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REVIEW

Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death

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Sudden cardiac death, frequently due to ventricular arrhythmias, is a significant problem globally. Most affected individuals do not arrive at hospital in time for medical treatment. Therefore, there is an urgent need to identify the most-at-risk patients for insertion of prophylactic implantable cardioverter defibrillators. Clinical risk markers derived from electrocardiography are important for this purpose. They can be based on repolarization, including corrected QT (QT_c) interval, QT dispersion (QT_D), interval from the peak to the end of the T-wave ($T_{peak} - T_{end}$), ($T_{peak} - T_{end}$)/QT, T-wave alternans (TWA), and microvolt TWA. Abnormal repolarization properties can increase the risk of triggered activity and re-entrant arrhythmias. Other risk markers are based solely on conduction, such as QRS duration (QRS_d), which is a surrogate marker of conduction velocity (CV) and QRS dispersion (QRS_D) reflecting CV dispersion. Conduction abnormalities in the form of reduced CV, unidirectional block, together with a functional or a structural obstacle, are conditions required for circus-type or spiral wave re-entry. Conduction and repolarization can be represented by a single parameter, excitation wavelength ($\lambda = CV \times$ effective refractory period). λ is an important determinant of arrhythmogenesis in different settings. Novel conduction–repolarization markers incorporating λ include Lu *et al.*' index of cardiac electrophysiological balance (iCEB: QT/QRS_d), [$QRS_D \times (T_{peak} - T_{end})/QRS_d$] and [$QRS_D \times (T_{peak} - T_{end})/(QRS_d \times QT)$] recently proposed by Tse and Yan. The aim of this review is to provide up to date information on traditional and novel markers and discuss their utility and downfalls for risk stratification.

Keywords Cardiac arrhythmia • Repolarization • Conduction • Depolarization • Dispersion • Risk stratification • Sudden cardiac death

Short- or long-QT intervals increase the risk of developing malignant ventricular arrhythmias

The opening and closing of ion channels located in the plasma membrane mediate inward and outward transmembrane currents, in turn determining the QT duration. This interval shortens with an increasing heart rate. Its interpretation therefore requires correction that can be made using by different formulae (*Table 1*). The most popular method is Bazett's formula, which is given by the QT interval divided by the square root of the RR interval.[1] The disadvantage of this method is that QT interval is overestimated at high heart rates and underestimated at low heart rates. Fridericia formula divides the QT interval by the cubic root of the RR interval, and works better for slow heart rates. Other methods include the Framingham and Hodges formulae. The AHA/ACCF/HRS Recommendations published in 2009 proposes an upper normal limit of a corrected QT (QT_c) interval of 450 ms for men and 460 ms for women, and a lower limit of 390 ms for both genders.[2,3] The newest European Society of Cardiology guideline produced in 2015 suggests upper and lower limits of 480 and 360 ms, respectively, for both males and females.[4] The risk of developing malignant ventricular arrhythmias increases at either extreme of the QT interval, as exemplified by the long- and short-QT syndromes (LQTS and SQTS).

The cellular origin of the T-wave has been the subject of intense debate for several decades.[5–7] The original theory was that its inscription is generated by a repolarization gradient between the cardiac apex and base.[8] Later work suggested that the distinct electrophysiological properties of ventricular cardiomyocytes from different regions, such as epicardium, mid-myocardium (M), and endocardium were responsible.[9] M-cells takes the longest to

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Table 1 Different methods for QT correction

QT correction method	Formula
Bazett	$QT/RR^{1/2}$
Fridericia	$QT/RR^{1/3}$
Framingham	$QT + 0.154\ (1000 - RR)$
Hodges	$QT + 105\ (1/RR - 1)$

repolarize compared with the remaining cell types, but whether this intramural repolarization delay occurs *in vivo* is controversial.[10] Indeed, it may be unmasked only under non-physiological conditions such as gap junction inhibition.[11]

