

Electrocardiographic Markers of Sudden Cardiac Death (Including Left Ventricular Hypertrophy)



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KEYWORDS

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy • Brugada syndrome
- Depolarization markers • Electrocardiogram • Left ventricular hypertrophy • Repolarization markers
- Sudden cardiac death

KEY POINTS

- The electrocardiogram provides significant information regarding the diagnosis and screening for patients at risk of sudden cardiac death.
- Left ventricular hypertrophy is an underestimated cause of sudden cardiac death that can easily be diagnosed by the electrocardiogram.
- The electrocardiogram also provides specific signs of inheritable cardiac disorders such as arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, Brugada syndrome, and others.

MAIN CAUSES OF SUDDEN CARDIAC DEATH

The main cause of sudden cardiac death (SCD) is structural heart disease, mostly atherosclerotic heart disease, which represents approximately 85% of all cases (approximately 280,000 SCD per year in the United States). The remaining 15% is caused by cardiopathies without apparent structural heart disease (approximately 53,000 SCD per year). Besides structural heart disease, the other main cause of SCD is atherosclerotic heart disease, which includes coronary artery disease (CAD), followed by others such as nonischemic dilated cardiomyopathy/dilated

cardiomyopathy, hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), coronary artery anomalies, myocarditis, mitral valve prolapse, symptomatic moderate to severe calcified aortic stenosis (frequently bicuspid), congenital heart diseases before and after surgical correction, commotio cordis or cardiac concussion, and Wolf-Parkinson-White syndrome. Among the causes of SCD without apparent structural heart disease, channelopathies or “primary electrical” diseases stand out, such as Brugada syndrome and sudden unexplained nocturnal death syndrome. Both sudden

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unexplained nocturnal death syndrome and Brugada syndrome are phenotypically, genetically, and functionally the same disorder,¹ idiopathic ventricular fibrillation (VF), early repolarization syndrome/J wave syndrome, congenital or acquired long QT syndrome (LQTS), congenital short QT syndrome, catecholaminergic polymorphic ventricular tachycardia (VT), familial progressive cardiac conduction defect/disorder, or Lenègre disease.² Genetic screening and identification of the causal mutation are crucial for risk stratification and family counseling. Also, Lev's disease (acquired complete atrioventricular heart block due to idiopathic fibrosis and calcification of the electrical conduction system of the heart, most common in the elderly, and often described as senile degeneration of the conduction system), familial sick sinus syndrome, overlapping syndromes, short-coupled variant of Torsades de Pointes (TdP) with a normal QT interval or Leenhardt syndrome³ with or without early repolarization on inferolateral leads,⁴ sudden infant death syndrome, sudden unexpected death in infancy, and inborn errors of metabolism.⁵

More than 122 years after the discovery of the standard 12-lead electrocardiogram (ECG) by Willem Einthoven,⁶ it remains the most common test that is used in the diagnostic armamentarium of the practicing clinician. Because SCD is a complex, multifactorial syndrome, its pathophysiology and triggers are poorly understood. Because SCD has a multifactorial risk profile, it stands to reason that using multiple risk markers, reflecting different facets of the heart's electrical activity, would convey more information than a single marker. At this time, no individual ECG finding has been found to be able to adequately stratify patients with regard to risk for SCD. However, one or more of these candidate surface ECG parameters may become useful components of future multifactorial risk stratification models.⁷

Currently, there is a trend of decreasing the incidence of fast VT/VF. At the same time, there is an increase in pulseless events (ie, cardiac arrest). More people in heart failure have asystole so defibrillation does not work. **Fig. 1** shows the causes of SCD and distribution of arrhythmias.

ELECTROCARDIOGRAPHIC MARKERS OF SUDDEN CARDIAC DEATH: ROLE OF THE ELECTROCARDIOGRAM AS A PART OF A RISK STRATIFICATION OF SUDDEN CARDIAC DEATH

Electrocardiographic depolarization and repolarization disorder and ECG markers of SCD

I. ECG markers of repolarization disorders in SCD

- Prolonged QT/QT corrected QT (QT_c) interval
- Short QT–QT_c interval

2. Prolonged JT-corrected JT (JT_c)
3. Prolonged QT dispersion
4. Inferolateral early repolarization syndrome/J wave syndrome
5. Interval from the peak to the end of the T-wave (T_{peak} – T_{end}) or Tpe
6. T_{peak} – T_{end}/QT ratio
7. Macrowave alternans or T wave alternans
8. Microwave alternans or T wave alternans

II. ECG markers of depolarization disorders in SCD

1. Prolongation of QRS duration (QRS_d)
2. QRS prolongation in right precordial leads (from V1 to V3).
3. An S-wave (≥ 0.1 mV and/or ≥ 40 ms) in lead I
4. QRS dispersion
5. Narrow and wide QRS fragmentation (fQRS and fQRS wide)
6. Epsilon waves
7. Presence of ventricular late potentials (LPs) using high-resolution or signal-averaged ECG

Electrocardiographic Markers of Repolarization Abnormalities in Sudden Cardiac Death

The QT interval or electric systole

The QT interval is the interval that extends between the first recognizable part of the QRS complex onset up to the last recognizable portion of the T wave (the latter may be hard to determine accurately). The end of T is defined as the return of the T wave to the T-P baseline. The QT interval represents the time between ventricular (electric) depolarization onset and (electric) repolarization offset (terminal part). Therefore, one should correct the QT interval according to the heart rate, the so-called QTc. Several mathematical formulas have been proposed. The most commonly used formula is the one proposed by Bazett in the 1920s.⁸ Bazett's formula uses the QTc measurement divided by the square root of RR:

$$\text{QTc} = \frac{\text{Measured QT interval}}{\sqrt{\text{RR}}}$$

Bazett's formula correction of QT interval has been criticized because it tends to provide an inappropriately short QTc at low heart rates. Consequently, it is inappropriate for QTc measurements at higher rates. Several formulae have been proposed to correct the QT interval for the physiologic effect of heart rate changes (QTc), but none

1. The QT interval or electric systole

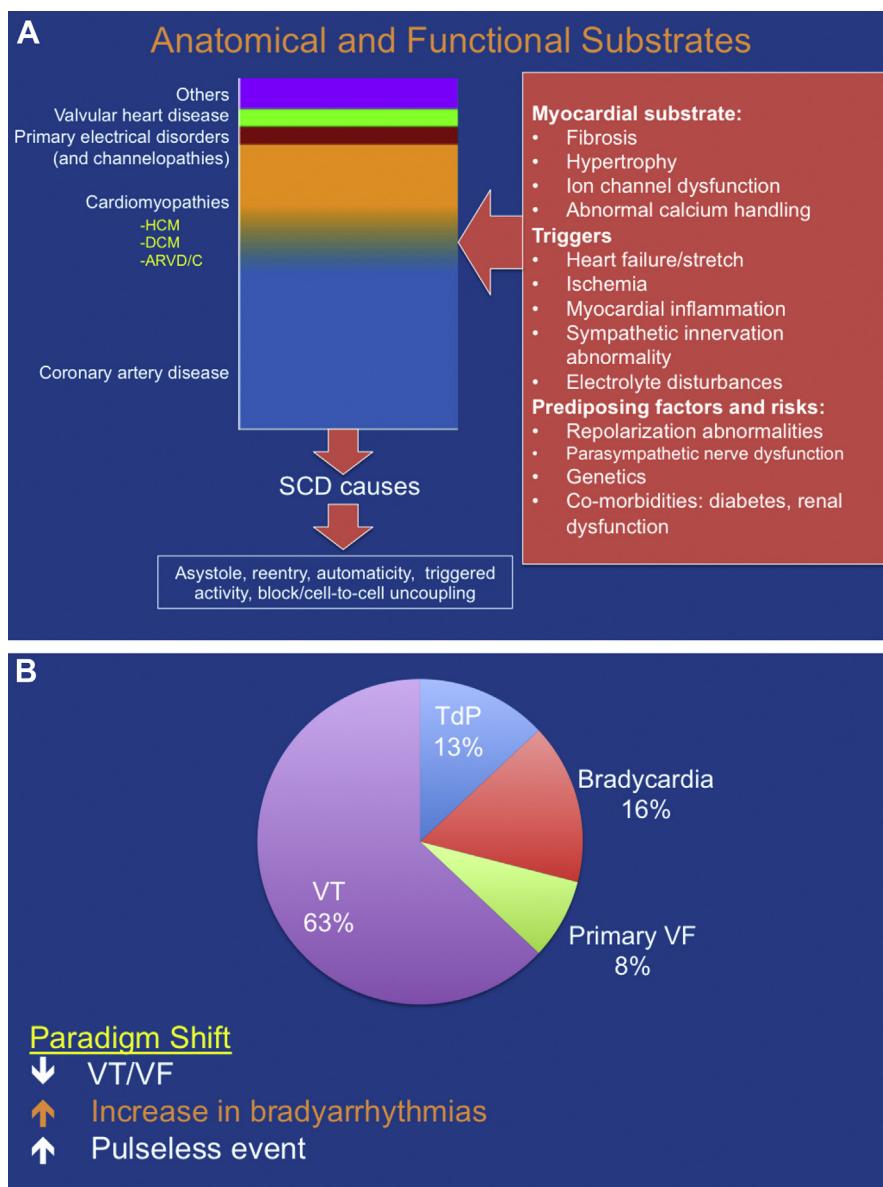


Fig. 1. (A) Causes of SCD. (B) Distribution of arrhythmias in SCD. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; TdP, Torsades de pointes; VT/VF, ventricular tachycardia/ventricular fibrillation. ([A] From van der Bijl P, Delgado V, Bax JJ. Noninvasive imaging markers associated with sudden cardiac death. Trends Cardiovasc Med 2016;26(4):348–60; with permission and [B] Data from 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;117:151–9).

of them are perfect. Bazett's correction is used for automated analysis in large clinical trials because it is simple and is incorporated into automatic measurement by most of the commercially available ECG mechanisms. None of the formulas has been shown to be superior to the others, and each carry its own limitations. Bazett's formula is more popular, but Fridericia's correction is preferred because it is more accurate at physiologic heart rate.

Fridericia's formula ($QTcF = \frac{QT}{\sqrt[3]{RR}}$) proposed an alternative correction using the cube root of RR.⁹ Apart from heart rate, the duration of the QT interval is also affected by methodological recording and errors of measurement of the QT interval, sympathovagal activity, drugs, genetic abnormalities, electrolyte disorders, cardiac or metabolic diseases, changes in cardiac afterload, and diurnal variation, which can account for 75 to 100 ms.

