

Review

Muhammad A. Hasan* and Derek Abbott

A review of beat-to-beat vectorcardiographic (VCG) parameters for analyzing repolarization variability in ECG signals

Abstract: Elevated ventricular repolarization lability is believed to be linked to the risk of ventricular tachycardia/ventricular fibrillation. However, ventricular repolarization is a complex electrical phenomenon, and abnormalities in ventricular repolarization are not completely understood. To evaluate repolarization lability, vectorcardiography (VCG) is an alternative approach where the electrocardiographic (ECG) signal can be considered as possessing both magnitude and direction. Recent research has shown that VCG is advantageous over ECG signal analysis for identification of repolarization abnormality. One of the key reasons is that the VCG approach does not rely on exact identification of the T-wave offset, which improves the reproducibility of the VCG technique. However, beat-to-beat variability in VCG is an emerging area for the investigation of repolarization abnormality though not yet fully realized. Therefore, the purpose of this review is to explore the techniques, findings, and efficacy of beat-to-beat VCG parameters for analyzing repolarization lability, which may have potential utility for further study.

Keywords: electrocardiography (ECG); QT interval variability; repolarization; vector electrocardiogram (VCG).

DOI 10.1515/bmt-2015-0005

Received November 8, 2014; accepted April 17, 2015; online first May 20, 2015

***Corresponding author: Muhammad A. Hasan**, PhD, Department of Electrical and Computer Engineering, Ryerson University, Toronto, ON M5B 2K3, Canada, Phone: +1-416-979-5000, ext. 2048, E-mail: mahasan@ryerson.ca; muhammad.hasan@adelaide.edu.au; Department of Electrical and Electronic Engineering, The University of Adelaide, Adelaide, SA 5005, Australia; and Centre for Biomedical Engineering (CBME), The University of Adelaide, Adelaide, SA 5005, Australia

Derek Abbott: Department of Electrical and Electronic Engineering, The University of Adelaide, Adelaide, SA 5005, Australia; and Centre for Biomedical Engineering (CBME), The University of Adelaide, Adelaide, SA 5005, Australia

Introduction

The biological signals are generated within the human body through different physiological processes. These signals are usually acquired in their raw form, and therefore, it is required to carry out signal processing and analysis to reveal pertinent details. In the case of an electrocardiographic (ECG) signal, the signal contains amplitude information without orientation of the heart vector direction. In clinical practice, the QT interval is measured as the duration of onset of Q wave and the offset of T wave in the heart's ECG electrical cycle, which represents the global electrical repolarization of the ventricles. Note that QT-interval variability analysis from a single ECG beat demonstrates the static picture of repolarization abnormalities, but the beat-to-beat QT interval variability (QTV) establishes the dynamic changes of the QT interval duration and repolarization labilities. Elevated beat-to-beat QTV is of interest as it has been associated with increased cardiovascular morbidity and mortality [10, 41, 42, 66, 72].

However, recent findings suggest that beat-to-beat QTV varies between leads in 12-lead ECG, where partial factors contributing to these QTV variations can be realized through the study of T-wave amplitude [37, 40, 41]. In particular, the magnitude and temporal pattern of beat-to-beat QTV varies significantly between leads in 12-lead ECG. Therefore, quantification of QTV in different leads is associated with their respective ECG leads. Consequently, QTV data from different studies in different leads may lead to inconsistencies. Thus, caution must be taken when comparing QTV results obtained from different leads across studies. Therefore, another modality called vector electrocardiography [or vectorcardiography (VCG)] may be useful for the analysis of dynamic changes of repolarization abnormalities. Here, VCG measures cardiac electrical forces with both magnitude and vectorial direction; it may be thought of as a methodological elaboration of the ECG.

These electrical forces are generated by billions of cardiac cells in the heart that can be modeled as a continuous series of vectors that form a resultant. Moreover, VCG aims at a spatial representation that reflects the electrical activity of the heart in the three (perpendicular directions of X, Y, and Z) spatial planes as shown in Figure 1. Note that VCG allows the concept of a dipole originated in the heart and uses orthogonal leads that define these three spatial planes: frontal, horizontal, and sagittal [31]. By contrast, the standard 12-lead ECG represents only the one-dimensional scalar value of the heart function, i.e., it represents only the magnitude and not the direction or spatial information of heart signal. Improved understanding for analysis and characterization of heart signals by considering both direction and magnitude of the ECG signals as a three-dimensional phenomenon may be then possible using techniques based on VCG.

Further, by observing QRS- and T-wave loops, we may obtain extra features, and this is of benefit for further observation and analysis during the progress of the ventricle activation front. This is because it may require a longer time for the evolution of the activation front to

proceed throughout the ventricular mass of the heart [62]. In addition, using VCG loops, it is easier to observe the direction and magnitude of the heart vector. Usually, recorded ECG cannot explain both the direction and magnitude of the heart vector. However, to observe the direction and magnitude of the heart vector, the VCG signal is required. Now, the VCG signal can be directly recorded *via* the Frank lead system or can be derived from the ECG signal using a transform method [singular value decomposition (SVD) or inverse Dower transform (IDT)] or *via* matrix coefficients (Kors). In addition, VCG loops may have clinical importance for detecting cardiac diseases such as myocardial infarction or myocardial injury in coronary surgery over conventional ECG analysis [19, 94], which is not easy to observe from a scalar ECG signal. Therefore, it has been proposed over recent decades by various researchers that VCG has significant utility compared to the standard 12-lead standard ECG [13, 14, 60, 84]. As VCG represents the spatial and temporal information of the heart action, it is thought to be a very promising tool for diagnosis of heart diseases [12, 73, 93, 96] and also can be extended as a marker for biometrics [1].

Therefore, this paper focuses on a review of techniques, findings, and efficacy of beat-to-beat VCG approach for analyzing repolarization abnormalities.

Synthesis of VCG

VCG from Frank (X, Y, and Z) lead

For clinical studies, the VCG signal is recorded directly from the surface of the body. However, in older studies, VCG was recorded from the body using a special approach that directly provided the three orthogonal components of the dipole vector, based on the Frank VCG lead system [25]. This system consists of seven electrodes. There are five electrodes in the transverse plane; one electrode is on the back of the neck and one on the left foot, as shown in Figure 2. By utilizing the Frank VCG lead system, a three-dimensional representation of electrical heart activity can be found directly by measuring ECG in three different directions (Figure 2), i.e., right-to-left (X-axis), head-to-feet (Y-axis), and front-to-back (Z-axis).

There are a number of reasons why the Frank VCG lead system is no longer used for clinical practice, mainly due to its non-standard lead configuration. Hence, an important current issue is to derive VCG from standard 12-lead ECG for improving diagnosis of heart signals. Although, a study demonstrated quantitatively for deriving VCG signal

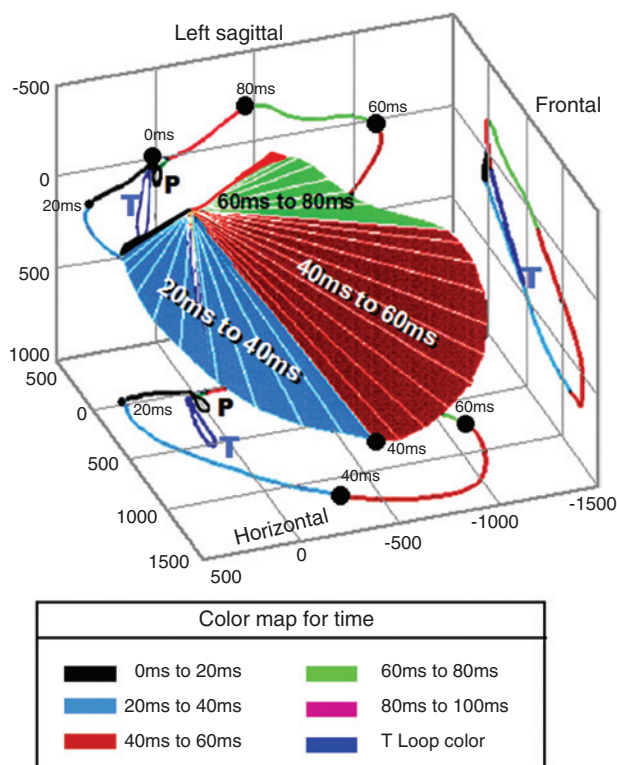


Figure 1: The basic principle of vectorcardiography (after [31]). Electrical activity of the heart in the three perpendicular directions X, Y, and Z. The P, QRS, and T wave loops are observed in three different planes (sagittal, frontal, and horizontal).

