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 “tumul-
tuous,” “tremulous,” and “irregular” behavior of the ventri-
cles.1 First documentation of the onset of ventricular fibrilla-
tion (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 termi-
nation of electrical stimulation and resulted in cardiac arrest
that could not be checked by vagal stimulation.

Intensive investigation of the newly described phenomena
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 phenom-
enon 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 cardia-
card origin resulted from one of the following:5 (1) abnormal

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Impulse transmission in the nerve fibers, (2) conduction
of abnormal stimuli from external source; or (3) mor-
phological 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 Kronecker and
Schmey5 and Langendorff7 supported the neurogenic theory
by the observation of anatomical heterogeneity of suscepti-
bility 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 fa-
radizations 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 condi-
tion 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 sys-
tem 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 sympa-
thetic 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-

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farcted myocardium.18,19 Injury and inflammation of peripheral nerve fibers in the heart are likely to initiate an increase in nerve growth factor (NGF) production,20 which would stimulate sympathetic nerve sprouting. Such a response could enhance the negative feedback control of inflammation.21 And indeed, in a canine model of chronic infarct and atrioventricular block induced by left anterior descending coronary artery ligation and catheter ablation, respectively,22,23 Chen’s group observed a significant increase in nerve densities. Immunolabeling with the growth-associated protein 43 (GAP43),24 tyrosine hydroxylase (TH), and tenascin-X (TnX)25 suggested an elevated level of nerve sprouting.22 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 \( I_{Ca,L} \), \( I_{Kr} \), and \( I_{Cf} \). Superimposed with electrical remodeling of a number of ionic channels in the infarction border zone, the resulting heterogeneity is likely to contribute to enhanced propensity to arrhythmias, which was demonstrated in this model.22 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.22 Thus, morphological changes in the nervous system of the heart were demonstrated to result in fibrillation, contrary to the myogenic theory.8,9

Similar findings were presented from a canine model of atrial fibrillation produced by prolonged right atrial pacing. Chang et al26 observed a dramatic increase in the density of GAP43-immunopositive and TH-immunopositive nerve fibers.26 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.26 These immunohistochemical studies support earlier positron-emission tomography imaging data, which presented evidence of heterogeneity of changes in atrial sympathetic innervations.27 Chemically induced heterogeneous sympathetic denervation was shown to create a substrate for atrial fibrillation.28 Thus, another dimension of remodeling associated with prolonged electrical pacing was presented, in addition to the well-established electrical and anatomical remodeling.29

And finally, Liu et al15 applied a similar protocol to the classical Anichkov1 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,15 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 \( I_{Cf} \) density.

These studies15,16,22,23,26 reopen an old and well-forgotten 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.30 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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