Common inflammatory pathways between coronary artery disease and aortic valve stenosis

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• Acquired nonrheumatic aortic valve stenosis (AVS) is the most common valvular heart disease in the Western world
  

• Considered a passive, age-related degenerative disease

• Recent studies have shown that the pathogenesis of AVS resembles that of atherosclerosis, ranging from endothelial dysfunction to calcification
  
From a clinical point of view, it is of great importance to:

1) identify patients with mild or moderate AVS who have increased risk for subclinical coronary atherosclerosis

2) investigate the effect of atherosclerosis risk factors on the incidence and rate of progression of AVS
• Common histopathological evidence

• Predisposing factors of progression of aortic valve stenosis

• Aortic valve stenosis and cardiovascular outcome

• Clinical evidence of coronary artery disease in patients with aortic valve stenosis
• Common histopathological evidence

• Predisposing factors of progression of aortic valve stenosis

• Aortic valve stenosis and cardiovascular outcome

• Clinical evidence of coronary artery disease in patients with aortic valve stenosis
Φλεγμονή και Στένωση Αορτικής Βαλβίδας

• Διήθηση λεμφοκυττάρων μακροφάγων,
  νεοαγγειογένεση σε ασθενείς με στένωση αορτικής βαλβίδας.
  • Μόρια προσκόλλησης στα ενδοθήλια των νεοαγγείων.

26 ασθενείς στένωση AV
14 ασθενείς ανεπάρκεια AV

Mazzone et al, J Am Coll Cardiol 2004;43:1670–6
Neoangiogenesis is most intense in moderate forms of AS and is distinctly associated with the inflammatory process, suggesting that the growth factors and cytokines excreted by inflammatory cells contribute to its existence.

The angiogenic process was associated with inflammation, but not with calcification or fibrosis, suggesting the presence of a distinct angiogenic response in the evolution of AVS.

**In Vivo Aortic Valve Thermal Heterogeneity in Patients With Nonrheumatic Aortic Valve Stenosis**

The First In Vivo Experience in Humans

Konstantinos Toutouzas, MD,* Maria Drakopoulou, MD,* Andreas Synetos, MD,* Eleftherios Tsiamis, MD,* George Agrogiannis, MD,¶ Nikolaos Kavantzas, MD,¶ Eustratios Patsouris, MD,¶ Dimitris Iliopoulos, MD,¶ Stergios Theodoropoulos, MD,¶ Magdi Yacoub, MD,¶ Christodoulos Stefanadis, MD*  

*Athens, Greece; and London, United Kingdom

<table>
<thead>
<tr>
<th>Grade</th>
<th>AVS (n = 75)</th>
<th>AVI (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Histological features, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>0 (0%)</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Mast cells</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Calcium deposits</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Immunohistological features, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td>0 (0%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0 (0%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0 (0%)</td>
<td>2 (0%)</td>
</tr>
</tbody>
</table>

*p < 0.05 for comparisons between aortic valve stenosis (AVS) and aortic valve insufficiency (AVI).

CD3 = cluster of differentiation 3; IL = interleukin; TNF = tumor necrosis factor.

- leaflets of AVS had increased inflammatory cell infiltration, calcium deposit, and anti-VEGF expression compared to leaflets of aortic valve insufficiency.
Figure 1: Representative Photomicrographs of HE Staining in Examined Specimens of Aortic Valves

(A) Hematoxylin and eosin (HE) staining in aortic valve stenosis showing intense inflammation (×200). (B) The HE staining in aortic valve insufficiency showing normal valvular stroma with sparse cellularity (×200).

Figure 2: Representative Photomicrograph of CD3-Positive Leukocytes in Examined Specimens of Aortic Valves

Intense expression of cluster of differentiation 3 (CD3)-positive leukocytes in aortic valve stenosis.

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Figure 3  Representative Photomicrographs of Anti–TNF-α Staining in Examined Specimens of Aortic Valves

(A) Anti–tumor necrosis factor (TNF) α staining in aortic valve stenosis. Arrows indicate positivity to anti–TNF-α. (B) Anti–TNF-α staining in aortic valve insufficiency showing negative staining for anti–TNF-α (×400).

