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Electrocardiogram-based Parameters for the Prediction of Sudden Cardiac Death: A Review

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ABSTRACT

There has recently been a resurgence of interest in electrocardiogram-based (ECG-based) parameters in predicting Sudden Cardiac Death (SCD) risk. Accurate and timely SCD predictions are essential clinical practice for physicians to provide effective prevention and treatment. An ECG is a non-invasive and inexpensive diagnostic test, and has been firmly established as a clinical tool for assessing the risk of cardiac disease. The electrocardiographic signal derived from the ECG recording consists of a distinctive waveform that depicts the electrical activity of the heart, which can be analyzed for the identification of abnormalities in the heart rhythm. The parameter or characteristic found in the ECG signal might be important for predicting the SCD. A number of systematic reports by expert meetings and review articles in indexed journals identified ECG-based parameters as QRS duration, QT interval, Signal Average ECG (SAECG), T-wave alternan (TWA), Heart Rate Variability (HRV), Heart Rate Turbulence (HRT), T-peak to T-end (Tpe), fragmented QRS complexes (fQRS), and Early Repolarization (ER). This article reviews the mechanism and morphology of these parameters, which may potentially have a role to play in a future algorithm designed to identify early signs of SCD. As of now, none of the ECG-based parameters have been found to be sufficiently stable to predict the SCD risk. Nevertheless, the combination of two or more of the parameters listed, as suggested in many studies, may become a useful component for predicting SCD in the future.

Keywords: SCD prediction; electrocardiogram signal; ECG-based parameter, automated ECG analysis

INTRODUCTION

Sudden cardiac death (SCD) is a life-threatening event which may lead to loss of life if no emergency treatment is administered immediately. The incidence occurs in a short period of time, generally within an hour or less after symptom onset due to the cardiac cause and signaled by syncope (Chugh 2010; Mehra 2007; Zipes & Wellens 1998). SCD is mainly caused either by ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia, asystole, pulseless electrical activity (PEA), or non-arrhythmic causes (Fishman et al. 2010; Goldberger et al. 2008). Upon the occurrence of the condition, the blood flow to the brain will be reduced so drastically that a person will lose consciousness with no pulse and no breathing. Oxygen level will be decreased, which may cause brain injury if it is not treated within five minutes (Vijaya et al. 2012).

Recent studies of global pattern show that cardiac disease continues to be the world's leading killer, with SCD is responsible for half of all cardiovascular deaths, which mostly occurred in individuals who do not have high-risk profiles (Al-Khatib et al. 2007; Liew 2011; Narayanan & Chugh 2015; Zipes & Wellens 1998). Due to the low survival rates of SCD preceding episodes, considerable efforts have been directed towards risk prediction and prevention. If any inconsistency in cardiac activity is detected at an early stage, appropriate medical treatment may be delivered by medical experts to the patient on time.

There is an interaction between SCD and myocardial infarction (MI). Both are initial manifestations of coronary artery disease (CAD) (Sara et al. 2014). SCD is most commonly associated with CAD, with a small proportion is due to other cardiomyopathies (Chugh 2010; Narayanan & Chugh 2015). Unlike MI, SCD is the indication of a fatal heart rhythm disorder. Acute myocardial infarction (AMI), on the other hand, occurs when there is a blockage in one or more of the coronary arteries, causing damage to the heart muscle. Although there is a clear distinction of definitions between them, the subgroup of patients suffering from SCD will initially suffer from AMI, mostly within the first hour of AMI incident (Chugh 2010; John et al. 2012).

The prediction and prevention of SCD has become an area of active investigation. This is demonstrated by increasing awareness among the

