Mechanisms of aortic valve calcification: the LDL-density-radius theory: a translation from cell signaling to physiology

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Submitted 28 August 2009; accepted in final form 16 October 2009

Rajamannan NM. Mechanisms of aortic valve calcification: the LDL-density-radius theory: a translation from cell signaling to physiology. Am J Physiol Heart Circ Physiol 298: H5–H15, 2010. First published October 23, 2009; doi:10.1152/ajpheart.00824.2009.—Recent epidemiologic studies have revealed the risk factors associated for vascular atherosclerosis, including the male sex, smoking, hypertension, and elevated serum cholesterol, similar to the risk factors associated with the development of AV stenosis. An increasing number of models of experimental hypercholesterolemia demonstrate features of atherosclerosis in the AV, which are similar to the early stages of vascular atherosclerotic lesions. Experimental and clinical studies demonstrate that the hypercholesterolemic AV develops an atherosclerotic lesion which is proliferative and expresses high levels of osteoblast bone markers which mineralize over time to form bone. Calcification, the end-stage process of the disease, is necessary to understand as a prognostic indicator in the modification of this cellular process before it is too late. In summary, these findings suggest that medical therapies may have a potential role in patients in the early stages of this disease process to slow the progression to severe aortic stenosis and to delay the timing of the need for surgery. The translation of these experimental studies to clinical practice will be important to understand the potential for medical therapy for this disease process.

Valvular heart disease; lipids; pathophysiology atherosclerosis; experimental models

With the decline in incidence of rheumatic carditis, calcific aortic stenosis (AS) has become the most common indication for surgical valve replacement in the United States. Numerous epidemiologic studies identified risk factors for AS disease development, which are similar to those of vascular atherosclerosis, including smoking, the male sex, body mass index, hypertension, elevated lipid and inflammatory markers, metabolic syndrome, and renal failure (5, 6, 12, 14, 17, 19, 24, 28, 40, 53, 61, 83–86, 107, 112). 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 (AV) leaflet. Understanding calcification as the critical end-stage process that causes progression to severe stenosis and leads to poor outcomes as defined by Rosenhek and colleagues (95) is becoming important in the results of the randomized trials for treating AS with medical therapy. Over the past decade, there have been a growing number of experimental studies in ex vivo and in vitro models that are defining the molecular signaling markers in calcific AS. In addition, there are a growing number of retrospective and prospective studies testing the hypothesis that atherosclerotic calcific AS may be targeted with medical therapy. This review discusses the experimental evidence defining the cellular mechanisms of calcification and the translational implications of the current and future clinical trials testing medical therapies in the development of AV disease.