Figure 6  Representative Photomicrographs of VEGF Staining in Examined Specimens of Aortic Valves

(A) Marked vascular endothelial growth factor (VEGF) immunoreactivity in neovascularism in severe aortic stenosis (×400). (B) Aortic valve insufficiency showing no VEGF immunoreactivity (×400).
In Vivo Aortic Valve Thermal Heterogeneity in Patients With Nonrheumatic Aortic Valve Stenosis

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Figure 5  DT in Leaflets With Intense Versus Low Expression of Inflammatory Indexes

Mean temperature difference (DT) in leaflets with intense versus leaflets with low expression of CD3 (A), TNFα (B), IL-6 (C), and vascular endothelial growth factor (VEGF) (D). The bottom of the boxes represents the first quartile; the top of the boxes represents the third quartile, and the line in the box represents the median value. Abbreviations as in Figures 2, 3, and 4.
Prevalence and pathology of heterotopic ossification in 347 surgically excised heart valves (256 aortic, 91 mitral) in 324 consecutive patients

Higher vascular density in aortic valves with high-grade stenosis compared to the moderate-grade stenosis

Capillary-like sprouts from the at day 10 (A) and day 21 (B) observed with a phase contrast microscope.

ex vivo model

• AR and CNT have lower degree of inflammatory cell infiltrate and apolipoprotein deposition vs AVS

W. Lars et al. / Cardiovascular Pathology 16 (2007) 171–178

• Early lesions of AVS were characterized by accumulation of lipid and infiltration of macrophages and T lymphocytes, whereas,
• late lesions were characterized by formation of calcific plaques, proliferation of fibrous connective tissue and little lipid accumulation

• enhanced expression of MMP-2 and MMP-9 in AVS, confirming the hypothesis of implication of chronic inflammation in AVS


Both inflammation and neoangiogenesis are implicated in the pathogenesis of sclerotic aortic valve leaflets, resembling that of an active or unstable atherosclerotic plaque.
Activation of the complement cascade with ensuing inflammatory response contributes to AVS at its various stages of progression.

Interestingly, C5b-9 was found already in early aortic valve lesions

its deposition was augmented in advanced stenotic valves

suggesting acceleration of the complement activation as the disease advances
Stenotic aortic valves have shown a higher density of C. pneumonia in areas with fibrosis and calcification in relation to preserved areas.

calcification is the dominant feature


calcified regions of aortic valve leaflets have features resembling those of arterial atherosclerotic plaques, such as inflammatory infiltrates and lipid content.

However, calcification during the atherosclerotic process is distinct from the calcification process in a degenerating aortic valve.
Pathogenesis of AVS may additionally involve active bone formation

Osteoblast phenotype is associated with AVS

Stimulation of human aortic valve interstitial cells by a physiologically relevant bacterial product triggers proinflammatory and proosteogenic gene and protein expression.

Interestingly, heterotopic ossification, associated with inflammation and neoangiogenesis, has been described, suggesting an unexpected process of tissue repair in endstage calcified heart valves
Calcification and Lipid deposition

- close association between calcification and lipid deposition, both of which are invariably present in stenotic valves
- Moreover, stenotic aortic valves have a much larger amount of lipids than non-stenotic valves.
- accumulation of three apolipoproteins, in aortic valvular lesions, that have been previously implicated in the pathogenesis of atherosclerosis
  

- aortic valves with stenosis contained markedly higher amounts of lipids than healthy valves

• experimental model of acquired AVS in rabbits receiving high-cholesterol diet + supplements of vitamin D2

• animals not receiving vitamin D2 did not display any significant degree of AVS after 12 weeks of treatment


significant role of calcium in the development of AVS although lipid accumulation is a common finding in both diseases, it seems that its role in the degree of calcification in aortic valve leaflets still needs to be determined,
• Common histopathological evidence

• **Predisposing factors of progression of aortic valve stenosis**

• Aortic valve stenosis and cardiovascular outcome

• Clinical evidence of coronary artery disease in patients with aortic valve stenosis
• Clinical risk factors of AVS share considerable overlap with those of coronary artery disease
  • older age,
  • male gender,
  • increased serum low-density lipoprotein (LDL) concentration,
  • smoking,
  • hypertension,
  • diabetes mellitus


• the factors affecting the progression of AVS have not been extensively investigated.
Factors affecting the progression of AVS

- Age and coexistence of CAD were associated with a more rapid increase in AVS gradient
  

- A strong influence of LDL cholesterol level on the progression of aortic valve calcification
  