medical community and researchers to enhance methodologies for the identification of early SCD predictors. (Just 2017) quoted that "Having a platform to stratify patients according to risk is key to the success of any population health management initiative". Risk stratification is a process of separating patients' populations into high risk, low risk, and the ever-important rising-risk groups. The left ventricular ejection fraction (LVEF) measurement has been reported as commonly used for risk stratification in clinical practice but is only effective in a small subgroup of patients (Abdelghani et al. 2016; Chugh 2010; Fishman et al. 2010). Therefore, there is a significant room for improvement in SCD risk stratification as relying on LVEF alone is insufficient. Prior knowledge gained from reports and recommendations by medical experts on the risk factors and risk stratification tools offers a basic concept on the analysis of the SCD prediction, which is subsequently disseminated for more effective prevention. Currently, the efficacy of ECG-based parameters as predictors for SCD risk stratification has been addressed by many studies (Abdelghani et al. 2016; Goldberger et al. 2008; Liew 2011; Narayanan & Chugh 2015). The most recent work by (Holkeri et al. 2019) used electrocardiographic risk score and evaluated its ability to identify subjects at high risk of SCD in the Finnish populations. Their finding has shown that the combination of several ECG abnormalities from the ECG-based parameters may improve SCD risk stratification.

Numerous invasive and noninvasive methods have been developed to identify patients at risk. However, over the past three decades, noninvasive methods for predicting SCD have clearly been more appealing in the clinical strategy for extensive screening as the procedures do not involve the introduction of instruments into the body. This is demonstrated by a multifold of non-invasive markers derived mainly from surface ECG correlated with SCD, cardiac and total mortality, which are deployed globally by clinicians (Fishman et al. 2010). Moreover, the noninvasive methods are inexpensive, expeditious, attainable, and familiar to all physicians.

This paper reviews the current knowledge based on the potential of ECG-based parameters to predict SCD. The mechanism and historical overview of ECG are described briefly in the section. The third section introduces the role of the automated ECG analysis in the SCD prediction. In the fourth section, nine ECG-based parameters that have been identified as the SCD predictors are comprehensively discussed. These include the significance and recommendations of each parameter as a predictor candidate of SCD. Finally, the summary is presented in the last section with additional information on the selected publications, as shown in Table 2. This table summarizes the associations and limitations of ECG-based parameters for SCD prediction.

ECG HISTORICAL AND MECHANISM OVERVIEW

The heart contains two upper chambers called atria, and two lower chambers called ventricles. The right and left atria serve as volume reservoirs for blood that is sent to the ventricles. Meanwhile, the right and left ventricles serve as pumping chambers for the heart (Wilkins 2005). A natural electrical system causes the heart muscle to contract and pump blood to the body and lungs, which can be sensed using electrodes that are placed in specific locations on the skin between the extremities and torso. The output derived from the electrodes known as leads are then amplified, filtered, and displayed by an electrocardiographic recording (Mirvis & Goldberger 2012).

The mechanism of the electrocardiogram, generally known as ECG, is a graphical depiction of electrical pulses derived from the heart, and was first discovered by Willem Einthoven in the early 1900s using a string galvanometer (Rivera-Ruiz et al. 2008). Einthoven's contribution in ECG constitutes essential knowledge in the cardiology field and the technology has subsequently become the most common and practical tool for the diagnosis of cardiac abnormalities. The complete ECG cycle consists of a P-wave, a QRS complex, an ST segment, and a T-wave. The annotation of each point and the intervals are shown in Figure 1.

The P-wave is an electrical recording of the activity in the upper chambers. The QRS complex is

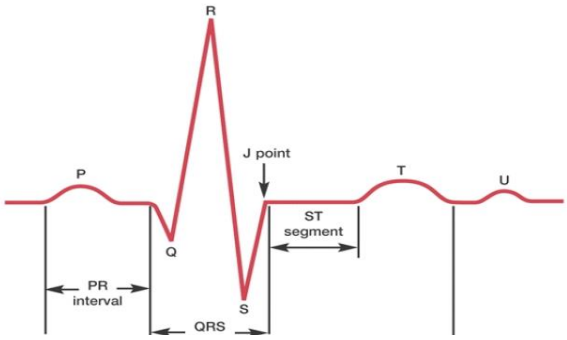

FIGURE 1. A typical cycle in the ECG waveform

a recording of the electrical activity of the lower chambers (ventricles) and has the most prominent feature (Baura 2012). Thus, the QRS complex is commonly used in ECG analytic algorithms and the broader area of automated electrocardiogram analysis (Bansal et al. 2009; Chang & Young 2009; Köhler et al. 2002). The ST segment appears as a straight line between the end of the S-wave (the J point) and the beginning of the T-wave. It represents the interval between ventricular depolarization and repolarization. The T-wave corresponds to the period in which the ventricles are electrically relaxed and are preparing for a new contraction

(Mirvis & Goldberger 2012). The lowest amplitude is the U-wave, where the location is between the T-wave end (T offset) and the P-wave onset. It is frequently absent in the limb leads. Commonly, the subtle appearance of U-wave is almost unnoticeable and overlooked by ECG readers and automated systems (Rautaharju et al. 2009). However, disproportionally large or inverted U-waves are signs of abnormality (Pérez Riera et al. 2008; Sovari et al. 2007).

