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The value of the 12-lead electrocardiogram in the prediction of sudden cardiac death

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Sudden cardiac death (SCD) can be caused by several clinical conditions, overt or misconceived, which recognize different pathophysiologies determining the development of fatal arrhythmic events. In the various forms of structural heart disease such as ischaemic heart disease, cardiomyopathies (e.g. hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy), channelopathies (e.g. long-QT syndrome, congenital short QT, Brugada syndrome, early repolarization (ER) syndrome, and idiopathic ventricular fibrillation) but also in the apparently healthy subject, the 12-lead electrocardiogram (ECG) has proved, over the years, to be a reliable and readily available method for stratifying the risk of adverse arrhythmic events and consequently SCD. Several electrocardiographic markers have been shown to be associated with adverse outcomes in different types of patients. Although with different sensitivity and specificity in each clinical condition, depolarization abnormalities, such as QRS fragmentation, Q waves, QRS duration, left posterior fascicular block, low QRS voltage, and left ventricular hypertrophy and similarly repolarization abnormalities as ER pattern, T wave alternans, QT interval, and QT dispersion, have shown significant efficacy in predicting SCD. Despite the advancement of techniques especially in the field of imaging, the correct interpretation of the 12-lead ECG remains, therefore, an effective tool for assessing the possible prognostic outcome in terms of arrhythmic risk and SCD in different types of patients.

General consideration

Sudden cardiac death (SCD) is a dramatic event that does not recognize a single possible cause but can be attributed to a multitude of triggers and underlying syndromes with different pathophysiology that are often not fully understood. Sudden cardiac death can be the ultimate expression of some overt structural heart diseases such as coronary artery disease (CAD), cardiomyopathies, myocarditis, and congenital heart disease. Even in patients without manifest structural heart disease, SCD could be

the worst expression of a primarily electric disease also known as channelopathies such as long-QT syndrome (LQTS), congenital short QT (SQTS), Brugada syndrome (BS), early repolarization syndrome (ERS), idiopathic ventricular fibrillation (IVF), and many others.

Regardless of the underlying pathology, whether it is known or not, we need to identify markers that can predict the risk of SCD in different patient population. Despite the advancement of our knowledge and modern imaging methods, the electrocardiogram (ECG) has been and continues to be considered one of the main screening methods that can provide useful information in assessing arrhythmic risk in different types of patients. It has obviously not been possible to identify a single electrocardiographic marker that can satisfactorily stratify arrhythmic risk, but

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several parameters have been evaluated (Table 1), on surface ECG, over the years that are certainly useful for the overall evaluation of different index cases.

Depolarization abnormalities

QRS fragmentation

In the absence of bundle branch block with a QRS duration (QRSd) <120 ms, the evidence of an additional R′, an RSR′ with or without Q waves, or the presence of notching of R wave or nadir of S wave in two contiguous leads enable us to identify a narrow fragmented QRS (fQRS) (Figure 1). Similar ECG patterns could be applied to a QRS with a duration >120 ms. Indeed, the diagnosis of broad fQRS can be made in the presence of a wide QRS associated with the evidence of two R waves in the context of an RSR morphology, or with the evidence of more than two notches at the level of the R or S waves in two contiguous leads. The first accepted classification of the different patterns of fQRS was proposed in 2007 and was subsequently followed by some modifications that enhanced the amplitude of the deflections than their number and morphology. The fQRS is the expression of slow conduction or disarray of the electrical stimulus through the myocardium; indeed, it has been related to myocardial scarring, ventricular aneurysm, or the reduction of left ventricular (LV) longitudinal strain at the speckle tracking evaluation. Although not specific to any disease, in particular, fQRS has been

investigated as a prognostic marker of SCD in numerous diseases such as ischaemic cardiomyopathy, dilated cardiomyopathy (DCM), and arrhythmogenic cardiomyopathy (ACM). Strauss et al., in 2008,[1] demonstrated a clear correlation of some QRS characteristics, such as QRS amplitude, duration, and notching of each (Q, R, S) wave, with the presence of ventricular myocardial scar on cardiac magnetic resonance (CMR) in patients with either ischaemic or non-ischaemic cardiomyopathy (NICM). In 2015, Bulut et al.[2] have shown that during cardiac rehabilitation in ST elevation myocardial infarction (STEMI) patients, the number of fQRS diminished as a likely sign of an improved conduction velocity through the peri-infarct zone. A recent meta-analysis by Rosengarten et al.[3] demonstrated that fQRS was associated with an approximately two-fold risk of SCD in patients with ischaemic cardiomyopathy and NICM. In 2014, Kang et al.[4] demonstrated that fQRS in inferior leads was significantly associated with major adverse events and ventricular arrhythmias (VAs) in patients with hypertrophic cardiomyopathy (HCM). Several studies in patients with BS have concluded that fQRS could be used as a helpful predictor of ventricular fibrillation (VF) and appropriate device intervention in these patients.[5] The FinGesture study, which analysed subjects who died of witnessed SCD, demonstrated a higher prevalence of anterior fQRS on previous ECGs, in patients who died suddenly during physical activity than in patients who died suddenly at rest.[6] Finally, Narayanan et al.[7] demonstrated that fQRS, especially in lateral leads, was associated with an increased risk of SCD among obese/overweight subjects in the general population.

