

Cardiac regulation and electrocardiographic factors contributing to the measurement of repolarization variability

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Abstract

Cellular and macroelectrical instability within the heart ventricles during repolarization is described as a potential triggering mechanism of life-threatening arrhythmias. Although this phenomenon was observed in animal and in vitro studies, significant efforts have been put into the design of computerized technologies to quantify very subtle variations of the repolarization signal from the surface electrocardiograms. These technologies aim at capturing repolarization instability of ventricular repolarization while controlling for the normal variability. Currently, the methods have focused on the autonomic regulation of the heart rate as a primary confounding factor (such as in the QT variability index). However, there are other factors that can influence the measurements of beat-to-beat variability of the repolarization segment. Among them, the amplitude of the repolarization signal, the selected lead, and the heart vector orientation are very important and too often neglected in clinical investigations. We will discuss these factors and provocatively describe why they should be cautiously considered to avoid erroneous measurements of repolarization instability.

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Keywords:

QT variability; QT/R-R coupling; Risk stratification; Electrocardiogram; Heart rate variability

1. Introduction

Although microvolt T-wave alternans (TWA) is an accepted investigational tool for primary and secondary prevention of fatal arrhythmias and sudden cardiac death, the interest for extending the analysis of alternating repolarization oscillations to nonalternating repolarization variability has been steadily growing during the past decade. This interest has been primarily driven by the current limitations of the clinical method for measuring TWA. Indeed, TWA identification still requires the use of special electrocardiogram (ECG) equipment. T-wave alternans measured from Holter ECG recorders and other ambulatory recordings remains under evaluation.^{1–4} Furthermore, the clinical TWA test is a provocative test requiring the gradual elevation of the patient heart rate above 100 beats/min and thus excludes the patients who have chronotropic incompetence, intolerance to exercise, large numbers of ventricular ectopic beats, and/or atrial fibrillation.⁵ Finally, there is a considerable variation in reported diagnostic performances of this test. In average, it has a high negative predictive values (~95%), but

it suffers from a low average positive predictive value (PPV, <30%).⁶ In 2008, Gold et al⁵ emphasized the role of drug therapy as a potential explanation for the disparity of results and the TWA-reducing role (blunting heart rate response during exercise) of β -blockers in particular. In the Alternans Before Cardioverter Defibrillator (ABCD) trial, Costantini et al⁷ confirmed this statement while reporting low PPV and high negative predictive value of the TWA test in patients with ischemic heart disease and nonsustained ventricular arrhythmias. The reason for the large variation of the PPV of the TWA test between studies remains to be fully elucidated.

It is in this context that the analysis of the nonperiodic ventricular repolarization (VR) instability is presented as a unique opportunity for complementing the usefulness of the TWA tests.⁸ A series of ECG signal processing techniques have been designed, and they commonly reported an increased nonalternating repolarization instability in patients with an increased risk for life-threatening arrhythmias. This result was shown in patients after myocardial infarction and with a low ejection fraction (Multicenter Automatic Defibrillator Implantation Trial II type population),^{9,10} in patients with hypertrophic cardiomyopathy,¹¹ in long QT syndrome patients,^{12,13} in ischemic and nonischemic cardiomyopathy patients,¹⁴ and finally in individuals exposed to drugs with arrhythmogenic properties.¹⁵

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In this article, we aim at briefly reviewing the factors that can influence cardiac variability and discuss their potential contribution to the measurements of repolarization variability. We will discuss the technical challenges associated with the measurement of nonalternating repolarization instability and on-purpose provocatively present the factors that are too often overlooked.

2. The regulation of the heart and its VR: a brief overview

Cardiac regulation is realized by a set of mechanisms and feedback systems described as the nervous, the endocrine, and the serum controls. The serum control happens through the extracellular potassium, calcium, magnesium, and sodium concentrations. A modification of their concentrations may lead to abnormal ion exchange and lethal outcome (hypokalemia or hypocalcemia can precipitate arrhythmias). The endocrine control occurs via the adrenal medulla and the thyroid. The nervous control is the most predominant controlling mechanism. It includes the autonomic nervous system (ANS) and the cardiac reflexes. The first one is driven by the sympathetic and the parasympathetic balances, whereas the second one relies on chemoreceptor and the

baroreceptor monitors pH and blood pressure. Obviously, these factors have an impact on all cells of the heart. In this article, we will focus on the cardiac VR process understanding that electrical activities of the atria and depolarization of the ventricles are intrinsically dependent on these regulatory mechanisms as well.

