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Screening Risk for Sudden Cardiac Death

Signals from the brain may contribute to arrhythmias, but an algorithm can screen patients for risk.

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A quiet revolution is going on in the world of patient risk stratification. It is becoming increasingly apparent that, while sudden cardiac death (SCD) manifests in the heart, it is triggered by the brain via the autonomic nervous system (ANS). Techniques taking this into account have the potential to be far more accurate and robust than other existing methods. They have the potential to impact a range of areas in medicine, from SCD risk stratification to triage of battlefield and civilian trauma victims. ANS can also help diagnose autonomic neuropathy, including cardiac autonomic neuropathy (CAN), which carries with it an elevated risk of adverse cardiac events and death.

Brain Control Over Arrhythmias

Intuitively, we know the brain influences the heart rate and rhythm. Heart rate increases in concert with emotional highs and lows, emotional stress can trigger atrial fibrillation, and there are well-known data regarding increased patient mortality in depressed or emotionally stressed patients. Recent work has taken this understanding a step further. Back in the 1990s, James Skinner, Ph.D., performed two fascinating experiments. First, in the swine model, he traced the cardiac innervation back to the brain in normal animals and found that if he stimulated along that tract, even as high up as its origin in the mesial frontal cortex, he could induce ventricular arrhythmias and even sustained ventricular fibrillation (VF) in animals with normal hearts.

Conversely, if he severed all nerve connections, he could even tie off the left anterior descending artery and cause an acute myocardial infarction – a maneuver that causes VF frequently in pigs – and, yet, would never get VF. This suggested that while VF occurs in the heart, the brain initiates it.

Recent human clinical data seem to confirm this. Data from the National Implantable Cardioverter Defibrillator (ICD) Registry reveal more than 75 percent of patients who receive prophylactic ICDs based upon the combined MADIT II/SCD-HeFT trial criteria (which included having a cardiomyopathy) have never needed the ICD to fire for ventricular tachycardia (VT) or VF. Conversely, it has been known for some time almost 80 percent of people who suffer SCD each year do not meet these implant criteria, because they did not have a cardiomyopathy. These data point to the fact that having a “bad heart” is neither necessary nor sufficient to produce VF.

Developing a Screening Method

Unfortunately, existing risk stratification technologies have been hampered by inadequate sensitivity and specificity, difficult to perform tests, or both. As such, newer risk stratification efforts have centered on the brain-heart axis and the ANS. The thought being that, if it could be

determined which patients have the kind of “neural wiring” that can lead to VF, then preventive therapy, such as an ICD, could be selectively targeted to them.

One attractive “window” into the brain and ANS is the heart rate variability (HRV) signal. While a heart disconnected from the central nervous system will beat relatively steadily, almost like a metronome, a heart connected to the central nervous system starts to exhibit seemingly random variations in rate, known as HRV. There are several known sensory-motor loops that control heart rate, such as temperature, pH, baroreceptor reflex, etc. It has been realized their behavior, like that of many biological organisms, is governed by a branch of mathematics called nonlinear dynamics (commonly referred to as chaos theory). The seemingly random variations are actually ordered, and this order can be brought out and characterized using the right analytical tools.

Based on physiologist Walter Canon’s cerebral defense theory and subsequent work looking at the nonlinear mathematics of HRV, Skinner developed a theory. He postulated the degree of cooperativity among those sensory-motor loops would be reflected in the degrees of freedom of the HRV signal, which could, in turn, be modeled using nonlinear mathematics. It is the brain’s influence on the heart that causes the variations in heart rate in the first place.

The Brain Can Create VF

As we are discovering in many branches of biology and medicine, in healthy organisms there are multiple systems working in opposition and more or less independently (e.g., the sympathetic and parasympathetic nervous systems). If and when these systems begin to coordinate to a high degree, it is a sign that the organism is not doing well. Think of it as the brain “marshaling the forces” to work together to keep the organism alive.

Unfortunately, the price we pay for this hypercoordination is a tendency for the brain-heart innervation described above to activate in a way that can lead to VF, most likely by affecting cardiac refractory periods and conduction times. Those individuals with the capability to hypercoordinate in this way can produce VF, while those who don’t, will not.