The normal range of the QT/QTc interval in adults varies between 350 ms and 470 ms or greater (for men) and 480 ms or greater (for women). Both short and long QT intervals can cause a variety of life-threatening ventricular arrhythmias. Other authors consider a QTc "borderline" value to be QTc of 440 ms or greater.¹⁰

Prolonged corrected QT interval

QT (QT_c) interval prolongation is defined as a QTc of 470 ms or greater in men and 480 ms or greater in women, although arrhythmias are most often associated with values of 500 ms or greater. The severity of proarrhythmia at a given QT interval varies from drug to drug and from patient to patient, including their genetic background. Unfortunately, the extent of QT prolongation and risk of TdP with a given drug is not always linearly related to the dose or plasma concentration of the given drug because patient and metabolic factors such as enzymes (ie, CYP3A4) play a significant role (eg, gender, race, electrolyte status, etc). Furthermore, there is not a simple relation between the degree of drug-induced QT prolongation and the likelihood of the development of TdP, which can occasionally occur without any substantial QT interval prolongation. **Table 1** shows the value of QTc to be very prolonged, prolonged, normal, and very short (congenital short QT syndrome).

Measurement of the QT interval

The QT interval should be measured in leads II or V5 or on the lead with the largest T wave. Traditionally, lead II has been used for QT interval measurement because in this lead, the vectors of repolarization usually result in a long single wave rather than discrete T and U waves.¹¹ Several successive beats should be measured using the maximum interval. U waves 1 mm or greater that are fused to the preceding T wave should be included in the measurement. U waves less than 1 mm and those that are separate from the preceding T wave should be excluded. When

measuring the QT interval, the ECG is best recorded at a paper speed of 50 mm/s and at an amplitude of 0.5 mV/cm using a multichannel recorder capable of simultaneously recording all 12 leads. A tangent line to the steepest part of the descending portion of the T wave is then drawn. The intercept between the tangent line and the isoelectric line is defined as the end of the T wave (**Fig. 2A**).

Prolonged JT-JTc

The QTc interval constitutes the classical measurement of ventricular repolarization; however, this parameter also includes ventricular depolarization. Thus, in the presence of wide QRS complex (≥ 120 ms) such as right or left bundle branch block, nonspecific intraventricular conduction disturbance or Wolff-Parkinson-White syndrome (ventricular preexcitation), the measurement of ventricular repolarization by QTc may be incorrect or is subject to measurement error. In such cases, the measurement of JTc is more accurate than the QTc interval because it excludes depolarization. Additionally, the JTc interval could be a better parameter than the QTc interval for a more accurate measurement of repolarization time in normal healthy subjects, such as physically fit university students.¹² The JT and JTc interval extends from the J-point to the end of the T wave (see **Fig. 2B**).

The JTc interval is calculated by subtracting the QRS duration from the QTc interval in leads II, V2, and V6. The normal JTc value is between 320 and 400 ms. The measurement of JTc may be useful to identify LQTS cases with borderline values, where the QTc interval could be normal at rest on the ECG.

Prolonged QT Dispersion

QT dispersion is defined as the maximum – minimum QT intervals on the 12-lead surface ECG. The normal range for QT dispersion is 40 to 50 ms with a maximum of 65 ms. The QT dispersion values of 65 ms or greater carry a high risk of ventricular arrhythmias and is a risk marker for SCD. An increased QT dispersion reflects inhomogeneity of ventricular action potentials and may be a marker for SCD, which is considered to be an indirect measure of spatial heterogeneity of repolarization, and may be useful in assessing drug efficacy and safety. Patients who received class 1A antiarrhythmic drugs and developed TdP had significantly increased precordial QT dispersion. In contrast, patients receiving amiodarone or class 1A antiarrhythmics without TdP did not have increased QT dispersion, although the QT interval

Table 1
QT/QT_c interval values for men and women

	Men	Women
Normal QT interval (ms)	360–390	370–400
Long QT interval (ms)	450–470	460–480
Very long QT (ms)	≥ 470	≥ 480
Congenital short QT syndrome (ms)	<330	<340

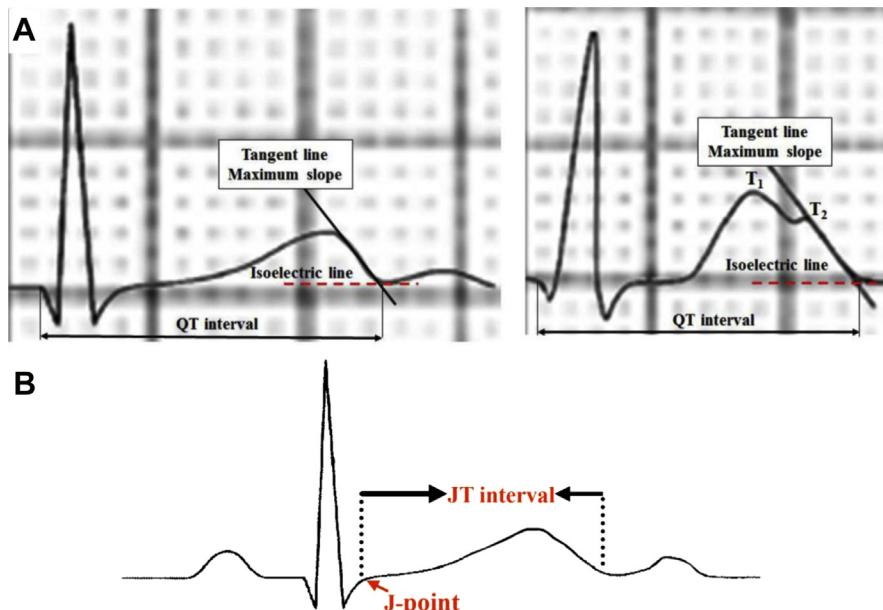


Fig. 2. (A) Intersection between the tangent line and the isoelectric line (*T-P*) is considered the end of the wave *T*. (B) The *JT* interval extends from the *J-point* to the end of the *T* wave.

was noticeably prolonged. Thus, spatial heterogeneity/dispersion of the ventricular repolarization may predispose to QT prolongation and increase the risk of *TdP*.

Early Repolarization

Early repolarization or inferolateral J-point elevation

Early repolarization is defined as QRS-ST junction (*J-point*) with terminal slurring or notch in at least 2 successive inferior (II, III, aVF) and/or lateral (I, aVL, V4, V5, V6) leads with a value of 1 mV or greater from baseline. The new definition of the early repolarization pattern¹³ requires the peak of an end-QRS notch and/or the onset of an end-QRS slur as a measure, denoted *Jp*, to be determined when an interpretation of early repolarization is being considered. Early repolarization may be present if *Jp* is 0.1 mV or greater in at least 2 successive leads; however, ST-segment elevation is not a required criterion.

Early Repolarizations Electrocardiographic Variants

- I. Classic definition of early repolarization^{14–16}
 - A. QRS with ST-segment elevation without *J* wave
 - B. QRS with ST-segment elevation with *J* wave
- II. New definition of early repolarization without ST-segment elevation

- C. Slurred QRS downslope without ST-segment elevation (also called lambda-wave)
- D. QRS notching *J* wave without ST-segment elevation

Inferior *J-point* elevation is associated with a higher risk of SCD.¹⁷ *J-point* elevation in patients with idiopathic VF had higher amplitude and wider distribution than those with an established cause of cardiac arrest.

J wave amplitude of 0.2 mV of greater

J wave amplitude was variable on serial ECGs; at least 1 ECG failed to demonstrate early repolarization in 58% of patients.¹⁸ The underlying pathophysiological mechanism(s) of *J* wave in anterior leads are different from inferolateral leads because the onset mode of premature ventricular contractions differ between the two groups.¹⁹

Fig. 3 illustrates the morphology and patterns of malignant *J* wave: early repolarization in inferior leads or global early repolarization pattern, terminal notching of QRS complex, *J* wave amplitude of more than 0.2 mV, and horizontal or downward direction of ST-segment elevation signifying higher risk features for SCD in early repolarization patients.

The characteristics of benign early repolarization pattern is predominantly observed in young (<45 years of age), physically active individuals and highly trained athletes, as well as black

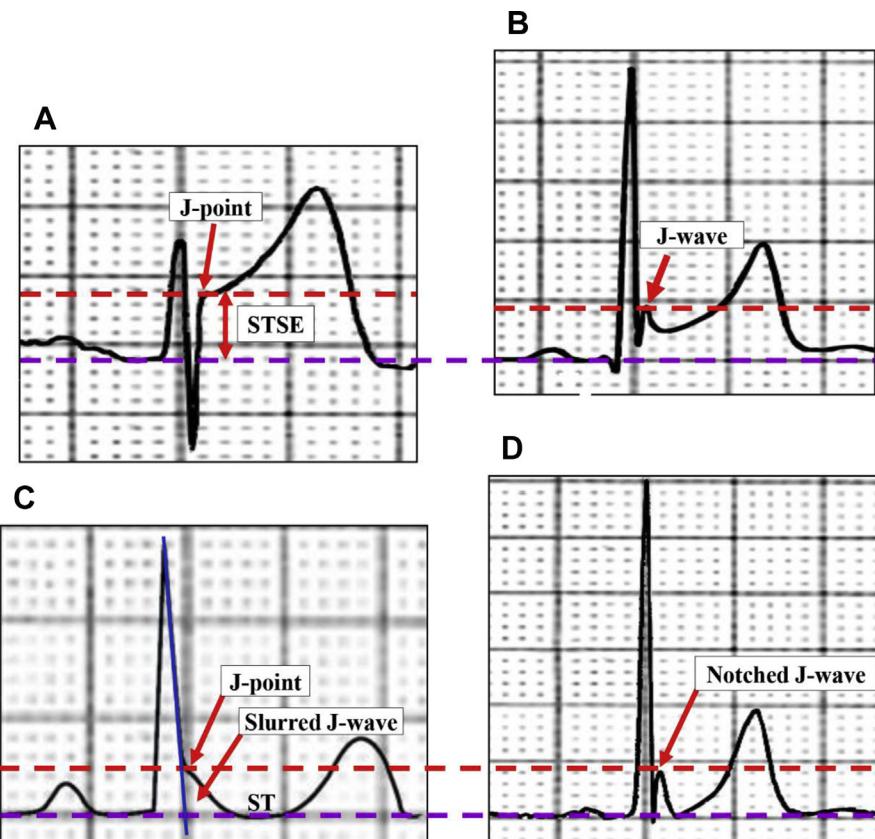


Fig. 3. The 4 different ECG patterns of J wave morphology. The upper red line indicates ST-segment elevation degree without (A) and with (B) J wave, the slur (C) or notch (D) amplitude, J peak (Jp), whereas the lower purple line indicates the baseline used as a reference with respect to which amplitudes should be measured. The blue line indicates tangent to the descendant ramp of the R-wave downslope. (Data from Macfarlane P, Antzelevitch C, Haissaguerre M, et al. Consensus paper: early repolarization pattern. *J Am Coll Cardiol* 2015;66(4):470–7.)

men. It is found on the ECG in about 1% of those with chest pain; frequent sinus bradycardia and phasic arrhythmias; axes of QRS orientation in the same direction in the frontal plane; R wave of higher voltage in left precordial leads; notching or slurring of R wave in the terminal descending limb; “fishhook” deformity at the J-point; rapidly ascending ST-segment elevation after the J-point (upwardly concave) followed by tall, pseudosymmetric, broad-based and upright T waves (degree of ST elevation is <25% of the T wave amplitude in V6); deep (≥ 2 mm) and narrow (<4 ms) Q waves followed by an R wave of great voltage in the left precordial leads; QRS transition in precordial leads of sudden occurrence; J-point and ST-segment modest elevation, usually less than 2 mm (although precordial ST-segment elevation may be up to 5 mm in some instances) concave to the top in middle and/or left precordial leads (V2-V6) and

less than 0.5 mm possibly in the inferior leads; reduction in J-point and ST-segment elevation by sympathetic activity and sympathomimetic drugs; absence of reciprocal changes or mirror image (exception in VR lead); and near symmetric T waves with greater width (duration) and polarity matching QRS and relatively temporal stability (no progression on serial ECGs²⁰; **Figs. 4–7**). **Table 2** shows the important characteristics for the differential diagnosis between benign and malignant early repolarization pattern.

