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Pathophysiologic Mechanisms of Age – Related Aortic Valve Calcification

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1. Introduction

Tricuspid aortic valve is a flexible membrane that opens and closes 100,000 times a day (Fig. 1) [1].
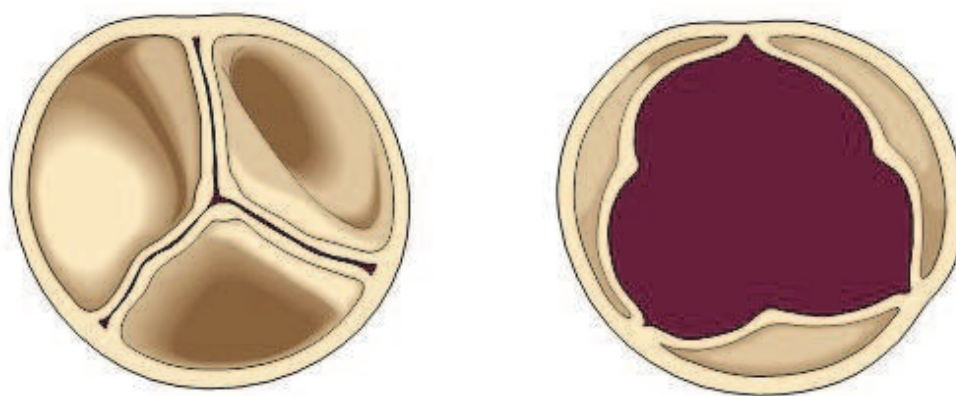

Fig. 1. Normal tricuspid aortic valve in closed and open position.

Aortic stenosis is the most common valvular lesion in Europe and North America [2]. As incidence of acute rheumatic fever has declined, calcific aortic stenosis (CAS) has become the most common indication for surgical valve replacement in the United States (Fig. 2) [3]. Regarding population aged>65 years, its incidence is 2-7% [2]. Interestingly, aortic sclerosis (aortic valve calcification without hemodynamic compromise) is present in more than 25% of patients older than age 65 years [5].

Recent studies provide evidence that atherosclerosis and CAS share common features in relation to risk factors and histopathologic lesions [3]. Moreover, histopathologic evidence suggests that early lesions in CAS are not just a result secondary to aging, but an active cellular process. Recent research implies that the classical "response to injury hypothesis", initially described in atherosclerosis, seems to represent the cornerstone of pathophysiology [4].
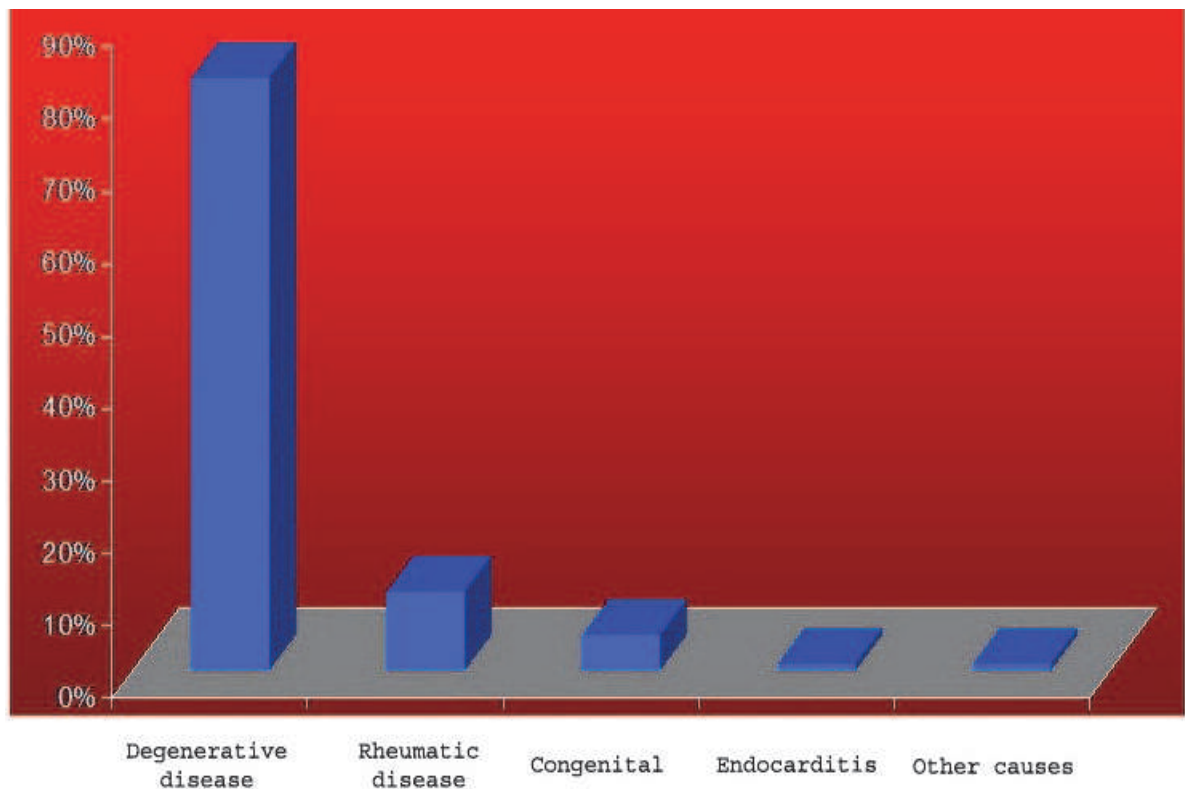
Fig. 2. Causes of aortic valve stenosis.

