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Interstitial Fibrosis in Cardiac Pathophysiology: The Silent Architect of Myocardial Remodeling.

Kim Eagle *

Cardiovascular Center, University of Michigan Health System, USA

***Correspondence to:** Kim Eagle, Cardiovascular Center, University of Michigan Health System, USA. Email: keagle@med.umich.edu

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Introduction

Interstitial fibrosis is an insidious and often overlooked process in the progression of many chronic diseases, especially within the cardiovascular system. It plays a pivotal role in the pathological remodeling of tissues, particularly in the heart, where it contributes significantly to cardiac dysfunction, heart failure, and arrhythmogenesis. Despite its profound clinical implications, interstitial fibrosis often remains a silent entity, detectable only through invasive biopsy or advanced imaging techniques until the onset of significant clinical symptoms. This article delves into the pathogenesis, mechanisms, diagnostic challenges, and emerging therapeutic interventions targeting interstitial fibrosis, focusing especially on its impact on cardiac health.At its core, interstitial fibrosis is characterized by the excessive deposition of extracellular matrix components, primarily collagens, in the interstitial space between parenchymal cells. In the myocardium, this matrix accumulation disrupts the normal architecture and mechanical function of the heart, reducing compliance, impairing relaxation, and increasing myocardial stiffness. Over time, this contributes to diastolic dysfunction and eventually heart failure with preserved ejection fraction (HFpEF), a condition increasingly recognized as a major public health challenge.

The pathophysiological cascade leading to interstitial fibrosis is complex and multifactorial. It begins with cellular injury or stress, which triggers a reparative response. Fibroblasts, the primary effector cells in this process, are activated and transform into myofibroblasts—specialized cells capable of producing large amounts of extracellular matrix proteins. Under normal conditions, this response is self-limiting and aids in tissue repair. However, in chronic conditions such as hypertension, diabetes mellitus, ischemic heart disease, and aging, the stimuli for fibroblast activation persist, leading to continuous matrix deposition and fibrosis.A critical factor in this progression is the dysregulation of molecular signaling pathways, particularly those involving transforming growth factor-beta (TGF-β), angiotensin II, and endothelin-1. These mediators stimulate fibroblast proliferation, migration, and matrix synthesis, thereby promoting fibrotic remodeling. Additionally, the renin-angiotensin-aldosterone system (RAAS) plays a central role in cardiac fibrosis. Angiotensin II and aldosterone not only increase blood pressure but also have direct profibrotic effects on cardiac cells. This has led to the widespread use of RAAS inhibitors, such as ACE inhibitors and angiotensin receptor blockers, as cornerstone therapies in managing patients with heart failure and fibrotic remodeling.

Another key player in the development of interstitial fibrosis is oxidative stress. Reactive oxygen species (ROS) generated during chronic inflammation or ischemia can damage cellular components and further activate profibrotic pathways. This is often seen in patients with metabolic syndrome or type 2 diabetes, where hyperglycemia-induced oxidative stress contributes to myocardial fibrosis and stiffening of the ventricles. Similarly, chronic pressure overload in hypertension induces mechanical stress that stimulates fibroblast activation and matrix production.Diagnosing interstitial fibrosis remains challenging due to its asymptomatic nature in early stages and the lack of highly sensitive, non-invasive biomarkers. Cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement and T1 mapping has emerged as a powerful tool for detecting myocardial fibrosis. These imaging

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modalities can quantify extracellular volume, providing indirect evidence of interstitial fibrosis. Serum biomarkers such as procollagen peptides and galectin-3 are also being explored for their diagnostic and prognostic value, though their use in routine clinical practice remains limited.

Histopathological analysis of myocardial tissue obtained through endomyocardial biopsy remains the gold standard for diagnosing interstitial fibrosis. However, due to the invasive nature and potential complications of this procedure, it is rarely performed unless clinically indicated. Thus, there is a growing emphasis on developing reliable, non-invasive diagnostic techniques to detect and monitor fibrosis progression in patients at risk.The clinical consequences of interstitial fibrosis are far-reaching. In the heart, it reduces myocardial compliance, leading to impaired ventricular filling and diastolic dysfunction. This is particularly evident in HFpEF, a condition characterized by symptoms of heart failure despite a normal ejection fraction. In addition to diastolic dysfunction, fibrosis also increases the risk of arrhythmias. The fibrotic tissue disrupts the normal conduction pathways of the heart, creating areas of slow conduction and re-entry circuits that predispose to atrial and ventricular arrhythmias.

Moreover, interstitial fibrosis is not confined to the myocardium alone. It also affects other organs, including the lungs, kidneys, and liver, where it contributes to the progression of chronic diseases such as pulmonary fibrosis, chronic kidney disease, and cirrhosis. In these contexts, fibrosis similarly results from sustained injury and inflammation, underscoring the systemic nature of this pathological process.Given its central role in disease progression, interstitial fibrosis has become a prime target for therapeutic intervention. Current strategies focus on halting or reversing fibrosis by targeting the underlying mechanisms of fibroblast activation and matrix deposition. As mentioned earlier, RAAS inhibitors remain a cornerstone in the management of cardiac fibrosis. More recently, mineralocorticoid receptor antagonists such as spironolactone and eplerenone have shown promise in reducing myocardial fibrosis and improving diastolic function.

Conclusion

Interstitial fibrosis is a pivotal but often silent contributor to the pathogenesis of numerous chronic diseases, particularly in the cardiovascular system. Its presence in the myocardium leads to significant structural and functional alterations, resulting in heart failure, arrhythmias, and increased mortality. Although the exact mechanisms of fibrosis are complex and multifaceted, advances in molecular biology, imaging, and therapeutics are gradually unraveling its intricacies. A deeper understanding of interstitial fibrosis not only offers new avenues for therapeutic intervention but also emphasizes the need for early detection and prevention. As we continue to explore the cellular and molecular underpinnings of this condition, the prospect of halting or even reversing fibrosis becomes increasingly tangible, offering hope to millions affected by its debilitating consequences

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