DOI: 10.15825/1995-1191-2022-1-96-106

STRUCTURAL VALVE DEGENERATION: ARE THERE COMMON MECHANISMS WITH ATHEROSCLEROSIS AND CALCIFIC AORTIC STENOSIS?

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Current research shows that some of the pathogenetic processes behind structural destruction of bioprosthetic valves are largely similar to those involved in the development of atherosclerotic vascular lesions and native valve calcification. These processes include lipid and leukocyte infiltration, typical for both prosthetic and native tissues. They are accompanied by formation of foam cells, excessive production of matrix-degrading enzymes and increased oxidative stress. This fact suggests that some approaches to conservative treatment of atherosclerosis may be useful for prolonging the lifespan of bioprosthetic valves.

Keywords: bioprosthetic heart valves, structural valve degeneration, atherosclerosis, calcific aortic stenosis, conservative therapy, pathophysiology, risk factors.

INTRODUCTION

To date, the main way of correcting severe valvular heart disease is by replacing the affected valves [1–3]. According to various estimates, 250,000 to 400,000 such operations are performed annually in the world [4–7], about 10,000 in Russia. Moreover, there seems to be higher number of interventions on the heart valve apparatus across the globe. This is associated with increased accessibility of surgical care in developing countries, as well as the aging population of Western countries, accompanied by increasing prevalence of acquired valve defects [7]. By the year 2050, expectations are that annually 850,000 valves will be implanted [4]. Mechanical valves (MV) and bioprosthetic heart valves (BHV) are used as substitutes for native valves [9, 10]. Silence, optimal hemodynamic parameters and low thrombogenicity favorably distinguish BHVs from MVs [10]. At the same time, BHVs have a significant drawback – limited period of functioning, which is caused by occurrence of degenerative changes in the prosthetic biomaterial over time [9, 10]. In some sources, this phenomenon is called structural valve degeneration (SVD) [11, 12]. Due to SVD, 20% to 50% of conventional stented bioprostheses require replacement as early as 15 years after implantation [6]. Moreover, faster rates of SVD directly correlate with younger age [5, 6]. This peculiarity of BHVs predetermines the need for reprosthetic surgeries and is a significant limitation for the wide use of this type of medical devices, especially in young patients [1–3].

It is important to emphasize that the mechanisms responsible for SVD development are poorly understood and studied. As recently as 15–20 years ago, many researchers believed that only passive physical and chemical processes were behind the destruction and calcification of the biological component of BHVs [13–15], but these views are now regarded as simplistic [16]. Numerous original studies conducted over the past two decades show that the recipient's immune response may significantly contribute to the degeneration of the biological tissues of BHVs. Thus, researchers today increasingly consider SVD as an active cell-regulated process [9, 17], whose pathophysiology partially resembles that of atherosclerosis (ATS) and calcification of native aortic valves (AVs) [6, 18, 19].

Given the increase in the number of BHVs used in global surgical practice in recent decades [4, 20], there is an increasing need to find methods to reduce the rate of SVD, which is the main cause of BHV dysfunction. At the same time, the concept of SVD as an active cell-regulated process opens up new opportunities in the development of ways to modify the xenobiomaterial used for valve prosthetics, as well as medication support for operated patients in order to prevent early failure and increase the duration of BHVs functioning. Thus, our review concentrates on the analysis of current information on SVD pathophysiology and the similarity of the mechanisms behind it with those responsible for ATS and calcific aortic stenosis (CAS). Recent advances in the development of methods to reduce the immune response to BHV tissues are also reviewed.

SVD, ATS AND CAS: WHAT DO THEY HAVE INCOMMON?

It is known that ATS and CAS share many common risk factors, such as age, smoking, hypertension, metabolic syndrome, diabetes mellitus and hypercholesterol-

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emia [21, 22]. Some clinical studies have also indicated the association of the latter with SVD and deterioration of the hemodynamic parameters of BHVs due to degeneration of the prosthetic biomaterial [23–27]. Given that SVD, ATS and CAS share common risk factors, it can be assumed that these pathological conditions partially share similar mechanisms.