176 asymptomatic patients with mild to moderate AVS

- 5 years
- Patients showed rapid progression of valvular disease,
- 46% developing severe AVS
- Increased mortality
- Significant valve calcification, CAD and rapid progression of aortic jet velocity indicated poor outcome

170 patients who had paired echocardiograms

- initial AVA,
- current smoking
- serum calcium level

- independent predictors of amount of AVA reduction per year

- Patients with high cholesterol levels had X2 the rate of progression compared with those with lower cholesterol level
- although cholesterol was not an independent predictor in the multiple regression analysis
Clinical Factors, But Not C-Reactive Protein, Predict Progression of Calcific Aortic-Valve Disease

The Cardiovascular Health Study

Gian M. Novaro, MD,* Ronit Katz, PhD,† Ronnier J. Aviles, MD,‡ John S. Gottdiener, MD,§ Mary Cushman, MD, MSc,‖ Bruce M. Psaty, MD, PhD,¶ Catherine M. Otto, MD,# Brian P. Griffin, MD**

Weston, Florida; Seattle and Bellevue, Washington; Baltimore, Maryland; Colchester, Vermont; and Cleveland, Ohio

Table 4
Multivariate-Adjusted ORs for Incident Aortic Stenosis in Subjects Who Have Normal Aortic Valves or Aortic Sclerosis at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (log)</td>
<td>0.092</td>
<td>0.85</td>
<td>0.70–1.03</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>1.13</td>
<td>1.09–1.16</td>
</tr>
<tr>
<td>Male gender</td>
<td>&lt;0.001</td>
<td>3.05</td>
<td>1.76–5.27</td>
</tr>
<tr>
<td>African-American ethnicity</td>
<td>0.035</td>
<td>0.49</td>
<td>0.25–0.95</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.110</td>
<td>1.62</td>
<td>0.90–2.94</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.013</td>
<td>0.96</td>
<td>0.94–0.99</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.108</td>
<td>1.54</td>
<td>0.91–2.60</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.059</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
</tbody>
</table>

Factors included in the model were current smoking, hypertension, and prevalent coronary heart disease.


- 9% rate of progression from aortic sclerosis to aortic stenosis
- 5-year follow-up period
• Retrospective study
• Patients treated with statins had reduced AVS progression
• Only a modest relationship between the change in LDL cholesterol level and the aortic valve area

- echocardiography- none of the atherosclerosis risk factors were associated with AVS progression


- mitral annular calcification was independently associated with progression to AVS. 15.9% patients developed AVS and almost all patients had aortic sclerosis.


- one-third of the patients with aortic sclerosis developed some degree of AVS in a follow-up of four years confirming the hypothesis that aortic sclerosis may be an important precursor of AVS


confirming the hypothesis that aortic sclerosis may be an important precursor of AVS
• Common histopathological evidence

• Predisposing factors of progression of aortic valve stenosis

• Aortic valve stenosis and cardiovascular outcome

• Clinical evidence of coronary artery disease in patients with aortic valve stenosis
Aortic valve stenosis has been demonstrated to be an independent predictor of cardiovascular events in recent studies.