Pre-clinical and clinical predictors of arrhythmic risk: the need for new indices

Pre-clinical animal models have been useful for the studying the mechanisms of cardiac arrhythmogenesis in a number of settings and provide a platform for testing the arrhythmogenic potential of pharmacological agents.[12–16] Experiments in these systems have demonstrated different pro-arrhythmic factors, such as reduced CV,[17] increased CV dispersion, increased or decreased action potential duration (APD),[18] increased transmural dispersion of repolarization (TDR) given by the maximum APD difference across the myocardial wall,[19,20] increased critical interval for re-excitation given by APD—effective refractory period (ERP) difference,[21] reduced λ,[17] and reduced λ-TRIaD (λ, triangulation, reverse use dependence, instability, and dispersion).[22] Abnormal cardiac dynamics, reflected by increased APD, ERP, or λ restitution gradients have also been associated with arrhythmogenesis.[21,23–26]

The difference between triggers and markers of arrhythmias and sudden death can be distinguished. Triggers refer to events that produce the electrophysiological abnormalities initiating arrhythmogenesis, such as sleep,[27] emotional stress, or exercise.[28] These may produce myocardial ischaemia that can promote slowed conduction, reflected in prolonged QRS_d, as well as TWA. Both prolonged QRS_d and TWA have been long recognized as a marker of sudden cardiac death.[29,30] Although both can generate arrhythmias, they are downstream of the triggering events detailed above.

Repolarization markers

Traditional clinical markers for arrhythmic risk prediction have largely focused on abnormal repolarization, of which QT and QT_c are archetypal examples.[31] However, the limitations of QT_c in predicting arrhythmogenicity led to the development of other markers, such as QT dispersion (QT_D),[32] the interval from the peak to the end of the T-wave[33] ($T_{peak} - T_{end}$), ($T_{peak} - T_{end}$)/QT ratio,[34] JT_{peak}/JT, ($T_{peak} - T_{end}$)/JT_{peak} and T_{peak}/JT ratios, principal component analysis (PCA) ratio,[35] and J- and T-wave heterogeneities.[36] Dynamic changes such as TWA,[37,38] microvolt TWA,[39] the restitution markers Regional Restitution Instability Index (R2I2), and peak electrocardiography (ECG) restitution slope (PERS)[40,41] (*Table 2*). These will be discussed in turn.

QT_c and QT_d

QT_c was originally devised for identifying patients suffering from cardiac ion channelopathies such as LQTS and SQTS, but its use has been extended to a wide range of clinical conditions such as heart failure,[31] diabetes mellitus,[73] and obesity.[74] Prolonged QT interval reflects prolonged APDs at the cellular level. This can lead to reactivation of the L-type calcium channels,[75] and subsequent development of early after depolarization and triggered activity. However, malignant arrhythmias such as *torsade de pointes* (TdP) can occur despite a normal or even a shortened QT interval.[22,76] Moreover, QT interval has a low sensitivity and specificity for a multitude of reasons, such as difficulty and inaccuracy in determining the end of the T-wave, and it is altered by both autonomic input and heart rate. QT_{peak} was studied as a potential marker because T_{peak} is easily determined compared with T_{end}.[77] However, it was not altered by exercise or the presence of heart failure and was therefore inferior to QT_c in risk prediction. It was also recognized that QT_c provided no information on the heterogeneity of repolarization across the heart, yet it is increased heterogeneities in repolarization that elevate arrhythmic risk. This can occur when APD prolongation is non-uniform across the myocardium or when discordant alternans are observed, both of which can produce unidirectional conduction block and re-entry.[24]

