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Cardiac Fibrosis: New Treatments in Cardiovascular Medicine

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ABSTRACT: Almost 6 million people in the United States have heart failure. When heart failure develops, cardiac output decreases and compensatory mechanisms activate. One of these mechanisms is cardiac fibrosis, a scarring process that over time impacts cardiac structure and function. Historically, cardiac fibrosis has not been a focus for treatment; however, it is now believed that therapy directed at cardiac fibrosis could reduce the progression of heart failure and other cardiovascular diseases. Medications that target the renin-angiotensin system, transforming growth factor-beta, and endothelin are in various stages of development.

Heart failure is a complex clinical syndrome in which structural or functional abnormalities impair the heart's ability to fill with or pump blood.[1,2] Affecting nearly 6 million people in the United States, heart

failure is the leading reason for hospitalization in patients aged 65 years and older, as well as a major cause of impaired quality of life and chronic disability.[1-3]

Heart failure can result from systolic dysfunction, diastolic dysfunction, or both.[1] The most common risk factors for developing heart failure include coronary heart disease (often with myocardial infarction [MI]), hypertension, diabetes, and cardiomyopathy.[3,4]

Heart failure is initiated by any event that impairs the heart's ability to contract and/or relax, resulting in reduced cardiac output.[1] As cardiac output decreases, compensatory mechanisms activate to restore cardiac output through increased preload, tachycardia, vasoconstriction, ventricular hypertrophy, and remodeling.[1,4] At the cellular level, ventricular hypertrophy and remodeling are accompanied by cardiomyocyte hypertrophy, necrosis, apoptosis, fibroblast proliferation, and increased deposition of fibrous collagen, the last two of which are collectively termed *cardiac fibrosis*.[4] This article will focus on cardiac fibrosis, including its mediators, assessment, and potential treatments.

Structure of the Heart Wall

The heart wall is composed of three layers: the epicardium (outer layer), the myocardium (middle layer), and the endocardium (interior layer).[5] Fibrosis can occur in any layer and in various locations of the heart (i.e., the four heart chambers and valves).[3] The discussion in this article will be limited to myocardial fibrosis.

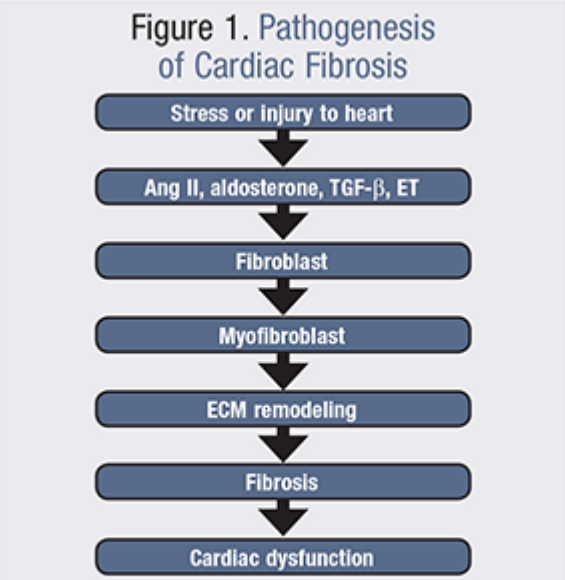
The myocardium contains a variety of cell types, including cardiomyocytes and fibroblasts.[6] Fibroblasts are found within the heart's connective tissue and account for approximately two-thirds of cardiac cells.[6-8] Fibroblasts are involved in many aspects of cardiac function, including regulating the balance of the extracellular matrix (ECM), ECM remodeling, electrical activity, production of growth factors and cytokines, and intercellular signaling.[6]

The structural component of the myocardium is the ECM.[1] Collagen, a fibrous protein found in ECM and connective tissue, is composed of amino acids.[1]

Pathogenesis of Cardiac Fibrosis

Ventricular remodeling, a natural compensatory process that precedes the development of heart failure symptoms, results in progressive changes in the structure and function of the heart, including cardiac hypertrophy, loss of cardiac muscle cells, and ECM alterations.[1] Some types of hypertrophy are accompanied by fibrosis.[1]

Cardiac fibrosis occurs when fibroblasts are activated to myofibroblasts and produce elevated amounts of ECM proteins that form scar tissue and alter normal degradation of ECM (**FIGURE 1**).[4,7,8] Both processes lead to a buildup of collagen, which impacts both systolic and diastolic function.[7,9]



Ang II: angiotensin II; ECM: extracellular matrix; ET: endothelin; TGF-β: transforming growth factor-β.
Source: References 7, 8, 11.

