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Review Article

Calcified Aortic Stenosis: From Understanding Pathogenesis to the Development of a Conservative Treatment Strategy (on the 120th Anniversary of the Publication of J.G. Mönckeberg)

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Abstract

In recent decades, there has been a shift in the understanding of aortic stenosis that develops in elderly and older individuals. In Russia, this condition has been traditionally associated with atherosclerosis, while internationally, since the first description by J.G. Mönckeberg (1904), this heart defect has been interpreted as degenerative, resulting from wear and tear of the aortic valve followed by dystrophic petrification. However, even this concept is now considered outdated. New data have highlighted the process in the aortic valve as an active inflammation, a nosologically distinct disease. The role of cellular, particularly lymphocytic, infiltration, genetic predisposition to pathological fibrosis in the valve, specific endothelial damage, activation of mechanisms of ectopic ossification, and more, have been demonstrated. The link with osteoporosis has also become evident. Interest in "Mönckeberg's disease" is further fueled by the belief among pharmacologists that it is feasible to develop methods for preventing the calcification of intracardiac structures. However, this is a matter for the future. Currently, in everyday practice, doctors still lack guidelines for managing patients with senile aortic stenosis. This review is dedicated to addressing this issue.

Keywords: Calcified Aortic Stenosis; Osteoporosis; Bicuspid Aortic Valve; Angiotensin-Converting Enzyme Inhibitors

Abbreviations

AV: Aortic Valve; AS: Aortic Stenosis; CAS: Calcified Aortic Stenosis; LDL: Low-Density Lipoproteins; ACE: Angiotensin-Converting Enzyme; SAL: Sclerosis of Aortic Leaflets; EchoCG: Echocardiography; RAS: Renin-Angiotensin System

In the last 30-35 years, significant progress has been made in studying the calcification of the aortic valve (AV) and the resulting aortic stenosis (AS). In Russia, the term "atherosclerotic heart defect" has become so ingrained in the consciousness of physicians that it continues to be used not only in medical documentation but also in conference presentations and scientific articles. Meanwhile, abroad, the atherosclerotic hypothesis is not only not raised but has never been seriously discussed, except in rare cases of AV lesions in patients with severe familial hypercholesterolemia [1]. There, the term "calcifying aortic valve disease," a continuum from asymptomatic leaflet sclerosis to manifest calcified aortic stenosis (CAS), is widely studied [2]. In other words, the Soviet concept of pathogenesis has not been confirmed, and it is necessary to align Russian cardiologists and therapists with the modern understanding of this issue.

In 2004 and 2014, we published anniversary articles dedicated to the centennial of the first scientific publication on this disease. A decade later, we would like to refresh the knowledge on senile AS, but it is worth starting with at least a brief reminder of who the pioneer of this pathological process was. Johann Georg Mönckeberg was born in 1877 in Hamburg. His father later became the mayor, after whom the main shopping street of the city, Mönckebergstraße, was named in memory of how this distinguished senator rid Hamburg of slums, fought the consequences of the cholera outbreak in 1892, began the construction of the main train station, and supported the city's subway construction program before World War I. While finishing his studies at the University of Strasbourg, Mönckeberg Jr., as a student, published his first scientific work at the age of 22.

After receiving his doctorate in Bonn in 1900, he returned to Hamburg and began working at the relatively small Eppendorf Hospital (now one of the largest in Germany), where in 1903 he wrote his famous article on arteriosclerosis – a specific form of damage to the middle layer of arteries (unlike atherosclerosis) of the elastic and elastic-muscular type, characterized by signs such as media necrosis, media sclerosis, and media calcification. A year later, his article "The Normal Histological Structure and Sclerosis of the Aortic Valve," which initiated a century-long study of senile AS, was published [3]. Although his scientific interests would later cover all aspects of pathomorphology, vascular system pathology, including studies on the cardiac conduction system, remained his primary focus, with 59 of his 86 publications devoted to vascular pathology.

As an original researcher, Mönckeberg specialized in general pathology and soon gained authority, as evidenced by his career trajectory: in 1908, he became an extraordinary professor in Giessen, in 1912, he was appointed professor of pathology at the Düsseldorf Medical Academy, and in 1916, he assumed the chair of pathology in Strasbourg. During this time, the country was at war, with Strasbourg at the center of events. According to contemporaries, Mönckeberg was not only actively involved in providing medical care to the army of the collapsing German Empire but also worked with live patients.