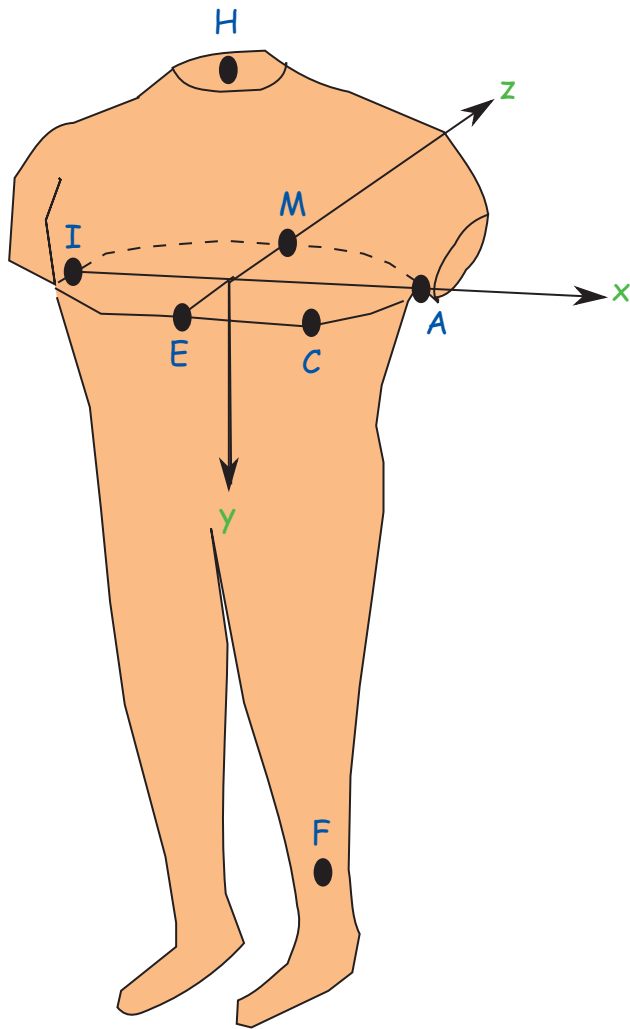


Figure 2: Frank VCG lead system (adapted after [1]). The Frank VCG lead system consists of seven unipolar electrodes, and signals are viewed in three (X, Y, and Z) directions.

using the non-linear optimization technique from three-lead ECG (I, II, V_2), which is believed to have higher correlation with the corresponding measured scalar leads [77]. However, this study needs further research for deriving beat-to-beat VCG signal from multiple databases, as the technique is based on a median beat of three-lead ECG.

VCG from 12-lead ECG

To derive VCG from standard 12-lead ECG, several techniques have been proposed [33, 63, 78, 79]. However, existing methods are limited and not yet standardized. One of the techniques suggested by Edenbrandt and Pahlm [23] is called the IDT, which is the pseudo-inverse of the matrix

proposed by Dower [22]. Another technique was introduced by Kors et al. [54] for synthesizing the VCG from standard 12-lead ECG. These simple estimated transformation matrices are most commonly used to synthesize the VCG from 12-lead ECG. However, a number of studies have investigated the reliability of these estimated matrices, where the findings showed that this type of transformation has a number of limitations in achieving orthogonal VCG reconstruction [32, 33, 63]. The main problem of the proposed transform matrices is due to estimation during reconstruction that gives rise to potential information loss or even unwanted information. Furthermore, the derived orthogonal leads from 12-lead ECG by applying these matrices may differ from those obtained from the actual VCG leads.

However, an alternative technique using SVD is suggested by Acar and Koymen [2] for deriving the VCG from 12-lead standard ECG for a single ECG beat. Here, the SVD is applied to the eight independent leads (I, II, V_1 , V_2 , V_3 , V_4 , V_5 , and V_6) of the standard 12-lead ECG configuration to obtain eight decomposed signals. The first three decomposed signals comprise an ECG dipole (see Figure 3), and 99% of the ECG energy can be represented in a three-dimensional minimum subspace [2], which are similar to the orthogonal components obtained from the Frank VCG. However, the method of Acar et al. [3], for single ECG beat analysis, does not provide detailed analysis on a beat-by-beat basis and does not completely provide the characteristics of beat-to-beat VCG based analysis. This is an issue as cardiac electrical activity is not regular or stationary but has non-linear characteristics. Therefore, to address this problem, our recent article [39] considered and extended beat-to-beat VCG analysis by employing an SVD approach, which was introduced by Acar and Koymen [2]. For extracting the beat-to-beat QT intervals, we have used the T-wave template matching algorithm proposed by Berger et al. [10]. We computed the beat-to-beat QT interval for each individual lead in 12-lead ECGs by adopting an approach that has been previously described [40]. Thus, we are able to obtain beat-to-beat QRS- and T-wave signals from standard 12-lead ECGs for beat-to-beat VCG analysis.

Moreover, in the reconstructed VCG, the signals are resolved into three components (X, Y, and Z directions). These three orthogonal signals facilitate the construction of ventricular depolarization (QRS wave) and the repolarization (T wave) loop (see Figure 3) for various VCG-based parameter extractions. These parameters and indices may be essential factors for characterizing the temporal and spatial changes in the QRS and T loops in ventricular depolarization and repolarization.

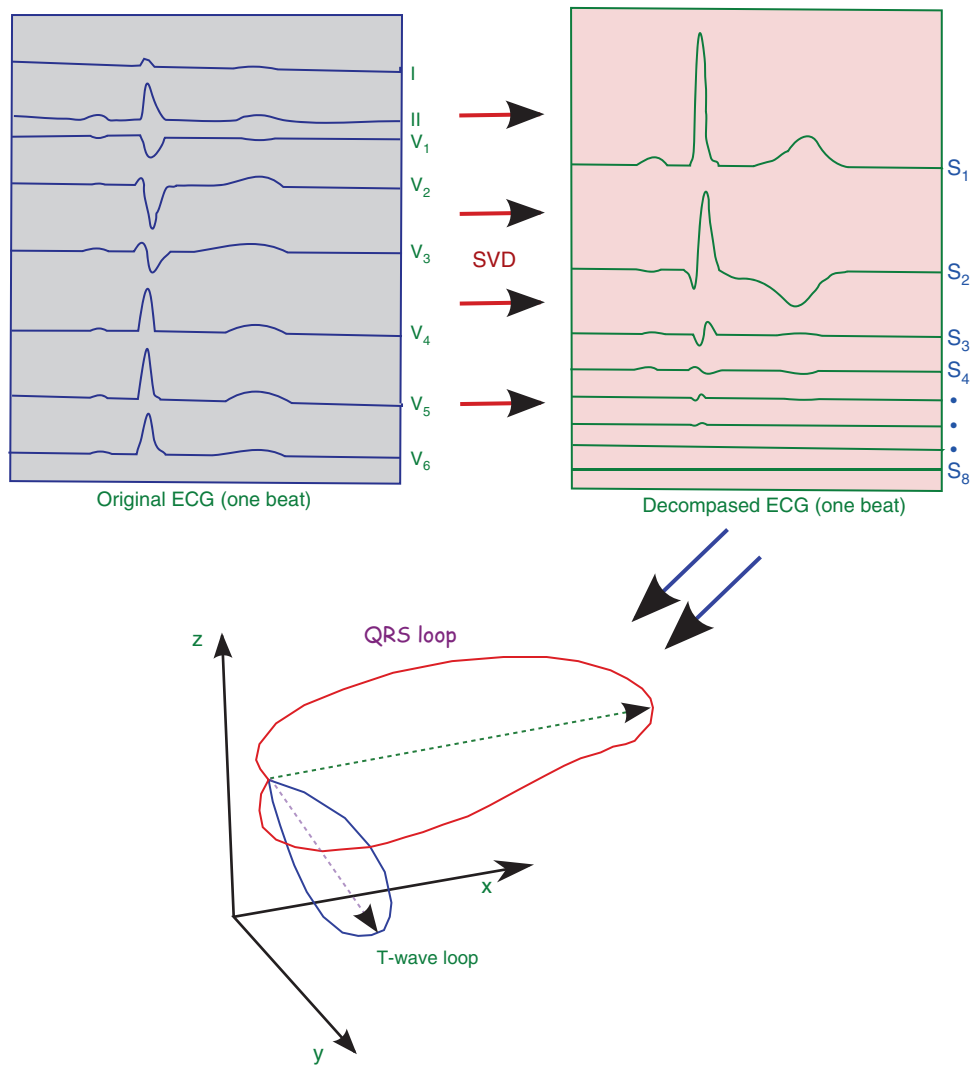


Figure 3: Eight independent leads.

Eight independent leads as input (top left) and eight decomposed ECG signal (top right) for a single-beat ECG after applying SVD transformation. The QRS and T wave loop for a single-beat ECG (bottom), where arrow refers the main vector of QRS and T wave.