AV Cardiovascular Risk Factors

Otto et al. (83) and Stewart et al. (107) described the risk factors for calcific AS identified in the Cardiovascular Health Study. The investigators examined 5,621 patients older than the age of 65 yr and found by Doppler echocardiography that the prevalence of AV sclerosis was 29% and AV stenosis was 2% in this population. The investigators demonstrated that the clinical risk factors important for the development of atherosclerosis are also the independent risk factors for AV stenosis including age, the male sex, height (inverse relationship), history of hypertension, smoking, elevated serum levels of lipoprotein(a), and LDL levels (107). Data from several studies have confirmed that all of these traditional risk factors including metabolic syndrome (14) and renal failure (84), which are important in the development of vascular atherosclerosis, are also implicated in the development of calcific AS (5, 6, 12, 14, 17, 19, 24, 28, 40, 53, 61, 83–86, 107, 112). These findings provide the foundation to study targeted strategies for medical therapy, including, for example, medications for hyperlipidemia, hypertension, and diabetes. There are a growing number of experimental in vivo models of calcific AS that demonstrate primarily that lipids (2, 26, 27, 90, 93, 103, 109), diabetes
Lipids and other cardiovascular risk factors induce oxidative stress (57, 94, 109) in the AV endothelium similar to vascular endothelium (111), which in turn activates the secretion of cytokines and growth factors important in cell signaling. The early atherosclerotic and abnormal oxidative stress environment also plays a role in the activation of the calcification process in the myofibroblast cell. Cardiovascular risk factors, cell proliferation (35), and cyclic stretch (9) play a role in the activation of these cells to transition to a calcifying phenotype. There is also increasing evidence that these cells undergo specific differentiation steps toward the development of this bone phenotype as shown in vitro studies (11, 54, 116). The signaling molecules important in the development of vascular atherosclerosis are also important in the development of valve calcification including matrix metalloproteinase (43, 49); interleukin-1 (47); transforming growth factor-β (44); purine nucleotides (80, 81); receptor activator of NF-κB (46); osteo-protegrin (46); elastolytic cathepsins S, K, and V and their inhibitor cystatin C in stenotic AVs (39) Toll-like receptors (114); TNF-α (48); MAPK (35); and the canonical Wnt pathway (16, 91, 103). Similar to vascular atherosclerosis, these events are potential cellular targets for pharmaceutical agents to slow this disease process. 3-Hydroxy-3-methyl-glutaryl-CoA reductase agents, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (ARBs) provide an interesting approach for targeting in this disease. A number of experimental studies have tested the effects of statins and ARBs in vivo and in vitro (4, 55, 63, 81, 82, 91, 93, 94, 113). The results from these experimental studies demonstrate an in vivo reduction in the atherosclerotic bone-forming lesion (4). Furthermore, in vitro, specific signaling pathways targeted with atorvastatin show improvement in the extracellular nucleotide regulation of bone formation in the AV myofibroblast cell (80, 82). Furthermore, there is evidence that the angiotensin-converting enzyme pathway is upregulated and colocalized with LDL in calcified human ex vivo AVs and may also play a role in future potential medical therapy (75).

**Cellular Mechanisms of AV Calcification: The Osteoblast Phenotype**

The hallmark of AV stenosis is calcification, which for years was thought to be due to a passive process but currently is defined as a bone formation process. Calcification is the hallmark of this disease in terms of phenotype (92) and survival in this patient population (95). There is also growing evidence in the field of genetics and AVs that there are an increasing number of genetic abnormalities important in this disease process: vitamin D receptor (78), estrogen receptor (69), polymorphisms in lipoprotein metabolism (7, 71) and loss of function mutation in the Notch1 receptor (32), polymorphisms in the angiotensin-converting enzyme pathway (77), polymorphisms in the inflammatory signaling pathways (79), and polymorphisms in genes regulating oxidative stress (64). In addition, a study from France demonstrated the familial aggregation of this disease in families (87). The traditional cardiovascular risk factors (5, 6, 12, 14, 17, 19, 24, 28, 40, 53, 61, 83–86, 107, 112) and the genetic studies (19–27) are important in the development of the final common pathway: the osteoblast phenotype (60, 92). These studies show that there are evolving mechanisms for AV calcification that include cardiovascular risk factors and genetics to active specific cell signaling pathways in this disease process.

The understanding of these signaling pathways, atherosclerotic and osteoporotic risk factors, and genetics is shown in Fig. 1, which outlines the interactions of the interrelated concept of traditional cardiovascular risk factors and genetic risk factors and identified cellular targets for the treatment of AV disease. The normal AV is located at the top of the figure. In the presence of lipids, the AV endothelium is activated and abnormal oxidation states develop. The myofibroblast cells then begin to proliferate and synthesize extracellular bone matrix proteins with the upregulation of the Wnt/lipoprotein receptor-related protein 5 (Lrp5) activation (16, 91, 103). These proteins over time mineralize and calcify, and a calcified AV develops as shown at the bottom of the figure. The calcified valve at the bottom of Fig. 1 demonstrates the osteoblast bone formation in the leaflets of the valve. The arrows show the valves after improvement with medical therapy (4, 55, 63, 81, 82, 91, 93, 94, 113) using statins, angiotensin-converting enzyme I, ARB, or lipid lowering (58).