The main limitation of the fQRS is that it is frequently observed in apparently healthy individuals. Terho et al.[8] noted inferior fQRS in 15.6%, anterior in 2.9%, and lateral in 0.5% in a general population sample of over 10 000 middle-aged subjects without known cardiac disease. We can speculate that fQRS could be related to other causes in the patients without late gadolinium enhancement (LGE) (interstitial fibrosis, different geometry of LV, and anisotropic conduction). Further studies should explore the potential prognostic utility of the different fQRS morphologies, distinguishing malignant phenotypes caused by myocardial scarring from benign normal variants.

Q waves

Pathological Q waves are defined as Q waves in at least two continuous leads meeting the following criteria: an amplitude greater than 20 ms in duration in leads V2 and V3,

Table 1. ECG markers of sudden cardiac death

| Depolarization abnormalities	Repolarization abnormalities
• Fragmented QRS	• Early repolarization pattern
• Q waves	• T peak–T end
• QRS duration	• T wave alternans
• Left posterior fascicular block	• QT interval (long-QT and short-QT)
• Low QRS voltage	• QT dispersion
• Left ventricular hypertrophy	
• Signal-averaged electrocardiogram and very late potential	
• Epsilon wave	
• Brugada pattern	
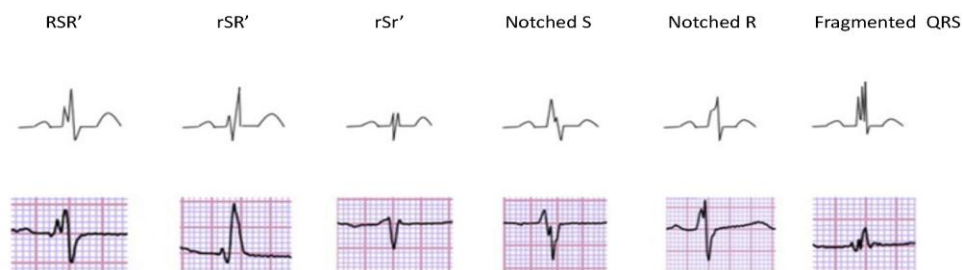
Figure 1 QRS fragmentation morphology.

≥40 ms and at least 0.1 mV deep in lead III and ≥30 ms and deeper than 0.1 mV in other leads. It is well known that pathological Q waves in patients with ischaemic cardiomyopathy represent the ECG signs of myocardial scar and, subsequently, they could be the mark of non-viable myocardium the extent of which affects the patient's prognosis. There are also several evidence that Q waves could also be the ECG expression of cardiomyopathies. Chen *et al.*[9] demonstrated that the presence of pathological Q waves in lead D III may distinguish patients with HCM from athletes regardless of other ECG markers. The prevalence of pathological Q waves in HCM patients reaches 42% and 10 25% in DCM. The presence of Q waves in cardiomyopathies is also related to the evidence of LGE on CMR but with a scarce correlation with the LGE location and extent in contrast to what is seen in ischaemic cardiomyopathy. Holmström *et al.*[10] demonstrated that in more than 5000 autopsied SCD victims, the presence of pathological Q waves was associated with the evidence of myocardial fibrosis.

Recently, Pelli *et al.*[11] examining the ECGs from 1477 implantable cardiac defibrillators (ICDs) patients and 700 control patients, found that pathological Q waves were a strong ECG predictor of ICD benefit in primary prophylactic ICD patients. These results provide potentially useful, non-invasive early recognition of patients with fibrotic cardiomyopathy (ischaemic or not) and its related risk for SCD.

