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Role of the brain in ventricular fibrillation and hypertension: From animal models to early human studies

Sudden cardiac death is caused by ventricular fibrillation (VF), not by myocardial ischemia. Ventricular tachycardia, the precursor to VF, results dynamically from a "rotor"[1,2] that occurs in the excitable medium of the myocardium. The rotor is a self-sustaining vortex with its wave front of depolarization extending outward from a pivot point, with the inner circles moving more slowly than the outer. The rotor is a couple of centimeters in diameter, and the pivot point meanders randomly. When its outer edges strike nonexcitable tissues, such as an artery or an old infarction, the initial rotor breaks up into secondary and tertiary rotors to produce the disorganized excitability of VF.

VENTRICULAR FIBRILLATION IS A BRAIN PROBLEM

Pathology studies have shown that sudden cardiac death is often, but not always, associated with infarction or thrombosis in the heart. One seventh of patients experiencing sudden cardiac death have no detectable cardiovascular pathology, and half have insignificant pathology compared with controls.[3]

In a compelling experiment, Ebert and associates[4] showed that if all the nerves projecting to the heart (including the intrinsic ones) are blocked, then coronary artery occlusion and ischemia do not result in VF—not in a single case among 13 anesthetized dogs. This demonstrated that VF is clearly a brain problem, not a heart problem.

Joaquin Fuster showed in an early report[5] that brief electric pulses delivered through an electrode in the hypothalamus, which activated local neurons and fibers of passage, would elicit ventricular tachycardia. This evocation of arrhythmogenesis in a normal heart was later confirmed by others and shown to result in lethal VF if stimulation continued for longer periods (see review by Skinner[6]). **Figure 1A** presents an example of one such brain stimulation.[6]

A CEREBRAL DEFENSE SYSTEM?

Skinner and Reed[7] backtracked from the cutting of nerves in the periphery to blocking the higher cerebral sources of the nerves. We obtained results similar to those of Ebert et al, but in conscious animals, ie, in a conscious pig model of left anterior descending coronary artery occlusion.[7] This work, however, was guided by previous results that had considered Walter B. Cannon's early theory about brain-heart relationships.[8]

Cannon suggested that the focus of natural selection that led to the hypertrophy of the human brain was a "cerebral defense system" in which novel stimuli evoked cerebral "orchestration" of both the sensory input channels and the autonomic output channels. He believed that this orchestration had important survival value in moments of crisis, as it led to superior escape from predators or superior attack of prey.

Skinner and Lindsley[9] studied this hypothesized orchestrator, which Cannon proposed to lie in the most recently encephalized centers of the brain. We found it to be located in the orbitofrontal cortex and to control sensory input by thalamic inhibition in channels conveying irrelevant information—ie, the regulation of sensory input by the cerebral defense system worked by selective *in*attention.[10] Thus it was knowledge of where the autonomic output arose (the frontal cortex) that guided Skinner and Reed[7] in locating the descending projections to the peripheral nerves that, when blocked, would prevent VF in the conscious pig model of heart attack.

Insights from sleep

Sleep is initiated by the frontal lobes, as blockade in these structures, or blockade of their connections with the nonspecific nuclei of the thalamaus, will pre-

* Dr. Skinner reported that his employer, Vicor Technologies, holds patents for the nonlinear PD2i algorithm discussed in this article.

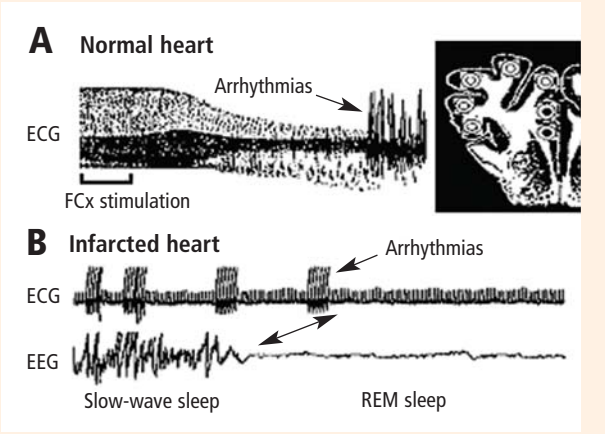

FIGURE 1. (A) Effect of electrical stimulation of the frontal cortex (FCx) on the electrocardiogram (ECG) of the normal heart in an unanesthetized pig.[6] (B) Salutary effect (after a 10-second latency, indicated by double-headed arrow) of rapid eye movement (REM) sleep on arrhythmogenesis in the acutely infarcted pig heart.[12]