Interval from the Peak to the End of the T Wave or Tpe

Analysis of both the QT subintervals J-T_{peak} and T_{peak}–T_{end} can differentiate drugs that selectively block hERG K⁺ channels (high TdP risk) from drugs that block hERG and late Na⁺ or Ca⁺⁺

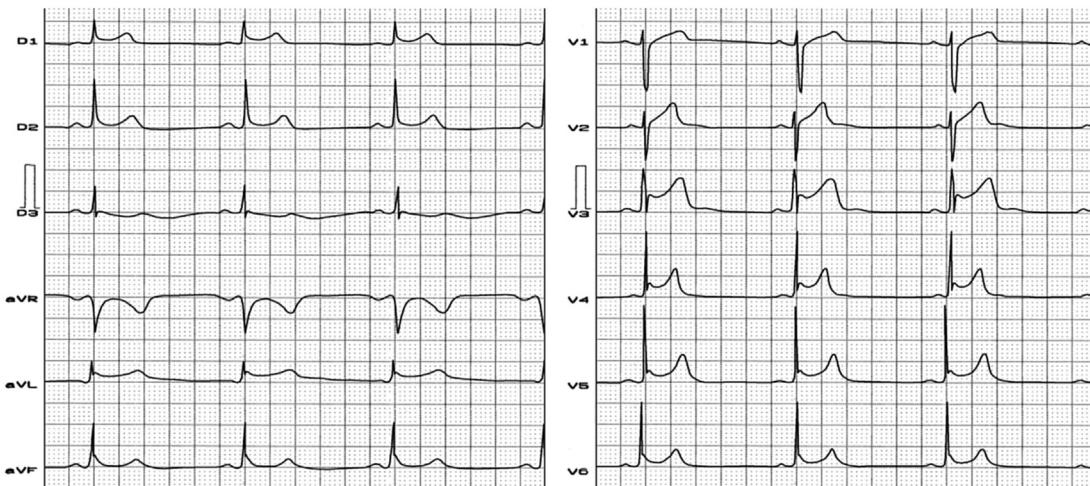


Fig. 4. Example of a typical electrocardiogram (ECG) in a 24-year-old African American professional basketball player with benign early repolarization pattern. His height and weight are 1.91 m and 82 kg. The ECG diagnosis is sinus bradycardia (heart rate, 50 beats/min). J-point and ST-segment elevation concave upward followed by tall T waves (with elevation > 4 mm), notch or slurring of terminal portion of the QRS complex (J-point) and mirror image only in aVR. Interpretation is sinus bradycardia with early repolarization syndrome (pattern).

currents (low TdP risk). Tpe becomes relatively shorter after I_{Kr} inhibition by dl-sotalol. The most pronounced repolarization changes were present in the ascending segment of the minimal T wave representation.²¹

The Tpe interval in the precordial leads was highly related to malignant ventricular arrhythmias in a large cohort of patients with Brugada syndrome. This simple ECG parameter could be used for risk stratification in high-risk patients. The Tpe interval from lead V1 to lead V4, maximum value of the Tpe interval, and Tpe dispersion in all precordial leads were significantly

higher in patients with SCD or appropriate implantable cardioverter-defibrillator (ICD) therapy, and those with syncope compared with asymptomatic patients. A maximum value of the Tpe interval of 100 ms or greater was present in 47 of 226 asymptomatic patients (21%), in 48 of 73 patients with syncope (66%), and in 22 of 26 patients with SCD or appropriate ICD therapy (85%), respectively. In a multivariate analysis, a maximum value of the Tpe interval of 100 ms or greater was independently related to arrhythmic events.²² Fig. 8 shows a representation of this case.

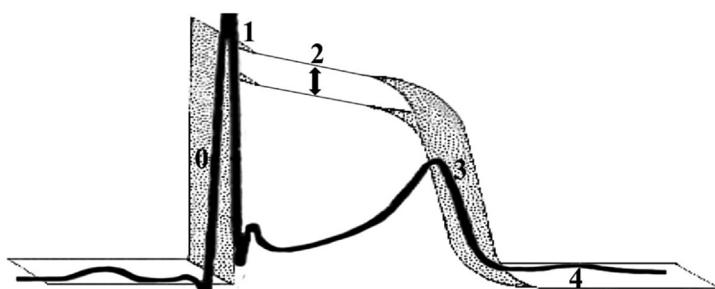


Fig. 5. Theoretic electrophysiologic explanation of ST-segment elevation on electrocardiograms in athletes. In "benign" early repolarization, there is a voltage gradient; however, no dispersion of duration of action potentials in ventricular wall thickness is observed. Therefore, these patients demonstrate notching or slurring in the R wave in the descending branch, ST-segment elevation concave upward, followed by T waves of greater voltage and polarity matching QRS with no risk of developing arrhythmias.

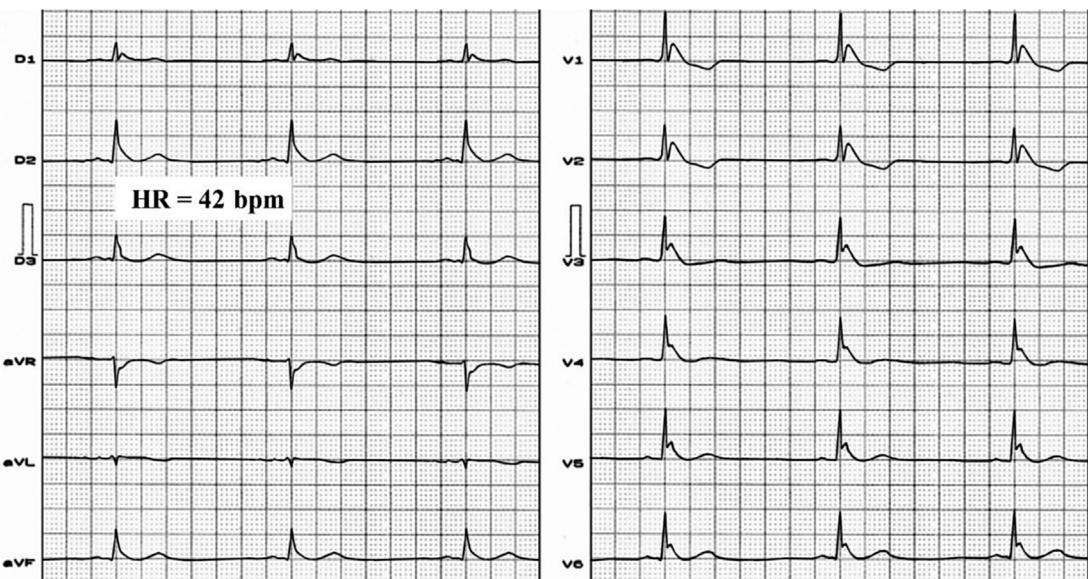


Fig. 6. Typical example of “malignant” early repolarization pattern in a patient with symptomatic idiopathic ventricular fibrillation. Sinus bradycardia (heart rate [HR], 42 beats/min), and J wave (slurred and notched) across pre-cordial leads and inferior leads are present.

RISK PREDICTION OF VENTRICULAR ARRHYTHMIAS AFTER MYOCARDIAL INFARCTION

Prolonged QTc is a known risk marker for mortality and ventricular arrhythmias. QTc does not constitute a high predictive value for arrhythmic

events in patients after myocardial infarction. The terminal part of the QT interval, T_{peak} to T_{end} , or Tpe may have a more accurate value in predicting adverse outcomes. Tpe predicts malignant arrhythmias in patients after myocardial infarction independent of the left ventricular ejection fraction (LVEF). Tpe may contribute in the risk

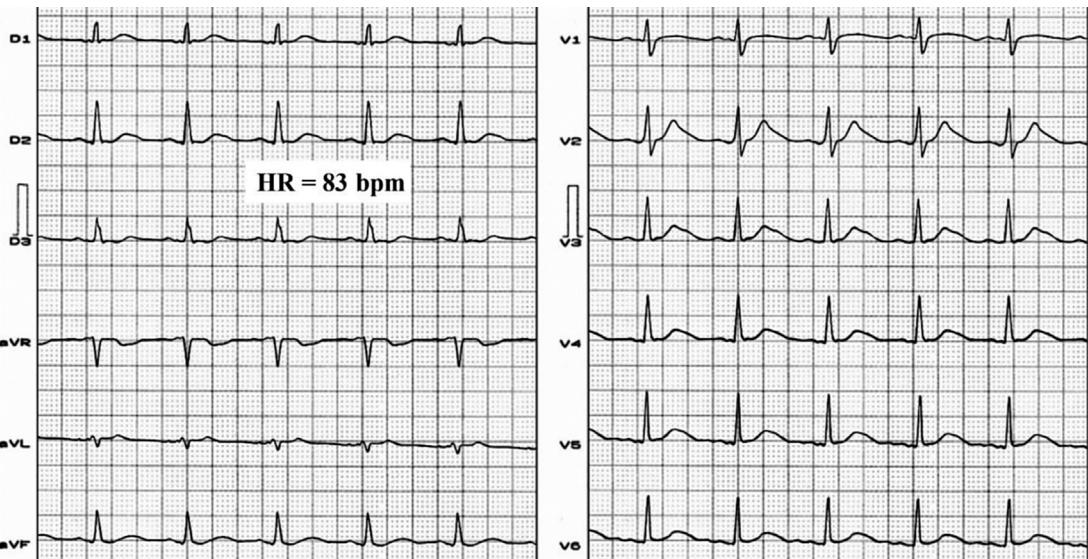


Fig. 7. Electrocardiogram of the same patient as in **Fig. 6** performed 2 days after oral quinidine administration (1500 mg/d). Interpretation is sinus rhythm with a heart rate (HR) of 83 beats/min. The J wave disappeared because quinidine reduced the magnitude of the I_{to} channel, a mediator of phase 1 of action potential.