In the early 1920s, he developed an illness initially diagnosed as severe influenza, leading to his resignation and a period of recovery before resuming research in Tübingen and then Bonn. However, in 1923, he experienced a new episode of "influenza," and although he was offered to move to Hamburg to work again at Eppendorf Hospital, he was too ill to accept. Symptoms of uremia began to progress, and Mönckeberg passed away in March 1925.

In the aforementioned 1904 article, Mönckeberg reported autopsy findings of two elderly men with massive petrification of the aortic valve, noting the intact mitral valve. While the possibility of a preceding inflammatory process was not excluded, the main hypothesis proposed was that calcification could result from age-related wear and tear, a consequence of senile degeneration of valve structures. This view became established abroad (literally until the end of the 20th century, the term "degenerative calcified aortic stenosis" was commonly accepted there). From that time, the question of the nature of senile AS became a subject of debate and extensive study.

The early stage of the discussed disease is sclerosis, which histologically appears as thickening on the aortic surface of the leaflet, gradually spreading to the underlying fibrous layer. At first glance, the changes resemble atherosclerosis: accumulation of atherogenic lipoproteins, including low-density lipoproteins (LDL) and lipoprotein(a), infiltration by inflammatory cells, and microscopic calcification [4,5]. However, this first impression is misleading.

Sclerosis of the leaflets is initiated by endothelial damage due to increased mechanical stress, cavitation factors, and platelet dysfunction, but there is evidence that endothelial cells also die through apoptosis mechanisms [6]. Mechanical stress on the valve is highest on the aortic side of the leaflets in the region of their attachment to the aortic root. The hemodynamic impact on the non-coronary leaflet is usually more pronounced than on the left and right coronary leaflets, due to the absence of diastolic coronary blood flow in this Valsalva sinus. This likely explains why the non-coronary leaflet is often involved in the sclerosis process earlier than its "sisters." The mechanical concept partly explains age differences in the onset of calcification in people with tricuspid and bicuspid valves, despite identical histological changes: in patients with a bicuspid valve, which is subjected to higher mechanical loads, calcification often develops two decades earlier [7]. Almost all patients with this congenital defect eventually acquire significant aortic stenosis, while in people with a tricuspid valve, it develops much less frequently and is less severe [8].

Within each leaflet, there is focal accumulation of extracellular lipids in the subendothelial area, displacing the outer elastic mem-

brane toward the fibrous layer [9]. The presence of lipoprotein (a), apolipoproteins B and E in close proximity to these accumulations suggests that plasma lipoproteins are the sources. Oxidized LDL, known for their pro-inflammatory and growth-stimulating properties, have also been identified as factors that transform macrophages into foam cells, analogous to early atherosclerotic changes. However, the primary focus is on the initial infiltration by inflammatory cells, predominantly present in the early stages of AV involvement. Monocytes penetrate the endothelial layer and differentiate into M1 phenotype macrophages [10]. Activated T-lymphocytes release cytokines such as transforming growth factor β1 and interleukin-1β, associated with increased synthesis of matrix metalloproteinases [11], contributing to extracellular matrix formation, leaflet connective tissue remodeling, and local calcification.

At the sclerosis stage, angiotensin-converting enzyme (ACE) has been detected in aortic leaflets. Although some evidence suggests that a certain amount of ACE is produced directly in the valve, it is mostly extracellularly located near apolipoprotein B, implying its external introduction with LDL cholesterol particles. Additionally, angiotensin II, which stimulates monocyte infiltration and uptake of modified LDL in atherosclerotic lesions, has been found in early sclerotic changes in the AV, suggesting ACE activity.

Fibrosis progression is promoted by oxidative stress [12]. In the damaged AV, some fibroblasts differentiate into myofibroblasts, which possess some characteristics of smooth muscle cells. In particular, they begin to synthesize markers of smooth muscle cells, such as α-actin, vimentin, and desmin. This leads to a significant increase in collagen and extracellular matrix synthesis, placing the disease alongside other fibrotic processes such as fibromatosis, systemic progressive sclerosis, Dupuytren's contracture, and scleroderma [13]. It turns out that these myofibroblasts in actively thickening leaflets express type 1 receptors for angiotensin II (AT1 receptors), which again suggests the involvement of ACE in the development of this heart defect. Further research will be needed to better define the potential role of the renin-angiotensin system in the pathogenesis of calcifying aortic valve disease.

