

Structural degeneration of biological conduits: an analytical review of calcification mechanisms

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Received 15 May 2026. Revised 10 June 2026.
Accepted 11 June 2026.

How to cite: Nichay N.R. Structural degeneration of biological conduits: an analytical review of calcification mechanisms. *Patologiya krovoobrashcheniya i kardiokhirurgiya* = *Circulation Pathology and Cardiac Surgery*. 2026;30(2): 20-33. (In Russ.)
<https://doi.org/10.21688/1681-3472-2026-2-20-33>

Funding

Research was carried out within the state assignment of Ministry of Health of Russian Federation (theme No. 124022500251-0). The funding source had no involvement in the study design; collection, analysis of data; writing of the report; or decision to submit the article for publication.

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Abstract

Introduction: In congenital heart surgery, pulmonary valve replacement remains the most common valve substitution procedure. Pulmonary valved conduit implantation is essential for correcting most complex congenital heart defects and is performed five times more frequently than other valve replacements in children. However, all pulmonary valved conduits lack growth potential and inevitably undergo structural valve degeneration (SVD), limiting their long-term durability. Calcification constitutes the principal manifestation and predominant pathophysiological process of SVD.

Objective: To provide a comprehensive overview of the factors contributing to pathological calcification and their role in the pathogenesis of mineralization in biological conduits.

Materials: Literature sources, including both clinical and experimental studies, were analyzed.

Results: This narrative review examines the key drivers of pathological calcification, including recipient metabolic and immune factors, biomaterial structure and composition, and mechanical stress on the implant.

Conclusions: Understanding the basic mechanisms of biomaterial mineralization is essential for addressing early prosthesis dysfunction. Strategies targeting these mechanisms could underpin the development of next-generation conduits with greater resistance to tissue mineralization and improved long-term durability.

Keywords: biological heart valves; mineralization mechanisms; pathological calcification; pulmonary valve conduit; structural valve degeneration



Структурная дегенерация биологических кондуитов: аналитический обзор механизмов кальцификации

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Поступила в редакцию 15 мая 2026 г.
Исправлена 10 июня 2026 г. Принята к печати 11 июня 2026 г.

Цитировать: Ничай Н.Р. Структурная дегенерация биологических кондуитов: аналитический обзор механизмов кальцификации. *Патология кровообращения и кардиохирургия*. 2026;30(2):20-33.
<https://doi.org/10.21688/1681-3472-2026-2-20-33>

Финансирование

Исследование проводилось в рамках государственного задания Министерства здравоохранения Российской Федерации (тема № 124022500251-0). Источник финансирования не принимал участия в разработке дизайна исследования, сборе и анализе данных, написании отчета или принятии решения о публикации статьи.

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Аннотация

Актуальность. В хирургии врожденных пороков сердца (ВПС) протезирование легочной артерии остается наиболее частой процедурой замены клапана. Имплантация легочного кондуита является важной частью коррекции большинства сложных ВПС и выполняется в пять раз чаще, чем протезирование других клапанов у детей. Однако все клапаносодержащие легочные кондуиты, помимо отсутствия потенциала к росту, неизбежно подвержены структурной дегенерации, ограничивающей их долговечность. Кальцификация представляет собой основное проявление и ведущий патофизиологический механизм дегенеративных изменений.

Цель. Представить всестороннее описание детерминантов патологической кальцификации и их роли в патогенезе минерализации биологических кондуитов.

Материалы. Проанализированы литературные источники, включающие как клинические, так и экспериментальные данные.

Результаты. В этом аналитическом обзоре рассматриваются основные механизмы патологической кальцификации, обусловленные как факторами метаболизма и иммунного ответа реципиента, структурой и химическим составом биоматериала, так и механическим воздействием на трансплантат.

