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Review Article

Biomechanical Changes in Cardiac Structure and Activation of Metabolic Pathways in Aortic Stenosis

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Abstract

Degenerative Aortic Stenosis (AS) is the most prevalent valvular heart disease in the Western world and represents a paradigmatic model of chronic pressure overload. Sustained increases in left ventricular wall stress induce concentric hypertrophy, interstitial fibrosis, and alterations in the extracellular matrix. In parallel, metabolic reprogramming occurs, characterized by shifts in substrate oxidation, mitochondrial dysfunction, and activation of signaling pathways such as AMPK, mTOR, Notch1, transforming growth factor-β (TGF-β), and Sphingosine-1-Phosphate (S1P). In addition, the natriuretic peptide system modulates the initial adaptive response. This review integrates the biomechanical and metabolic mechanisms involved in the progression from compensated hypertrophy to heart failure in aortic stenosis.

Introduction

Calcified Aortic Stenosis (AS) is currently recognized as an active and complex disease characterized by chronic inflammatory processes, osteogenic differentiation of valvular interstitial cells, and progressive remodeling of the aortic valve [1,2]. This process leads to narrowing of the valvular orifice and, consequently, to progressive obstruction of the left ventricular outflow tract. From a hemodynamic perspective, this obstruction produces a chronic increase in left ventricular afterload, resulting in elevated myocardial wall stress. According to Laplace's law, wall stress is directly proportional to intracavitary pressure and ventricular radius and inversely proportional to wall thickness [3]. As a compensatory mechanism to counteract this sustained increase in afterload, the myocardium develops concentric Left Ventricular Hypertrophy (LVH), characterized by increased wall thickness without significant dilation of the ventricular cavity [4]. Initially, this process is adaptive, as it reduces wall stress and helps maintain cardiac output. However, over time, sustained hypertrophy becomes associated with structural, molecular, and metabolic alterations that drive the transition from a compensated state to myocardial dysfunction and the development of heart failure [5].

Ventricular Biomechanics in Aortic Stenosis

Pressure Overload and Mechanotransduction

Chronic elevation of ventricular afterload induces a complex mechanotransduction response in car-diomyocytes. This process involves the conversion of mechanical stimuli, such as stretch or increased wall tension, into intracellular biochemical signals that regulate gene expression and cellular growth. In this context, several mechanoreceptors located in the sarcolemma and cytoskeleton, including integrins and focal adhesion complexes, play a key role in detecting changes in the mechanical environment of the myocardium [6,7]. Activation of these mechanical sensors

triggers multiple intracellular signaling cascades. Among the most relevant are the MAPK/ERK and calcineurin-NFAT pathways, which promote cardiomyocyte hypertrophy through increased protein synthesis and regulation of genes associated with cellular growth [8,9]. In addition, mechanosensitive ion channels, particularly those belonging to the Transient Receptor Potential Canonical (TRPC) family, contribute to stretch-induced calcium influx, thereby facilitating activation of hypertrophic signaling programs and modulating excitation–contraction coupling [10].

Structural Remodeling and Fibrosis

As pressure overload persists, left ventricular hypertrophy is accompanied by deeper structural alterations in myocardial tissue. One key process during this stage is remodeling of the extracellular matrix, primarily mediated by the activation of cardiac fibroblasts and their differentiation into myofibroblasts. This process is largely regulated by profibrotic cytokines, particularly transforming growth factor-β (TGF-β) [11,12]. Activation of these pathways leads to increased synthesis and deposition of collagen, particularly type I collagen, within the myocardial interstitium. Progressive accumulation of extracellular matrix components increases myocardial stiffness and alters ventricular mechanical properties, promoting the development of diastolic dysfunction [13]. Histological studies in patients with severe AS have demonstrated diffuse interstitial fibrosis even at early stages of the disease, before a significant reduction in left ventricular ejection fraction becomes evident [14]. These findings suggest that structural myocardial alterations precede the most overt clinical manifestations of functional deterioration.