Descriptive studies of patient specimens have defined the critical features of AV calcification including osteoblast expression, cell proliferation, and atherosclerosis (16, 18, 43, 60, 72, 92, 93). The concept of bone calcification within the heart has been first defined by vascular biologists. Demer (23) was the first to define lipids in the development of vascular and valvular calcification. These studies (108) demonstrate that calcifying vascular cells have the multipotential ability to differentiate to calcifying phenotypes. Towler et al. (103) further confirmed this hypothesis that vascular calcification differentiates via the Msx2/Wnt pathway in a diabetic mouse model. Further confirmation of this hypothesis in the vasculature was studied concurrently by Giachelli’s group (33) in models of renal vascular disease. Mohler et al. (59) and O’Brien et al. (72) described the expression of the bone matrix protein osteopontin in the diseased calcific AVs. Subsequently, other studies (16, 52, 60, 89, 92, 106) have described the presence of bone in calcifying human AV lesions. Cardiovascular calcification is composed of hydroxyapatite deposited on a bone-like matrix of collagen, osteopontin, and other noncollagenous bone matrix proteins (59, 60, 72). These findings have been confirmed histologically with the documentation of osteoblast bone formation in calcified AV that were removed at the time of surgical valve replacement (60, 72, 92). We used multiple techniques to assess for the osteoblast phenotype including RT-PCR analysis, bone histomorphometry, and microcomputed tomography to demonstrate that an osteoblast-like cellular pathway was present in calcified AVs (92). The gene expression of osteopontin, bone sialoprotein, and Cbfal (the osteoblast-specific transcription factor for bone formation) were increased in the calcified AV compared with control valves from heart transplantation recipients (92). These findings show that the myo-
fibroblast cell residing in the AV have the potential to differentiate into bone-forming cells which mineralize over time and express an ossification phenotype similar to the mechanisms important in vascular calcification.

Figure 2A demonstrates the cellular architecture of the AV including the endothelial layer (22), the subendothelial space, and the myofibroblast cell (45, 54) that resides below the endothelial cells located in the AV fibrosa. Atherosclerotic risk factors activate endothelial dysfunction in vascular and valvular heart disease, which is an important initiating event in both of these processes. Figure 2B demonstrates the influence of inflammation and lipids in the AV endothelium and the activation of a number of different signaling pathways important in the calcification process. The myofibroblast cell that resides below the endothelial cell layer has the multipotential ability to differentiate into other phenotypes (54). Figure 2C shows the myofibroblast cell differentiating into a calcifying and mineralizing osteoblast-like cell. The cellular and genetic studies have demonstrated that AV calcification has an active cellular biology which is evolving into a multifactorial etiology for the activation and progression of this disease.

**Endochondral Signaling Pathways in the Bone and Heart**

The LRP5 pathway regulates bone formation in different diseases of bone (13, 34). The discovery of the LRP5 receptor in the gain-of-function (13) and loss-of-function (34) mutations in the development of bone diseases resulted in a number of studies that have shown that activation of the canonical Wnt pathway is important in osteoblastogenesis (8, 29, 41, 110). Three studies to date have confirmed the regulation of the LRP5/Wnt pathway for cardiovascular calcification in vivo and ex vivo (16, 91, 103). The LRP5 receptor signaling in bone is mediated via the canonical Wnt pathway. In this pathway,
Wnt proteins bind to receptors composed of a frizzled protein and either of the LDL receptor-related proteins LRP5 or LRP6. Signaling via Disheveled and/or Axin then results in the inactivation of a multiprotein complex including Axin, adenomatous polyposis coli, and glycogen synthase kinase-3β that normally renders β-catenin unstable. By inhibiting this complex, Wnt signals lead to the accumulation of β-catenin in the cytosol and its entry into the nucleus. Once in the nucleus, β-catenin binds to proteins of the T-cell factor/lymphoid-enhancer factor-1 family and modulates the expression of several target genes that include cyclin D, Cbfa1, and Sox9. Bone and cartilage are major tissues in the vertebrate skeletal system, which is primarily composed of three cell types: osteoblasts, chondrocytes, and osteoclasts. In the developing embryo, osteoblast and chondrocytes both differentiate from common mesenchymal progenitors in situ, whereas osteoclasts are of hematopoietic origin and brought in later by invading blood vessels. Osteoblast differentiation and maturation lead to bone formation controlled by two distinct mechanisms: intramembranous and endochondral ossification, both starting from mesenchymal condensations.

