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The Role of Myocardial Fibrosis in the Pathogenesis of Atrial Fibrillation

Hazarapetyan LG, Zevejan PH and Grigoryan SV*

Department of Cardiology, Yerevan State Medical University, Armenia

***Corresponding author:** Svetlana Grigoryan, Department of Cardiology, Yerevan State Medical University, Yerevan, 5 P. Sevak Street, Yerevan, Armenia, Tel: 374-91-415-123; Email: s.grigoryan@interdiagnostika.com

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Abstract

The article discusses the role of atrial myocardial fibrosis in the occurrence and maintenance of atrial fibrillation (AF). The participation of such mechanisms as the profibrotic renin-angiotensin-aldosterone system (RAAS), transforming growth factor (TGF-β1) and their relationship to developing fibrosis was revealed. A relationship has been shown between atrial fibrosis and atrial remodeling.

Keywords: Myocardial Fibrosis; Atrial Fibrillation; Heart Remodeling; Recurrence of Atrial Fibrillation

Abbreviations: AF: Atrial Fibrillation; AT1R: Angiotensin Type I Receptor.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with heterogeneous clinical manifestations and severe complications. The process of atrial remodeling is the basis of the occurrence and recurrence of AF, which affects the electrical, contractile, structural function and leads to their morphological changes in atrium [1]. It was revealed that in patients with AF, hemodynamic overload of the atria is observed. Constantly increased intra-atrial pressure leads to thinning of the atrial wall, to decrease in the number of contractile myocardial cells and the development of diffuse atrial sclerosis. The specific gravity of the fibrous tissue of such atria is much higher than normal. It is believed that the development of fibrosis has several causes: 1) a consequence of the inflammatory process ("atrial myocarditis" as the cause of AF); 2) hyperactivation of the renin-angiotensin-aldosterone system with the negative effects of excessive formation of angiotensin and aldosterone; 3) an increase in other biologically active agents capable of inducing fibrosis, such as galectin-3 [2]. The process of fibrosis is characterized by the proliferation and differentiation of fibroblasts and myofibroblasts, followed by an increase in collagen synthesis to form fibrous tissue. In patients with AF, An increase of atrial fibrosis is observed at biopsy and autopsy in AF patients [3].

The relationship between the volume of fibrosis in the left atria and the number of cases of postoperative AF was revealed. With a fibrosis volume of up to 15%, AF developed in 16% of patients in the postoperative period; with a volume of fibrosis of 15–23% - in 21% of patients and with a volume of fibrosis of 23–32% [4]. This significantly increases the risk of recurrence of AF [5]. Atrial fibrosis is a multifactorial process resulting from complex interactions between neurohormonal and cellular mediators [6]. Fibrosis is understood as an increase in the level of the collagen fraction by 2-3 times, i.e. the predominance of collagen synthesis over its breakdown. It has been proven that the more collagen, the higher the rigidity of not only the vascular wall, but also the myocardial wall [7]. Several profibrotic signaling pathways are known to promote the transition of profibrotic molecules

and mediators to atrial fibrosis. For example, angiotensin II, a well-known profibrotic molecule, plays a central role in collagen production. It acts by binding to 2 different subtypes of receptors: angiotensin type I receptor (AT1R) and type II (AT2R). AT1R realize the profibrogenic effects of angiotensin II by stimulating fibroblast proliferation, hypertrophy and apoptosis of cardiomyocytes [8]. Activation of type 1 AT II receptors stimulates the accumulation of extracellular matrix proteins and fibrosis. The influence of angiotensin II on the composition of the extracellular matrix and collagen expression is partially mediated by local synthesis of the cytokine transforming growth factor-beta-1TGF-β1. Which, being a profibrotic cytokine, controls the production and composition of the extracellular matrix.

TGF-β1 is secreted by both cardiomyocytes and fibroblasts and is the main mediator of angiotensin II regulatory signals for autocrine (influence on the angiotensin II producing cell itself) and paracrine (influence on neighboring cells) regulation mechanisms [9]. The main cardiac effects of TGF-β1 are: hypertrophy, fibrosis and apoptosis. Excessive expression of TGF-β1 enhances the synthesis of the extracellular matrix and stimulates the progression of organ fibrosis. It is known that the level of TGF-β1 in patients with AF is higher than in patients with sinus rhythm. In addition, activation of TGF-β1 receptors also results in the expression of connective tissue growth factor, which is released locally, further stimulating extracellular matrix proteins and enhancing the progression of atrial fibrosis. As a result, the accumulation of fibrillar and non-fibrillar collagen leads to the progression of atrial fibrosis and the maintenance of AF, i.e. either to its reccurence, or to the transition to a permanent form of AF. The relationship between TGF-β1 and RAAS is quite interesting; angiotensin II stimulates the synthesis of TGF-β1, which is a potent stimulator of fibroblast activity. Conversely, TGF-β1 reciprocally enhances the production of angiotensin II and additional profibrogenic factors; thus, a positive feedback loop is formed [10]. It appears that fibrosis progresses despite compensatory changes in TGFβ1 signaling pathways, and high blood levels of TGFβ1 are a potential non-invasive predictor of atrial electrical and structural remodeling in AF.

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