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Mechanisms of Fibrillation: Neurogenic or Myogenic? Reentrant or Focal? Multiple or Single?: Still Puzzling After 160 Years of Inquiry

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The mechanisms of initiation and maintenance of ventricular fibrillation (VF) we have been hotly debated since Hoffa and Ludwig first observed and documented the bizarre chaotic action of ventricles after exposure to electrical current.[1] During this initial period of inquiry the majority of prominent physiologists favored a neurogenic origin of arrhythmogenesis with abnormal impulse formation within a specialized network of nerve cells, which were considered the primary culprit of arrhythmogenesis. Vulpian, in his work *Note sur les effets de la faradisation directe des ventricules du coeur le chien* in 1874, however, was the first to suggest a myogenic origin of arrhythmogenesis, postulating that the cardiac muscle fibers themselves and not a specialized nerve network were responsible for initiating and sustaining abnormal cardiac rhythms.[2] In line with this observation he coined the term "*mouvement fibrillaire*" or fibrillation to emphasize the myogenic nature of the process that he had observed. A former student of Ludwig, John McWilliam of Scotland presented similar observations supporting the myogenic nature of fibrillation and was the first to suggest in his work titled *Fibrillar contraction of the heart* in 1887 that disturbances in impulse propagation were responsible for the onset of fibrillation.[3] In addition to the neurogenic versus myogenic argument, focal activity versus reentrant theories as the mechanism of fibrillation have been the center of debates since the early 20th century.

Most physiologists at the turn of the 20th century assumed arrhythmias in general, including fibrillation, were caused by a rapidly firing single focus. The concept of reentry, however, became established with work of George Ralph Mines, Thomas Lewis, and Walter Garrey in the 1910s. Garry was able to show that a minimal mass of tissue was required for maintenance and that a single rapidly firing foci was not always the cause of fibrillation.[4] Mines was one of the first to propose the basic concept of the reentrant arrhythmias and is credited for the discovery of the vulnerable period.[5,6] He also noted "the favorable conditions of slow conduction and short refractory periods … suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically."[6] The current basic electrophysiological mechanism of VF initiation include the mother reentry hypothesis, as first proposed by Lewis to explain atrial flutter and fibrillation in 1925[7] and extrapolated by Gurvich in 1957 to ventricular fibrillation.[8] Modern imaging results presented by Jalife provided convincing evidence in support of this hypothesis now known as "mother rotor."[9] An alternative reentrant theory of VF was advanced by Moe in 1964 and is currently known as multiple wavelet hypothesis.[10]

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Carl Wiggers was the first to apply imaging for documenting initiation and progression of VF. He described spatio-temporal characteristics of 4 distinct phases of VF based on epicardial motion recorded on film with high-speed cinematography.[11] Although it is known since Vulpian that VF progresses in stages, the mechanisms and underlying driving force behind transition and maintenance are poorly understood.

At the end of the 20th century, the predominant consensus has attributed VF initiation and maintenance to the myogenic theory of fibrillation with a single or multiple reentry circuits as a core mechanism. Twenty-first century studies both basic and clinical, however, have re-invigorated both the neurogenic versus myogenic and focal versus reentry debates. New evidence has been presented in support of the critical role of the specialized conducting system and triggered activity in initiation of VF. Haissaguerre helped revive the debate with the identification and ablation of Purkinje potentials in patients resuscitated from idiopathic VF implicating focal, triggered activity arising from the Purkinje system as a source of arrhythmogenesis.[12] Application of Lugols' solution to the sub-endocardium of canine hearts resulting in a chemical ablation of the Purkinje network has been shown to increase the VF threshold making it much more difficult to induce and maintain VF as opposed to canines not receiving chemical ablation.[13]

Chen has provided compelling evidence on the critical role of the autonomic nervous system associated with myocardial injury and VT/VF formation in post-MI canine models further implicating the importance and re-emergence of the neurogenic theory.[14,15] Chen's group conducted experiments in the canine model of AV block and myocardial infarction, in which continuous infusion of nerve growth factor near the left stellate ganglion facilitated nerve sprouting and hyper-innervation. Interestingly, experimental groups with chronic nerve growth factor infusion were noted to have a much higher incidence of VT/VF when compared with control groups.[16] Left stellate ganglion nerve activity was monitored throughout and displayed a relationship between sympathetic discharges and VT/VF initiation illuminating the direct role of the autonomic nervous in arrhythmogenesis.[16] Anatomic therapeutic approaches to rhythm disorders are now actively pursued with goal of denervation of the autonomic influence on the heart in patients at risk. Left cardiac sympathetic denervation is currently being evaluated as a method of therapy in patients with long QT syndrome and catecholinergic polymorphic ventricular tachycardia via VATS and has been shown to have promising results of preventing malignant ventricular arrhythmias.[17,18]

Much work has been done in elucidating the mechanisms at play in the formation of short duration VF (<1 min) and both multiple wavelet and mother rotor hypotheses are thought to play a role in this initial time period.[19] The mechanisms of long duration VF (>1 min), however, remain under-investigated and thus poorly understood. Although the Purkinje system has been brought into the spotlight highlighting the role of the specialized nervous system in VF, the mechanism of how it participates has remained controversial.

In this issue of the Journal, Robichaux *et al*.[20] have provided an elegant study in an *in vivo* canine model characterizing the role of focal, triggered activity from the Purkinje fibers in the initiation and maintenance of long duration VF (LDVF). In this study using a 64-electrode basket catheter in the LV, a 12-lead ECG, and RV catheter, 6 canines had VF induced and activation sequences of 15 successive cycles after initiation of VF were observed after 1, 2, 3, 5, 7, and 10 min of LDVF. The findings of the study can be summarized into the following: (1) during the first 3 min of VF reentry with complex endocardial patterns were noted to be the predominant mechanisms of VF maintenance; (2) after 3–7 min of VF, complex endocardial patterns were replaced by highly organized activation sequences and was termed ventricular electrical synchrony or VES. Although the

time frame to reach VES varied, once this pattern began it was generally seen at all subsequent time points; (3) activations of the Purkinje system were always noted before ventricular activations when they occurred spreading through the P–V junctions; and (4) activation sequences between LV and RV were dissociated during VES. Overall, these findings provide reasonable evidence that the Purkinje system is key in the maintenance of LDVF and insight into the role and success of ablation of the Purkinje system in idiopathic VF.

Chen *et al.*[21] defined 2 types of VF that have different characteristics and termed type 1 and type 2 VF, with type 1 thought to be secondary to multiple wavelets and type 2 thought to be driven by a focal source with transition typically seen from type 1 to type 2 as VF progresses depending on the degree of local anatomical and functional heterogeneity located within the tissue. A third mechanism is now apparent and is implicated by automaticity driven by the specialized conduction system of Purkinje fibers. These findings have potentially important clinical implications. In patients who are at higher risk of SCD as evaluated by traditional methods, how aggressive should we be in identifying possible arrhythmogenic sources within the Purkinje system and ablating during EPS? Are some areas of the Purkinje system more susceptible to VF maintenance than others? Prophylactic ablation of “susceptible” regions of the Purkinje system if identified may be a new avenue of preventing VF as earlier stages of VF are more likely to self-terminate, particularly in the setting of normal anatomy, oxygenation, and LV function. Although these findings provide insight into the general mechanism of LDVF, many questions remain due to exceedingly difficult methodological obstacles. Thus, undoubtedly the debate between the neurogenic and myogenic camps and the focal and reentrant camps will continue. But these debates are likely to bring about new approaches to pharmacological, device and ablation therapies to prevent sudden cardiac death.

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