The role of lipid signaling of the LRP5 receptor has been defined in experimental in vitro and in vivo lipid models of vascular atherosclerosis. LRP5 binds apolipoprotein E-containing lipoproteins in vitro and is widely expressed in many tissues including hepatocytes, adrenal gland, and pancreas (50). The production of mice lacking LRP5 revealed that LRP5 deficiency led to increased plasma cholesterol levels in mice fed a high-fat diet, secondary to a decreased hepatic clearance of chylomicron remnants and also marked an impaired glucose tolerance (30). The LRP5-deficient islets also demonstrated a reduction of intracellular ATP and calcium in response to glucose and thereby decreasing glucose-induced insulin secretion (30). Furthermore, experimental hypercholesterolemia is associated with the increase in LRP5 receptor expression and the activation of cell proliferation and extracellular matrix production critical in bone formation (91). These studies provide evidence that the lipoprotein metabolism is regulated by the fifth family member of the LDL coreceptor family LRP5 in these knockout mouse studies.

Figure 2D demonstrates the secretion of Wnt (88) from the endothelial cells into the subendothelial space to bind and form the Lrp5/Wnt/Frizzled complex on the myofibroblast extracellular membrane. F: transcriptional activation of the Cbfa1 osteoblast differentiation pathway in the myofibroblast cell. LEF, lymphoid enhancer factor; TCF, T-cell factor.
**Phenotypic Expression of Calcification in the Heart: The Bernoulli Equation**

Fluid hemodynamics in the heart is dependent on multiple factors as derived by the Bernoulli’s equation for fluid flow (10). Bernoulli described flow through a column that is directly proportional to the change in pressure across the column and indirectly proportional to the resistance. The formula for flow (Q) through the heart is similar to Ohm’s law for electricity as shown in Eq. 1, where \( \Delta P \) is change of pressure and \( R \) is resistance:

\[
Q = \frac{\Delta P}{R} \tag{1}
\]

The entire formula for resistance for steady-state flow through a circular tube is shown in Eq. 2, where \( \eta \) is viscosity, \( r \) is the radius of the tube, and \( L \) is length:

\[
R = \frac{8\eta L}{\pi r^4} \tag{2}
\]

Equations 1 and 2 can be combined to give the flow rate through a circular tube in terms of a pressure drop that is described as Poiseuille’s law:

\[
Q = \frac{\pi r^4}{8\eta L} \Delta P \tag{3}
\]

The differences in the rate of fluid flow are dependent on the radius of the anatomic structure, which is inversely proportional to the resistance. In addition, it is important to note the inverse \( r^4 \) dependence of the resistance to fluid flow. If the radius of the tube is halved, the pressure drop for a given flow rate and viscosity is increased by a factor of 16. Since the flow rate is then proportional to the fourth power of the radius, the size of the radius becomes important as blood flows through the heart.

For example, the average diameter of a left main coronary artery is 4.5 ± 0.5 mm (25), and the average diameter of the left ventricular outflow tract is 2.0 ± 0.2 cm (76). From a circulatory perspective, these differences in the radii lengths become relevant as the effect of the calcification is correlated with the hemodynamic flow properties. These differences in radii will have different effects on resistance. This concept becomes important as the rates of occlusion for vascular occlusion versus valvular stenosis are considered in the treatment of these two disease processes. Vascular occlusion occurs secondary to an increase in vascular atheroma, which in many cases is a calcified artery, similar to valvular atherosclerosis and eventual calcification; however, both have different rates of progression depending on risk factors, genetics, and signaling events. The treatment of these two diseases will have different rates of improvement because of multiple factors including risk factors, genetics, and the anatomic location of the disease that affects the physiology of flow. If both disease processes are treated at the same time, vascular occlusion will respond faster than the valve stenosis because of the size of the radius. Therefore, the fundamental difference in treating these two different diseases will be dependent not only on the targeting biological signaling events important in calcification but also on the understanding that the differences in rate of improvement depends on the size of the radius for the different disease processes. A theoretical understanding of the effect of fluid hemodynamics on the calcification phenotype and the signaling mechanisms involved in the development of calcification provide the foundation for why randomized vascular trials demonstrate positive results more rapidly than randomized valvular trials, if the trials are designed the same.

