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Myocardial fibrosis predicts ventricular tachyarrhythmias

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ABSTRACT

Myocardial fibrosis is a common pattern in the setting of different heart diseases, and promotes ventricular tachyarrhythmias by creating a vulnerable substrate for reentrant activity and by favoring the emergence of triggers. Currently, late gadolinium enhancement (LGE) cardiac magnetic resonance is considered the reference method for the noninvasive assessment of ventricular fibrosis. Several studies and meta-analyses have shown that ventricular fibrosis detected by LGE is a powerful predictor of ventricular tachyarrhythmic events in ischemic, non-ischemic dilated cardiomyopathy and hypertrophic cardiomyopathy patients. Both the presence and extension of ventricular fibrosis were shown to correlate with the occurrence of ventricular arrhythmias and sudden cardiac death, irrespective of the grade of left ventricular dysfunction. Based on these results, the assessment of ventricular fibrosis has been suggested as a candidate marker to improve the decision making for implantable cardioverter-defibrillator therapy in patients with left ventricular dysfunction. These points will be discussed in the review.

Key words: Arrhythmias, Cardiomyopathy, Fibrosis, Implantable cardioverter-defibrillator, Late gadolinium enhancement, Sudden cardiac death.

Introduction

The presence of ventricular fibrosis is a common finding in the setting of ischemic cardiomyopathy (ICM). However, recognition of myocardial fibrosis in the absence of ischemia is increasing in a variety of conditions, such as nonischemic dilated cardiomyopathy (NICM), hypertrophic cardiomyopathy (HCM), hypertensive heart disease and heart failure [1]. Ventricular fibrosis may occur with distinct features across different heart diseases and phases of the disease. Whatever the pattern of its presentation, fibrosis, and mostly diffuse and patchy fibrosis, promotes ventricular arrhythmias by harboring critical reentrant pathways and favoring the emergence of arrhythmogenic triggers [2,3]. Given the recognized role of fibrosis in the genesis of arrhythmias, in the last few years we have witnessed the emergence of several methods for the assessment of ventricular fibrosis, and in particular of non-invasive techniques for clinical use [1,4]. Clinical studies applying non-invasive techniques indicated that the presence of ventricular fibrosis could be a strong predictor of ventricular arrhythmias and sudden cardiac death (SCD) in several cardiac diseases, suggesting the potential of fibrosis as risk stratification marker [5].

In this review we will discuss the mechanistic link between fibrosis and ventricular tachyarrhythmias, the methods available for the clinical detection of fibrosis, the clinical evidence supporting fibrosis prognostic power in predicting ventricular tachyarrhythmias, and the clinical implications of the use of fibrosis as marker for SCD risk stratification.

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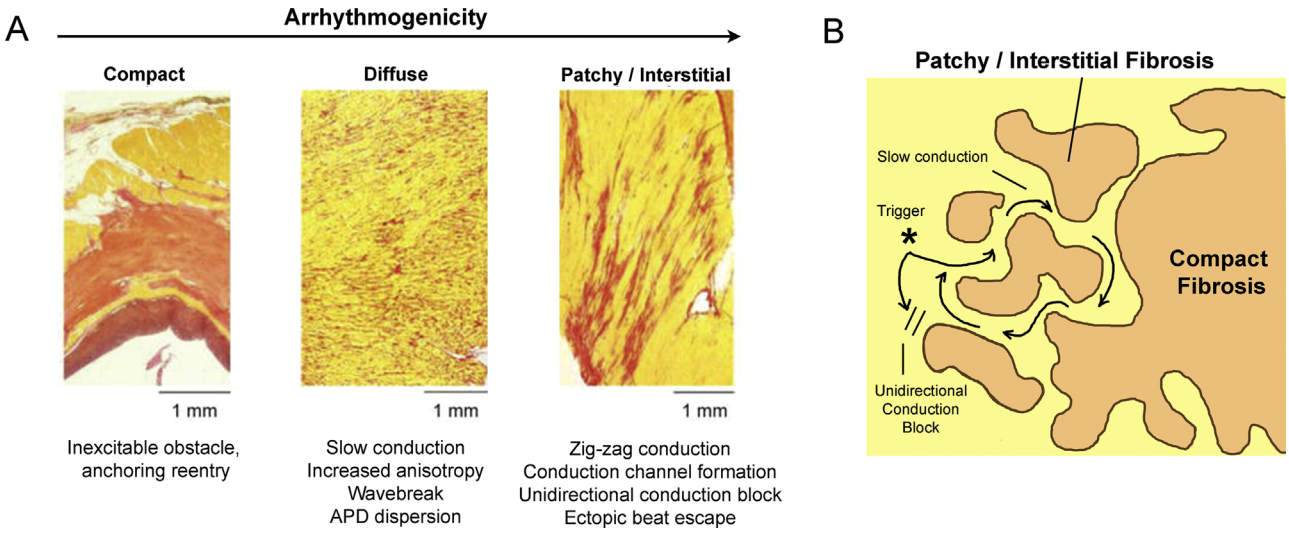

