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Abstract	
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Temporal beat-to-beat Variability of Repolarization Changes Predict Non-sustained Ventricular Tachycardia in Ischemic Heart Disease Patients

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Abstract

Beat-to-beat variability of repolarization (BVR) is a promising marker of increased arrhythmia risk. BVR analysis could improve non-invasive risk stratification and may be valuable in the management and prevention of ventricular tachycardia (VT). We investigated the temporal evolution in BVR before spontaneous non-sustained ventricular tachycardia (nsVT) in patients with Ischemic Heart Disease (IHD).

24h Holter recordings from 20 IHD patients were collected prior to implantable cardioverter-defibrillator (ICD) implantation. After R-peak detection, Q-wave onset and T-wave offset were determined with a semi-automated template matching technique. The QT-annotation was manually verified and adjusted if necessary. Episodes of nsVT were semi-automatically identified and BVR was assessed at time points 1, 5 and 30 minutes prior to nsVT, and at a fixed moment during sleep (03:00am).

Resting BVR, measured at 03:00am, was 7.26 ± 3.88 ms and was significantly ($p<0.05$) higher at 5 minutes (14.40 ± 7.61 ms) and 1 minute (18.01 ± 6.48 ms), but not at 30 minutes (8.90 ± 4.93 ms) prior to nsVT.

These preliminary results reinforce the value of BVR analysis in the risk stratification of IHD patients; and identify a novel prediction method of impending VT that could be used for real-time analysis and monitoring.

1. Introduction

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide, accounting for 11.2% of all deaths globally in 2011 [1]. A significant portion of these deaths are caused by ventricular tachycardia's (VT) [2].

Currently, risk stratification focusses on identifying patients eligible for an implantable cardioverter-defibrillator (ICD) [3]. It is almost solely based on left ventricular function assessment and lacks sensitivity and specificity. Non-invasive, ECG-based, biomarkers may improve the management and outcome of IHD patients by better risk stratification and allowing preventive care of imminent VT.

The prolongation of myocardial repolarization, quantified as the QT-interval, has been used broadly as a non-invasive biomarker to predict mortality. However, there are several clinical and experimental studies that question the predictive value of a prolonged QT-interval. In 1997, Gilmour et al. concluded that the repolarization prolongation itself was not sufficient for the initiation of ventricular arrhythmias [4]. Therefore, in attempt to address this issue, numerous biomarkers have been proposed to improve the predictive value with respect to the prolongation of repolarization.

Beat-to-beat variability of repolarization (BVR), quantified as short-term variability of the QT interval (STV_{QT}), is a relatively new ECG-based biomarker that captures the repolarization instability [5]. It has shown to improve the diagnostic screening of patients with documented drug-induced proarrhythmia, heart failure and congenital long-QT syndrome [6]. Furthermore, it seems to be superior to the QT-interval in terms of identifying patients at risk for ventricular arrhythmias [6].

One of the current limitations of the analysis of BVR is the requirement of separate software and dedicated personnel [6]. We tried to overcome this limitation by developing an easy to use graphical user interface for semi-automated analysis of the ECG signals.

In this paper we used the newly developed semi-automated framework to investigate the temporal evolution in BVR before spontaneous non-sustained ventricular tachycardia (nsVT) in patients with IHD.

2. Materials & Methods

2.1. Patient population

The study population included 20 patients with IHD. The mean age was 65.6 ± 8.9 years and 15% were female. Details of the clinical data are shown in Table 1. 24 hour digital 2-lead Holter recordings were collected prior to ICD implantation.

Table 1: Clinical data of patients with IHD.

Variable	Number
Group size	20
Age (y)	65.6 ± 8.9
Women/men	3/17
LVEF (%)	32.9 ± 12.6
NYHA class	
I	6
II	8
III	6

2.2. ECG analysis

The analysis was usually performed on lead A, corresponding to lead II of the standard 12-lead clinical ECG, unless the QRS-complexes were too small or the signal quality was not sufficient in the region of interest. In the latter case, lead B, corresponding to lead V1 was used.

Since a 24 hour signal collection inevitably contains a fair amount of noise, preprocessing was necessary to improve the signal quality. Baseline wander and power line interference were removed with respectively a high-pass Butterworth filter with a cut-off frequency of 0.5 Hz and a notch filter.

The R-peaks are detected by an in-house developed algorithm based on the Pan-Tompkins algorithm [7]. The latter requires an extensive number of filters to emphasize the QRS-complexes, while in the used algorithm this is done by an enveloping procedure. The entire algorithm consists of five steps, which will be described in the next paragraph.

