VIEWPOINT

Risk stratification for arrhythmic sudden cardiac death

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Reviews of risk stratification for death from fatal ventricular arrhythmias echo a common conclusion: we need better means for risk stratification.[1–3] However, because a large number of clinical studies have already addressed the question of risk stratification, we believe it is evident that (1) assessing the risk for death from fatal ventricular arrhythmias is difficult, and (2) the current methods for investigating risk stratification bear critical examination and extension.

Although there are many potential reasons to improve risk stratification methods, the implantable cardioverter-defibrillator (ICD) introduced a practical objective: the identification of patients whose lives could be meaningfully prolonged by an ICD. Hence, in discussing the issue of risk stratification, we focus on issues that specifically arise in the context of cardiac arrest due to unexpected ventricular tachyarrhythmia. The task is especially difficult because often it is not possible to assess the relative incidence of cardiac arrest compared to other reasons for mortality outside of the hospital. In this essay, we suggest approaches that are complementary to methods currently used for risk stratification.

A great number of different measures have been proposed for risk stratification[1–7] based on age, sex, social history, left ventricular ejection fraction, signal-averaged ECG, baroreceptor sensitivity, electrophysiologic testing, high frequency of premature ventricular complexes (PVCs), T-wave alternans, heart rate turbulence, genetic abnormalities, and recovery of heart rate following exercise. As well, various measures of heart rate variability, ranging from statistical assessment of the intervals between heartbeats, to the power spectra of the heart rate, to measures involving more esoteric concepts such as entropy or short- or long-range scaling behavior, also have been used. It is a formidable challenge to determine how best to combine these measures to assess the risk of ventricular tachyarrhythmia.

After reviewing current approaches of risk stratification, we apply a previously published method, the heartprint,[8,9] to provide an example in which patients, who appear to be similar using currently accepted criteria, may have quite different dynamic characteristics of their arrhythmias. This example suggests the need for a more personalized approach in which dynamic analysis of arrhythmias in individuals is combined with other methods of risk stratification.

Clinical studies of risk stratification

Clinical studies of risk stratification for sudden cardiac death provide an essential component for clinical decisions. To date, basically three different types of clinical studies have been used to make inferences concerning risk stratification and therapy.

1. *Retrospective or prospective observational studies of risk stratification in large preselected populations.* In this type of study, initial evaluations of patients document some subset of characteristics and assess the mortality or morbidity over time. Typically, in any study there might be some large numbers of different characteristics under consideration, and multivariate statistical methods must be used to determine measures that offer independent predictive power. The prospective analysis of heart rate variability and baroreceptor sensitivity in patients following myocardial infarct in the Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study typifies this approach.[4]

In contrast to observational studies that compare a number of different risk factors but in which there is no specific intervention, other studies analyze the efficacy of interventions. We distinguish two cases.

2. *Prospective clinical trials in which one therapy is administered based on the outcome of two or more identified risk factors.* This type of study is used to compare the efficacy of risk factors in refining the selection of patients for therapy. For example, the Alternans Before Cardioverter Defibrillator (ABCD) trial compares T-wave alternans with electrophysiologic testing in predicting ventricular arrhythmias in patients with ischemic heart disease, left ventricular dysfunction, and nonsustained tachycardia.[6] Both tests are administered, and patients with positive results in either test receive an implantable defibrillator. This type of study can help determine which risk stratification methods are optimal in a clinical setting.

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3. *Prospective clinical trials in which two or more different therapies are tested in a cohort of patients all of whom fulfill the same entrance criteria.* In this case, risk stratification is implicit in the selection criteria. Positive results showing reduced morbidity and mortality in one treatment arm can be used clinically as the basis for treatment. For example, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) compared the efficacy of ICDs with standard therapy in postinfarction patients with left ventricular ejection fraction <30%. The finding of improved survival of ICD patients in a 20-month follow-up period has lent support to the use of ICDs in patients who meet the entrance criteria.[2,5] Subsequent analysis of the MADIT-II data using multivariate proportional hazards model for the time to ICD therapy may be useful in further assessment of the time-dependent factors in disease progression and thus might help refine future treatment strategies.[10]

Clinical studies such as the ABCD and MADIT-II are examples of "pragmatic" trials.[11] Pragmatic trials provide the physician with scientific evidence upon which to base clinical decisions, adding a measure of concreteness in making difficult therapeutic decisions. However, we believe a number of deficiencies inherent in pragmatic clinical trials reduce their utility.