Fig. 1 – Proarrhythmic effect of fibrotic patterns. A. Different types of fibrosis in human cardiac tissue from explanted hearts visualized by light microscopy (red, collagen stained with picrosirius red). Collagen patterns are indicated with the corresponding arrhythmic mechanisms. B. Schematic draw of the role of fibrosis patterns in the onset of reentry-based ventricular tachyarrhythmia. Patchy fibrosis around the compact scar leads to conduction slowing, unidirectional conduction block and trigger escape, favoring the onset of reentrant activity. Modified with permission from de Jong et al. [6]. APD, action potential duration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fibrosis as a determinant of ventricular tachyarrhythmias

Fibrosis is a scarring process, characterized by cardiac fibroblast activation and differentiation into myofibroblasts, loss of extracellular matrix homeostasis and excess deposition of collagen. Fibrosis presents in two forms, replacement and reactive interstitial fibrosis. Replacement fibrosis occurs in response to cardiac injury (e.g., following myocardial infarction), which activates a reparative response where dead cells are replaced and a collagen-based scar is formed. Reactive fibrosis is characterized by the expansion of the cardiac interstitial space without significant myocyte loss, and is activated by pressure or volume overload, ischemia and cardiomyopathies. Under disease adverse remodeling and cardiac fibrosis can become a persistent process, resulting in distorted cardiac architecture and function. This leads to mechanical stiffness and diastolic dysfunction and supports the development of cardiac arrhythmias.

Fibrosis and myofibroblast activation can favor the onset and maintenance of cardiac arrhythmias by different mechanisms. Increased collagen deposition with fibrosis results in myocyte electrical decoupling, affecting both conduction and impulse formation [2,3]. The degree of arrhythmogenicity depends on the amount of fibrosis, with maximal arrhythmia propensity for intermediate amounts of fibrosis [3], but also on the texture of fibrosis. Compact fibrosis with large areas completely deprived by myocytes can favor arrhythmias by anchoring reentrant waves. Heterogeneous fibrosis with diffuse and patchy/interstitial forms plays the major arrhythmogenic role [6] (Fig. 1). The presence of non-conducting collagen septa between myocytes leads to conduction slowing and augmented anisotropy, and promotes the escape of ectopic beats, such as after depolarization-induced premature beats, and the formation of unidirectional conduction block by reducing source-sink mismatch [2,3]. The critical role of tissue heterogeneity in reentry-based ventricular tachycardia in patients with structural heart disease was pointed out by several clinical studies [7] and by computer simulations [8,9]. Voltage mapping and contrast-enhanced cardiac magnetic resonance (CMR) showed that scar heterogeneity was present in human infarcts where the compact scar was surrounded by a gray zone with surviving myocardial fibers (Fig. 2). Areas with intermediate fibrosis harbored conduction channels and slow conduction isthmuses, which constituted the crucial part of the reentrant circuits.

Additional mechanisms related to fibroblast activation, such as myocyte-myofibroblasts coupling and fibroblast-secreted paracrine factors, may further alter myocyte electrophysiology in a proarrhythmic way [2,10], although the action of these mechanisms in the intact heart is controversial. Myocyte depolarization induced by heterocellular coupling with myofibrobasts and secretion of cytokines may lead to augmented automaticity, conduction slowing and alteration of refractoriness [2,10].

Direct and indirect mechanisms synergistically concur to generate a “perfect storm” for cardiac arrhythmias, creating a vulnerable substrate for reentrant activity with slow conduction and unidirectional conduction block, and promoting the emergence of triggers [2].

Fibrosis detection

The presence of ventricular fibrosis was initially assessed by invasive techniques. Among these, endomyocardial biopsy is considered the gold standard, but the procedure is associated