Cardiac fibrosis, which is part of the normal aging process, is associated with many cardiovascular diseases, including heart failure, hypertension, and cardiomyopathies; it also is found in hearts that have been damaged by MI or radiation.[3,10-12] Fibrosis progresses over time and is accompanied by ongoing deterioration of heart function.[13]

Types of Fibrosis

Two forms of fibrosis—replacement fibrosis and reactive interstitial, or perivascular, fibrosis—have been identified.[10] *Replacement fibrosis* occurs in response to an injury causing cardiomyocyte death, as in the case of MI; a reparative response is activated in the heart, causing replacement of dead cells and formation of a collagen-based scar.[10,14] In *reactive interstitial fibrosis*, the cardiac interstitial space expands without significant cardiomyocyte loss.[3,14] Reactive fibrosis allows the heart to adapt to injury and retain its pressure-generating ability.[14] Pressure or volume overload, ischemia, and cardiomyopathies are examples of reactive fibrosis.[14]

Mediators of Fibrosis

Increases in various circulating hormones, cytokines, and proteins triggered by stress or injury contribute to fibroblast activation and differentiation and, ultimately, to cardiac fibrosis.[7,8] Although many substances have been identified as playing a part in this process, several studies suggest that the renin-angiotensin system (RAS), transforming growth factor (TGF)-beta, and endothelin (ET) are key elements in the cascade. These elements will be the focus of this discussion.[8]

The RAS regulates the production and activity of fibroblasts.[11] When the heart is injured, macrophages and fibroblasts produce renin and ACE, which in turn generate angiotensin II (Ang II).[9] Ang II interacts with Ang II receptor type 1 (AT_1) receptors, which promote hypertrophy, stimulate

fibroblast proliferation, and increase collagen synthesis.[9,15] In addition, Ang II suppresses collagenase (an enzyme that breaks down collagen), which may lead to increased collagen accumulation and fibrosis.[13]

Aldosterone has also been identified as a mediator of fibrosis. It affects fibroblast proliferation and collagen deposition in the ECM, heightening expression of cytokines and chemokines, signaling macrophages, and activating cardiomyocyte fibrogenic signals.[1,9,12,13]

TGF-beta is a cytokine in the heart that is activated by cardiac injury, generation of reactive oxygen species, Ang II, high glucose, altered pH, and certain proteases.[4,9] Once activated, TGF-beta increases ECM production and decreases ECM breakdown.[4,9]

ET is a protein that is released by endothelial cells in the heart.[8] It has been found to increase fibroblast differentiation into myofibroblasts and the production of ECM.[8]

Assessment of Fibrosis

Historically, the only measures of cardiac fibrosis have been echocardiograms that indirectly measure left ventricle mass and endomyocardial biopsies that measure collagen volume fraction (CVF).[11] Newer techniques involve laboratory assessment of biomarkers and cardiac imaging.[11]

Several biomarkers for fibrosis have been identified, most of which are focused on ECM structure.[11] Researchers can measure biomarkers of the synthesis and degradation of collagen types I and III, the main components of ECM.[11] Collagen types I and III are synthesized as procollagens, which are then processed into mature collagen molecules by a peptidase cleaving their propeptide domain.[6,11] During collagen synthesis, propeptides from the amino-terminals (PINP and PIIINP) or carboxy-terminals (PICP and PIIICP) of collagen types I and III are released and measured as biomarkers.[6] During collagen degradation,

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