Ventricular Fibrillation

Rotors or Foci? Both!

See Article by Panitchob et al

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As to the fundamental mechanisms of fibrillation we have plenty of theories, but none is universally accepted… we may note in passing that they all center around two ideas … (a) that the impulses arise from centers or pacemakers, or (b) that the condition is caused by re-entry of impulses and the formation of circles of excitation. Each of these views, again, has two groups of exponents … (a) those who believe that a single focus, or excitation ring, occurs, and (b) those who favor the idea that multiple foci, or numerous circus rings, are developed.

—Carl J. Wiggers, 1940[1]

Ventricular fibrillation (VF) was likely recognized as early as 3500 BCE when the Ebers Papyrus[2] described key features of fibrillation as follows:

"If the heart trembles, has little power and sinks, the disease is advancing and death is near."

The modern scientific effort to understand fibrillation did not begin until 1543, when Vesalius[3] described worm-like movements in animal hearts during dissection just before they died. Erichsen[4] in 1842 documented tumultuous, tremulous, and irregular behavior of ventricles consequent to coronary ligation. Hoffa and Ludwig[5] first recorded VF using a kymograph (mechanical wave recorder) in 1850 (Figure, left). Interestingly, Hoffa, who was Ludwig's pupil at the time, meant to stimulate neurons but accidentally stimulated the myocardium. They showed that irregular contractions of the ventricles could be induced by faradization (electric stimulation) and resulted in cardiac arrest that could not be checked by vagal stimulation. These studies of autonomic control of the heart suggested a neurogenic VF mechanism.

The term fibrillation was coined by Vulpian[6] in 1874, referring to arrhythmia as mouvement fibrillaire and described the progression of VF as having at least 3 distinct phases. In 1887, MacWilliam[7] described ventricular and atrial fibrillation as 2 distinct phenomena and observed that stimulation of vagus had no effect on VF but could arrest atrial fibrillation. He also showed that VF could be terminated by repetitive electric shocks applied through a large pair of electrodes, 1 located on the ventricular apex and other in the sixth or seventh dorsal vertebra. The work of Vulpian and MacWilliam put to rest the neurogenic theory of VF and suggested a myogenic VF mechanism that remained dominant for over a century. In 1911, Levy and Lewis[8] used the ECG to document arrhythmia during chloroform anesthesia and observed that ventricular tachycardia often preceded VF. However, it was Hoffman[9] in 1912 who recorded the first ECG of VF in a human.

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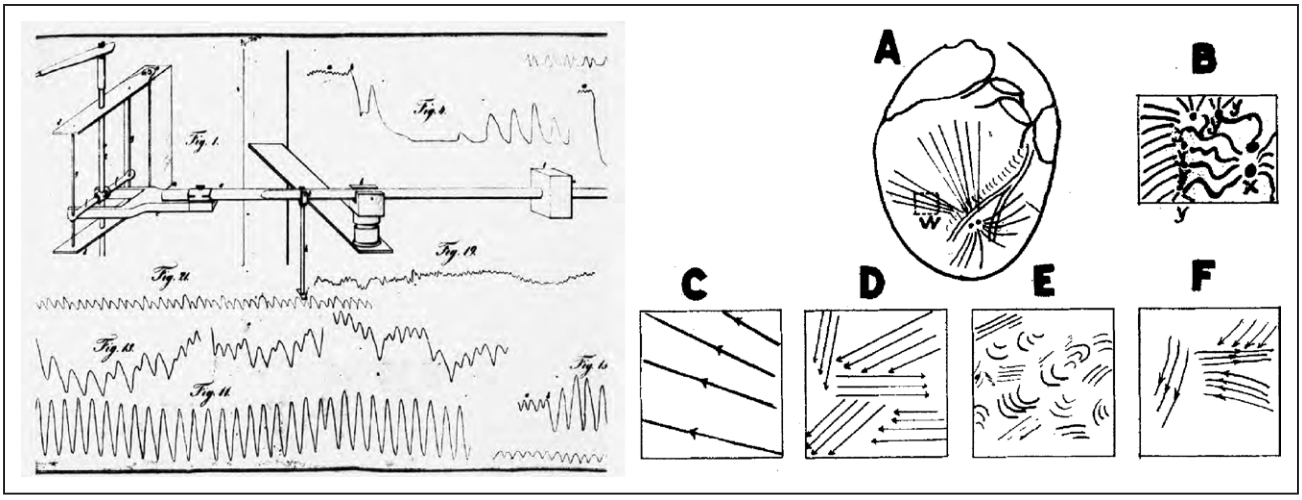

