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CARDIAC FIBROSIS IN THREE DIMENSIONS-MECHANISTIC INSIGHTS INTO ARRHYTHMIC RISK DUE TO HYPERTROPHY

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Sudden cardiac death, predominantly due to ventricular tachycardia and fibrillation (VT/VF), has a staggering death toll, by some estimates up to 10 million deaths/year worldwide(Rubart & Zipes, 2005). Underlying heart disease increases the risk of VT/VF and arrhythmic death.(Rubart & Zipes, 2005) Physiological (uniform/orderly) impulse propagation in the myocardium is critically dependent on proper organization of the myocardial bundles and cell-cell communication.(Kleber & Rudy, 2004) Myocardial fibrosis is a major structural alteration of the myocardium as a result of various disease processes. Cardiac injury (e.g. infarction, focal inflammation) results in the formation of a fibrotic scar.(Rutherford *et al.*, 2012) Other cardiac diseases such as hypertension that are associated with cardiac hypertrophyare also associated with myocardial fibrosis. Fibrosis is a central problem in arrhythmia biology, by distorting myocardial architecture and interrupting electrical propagation pathways it setsthe stage for non-uniform impulse propagation. These altered 'zig zag' conduction pathways form reentrant circuits that sustain VT/VF.(Nguyen *et al.*, 2014) The pattern and location of fibrosis also profoundly influences the formation of arrhythmogenic circuits in the heart.(Nguyen *et al.*, 2014) Fibrotic scars secondary to myocardial infarction have been the subject of intense study over several decades. These scars (usually encompassing a perfusion bed of a coronary artery) contain strands of viable myocardial bundles interspersed with fibrotic tissue that can create reentrant circuits(Janse & Wit, 1989). The translational potential of understanding myocardial scars by the experimental mapping of reentry in experimental models has resulted in substantial clinical benefit.(Ajijola *et al.*, 2013) Clinical translation of these experimental findings resulted in mapping of VT circuits in humans. The development of catheter ablation of VT as a clinical therapy followed and is an excellent example of the direct beneficial consequence of these scientific advances.(Shivkumar, 2019)

In contrast to fibrosis/scars secondary to infarction, patchy fibrosis seen with diseases such as hypertrophy can result in complex circuits and set the stage for additional electrophysiological effects such as triggered activity (Qu *et al.*, 2022) secondary to

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myofibroblast-myocyte interactions and source sink effects.(Nguyen *et al.*, 2012) Complex fibrosis (as seen in cardiac hypertrophy) has been the subject of intense experimental investigation. In this issue of the *Journal* (ref to be inserted by Journal), Khwaounjoo et al report the risk of VT/VF in the spontaneous hypertensive rat (SHR), a well-established model, characterizing the three-dimensional aspects of fibrosis and associated electrophysiological changes with mapping. They demonstrate proarrhythmic changes with increasing age and hypertensive heart disease in great detail, placing the structural and electrophysiological variables in context. Their study strongly supports the concept that arrhythmic risk is predicted by several left ventricular measures, but most importantly fibrosis. The strength of the study is extremely detailed quantification of structure, fibrosis and epicardial action potential duration dispersion. The study exclusively uses programmed electrical stimulation induced VT/VF risk as a surrogate for spontaneous VT/VF risk. Therefore, their results are relevant only to SHR producing a vulnerable substrate via fibrosis but does not explore whether SHR also promotes the other contributors to arrhythmogenesis, such as the emergence of triggers. Studies in SHR model (also cited by the authors) show the emergence of oxidative-stress induced early afterdepolarizations as a result of the source-sink mismatches caused by fibrosis, directly inducing spontaneous VT/VF.(Nguyen *et al.*, 2016) Thus taken together the data in the present study provides a comprehensive picture of the well characterized SHR model. The emerging paradigm would be that aging and hypertrophy cause both fibrosis and dispersion of repolarization. Changes secondary to fibrosis such as conduction block, combined with source-sink mismatch and enhanced formation of triggers can act in concert to provide both the trigger and the substrate for lethal arrhythmias (Figure).