Table 2
Important characteristics for the differential diagnosis between a benign and a malignant ERP

	Malignant ERP	Benign ERP
Resuscitation from cardiac arrest or documented VF	Very suggestive	Asymptomatic
Positive family history for SCD in young relative	Possible	Absent
Sinus bradycardia	Absent	Common
Axes of QRS, ST segment, and T wave morphology	Frequently discordant	Often concordant
Mirror or reciprocal image	Frequently in several leads	Only aVR
Transient augmentation of J waves	Characteristic (present)	Absent
Short coupled PVCs	Frequent (present)	Absent
Coexisting channelopathies such as Brugada syndrome, SQTS, idiopathic VF	Frequent (present)	Rare
Degree of ST segment elevation/ high-amplitude J waves in the inferior leads	J waves >2 mm ²⁸	<2 mm
Widespread J waves in inferolateral leads and/or globally across all the leads	Strong signal ^{29,30}	Absent
ST segment upstroke (positive convex or lambda wave shape (sharp monophasic or biphasic waveforms)	It is the rule ³¹	Absent; the ST segment is concave upward followed by a T wave of high voltage and polarity matching QRS (concordance)
J waves in the inferior leads	Also present	Possible
J waves in lateral leads, tall R waves, rapidly ascending ST segments followed by tall T waves	Absent	Characteristic ^{32,33}
In a population of athletes, ERP is associated with increased QRS voltages, ST-segment elevation, and LV remodeling	Absent	Characteristic ³⁴
T wave voltage +	Lower ³⁵ (T wave amplitude of $\leq 10\%$ of the R-wave voltage in the same lead)	Higher
Lower T_R ratio in II or V5 +	Yes	No
Longer QTc interval	Yes	No

Abbreviations: ERP, early repolarization pattern; LV, left ventricle; PVC, premature ventricular contraction; SCD, sudden cardiac death; SQTS, short QT syndrome; VF, ventricular fibrillation.

stratification to identify patients after myocardial infarction with malignant arrhythmias and an indication for ICD therapy.²³

The $T_{peak}-T_{end}/QT$ Ratio

The $T_{peak}-T_{end}/QT$ ratio is measured in leads V2 and V6, which are considered to reflect the

transmural axis of the left ventricle in Brugada syndrome and other channelopathies.²⁴

In patients with inducible VT/VF at electrophysiology study (EPS), the mean \pm standard deviation values are: V2 = 0.227 ± 0.034 ; V6 = 0.206 ± 0.012 . In patients with noninducible VT/VF at EPS the mean \pm standard deviation values are: V2 = 0.206 ± 0.012 ; V6 = 0.180 ± 0.014 .

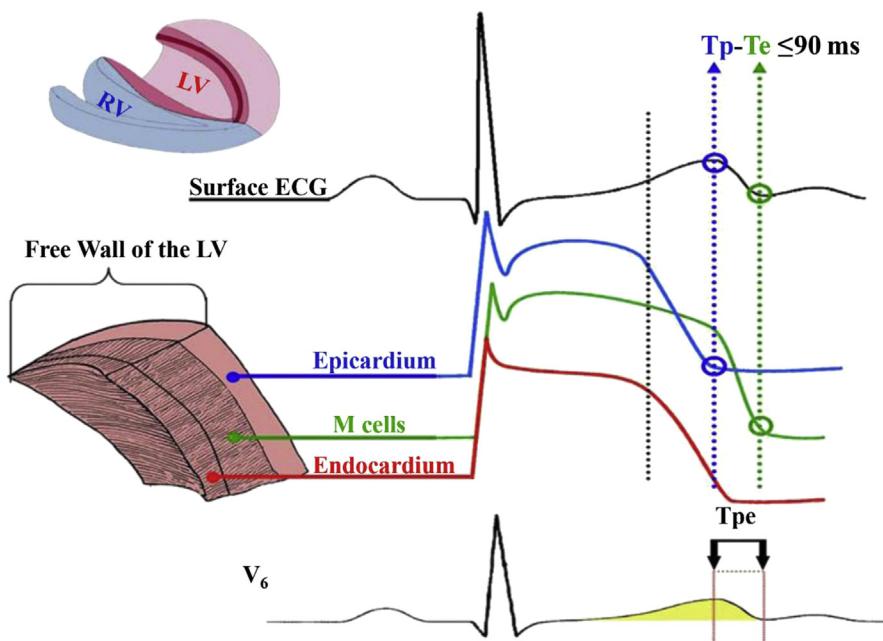


Fig. 8. Representation of the $T_{\text{peak}}/T_{\text{end}}$ interval (T_{pe}). This is the interval between the apex to the end of the T wave ($T_{\text{peak}} - T_{\text{end}}$ interval or T_{pe}). The wall of the heart consists of 3 layers: the epicardium (external layer), the myocardium (middle layer with M cells) and the endocardium (inner layer). T_{pe} may correspond to transmural dispersion of repolarization and, consequently, the amplification of this interval is associated to malignant ventricular arrhythmias. The normal value of the $T_{\text{peak}}/T_{\text{end}}$ interval (T_{pe}) is 94 ms in men and 92 ms in women when measured in lead V5. In congenital short QT syndrome this parameter is greater than 92 ms in women and greater than 94 ms in men (measurement in V5). ECG, electrocardiogram.

$T_{\text{peak}}-T_{\text{end}}/\text{QT}$ ratio was associated with VT/VF inducibility in Brugada syndrome. The utility of $T_{\text{peak}}-T_{\text{end}}/\text{QT}$ ratio as a new marker of arrhythmogenesis in Brugada syndrome warrants a large patient cohort.²⁵

Macrowave T Wave Alternans or Macroscopic T Wave Alternans

Macrowave T wave alternans or macroscopic T wave alternans is a beat-to-beat variation in the polarity and shape/morphology of the ST segment and T wave in 12-lead ECG as shown in **Fig. 9**. In long lead II, a T wave with positive polarity followed by of the next negative T wave polarity, that alternates sequentially. This variety was described for the first time by Schwartz and Malliani,²⁶ in patient carriers of congenital LQTS. These authors showed that changes in T wave

polarity may be reproduced experimentally, by stimulation of the left stellate ganglion. T wave alternans consist of polarity or voltage modifications in the ST segment, T wave or ST-T wave, which represents ventricular repolarization (T wave) along with the ST segment preceding it and the U wave. The phenomena corresponds to ST segment (phase 2), T wave (phase 3), and U wave (phase 4) of an action potential.

Micro T Wave Alternans

Micro T wave alternans are a variant of T wave alternans that detects T wave alternans signals as small as one-millionth of a volt (millivolt). Although T wave alternans seems to be a useful marker of susceptibility for malignant ventricular arrhythmias and cardiovascular death, so far there is no sufficient evidence from randomized clinical trials to



Fig. 9. Macrowave T wave alternans.

support its use in guiding therapy.²⁷ It is not used in daily clinical practice except for academic centers. A T wave alternans level of 1.9 μ V or greater with sufficient signal-to-noise ratio for greater than 2 minutes is defined as a positive test result, whereas a T wave alternans level of less than 1.9 μ V is considered negative. Recently, Takasugi and colleagues²⁸ reported that μ V T wave alternans is far more prevalent in LQTS patients than previously reported and is strongly associated with a history of TdP. T wave alternans should be monitored from precordial leads in LQTS patients. Highest T wave alternans levels were recorded in precordial leads (V1-V6) in 93.8% of patients, most frequently in lead V2 (43.8%). A single ECG lead detected only 63.6% or less of T wave alternans of 42 μ V or greater episodes, whereas the combined leads V2 to V5 detected 100% of T wave alternans of 42 μ V or greater. None of the healthy subjects had T wave alternans of 42 μ V or greater. The use of a limited set of ECG leads in conventional monitoring has led to an underestimation of T wave alternans and its association with TdP.

ELECTROCARDIOGRAPHIC MARKERS OF SUDDEN CARDIAC DEATH: DEPOLARIZATION ABNORMALITIES

Prolongation QRS Duration

There is conflicting data regarding the relationship between prolonged QRSd and arrhythmic events, including SCD in heart failure patients with or without ICDs. Dhar and colleagues²⁹ studied the prognostic significance of prolonged QRSd relative to arrhythmic outcomes in medically and ICD-treated patients enrolled in the MADIT II trial (Multicenter Automatic Defibrillator Implantation Trial). Using a Cox proportional hazards model adjusting for ejection fraction, heart failure class, and blood urea nitrogen, the authors estimated the association of prolonged QRSd of 140 ms or greater with SCD in the medically treated arm and SCD or first appropriate ICD therapy for rapid VT/VF (ie, cycle length ≤ 260 ms) in the ICD-treated arm. In the medically treated arm, prolonged QRSd was a significant independent predictor of SCD. However, in the ICD-treated arm, prolonged QRSd did not predict SCD or rapid VT/VF. The authors concluded that in patients with prior myocardial infarction and an LVEF of 30% or less, a prolonged QRSd does not predict SCD, VT, or VF in ICD-treated patients; however, it does predict SCD in medically treated patients. This highlights the noncorrespondence of VT/VF and SCD and the need for caution in the risk

stratification of SCD when using nonrandomized databases that include only patients with ICDs.

To assess the potential improvement in SCD risk prediction, one should add ECG risk markers from the 12-lead ECG (resting heart rate, QRSd, and JTc intervals) to the LVEF. From the ongoing Oregon Sudden Unexpected Death Study, SCD cases with available pre-event LVEF were compared with matched control subjects with CAD. The authors concluded that combining these 3 selected 12-lead ECG markers with LVEF improves SCD risk prediction. In other words, when the ECGs markers are combined, it has cumulative effects on the risk of SCD prediction.³⁰

In Brugada syndrome, a prolonged QRSd, measured from QRS onset to the J-point in leads V2 and II from a standard 12-lead ECG, is associated with symptoms and could serve as a simple noninvasive ECG risk marker of vulnerability to life-threatening ventricular arrhythmias.³¹ The mean QRS interval is 129.0 ± 23.9 ms in symptomatic patients with Brugada syndrome versus 108.3 ± 15.9 ms in asymptomatic patients³² (**Figs. 10** and **11**).

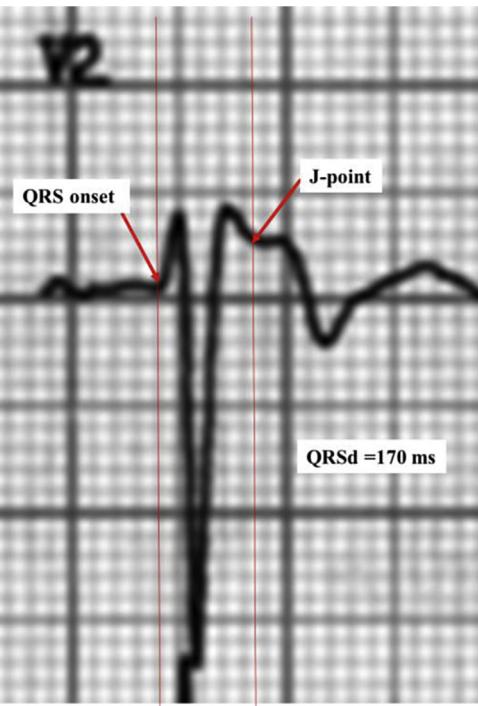


Fig. 10. Prolonged QRS duration measured from lead II or lead V2 of 120 ms or greater in a patient with Brugada syndrome.