2. Anatomy - histology

Aortic valve is normally tricuspid, although in 1% of the population it is found to be congenitally bicuspid.

The internal collagen framework of the leaflets is arranged in three layers: fibrosa, spongiosa and ventricularis.

Fibrosa with its dense connective tissue provides strength, spongiosa with its loose matrix of glycoproteins provides a cushion for the mechanical forces, and ventricularis provides elasticity for changes of shape during opening and closing [6].

All three layers of aortic valve are avascular and are innervated by adrenergic and cholinergic neural networks [6].

In aortic sclerosis and stenosis, calcified nodules are initially observed at the base of the cusps and their presence is gradually extended towards the orifice. All three cusps are usually affected but one or more may be dominant. Heavy calcification is associated with hemodynamic impairment leading ultimately to need for valve replacement [7].

3. Calcific aortic stenosis (CAS) and atherosclerosis

3.1 Risk factors

Several studies suggest that traditional risk factors for atherosclerosis such as male gender, hypertension, dyslipidemia and renal failure are implicated in pathogenesis of CAS (Fig. 3) [2, 3, 8].

In addition, as we will discuss later, histologic lesions of CAS and atherosclerosis share common features. Inflammatory infiltration, lipid accumulation, cellular apoptosis and profileration and remodeling of extracellular matrix are present in both situations. Genetic

Fig. 3. Risk factors for calcific aortic stenosis.

polymorphisms and activation of certain pathways such as renin-angiotensin system seem to play vital role and elucidation of their participation in pathophysiology of CAS comprises major challenge [2, 6].

3.2 Similarities in histopathology

CAS and atherosclerosis present characteristic lesions with fibromyxomatous degeneration, inflammatory infiltration and lipid accumulation. Mechanical forces play significant role in progression of lesions [9].

However, pattern of disease is more diffuse in CAS in relation to atherosclerosis where lesions are characterized by necrotic core and fibrous cap. In addition, calcification is more prominent in aortic cusps and is observed even in early stages of pathophysiologic process [6].

Neoangiosis comprises, also, a common feature in CAS and atherosclerosis. Nevertheless, there are some differences. Normal valves are avascular in contrast to artery wall which is supplied by vasa vasorum. New vessels in atherosclerotic lesions are, actually, branches of vasa vasorum and present some defective characteristics as their wall is thin and friable resulting very often in intraplaque hemorrhage. Angiogenesis in calcified valves is not completely understood but it seems to be more organized. Several growth factors such as VEGF (vascular endothelial growth factor) are implicated in formation of vessels which have developed interendothelial junctions and partial basement membrane – like structures [10-12].

4. Pathophysiology of Calcific aortic stenosis (CAS)

Several factors lead to activation of endothelium with subsequent expression of significant factors such as cytokines and adhesion molecules. Subendothelial accumulation of lipids and inflammatory cells comprise the early lesions which trigger a "response to injury". This phase includes remodeling of extracellular matrix and transformation of quiescent valvular interstitial cells to activated interstitial cells (VICs) that consequently gain osteoblastic phenotype (Fig. 4).
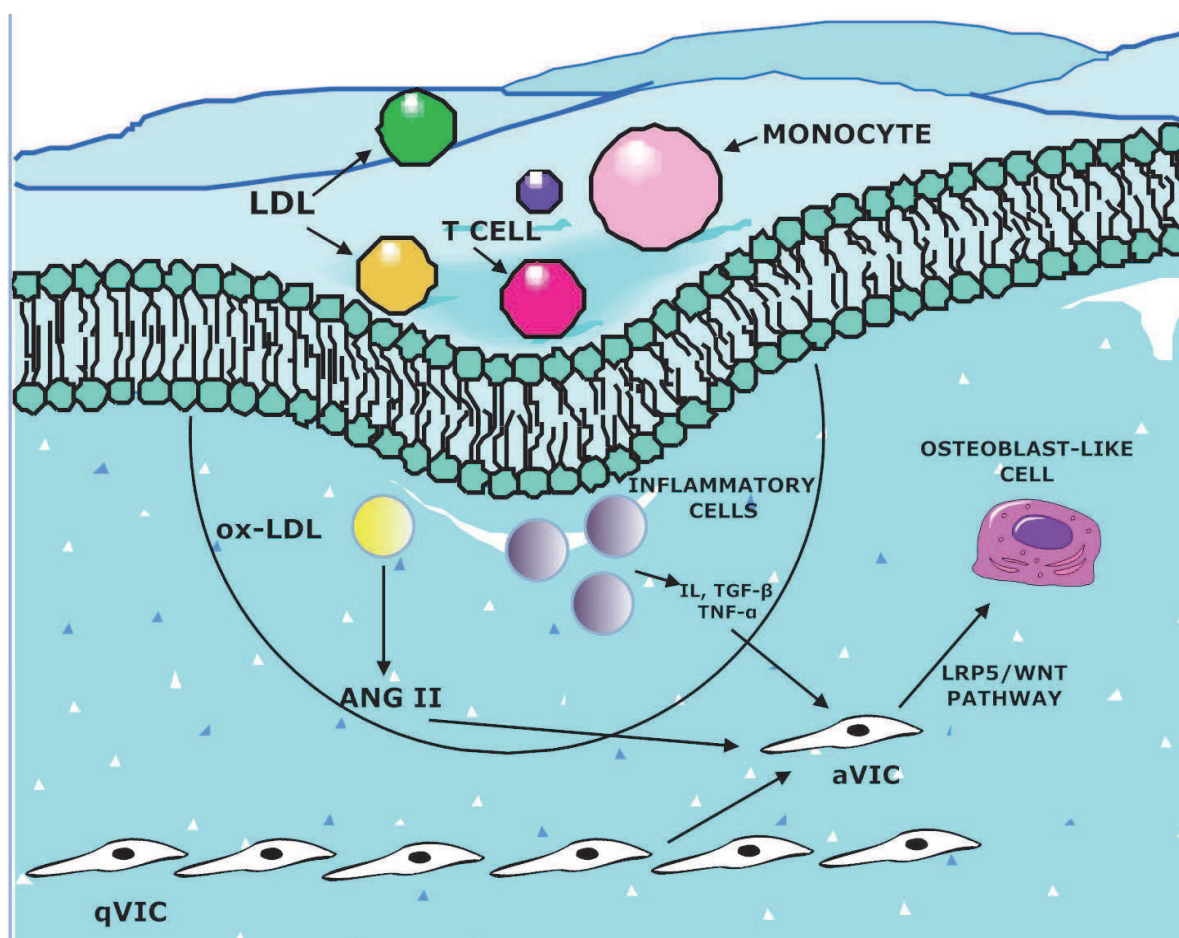