First, the upper (U) and lower (L) ECG envelopes are computed by means of the secant method with a user-defined window size. Second, these envelopes are used to obtain a flattened version of the signal: $F(t) = U(t) - L(t)$. An example is shown in Figure 1. Third, an adaptive thresholding procedure is applied on the F_{ecg} signal to locate the QRS-complexes. Missing, ectopic and false peaks are corrected by means of a search back procedure in the fourth step. Finally, the R-peak locations in the original ECG signal are defined by a local maximum search.

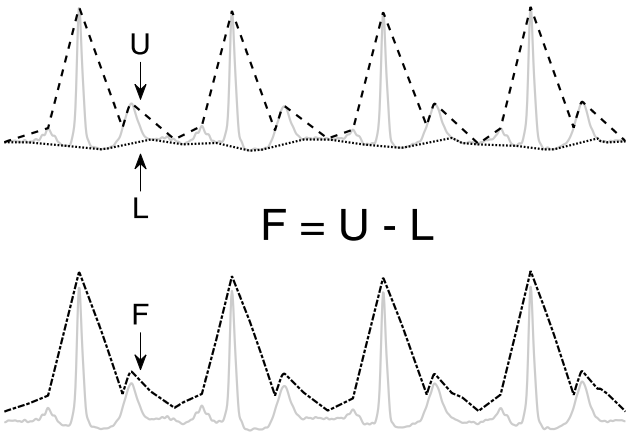

Figure 1: The flattened ECG (F) is constructed by subtracting the lower envelope (L) from the upper envelope (U). This procedure highlights the QRS-complex and obscures the other waveforms.

Detected R-peaks have to be corrected in case of errors. Additionally, only Normal-to-Normal (NN) intervals are taken into account for QT-analysis. Hence, (ventricular) ectopic beats were removed. The interface provides the possibility to graphically add, adjust or remove annotations. Adjustments were done by a drag-and-drop like feature. All corrections were carried out by one trained medical doctor.

After the R-peak detection and/or correction, the QT-intervals were derived. The detection of the Q-wave onset (Q_{on}) and the T-wave offset (T_{off}) was done in a semi-automated fashion, similar to the commonly used template matching method presented by Berger et al. [8]. The steps involved are:

(1) The creation of a template heartbeat ($\varphi(\mathrm{n})$) by computing the trimmed mean of all heartbeats (x_i). A window of one second, 0.35 s before and 0.75 s after each R-peak (R_i), was defined to select the heartbeats.

(2) The manual selection of the Q_{on} and T_{off} on the template heartbeat.

(3) The matching of all heartbeats with the template. Per heartbeat, an error function ($\varepsilon_i(\alpha)$) is defined for both the Q_{on} and T_{off}:

$$Q_{on} \quad \varepsilon_i(\alpha) = \sum_{j=1}^{R_\varphi - Q_{on}} [\varphi(R_\varphi - j) - x_i(R_i - \alpha j)]^2 \quad (1)$$

$$T_{off} \quad \varepsilon_i(\alpha) = \sum_{j=1}^{T_{off} - R_\varphi} [\varphi(R_\varphi + j) - x_i(R_i + \alpha j)]^2 \quad (2)$$

where α is the time-stretching factor. The error function is thus the sum of squared differences between the template and the stretched or compressed heartbeat i.

(4) A progressive search in the interval [0.9 1.1] is conducted in order to find the value of α that minimizes $\varepsilon_i(\alpha)$.

(5) These values of α are multiplied with the respective QR_φ- or RT_φ-interval to locate the Q_{on} and T_{off} of each heartbeat.

In case of erroneous location of Q_{on} or T_{off}, correction is needed. All points were examined by a cardiologist and could be adjusted by the same drag-and-drop like feature, as previously described for the R-peak correction.

nsVT episodes were semi-automatically identified based on the tachogram. An overview of the nsVT characteristics is given in Table 2. Hereafter, BVR was assessed at time points 1, 5 and 30 minutes prior to an nsVT episode, and at rest: a fixed moment during sleep (03.00am). BVR, quantified as STV_{QT}, was calculated from 31 consecutive beats using the following formula:

$$STV_{QT} = \frac{\sum_{n=1}^{30} |QT_{n+1} - QT_n|}{(30 \times \sqrt{2})} \quad (3)$$

where QT quantifies the duration of ventricular repolarization. BVR indicates the average dispersion of the repolarization time perpendicular to the line-of-identity in a Poincaré plot.

Table 2: nsVT characteristics

Variable	Number
HR (bpm)	146 ± 9
Cycle length (ms)	424 ± 24
# beats	49 ± 7
Duration (s)	20 ± 3

2.3. Statistical analysis

All variables are reported as mean ± SD. Repeated measures ANOVA was used to assess significance levels between BVR values at different points in time prior to nsVT. P-values lower than 0.05 were accepted as statistically significant. All programming and calculations were done using MATLAB R2017b.

