Fibrillation or Neurillation
Back to the Future in Our Concepts of Sudden Cardiac Death?
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“If the heart trembles, has little power and sinks, the disease is advancing . . . and death is near . . . .”
—The Papyrus Ebers (circa 3500 BCE)

Numerous concepts of cardiac electrophysiology have been advanced, enshrined, and then laid to rest. Other theories have withstood the test of time despite the restless energy of inquisitive doubt of future generations. Until recently, one such concept has been the foundation of the mechanisms of fibrillation, which was imprinted in the very name to emphasize its fibrillar or myogenic nature.

It was apparently known to ancient Egyptians and Chinese that an irregular heartbeat is associated with death. However, scientifically rigorous description of a causal relationship was presented only in the middle of the 19th century. Erichsen described in 1842 that coronary artery ligation led to “tumultuous,” “tremulous,” and “irregular” behavior of the ventricles.1 First documentation of the onset of ventricular fibrillation (VF) during electrical stimulation was recorded in 1849 using Ludwig’s “kymographion” by his associate Hoffa.2 Interestingly, at the time, Hoffa was assigned to investigate autonomic nervous system effects on cardiac activity, which had been discovered a year earlier by Ludwig himself.3 Hoffa described irregular contractions induced by “faradization” (electrical stimulation), which persisted even after the termination of electrical stimulation and resulted in cardiac arrest that could not be checked by vagal stimulation.

Intensive investigation of the newly described phenomenon led to the introduction of numerous terms, which aimed to capture the mechanistic and/or anatomic nature of the irregular contractions and resulting cardiac arrest.4 The main disagreement gravitated toward one question: is the phenomenon neurogenic or myogenic in nature? In other words, is irregular activity due to abnormal behavior of cardiac muscle itself or due to abnormal activity of the autonomic nervous system that controls the heart? Initially, the neurogenic theory of VF seemed more convincing and persisted despite ample evidence to the contrary. Most of the investigators favoring a neural origin concluded that irregular contractions and cardiac arrest resulted from one of the following:5: (1) abnormal impulse transmission in the nerve fibers, (2) conduction of abnormal stimuli from external nervous source; or (3) morphological changes in specialized nervous centers, which regulate cardiac behavior. In support of the neurogenic theory of VF, See and Gley argued that the susceptibility to VF can be altered via depression of the nervous system by systemic hypothermia or large doses of chloral.6 Kroncke and Schmey5 and Langendorff7 supported the neurogenic theory by the observation of anatomical heterogeneity of susceptibility to VF, which they related to the different density of nerve fibers through the heart.

However, a myogenic theory eventually prevailed and dominated for more than a century. Vulpian was the first to present observations that he explained on the basis of the myogenic nature of irregular rhythm induced by faradization. He observed the following: (1) VF can be induced from any region of the ventricles, (2) induction depended on current strength, (3) VF self-terminates in guinea pigs, but not in dogs, and (4) neither vagal stimulation nor additional faradizations could arrest VF.8 Based on his observations, Vulpian introduced the term “fibrillation” to emphasize the myogenic nature of the phenomenon. Unfortunately, his work was largely ignored until MacWilliam provided a more convincing repudiation of the neurogenic theory:9 “The state of arrhythmic fibrillar contraction is essentially due to certain changes occurring within the ventricles themselves. It is not due to the passage of any abnormal nerve impulses to the ventricles from other parts, or to the interruption of any impulses normally transmitted to the ventricles. The condition is not due to injury or irritation of the nerves that pass over the ventricles from the base of the heart. The arrhythmic fibrillar contraction is not necessarily dependent on the destruction or paralysis of a coordinating center located in any particular part of the ventricles.”

For a long time, it was widely accepted that Vulpian and MacWilliam had firmly established the myogenic theory of fibrillation,9 which implied that the autonomic nervous system had a limited role in VF. Predominant theories of initiation and maintenance of fibrillation, such as “mother rotor”10–12 or restitution13,14 hypotheses, are based entirely on the myogenic nature of fibrillation. A study in this issue of Circulation Research15 casts some degree of doubts on this dogma. Several preceding studies from Chen’s laboratory16 presented evidence of induced nerve sprouting and sympathetic hyperinnervation in canine models of ventricular and atrial fibrillation. Now they have extended these findings to the classical Anichkov rabbit hypercholesterolemia model17 of atherosclerosis and sudden cardiac death.