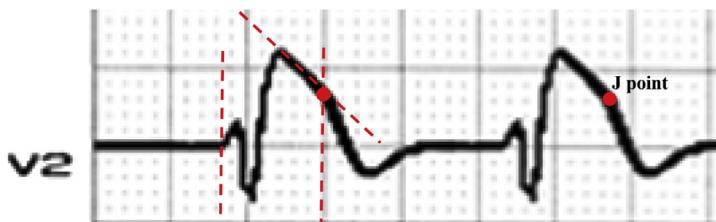


Fig. 11. Vertical dotted lines show the onset and termination of the QRS complex in lead V2. In this case the QRS duration is 165 ms. The oblique line is the tangent line that we use to determinate the end of QRS and the beginning of repolarization (J-point).

Right Precordial QRS Duration Prolongation (Parietal Block)

When the equation $\text{QRSd}_{\text{V1+V2+V3}} / (\text{V4+V5+V6})$ is 1.2 or greater, in carriers of ARVC/D genes, this ECG sign constitutes a sign of high sensitivity for ARVC/D diagnosis and is present in 98% of subjects. Selective prolongation of QRSd is considered typical of ARVC/D, but it is also observed in Brugada syndrome.³³ This author identified selective prolongation of QT interval duration in the right precordial leads (V1–V3) in comparison with the left ones (V4–V6); thus, it is not a specific marker. This longer QRSd complex in the right precordial leads is due to the so-called right parietal (focal or right divisional) block characteristic of ARVC/D: $\text{QRSd}_{\text{V1+V2+V3}} / (\text{V4+V5+V6})$ of 1.2 or greater. Because the QT interval is the result of ventricular depolarization (QRS) plus ventricular repolarization (ST/T), we believe that this selective prolongation represents a certain degree of parietal (intramural) or partial ($\text{QRSd} \leq 120$ ms) block in the right ventricular outflow track, as the one observed in ARVC/D.

A $\text{QRSd}_{\text{V1+V2+V3}} / (\text{V4+V5+V6})$ of 1.2 or greater is observed in approximately 65% of cases of ARVC/D.³⁴ The presence of QRSd from V1 to V3 greater than V4 to V6 has 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVC/D³⁵ (Fig. 12).

In ARVC/D, there is evidence of peripheral right bundle branch block, as it was initially reported by Guy Fontaine, topographic incomplete or complete right bundle branch block occurs in the fascicular portion of the right branch and/or in the right ventricular free wall after the trunk of the branch splits at the base of the papillary muscle of the tricuspid valve. This mechanism seems to be due to the presence of dysplasia in the free wall, in the right ventricular outflow tract, in the right ventricular inflow tract, or in the apical region (triangle of dysplasia), an area where there is dysplasia. The mechanism of the right conduction defect is not a disease of the bundle branch itself, but a distal block probably situated at the junction of the right bundle to the right ventricular wall. This

hypothesis is supported by the histologic appearances of the dysplastic zones.³⁴

In ARVC/D, among those without right bundle branch block, a prolonged S-wave upstroke in V1 through V3 of 55 ms or greater was the most prevalent ECG feature (95%) and correlated with disease severity and induction of VT on EPS. This ECG feature also best distinguished ARVC/D (diffuse and localized) from right ventricular outflow tract.^{34,36} Fig. 13.

An S-Wave 0.1 mV or Greater and/or 40 ms or Greater in Lead I

Calò and colleagues³⁷ analyzed data from 347 consecutive patients with spontaneous type 1 Brugada syndrome by ECG parameters but

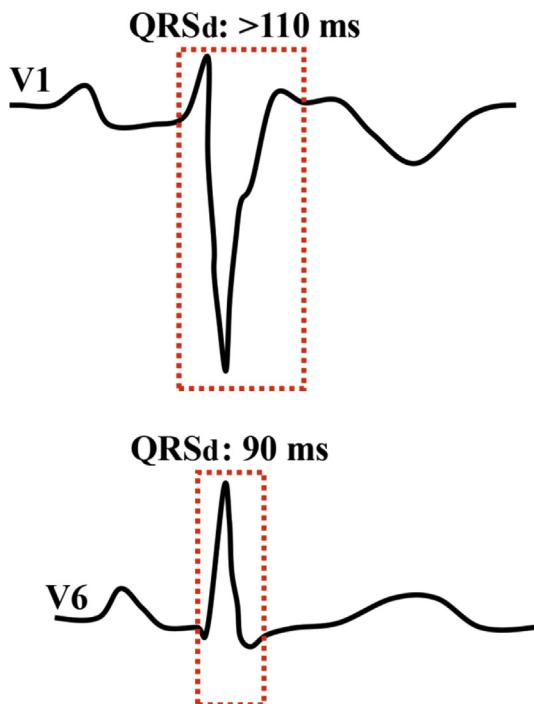


Fig. 12. Electrocardiographic measurement in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia.

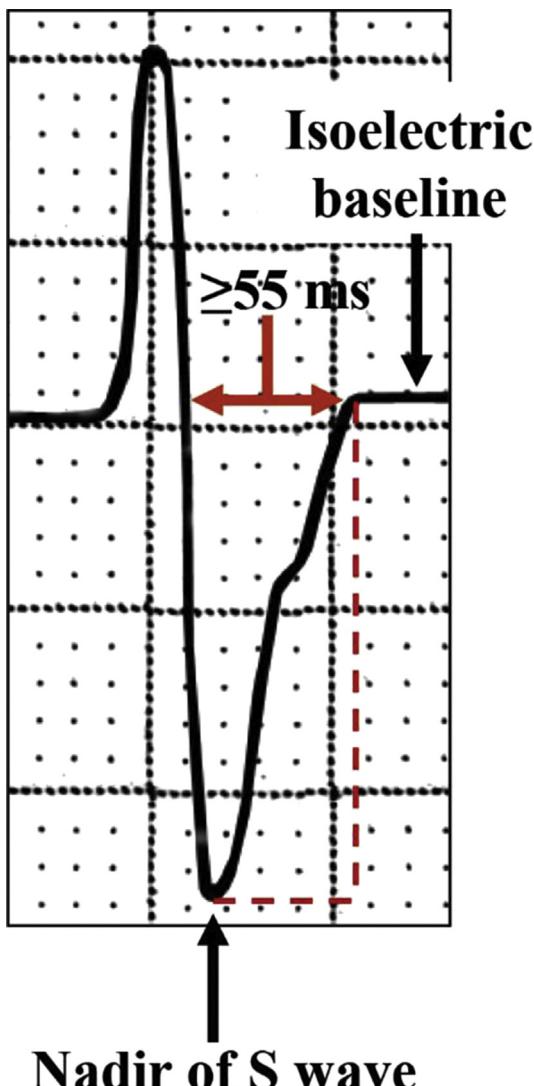


Fig. 13. Prolonged S-wave upstroke in leads V1 through V3 of 55 ms or greater.

with no history of cardiac arrest (including 91.1% asymptomatic at presentation, 5.2% with a history of atrial fibrillation, and 4% with a history of arrhythmic syncope). The most powerful marker for VF/SCD was the presence of S-wave (≥ 0.1 mV and/or ≥ 40 ms) in lead I. In the multivariate analysis, the duration of S-wave in lead I of 40 ms or greater and atrial fibrillation were independent predictors of VF/SCD during follow-up. Electroanatomic mapping in 12 patients showed an endocardial activation time significantly longer in patients with an S-wave in lead I, mostly because of a significant delay in the anterolateral right ventricular outflow tract.³⁷

QT Dispersion

QT dispersion is an indirect measure of spatial heterogeneity of repolarization, which may be useful in assessing drug efficacy and safety. In an important study, patients who received class 1a antiarrhythmic drugs and developed TdP had significantly increased QT interval dispersion. In contrast, patients receiving amiodarone or class 1A antiarrhythmics without TdP did not have increased QT dispersion, although the QT interval was noticeably prolonged. Thus, spatial heterogeneity/dispersion of ventricular repolarization may be promoted in addition to QT prolongation for the genesis of TdP. The most critical adverse effects of class III drugs are marked QT interval prolongation and TdP.³⁸ Although the use of QT dispersion in the assessment of drugs that prolong the QT interval needs further confirmation, it may provide information about the clinical significance of QT prolongation. Thus, the use of QT dispersion in the assessment of drugs that prolong the QT interval needs further confirmation, and may provide information about the clinical significance of QT prolongation to identify individual patients at risk of TdP and SCD.

Narrow QRS, Fragmented QRS Complex/Wide QRS Fragmentation

Narrow QRS fragmentation definition

The presence of notched R or S waves without accompanying typical bundle branch blocks, or the existence of an additional wave like RSR' pattern within the QRS complex 1 or more R' or notching of S or R wave with a normal QRSd (<120 ms) present in at least 2 contiguous (successive) leads. This has been defined as narrow fQRS. fQRS includes various morphologies of the QRS (<120 ms), which included an additional R wave (R') or notching in the nadir (lowest point) of the S wave, or greater than 1 R' (fragmentation) in 2 contiguous leads, corresponding with a major coronary artery territory. fQRS can be caused by zigzag conduction around the scarred myocardium, resulting in multiple spikes within the QRS complex.^{39,40} Narrow fQRS is a simple, inexpensive, and readily available noninvasive ECG parameter.

Wide fQRS definition

Fragmentation of wide complex QRS (≥ 120 ms) consists of various RSR patterns, with more than 2 R waves (R'') or more than 2 notches in the R wave, or more than 2 notches in the downstroke or upstroke of the S wave (Fig. 14).

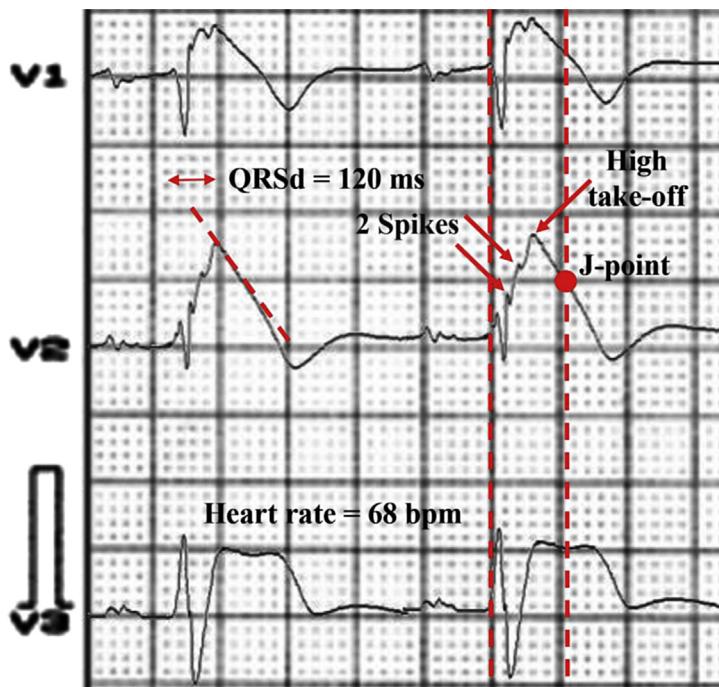


Fig. 14. Wide QRS fragmentation in a symptomatic patient with Brugada syndrome. Dotted lines show the onset and the end of the QRS complex.