ATS and CAS are slowly progressive chronic inflammatory diseases characterized by lipid accumulation and activation of processes of maladaptive extracellular matrix remodeling in affected parts of vascular wall and AV leaflets respectively [28]. Intensive lipid and leukocytic infiltration accompanied by formation of foamy cells, which are lipid-laden macrophages, act as key histopathological events uniting the pathogenesis of ATS and CAS [28–33]. Through the release of proinflammatory cytokines, macrophages and foamy cells induce excessive activation of resident smooth muscle cells (SMCs) of vessels and valve interstitial cells (VICs) of valves, which becomes the main driving force behind the pathological changes observed in the development of the diseases under consideration [28–33].

In its turn, SVD is a process of gradual and irreversible destruction of the biological component of BHVs, apparently caused mainly by passive cell-independent mechanisms [14, 15]. At the microstructural level, SVD is mainly manifested by stratification, fragmentation and calcification of collagen and elastin fibrils of the extracellular matrix, and at the macrostructural level by perforations, tears and/or mineralization of the flaps, which eventually cause prosthesis dysfunction due to stenosis and/or transprosthetic regurgitation [11, 12]. However, like the affected areas of vessels and native valves, the tissues of implanted BHVs are subject to infiltration by immune cells, among which macrophages are the predominant type [34–41]. Also, some authors note the presence of lipid stains and foamy cells in explanted BHVs due to dysfunction [34, 41, 42], which is a key sign of atherogenic processes. It should be noted that cellular and lipid infiltrates in BHVs are usually co-localized with areas of damaged or calcified matrix.

Although the primary role of lipids and immune cells (particularly macrophages and foam cells) in the progression of ATS and CAS is generally understood [28–33], their contribution to BHV degeneration is largely unclear. Apparently, macrophages and other immune cells can contribute to additional destruction and calcification of the prosthetic biomaterial through several mechanisms. For instance, macrophages and foam cells are capable of producing numerous matrix-degrading enzymes, including almost the entire spectrum of matrix metalloproteinases (MMPs) and cathepsins B/K/L/S/V [43–46]. Increased expression of a number of MMPs and cathepsins has been noted in resected atherosclerotic plaques [47] and stenotic AVs [29], but BHVs have hardly been studied for the presence of proteolytic enzymes in their tissues. Nevertheless, BHV-infiltrating macrophages and foam cells have been shown to actively secrete MMP-9 [41] and plasminogen proenzyme [40]. It has been shown that non-calcified pericardial BHVs explanted due to leaflet ruptures show higher MMP-9 content compared to calcified prostheses and intact bovine (cattle) pericardium [48]. It is also known that activated macrophages and granulocytes create high concentrations of reactive oxygen species (ROS) in the surrounding space, sufficient to cause DNA damage and death of co-cultured monocytes [49]. As in the case of atherosclerotic plaques and calcified AV leaflets [28, 29], ROS provoke increased oxidative stress in degenerating BHV tissues and immune cells infiltrating them, presumably contributing to oxidative damage of the prosthetic biomaterial [50, 51] and its dystrophic calcification, partially caused by mineralization of apoptosed macrophages [40]. Finally, macrophages can produce calcium-binding proteins, in particular osteopontin and osteonectin [52, 53], as well as produce vesicles resembling matrix vesicles secreted by bone osteoblasts, which mediate bone biomineralization [54, 55]. It is important to note that a number of non-collagenous bone matrix proteins, including osteopontin, osteonectin and osteocalcin, were detected by immunohistochemistry in the tissues of explanted BHVs, and their expression levels correlated with the degree of cellular infiltration and calcification of the leaflets [56]. Again, this pattern largely resembles that of mineralization of native AVs [57, 58].