Table 1 summarizes the morphological meaning of each wave, intervals and normal values for a healthy adult. Normal ECG values provide important information in clarifying diagnostic criteria but the ranges vary depending on age and gender (Rijnbeek et al. 2014).

TABLE 1. Denotations and the normal values of ECG waves and intervals for the adult

Waves /Intervals	Denotations	Normal value
P-wave	Sequential depolarization of the right and left atria.	< 121 ms (Rijnbeek et al. 2014)
QRS complex	Right and left ventricular depolarization.	
ST-T wave	Ventricular repolarization.	
U-wave	After depolarization event at the beginning of diastole.	< 25% of the T-wave amplitude (Pérez Riera et al. 2008)
PR interval	Time interval from onset of atrial depolarization (P wave) to onset of ventricular muscle depolarization (QRS complex).	120-200 ms (Yanowitz 2018)
QRS duration	Duration of ventricular muscle depolarization (width of the QRS complex).	80-100 ms (Goldberger et al. 2008)
QT interval	Duration of ventricular depolarization and repolarization.	Men < 450 ms and women < 460 ms (for HR 60-100 bpm) (Algra et al. 1991)
RR interval	Rate of ventricular cycle.	50-90 bpm (resting ECG) (Spodick 1993)

Early electrocardiographs were developed using analog electronics and printed on a graph paper at a standard scale. Each small box on the graph (1 mm) represents 40 ms of time for the x-axis and 0.1 mV of voltage for the y-axis. The trace can be measured manually using a Vernier caliper. Today, the electrocardiographs use an analog-to-digital converter to convert the signal into digital, which can be manipulated by digital electronics (Mortara 1989). The growth of technology in recent years has permitted the digital recording of ECG signals and a more accurate analysis can be carried out using a computer or an automated system.

AUTOMATED ECG ANALYSIS IN SCD PREDICTION

The automated ECG program was developed in the 1960s (Stallmann & Pipberger 1961) and thereafter, the technology has continued to advance in numerous ways. Automated ECG interpretation utilizes artificial intelligence, pattern recognition software, and knowledge bases to provide analysis and diagnosis of ECG signal. Many reports and studies have demonstrated that certain parameters on ECG-based investigations can contribute vital information on underlying cardiac substrate abnormality that may predispose to ventricular arrhythmias and SCD (Fishman et al. 2010; Huikuri et al. 2003; Liew 2011; Narayanan & Chugh 2015). Prior to the investigations, an analysis of ECG requires patients' data from monitoring and recording, which can be retrieved by using stress testing, resting interpretation, ambulatory monitoring, or intensive care monitoring (So¨rnmo & Laguna 2006).

Nowadays, the vast majority of ECG system monitoring utilizes the automated ECG analysis. In the case of automated SCD detection, non-invasive methods based on signal processing techniques are becoming studies of growing interest. These methods include time domains, frequency domains, time-frequency domains and non-linear domains. For example, study in (Khazaei et al. 2018) has developed an algorithm that uses the nonlinear-based features of heart rate variability (HRV). The HRV was derived from the ECG signal and the algorithm was able to detect SCD indication six minutes prior to SCD onset. They used the one-way ANOVA to minimize the dimension of the feature space and eventually applied the machine learning algorithms (Decision Tree, K-nearest Neighbor, Naive Bayes, and Support Vector Machine) for classification. Similar work was also carried out by (Murugappan et al. 2015) using HRV in predicting the SCD five minutes before the sudden cardiac arrest (SCA) onset. The work employed time domain features extraction and classified the features using simple machine learning algorithms (K-nearest neighbor and Fuzzy classifier). In their study, the extracted features are statistically validated using the one-way ANOVA. For another example, the study in (Shen et al. 2016) applied an ECG biometric algorithm to detect the SCD event. To analyze the detection, two different techniques were used: modified zero-crossing and wavelet based. Eventually, their study found that the modified zero-crossing approach showed higher performance than the wavelet analysis.

