Electrocardiographic Arrhythmia Risk Testing

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Abstract: Among the most compelling challenges facing cardiologists today is identification of which patients are at highest risk for sudden death. Automatic implantable cardioverter-defibrillators are now indicated in many of these patients, yet the role of noninvasive risk stratification in classifying patients at high risk is not well defined. The purpose of this review is to evaluate the various electrocardiographic (ECG) techniques that appear to have potential in assessment of risk for arrhythmia. The resting ECG (premature ventricular contractions, QRS duration, damage scores, QT dispersion, and ST segment and T wave abnormalities), T wave alternans, late potentials identified on signal-averaged ECGs, and heart rate variability are explored. Unequivocal evidence to support the widespread use of any single noninvasive technique is lacking; further research in this area is needed. It is likely that a combination of risk evaluation techniques will have the greatest predictive power in enabling identification of patients most likely to benefit from device therapy. (Curr Probl Cardiol 2004;29:357-432.)

Over the past decade advances in technology have provided cardiologists with improved therapeutic options for patients at risk for sudden cardiac death (SCD). The automatic implantable cardioverter-defibrillator (ICD) has changed the landscape of electrophys-

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iology in that implantable devices are now indicated for most patients at highest risk for life-threatening ventricular arrhythmias. In 2002 the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II investigators found that in patients with a history of myocardial infarction (MI) and left ventricular ejection fraction (LVEF) of 30% or less there was a 31% decrease in mortality after implantation of an ICD. Practice guidelines for ICD implantation now include this patient group under a new class IIa recommendation.

Implantation of ICDs based on this new indication will substantially increase medical expenditures for ICDs in years to come. It is not yet known which patients with previous MI and LVEF of 30% or less benefit the most from ICD therapy. To date, most studies have analyzed age, gender, LVEF, New York Heart Association class, QRS duration, interval since previous MI, and presence of hypertension, diabetes, left bundle branch block (LBBB), or atrial fibrillation; risk stratification in patients with previous MI and LVEF greater than 30% has not been well-defined. In addition, patients with nonischemic cardiomyopathy are at increased risk for sudden death, but methods for risk stratification are not well-established. Screening for patients at risk remains elusive, because many patients who die suddenly do not have a known history of MI or heart disease. Alternate means of risk stratification are critical, because most patients who die suddenly do not meet current ICD criteria. Thus one of the most compelling challenges in cardiology today can be summarized with the question, Which patients are at highest risk for sudden death, and how can we identify them?

Noninvasive risk stratification is critical to the process of deciding who should receive device therapy, particularly because questions have been raised about the usefulness of invasive electrophysiologic testing for risk stratification. However, most proposed noninvasive techniques lack unequivocal evidence for widespread use. The purpose of this review is to critically evaluate the various electrocardiographic (ECG) techniques currently available to assist health care providers to better identify patients who can benefit from device therapy. The routine resting ECG will be explored, with evaluation of the roles of premature ventricular contractions (PVCs), QRS duration, damage scores, QT dispersion (QTD), and ST segment and T wave abnormalities as prognostic factors. Then more advanced techniques of acquired ECG data will be evaluated, including T wave alternans (TWA) and late potentials (LPs) identified on signal-averaged ECGs (SAECGs). Finally, heart rate variability (HRV), as measured with a variety of techniques, will be discussed as both a clinical research tool and a potential clinical risk factor for cardiovascular...
(CV) death. For each ECG technique, an internet search of MEDLINE was conducted with the name of the method and “Prognosis” or “Outcomes.” Relevant clinical research studies were then summarized, and are referenced throughout the review. The history of each technique, its physiologic or pathophysiologic features, and current guidelines for its use are explored.

This review does not discuss the use of exercise testing, Holter monitoring, or genomics in assessing risk for arrhythmia. Patients can be stratified according to responses to exercise testing and Holter monitoring, and usage guidelines are available for both techniques. Genomics and proteomics have incredible potential, and will probably guide treatment decisions in the future, but are currently not clinically useful.

Test Characteristics

Test characteristics must be considered when assessing studies of diagnostic or prognostic tools. They are essential when attempting to describe how well a test predicts events that occur over time, and are affected by interacting factors. Simple calculations of sensitivity and specificity can be misleading, because the follow-up times of the studies vary. Predictive accuracy is greatly affected by disease prevalence and, in follow-up studies, by disease incidence. Range of characteristic curves should not be affected by disease incidence or prevalence; however, they do not account for time or for the interaction of other factors. Even univariate survival techniques, such as Kaplan-Meier survival curves, can be misconstrued, particularly when the plotted arms have different mean ages and differ in other characteristics. The optimal studies use multivariate Cox hazard models adjusted for age, gender, and other factors to provide hazard ratios. These conclusions guided the choice of studies included in this review and the extent to which the studies are relied on.

End Points

End points must be taken into account when determining whether the various ECG techniques presented are useful clinical predictors of which patients are most likely to benefit from ICDs. Because it is clear from the literature that the risk factors for SCD are largely the same as those for generalized CV death, some investigators have suggested that there is no way to identify patients specifically at risk for SCD and that research efforts should focus on CV death. While all-cause mortality and CV mortality are valuable end points, the purpose of this review is to specifically identify patients who would benefit from device therapy. Therefore SCD is a more appropriate end point, when available.
However, it should be noted that the definition of “sudden” varies greatly. For example, in the Framingham Heart study, SCD was defined as “death in a matter of minutes...attributed to no other causes by the physician who completed the death certificate,” whereas in the United Kingdom Heart Disease Prevention Project the World Health Organization definition used was “death attributed to coronary heart disease occurring definitely or possibly within 24 hours of the onset of acute symptoms.” The United States Pooling Project defined SCD as when a patient in “apparent good health was observed to die within 3 hours of onset of symptoms with no history that violence or accident played any role in the fatal outcome.” This makes it difficult to compare the results from these studies.

The Multiple Risk Factor Arrhythmia Trial (MRFAT) used a more reliable arrhythmic events category, which included ECG documentation of cardiopulmonary resuscitation or SCD. It is also plausible to evaluate ECG testing in patients in whom an ICD has already been implanted; shock or pacing therapies could be considered end points in themselves. This requires interrogating the devices after each event to determine appropriateness of therapy. However, this can be controversial. For example, a device could be activated for a nonfatal event, such as a prolonged bout of ventricular tachycardia (VT) that might have ended spontaneously without requiring a life-saving intervention.

In screening candidates for device therapy, testing should predict those patients who are likely to die of arrhythmia rather than those who have a low life expectancy for other reasons. For example, LVEF alone may not be the best guide for device implantation, because many patients with low LVEF die of congestive heart failure (CHF) rather than from arrhythmia. The ICD is most cost-effective in patients at primary risk for arrhythmic death. The best screening test would predict sudden death or death from arrhythmia, but would not predict, or would minimally predict, other causes of death.

**Target Population**

While patients with left ventricular (LV) dysfunction and previous MI are at increased risk, it is still useful to evaluate the arrhythmic risk technologies in general populations. There may be other unsuspected patient groups at high risk that may be identified in a larger study. Furthermore, there is the opportunity to perform subset analysis in populations at high risk. These subtleties require carefully designed prospective trials.
**MRFAT**

It is difficult to perform an appropriately designed trial with a head-to-head comparison of numerous technologies. The Finnish trial MRFAT\(^{11}\) achieved this goal and targeted an important group, patients post-MI given \(\beta\)-blockers. Other specific populations must be studied in a similar manner, because it appears that patients with ischemic and nonischemic cardiomyopathy have different mortality rates and possibly different factors associated with their death. MRFAT provides a model for performing studies to evaluate arrhythmic risk evaluation technologies, and in addition to referencing MRFAT throughout this review it is discussed in detail at the end of the review.

**Resting ECG**

The low cost and accessibility of the resting ECG make it an attractive screening test for arrhythmic risk. This section addresses static ECG findings rather than dynamic ECG changes. QT prolongation has been the subject of many reviews, and is not discussed here. We have previously reviewed the resting ECG in detail,\(^{12}\) and will focus here on abnormalities that predict SCD.

The most important findings come from research in the United Kingdom; Manitoba, Canada; and Framingham, Massachusetts. The Scottish Heart Health Study\(^ {13}\) correlated SCD rates in men with common findings on the resting ECG classified by Minnesota Code. Over 4 years the unadjusted relative risk was 4.0 for Q waves, 1.6 for LV hypertrophy (LVH) by voltage, and 3.5 for ST depression. The investigators used the World Health Organization definition of SCD, including deaths up to 24 hours after an acute event. The Manitoba study also used this definition, and reported 30-year follow-up in nearly 4000 men.\(^ {14}\) Seventy incidences of SCD occurred in men without previous heart disease. Thirty-one percent had major ST segment and T wave abnormalities, 16% had PVCs, 13% had LVH by voltage, 7% had LBBB, and 6% had marked left axis deviation. Each abnormality except left axis deviation was a significant predictor of SCD, and more than one abnormality greatly increased the risk.

More recent studies have used a narrower definition of SCD that includes death up to 1 hour after the acute event. Data from the British Regional Heart Study were used to identify independent risk factors for SCD in 7735 middle-aged men who were followed up for 8 years.\(^ {15}\) Independent ECG risk factors for SCD included any rhythm other than
sinus rhythm (risk ratio, 3) and heart rate of 90 or more beats per minute (bpm; risk ratio, 5).

The Framingham investigators studied 2011 men and 2534 women, and assessed short-term risk over 2 years versus long-term risk with 28 years of follow-up. Table 1 summarizes the findings. Of note, significant ECG abnormalities had more prognostic value over the short term versus the long term.

### PVCs

**Definition and historical perspective.** PVCs are common ECG findings in patients with and without structural heart disease, and pose a common dilemma for health care practitioners because their clinical significance is controversial. The “PVC hypothesis” was popularized by Lown and Wolf and by others more than 30 years ago, and was accepted as dogma well into the late 1980s. Sudden death in MI survivors was thought to be secondary to ventricular fibrillation (VF), and PVCs would precede those events and therefore identify those patients at risk. It was argued that the suppression of PVCs with antiarrhythmic medications should prevent VF. The rationale for this concept was so compelling that it was quickly extrapolated to all patients with PVCs, whether or not they had structural heart disease. The disappointing results of the Cardiac Arrhythmia Suppression Trial (CAST) and CAST II put the entire causal role theory of PVCs in doubt. The PVC hypothesis is an example of why the evidence-based approach to treatment is more appropriate than a mechanistic approach.

**Pathophysiologic features.** PVCs may be the expression of an irritable focus or a reentrant pathway leading to VT and VF. This is consistent

<table>
<thead>
<tr>
<th>Risk for sudden cardiac death</th>
<th>Long-term risk (RR)</th>
<th>Short-term risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Intraventricular block</td>
<td>1.7</td>
<td>4.1</td>
</tr>
<tr>
<td>ST depression inclusive of LVH</td>
<td>2.1</td>
<td>5.0</td>
</tr>
<tr>
<td>ST-T abnormality</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Intraventricular block</td>
<td>3.1</td>
<td>7.3</td>
</tr>
<tr>
<td>ST depression inclusive of LVH</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>ST-T abnormality</td>
<td>2.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

ECG, Electrocardiogram; RR, relative risk; OR, odds ratio; LVH, left ventricular hypertrophy.
with the knowledge that ectopic beats can lead to tachyarrhythmias in other circumstances, PVC prevalence increases with age, irrespective of underlying disease, including coronary artery disease, hypertension, decreased lung function, accompanying ECG abnormalities, and nearly every form of structural heart disease. However, the prognostic significance of these findings in different populations has been inconclusive owing to conflicting results. The most studied group is patients who have had a recent MI. In the acute phase of MI, PVCs are seen in 80% to 90% of patients, and have been related to residual ischemia, degree of coronary artery narrowing, degree of LV involvement, and interval since MI. Lown and Wolf proposed a grading system for categorizing PVCs in patients post-MI that aimed to identify those characteristics of ectopy that are more ominous. This system identified certain features such as increased frequency (>30/hr), multiform PVCs, repetitive forms (eg, couplets, salvos), and early PVCs (ie, R-on-T) as having increasing prognostic significance.

**Prospective studies.** The data in patients without CV disease have been conflicting. In a prospective study of 15,637 apparently healthy white men screened for the Multiple Risk Factor Intervention Trial, 2-minute resting rhythm strips demonstrated that frequent or complex PVCs were associated with a significant and independent risk for SCD but not non-SCD. The prevalence of any PVCs in this large study was 4.4%. In a study of the association between PVCs and all-cause mortality in 481 presumed healthy persons the presence of PVCs, particularly complex forms, was associated with a high incidence of death from MI, especially in those younger than 56 years. The Tecumseh study was another early study that suggested an association between PVCs on the routine ECG and SCD, and the North Carolina factory workers study reported an association with other ECG abnormalities.