- The mortality rate is increased in severe symptomatic AVS if untreated.
- Mild to moderate AVS is associated with increased risk of adverse cardiovascular events.
- The mechanisms involved in this clinical outcome in mild to moderate AVS are not completely defined.
- This risk is attributed to rapid progression of AVS, but also to the presence and progression of subclinical CAD.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study Population</th>
<th>End-points</th>
<th>Mean follow-up</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow(1998)[13]</td>
<td>1797 patients, 165 with mild, 96 with moderate, 301 with severe and 1496 without AVS.</td>
<td>Myocardial infarction, sudden cardiac death.</td>
<td>48±30 months</td>
<td>The incidence of coronary events increased with the degree of stenosis (no AVS:41%, mild:62%, moderate:80%, severe:93%, p&lt;0.01).</td>
</tr>
<tr>
<td>Aronow(1999)[45]</td>
<td>1980 patients, 981 with mild and 999 without AVS.</td>
<td>Myocardial infarction, sudden cardiac death.</td>
<td>46±28 months</td>
<td>Patients with mild AVS had a 1.8 times higher chance of developing a coronary event than those without AVS.</td>
</tr>
<tr>
<td>Otto(1999)[48]</td>
<td>5621 patients, 3919 with normal aortic valves, 1610 with sclerotic valves and 92 with AVS.</td>
<td>Death, cardiovascular events</td>
<td>5 years</td>
<td>Consistent stepwise increase in deaths from any cause and cardiovascular causes with increasing aortic valve abnormality (p&lt;0.001).</td>
</tr>
<tr>
<td>Chandra(2004)[47]</td>
<td>425, 203 with mild and moderate AVS. Patients with (peak velocity&lt;2 m/s excluded).</td>
<td>Death, myocardial infarction.</td>
<td>1 year</td>
<td>Higher incidence of cardiovascular events (16.8% vs. 7.1%, p &lt;0.002) and worse event-free survival (normal valves =93%, mild AVS=85%, moderate-severe AVS=77%, p&lt;0.002) in patients with AVS.</td>
</tr>
<tr>
<td>Olsen(2005)[16]</td>
<td>960 patients, 388 with aortic valve sclerosis, 557 without AVS.</td>
<td>Cardiovascular death, myocardial infarction, stroke.</td>
<td>60 ±4 months</td>
<td>Composite end points occurred in 15.4% of patients with aortic valve sclerosis compared with 8.3% of patients without aortic valve sclerosis (p&lt;0.001).</td>
</tr>
<tr>
<td>Taylor(2005)[49]</td>
<td>2279 patients, 175 with mild AVS, 2104 without AVS.</td>
<td>Myocardial infarction, cardiovascular death, revascularization.</td>
<td>3 years</td>
<td>CAD events incidence rates were &gt;4 times higher for AVS.</td>
</tr>
<tr>
<td>Barasch(2006)[46]</td>
<td>3929 patients, 2075 with AVS.</td>
<td>Cardiovascular death, mortality, cardiovascular events.</td>
<td>6.6 years</td>
<td>AVS was associated with incident congestive heart failure and death (HR 1.50, 95%, p&lt;0.05).</td>
</tr>
<tr>
<td>Völzke(2009)[50]</td>
<td>2081 patients, 528 with isolated AVS, 35 with isolated mitral annular calcification and 89 with both diseases.</td>
<td>Mortality, cardiovascular death.</td>
<td>8.6 years</td>
<td>Mortality rates were higher for AVS (incidence rate ratio 3.49, p&lt; 0.001).</td>
</tr>
</tbody>
</table>
The presence of mild AVS was associated with a 50% increase in cardiovascular death and myocardial infarction.

A stepwise increase in deaths with increasing aortic valve abnormality.

*P<0.001 for the comparison with the group with normal aortic valves.
†The rates were calculated for subjects at risk for new events.
‡P<0.01 for the comparison with the group with normal aortic valves.
§P=0.02 for the comparison with the group with normal aortic valves.

• the incidence of new coronary events increased with the severity of AVS
• mild AVS had 1.8 times higher risk of developing a new coronary event than those without AVS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age-adjusted Simple Models</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve sclerosis</td>
<td>4.26 (2.15–8.04)</td>
<td>3.82 (1.83–7.97)</td>
</tr>
<tr>
<td>Women</td>
<td>0.59 (0.36–0.99)</td>
<td>0.80 (0.41–1.54)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1.92 (1.13–3.25)</td>
<td>1.80 (0.96–3.38)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>1.02 (1.01–1.03)</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td>Hypertension medication status</td>
<td>2.00 (1.13–3.53)</td>
<td>1.68 (0.85–3.32)</td>
</tr>
<tr>
<td>Current smoker status</td>
<td>3.30 (1.78–6.15)</td>
<td>2.65 (1.41–4.97)</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dl)</td>
<td>0.97 (0.96–0.99)</td>
<td>0.99 (0.97–1.01)</td>
</tr>
<tr>
<td>Low-density lipoprotein (10 mg/dl)</td>
<td>1.1 (0.99–1.02)</td>
<td>1.1 (0.99–1.01)</td>
</tr>
<tr>
<td>Intimal-medial thickness (mm)</td>
<td>4.83 (1.03–22.62)</td>
<td>0.67 (0.01–5.08)</td>
</tr>
<tr>
<td>Fibrinogen (10 mg/dl)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.1 (1.0–1.1)</td>
</tr>
<tr>
<td>von Willebrand Factor (10%)</td>
<td>1.01 (1.00–1.02)</td>
<td>1.03 (1.00–1.05)</td>
</tr>
</tbody>
</table>

*Hospitalized myocardial infarction or fatal CHD.
†Covariates as major risk factors of CHD are put into the model one at a time, along with the age variable. If a covariate was significant in the simple model, it was put into the multivariable model. Also, variables that have relevant clinical meanings from previous studies, although not significant in the present analyses, are still included in the model.
‡Values are expressed as hazard ratio (95% confidence interval).

