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Review

Cardiac fibrosis as a determinant of ventricular tachyarrhythmias

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ABSTRACT

Animal and emerging clinical studies have demonstrated that increased ventricular fibrosis in a setting of reduced repolarization reserve promotes early afterdepolarizations (EADs) and triggered activity that can initiate ventricular tachycardia and ventricular fibrillation (VT/VF). Increased ventricular fibrosis plays a key facilitatory role in allowing oxidative and metabolic stress-induced EADs to manifest as triggered activity causing VT/VF. The lack of such an arrhythmogenic effect by the same stressors in normal non-fibrotic hearts highlights the importance of fibrosis in the initiation of VT/VF. These findings suggest that antifibrotic therapy combined with therapy designed to increase ventricular repolarization reserve may act synergistically to reduce the risk of sudden cardiac death.

Contents

1. Introduction

Classically, increased cardiac fibrosis has been shown to be associated with altered cardiac conduction, causing conduction slowing, block, and reentry in studies on isolated animal and diseased human cardiac tissues [1–3]. Interestingly, similar findings were also demonstrated in isolated Langendorff-perfused explanted human hearts with dilated cardiomyopathy [4,5]. While alterations of cardiac conduction [6,7] and the resulting reentrant wavefront of excitation [8] are uniformly accepted as arrhythmic consequences of increased cardiac fibrosis, recent experimental and computational studies indicate that fibrosis may also importantly modulate the formation of cardiac afterpotentials, notably early afterdepolarizations (EADs), that lead to triggered activity causing atrial fibrillation (AF) [9] and ventricular fibrillation (VF) [10–12]. Taken together,

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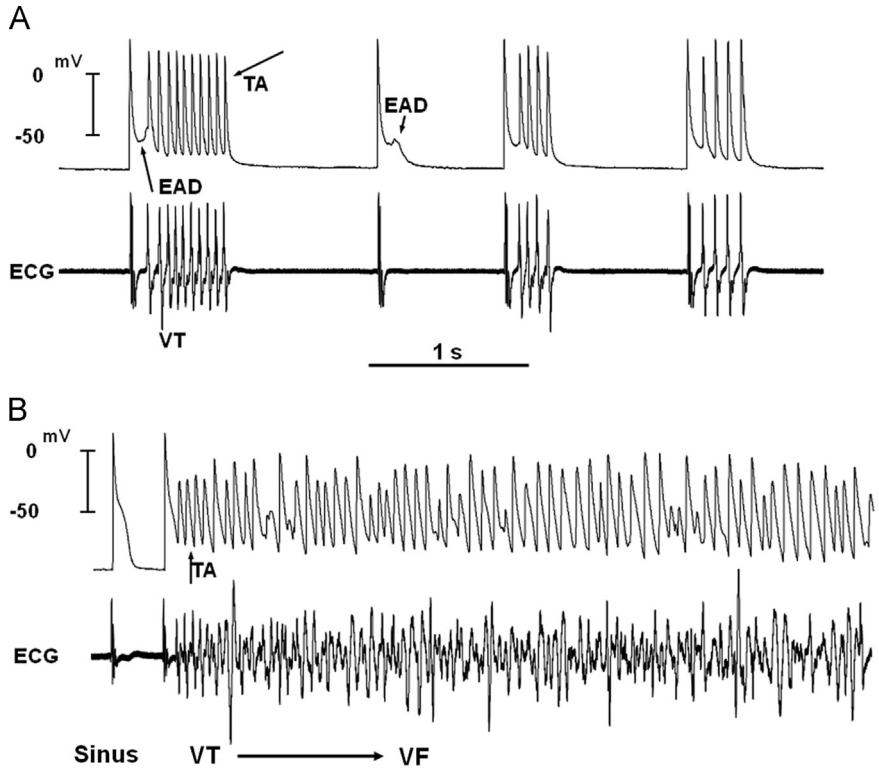