Myocardial ischemia and infarct are known to result in the injury of sympathetic nerves and sympathectomy of nonin-
farcted myocardium. Injury and inflammation of peripheral nerve fibers in the heart are likely to initiate an increase in nerve growth factor (NGF) production, which would stimulate sympathetic nerve sprouting. Such a response could enhance the negative feedback control of inflammation. And indeed, in a canine model of chronic infarct and atrioventricular block induced by left anterior descending coronary artery ligation and catheter ablation, respectively, Chen’s group observed a significant increase in nerve densities. Immunolabeling with the growth-associated protein 43 (GAP43), tyrosine hydroxylase (TH), and tenascin-X (TnX) suggested an elevated level of nerve sprouting. Yet, spatial heterogeneity throughout the injured myocardium could also result in a profound heterogeneity of myocardial excitability and refractoriness via patchy, dispersed β-adrenergic stimulation of ICaL, IKs, and ICa. Superimposed with electrical remodeling of a number of ion channels in the infarction border zone, the resulting heterogeneity is likely to contribute to enhanced propensity to arrhythmias, which was demonstrated in this model. Interestingly, additional stimulation of nerve sprouting by NGF infusion to the left stellate ganglion superimposed with infarct dramatically increased the frequency of ventricular arrhythmias and sudden cardiac death. Thus, morphological changes in the nervous system of the heart were demonstrated to result in fibrillation, contrary to the myogenic theory.

Similar findings were presented from a canine model of atrial fibrillation produced by prolonged right atrial pacing. Chang et al observed a dramatic increase in the density of GAP43-immunopositive and TH-immunopositive nerve fibers. They also observed a profound difference in the rates of nerve sprouting between the right and left atria, which enhanced the normal significant right-left atrial asymmetry of nerve densities. These immunohistochemical studies support earlier positron-emission tomography imaging data, which presented evidence of heterogeneity of changes in atrial sympathetic innervations. Chemically induced heterogeneous sympathetic denervation was shown to create a substrate for atrial fibrillation. Thus, another dimension of remodeling associated with prolonged electrical pacing was presented, in addition to the well-established electrical and anatomical remodeling.

And finally, Liu et al applied a similar protocol to the classical Anichkov model of atherosclerosis, which in 1913 yielded clear evidence that cholesterol alone can cause atherosclerosis in the rabbit heart. They reported that, in the Anichkov model, a cholesterol-rich diet results in a significant increase in the density of both GAP43-positive and TH-positive nerve fibers, which suggests nerve sprouting and sympathetic hyperinnervation in response to hypercholesterolemia. Furthermore, they found a dramatic increase in the incidence of ventricular fibrillation, which was associated with enhanced dispersion of repolarization, prolongation of action potential duration and the QT interval, and increased ICa density.

These studies reopen an old and well-forgetten page in the history of VF, dating back to the 19th century. It is clear that, in addition to the electrical, structural, and mechanical remodeling documented in numerous models of chronic atrial and ventricular arrhythmias, one has to consider neural remodeling. The relationship among these remodeling processes and inflammatory responses is likely to be the focus of follow-up studies, which will shed light on the nature of fibrillation or perhaps “neurillation,” if neurogenic factors of the arrhythmia will be found to play as important a role as myogenic factors. These studies provide new, promising insights into the still-puzzling efficacy of β-blockers in the prevention of sudden cardiac death. Furthermore, one could speculate that the cardiac model of nerve sprouting presented here may help to unravel the mechanisms of neural repair and regeneration.

References


Key Words: cardiac electrophysiology, ventricular fibrillation, neural repair, nerve sprouting, regeneration
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Circ Res. 2003;92:1062-1064
doi: 10.1161/01.RES.0000075793.51113.6A

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