These nervous, endocrine, and serum controls are part of the physiological regulating factors, but clinical and technical factors are also important when measuring VR variability. Fig. 1 provides a schematic description of these factors and their known interactions (circles with a common surface represents potential interactions). The right part of the figure describes the various electrocardiographic expressions of the presence of myocardial substrate or vulnerability to cardiac arrhythmias: QT/QTc prolongation, abnormal repolarization heterogeneity, and exercise-induced ST elevation/depression. They reveal the existence of myocardial substrate, whereas TWA, abnormal QT/R-R dynamicity, increased QT and T-wave variability, and ST changes are associated with the presence of myocardial vulnerability.

The effect of other factors, such as the autonomic balance,¹⁷ the repolarization adaptation to heart rate,¹⁸ and the heart rate dependency, is more difficult to assess because their level is subject dependent.

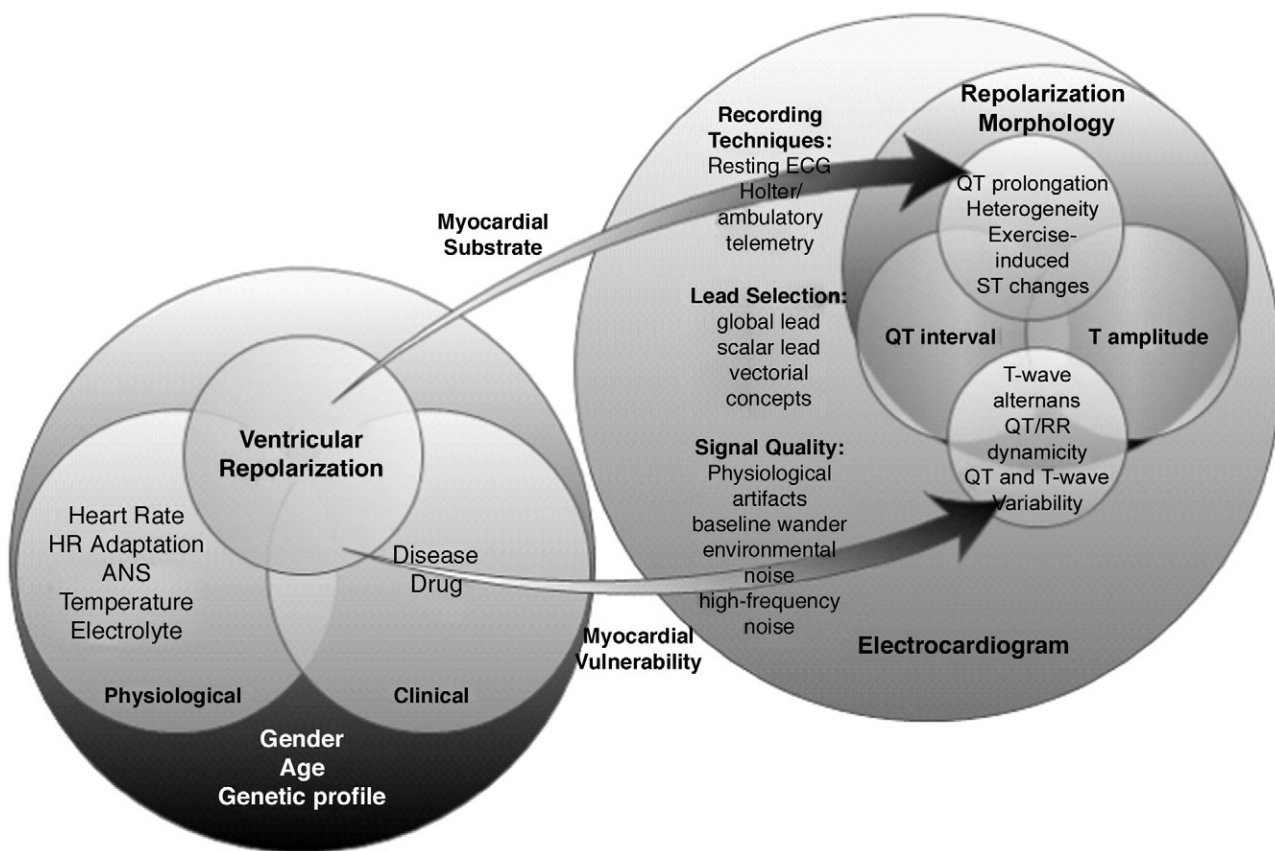


Fig. 1. Schema summarizing the list of factors influencing the VR process of the heart and the various electrocardiographic signs revealing the presence of myocardial arrhythmogenic substrate or myocardial vulnerability. In this schema, circles with common areas represent interaction between the associated groups of factors. For instance, a drug is defined as a clinical factor that can influence the VR directly or by modifying heart rate (HR), HR adaptation, and the ANS. Also, the effect of a drug might be dependent on an individual's age, sex, and genetic profile and electrolyte balance. The physiological and clinical factors can depend on the genetic makeup, age, and sex of a given individual. Reprinted with permission from Couderc.¹⁶

3. Physiological and clinical sources of repolarization variability

The morphology and the timing of the action potentials from the myocardial cells within the ventricles, during the repolarization process, produce the voltage gradient responsible for the inscription of the T wave on the ECG. The shape and duration of the T waves depend on the associated activation sequence, that is, the sequence in which the heart muscle is repolarized. Among the factors affecting the T-wave morphology, the body position,¹⁹ temperature,²⁰ electrolytes,²⁰ the recording technique, the lead choice,²¹ the subject age and sex,²² and the individual genetic profile are important.

3.1. Heart rate

The major component involved in the variability of the repolarization interval (including the scalar QT interval duration) is the heart rate. This relationship is visually obvious on the surface ECGs, but the accurate characterization of the QT/RR coupling remains an unresolved problem of modern quantitative electrocardiography. Several groups have worked on the definition of mathematical models describing this relationship. The works from Nollo et al,²³ Speranza et al,²⁴ and Lombardi et al²⁵ represent pioneering efforts for the understanding of the dual control of the ANS on the cycle length and the VR. These investigations described a common synchronicity between the beat-to-beat variability