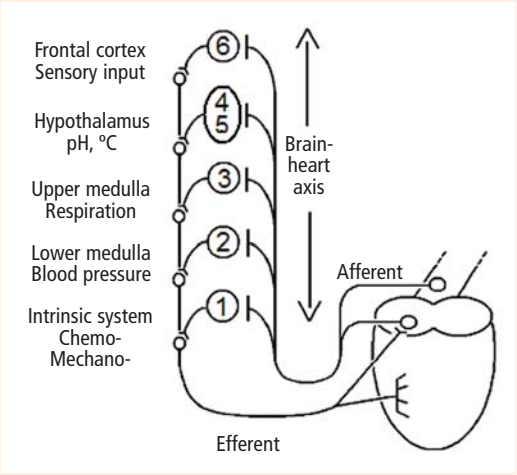

FIGURE 2. The sensory-motor loops of the brain-heart axis that compete with one another to control the heartbeat intervals.

vent occurrence of the sleep spindles that initiate the sleep process.[11] **Figure 1B** depicts the salutary effect of a particular sleep state (rapid eye movement [REM] sleep) on cardiac arrhythmias resulting from an acute myocardial infarction.[12] The 10-second latency between the onset of REM sleep and the salutary effect on arrhythmogenesis (double-headed arrow in figure) suggests that the release of a neuroendocrine molecule may underlie the effect.

Brain-heart axis

A brain-heart axis regulates the vulnerability of the heart, especially the ischemic heart, to lethal arrhythmogenesis. As illustrated in **Figure 2**, blockade at any point in the descending pathway will prevent VF in the conscious pig model of heart attack, and, conversely, electric stimulation will evoke lethal arrhythmias. Thus, by Cartesian logic, the brain–VF relationships are both necessary and sufficient (causal), whereas ischemia–VF relationships are not. So what normally causes the brain-mediated VF that is especially easy to evoke in the ischemic heart?

STRESS AS AN ENABLER OF VENTRICULAR FIBRILLATION: EVIDENCE FROM ANIMAL MODELS

Cannon's subjects would be expected to be "stressed" by the sudden appearance of a novel stimulus in a jungle setting. For example, a monkey sitting quietly in a tree would not know whether to move toward or away from an object producing a novel stimulus, but meanwhile its heart would be racing and it would feel anxious. With the additional evolution of the frontal lobes, as in the human primate, any stimulus event may come to evoke anxiousness.

For example, complex "stressor events" are known to have a relationship to the incidence of sudden cardiac death (VF) in humans. Bereavement, job insecurity, marital strife, and recently having moved are among the defined psychosocial stressors that Rahe et al[13] found were statistically related to the incidence of sudden cardiac death. Although pigs are not capable of being stressed by bereavement, job insecurity, or marital strife, as these events require considerable neocortex for their perception, Skinner and associates[14] considered another psychosocial stressor identified by Rahe et al—"recently having moved"—as a possible way to simulate human psychosocial stress in pigs. In our conscious pig model of heart attack, we found that coronary occlusion always resulted in VF in pigs unadapted to the laboratory, whereas it did not result in VF—not in 1 of 16 animals—among those pigs that had been adapted to the laboratory by having been fed and played with daily for about 1 week.[14] A subsequent study showed that this daily adaptation to the unfamiliar surroundings of the laboratory systemically reduced the sympathetic drive on the myocardium at rest and did this (ie, reduced phosphorylase activation) without changing heart rate or blood pressure.[15]

THE SEARCH FOR A CEREBRAL MEDIATOR OF THE STRESS RESPONSE

Meanwhile, the search was on by Skinner and associates for a cerebral mediator of the stress response.