QRS duration

Despite conflicting data from various trials, QRSd is recognized as one of the electrocardiographic predictors of SCD. QRSd expresses delayed depolarization and impulse propagation through the myocardium. It was initially recognized that prolonged duration of QRS complex >120 ms in HCM carries a higher risk of adverse cardiovascular events when compared with a QRS interval <120 ms in this patient population. Similarly, in the LIFE study that enrolled hypertensive patients, it was demonstrated that even a 10 ms increase in QRSd, entailed a higher risk of SCD.[12] It is well demonstrated that in heart failure (HF), especially in patients with left conduction delay, the wider the QRS interval the higher the risk of SCD.[13] We also have to consider that for QRS interval >200 ms, there is also a higher defibrillation threshold at the time of ICD implantation. Data derived from a few trials use a QRSd ≥ 110 ms as a reference value of wide QRS even without criteria for the diagnosis of complete or incomplete bundle branch block, for the prediction of SCD in the general population.[14] These data were recently confirmed in a large population study composed of three population cohorts of different eras, re-evaluating the ECG of each patient, and it was shown that the QRSd was consistently associated with SCD even with more statistical significance compared with QTc and JTc intervals.[15]

Left posterior fascicular block

The electrocardiographic characteristic to correctly diagnose a left posterior fascicular block (LPFB) are QRSd <110 ms; QRS frontal axis between 100° and 180°, rS pattern in leads I and aVL; and qR morphology in leads II, III, and aVF (*Figure 2*). We also have to underscore that to make a correct electrocardiographic diagnosis of LPFB,

Figure 2 Left posterior fascicular block.

some clinical conditions such as right ventricular (RV) hypertrophy, a vertical heart in long-limbed subjects, and a large lateral infarction must be excluded. The LPFB is the rarest conduction disturbance within the intraventricular conduction system. This statistic is easily explained, on the one hand, by the anatomical conformation of the fascicle itself, which is shorter and wider than the right bundle, and the anterior fascicle, which being thinner and longer is more exposed to blockages in their course, and on the other hand, by the rarer exposure of the posterior fascicle to various pathophysiological processes. Indeed, the posterior fascicle lies in the posterior portion of the inflow tract of LV without any other dangerous structure. This site is much less prone to the effects of turbulent flow than the outflow tract, and furthermore, the left posterior branch benefits from a double coronary blood flow supply from the posterior and anterior descending coronary arteries. Due to this peculiar conformation, when LPFB occurs, it is usually an expression of extensive damage to the conduction system that has usually already involved other intraventricular fibres. In association with other conduction delays, the LPFB may be the forewarning of extensive damage to cardiac structure. It has, however, been seen that in several cardiomyopathies the portion of the ventricular myocardium affected early by pathology, as witnessed by the presence of LGE on magnetic resonance imaging, is precisely the basal infero-posterior region supplied by the posterior fascicle. Based on this hypothesis, Calò *et al.*, in a retrospective study, analysed ECGs of young patients who had died of SCD or had suffered aborted cardiac arrest (ACA) and compared them with tracings of apparently healthy patients, focusing their attention on the hypothesis that LPFB could be an early expression of structural pathology. The prevalence of LPFB in patients with resuscitated SCD was 100-fold higher than in the control group, and in patients with ACA, CMR analysis showed structural pathology in all of the subjects (mainly LGE in the inferolateral and infero-septal location). Perhaps even more significant in the study was the evidence that in the control group (apparently healthy), those with evidence of LPFB also had evidence of LGE on CMR [performed for various reasons such as a family history of SCD and evidence of left ventricular hypertrophy (LVH)].[16] More recently Nyholm *et al.*[17] analyse ECGs from a large number of patients and they found that higher degrees of fascicular blocks were associated with increased risk of syncope, pacemaker (PMK) implantation, and complete heart block, but the association with death was negligible except for patients with LPFB. These data suggest a role

for LPFB in the early identification of patients at increased risk of SCD and with a possible underlying organic pathology gleaned by an easily available screening medium such as the ECG.

Low voltage QRS

Low QRS voltage (LQRSV) on ECG was initially defined as the sum of the S-wave amplitude in lead V1 and R wave in V5 or V6 ≤ 15 mm (Sokolow/Lyon index). Other definitions of LQRSV have been proposed and validated as, for example, the nadir-to-peak QRS amplitude <5 mm in all the limb leads and <10 mm in all the precordial leads. To have a more reliable and sensitive quantification of LQRSV, it can also be used as the combined definition of QRS amplitude in each limb lead <5 mm and a Sokolow-Lyon index ≤15 mm. LQRSV can be found in isolation in precordial leads, limb leads, or in both (*Figure 3*). The presence of LQRSV was described in different groups of patients.[18,19] LQRSV has been extensively studied in ACM. Initially, it was seen that LQRSV at the level of the right precordial leads and even more when the precordial QRS amplitude ratio was applied (the ratio between the sum of QRS amplitude in leads V1–V3 and the total sum of V1–V6 QRS amplitude), with a value ≤0.48, was found to have a linear relationship with RV dilation and dysfunction in addition to a large scar area. With the evolution of the diagnosis and definition of ACM, LQRSV, especially in limb leads, has been shown to correlate with biventricular involvement, LV involvement, and the extension of the LGE on CMR.[20] As assessed by trials, these are all negative prognostic markers in the evolution of the pathology both in a proarrhythmic and mechanical dysfunction sense. In cardiac amyloidosis, the deposition of proteinaceous material in both the light chain associated form (AL) and the transthyretin-associated form (ATTR wild type or mutated) fictively increases the thickness of the heart walls, which, instead, lose their muscle tissue component. For this reason, peculiar electrocardiographic patterns such as a pseudo-infarct pattern and the presence of LQRSV especially when considered in relation to the calculated cardiac mass can be noticed. LQRS is more frequent in the AL form compared with ATTR (60% vs. 25%), probably due to the overt prevalence of cardiac involvement in the AL amyloidosis. The prognostic value of LQRSV was confirmed in both amyloidosis forms by Mussinelli *et al.*[21] who demonstrated how the presence of LQRSVs in peripheral