Metabolic Reprogramming in Pressure-Overload Hypertrophy

Changes in Energy Metabolism

The healthy adult myocardium primarily generates ATP through fatty acid β-oxidation, a highly efficient process under physiological conditions [15]. However, in the setting of pressure-overload-induced hypertrophy, as occurs in aortic stenosis, metabolic reprogramming takes place, characterized by a shift toward increased glucose utilization as the primary energy substrate. This phenomenon resembles the metabolic profile of the fetal heart and is accompanied by reexpression of fetal genes involved in energy metabolism [16]. Among the molecular mechanisms contributing to this metabolic transition is reduced activity of peroxisome proliferator-activated receptor-α (PPAR-α), together with alterations in transcriptional coactivators such as PGC-1α, which play a central role in regulating mitochondrial biogenesis and fatty acid oxidation [17].

AMPK and Cellular Energy Sensors

AMP-Activated Protein Kinase (AMPK) functions as a central sensor of cellular energy status. When the ATP/AMP ratio decreases, AMPK becomes activated to restore energy balance by stimulating catabolic processes and inhibiting anabolic pathways [18]. In the context of pressure overload, early AMPK activation may represent an adaptive mechanism. It promotes glucose uptake, improves metabolic efficiency, and stimulates autophagic processes that facilitate removal of damaged organelles [19]. However, in more advanced stages of disease, AMPK regulation may become disrupted, leading to disorganization of cellular energy metabolism and reduced mitochondrial oxidative phosphorylation capacity [20].

Mitochondrial Dysfunction and Oxidative Stress

Chronic cardiac hypertrophy is also associated with alterations in mitochondrial structure and function. In particular, dysfunction of the mitochondrial electron transport chain has been described, reducing the efficiency of ATP production and promoting generation of Reactive Oxygen Species (ROS) [21]. Increased oxidative stress has multiple pathological consequences. Among these is activation of proinflammatory transcription factors such as NF-κB, which promote a state of chronic low-grade inflammation within myocardial tissue [22]. This inflammatory environment contributes to perpetuation of adverse cardiac remodeling, promoting both hypertrophy and interstitial fibrosis.

Specific Molecular Pathways in Aortic Stenosis

Sphingosine-1-Phosphate (S1P)

Sphingosine-1-Phosphate (S1P) is a bioactive sphingolipid involved in the regulation of cellular pro-liferation, survival, and fibrogenic processes [23]. In experimental models of pressure overload, activation of sphingosine kinase-1 increases S1P production, contributing to cardiac hypertrophy through activation of S1P receptors S1PR1-3 [24,25]. In addition to its direct effects on cardiomyocytes, S1P also enhances TGF-β-mediated signaling, promoting fibroblast activation and extracellular matrix deposition within the myocardium [26].

Atrial Natriuretic Peptide (ANP)

Increased intracardiac pressure and atrial stretch stimulate the release of Atrial Natriuretic Peptide (ANP) [27]. This peptide exerts multiple physiological effects, including diuretic, natriuretic, and vasodilatory actions. At the cellular level, ANP activates particulate guanylate cyclase, leading to increased intracellular Cyclic Guanosine Monophosphate (cGMP) levels [28]. cGMP-mediated signaling exerts antihypertrophic and antifibrotic effects in the myocardium, suggesting a compensatory role in response to pressure-overload-induced remodeling. Clinically, circulating levels of ANP and B-type Natriuretic Peptide (BNP) correlate closely with the severity of aortic stenosis and patient prognosis [29].

Notch1 and Valvular Calcification

The Notch signaling pathway plays a crucial role in cardiovascular development and tissue homeostasis. Mutations in the NOTCH1 gene have been associated with earlyonset valvular calcification [30]. Loss or reduction of Notch signaling promotes osteoblastic differentiation of valvular interstitial cells through activation of osteogenic transcription factors such as Runx2 [31]. Beyond its role in the valve, Notch signaling also influences myocardial biology by modulating hypertrophic responses and promoting cellular survival mechanisms under hemodynamic stress [32].