Both novel stimuli and conditioned stressors were found to evoke a cortical event-related slow potential (of greatest amplitude in the frontal lobes) that was mediated by the following:

- Noradrenergic release[16]
- Slow postsynaptic potentials in the dendrites of pyramidal neurons[17]
- Cyclic AMP as the intracellular messenger[18]
- Activation of a slow outward membrane current (K^+).[19]

Focus on intracerebral beta-receptors

When it was realized that these neurophysiologic and neurochemical results implicated a cerebral beta-receptor as a way to intervene in the stress response, experiments were quickly performed[20,21] to determine where the site of action was, since beta-blockers had already been determined in the Beta-Blocker Heart Attack Trial to prevent VF (ie, reduce mortality by 26% in post-myocardial infarction patients).[22] What was not known was whether the target receptor of the beta-blockers is in the brain or the heart. In the pig model, short-term injections of propranolol into either the interstitial compartment of the brain or the larger compartment of the circulation soon made clear that it is the blockade of the intracerebral beta-receptors, not the cardiac beta-receptors, that results in the antimortality effect.[20,21]

This interpretation is further supported by observing the antimortality efficacy of different beta-blockers with varying lipophilicities. Fat-soluble molecules get into the brain at higher levels. The straight-line negative slope that Hjalmarson[23] found for this comparison indicates that the more lipophilic beta-blockers have a much greater efficacy for preventing VF in post-myocardial infarction patients.

Blood pressure elevations maintained by hypothalamic fibers of passage

Since beta-blockers were first developed using bioassay models of hypertension, there was reason to suspect that this same cerebral defense system, which involves the frontal lobes, might also play a role in the maintenance of hypertension, especially since hypertension is a harbinger for sudden cardiac death. Skinner and associates[24] showed that blood pressure elevations are not maintained by the hypothalamus, as was previously interpreted by others after they placed permanent lesions in this structure, but rather that it is blockade of the fibers of passage through the hypothalamus that produces normalization of blood pressure. These hypothalamic fibers of passage were understood to arise from the frontal cortex because blockade of that structure also normalized blood pressure in the several animal models of hypertension that were studied. Even more convincingly, we found that cryoblockade in the hypothalamus, at temperatures that blocked the local synaptic activity but not the fibers of passage, had no effect on blood pressure elevations, whereas cooling only 5°C more, which also blocked the fibers of passage, quickly normalized blood pressure in the various hypertensive models.[24]

The above result explains why reducing blood pressure elevations with a neuroactive beta-blocker also has an antimortality effect. That is, both hypertension and lethal arrhythmogenesis originate in the same noradrenergic frontocortical tissues. In contrast, reducing blood pressure with a diuretic (which reduces blood volume by expelling water) has no effect on mortality. It was interpreted that hypertension per se does not lead to sudden cardiac death but rather that activation of the frontal cortices produces both, in parallel.

A UNIFYING INSIGHT: BETA-BLOCKERS ARE ANXIOLYTIC

A single piece of scientific evidence ties all of this brain-heart business together and makes it consistent—the unexpected finding that beta-blockers are also anxiolytic (ie, anti-"stress"). Beta-blocker pills have been used by actors for decades to reduce stage fright. This anecdotal efficacy has gained scientific support more recently in studies that have shown beta-blockers to prevent the behavioral (psychiatric) sequelae in posttraumatic stress disorder.[25] Anxiety reduction in humans is perhaps somewhat predicted by the action that beta-blockers have in pigs that are unadapted to the laboratory. That is, with this deleterious brain state of "stress," VF always occurs after coronary artery occlusion, whereas with this deleterious brain state *and* intracerebral beta-blockade, VF does not occur.

But the beta-blocker effect did not have to be mediated through the perception of anxiety—it just turned out that way. The antimortality effect could have worked farther downstream in the brain-heart axis **(Figure 2)** without there being any anxiolytic effect, but it didn't—there is an anxiolytic effect, and this means that the drug is likely working on the higher cerebral centers underlying the perception of anxiety to reduce mortality. The frontal cortex, the highest center in the brain-heart axis, is well recognized as underlying the perception of anxiety, as frontal lobotomies were at one time prescribed to alleviate it.