We evaluated the prognostic significance of various patterns and morphologic features of PVCs on routine ECGs in 42,330 male veterans. Complex PVCs were defined as those that demonstrated multiform anatomy and repetitive forms (ie, couplets, salvos). PVCs were present in 1726 (4%) patients. The age-adjusted hazard ratio for PVCs in all patients was 2 for all-cause and CV mortality. Complex PVCs showed a trend toward greater mortality. Figure 1 illustrates these findings. These results are consistent with those of the Framingham Heart Study. After adjusting for age and risk factors, there was a significant and independent association between asymptomatic complex PVCs in men without clinically apparent coronary heart disease and the risk for MI and CV death.
This association was not seen in women or in men with known coronary artery disease.

J. S. Alpert: The problem with using PVCs as a marker for sudden death is that specificity and positive predictive value are not high. PVCs are commonly observed in persons older than 60 years, including apparently healthy subjects. Most of these individuals will not experience sudden death. Therefore administration of antiarrhythmic agents in all patients with PVCs is not a good strategy, inasmuch as most of those treated will be free of sudden death without therapy.

QRS Duration

Definition and historical perspective. With recent advances in biventricular pacing for resynchronization, there has been a resurgence of interest in the prognostic implications of QRS duration. Biventricular pacing therapy for heart failure relies on the premise that multiple site pacing can correct the mechanical dyssynchrony in patients with intraventricular conduction delay. Patients with QRS prolongation appear to
have a more predictable response to therapy. The new Medicare guidelines for insurance coverage for ICD placement include patients with previous MI, LVEF 30% or less, and QRS duration of greater than 120 ms.

**Pathophysiologic features.** QRS prolongation may be secondary to bundle branch block, abnormal conduction (Wolff-Parkinson-White syndrome, electronic pacing), LVH, or generalized conduction system disease. It has also been hypothesized that ventricular dilatation can lead to conduction delays. Synchronous pacing can result in ventricular remodeling and improvement in function, even when the primary pathophysiologic features have not been altered. The duration of this effect has yet to be determined.

**Prognostic studies.** Some studies that evaluated QRS duration in more general populations have produced conflicting results. Most studies have focused on patients with bundle branch block; here we focus on those studies that specifically considered QRS duration.

Kreger et al analyzed a Framingham cohort of 5209 men and women and found that QRS duration was not associated with major CV end points over 18 years of follow-up. The finding that QRS duration was not predictive in this large population cohort is in contrast to the findings of other studies.

Several studies have demonstrated the prognostic value of QRS duration in the setting of acute MI. Brilakis et al found that prolonged QRS duration in the absence of bundle branch block was independently associated with higher in-hospital and overall mortality in patients with non-ST elevation MI. A Global Utilization of Strategies to Open Occluded Coronary Arteries sub-study of patients with ST elevation MI found that QRS duration was a strong predictor of death. Pudil et al found similar results in 1100 patients treated with thrombolysis.

Greco et al studied the effect of QRS duration over 10 years in patients post-MI. Survival was 55% in patients with QRS less than 120 ms, 24% with QRS 120 to 140 ms, and 4% with QRS greater than 140 ms. Sudden death accounted for 42% of fatalities in those with prolonged QRS duration. Freedman et al analyzed the ECGs for 15,609 patients enrolled in the Coronary Artery Surgery Study. LBBB carried a relative risk of 5, and right bundle branch block (RBBB) carried a relative risk of 2. LBBB but not RBBB remained an independent predictor at Cox analysis adjusted for heart failure and coronary disease.

Brophy et al showed that prolongation of QRS was associated with twice the mortality in patients with acute CHF. Shenkman et al found a linear relationship between increased QRS duration and decreased
LVEF. QRS greater than 120 ms was associated with increased mortality. Shamin et al\textsuperscript{53} studied 241 patients with heart failure followed up for 2.5 years, and showed that increasing QRS duration was associated with increased mortality. A separate study found that prolongation of QRS over time predicted mortality and that a greater than 20\% increase in duration was associated with the worst prognosis.\textsuperscript{54} Iuliano et al\textsuperscript{55} found QRS duration stratified risk in patients with similar LVEF. Silvet et al\textsuperscript{56} observed a cohort of 2265 patients and demonstrated that QRS prolongation independently predicted higher mortality in patients with decreased LVEF.

Unverferth et al\textsuperscript{57} analyzed variables that influence prognosis in patients with nonischemic cardiomyopathy, including findings at history and physical examination, ECG, echocardiography, cardiac catheterization, Holter monitoring, and endomyocardial biopsy. The most powerful predictor of prognosis was intraventricular conduction delay.

We sought to evaluate the prognostic power of QRS duration in a broad clinical population. Patients with bundle branch block, electronic pacing, or Wolff-Parkinson-White syndrome were excluded, leaving 44,280 patients for analysis; mean follow-up was 6 years. ECGs were classified in quartiles according to QRS duration. After adjustment in a Cox model for age, gender, and heart rate, the QRS duration score was a strong independent predictor of CV mortality, with a hazard ratio of 1.6. With increasing QRS duration there was a graded increase in CV risk (Figure 2). QRS duration greater than 130 ms was associated with a 240\% increased risk for CV death.

**Damage Scores**

**Definition and historical perspective.** A number of ECG classification systems known as damage scores have been developed to estimate cardiac injury, infarct size, and LV function. Many studies have documented an association between damage scores and clinical outcome, imaging results, and autopsy data. Using the presence of Q waves or a Q wave score representing anatomically based regions of the ECG is a straightforward approach to evaluating myocardial damage. Other scoring systems incorporate more information than just the presence or absence of Q waves. The most studied damage scores are the Simplified Selvester Score and the Cardiac Infarction Injury Score. Initially developed for estimating MI size, the Selvester Score is based on the duration of the Q and R waves and on the ratios of the R to Q amplitude and R to S amplitude in each of 10 leads.\textsuperscript{58,59} It achieved a 95\% specificity for diagnosing MI, and is highly predictive of infarction size.\textsuperscript{60-63} Rautaharju
et al.\textsuperscript{64} developed the Cardiac Infarction Injury Score to better classify myocardial damage and thus improve the diagnosis of MI. This score is based on the duration of Q waves, amplitude of T waves, and ratio of Q to R amplitude in specific ECG leads. It has a sensitivity of 85\% and specificity of 95\% for diagnosing a previous MI.

**Pathophysiologic features.** Diagnostic Q waves (30-40 ms duration, 25\%-33\% of the following R wave amplitude) are associated with underlying myocardial damage. The loss of muscle and the unopposed depolarization of the opposite wall results in the downward deflection. Q waves correlate with LVEF and with location of infarct 80\% of the time.\textsuperscript{65} Q waves in multiple regions are associated with increased mortality.\textsuperscript{66} Even in asymptomatic populations, Q waves and QS patterns are associated with CV mortality and all-cause mortality.\textsuperscript{67} When followed over time, Q waves may predict stroke, CHF, or death.\textsuperscript{68,69} Despite Q wave regression, the increased risk remains.

**Clinical and prognostic studies.** The Selvester Score, the Cardiac Infarction Injury Score, and Q wave score are predictive of CV mortality. In reports from Framingham and Holland, the Selvester Score was significantly associated with cardiac death.\textsuperscript{70,71} In a study of 3395 patients post-MI an elevated Cardiac Infarction Injury Score was associated with higher relative risk for mortality.\textsuperscript{72} It identified a relative risk of 6 in a

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**FIG 2.** Kaplan-Meier survival curves for computer-measured QRS duration in a general Veterans Affairs medical population. CV, Cardiovascular.
population of Dutch men followed up for 25 years. Similar results were obtained in a 28-year follow-up of more than 3000 healthy middle-aged men and women. Multiple studies have demonstrated that Q wave-based scores also have predictive ability. Table 2 summarizes the major prognostic studies.

To compare different scoring methods we analyzed ECGs from 46,933 veterans, using computerized measurements and algorithms. The simplified Selvester Score, the Cardiac Infarction Injury Score, and Q wave score were calculated. Over a mean follow-up of 6 years the Cardiac Infarction Injury Score outperformed all other ECG classifications in

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Follow-up (y)</th>
<th>End points</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Domburg et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>3395 patients post-MI</td>
<td>3</td>
<td>Total and CV mortality</td>
<td>RR of CIIS &gt;40, 30-40, and 20-30, twofold</td>
</tr>
<tr>
<td>Dekker et al&lt;sup&gt;73&lt;/sup&gt;</td>
<td>1713 middle-aged and elderly men</td>
<td>5-30</td>
<td>Angina, MI, CV mortality</td>
<td>5-year RR of CAD with CIIS ≥20 vs &lt;5, sixfold</td>
</tr>
<tr>
<td>Dekker et al&lt;sup&gt;72&lt;/sup&gt;</td>
<td>3091 healthy men and women</td>
<td>28</td>
<td>CAD, and CV mortality</td>
<td>CIIS &gt;10 vs ≤0 had higher CV mortality (RR 3 for men, 6 for women)</td>
</tr>
<tr>
<td>Jones et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>243 patients post-MI</td>
<td>30</td>
<td>CV mortality</td>
<td>SSS significantly associated with death</td>
</tr>
<tr>
<td>Fioretti et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>474 patients post-MI</td>
<td>1</td>
<td>CV mortality</td>
<td>SSS not significant at multivariate analysis</td>
</tr>
<tr>
<td>Kannel and Abbott&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Framingham study</td>
<td>10</td>
<td>CV mortality, SCD</td>
<td>Risk increased twofold to fourfold in those with LVH or Q waves.</td>
</tr>
<tr>
<td>Pedoe&lt;sup&gt;9&lt;/sup&gt;</td>
<td>8228 men</td>
<td>4</td>
<td>CV mortality</td>
<td>Q waves, abnormal ST, or T waves predict SCD</td>
</tr>
<tr>
<td>Ostor et al&lt;sup&gt;75&lt;/sup&gt;</td>
<td>7735 middle-aged men</td>
<td>10</td>
<td>Fatal CAD, nonfatal MI</td>
<td>Q waves increase risk 2.5-fold</td>
</tr>
<tr>
<td>Cullen et al&lt;sup&gt;76&lt;/sup&gt;</td>
<td>2119 patients</td>
<td>13</td>
<td>CV mortality</td>
<td>Q and QS pattern predictive</td>
</tr>
<tr>
<td>Menotti and Seccareccia&lt;sup&gt;67&lt;/sup&gt;</td>
<td>12,180 men, 10,373 women</td>
<td>6</td>
<td>CAD, CV mortality, all-cause mortality</td>
<td>Q waves and blocks strongest predictors of events</td>
</tr>
<tr>
<td>Tervahauta et al&lt;sup&gt;77&lt;/sup&gt;</td>
<td>697 men</td>
<td>5</td>
<td>MI, all-cause mortality</td>
<td>Q waves predictive</td>
</tr>
<tr>
<td>Reunanen et al&lt;sup&gt;78&lt;/sup&gt;</td>
<td>5738 men, 5224 women</td>
<td>5</td>
<td>CV mortality</td>
<td>Men with Q waves at 20-fold increased risk for CV death</td>
</tr>
</tbody>
</table>

**TABLE 2.** Prognostic studies of electrocardiographic damage scores

CAD, Coronary artery disease; CIIS, Cardiac Infarction Injury Score; CV, cardiovascular; MI, myocardial infarction; LVH, left ventricular hypertrophy; SSS, Simplified Selvester Score; RR, relative risk.
enabling determination of prognosis, although all were predictive. Increasing tertiles of the score were associated with an additional 39% increase in relative risk. The annual mortality for patients with a high-risk Cardiac Infarction Injury Score was 4.5%, compared with 0.3% for those in the low-risk group (Figure 3).

J. S. Alpert: It is not surprising that larger infarct size on the ECG is associated with a worse long-term prognosis, because infarct size is the reciprocal of residual LV function, a variable (eg, LVEF) that has been known for three decades to correlate with survival after MI. The sum of all R wave voltage in a 12-lead ECG correlates moderately with LVEF.

**QT Dispersion**

*Definition and historical perspective.* QT dispersion is defined as the difference between the maximum and minimum QT interval measurements on a standard 12-lead ECG. It may reflect underlying heterogeneity
of ventricular repolarization and vulnerability to ventricular arrhythmias. Despite much research on this topic over the last decade, the prognostic significance and clinical utility of this measurement remain unclear. This has led to debate as to whether QTD should be regarded as the “electrophysiological Holy Grail” or as “the greatest fallacy in ECG in the 1990s.” Some of its harshest critics argue that QTD reflects nothing more than random measurement error.