Observation

For both narrow and wide fQRS, it is necessary to exclude typical bundle branch block (right bundle branch block or left bundle branch block) pattern ($\text{QRS} \geq 120 \text{ ms}$) and incomplete right bundle branch block. The presence of fQRS has been investigated among the patients with ischemic and nonischemic cardiomyopathy, suggesting that this ECG parameter may suggest an adverse prognosis and risk of SCD, risk of ICD therapy, and response to cardiac resynchronization therapy. In addition, there is evidence that fQRS could play an important role as a screening and prognostic tool among the patients with tetralogy of Fallot, channelopathies, hereditary cardiomyopathies such as ARVC/D, HCM, several scenarios of CAD, hypertension, collagenopathies, cardiomyopathies such as chronic Chagas myocarditis (in Latin America), sarcoidosis, amyloidosis, and so on (Fig. 15). However, fQRS is not specific for any cardiac pathology. Rather, it is a marker of slow conduction that could be present.

Technical problems that affect fragmented QRS complexes

A low-pass filter (35 Hz) is usually used to reduce electrical and musculature noises when recording the ECG, but the cutoff frequency of the low-pass filter influences detection of fQRS. When a low-pass filter is used, the number of

spikes within the QRS complex could be reduced. Increasing the cutoff frequency of the low-pass filter from 35 to 150 Hz unmasked 3 additional spikes within the QRS complex that are frequently observed.⁴¹

Major causes of fragmented QRS complexes

Congenital heart disease

Tetralogy of Fallot in adults Although a QRSd of 180 ms or greater has a prognostic value in adults with tetralogy of Fallot, its sensitivity to predict mortality is low. Fragmented QRS complexes are related to myocardial fibrosis scar or site of ventriculotomy and dysfunction in patients with tetralogy of Fallot. The extent of fQRS is superior to QRSd in predicting mortality in adult patients with tetralogy of Fallot and may be used in risk stratification.⁴² The presence of fQRS on ECG may be a useful tool in daily clinical practice to identify patients at risk for developing ventricular tachyarrhythmia and those with congenital heart disease, in addition to known predictors of ventricular tachyarrhythmias.⁴³

Channelopathies

- Brugada syndrome: Fragmented QRS and early repolarization pattern are common ECG findings in patients at a high risk of Brugada syndrome, occurring in up to 27% of cases. When combined, fQRS and an early repolarization pattern confer a higher risk of

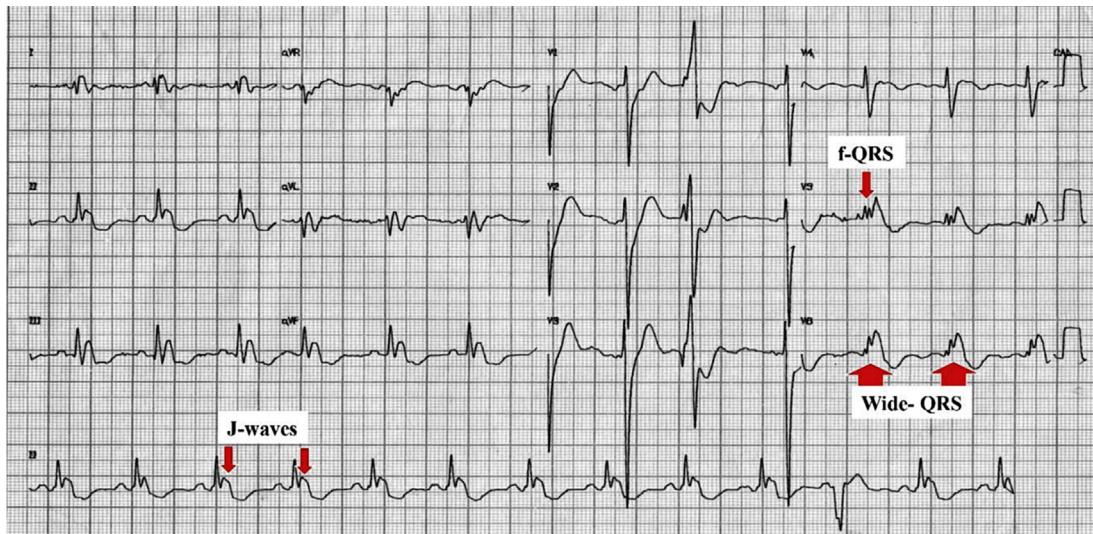


Fig. 15. Electrocardiogram (ECG) in a patient with severe coronary artery disease. Association of QRS fragmentation in at least 2 contiguous leads on the 12-lead ECG plus wide QRS complexes plus J waves of 0.1 mV or greater combined with a descending/horizontal ST segment and inverted T waves in left precordial leads (V5-V6) constitute a malignant early repolarization pattern, because they identify patients with a higher risk of fatal arrhythmias after coronary artery bypass grafting. All of these are components of multifactorial risk for increased morbidity and mortality, sudden cardiac death, and recurrent cardiovascular events.

appropriate ICD interventions during a long-term follow-up.^{44,45} The presence or absence of inferolateral early repolarization and fQRS predicted a worse or better prognosis.⁴⁶

- Idiopathic VF: Patients with idiopathic VF with the combined appearance of fQRS and J wave in resting ECG are at an increased risk of VF and SCD. This subgroup of patients with idiopathic VF has a unique clinical feature and is discussed elsewhere.⁴⁷
- Early repolarization syndrome.⁴⁸
- LQTS: Acquired predisposing factors promoted repolarization abnormality (especially prolongation of QT and Tpe intervals), and the existence of fQRS plays an important role in the development of TdP in patients with acquired LQTS.⁴⁹

Hereditary cardiomyopathies

- HCM: HCM is the most common cause of SCD in the young, particularly among athletes. Identifying high-risk individuals is very important for SCD prevention. QRS may have a substantially higher sensitivity and diagnostic accuracy compared with pathologic Q waves for detecting myocardial fibrosis in HCM.^{40,50} In patients with HCM and apical aneurysm, fQRS is associated with an increased risk of VT.⁵¹ fQRS predicts heart failure progression in patients with HCM.⁵² Fragmented QRS and T wave

inversion in multiple leads are more common in high-risk patients.⁵³ The presence of a fQRS may be a good candidate marker for prediction of nonsustained or sustained VT, SCD, or appropriate ICD therapies in patients with HCM.⁵⁴ fQRS predicts arrhythmic events in patients with obstructive HCM and should be implemented in the risk stratification model.⁵⁵

- ARVC/D: The fQRS complex on standard 12-lead ECG predicts fatal and nonfatal arrhythmic events in patients with ARVC/D. Therefore, large-scale and prospective studies are needed to confirm those findings.⁵⁶ fQRS in ARVC/D has a high diagnostic value, similar to epsilon wave potentials by a highly amplified and modified recording technique.⁵⁷
- Idiopathic dilated cardiomyopathy: In idiopathic dilated cardiomyopathy, approximately 30% of cases have a genetic background and, like HCM, fQRS plays an important marker in identifying high-risk patients.

Acquired diseases

- CAD: Based on current evidence, fQRS is associated with increased major adverse cardiovascular events, mortality, Q wave myocardial infarction, anterior wall myocardial infarction, and decreased LVEF in CAD. fQRS is a reliable marker in patients with CAD who may be at risk of arrhythmic events.⁵⁸

- Acute myocardial infarction
 - ST-segment elevation myocardial infarction: The number of leads with fQRS on ECG is an independent predictor of in-hospital all-cause mortality in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention.⁵⁹
 - Non-ST-segment elevation myocardial infarction: The fQRS complexes are commonly present in non-ST-segment elevation myocardial infarction and the fQRS complexes are an independent predictor of major adverse cardiac events in non-ST-segment elevation myocardial infarction patients.⁶⁰
 - Remote myocardial infarction: Defined fQRS has higher sensitivity and negative predictive value compared with the Q wave.³⁹
 - Coronary slow flow: This phenomenon is a delayed anterograde progression of contrast agent to the distal branch of a coronary artery in the absence of obstructive CAD; a narrow fQRS may be a potential indicator of myocardial damage in patients with coronary slow flow.⁶¹
 - Left ventricular aneurysm: fQRS in V5 to V6 in the absence of bundle branch block suggests left ventricular aneurysm.⁶²
 - Hypertensive heart disease: The left ventricular mass index in hypertensive patients who had fQRS on their ECGs was significantly higher than that of the patients who did not, and fQRS on ECG was an important indicator of left ventricular hypertension in hypertensive patients.⁶³ Carboxy-terminal propeptide of type 1 procollagen is a marker of extracellular collagen synthesis. fQRS on the ECG has been demonstrated as a marker of myocardial fibrosis. Serum propeptide of type 1 procollagen level is a strong and independent predictor of fQRS. Discriminative performance of serum propeptide of type 1 procollagen levels for the presence of fQRS is high. The fQRS may indicate myocardial fibrosis in patients with hypertension.⁶⁴
 - Chronic Chagas' cardiomyopathy: The fQRS is highly prevalent among patients with chronic Chagas' cardiomyopathy. It is a poor predictor of appropriate therapies delivered by ICD in this population.⁶⁵
 - Obstructive sleep apnea: Patients with obstructive sleep apnea show leftward shift of electrical axis, low QRS voltage, QRSD prolongation, and fQRS, suggestive of depolarization disturbance and indicative of electrical remodeling.⁶⁶ Both parameters (fQRS and QRSD prolongation) are related to an increased cardiovascular mortality. Consequently, it seems reasonable to recommend a more detailed evaluation of patients with obstructive sleep apnea with fQRS or prolonged QRS complexes with respect to the presence of cardiovascular diseases.⁶⁷
 - Systemic lupus erythematosus: Cardiac involvement is present in more than one-half of the patients with systemic lupus erythematosus. The frequency of fQRS is higher in patients with systemic lupus erythematosus (41% of cases). fQRS may be used for the early detection in patients with systemic lupus erythematosus.⁶⁸
 - Ankylosing spondylitis: Inflammatory diseases may cause fibrosis. The presence of fQRS may be a simple and cost-effective method for predicting cardiac fibrosis in ankylosing spondylitis patients. fQRS can be a predictive marker for fibrosis in patients with this disease.⁶⁹
 - Extracardiac sarcoidosis: fQRS is associated with cardiac events in extracardiac sarcoidosis.⁷⁰
 - Light-chain cardiac amyloidosis: The presence of fQRS may improve diagnosis and prognostic risk stratification in this entity.⁷¹
 - Psoriasis vulgaris: It was suggested that the presence of fQRS in the ECG may be related to myocardial fibrosis in patients with psoriasis who do not have cardiovascular disease. fQRS could be used as a predictive marker for myocardial fibrosis in patients with psoriasis.⁷²
- In summary, fQRS reflects intramyocardial conduction delay owing to myocardial fibrosis and/or the presence of scar tissue. Thus, it is conceivable that it increases the risk of malignant arrhythmias, but is a non-specific marker.