The study of BHV flaps by immunohistochemical staining showed that lipid deposits found in them consist mainly of oxidized low-density lipoproteins (oxLDL) [41, 42], which is also typical of ATS-affected vessels and calcified AV flaps [28–33]. The contribution of oxLDL to the development of SVD and to BHV dysfunction is still unknown. Potentially, lipid infiltration of BHV flaps can accelerate their degeneration by stimulating inflammatory activation of implant-infiltrating macrophages, formation of froth cells and their increased production of proteolytic enzymes. Experimental data support this hypothesis: the results of immunohistochemical staining of tissues of explanted BHVs show that macrophages penetrating them in the presence of oxLDL express high MMPs-9 levels, which is not observed in the samples without pronounced lipid infiltration [41]. These findings are consistent with the results of studies that have indicated an important role of oxLDL in stimulation of MMP secretion by immune cells [59–63]. It is also known that oxLDL enhance the production of various proinflammatory cytokines and chemokines by macrophages, such as interleukin-1β/-6/-8, tumor necrosis factor alpha, monocyte chemoattractant protein-1, macrophage inflammatory proteins, etc. [32, 62–64]. The release of cytokines and chemoattractant molecules may help recruit new immune cells in the inflammation site, although this process has not been studied in BHV tissues.

Notably, clinical studies reveal an association between BHV degeneration and lipid metabolism disor-

ders. For example, it was found that the risk of early SVD is higher in patients with increased low-density lipoproteins (LDL) and apolipoprotein B in relation to high-density lipoproteins and apolipoprotein A-I, respectively [65, 66]. In addition, elevated circulating levels of proprotein convertase subtilisin/kexin type 9 also correlate with the more rapid SVD and deterioration of the hemodynamic characteristics of BHVs [66, 67]. Finally, a macrophage-produced and/or LDL-borne enzyme, lipoprotein-associated phospholipase A2 (Lp-PLA2), seems to be associated with BHV degeneration [42]. It is known that Lp-PLA2 is involved in the development of both ATS and CAS by enhancing inflammation and calcification of native tissues through generation of such proinflammatory, proapoptotic and proosteogenic mediators as lysophosphatidylcholine and oxidized fatty acids [29, 68].

Probably, another mechanism can unite SVD and CAS pathogenesis. It has been established that the degree and rate of progression of native AV calcification correlate with the presence of intraleaflet haemorrhage (ILH) in the valve tissues [69], with the areas with ILH usually co-localized with calcium deposits [70, 71]. The relationship between ILH and AV mineralization is poorly studied [72]. It is assumed that iron accumulation in the matrix, which originates from the dead erythrocytes and induces differentiation of VICs into osteoblast-like cells through elevated oxidative stress, promotes calcification enhancement [72]. Recently, a group of researchers from China noted that there are also erythrocyte iron deposits co-localized with mineralized matrix areas in the flaps of explanted BHVs [73]. Probably, the iron accumulated in BHVs contributes to ROS generation through Fenton and Haber-Weiss redox reactions and subsequent oxidation-conditioned degeneration of the prosthetic biomaterial [50, 51]. In addition, fragments of erythrocytes diffusing into loosened tissues and then dying in them can serve as calcium phosphate nucleation nuclei.

Some commonalities of pathophysiological features characteristic of SVD with those of other inflammatory diseases of the cardiovascular system can also be seen in the results obtained by a group headed by Dr. Skowasch (Skowasch et al.) [74]. These studies showed increased expression of C-reactive protein (CRP) by BHV-infiltrating cells, and CRP levels in BHV-degenerating tissues correlated with those in the blood serum [74]. In addition to those described above, other mechanisms typical of ATS and CAS pathogenesis may also be involved in SVD. For example, activation of renin-angiotensin-aldosterone system [75–77] and autotoxin accumulation [78] are largely responsible for elevated oxidative stress and, as a consequence, inflammatory and fibroproliferative processes in the affected vessels and AVs. Presumably, these same factors may also play a role in the development of SVD, but their involvement in BHV degeneration has not yet been studied.