Method. Factors such as small sample size, difficulty in accurately measuring reproducible QT intervals, and use of different patient populations may explain the controversy. The fundamental problem in the application of QTD to clinical practice is the difficulty of accurately and reliably measuring QT intervals. Both manual and computerized measurements are potentially unreliable, with high interobserver, intraobserver, and even day-to-day intrapatient variability. This lack of reliable reproducibility has been demonstrated in patients with abnormal and normal ECGs. Experts have concluded that all QT measurements, whether done by hand or computer, are limited by low T wave amplitude, superimposed U and P waves, and abnormal T wave anatomy, all problems that are difficult to overcome. Because of these problems there is currently no consensus in the literature on the reference values for QTD in normal populations, let alone in diseased cohorts. Published studies of healthy subjects have reported mean QTD values ranging from 10 to 71 ms.

Prognostic studies. The prognostic power of QTD measurement has been studied in elderly patients; patients with LV dysfunction, diabetes, or structural heart disease; patients who have received transplanted organs; and apparently healthy patients. Okin et al reported data from the Strong Heart Study, a community-based study of CV disease and risk factors in Native Americans. They concluded that, although QTD measurement is a significant predictor of CV mortality, it is not useful in predicting all-cause deaths. In a later analysis QTD was assessed in 1839 Native Americans. Increased QTD was a significant predictor of mortality in women, but not in men.

Using a QTD cut-off value of 61 ms, Zabel et al found no correlation between QTD and mortality in a prospective study of 280 infarct survivors. Puljevic et al evaluated QTD in 145 patients 3 months after MI. QTD significantly increased with the severity of arrhythmia, and VT was associated with a QTD measurement of greater than 80 ms.

We performed a study to evaluate the relationship between computerized measurements of QTD and CV death in a general medical population of 38,679 male veterans over a mean follow-up of 6 years. Patients with
paced rhythms, Wolff-Parkinson-White syndrome, bundle branch block, or atrial fibrillation were excluded. Of interest, 2.8% of the patients had a QTD of zero, indicative of failure of the computer software to detect T waves in sufficient leads to estimate QTD. In the remaining patients the mean values of QTD and corrected QTD were lower among those who survived compared with those who died (31 vs 34 ms and 33 vs 37 ms, respectively). In Cox regression analyses QTD adjusted for both age and heart rate and age-adjusted corrected QTD were significant, independent, but weak predictors of CV mortality. Those in the 90th percentile had a 2% annual CV mortality, and hazard ratio of 1.5.

**ST Abnormalities**

**Combined ST-T-wave abnormalities.** The Belgian Nutrition and Health Study examined the ECGs of 9117 apparently healthy men and women. At baseline the prevalence of an ECG demonstrating ischemia, according to Minnesota Code, was 8.4% in men and 10.6% in women. After correction for cardiac risk factors the mortality risk ratio over 10 years in men was twice that in women. Both men and women with major ST segment and T wave abnormalities were at fourfold increased risk for cardiac death.

A study of Western Electric Company employees in Chicago, Illinois, included 1673 men, ages 40 to 55 years, with no evidence of congestive heart disease (CHD) and no major ECG abnormalities during the initial 5 years. Nonspecific minor ST-T segment abnormalities were noted in more than 10%. Men with three or more annual recordings of minor ST-T abnormalities were at twice the risk for CV death.

The Finnish cohort of the Seven Countries Study included 697 men, ages 65 to 84 years. After 5 years there were 74 fatal MIs and 207 deaths. Highest risk was observed among men with Q waves together with ST or T wave changes. Men with ST-T–wave changes without Q waves also were at increased risk, whereas men with only Q waves were not at increased risk.

As part of the Reykjavik study, 9139 men were followed up for 4 to 24 years. The prevalence of silent ST-T wave changes among men without overt CHD was strongly influenced by age, increasing from 2% at age 40 years to 30% at age 80 years. After adjustment for other risk factors, these changes were associated with a risk ratio of 2 for cardiac death.

**Comparison of ST segments and T waves.** In a prospective study, 7985 women and 9630 men without other ECG abnormalities or heart disease were followed up for more than 20 years. ECGRs for persons with minor Minnesota Code ST segment or minor T wave abnormalities were
compared with normal ECGs. For CV mortality, age-adjusted hazard ratio was about 2, and there was a trend for T waves to be more predictive.

In the Framingham Study, 14% of 5127 men and women had or developed ST and T wave abnormalities. Over 30 years CHD developed in 760 men and 578 women. T wave abnormalities alone carried a significantly increased risk for coronary morbidity and mortality, independent of known risk factors, although the combination of S-T and T waves was most hazardous.

In the Copenhagen City Heart Study 5243 men and 6391 women were followed up for 7 years. T wave inversions alone or in combination with ST depression provided independent prognostic information. LVH with both ST depression and T wave inversions were of the greatest prognostic value, with an age-adjusted relative risk of four times for CV disease.

Dekker et al evaluated T wave amplitude and ST segments in ECG lead I and correlated them with angina pectoris, first MI, SCD, and death from coronary artery disease in 876 men. Men with T wave amplitude of 0.15 mV or greater were at lower risk for MI, CHD, death, and SCD compared with men with T wave amplitude of 0.05 to 0.15 mV. In men with T wave amplitude of 0.05 mV or less, relative risk was 2.0. In men with ST segment depression, relative risk was slightly greater and independent of T wave amplitude.

Our research group analyzed the first ECGs digitally recorded in 46,950 veterans. Female and male patients with paced rhythms, prolonged QRS, atrial fibrillation, LVH, and diagnostic Q waves were excluded, leaving data for 31,074 men for analysis. After adjusting for age and heart rate in a Cox model, major abnormalities in both ST segments and T waves carried the greatest hazard, at 3.2. Minor ST depression combined with major T wave abnormalities carried a hazard of 3, whereas minor T wave abnormalities combined with major ST depression carried a hazard of only 2. Similar results were found in the presence of Q waves, LVH, or bundle branch block. Our findings confirm those of others that T wave abnormalities appear to have more prognostic power than ST segment depression on routine resting ECGs.

T Wave Abnormalities

T wave amplitude. Jacobsen et al examined T wave amplitude in 468 patients with acute coronary syndromes. Thirteen categories of T wave abnormalities were tested prospectively, and six were associated with the 1-month combined end point of refractory angina, MI, or death. In this
study, T wave abnormalities had no prognostic value when ST depression was also present.

The MRFIT research group looked at the prognostic significance of isolated T wave abnormalities in healthy middle-aged men. Digitized ECGs were performed in 12,866 men followed up for 6 years. Minnesota coding, simple amplitude criteria, and T wave axis were calculated, and Minnesota Code T wave abnormalities were associated with the greatest hazard for fatal and nonfatal coronary disease.

We analyzed the first ECGs digitally recorded in 46,950 veterans, and after excluding potential confounders, 31,074 subjects were evaluated. After adjusting for age and heart rate in a Cox regression model, T wave amplitude in lead I was the most significant predictor of CV death. For every 1-mm decrease in T wave amplitude there was a 32% increase in mortality (Figure 4). T wave amplitude in lead I also outperformed other significant ECG findings in multivariate analysis, including ST depression, QT interval, LVH, and QRS duration.

**T wave axis.** The Rotterdam study examined ECGs for 2352 men and 3429 women, with follow-up for 4 years. Participants with an
abnormal frontal plane T wave axis (11%) were at increased risk for SCD (hazard ratio, 4), higher total CV mortality, and nonfatal cardiac events. The risk associated with an abnormal T wave axis was higher than those for any other CV risk factor, and appeared to be independent.

T wave axis deviation was measured in 4173 older subjects free of heart disease at baseline in the Cardiovascular Health Study. The prevalence of marked T wave axis deviation was 12%. Adjusting for clinical risk factors and other ECG abnormalities, there was a nearly twofold excess risk for CV death.

One interesting approach to the T wave is to consider the spatial divergence between the T wave vector and the QRS vector (Figure 5). In theory, in healthy subjects these vectors should be almost in the same spatial alignment.

The Rotterdam study categorized subjects as having normal, borderline, or abnormal spatial QRS-T angles. Abnormal angles were correlated with a hazard ratio of 6 for SCD. None of the classic CV and ECG predictors provided larger hazard ratios.

We analyzed the first ECGs digitally recorded in 46,950 veterans, and after eliminating potential confounders assessed 31,074 patients. After adjusting for age and heart rate in a Cox regression model, spatial QRS-T angle difference was the most significant predictor of CV mortality, outperforming all other ECG findings, including T wave and QRS
amplitude and axis, QRS duration, QT interval, QTD, and ST depression. Similar results were found when those with Q waves, RBBB, intraventricular conduction defect, and LVH were included. Figure 6 illustrates our finding that spatial QRS-T angle is a significant and independent predictor of CV death. It can be easily calculated as part of the computerized interpretation program for all 12-lead ECGs.

**T wave anatomy.** Inasmuch as nonuniform recovery of ventricular excitability facilitates the reentry circuits, leading to development of ventricular tachyarrhythmias, the anatomy of T waves has been explored, in particular with use of principal component analysis.\(^{108,109}\) Whereas Okin et al\(^ {93}\) have reported its utility, no studies have used sudden death or arrhythmic events as end points.

**Summary**

The routine resting ECG is readily available, noninvasive, and inexpensive, making it the most widely used CV test. Not only is it useful as a diagnostic tool, particularly when dynamic changes are noted in patients with chest pain, but static findings on the routine ECG are a simple way of stratifying patient risk for CV mortality. Whereas most studies use total
or CV mortality as an end point, there is substantial evidence to suggest that some ECG characteristics have predictive value for SCD.

PVCs found on a routine ECG appear to provide prognostic information and predict SCD and CV mortality; however, attempts to treat arrhythmias with medications have failed to produce beneficial results. It is unclear that PVCs are a useful risk marker to guide ICD therapy.

Repolarization abnormalities in general appear to be more predictive than depolarization abnormalities. QTD appears to be a weak predictor, and is limited methodologically. There is strong evidence that QRS duration is predictive of risk for SCD and CV mortality in patients post-MI with heart failure, and it also appears to have predictive power in a broader population of patients. However, in some studies repolarization abnormalities have demonstrated better predictive ability compared with QRS duration. Among ECG measurements of repolarization, T wave abnormalities appear to be the most predictive, with reduced T wave amplitude associated with the highest hazard for CV death.

Spatial QRS-T wave angle carries a sixfold elevated risk for SCD, and may be an even better predictor than T wave amplitude. It is a promising marker that considers both depolarization and repolarization abnormalities. The Cardiac Infarction Injury Score is another valuable marker that performs well, and incorporates information from several parts of the ECG. These two markers require computerization to be measured from a standard ECG, and are not currently in regular clinical use, but they should be studied prospectively in appropriate target populations to better determine their value in enabling identification of patients who would benefit from ICD therapy.

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**J. S. Alpert:** The major problem with the simple and straightforward ECG variables as predictors of sudden death is that they are not predictive enough to be helpful in day-to-day clinical medicine. The risk ratios for any of these variables with respect to prediction of sudden death are rarely more than 2.0, and are often less than 2.0. Therefore many patients who test positive for these ECG markers will not experience sudden death. As pointed out, their specificity and positive predictive value for sudden death are not high. They represent clues that should be factored into the overall clinical equation leading to a specific therapeutic strategy. However, they are not themselves definitive in predicting which patients will experience sudden death.
Late Potentials

Definition and history. LPs represent delayed ventricular activation, which possibly predisposes to sustained ventricular arrhythmias. They were first reported by Berberi et al.\textsuperscript{110} and Simson et al.\textsuperscript{111} from ECGs recorded on the chest wall in the dog, and were subsequently demonstrated in human beings.\textsuperscript{112,113} Over the last 25 years several signal processing techniques for examining the region around the terminal portion of the QRS complex have been developed. The SAECG is a noninvasive, inexpensive ECG recorder that incorporates high-gain amplification, high-frequency (HF) digital sampling rates, and signal-averaging techniques. From ECG recordings on the body surface, the SAECG can detect low-amplitude, HF signals in or near the terminal portion of the QRS complex.