Заключение. Понимание основных механизмов минерализации биоматериала является необходимым условием для решения проблем, связанных с ранней дисфункцией протеза. Стратегии, нацеленные на эти механизмы, могут лечь в основу разработки кондуитов нового поколения с повышенной устойчивостью к минерализации ткани и увеличенной долговечностью.

Ключевые слова: биологические клапаны сердца; легочный клапаносодержащий кондуит; механизмы минерализации; патологическая кальцификация; структурная клапанная дегенерация



Introduction

The era of biological heart valve prostheses began in the 1960s, when the first surgical procedures using aortic and pulmonary homografts were performed [1]. In the following decades, chemically preserved xenogenic prostheses became commercially available and gained widespread use [2]. In congenital heart surgery, pulmonary valve replacement is the most frequently performed valve replacement procedure [3]. Implantation of a valved pulmonary conduit constitutes an essential component of the repair of most complex congenital heart defects requiring reconstruction of the right ventricular outflow tract, and it is performed five times more often than replacement of other heart valves in pediatric patients [4].

Despite the variety of currently available bioprostheses and conduits, none fully meets all the criteria of an ideal prosthesis [4–6]. In addition to lacking growth potential, all valved pulmonary grafts inevitably undergo degenerative changes, resulting in the need for reoperations, particularly in younger children [7–9]. The main causes of conduit dysfunction in the pediatric population include calcification, neointimal proliferation, infective endocarditis, and thrombosis [10–12]. The subject of this analytical review is pathological calcification as the most frequent cause of pulmonary prosthesis dysfunction in children [7; 13].

Calcification, or mineralization, is the process of formation of nodular deposits of calcium phosphate and other calcium-containing compounds in tissues or biomaterials [14; 15]. Under physiological conditions, this process plays a key role in skeletal development by ensuring the structural strength and functional integrity of skeletal tissues. However, pathological, or ectopic, mineralization devel-

ops in tissues and anatomical sites where calcification is not a normal physiological phenomenon [16]. In the context of bioprosthetic heart valves, pathological calcification is the most common form of structural biomaterial degeneration. It is characteristic of all types of pulmonary conduits and affects both the leaflets and the conduit wall (Fig. 1) [13]. The aim of this analytical review is to provide a comprehensive description of the determinants of pathological calcification and their role in the pathogenesis of biological conduit mineralization.

Determinants of Pathological Calcification

Initially, calcification of bioprosthetic heart valves was regarded as a passive degenerative process. Studies by Schoen F.J. and Levy R.J. systematized concepts regarding the mechanisms of mineralization and proposed a model incorporating several determinants of this process [2]. This model suggests that the initial sites of mineral nucleation are associated with elevated intracellular calcium levels in devitalized cells and cell debris present within the biomaterial. The authors also emphasized the role of collagen fiber mineralization. The model includes host-related, implant-related, and mechanical injury factors.

However, the mechanism of biomaterial calcification should not be considered solely as passive deposition of calcium salts. Rather, it is a complex multifactorial pathological process whose determinants are currently divided in the literature into two main categories (Table 1): material-related and host-related [2; 15]. The first category includes structural features of biomaterials and their physicochemical properties that determine their high susceptibility to calcification. The second category comprises recipient-related factors influencing



Fig. 1. Calcified glutaraldehyde-treated bovine jugular vein conduit, 9 years after implantation for RVOT reconstruction (Ross procedure): A, B – CT images; C – macrophotograph of the explanted conduit. Red arrows indicate large calcium deposits in the conduit wall and leaflets (data sourced from the archive of the Meshalkin National Medical Research Center)

Table 1. Determinants of pathological calcification of biological pulmonary conduits