Therefore, QT dispersion (QT_D) was introduced for assessing arrhythmic risk in LQTS in clinical practice.[78] QT_D is defined as the maximum difference between QT intervals in two leads of the 12-lead ECG. A review found that normal subjects had a mean value of 33 ms (range 10–71 ms).[79] In otherwise healthy individuals, QT_D values >58 and >80 ms were shown to increase the risk of cardiovascular mortality by three- and four-fold, respectively, when compared with subjects with QT_D values <30 ms.[32,80] QT_D was found to be significantly longer in LQTS patients who developed TdP than those without TdP. However, logistic regression analysis showed that it was not a reliable predictor of arrhythmogenicity.[81] Similarly, in a cohort of patients with hypertrophic cardiomyopathy, neither QT_c nor QT_D distinguished mutation carriers for HOCM with SCD/ ventricular tachycardia (VT) from those without SCD/VT.[82] Nevertheless, QT_D was shown to be a prognostic marker for fatal and non-fatal cardiovascular events in diabetic patients, whether or not they were complicated by hypertension, and was better than QT_c in this regard.[83,84] In a 23-year follow-up study, it was found that QT_D was an independent predictor of cardiovascular morbidity and mortality in type 1 diabetes, but not type 2 diabetes.[73] Athletes undergoing exercise training showed increased QT_D associated with cardiac hypertrophy.[85] Whether this is associated with increased risk of ventricular arrhythmias has not yet been determined. Finally, non-linear measures of chaos in QT intervals have also been associated with increased cardiovascular mortality.[86]

$T_{peak} - T_{end}$ and $(T_{peak} - T_{end})/QT$

$T_{peak} - T_{end}$ is defined as the interval between the peak of the T-wave and the end of the T-wave, representing the dispersion of repolarization.[33] $T_{peak} - T_{end}$ was initially suggested as a marker for TDR, based on observations in coronary-perfused canine wedge

Table 2 Summary of different clinical markers based on repolarization or conduction alone, both repolarization and conduction, and others

Classification of risk marker	Clinical risk marker	Definition	Pre-clinical marker correlate	References
Repolarization	Corrected QT interval (QT_c)	QT interval corrected for heart rate	Action potential duration (APD)	31
	QT dispersion (QT_D)	Maximum difference between QT intervals in two leads of the 12-lead ECG	Difference in APD values between two regions	32,42
	$T_{peak} - T_{end}$	Interval from the peak to the end of the T-wave	Global dispersion of repolarization (TDR)	33
	$T_{peak} - T_{end}$ dispersion	Maximum difference between $T_{peak} - T_{end}$ in two leads of the 12-lead ECG	Global dispersion of repolarization (TDR)	43
	$(T_{peak} - T_{end})/QT$	Interval from the peak to the end of the T-wave divided by QT interval	Dispersion of repolarization divided by APD	34
	JT_{peak}/JT, $(T_{peak} - T_{end})/JT_{peak}$ and T_{peak}/JT ratios	JT_{peak}: interval from J-point to peak of the T-wave JT: interval from J-point to end of T-wave	Dispersion of repolarization normalized to JT interval	44–49
	$JT_{peak} - JT_{end}$ dispersion	Maximum difference between $JT_{peak} - JT_{end}$ in two leads of the 12-lead ECG	Global dispersion of repolarization (TDR)	43
	T-wave alternans (TWA)	T-wave duration difference between alternate beats	APD alternans	23,50
	Microvolt TWA	T-wave duration difference between alternate beats at the microvolt level	APD alternans	51
	Regional restitution instability index (R2I2)	Gradients of QRS onset to T_{peak} (QT_{peak}) plotted against T_{peak} to QRS onset ($T_{peak}Q$)	APD restitution gradient	40
	Peak ECG restitution slope (PERS)	Peak restitution curve slope taken as a mean across the 12 ECG leads	Maximum APD restitution gradient	41
	J-wave heterogeneity	Based on second moment analysis: maximum of the heterogeneity waveform in the J-point	Dispersion of the junction between depolarization and repolarization	52
	T-wave heterogeneity	Based on second moment analysis: maximum of the heterogeneity waveform in the interval between the J-point and the end of the T-wave	Dispersion of APD	36
Conduction	QRS_d	QRS duration, the interval between start and end of QRS complex	Conduction velocity (CV)	30
	QRS_D	QRS dispersion, maximum difference between QRS durations measured in the right and left precordial leads	• Phase difference in conduction times of neighbouring regions • CV difference between two regions • Standard deviation of the mean CV	53,54
	R-wave heterogeneity	Based on second moment analysis: maximum value of the heterogeneity waveform in the interval from the beginning of the Q wave to the end of the S wave	Dispersion of dV/dt_{max}	36
	QRS scoring (estimation of scar size)	See reference[55]		55–58
Repolarization and conduction	index of cardiac electrophysiological balance (iCEB)	QRS_d/QT	Excitation wavelength (λ, CV × effective refractory period) λ-TRIaD (triangulation, reverse use dependence, instability, and dispersion)	59
	$(T_{peak} - T_{end})/QRS_d$	–	APD dispersion, CV	60,61
	$(T_{peak} - T_{end})/(QT \times QRS_d)$	–	APD dispersion, APD, CV	60,61
	$QRS_D \times (T_{peak} - T_{end})/QRS_d$	–	Dispersion of CV and APD, CV	62

