REVIEW ARTICLE

Electrocardiographic Predictors of Arrhythmic Death

Michael G. McLaughlin, M.D. and Peter J. Zimetbaum, M. D.

From the Beth Israel Deaconess Medical Center, Boston, MA

Sudden Cardiac Death (SCD) refers to death that occurs within 1 hour of the onset of symptoms. Because the majority of SCD occurs as an unwitnessed out-of-hospital event, data on the exact mechanisms are limited. However, in small series of patients who experienced SCD while wearing an ambulatory monitor^{1,2} more than 80% of SCD episodes were noted to be due to ventricular tachyarrhythmias; therefore, SCD usually implies arrhythmic death and the terms are often used synonymously.

SCD is among the leading causes of death in the developed world, including 350,000–400,000 cases annually in the United States.^{3,4} Prevention efforts are limited by the unpredictable onset of lethal arrhythmias and the rapid progression to death. Arrhythmia suppression with antiarrhythmic medications has proven ineffective and, in some cases, hazardous.⁵ Thus, current management strategies have two major components: aggressive treatment of the risk factors and cardiovascular conditions that predispose to SCD (e.g., hypertension, coronary heart disease, and heart failure); and in patients at high risk for arrhythmic death, the increasing use of implantable cardioverter defibrillators (ICDs).

Although ICDs have proven to be powerful tools in both the primary^{6–10} and secondary prevention of SCD,^{11,12} identifying the patients who should receive an ICD remains a challenge. Current guidelines for ICD implantation include patients at the highest risk of SCD, but this represents only a minority of those who will have an event.¹³ Paradoxically, many of the patients who are covered by these guidelines will never experience SCD.

This paradox is a reflection of the manner in which ICD indications have evolved. ICD indications are derived from randomized trials that,

by their inclusion criteria, defined populations in whom prophylactic ICD implantation resulted in survival benefit. In successive trials, these inclusion criteria have steadily broadened (e.g., elimination of the requirement for NSVT and inducible arrhythmias, inclusion of patients with nonischemic cardiomyopathy). Although the populations defined by these less restrictive criteria have benefited from ICD therapy, compared to earlier trials with more narrowly defined populations the absolute reduction in mortality is lower, and the number of patients needed to treat in order to save one life is higher.¹⁴

Without more specific tools for risk stratification, expanding indications for ICD placement will incur extraordinary expense and result in ICD placement in larger numbers of patients who will not experience SCD. Therefore, attention has now turned to the development of refined risk stratification strategies for identifying low risk patients within an otherwise high risk cohort. Such strategies will require specific markers with a high negative predictive value.

Electrocardiography offers a wealth of information on cardiac structure and electrophysiologic properties. The standard 12-lead electrocardiogram (ECG), the signal averaged ECG (SAECG), exercise treadmill testing, and continuous Holter monitoring each provides information on such cardiac features as conduction abnormalities, afterpotentials, ventricular ectopy, repolarization abnormalities, and autonomic function. These features, in turn, are associated with either the substrate or the triggers that produce lethal arrhythmias (Table 1). This review will evaluate the relationships between these electrocardiographic phenomena and arrhythmic death.

Address for reprints: Michael McLaughlin, M.D., Beth Israel Deaconess Medical Center, Division of Cardiology-Electrophysiology Lab, 185 Pilgrim Road, Baker 4, Boston, MA 02215. Fax: 781-453-5260; E-mail: mmclaug2@bidmc.harvard.edu

Table 1. Associations between Electrocardiographic Findings and Mortality

Finding	Correlation	Population	Comments	References
IVCD	HR = 1.44	CAD, EF $\leq$ 40, NSVT	Most patients >1 year post-MI. Minority treated with thrombolytics or PCI.	17
LBBB	HR = 1.49			
RBBB	NS (All for SCD)			
TWA	RR = 10.9 (Arrhythmic events) PPV = 19% NPV = 97% (Arrhythmic event) HR = 4.8	Mixed: Patients referred for EPS for a variety of indications Meta-analysis of 19 studies, 2608 patients, most with CHF and/or prior MI. MADIT-II patients (EF $\leq$ 30 and a Prior MI)	30% of patients had no structural heart disease. 31% undergoing EPS for SVT End point "arrhythmic event" varied slightly among studies Indeterminate TWA results were excluded from analysis Identified low-risk patients within this high risk cohort	24 28 29
NSVT	RR = 2 (SCD) NS RR = 1.8–8.6 (SCD) NS	Post-MI, prior to reperfusion era Post-MI, treated with thrombolytic therapy Hypertrophic cardiomyopathy Nonischemic cardiomyopathy, valvular Disease	RR significantly greater in patients with both NSVT and EF $\leq$ 40 NSVT is common in these populations	31,32 34,35 36,37 38–42
HRV	RR = 2.8 (total mortality) RR = 2.8–3.5 (total mortality) RR = 3.2 (Cardiac mortality)	Post-MI, prior to reperfusion era Post-MI, treated with thrombolytic therapy Post-MI, with and without thrombolytic therapy	 RR = 6.7 in patients with EF < 35	43 46 47
SAECG	RR = 1.6 (SCD) NS	CAD, EF $\leq$ 40, NSVT Post-MI, primary reperfusion era	Most patients >1 year post-MI. minority treated with thrombolytics or PCI Low risk cohort (<1% annual event rate)	52 53

