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REVIEW TOPIC OF THE WEEK

Myocardial Interstitial Fibrosis in Heart Failure

Biological and Translational Perspectives

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ABSTRACT

Myocardial interstitial fibrosis contributes to left ventricular dysfunction leading to the development of heart failure. Basic research has provided abundant evidence for the cellular and molecular mechanisms behind this lesion and the pathways by which it imparts a detrimental impact on cardiac function. Translation of this knowledge, however, to improved diagnostics and therapeutics for patients with heart failure has not been as robust. This is partly related to the paucity of biomarkers to accurately identify myocardial interstitial fibrosis and to the lack of personalized antifibrotic strategies to treat it in an effective manner. This paper summarizes current knowledge of the mechanisms and detrimental consequences of myocardial interstitial fibrosis, discusses the potential of circulating and imaging biomarkers available to recognize different phenotypes of this lesion and track their clinical evolution, and reviews the currently available and potential future therapies that allow its individualized management in heart failure patients.
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Beyond the cardiomyocyte-centric view of heart failure (HF), it is now accepted that alterations in the interstitial extracellular matrix (ECM) and the coronary microcirculation also play a major role in the development of pathological structural myocardial remodeling that determines the evolution of HF. Myocardial interstitial fibrosis (MIF) is defined by the diffuse, disproportionate accumulation of collagen in the myocardial interstitium. MIF contributes to left ventricular (LV) dysfunction in many disorders and predisposes patients to develop HF with either preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). Although ample research evidence explains the mechanisms of MIF, translation of this knowledge to improved diagnostics and therapeutics for HF has not been fully realized. This review summarizes the knowledge regarding mechanisms involved in the pathogenesis and consequences of MIF in HF, discusses the potential of circulating and imaging biomarkers available to recognize different MIF phenotypes and track their evolution, and reviews the available and future therapies that may allow individualized HF management targeting MIF.

HISTOCHEMICAL ASPECTS OF MYOCARDIAL INTERSTITIAL FIBROSIS. Histologically MIF is defined by the diffuse deposition of excess fibrous tissue (i.e., collagen types I and III fibers) relative to the mass of cardiomyocyte within the myocardial interstitium. There are 2 principal types of MIF (1). In the reparative or replacement fibrosis, MIF replaces small foci of dead cardiomyocytes, forming microscars (2,3) (**Figure 1**). In the reactive fibrosis,

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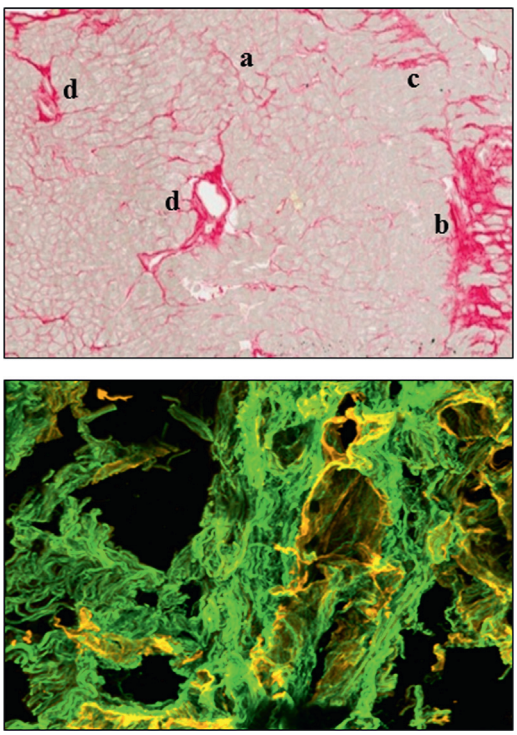
accumulation of fibrous tissue in the perivascular space around intramural coronary arteries and the perimysium and endomysium changes the normally thin fibrous tissue layer around the cardiac muscle bundles and individual cardiomyocytes into thicker sheaths (2,3) (**Figure 1**). It is unclear whether these 2 types represent truly different entities as they coexist in most patients.

Quantitatively, MIF is characterized by the increase in the percentage of total myocardial tissue occupied by collagen fibers, denoted as collagen volume fraction (CVF) and determined in myocardial samples by collagen-specific stains (4). Although MIF is patchy, the area of fibrosis increases from the outer to the inner third of the ventricular free wall, probably due to transmural pressure gradient, wall stress, and coronary microcirculation alterations that are present in ischemic and nonischemic cardiac diseases (3,5).

There are also qualitative changes in the collagen composition. In HF with hypertensive heart disease (6) or aortic stenosis (7), the collagen type I VF (C_IVF)-to-collagen type III VF (C_{III}VF) ratio is abnormally increased due to an excess of collagen type I fibers. However, in ischemic cardiomyopathy, the C_IVF-to-C_{III}VF ratio is decreased due to an excess of collagen type III fibers (8), suggesting that collagen dysregulation may depend on the underlying clinical scenario. The physicochemical properties of collagen fibers also vary. The insolubility and stiffness of fibers depend on the degree of intermolecular covalent linkage, or cross-linking, among their constitutive fibrils (9). Increased cross-linking is reported in patients with HF and increased LV stiffness (10–12). These observations suggest that both the extent of fibrosis and its composition are relevant. Additionally, it is likely that these alterations are dynamic, which are reflected in variable MIF phenotypes over time.

FIGURE 1 Myocardial Interstitial Fibrosis Shown on Endomyocardial Biopsy



(Upper) Endomyocardial tissue from a patient with severe aortic stenosis and heart failure showing myocardial interstitial fibrosis. Sections were stained with picrosirius red, and collagen fibers were identified in red. Collagen deposits were identified as thin bands surrounding individual cardiomyocytes or groups of cardiomyocytes **(a)**, micro-scars **(b)**, and large strands diffusely localized across the interstitium **(c)** and around intramyocardial vessels **(d)**. (Magnification ×40). **(Lower)** Endomyocardial tissue from the same patient. Sections were stained with specific monoclonal antibodies against collagen types I and III, and fibers were identified in **green** and **yellow**, respectively, shown on confocal microscopy. (Magnification ×60). Reprinted with permission from Echegaray et al. (7).

ABBREVIATIONS AND ACRONYMS

CITP = collagen Type I telopeptide

CMR = cardiac magnetic resonance

CVF = collagen volume fraction

ECM = extracellular matrix

ECV = extracellular volume

HF = heart failure

MIF = myocardial interstitial fibrosis

MMP = matrix metalloproteinase

PICP = carboxy-terminal propeptide of procollagen Type I

PIIINP = amino-terminal propeptide of procollagen Type III

MECHANISMS OF MYOCARDIAL INTERSTITIAL FIBROSIS. MIF represents a final common lesion following a variety of injuries caused by an intrinsic cardiac disease or by systemic factors activated in the context of extracardiac comorbidities such as arterial hypertension, diabetes mellitus, and chronic kidney disease (13). The process of MIF develops in several phases (**Central Illustration**).

Triggering stimuli. Cardiomyocyte death is often the triggering event responsible for the initiation of fibrosis in reparative MIF. In reactive MIF, varied stimuli (e.g., pressure overload, ischemia, or metabolic injury) may trigger the fibrotic response in the absence of cell death (2,3,13). Several cell types are implicated in the fibrotic response, either directly by producing fibrous tissue (myofibroblasts) or indirectly by secreting profibrotic mediators (macrophages, mast cells, lymphocytes, cardiomyocytes, and vascular cells) (2,3,13).

Generation of myofibroblasts and profibrotic activation. Beyond resident fibroblasts, circulating and resident fibroblast progenitor cells, including fibrocytes, epicardial epithelial cells undergoing