SVD, ATS AND CAS: FUNDAMENTAL DIFFERENCES

Despite the obvious similarity of a number of processes uniting the pathophysiology of SVD, ATS and CAS, they have notable differences. The most important of these is the absence of a fibroproliferative response to inflammatory infiltration on the part of BHV tissues, since they usually do not have living mesenchymal cells that could mediate it. A possible exception is only homovital allogeneic valve conduits, which have in their tissues significant populations of endothelial cells, SMCs and VICs of donor origin. Also living cells in allografts can be preserved after antibiotic treatment and cryopreservation, though their quantity in this case is usually small [79, 80]. Small clusters of cells with endothelial and fibroblast phenotype were also detected in xenogeneic BHVs [39, 81, 82], but there are no examples in current literature of when their number would be comparable with that in native tissues.

Hypothetically, fibrosis and ossification of BHV flaps controlled by myofibroblasts and osteoblast-like cells, respectively, can occur during SVD [6]. At least all necessary components for this are present in BHV tissues [83]. Nevertheless, it seems extremely unlikely that a small population of mesenchymal cells can contribute to fibrous and/or osteogenic remodeling of the prosthetic biotissue matrix in such a way that it would be visible against the background of passive degenerative-dystrophic processes. Modern research supports these views. For example, a group of scientists from Japan could not find cells with myofibroblast or SMC phenotypes in explanted BHVs, while fibrosis and mineralization of their flaps, apparently, were associated with deposition of fibrinogen from blood plasma and macrophage apoptosis [40]. Another research group attempted to study the expression of components of the cytokine system OPG/RANKL/RANK in explanted BHV tissues (the latter is known to be responsible for osteogenic differentiation of cells in native AVs), which showed that this system is not involved in SVD [84].

Another important difference SVD has from ATS and CAS lies in the triggers of the processes of lepid accumulation and leukocyte infiltration. For instance, endothelial dysfunction, accompanied by changes in the endothelial layer secretory profile and/or its partial loss, is the main cause of pathological changes in the affected vessels and AVs [28, 29]. Because of this, LDL start penetrating into the subendothelial space and deeper layers of the vascular wall or cusps. Oxidizing, they provoke intense aseptic inflammatory reactions with further recruitment of immune cells. With the exception of homovital allogeneic valve conduits, BHVs lack endothelial lining (although small reendothelized areas may occur on their surface [40]), thus, the considered mechanism cannot be involved in their case. Analysis of current literature sources shows that the main trigger of inflammatory

infiltration of xenogeneic BHVs is most likely residual xenoglycans, the end links of the polysaccharide chains of which are represented by sugars such as galactose-alpha-1,3-galactose and N-glycolylneuraminic acid [85]. Moreover, the main trigger of immune response to allogeneic valve substitutes seems to be residual molecules of human leukocyte antigen [86–88]. Lipid infiltration of LDL in this case is secondary to macrophage infiltration [41, 83].

Based on the above, we conclude that unlike in contrast to ATS and CAS, SVD is unlikely to be mediated by resident or alien mesenchymal cells. Thus, immune cells, primarily macrophages, are responsible for cell-mediated degradation of BHVs. The main trigger of inflammatory infiltration of both xenogeneic and allogeneic BHVs are foreign carbohydrate and protein molecules, which allows to consider the active processes behind SVD not as an ATS-like process, but rather as one of the variants of chronic implant rejection [9, 17], which has some features of atherosclerotic lesion. A comparative characteristic of SVD, ATS and CAS is shown in Table.