SCD = sudden cardiac death; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block; TWA = T wave alternans; NSVT = nonsustained ventricular tachycardia; HRV = heart rate variability; SAECG = signal averaged ECG; RR = relative risk; NS = nonsignificant; CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; MI = myocardial infarction; EPS = electrophysiology study; SVT = supraventricular tachycardia; PCI = percutaneous coronary intervention.

12-LEAD ECG

The 12-lead ECG is rapid, inexpensive, and widely available. This simple tool provides a great deal of information on cardiac structure and electrical properties. As with many of the predictors discussed in this review, the prognostic significance of specific ECG abnormalities depends in part upon the nature and extent of associated cardiac disease. Among patients with prior myocardial infarction or nonischemic cardiomyopathy, QRS prolongation (due to LBBB or IVCD, but not RBBB) is associated with an increased risk of arrhythmic death. Repolarization abnormalities (QT prolongation, T wave

alternans) occur in patients both with and without structural heart disease, and these findings are discussed separately in later sections.

Conduction Abnormalities: QRS Prolongation

QRS prolongation is due to delayed propagation of the depolarization wave across the ventricular myocardium, caused either by defects within the His-Purkinje system or by conduction delay through the myocardium itself. QRS prolongation

may be direct evidence of electrophysiologic abnormalities that increase susceptibility to ventricular arrhythmias, or alternatively may reflect cardiac structural abnormalities that are themselves the substrate for arrhythmias. In either case, in patients with certain forms of cardiac disease, the presence of a widened QRS due to left bundle branch block (LBBB) or intraventricular conduction delay (IVCD) predicts an increased risk of arrhythmic death.¹⁵ In contrast, right bundle branch block (RBBB) is not associated with an increased risk of arrhythmic events. Evidence supporting the prognostic significance of QRS prolongation comes from observational cohorts of patients with CHD, cardiomyopathy, and hypertensive heart disease, and from subgroup analyses of ICD trials.

The CASS trial enrolled patients with multivessel coronary artery disease who were randomly assigned to either coronary artery bypass grafting or medical therapy. In a registry of 15,609 patients initially evaluated for this study, 522 patients with LBBB or RBBB were identified.¹⁶ In multivariate analysis 2-year mortality was significantly higher in patients with LBBB compared to those with normal conduction. Patients with RBBB did not have increased mortality. This report, however, did not distinguish sudden from nonsudden death.

These results were extended in a report from the MUSTT trial and registry, in which rates of both arrhythmic and total mortality were compared between patients with normal conduction and a variety of conduction disorders. All patients had a prior myocardial infarction and left ventricular dysfunction.¹⁷ This cohort included the 1638 patients from the trial and registry who did not receive either an antiarrhythmic drug or an ICD. The incidence of IVCD, LBBB, RBBB, and LAFB were 17%, 8%, 5%, and 12%, respectively. In multivariate analysis both LBBB and IVCD independently predicted an increased risk of arrhythmic death (49% and 44% increase compared to patients with normal conduction, respectively). Neither RBBB nor LAFB predicted arrhythmic or total mortality.

An association between QRS prolongation and arrhythmic risk is further supported by subgroup analyses from major ICD trials. In MADIT II⁸ enrolling patients with prior MI and LV systolic dysfunction, and DEFINITE,¹⁸ which enrolled patients with nonischemic cardiomyopathy, there were trends towards greater mortality reduction with ICD therapy among patients with QRS duration ≥ 150 and ≥ 120 ms, respectively. In SCD-

HeFT,⁹ which enrolled patients with heart failure and either ischemic or nonischemic cardiomyopathy, patients with a QRS ≥ 120 ms had a greater mortality reduction with ICD placement than those with normal conduction.

