Predicting Sudden Death Risk for Heart Failure Patients in the Implantable Cardioverter-Defibrillator Age

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One-third to one-half of patients with chronic, dilated heart failure will die suddenly or be resuscitated from a cardiac arrest or sustained ventricular tachycardia (VT). Implantable cardioverter-defibrillators (ICDs) offer excellent protection from sudden death by providing effective termination of the arrhythmia when it occurs, but they are not without problems. Approximately one-third of patients will experience some adverse effect, including inappropriate shocks, lead problems, and infection. The implantation and testing procedure occasionally precipitates hemodynamic deterioration. DDD or VVI pacing from the right ventricular lead of the ICD may have adverse hemodynamic effects, including increasing dysynchrony of left ventricular contraction, and may have contributed to the aggravation of heart failure observed in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II).

As with any therapy, wider use in lower risk patients increases the number of patients who might not benefit but who still suffer adverse effects. On the other hand, many sudden deaths will be prevented, and the balance, to this point, has been positive. The substantial costs of the ICD hardware, implantation, and follow-up are also a concern. Thus, identifying those patients with depressed ventricular function who are most likely to benefit, or perhaps more importantly, those who are unlikely to benefit, is of interest.

The development of tests to identify patients at high risk for fatal arrhythmias typically follows a progression (Table). Retrospective studies determine if a positive test is more common in known high-risk groups (e.g., cardiac arrest survivors) compared with lower risk groups. Second, predictive accuracy is evaluated prospectively, often as a substudy of a larger trial. Finally, the test is used to select a high-risk group for testing of a therapy. Despite the extremely high efficacy of ICDs for terminating arrhythmias, benefit cannot be automatically assumed. A new test might select patients at high risk for hemodynamic deterioration or catastrophic events with imminent death even if an arrhythmia is terminated.

With attempts to risk stratify heart failure populations, 3 general themes have emerged. First, the etiology of heart failure makes a difference. Patients with coronary artery disease and prior infarction are at risk for ventricular fibrillation during myocardial ischemia and from reentry in the old infarct causing VT. These mechanisms of arrhythmia are uncommon in “noncoronary” causes of heart failure, such as valvular heart disease, and idiopathic or familial cardiomyopathies. Secondly, the severity of electrophysiological abnormalities parallels the severity of heart failure. Thus, markers for arrhythmias are also associated with death from pump failure. Third, noninvasive tests based on the ECG recordings (T-wave alternans, signal averaged-electrocardiograms, and heart rate variability) are not interpretable in more than 20% to 30% of patients because of atrial fibrillation or limitations peculiar to the test.

The severity of left ventricular (LV) dysfunction and LV size alone is a marker of risk, but it identifies a broad segment of the heart failure population. In patients with prior infarction and LV ejection fraction ≤0.30, but without any recent New York Heart Association class IV heart failure symptoms, ICDs reduced mortality to 16% from 22% at 2 years in the MADIT II study. Nonsustained VT and frequent ventricular ectopy increase in prevalence with heart failure severity and have predicted sudden and non-sudden death. ICDs did not improve survival compared with no antiarrhythmic therapy or with amiodarone in patients with nonischemic cardiomyopathy selected for nonsustained VT (S. Adam Strickberger, MD, Washington Hospital Center, Washington, DC, oral and electronic communication, 2001) or depressed ventricular function.

Invasive electrophysiological studies detect potential reentry circuits after myocardial infarction. Approximately one-third of patients with prior infarction, LV ejection fraction ≤0.40, and spontaneous nonsustained VT have inducible sustained VT, predicting a 6% to 9% per year risk of spontaneous sustained VT or sudden death. ICDs reduce this risk to less than 3% to 5% per year. Electrophysiological study is not a useful screening tool in noncoronary causes of heart failure; fewer than 5% of patients have inducible monomorphic VT. When heart failure is advanced, the sensitivity of electrophysiological testing decreases, thereby failing to identify many high-risk patients even in the postinfarction group.

Given these limitations, other noninvasive predictors have been sought. Abnormalities of cardiac repolarization are common in heart failure. Dispersion of the QT interval in the surface ECG was initially associated with high-risk
patients, but was of no value in a prospective study of 703 patients.\textsuperscript{17} Detection of small oscillations in the T-wave amplitude (T-wave alternans) during exercise is linked to susceptibility to ventricular arrhythmias.\textsuperscript{12} It is associated with high-risk groups and was a marker of risk in a prospective study of 85 patients with nonischemic cardiomyopathy.\textsuperscript{12} Trials to determine if T-wave alternans testing can be used to select patients for ICD therapy are in progress.