Factor	Determinants
Recipient-dependent factors	
Mechanical impact	Cyclic mechanical stress [2; 51; 59; 102; 105; 106] Turbulent flow [1; 43; 107; 108]
Immune response	Activation of cellular immunity [17; 19–23; 33–35] Activation of humoral immunity [17; 19–21] Proteolytic enzymes [18; 26–30] Oxidative stress [31; 32]
Metabolic features	Calcium and phosphorus metabolism [49; 51; 55; 57]
Material-related factors	
Biomaterial composition	Extracellular matrix structure and cellular filling [15; 35; 49; 66; 77–79]
Chemical treatment of biomaterial	Cross-linking type [49; 72] Imbalance of tissue protein charges [49; 59; 69] Cell devitalization [15; 69; 85]
Conduit production technology	Conduit joining sutures [91]
Conduit thrombosis	Thrombotic masses [36–38]
Conduit-associated endocarditis	Bacterial colonization [39; 40]

mineralization processes after implantation of an artificial heart valve. This group includes the mechanical effects of cyclic loading, activation of the immune system, oxidative stress, and the influence of the recipient's metabolic rate.

Metabolic and Immune Response Factors

Over the past decade, substantial evidence has accumulated indicating a key role of the immune response in the calcification and degradation of bioprosthetic heart valves [17; 18]. According to previously published data, calcified bioprostheses are characterized by significant infiltration with immune cells, including T lymphocytes, macrophages, B lymphocytes, neutrophils, and plasma cells, as well as by a concomitant increase in tissue cytokine concentrations [17; 19]. In a large cohort study, Senage T. et al. [20] demonstrated that the level of antibodies specific to bioprosthetic xenoantigens increases significantly as early as one month after implantation. By depositing within the biomaterial tissue, these antibodies mediate bioprosthetic dysfunction through mineralization, as confirmed by the detection of Neu5Gc, anti-Neu5Gc IgG, and complement in calcified implants.

Experimental studies in animal models have also demonstrated activation of the immune response to preserved biomaterials. In their study, Manji R.A. et al. showed that xenogeneic tissues treated with glutaraldehyde (GA) induce both cellular and humoral immune responses [21]. The authors investigated two experimental groups of rats: the syngeneic group received

GA-treated segments of rat aortic root, whereas the xenogeneic group received similar vascular segments from guinea pigs. The results revealed a significant increase in macrophage and T-lymphocyte infiltration in xenogeneic grafts compared with syngeneic ones. In addition, animals in the xenogeneic group exhibited increased IgG levels, which decreased following steroid therapy. An important conclusion of the study was the demonstrated linear correlation between the degree of tissue calcification and the intensity of cellular infiltration, particularly by macrophages [21].

The foreign body reaction also exerts a substantial effect on graft mineralization processes, which is especially evident in studies of synthetic materials. Despite the absence of biological antigens capable of eliciting a classical antigen–antibody reaction, the non-biodegradable nature of synthetic implants induces chronic inflammation, leading to fibrous encapsulation and calcification of the prosthetic tissue [22; 23]. Activated macrophages and foreign body giant cells release cytokines and growth factors, thereby creating a microenvironment that promotes fibroblast differentiation into osteoblast-like cells and stimulates tissue mineralization and heterotopic ossification [24; 25]. Histological studies demonstrate that all layers of synthetic grafts are susceptible to calcification [23; 25].

Another potential mechanism by which the inflammatory response contributes to calcification involves proteolytic enzymes such as matrix

metalloproteinases (MMPs), as well as calcium-binding proteins, including osteopontin and osteonectin, produced by macrophages and T cells. MMPs play a key role in collagen and elastin degradation, leading to the exposure of nucleation sites for mineral crystal formation [18; 26; 27]. Osteonectin and osteopontin have a high affinity for calcium and are involved in the regulation of osteoblast-like cell differentiation [28–30].

Oxidative stress, which plays a central role in the pathogenesis of various diseases, including inflammatory and metabolic disorders, contributes to collagen degradation and increases valve tissue susceptibility to collagenase. Pathways mediated by hydroxyl and tyrosyl radicals are particularly important, as they enhance biomaterial calcification processes [31; 32].