ATS THERAPY IN SVD INHIBITION

To date, there are no conservative therapies to slow down SVD. Nevertheless, the partial similarities between SVD and ATS suggest that anti-atherosclerotic drugs may be effective in inhibiting BHV degeneration. Some authors had previously believed that better clinical results could be achieved with lipid-lowering therapy in patients with appropriate indications [89]. Two small-scale retrospective studies demonstrated lower rates of increase in peak flow velocity, decrease in effective valve opening

Table

Comparative characteristics of some pathophysiological features between SVD, ATS and CAS

Sign	Structural valve degeneration	Atherosclerosis	Calcific aortic stenosis
Presence of inflammatory cellular infiltrates.	Present, but not in all cases.	Always present.	Always present.
Deposition of oxidized low-density lipoproteins and formation of foam cells.	Noted by several research groups, but apparently, rarely accompanies cellular infiltration in prosthetic biotissues.	A key sign of the disease.	Key sign of the disease.
Increased production of proteolytic enzymes, proteolysis activation.	A significant increase in MMP-9 expression was detected in some samples. However, interaction of proteolytic enzymes with stabilized matrix is poorly studied.	Increased expression of various MMPs, cathepsins and other matrix-degrading enzymes. Active matrix remodeling.	Increased expression of various MMPs, cathepsins and other matrix-degrading enzymes. Active matrix remodeling.
Release of inflammatory mediators, including various cytokines and chemokines.	Virtually unexplored. At least one study noted an increase in CRP expression in degenerating bioprostheses. There is indirect evidence pointing to the involvement of Lp-PLA2 in the destruction of prosthetic biotissues.	Increased production of a wide range of cytokines, chemoattractant and other proinflammatory agents.	Increased production of a wide range of cytokines, chemoattractant and other proinflammatory agents.
Increase in intracellular oxidative stress, intensification of extracellular oxidation.	Oxidation-dependent damage to the prosthetic biotissue has been noted in at least two studies.	One of the main mechanisms of pathogenesis.	One of the main mechanisms of pathogenesis.
Involvement of noncollagenous bone matrix proteins in biomineralization.	Increased expression of osteopontin, osteonectin, and osteocalcin was detected in calcified areas of the matrix.	Involved in those cases where calcification in atherosclerotic plaque is observed.	One of the main participants in aortic valve calcification processes.
Initiating causes of lipid and leukocyte infiltration.	Residual xenoglycans and other foreign molecules.	Endothelial layer dysfunction and damage.	Endothelial layer dysfunction and damage.
Active fibroproliferative response to inflammatory infiltration on the tissue side.	Probably impossible due to the complete absence or extremely small population of mesenchymal cells. Passive mechanisms (stratification of biotissue fibers, deposition of fibrinogen and other proteins from blood plasma) are responsible for leaflet fibrosis.	One of the main mechanisms of disease development; it is mediated by activated valvular interstitial cells.	One of the main mechanisms of disease development; it is mediated by activated valvular interstitial cells.
Heterotopic ossification	Apparently, it cannot be realized because no osteoblast-like cells are found in the prosthetic tissues.	Partial mineralization is due to the activity of smooth muscle cells with an osteogenic phenotype.	One of the main mechanisms of aortic valve calcification.

area and increase in regurgitation in patients with BHVs that were treated with statins compared to patients in the control group [90, 91]. In another study, statins reduced plasma CRP levels in patients with BHVs, indicating their anti-inflammatory effect [74]. However, the results of the latest and the largest observational study to date, which included data on 1193 patients, was unable to show whether lipid-lowering therapy could delay the SVD process for BHVs in the aortic position at 1, 5 and 10 years after implantation [92]. Therefore, the use of statins for prevention of early failure of BHVs became skeptical [92, 93].

