Prognostic Value of Intra-QRS and ST-T Micro-Variability – A 2 Year Follow-Up

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Abstract

Previously, we found that patients with malignant ventricular arrhythmias show an increased beat-to-beat micro-variability of de- and repolarization, indicated by an increased variability of QRS duration and an increased intra-QRS (QVI)and ST-T (TVI) variability compared to healthy subjects. In this study we investigated the prognostic value of the previously found markers QVI and TVI of beat-to-beat variability in terms of mortality. Patient (960) assignment had to be to one of the following subgroups: (a) no organic heart disease, (b) coronary artery disease, or (c) spontaneous or inducible ventricular tachycardia or ventricular fibrillation. High-resolution ECGs were recorded Beat-to-beat micro-variability measurement was based on 200 consecutive sinus beats per individual. Total and cardiac mortality was highest in the group with malignant arrhythmias (13.3% and 12%). The Cox proportional hazards regression model on the singular factors of QVI and TVI revealed a connection to survival. This was valid for both the 1-year (QVI p=0.006, TVI p=0.009) and 2-year (QVI p=0.015, TVI p=0.008) follow-up. We conclude that increased QRS- and T-variability indicating increased anisotropy of de- and repolarisation is associated with an increased mortality.

1. Background

High-resolution electrocardiography may be used for the detection of fractionated micropotentials, which serve as a non-invasive marker for an arrhythmogenic substrate and for an increased risk for malignant ventricular tachyarrhythmias. Beat–to–beat variation of cardiac excitation and depolarization has been associated with electrical instability and an increased risk for arrhythmias [1]. Rosenbaum et al. [2] have shown that increased beat–to–beat microvariations of the T–wave, although visually inapparent, are associated with a decreased arrhythmia–free survival. Their method to quantify periodic electrical alternans of the T–wave amplitude has gained growing clinical acceptance as a non–invasive, electrocardiographic risk marker. Earlier high–resolution electrocardiographic studies already demonstrated periodic and non-periodic behaviour of ventricular late potentials at the terminal QRS [3–5]. Previous work of our group showed a significantly higher beat–to–beat variation of the duration of the filtered QRS [6] and an increased total beat–to–beat microvolt variation of the QRS [7, 8] and the ST-T segment among patients with an increased risk for ventricular tachycardias compared to healthy subjects.

In this study we investigated the prognostic value of the previously found markers of beat-to-beat variability in terms of mortality.

2. Subject data

Patient inclusion criteria were the registration of an antiarrhythmia free high resolution ECG with more or equal to 200 sinus beats. Age had to be less than 80 years and an assignment to the target groups of (a) no organic heart disease, (b) coronary artery disease, or (c) spontaneous or inducible ventricular tachycardia or ventricular fibrillation had to be possible.

Screening. Screening included 1411 patients. In 219 patients atrioventricular block, a pacemaker, antiarrhythmic medication, absolute arrhythmia, or technical problems were the cause of not evaluating the high resolution ECG recording. Thirty-six recordings had less than 200 usable QRS complexes as a result of visually evaluating all ECGs and excluding segments marked as noisy. For one patient beat extraction failed, caused by a change of QRS morphology. Twenty-four cardiac patients were excluded for missing invasive cardiac diagnosis. Thirty-one patients were older than 80 years. Follow-up status could not be determined for 78 patients (5.5%). Of the remaining 1022 patients, in whom the ECG recording could have been evaluated, 62 could not be assigned to one of the target groups. These 62 split into 9 patients with a dilative cardiomyopathy, one with arrhythmogenic right

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ventricular disease (ARVD??), 10 with congenital heart disease, 17 with a disorder of the cardiac rhythm (8 Wolf-Parkinson-White syndrome, 3 QT syndrome, 1 secondary ventricular fibrillation, 5 unclear cause), and 25 patients with other diagnosis that did not meet the inclusion criteria. Patients with dilative cardiomyopathy and no other disease (e.g. VT/VF) were excluded as their number was too low for statistical evaluations and previous studies [9] already showed an increase of the variability of QRS duration in this group.