Sclerosis leads to valve thickening due to intense interstitial fibrosis, but true leaflet stiffness is, of course, caused by active calcification, which begins at the early stages of the disease. Tiny, practically dust-like calcifications arise in areas of lipoprotein accumulation and inflammatory infiltration. It has been shown that macrophages express osteopontin – a protein necessary for bone tissue formation [14] and now considered a target for conservative tactics in the development of calcification [15]. The concentration of osteonectin – a key protein involved in bone mineralization – increases in the leaflets [16]. Recently, it has been discovered that embryonic glycoprotein tenascin C, which also stimulates bone formation and tissue mineralization, begins to form in thickening valves [17]. As a result, myofibroblasts begin to acquire the phenotype of osteoblasts, forming bone tissue foci around themselves [18]. It is well known that smooth muscle cells, which are essential participants in atherogenesis and constitute the basis of the media in both muscular and elastic arteries, are minimally represented in the valvular structures of the heart [19].

As the disease progresses, active bone formation becomes increasingly apparent. In an assessment of AVs taken from 347 individuals during valve replacement surgery, the majority had signs of calcification, with 13% exhibiting plate-like or endochondral bone tissue, including hematopoietic remodeling, i.e., elements of red bone marrow [20]. As early as 2001, we perhaps for the first time in the world formulated an integral definition of senile aortic stenosis, combining patho- and morphogenesis with hereditary predisposition and hemodynamic characteristics. At that time, the assertion in it about ectopic ossification in the leaflets, with subsequent "hydroxyapatite thickening," sounded almost revolutionary in the homeland of the "atherosclerotic hypothesis," but now it is confirmed by numerous foreign data [21,22].

Moreover, both Russian and foreign researchers have identified the influence of general mineral metabolism on the process under discussion: patients with impaired calcium-phosphorus metabolism have a higher prevalence of calcifying AV disease and accelerated stenosis progression [23]. It is also significant that patients with osteoporosis have a higher prevalence of any valve calcification, and this has been actively studied in recent years in connection with the search for therapeutic approaches [24]. However, the question of whether this observation represents a true causal relationship or is simply a random association due to the high prevalence of both conditions in the elderly remains unresolved.

Today, global interest is focused less on stenosis itself, as by that stage the opportunity to help the patient has often passed, leaving surgery as the only option. The main attention is on the pre-stage

of this condition – aortic leaflet sclerosis (SAL), which is present in a quarter of people aged 65 to 74 and nearly half of those over 84 years old. Risk factors are similar to those for atherosclerosis [25]. According to the Cardiovascular Health Study, which included 5,621 patients over the age of 65, these factors include older age, male gender, smoking, hypertension, and hyperlipidemia [26], as well as type 2 diabetes [27]. While SAL is clinically asymptomatic, its presence is associated with increased morbidity and mortality, even when accounting for coexisting cardiovascular risk factors. The same study showed that it increases the risk of myocardial infarction by 40% and the risk of death by 50% in patients without a pre-existing diagnosis of coronary artery disease at the start of the study. In another prospective study involving 2,000 elderly patients, those with AV sclerosis had a 1.8 times higher likelihood of developing new coronary events [28].

The mechanism of adverse outcomes in patients with SAL is not entirely clear. It is obvious that valve damage cannot be the main cause, as AV hemodynamics remain functional. Moreover, embolization from the damaged valve or thrombus detachment into the coronary arteries is also unlikely, as there is no reason to believe that the sclerosed leaflets are unstable or thrombogenic [29].

One hypothesis explaining the dramatic correlation suggests that SAL serves as a trigger for a general systemic inflammatory process, leading not only to AV calcification but also to atherosclerosis [30]. This is somewhat supported by the fact that almost half of patients with CAS have such severe coronary atherosclerosis that valve replacement surgery is often combined with simultaneous angioplasty. However, in the other half of the patients needing valve replacement, this concept is contradicted: their coronary arteries are relatively intact. Another factor in favor of the "trigger hypothesis" is the association of SAL with markers of endothelial dysfunction, homocysteine levels, and C-reactive protein. Another possible explanation for the increased cardiovascular risk associated with AV sclerosis is genetic polymorphism, linking CAS and atherosclerosis [31].