The more substantial mortality reduction with ICD placement among patients with QRS prolongation suggests that, compared to those patients with normal conduction, these patients have a greater baseline risk of arrhythmic death. In contrast, however, in PainFREE RxII, patients with QRS ≥ 120 ms did not have an increased incidence of VT or VF compared to patients with a normal QRS.¹⁹ Of note, these four studies generally analyzed patients with QRS prolongation as a single group, and the number of patients with each type of abnormality would have been small, thus diluting the impact of the specific abnormalities previously linked to arrhythmic risk (LBBB and IVCD). In addition, the populations of these ICD trials are not directly comparable to one another, as the patients in MADIT-II, DEFINITE, and SCD-HeFT had more advanced disease and more severe LV dysfunction than those in PainFREE RxII.

Thus, among patients with ischemic and nonischemic cardiomyopathy QRS prolongation is associated with an increase in total mortality and predicts up to a 49% increase in arrhythmic death. When analyzed according to specific types of conduction abnormalities, this association is limited to patients with LBBB or IVCD. RBBB is not independently predictive of SCD. Finally, the prognostic significance of conduction abnormalities is likely modified by the magnitude of QRS prolongation, the degree of LV dysfunction, and the presence of heart failure.

EXERCISE TREADMILL TESTING

T Wave Alternans

T wave alternans (TWA) refers to variations in T wave morphology that occur in an alternating, beat-to-beat pattern. TWA is a manifestation of more complex phenomena occurring on several levels. The cellular events that produce TWA are being elucidated in animal models. Impaired intracellular calcium cycling results in beat-to-beat alterations in the action potential, most significantly during repolarization.²⁰ Although the term alternans refers to temporal variations in repolarization, action potential alternans occurs nonuniformly throughout

the myocardium, producing spatial heterogeneities as well. Large spatial gradients of repolarization can cause unidirectional block, reentry, and an increased susceptibility to malignant arrhythmias.²¹ TWA and its association with arrhythmias were first described nearly 100 years ago,²² but TWA of sufficient magnitude to be seen on visual inspection is rare. More recently, TWA on the magnitude of microvolts has been demonstrated with computer assisted spectral analysis. Because action potential alternans, which underlies TWA, enhances heterogeneities of repolarization and arrhythmia susceptibility, TWA has been studied as a tool for predicting SCD.

A seminal study first evaluated the relationship between TWA and a more established predictor of SCD, inducible VT.²³ Among 83 patients referred for electrophysiology study (EPS), the presence of TWA correlated well with VT inducibility (RR of inducible VT = 5.2, compared to patients without TWA). Over 20 months of follow-up, TWA also predicted higher rates of arrhythmic events. Arrhythmic events occurred in 81% of patients with TWA, and 6% of those without this finding. In this cohort, TWA was essentially equal in prognostic power to inducible VT.

Since this initial report, a number of studies have confirmed the predictive accuracy of TWA for arrhythmic events, and when compared to other invasive (EPS) and noninvasive (SAECG, HRV) risk-stratifying tests, TWA has performed better.^{24–27} As an example, among 313 patients referred for diagnostic EPS, the presence of TWA predicted arrhythmic events (SCD, sustained ventricular tachycardia, ventricular fibrillation, or appropriate ICD therapy) with a relative risk of 10.9. In comparison, for EPS and SAECG the relative risks were 7.1 and 4.5, respectively.²⁴

A meta-analysis including 2608 patients from 19 studies assessed the prognostic value of TWA in a variety of clinical settings.²⁸ In this report, the overall positive and negative predictive value of TWA for ventricular arrhythmias were 19% and 97%, respectively, and the predictive power of TWA was similar in patients with ischemic or nonischemic cardiomyopathy. In three studies limited to patients with a prior myocardial infarction, the positive predictive value was lower (6%), but the negative predictive value was higher (99%). The high negative predictive value of TWA represents, perhaps, its greatest clinical potential, in that it may identify low-risk patients within a given cohort. However,

these studies included relatively low-risk cohorts, in which only a minority of patients had an LVEF $\leq 40\%$ and few would have met current indications for ICD implantation.

The negative predictive value of TWA in a more select population of post-MI patients was illustrated in a prospective multicenter registry.^{29,30} Among a subset of 177 patients in this registry who met MADIT-II indications for ICD placement, 32% had a normal TWA study.²⁹ Over an average follow-up of 20 months, total mortality was lower in patients with a negative TWA (3.8% vs 17.8% in patients with an abnormal or indeterminate TWA, HR = 4.8).