Clinical patient data. The study included 960 patients separated into three target groups: (a) 176 subjects without an organic heart disease, (b) 627 patients with coronary artery disease, and 157 patients with spontaneous or inducible ventricular tachycardia or ventricular fibrillation. The subjects of group (a) were healthy volunteers (61) and patients (115) without an organic heart disease. The mostly younger volunteers (mean age: 24.3 ± 4.1 years) had a normal resting and exercise ECG, a normal echocardiogram, and no cardiac symptoms or coronary risk factors. The subgroup with no organic heart disease consisted of subjects for whom coronary artery disease or other important heart disease were ruled out by clinically indicated coronary angiography. For 27 patients of this subgroup benign supraventricular arrhythmias or electrophysiological ablation therapy (9) were the reason for angiography. This explains the relatively high rate (7%) of syncopes found anamestically in this group. The other 88 patients of this subgroup had a coronary angiography as a cause of cardiac troubles or a suspicion of coronary artery disease in the context of a pre-operative diagnosis. Of the patients of group (b) 89.6% (562/627) had a previous myocardial infarction. Of these 562 cases 429 had an open infarct vessel, for 332 patients it was revascularized by primary percutaneous transluminal coronary angioplasty (PTCA) in the event of acute myocardial infarction, or by medicinal thrombolysis or spontaneous lysis. For 97 patients the infarct vessel was treated later by elective coronary angioplasty or coronary bypass surgery. In 27 of the 562 cases (4.8%) with a clinically documented myocardial infarction no repeated coronary angiography was performed so that the status of the infarct vessel was not determined.

3. ECG recordings

High–resolution electrocardiograms were recorded during sinus rhythm from bipolar orthogonal X, Y, Z leads using the Predictor system (Corasonix Inc., Oklahoma, USA). A/D resolution was 16 bit with an antialiasing filter (0.05-300Hz). Before ECG recording antiarrhythmic drugs were stopped for at least four half–lives. The skin was carefully prepared and recordings were done with

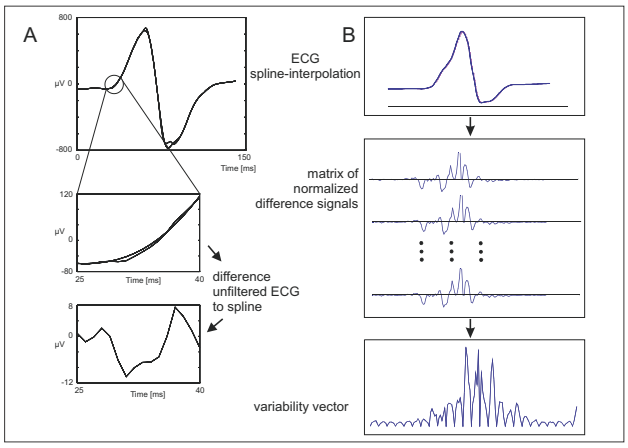

Figure 1. Diagram of the spline–filtering procedure. The upper left panel (A) shows both signals, the QRS–complex (sum of the three leads) and the cubic spline. A zoom–in makes the differences more apparent. The right panel (B) shows the calculation of the variability vector.

the subjects in reclining position in a Faraday cage. For the beat–to–beat recordings of 6 to 30min duration the sampling rate was 1000Hz. QRS triggering, reviewing of the ECG, and arrhythmia detection was done on a high–resolution ECG analysis platform developed by our group [10]. The three leads were summed into a signal $V = X + Y + Z$. From each recording 200 consecutive sinus beats preceded by another sinus beat were selected for subsequent beat–to–beat variability analysis. In a first step the signals were aligned by maximizing the cross–correlation function [11] between the first and all following beats. Prior to the quantification of signal variability the beats were pre-processed to suppress the main ECG waveform, bringing the beat–to–beat micro-variations into clearer focus. To achieve this, the individual signal was subtracted from its cubic spline smoothed version (spline filtering, spline interpolation through every seventh sample using the not–a–knot end condition) [12], compare Figure 1 panel (A). This method resembles a waveform adaptive, high–pass filtering without inducing phase–shift related artefacts. Next, for each individual beat the amplitude of the difference signal was normalized to zero mean and a standard deviation of 1μV, see Figure 1 panel B. Beat–to–beat variation of each point was measured as the standard deviation of the amplitude of corresponding points across all 200 beats.

