Synergism between Enhanced Late Inward Currents and Tissue Fibrosis in the Initiation of Spontaneous Ventricular Tachyarrhythmias

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Sudden cardiac death (SCD) death is a major worldwide public health problem that often arises in patients with diverse cardiac diseases associated with enhanced cardiac tissue fibrosis and altered cardiac sarcolemmal ionic current conductances. It is now clear that the major cause of SCD is ventricular tachycardia (VT) degenerating to ventricular fibrillation (VF), although bradyarrhythmias may also promote the fatal event albeit, to a much lesser extent than the VT/VF [1]. SCD occurs in approximately 180,000-250,000 cases annually in the United States, and an estimated 4-5 million cases worldwide [2]. The prevalence of cardiovascular diseases potentially associated with lethal arrhythmia is estimated at approximately 13 million US individuals, which is about 5% of the middle-aged population [3]. Sarcolemmal ion channels of cardiac myocytes are responsible for the genesis of cardiac action potential (AP) and their genetic (channelopathy) or disease-induced alterations promote arrhythmogenic changes including triggered activity caused either by early or delayed after depolarizations (EAD and DAD respectively) predisposing the heart to life-threatening VT/VF. Four major classes of genetically-based ion channel abnormalities have been described that predispose the heart to VT/VF: the long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) [4]. Initially it was thought that patients at increased risk of VT/VF with genetic abnormalities in sarcolemmal ionic currents (i.e. channelopathies) had structurally normal hearts. However recent studies based on post-mortem histological analysis of patients with NA channelopathies (i.e. BrS), provided compelling evidence that these patients had focal areas of increased ventricular tissue fibrosis and reduced gap junctional connexin-43 (Cx43) indicating the potential dual contributions of fibrosis and channelopathy to the development of VT/VF [5]. Diverse etiological factors including myocardial infarction or drug-induced altered ion channel conductances are also thought to interact with cardiac tissue fibrosis to promote VT/VF [6]. In this article, I will make the case for the presence of a synergism between ionic current abnormality caused by enhanced late Na current so to mimic LQT3 and enhanced late Ca current as a surrogate of LQT8 (Timothy syndrome) and increased ventricular tissue fibrosis in the promotion of VT/VF. The cellular basis of the synergism is then briefly discussed.

Fibrosis and Reentry

Rapid ventricular pacing-induced VT/VF caused by unidirectional conduction block and reentry in human hearts with increased fibrosis is well-documented. Indeed we [7] and others [8] have shown in explanted arterially perfused human hearts with cardiomyopathy and increased fibrosis rapid pacing-induced reentrant VT/VF. However, studying VT/VF mechanism with the pacing protocol does not provide insight into the mechanism of VT/VF that arises spontaneously without recourse of artificial pacing protocol. Recent experimental findings in isolated whole heart studies indicate that fibrosis, in addition to the alterations of the conduction velocity, also importantly modulate the formation of cardiac afterpotentials notably EADs that lead to triggered activity causing rapid VT that degenerates to VF. These findings extend previous cardiac monolayer studies that showed myofibroblast coupling to cardiomyocytes through gap junction formation imparts enhanced automaticity to cardiomyocytes when coupled to a finite (critical) number of myofibroblasts [9]. Taken together, these findings indicate that increased cardiac fibrosis promotes arrhythmias not only by the mechanism of reentry but also by the mechanism of triggered activity and enhanced automaticity potentially making cardiac fibrosis a highly effective arrhythmogenic target [10].