VCG-based parameters

Several VCG-based parameters were proposed in last few decades for identifying and characterizing various cardiac patients [3, 39, 50, 58, 68, 96, 97]. A brief description of several VCG-based parameters is given below.

Total cosine R to T

Total cosine R to T (TCRT) measures the vector deviation between the depolarization and the repolarization waves by calculating cosine values between the dominant QRS

loop vectors and the main T-wave loop vectors within the optimized decomposition space [3]. Note that TCRT values are limited to the range of -1 to +1 range. Minus one corresponds to an angle of 180° , indicating that the QRS- and T-wave loops are pointing in opposite directions. By contrast, +1 corresponds to an angle of 0° , indicating that the QRS- and T-wave loops are pointing at the same direction. In [3], the mean value of TCRT was found to be negative in hypertrophic cardiomyopathy (HCM) patients but positive in healthy subjects. The negative TCRT value in HCM patients indicates increased deviation between repolarization (QRS) and depolarization (T) waves in terms of their principal direction in a three-dimensional time-orthogonal space.

T-wave morphology dispersion

T-wave morphology dispersion (TMD) represents the variation of morphology of T-waves between different ECG leads during complete ventricular repolarization [3]. It is computed as the average of angles between all possible pairs of the reconstruction vector, as shown in Figure 4. A small TMD value implies the reconstruction vectors of different ECG leads are close to each other or T-wave morphologies in different ECG leads are similar. The TMD is defined as the mean of all θ_{ij} excluding V_1 as follows:

$$\text{TMD} = \frac{1}{21} \sum_{i,j} \in \Gamma, \text{ where } \Gamma = \{I, II, V_1, V_2, V_3, V_4, V_5, V_6\}. \quad (1)$$

In the study by Acar et al. [3], a significantly increased TMD value was observed in HCM patients compared to healthy subjects, which basically reflects the spatial and temporal variations of repolarization (T-wave) pattern in HCM patients.

Percentage of loop area

Generally, percentage of loop area (PL) is computed as the ratio of the T-wave loop area to the area of the surrounding rectangle, where the rectangular area is divided into 100 equal rectangular cells, as shown in Figure 5. This parameter defines the regularity of the T-wave loop [3]. For large PL, the T-wave loop is considered to be smooth and connected, but a lower value of PL is due to a more irregular T-wave loop. A higher PL value was found in

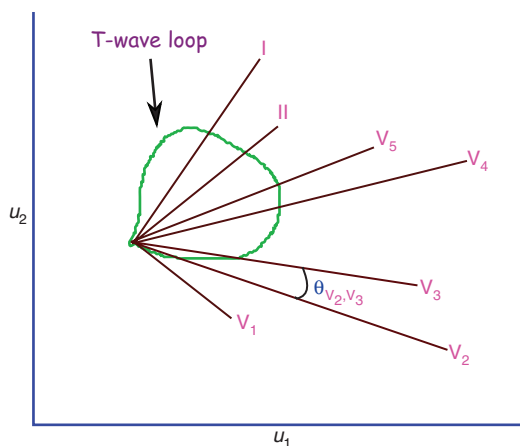


Figure 4: T-wave morphology dispersion. Projection of different constructed ECG leads on u_1 and u_2 planes for T-wave loop.

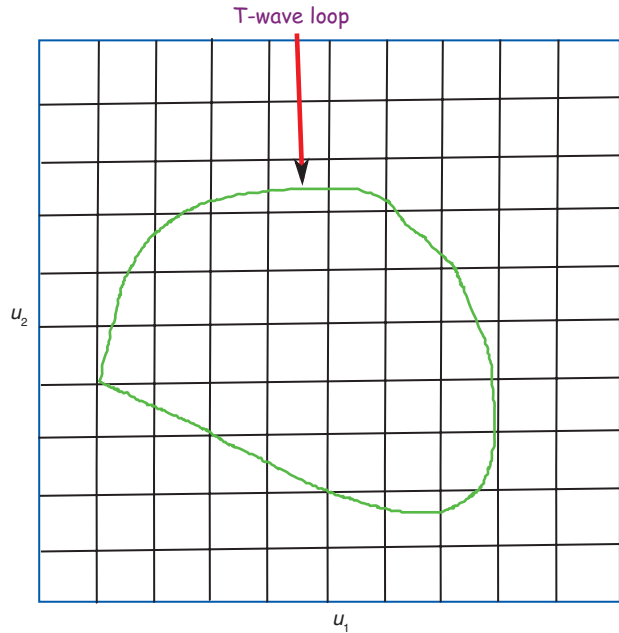


Figure 5: Percentage of loop area (PL). Projection of T-wave loop on u_1 and u_2 planes.

healthy subjects compared to HCM patients that indicates a smooth and connected T-wave loop (not crossing itself) in normal ECGs compared to HCM ECGs [3].

Lead dispersion

Lead dispersion (LD) measures temporal variation in inter-lead relationships during ventricular repolarization [3]. This is the measurement of the temporal homogeneity of the propagation of the repolarization wave. If the value of LD is significantly different between two groups of subjects, then T-wave loops are discriminative. In the study by Acar et al. [3], the mean values of LD were similar in healthy subjects and HCM patients, which shows that the loop itself is not discriminative for healthy subjects and HCM patients. However, Lin et al. [59] demonstrated a significantly higher LD in patients with ventricular tachycardia (VT)/ventricular fibrillation (VF) compared to patients without VT.

Azimuth and elevation

Generally, the spatial orientation of the maximum T-wave vector is defined by its azimuth and elevation. Usually, the azimuth is considered as the angle in the transverse plane. The value of azimuth can be interpreted as follows: 0° , left; $+90^\circ$, front; -90° , back; and 180° , right.

In addition, the elevation is defined as the angle from 0° (caudal direction) to 180° (cranial direction), basing the elevation of the T-wave on the angle in the cranio-caudal direction. Significant leftward azimuthal orientation was found compared with left circumflex artery patients and downward elevation compared with both right coronary artery and left coronary artery patients [75].

Complexity ratio

The index complexity ratio (CR) reflects the complexity of repolarization. The principal component analysis provides the identification of a set of eight values, which represent the relative magnitude of spatial components of repolarization [70]. This parameter describes the global shape abnormalities of the repolarization wave, which is defined as the second component divided by the first component of eigenvalue decomposition given as a percentage. The relative contribution of these components can be used to estimate the complexity. This index may provide identification of patients with abnormal repolarization. In the study by

Zabel et al. [96], the CR value was found to be significantly different in all patient groups, but it was not significant in patients with and without arrhythmic events.

However, in this article, a brief description of VCG-based parameters is discussed in the following sections based on a single-beat and a beat-to-beat basis.

Single-beat VCG-based parameters

Patients with various cardiac condition (arrhythmogenesis, myocardial infarction, heart failure, hypertrophic cardiomyopathy) were investigated using several VCG parameters in several studies [3, 27, 59, 96]. A summary of the VCG-based parameters employed in single-beat analysis is given in Table 1.

Beat-to-beat VCG-based parameters

The analysis of VCG parameters based on single-beat ECG for different cardiac conditions and the investigation of

Table 1: Analysis of single-beat VCG-based parameters and their findings.

Study	VCG parameters	Groups	Main findings
[3]	1. TCRT 2. TMD 3. LD 4. PL	Supine resting healthy subjects (n=76) HCM (n=63)	The proposed VCG parameters (TCRT, TMD, and PL) were able to show the prognostic capabilities for differentiating patients with HCM from healthy subjects. However, the parameter LD was found to be similar for both studied subjects.
[96]	1. TCRT 2. TMD 3. CR 4. Normalized T-wave loop area (NTLA)	Consecutive post-MI patients (n=280) Men (n=229) Women (n=51)	The TCRT parameter was found to be a strong risk predictor in this study. However, the TMD value did not show significant differences in studied groups. In patients with and without arrhythmic events, the CR value was not promising. However, it showed significant differences in all patient groups. Finally, the NTLA value was significantly differences in the patient group with events ($p<0.05$).
[27]	1. TCRT 2. TMD 3. NTLA	HCM (n=54) Healthy subjects (n=70)	Significantly lower TCRT, higher TMD, and decreased NTLA values were found in HCM patients compared to healthy subjects ($p<0.01$) in supine position, which suggests that these parameters might be useful for assessing repolarization abnormalities of HCM patients.
[97]	1. TCRT 2. TMD 3. CR 4. NTLA	Male US veterans (n=772) Dead (n=252) Alive (n=520)	Significantly lower TCRT, higher TMD, and increased CR values were found in increased risk of death subjects ($p<0.02$), which demonstrates the reproducibility of the proposed parameter. However, no significant repolarization heterogeneity was found in patients who had events (death) during long-term follow-up.
[95]	1. TCRT	Post-MI patients (n=280) with 27 events (death or non-fatal sustained VT/VF)	TCRT value was found to be univariately associated ($p=0.0002$) with the events.
[8]	1. TCRT	MI patients (n=334)	Reduced TCRT value was observed in cardiac and arrhythmic death in patients post-MI, which reflects increased repolarization heterogeneity in MI patients.