Fig. 4. Schematic illustration of pathophysiology of calcific aortic stenosis (ox-LDL: oxidized LDL, ang II: angiotensin II, qVIC: quiescent valvular interstitial cell, aVIC: activated valvular interstitial cell).

Expression of bone regulatory factors is related to formation of calcified nodules, lesions which represent later stages of aortic stenosis [8].

We will discuss further in detail all aspects of pathophysiologic process.

4.1 Endothelium

Abnormal activation of aortic valve endothelium was observed initially in experimental hypercholesterolemia rabbits [3].

Recent research has shown increased E-selectin plasma levels in patients with severe CAS which normalize after aortic valve surgery [13,14]. In addition, high levels of endothelial microparticles have been found in these patients. Endothelial microparticles are small vesicles that consist of a plasma membrane surrounding a small amount of cytosol. The membrane of the endothelial microparticle contains specific receptors and cell surface molecules which enable the identification of the endothelial origin of the microparticle. Inflammatory infiltration in calcified aortic valves has been related to circulating levels of endothelial microparticles [13, 15]. Several endothelial markers such as CD31, CD34, von Willebrand factor, and CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule) were markedly expressed in tissue samples of human aortic valves that were from patients undergoing valve replacement for severe calcific, non-rheumatic aortic stenosis [13].

Remarkably, decreased availability of nitric oxide and prostacyclin was noticed in these specimen. These molecules are considered to be major modulators of inflammatory processes [1].

4.2 Valvular Interstitial Cells (VICs)

Valve integrity is determined by extracellular matrix. Moreover, quality and quantity of extracellular matrix components are depended on function of VICs [16].

Not surprisingly, age – related reduction of this cellular population is accompanied by fibrous degeneration [17].

VICs are elongated, spindle – like cells and most of them are located in fibrosa. They display morphological and functional characteristics of fibroblasts, smooth muscle cells and myofibroblasts [17].

Five distinct phenotypes of VICs have been recognized:
1. Embryonic progenitor endothelial/mesenchymal VICs
2. Quiescent VICs
3. Activated VICs
4. Adult progenitor VICs
5. Osteoblastic VICs

These cells present plasticity and are capable of changing their phenotype under certain circumstances (Fig. 5) [18].

VICs preserve stability and integrity of the valves and are involved in synthesis and remodeling of extracellular matrix [17].