Based upon its high negative predictive value, TWA is currently the most promising potential tool for selecting low-risk patients from within otherwise high-risk populations. However, there are features that will limit its applicability in some populations. First, TWA is most accurately assessed during graded exercise, and therefore is not easily measured in patients with chronotropic incompetence. Similarly, TWA cannot be measured in patients with atrial fibrillation. Finally, there is a high rate of indeterminate test results (up to one-third in some series). It is not clear how such tests should be interpreted or categorized in research trials or in practice. At present, many investigators,^{29,30} include indeterminate results as abnormal, and focus on the negative predictive value of normal studies.

In order to define the role of TWA in risk-stratification algorithms, several issues need to be clarified, including defining the populations in which TWA is adequately predictive of arrhythmic risk to change management recommendations (e.g. post-MI, nonischemic cardiomyopathy, heart failure); comparing TWA to other established risk-stratification tools (e.g., EP study and SAECG); and assessing the appropriate time points after cardiac events at which TWA should be tested. To answer these questions, large prospective trials in clearly defined patient populations are currently underway.

AMBULATORY MONITORING

Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia (NSVT) is a common finding in a wide variety of structural heart disease. Definitions of NSVT vary, but one

commonly applied standard is three or more successive ventricular beats at a heart rate of ≥ 120 beats/min. The prognostic significance of NSVT depends largely on the nature of the associated cardiac abnormality.

NSVT has been most extensively studied in patients with a prior myocardial infarction. In this setting, the prognostic value depends upon the temporal relationship of NSVT to the MI. NSVT is very common in the first 48 hours after an infarction. At this early time point, the arrhythmia is usually due to abnormal automaticity or triggered activity originating in the ischemic or infarcted territory. These arrhythmogenic phenomena are transient and resolve as the infarction evolves and scar formation occurs. Early NSVT, therefore, is not predictive of long-term arrhythmic risk. In contrast, NSVT that occurs later is more likely due to reentry within a region of myocardial scar, representing permanent substrate for malignant arrhythmias and therefore increased risk of SCD.

In a series of 820 patients with a myocardial infarction, prior to the use of current reperfusion therapies, Holter monitoring an average of 11 days postinfarction revealed NSVT in 90 patients and sustained VT in two.³¹ Over an average follow up of 31 months, the 92 patients with sustained or non-sustained VT had a nearly twofold increase in mortality compared to patients without ventricular arrhythmias. The prognostic significance of NSVT is even greater in CAD patients with systolic dysfunction ($EF < 40\%$), in whom there is a greater than fivefold increase in mortality compared to post-MI patients without NSVT.^{31,32}

Despite its proven predictive power, the utility of NSVT in risk-stratification is limited for several reasons. A risk-stratifying tool should either identify high-risk patients in a low-risk cohort, or select low-risk patients with other high-risk findings. Many of the patients in whom NSVT is most predictive of SCD (those with prior infarction and reduced systolic function), are already known to be at high risk of SCD and meet current criteria for primary prevention of SCD with an ICD. In order to be of value in this population, NSVT would have to have a high negative predictive value. However, due its intermittent nature, screening for NSVT is not sensitive and has a poor negative predictive value. In one report, NSVT was reproducible in only 50% of patients who underwent repeat Holter monitoring.³³ Furthermore, NSVT appears to be both less common and less predictive of arrhythmic events

in patients treated with primary reperfusion therapies.^{34,35} At present, when NSVT is seen in patients with a prior infarction and mild to moderate LV dysfunction, who do not otherwise meet criteria for ICD placement, it may be considered a reason for further evaluation (e.g., electrophysiology study).

NSVT is also a common finding in patients with hypertrophic cardiomyopathy (HCM). In one series of 99 patients, NSVT was noted in 19% of the population.³⁶ At a follow up of 3 years, annual mortality was 8.6% in those patients with NSVT, compared to 1% in those without this finding. In a more recent series, NSVT also predicted a higher rate of SCD but the magnitude of risk was much lower (1.6% vs 0.9% in patients without NSVT).³⁷

In contrast to patients with prior MI or HCM, NSVT is not predictive of arrhythmic events in patients with nonischemic cardiomyopathy or valvular disease, including mitral valve prolapse, mitral regurgitation, and aortic stenosis. NSVT is common in all of these patient populations, with a prevalence of up to 80% in patients with idiopathic dilated cardiomyopathy,³⁸ but is not independently predictive of mortality.³⁸⁻⁴²

Heart Rate Variability

In healthy individuals, there is a natural variation in heart rate (or the RR interval) that is controlled by fluctuations in parasympathetic and, to a lesser extent, sympathetic input to the sinus node. Thus, measures of heart rate variability (HRV) represent a surrogate for evaluation of autonomic function. Autonomic balance also affects the initiation and perpetuation of ventricular arrhythmias through modulation of electrophysiologic properties, including ventricular refractory periods, afterpotentials, automaticity, and fibrillation thresholds. HRV, therefore, has been studied as a tool for predicting the likelihood of malignant arrhythmias.