3. Results

QT Poincaré plots from a representative patient at 03.00am and 1 minute prior to nsVT are displayed in Figure 2.a and 2.b respectively. We have found that resting BVR (7.26 ± 3.88 ms) was significantly increased at 5 minutes (14.40 ± 7.61 ms) and 1 minute (18.01 ± 6.48 ms), but not at 30 minutes (8.90 ± 4.93 ms) prior to nsVT (Figure 2.c). Additionally, all patients showed an increased BVR at 1 minute prior to nsVT compared to 30 minutes prior to nsVT and resting BVR.

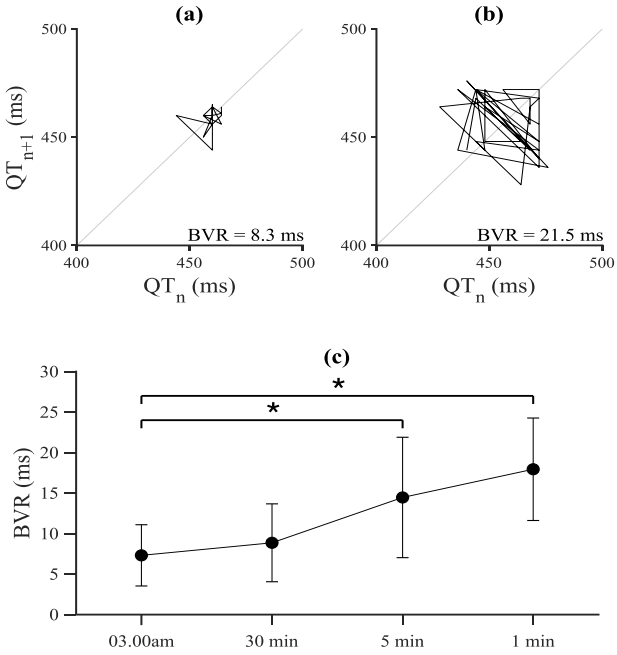

Figure 2: Poincaré plot of QT from a representative patient with IHD. Increased dispersion of the repolarization time, and thus the BVR values, from 03.00am (*a*) to 1 minute prior to nsVT (*b*) is clearly present. This increase is also found in the entire population for 1 minute and 5 minutes prior to nsVT (*c*). *p < 0.05 vs. 03.00am.

4. Discussion

We have shown that a significant increase in BVR precedes nsVT events in IHD patients. This indicates that the assessment of BVR could improve risk stratification of IHD patients and identifies a novel prediction method for impending VT.

BVR has proven to be a sensitive predictor of lethal ventricular arrhythmias in animal models [9], where it reflects the electrical substrate of repolarization heterogeneity and impaired reserve that precedes re-entrant arrhythmia [5]. The temporal changes in BVR we observe likely reflect the dynamic substrate of repolarization heterogeneity preceding arrhythmic re-entry.

Temporal variations in BVR have been recently described in relation to diurnal rhythms in high risk patients, and suggested as an assessment marker [10]. We have used a more clinically relevant concept of impending nsVT to demonstrate the clinical relevance of temporal BVR in improving risk stratification of IHD patients.

Changes in cardiac cycle duration frequently precede ventricular arrhythmias and detailed analysis of these changes that have clinical value have been proposed for integration into monitoring devices, such as ICD software. We have shown that a significant increase in

BVR already occurs at 5 minutes prior to the nsVT event. As such, monitoring BVR could allow for some much needed time to respond to impeding arrhythmia. It might be enough for a doctor to take action in a hospital or to alarm relatives when at home.

In this paper we used a robust, semi-automated fiducial point detection technique with manual corrections. Future research should investigate the influence of fully automated fiducial point detection algorithms on the BVR analysis. If accuracy and robustness can be guaranteed, this would allow BVR to be monitored in real-time and strengthen the case to be integrated in wearable devices.

The major limitation of this study is the small patient cohort. Therefore, while the results presented in this study are promising, the findings are still preliminary. In order to have more clinical value, they need to be verified in larger patient cohorts and other high-risk patients.

5. Conclusion

The presented results suggest that temporal changes in pre-arrhythmic BVR could be used to predict imminent nsVT events in IHD patients. These preliminary results set a strong precedent that both reinforces the value of BVR analysis in the risk stratification of IHD patients; and identifies a novel method of impending VT prediction that could be used for real-time analysis and monitoring. The obtained results need to be verified in larger patient cohorts and other high-risk patients.

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