1. *Lack of homogeneity in the selected patients.* Selection criteria in clinical trials isolate individuals who would be expected to respond to therapies in similar fashion. However, heterogeneities arise from a large number of factors, including differences in age, sex, environmental risk factors, genetics, and existing cardiac or other pathologies. In clinical trials related to sudden cardiac death, the heterogeneity manifests itself in the observation that, in most studies, only a small percentage of individuals suffer cardiac arrest in a given year (it is impossible to predict which ones on an individual basis).
2. *Incomplete data on each patient and lack of access to original data.* Clinical trials that are performed over long periods and involve a large number of patients are difficult and expensive to undertake. Many clinical trials are undertaken by individuals and sponsors that have a large financial or intellectual stake in the outcome. These studies typically focus on a small number of risk criteria and therapies, and original raw data rarely, if ever, are available to the medical community.
3. *Absence of an analysis of what happens in an individual patient.* Of necessity, clinical trials involve a large number of patients, and it is difficult to analyze each patient in detail. If the patient population were sufficiently homogeneous, this issue would not be a problem. However, such a degree of homogeneity is not possible in clinical studies of the kind described here, and the variability between patients is rarely understood.

Nonlinear dynamics perspective

In order to analyze why any given patient undergoes a cardiac arrest at some given time (rather than another time or not at all), it is necessary to develop theoretical insights into the mechanisms of arrhythmia in a given patient and the mechanisms for transition between rhythms. The mathematical field of nonlinear dynamics offers a language and theoretical approach suitable for this task. In the context of nonlinear dynamics, changes in the dynamics may occur as a consequence of a change in the parameters of a system. Thus, changes in activity, drugs, and circulating hormones as well as anatomic changes due to disease processes or surgery can lead to transitions of dynamic behavior in the heart.

One of the earliest uses of nonlinear dynamic concepts in cardiology was the formulation of a mathematical model for AV heart block by Mobitz, who made the observation that different patterns of block would be found at different heart rates.[12] The power of the mathematics arises from the observation that once the AV nodal conduction is determined by delivering single premature beats to the atria, the ventricular response can be computed for any sinus or pacing frequency under the assumption that AV nodal properties do not change at the altered sinus rate.[13,14]

Another example that is more relevant to the current essay is the occurrence of alternans in action potential duration in a variety of circumstances. Because it has been hypothesized that the instability leading to action potential duration alternans may lead to T-wave alternans and to further instabilities resulting in ventricular tachyarrhythmia, it clearly is of interest to understand the mechanisms leading to alternans.[15–17] Based on the measurement of the action potential duration and propagation velocity to single premature beats, using nonlinear dynamics it is possible to compute the sinus or pacing frequencies that would lead to alternans as a consequence of an instability in the dynamics.

Insights about dynamics derived from simple mathematical models or idealized experiments have proved difficult to apply clinically. However, it should be possible to use mathematics to extend the classic approaches championed by Pick and Langendorf[18] and by Schamroth[19] to understand the mechanisms of the arrhythmias in individual patients. In contrast to earlier work that concentrated on comparatively short records, computer-aided data analysis and modeling will be needed to correlate the anatomic and physiologic substrate of arrhythmia with observed data over long times. In previous work, we proposed a new method—the heartprint (see description following)—to perform a computer-based, beat-by-beat analysis of ventricular arrhythmias over long times.[8,9] The heartprint reflects the dynamics of PVCs based on a Holter tape record over a 24-hour period. The heartprint of a patient with parasystole[8] is very different from the heartprints of sudden cardiac death patients who exhibited long QT syndrome, torsades de pointes, fixed coupling intervals, and persistent bigemi-