Pathophysiologic features. LPs are thought to represent slow or delayed conduction through the myocardium. They can be thought of as small action potentials from myocytes isolated by fibrosis that depolarize late, after the majority of myocytes that constitute the QRS complex have depolarized. Numerous studies have provided convincing evidence that delayed conduction has an important role in the genesis of ventricular arrhythmias.\textsuperscript{114,115} Many investigators have used direct epicardial and endocardial mapping techniques to record delayed, fragmented electrical activity in patients and animals with ventricular arrhythmias.\textsuperscript{116} Additional studies have corroborated the capacity of the highly amplified SAECG to detect such delayed activity. Several investigators have used both the body surface SAECG and endocardial catheter techniques to record delayed potentials in human beings and animals with ventricular tachyarrhythmias.\textsuperscript{117,118} They found a close temporal correlation between the delayed potentials recorded by the invasive techniques and the SAECG.

Methods. Lead systems.

For recording LPs from the surface of the body most investigators use an XYZ lead system formed by three orthogonal bipolar electrode combinations. Signals from the three bipolar electrodes can be combined into a spatial vector magnitude that equals the square root of $X^2 + Y^2 + Z^2$, yielding a composite waveform. Others have used a variety of precordial lead systems to achieve closer proximity to the left ventricle. Some have suggested that a precordial lead system has advantages\textsuperscript{119}; others have shown there is no advantage.\textsuperscript{120} Most current systems use orthogonal, bipolar XYZ ECG leads, which are recorded, averaged,
filtered, and combined into a vector magnitude called the filtered QRS complex.

**Amplification.**

ECG electrode signals are initially amplified 10 to 100 times with a wide-frequency band pass before analog to digital conversion. Some investigators further amplify the signals after analog to digital conversion.

**Analog to digital conversion.**

A computer is used to convert the original continuous analog ECG signal into a digital signal of voltages sampled at frequent, fixed intervals. As with all digitized signals, resolution is governed largely by sampling interval. Sampling rates for LP evaluations vary from 1000 samples to 10,000 samples per second, whereas standard computerized exercise ECG equipment is limited to 250 to 500 samples per second.

**Noise.**

Numerous sources of noise are encountered in highly amplified recordings. Artifact from respiratory muscles is independent of electrical activity arising from the heart, and cancels out with signal averaging. Electronic noise arising from the electrodes is lessened with proper skin preparation. Electrical power lines and other nearby electronic equipment can create noise, which can be reduced by using shielding or filters. The greatest reduction of noise is achieved by increasing the number of cycles averaged.

**Filtering.**

Filters have a great effect on the recognition and measurement of LPs. Most studies use high band pass filters (cutoff ranging from 25 to 100 Hz), which enable higher frequency signals derived from the depolarization phase of the action potential to pass without attenuation while reducing the low-frequency (LF), large-amplitude signals originating from the plateau or repolarization phase of the action potential. Most current systems also use a bidirectional digital filter to reduce artifact, but differing results are still reported with the various filters.\(^{121}\)

**Averaging.**

After analog to digital conversion, signals are averaged. To use signal averaging techniques the waveform must be periodic and have a specific feature, like the R wave, that can be used as a reference point so that each waveform can be appropriately aligned.\(^{122}\) Computer template recognition is currently used to align QRS complexes and to reject ectopic and noisy beats. A frequent sampling interval produces a relatively smooth and continuous waveform. The net effect after averaging is an increase in the signal-to-noise ratio. Most systems include 100 to 400 beats on average, although some average up to 1000 beats.
Quantitative analysis.
Initially investigators visually identified LPs, but currently computer algorithms are used. A ventricular LP is seen as low-amplitude electrical activity in the terminal portion of the QRS complex that may extend into the ST segment. Inasmuch as LPs are depolarization phenomena, it becomes a matter of semantics as to whether they are considered part of the QRS complex (late depolarizations) or as occurring in the ST segment (during repolarization). There are no absolute criteria to define LPs, because often there is no clear distinction between the end of the QRS and the beginning of the LP. The two methods used to characterize LPs are either time domain or frequency domain techniques. The relative merits of the two techniques have been reviewed, but the optimal means for assessing LPs remains uncertain.

LP variables from both techniques are described in Table 3.

Time domain techniques.
The duration of the filtered QRS complex (HFQRSD) is a computer algorithmic measurement end point that can vary with the equipment, filters, and software used. The difference between HFQRSD and standard QRS duration is also an indicator of LP activity. Examples of a normal and abnormal SAECG are presented in Figure 7. The vector magnitude of the

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Definition</th>
<th>Meaning</th>
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</thead>
<tbody>
<tr>
<td>QRSD (ms)</td>
<td>QRS duration as determined after wide bandpass filtering (0.05-300 Hz) and using standard computer algorithms</td>
<td>“Normal” QRS duration (abnormal when &gt;120 ms)</td>
</tr>
<tr>
<td>HFQRSD (ms)</td>
<td>RMS of noise determined, then move backward from end of ST segment until standard deviation of noise is exceeded by 2.5 times.</td>
<td>High-frequency total QRS duration (abnormal when &gt;112 ms)</td>
</tr>
<tr>
<td>HFDIF (ms)</td>
<td>Difference between QRSD and HFQRSD (HFQRSD usually smaller than QRSD)</td>
<td>Longer HFDIF is marker for more late potential activity</td>
</tr>
<tr>
<td>HFD40 (μV)</td>
<td>Duration of high-frequency components &lt;40 μV in amplitude, occurring in terminal portion of filtered QRS complex; HFD40 determined backward from HFQRSD offset point.</td>
<td>High-frequency component &lt;40 μV; &gt;40-42 ms usually considered abnormal</td>
</tr>
<tr>
<td>HFRMS (μV)</td>
<td>RMS of last 40 ms of total high-frequency duration</td>
<td>High-frequency root mean squared: &lt;25 μV usually considered abnormal</td>
</tr>
<tr>
<td>Area ratio</td>
<td>Area under curve for frequencies between 20 and 50 Hz divided by area under curve for frequencies between 0 and 20 Hz</td>
<td>Usually abnormal when &lt;20</td>
</tr>
</tbody>
</table>
terminal 40 ms of the filtered and averaged QRS complex (HFRMS) is also a marker of LPs. The greater the amplitude the more the QRS complex is included in the measurement and the more normal it is. Another indicator is HFD40, a measurement in milliseconds of the HF signal contained in the terminal portion of the QRS complex. Examples of abnormal HFRMS and HFD40 measurements are illustrated in Figure 8 and Figure 9.

**Frequency domain techniques.**

Fast Fourier transform analysis of the SAECG is another method used to quantitate LP activity. It is a powerful computer-based mathematical algorithm that can determine the amplitudes and frequencies of the various harmonic components that comprise a complex periodic signal such as the ECG. The area ratio is expressed as the area under the curve for frequencies between 20 and 50 Hz divided by the area under the curve.
for frequencies between 0 and 20 Hz. This has the advantage over time
domain systems of being less filter-dependent, while yielding more
quantitative information. Other methods of estimating the spectra of short

FIG 8. Abnormal HRMS on a signal-averaged electrocardiogram.
ECG segments that have been used include moving time window techniques, such as spectrotemporal mapping,\textsuperscript{124} spectral turbulence analysis,\textsuperscript{125} and autoregressive methods.\textsuperscript{126}

FIG 9. Abnormal signal-averaged electrocardiogram, owing to HFD40.
Reproducibility.

A limited number of studies have evaluated the reproducibility of methods for demonstrating LPs. Reproducibility depends on several factors, including electrode position, noise, stability of medical conditions, and the criteria for characterizing the LPs. Any visual analysis used also depends on the experience of the readers.

Comparison between recording systems.

A European multicenter study assessed three separate systems and compared four methods of identifying LPs, and found significant differences in analyzing LP activity. Atwood et al evaluated 113 consecutive patients without resting QRS conduction abnormalities referred for Holter monitoring using four different lead systems and multiple measurements of LPs. They found that the LV leads tended to yield more abnormal measurements than the orthogonal system did and that the various measurements failed to agree with each other.

Clinical studies. Numerous studies have demonstrated a link between LPs and ventricular arrhythmias, MI, and ischemia. LPs have also been associated with ablations, antiarrhythmic drugs, LV function, cardiac transplantation rejection, LVH, and bundle branch block. In addition, LPs have been studied in a variety of disease states, including muscular dystrophies, right ventricular dysplasia, collagen vascular diseases, thrombolysis post-MI, and syncope. In this review we focus on studies in patients post-MI and with CHF with adequate population size and those that focus on hard outcomes. A summary of the studies in Table 4 provides information on study size, years of follow-up, and LP variables that were predictive.

Patients post-MI.

Kanovsky et al performed one of the early studies that showed that the SAECG could be used to identify patients at risk for VT after MI. Holter monitoring, cardiac catheterization, and SAECG data were retrospectively analyzed in 174 patients post-MI, 98 of whom had recurrent sustained VT. At multivariate logistic regression, LPs and PVC rate greater than 100 per hour were found to be independent predictors for development of VT. Although limited by workup bias, because only patients who required either cardiac catheterization or an electrophysiologic study (EPS) were included, this study set the stage for further important research. Kuchar et al evaluated 210 consecutive patients post-MI with radionuclide left ventriculography, Holter monitoring, and SAECG. Stepwise logistic regression showed that each of the noninvasive tests was independently predictive of arrhythmic events (SCD, requirement for cardiopulmonary resuscitation). A study of 306 survivors of
transmural MI (LPs found in 26%) noted that the 2-year probability of remaining free from SCD or nonfatal ventricular arrhythmia was only 79% in patients with LPs and 96% in patients without LPs. Although there was a correlation, multiple logistic regression analysis showed that
LPs were not independent predictors of either mortality or VT events. On the other hand, in a series of 171 consecutive survivors of acute MI in which 6% of the patients sustained VT or SCD, LPs demonstrated a relative risk for arrhythmic events of 7.7. Another study of 145 patients 3 months after MI showed that LPs were associated with VT, with sensitivity of 50% and specificity of 90%.

Verzoni et al observed 220 patients after acute MI with serial SAECGs over 1 year to evaluate changes in LPs. Although 20% of patients had spontaneous normalization of SAECGs after 6 months, the mean values of HFQRSD, HFD40, and HFRMS did not change significantly. Patients with subsequent arrhythmic events had longer values for each LP parameter compared with those patients without events. The sensitivity and specificity of LPs to predict arrhythmic events was 83% and 73%, respectively. This study confirmed that dynamic changes in LPs are seen during the first year after MI, but clearly demonstrated strong predictive ability of LPs. Kuchar et al further evaluated the loss of LPs in a study of 243 patients followed up after MI. Of 92 patients with LPs at hospital discharge, 23 no longer had LPs at 6-week follow-up. The risk for arrhythmic events during median follow-up of 31 months was similar in patients with and without loss of LPs (9% vs 11%), but was significantly greater than in patients with no LPs at discharge (2%). Kozar et al recorded SAECGs in 261 patients 1 week post-MI in the morning and evening to evaluate the diurnal variation in LPs. The rate of development of VT and SCD was significantly higher in patients with persistent LPs in both morning and evening.

Several larger patient series support the prognostic potential of LPs. The German Post-MI Late Potential Study was a prospective series of 778 males who survived the acute phase of MI. Cox regression analysis showed that LPs were independently predictive of arrhythmic events (VT, VF, or SCD in 4.2% of patients), with a hazard ratio of 5. A sub-study of CAST evaluated 1158 patients, and serious arrhythmic events (nonfatal VT, SCD) occurred in 45 patients during 1-year follow-up. Cox regression analysis of six SAECG variables, and clinical, LVEF, and ambulatory ECG variables indicated that the HFQRSD at 40 Hz of 120 ms or greater was the most predictive for arrhythmic events. Zimmerman et al assessed the long-term prognostic value of LPs after a first acute MI over a 6-year follow-up period. LPs were associated with a fivefold increase in risk for arrhythmia.

The most recent and well-designed study of the predictive power of arrhythmia risk markers after acute MI was performed in 700 consecutive patients as part of MRFAT. SCD was predicted by an abnormal
SAECG, but the positive predictive accuracy and sensitivity were relatively low.

**Patients with CHF.**

There are fewer studies in patients with CHF, but valuable results do exist. A study of SAECGs in 62 patients being evaluated for heart transplantation found no significant difference in the risk for SCD in those with and without LPs.\(^{148}\) In 151 patients with less severe CHF (ischemic, idiopathic), SAECG again failed to identify patients with CHF at high risk for SCD.\(^{149}\) A study of 131 patients with idiopathic dilated cardiomyopathy with a 4-year follow-up demonstrated the prognostic value of SAECG.\(^{150}\) Patients with LPs were at three times increased risk for CV death. Another study of patients with idiopathic dilated cardiomyopathy evaluated 82 patients and 72 healthy control subjects.\(^{151}\) Multiple LP parameters were evaluated, but did not independently predict arrhythmic events.