Abnormal ventricular depolarization can be analyzed from signal-averaged ECG (SAECG) recordings of the QRS complex. Prolonged QRS duration is associated with arrhythmias and mortality in patients with coronary artery disease.\textsuperscript{18} Patients with an abnormal SAECG before coronary artery bypass surgery, however, do not benefit from ICD placement at the time of surgery.\textsuperscript{19} In heart failure populations, the predictive value of this test is unclear.\textsuperscript{12,20}

Neurohumoral activation is associated with heart failure severity and mortality; sympathetic activation promotes arrhythmias.\textsuperscript{21,22} Heart rate variability reflects neurohumoral activity and its interaction with the sinus node. Heart rate variability declines with the severity of heart failure, consistent with increased sympathetic activation, and has been associated with increased mortality and, in some but not all studies, increased risk of sudden death.\textsuperscript{3,21,22} Clinical use has been limited for several reasons. Sinus rhythm is required. Ectopic beats, frequent in heart failure, impede analysis and introduce potential error. Physical activity, posture, and respiratory effort influence heart rate variability and are difficult to standardize during long ambulatory recordings. A number of different computational approaches to analysis have been used, and a clear standard has yet to emerge.

In this issue of *Circulation*, La Rovere and colleagues\textsuperscript{3} present an evaluation of short-term analysis of heart rate variability for predicting sudden death in chronic heart failure. They standardized the recording conditions, studying subjects in the morning after 30 minutes of supine rest and during controlled breathing. Brief, 5-minute recordings were analyzed. Both time domain (mean R-R interval and standard deviation of the R-R interval) and frequency domain (spectral analysis) analyses were performed. Cut-off values were defined in an initial cohort of 202 patients and tested in a second prospective cohort of 242 patients. Approximately half of the patients had ischemic cardiomyopathy. Sudden death was predicted by reduced power in the low frequency heart rate variability spectrum (0.04 to 0.15 Hz) and ≥83 ventricular premature beats/h on a 24-hour Holter recording. Either risk factor identified 37% of the sample population who had a 3-year sudden death risk of 23% compared with a 3% risk of sudden death in 63% of the sample without these risk factors.

The patient population is mixed, and whether the findings apply similarly to both the coronary and noncoronary artery disease patients requires further study. The short-term duration of the recordings has appeal. The recording methods and analysis of heart rate variability are sophisticated and may not be easily implemented. The cut-off values were redefined for the validation cohort, so the predictive accuracy noted above is likely an optimistic estimate of what would be observed in practice. Whether this method should be used to select therapy remains to be determined.

As long as the risks, impact on quality of life, and costs of ICDs continue to be more than minimal concerns, refining patient selection will remain of interest. However, it is a moving target. During the 10-year course of their study, La Rovere and coworkers\textsuperscript{5} observed a decrease in mortality and an increase in use of β-adrenergic blocker therapy. Ten years ago, ICDs required a thoracotomy for placement and were reasonable options only for patients at the highest risk who had been resuscitated from a cardiac arrest. ICDs are now warranted for many patients with depressed ventricular function who have not had a cardiac arrest. As lower risk populations are evaluated, identification of those higher risk subgroups most likely to benefit may assume more importance. At the other extreme, patients with end-stage heart failure often will have risk markers for sudden death but no benefit of an ICD when death from pump failure intervenes. New strategies for selecting patients for ICDs will continue to require evaluation in clinical trials.

| TABLE 1. Risk Factors for Sudden Death in Patients With Depressed Ventricular Function |
|---------------------------------|-----------------|----------------|----------------|----------------|
| LV size/EF                      | C/NC            | C/NC           | C              | C? (early after MI) |
| BNP                             | C/NC            | ?              | ?              | ?              |
| Holter ECG                      | C/NC            | C/NC           | C (with EPS)   | +/-            |
| HRV                             | C/NC            | C/NC           | ?              | ?              |
| TWA                             | C/NC            | NC             | ?              | ?              |
| SAECG                           | C/NC            | C/NC?          | ?              | ?              |
| QT dispersion                   | C/NC            | No             | …              | …              |
| EPS                             | C              | C              | C              | ?              |

LV indicates left ventricular; EF, ejection fraction; C, coronary artery disease patients; NC, noncoronary artery disease patients; C/NC, shown for both coronary and noncoronary artery disease patients or in studies including both groups with the finding not stated to be confined to one disease etiology; MI, myocardial infarction; BNP, brain natriuretic peptide; EPS, electrophysiologic study; HRV, heart rate variability; TWA, T-wave alternans; SAECG, signal averaged ECG; and ?, unknown.
References


Key Words: Editorials ■ death, sudden ■ heart failure ■ defibrillation
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