It is also worth highlighting that additional pathophysiological mechanisms are likely to be operational in the genesis of arrhythmias relating to fibrosis. Even in the presence of a discrete region of scar tissue in the heart creating the substrate for VT, it is known that reentrant arrhythmias require areas of functional block/conduction changes that allow impulse propagation in preferential directions.(Tung *et al.*, 2012; Ajijola *et al.*, 2013; Tung *et al.*, 2013) Thus, clinical occurrence of VT reflects the balance between macro structure and functional control in real life. Neural remodeling is a key contributor to functional control of circuits and arrhythmogenesis in the setting of scars.(Fukuda *et al.*, 2015; Zhu *et al.*, 2022)

To conclude, the current publication provides much needed data on the complex changes to the myocardial architecture in the setting of cardiac hypertrophy. Future studies should build on this framework to further elucidate the arrhythmic implications of fibrosis. Experiments that can address functional changes relating to cardiac innervation (and functional control) as it has been done in post-infract scars(Zhu *et al.*, 2022) will add an important dimension to our understanding of this disease. The authors are to be congratulated for this elegant study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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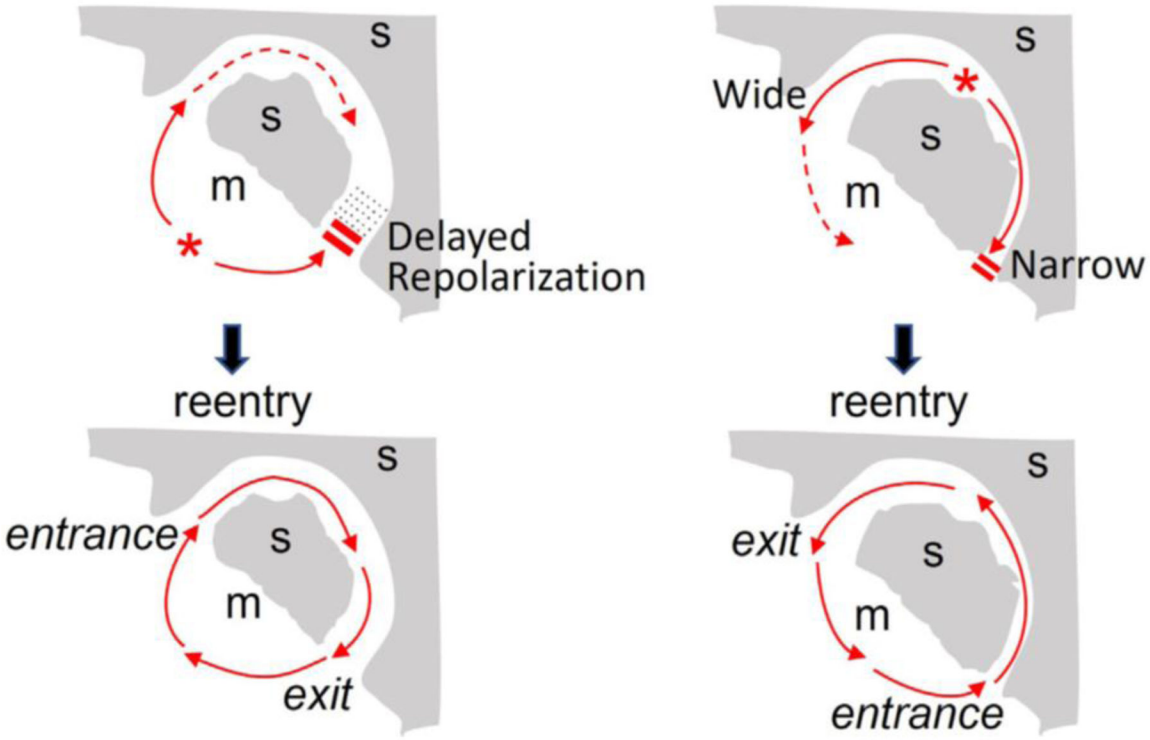

Figure:

Reentry initiation via trigger (premature ventricular complex [PVC]) and substrate interactions. Schematic diagrams showing a PVC (*) inducing anatomic reentry using a myocardial channel (m) embedded in a scar (s) (gray shading) via two mechanisms: delayed repolarization mediated unidirectional conduction block (left) and narrow exit (source-sink mismatch) mediated unidirectional conduction block (right). Image modified from ref(Qu *et al.*, 2022).