(Table 1: continued)

Study	VCG parameters	Groups	Main findings
[18]	1. TCRT	Male (n=8) Female (n=2)	The effortful mental arithmetic and isometric handgrip exercise tasks appeared to be inhomogeneous of TCRT values compared to the effortless control condition.
[58]	1. TCRT 2. TMD 3. NTLA 4. LD	End-stage renal disease patients Survivors (n=171) All-cause death (n=154)	No significant TCRT and TMD differences were found between survivors and all-cause death patients that suggest these parameters may not be useful for studying this type of patients. Further, same scenario occurred between cardiovascular mortality and non-cardiovascular mortality. However, the parameter LD demonstrated as an independent predictor of repolarization heterogeneity between survivors and all-cause mortality.
[26]	1. TCRT	Near-consecutive cohort of patients Healthy subjects (n=33) Patients (n=121)	The TCRT value may distinguish a primary from secondary T-wave abnormalities.
[51]	1. TCRT	Type 1 diabetic patients (n=16) Healthy subjects (n=8)	The TCRT values were significantly lower in the diabetic patients compared to healthy subjects ($p<0.05$), which indicates about the prognostic capability of this parameter in clinical application.
[46]	1. TCRT	Acute MI patients (n=45) Healthy subjects (n=25)	Computation of TCRT was failure in several AMI patients. However, small improvements of the basic TCRT algorithm may decrease the failures up to 82%.
[59]	1. TCRT 2. TMD 3. NTLA 4. LD	Heart failure patients With VT/VF (n=27) Without VT as control (n=54)	The TCRT, TMD, and NTLA values were not significantly different between these studied groups ($p>0.05$). However, significantly higher LD was found in patients with VT/VF compared to without VT.
[43]	1. TCRT 2. TMD 3. PL 4. LD	Patients with systolic heart failure (n=650)	The TCRT value was unable to demonstrate the differences between all-cause mortality and survival groups ($p=0.07$). However, opposite scenario was found between cardiovascular and non-cardiovascular death. Similarly, TMD, PL, and LD were also not to be found significant differences between all-cause mortality and survival groups ($p>0.05$) as well as between cardiovascular and non-cardiovascular death ($p>0.05$).
[44]	1. TCRT	Patients after MI With VT (n=30) Without VT (n=13)	Significant differences of TCRT values were observed between group of patients with VT and group of patients without VT.
[68]	1. TCRT 2. TMD	Total adults (n=5917) Men (n=2674) Women (n=3243)	The TCRT value was not statistically significant different in men (all-cause and cardiovascular mortality). However, was significant different in women (all-cause and cardiovascular mortality). Similarly, women showed higher value of TMD than men in all-cause and cardiovascular mortality.
[76]	1. Spatial QRS-T angle 2. Azimuth and elevation	Population (n=660)	Spatial QRS-T was found to be strongly depends on sex. In addition, the direction of azimuth showed toward anterior in male than in female group. Further, the elevation appeared to be significant differences between men and women.
[75]	1. Azimuth and elevation	Patients with stable CAD (n=35) Healthy subjects (n=10)	Azimuth was found to be significant leftward compared with left circumflex artery patients and elevation was more downward compared with both the right coronary artery and right coronary artery patients.
[21]	1. Spatial QRS-T angle	Healthy school-age children Male (n=348) Female (n=298)	Significantly higher spatial QRS-T angle was found in boys compared to girls ($p=0.031$), which shows that the direction of depolarization and repolarization for boys appears to be close to each other.
[88]	1. Azimuth and elevation	Patients with structurally normal hearts (n=19)	Significantly increased elevation and azimuthal orientation was observed with increased HR, which indicates that the T-wave vector appears to move slightly upward and forward.

prognostic capabilities have received significant interest. However, little is known of VCG parameter analysis based on beat-to-beat cases. In addition to that, how these VCG parameters are influenced by beat-to-beat ECG is not completely understood. Nevertheless, recently, a few studies have investigated beat-to-beat VCG parameters in different cardiac populations and tested their independent predictive power for classifying patients [38, 39, 86]. A brief description of relevant beat-to-beat VCG-based

parameters and their relationship to the findings in a number of studies is summarized in Table 2.

Another interesting study was carried out by Karsikas et al. [47], where beat-to-beat variability of QRS-T angle was observed during an incremental exercise test. This study reported that the TCRT trend during exercise was negative and became more negative in healthy subjects compared to the patients with coronary artery disease (CAD). However, theoretically, TCRT ought to be toward a positive value in

Table 2: Analysis of beat-to-beat VCG-based parameters and their findings.

Study	VCG parameters	Groups	Main findings
[47]	1. TCRT 2. Cos (QRST angle) 3. Cos (plane angle)	CAD (n=10) Healthy subjects (n=10)	A negative trend of TCRT was observed during exercise, and it was more negative in healthy subjects compared to CAD patients.
[86]	1. R-peak cloud volume 2. T-peak cloud volume 3. T-/R-peak cloud volume	Structural heart diseases (n=414)	Increased volume of T-peak cloud seemed to be associated with higher risk of ventricular tachyarrhythmia.
[35]	1. R-peak cloud volume 2. T-peak cloud volume 3. T-/R-peak cloud volume	Patients with structural heart disease and ICD (n=81)	Higher volume of T-peak cloud appeared to be associated with higher risk of sustained ventricular tachyarrhythmias.
[69]	1. Spatial QRS-T angle 2. T-wave PCA	HCM (n=56) Healthy subjects (n=56) Athletes (n=69)	The suggested VCG parameters (spatial QRS-T angle, T-wave PCA) were found to be useful for detecting the HCM patients.
[50]	1. TCRT 2. QRS-T angle 3. TCRT/RR 4. QRS/RR	Exercise ECG recordings (n=1297) Men (n=872) Women (n=425)	Beat-to-beat VCG parameters from exercise ECG (TCRT-RR and QRST-RR) were found to be associated with mortality, especially with cardiac mortality and sudden cardiac death.
[49]	1. TCRT/RR 2. QRST/RR	Healthy subjects during exercise (n=40) Men (n=20) Women (n=20)	The suggested VCG parameters were found to be affected by HR and gender effect. Further, hysteresis was found in the TCRT/RR slopes for delayed rate adaptation.
[16]	1. Maximum magnitude of the depolarization vector of QRS loop 2. Volume of QRS loop 3. Planar area of QRS loop 4. Ratio between the area and perimeter of QRS loop 5. Ratio between the major and minor axes of QRS loop 6. QRS loop energy	Ischemic patients (n=80) that underwent PTCA	The proposed VCG parameters explained more about the morphological changes of QRS loop and reflects the modifications in the levels of cardiac ischemic before, during, and after PTCA.
[39]	1. DV_{QRS} 2. DV_T 3. MLL_{QRS} 4. MLL_T 5. TMD 6. TMP_{pre} 7. TMD_{post} 8. PL 9. TCRT	MI patients (n=84) Healthy subjects (n=69)	Most of the VCG parameters showed independent prognostic capabilities for diagnosing MI patients. However, TCRT did not seem to be capable of characterizing the MI patients from healthy subjects.
[85]	1. Mean spatial TT' angle 2. Normalized variances of T-wave loop area 3. Spatial T-vector amplitude 4. $T_{peak}-T_{end}$ area	Healthy subjects (n=160) Men (n=80) Women (n=80)	Healthy men showed higher repolarization lability of several VCG parameters than healthy women, where caution should be paid for gender-specific risk stratification study.

healthy subjects, compared to the CAD patient, due to the homogeneity of repolarization lability in healthy subjects, which was investigated by several studies for a single-beat ECG analysis [3]. The greater trend of TCRT toward a negative value might be found in healthy subjects due to a consequence of the experimental setup. Nevertheless, the study of Karsikas et al. [47] highlights that further research is required for beat-to-beat analysis for QRS-T angle measurements to assess the reliability of this parameter.

Two further different studies have found that the beat-to-beat three-dimensional ECG variability predicts ventricular arrhythmia (VA) in patients with structural disease and implanted implantable cardioverter defibrillator (ICD) using the same (R-peak cloud volume, T-peak cloud volume, T/R-peak cloud volume) VCG-based parameters [35, 86]. They suggested that large T-peak cloud volume (this cloud volume was computed as the volume within the convex hull) is associated with the increased risk of VA. However, this study was limited to an analysis of 30 consecutive beats. The VCG analysis of a higher number of beats may increase the validity of the outcome significantly.