Calcified nodules consist of nonviable myofibroblasts and crystals of hydroxyapatite. Viable osteoblast-like cells surround these structures expressing bone regulatory proteins. Alkaline phosphatase constitutes unquestionable proof of bone formation in areas of tissue injury [1].
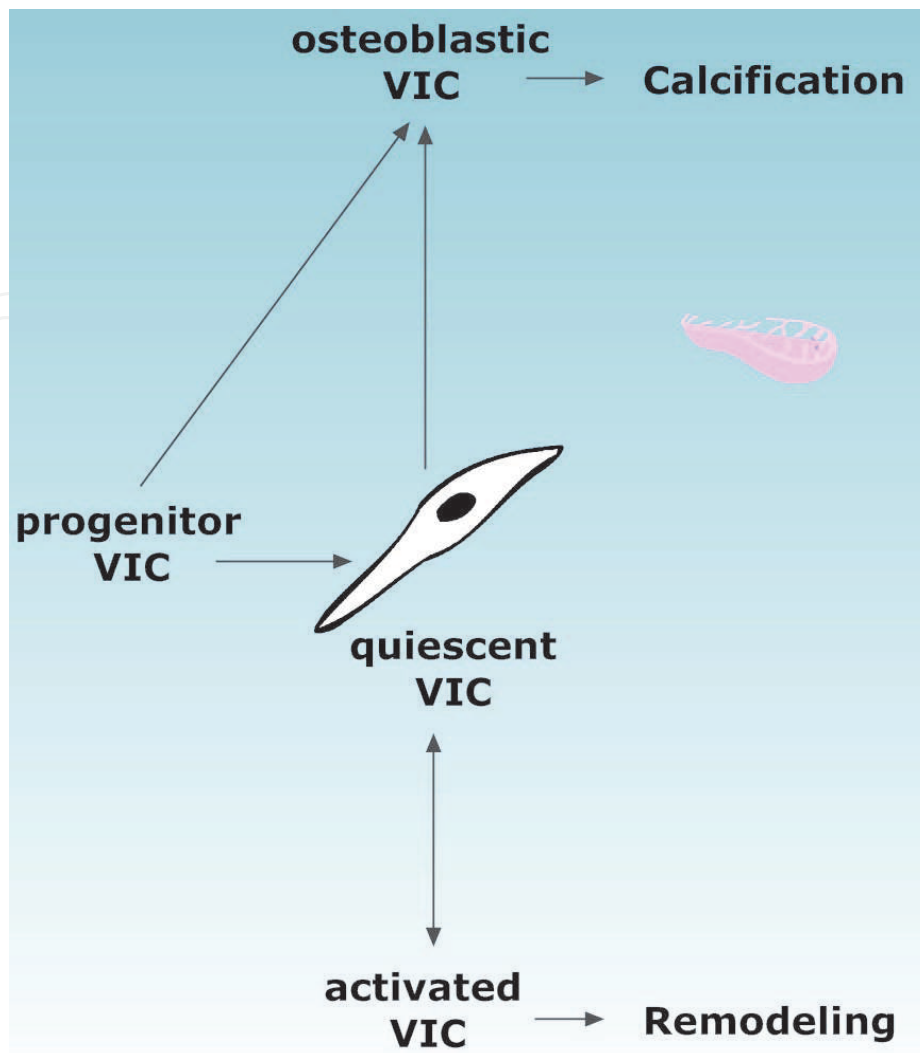
Fig. 5. Subtypes of Valvular Interstitial Cells.

VICs resemble to vascular smooth muscle cells (VSMCs) but their embryology is different. VSMCs derive from cardiac neural crest and lateral mesoderm-derived mesenchyme [6]. Myocardin-related transcription factor-B is the master regulator of differentiation of VSMCs that originate from the neural crest [19]. On the other hand, endothelial to mesenchymal transformation (EMT) phenomenon is considered to be responsible for the origin of VICs. The process seems to be regulated by TGF-β (transforming growth factor-β), NOTCH1, and Wnt/β-catenin signals [20].

4.3 Mechanical forces

Aortic valve cusps are subjected to unceasing influence of severe mechanical forces during lifetime. It is believed that the attachment area of the aortic leaflets to the aortic root encounters the strongest mechanical influence, which may provoke endothelial dysfunction. As we aforementioned, activation of endothelium is related to expression of adhesion molecules and cytokines that initiate several pathophysiologic processes [3].

Leucocyte infiltration and lipid accumulation take place initiating tissue injury with reactive fibro-proliferative changes. Alteration of valve morphology leads to further increase of local shear stress and ultimately a vicious circle is set up [13].

Preliminary studies suggested the 'wear and tear' theory in order to underline significance of mechanical stress in pathogenesis of aortic stenosis [4].

However, mechanical stress does not necessarily hold primary role in pathogenesis. Genetically predisposed individuals in atherosclerosis and aortic valve sclerosis are very prone to mechanical forces that trigger effortlessly key molecular signaling pathways in both diseases [13].

4.4 Genetic influence
4.4.1 Inhibitory proteins

Activation of signaling pathways is depended on expression of inhibitory proteins. Recent evidence has shown that BMP (bone morphogenetic protein), a major bone regulator, is inhibited by several proteins such as noggin, chordin, follistatin, gremlin and Smad proteins. Relative deficiency of these factors could be responsible for aortic valve ossification [1].

4.4.2 Lipoproteins

Determination of allelic variants of lipoproteins in patients suffering from aortic stenosis comprises an interesting research topic. Although a higher prevalence of apoE2 [21] and apoE4 [22], has been observed in some studies, these results have not been affirmed by other researchers.

4.4.3 Inflammatory factors

Inflammation is a prerequisite for aortic valve calcification. Specific genetic variants may trigger intense immune response with devastating results. Polymorphisms of the interleukin-10 gene promoter as well as simultaneous presence of the rare chemochine receptor 5 and connective tissue growth factor alleles are associated with severe calcium burden in patients with aortic stenosis [13].

4.4.4 Bone metabolism

Regarding bone metabolism genomics, vitamin D receptor genetic polymorphism has been extensively investigated [23]. High incidence of the B allele has been found in aortic stenosis and is related with reduced calcium absorption, bone resorption and increased expression of parathormone [3, 13].

Runx2, also designated Cbfa1, belongs to the Runt domain family and is the master transcription factor for bone formation inducing transcription of osteoblast-related genes that enhance mineralization such as osteocalcin gene [24]. Trancriptional activity of Runx2 may be suppresed by Notch1 signaling. Recent research demonstrated that a nonsense mutation of the NOTCH1 gene is associated with enhanced calcium deposition in aortic valves probably via reduced inhibition of Runx2 expression [25].

Finally, a polymorphism of the alpha estrogen receptor, in post-menopausal women is related to increase of cholesterol levels and predisposition to aortic valve calcification [26].

4.4.5 Cell cycle proteins

Finally, some cell cycle regulatory proteins are considered to participate in pathophysiologic process. P21$^{WAF1/CIP1}$ (cyclin-dependent proteinkinase inhibitor p21), and 14-3-3 belong to this category and their expression is reduced in areas of calcification [27].