To date, it is still not possible to draw a definitive conclusion about the effectiveness of statins in slowing down the SVD process due to the limited number of studies and the inconsistency of their results. There is a possibility that lipid-lowering therapy can be effective only for a subset of patients, for example, young people, whose immune system is more reactive, and the processes of degeneration of BHVs, presumably, are more associated with their cellular infiltration rather than fatigue breakdown of the prosthetic biomaterial. Thus, according to Dr. G. Nollert and his group (Nollert et al.) [27], cigarette smoking, high cholesterol and triglyceride levels were associated with accelerated BHV failure in patients aged 57 years or younger. No such association was observed in patients older than 57 years. However, it should be noted that the 2010 observational study included patients older than 63 years [92].

OTHER WAYS TO REDUCE INFLAMMATORY RESPONSE TO BIOPROSTHETIC VALVES

Since SVD somewhat resembles chronic immune rejection of living organ and tissue transplants, it is logical to assume that immunosuppressive therapy may be useful in delaying valve degeneration. This hypothesis is supported by experiments on laboratory animals. Specifically, experiments with inbred rats showed a direct correlation between the inflammation intensity and degree of calcification in glutaraldehyde-preserved guinea pig aortic valve, as well as reduced inflammatory response and degree of implant degeneration in patients who had been given steroid treatment [94]. A number of clinical observations also suggest that long-term use of corticosteroids reduces the rate of bioprosthetic valve calcification in young patients [95, 96]. However, immunosuppressive therapy can hardly be considered a viable option: due to significant side effects, this strategy is not applicable to most patients with bioprosthetic valves. In addition, the efficacy of immunosuppression in inhibiting bioprosthetic valve degeneration has not been validated by clinical trials.

An acceptable alternative to immunosuppressive therapy is decellularization or additional enzymatic treatment of prosthetic biomaterial aimed at eliminating xenoglycans, the most immunogenic components of animal biotissues [85]. Also, over time, it will probably become possible to obtain biomaterial from genetically modified animals whose tissues do not express the most immunoreactive carbohydrate xenoglycans [85]. Currently, porcine [97] and cattle [98] knockout for galactose-alpha-1,3-galactose and N-glycolylneuraminic acid have already been bred. The first experimental models of BHVs from the tissues of knockout pigs have also been made [99]. If future clinical trials prove the benefits of using BHVs created from the tissues of modified animals, they are likely to enter clinical practice [100].

CONCLUSION

According to current views, SVD is not simply a passive degenerative-dystrophic process and is partly realized through cell-dependent mechanisms. The triggers and nature of cellular infiltration of bioprosthetic valves allow us to attribute this reaction, occurring both on chemically stabilized xenogeneic biological tissues and on unfixed allogeneic biomaterial, to chronic immune rejection. It is noteworthy that some of the identified mechanisms resemble those involved in vascular ATS and native aortic valve calcification. They include lipid accumulation, foam cell formation, increased production of matrix-destroying enzymes, release of inflammation mediators and elevated oxidative stress. The clinical significance of these phenomena is still poorly understood.

Unfortunately, there are currently no drug therapies that can delay bioprosthetic valve deterioration. Suggestions that lipid-lowering therapy might be useful in this regard have not been confirmed, although there is a possibility that it might still play a role in patients younger than 57 years of age. Besides, there are opinions that special biomaterial processing aimed at eliminating immunogenicity and the manufacture of bioprosthetic valves from the tissues of genetically modified animals, will reduce the inflammatory response to the implants and increase their shelf-life in young patients. Given the global trend towards an increase in the number of heart valve replacement surgeries and an increase in the proportion of bioprosthetic valves used for this purpose, even a slight improvement in the latter, accompanied by an increase in their average lifespan by 3–5 years, will have a significant clinical impact.

The work was carried out within the framework of a comprehensive program of fundamental scientific research of the Siberian Branch of the Russian Academy of Sciences on the fundamental theme NII KPSZ No. 0546-2015-0011 "Pathogenetic substantiation of development of bio implants for cardiovascular surgery, with implementation of a patient-centered approach using mathematical modeling, tissue engineering and genomic predictors".

The authors declare no conflict of interest.

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The article was submitted to the journal on 10.12.2021