In the same year, in 2010, Kenttä et al. [50] studied the beat-to-beat rate dependency and gender affect on spatial angle (TCRT or QRS-T angle) between QRS-T loops during exercise ECG. They suggested that the beat-to-beat individual patterns of TCRT and QRS/T angle are influenced by heart rate (HR) and gender. However, further study is required for ultimate validation before considering clinical implementation. Another study by Kenttä et al. [49] suggests that spatial angles (TCRT and QRS-T angles) might be strong predictors of sudden cardiac death for risk stratification where a larger database was used for analysis.

Correa et al. [16] introduced six (maximum magnitude of the depolarization vector of QRS loop, volume of QRS loop, planar area of QRS loop, ratio between the area and the perimeter of QRS loop, ratio between the major and the minor axes of QRS loop, and QRS loop energy) different VCG-based parameters to investigate the morphological changes in the QRS loop for ischemic patients that underwent percutaneous transluminal coronary angioplasty (PTCA). They showed that VCG-based parameters were significantly different before, during, and after PTCA. However, they considered only the QRS-loop VCG parameters for ischemic patients and the morphological changes in repolarization loop descriptors. Therefore, it might be interesting if future analysis can be extended by considering the T-wave loop as well.

Hasan et al. [39] proposed two new descriptors along with some existing depolarization and repolarization

indices for beat-to-beat VCG analysis. Point-to-point distance variability (DV) is one of them, which was determined based on the coefficient of variance of point-to-point distance from each loop to the mean loop of QRS- and T-wave loop. In addition, another new descriptor was mean loop length (MLL), which was calculated for the mean loop of the QRS and the T loop by adding the distance from each point to the next point in the loop. Significantly higher DV of the QRS- and T-wave loop was found in MI patients compared to healthy subjects [39]. However, the beat-to-beat TCRT value was not significant for identifying the MI patients in this study, which brings to attention the need for requiring further research before using these parameters for analyzing repolarization heterogeneity and cardiac risk stratification study.

Recent research in 2013, Sur et al. [85] suggested several VCG-based parameters for the analysis of ventricular depolarization and repolarization in healthy subjects based on gender. In this work, they suggested that the repolarization lability is gender dependent, with mostly men having higher repolarization lability than the women. In addition, Correa et al. [15] also studied seven VCG-based parameters (maximum vector magnitude, volume, planar area, maximum distance between centroid and loop, angle between XY and optimum plane, perimeter, and area-perimeter ratio). In this study, they demonstrated that several VCG-based parameters are found to be a significant marker for differentiating healthy subjects from ischemic patients. The details of the VCG-based parameters list are given in the Table 2 and their findings.

Factors affecting VCG

The factors that affect the VCG-based parameters are significantly lower than the standard ECG parameters. However, several factors need to be considered for the analysis of VCG-based parameters in clinical studies. Brief descriptions of the factors that may affect the VCG parameters are given below.

Heart rate dependency

The relationship between HR and VCG-based parameters has been investigated by a few studies [50, 76, 88]. Some of the studies demonstrated that the VCG parameters are dependent on the HR. Scherptong et al. [76] investigated VCG parameters (QRS-T angle and spatial ventricular

gradient) on a young healthy population. They showed a significant influence of HR on the spatial ventricular gradient magnitude, with an apparent inverse relation between HR and the spatial ventricular gradient. They concluded that the increased HR is associated with decreased spatial ventricular gradient magnitude.

Kenttä et al. [50] investigated the affect of HR on spatial VCG parameters during exercise ECG for healthy subjects and concluded that the HR has significant influence on VCG parameters (TCRT and QRS-T angle). Particularly, HR affects TCRT during exercise and recovery periods. In a supine position, the TCRT values were found to be higher compared to sitting and standing positions [7]; however, HR is increased during the exercise. As a result, the QRS-T angle increased, decreasing the value of TCRT. Thus, TCRT is influenced by HR. Vahedi et al. [88] also found that some computed VCG parameters (QRS_{area} , T_{area} , and $T_{amplitude}$) were also influenced by HR, where a decrease in heterogeneity of ventricular activity was observed due to increased HR.

Respiration

Respiration is one of the most important factors that may affect VCG loops or parameters. Respiratory activity influences ECG measurements with respect to both beat morphology and HR. The morphological beat-to-beat variations can be found in the ECG, during the respiratory cycle, and are mainly due to chest movements and changes in the position of the heart. The respiratory frequency is generally estimated from the respiration signal. As a result, the derived VCG loops are not synchronized due to the respiratory-induced changes or respiratory frequency in the electrical axis of the heart [74]. In addition, cardiac motion abnormalities may have some affect on VCG parameters during the process of magnetic resonance imaging (MRI). Due to the respiratory motion or irregular cardiac rhythms, the imaging of the heart is inherently prone to imaging artifact [64]. Thus, one needs to take into account the respiratory signal or respiratory frequency for the analysis of VCG loops. Thereby, the VCG analysis results may be affected. However, in 1998 and 2000, the articles published by Sörnmo [81] and Astrom et al. [5] developed the method for reducing the affect of respiration and muscular activity on VCG loops in a beat-to-beat manner. Mainly, they reduced the respiration influence by performing spatial and temporal maximum-likelihood (ML) alignment of the VCG loops, and this alignment was based on scaling, rotation, and time synchronization of the loops. Moreover, the affect

of respiration on VCG loops has been validated further, and the respiration frequency was estimated in the article proposed by Leanderson et al. [57]. In 2006, Bailón et al. [6] also estimated the respiratory frequency from VCG during the stress testing, which has demonstrated the influence of respiration and existence in the VCG loops. Recently, in 2009, Karsikas et al. [47] suggested that respiration significantly affects the beat-to-beat variability of all the QRS-T angle measures. Therefore, this study suggested that care should be taken when considering the reliability of VCG angle measures for one-beat analysis as compared to beat-to-beat analysis.

Nevertheless, this proposed ML VCG loop alignment technique was limited [5, 81]. For example, the proposed technique reduces the ability to include *a priori* information in any of the transformations. In addition, for low-quality signals, such as fetal ECG signal, the reliability of this method is reduced. To address this situation, in 2013, Vullings et al. [91] introduced the generic Bayesian framework to derive the beat-to-beat VCG loop alignment, where the existing ML method can also be derived. This Bayesian probability theory was applied to derive maximum *a posteriori* estimation for robust VCG loop alignment.

Gender

The problem of gender influence on VCG parameters is not fully understood yet. However, several studies have attempted to explore the relation between gender and VCG-based parameters. In 1968, a study was carried on 101 healthy male and 102 healthy female subjects to analyze VCG dependency on gender [82]. They found significant gender differences in several VCG-based parameters (maximal QRS and T vectors). In another study in 2002, Smetana et al. [80] observed substantial differences in repolarization homogeneity between male and female subjects. In 2008, Scherptong et al. [76] also tested spatial parameter dependency on gender and proposed that they are strongly sex dependent. Later, in 2012, Vahedi et al. [89] found that there were significant differences in spatial VCG-based parameters with gender and that the parameters are significantly higher in men compared to women. In agreement with the previous investigation, a recent study was conducted on healthy subjects for analyzing the VCG parameters by Sur et al. [85] in 2013. They concluded that healthy men showed higher repolarization lability for several VCG parameters compared to healthy women, which questions the factors that may contribute to influence the VCG parameters.

Age

Several researchers have investigated the influence of VCG parameters by considering the age effect [11, 24, 34]. All of the studies have found that the VCG-based parameters are age dependent. Guller et al. [34] observed that the size of the maximal spatial QRS vector was significantly decreased in first three days of a newborn baby. In their study, they found that the QRS duration is age dependent, and the most probable reason for the change in QRS configuration in newborn infants differences in the ventricular activation process. In addition, Brohet et al. [11] also demonstrated that infants younger than 6 months have higher levels of dispersion and disparate variation in VCG parameters (maximal spatial QRS vector, QRS-T angle) than older children.

VCG parameters for arrhythmic risk prediction

Many studies have demonstrated that several VCG parameters may have independent predictive power of cardiac events or mortality [4, 9, 45, 53, 67, 92]. Perkiömäki et al. [67] carried out a study for investigating the predictive power of the T-wave loop and QRS complex loop for cardiac mortality during follow-up of consecutive survivors of acute myocardial infarction (AMI). In this study, out of several other VCG parameters, they proposed that T-wave loop dispersion (TWLD) has independent predictive capabilities of cardiac death and clinical risk markers in patients with AMI. The TWLD parameter describes the irregularities of the T-wave loop during its course. Here, it was found that a negative correlation between TWLD and the height of the T-wave loop, and the height/width ratio of the T-wave loop also independently predicted cardiac mortality when adjusted for clinical risk markers. However, the computation of T-wave loop height and width requires further validation. Because, according to the description in this study, the value of height and width may be changeable and the ratio of height/width can differ in beat-by-beat ECG. However, this study successfully demonstrated that the changes in T-wave shape have the predictive power for cardiac mortality.

