 is shown as one example of how a genetic abnormality might contribute to both valvular morphological abnormalities and valvular calcification. The reader is cautioned that NOTCH1 is presented as a proof-of-principle only, as mutations in this gene have to date been associated with valvular lesions in just 2 families. NOTCH1 normally inhibits osteoblast differentiation by repressing the hairy-related family of transcription factors (Hrt), thereby also repressing the Runx2/Cbfa1 pathway. The presence of normal NOTCH1 protein maintains the normal valve phenotype by allowing normal fibroblast differentiation and, secondarily, normal synthesis of structural collagen and elastin. Mutations in the NOTCH1 gene (which are associated with bicuspid aortic valves) lead to osteoblastic differentiation because the NOTCH1 protein is no longer able to repress Hrt and the Runx2/Cbfa1 osteoblast differentiation pathway. Particularly in the setting of lipid/inflammatory stimulation of osteoblastogenesis, the proosteoblastic phenotype resulting from mutations in NOTCH1, its downstream regulatory factors, or other genetic abnormalities, may also lead to pathological calcification.
Aortic sclerosis and stenosis have been considered to be a continuum of the same disease process, as supported by a recent study demonstrating a rate of progression of echocardiographically-identified aortic sclerosis to AS in an elderly cohort of ~15% over 7 years. However, although tricuspid and bicuspid aortic valve lesions share many common epidemiologic risk factors and histopathologic lesion characteristics, it may be that genetic factors, as typified by NOTCH1 mutations, are more potent and more prevalent in the subset of patients who progress from aortic sclerosis to AS. Thus, it might be that currently-proposed pharmacological therapies directed against atherogenic risk factors31–36,62 are relatively less effective in the subset of AS patients with a genetic defect affecting valve morphology and/or may need to be started at an earlier time point to achieve a therapeutic benefit.33,37

Summary

The past 10 to 15 years have been marked by significant advances in our understanding of the pathogenesis of calcific aortic valve disease. A proposed scheme integrating lipids, the renin–angiotensin system, inflammation, signaling pathways, and genetic predisposition in the pathogenesis of valve calcification is shown in Figure 2. A number of risk factors for this disease have been identified, and the histological features of valve lesions have been better delineated. More recent studies have led to an emerging understanding of the roles of separate cell-signaling pathways involving Wnt and Runx2/Cbfal in disease pathogenesis. Both of these pathways appear to be activated by atherogenic factors, whereas a recent study has linked a specific genetic defect with activation of the Runx2/Cbfal pathway. As a result, we have moved well beyond the old paradigm that considered aortic valve disease development to be a fait accompli to understanding that it is actively mediated, with many mechanisms similar to those operative in atherogenesis. Recent data should now guide us toward a more nuanced view, which considers the interplay in valve disease pathogenesis between lipid/inflammatory mediators as well as anatomic and genetic mechanisms unique to aortic valves.

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References


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