PI3K-Akt-mTOR

The PI3K-Akt-mTOR pathway is one of the principal regulators of cellular growth, protein synthesis, and cardiac hypertrophy [33]. Under conditions of pressure overload, this signaling cascade becomes activated and contributes to cardiomyocyte growth and ventricular remodeling. Experimental models have demonstrated that pharmacological inhibition of mTOR can attenuate pressure-overload-induced cardiac remodeling, reducing both hypertrophy and myocardial fibrosis [34,35]. These findings suggest that this pathway may represent a potential therapeutic target in diseases characterized by pathological ventricular hypertrophy.

TGF-β

Transforming growth factor-β (TGF-β) is a central mediator of both valvular and myocardial fibrosis [36]. Its activation may occur in response to mechanical stimuli associated with pressure overload. Once activated, TGF-β promotes the transition of fibroblasts into myofibroblasts-cells highly specialized in extracellular matrix production-leading to progressive collagen deposition and increased tissue stiffness [37].

RISK and SAFE Pathways

The signaling pathways known as RISK (Reperfusion Injury Salvage Kinase) and SAFE (Survivor Activating Factor Enhancement) play important roles in cellular protection against various stress conditions. The RISK pathway primarily involves PI3K-Akt activation, whereas the SAFE pathway is mediated through STAT3 signaling [38,39]. Under acute stress conditions, activation of these pathways may exert cardioprotective effects. However, in the context of chronic pressure overload, sustained activation may lose its protective efficacy and may even contribute to pathological hypertrophy and adverse myocardial remodeling [40-50]. We show a schematic drawing where the possible metabolic pathways involved in bone differentiation and calcification can be seen in (Figure 1).

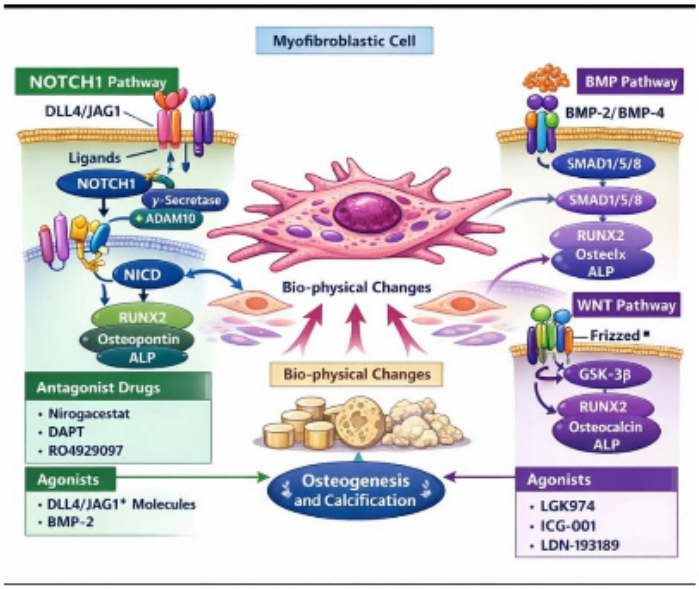

Figure 1: Metabolic pathways supposedly involved in aortic valve histopathology.

Clinical Implications

The clinical course of aortic stenosis and the response to treatment depend largely on the degree of myocardial remodeling present at the time of intervention. In particular, the reversibility of ventricular remodeling after aortic valve replacement is strongly influenced by the presence and extent of preexisting myocardial fibrosis. In this context, the identification of biomarkers capable of reflecting the metabolic and molecular processes involved in cardiac remodeling represents an important area of investigation. Molecules such as sphingosine-1-phosphate and natriuretic peptides may provide relevant information regarding the activity of these pathological pathways. Furthermore, the study of modulators of signaling routes such as Notch or TGF-β opens new perspectives for the development of targeted therapies aimed at intervening earlier in the remodeling process associated with aortic stenosis.

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