Figure. The first recordings of ventricular fibrillation were acquired by Hoffa and Ludwig using a kymograph (left).[5] Wiggers conducted the first imaging studies of ventricular fibrillation using fast cinematography (**right**). Reprinted from Wiggers[1] with permission. Copyright © 1940 Published by Elsevier, Inc.

In addition to the debate between a neurogenic or myogenic origin of VF, focal and reentrant mechanisms of VF have also been debated since the early days of VF research. At the turn of the 20th century, most researchers believed that fibrillation was induced by a rapidly firing single focus. However, Lewis, Mines, and Garrey in the 1910s conceptualized the reentrant mechanism of VF. Lewis introduced the primary ring hypothesis, suggesting that a single reentrant circuit was sufficient to maintain fibrillation. In 1913, Mines[10] described circus movement reentry and discovered the vulnerable period using rings of cardiac tissue isolated from tortoise and rays. He noted, "ordinarily, in the naturally beating heart, the wave of excitation is so long and so rapid that it spreads all over the ventricle long before it has ceased in any other part. Under the altered conditions of increased frequency, it is possible that this should no longer be the case, and thus that, the wave being slow and short, more than one could exist at one time in a single chamber..." Garrey[11] extended this idea in 1914 and published the first systematic study on the relationship between VF and the size of the heart. He proposed the critical mass hypothesis and noted, "the ease with which the fibrillatory process may be induced and with which the spontaneous recovery from the fibrillatory contractions takes place is inversely proportional to the mass of the fibrillating tissue." In contrast to Lewis, Garrey suggested that multiple reentrant sources are needed for initiation and maintenance of fibrillation.

Several years later, in 1930, Wiggers[12] thoroughly characterized VF in canines using high-speed cinematography and the ECG. He described VF induced by shock-on-T as a progression through 4 distinct stages, now referred to as the Wiggers stages of fibrillation (Figure, right). The first Wiggers stage (C)—the tachysystolic or undulatory phase—consisted of 2 to 8 peristaltic waves sweeping rapidly across the ventricles and lasting for several seconds. The second Wiggers stage (D), typically lasting 15 to 40 seconds, was convulsive incoordination and characterized by violent oscillations of more frequent contractions over a smaller area of myocardium. The third Wiggers stage (E) lasted 2 to 4 minutes with tremulous incoordination and involved more frequent contractions of smaller amplitude over an even smaller region. The fourth and final Wiggers stage (F) was atonic coordination, characterized by extremely weak and slow contractions over short distances, with increasing areas of quiescence, until the myocardium ceased to contract. The first 2 stages were marked by high ventricular activation rate (10 Hz), which gradually slowed during the last 2 stages because of ischemia. Wiggers was also the first to note that, "since sequential reentrant excitations travel over a bulky mass of ventricular muscle, one must not think in terms of 2-dimensional rings or circuits, but rather of massive wave fronts spreading in 3 dimensions."[12]

The conceptualization of focal and reentrant mechanisms of VF was refined as new generations of scientists extended the observations of their predecessors. The reentry mechanism split into the mother rotor hypothesis or the multiple persisting circuits hypothesis. In 1964, Han and Moe[13] postulated the multiple wavelet hypothesis using a 2-dimensional computer model of fibrillating myocardium. He suggested that multiple reentrant sources or wavelets were required to maintain fibrillation. In 1985, Allessie et al[14] mapped atrial excitation in canine hearts during acetylcholine-induced atrial fibrillation and provided the first experimental evidence of multiple propagating wavelets during fibrillation. A present-day refinement of the Moe multiple wavelet hypothesis is the restitution hypothesis of wavebreak, which postulates that rotors break

into multiple wavelets when the slope of the action potential duration restitution is steep. At the same time, others have provided experimental support for the mother rotor hypothesis, suggesting that multiple wavelets are spawned from a single, or a small number of, stable reentrant sources, termed rotors.[15]