4.5 Bone factors

Osteoblastic phenotype of VICs implies expression of bone proteins exhibiting regulatory or structural role.

Recent evidence suggests that aortic valve calcification is an active process involving chondro-osteogenic pathways. Calcified nodules are composed of hydroxyapatite crystals precipitated on a matrix of collagen, osteopontin (OP) and osteocalcin (OC) [3].

Aortic VICs in areas containing calcific deposits show significantly higher expression of bone regulatory factors such as BMP, Runx2, Osterix in relation to non-calcified areas (Fig. 6) [3,24].
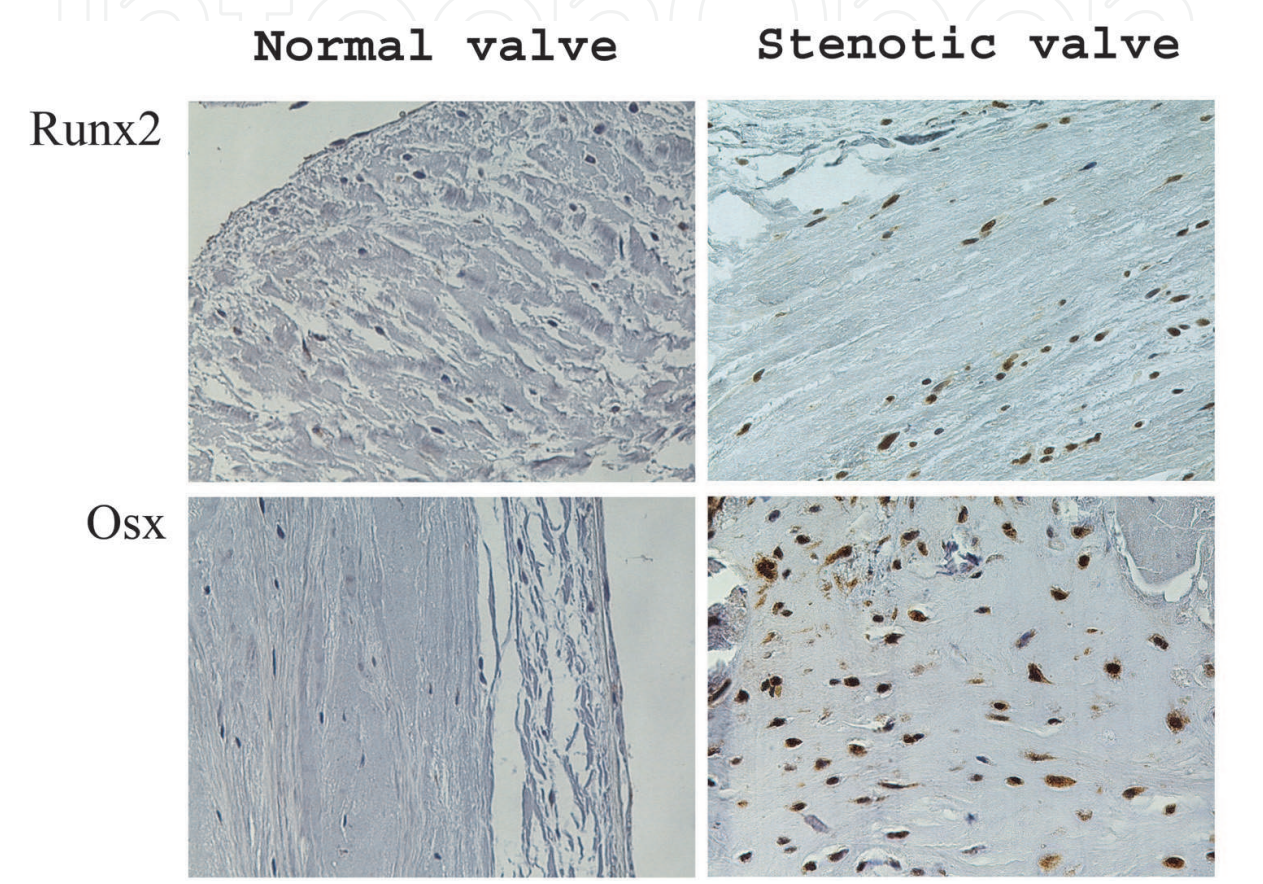

Fig. 6. Runx2 and Osterix immunoreactivity in normal and stenotic aortic valves (x400).

Sox9, a critical regulator of both early and late stages of chondrogenesis, is overexpressed in stenotic aortic valves [24].

Several lines of evidence suggest an important role of the OPG (osteoprotegerin)/RANKL (receptor activator of nuclear factor NF-κB ligand)/RANK (receptor activator of nuclear factor NF-κB) axis in valve pathology [28, 29]. Specifically, in cultured human aortic valve myofibroblasts, RANKL promotes calcium deposition in extracellular matrix and enhances the expression of osteoblast-related genes, promoting osteoblastic phenotype [30].

This phenotype of interstitial cells was also found to be related with high levels of Toll-like receptors (TLR) 2 and 4. Activation of these receptors may lead to increased expression of cytokines and osteogenic factors such as BMP-2 and Runx2 [31].

4.6 Lipids

Initially, Otto et al. noted the association of lipid metabolism with CAS. Accumulation of intracellular and extracellular lipids was constant finding in pathologic specimens [32].

Involvement of the Lrp5 receptor (low-density lipoprotein receptor-related protein 5) in valve calcification has been implicated in several studies [3].