Similarly, the abnormal spatial QRS-T angle was studied by Kardys et al. [45] for cardiovascular risk prediction in a large data set for an elderly population. Here, the spatial QRS-T angle was considered as the angle between the mean spatial QRS axis and the mean spatial T axis.

The main contribution of this study was the population sets for increasing the statistical power and data analysis technique. However, a methodological limitation needed to be investigated and included in this study by observing the variations of QRS-T angle rather taking only the mean value of spatial QRS-T angle. This is due to variations of spatial QRS-T angle may provide an additional contribution to the prediction of high risk of cardiac mortality. This limitation was also found in another study [92], which is in line with the previous findings. However, the proposed spatial QRS-T angles for risk prediction can be used for further stratification of patients with standard ECG abnormalities as well as for clinical application.

Risk stratification study was conducted by Huang et al. [43] by proposing several VCG parameters (TCRT, TMD, LD, PL, and PO) for cardiovascular mortality in patients with systolic heart failure. However, only one parameter (TCRT) was found to be risk predictor for cardiovascular mortality in this proposed study, where other VCG parameters appeared to be not significant. The discrepancy in this result may be due to the selection of the data set, where the diversity of disease etiologies (including ischemia and non-cardiomyopathy) and different causes of death (including arrhythmia and pumping failure) may explain the discrepancy.

Moreover, the spatial ventricular gradient (sum of the areas within QRS complex and T wave) from VCG is potentially useful for assessing the abnormalities in repolarization properties before and after the ablation in patients with Wolff-Parkinson-White (WPW) syndrome. Mikio et al. [65] demonstrated that the directions of spatial ventricular gradient appears to be abnormal before ablation in patients with manifest WPW syndrome compared to healthy subjects. Moreover, the VCG approach is found to be more sensitive than ECG for the identification of pre-excitation site in WPW syndrome [28].

Computational methods for the diagnosis of cardiac diseases using VCG parameters

Several techniques are applied to transform VCG from multichannel ECG signal. However, it has been shown to have limitations in very-high-field MRI, specially, when two or three ECG leads are used for analyzing VCG [55]. Therefore, Gregory et al. [30] proposed a technique for MRI synchronization in high-field MRI that may even deal with arrhythmic beats (premature ventricular

contraction), commonly found in patients with ischemic histories or during stress perfusions studies. The computational methods are found to be promising for cardiac diseases and therapy planning through VCG analysis [83, 90]. Villongco et al. [90] also showed that patient specific models of ventricular depolarization can be used for estimating the left-bundle branch block and right ventricular-paced activation sequences from VCG parameters for a single dominant excitation wave. However, most cardiac diseases and activation sequences generally involve complex wave dynamics with multiple wavefronts, where the proposed single activation site and fixed dipole equivalent source model may be ineffective in describing the ventricular depolarization patterns in detail.

TCRT and TMD versus other non-invasive risk stratification methods

Whether it is better to use the scalar ECG parameters (such as HRV, QT dispersion, QTV, T-wave inversion, ST depression) or the VCG parameters (such as TCRT, TMD) for cardiac risk prediction is a controversial issue because both approaches have pros and cons in methodological steps and dependency on the quality and appropriate data sets [29, 61, 67, 71, 87, 98]. However, VCG parameters (TCRT and TMD) are found to be advantageous over other non-invasive risk predictors' parameters [43, 70, 92]. The main reason may be the computational feasibility with fewer errors in the parameters (TCRT/TMD) compared to other ECG parameters. One of the critical problems is in finding an accurate T-wave end for extracting other non-invasive ECG parameters for risk stratification [20, 56], which is considered to be a major source of inaccuracy in automatic QT extracted measurements [48, 52]. Proper identification of T-wave offset becomes a difficult task because of the slow transition of cardiac cells to the termination of the ventricular repolarization process, where accurate localization of the T-wave end point becomes a challenging task. In addition, breathing (inspiration and expiration) may have also some effect on the accuracy of the detected T-wave offset. Therefore, estimating the variability of repolarization can be affected to some extent by the challenge of T-wave end detection in ECG [17]. Meanwhile, VCG parameters may not need exact identification of the T-wave end [70] that improves the reproducibility of VCG-based parameters over other non-invasive ECG parameters for risk stratification study.

Future directions

As mentioned, the characteristics of beat-to-beat VCG-based parameters appear to be inconsistent. Therefore, future study may address this issue and validate the existing findings. Currently, measurements and analyzing techniques are offline. In the future, with advances in low-cost computing hardware, real-time three-dimensional visualization of VCG loops may provide better interpretation of VCG and may be of benefit for remote health-monitoring systems. The quantification of the spatial QRS-T angle is not currently familiar to most clinicians and it is not routinely available from the computerized electrocardiographic analysis software currently in use. Therefore, in future, it might be incorporated in the commercial computerized software with detailed interpretation so that clinicians can make proper decision for diagnosis of cardiac patients. In addition, it can be used for biometric identification as an alternative identification technique in parallel with the existing system. Finally, we may expect that, in the future, the developed algorithm can be implemented into a field programmable gate array board (e.g., [36]) for speeding the process and classification and for many other diagnostic purposes.

Conclusion

In conclusion, the concept of VCG analysis is a known approach for testing the homogeneity of repolarization lability. In addition, most of the earlier VCG studies were limited to a static beat. However, literature clearly shows that the beat-to-beat variability of VCG-based parameters does not exactly follow the same pattern but sometimes provides new information. In addition to that, factors that may contribute for affecting the VCG parameters need to be considered. Therefore, further research is required to validate the hypothesis for repolarization abnormalities using the VCG approach in a beat-to-beat manner.

Acknowledgments: Thanks are due to the editor and reviewers for their valuable comments for improving this manuscript.

Conflict of interest statement

Competing interests: The authors declare that they have no competing interests.

Author's contributions: M.A.H. designed the study. M.A.H. and D.A. carried out the interpretation. M.A.H. drafted the manuscript. M.A.H. and D.A. edited and revised the

manuscript. D.A. supervised the study. All authors read and approved the final manuscript.