More recently, there has been renewed interest in neurogenic mechanisms of VF, including studies of the role of the autonomic nervous system and the specialized conducting (Purkinje) system of the ventricles.[16,17] In particular, recent studies have shown that abnormal focal activity because of highly active Purkinje fibers is important in maintaining VF.[17] Indeed, catheter ablation of Purkinje fibers to suppress VF in patients with ischemic heart disease has proven effective.[18] Aberrant Purkinje fiber activity is thought to motivate multiple wavelet activity and to also participate in maintaining large rotors.[19] Although the influence of the Purkinje system in maintaining fibrillatory activation is much more appreciated now than in prior decades, the mechanisms that maintain long-duration VF (>1 minute), and the involvement of the Purkinje system, remain an active area of research.

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Panitchob et al[20] mapped VF in 6 healthy canines using a 64-electrode endocardial basket catheter and 54 6-electrode transmural plunge needles inserted into the left ventricle. They showed that the early onset of VF is marked by a chaotic endocardial activation pattern that gives way to regular and eventually synchronized activation patterns as the VF progresses. The chaotic activation pattern of early VF typically lasted 2 minutes and was marked by irregular cycle lengths without an endo-to-epi activation rate gradient. The chaotic pattern was associated with intramural reentry or wandering wavelet reentry. This observation is consistent with the results of previous epicardial mapping studies of fibrillating swine hearts.[21,22] In particular, panoramic optical mapping of nearly the entire epicardium of fibrillating hearts enabled the tracking of rotors through fragmentation and collision events.[21] This provided a comprehensive analysis of rotor movement and lifespan during perfused VF—a condition similar to the short-duration VF phase described by Panitchob et al. Panoramic mapping revealed that shorter-lived rotors were common and that, on average, a dozen of such rotors were present within the epicardium during early (perfused) VF.[21] Might Panitchob et al have also made this same observation if they had panoramically mapped the epicardium of the canine hearts they studied? It is reasonable to suspect so.

Panitchob et al[20] further observed that a regular activation pattern dominated at the 3-minute mark and was characterized by repeatable cycle lengths and an emerging activation rate gradient driven by the Purkinje system. Moreover, the regular pattern on the endocardial surface was consistent with a stable mother rotor. The synchronized pattern emerged later in VF (>5 minutes) and was characterized by irregular cycle lengths and synchronized activation of the entire endocardium. The synchronized activation pattern was thought to be the result of focal activity in the Purkinje system. The authors further showed that defibrillation shocks elicited responses dependent on VF duration. Failed defibrillation shocks changed chaotic and regular activation pattern to a synchronized pattern in long-duration VF (7 minutes) but not in short-duration VF (10 seconds). An impressive aspect of the study is that Panitchob et al carefully quantified the stages of VF that were first qualitatively described by Wiggers. In doing so, they have provided the research community with new opportunities to further study and understand the details of how VF progresses from the spark of initiation to the cessation of the last wave front.

In considering the substantial experimental advances and the multitude of decades of inquiry into the mechanisms of VF, it is striking that the general sentiment expressed in 1940 by Wiggers is still valid: no theory of fibrillation is universally accepted. Perhaps, there is no overarching single answer to what maintains fibrillation. It is likely that mechanisms that maintain VF may lie along a spectrum and alternate between reentrant and focal sources depending on the degree of transmural dissociation caused by progressing ischemia. Future studies are required to dissect the causes of transitions between reentrant and focal mechanisms that maintain VF. Doing so could have a dramatic impact on approaches used to resuscitate patients who succumb to sudden cardiac arrest.

AFFILIATIONS

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DISCLOSURES

None.

FOOTNOTES

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