**Clinical Studies in AV Disease**

The pioneers in valve clinical trials designed studies before the publication of many of the experimental models. The trials were designed with the traditional trial design for lipid lowering using vascular and valvular end points. The first randomized prospective study testing the effects of statins in AV disease was published in 2005 (21). In this double-blind, placebo-controlled trial, patients with calcific AS were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. Aortic-valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical-computed tomography, respectively. The primary end points were a change in aortic-jet velocity and aortic-valve calcium score; secondary end points were traditional vascular end points. The Scottish Aortic Stenosis Lipid-Lowering Therapy, Impact on Regression (SALTIRE) investigators demonstrated a trend in the slowing of the progression of the AV stenosis but not a statistically significant study for primary end points. The vascular end points demonstrated a statistically significant improvement. The SALTIRE investigators concluded that intensive lipid-lowering therapy does not halt the progression of calcific AS or induce its regression (21), and the reason for this negative trial is the timing of therapy (67).

In the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) trial, Moura et al. (65) performed a prospective trial of AS with rosuvastatin targeting the serum LDL-slowed progression of echo hemodynamic measurements and improved inflammatory biomarkers, providing the first clinical evidence for targeted therapy in patients with asymptomatic AS. The aim of the study was to assess rosuvastatin on the hemodynamic progression and the inflammatory markers of AS by treating LDL in patients with AS according to the National Cholesterol Education Program-ATPIII guidelines for one year. Prospective treatment of moderate AS with rosuvastatin targeting serum LDL did slow the progression of the echocardiographic parameters of AS, improved inflammatory biomarkers, and improved vascular end points, showing the first clinical evidence for targeted therapy in asymptomatic moderate to severe AS (65).

The most recent clinical trial, Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (SEAS) (98), was a randomized, double-blind trial involving 1,873 patients with mild-to-moderate, asymptomatic AS. Again, similar to SALTIRE, there were fewer patients with ischemic cardiovascular events in the simvastatin-ezetimibe group (148 patients) than in the placebo group (187 patients); the authors noted that this is mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin-ezetimibe group (105 vs. 70, \( P = 0.01 \)). The investigators concluded that the medication did not reduce the composite outcome of combined aortic valve events in patient with AS including echo progression and vascular end points. These three clinical trials had different results. However, the design of the
clinical trials for SALTIRE and SEAS was the traditional vascular trial studies. RAAVE was designed by clinical echocardiographers and a valve biologist with the perspective of many years of testing the effects of statins in vivo animal models. Therefore, the results are positive with the design of the trial to include the cellular and hemodynamic mechanisms of AV disease.

Translating Experimental Studies into the Treatment of Valvular Heart Disease: The LDL-Density-Radius Theory

Lessons from the experimental studies have evolved into a series of clinical parameters, which provide the foundation for an algorithm to treat AV disease: the LDL-density-radius theory. From a valve biologist perspective, the possibility for medical therapy for AV disease resides in two fundamental differences in vascular versus valvular biology: first is calculating the magnitude of the LDL lowering necessary to treat the process, and second is the difference in the radius between the AV and that of the vessel. These differences are important to understand the final analysis of these trials and the future trial design for AV disease.

The hypothesis to measure the effects of lipid lowering in slowing the progression of calcific AS is dependent on two axioms: biology and hemodynamics. The experimental data demonstrate that lipids activate bone differentiation within the valve myofibroblast (91) and atheroma in the vessel. The first axiom is the LDL density theory. The first axiom accounts for the effect of LDL biology in atherosclerosis. If the risk factors of elevated cholesterol and LDL are important in this disease, then measuring lipid lowering using standard established assays for LDL in the treatment of valve disease becomes necessary. This approach does not take into account the effect of other inflammatory contributors to this disease including high-sensitive C-reactive protein (42), HDL (115), homocysteine (1, 36), CD40 (31, 65, 66, 70), and small-particle LDL (15, 62), which also contribute to the pathogenesis of valvular heart disease but are not routinely measured in everyday clinical practice.