References

- [1] Abdelraheem M, Selim H, Abdelhamid TK. Human identification using the main loop of the vectorcardiogram. *Am J Signal Process* 2012; 2: 23–29.
- [2] Acar B, Koymen H. SVD-based on-line exercise ECG signal orthogonalization. *IEEE Trans Biomed Eng* 1999; 46: 311–321.
- [3] Acar B, Yi G, Hnatkova K, Malik M. Spatial, temporal and wave-front direction characteristics of 12-lead T-wave morphology. *Med Biol Eng Comput* 1999; 37: 574–584.
- [4] Aro AL, Huikuri HV, Tikkanen JT, et al. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. *Europace* 2012; 14: 872–876.
- [5] Astrom M, Santos EC, Sörnmo L, Laguna P, Wohlfart B. Vectorcardiographic loop alignment and the measurement of morphologic beat-to-beat variability in noisy signals. *IEEE Trans Biomed Eng* 2000; 47: 497–506.
- [6] Bailón R, Sörnmo L, Laguna P. A robust method for ECG-based estimation of the respiratory frequency during stress testing. *IEEE Trans Biomed Eng* 2006; 53: 1273–1285.
- [7] Batchvarov V, Dilaveris P, Färbom P, et al. New descriptors of homogeneity of the propagation of ventricular repolarization. *PACE* 2000; 23: 1968–1972.
- [8] Batchvarov VN, Hnatkova K, Poloniecki J, Camm AJ, Malik M. Prognostic value of heterogeneity of ventricular repolarization in survivors of acute myocardial infarction. *Clin Cardiol* 2004; 27: 653–659.
- [9] Beckerman J, Yamazaki T, Myers J, et al. T-Wave abnormalities are a better predictor of cardiovascular mortality than ST depression on the resting electrocardiogram. *Ann Noninvasive Electrocardiol* 2005; 10: 146–151.
- [10] Berger RD, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation* 1997; 96: 1557–1565.
- [11] Brohet CR, Hoeven C, Robert A, Derwael C, Fesler R, Brasseur LA. The normal pediatric Frank orthogonal electrocardiogram: variations according to age and sex. *J Electrocardiol* 1986; 19: 1–13.
- [12] Carlson J, Havmoller R, Herreros A, Platonov P, Johansson R, Olsson B. Can orthogonal lead indicators of propensity to atrial fibrillation be accurately assessed from the 12-lead ECG? *Europace* 2005; 7: S39–S48.
- [13] Chou T-C. When is the vectorcardiogram superior to the scalar electrocardiogram? *J Am Coll Cardiol* 1986; 8: 791–799.
- [14] Correa R, Arini PD, Correa LS, Valentinuzzi M, Laciari E. Novel technique for ST-T interval characterization in patients with acute myocardial ischemia. *Comput Biol Med* 2014; 50: 49–55.
- [15] Correa R, Arini PD, Valentinuzzi ME, Laciari E. Novel set of vectorcardiographic parameters for the identification of ischemic patients. *Med Eng Phys* 2013; 35: 16–22.
- [16] Correa R, Laciari E, Arini P, Jané R. Analysis of QRS loop in the vectorcardiogram of patients with Chagas' disease. In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2010: 2561–2564.
- [17] Couderc J-P. Cardiac regulation and electrocardiographic factors contributing to the measurement of repolarization variability. *J Electrocardiol* 2009; 42: 494–499.
- [18] Critchley HD, Taggart P, Sutton PM, et al. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. *Brain* 2005; 128: 75–85.
- [19] Dahlin L-G, Ebeling-Barbier C, Nylander E, Rutberg H, Svedholm R. Vectorcardiography is superior to conventional ECG for detection of myocardial injury after coronary surgery. *Scand Cardiovasc J* 2001; 35: 125–128.
- [20] Daskalov I, Christov I. Automatic detection of the electrocardiogram T-wave end. *Med Biol Eng Comput* 1999; 37: 348–353.
- [21] Dilaveris P, Roussos D, Giannopoulos G, et al. Clinical determinants of electrocardiographic and spatial vectorcardiographic descriptors of ventricular repolarization in healthy children. *Ann Noninvasive Electrocardiol* 2011; 16: 49–55.
- [22] Dower GE, Machado HB, Osborne J. On deriving the electrocardiogram from vectorcardiographic leads. *Clin Cardiol* 1980; 3: 87.
- [23] Edenbrandt L, Pahlm O. Vectorcardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. *J Electrocardiol* 1988; 21: 361–367.
- [24] Edenbrandt L, Jonson B, Lundh B, Pahlm O. Sex- and age-related normal limits for the QRS complex in vectorcardiography. *Clin Physiol* 1987; 7: 525–536.
- [25] Frank E. An accurate, clinically practical system for spatial vectorcardiography. *Circulation* 1956; 13: 737–749.
- [26] Friedman HS. Determinants of the total cosine of the spatial angle between the QRS complex and the T-wave (TCRT): implications for distinguishing primary from secondary T-wave abnormalities. *J Electrocardiol* 2007; 40: 12–17.
- [27] Gang Y, Hnatkova K, Guo X, et al. Reproducibility of T-wave morphology assessment in patients with hypertrophic cardiomyopathy and in healthy subjects. *Comput Cardiol* 2001; 393–396.
- [28] Giorgi C, Nadeau R, Primeau R, et al. Comparative accuracy of the vectorcardiogram and electrocardiogram in the localization of the accessory pathway in patients with Wolff-Parkinson-White syndrome: validation of a new vectorcardiographic algorithm by intraoperative epicardial mapping and electrophysiologic studies. *Am Heart J* 1990; 119(Pt 1): 592–598.
- [29] Goldenberg I, Mathew J, Moss AJ, et al. Corrected QT variability in serial electrocardiograms in long QT syndrome the importance of the maximum corrected QT for risk stratification. *J Am Coll Cardiol* 2006; 48: 1047–1052.
- [30] Gregory TS, Schmidt EJ, Zhang SH, Ho Tse ZT. 3DQRS: a method to obtain reliable QRS complex detection within high field MRI using 12-lead electrocardiogram traces. *Magn Reson Med* 2014; 71: 1374–1380.
- [31] Grishman A, Donoso E. Spatial vectorcardiography. II. Mod Concepts Cardiovasc Dis 1961; 30: 693–696.
- [32] Guillem MS, Climent AM, Bollmann A, Husser D, Millet J, Castells F. Limitations of Dower's inverse transform for the study of atrial loops during atrial fibrillation. *PACE* 2009; 32: 972–980.
- [33] Guillem MS, Sahakian AV, Swiryn S. Derivation of orthogonal leads from the 12-lead electrocardiogram. Performance of an atrial-based transform for the derivation of P loops. *J Electrocardiol* 2008; 41: 19–25.
- [34] Guller B, Lau FY, Dunn RF, Pipberger HA, Pipberger HV. Computer analysis of changes in Frank vectorcardiograms of 666 normal infants in the first 72 hours of life. *J Electrocardiol* 1977; 10: 19–26.

- [35] Han L, Tereshchenko LG. Lability of R-and T-wave peaks in three-dimensional electrocardiograms in implantable cardioverter defibrillator patients with ventricular tachyarrhythmia during follow-up. *J Electrocardiol* 2010; 43: 577–582.
- [36] Hasan M, Reaz M. Hardware prototyping of neural network based fetal electrocardiogram extraction. *Meas Sci Rev* 2012; 12: 52–55.
- [37] Hasan MA, Abbott D, Baumert M. Beat-to-beat QT interval variability in the 12 lead ECG. *Comput Cardiol* 2011; 61–64.
- [38] Hasan MA, Abbott D, Baumert M. Beat-to-beat spatial and temporal analysis for QRS-T morphology. In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2012: 4193–4195.
- [39] Hasan MA, Abbott D, Baumert M. Beat-to-beat vectorcardiographic analysis of ventricular depolarization and repolarization in myocardial infarction. *PLoS One* 2012; 7: e49489.
- [40] Hasan MA, Abbott D, Baumert M. Relation between beat-to-beat QT interval variability and T-Wave amplitude in healthy subjects. *Ann Noninvasive Electrocardiol* 2012; 17: 195–203.
- [41] Hasan MA, Abbott D, Baumert M. Beat-to-beat QT interval variability and T-wave amplitude in patients with myocardial infarction. *Physiol Meas* 2013; 34: 1075–1083.
- [42] Hinterseer M, Thomsen MB, Beckmann B-M, et al. Beat-to-beat variability of QT intervals is increased in patients with drug-induced long-QT syndrome: a case control pilot study. *Eur Heart J* 2008; 29: 185–190.
- [43] Huang HC, Lin LY, Yu HY, Ho YL. Risk stratification by T-wave morphology for cardiovascular mortality in patients with systolic heart failure. *Europace* 2009; 11: 1522–1528.
- [44] Kania M, Fereniec M, Janusek D, et al. Optimal ECG lead system for arrhythmia assessment with use of TCRT parameter. *Biocybern Biomed Eng* 2009; 29: 75–82.
- [45] Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J* 2003; 24: 1357–1364.
- [46] Karsikas M, Huikuri H, Seppanen T. Improving reliability of “total-cosine-R-to-T” (TCRT) in patients with acute myocardial infarction. *Comput Cardiol* 2008; 373–376.
- [47] Karsikas M, Noponen K, Tulppo M, Huikuri HV, Seppanen T. Beat-to-beat variation of three-dimensional QRS-T angle measures during exercise test. *Comput Cardiol* 2009; 125–128.
- [48] Kautzner J, Yi G, Camm A, Malik M. Short-and long-term reproducibility of QT, QTc, and QT dispersion measurement in healthy subjects. *PACE* 1994; 17: 928–937.
- [49] Kenttä T, Karsikas M, Junttila MJ, et al. QRS-T morphology measured from exercise electrocardiogram as a predictor of cardiac mortality. *Europace* 2011; 13: 701–707.
- [50] Kenttä T, Karsikas M, Kiviniemi A, Tulppo M, Seppänen T, Huikuri HV. Dynamics and rate-dependence of the spatial angle between ventricular depolarization and repolarization wave fronts during exercise ECG. *Ann Noninvasive Electrocardiol* 2010; 15: 264–275.
- [51] Koivikko M, Karsikas M, Salmela P, et al. Effects of controlled hypoglycaemia on cardiac repolarisation in patients with type 1 diabetes. *Diabetologia* 2008; 51: 426–435.
- [52] Kors J, van Herpen G. Measurement error as a source of QT dispersion: a computerised analysis. *Heart* 1998; 80: 453–458.
- [53] Kors JA, Kardys I, van der Meer IM, et al. Spatial QRS-T angle as a risk indicator of cardiac death in an elderly population. *J Electrocardiol* 2003; 36: 113–114.
- [54] Kors JA, Van Herpen G, Sittig AC, Van Bommel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* 1990; 11: 1083–1092.
- [55] Krug J, Rose G, Stucht D, Clifford G, Oster J. Limitations of VCG based gating methods in ultra high field cardiac MRI. *J Cardiovasc Magn Reson* 2013; 15(Suppl 1): W19.
- [56] Laguna P, Thakor N, Caminal P, et al. New algorithm for QT interval analysis in 24-hour Holter ECG: performance and applications. *Med Biol Eng Comput* 1990; 28: 67–73.
- [57] Leanderson S, Laguna P, Sörnmo L. Estimation of the respiratory frequency using spatial information in the VCG. *Med Eng Phys* 2003; 25: 501–507.
- [58] Lin CY, Lin LY, Chen PC. Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in patients initiating haemodialysis. *Nephrol Dialysis Transplant* 2007; 22: 2645–2652.
- [59] Lin YH, Lin LY, Chen YS, et al. The association between T-wave morphology and life-threatening ventricular tachyarrhythmias in patients with congestive heart failure. *PACE* 2009; 32: 1173–1177.
- [60] Lingman M, Hartford M, Karlsson T, et al. Transient repolarization alterations dominate the initial phase of an acute anterior infarction—a vectorcardiography study. *J Electrocardiol* 2014; 47: 478–485.
- [61] Malik M, Hnatkova K, Batchvarov VN. Post infarction risk stratification using the 3-D angle between QRS complex and T-wave vectors. *J Electrocardiol* 2004; 37(Suppl): 201–208.
- [62] Malmivuo J, Plonsey R. *Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields*. Oxford: Oxford University Press 1995.
- [63] Man S, van Zwet E, Maan A, Schali J, M, Swenne C. Individually improved VCG synthesis. *Comput Cardiol* 2009; 277–280.
- [64] Maredia N, Radjenovic A, Kozerke S, Larghat A, Greenwood JP, Plein S. Effect of improving spatial or temporal resolution on image quality and quantitative perfusion assessment with k-t SENSE acceleration in first-pass CMR myocardial perfusion imaging. *Magn Reson Med* 2010; 64: 1616–1624.
- [65] Mikio S, Inden Y, Sawada T, et al. Comparison of vectorcardiographic and 12-lead electrocardiographic detections of abnormalities in repolarization properties due to preexcitation in patients with Wolff-Parkinson-White syndrome. *Jpn Heart J* 2000; 41: 295–312.
- [66] Murabayashi T, Fetics B, Kass D, Nevo E, Gramatikov B, Berger RD. Beat-to-beat QT interval variability associated with acute myocardial ischemia. *J Electrocardiol* 2002; 35: 19–25.
- [67] Perkiömäki JS, Hyytinen-Oinas M, Karsikas M, et al. Usefulness of T-wave loop and QRS complex loop to predict mortality after acute myocardial infarction. *Am J Cardiol* 2006; 97: 353–360.
- [68] Porthan K, Viitasalo M, Julia A, et al. Predictive value of electrocardiographic QT interval and T-wave morphology parameters for all-cause and cardiovascular mortality in a general population sample. *Heart Rhythm* 2009; 6: 1202–1208.
- [69] Potter SLP, Holmqvist F, Platonov PG, et al. Detection of hypertrophic cardiomyopathy is improved when using advanced rather than strictly conventional 12-lead electrocardiogram. *J Electrocardiol* 2010; 43: 713–718.
- [70] Priori SG, Mortara DW, Napolitano C, et al. Evaluation of the spatial aspects of T-wave complexity in the long-QT syndrome. *Circulation* 1997; 96: 3006–3012.
- [71] Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003; 348: 1866–1874.