leads correlated with more severe cardiac involvement and consequently to adverse outcomes. In HCM, the presence of LQRSV was associated with the end-stage evolution and had a good correlation with the extent of fibrosis assessed by LGE on CMR. Based on these observations, Biagini *et al.*,[22] in their large cohort study, claimed that LQRSV was independently related to SCD in HCM patients. In patients with congestive HF due to dilated and hypokinetic LV, already in 1982, was described a classic electrocardiographic triad composed of LQRSV in limb leads with normal QRS precordial amplitudes or LQRSV in limb leads with high QRS complexes in the precordial leads with poor R-wave progression. These observations were confirmed later with the significant association of LQRSV on ECG in patients with DCM who experience LV reverse remodelling.[23] Even in Takotsubo syndrome, it has been shown that the presence and persistence of LQRV, expressing oedema and/or fibrosis, could predict the possibility of recovery of ventricular systolic function earlier than other markers.[24] Finally, it has been shown that in so-called non-ischaemic left ventricular scar (NLVS), which appears to be responsible for ~1–3% of SCDs, the presence of LQRSV is a frequent finding. NLVS is characterized by idiopathic fibrosis (autopsy or CMR detection) frequently localized at the posterolateral region of the LV in the sub-epicardial or mid-wall region. In different trials, it was demonstrated that LQRSV was the commonest finding on surface ECG of patients with the diagnosis of NLVS performed by CMR or by post-mortem examination.[25] It can, therefore, be speculated that LQRSV could be an early indicator of structural LV pathology.

Left ventricular hypertrophy

The association of LVH diagnosed through ECG criteria and SCD has been known for about 50 years. The pathophysiological mechanisms of LVH leading to arrhythmogenesis and SCD are due to an increase in myocardial cell size, without an increase in the myocardial cell numbers. This could lead to subendocardial ischaemia, fibrosis, diastolic dysfunction, myocardial remodelling, myocardial disarray, and arrhythmogenesis. Due to the augmentation of LV mass, there may be prolongation of action potential (AP) duration which facilitates the occurrence of re-entrant arrhythmias. In LVH, there is also an electrical remodelling due to impaired ion channel and connexin expression. Moreover, in hypertrophied cells, there is an increase in intracellular calcium that facilitates delayed afterdepolarization and triggered activity. These elements lead to an increased anisotropy and excitability in LVH which increases the risk of VAs. Various electrocardiographic criteria expressing LVH have been validated and confirmed by echocardiography or CMR. The most widely used are the Sokolow–Lyon amplitude calculated as SV1 + RV5 or SV1 + RV6 with a cut-off for LVH that is ≥3.5 mV; Cornell amplitude calculated as SV3 + RaVL with a cut-off for LVH that is >2.0 mV in women and >2.8 mV in men; R amplitude in lead aVL with a cut-off for LVH >1.1 mV; Peguero–Lo Presti amplitude as the deepest S among all 12 leads + SV4 with a cut-off for LVH that is ≥2.3 mV in women and ≥2.8 mV in men. Another marker of LVH is the ST strain, defined as ≥1 mm concave down-sloping ST-segment depression with asymmetrical T-wave inversion in the lateral leads. This pattern can be found both
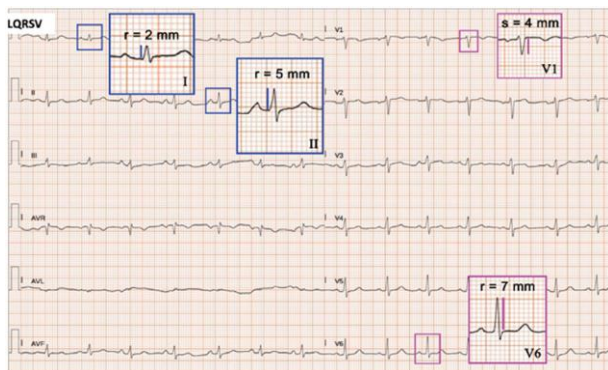