The largest study in patients with CHF was part of the Multicenter Unsustained Tachycardia Trial (MUSTT).\(^{152}\) SAECG tracings from 1925 patients with nonsustained VT, coronary artery disease, and LV dysfunction were analyzed by a blinded core laboratory. At Cox proportional hazard modeling, HFQRSD greater than 114 ms was predictive of arrhythmic death or cardiac arrest and cardiac death, independent of clinical variables, ICD implantation, and antiarrhythmic drug therapy. An abnormal SAECG was predictive of significantly higher 5-year rates of arrhythmic death or cardiac arrest, cardiac death, and total mortality. Patients with ejection fraction less than 30% and an abnormal SAECG (21% of the population) constituted a subset at particularly high risk, with an arrhythmic or cardiac death rate of 45%.

**Guidelines and Statements**

In 1990 the European Society of Cardiology, the American Heart Association, and the American College of Cardiology (ACC) reported standards for acquisition and analysis of SAECG data and to define the role of LPs in clinical decision making.\(^{153}\) In 1995 a Current Procedural Terminology code was given for billing both technical and professional components. The most recent recommendations come from a 1996 ACC expert consensus document.\(^{154}\) In this assessment the experts determined that, although many published reports describe the performance of the SAECG in a variety of patients, there are few prospective prognostic studies. The committee concluded that publishing recommendations for the use of the SAECG in most clinical areas was premature because firm
indications could not be established. Their limited recommendations for
use of the SAECG are presented in Table 5.

Summary

LPs appear to be signals derived from slowly conducting myocardium
that may predispose to ventricular arrhythmias. There is strong correlation
between signals recorded from the body surface and delayed potentials
recorded from invasive mapping studies. Problems with the methods for
detecting LPs remain. The optimal lead system for LP evaluation has not
been identified, although standard orthogonal lead systems may be
adequate, and the best techniques to identify and define LPs have not been
determined. The conflicting results of studies of different systems and
techniques point out the lack of a true standard. Continued efforts to
identify the optimal method for recording and analyzing SAECG data are
needed.

Despite these limitations there is evidence from the clinical literature
that the SAECG may be a valuable prognostic tool. Most studies in
patients post-MI have demonstrated an association between LPs and
arrhythmic events. The large multicenter MUSTT study of patients with
ischemic cardiomyopathy provides some of the best evidence for the
prognostic value of the SAECG. Although conflicting results were
obtained in other small studies, mostly of nonischemic cardiomyopathy,
MUSTT provides strong evidence for a role for SAECG in ischemic cardiomyopathy.

The most recent and comprehensive post-MI study (MRFAT) and the ischemic cardiomyopathy study (MUSTT) both found a commercially available SAECG device to have independent prognostic power for arrhythmic events. The most important criterion was prolonged HFQRS. Further studies are needed, but the available data suggest that the simple measurement of QRS duration on the filtered SAECG is a potentially valuable test for identifying patients at high risk for arrhythmic events.

**T Wave Alternans**

**Definition and history.** T wave alternans (TWA), a beat-to-beat fluctuation in the amplitude or shape of the T wave, has been noted since the early days of ECG.\(^{155}\) Since its early description TWA has been associated with pathologic findings including autonomic imbalance,\(^{156}\) electrolyte abnormalities,\(^{157,158}\) coronary spasm,\(^{159,160}\) and SCD.\(^{161}\) The earliest laboratory studies noted it is a feature of myocardial ischemia\(^{162,163}\) and focused on its relationship to arrhythmias and arrhythmic risk.\(^{164,165}\) Although the exact cause of TWA remains elusive, it is thought to correlate with negative clinical outcomes, and hence is a subject of great interest among investigators.

**Physiologic features.** Despite lack of complete understanding of the physiologic basis of TWA, there are several hypotheses to explain the beat-to-beat pattern. The T wave is a symbol of transmural dispersion of repolarization that results from differences in size, duration, and shape of the phase three plateau cellular action potentials.\(^{166-168}\) This dispersion of repolarization is affected by alterations in cellular calcium,\(^{169}\) inhibition of adenosine triphosphate production\(^{170}\) and impairment of connexins (membrane ion channel proteins that control conduction).\(^{171}\) TWA results from changes in the electrical conduction pattern of the myocardium between consecutive beats. These changes can be represented by alternating action potential amplitudes, alternating changes in the T wave spatial direction (or angle) of repolarization, or both.

Heterogeneities of repolarization can cause spatially discordant alternans, which can be amplified and form a substrate for reentrant excitation.\(^{172}\) Although TWA appears to be a possible cause of arrhythmias, it may just be a reflection of arrhythmogenic substrate. In response to ischemia, action-potential duration differences occur in an alternating beat-to-beat pattern and with spatial heterogeneity.\(^{173}\) Scars, PVCs, or sympathetic stimulation can also result in alternans.
Animal studies linking TWA to arrhythmias.

Several animal studies have been conducted to address the physiologic basis of TWA. In a canine model of experimental MI, Rosenberg et al.\textsuperscript{174} studied the beat-to-beat variability in local activation time during sustained monomorphic VT, and during ventricular pacing and sinus rhythm as controls. The mean variability of local activation time during VT was much higher (3.2 ms) compared with ventricular pacing (0.2 ms) and sinus rhythm (0.7 ms). In addition, oscillations in local activation time manifested alternans-type periodicity. Inasmuch as beat-to-beat variability and activation-time alternans are common during sustained monomorphic VT and are negligible during sinus rhythm or ventricular pacing, they may be intrinsic to reentry. Other animal studies have established a mechanism linking TWA to the pathogenesis of SCD. Surface ECGs from guinea pig hearts during pacing with simultaneously recorded action potentials demonstrated discordant alternans of the repolarization phase of the action potential above a critical threshold heart rate (about 200 bpm).\textsuperscript{175} Membrane repolarization alternated with the depolarization between neighboring cells, creating large spatial gradients of repolarization. In the presence of discordant alternans a small acceleration of the pacing cycle length produced unidirectional block of an impulse propagating against steep gradients of repolarization leading to reentry, which initiated VF.

Methods. Because the exact cause of TWA is uncertain, it is also difficult to determine the best measurement technique. The multiple methods for measuring TWA that are available differ substantially, because they focus on different causes of TWA. TWA can be due to either alternating beat-to-beat changes in action potential amplitudes of T waves or alternating beat-to-beat changes in the T wave spatial direction (known as T wave “wobble”).\textsuperscript{176} For the former, SAECGs are used to average the ECG complexes and T wave amplitudes, and the standard deviation of the waveforms is the marker of beat-to-beat variability. For the latter, T wave spatial angle is usually interpreted as alternations in T wave amplitude when it is measured in one lead rather than spatially.\textsuperscript{177} Three-dimensional leads can also be used, and the actual T wave spatial vector amplitude derived and measured.

Since macroscopic or visible alternations of T waves are rare, specialized technology has been developed to detect subtle microvolt differences. Older studies used vectocardiographic leads (orthogonal leads, body surface maps including 12-lead ECGs) to measure the variability of the T wave spatial angle or amplitude.\textsuperscript{178,179} This technology was easily applied during exercise with standard signal averaging techniques.
focusing its use on diagnosis of ischemia. Other studies used fast Fourier transform spectral analysis to indirectly calculate the power spectra of beat-to-beat fluctuations in the T wave amplitude with the vector magnitude from three-dimensional ECG leads over 128 consecutive beats. Modified moving average is a newer technique that uses a nonspectral method and averts the need to increase and stabilize heart rate, and enables TWA measurement to be made from an ambulatory ECG. A stream of digitized beats is divided into odd and even bins, and each bin is averaged, creating odd beat and even beat amplitude averages, which are then subtracted to give the TWA.

Mathematical algorithms such as autocorrelation, autoregression, and complex demodulation are applied to decrease background noise and measure the alternans ratio (the extent to which measured alternans exceeds noise) and convey the statistical degree of confidence in the alternans measurement. Sophisticated noise reduction techniques combined with commercially available analytic tools enable measurement of microvolt TWA during routine exercise testing. This advancement is important, because TWA often only appears at heart rate greater than 90 bpm.

**TWA detection: Exercise or atrial pacing?**

Exercise or atrial pacing is often used to increase the heart rate sufficiently for TWA to be detected. In a study of 30 patients with a history of ventricular tachyarrhythmias, heart rate thresholds for the onset of TWA were comparable between submaximal exercise (100 ± 14 bpm) and atrial pacing (97 ± 9 bpm). The concordance rate for TWA with the two techniques was 84%.

Although both methods appear to provide similar results, there is evidence that exercise is better for prognostication. A cohort study of 251 patients with high-risk ischemic heart disease showed that bicycle exercise and pacing TWA were both predictive of EPS results (odds ratio, 3). However, exercise TWA was a significant predictor of the primary end point of death, sustained ventricular arrhythmia, or appropriate ICD therapy (hazard ratio, 2), whereas pacing TWA had no prognostic value (hazard ratio, 1.1). These findings suggest that TWA has the greatest clinical utility with exercise.

**Clinical studies.** Prognostic studies with TWA are summarized in Table 6. TWA is a predictor of inducible ventricular arrhythmias, with a relative risk of 5 in 83 patients referred for EPS. Arrhythmia-free survival at 20 months was significantly lower among patients with TWA (19%) compared with those without TWA (94%). Similar results were obtained in a small study of patients undergoing EPS.

Gold et al reported a larger prospective multicenter trial of 313
patients undergoing EPS. Kaplan-Meier survival analysis of the primary end point of SCD, sustained VT, VF, or appropriate ICD therapy showed that TWA was predictive of events, with a relative risk of 11. Meanwhile, EPS had a relative risk of 7, and SAECG had a relative risk of 5.

**Patients with cardiomyopathy.**

Patients with nonischemic cardiomyopathy have been evaluated separately in some studies. In an interesting study of 104 patients with nonischemic cardiomyopathy undergoing TWA exercise testing, the

### TABLE 6. Clinical studies evaluating prognostic power of T wave alternans

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Patient type</th>
<th>Follow-up (y)</th>
<th>End points</th>
<th>Measurements*</th>
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<tbody>
<tr>
<td>Rosenbaum et al</td>
<td>1994</td>
<td>83</td>
<td>Undergoing EPS</td>
<td>1.7</td>
<td>Inducibility in EPS and arrhythmia-free survival</td>
<td>Microvolt-TWA (&lt;15 µV) (RR, 5.2)</td>
</tr>
<tr>
<td>Gold et al</td>
<td>2000</td>
<td>313</td>
<td>Undergoing EPS</td>
<td>1.1</td>
<td>SCD, VT, VF, appropriate ICD therapy</td>
<td>TWA (RR, 11)</td>
</tr>
<tr>
<td>Kitamura et al</td>
<td>2002</td>
<td>104</td>
<td>Nonischemic CM</td>
<td>2</td>
<td>VT, VF, SCD</td>
<td>TWA with onset HR ≤100 bpm</td>
</tr>
<tr>
<td>Hohnloser et al</td>
<td>2003</td>
<td>137</td>
<td>Nonischemic CM</td>
<td>1.2 ± 0.5</td>
<td>VT, VF, SCD</td>
<td>Microvolt-TWA</td>
</tr>
<tr>
<td>Klingenhheben et al</td>
<td>2000</td>
<td>107</td>
<td>CM</td>
<td>1.5</td>
<td>VT, VF, SCD</td>
<td>TWA</td>
</tr>
<tr>
<td>Ikeda et al</td>
<td>2000</td>
<td>102</td>
<td>Post-MI, CM</td>
<td>1</td>
<td>VT, VF</td>
<td>TWA, low PPV (28%) but high NPV (98%)</td>
</tr>
<tr>
<td>Tapanainen et al</td>
<td>2001</td>
<td>379</td>
<td>Post-MI, CM</td>
<td>1</td>
<td>TM</td>
<td>TWA not predictive</td>
</tr>
<tr>
<td>Rashba et al</td>
<td>2002</td>
<td>108</td>
<td>CAD and LVEF (40%)</td>
<td>1.5</td>
<td>TM, VT/VF, appropriate ICD therapy</td>
<td>TWA predictive with normal QRS (hazard ratio, 6) and not useful with QRS ≥120 ms</td>
</tr>
<tr>
<td>Hohnloser et al</td>
<td>2003</td>
<td>129</td>
<td>Post-MI, CM, and LVEF (30%)</td>
<td>2</td>
<td>Cardiac arrest, SCD, sustained VT</td>
<td>TWA (RR, 5.5)</td>
</tr>
</tbody>
</table>

*Measurements that were significantly associated with endpoints are listed unless otherwise indicated.