Fig. 1. Simultaneous microelectrode and ECG recordings at the onset of VT/VF in an aged rat heart exposed to 0.1 mM H_2O_2. Panel A, onset of early afterdepolarization (EAD)-mediated triggered activity (TA) causing ventricular tachycardia (VT) 5 min after H_2O_2 exposure. Note the smooth emergence of EAD (upward-pointing arrow) during the isoelectric interval on the ECG followed by a run of 10 TA (downward-pointing arrow) causing non-sustained VT on the ECG. The onset of the EAD precedes the QRS complex of the VT by 8 ms, indicating absence of electrical activity elsewhere in the heart. Two additional short runs of VT with 4 beats each are also shown that follow a single subthreshold EAD (downward-pointing small arrow) with no TA. Panel B shows the degeneration of the TA to VF 15 min after H_2O_2 exposure. (From Ref. [10].)

these findings indicate that increased cardiac fibrosis promotes tachyarrhythmias not only by the mechanism of reentry but also by the mechanism of triggered activity, potentially making cardiac fibrosis a highly effective antiarrhythmic target.

In this review, we demonstrate how the interaction of fibrotic ventricles with oxidative or metabolic stress leads to the emergence of EADs, triggered activity, and VF. Specifically, we describe the dynamic scenario starting from cellular EADs that promote triggered activity causing focal ventricular tachycardia (VT), which then degenerates to VF. We also discuss recent experimental and clinical studies that show the potential antiarrhythmic benefits of drug-induced prevention and/or reduction of ventricular fibrosis [13–17].

1.1. The pathology of fibrosis

Cardiac fibrosis develops when the body's natural wound-healing process becomes altered, causing abnormally elevated fibrosis by mechanisms that still remain poorly defined. Under normal (adaptive) conditions of wound healing, specialized cells known as fibroblasts become activated and transform into myofibroblasts. The myofibroblasts then undergo proliferation, causing increased synthesis of collagen protein in the extracellular matrix composed predominantly of type I collagen and to a lesser extent type III collagen (normal wound healing process). What is initially an adaptive process, perhaps meant to enhance tensile strength, can progress to maladaptive (pathologic) conditions when the "healing" process persists with the development of excessive myocardial fibrosis [15,18–20]. While resident cardiac fibroblasts may be activated and transformed into myofibroblasts, there is also the potential of participation by fibroblasts originating from either endothelial cells via endothelial–mesenchymal transition (EndMT) or from the bone marrow [21,22] and the spleen [23]. For example, it has been shown that transforming growth factor-beta 1 (TGF-β1) induces endothelial cells to undergo EndMT, whereas bone morphogenic protein 7 (BMP-7) preserves the endothelial phenotype. The demonstration that the systemic administration of recombinant human BMP-7 (rhBMP-7) significantly inhibits EndMT and the progression of cardiac fibrosis in mouse models of pressure overload provides new insights into the progression of pathological (maladaptive) cardiac fibrosis [24].

1.2. Aged heart animal model of fibrosis

Atrial and ventricular fibrosis may indeed increase with aging, but fibrosis per se does not promote cardiac arrhythmia [25–28]. Instead, fibrosis provides a substrate that when coupled to a mild form of stress (oxidative or metabolic), which is of no arrhythmic consequence in non-fibrotic hearts, promotes EADs and triggered activity causing VT and VF in fibrotic hearts, as shown in Fig. 1. We describe the key role played by increased ventricular fibrosis using the aged rat model exposed to either oxidative stress caused by either hydrogen peroxide (H_2O_2) [10] or glycolytic inhibition (GI) induced by replacing glucose with pyruvate [12]. This substitution deprives the sarcoplasmic reticulum (SR) of high-energy phosphate (ATP) needed for proper reuptake of intracellular calcium from the cytoplasm [29,30].

2. Oxidative stress

Hydrogen peroxide (H_2O_2) is shown to readily promote EADs and triggered activity in isolated rat and rabbit ventricular myocytes by increasing both the L-type Ca channel ($I_{Ca\text{-}L}$) and late sodium currents ($I_{Na\text{-}L}$) [31–35]. However, this same stress fails to cause EADs in normal non-fibrotic cardiac tissue [10,12]. The discrepancy between non-fibrotic and fibrotic heart tissues in