Figure 3 Low QRS voltage.

in a form of hypertrophy secondary to an increased after-load [e.g. arterial hypertension or aortic stenosis (AS)] and in congenital forms such as in HCM.[26,27] There are also more peculiar signs of hypertrophy such as in apical forms of HCM in which there are often giant negative T waves in V2–V5 leads. ECG signs of LVH are associated with adverse outcomes. Shah *et al.*[28] in 2014 demonstrated that in patients with AS and LVH confirmed by echocardiography and CMR, the strain pattern on surface ECG was correlated with mid-wall fibrosis detected by LGE on CMR and it could be a good predictor of adverse outcomes. In a large registry that analysed the various ECG indices of LVH in relation to SCD, it was shown that all signs of LVH expressed by the above-mentioned scores were associated with increased SCD except for R voltage in aVL during an extended follow-up of almost 14 years.[29] In 2020, in a trial of 42 young HCM patients, some ECG characteristics were studied and summarized in an ECG score which also included QRS voltage amplitude. In the trial was demonstrated that an ECG score >2 points was related to LGE on CMR and consequently with HCM prognosis.[30]

Signal-averaged electrocardiogram and very late potential

The signal-averaged electrocardiogram (SAECG) is an amplified ECG that can detect abnormal microvolt-level potentials that can normally not be seen on a surface ECG. These microvolt potentials are the so-called very late potentials (VLPs) because they occur during the terminal portion of the QRS complex. These VLP are the manifestation of a portion of slow conduction. The slow conduction determines a delayed depolarization through the myocardium that could be the substrate for VA due to a re-entry circuit. It is well known that VLP has been demonstrated to predict the inducibility of ventricular tachycardia (VT) in the electrophysiological laboratory. VLPs have proved to be a useful tool in predicting malignant VA in patients with BS.[31] Even though with some contrasting evidence, it was noticed that the association of SAECG and reduced ejection fraction have the potential to identify patients at risk of SCD even in the context of a defined syndrome.[32] Even in patients with recent myocardial infarction (MI), SAECG achieved contrasting results in predicting survival and arrhythmic risk stratification. In the evaluation of results regarding SAECG, we must consider the difficulties in acquiring a correct record of the ECG trace which have to last for almost 5–20 min to have a correct identification of threshold amplitude signals. For these reasons, SAECG, which was previously considered as a minor criterion in the diagnosis and as a parameter that could also potentially be used in a prognostic sense in arrhythmogenic right ventricular cardiomyopathy (ARVC), has instead been removed as a criterion in the latest ARVC consensus statement.[33]

Epsilon wave

The epsilon wave is defined as a reproducible, low-amplitude positive deflection at the end of the QRS where the ST segment begins. It is the manifestation of a late depolarization of the free wall of the RV myocardium, which is mainly recorded in leads V1–V4. The epsilon wave may be isolated but two or more waves may also be present at the QRS complexes of the same lead. The epsilon wave has always been considered as an electrocardiographic marker for the diagnosis of ARVC (previously as a major criterion currently considered as a minor criterion).[33] The epsilon wave was also described in other structural cardiac conditions like inferior acute MI in association with the involvement of the right ventricle, Uhl's anomaly, Fallot tetralogy, giant cell myocarditis, BS, myocardial engagement of sickle cell anaemia, and cardiac sarcoidosis (CS). The presence of epsilon waves has also been found in endurance athletes or in relatives of probands with ACM often manifested during exercise tests. In these cases, subjects who had manifested an epsilon wave after exercise had positive genetics for mutations at the level of the sodium or potassium ion channels.[34] Authors agree that epsilon waves often represent the ECG manifestation of a fibro-fatty tissue or infiltration of myocardial tissue from which it derives slow conduction and consequently late depolarization prone to trigger VA through a re-entry circuit. Mainly in ACM but also in CS or BS, it was suggested that the presence of epsilon waves could have a prognostic impact on the development of arrhythmias.