A number of studies have confirmed the role of the immune response to suture-related injury in calcium deposit formation [33–35]. Immune cells, including macrophages and lymphocytes, are activated in response to tissue and endothelial damage, thereby initiating an inflammatory cascade that creates a favorable microenvironment for mineralization [18].

Recent studies have demonstrated an association between subclinical leaflet thrombosis and bioprosthetic calcification [36; 37]. Carlidge T.R.G. et al. [38] identified a spatial overlap between mineralization zones and thrombotic deposits on valve leaflets. The authors concluded that thrombi may act as a potential trigger of mineralization. In addition, fibrin clots forming on the biomaterial surface create favorable conditions for asymptomatic bacterial colonization [39; 40], thereby contributing to accelerated structural tissue degeneration. Thus, subacute or subclinical endocarditis may also be one of the causes of early calcification of a biological valve [39].

More rapid and aggressive mineralization of bioprosthetic tissue has been observed in children and adolescents [13; 41–43]. This phenomenon is likely driven by increased activity of both the immune system [44] and metabolic processes [45; 46]. The specific features of mineral metabolism in young patients, especially children, are directed toward physiological skeletal formation, which may promote pathological biomaterial mineralization [47; 48]. Similar patterns have also been identified in laboratory studies using animal models [49; 50]. In experimental settings, attempts to reduce bioprosthetic mineralization through systemic administration of anti-calcification agents such as

bisphosphonates resulted in growth retardation in animals [14].

The rate and extent of dystrophic mineralization increase significantly in the presence of elevated blood calcium and/or phosphorus levels. *In vitro* studies have demonstrated that the rate of hydroxyapatite crystal growth on GA-treated bovine pericardium was linearly proportional to the degree of calcium phosphate supersaturation in solution at stable calcium and phosphorus concentrations [51]. Earlier experimental studies indicate a key role of phosphorus ions in the initiation of the mineralization process [49]. An increase in inorganic phosphate concentration in the surrounding environment promotes accelerated nucleation of mineral crystals within implant tissues, which may explain the more aggressive development of calcification under certain metabolic conditions. Age-related changes in blood phosphorus levels are substantial: from the neonatal period to old age, the physiological phosphate level decreases by at least twofold, whereas calcium levels fluctuate within a relatively narrower range [52]. Phosphate concentrations are highly labile and depend not only on age but also on sex, renal function, hormonal status, and other factors [53; 54]. The influence of serum phosphorus levels on tissue mineralization has been confirmed experimentally. Thus, *in vitro* incubation of alkaline phosphatase (ALP)-collagen conjugates in sera from young and old rats showed that serum phosphorus plays a significant role in *de novo* mineral nucleation [55]. This conclusion is supported by the results of elemental analysis of biomaterials implanted subcutaneously in young and old rats: in young animals, phosphorus predominated over calcium in mineral particles, whereas in old rats, the surface particles contained twice as much calcium as phosphorus [49].

In addition, ALP may indirectly affect calcification by regulating circulating inorganic phosphate levels. By dephosphorylating organic phosphate compounds, this enzyme increases the concentration of circulating inorganic phosphates [49]. ALP levels peak before the age of 4 years and during puberty, then decline after 18 years of age and stabilize, correlating with normalization of plasma phosphate concentrations [56]. Physiologically high levels of circulating inorganic phosphates and ALP in pediatric patients predispose to bioprosthetic mineralization. Notably, increased activity of this enzyme has also been observed in adult patients with bioprosthetic dysfunction due to severe calcification [57].

Another characteristic feature of young age is the high rate of biomaterial remodeling accompanied by differentiation of vascular interstitial cells into myofibroblasts [58]. Myofibroblasts are capable of expressing osteoblastic markers such as osteocalcin and bone sialoprotein, ultimately leading to the formation of nodular bone-like calcified deposits within the structure of valve tissue [59].