What is the rate of SAL progression to CAS, the transition from sclerosis to stenosis? In the largest study to date, involving more than 2,000 patients with aortic sclerosis, the frequency and rate of heart defect development were studied: over 8 years, severe AS developed in 3%, moderate AS in 2.5%, and mild AS in 10.5% of the study participants [32]. While the relative numbers may not seem particularly impressive, these figures reflect a significant number of patients overall, and it is clear that the number of those whose sclerosis progresses to some degree of valve obstruction will increase with longer follow-up.

Moving on to the discussion of CAS itself, it must be noted that this is not a rare pathology. In the general population, its prevalence is 2% to 5% among those over 65 years old, and today it ranks third after hypertension and coronary artery disease among cardiovascular diseases in the elderly [33]. Prospective studies on the rate of hemodynamic progression of AS show that the average rate of increase in transaortic flow velocity is 0.3 m/s per year, and the increase in mean transaortic gradient is 7 mm Hg per year, while AV area decreases by 0.1 cm^2 per year [34]. While early publications on the natural course of AS in patients with severe but asymptomatic CAS reported sudden cardiac death rates of up to 20%, more recent authors report a much lower – no more than 1% – likelihood of sudden death in patients without clinical signs of the defect [35].

Although manifesting symptoms of the disease are always considered to be syncope, angina pectoris, and arrhythmias, the disease often clinically debuts with dyspnea on exertion and decreased exercise tolerance. Suspecting senile AS and establishing it as a preliminary diagnosis can be based on the following "criteria":

- A harsh systolic murmur over the aortic points, often radiating to the apex of the heart, neck vessels, and axillary region.
- Age of the patients: 65 years and older.
- Absence of a history of rheumatic fever.
- Combination of angina pectoris, dyspnea, palpitations ("irregular heartbeats") with syncope (dizziness) during exertion.
- Anamnestic data on embolic complications (such as stroke, myocardial infarction, sudden vision loss, hospitalization due to acute occlusion of one of the limb arteries, etc.) or gastrointestinal bleeding that developed after the age of 60-65 and was not associated with peptic ulcer disease.
- The first detection of a heart murmur, according to history, after the age of 55.
- Spontaneous leveling of systemic arterial hypertension.

As can be seen, none of the listed points alone has diagnostic value, and each of them can be explained by pathogenesis other

than Mönckeberg's stenosis. However, together they form a clinical-anamnestic syndrome characteristic of the vast majority of our patients [36]. If we talk about a peculiar diagnostic rule, the first three signs are mandatory, while the remaining ones only increase the likelihood of this defect.

Timely diagnosis is crucial for promptly referring patients for a cardiothoracic surgeon consultation, as patients with severe CAS and clinical symptoms have a poor prognosis if valve replacement surgery is not performed or is delayed for any reason. In one study, among symptomatic patients who declined surgery, the average survival was only 2 years, and 5-year survival was less than 20% [37]. According to other data, only 40% of patients with clinically manifest AS survived for 2 years, and only 12% of them lived for 5 years [38]. During lectures, I am often asked what the indications for AV replacement are. The answer today can be formulated as follows: as long as the defect is asymptomatic, it is not treated; when it manifests with at least one symptom, the patient is operated on [39].

But is it always necessary to wait for obvious symptoms to resort to the help of surgeons, and even more so, therapists and cardiologists? After all, the first manifestation of the disease may be a fatal arrhythmia or an embolic stroke. Therefore, there is interest in obtaining objective markers capable of identifying those who need earlier valve replacement. In this regard, research on serum neurohormones is of interest, as they show a direct correlation between their levels and the severity of AS [40]. For example, brain natriuretic peptide in asymptomatic patients with normal exercise tolerance may reflect early signs of heart failure. A study of 130 patients with severe but asymptomatic AS over the course of a year found that brain and atrial natriuretic peptide levels not only increased in parallel with worsening ventricular dysfunction but also proved to be reliable predictors of clinical disease manifestation [41].