of the VR interval (QT and RT intervals) and the heart rate variability (RR intervals) based on the comparison of the peak locations of their respective power spectral density functions. To reduce repolarization variability due to measurements, Merri et al²⁶ investigated the variability of intervals inside the QT interval focusing their analysis on RT_m versus RR coupling and demonstrating that the QT dependency to heart rate primarily affects the early portion of the T wave (RT_m). Subsequently, Porta et al²⁷ confirmed this observation and demonstrated that RT_m was more robust than RT_{end} to ECG amplitude modulation synchronous with respiration, thus suggesting that a fraction of the RT_m variability might be the consequence of the presence of respiratory amplitude modulation. As a note, this study also quantified the increased robustness of RT_m to broadband noise in comparison to RT_{end}. These early works emphasized two very important points: (1) the variability of repolarization should not be dependent on the identification of the end of the T wave because it is very sensitive to signal noise and (2) the T-peak to T-end interval is rate independent in healthy individuals. One would note that most of these studies were based on short-term ECG signals (~300 seconds).

3.2. Autonomic regulation

The most clinically used technique to measure the autonomic nervous control on the beat-to-beat variation of the heart rate (heart rate variability) are the time and frequency-domain methods. The heart rate variability analysis is an evaluation of the changes in ANS regulation onto the sinoatrial node: parasympathetic activation corresponding to rapid dynamic control through acetylcholine targeting muscarinic receptors (high frequencies of the

power spectrum) and the sympathetic innervations has slower interaction via the β -adrenergic receptor.

As noted earlier, the effect of the autonomic regulation on the VR is not limited to the sinus nodal periodicity; there is a direct impact of the autonomic regulation on the cardiac cell of the ventricles. Almeida et al²⁸ analyzed short periods of ECG signals using the modeling technique described by Porta et al.²⁹ They described the presence of significant QT variability uncorrelated with sinus regulation suggesting the presence of direct regulation of the VR by the ANS.³⁰ The mechanisms involved in QT/RR coupling have been evidenced, but the understanding of the regulatory role of cardiac fat pads,³¹ intrinsic characteristics of myocardial fibers, and/or its modulation by the ANS³² remains to be fully understood. However, the QT/RR coupling is of great interest, and one would emphasize the interest from the medical community for the uncorrelated part of the beat-to-beat variability of the QT interval reflecting a possible impairment of the VR. This assumption is strengthened by the growing number of studies describing an increased repolarization variability in high-risk cardiac patients with a variety of clinical conditions. These studies consistently confirm the role of VR instability as a surrogate marker of cardiac vulnerability: QT variability,³³ TWA³⁴, and T-wave morphology instability.¹⁰