Epsilon Wave or Fontaine Wave

In approximately 30% of the severe cases of ARVC/D, a small deflection or zigzag may be observed at the end of the QRS in the V1 to V4 leads. They are delayed potentials, which appear after the end of ventricular depolarization (at the end of the QRS complex; **Fig. 16**) or postexcitation phenomenon that may be demonstrated by epicardial mapping, intracavitary electrode mapping, ECG, and signal-averaged ECG (SA-ECG).^{73,74} It was reported for the first time by Dr Guy Fontaine,⁷⁵ using the Greek letter epsilon (epsilon waves). Other terms include epsilon potentials,⁷⁶ ventricular postexcitation waves,⁷⁷ postexcitation (epsilon) waves,⁷⁸ or with the eponymous Fontaine wave⁷⁹; however, we

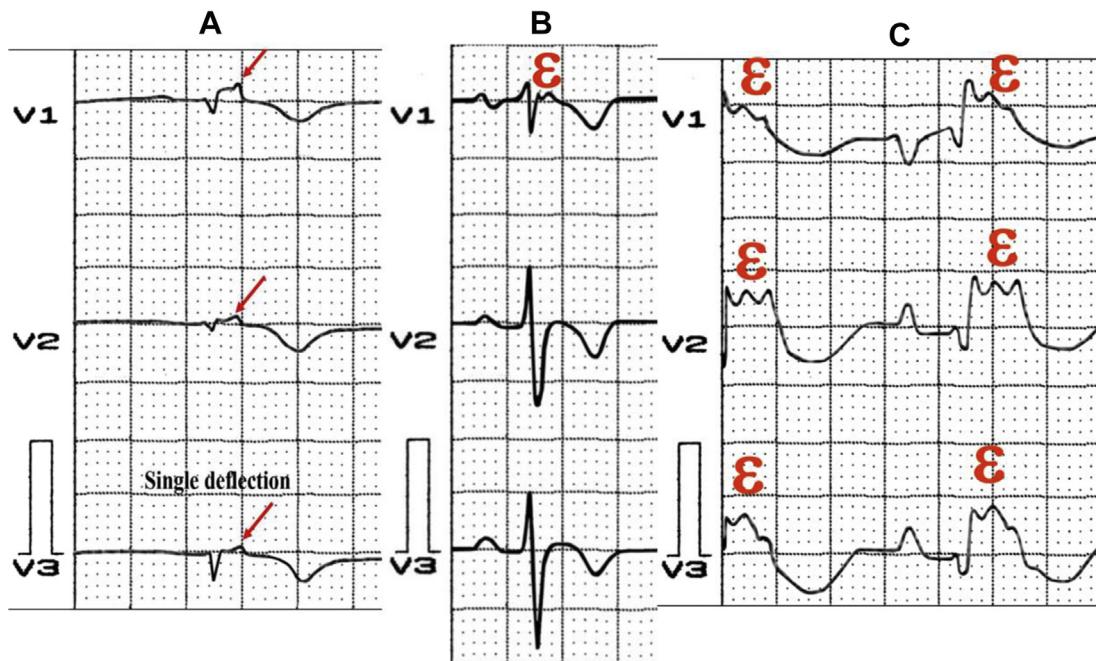


Fig. 16. Epsilon wave with single deflection. (A) Prominent upright deflections (red arrows) after the QRS complex in right precordial leads V1 through V3, associated with negative T waves. Epsilon waves are one of the major depolarization diagnostic criteria of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) following the task force. Epsilon waves can be recorded using a 12-lead electrocardiogram during sinus rhythm, and are useful for establishing a diagnosis of ARVC/D. (B) Sinus rhythm, right atrial enlargement, bizarre complete right bundle branch block, and a terminal notch located in the J-point (epsilon wave). The epsilon wave could be the result of delayed activation in the right ventricle. It is visible in leads V1 to V3 and in the frontal plane leads. T wave inversion is observed in leads V1 to V3, characteristic of ARVC/D. (C) Epsilon wave with multiple deflections inside of the QRS complex. ([A] Data from Anan R, Takenaka T, Tei C. Epsilon waves in a patient with arrhythmogenic right ventricular cardiomyopathy. Heart 2002;88(5):444.)

recommend using Epsilon wave to avoid confusion. It is a late depolarization of right ventricular fibers of right ventricular free wall (dysplastic triangle), registered mainly in leads V1 to V4. Epsilon waves are not the direct counterpart of late potentials, but reflect the delay in peripheral activation in the right ventricular free wall; therefore, it seems to be responsible for much of the genesis of negative T waves.⁷⁸ If we consider that epsilon waves are located after the J-point at the beginning of ST-segment only, the phenomenon theoretically could not be a depolarization criterion because ST segment occurs during the repolarization. **Fig. 16** explains depolarization and repolarization intervals on ECG.

Classification of Epsilon Waves by the Number of Deflections

We classified the epsilon waves according to the number of deflections: 1 (see **Fig. 16**), 2, or multiple deflections. **Fig. 17** shows an ECG of an 18-year-old Caucasian man with ARVC/D and severe right heart failure.

Sensitivity of Electrocardiography for the Detection of Epsilon Wave Frequency in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia With Standard 12-Lead Electrocardiogram With F-ECG and With R-ECG

Epsilon waves are observed in approximately 15% to 30% of the most severe cases of ARVC/D when the S-ECG is used.

Prognostic Significance of the Epsilon Wave in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Epsilon waves aid in the prognosis and risk stratification of patients with ARVC/D.⁸⁰ The detection of epsilon waves on the 12-lead ECG reflects significant right ventricular outflow tract involvement, which was associated with episodes of sustained VT, but not SCD or heart failure.⁸¹ The fQRS complex on S-ECG predicts fatal and nonfatal arrhythmic events in patients with ARVC/D.⁸² Therefore, large-scale and

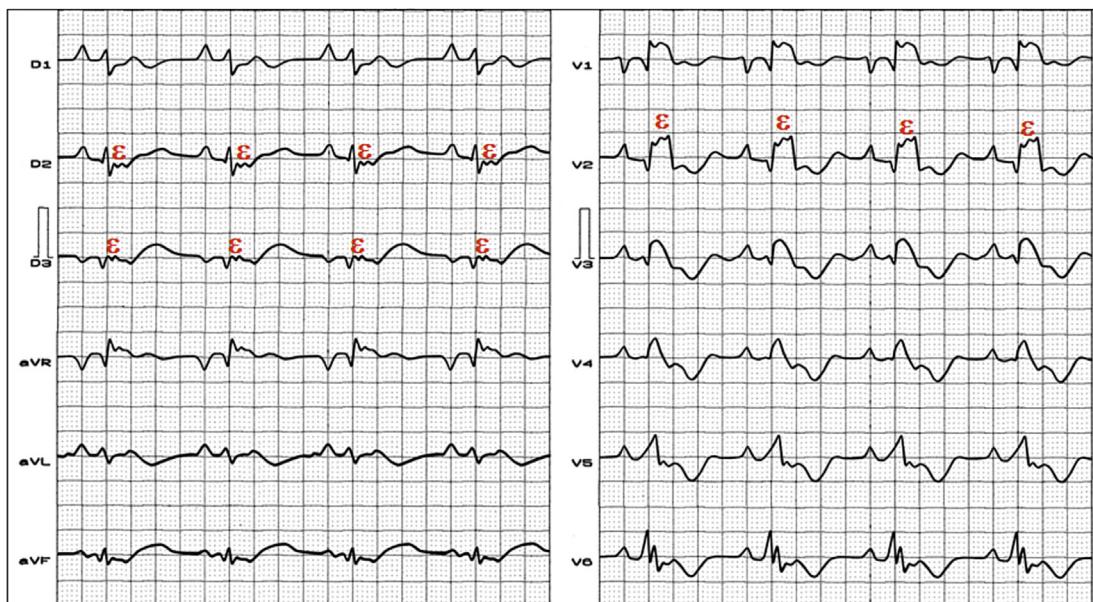


Fig. 17. An 18-year-old female Caucasian with a weight of 53 Kg and height of 1.52 m. Electrocardiographic diagnosis, sinus rhythm; heart rate, 60 beats/min; P wave, SAQRS near 0° ; voltage, 3 mm; duration, 130 ms; negative polarity in V1 and positive in V2, q wave in V1 and V2, batrial enlargement? Or a significant right ventricular enlargement? QRSD: 230 ms (complete right bundle branch block); epsilon waves are observed in numerous leads inside and outside of the QRS (arrows).

prospective studies are needed to confirm these findings.⁵⁶ fQRS is a valuable marker to predict total mortality and major adverse cardiac events in patients with CAD.⁸³

Sarcoidosis

Multivariate analyses revealed that fQRS complexes are an associated risk factor for developing cardiac events in extracardiac sarcoidosis.⁷⁰

Brugada syndrome

In Brugada syndrome, the presence of fQRS and early repolarization correlates with increased risk in several studies.^{84,85} On multivariable analysis, a history of VF and syncope episodes, an inferolateral early repolarization pattern, and fQRS were independent predictors of documented VF and SCD.⁴⁶ In a large multicenter, observational, long-term study, the ECG findings that were useful for predicting adverse outcome in patients with ARVC/D were: T wave inversion in the inferior leads, a precordial QRS amplitude ratio of 0.48 or greater, and fQRS.⁸⁶

Pathognomonic Features

Despite being characteristic of ARVC/D, epsilon waves are not pathognomonic, because

they have been described in other pathophysiological conditions associated with myocardial damage.

Physiologic Epsilon Waves

Ventricular hypertrophy in elite endurance senior athletes

Epsilon wave was found in 3 senior athletes (1.57%) from 347 elite endurance athletes (seniors, 190; juniors, 157), with a mean age of 20 years and 200 subjects with a mean age of 21 years, belonging to a control group of 505 normal sedentary population.⁸⁷ Bizarre QRS, ST-T patterns suggestive of abnormal impulse conduction in the right ventricle, including the right outflow tract, associated with prolonged QTc interval in some cases were observed in highly trained endurance athletes. The genetic analyses, negative in most athletes, identified surprising mutations in SCN5A and KCN genes in some cases.⁸⁷

Pathologic Epsilon waves

1. Giant cell myocarditis: Epsilon waves are a major diagnostic criterion for ARVC/D, but also other cardiac pathologies such as giant cell myocarditis can cause severe right

- ventricular conduction disturbances manifesting with epsilon waves and VT on surface ECG.⁸⁸
2. Sickle cell anemia.⁸⁹
 3. Brugada syndrome: It is believed that Brugada syndrome and ARVC/D are different clinical entities with respect to the clinical presentation and the genetic predisposition. The coexistence of these 2 relatively rare clinical entities was also reported.⁹⁰ In clinical practice, there may be cases where the dividing line is not so clear.^{91,92} Epsilon waves seem to be rare in patients with Brugada syndrome and were found in 2 of 47 patients by Letsas and colleagues,⁹³ and in 1 patient from a total of 12 unrelated index patients with Brugada syndrome that were included in the study by Yu and colleagues.⁹⁴
 4. Idiopathic VF in the absence of Brugada syndrome phenotype with loss-of-function mutation of the SCN3B-encoded sodium channel beta-3 subunit.⁹⁵
 5. During exercise testing or treadmill stress testing in asymptomatic gene carriers: Depolarization abnormalities during exercise testing in asymptomatic gene carriers were found to develop more frequently compared with healthy controls; epsilon waves appeared in 4 of 28 (14%).⁹⁶ Recently, Adler and colleagues⁹⁵ uncovered epsilon waves in asymptomatic patients carrying mutations in the PKP2 gene. This finding suggests that exercise testing may be valuable for the diagnosis of ARVC/D and that exercise-induced epsilon waves may be

found in various genetic subtypes of this disease.

