Introduction

Left ventricular outflow tract obstruction in adults is most often caused by aortic stenosis (AS). However, obstruction may also occur above the valve (supravalvular stenosis) or below the valve (subvalvular stenosis). AS is the most common heart valve disease in adults. It is the third cause of cardiovascular diseases after arterial hypertension and coronary artery disease. According to the Euro Heart Survey on Valvular Heart Disease, AS is the most common among single native left-sided valve diseases (43.1%). It presents primarily as degenerative AS in adults of advanced age: 2% to 7% of the patients are older than 65 years. Degenerative changes of aortic valve are observed in 20% to 30% of the patients aged more than 65 years and in about 50% of those aged more than 85 years. In 15% of the patients aged less than 65 years, AS develops within 7 years.

Etiology and pathogenesis

There are 3 primary causes of AS:

1. calcific disease of a trileaflet valve
2. congenital abnormal valve with calcification (unicuspid or bicuspid)
3. rheumatic valve disease.

Rare causes of AS include metabolic syndromes (Fabry disease), nonspecific infectious diseases, lupus erythematosus, Paget disease, hyperuricemia, changes due to medication, and after-radiation therapy. Calcific AS develops in patients with end-stage renal disease.

According to the Euro Heart Survey on Valvular Heart Disease, degenerative etiology in AS is predominant (81.9%), followed by rheumatic origin (11.2%); endocarditis accounts for 0.8% of the cases; congenital AS with bicuspid aortic valve occurs in 5.4% of the patients; while other causes are observed in 0.6% of the patients.

Calcific disease

Normal aortic valve is a structure consisting of several layers: valvular endothelial cells at blood-contacting surface, valvular interstitial cells, and valvular extracellular matrix including collagen, elastin, and amorphous extracellular matrix with glycosaminoglycans. Valvular interstitial cells play a crucial role in valve function. They synthesize extracellular matrix and regulate matrix enzymes, which mediate remodeling of collagen and other matrix components.

Degenerative aortic valve disease is characterized by aortic valve leaflet thickening and calcification with normal function at the beginning. It is called aortic valve sclerosis. Progression of degenerative process is characterized by formation of calcium nodules, including the formation of actual bone and new blood vessels. In end-stage disease, large nodular calcific masses are observed in aortic leaflets. Risk factors and mediators leading to calcific AS are similar for atherosclerosis (older age,
male sex, hypercholesterolemia, hypertension, smoking, and diabetes). \(^2\)

AS is a persistent disease connected with activation of 3 processes: lipid accumulation, inflammation, and calcification. \(^3,4\) Mechanical stress (e.g., elevated stretch, shear stresses) on aortic valve leads to valvular endothelial dysfunction, followed by deposition of low-density lipoprotein, lipoprotein A, with evidence of lipoprotein oxidation, as well as inflammatory cells with T-lymphocytes and macrophages, which in turn activate valvular interstitial cells resulting in their osteoblastic transformation. \(^5\) Cytokines, such as interleukin-1 and tumor necrosis factor-α, are markedly elevated in stenotic valves. \(^5,6\) Recent studies suggest that valve calcification is an actively regulated process, which involves local production of proteins that promote tissue calcification. Several extracellular matrix proteins typically found in bones, for example osteocalcin, osteopontin, osteonectin, bone morphogenetic protein, and metalloproteinases, are present in cardiovascular calcification, including cardiac valves. \(^12,16\) Osteopontin expression has been demonstrated in the mineralization zones of calcified aortic valves obtained during necropsy or surgery. \(^7\) There is a complex interaction between the receptor activator of nuclear factor kB (RANK) and its ligand (RANKL) and osteoprotegerin in relation to oxidative stress and inflammation. \(^17,18\) This interaction plays an important role in calcification.

Pathological angiogenesis has been observed in calcific AS. Inflammatory mediators cause an increase in vascular endothelial growth factor-A (VEGF-A) and transforming growth factor-β (TGF-β). \(^19,21\) VEGF-A and TGF-β induce fibrosis and contribute to the progression of calcific AS. TGF-β1 may contribute to the progression of calcific AS by initiating apoptosis-associated mineralization of aortic valve interstitial cells. \(^22\)

A number of authors have reported that the activation of angiogenesis in aortic valves occurs in a close association with valvular stenosis. Angiogenesis is involved in remodeling of the aortic valve and formation of calcified valves. \(^23\)

In later stages, the aortic valve shows extensive thickening and matrix remodeling due to increasing cell proliferation, matrix synthesis, and activation of matrix metalloproteinases. They degrade all components of the extracellular matrix including fibrillar collagen. \(^24\) A recent study suggested that metalloproteinases lead not only to matrix degradation, but may also directly promote the proliferation of fibroblasts to cause tissue thickening. \(^25\)