LRP5/Wnt signaling pathway has great importance in bone remodeling. Wnt3a protein is secreted by endothelial cells and has the ability to bind to LDL receptor-related proteins LRP5 or LRP6 complex on the myofibroblast extracellular membrane [33]. This signal results in cytoplasmic accumulation of catenin which subsequently enters nucleus and interacts with proteins of the T-cell factor/lymphoid-enhancer factor-1 family affecting expression of target genes such as cyclin D, Runx2, and Sox9 **(Fig. 7).**
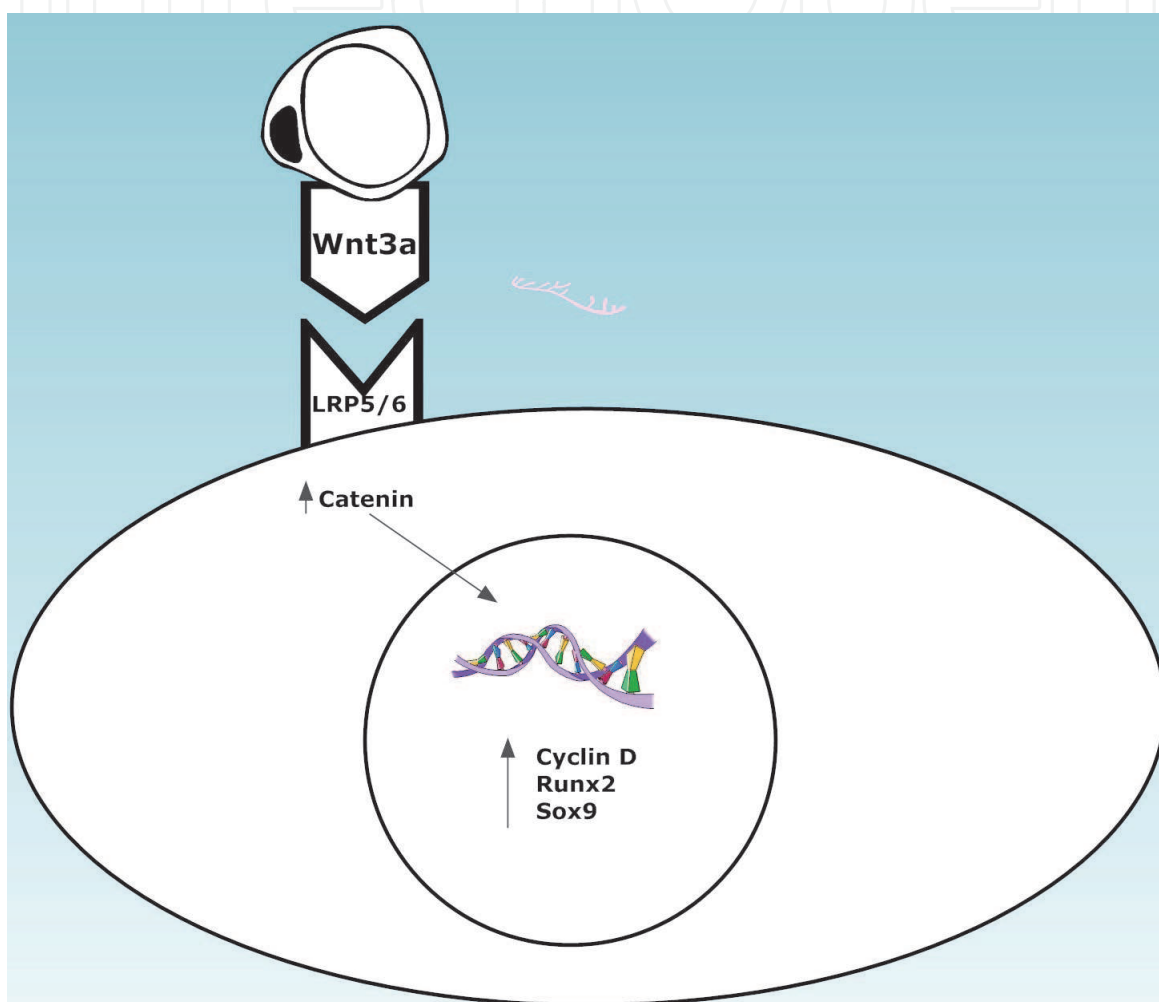

Fig. 7. Effects of LRP5/Wnt signaling pathway on gene expression.

The role of lipid signaling of the LRP5 receptor has been investigated in experimental models of vascular atherosclerosis. Relative deficiency of LRP5 is associated with reduction of intracellular ATP and calcium in response to glucose and thereby decreasing glucose-induced insulin secretion [8]. Interestingly, another study suggested that experimental hypercholesterolemia leads to increased LRP5 receptor expression which promotes cell proliferation and extracellular matrix remodeling. Mineralization, finally, ensues and progressive aortic stenosis is developed [8]. In addition, LRP5 plays significant role in the differentiation process of aortic VICs into osteoblasts, providing another link between lipid metabolism and aortic valve calcification [34].

A high total cholesterol/HDL ratio and small circulating LDL particles (<255A°) seem to be independently associated with rapid development of aortic sclerosis and stenosis.

High levels of angiotensin converting enzyme have been observed in valve lesions presenting increased LDL and apolipoprotein B concentration. It is speculated that plasma lipoproteins promote retention of angiotensin converting enzyme [13, 35].