The direction of the LDL affects the vascular lumen in an inward direction causing occlusion over time, as shown in Fig. 3A. The direction in which this LDL affects the valve is an upward direction along the y-axis, which corresponds to the aortic surface of the valvular fibrosa (74). Over time, the leaflets stiffen and can fuse in some valves (51). The overall effect on the radius is a reduction in the AV opening and an obstruction.
that leads to progressive stenosis (26) of the outflow tract (Fig. 3B). Figure 3C demonstrates a formula to calculate the percent reduction of the LDL density before and after therapy, similar to the calculation derived in the Reversal trial measuring reductions in atheroma volume in coronary artery disease (68). A calculation of the percent lowering of LDL density in a valve trial allows for the potential to calculate the improvement on the biological effect of LDL on this disease.

The second axiom for the theory is the radius theory. This hemodynamic radius principle is based on the biological direction of this disease. The second axiom calculates the biological effect of the changes in the radius for the specific anatomic location in the heart. Figure 3D shows the formula for Bernoulli flow through a pipe, as modified (37) for echocardiography. Figure 3D2 shows the formula to calculate AV areas by echocardiography using the Doppler technique (105). The derivation of the Bernoulli principle for this equation includes the drop of the calculation for the flow acceleration and the viscous friction because the velocity profile in the center of the lumen is usually so low that the effect of viscous friction becomes insignificant and not necessary to calculate. Clinically, the viscous friction factor has been ignored as part of the continuity equation in AV disease as defined by the echocardiography physiologists (38).

However, the concept of viscous friction becomes important when comparing vascular trials with valvular trials. The size of the radius plays a very important role in the time to see the treatment effects that are defined by vascular clinical end points such as ischemia and acute myocardial infarction. To date, SEAS and SALTIRE were designed using the vascular trial approach that includes randomizing patients to therapy versus no therapy and measuring echo and vascular end points. However, because the flow in the lumen of the vasculature is not flat due to a smaller radius (10), the viscous friction factor must be taken into account in evaluating the treatment effects within the vasculature as derived by Bernoulli’s original equation (10). Therefore, the treatment effect of LDL lowering will have a more rapid effect on the vasculature compared with the heart valve.

The importance of the smaller radius is shown in Fig. 3E, which is the calculation of the resistance of fluid through a pipe. If the size of the radius is significant in the calculation of flow, the inverse r^4 dependence of the resistance then becomes important in the treatment a smaller radius versus a larger radius in the AV area as viscosity increases by a factor of 16. Therefore, comparing the rates of improvement in a vascular trial versus a valvular trial will be different due to the differences in the size of the radius and the derivation of the modified Bernoulli equation for the echocardiographic formula for valve areas. The continuity equation drops the calculation of viscous friction because of the large size of the radius of the outflow tract of the left ventricle.

To measure the treatment effect for AV disease, Fig. 3F shows the calculation for the percent improvement for the AV area. Mathematically and biologically, clinical trials for AV disease may consider the following two axioms for targeting the disease biology in terms of the radial direction of disease and the magnitude of the LDL density to activate the atherosclerotic process according to Bernoulli’s original formula and the effect on resistance and fluid flow. The effect will require a longer period of time to see the slowing of progression in the AV area for the reasons described in the LDL-density-radius theory. Furthermore, the effect may be masked in the results of the published trials as the patients were randomized to treatment and the two axioms described in this theory are not accounted for in the randomization protocol.