In conclusion, the elementary knowledge for automated ECG analysis originated from the

morphological understanding of the wave and the signal processing study. The dynamic properties of the ECG signal expressed by the changes in rhythm and beat morphology produce important information on the cardiac condition. Automated ECG analysis significantly contributes to considerable advantages in the cardiovascular disease diagnosis compared to manual measurement, particularly when extraction of information is not readily available from the signal via visual assessment.

ECG-BASED PARAMETERS FOR SCD PREDICTION

Numerous studies have distinguished various ECG abnormalities associated with SCD. Although controversial results are encountered, these studies contribute vital information and guidance to the enhancement of SCD prediction techniques in the development of an automated system algorithm. Nine ECG-based parameters were discovered and five parameters were identified as highly quoted, including QRS duration, QT interval, Signal Average ECG (SAECG), T-wave alternan (TWA), and Heart Rate Variability (HRV). All publications were surveyed and nominated originally from systematic reports by expert meetings and review articles in indexed journals.

QRS Duration

A QRS duration (QRSd) is categorized as normal if it is between 80-100 ms, slightly prolonged if between 100-120 ms, and abnormal if it is more than 120 ms (Goldberger et al. 2008). QRS prolongation has been known to be associated with increased mortality (Huikuri et al. 2003; Liew 2011). A number of studies have reported that prolonged QRSd is a potentially significant predictor of SCD for most retrospective analyses, irrespective of the presence or absence of left bundle branch block (LBBB) and other known risk factors for SCD (Goldberger et al. 2008; Huikuri et al. 2003; Kurl et al. 2012). The longer QRS interval is found to be related to patients who suffer SCD in the setting of acute MI (Chugh 2010).

Conflicting results and limited observations justified by scientific statements from several reports and studies (Goldberger et al. 2008; Kashani & Barold 2005; Kurl et al. 2012) indicate that increased QRSd is not currently recommended as a SCD predictor. There is little evidence that showed the increase of QRSd has been associated with an increase in SCD among CAD patients (Liew 2011). In addition, the association of QRSd with SCD risk is not well documented in large population-based studies (Kurl et al. 2012). On top of unclear impact due to limited observations, the use of QRSd alone may have minimal benefit for risk stratification due to a strong overlap in cases and controls (Extramiana & Leenhardt 2011; Kashani & Barold 2005).

QT Interval

In cardiology, the QT interval is defined as the time between the start of the Q-wave and the end of the T-wave in the electrical cycle of the heart. Figure 2 shows the onset and the end of the Q-wave, where the tangent line for the steepest part of the T-wave intersects with the baseline of ECG (Postema & Wilde 2014). The prolongation of the QT interval corrected for heart rate, typically abbreviated as QTc, is considered normal under the heart rate of 60-100 bpm if the value is below 450 ms for males and 460 ms for females (Algra et al. 1991).

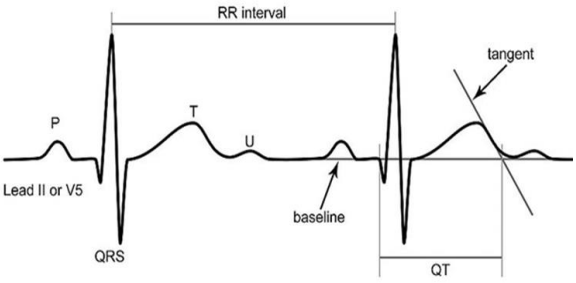

FIGURE 2. Measurement of QT interval on ECG Signal (Postema & Wilde 2014)

An abnormally prolonged QTc is a high risk of SCD and is only supported if the long-QT syndrome (LQTS) is present (Goldberger et al. 2008; Waddell-Smith et al. 2017). Increased QT intervals have been noted in patients with AMI. Another parameter associated with SCD prediction is QT dispersion (the maximal difference between QT intervals). However, the utility of this parameter as a SCD predictor is unclear. Despite being associated with increased mortality, a few observational studies have shown that QT dispersion does not have a prognostic value in arrhythmia risk, and have recommended that it not be included in routine ECG reports (Goldberger et al. 2008; Rautaharju et al. 2009).