CAD, Coronary artery disease; CM, cardiomyopathy; EPS, electrophysiologic study; HR, heart rate; LVEF, left ventricular ejection fraction; NPV, negative predictive value; PPV, positive predictive value; RR, relative risk; SCD, sudden cardiac death; TM, total mortality; TWA, T wave alternans; VF, ventricular fibrillation; VT, ventricular tachycardia; MI, myocardial infarction.
multivariate Cox hazards model revealed that both TWA with an onset heart rate of 100 bpm or less and LVEF are independent predictors of arrhythmic events.\textsuperscript{190} Hohnloser et al\textsuperscript{191} reported a prospective study of patients with dilated cardiomyopathy in which microvolt TWA was a significant univariate predictor of ventricular tachyarrhythmias and was the only significant independent predictor at analysis with the multivariate Cox hazards model. Klingengeheben et al\textsuperscript{192} found that in patients with CHF and no history of sustained ventricular arrhythmias, those with normal TWA test results had no ventricular arrhythmic events in the follow-up period. Only TWA was a significant and independent predictor of arrhythmic events.

**Patients with coronary disease.**

Ikeda et al\textsuperscript{193} prospectively assessed prognostic predictors in 102 patients post-MI and found that of the 15\% with symptomatic sustained VT or VF, the event rates were significantly higher in patients with TWA, LPs, or abnormal ejection fraction. The sensitivity and negative predictive value of TWA in predicting arrhythmic events were 93\% and 98\%, respectively; however, its positive predictive value was only 28\%. In a separate study of survivors of acute MI, sustained TWA during the pre-discharge exercise test did not indicate increased risk for death.\textsuperscript{194} It has been suggested that TWA should be used only in the absence of QRS prolongation, based on the results of the study by Rashba et al.\textsuperscript{195} In this study of patients with coronary artery disease and LVEF 40\% or less referred for EPS, TWA and QRS prolongation were both significant and independent predictors of arrhythmic events. TWA was a highly significant predictor of events in patients with a normal QRS duration (hazard ratio, 6), but not in patients with QRS prolongation.

In a retrospective analysis of MADIT, 129 patients were identified as undergoing microvolt TWA assessment.\textsuperscript{196} In patients negative for TWA, there was no cardiac arrest or SCD during follow-up, compared with an event rate of 15.6\% among the rest. While the authors concluded that TWA testing could help identify patients who are at low risk for ventricular tachyarrhythmias, reviewers have focused on the need for a randomized trial comparing MADIT II post-MI patients with and without TWA testing.\textsuperscript{197}

**Guidelines and Statements**

There are no expert committee statements specifically on TWA use, but Medicare has coverage guidelines for TWA (Table 7).\textsuperscript{198}
TWA has been proposed as a noninvasive test for assessment of susceptibility to ventricular arrhythmias. However, it is difficult to determine the value of TWA and to make clinical use of the technique. The pathophysiologic features of TWA are not fully understood, and it is uncertain whether TWA is a byproduct of arrhythmogenic substrate or a potential cause of arrhythmias. Furthermore, TWA on the surface ECG may reflect beat-to-beat differences in action potential amplitude or may be due to alternating changes in T wave spatial direction, and the methods to record these two phenomena differ. It also appears to be necessary to increase heart rate to induce TWA. It should be measured during exercise stress or, if exercise is not possible, during cardiac pacing.

Not only is there variability in the measurement and definitions of TWA, the evidence for the prognostic ability of TWA is limited. For patients referred for EPS, TWA seems to be predictive of greater inducibility of ventricular arrhythmias and less arrhythmia-free survival. In patients with nonischemic dilated cardiomyopathy, TWA appears to be predictive of ventricular arrhythmias. However, the results in patients post-MI and patients with ischemic cardiomyopathy are inconclusive.

The broad use of TWA testing is not supported by prospective outcome trials to date. Future research should center on determining the optimal testing approach and performing appropriately designed outcome trials.

**Summary**

TWA has been proposed as a noninvasive test for assessment of susceptibility to ventricular arrhythmias. However, it is difficult to determine the value of TWA and to make clinical use of the technique. The pathophysiologic features of TWA are not fully understood, and it is uncertain whether TWA is a byproduct of arrhythmogenic substrate or a potential cause of arrhythmias. Furthermore, TWA on the surface ECG may reflect beat-to-beat differences in action potential amplitude or may be due to alternating changes in T wave spatial direction, and the methods to record these two phenomena differ. It also appears to be necessary to increase heart rate to induce TWA. It should be measured during exercise stress or, if exercise is not possible, during cardiac pacing.

Not only is there variability in the measurement and definitions of TWA, the evidence for the prognostic ability of TWA is limited. For patients referred for EPS, TWA seems to be predictive of greater inducibility of ventricular arrhythmias and less arrhythmia-free survival. In patients with nonischemic dilated cardiomyopathy, TWA appears to be predictive of ventricular arrhythmias. However, the results in patients post-MI and patients with ischemic cardiomyopathy are inconclusive.

The broad use of TWA testing is not supported by prospective outcome trials to date. Future research should center on determining the optimal testing approach and performing appropriately designed outcome trials.

**TABLE 7.** Indications and limitations of Medicare coverage or medical necessity for T wave alternans testing

<table>
<thead>
<tr>
<th>Indications for coverage</th>
<th>Limitations of coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special circumstances in which predictability of VT or VF adds significantly to marginal clinical decisions</td>
<td>Test results will not alter treatment</td>
</tr>
<tr>
<td>Certain clinical situations</td>
<td>Test in routine physical examination or screening service without appropriate signs or symptoms</td>
</tr>
<tr>
<td>Unexplained syncope or presyncope</td>
<td></td>
</tr>
<tr>
<td>Complex ectopy where there is suspicion of congenital cardiac disorder or family history of sudden death</td>
<td></td>
</tr>
<tr>
<td>Sustained VT or VF, nonsustained VT and left ventricular dysfunction, paroxysmal VF</td>
<td></td>
</tr>
<tr>
<td>Risk for VT or VF, or sudden death (and results of test may affect patient treatment)</td>
<td></td>
</tr>
</tbody>
</table>

VT, Ventricular tachycardia; VF, ventricular fibrillation.

**J. S. Alpert:** TWA appears to be one of the more promising avenues of research in our efforts to find simple, inexpensive clinical markers for sudden...
death. Studies thus far have included small numbers of patients. Many cardiologists are hopeful that abnormal TWA study results combined with other abnormal clinical variables, such as QRS width and LVEF, will produce a useful index that will be reasonably predictive of sudden death and hence clinically helpful.

Heart Rate Variability

**Definition and history.** HRV in relation to mean heart rate reflects normal sympathetic and parasympathetic nervous system interaction, and hemodynamic responses to respiration, central pacemakers, and vascular reflexes. The earliest research in HRV involved measurement of sinus rate variability during a fixed respiratory rate and in response to the Valsalva maneuver. Because vagal tone influences heart rate during the Valsalva maneuver, early investigators concluded that abnormalities in HRV could predict future clinical manifestations of CHF. Once the effects of enhanced vagal tone on signal transduction were better understood, research in HRV then focused on arrhythmias and prevention of SCD.

**Physiologic features.** HRV occurs by multiple mechanisms. The HF component of HRV is related to both sinus arrhythmia and the Valsalva maneuver. Sinus arrhythmia is a fluctuation in heart rate that occurs with respiration. Inspiration inhibits vagal tone and increases heart rate. Peripheral reflexes due to chest stretch receptors and hemodynamic changes with inspiration also contribute to HRV. Because sinus arrhythmia is parasympathetically mediated, it can be blocked with atropine or vagotomy, which occurs after heart transplantation. Vagal tone increases with exercise training, and decreases with aging. Patients with diabetes and CHF may have parasympathetic dysfunction, with a corresponding reduction in sinus arrhythmia and an increased risk for SCD. The Valsalva maneuver is another contributor to the HF component of HRV, and the Valsalva index, which measures the ratio between the shortest and longest R-R intervals during the Valsalva maneuver, is an indicator of vagal tone.

In animal models, increased vagal tone antagonizes the effects of enhanced sympathetic tone, shortening ventricular refractoriness and increasing the baroreceptor response that prevents VF. Schwartz et al created a canine model of MI, and noted that animals whose heart rate decreased during an ischemic episode were less likely to develop VF than those whose heart rate did not change. By assessing baroreflex sensitivity, they could predict in which dogs VF would develop. Subsequent work validated these findings in human beings.
While the HF component of HRV has been explained by sinus arrhythmia and the Valsalva response, the LF variability component of HRV is more controversial. The two competing theories of LF variability are the central oscillator theory, which supports the prognostic value of spectral analysis, and the baroreflex feedback loop theory, which does not support spectral analysis. Malpas\textsuperscript{207} reviewed recent research examining the origin of variability associated with LF oscillations, and proposed a new hypothesis to account for LF variability. He argues that the vascular response to sympathetic activity may help determine the strength of oscillations. Whereas HRV was previously thought to reflect autonomic tone, Malpas concludes that there are additional non-baroreflex and non-autonomic pathways. This new hypothesis would weaken the rationale for using spectral analysis to estimate arrhythmic risk, but does not negate it.

**Methods.** HRV can be evaluated in a number of ways, including the time domain method and the spectral or frequency domain method, among others. Errors can occur by including artifacts, PVCs, or T waves in the analysis.

**Time domain.**

The simplest techniques for assessing HRV involve mathematical indices derived from the R-R interval. Two types of periodicities can be measured, depending on the duration of the data collection, that is, beat-to-beat short-term variability or long-term variability for periods greater than 10 seconds. Short-term variability, measured as the standard deviation of the difference in beat-to-beat R-R intervals, represents sinus arrhythmia. Long-term variability is measured as the standard deviation of all R-R intervals (SDNN, the square root of the mean squared differences of successive NN intervals from the mean, where NN refers to the R-R interval between normal beats). Long-term variability results from baroreflex and thermoregulatory effects.

**Spectral or frequency domain.**

Spectral analysis uses mathematical techniques to assess frequency-specific oscillations (ie, number of heart beats per second). The major mathematical technique is the Fourier transform algorithm, which can plot the relative energy component of different frequency components of HRV. Heart rate cycles are identified as HF (corresponding to respiration), LF (0.15-0.40 Hz, or two to nine cpm), very LF (VLF; 0.0033-0.04 Hz, about one cycle per 1 to 4 minutes), and ultra LF (up to 0.0033 Hz, about one cycle per 6 minutes). The LF bumps in the Fourier plot may represent thermoregulatory sympathetic discharges to protect from hypothermia, or sympathetic discharges to baroreceptors to maintain con-
sciousness during hemodynamic collapse, clearly a survival advantage in the context of human evolution. Figure 10 illustrates the frequency domain components and their possible significance. Spectral measures are collected over different time intervals (approximately 2.5-15 minutes), depending on the frequency being analyzed. The LF-HF ratio provides a measure of sympathovagal balance, estimating the relative influence of vagal modulation as opposed to sympathetic drive on the heart. Parasympathetic tone is primarily reflected in the HF component of spectral analysis. The LF component is influenced by both the sympathetic and parasympathetic nervous systems. However, these ratios and the peaks themselves are affected by many factors, including personality, anxiety, medications, and exercise. β-Blockers increase HRV and decrease the LF components of the spectral plot.

Nonlinear dynamics approaches.

HRV has also been analyzed with an approach based on the chaos theory, which is the qualitative study of unstable aperiodic behavior in deterministic nonlinear dynamic systems. A dynamic system may be defined as a simplified model for the time-varying behavior of an actual system, and aperiodic behavior occurs when no variable describing the state of the system undergoes a regular repetition of values. Fractals (short-term and long-term correlation properties or exponents of R-R intervals) and Poincare plots (plots of R-R to next R-R interval) are

**FIG 10.** Frequency domain components of heart rate variability. VLF, Very low frequency; LF, low frequency; HF, high frequency.
mathematical simplifications of unstable aperiodic behavior, and have been applied to spectral analysis of HRV. While some systems do follow nonlinear dynamics, most biochemical and biologic interactions can be modeled with traditional mathematics.

**Heart rate turbulence.**

This method of measuring HRV focuses on the percentage difference in R-R intervals in sinus beats that occurs before and after PVCs. A slope can also be calculated on the basis of a regression of multiple R-R intervals after a single PVC. Heart rate turbulence has been correlated with baroreflex sensitivity, and has been used as a measurement of HRV.

**Normal values for HRV.**

Determination of normal values and optimal time and frequency domain measurements should be made with appropriate control groups. It is important to control for age and various disease states, because these can affect HRV. Some normal values have been reported, but large, well-designed studies to establish normal values for HRV are lacking. Table 8 lists the various measurements of HRV and their normal values.

