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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardiac Fibrosis in Patients With Atrial Fibrillation

Mechanisms and Clinical Implications

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ABSTRACT

Atrial fibrillation (AF) is associated with structural, electrical, and contractile remodeling of the atria. Development and progression of atrial fibrosis is the hallmark of structural remodeling in AF and is considered the substrate for AF perpetuation. In contrast, experimental and clinical data on the effect of ventricular fibrotic processes in the pathogenesis of AF and its complications are controversial. Ventricular fibrosis seems to contribute to abnormalities in cardiac relaxation and contractility and to the development of heart failure, a common finding in AF. Given that AF and heart failure frequently coexist and that both conditions affect patient prognosis, a better understanding of the mutual effect of fibrosis in AF and heart failure is of particular interest. In this review paper, we provide an overview of the general mechanisms of cardiac fibrosis in AF, differences between fibrotic processes in atria and ventricles, and the clinical and prognostic significance of cardiac fibrosis in AF. (J Am Coll Cardiol 2015;66:943–59) © 2015 by the American College of Cardiology Foundation.

The mechanisms of atrial fibrillation (AF) are complex and associated with structural and electrical remodeling in the atria and ventricular myocardium. The key electrophysiological mechanisms of AF include: 1) focal firing due to triggered activity (early and delayed afterdepolarizations); 2) multiple re-entries due to shortening of the action potential; and 3) heterogeneity of impulse conduction caused by atrial fibrosis. Development and progression of atrial fibrosis are the hallmark of structural remodeling in AF and are considered to be the substrate for AF perpetuation. Advanced atrial fibrosis is associated with more frequent paroxysms of AF, transformation of the arrhythmia into a permanent type, and reduced effectiveness of antiarrhythmic drug therapy (1,2).

Despite a large body of experimental and clinical evidence supporting the role of atrial fibrosis in AF, data on fibrotic processes in the ventricles of patients with AF are limited. The available data indicate that ventricular fibrosis may be at least partly responsible for the impaired cardiac relaxation and contractility seen in many patients with AF. Cardiac fibrosis may be implicated in complex interactions between AF and heart failure (HF), each of which can be the cause and the consequence of the other. Given that AF and HF coexist at high frequency, and their clear prognostic significance (e.g., increased risk of hospitalization or death related to HF deterioration), a better understanding of the role of cardiac fibrosis in the pathogenesis of AF and its complications is important (3). The present review focuses on general

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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack

CMR = cardiac magnetic resonance

CTGF = connective tissue growth factor

DE-CMR = delayed gadolinium enhancement cardiac magnetic resonance

ECM = extracellular matrix

HF = heart failure

miR = microribonucleic acid

MMP = matrix metalloproteinase

NADPH = nicotinamide adenine dinucleotide phosphate

PDGF = platelet-derived growth factor

TGF-β_1 = transforming growth factor beta-1

mechanisms of cardiac fibrosis in AF, differences between fibrotic processes in the atria and ventricles, and the clinical and prognostic effect of cardiac fibrosis in AF.

MECHANISMS OF CARDIAC FIBROSIS

Progressive accumulation of fibrotic tissue in myocardium is 1 of the major components of cardiac remodeling. Formation and redistribution of connective tissue fibers modulate myocardial geometry to adapt to new conditions of (patho)physiological functioning and to prevent or minimize the effects of new mechanical, chemical, and electrical stimuli. This adaptation process involves both the cellular components of the myocardium and the extracellular matrix (ECM), an acellular component of the heart, containing a variety of fibers, with collagen predominant (4).

Excessive ECM production in adults is commonly associated with the pathogenesis of cardiovascular diseases, resulting in abnormalities of cardiac contraction and relaxation, and thus inevitably leading to HF (5). Although collagen deposition in the healthy heart is restricted to maintenance of heart architecture, during progression of various cardiac disorders, the collagen network undergoes quantitative and qualitative changes leading to excessive accumulation of collagen, either in regions of cardiomyocyte loss (e.g., in myocardial infarction, reparative fibrosis) or diffusely, in areas of the myocardium not involved in the focal injury (e.g., in dilated cardiomyopathy, reactive fibrosis) (4,5).

CARDIAC FIBROBLASTS AND MYOFIBROBLASTS. Both cellular and extracellular components take part in the remodeling process. Cardiac fibroblasts play a pivotal role in formation of the ECM. They are numerous within the myocardium and can account for up to 60% of cells in cardiac muscle (6). Thus, cardiac fibroblasts outnumber even cardiomyocytes, although the latter cells largely determine total myocardial mass.

The population of cardiac fibroblasts in healthy adult hearts is maintained at a relatively low level and is predominantly composed of resident fibroblasts and cells undergoing an epithelial-to-mesenchymal transition. In pathological conditions, fibroblasts dramatically increase in number via differentiation from several cell lineages, including monocytes, endothelial cells, bone marrow–circulating progenitor cells, and pericytes (7–9).

The physiological functions of fibroblasts extend beyond metabolism of the ECM. Tight connections between the fibroblasts, fibers of the ECM, and other cellular components form a multidimensional network that acts as an integral sensor of dynamic changes in the various mechanical, chemical, and electrical stimuli in the myocardium. In response to these stimuli, this complex system adjusts ECM turnover and regulates cardiomyocyte hypertrophy and, to a smaller extent, cardiomyocyte proliferation; it also triggers activation of fibrotic and inflammatory pathways. Of note, cardiac fibroblasts exhibit various phenotypes depending on the surrounding microenvironment (10).

Cardiac fibroblasts might also contribute to electrical remodeling in AF due to their different electrophysiological properties compared with the surrounding cardiomyocytes. Fibroblasts are essentially nonexcitable cells but can transfer currents between cardiomyocytes via connexins in vitro. This action may result in heterogeneity of current conduction, shortening of action potentials, depolarization of resting cardiomyocytes, and induction of spontaneous phase 4 depolarization (11). Consequently, fibroblasts might be directly involved in the occurrence and perpetuation of re-entry, although further research is needed to provide in vivo evidence for this claim. Interestingly, computer modeling found proliferation of myofibroblasts in AF and their electrical interaction with cardiomyocytes to be sufficient for re-entry formation, even in the absence of fibrosis (12).

Myofibroblasts are cells that play a particularly significant role in cardiac fibrosis. They are derived from cardiac fibroblasts but have an ~2-fold higher capacity to synthesize collagen. Compared with cardiac fibroblasts, myofibroblasts do not appear in healthy myocardium, are more responsive to proinflammatory and profibrotic stimuli, and are capable of synthesizing a large variety of cytokines and chemokines (13). Importantly, myofibroblasts contain alpha-smooth muscle actin and adhesion complexes (fibronexus). The latter binds myofibroblast internal microfilaments to ECM proteins that help to provide contractile force to the surrounding ECM.

A range of growth factors, cytokines, and hormones, as well as mechanical stretch and hypoxia, regulate ECM turnover and cardiac fibroblast activity. These factors determine fibroblast gene expression, their differentiation, and the level of collagen synthesis.

TRANSFORMING GROWTH FACTOR-β_1 SIGNALING. Among the numerous regulatory factors, angiotensin II and transforming growth factor beta-1 (TGF-β_1) (**Figure 1**)