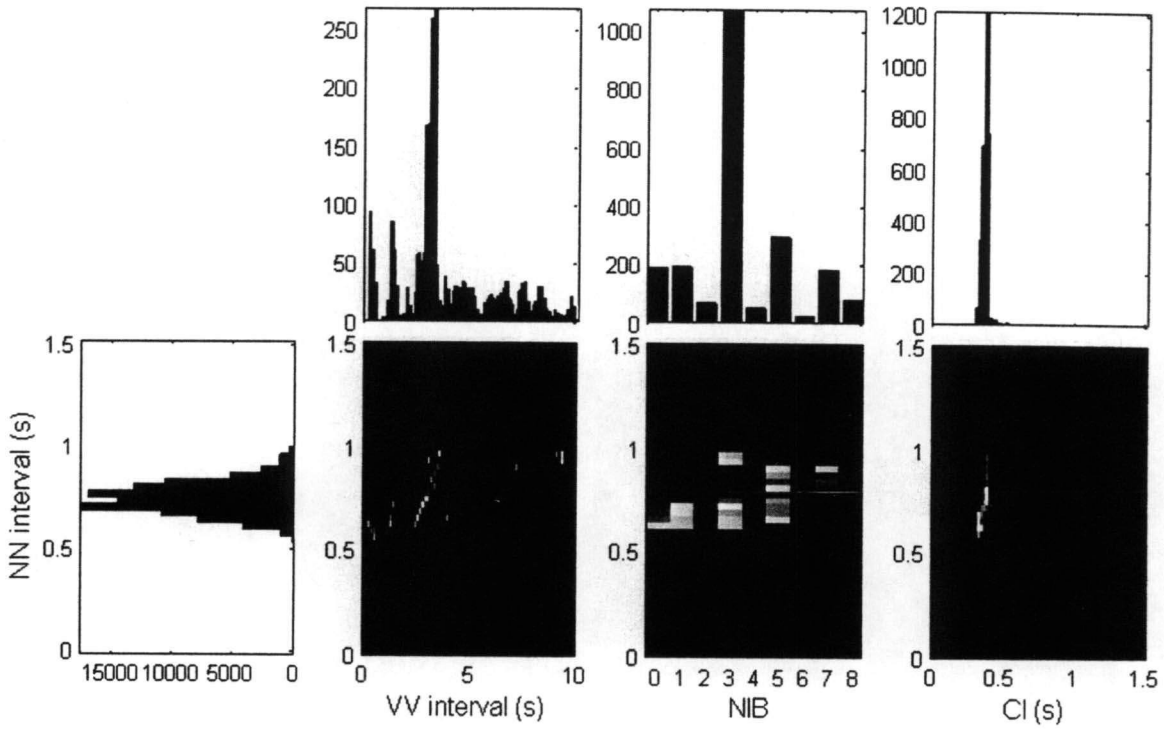

Figure 1 Heartprint of record e179a from the Cardiac Arrhythmia Suppression Trial (CAST) RR interval substudy database.[21] The heartprint, in which the redder colors represent more events, shows a large range of sinus rates with NN intervals between 0.53 and 1 second, the number of sinus intervening beats (NIB) between two ectopic V beats were mostly the odd numbers 3, 5 and 7, and the coupling interval (CI) was relatively fixed.

nal rhythms consistent with a mechanism of early afterdepolarization-induced PVCs leading to torsades de pointes.[9]

To illustrate the nonlinear dynamics perspective on clinical data, we consider the Cardiac Arrhythmia Suppression Trial (CAST). CAST was based on the hypothesis that drugs that decreased the frequency of PVCs would lead to a reduction in sudden cardiac death in patients with prior myocardial infarction.[20] However, the clinical trial involving approximately 1,500 postinfarction patients found increased mortality in those patients who received medications that reduced the incidence of PVCs.

To study the arrhythmias in individual patients, we have accessed the CAST data available at the PhysioNet website (www.physionet.org).[21] Figures 1 and 2 illustrate the heartprints of two male patients who had frequent ventricular ectopy that was reduced by encainide. The heartprint represents the dependencies between the intervals between two normal beats (NN) and three other intervals: the time between two premature ectopic V beats (VV), the number of intervening normal beats (NIB) between two consecutive premature V beats, and the coupling interval, that is, the time from a sinus beat (N) to the premature V beat. The ordinate of the three colored plots is the NN interval. The incidence of the VV intervals, NIB values, and coupling interval are indicated in the three colored plots, respectively, where the relative frequency of occurrence is indicated by the color (e.g., red is associated with higher incidence and dark blue with the lowest). The histograms above the colored plots are those of the VV intervals, the NIB values, and the coupling interval, respectively; the histogram to the left gives that of the NN values. The most striking aspect of Figures 1 and 2 is that the patients displayed very different qualitative features of their heart dynamics. In Figure 1, the rhythm is largely concealed bigeminy in which the NIBs were mostly odd numbers 3, 5 and 7, and the coupling interval was fixed. In contrast, in Figure 2 there were many different NIB values, and the coupling interval was variable.

We do not have sufficient information about the manifestation of arrhythmias using the heartprints to propose a mechanism for the arrhythmias in these patients. However, the analysis indicates that the mechanism of the arrhythmias likely is different in both patients. If the mechanisms of arrhythmia in different patients are different, there is no reason to expect that a single intervention would be efficacious in all individuals meeting the entrance criteria.