An Algorithm to Predict SCD

Skinner refined an existing measure of the degrees of freedom of a system, the correlation dimension (D2), calling it the “point correlation dimension” or PD2i. He showed it measures the degrees of freedom of a system much more accurately than competing methods and can track changes beat by beat. In addition, the results are very simple to interpret. Either the minimum PD2i recorded is below the predetermined cutoff (positive result), or it is not (negative result).

Published data from clinical trials have shown PD2i to be a highly accurate predictor of SCD, with a sensitivity approaching 100 percent and a specificity of about 86 percent. The analysis is performed on a single-channel recording of 1,000 heartbeats in sinus rhythm – approximately 15 minutes of electrocardiogram (ECG) at resting heart rates. The algorithm can use recordings made at rest and is relatively impervious to noise and nonstationarities in the data. This has helped set it apart from other nonlinear measures and seems to account for its high level of accuracy.

Triaging the Severely Injured

The U.S. Army Institute of Surgical Research (USAISR) also has been looking for predictors of severity of injury in combat casualties to assist in the triage process. Just as in the SCD prediction arena, the USAISR found a nonlinear dynamics approach to HRV seems to offer the best hope. It provided good results in testing, but the military found the measures it was using did not perform well in real-life conditions of noisy data. Moreover, unlike in SCD prediction, trauma victims need to be assessed rapidly, so whatever measure is chosen needs to be able to work on data sets of limited duration.

The PD2i algorithm was able to accurately identify, retrospectively, those patients who needed lifesaving intervention using noisy data. The algorithm did this with as little as 200 heartbeats – around 90 seconds of data – from a tachycardic, injured patient. Further studies showed that by continuously calculating nonlinear parameters, including PD2i, in a “rolling window” fashion, one could track the progress through treatment. This potentially provides physicians with a parameter to follow as they initiate treatment. It also opens up the possibility of a new parameter for intraoperative and intensive care unit (ICU) monitoring. Again, the idea behind all of these applications is the same as with SCD, only on a more acute scale. The sicker the patient is, the more the brain needs to “marshal the forces” of the various compensatory mechanisms to keep the injured person alive. This will be reflected in the HRV signal.

Screening for Neurologic Disorders

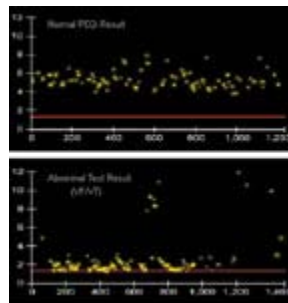
Nonlinear measures such as PD2i also may have benefit in identifying purely neurologic disorders. Recent studies reveal PD2i to be able to detect the presence of autonomic neuropathy, including cardiac autonomic neuropathy, quite early in the course of the disease. Further work is planned in the areas of diagnosing and tracking the progression of concussion, and in assessing the severity of neurotrauma.

Vicor Technologies incorporated the PD2i algorithm into its PD2i Analyzer, an HRV diagnostic, which received U.S. Food and Drug Administration (FDA) clearance in December 2008. The company is working with the USAISR to develop a PD2i system to triage combat and civilian trauma victims. That system is pending FDA clearance, which is expected in 2010.

Editor's Note: Dr. Weiss previously served as medical director of the electrophysiology laboratory at the Boca Raton Community Hospital in Boca Raton, Fla., and was a partner at Florida Arrhythmia Consultants. He is now the chief medical officer of Vicor Technologies Inc. He previously served as a consultant to medical device manufacturers, such as Medtronic, St. Jude Medical and Guidant. Additionally, he served as a clinical investigator in the MADIT II (Multicenter Automatic Defibrillator Implantation Trial) and SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) trials.



The electrocardiogram has been in clinical use for about 100 years, but new computer analysis software is helping extract additional information from the electrical signals for more accurate diagnoses.



The PD2i plot at the top is taken from normal healthy subject. Below is the PD2i plot from a patient who suffered ventricular tachycardia/fibrillation. It shows repeated low-dimensional excursions below a diagnostically relevant PD2i of less than 1.4.



*The Vicor PD2i Analyzer uses a single-channel recording of 1,000 heartbeats in sinus rhythm at resting heart rates to screen patients for the risk of sudden cardiac arrest. This article appeared in *Diagnostic and Invasive Cardiology*, May/June 2010 Issue*