Brugada pattern

Type 1 Brugada pattern is characterized by ST elevation of at least 2 mm with a downward convex morphology, followed by a descending negative T wave, with little or no isoelectric separation. The type 2 pattern has a 'saddleback' appearance with a high take-off ST-segment elevation of at least 2 mm, a trough displaying an ST elevation greater than or equal to 1 mm, and then either a positive or biphasic T wave. The cellular basis for this phenomenon is caused by a loss of function of Na^+ channels and/or a gain of function of I_{to} (potassium channels). I_{to} channel densities are heterogeneously distributed across the myocardial wall being much higher in the basal epicardium of the right ventricle outflow tract (RVOT). This produces a transmural voltage gradient that could be responsible for the presence of J point elevation on surface ECG. Reduction of I_{Na} could unmask the difference of entity in I_{to}, through the myocardial wall leading to premature repolarization, and focal AP shortening. Contributing to this is also the inhibition of I_{CaL} which is voltage regulated. In alternative to the repolarization hypothesis, experts advocate depolarization abnormalities related to ionic channelopathy and structural abnormalities in the RVOT such as the presence of fibrosis or the reduction in the expression of connexin-43 contributing to the arrhythmogenicity of Brugada pattern. The reduction in I_{Na} linked to an *SCN5A* mutation leads to a reduction in the upstroke velocity of AP Phase 0, and slow electrical conduction that involves the RVOT. Both the depolarization and repolarization abnormalities contribute to an increase in the transmural gradient of the membrane potential. The heterogeneity in the electrical conduction may lead to VA due to a Phase 2 re-entry mechanism. The presence of spontaneous type 1 Brugada pattern is considered diagnostic of BS. In type 2, on the other hand, the diagnosis of BS requires a clinical–anamnestic correlation and/or the need to unreveal a spontaneous type 1 by means of a prolonged ECG recording or to elicit the presence of the pattern by means of a pharmacological test.

It has also been shown that there is a difference in the risk of SCD and adverse arrhythmic events in patients carrying a spontaneous type 1 pattern compared with those who have a drug-induced form. In particular, a spontaneous type 1 ECG resulted in a two- to six-fold relative risk for serious adverse events (SAEs). In a recent review involving 4099 patients, Rattanawong et al.[35] found that patients with spontaneous type 1 ECG had a 2.4% annual incidence of SAEs compared with 0.65% for those with drug-induced Brugada patterns. Similarly, data from the Brugada-RISK group demonstrated that patients with a spontaneous type 1 ECG pattern had a lower mean reduced survival compared with patients without this pattern (8.8 vs. 9.8 years; $P < 0.001$) with a heart rate (HR) of 3.80. The 5-year predicted risk of an event in patients with spontaneous type 1 ECG pattern and none of the other study identifiable risk factors was 5.9%. In the risk stratification of SCD or SAEs in BS, many other clinical and electrocardiographic variables that better identify patients at major risk are included (e.g. family history, syncope, early repolarization pattern (ERP) pattern in limb leads, etc.),[36] but the presence of a spontaneous type 1 pattern represents albeit downsized compared with the past one of the major determinants of the arrhythmic risk.[37]

Repolarization abnormalities

Early repolarization pattern

The electrocardiographic characteristic of ERP is the presence of J point elevation with an end-QRS notch or slur (the J wave) on the downslope of a prominent R wave ≥1 mm involving ≥2 leads (excluding V1–V3), where the QRSd is <120 ms. Departing from the classical definition of ERP, several electrocardiographic patterns have been identified as variants of the classical form that show a widening of the terminal portion of the QRS (the so-called reverse delta wave or lambda wave) or a notch of the J point without the latter being elevated. Depending on different morphologies of the ST segment following the J point, we can define a 'malignant' or 'benign' early repolarization (ER) (Figure 4). The malignant form is represented by a down-sloping or flat ST segment; the benign one is characterized by an upsloping ST segment more evident in infero-lateral leads. Other ECG peculiarities of high-risk ERP are the presence of a J point elevation >2 mm and a dynamic change in ST morphology, convex upstroke ST segment, lambda wave shape, low T-wave voltage (≤10% of the R wave in the same lead), widespread J waves across the majority of the leads, reciprocal images on the opposite leads, and a coexisting known cardiac disease. Pathophysiology studies have demonstrated a complex relationship between transient outward potassium currents (in Phase 1 of the myocardial cell AP) and calcium currents (between Phase 1 and Phase 2) of the myocardial cell AP as well as an involvement of the sub-epicardial Purkinje fibre network in the genesis of ERP and the resulting arrhythmias. Genetic studies in patients with IVF and evidence of ERP on ECG have also demonstrated several mutations in potassium and calcium channels as potentially pathogenetic. Not all authors agree with the definition of ER, but some argue that we should talk about late depolarization or more generally 'J waves'. ERP was previously considered a benign finding typical of young men, athletes, and more prevalent in dark-skinned population than in 2008 Haïssaguerre et al.[38] reveal that in patients with a history of IVF there was an increase incidence of ERP. In agreement with this evidence is the definition of ERS, the diagnosis of which can be made in the presence of an ECG pattern of ERP in patients with resuscitated cardiac arrest due to VF or polymorphic ventricular tachycardia (PVT) in the absence of any other cause. Alternatively, post-mortem diagnosis can be made in patients who died from SCD with a negative autopsy and by reviewing the patient's ECGs that should show the pattern of ERP. In 2016, Mellor et al. analysed the ECG of first-degree relatives of subjects who died from a sudden arrhythmic death syndrome (SADS) and compared them with matched controls. They show an increased prevalence of ER in SADS family members compared with controls irrespective of the underlying arrhythmic family syndrome.[39] These data
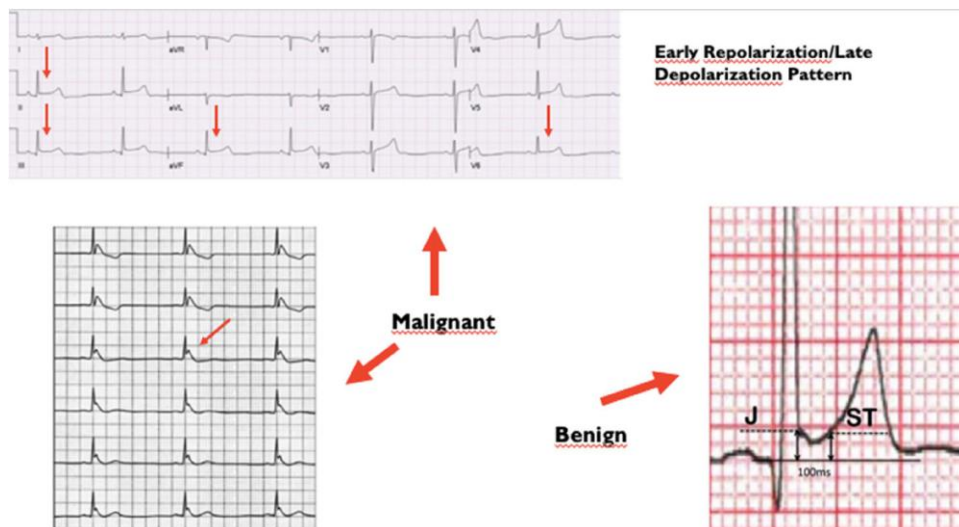