Continued

Table 2 *Continued*

Classification of risk marker	Clinical risk marker	Definition	Pre-clinical marker correlate	References
	$QRS_D \times (T_{peak} - T_{end})/(QRS_d \times QT)$	–	CV and APD, and their dispersion	62
Others	Ventricular premature beats (VPBs)	Premature QRS complex	Premature action potential	63–68
	Non-sustained VT	≤5 closely coupled QRS complexes	≤5 closely coupled action potentials	69,70
	Heart rate variability (HRV)	Several definitions	–	71
	Ventricular ectopic QRS interval (VEQSI)	Duration of the broadest VPB	Duration of the longest premature action potential	72

preparations that the end of AP repolarization at the epicardium coincided with the T_{peak} and at the M-cell coincided with T_{end}.[87] Subsequent experiments in swine showed that T_{peak} coincided not with full epicardial repolarization but rather with the earliest end of repolarization, whereas T_{end} coincided with the latest end of repolarization rather than full M-cell repolarization. In other words, $T_{peak} - T_{end}$ was a marker for global, rather than transmural, dispersion of repolarization.[33,88–90] $T_{peak} - T_{end}$ is also lead-dependent because the dispersion of repolarization varies with different cardiac regions.[91] Therefore, it was proposed that it should be determined from the right precordial leads (V_4 to V_6) for right ventricular disorders such as BrS, from the left precordial leads (V_1 to V_3) for other disorders such as LQTS.

Prolonged $T_{peak} - T_{end}$ elevates arrhythmic risk because increased dispersion of repolarization predisposes to the development of unidirectional block and therefore reentry.[89,92–94] This has been observed in LQTS1 and LQTS2 at baseline.[95] Exercise is known to trigger ventricular arrhythmias in LQTS1 but not LQTS2. Greater increases in $T_{peak} - T_{end}$ were observed in LQTS1 only, suggesting that it could be a useful risk marker for arrhythmogenesis in this LQTS subtype. Moreover, $T_{peak} - T_{end}$ has been successful in stratifying arrhythmic risk within a population of LQTS individuals, where patients with TdP had larger $T_{peak} - T_{end}$ than those without TdP.[81] $T_{peak} - T_{end}$ is also increased in SQTS and Brugada syndrome,[96,97] consistent with pre-clinical data that TDR is amplified in this condition.[18,60,98] Outside of congenital arrhythmic syndromes, it has successfully distinguished between the following three groups of hypertrophic cardiomyopathy patients, mutation carriers with history of SCD/VT, carriers without SCD/VT and neither carriers nor history of SCD/VT.[82] Furthermore, $T_{peak} - T_{end}$ predicted mortality in both ST elevation and non-ST elevation myocardial infarction (MI).[99] The Copenhagen study found an inverted U relationship between $T_{peak} - T_{end}$ and the risk of all-cause and cardiovascular mortality, atrial fibrillation and heart failure.[100]