3.3. QT hysteresis

The time of adaptation of the QT interval to heart rate has been documented using endocardial action potential duration recordings under specific pacing protocol by Franz et al¹⁸ in 17 subjects. The investigated pacing protocol included abrupt sustained rate acceleration and deceleration evidencing non-steady-state and steady-state action potential duration. The time of steady-state adaptation was found to be several minutes (2-3 minutes) in this specific study. Any ECG recorded within few minutes after a rapid heart rate change (deceleration or acceleration) would provide non-steady-state QT interval measurements. Repolarization restitution time was shown to be different between individuals.³⁵ Also, the repolarization adaptation is faster when the heart rhythm is increased than when it is decreased leading to a “hysteresis” effect.³⁶ These nonlinear changes of the QT interval duration in response to heart rate are expected to impact the measurements of the repolarization variability. However, the current techniques designed to measure QT or repolarization variability have neglected to distinguish the effect of the QT hysteresis. Interestingly, it was shown that Long QT syndrome (LQTS) patients have an impaired QT hysteresis, which was presented as a potential arrhythmogenic factor even if it would be associated with a reduced variability of the repolarization (smaller range of variability after abrupt changes in heart rate).³⁷

Pueyo et al³⁸ have reported an elegant study in which a modeling technique of the QT/RR relationship is proposed including rate dependency, RR-independent variation, and hysteresis effects of the QT interval. This approach is based on a weighted average method in which the distribution of weighting factors leads to the lowest residual fitting. Such

technologies are important because they may provide a better approach for separating rate-related variability from abnormal variability. However, these models remain to be evaluated in a larger number of recordings, and their reproducibility should be established.

3.4. Instability of the VR process

The relationship between beat-to-beat oscillation of the repolarization interval and an increased risk for malignant ventricular arrhythmias has been the basis of most work related to alternating and nonalternating repolarization instability. The primary source of the electrophysiological variability of the VR process is linked to the beat-to-beat variation of the action potential duration within the ventricles and the development of early after-depolarization. The presence of such variability has been supported by animal³⁹ and human studies.^{40,41} The very recent study from Tereshchenko et al⁴² represents a unique clinical study describing a link between intracardiac repolarization (QT) variability and QT variability from the surface ECGs. The study assessed the correlation between the QT variability index from Berger et al¹⁴ and the variability measured from far-field and near-field intracardiac electrograms. In a large cohort of 298 implantable cardiac defibrillator patients, the study demonstrated a strong correlation between QT variability index measured at these different sources even if, as noted by the authors, there were obvious differences in position of lead axis, in electrogram signal processing and spatial scale (amplitude of signals).

4. Technical sources and artifacts leading to repolarization variability

4.1. Lead selection

Based on healthy individuals, Porta et al⁴³ evaluated the role of lead selection into the measurement of variability of the repolarization segment (RT apex). Fig. 2 describes the beat-to-beat variation of the RT interval for 3 recorded leads (X, Y, and Z) and their associated spectral profiles. The graphs reveal clear differences between leads with a prominent contribution of respiratory frequency in lead Z (~0.2–0.3 Hz). The difference between leads was explained by the contribution of the heart mechanical movements. Such observation emphasizes the importance of lead selection and the impact of using different leads when comparing groups. Furthermore, the heart main vector orientation can change after a modified balance of gradient voltage inside the ventricle. Postmyocardial infarction patients may have an ischemia leading to the rotation of the main heart vector. In such case, the selection of the lead to measure the repolarization variability should be cautiously selected to avoid any bias in repolarization variability measurements.