Figure 4 Early repolarization/late depolarization pattern.

suggest that the feature of ER or late depolarization encountered could have the potential to better stratify the arrhythmic risk in patients. In ischaemic heart disease, a higher prevalence of ERP has been demonstrated in patients with CAD than in control groups, and it has also been shown that the presence of ERP increases the risk of VF within 48 h from acute MI.[40] In HCM, J-wave patterns such as notch or slur of the QRS were associated with increased LV mass on CMR and with a higher incidence of major cardiac events.[41] Finally, even in patients with BS, a recent meta-analysis showed that ERP in the infero-lateral leads conferred an approximately five-fold increased risk of major arrhythmic events compared with patients who did not present this pattern on ECG.[42]

T peak–T end

The interval from the peak of the T wave from the end to the T wave was shown to be associated with the dispersion of the repolarization across the three layers of the heart wall, and consequently, the lengthening of this interval could predispose to the occurrence of VA probably due to a mechanism of Phase 2 re-entry. On surface ECG, the T peak–T end (Tpe) interval is usually measured in precordial leads. The accepted normal value in men is 94 and women is 92 ms. Although not fully validated in all subpopulations of patients, there is a common consensus that amplification of this interval above 100 ms is pathological. Even if some studies conducted in the general population and in patients with known cardiovascular disease have been questioned, the validity of the peak T end as a risk marker for SCD, over the years, various evidence have built up on the value that this ECG parameter can assume. In 2007, it was demonstrated, in a population of patients with congenital or acquired long-QT, that the best single discriminator for the risk of torsade de pointe (TdP) in these patients was a Tpe interval longer than 117 ms.[43] In the same way, in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI), patients with pre-pPCI Tpe interval above 100 ms were associated with increased mortality.[44] In patients with LV dysfunction and a left ventricular ejection fraction $\leq$ 35% who had an ICD in primary prevention, Tpe with a mean value of 107 ms was associated with an increased risk of VT/VF and mortality.[45] However, Tpe is subject to variation with HR, as well as having substantial inter-individual measurement variability. Therefore, over the years, it has been hypothesized to normalize the Tpe by dividing it by the measure of QT interval as an expression of the duration of the AP to improve the predictive value of the Tpe itself with regard to SCD. The optimal ratio was calculated between 0.17 and 0.23. In patients with BS undergoing electrophysiological study, a high Tpe/QT ratio was associated with VT/VF inducibility.[46] Similar results occurred in STEMI patients undergoing pPCI, in whom a Tpe/QT ratio $\geq$ 0.29 was associated with major adverse cardiovascular events during follow-up.