A wide array of measures of HRV has been defined. Full discussion of the various measures is beyond the scope of this review, but they fall into two broad categories, time domain measures and frequency domain measures. Time domain measures are direct assessments of the variation of RR intervals over time. Examples include the standard deviation of RR intervals and the root mean square of successive RR intervals, although a number of more complex measures have been developed.

Frequency domain measures compute power spectral density. In general, lower values, reflecting

less HRV, are abnormal. Using fast Fourier transformations or regression analysis on a sequence of RR intervals, these methods assess cyclical variations in RR intervals at different frequencies or cycle lengths. High frequency (or short cycle length) patterns reflect vagal influence, while low frequency (long cycle length) patterns reflect both vagal and sympathetic influences. Thus, the relative proportion of low to high frequency spectral power serves as an index of sympathovagal control of HR.

Like other predictors of SCD, HRV has been most extensively studied in patients with a prior myocardial infarction. The first large study enrolled 808 patients with a recent MI.^{43,44} HRV was assessed by a number of time and frequency domain methods. Time domain measures were generally more predictive of long-term mortality. At a mean follow up of 31 months, patients with the reduced HRV had significantly greater total mortality compared to those with normal HRV (34% vs 12%). Patients in this study did not undergo primary reperfusion therapy, possibly limiting the applicability of these findings to modern populations. However, time domain measures of HRV had similar predictive power for long-term mortality in subset analyses from the thrombolysis trials GUSTO-I⁴⁵ and GISSI-2.⁴⁶

HRV has been shown to provide independent and additive predictive value when compared to other high-risk findings, including left ventricular dysfunction and ventricular ectopy. In the largest prospective analysis, 1284 post-MI patients had HRV assessed within 28 days of the MI. In multivariate analysis, low HRV predicted a 3.2-fold increase in cardiac mortality, and among those patients with LVEF <35%, the increased risk was 6.7-fold.⁴⁷

The above studies largely describe an association between reduced HRV and total or cardiac mortality. The relationship between HRV and arrhythmic death was assessed in a separate study of 416 post-MI patients.⁴⁸ Reduced HRV was strongly associated with arrhythmic events, and in multivariate analysis was a more powerful predictor of events than reduced EF, abnormal SAECG and NSVT.

In DINAMIT, however, the predictive power of reduced HRV after MI did not result in effective patient selection for primary prophylaxis with ICD therapy.⁴⁹ Post-MI patients with an LVEF <35% and either reduced HRV or an elevated resting HR were randomly assigned to ICD therapy or standard medical therapy. Although ICD placement did re-

duce arrhythmic deaths, it did not reduce total mortality, suggesting that the patient enrollment criteria, including reduced HRV, may have selected a population at high risk of both arrhythmic and nonarrhythmic death.

This hypothesis is supported by a prospective study of HRV in 433 patients with stable class I-III heart failure.⁵⁰ Patients with significantly reduced HRV by a time-domain measurement (SDNN < 50 ms) had a striking 51.4% annual mortality, compared to 5.5% among patients with SDNN >100 (normal). In multivariate analysis, reduced HRV was independently predictive of total mortality; however, this was due to an increased risk of death from progressive heart failure. HRV was not independently associated with SCD in this population.

To define the role HRV may play in risk stratification for arrhythmic death, questions requiring further study include the optimal time point after an MI at which HRV should be measured; the optimal method for measuring HRV; the population in which HRV is most useful; and the relationship between HRV and established markers of arrhythmic risk. Furthermore, an important limitation on the clinical application of HRV is its dependence upon the clinical conditions during which it is measured. Due to the direct relationship between autonomic factors and HRV, both physical and emotional condition can impact HRV, leading to substantial inter- and inpatient variability.

SAECG

The SAECG is a tool for identifying "late potentials" in a QRS complex. Two hundred to four hundred ventricular beats from a surface ECG are analyzed with signal processing algorithms to generate a single, high-resolution QRS complex. By averaging out ambient noise, a high-resolution tracing is generated that can identify microvolt-level activity at the terminal portion of the QRS complex. When present, these potentials represent myocardial regions of delayed activation or slowed conduction, usually due to local inflammation, edema, fibrosis, or scar. Thus, the presence of late potentials can be interpreted as identifying potential substrate for reentrant ventricular arrhythmias.