In order to measure QTc effectively, a few studies suggested the use of leads II and V5 (as a second choice) with tangent technique and corrected with the Bazett formula (Waddell-Smith et al. 2017). The reasons behind the focus on lead II and V5 are that these leads best correlate with genotype status in LQTS and show fewer baseline movements (Berger et al. 2011; Mönnig et al. 2006). Besides Bazett formula, Fridericia, Framingham and Hodges are used as alternative formulas depending on the appropriateness of the use (Goldenberg et al. 2006; Waddell-Smith et al. 2017). In order to achieve accurate QTc measurement, another factor that needs to be considered is to get the minimal artefact and high resolution. This is best done during a stable sinus rhythm (Waddell-Smith et al. 2017). The QT interval studies concerning its association with SCD seem to have conflicting results, indicating that it is

useful for some populations only (Abdelghani et al. 2016; Liew 2011).

Signal averaged ECG (SAECG)

SAECG is an amplified and processed ECG that can identify abnormal microvolt-level potential at the end of the QRS complex, known as ventricular late potential (VLP) (Abdelghani et al. 2016; Al-Khatib et al. 2007). Normally, the VLP is undetected using the standard 12-lead ECG due to very low amplitude. Thus, it requires an amplified high-resolution ECG recording (Liew 2011).

The use of SAECG as a SCD predictor has controversial outcomes. A number of studies have concluded that abnormal SAECG tend s to be associated with SCD according to prospective analyses, but that potential utility has not been demonstrated (Chugh 2010; Goldberger et al. 2008). An expert meeting of Duke Clinical Research Institute, the USA in 2007 (Al-Khatib et al. 2007) reported that the majority of previous studies had shown the prognostic value of SAECG in post-MI patients and concluded that SAECG could be a strong predictor of SCD. However, the positive predictive value was < 30%. A recent systematic literature review by (Abdelghani et al. 2016), concluded that SAECG may have some valuable information, but not a useful tool for SCD risk routine screening due to the technical challenges, high negative predictive value, and low positive predictive value.

T-wave alternan (TWA)

TWA is a periodic beat-to-beat variation of the amplitude and shape of the T-wave (Rosenbaum et al. 1996a). Specialized recordings must be utilized to elevate the heart rate in order to obtain a satisfactory result from TWA tests such as exercise stress, pharmacological stress, or atrial pacing (Haghjoo et al. 2006). Figure 3 shows the beat-to-beat morphology of TWA in ABAB type pattern observed on ECG trace.

A number of studies, along with a moderate amount of prospective data, have considered that the increased TWA amplitude is associated with SCD

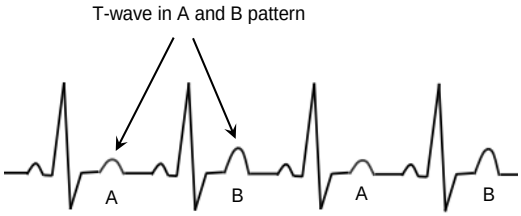

FIGURE 3. Morphology of the TWA in every other beat or AB-AB pattern (in amplitude and shape)

(Abdelghani et al. 2016; Goldberger et al. 2008; Rosenbaum et al. 1996b). Although the detection mechanism appears to be simple and reported as a more sensitive SCD predictor than SAECG, TWA has several limitations (Gold et al. 2000; Liew 2011). There have been some controversial results among post-AMI patients and insufficient evidence in a prospective and randomized trial for testing the predictive power (Gold et al. 2000; Huikuri et al. 2003). Another limitation is the high percentage of indeterminate tests resulting from atrial fibrillation, frequent ventricular ectopy, or patients' incapability of exercise (Al-Khatib et al. 2007). Therefore, for the time being, some observational studies (Al-Khatib et al. 2007; Chugh 2010) have suggested that the utility of TWA must be supported by additional data before it can be widely used for SCD risk stratification.