4. Follow-up results

During the two year follow-up period 45 cardiac and 16 non cardiac deaths occurred. This is equivalent to a cardiac mortality of 4.7% and a total mortality of 6.4%. Total and cardiac mortality was highest in the group with malignant arrhythmias (VT/VF, 13.3% and 12%) and about doubled

the mortality found with CAD patients without malignant arrhythmias. The most common causes of death within the VT/VF group were sudden cardiac death (SCD), defined as sudden death occurring within one hour after the onset of symptoms, and heart failure with 8 deaths (5.1%). One cardiac death within the VT/VF group could not be differentiated further. Thirteen patients had a deadly myocardial infarction (11 CAD group, 2 VT/VF group). The percentage of non cardiac deaths was 1.7% (16/960). Initially not expected two deaths (one cardiac) occurred in the group with no organic heart disease. Metastising breast cancer was the cause of death in the non cardiac case. For the 48 year old patient who died of cardiac causes, coronary artery disease was ruled out by coronary angiography at the time of inclusion. This patient had atrial hypertension, obesity and a stenosis of the renal artery as a first manifestation of atherosclerosis at that time. Clinically, a sudden cardiac death was observed in which pathophysiologically a primary arrhythmia and ventricular fibrillation on the basis of an early myocardial ischaemia may be possible.

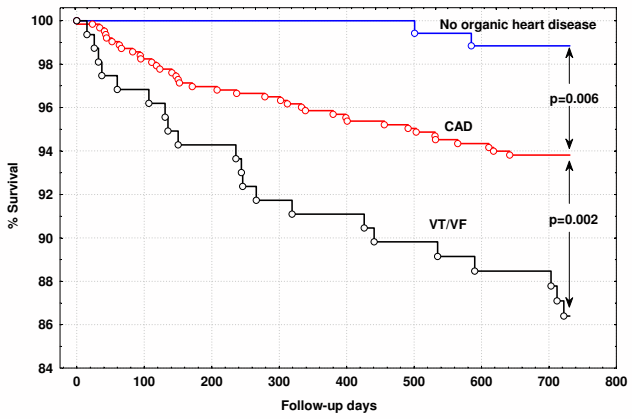

Figure 2. Kaplan–Meier survival curves for the three study groups (logrank test).

Figure 2 shows the survival of the three study groups for the follow-up period of two years. The mean follow-up time for the whole population was 682.2 days (15 to 731 days).

5. Total intra–QRS and ST–T microvariability

The median variability index of the QRS (QVI) for all 960 subjects was 38.27 (interquartile range: 30.16 to 47.78). This median value closely corresponds to the one found as an optimal single cut-off value for the smaller data set separating healthy subjects from patients with VT/VF [7]. The median variability index of the ST-T segment (TVI) was 30.64 (interquartile range: 21.83 to 50.79). For six recordings a variability index of the ST-T segment could not be calculated as ventricular extrasystoles with short coupling intervals reduced the number of usable beats to below 200. Four of these excluded patients were in the VT/VF group and one patient in each the CAD and no organic heart disease group. The median variability index of the ST-T segment was noticeably different from the optimal cut-off point of 12.6 found in the pre-study [7]. Figure 3 shows the differences of QVI and TVI of the three groups

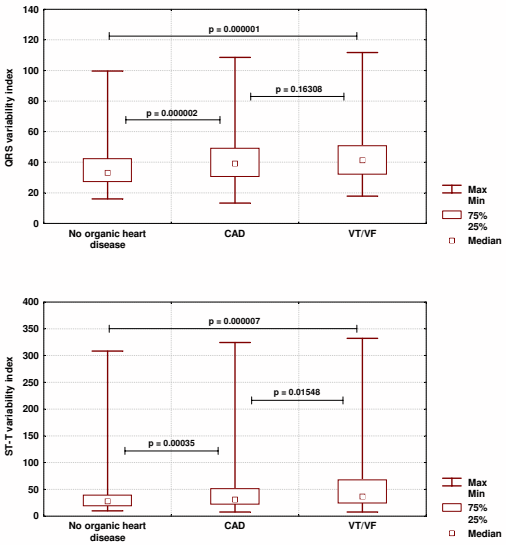

Figure 3. Total intra–QRS and ST–T microvariability of the three groups. Patients with CAD had a significantly increased microvariability both within the QRS and the ST–T segment (U–test).