The role of changes in neocortical gamma activity

The early realization that "intelligence" centers were part of the mechanism underlying sudden cardiac death and VF is what first led Skinner and associates[26] to examine the effects of beta-blockers on the olfactory bulb, a tissue that is often employed as a simple-system model of the more complex neocortex. We found in the conscious rabbit that the beta-blocker propranolol, when administered to the interstitial space of the olfactory bulb, would prevent the rabbit from learning anything new about an odor (eg, that the odor forewarned a noxious stimulus).[26] The important control observation was that blockade of the beta-receptor exerted its effect without reducing the cellular excitability and without preventing the raw perception of the odor and a sniffing response to it (ie, propranolol did not simply anesthetize the tissue). The rabbit could tell that the odor was there, but it could not learn what it signified.

The effect of the beta-blocker was on *learned* changes in the electric "gamma" activity in the bulb—ie, activity that oscillates within the higher frequency ranges (the gamma band). Gamma activity can also be recorded in the neocortex of humans and is recognized to be the low-voltage fast activity that we formerly called "EEG desynchronization," a cerebral reaction that always occurs in conjunction with attentive behavior.

What the learned changes in the gamma activity signify in the neocortex was later revealed by Gray and Singer,[27] who presented compelling evidence that it is the gamma activity that links various "cell assemblies" together in a "global phase synchrony" to form a more complex perception, that is, as more and more learned significance is attached to an initially simple sensory stimulus. This work is still fresh and productive in neuroscience, as evidenced in recent publications.[28,29]

Francis Crick, codiscoverer of the structure of DNA and later a theoretical neuroscientist, has stated that this "global phase synchrony" is a breakthrough discovery about higher cognitive processes of the brain.[30] Through studies of neocortical gamma activity we may someday come to understand what "stress" is and how it comes to organize the autonomic outflow that seems to cause VF in normal hearts and in ischemic hearts with lability of refractoriness.

HOW TO ASSESS THE IMPACT OF HIGHER CEREBRAL ACTIVITY ON THE HEART?

What is needed in medicine now, however, is not this complete understanding of the higher brain functions that lead to VF, but rather a simple way to assess the impact of the higher cerebral activity on the heart, especially the ischemic heart. It is known that there are at least the six sensory-motor loops shown in **Figure 2** that compete with one another to control the heart rate. In a person at rest there is a natural "jitter," or variation in the lengths of the heartbeat intervals, that results from this neural competition.

Skinner and associates[31] initially proposed to measure the neural impact on the heart by assessing the "degrees of freedom" in the heartbeat series, since conventional heart rate variability algorithms did not seem to work very well as a predictor of VF in our pig model. The degrees of freedom calculated from the heartbeat series, if they could be measured, would indicate how many of the different neural generators were contributing to the control of the heartbeats at any one moment.

We encountered several problems, however:

- Heartbeats are not randomly distributed around a mean (as is required for the use of measurement algorithms based on the linear stochastic model, eg, the mean, the standard deviation, the power spectrum, etc)
- The data do not remain stationary for very long, as is also required by linear stochastic algorithms as well as by most nonlinear ones
- Long data segments are required for most algorithms.

Applying nonlinear dynamics to assess heartbeat

A nonlinear algorithm, the point correlation dimension (PD2i), was finally developed[31] that did not require either random variation or stationary data yet did accurately express the degrees of freedom for various short segments of test data that had different known degrees of freedom. Skinner et al then tested this algorithm in our conscious pig model of heart attack.[31] If the left anterior descending coronary artery is closed 90%, then half of the unadapted (stressed) pigs will manifest VF within 24 hours and the other half will not (ie, they can be the controls). High-resolution digitization rates (> 500 Hz) were required to prevent discretization error, as the PD2i is a nonlinear algorithm and thus is sensitive to noise. We observed that the pigs that went into VF after 90% occlusion (pulsed-Doppler flow) had a low time-dependent excursion of the PD2i of the heartbeats that could predict the outcome before it happened. Those pigs that would not manifest VF were also accurately predicted. That is, with two common statistical tests of event predictability we found the PD2i to have a sensitivity of 100% and a specificity of 100%—a black-and-white result.[31]