Heart rate variability (HRV)

The HRV represents beat-to-beat variation of either the heart rate or the duration of the R–R interval from the ECG signal (Billman 2011). Analyses of HRV may provide quantitative information on cardiac autonomic activity and can be assessed using various techniques over a short duration (2 to 5 minutes) or longer period (24 to 48 hours) (Gang & Malik 2003; Goldberger et al. 2008).

Decreased HRV appears to be correlated with mortality, but probably not specific to SCD (Al-Khatib et al. 2007; Chugh 2010; Goldberger et al. 2008). A different case was found in previous observational studies among post-AMI patients, where low HRV predicted SCD (Al-Khatib et al. 2007; Huikuri et al. 2003). The practical use of HRV to predict SCD is limited due to the influence of a variety of factors such as age, gender, and medication (Liew 2011). In addition, this test cannot be evaluated in patients with active atrial fibrillation or frequent ectopy (Abdelghani et al. 2016). In CAD patients, the utility of HRV to predict SCD is poorly established and partly complicated by the effects of ischemia and balloon treatment on HRV indices (Liew 2011).

Despite the stated limitations, the advantages of HRV over other ECG markers in predicting SCD may need to be improved if adopted as a SCD predictor. Current studies have reported that a combination of HRV with other parameters such as TWA would enhance the prognostic value (Abdelghani et al. 2016; Murukesan et al. 2013).

Heart rate turbulence (HRT)

The derivation of the HRT term was first introduced by Schmidt et al. in 1999 (Schmidt et al. 1999). The study investigated the fluctuation of sinus rhythm cycle length after a single ventricular premature beat recorded in Holter ECG. The fluctuation is characterized by two numerical parameters, called turbulence onset and turbulence slope (Schmidt et al.

1999). HRT measures the vagal responsiveness. Hence the mechanism was said to have a close link with Baroreceptor Sensitivity (BRS) (Goldberger et al. 2008; Watanabe et al. 2002).

Several studies have shown that HRT is not a predictive parameter for SCD. This may be due to the short-term recording by previous investigations which resulted in an inadequate representation of the average HRT or a limited of ability to derive accurate data (Goldberger et al. 2008; Liew 2011). Based on a multitude of studies, it can be said that HRT has been mainly studied in the post-MI population. Therefore, generalizations to other populations are currently discouraged (Abdelghani et al. 2016). Furthermore, it is also affected by a number of factors, provocations, treatments, and pathologies (Bauer et al. 2008).

T-peak to T-end (Tpe)

The Tpe is the measurement of the interval starting from the peak to the end of the T-wave, as shown in Figure 4, where it indicates the quantity of transmural dispersions of repolarization in the left ventricle (Abdelghani et al. 2016). The prolongation of the interval has been demonstrated by many studies to predict ventricular tachyarrhythmia and sudden death, with almost every published trial showing that longer Tpe is associated with higher risk (Abdelghani et al. 2016; Rosenthal et al. 2015).

Investigation of this parameter as a SCD predictor began in 2011 by (Panikkath et al. 2011) using a population-based study of 353 SCD cases compared to 342 control subjects. They discovered that the Tpe prolongation measured in lead V5 appears to be strongly associated with SCD, regardless of age, sex, QTc, QRS duration, and left ventricle function. Overall, the studies reviewed here indicate the importance of Tpe as a useful risk component of the SCD predictor in the future, provided that the usage through optimal measurement method for standardization is clarified.

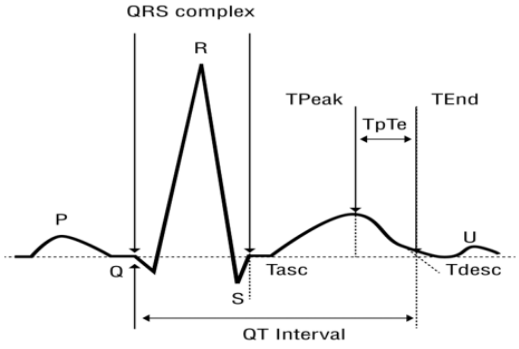

FIGURE 4. Measurement of Tpe or TpTe (Tasc: T-ascending; Tdesc: T-descending) (Park 2016)