4.2. T-wave amplitude

The analysis of T-wave amplitude dependencies to heart rate has been primarily investigated during postexercise period in healthy individuals describing that the amplitude of the T-wave and R-R interval dependency is inversely proportional.^{44,45} This relationship of T amplitude and RR

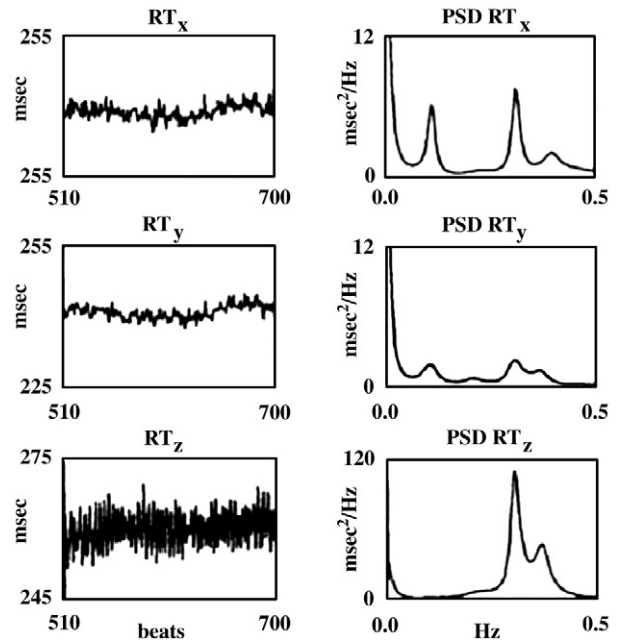


Fig. 2. Power spectrum density of the RT apex interval variability measured from different leads. From top to bottom, leads X, Y, and Z revealed very different temporal and spectral profiles (left to right columns). Reprinted with permission from Porta et al.⁴³

interval is inverted outside exercise periods: increased amplitude at slower heart rate (RR increased).⁴⁶ The mechanisms behind the inverted relationships of T amplitude and RR interval between repolarization steady-state and recovery periods are unknown.

Our investigation of T-wave amplitude in healthy subjects, LQTS patients, and subjects exposed to sotalol have shown an impairment of T-wave amplitude and heart rate dependency when potassium ion kinetics are blocked.⁴⁶ More precisely, T amplitude is increased when heart rate decreases in healthy subject, but this relationship is not observed in LQT2 (HERG/KCNH2) and in healthy individuals on sotalol. Thus, we suggested that blocking the rapid component of the delayed repolarizing potassium current (I_{Kr}) has a direct impact on T-wave amplitude. This result is important because changes in T amplitude could have the potential to generate a bias in repolarization variability measurements toward an increased variability in cardiac patients with abnormal ion kinetics and a lowering of the T-wave amplitude. Published methods for measuring repolarization variability do not systematically address the challenge of repolarization variability dependency to T-wave amplitude. Lower T-wave amplitude may contribute to inflate the estimation of the level of repolarization instability. The robustness of most computerized techniques to T-wave amplitude changes has not been reported, whereas low T-wave amplitude is often observed in ECG of cardiac patients.

4.3. Noise levels

High- and low-frequency noises are expected to affect the measurements of variability of the repolarization segment. As noted earlier, the identification of the end of the T wave is

usually not considered in repolarization variability methods because it is very sensitive to noise.²⁷ Consequently, most published methods for measuring variability rely on the overall morphology of the T wave rather than on measurement of an interval duration.^{2,33,41} Signal-to-noise ratio value in studies investigating the repolarization variability is rarely reported in parallel with variability measurements as far as the author could find in the literature. However, evaluating the correlation between noise level and repolarization variability measurements should be required to demonstrate the technology robustness.

5. Discussion

There is a growing clinical interest in assessing the level of repolarization instability from surface ECGs. Animal and human studies have demonstrated that repolarization instability exists at the cellular level, and local instability in the myocardium can be arrhythmogenic. From the surface ECGs, an increasing number of scientific reports describe repolarization variability as an independent predictor of cardiac events in various types of patients with ischemic and nonischemic cardiomyopathy. However, we are only at the dawn of the technologies for the quantitative estimation of the repolarization variability, and the definition of the appropriate technological requirements has not been clearly set. It is of paramount importance to define well these requirements. QT dispersion has been used for many years as a marker of ventricular heterogeneity, and it is only very recently that the limitations of such measurement have been highlighted. Thus, one would stress the need for better investigating the current limitations of repolarization variability methods.

To conclude, the measurement of repolarization variability can be affected by various factors; among them, we emphasized the role of the heart rate, the T-wave amplitude, and the signal noise level. Assessing the presence of a simple linear relationship between beat-to-beat variability measurements and these factors may provide important insights into the robustness of the evaluated technique. These steps are straightforward, yet they are usually overlooked in most clinical reports evaluating repolarization instability.

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