However, one problem with $T_{peak} - T_{end}$ is that it varies with species and heart rate, with significant inter-individual variability.[101] It was found that normalizing it with the QT interval, yielding $(T_{peak} - T_{end})/QT$, which has a relatively constant normal range between 0.17 and 0.23.[101] This index has been shown to predict arrhythmic risk in LQTS,[95] distinguishing patients with TdP from those without TdP.[81] It has also demonstrated utility predicting arrhythmic risk or mortality in Brugada syndrome,[101] and other clinical conditions such as ST elevation MI,[102] diabetes mellitus,[103] and paediatric sepsis.[104]

Novel repolarization indices: JT_{peak}/JT, $(T_{peak} - T_{end})/JT_{peak}$, and T_{peak}/JT ratios

Additional repolarization interval ratios such as JT_{peak}/JT, $(T_{peak} - T_{end})/JT_{peak}$, and T_{peak}/JT ratios have been proposed.[44–46] Fundamentally, JT_{peak} represents early repolarization, whereas $T_{peak} - T_{end}$ represents late repolarization.[47,48] In the context of QRS_d prolongation, the JT interval also better reflects the total duration of repolarization than the QT interval. It was found that JT_{peak}/JT, $(T_{peak} - T_{end})/JT_{peak}$, and T_{peak}/JT ratios had higher sensitivity and specificity than QT, QT_{peak}, JT, JT_{peak}, and $T_{peak} - T_{end}$, and the ratios QT_{peak}/QT, $(T_{peak} - T_{end})/QT_{peak}$, and $(T_{peak} - T_{end})/QT$, in distinguishing patients with prior MI from those without MI.[46] Results from a recent clinical trial suggested that long QT_c alone may be benign if it is not accompanied by corrected JT_{peak} prolongation.[49] Moreover, a recent study investigated $(T_{peak} - T_{end})$ dispersion and $JT_{peak} - JT_{end}$ dispersion as potential markers of abnormal repolarization, which are defined as the maximum dispersion observed across the different leads of the respective parameters.[43] Diabetic patients were shown to have higher values of QT_c, QT_D, $(T_{peak} - T_{end})$ dispersion, and $JT_{peak} - JT_{end}$ dispersion than non-diabetic patients.[43] Furthermore, 16.4 and 12.7% diabetic patients had $(T_{peak} - T_{end})$ dispersion and $JT_{peak} - JT_{end}$ dispersion, respectively, whereas only 7.3, 5.5, and 0% showed prolonged $T_{peak} - T_{end}$, QT_c, and QT_D, respectively. These findings suggest the former set of indices may have higher sensitivity in detecting repolarization abnormalities in diabetic patients.

Principal component analysis ratio and J- and T-wave heterogeneities

Advances in computing technology have permitted digitization of ECG recordings and more complex analyses of ECG waveforms. Principal component analysis is a technique used to quantify the relative weight of different components of repolarization from the ECG, representing the spatial complexity of repolarization.[105,106]

Previously, it was shown that the first component (eigenvector) of the T-wave accounted for most of the energy consumed for repolarization under normal conditions.[107] Increased contributions from second or later components, i.e. increased PGD ratios given by second component divided by first component, reflect greater heterogeneity of repolarization.[35]

Moreover, second central moment analysis measures the heterogeneities observed in different ECG leads simultaneously.[108] Such an analysis has been used subsequently to examine heterogeneities in J- and T-waves.[36] J- and T-wave heterogeneities indicate disarray of depolarization, of the junction between depolarization and repolarization[52] and of repolarization, respectively, all of which represent favourable substrates for reentry.[36] The Multilead ECG Template-Derived Residua algorithm was developed to remove intrinsic morphological differences to allow calculation of heterogeneities between different ECG leads.[108]