Early repolarization (ER)

Early repolarization (ER) is defined as the elevation of the QRS–ST junction (J point elevation) by 0.1 mV in two contiguous leads (other than V1 through V3) on 12-lead ECG (Jani T. Tikkanen, Olli Anttonen, M. Juhani Junttila, Aapo L. Aro, Tuomas Kerola, Harri A. Rissanen, Antti Reunanen 2009; Liew 2011). In previous research, ER was generally considered to be a benign entity, and was associated with idiopathic ventricular fibrillation (Ali et al. 2015; Haïssaguerre et al. 2008). Subsequently, this parameter is recognized by a number of studies that have a broader association with SCD (Narayanan & Chugh 2015; Nunn et al. 2011; Tikkanen et al. 2012). The mechanism underlying the ER contribution to predict SCD remains uncertain. Despite the simplicity and ease of measurement, research to seek the true potential of ER as a prediction tool for SCD will still be needed.

Fragmented QRS Complexes (fQRS)

The fQRS is another QRS morphology that can be defined as additional spikes or slurs of R-wave within the QRS complex, denoted as R'. It occurs with or without Q-wave in two or more contiguous lead within < 120 ms on 12-lead resting ECG (Chatterjee & Changawala 2010; Das et al. 2006; Haukilahti et al. 2016). The existence of fQRS was first remarked by Boineau and Cox in 1973 while experimenting with canine heart for acute ischemia (Boineau & Cox 1973).

Studies for this parameter are emerging, some of which have identified fQRS as an independent SCD predictor (Das & El Masry 2010). Besides the simplicity and ease of measurement, fQRS appears to be a promising tool to help identify patients at the highest risk for SCD. The QRS scoring systems derived from a number of fQRS studies have been recognized as having a role in risk stratification algorithm (Liew 2011). The combination with other repolarization abnormality markers like TWA will further enhance the predictive value of the fQRS for SCD (Das & El Masry 2010).

SUMMARY

This article dealt with statements, recommendations, and significance of the SCD prediction information from various publications using electrocardiographic parameters. The summary in Table 2 consists of selected publications, association and limitations of each of the ECG-based parameters to predict SCD in point form (except Tpe, ER, and fQRS). Among the nine parameters, QT interval, QRSd, SAECG, TWA, and HRV seem to have frequent applications until now. As for the others, although they are only being introduced in the medical research field, like Tpe, the investigations

to obtain valuable properties as SCD predictors are emerging.

Overall, the listed publications conveyed the knowledge in versatile aspects that proved beneficial for researchers and scientists to undertake further research in improving SCD prediction methods. To date, none of the ECG-based parameters have been found to be adequately stable to predict SCD risk patients. However, the combination of two or more of all the listed parameters, as suggested by many studies, may become a useful component in the future. In addition, if any research attempts to employ any of these parameters specifically in an automated system, further comprehensive studies on statistical analysis must be implemented in order to provide a solid justification on the utility of that candidate as an SCD predictor. Other tools such as artificial neural network, hybrid networks and modelling tools are also recommended as a decision-making tool to give greater assurance on the research outcome.

TABLE 2. Summary of selected important studies of ECG-based parameters for SCD prediction