Structure and Chemical Composition of the Implant

Various biomaterials are used in bioprostheses and pulmonary conduits, including the porcine aortic root, porcine and bovine pericardium, and the valved bovine jugular vein segment [5; 13; 60; 61]. These materials differ substantially in terms of species and tissue origin, which accounts for differences in tissue microstructure, the composition and relative proportions of extracellular matrix (ECM) proteins, and cellularity [49; 62]. The wall of the porcine aortic root consists predominantly of elastin and smooth muscle cells (SMCs) [63], whereas bovine pericardium is composed mainly of type I collagen [64; 65]. The bovine jugular vein contains both elastin and collagen fibers and is characterized by variability in the ratio of ECM components depending on individual factors such as the animal's age, breed, and diet [49; 63]. It is the ultrastructural features of cells and the ECM that provide both the substrate and scaffold for the initiation and growth of calcium phosphate crystals [15; 66].

All biomaterials used for manufacturing valved conduits and bioprostheses require chemical treatment aimed at increasing tissue stability and improving mechanical properties. The most commonly used preservative for xenogeneic tissues is glutaraldehyde (GA) [13; 51; 67]. GA effectively masks xenoantigens, thereby reducing tissue immunogenicity, prevents enzymatic degradation of the material, and enhances biomaterial stability [68; 69]. GA preservation leads to the formation of additional cross-links within collagen helices, thereby stabilizing the structure of collagen fibrils [70; 71]. During this reaction, GA interacts with the primary amines of lysine (Lys), hydroxylysine (Hyl), and the N-terminal amino acid residues of collagen, forming not only classical Schiff bases but also pyridinium cross-links [49; 70; 72]. This mechanism of covalent cross-linking provides long-term ECM stabilization, which is a key factor in improving the strength and biocompatibility of xenogeneic material.

However, GA-induced alterations in collagen structure promote tissue mineralization. Explanted dysfunctional valves have demonstrated calcified fibers whose diameter corresponds to that of type I collagen fibrils [73]. *In vitro* studies using supersaturated calcium phosphate solutions with constant calcium and phosphate ion concentrations showed that untreated pericardial patches did not undergo calcification [51]. Likewise, no signs of mineralization were observed in unfixed collagen matrices [74–76]. This phenomenon may be explained by disruption of the charge balance of tissue proteins under the influence of the preservative [49; 59]. GA treatment leads to the exposure of a large number of negatively charged groups that may serve as active binding sites for calcium ions and thus act as nucleation centers for mineral crystals [59; 69]. In addition, the pyridinium cross-link formed in collagen after GA fixation, which is specific to bone tissue, may itself promote calcium phosphate crystallization [72]. Positively charged pyridinium rings may serve as nucleation centers for mineral crystals through active binding of inorganic phosphates from the environment surrounding the implant. As a result, a pyridinium/phosphate complex is formed, which acquires a negative charge and is capable of additionally binding Ca^{2+} ions [49].

In contrast to collagen, which undergoes calcification only after GA treatment [74–76], elastin mineralizes both in the uncross-linked state and after aldehyde fixation [35; 66; 77; 78]. It has previously been shown that elastin does not enter into covalent binding with GA, but contains a substantial number of calcium-binding sites [49; 79]. Similar to GA-cross-linked collagen, the elastin structure contains a positively charged pyridinium ring [49], which forms the core of desmosine, the principal amino acid responsible for cross-linking of elastin fibers and their elastic properties [80]. The mechanism of calcium binding in elastin is similar to that in GA-treated collagen and is based on the interaction between the positively charged pyridinium ring and the phosphate anion. This results in formation of a complex that attracts Ca^{2+} ions from the surrounding environment [49]. Thus, the presence of pyridinium structures in elastin contributes to the formation of nucleation centers for mineral crystals, which explains the propensity of elastin fibers to mineralization regardless of chemical treatment.