T-wave alternans, microvolt T-wave alternans, regional restitution instability index, and peak electrocardiography restitution slope

T-wave alternans (TWA) has been associated with ventricular arrhythmias and sudden cardiac death.[50] They are due to alternations in repolarization time-course (measured as APDs) at the cellular level.[109] Traditionally, generation of APD alternans have been described by restitution, using a graphical method that relates APD to diastolic interval (DI). Restitution refers to the normal property of the myocardium where APD shortens with increasing heart rates and is thought to be an adaptive mechanism for maintaining diastolic filling time at such fast rates. APD alternans can be generated by APD restitution-dependent mechanisms when restitution gradients becomes greater than unity.[110–112] This is in keeping with clinical observations that a sudden increase in heart rate, which engages short DIs and the steeper portion of restitution curves, could produce or exacerbate TWA.[113] Alternans can also arise from mechanisms not involving APD restitution.[114–117] For example, abnormal Ca^{2+} handling involve an imbalance between Ca^{2+} release from the sarcoplasmic reticulum via ryanodine receptors and its subsequent reuptake by sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase.[118,119] Other mechanisms include cardiac memory, ventricular ERP (VERP) restitution, and mechano-electric feedback. The reader is directed to the following review articles for an in-depth discussion on the ionic and electrophysiological mechanisms involved in TWA generation.[24,109]

Alternans can be spatially concordant or discordant. Discordant alternans are thought to be more arrhythmogenic because they produce steeper gradients in repolarization and refractoriness. This can then lead to wavebreak, local conduction block of a premature extrasystole[120] to facilitate circus-type or spiral wave re-entry,[121–123] as well as Phase 2 re-entry.[124] TWA has been observed in a number of conditions, including electrolyte abnormalities, hypothermia, congenital arrhythmic syndromes such as long-QT and Brugada syndromes, and cardiac diseases such as coronary artery disease, post-MI, different forms of cardiomyopathy, vasospastic angina, and heart failure. There is accumulating evidence to suggest that different treatments can reduce TWA. For example, this has been observed using chronic vagal stimulation, which improved ventricular function and reduced both TWA and incidence of ventricular arrhythmias in heart failure patients.[125] Exercise rehabilitation also reduced TWA in patients with stable coronary artery disease.[126]

Microvolt TWA refers to small (as the name suggests, at the microvolt level) beat-to-beat differences in T-wave duration, amplitude, or morphology. Microvolt TWA has also been associated with TdP in LQTS.[39] The International Society for Holter and Non-invasive Electrocardiology issued its consensus guideline in 2011, discussing the use of spectral and modified moving average methods (in the frequency and time domains, respectively) to quantify microvolt TWA for arrhythmic risk stratification.[51] However, a sub-study of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) found no statistically significant difference in survival rates between heart failure patients who were microvolt TWA positive and those who were negative.[127]

Two ECG markers based on restitution have been devised to predict alternans formation.[40,41] Firstly, R2I2 is defined as the mean of the standard deviation of residuals from the mean gradient derived from each ECG lead over a range of DIs. It is obtained from QRS onset and T_{peak} measurements using a S1S2 protocol. QRS onset to T_{peak} (QT_{peak}) was used as a surrogate of APD, and plotted against T_{peak} to QRS onset ($T_{peak}Q$), a surrogate of DI. This then permitted the gradient, R2I2 to serve as an estimate of restitution gradients. Increased R2I2 was observed in patients with ischaemic cardiomyopathy compared with the control group. Secondly, PERS was defined as the peak restitution curve slope taken as a mean across the 12 ECG leads, reflecting maximum APD restitution gradients. Both were shown to independently predict patients at high risk of developing VT/VF and SCD.