Of course, in today's clinical practice, the diagnosis is confirmed by echocardiography (EchoCG). This method allows for accurate assessment of CAS severity using well-known parameters, as well as studying the degree of left ventricular myocardial hypertrophy, diastolic, and systolic function. EchoCG also helps to identify the presence of post-stenotic aortic aneurysm (more characteristic of rheumatic AS), coexisting mitral valve pathology, and signs of pulmonary hypertension. In patients with severe asymptomatic AS, EchoCG should be performed annually; in moderate AS – every 2 years; and every 5 years in patients with mild stenosis. If for some reason the ultrasound method cannot be performed, cardiac catheterization is used to assess the transvalvular gradient. Abroad, magnetic resonance imaging (MRI) is sometimes performed on CAS patients [42], but the indications for such an expensive study seem questionable.

Moving on to therapeutic strategies, it should be noted that there are currently no clear recommendations for medication therapy. In the case of manifest disease, surgery is indicated, with unique modern technologies, including 3D printing, improving the precision of procedures from preoperative planning to valve replacement itself [43]. Until recently, the focus was on active monitoring and refining indications for surgical intervention. However, in recent years, with the discovery of new pathogenic aspects, there has been a search for drugs that can prevent calcification and delay the onset of stenosis symptoms [44]. The most promising candidates are statins, bisphosphonates, and agents affecting the renin-angiotensin system (RAS).

Statins were initially considered particularly promising, as they are known to influence atherosclerosis not only by reducing hepatic cholesterol synthesis but also through direct anti-inflammatory effects on damaged vessels. However, the data obtained over the past decade are contradictory. Some researchers report a positive effect of statins on the course of AS, with a slowdown in disease progression [45]. Others, while acknowledging many other positive outcomes from these drugs in this patient category, are disappointed by the lack of significant impact on calcification rates from almost all statins [46].

The preventive use of bisphosphonates has only recently begun, but it is undeniable that proper treatment of osteoporosis will to some extent influence the prevention of calcifying AV disease [47].

Great interest is generated by RAS blockade, as the drugs used are well-studied and popular among practitioners. As discussed earlier, ACE plays a role in the early stages of the disease, possibly leading to increased AV leaflet sclerosis. This has led to experimental studies showing the preventive effect of ACE inhibitors on valve remodeling in animals. However, when AS becomes hemodynamically significant, the use of ACE inhibitors is limited (as is the case with many other cardiovascular drugs) due to the fixed cardiac out-

put. However, in recent years, more voices have been advocating for their expanded use [48]. What are the premises for this?

Firstly, drugs affecting RAS may be beneficial in AS due to their cardioprotective effects and favorable effects on left ventricular remodeling. A large Scottish study analyzed 2,117 patients with CAS (mean age 73±12 years, 46% male), 699 of whom were receiving ACE inhibitors or angiotensin II receptor blockers (ARBs). Cardiovascular events and all-cause mortality were assessed. Over an average follow-up period of 4.2 years, 1,018 (48%) patients experienced some cardiovascular event, and 1,087 (51%) died from various causes. Those receiving ACE inhibitors or ARBs had significantly lower rates of cardiovascular events (adjusted hazard ratio of 0.77) and all-cause mortality (adjusted coefficient of 0.76). This large-scale study demonstrated that therapy with drugs reducing RAS activity is associated with improved survival and reduced risk of cardiovascular events in AS patients [49].

It is known that aortic stenosis leads to myocardial hypertrophy, sometimes quite pronounced. It is believed that this reflects not only the left ventricle's response to transaortic resistance but also partly genetic factors, including the patient's gender. Regardless of AS severity, the structure and contractile function of the left ventricle influence both the presence of symptoms and the risk and outcome of surgical treatment. If today valve replacement is offered to asymptomatic patients with mild systolic dysfunction, tomorrow it may be offered at the stage of significant diastolic dysfunction.

It has been shown that when ACE inhibitors are prescribed at the early stages of CAS, they can maintain normal LV function for an extended period. Additionally, data suggest that if these drugs are prescribed due to hypertension in a patient with moderate stenosis and their condition remains satisfactory, discontinuing them is not necessary even with worsening valve obstruction [50]. Moreover, there is evidence that with careful titration, they can stabilize hemodynamics and increase exercise tolerance even in patients with critical stenosis who, for some reason, were denied surgery.

With each passing year, interest grows in finding ways to pharmacologically prevent intracardiac structure calcification and the resulting senile aortic stenosis.

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