4.7 Renin-angiotensin system

As we aforementioned, intense angiotensin-converting enzyme localization was observed in fibromyxomatous lesions. Lisinopril managed to attenuate presence of angiotensin-converting enzyme in experimental models [36]. Members of the renin-angiotensin system are implicated in mechanisms of repair of the aortic valve as a normal response to injury. However, hyperactivation of the renin-angiotensin system exerts deleterious effects leading to pathologic fibrosis [1].

4.8 Hemostasis

Role of hemostasis has not been fully elucitaded in CAS. Increased levels of von Willebrand factor as well as expression of fibrinolysis and platelet markers may be just a consequence of pathophysiologic process [13].

4.9 Neoangiosis

Several studies have confirmed neovessel formation in calcified valves [11, 37]. Angiogenesis may be implicated in calcification process by various ways including recruitment of inflammatory cells, transdifferentiation of pericytes of neovessel wall and secretion of cytokines from activated endothelial cells [24].

The whole process is related with increased levels of endothelial nitric oxide synthase, SPARC protein (secreted protein, acidic and rich in cysteine/osteonectin), VEGF and its receptors Flt-1 and Flk-1 [13]. VEGF-A exerts chemotactic activity for human monocytes via its receptor Flt-1, and also promotes their activation and migration [4].

Notably, low grade lesions are characterized by greater neoangiosis relatively to severe lesions suggesting a temporal pattern of the phenomenon in development of aortic stenosis [37].

Considering the fact that neoangiosis is characterized by a short time window as it takes place in days or months, potent therapeutic intervention must be timely and targeted [13].

4.10 Extracellular matrix remodeling

Recent studies have shown overexpression of elastolytic cathepsins S, K, and V and their inhibitor cystatin C in stenotic aortic valves [3].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of bioactive molecules. Several studies have demonstrated implication of MMP-1, MMP-3, MMP-9 in aortic stenosis [9, 38, 39]. In addition, MMP-1 colocalizes with TNF-a suggesting an association between extracellular matrix remodeling and inflammation [9]. Regarding MMP-2, there is no evidence so far for a potential involvement in progression of disease [40].

It is well known that MMPs activity is depended on their respective tissue inhibitors (TIMPs). There is much confusion about role of TIMPs in pathophysiology of aortic stenosis.

As previous studies [9, 41] have shown conflicting results, further research is needed in order to unravel a possible connection with valve remodeling.

Except MMPs, several other factors with degrading activity such as cathepsins S, K and V overwhelm calcified lesions. Cathepsin S expression is more prominent in severely calcified areas while cathepsin V is related to endothelial cells [42]. Moreover, colocalization of cathepsin G and TGF-1b in mast cells lends further support to hypothesis that inflammation is the underlying cause of calcification [43].

Another extracellular matrix glycoprotein, tenascin-C, presents abundant expression in calcified valves. Tenascin-C is a highly conserved, multifunctional protein implicated in cell proliferation, migration, differentiation, and apoptosis [44]. Emerging evidence suggests that tenascin-C enchances alkaline phosphatase activity and expression of MMPs promoting calcium deposition in degenerative lesions. In contrast, normal valves are deficient or present very low levels of tenascin C [1, 4].

Upregulation of cystatin C, a cysteine protease inhibitor, has been found in calcific human aortic valves. Its presence must not be considered circumstantial as previous study reported increased expression in mature osteoblasts [45].

Extracellular matrix proteins with lytic activity may exert favorable effects in a normal repair process. Nevertheless, overexpression of these factors or defective inhibitory mechanisms are responsible for valve injury [4].

4.11 Inflammation

Inflammation is considered to be the most significant aspect of pathophysiologic process.

Several inflammatory mediators have been observed in diseased valves such as terminal complement complex C5b-9, IL-1b, IL-6, IL-8, TNF-α (tumor necrosis factor-α) and Heat Shock Protein-60 [13].

In addition, high serum levels of soluble endothelial adhesion molecules have been found in patients with severe aortic stenosis who had no history of coronary artery disease. Intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin are characteristic representatives indicating an ongoing inflammatory response [4].

There is also intense expression of TGF-b1 [13] which binds to specific proteins of extracellular matrix. Lytic activity of MMPs induces release of TGF-β1 which in turn promotes cellular migration and aggregation as well as apoptosis of VICs [1, 46].

TLR on interstitial cells seem to play critical role in inflammatory response. In vitro studies have demonstrated that peptidoglycan or lipopolysaccharide stimulation of TLR activates NF-kB pathway with subsequent expression of cytokines and bone – related factors [47].

In addition, recent research has shown that aortic VICs in areas containing calcific deposits showed significantly higher Osterix and NFATc1 nuclear immunolocalization compared to non-calcified fibrocellular regions. NFATc1 is a member of a multigene family of transcription factors that belong to the Rel group and control T lymphocyte activation and differentiation [24].

Therefore, inflammation and osteogenesis are indissolubly related.

4.12 Oxidative stress

Oxidative stress has been implicated in aortic stenosis as several research projects have confirmed increase in reactive oxygen species, and a reduction in the expression and activity of antioxidant enzymes catalase and NADPH [48].

4.13 Infectious agents

Great effort has been made by several researchers in order to relate infectious agents with aortic stenosis but data are conflicting.

Bratos-Perez et al. studied aortic valve specimens collected at surgery and indicated the presence of nanobacteria, growing self-replicating calcifying nanoparticles, that potentially represent new pathogens. Their expression has been noticed already in carotid disease and abdominal aorta aneurysms [49].