In addition, elastin fibers contain numerous associated proteins, many of which are capable of binding calcium ions, including fibrillins, tenascins, and vitronectin [81; 82].

In particular, vitronectin has been proposed as a potential promoter of calcification. In an experimental model, its localization within the walls of elastin-containing tissues coincided with sites of incipient calcification [49].

Glycosaminoglycans, which are components of the ECM, also cannot be cross-linked by GA and are gradually lost during preparation, storage, and implantation of the bioprosthesis [83]. Degradation of glycosaminoglycans contributes to disruption of collagen integrity, resulting in exposure of additional regions of the three-dimensional structure and the formation of voids favorable for calcium phosphate crystal nucleation [69; 72].

Chemical treatment of the biomaterial also leads to cell devitalization, which potentiates graft mineralization [2; 49; 69]. Devitalized SMCs and cellular debris possess numerous Ca^{2+} -binding sites and act as active nucleators of hydroxyapatite crystals [15]. Under normal physiological conditions, intracellular calcium concentration is markedly lower than extracellular calcium concentration, a gradient maintained by mitochondria through calcium pumps [84]. *In vitro* studies have demonstrated that GA treatment causes cell death and inactivation of calcium pumps, leading to rapid influx of Ca^{2+} from the extracellular space into the cytoplasm [69; 85]. Increased intracellular calcium concentration raises the likelihood of its binding to phosphates localized in various cellular structures such as cell membranes and DNA, thereby promoting formation of crystallization nuclei [59; 86]. Cell injury is also associated with increased cytosolic phosphate content [6; 87]. The absence of vascularization in implanted bioprostheses prevents timely removal of cellular debris and devitalized cells by macrophages, as a result of which they become centers of hydroxyapatite crystal nucleation [86]. The presence of calcified particles in explanted valves, located between ECM fibrils and not locally associated with them, supports the cellular origin of calcium deposits [73]. Electron microscopy has revealed small calcium deposits spreading from cells into the adjacent ECM [87]. In some cases, small calcified deposits were found on the surface of mitochondria and cell nuclei [14].

In addition to enhancing mineralization of bioprosthetic tissue, one of the potential problems associated with GA fixation is the presence of free aldehyde residues in treated tissues or their release from polymeric cross-links [51; 69; 85]. Both free GA released from prosthetic tissues after implantation and aldehyde groups covalently bound to proteins exert cytotoxic

effects on recipient cells and inhibit tissue remodeling processes [35; 88–91]. The recipient response to the toxic effects of released GA, aimed at isolating the graft from surrounding tissues, leads to the formation of a dense, rigid fibrous capsule around the prosthesis [35; 91]. In combination with the fibrotic deformation characteristic of GA-treated xenogeneic materials [35; 91; 92], this process increases tissue stiffness, reduces elasticity, worsens the hemodynamic performance of the prosthesis, contributes to early prosthetic dysfunction, and increases the risk of tissue injury during repeat surgery. Strict adherence to the manufacturer's recommendations for rinsing the prosthesis before implantation minimizes the toxic effects of residual preservatives. In addition, preservation of the posterior wall of the native pulmonary artery facilitates tissue mobilization during right ventricular outflow tract re-replacement. The use of endovascular technologies in cases of pulmonary conduit dysfunction also reduces the need for repeat surgery, representing an effective alternative to open re-replacement of the right ventricular outflow tract [93–95].

Recent studies have shown that the manufacturing technology of valved conduits may also contribute to graft calcification. Xenopericardial conduits manufactured using multifilament suture material for leaflet fixation and conduit body construction are characterized by mineralization in the region of the conduit joining sutures irrespective of the type of biomaterial treatment [91]. The authors suggest that braided suture material serves as a nucleation center for hydroxyapatite crystals. Compared with monofilament suture, polyfilament multifilament has substantially more potential nucleation sites [96]. The voids within the braid create a capillary effect and provide spaces for cell accumulation [97]. Impregnation of the threads with plasma proteins and deposition of blood cells in these spaces initiate hydroxyapatite crystal nucleation [71; 98; 99]. The use of biomaterials without sutured leaflet fixation and with a native valve may reduce mineralization and improve prosthesis durability.