Late potentials are said to be present, and the SAECG abnormal, when one of the following is found: total duration of filtered QRS >114 ms, root mean square (RMS) voltage of the terminal portion of the QRS is <40 mV, or low amplitude (<40 mV)

signals persist for >38 ms at the end of the SAECG. Recognition of the potential link between late potentials and arrhythmic substrate has led to the extensive study of the predictive value of abnormal SAECG.

Initial studies documented higher incidence of late potentials in CAD patients with a history of sustained VT.⁵¹ Additional data further showed that an abnormal SAECG is an independent predictor of arrhythmic death and total mortality in post-MI patients. More recently, among 1925 patients from the MUSTT trial (CAD, EF < 40, and NSVT), an abnormal SAECG (filtered QRS > 114 ms) predicted a significant increase in 5-year incidence of SCD (28% vs 17%). The abnormal SAECG also provided additive prognostic value to the presence of very low EF (<30%), and patients with both of these abnormalities had a 36% 5-year incidence of arrhythmic death.⁵²

More recently, questions have been raised about the predictive value of the SAECG in the era of primary reperfusion.⁵³ The limitations of the SAECG in this setting was illustrated in a series of 1800 acute MI patients, 99% of whom were treated with primary reperfusion. In this cohort, 968 patients had a SAECG prior to discharge, 9.3% of which showed late potentials. Over an average follow-up of 34 months, SAECG abnormalities did not correlate with SCD and arrhythmic events. However, this was a low-risk cohort (average EF 57%, and average peak CK = 556), with an annual event rate of <1%. It is not known if the SAECG would perform better in a higher-risk cohort.

Special Circumstances

Arrhythmic death is most common in patients with CAD, and the above discussion largely focuses on ECG findings in this population. Several other conditions associated with electrocardiographic abnormalities and arrhythmic deaths are worth brief mention.

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a relatively rare disorder. It is characterized by fibrofatty replacement of the RV myocardium and ventricular arrhythmias. The prevalence is low, estimated to be approximately 1 in 5000. Case series, however, suggest that it may

Figure 1. Epsilon waves (arrows) in a patient with arrhythmogenic right ventricular dysplasia (ARVD).

be significantly more common in Northern Italy, where it was reported to account for up to 22% of SCD in young adults.⁵⁴ ARVD is a progressive disease, and the sensitivity of the ECG varies over time. Although up to 50% of affected patients may have a normal ECG at presentation, nearly all will have at least one of the following abnormal findings within 6 years of presentation: QRS > 0.11 ms, incomplete RBBB, epsilon wave (polyphasic deflection just after the QRS, usually in V₁ or V₂), or T wave inversions in the right precordial leads. In addition, the SAECG is often abnormal, and the presence of late potentials in patients with ARVD predicts a higher risk of malignant arrhythmias. (See Fig. 1)

Long QT Syndrome

Long QT syndrome is a disorder of ventricular repolarization, producing an abnormally long QT interval (>450 ms in men, >470 ms in women; >460 ms in children). QT prolongation is associated with a specific form of polymorphic ventricular tachycardia, called torsade de pointes. The

Figure 2. Long QT interval in a patient with a HERG mutation (LQT2) demonstrating notched or "bifid" pattern often seen with this genetic abnormality.

syndrome can be congenital or acquired. The congenital form has been associated with at least seven different sodium and potassium channel gene mutations.

The genetic abnormalities each impact cardiac myocyte ion currents, producing abnormal patterns of repolarization and a susceptibility to polymorphic VT. However, the various abnormalities produce distinct clinical manifestations, including subtle differences in T wave morphology and important differences in arrhythmia triggers (i.e., exertion vs sleep).^{55,56} A full discussion of the genetics is beyond the scope of this review. Diagnosis is based upon a combination of ECG and clinical criteria. (See Fig.2)

Brugada Syndrome

Brugada syndrome is another primary electrical disorder that occurs in patients without apparent structural cardiac abnormalities. The syndrome is defined by the presence of specific ECG abnormalities and malignant ventricular arrhythmias. The characteristic ECG abnormality is referred to as "pseudo-RBBB," with a terminal R-prime and downsloping ST elevations in the right precordial leads. In contrast to true RBBB, terminal S waves are not usually seen in I and V6. ECG abnormalities may be transient in some patients, and, challenge with a sodium channel blocker (e.g., procainamide, flecainide) can elicit the characteristic ECG abnormality. Patients with the characteristic ECG abnormalities but no history of arrhythmias are said to have a Brugada ECG pattern, while those with arrhythmias have Brugada syndrome.