1st author, year; Scope of study	Types of article	ECG-based parameters					
		QT interval/dispersion	QRS duration	SAECG	TWA	HRV	HRT
Gilman, 1994; Reviewed the efforts in identifying high-risk SCD patients, and highlighted the completed and ongoing efforts to prevent SCD (Gilman et al. 1994).	Review article			• Combination with EF was associated with arrhythmic event. • Less sensitive in anterior infarction than inferior infarction for post-MI patients.	• Merits further validation in large scale studies of unselected post-MI patients.	• Combination with SAECG yield more predictive.	
Huikuri, 2003; Analyzed problems of predicting arrhythmic deaths, advantages and limitations of the various methods of risk stratifications (Huikuri et al. 2003).	Review article	• Controversial results from observational & case control studies. • Methodological problems in measurement.	• Predicts arrhythmic mortality. • Prognostic power not tested in prospective trials.	• High -ve predictive accuracy in observational studies and MUSTT trial.	• +ve TWA predicts arrhythmia events among high-risk patients. • Partly controversial result among post AMI patients. • Predictive power not tested in randomized trials.	• Predict SCD in observational studies among post AMI patients. • Predictive power not tested in randomized trials.	
Al-Khatib, 2007; Reviewed current data on strategies of risk stratification for SCD (Al-Khatib et al. 2007).	Result of expert meeting	• Seems to be strongest predictor with LQTS patients. • Conflicting result with LVEF patients. • QT dispersion & QT variable likewise unclear. • Not proven to be clinically useful.		• Maybe a strong predictor in survivors of AMI. • Not a significant predictor of major arrhythmic events in MACAS.	• Predictor for VT events. • High percentage of indeterminate tests. • Absence of prospective and randomized trial. • Need additional data before establishing in clinical decision making.	• Reduced HRV associated with an increased risk of mortality among AMI. • Not significant predictor in several studies in MACAS.	• Absence of HRT after PVC was a significant predictor of all-cause mortality. • Not a significant independent predictor of major arrhythmic events in MACAS.
Goldberger, 2008; Discussed the risk stratification techniques for identifying patients at risk of SCD (Goldberger et al. 2008).	Scientific statement	• A risk factor for SCD by some retrospective analyses. • Clinical utility to guide selection of therapy has not yet been tested.	• Increased QRSd is likely a risk factor for SCD by most retrospective analyses. • Clinical utility to guide selection of therapy has not yet been tested.	• Likely a risk factor for SCD, based predominantly on prospective analyses. • Clinical utility to guide selection of therapy has been tested, but not yet demonstrated.	• Abnormal TWA is a risk factor for SCD by prospective studies. • Clinical utility to guide selection of therapy has been evaluated, but result are inconsistent.	• Low HRV is a risk factor for mortality, but likely is not specific for SCD. • Clinical utility to guide selection of therapy has been tested.	• Abnormal HRT is a likely risk factor for SCD. • Clinical utility to guide selection of therapy has not yet been tested.
Liew, 2011; Reviewed some evidence of ECG-based test as SCD predictors in patients with CAD and addressed the advantages & limitations(Liew 2011).	Review article	• Significantly associated with SCD. • Depends on genomic factor.	• Only small evidence associated with SCD in patients with CAD. • Increased of duration demonstrated in hypertensive patients undergoing intensive medical therapy for SCD risk.	• Easy & quick to perform. • High –ve predictive accuracy. • Combining with other tests improved the predictive accuracy.	• The MMA method of accessing TWA found to be strong, independent predictor. • Easy to perform. • High -ve predictive accuracy • Can only use with sinus rhythm and clean trace.	• Current practical use for risk stratification is limited. • Influenced by other variables (age, gender & medication). • Short-term measurement in risk prediction not fully tested.	• A powerful independent predictor of SCD risk by several large-scale by some studies. • Need 24hrs recording & presence of PVC. • Limited practical use at present due to unclear guidelines for risk stratification.
Abdelghani, 2016; Summarized the current knowledge pertaining to surface ECG predictors of SCD (Abdelghani et al. 2016).	Review article	• Conclusions are varying. • Maybe useful in some populations only.	• Consistently to be associated with increased all-cause mortality. • Mixed result with regard to SCD specifically related to arrhythmia.	• High –ve predictive value, low +ve predictive value, • Has some technical challenge. • Not a useful tool for routine screening for patient at SCD risk	• Increased amplitude of TWA was associated with SCD. • Can be assessed during exercise, atrial pacing or ambulatory Holter monitoring. • An independent predictor of risk for SCD.	• Must be combined with other ECG markers to achieve substantial prognostic value. • Cannot be evaluated in patients with active atrial fibrillation or frequent ectopy.	• Has been most extensively studied in the post-MI population. • Strong independent predictor of SCD risk. • Affected by several potential confounding variables. • Inadequate representation of average HRT due to short recording period.

Abbreviations: -ve = negative; +ve = positive; AMI = acute myocardial infarction; EF = ejection fraction; MACAS = Marburg Cardiomyopathy Study; MMA = modified moving average; MUSTT = Multicenter Unstained Tachycardia Trial; PVC = premature ventricular contractions; VT = ventricular tachycardia

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