Enhanced Late Na Currents in Structurally Normal Hearts

We tested the hypothesis that acute stress-induced increases of the late Na and Ca currents by diverse stressors (hydrogen peroxide, angiotensin II) promote EADs and EAD-mediated triggered activity and VT in structurally normal hearts. This hypothesis was tested in isolated and arterially-perfused rat and rabbit hearts in Langendorff setting. The hypothesis was defeated as normal hearts manifested strong resistance to initiate EADs, despite the fact that isolated ventricular myocytes from these same normal hearts readily manifested EAD and triggered activity. Furthermore, elevation of the stress level also failed to promote EADs in these structurally normal hearts [11-14]. Dynamic-clamp and simulation studies have shown that an isolated increase in either the late Ca or the late Na current readily promote EADs and triggered activity at the isolated myocyte level [13,15]. Consequently, tissue factors must have played a critical role in the failure of normal hearts to generate EADs with similar stressors that were capable of inducing EADs at the isolated single myocyte level. Tissue factors include the strong electrical coupling between the myocytes via Cx43 gap junctions that are present in normal non-fibrotic hearts. The strong electrical coupling with normal neighboring cells exerts a strong repolarizing current influence (sink effect) on the errant cells primed to initiate EADs. Such a strong repolarizing current in well-coupled tissue prevents the emergence of EADs at the tissue level resulting in failure to initiate VT/VF in normal non-fibrotic hearts. To study the influence of the modulatory effect of the sink on the ability of the source (EAD) to overcome it and propagate as a premature beat, our group simulated cardiac tissue of increasing dimensions. A central area of contiguous myocytes susceptible to EADs was surrounded by unsusceptible tissue, i.e. normal cells incapable of generating EADs. In 1D tissue the numbers of contiguous susceptible myocytes required for an EAD to trigger a propagating action potential were 70 cells. In 2D...
tissue, these numbers increased to 6,940 and in 3D tissue to 696,910. Most importantly these numbers were exponentially decreased in matrix with reduced gap junctional coupling, as it occurs in cardiac tissue fibrosis, and reduced repolarizing current, as it occurs in heart failure. Under these conditions, EADs readily emerged causing triggered beats [16]. These simulation results conclusively showed that the source-sink mismatch in well-coupled cardiac tissue powerfully protects the heart from EADs [16]. While structural and electrophysiological remodeling greatly decreases the number of cells for EAD formation, the chaotic nature of the EADs still requires synchronization mechanisms for EADs to overcome the robust protective effects of source-sink mismatch. Indeed, we found that such synchronization does occur because the dynamics of the EADs manifest chaotic irregular behavior capable of local synchronization causing strong sources. Under these conditions, the EAD-mediated triggered beats propagate in the tissue in the form of premature ventricular complexes or VT as we have shown in simulated and in experimental studies [12].

**Increased Ventricular Fibrosis without Channelopathy**

The fact that the mere presence of increased ventricular fibrosis is not arrhythmogenic is ascertained in clinical and animal models of age-induced fibrosis in rats [11] and rabbits [12]. In fact, these hearts manifest normal sinus rhythm during exposure to normal physiological solutions suggesting that the mere presence of increased tissue fibrosis is insufficient in and of itself to promote VT/VF. However, fibrosis facilitates wave break and reentry formation during rapid pacing but usually not during normal rhythm, as we have shown in explanted human hearts with fibrosis [7] and rat fibrotic hearts [13,17].

**Synergism caused by the Combined Enhanced Late Na Current and increased Ventricular Fibrosis**

We tested the synergism hypothesis in fibrotic rat and rabbit hearts by oxidative stress-induced rises in the late Na and Ca inward depolarizing currents with hydrogen peroxide or angiotensin II [14,18-20]. While the fibrotic hearts maintained normal rhythm when exposed to normal physiological solution, however, upon induction of enhanced late Na and Ca currents with oxidative [11,14] or metabolic stress [21] a synergism developed that promoted VT/VF in greater than 90 percent of the hearts studied [11,12]. The synergism resulted from reduced sink effect (repolarizing current) in fibrotic hearts caused by interstitial collagen deposition that separated myocardial bundle fibers and by reduced Cx43 expression [14]. This fibrotic remodeling effectively prevents electrotonic clamping of the voltage by the neighboring non-EAD generating normal cells allowing the cells primed to generate EADs to propagate and cause VT/VF. This synergism is consistent with predictions made by our simulation studies mentioned above.

**Therapeutic Implications**

The link between ventricular fibrosis and the risk of VT/VF in the setting of increased late inward Na and Ca currents suggests that targeting both fibrosis and block of the late currents may be important therapeutic strategies to prevent VT/VF. These therapeutic structural and ionic interventions do not disrupt the normal excitation-contraction coupling thus are highly likely to be devoid of any proarrhythmic effect. We have shown that increase in the repolarization reserve by blocking late inward Na current with late INa blocker, ranolazine suppressed and prevented oxidative stress-induced EADs, triggered activity, and VT/VF in aged fibrotic rat hearts [13]. In addition to increasing the repolarization reserve, new antifibrotic strategies are being developed that hold promise for future effective prevention of sudden cardiac death caused by VF. Animal studies in rats have shown pinfendine mitigates left ventricular fibrosis and dysfunction after myocardial infarction and reduces arrhythmias [22]. Furthermore, the extent of myocardial fibrosis determined by the late gadolinium enhancement cardiovascular magnetic resonance (CMR) technique in patients with hypertrophic cardiomyopathy showed that the extent of myocardial fibrosis was an independent predictor of adverse arrhythmic outcome [23]. It is hoped that these basic research findings will be translated to patients at risk of developing VT/VF. To the extent that such a translation will be successful it is anticipated that a more rational and effective care of patients at risk of VT/VF maybe developed.

**Acknowledgement**

Supported in part by NIH/NHLBI grant P01 HL078931 and UCLA Laubisch Endowment.

**References**


Citation: Karagueuzian HS (2016) Synergism between Enhanced Late Inward Currents and Tissue Fibrosis in the Initiation of Spontaneous Ventricular Tachyarrhythmias. J Hear Health 2(2): doi http://dx.doi.org/10.16966/2379-769X.120