5.1. Total intra–QRS and ST–T microvariability and mortality within a 2 year follow-up period

Using the Cox proportional hazards regression model on the singular factors of QVI and TVI revealed a connection to survival. This was valid for both the 1-year (QVI p=0.006, TVI p=0.009) and 2-year (QVI p=0.015, TVI p=0.008) follow-up. Nevertheless, the prognostic value of both parameters is below the invasively measured left ventricular ejection fraction (EF). Using Cox regression models with the factors QVI and EF and TVI and EF a significant connection to survival was only present after one year for QVI (p=0.033).

Using receiver operator characteristic curves it is possible to define cut-off values for QVI and TVI related to the total mortality. As already observed in the Cox model, the parameters QVI and TVI have a higher predictive value after one year, and thus the cut-off values based on the

one year mortality were used for the subsequent survival analysis, see Figures 4 and 5. Using the found cut-off values, the relative risk for death is 2.67 (95% CI: 1.44 to 4.99) for a patient with increased QVI after one year, it is 2.66 (95% CI: 1.41 to 4.94) for a patient with increased TVI after one year, and after two years it is 1.77 (95% CI: 1.07 to 2.94) for a patient with increased QVI and 2.37 (95% CI: 1.43 to 3.93) for a patient with increased TVI. A "normal" QVI $\leq$ 44.85 had 655 subjects (QVI: 32.72 $\pm$ 7.17) and an increased QVI value was present in 305 subjects (QVI: 55.78 $\pm$ 10.82). A "normal" TVI $\leq$ 46.56 had 677 subjects (TVI: 26.41 $\pm$ 8.81) and an increased TVI value was present in 277 subjects (TVI: 90.78 $\pm$ 50.75).

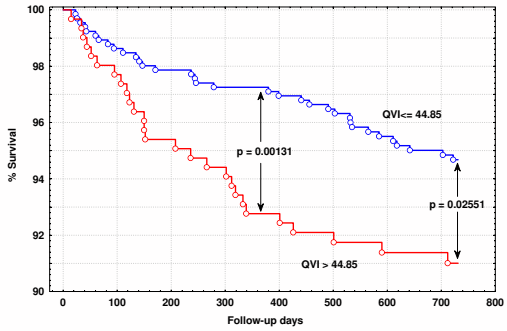

Figure 4. Kaplan–Meier survival curves for the group separation induced by the QVI cut–off point determined from a ROC curve (p values are from the logrank test).

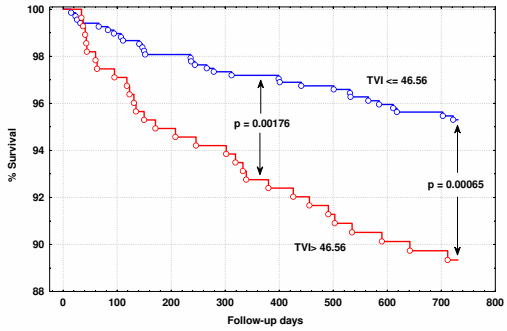

Figure 5. Kaplan–Meier survival curves for the group separation induced by the TVI cut–off point determined from a ROC curve (p values are from the logrank test).

6. Conclusion

The utility of the newly found markers of microvariability is demonstrated on a data set discriminating between healthy subjects and VT patients, this result contrasts the somewhat limited approach of Rosenbaum et al. [2], and shows the existence of intra-QRS variability. Furthermore these found parameters are markers for cardiac risk demonstrated during a two year follow-up. This very strong result emphasizes the significance of intra-QRS microvariability as an isolated marker of myocardial conduction inhomogeneity in comparison to microvariability measurements of the T-wave.

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