**Clinical Studies.** While there are many studies of the effects of training, medications, diabetes, genetics, and other factors on HRV, this review focuses on prognostic studies, which can help stratify patient risk for cardiac arrhythmias and SCD. These studies have examined patients post-MI, patients with stable ischemia, and patients with CHF, as well as apparently healthy individuals (Table 9).

**Patients with MI.**

Multiple prognostic studies have demonstrated an association between decreased HRV and both CV death and SCD. Farrell et al assessed HRV, ambulatory ECG variables, SAECGs, and ejection fraction in 416 patients, and found that impaired HRV was most predictive of future arrhythmic events when analyzed with a stepwise Cox regression model. Bigger et al studied 715 patients 2 weeks after MI to establish the association between six frequency domain measures of HRV and mortality during 4 years of follow-up. Each measure of HRV had a significant and at least moderately strong univariate association with all-cause mortality, cardiac death, and arrhythmic death. VLF was the only variable that was more closely associated with arrhythmic death than with cardiac death or all-cause mortality, and this tendency was still evident after adjusting for covariates. Katz et al observed 185 patients for 16 months after a first MI. Patients were instructed to take six deep respirations during 1 minute while changes in heart rate were measured. An abnormal test result was defined as a difference of less than 10 bpm between the
shortest and longest heart rate interval. Abnormal HRV was found in 65 patients, and was an independent and significant predictor of death.

Not all of the studies have demonstrated the value of HRV. Lanza et al.\textsuperscript{226} assessed HRV using time domain and frequency domain on 24-hour pre-discharge Holter recordings for 239 patients with a recent MI. Patients were followed up for 2 years, during which 26 deaths occurred, 19 of which were cardiac in origin and 12 were sudden. The average LF and LF-HF ratio were lower in patients who died, but HRV did not add independent prognostic information to LVEF and ventricular arrhythmias.

The Automatic Tone and Reflexes After Myocardial Infarction trial was a large, prospective, multicenter study of 1284 patients with a recent MI, in which all patients underwent noninvasive risk stratification testing.\textsuperscript{227} HRV was assessed by estimating SDNN during a 24-hour Holter

| **TABLE 8. Measurements of heart rate variability** |
|---------------------------------|------------------|-----------------|--------------|--------------|
| **Name**                        | **Description**  | **Recording**   | **Physiology** | **Normal***  |
| Sinus arrhythmia                | Heart rate change with respiration | 10-s ECG | Centrally mediated inhibition of vagal tone with inspiration | ± 3 bpm |
| Valsalva maneuver               | Ratio of longest and shortest R-R intervals | 2-min ECG | Hemodynamic response results in baroreceptor activation | |
| SDSD                            | Standard deviation of difference in beat-to-beat R-R intervals | 1 min to hrs | Beat-to-beat short-term variability of sinus arrhythmia (vagal) | |
| SDNN                            | Standard deviation of all normal to normal beat intervals | 1 min to hrs | >10 s or longer, due to baroreflex and thermoregulatory effects (LTV) | >50 ± 15 ms |
| HF bands                        | Spectral analysis (0.15-0.40 Hz) | 2.5 min to hrs | Sinus arrhythmia due to respiration | 15 ± 7 (ms\(^2\) × 10) |
| LF bands                        | Spectral analysis (0.04-0.15 Hz) | 2.5 min to hrs | | 14 ± 13 (ms\(^2\) × 10) |
| VLF bands                       | Spectral analysis (0.0033-0.04 Hz) | 2.5 min to hrs | | |
| ULF bands                       | Spectral analysis (<0.0033 Hz) | 2.5 min to hrs | | |
| LF-HF ratio                     | Spectral analysis | 2.5 min to hrs | | 1.2 ± 1 |

*ECG, Electrocardiogram; HF, high frequency; LF, low frequency; VLF, very low frequency; ULF, ultra low frequency; LTV, long-term variability; s, second; ms, millisecond. *Some measurements do not have established normal values.
Cardiac mortality was five times higher among patients with low HRV (<70 ms) than among patients with preserved values. In a multivariate model low HRV was significantly associated with increased mortality risk (risk ratio, 3).

Although traditional time and frequency domain HRV indexes are predictive, other investigators have demonstrated a possibly greater predictive ability of nontraditional measurements of HRV. A sub-study of the Trandolapril Cardiac Evaluation study was designed to determine
whether new analysis methods of HRV predict mortality in 159 patients with LVEF less than 35% after acute MI.\textsuperscript{228} None of the traditional HRV measurements differed between survivors and those who died, but the short-term fractal-like measurements were significant. Huikuri et al\textsuperscript{229} also compared the prognostic power of new fractal and traditional measures of R-R interval variability as predictors of death in 446 survivors of acute MI with depressed LV function. Time and frequency domain HRV measures, along with short-term and long-term correlation properties of R-R intervals were assessed from 24-hour Holter recordings. Reduced short-term HRV was the most powerful predictor of all-cause mortality, and predicted both arrhythmic death and nonarhythmic cardiac death. It remained an independent predictor of death after adjustment for other post-MI risk markers such as age, LVEF, functional class, and medications.

Most recently, Barthel et al\textsuperscript{230} studied 1455 survivors of acute MI, and calculated heart rate turbulence from Holter records. Seventy patients died during 22-month follow-up. At multivariate analysis heart rate turbulence was a stronger predictor of death than were LVEF, diabetes mellitus, or age, with a hazard ratio of 5.9.

**Patients with stable ischemia.**

Forslund et al\textsuperscript{231} assessed the prognostic effect of HRV in patients with stable angina pectoris. Testing included Holter monitoring and exercise tests at baseline and after 1 month of treatment in 641 patients with stable angina pectoris. Patients who died of CV causes (27 cardiac-related deaths and 26 MIs during the 3-year follow-up) had lower total power and HF, LF, and VLF components of HRV. Cox analyses showed that low HRV (measured by total power, HF, LF, and VLF) independently predicted cardiac-related death but not non-fatal MI.

**Patients with CHF.**

HRV has been studied extensively in patients with chronic CHF. Szabo et al\textsuperscript{232} studied 159 patients with stable heart failure. They found that HRV enabled prediction of death only by progressive pump failure, whereas LVEF was predictive of SCD. Many other studies have shown various measures of HRV to predict total mortality, cardiac-related death, and SCD. Time and frequency domain analyses of HRV on 24-hour ECG recordings were assessed in 116 patients with idiopathic dilated cardiomyopathy followed up for 4 years by Fauchier et al.\textsuperscript{233} Using multivariate analysis, reduced SDNN (less than 100 ms) and VT were predictive of SCD or arrhythmic events.

Ponikoski et al\textsuperscript{234} evaluated whether HRV could predict survival in 102 consecutive patients with heart failure followed up for 2 years. HRV
measurements (total power, LF, HF) were derived from 24-hour ECG monitoring. At multivariate analysis, HRV parameters (SDNN, standard deviation of all NN intervals [SDANN], LF) were predictive of survival independently of functional class, LVEF, peak oxygen consumption, and VT on Holter monitoring. One-year survival in patients with SDNN less than 100 ms was 78%, compared with 95% in those with SDNN greater than 100 ms. Sixty-four patients with CHF underwent clinical assessment, 24-hour Holter monitoring, and echocardiography by Wijbenga et al.\textsuperscript{235} Patients who died or required heart transplantation had less HRV than did survivors, and reduced HRV index was independently related to survival.

UK-Heart was a prospective study of 433 outpatients with CHF and mean LVEF of 41%.\textsuperscript{236} During 18 months of follow-up, SDNN was a significant predictor of all-cause mortality with multivariate analysis. The annual mortality rate for the study population in SDNN subgroups was 6% for greater than 100 ms, 13% for 50 to 100 ms, and 51% for less than 50 ms.

Lanza et al.\textsuperscript{237} measured time domain and frequency domain HRV with 24-hour Holter recordings in 56 patients with idiopathic dilated cardiomyopathy. There were eight cardiac deaths and 11 arrhythmic events including SCD over 18 months of follow-up. At multivariate Cox analysis, no variable showed an independent association with cardiac death, but a LF-HF ratio less than 1.2 was the only variable independently predictive of arrhythmic events (risk ratio, 8). Boveda et al.\textsuperscript{238} prospectively enrolled 190 patients with a mean LVEF of 28%, and time domain measures of HRV were obtained from 24-hour Holter ECG recordings. Independent predictors for all-cause mortality were ischemic heart disease, cardiac enlargement, and SDNN less than 67 ms.

Ho et al.\textsuperscript{239} evaluated both traditional and nontraditional measures of HRV in 69 patients with heart failure and in control subjects in the Framingham Heart Study matched by age and sex. They obtained time domain measures (mean and standard deviation of heart rate), frequency domain measures (power in the VLF, LF, and HF bands, and total spectral power over all three bands), and measures based on nonlinear dynamics (approximate entropy, a measure of complexity, and detrended fluctuation analysis). With use of Cox proportional hazards models, the conventional measures (standard deviation of heart rate, LF, VLF, and total power) and the nonlinear measure (detrended fluctuation analysis) were predictors of survival over a mean follow-up of 1.9 years; other measures, including approximate entropy, were not predictive. Their results demonstrate that HRV analysis of ambulatory ECG recordings based on fully automated
methods can have prognostic value in a population-based study and that nonlinear HRV indices may also provide prognostic information.

A Dutch study reported an assessment of nonlinear Poincare plots in 95 patients with mild to moderate heart failure followed up for 4 years with Holter monitoring.\textsuperscript{240} None of the conventional time and frequency domain measures of HRV were related to survival. In contrast, abnormal Poincare plots identified a significantly higher risk for all-cause CV death (hazard ratio, 6) and for sudden death (hazard ratio, 7) compared with normal plots. At multivariate analysis, abnormal Poincare plots still had independent prognostic value, both for all-cause CV mortality and for SCD (hazard ratio, 5).

A more recent and larger study by Makikallio et al\textsuperscript{241} evaluated whether traditional and fractal analyses of HRV from 24-hour Holter recordings predicted mortality among 499 patients with heart failure and LVEF less than 35\%. The conventional (standard deviation of R-R intervals, HRV index, frequency domain indexes) and fractal (short-term fractal scaling exponent of R-R intervals) HRV indexes predicted mortality at univariate analysis, but after adjusting for age, functional class, medication, and LVEF in the multivariate proportional hazards analysis, the reduced short-term fractal exponent remained the only independent predictor of mortality (risk ratio, 1.4; 95\% confidence interval, 1.0-1.9; \( P < .05 \)). In another study of 55 patients at high risk with reduced ejection fraction and an ICD, the fractal measurement again performed best.\textsuperscript{242} Ten-minute, high-resolution ECGs were performed initially and after 2 years of follow-up. The end point of device shock or death was seen in 23 patients, and these patients had significantly lower short-term fractal exponents. None of the spectral or frequency HRV parameters differed significantly between patients with and without events. In the Cox model adjusted for age, gender, LVEF, VT, and \( \beta \)-blocker usage, only the short-term scaling exponent was an independent predictor of the end point (hazard ratio, 1.20).

\textbf{Apparently healthy individuals and the elderly.}

Whereas the previous studies stratified patients already at risk for future cardiac events, the following studies focus on apparently healthy persons, to determine whether measurements of HRV still provide prognostic information. Huikuri et al\textsuperscript{243} evaluated 347 subjects older than 64 years with 24-hour ECG recordings, and observed them for 10 years. Among all analyzed variables, HRV was the best univariate predictor of all-cause mortality (odds ratio, 8). Makikallio et al\textsuperscript{244} evaluated a similar group of 325 subjects older than 65 years with 24-hour Holter recordings, and also observed them for 10 years. At univariate and multivariate analyses, a
reduced short-term fractal scaling exponent was predictive of cardiac death (risk ratio, 2.5) and provided even stronger prediction of SCD (risk ratio, 4). Finally, ambulatory ECGs were obtained in 2501 participants in the Framingham Heart Study without clinical heart disease, which were reprocessed to assess HRV. During a mean follow-up of 3.5 years, cardiac events occurred in 58 subjects. After adjustment for other risk factors, all HRV measures except the ratio of LF to HF power were significantly associated with increased risk for cardiac events.

**Guidelines and Statements**

The last clinical guidelines regarding HRV were part of the ambulatory ECG guidelines from the ACC and American Heart Association in 1999, and a clinical competence statement was published in 2001. The clinical indications for measuring HRV are listed in Table 10.