Three different types of ECG abnormalities have been described. In Type 1, which is the most common and carries the worst prognosis, there is a terminal r-prime, at least 2 mm of ST elevation at the

Figure 3. Brugada Syndrome, Type 1 ECG.

J-point, and a slow downward sloping of the ST segment (Fig. 3). Type 1 is sometimes referred to as the "coved-type." In Type 2 and Type 3, the ST segment is "saddle-type," with initial downward sloping followed by an upturn in the T wave. If this "saddle-type" abnormality is present with >2 mm of ST elevation, it is referred to as Type 2, and with <2 mm ST elevation it is called Type 3.

Type 1 Brugada ECG abnormalities are required for the diagnosis, while Type 2 and 3 are considered suspicious, but not diagnostic. Patients with a Type 2 or 3 ECG who are suspected of having Brugada syndrome should undergo pharmacologic challenge to see if the ECG converts to a Type 1 pattern.

Rates of SCD in asymptomatic patients with Type 1 Brugada ECG abnormalities vary significantly in different case series, probably due to variations in diagnostic criteria and referral bias. Annual SCD rates in this population have been reported between 0.3% and 4% per year. (See Fig.3)

Tetralogy of Fallot

Ventricular arrhythmias and SCD are a potentially devastating late complication following Tetralogy of Fallot repair. QRS prolongation may identify patients at risk for this late complication, as evidenced by two recent studies. Among 178 survivors of Tetralogy of Fallot repair, QRS >180 ms was 100% sensitive and 94.7% specific for life-threatening ventricular arrhythmias.⁵⁷ In a larger cohort of 793 patients, in multivariate analysis QRS >180 ms independently predicted VT and SCD (RR 41.9 and 2.29). In the second report, QRS width increased more rapidly over the 10-year study period in patients who developed VT or SCD.⁵⁸

REFERENCES

1. Olshausen KV, Witt T, Pop T, et al. Sudden cardiac death while wearing a Holter monitor. *Am J Cardiol* 1991;67:381-386.
2. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;117:151-159.
3. Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001;104:2158-2163.
4. Centers for Disease Control and Prevention (CDC). State-specific mortality from sudden cardiac death—United States, 1999. *Morb Mortal Wkly Rep* 2002;51:123-126.
5. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781-788.
6. Moss AJ, Hall WJ, Cannom DS, et al., for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-1940.
7. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;341:1882-1890.
8. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
9. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
10. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
11. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;21:2071-2078.
12. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-1583.
13. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Structure, function, and time-dependence of risk. *Circulation* 1992;85(Suppl. 1):I2-I10.
14. Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: Expanding indications and technologies. *JAMA* 2006;295:809-818.
15. Elhendy A, Hammill SC, Mahoney DW, et al. Relation of QRS duration on the surface 12-lead electrocardiogram with mortality in patients with known or suspected coronary artery disease. *Am J Cardiol* 2005;96:1082-1088.
16. Freedman R, Alderman E, Sheffield L, et al. Bundle branch block in patients with chronic coronary artery disease: Angiographic correlates and prognostic significance. *J Am Coll Cardiol* 1987;10:73-80.
17. Zimetbaum PJ, Buxton AE, Batsford W, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. *Circulation* 2004;110:766-769.
18. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2005;350:2151-2158.
19. Buxton AE, Sweeney MO, Wathen MS, et al. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators. *J Am Coll Cardiol* 2005;46:310-316.
20. Diaz ME, O'Neill SC, Eisner DA. Sarcoplasmic reticulum calcium content fluctuation is key to cardiac alternans. *Circ Res* 2004;94:650-656.
21. Pastore JM, Girouard SD, Laurita KR, et al. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. *Circulation* 1999;99:1385-1394.
22. Herring H. Experimentelle Studien an Saugtieren über das Electrocardiogram. *Z Exper Med* 1909;7:363.
23. Rosenbaum DS, Jackson LE, Smith JM, et al. Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994;330:235-241.
24. Gold MR, Bloomfield DM, Anderson KP, et al. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for