T wave alternans

T wave alternans (Twa) is a macroscopic beat-to-beat variation of T wave on the same lead. Variability can be in polarity, shape, and morphology, at the level of the ST-T wave. It was also described as the micro-Twa that detects Twa signals as small as one-millionth of a volt. Twa could

be a frequent and not definitely pathologic finding with elevated HR but is always pathological at an HR < 110 b.p.m. The limitation of this parameter is that it is considered useful only in patients with a narrow QRS (<120 ms). The presence of Twa is attributed to the dispersion of repolarization due to an alteration in calcium cycle handling and its interaction with late potassium current. The alteration in AP could predispose to the development of VA. The phenomenon of the Twa was first described in a small cohort study of LQTS patients in which Takasugi *et al.*[47] demonstrated that microvolt Twa was more prevalent in patients with a history of TdP. In patients with a recent MI, the evidence of Twa was a strong predictor of arrhythmic events if measured 30 days after the event. In MASTER I trial that analyses a population composed of 575 post-MI patients with LV systolic dysfunction, Twa was not associated with VA but was associated with a two-fold increase in total mortality.[48] Even if the SCD-HeFT substudy failed to demonstrate the utility of Twa in the prediction of arrhythmic events in HF patients, other trials demonstrated that in HF patients there was a strong correlation of Twa with SCD in primary prevention but there was a minimal reliance on ICD endpoints (e.g. appropriate shock).[49,50]

QT interval and QT dispersion

The QT interval is the interval that is measured between the first visible wave of the QRS complex up to the last recognizable portion of the T wave. The correct point is the end of the T wave which is defined as the return of the latter to the T-P baseline. The QT interval represents the time between ventricular depolarization onset and repolarization offset. Both short- and long-QT intervals can cause a variety of life-threatening VA. Several mathematical formulas have been proposed for the correction of the QT interval according to HR. The most commonly used formulas are Bazett's and Fridericia's. The QT interval could be influenced by many variables such as sympathovagal activity, electrolyte imbalances, drugs, and cardiac and metabolic diseases. The accepted normal range of the QT/QTc interval in adults varies between 350 ms and ~460 ms. Other authors consider a QTc 'borderline' value to be QTc of 440 ms or greater. The earliest acquired evidence concerning the arrhythmogenicity of the increased QT interval comes, as a matter of course, from congenital LQTS. Indeed, it has been shown that there is a progressively increasing arrhythmic risk for each increase in the absolute value of the QT interval. In LQTS, the highest risk category corresponds to a QT interval $\geq$500 ms with an annual risk of adverse events of about 2% and an absolute risk 2–3 times higher than patients with an interval of <500 ms.[51] In an attempt to evaluate certain ECG parameters for arrhythmic risk stratification in BS, Tse *et al.*[52] demonstrated that in patients with VT or VF, the QT interval was on average longer than in patients who had not had arrhythmic events. In patients with STEMI, trials have shown that QT interval prolongation is a strong predictor of intra-hospital mortality and VA. In the study by Rivera-Fernández *et al.*,[53] the mortality in STEMI patients who had an increased QTc interval prior to hospital admission was 20% vs. 4.5% in patients with a normal QTc interval.

The short QT interval is a very rare condition (about 0.2% of the general population), found almost exclusively in the

form of the syndrome that takes its name. Indeed, the presence of a short QT interval, defined as a QT interval <330 ms or <360 ms in the presence of ACA or known family history (genetic or ECG evidence), allows the diagnosis of SQTS to be made. As mentioned above, the dispersion of the AP and the reduced adaptation of the QT interval to HR underlie the syndrome's strong arrhythmogenic tendency.[54]

QT dispersion is defined as the maximum—minimum QT intervals on the 12-lead ECG. The normal range for QT dispersion is 40–50 ms with a maximum of 65 ms. QT dispersion values greater than 65 ms identify a high risk of VA and SCD but probably only grossly abnormal values (>100 ms), outside the range of measurement error may potentially have practical value by reflecting abnormal repolarization. An increased QT dispersion reflects a different timing in ventricular AP throughout the myocardial wall and may be a marker of risk for SCD mainly due to the predisposition to TdP. The QT dispersion as a marker of altered propagation of the AP was implicated in the pathogenesis of the occurrence of VA in different conditions such as BS, LQTS, SQTS, catecholaminergic PVT, probably due to early after depolarization, Phase 2 reentry, and subsequent triggered activity. Even in HCM patients, Magrì et al.[55] demonstrated, in a population of 221 subjects during a follow-up of more than 4 years, that QT interval dispersion (with a cut-off of 93 ms) was associated with an increased risk of SCD calculated using the HCM Risk SCD score.

Conclusion

The ECG provides both diagnostic and prognostic information and, therefore, is a powerful diagnostic tool to prevent SCD. We believe that the renaissance of the ECG signs is necessary for helping cardiologists to properly judge ECG findings that can often save a life.

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Data availability

No new data were generated or analysed in support of this research.

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