Clinical Application of the Algorithm

The application of this proposed algorithm to calculate the hemodynamic and biological effect of lowering lipid density on the radius can be performed using end points from the different trials. Table 1 demonstrates an example of how to test this theory with the formula using values from the mean end-point results of the three different trials: SALTIRE, RAAVE, and SEAS. (Published mean end-point data were provided to the author from the investigators of the SEAS and SALTIRE trials for this analysis. The author is a coinvestigator for the RAAVE trial.) The calculation of the percent change in LDL and the percent change in aortic valve area (AVA) indicate that the lower percent change in AVA represents the percent improvement needed to demonstrate the potential to treat atherosclerotic AV disease responsive to medical therapy. The RAAVE trial provides a small open-label, prospective trial showing the effect of lowering LDL in AS patients with high-lipid levels, which tests the hypothesis of the LDL-density-radius theory. The trend demonstrates that the smaller the percent change in the AVA in the treatment group of

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<th>LDL</th>
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<tr>
<td>Baseline, mg/dl</td>
<td>End of trial, mg/dl</td>
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<td>SALTIRE</td>
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<tr>
<td>Control</td>
<td>133</td>
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<tr>
<td>Atorvastatin (80 mg)</td>
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<td>RAAVE</td>
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<td>Control</td>
<td>119</td>
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<td>Rosuvastatin (20 mg)</td>
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<td>SEAS</td>
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<td>Control</td>
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<td>Simvastatin (40 mg)-ezetimide (10 mg)</td>
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Application of the LDL-density-radius theory. Calculations demonstrate the significance of the hemodynamic and biological differences between aortic valve clinical trials vs. vascular clinical trials. AVA, aortic valve area; SALTIRE, Scottish Aortic Stenosis Lipid-Lowering Therapy, Impact on Regression trial; RAAVE, Rosuvastatin Affecting Aortic Valve Endothelium trial; SEAS, Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis trial.
RAAVE, the slower the progression. These preliminary calculations are shown in Table 1, which demonstrates that these calculations may allow for the effect of the radius and the LDL to interpret the results from a biological and hemodynamic perspective for present and future valvular heart disease trials. An application of this formula with appropriate statistical analysis is necessary to confirm this hypothesis, and a formal subanalysis of SEAS and SALTIRE will help to solidify this theory. The approach to test this theory would be to perform a formal subgroup analysis of the SEAS and SALTIRE trials: first, to calculate the data using the LDL-density-radius theory from the randomized groups in each trial; second, to calculate groups using the theory separating the patients similar to the RAAVE trial by analyzing the effects of the elevated LDL patient population compared with the normal LDL patient population at baseline; and third, to calculate the percent change in AV area and LDL to test the biological and hemodynamic perspective for this theory in each of the published trials and also in future trials. The potential anticipated results after testing this algorithm in the already published trials may show a potential trend demonstrating the slowing of the progression of AS.

In Summary

For the past 40 years, catheter hemodynamics, echocardiography, and timing of surgery have evolved as the diagnostic and therapeutic approach for calcific AS. In the past decade, with the advent of experimental models and genetic testing, there is a recognition that the AV has an active cellular biology that incorporates three main processes for the development of calcific AS, which include traditional cardiovascular risk factors, genetics, and cellular signaling pathways to differentiate the valve into the osteoblast phenotype. The future management of this disease process will include an understanding of these different mechanisms for future medical therapy of this disease. If the physician can define the traditional risk factors in patients who present with an AV murmur, then targeting these risk factors may slow the progression. The stethoscope can become an inexpensive screening tool for this pathological process and possible preclinical atherosclerosis. If there are no identifiable risk factors, then genetic considerations may play a role. Progress in this field will make a difference for the future delay in the timing of surgery for these patients in the future.

GRANTS

This work was completed with the support of an American Heart Association Grant-in-Aid 0555714Z and National Heart, Lung, and Blood Institute Grants 5K08-HL-073927-04 and 1R01-HL-085591-01A1.

DISCLOSURES

N. M. Rajamannan is an inventor on a patent for the use of statins in degeneration of aortic valve disease. This patent is owned by the Mayo Clinic, and N. M. Rajamannan does not receive any royalties from this patent.

REFERENCES

Review

Mechanisms of Aortic Valve Calcification