Despite the usefulness of repolarization markers, repolarization abnormalities such as TDR did not consistently predict arrhythmogenicity in mouse models of LQTS or SQTS.[128] This is because APD does not always coincide with ERP, as in the case of acquired LQTS. In acquired SQTS produced by hyperkalaemia, although abnormal TDR was observed. ERP appeared to be central in determining arrhythmic tendency as hypercalcaemia treatment produced anti-arrhythmic effects by correcting for ERP without influencing the abnormal TDR.[18] In other cases such as Brugada syndrome, conduction abnormalities in the form of CV reduction and CV dispersion were not taken into account. Indeed, ventricular arrhythmias to occur despite normal repolarization gradients in Brugada patients.[129]

Conduction markers

Normal cardiac excitation involves the an orderly wave of depolarization that is conducted from the sinoatrial node to the ventricular myocardium.[130] Abnormalities in this depolarization or conduction process can predispose to the development of arrhythmias.[131,132] Markers based on such abnormalities include QRS duration (QRS_d), QRS dispersion (QRS_D), R-wave heterogeneity, and QRS scoring.

QRS_d, QRS_D, and R-wave heterogeneity

CV dispersion is a broad term encompassing phase difference in conduction times of neighbouring regions,[133] difference in CV

across the myocardial wall[93] and standard deviation of the mean CV.[134] Increased CV dispersion has been observed in a pharmacological model of gap junction and sodium channel inhibition,[135] and genetic systems with downregulation of connexin 43, the principal component of gap junctions.[93,133,134] In these models, arrhythmogenesis took place despite unaltered CV,[133,136–140] thereby implicating CV dispersion as an additional pro-arrhythmic factor that must be taken into account. Electrocardiographically, can be used as a surrogate of CV dispersion, and is defined as the maximum difference between QRS_d measured in the right and left precordial leads.[53] It was first noted in arrhythmogenic right ventricular cardiomyopathy, a condition characterized by fibro-fatty replacement of right ventricular myocardium that leads to asynchronous activation.[53,54] QRS_D was found to be the strongest independent predictor of SCD when compared with other parameters such as QT_D, negative T-wave beyond the V_1 lead, and syncope.[141] QRS_D also predicted SCD in congestive heart failure[142] and correlates well with left ventricular systolic dysfunction.[143] Finally, R-wave heterogeneity represents disarray or dispersion in depolarization, which is pro-arrhythmic.[36]

QRS scoring

The Selvester QRS scoring system was first devised to quantify and localize myocardial scarring based on subtle changes in ventricular depolarization as determined from the ECG.[56–58] The revised system permits this analysis even in the presence of confounders, such as bundle branch and fascicular blocks and ventricular hypertrophy.[55] This was validated against the use of cardiac magnetic resonance imaging with late gadolinium enhancement in patients with ischaemic and non-ischaemic cardiomyopathy.[55,58] Increases in this revised QRS score were shown to predict the occurrence of ventricular arrhythmias, the need for ICD shocks, prognosis,[144] and reduced reverse LV remodelling.[145] These were also associated with TWA in heart failure with preserved ejection fraction.[56]

Novel conduction–repolarization indices for risk stratification: the importance of conduction slowing and conduction dispersion

From the above considerations, it is clear that both conduction and repolarization, represented by λ, is required to explain arrhythmogenesis. Indeed, pre-clinical studies demonstrated that λ was the best predictor of arrhythmic tendency, increasing with pro-arrhythmic conditions and decreasing by anti-arrhythmic therapy.[18,25] However, a major disadvantage of λ is that it must be determined invasively by electrophysiological studies in the clinical setting. Based on the principle of λ, Lu *et al.* proposed a novel index of cardiac electrophysiological balance (iCEB), given by QT/QRS_d (both QT and QRS in milliseconds, with a dimensionless index).[59] This has demonstrated utility in predicting cardiac arrhythmias after administration of drugs such as dofetilide, digoxin, and isoprenaline in rabbit perfused-wedge preparations.[59] It was subsequently validated in humans also in the presence of drugs, LQTS, and Brugada syndrome.[146]