- arrhythmia risk stratification. *J Am Coll Cardiol* 2000;36:2247-2253.
25. Ikeda T, Sakata T, Takami M, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. *J Am Coll Cardiol* 2000;35:722-730.
26. Estes NA3rd, Michaud G, Zipes DP, et al. Electrical alternans during rest and exercise as predictors of vulnerability to ventricular arrhythmias. *Am J Cardiol* 1997;80:1314-1318.
27. Hohnloser SH, Klingenhoben T, Li YG, et al. T wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: Prospective comparison with conventional risk markers. *J Cardiovasc Electrophysiol* 1998;9:1258-1268.
28. Gehi AK, Stein RH, Metz LD, et al. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: A meta-analysis. *J Am Coll Cardiol* 2005;46:75-82.
29. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: A solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004;110:1885-1889.
30. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:456-463.
31. Bigger JT. Prevalence, characteristics and significance of ventricular tachycardia detected by 24 hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. *Am J Cardiol* 1986;58:1151-1160.
32. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: Two year follow-up. *Am J Cardiol* 1984;54:31-36.
33. Senges JC, Becker R, Schreiner KD, et al. Variability of Holter electrocardiographic findings in patients fulfilling the noninvasive MADIT criteria. Multicenter Automatic Defibrillator Implantation Trial. *Pacing Clin Electrophysiol* 2002;25:183-190.
34. Hohnloser SH, Klingenhoben T, Zabel M, et al. Prevalence, characteristics and prognostic value during long-term follow-up of nonsustained ventricular tachycardia after myocardial infarction in the thrombolytic era. *J Am Coll Cardiol* 1999;33:1895-1902.
35. Maggioni AP, Zuanetti G, Franzosi MG, et al. Prevalence and prognostic significance of ventricular arrhythmia after acute myocardial infarction after acute myocardial infarction in the thrombolytic era. GISSI-2 results. *Circulation* 1993;87:312-322.
36. Maron BJ, Savage DD, Wolfson JK, et al. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: A prospective study. *Am J Cardiol* 1981;48:252-257.
37. Adabag AS, Casey SA, Kuskowski MA, et al. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;45:697-704.
38. Singh SN, Fisher SG, Carson PE, et al. and the Department of Veteran Affairs CHF-STAT Investigators. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. *J Am Coll Cardiol* 1998;32:942-947.
39. Larsen L, Markham J, Haffajee CI. Sudden death in idiopathic dilated cardiomyopathy: Role of ventricular arrhythmias. *Pacing Clin Electrophysiol* 1993;16:1051-1059.
40. Kligfield P, Levy D, Devereux RB, et al. Arrhythmias and sudden death in mitral valve prolapse. *Am Heart J* 1987;113:1298-1307.
41. Kligfield P, Hochreiter C, Niles N, et al. Relation of sudden death in pure mitral regurgitation, with and without mitral valve prolapse, to repetitive ventricular arrhythmias and right and left ventricular ejection fractions. *Am J Cardiol* 1987;60:397-399.
42. Wolfe R. Arrhythmias in patients with valvar aortic stenosis, valvar pulmonary stenosis, and ventricular septal defect. Results of 24-hour ECG monitoring. *Circulation* 1993;87:189-1101.
43. Kleiger RE, Miller JP, Bigger JT Jr, et al., and the Multicenter Postinfarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256-262.
44. Bigger JT Jr, Fleiss JL, Steinman RC, et al. Correlation among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am J Cardiol* 1992;69:891-898.
45. Singh N, Mironov D, Armstrong PW, et al. for the GUSTO ECG Substudy Investigators. Heart rate variability assessment early after acute myocardial infarction: Pathophysiologic and prognostic correlates. *Circulation* 1996;93:1388-1395.
46. Zuanetti G, Neilson JMM, Latini R, et al on behalf of the GISSI-2 Investigators. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. *Circulation* 1996;94:432-436.
47. La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;351:478-484.
48. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687-697.
49. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-2488.
50. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). *Circulation* 1998;98:1510-1516.
51. Breithardt G, Borggrefe M, Karbenn U, et al. Prevalence of late potentials in patients with and without ventricular tachycardia: Correlation with angiographic findings. *Am J Cardiol* 1983;49:1932-1937.
52. Gomes JA, Cain ME, Buxton AE, et al. Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. *Circulation* 2001;104:436-441.
53. Bauer A, Guzik P, Barthel P, et al. Reduced prognostic power of ventricular late potentials in post-infarction patients of the reperfusion era. *Eur Heart J* 2005;26:755-761.
54. Corrado D, Basso C, Schiavon M, et al. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;339:364-369.
55. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995;92:2929-2934.

56. Moss AJ. T-wave patterns associated with the hereditary long QT syndrome. *Card Electrophysiol Rev* 2002;6:311–315.
57. Gatzoulis MA, Till JA, Somerville J, et al. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation* 1995;92:231–237.
58. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. *Lancet* 2000;356:975–981.