**Summary**

Two major questions concerning HRV remain to be clarified. First, many methods to measure HRV have been reported, and it is difficult to conclude which is most appropriate for establishing normal values. There is a need to standardize the measurement of HRV and to quantify normal values by patient age and gender. Time and frequency domain measures of HRV have been most commonly used, but recent studies show that new analysis methods based on nonlinear dynamics may be more powerful in terms of risk stratification. Second, the sensitivity, specificity, and predictive accuracy of this test require much more prospective investigation. Studies should be undertaken to determine the value of measuring HRV in various situations, particularly in patients after acute MI.

<table>
<thead>
<tr>
<th>TABLE 10. Indications for measurement of heart rate variability to assess risk for future cardiac events in patients without symptoms from arrhythmia</th>
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<tbody>
<tr>
<td>Class I (definitely indicated)</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Class IIa (probably indicated)</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Class IIb (possibly indicated)</td>
</tr>
<tr>
<td>Patients post-MI with left ventricular dysfunction</td>
</tr>
<tr>
<td>Patients with congestive heart failure</td>
</tr>
<tr>
<td>Patients with idiopathic hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Class III (definitely not indicated)</td>
</tr>
<tr>
<td>Patients post-MI with normal left ventricular function</td>
</tr>
<tr>
<td>Patients with diabetes, to evaluate for diabetic neuropathy</td>
</tr>
<tr>
<td>Patients with rhythm disturbances that preclude heart rate variability analysis (eg, atrial fibrillation, frequent premature ventricular contractions)</td>
</tr>
</tbody>
</table>

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survivors of cardiac arrest, and asymptomatic patients with low LVEF. Correlations of this test with other risk stratification measurements will be necessary to evaluate its independent predictive value. The preliminary data available do not enable definitive conclusions.

One of the leading research groups in HRV recently made some provocative observations in a review questioning whether HRV should be considered a clinical tool or a “research toy.” They note that the mechanisms responsible for the association between HRV and death are not completely established. While reduced HRV has been most commonly associated with risk for arrhythmic death, it may also predict vascular causes of death, progression of coronary atherosclerosis, and death from heart failure. Before the measurement of HRV can be applied to clinical practice and used to direct therapy, for example, ICD implantation, more precise insight into the pathophysiologic link between HRV and mortality are needed.

HRV is an interesting method for evaluation of parasympathetic and sympathetic effects on heart rate in human beings, and preliminary data suggest it could become an important prognostic risk factor for CV death. However, there are substantial unanswered questions that preclude HRV from being a standard clinical test at present; until more data are known it should be considered a clinical research tool.

**MRFAT**

MRFAT deserves detailed review, because it is the only prospective study that has directly compared most of the available noninvasive techniques for evaluating risk for arrhythmia. Also, the comparison was not part of a randomized trial evaluating an intervention. Furthermore, there was a target population who were closely followed and assessed for carefully defined end points.

The participating Finnish investigators applied a protocol that included LVEF at echocardiography, HRV, Holter monitoring, baroreflex sensitivity, SAECG, QTD, and QRS duration in 675 patients post-MI, most of whom were given β-blockers according to clinical practice, not protocol. End points included SCD, non-SCD, and arrhythmic events, separately defined as successful cardiopulmonary resuscitation or probable arrhythmic death based on ECG recordings. During a mean follow-up of 3.6 years, there were 37 non-SCDs (5.5%), 22 SCDs (3.2%), and 17 arrhythmic events (2.5%). All arrhythmia risk variables are listed with the results for the major end points in Table 11. SCD was weakly predicted only by reduced LVEF (<40%), nonsustained VT, and abnormal SAECG, but not by autonomic markers or standard ECG variables. The
hazard ratios for arbitrary cut points are listed in Table 12. The positive predictive accuracy and sensitivity of ejection fraction, nonsustained VT, and abnormal SAECG as predictors of SCD were low: 8% and 45%, 12% and 19%, and 13% and 32%, respectively.

These investigators concluded that arrhythmia risk variables, particularly autonomic and standard ECG markers, have limited predictive power in identifying patients at risk for SCD after MI in the era of β-blocker therapy. Similar carefully designed and accomplished prospective evaluations of noninvasive screening techniques are needed, particularly in other groups of patients who are candidates for an ICD.

**Conclusion**

Patients with coronary artery disease and decreased LVEF are at increased risk for ventricular arrhythmias and SCD. The MADIT II study demonstrated a significant decrease in mortality with prophylactic ICD implantation in patients with a history of MI and LVEF of 30% or less. Further studies of noninvasive assessment may aid in identifying patients most likely to have the greatest benefit from ICD therapy. Noninvasive assessment may also identify patients at high risk with coronary artery disease and more preserved LV function than studied in MADIT II. These tests may also be applied to patients with nonischemic cardiomyopathy.

In our evaluation of the available experimental data, we attempted to focus on SCD as an end point of CV death as the next best alternative.

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**TABLE 11. Arrhythmia risk variables from MRFAT**

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 574)</th>
<th>Non-SCD (n = 37)</th>
<th>SCD (n = 22)</th>
<th>Arrhythmic event (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>46 ± 9</td>
<td>37 ± 11</td>
<td>41 ± 11</td>
<td>39 ± 12</td>
</tr>
<tr>
<td>Holter monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT*</td>
<td>24 (4%)</td>
<td>5 (14%)</td>
<td>4 (18%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>10 PVCs/hr</td>
<td>72 (13%)</td>
<td>12 (32%)</td>
<td>5 (23%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>9.3 ± 8.1</td>
<td>5.3 ± 6.0</td>
<td>8.2 ± 12.3</td>
<td>8.7 ± 13.8</td>
</tr>
<tr>
<td>ECG markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>89 ± 16</td>
<td>103 ± 22</td>
<td>93 ± 19</td>
<td>95 ± 22</td>
</tr>
<tr>
<td>QT dispersion (ms)</td>
<td>74 ± 39</td>
<td>91 ± 33</td>
<td>80 ± 48</td>
<td>87 ± 48</td>
</tr>
<tr>
<td>Signal-averaged ECG</td>
<td>98 ± 18</td>
<td>116 ± 25</td>
<td>103 ± 22</td>
<td>102 ± 23</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>47 ± 33</td>
<td>44 ± 33</td>
<td>49 ± 44</td>
<td>43 ± 33</td>
</tr>
<tr>
<td>RMS last 40 ms</td>
<td>29 ± 10</td>
<td>29 ± 15</td>
<td>36 ± 20</td>
<td>33 ± 14</td>
</tr>
<tr>
<td>Duration &lt;40 μV/ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MRFAT, Multiple risk factor arrhythmia trial; SCD, sudden cardiac death; PVC, premature ventricular complexes; SDNN, standard deviation of normal beat to normal beat duration. *Three or more consecutive PVCs that last no more than 30 s and terminate spontaneously. At least two consecutive cycles must last <550 ms (equivalent to ≥110 bpm), and average rate of entire episode must be >100 bpm.
More and better studies are clearly needed in this area, but this review can come to a relative consensus on which tools and variables are the most effective predictors and help to focus further research.

The routine resting ECG is readily available, noninvasive, and inexpensive, and thus is the most widely used CV test. It is the optimal tool for risk assessment if the analysis can provide adequate predictive power. Reduced T wave amplitude is the highest hazard for CV death among standard ECG variables. QRS duration on resting ECGs has prognostic value, but signal-averaged ECGs appears more prognostic. QTD appears to be a weak predictor, and has methodologic limitations. PVCs found on a routine ECG appear to provide prognostic information, and complex PVCs may provide additional information, but more studies are needed to establish a clear role for PVCs as a predictive marker. Abnormal spatial QRS-T wave axis carries a six times elevated risk for SCD and is a promising marker. Scores such as the Cardiac Infarction Injury Score combine multiple ECG variables and outperform most of the individual

| TABLE 12. Arrhythmia risk variables as predictors of sudden cardiac death and arrhythmic events from MRFAT |
|---------------------------------------------------------------|----------------|----------------|
|                                | **SCD** (n = 22) | **Arrhythmic Events** (n = 17) |
| Univariate analysis                              |                |                |
| Ejection fraction <0.40                        | 2.7            | 3.6            |
| Holter monitor                                  |                |                |
| Nonsustained VT                                | 4.2            | 5.8            |
| PVCs >10/hr                                    | 1.7            | 1.8            |
| SDNN <70 ms                                    | 1.8            | 2.2            |
| ECG markers                                    |                |                |
| Abnormal SAECG                                 | 5.4            | 3.6            |
| 12-lead ECG                                    |                |                |
| QRS duration 120 ms                            | 2.4            | 3.2            |
| QT dispersion 90 ms                            | 1.0            | 2.0            |
| Multivariate analysis                          |                |                |
| Ejection fraction <0.40                        | 2.2            | 3.2            |
| Holter monitor                                  |                |                |
| Nonsustained VT                                | 4.1            | 7.4            |
| PVCs >10/hr                                    | 2.2            | 2.6            |
| SDNN <70 ms                                    | 1.3            | 2.0            |
| ECG markers                                    |                |                |
| Abnormal SAECG                                 | 4.6            | 4.5            |
| 12-lead ECG                                    |                |                |
| QRS duration 120 ms                            | 1.7            | 2.2            |
| QT dispersion 90 ms                            | 1.1            | 1.4            |

* MRFAT, Multiple Risk Factor Arrhythmia Trial; SCD, sudden cardiac death; VT, ventricular tachycardia; PVC, premature ventricular contraction; SDNN, standard deviation of normal beat to normal beat; SAECG, signal-averaged electrocardiogram.
markers. Both the QRS-T wave angle and the Cardiac Infarction Injury Score require computerized measures from a standard ECG, but most ECG programs can be easily be modified to use these unconventional but more sensitive and specific ECG characteristics to estimate risk, in addition to making the usual interpretive statements.

The more advanced ECG techniques require more than a simple ECG, but are also relatively straightforward and inexpensive compared with the invasive approach to arrhythmia assessment. TWA can be done during exercise stress testing, and appears to have some predictive ability, but it has methodologic limitations, and studies show conflicting results in different patient groups. HRV can be determined with ambulatory ECG monitoring, and there have been some promising results, but it also has significant limitations. The pathophysiologic features are not fully understood, and a standard measurement technique is lacking, which may explain why evaluation of the literature is inconclusive. It deserves further study. The detection of LPs is also limited by a standard approach to measurement, but may be the most promising of the more advanced ECG techniques. Recent studies in patients post-MI and patients with ischemic cardiomyopathy have provided strong evidence of an independent prognostic role of LPs. Commercially produced SAECG technology is available, and, although QRS duration on resting ECG has predictive power, the SAECG appears to have more prognostic value.

As a prospective study designed to evaluate most of the noninvasive arrhythmic risk technologies, MRFAT presents a good evaluation of risk stratification of patients post-MI in the current β-blocker era, with SCD as the primary end point. Most ECG variables were not predictive in this population. Only reduced LVEF, nonsustained VT, and the SAECG were predictive of SCD. Yet, despite limited results, MRFAT provides a model for future investigations. Similar studies in other high-risk populations, such as patients post-MI with cardiomyopathy, may provide more impressive results.

Multiple noninvasive assessment tools need to be further evaluated. Experience shows that a single marker is unlikely to be sufficient; rather, a combination of risk evaluation techniques is most likely to have the greatest predictive power. A scoring system that incorporates multiple variables may help physicians decide which patients are the best candidates for ICD implantation. Once an evaluation strategy or score is developed, it can be tested in large prospective studies.

With this review as a guide, we can focus on the most promising techniques to predict the occurrence of SCD. Table 13 lists our conclusion as to which markers of elevated arrhythmic risk should be evaluated.
Variables from multiple noninvasive methods are included, and all have shown some promise as independent predictors. Evaluation in patients post-MI, with and without cardiomyopathy, would be the optimal study population, on the basis of previous studies that focused on those groups.

J. S. Alpert: Dr. Engel and his colleagues at Stanford have written a superb review of the clinical variables that have been suggested as potential markers for predicting sudden death in patients with heart disease. However, none have yet shown adequate specificity and positive predictive value for the devastating complication of sudden death. Nevertheless, research continues in an effort to find a single variable or a set of multiple variables that will enable clinicians to identify patients who are at high risk for sudden death.

**REFERENCES**

5. Moss AJ. Dead is dead, but can we identify patients at increased risk for sudden cardiac death? J Am Coll Cardiol 2003;42:659-60.


40. Hesse B, Diaz LA, Snader CE, Blackstone EH, Lauer MS. Complete bundle branch


55. Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN. Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS...


116. Gardner PI, Ursell PC, Fenoglio JJ, Wit AL. Electrophysiologic and anatomic basis...


131. Denes P, Santarelli P, Hauser RG, Uretz EF. Quantitative analysis of the high