Recently, Tse proposed that iCEB should be modified from QT/QRS_d to produce the following indices: $(T_{peak} - T_{end})/QRS_d$ and $T_{peak} - T_{end}/(QT \times QRS_d)$.[60,61] This is based on pre-clinical findings that increased dispersion of repolarization is a pro-arrhythmic factor,[18,21] in keeping with clinical studies demonstrating that $T_{peak} - T_{end}$ and $(T_{peak} - T_{end})/QT$ were superior to the QT_c in arrhythmic risk stratification.[147] Moreover, Tse and Yan further modified Tse's indices, yielding $QRS_D \times (T_{peak} - T_{end})/QRS_d$ and $QRS_D \times (T_{peak} - T_{end})/(QT \times QRS_d)$.[62] Their reasoning was that increased CV dispersion is also an important determinant of ventricular arrhythmogenesis, but these indices remain to be validated clinically. Future work can take advantage of the ability of cardiac magnetic resonance imaging to characterize structural abnormalities with high resolution, in combination with magnetocardiography for risk stratification.[55,148,149]

Other risk markers: ventricular ectopy, non-sustained ventricular tachycardia, heart rate variability, and ventricular ectopic QRS interval

In addition to repolarization and conduction abnormalities, other markers have been associated with increased arrhythmic risk, including ventricular ectopy (ventricular premature beats, VPBs), the presence of non-sustained VT (NSVT), heart rate variability (HRV), and the ventricular ectopic QRS interval (VEQSI). In 1969, a higher incidence of SCD was observed in individuals who had ventricular ectopy compared with those who did not.[63] Furthermore, in patients with coronary artery disease, the presence of VPBs increases the risk of death by two-fold, even correcting for the risk factors of CAD.[64] Apart from the presence of VPB, its morphology is also important,[65] such as higher QRS_d[66,67] and notching of the peak.[68] Furthermore, a higher risk of death is observed in patients with NSVT compared with those without NSVT.[150] NSVT was predictive of all-cause and arrhythmic mortality,[69] but not after adjusting for ejection fraction.[70] HRV initially demonstrated promise but was later shown not to be predictive of arrhythmic mortality.[67,71] Finally, VEQSI, defined as the duration of the broadest VPB, was shown to be a marker of structural heart disease, correlated with left ventricular function and distinguished post-MI patients with prior life-threatening events from those without previous episodes of ventricular arrhythmias.[72]

Conclusion

In this article, we reviewed the different clinical markers based on abnormalities in repolarization, conduction, or both. It was emphasized that dispersions of repolarization and conduction should all be taken into consideration for accurate prediction of an individual's arrhythmic potential. These ECG markers of varying complexity can be used in different settings. Clearly, in daily patient care by the bedside or in the clinic, patients may initially require a quick evaluation of arrhythmic risk. Traditionally, this has involved determination of QT_c. We propose that both QRS prolongation and iCEB be

incorporated in this initial risk stratification. Invasive electrophysiological studies, where patients' hearts can be subjected to stimulation protocols such as S1S2 pacing, will continue to provide important information for risk stratification. Their use can yield the novel markers, such as R2I2 and PERS recently proposed.[40,41] These invasive markers can be combined with complex non-invasive markers, which require calculations and derivation of information from several precordial leads. This holistic approach would then represent a comprehensive risk assessment of the patient. However, at the moment, these complex markers are used in epidemiological studies and not routinely. Eventually, once these have proved their clinical utility in terms of sensitivity and specificity, we expect these markers to be used widely in clinical practice. This will require the development of user friendly apps on mobile devices. These apps can be designed to automatically calculate the indices when the basic parameters are input by the clinician, yielding useful information such as 'high, 'medium or low risk' of developing ventricular arrhythmias to facilitate and streamline patient management.

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