We then tested the nonlinear PD2i algorithm in a retrospective clinical study of human subjects.[32] We studied 24-hour electrocardiographic recordings (analog Holter tapes, digitized at 500 Hz) in which the patient had manifested VF on the day of the recording. Control tapes were found that were matched to the VF subjects on important clinical variables: number and degree of coronary artery narrowings, degree and type of cardiac arrhythmias (ie, nonsustained ventricular tachycardia), low ejection fraction, etc. The only difference was that the controls did not manifest VF for at least the 3 years of follow-up after their Holter tape recording. The results were the same as for the pig model—the VF and non-VF patients were predicted by the PD2i of the heartbeat intervals with a sensitivity of 100% and a specificity of 100%.[32]

Only a few tapes were rejected from study because of overly high arrhythmia rates. Arrhythmias of the usual types encountered in high-risk subjects were well tolerated,[32] as the PD2i algorithm internally rejects analysis of such aberrant beats. Tolerance of small amounts of continuous noise in the data (± 5 integers) was designed into the algorithm by setting slopes in the correlation integral less than 0.5 to 0.

Figure 3 presents an example of the "jitter" in the heartbeat (R-R) intervals and its corresponding "degrees of freedom" (PD2i) for three randomly selected 15-minute segments (A, B, and C in the figure) taken from a 24-hour Holter tape. This recording is from a patient who had manifested VF just after the C segment. It is clear that there are low excursions of PD2i values in time (asterisks in figure) throughout all of the segments. Excursions of PD2i values to levels this low never occurred in patients who did not manifest VF within the 3 years of follow-up—another black-and-white result.[32]

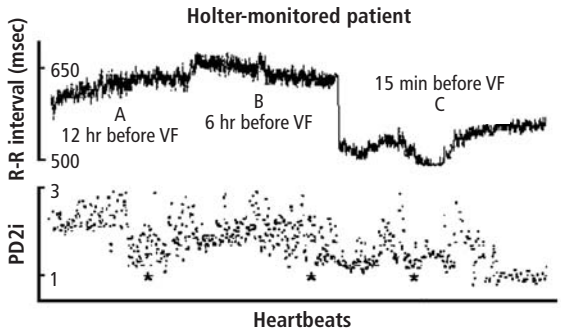

FIGURE 3. The R-R intervals (top panel) and corresponding PD2i series (bottom panel) of heartbeats in a patient with ventricular fibrillation (VF). Reprinted from reference 32, copyright 1993, with permission from Elsevier.

CONCLUSIONS AND FUTURE DIRECTIONS

Future studies of the brain-heart axis involved in VF initiation may lead to important insights into consciousness itself, especially those studies related to the selective attention and complex perception that are involved in anxiety and psychosocial stress. The study of neocortical gamma activity is an important lead in this direction. Until these insights come, however, the application of nonlinear dynamics to assess heartbeats, as with the PD2i algorithm, appears to constitute a new clinical paradigm in which to determine the impact of the brain on the heart, especially the heart at risk of VF. Salutary molecules released during particular brain states, such as REM sleep, may become the basis for important new cardiovascular drugs to treat lethal arrhythmogenesis, the ischemic myocardium, or both. Furthermore, the state-dependent release of natural biomolecules may be a new paradigm for the discovery of important new drugs. See the next article in this supplement for a detailed review of these new paradigms.

After examining all of the neuroanatomic, neurochemical, neurophysiologic, and neurobehavioral correlates of the sensory and autonomic regulation that occurs during defined defensive events, it now seems that Cannon was right: the cerebral defense system was the focus for the natural selection that gave us our big brains (especially the frontal cortex). At the same time, natural selection also gave us psychosocial stress and sudden cardiac death as unfortunate side effects of human intelligence.

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