Mechanical Factors

Cyclic mechanical stress has a direct effect on the calcification process of bioprostheses. During each cardiac cycle, bioprostheses are subjected to substantial mechanical loads, with maximal stresses localized in the regions of greatest leaflet flexion. Prosthetic valve leaflets experience high transient stresses at closure, as well as cyclic bending and compressive stresses during

valve opening [100; 101]. Concentration of high stresses accelerates structural fatigue damage to the tissue and may initiate biomaterial calcification. After examining 64 pairs of Hancock I bioprostheses (Medtronic Inc., Minneapolis, MN, USA) that had been located in the inflow and outflow pathways of the HeartMate XVE left ventricular assist device (Thoratec, CA, USA), Liao K.K. et al. noted more pronounced calcification of inflow valves compared with outflow valves [102]. This difference was attributed to the substantially higher mechanical pressure experienced by inflow valves. In particular, differences in the degree of calcification were associated with the higher closing pressure and greater pressure gradient to which inflow valves are exposed relative to outflow valves [102].

The commissural regions and leaflet bases of bioprosthetic valves are subjected to increased mechanical loads during each cardiac cycle [59; 73; 102], which contributes to ECM damage in these areas [103; 104]. Microdamage to collagen fibers leads to exposure of chemically active sites that serve as foci for crystal nucleation from calcium and phosphate ions diffusing into the tissue [2; 51; 59; 105]. In an experimental study using a calcifying solution, Zareian R. et al. [103] evaluated the effect of stent crimping on premature biomaterial mineralization. The results showed that ECM damage caused by mechanical stress promotes increased calcium salt deposition in the tissue and leads to extension of mineralization into deeper layers. In the study by Vaesken A. et al. [99], it was found that during transcatheter valve crimping at the time of assembly, the biological material is exposed to additional mechanical load and undergoes degradation even before implantation. It was also demonstrated that tissue deformation itself in regions of folds and bends enhances material mineralization [106].

The formation of turbulent flow and greater energy loss resulting from the use of oversized prostheses and the need for their implantation in an extra-anatomical position also increase the risk of calcification of graft structures, prosthetic infective endocarditis, and consequently early reinterventions [1; 43; 107; 108]. The "dead space" created by the use of disproportionately large grafts leads to substantial deterioration of hemodynamic performance in the implantation zone and causes not only thrombotic deposits in the sinuses and on the prosthetic wall, but also dynamic obstruction due to graft pulsation, conduit kinking, and sternal compression [4; 109; 110]. For this reason, many authors do not recommend implantation of pulmonary conduits exceeding a Z-score of +2 when

calculated according to the patient's actual body surface area [4; 111–113].

Pathogenesis of Biomaterial Mineralization

The similarity of the pathogenetic mechanisms of calcification observed across various experimental models and bioprostheses used in clinical practice indicates the presence of a common pathophysiological basis [14]. From a physicochemical perspective, mineralization of biological conduits is characterized by the formation and propagation of calcium phosphate deposits both on the surface of and within prosthetic tissues [51]. Calcification develops when the biomaterial contains specific binding sites for calcium and phosphorus ions and when the recipient environment contains these ions in concentrations and ratios sufficient for the formation of insoluble calcium phosphate compounds [49; 77]. Once these conditions are met, the process of biomaterial calcification is initiated and may begin either intracellularly or within the extracellular matrix (ECM) [15].

As described above, GA preservation of biomaterials leads to tissue cell devitalization, alters the conformation of collagen fibers, and promotes the formation of hydroxyapatite crystallization centers within the collagen matrix [59; 69; 72]. Devitalization of SMCs is accompanied by intracellular accumulation of Ca^{2+} ions followed by mineralization of cellular structures [2; 15; 49]. In addition, after GA fixation, the calcium-binding capacity of the biomaterial increases owing to a shift in the charge balance of collagen proteins toward a greater number of negatively charged groups [49; 59].