- [72] Raghunandan D, Desai N, Mallavarapu M, Berger RD, Yeragani VK. Increased beat-to-beat QT variability in patients with congestive cardiac failure. *Ind Heart J* 2004; 57: 138–142.
- [73] Rautaharju PM, Warren J, Wolf H. Waveform vector analysis of orthogonal electrocardiograms: quantification and data reduction. *J Electrocardiol* 1973; 6: 103–111.
- [74] Riekkinen H, Rautaharju P. Body position, electrode level, and respiration effects on the Frank lead electrocardiogram. *Circulation* 1976; 53: 40–45.
- [75] Rubulis A, Jensen SM, Näslund U, Lundahl G, Jensen J, Bergfeldt L. Ischemia-induced repolarization response in relation to the size and location of the ischemic myocardium during short-lasting coronary occlusion in humans. *J Electrocardiol* 2010; 43: 104–112.
- [76] Scherptong RW, Henkens IR, Man SC, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J Electrocardiol* 2008; 41: 648–655.
- [77] Schreck DM, Fishberg RD. Derivation of the 12-lead electrocardiogram and 3-lead vectorcardiogram. *Am J Emerg Med* 2013; 31: 1183–1190.
- [78] Shvilkin A, Bojovic B, Vajdic B, Gussak I, Zimetbaum P, Josephson ME. Vectorcardiographic determinants of cardiac memory during normal ventricular activation and continuous ventricular pacing. *Heart Rhythm* 2009; 6: 943–948.
- [79] Shvilkin A, Bojovic B, Vajdic B, et al. Vectorcardiographic and electrocardiographic criteria to distinguish new and old left bundle branch block. *Heart Rhythm* 2010; 7: 1085–1092.
- [80] Smetana P, Batchvarov VN, Hnatkova K, Camm AJ, Malik M. Sex differences in repolarization homogeneity and its circadian pattern. *Am J Physiol Heart Circul Physiol* 2002; 282: H1889–H1897.
- [81] Sörnmo L. Vectorcardiographic loop alignment and morphologic beat-to-beat variability. *IEEE Trans Biomed Eng* 1998; 45: 1401–1413.
- [82] Sotobata I, Richman H, Simonson E, Fukumoto A. Sex differences in the vectorcardiogram. *Circulation* 1968; 37: 438–448.
- [83] Sovilj S, Magjarević R, Lovell NH, Dokos S. A simplified 3D model of whole heart electrical activity and 12-lead ECG generation. *Comput Math Methods Med* 2013; 2013: 1–10.
- [84] Strauss DG, Olson CW, Wu KC, et al. Vectorcardiogram synthesized from the 12-lead electrocardiogram to image ischemia. *J Electrocardiol* 2009; 42: 190–197.
- [85] Sur S, Han L, Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. *PLoS One* 2013; 8: e57175.
- [86] Tereshchenko LG, Han L, Cheng A, et al. Beat-to-beat three-dimensional ECG variability predicts ventricular arrhythmia in ICD recipients. *Heart Rhythm* 2010; 7: 1606–1613.
- [87] Turrini P, Corrado D, Basso C, Nava A, Bauce B, Thiene G. Dispersion of ventricular depolarization-repolarization a non-invasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2001; 103: 3075–3080.
- [88] Vahedi F, Haney MF, Jensen SM, Näslund U, Bergfeldt L. Effect of heart rate on ventricular repolarization in healthy individuals applying vectorcardiographic T vector and T vector loop analysis. *Ann Noninvasive Electrocardiol* 2011; 16: 287–294.
- [89] Vahedi F, Odenstedt J, Hartford M, Gilljam T, Bergfeldt L. Vectorcardiography analysis of the repolarization response to pharmacologically induced autonomic nervous system modulation in healthy subjects. *J Appl Physiol* 2012; 113: 368–376.
- [90] Villongco CT, Krummen DE, Stark P, Omens JH, McCulloch AD. Patient-specific modeling of ventricular activation pattern using surface ECG-derived vectorcardiogram in bundle branch block. *Progr Biophys Mol Biol* 2014; 115: 305–313.
- [91] Vullings R, Mischi M, Oei SG, Bergmans JWM. Novel Bayesian vectorcardiographic loop alignment for improved monitoring of ECG and fetal movement. *IEEE Trans Biomed Eng* 2013; 60: 1580–1588.
- [92] Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. *Heart Rhythm* 2005; 2: 73–78.
- [93] Yang H, Bukkapatnam ST, Komanduri R. Spatiotemporal representation of cardiac vectorcardiogram (VCG) signals. *Biomed Eng Online* 2012; 11: 1–15.
- [94] Yang Q, Kiyoshige K, Fujimoto T, et al. Vector u loop in patients with old myocardial infarction. *Clin Cardiol* 1989; 12: 277–282.
- [95] Zabel M, Malik M. Practical use of T wave morphology assessment. *Cardiac Electrophysiol Rev* 2002; 6: 316–322.
- [96] Zabel M, Acar B, Klingenhöben T, Franz MR, Hohnloser SH, Malik M. Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. *Circulation* 2000; 102: 1252–1257.
- [97] Zabel M, Malik M, Hnatkova K, et al. Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. *Circulation* 2002; 105: 1066–1070.
- [98] Zhang Z-m, Prineas RJ, Case D, Soliman EZ, Rautaharju PM. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). *Am J Cardiol* 2007; 100: 844–849.