6. Postoperative tetralogy of Fallot.⁹⁷
7. Right ventricular myocardial infarction.⁹⁸
8. Inferior or lateral old (remote) posterior myocardial infarction.⁹⁹
9. Infiltrative diseases, such as cardiac sarcoidosis.¹⁰⁰ Increasing evidence suggests that cardiac sarcoidosis might produce the pathologic substrate of myocardial inhomogeneity causing epsilon waves. Therefore, differentiating these 2 entities is of paramount clinical importance.¹⁰¹

Epsilon Wave and Relationship to Ventricular Tachycardia

The presence of these waves indicate slow and fragmented conduction, which favors reentry circuits, which in turn result in sustained VT runs with complete left bundle branch block morphology, suggesting origination in the right ventricle.^{89,102} The tracing should run at a double velocity (50 mm/s) and voltage (20 mm/s) to compare the duration of QRS complexes (QRSd) in different leads, as well as to try to record epsilon waves. **Fig. 18** shows more clearly the epsilon wave with double velocity and double voltage. The rate of widespread T wave inversion (exceeding V3) was significantly higher in patients with epsilon waves than in those without. Because these waves are of relatively low voltage, they may go undetected by S-ECG or unnoticed by the interpreter.⁹⁹

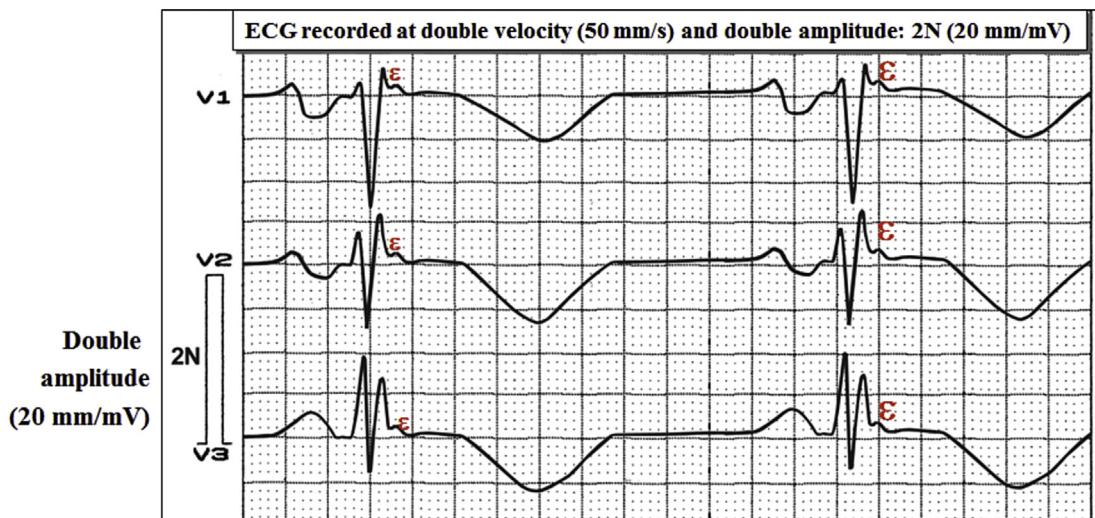


Fig. 18. Epsilon wave with double velocity and voltage. ECG, electrocardiogram.

PRESENCE OF VENTRICULAR LATE POTENTIALS USING HIGH-RESOLUTION OR SIGNAL-AVERAGED ELECTROCARDIOGRAPHY

Sufficient data are available to recommend the use of high-resolution or SA-ECG in patients recovering from myocardial infarction without bundle branch block to help determine the risk for developing sustained ventricular tachyarrhythmias.⁴⁰ However, no data are available about the extent to which pharmacologic or nonpharmacologic interventions in patients with LPs have an impact on the incidence of SCD. Therefore, controlled, prospective studies are required before this issue can be resolved.

Value of the Signal-Averaged Electrocardiogram in the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

SA-ECG or high-resolution ECG is observed more frequently by using this method in cases of ARVC/D. In ARVC/D, SA-ECG frequently is associated to LPs. The epsilon wave may be observed in surface ECG; however, it is seen much more frequently in SA-ECG. SA-ECG is used to detect LPs and epsilon waves in ARVC/D carriers. Patients with positive SA-ECG (presence of LPs) have a significantly increased risk of sustained VT and/or SCD in comparison with those with normal SA-ECG or branch block.

Electrocardiographic predictor of sudden death in left ventricular hypertrophy

The association of SCD/LVH diagnosed from the 12-lead ECG was first reported 47 years ago in a prospective study. A population-based study from Michigan showed an association of LVH by ECG with 98 coronary heart disease deaths (45 SCD events) observed over a 6-year duration, and predicted an SCD rate of 48 per 1000 over this time frame, compared with 2.6 per 1000 with a normal ECG.^{40,103,104}

Advantages of the electrocardiograph for the diagnosis of left ventricular hypertrophy

- Low cost.
- Easily available to perform at any medical facility globally.
- High specificity (close to 99%).
- Simple diagnostic criteria.
- Possibility of identifying ischemia, necrosis, arrhythmias, and associated dromotropic disorders immediately.
- Independent from the experience of the observer and the quality of the equipment.

- Irreplaceable in apical HCM when revealing the typical giant negative T waves from V2 to V5 accompanied by positive voltage criteria.
- Preparticipation screening is a life-saving and cost-effective strategy in young athletes in whom SCD is mostly caused by ECG-detectable myocardial diseases.¹⁰⁵ The addition of an ECG to preparticipation screening saves 2.06 life-years per 1000 athletes at an incremental total cost of \$89 per athlete and yields a cost effectiveness ratio of \$42 900 per life-year saved (95% CI, \$21 200–\$71 300 per life-year saved) compared with cardiovascular-focused history and physical examination alone.¹⁰⁶ However, controversies continue on the role and value of ECG screening in the preparticipation of athletes.

The main method to diagnose LVH is echocardiography, which allows measuring the thickness of the muscle of the heart. Two-dimensional echocardiography can produce images of the left ventricle. The thickness of the left ventricle as visualized in echocardiography correlates with its actual mass. A normal thickness of the left ventricular myocardium is from 6 to 11 mm (as measured at the very end of diastole). If the myocardium is more than 1.1 cm thick, the diagnosis of LVH can be made by echocardiography. Echocardiography, if available, should be the test of choice to assess for LVH. It is much more sensitive than ECG and can also detect other abnormalities such as left ventricular dysfunction and valvular disease.

Cardiac MRI is the gold standard test for LVH, because it is even more accurate and reproducible than echocardiography.¹⁰⁷ It can precisely estimate a patient's left ventricular mass and assess for other structural cardiac abnormalities. The use of MRI, however, is significantly restricted in clinical practice owing to its high cost and limited availability and expertise to evaluate the test.

A QRS-T angle between 90° and 180° (QRS/ST-T angle broadening: ST-segment depression and T wave inversion in the left precordial leads and in the limb leads in which major QRS deflections are upright) is associated with an increased risk of SCD, independent of the LVEF¹⁰⁸ (Fig. 19). Prolonged QTc is an independent marker of SCD among subjects with LVH.¹⁰⁹ In the setting of aggressive antihypertensive therapy, a prolonged QRSc identifies hypertensive patients at higher risk for SCD.¹¹⁰ The presence of cardiac sympathetic hyperactivity may predict SCD in the asymptomatic hemodialysis patients with LVH.¹¹¹

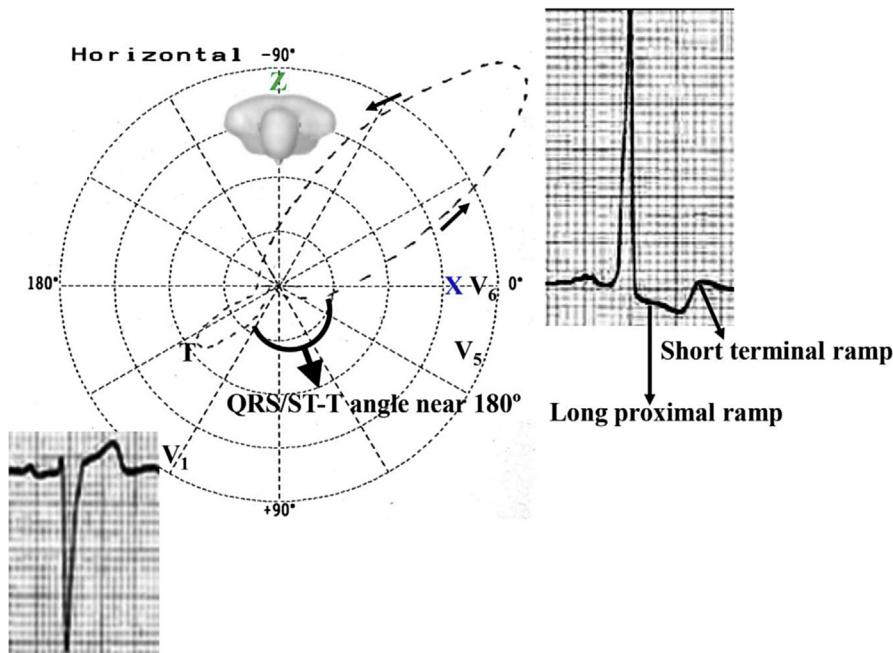


Fig. 19. Left ventricular strain pattern. Deviation of the ST-segment and the Twave/loop in the opposite direction to the main QRS vector causes widening QRS amplitude and wide QRS/T angle between 90° and 180°. This is called left ventricular strain pattern. A $^{QRS}_{ST-T}$ angle of 90° or greater and a Twave upright in V2 and more negative than -0.1 mV in V6, and ST segment depression with upward convexity and Twave inversion in the left precordial leads.

SUMMARY

Although the ECG was invented more than 100 years ago, it remains the most commonly used test in clinical medicine. It is easy to perform, relatively cheap, and results are readily available. Interpretation of the ECG, however, needs expertise and knowledge. Amazingly, new data, phenomenon, and syndromes are continuously discovered by the ECG. It is important to differentiate between normal and abnormal ECGs first and then try to correlate the findings with clinical pathologies. Today, the ECG is also an integral part of the screening model for a variety of conditions such as channelopathies, athletes, preoperative risk profile, and remains the cardiologist's best friend.¹¹²

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