SciForschen
Open HUB for Scientific Research

ISSN 2379-769X

Journal of Heart Health

Short Communication Volume: 2.2 Open Access

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

Karagueuzian HS*

UCLA Cardiovascular Research Laboratory, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

***Corresponding author:** Karagueuzian HS, MSc, PhD, FHRS, FACC, UCLA Cardiovascular Research Laboratory, MRL 3774, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA, Tel: 310-825-9360; Fax: 310-206-5777; **E-mail:** hkaragueuzian@mednet.ucla.edu

Received date: 14 Mar 2016; **Accepted date:** 22 Mar 2016; **Published date:** 24 Mar 2016.

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

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 ventricular 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 channelopathy (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 after potentials 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 antiarrhythmic 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 errand 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 ageing-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 blockade, 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 pirfenidone 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

1. Huikuri HV, Castellanos A, Myerburg RJ (2001) Sudden death due to cardiac arrhythmias. N Engl J Med 345: 1473-1482.
2. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, et al. (2008) Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 51: 213-228.
3. Arking DE, Chugh SS, Chakravarti A, Spooner PM (2004) Genomics in sudden cardiac death. Circ Res 94: 712-723.
4. Behere SP, Weindling SN (2015) Inherited arrhythmias: The cardiac channelopathies. Ann Pediatr Cardiol 8: 210-220.
5. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, et al. (2015) Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. J Am Coll Cardiol 66: 1976-1986.
6. Weiss JN, Garfinkel A, Karagueuzian HS, Nguyen TP, Olcese R, et al. (2015) Perspective: a dynamics-based classification of ventricular arrhythmias. J Mol Cell Cardiol 82: 136-152.
7. Wu TJ, Ong JJ, Hwang C, Lee JJ, Fishbein MC, et al. (1998) Characteristics of wave fronts during ventricular fibrillation in human hearts with dilated cardiomyopathy: role of increased fibrosis in the generation of reentry. J Am Coll Cardiol 32: 187-196.
8. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, et al. (1993) Slow conduction in the infarcted human heart. 'Zigzag' course of activation. Circulation 88: 915-926.
9. Miragoli M, Salvarani N, Rohr S (2007) Myofibroblasts induce ectopic activity in cardiac tissue. Circ Res 101: 755-758.
10. Karagueuzian HS (2011) Targeting cardiac fibrosis: a new frontier in antiarrhythmic therapy? Am J Cardiovasc Dis 1: 101-109.
11. Morita N, Sovari AA, Xie Y, Fishbein MC, Mandel WJ, et al. (2009) Increased susceptibility of aged hearts to ventricular fibrillation during oxidative stress. Am J Physiol Heart Circ Physiol 297: H1594-H1605.
12. Sato D, Xie LH, Sovari AA, Tran DX, Morita N, et al. (2009) Synchronization of chaotic early afterdepolarizations in the genesis of cardiac arrhythmias. Proc Natl Acad Sci U S A 106: 2983-2988.
13. Morita N, Lee JH, Xie Y, Sovari A, Qu Z, et al. (2011) Suppression of re-entrant and multifocal ventricular fibrillation by the late sodium current blocker ranolazine. J Am Coll Cardiol 57: 366-375.
14. Bapat A, Nguyen TP, Lee JH, Sovari AA, Fishbein MC, et al. (2012) Enhanced sensitivity of aged fibrotic hearts to angiotensin II- and hypokalemia-induced early after depolarization-mediated ventricular arrhythmias. Am J Physiol Heart Circ Physiol 302: H2331-H2340.
15. Madhvani RV, Angelini M, Xie Y, Pantazis A, Suriany S, et al. (2015) Targeting the late component of the cardiac L-type Ca^{2+} current to suppress early afterdepolarizations. J Gen Physiol 145: 395-404.
16. Xie Y, Sato D, Garfinkel A, Qu Z, Weiss JN (2010) So little source, so much sink: requirements for afterdepolarizations to propagate in tissue. Biophys J 99: 1408-1415.

17. Hayashi H, Wang C, Miyauchi Y, Omichi C, Pak HN, et al. (2002) Aging-related increase to inducible atrial fibrillation in the rat model. J Cardiovasc Electrophysiol 13: 801-808.

18. Xie LH, Chen F, Karagueuzian HS, Weiss JN (2009) Oxidative-stress-induced afterdepolarizations and calmodulin kinase II signaling. Circ Res 104: 79-86.

19. Pezhouman A, Singh N, Song Z, Nivala M, Eskandari A, et al. (2015) Molecular Basis of Hypokalemia-Induced Ventricular Fibrillation. Circulation 132: 1528-1537.

20. Nguyen TP, Sovari AA, Pezhouman A, Iyer S, Cao H, et al. (2016) Increased susceptibility of spontaneously hypertensive rats to ventricular tachyarrhythmias in early hypertension. J Physiol 594: 1689-1707.

21. Morita N, Lee JH, Bapat A, Fishbein MC, Mandel WJ, et al. (2011) Glycolytic inhibition causes spontaneous ventricular fibrillation in aged hearts. Am J Physiol Heart Circ Physiol 301: H180-H191.

22. Nguyen DT, Ding C, Wilson E, Marcus GM, Olgin JE (2010) Pirfenidone mitigates left ventricular fibrosis and dysfunction after myocardial infarction and reduces arrhythmias. Heart Rhythm 7: 1438-1445.

23. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, et al. (2010) Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 56: 867-874.