• association of mild to severe with all-cause and cardiovascular Mortality
• 8.6 years follow-up
3929 patients with a follow-up of 6.6 years

AVS was associated with incident congestive heart failure and death

Patients with AVS had a higher incidence of cardiovascular events and worse event-free survival by multivariable analysis AVS presence of CAD, presentation with acute MI at the time of admission, increasing tertiles of C-reactive protein, congestive heart failure, and age were independent predictors of adverse cardiovascular outcomes at 1 year follow-up.

AVS is not the mediator of adverse outcomes but rather a marker of the presence of CAD.

Figure 5. Cox multivariate analysis: one-year outcome of cardiac death and nonfatal myocardial infarction (MI). C.I. = confidence interval, CRP = C-reactive protein. Tertiles <0.32; 0.32 to 1.18; >1.18 (mg/dl).

Chandra HR., J Am Coll Cardiol 2004;43(2):169-75
• The significance of subclinical CAD diagnosis seems to be crucial in this group of patients.

• Although the progression of mild to moderate AVS can be easily evaluated by Doppler examination, the identification of patients with increased risk to present with an adverse cardiovascular event prior to the progression of significant AVS is usually underestimated, as a diagnostic algorithm has not been established.
• Common histopathological evidence

• Predisposing factors of progression of aortic valve stenosis

• Aortic valve stenosis and cardiovascular outcome

• Clinical evidence of coronary artery disease in patients with aortic valve stenosis
Mild AVS had 38% sensitivity and 86% specificity for the diagnosis of obstructive CAD.

Mild AVS predicted obstructive CAD in patients aged<60 years, it did not reach statistical significance in patients aged>60 years.

Patients with a two or three vessel disease had a higher rate of AVS than those with a single-vessel disease or no significant stenosis in the coronary tree.

• Retrospective study
• patients with AVS had a higher positive rate of coronary angiography and multivessel CAD than patients without AVS
• The sensitivity, specificity, positive predictive value and negative predictive value of AVS in diagnosing CAD were 63.8, 71.3, 61.7 and 73.1%


Prevalence and significance of AVS in 357 patients with suspected CAD
• AVS is an independent echocardiographic predictor of significant CAD
• predictive value of AVS for the presence of CAD was more prominent in females and in subjects aged<65 years.

• Association between AVS and the extent of coronary atherosclerosis
• Patients with AVS had higher rate of three vessel disease and higher Gensini score to patients without

Soydine S Cardiology 2006;106(4):277-82.

• Valvular atherosclerotic changes are strongly analogous with coronary
• atherosclerosis and generalized atherosclerotic processes
• Gensini score was significantly higher in patients with aortic sclerosis

• aortic valve calcification without obstruction detected by echocardiography is a marker of significant CAD in patients undergoing coronary angiography

• the group with mild AVS had a higher prevalence of significant CAD compared with the control group, suggesting that AVS can serve as a window to atherosclerosis of the coronary arteries

<table>
<thead>
<tr>
<th>Prevalence of coronary artery disease in patients with and without AVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Significant CAD</td>
</tr>
<tr>
<td>Significant LAD</td>
</tr>
<tr>
<td>1-Vessel CAD</td>
</tr>
<tr>
<td>2-Vessel CAD</td>
</tr>
<tr>
<td>3-Vessel CAD</td>
</tr>
<tr>
<td>Left main CAD</td>
</tr>
</tbody>
</table>

AVC, aortic valve calcification; CAD, coronary artery disease; NS, not significant; LAD, left anterior descending.

no significant association between the total heart calcification score index, assessed by echocardiography, and angiographically detected CAD

Corciu. Int J Cardiol 2009; in press
• Echocardiographic detection of aortic valve calcification may provide a new surrogate marker of the extent of coronary atherosclerosis

• The presence of mild AVS, may be an indication of underlying significant subclinical CAD------further evaluation and aggressive treatment

• both diseases share common risk factors

• Whether modification of these risk factors reduces equally the incidence and rate of progression of AVS and atherosclerosis is still controversial.