Nevertheless, role of infectious microorganisms has not been clarified and further evidence is needed.

4.14 Autonomic nervous system

Aortic valve is innervated by adrenergic and cholinergic neural networks. Upregulation of b-adrenergic receptors, especially b2, was observed in areas of calcifcation [50]. In addition, a stable analogue of the purinergic receptor P2Y (ATP-g-S) may cause the transdifferentiation of cultured interstitial aortic valve cells into osteoblasts [51].

5. Treatment effects on pathophysiologic mechanisms

Study of effects of therapeutic strategies on progression of aortic stenosis has provided significant evidence regarding pathophysiology of disease.

5.1 Statins

Role of statins has been studied extensively but findings are inconsistent in patients with moderate to severe degrees of aortic stenosis [13].

Atorvastatin was shown to attenuate leucocyte infiltration and expression of bone regulatory factors in aortic valves of experimental models with hypercholesterolemia [3]. These effects are attributed to modulation of Lrp5 pathway [30] and endothelial nitric oxide synthase [52].

Previous reports suggest that expression of MMPs, in particular MMP-1, MMP-2, MMP-3, and MMP-9, is reduced by VICs and macrophages under the effect of statin treatment [1].

As we aforementioned, TGF-β is an important regulator of cellular proliferation and differentiation and modulator of inflammation and extracellular matrix remodelling. Statins exhibit variable effects on TGF-β expression in aortic valves. Several studies provide evidence that levels of TGF-β in human VICs are reduced with implementation of statin treatment in initial stages of disease [53]. This results in attenuated presence of ALP (alkaline phosphatase) and osteocalcin in calcified lesions [53]. However, these findings were not confirmed in late stages of disease indicating the narrow therapeutic time window of statins [54].

Atorvastatin extenuates the activity of alkaline phosphatase in cultured interstitial aortic cells [48] in contrast to bone tissue where it exerts opposite effect. [55]. Statins, also, reduce the expression of RGS (regulators of G protein-mediated signaling) proteins in calcified valves triggering activation of extracellular-regulated kinases [56] that enhance proliferation of myofibroblasts [13]. Increased expression of BMP-2, a major osteogenic stimulus. has been observed in experimental models treated with HMG-CoA reductase inhibitors [54]. These contradictory findings, called 'statin paradox', suggest that beneficial impact could be time-depended and beyond this time window statins exhibit neutral or even harmful effect. A possible explanation is that different cell populations prevail during several stages of pathophysiologic process resulting in variable response to statin treatment. This could be

related to the results of several trials that failed to demonstrate positive therapeutic effects [13]. In SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) and SEAS (simvastatin and ezetimibe in aortic stenosis study) studies, statin therapy had no effect on the rate of progression of aortic stenosis. Further projects such as ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial are under way to try to define the role of statins in pathophysiologic process. Meanwhile, there is no indication for statin use specific to aortic stenosis [4].

In conclusion, statins exhibit pleiotropic activities and their role must be further analyzed. Inhibition of the HMG-CoA reductase influences not only cholesterol synthesis but also biosynthesis of isoprenoid compounds that are implicated in inflammation and osteogenesis [13].

5.2 Angiotensin Converting Enzyme Inhibitors (ACEI)

As we discussed earlier, angiotensin converting enzyme exhibits intense presence in diseased valves and there is much evidence regarding its involvement in pathophysiology.

Preliminary reports suggest that olmesartan, an angiotensin type 1 receptor antagonist, preserves endothelial integrity and inhibits transdifferentiation of VICs into myofibroblasts or osteoblasts [58].

5.3 Smoking cessation

Smoking, the single most preventable cause of death in Western World, is a leading risk factor not only for atherosclerosis but also for aortic stenosis. Tobacco components, mostly nicotine and acetaldehyde, have the ability to induce TGF-b1 expression in cultured fibroblasts and mast cell activation. These effects are enough to cause increased collagen burden favoring valve calcification [13].

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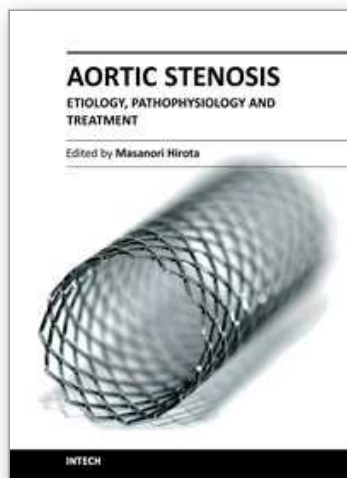
Aortic Stenosis - Etiology, Pathophysiology and Treatment

Edited by Dr. Masanori Hirota

Currently, aortic stenosis (AS) is the most prevalent valvular disease in developed countries. Pathological and molecular mechanisms of AS have been investigated in many aspects. And new therapeutic devices such as transcatheter aortic valve implantation have been developed as a less invasive treatment for high-risk patients. Due to advanced prevalent age of AS, further discovery and technology are required to treat elderly patients for longer life expectancy. This book is an effort to present an up-to-date account of existing knowledge, involving recent development in this field. Various opinion leaders described details of established knowledge or newly recognized advances associated with diagnosis, treatment and mechanism. Thus, this book will enable close intercommunication to another field and collaboration technology for new devices. We hope that it will be an important source, not only for clinicians, but also for general practitioners, contributing to development of better therapeutic adjuncts in the future.

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