After implantation and contact with blood, nonspecific adsorption of plasma proteins occurs on the biomaterial surface, along with infiltration by inflammatory cells [18; 114]. Adsorption of recipient plasma proteins initiates a number of downstream biological processes, including activation of the complement system and platelets, triggering of the coagulation cascade, and cell adhesion [97]. Monocytes and macrophages are recruited to the biomaterial surface via the layer of adsorbed proteins [115]. Adhesion of these cells and their infiltration into the prosthetic tissue are accompanied by ECM degradation. Monocytes and macrophages disrupt ECM proteins by means of invadopodia [18]. During phagocytosis, they also release proteolytic enzymes such as matrix metalloproteinases (MMPs) and produce reactive oxygen and nitrogen species [116]. MMP-dependent proteolysis, together with fibrinolysis, leads to cleavage of the major ECM components, including elastin fibers and fixed

collagen [117]. Reactive oxygen and nitrogen species generated during phagocytosis cause oxidative damage to collagen and disruption of GA-induced cross-links, resulting in demasking of xenoepitopes and increased susceptibility of the ECM to further degradation [118].

Mechanical loading also contributes to damage and rupture of ECM fibers [105]. In addition, cyclic loading and hemodynamic pressure reduce the effectiveness of GA fixation, leading to exposure of an increasing number of xenoantigens and, consequently, amplification of the immune response to the biomaterial [117; 119].

ECM degradation and disruption create spatial conditions favorable for tissue calcification. Calcium ions and phosphates, both abundantly present within the ECM itself and supplied from surrounding tissues, form a microenvironment conducive to pathological biomaterial mineralization [48; 49]. The concentration of the ions constituting these salts in biological fluids exceeds the solubility limit of the resulting minerals [51]. At the same time, calcium-binding proteins produced by macrophages further enhance hydroxyapatite nucleation [28; 29].

According to the classical concept of tissue mineralization, biomaterial calcification develops in two stages: initiation of calcium phosphate deposition, characterized by formation of a crystalline nucleus, and subsequent crystal growth, associated with a quantitative increase in the mass of mineral structures [120]. The second stage of calcification is generally considered to be largely resistant to inhibition. Once the nucleation stage of the calcium phosphate crystal has occurred, its further growth becomes essentially irreversible [15], ultimately leading to structural damage of xenogeneic conduit tissue [49].

Conclusion

Biomaterial mineralization in a blood-contacting environment under conditions of constant hemodynamic loading is a complex multifactorial pathological process. Despite ongoing research in this field, we remain far from a complete understanding of all aspects of calcification of bioprosthetic heart valve tissues [117].

Based on currently available data, several approaches to the prevention of pathological calcification have been proposed [14]. Systemic therapy aimed at suppressing calcification and local drug delivery strategies have not progressed because of the high risk of adverse effects and technical challenges [14; 74; 121]. Therefore, modification of the biomaterial itself appears to be the most promising and practically feasible approach. Over the past decades, various methods have been proposed to alter the calcifiable substrate or to immobilize inhibitors of Ca^{2+} binding. Although these approaches have been successfully tested in rat subcutaneous implantation models and have demonstrated promising results, their potential clinical application remains far from optimal [15]. At present, there is no effective method in clinical practice for preventing biomaterial mineralization [67; 122].

Thus, calcification of biological conduits remains an unresolved problem requiring further research and the development of innovative bioprosthesis manufacturing strategies. Investigation of the mechanisms linking tissue structural features, chemical composition modification, and the recipient immune response with calcification and adverse prosthetic remodeling will provide the basis for the development of new preservation methods aimed at preventing graft dysfunction.

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