The authors underline the role of the renin-angiotensin system. Angiotensin II leads to oxidative stress and inflammation and contributes to accelerated degeneration of valve leaflets. \(^26\) Angiotensin-converting enzyme (ACE) and angiotensin I have been found to be increased in stenotic valves. A retrospective clinical study suggested that angiotensin type I receptor blockers, but not ACE inhibitors, slow down calcific process at an early stage of AS. \(^27\)

Oxidative stress has been demonstrated in abnormal endothelial nitric oxide synthase function, which decreases normal physiological levels of nitric oxide along the valve endothelium. \(^28,29\) In calcific AS, the levels of superoxide and hydrogen peroxide are markedly increased.

The presence or progression of calcific AS has been associated with several clinical, genetic, and anatomic factors. Genetic factors play a role in selected patients. Mutations of NOTCH1 are associated with abnormal aortic valve (bicuspid aortic valve with or without aortic aneurysm) and severe aortic calcification. \(^30\) Apolipoprotein E gene polymorphism, interleukin-10, vitamin D receptor, and ACE are factors predisposing to the development of aortic calcification. \(^31,32\)

Increasing age is one of the strongest predictors of cardiovascular calcification. Several regulatory mechanisms decay to exhaustion. Normal endothelial cells are damaged by blood flow; however, the endothelial surface is preserved and crusted with dividing endothelial cells and circulating progenitor cells. The number of progenitor cells and the ability of endothelial cells to divide decrease during aging. The lack of appropriate repair processes leads to calcification. \(^33,34\) The degenerative process spreads from the basal attachment of the leaflets to their edges.

**Congenital abnormal valve** The most frequent cause of congenital AS is bicuspid valve accounting for about 1% to 2% of the cases worldwide. Most frequently, it arises from right coronary and noncoronary leaflet fusion. Patients with bicuspid aortic valve are more often exposed to degenerative changes and more often develop AS and aortic regurgitation. These valve diseases are observed in the 4th or 5th decade of life. They usually occur in isolation but are associated with other abnormalities in 20% of the cases, the most common being coarctation of the aorta or patent ductus arteriosus. \(^25\)

**Rheumatic valve disease** Rheumatic valve disease results from adhesion and fusion of the commissures between the leaflets with small central orifice. Nowadays, rheumatic fever is very rare. Contrary to degenerative aortic valve, rheumatic changes spread from the edges of leaflets and their commissures. Rheumatic disease nearly always affects the mitral valve first, so that rheumatic aortic valve disease is accompanied by rheumatic mitral valve changes. \(^35\)

**Pathophysiology** AS, regardless of the etiology, results in the obstruction in the left ventricular emptying. Left ventricular pressure is much greater than aortic pressure during the left ventricular ejection. Normally, the pressure gradient across the aortic valve during ejection is very low (a few mmHg); however, it can become high during stenosis. The high pressure gradient across
The increased risk of bleeding appears to be due to pathological function of platelets and decreased concentration of the von Willebrand factor. This abnormality results from mechanical disruption of von Willebrand multimers during turbulent passage through the narrowed valve. The severity of the von Willebrand factor abnormality is directly related to the severity of AS and transvalvular gradient.\(^3\)\(^3\)

**Conclusions**  The knowledge of the pathogenesis and mechanisms of developing AS is particularly important. Reduction in risk factors of, for
example, hypercholesterolemia, diabetes, or hypertension, and suppressing the inflammatory process seem to be potential novel strategies for preventing the progression of calcific AS.

REFERENCES


ARTYKUŁ POGLĄDOWY

Patogeneza i patofizjologia stenozy aortalnej u dorosłych

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STRESZCZENIE
Zwężenie zastawki aortalnej należy do najczęściej spotykanych wad zastawkowych serca. Obecnie dominuje postać degeneracyjna tej wady. Jest to przewlekła choroba związana z aktywacją 3 głównych procesów: gromadzenia lipidów, nacieczenia zapalnego i kalcyfikacji. Ostatnie badania sugestują, że zwężenie zastawki jest aktywnym procesem, w którym dochodzi do przebudowy w obrębie substancji pozakomórkowej, rozwoju angiogenezy, a także — w wyniku działania mediatorów zapalnych — do kostnienia. Wiele mechanizmów i czynników ryzyka biorących udział w patogenezie zwężenia zastawki aortalnej przypomina rozwój miażdży. Znajomość tych procesów może odgrywać ważną rolę w prewencji i zastosowaniu właściwej terapii u chorych, szczególnie w początkowym okresie rozwoju stenozy aortalnej.

SŁOWA KLUCZOWE
stenoza aortalna, wady zastawkowe serca