Toward a personalized medicine

The observation that patients who appear to be similar with respect to commonly used clinical measures may really have different mechanisms of arrhythmia, and hence may respond differently to therapy, points to the need for development of measures that reflect more accurately the underlying pathophysiologic processes in individual patients to complement currently accepted criteria. Advances in genomics and the recognition of mutations in ionic channels should increasingly provide genetic information in individual patients that may be helpful in assessing cardiac risk factors.[7,22] We propose that the development of quantitative

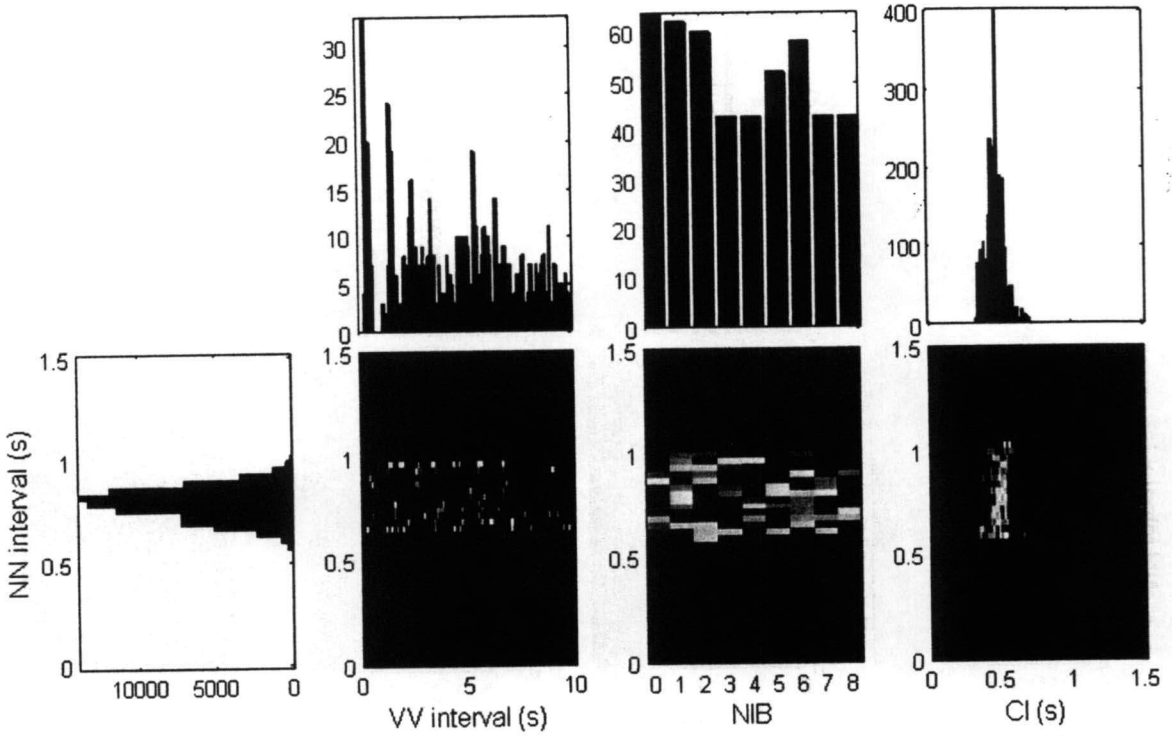

Figure 2 Heartprint of record e254a from the Cardiac Arrhythmia Suppression Trial (CAST) RR interval substudy database.[21] The NN intervals are between 0.55 and 1 second, there was a wide range of NIB values, and the coupling interval (CI) was highly variable.

mathematical methods for analyzing heart rate variability and for analyzing and modeling complex arrhythmia on a beat-by-beat basis based on Holter or other long-term recordings should provide important information about cardiac risk. Because it will be a formidable challenge to combine the information from these various measures, it is essential that multivariate analyses be performed to examine interactions between multiple risk factors.[10] Also, risk is not constant but evolves in a dynamic fashion following cardiovascular events and as patients age. Consequently, it will be necessary to perform analyses that carry out dynamic risk profiling over time and carry out time-dependent multivariate analyses in which the predictive power combinations of relevant variables are statistically tested as a function of time.[1,10] However, because it is difficult to perform such studies, it is important that data from clinical trials be made available to qualified investigators. These data should include as large a percentage as possible of the various measures proposed for risk stratification. Retrospective multivariate data analyses (e.g., as carried out by Singh et al[10]) could compare hypothesized risk factors on the same dataset. Ready availability of previous data will be useful for assessing novel proposals for risk stratification.

Conclusion

Researchers and clinicians should recognize that arrhythmic cardiac death is a heterogeneous phenomenon. The transitions between rhythms capable of sustaining life and those that lead to death occur via a variety of different scenarios that are amenable to analysis. Although for now it will be necessary to rely on criteria for risk stratification based on large clinical studies, in the future, individualized analyses that combine traditional clinical measures of cardiac risk with genetic and mathematical analyses that offer insight into the pathophysiology in individual patients should provide improved methods of risk stratification.

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