Evaluation of Ventricular Repolarization Variability in Patients With Nonischemic Dilated Cardiomyopathy From Vectorcardiography

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Abstract

Ventricular repolarization variability (VRV) has predictive value for mortality in patients with ischemic heart disease. However, the potential for risk stratification in patients with nonischemic cardiomyopathy remains unclear. To investigate the predictive value of VRV for all-cause mortality in patients with nonischemic dilated cardiomyopathy, we analyzed the Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE).

The Telemetric and Holter ECG Warehouse (THEW) data set E-HOL-03-0401-017 was used for analysis. The data set comprises 393 recordings from 236 patients (67 women, age 60 ± 14 *years; 168 men, age:* 58 ± 12 *years; 1 record not specified). All patients had a left ventricular ejection fraction* < 36 *% and were randomized to receiving standard medical therapy with or without an ICD. 24h-Holter 3-lead (Frank lead system) ECGs were performed at enrollment and after up to 5 years' follow-up. The all-cause mortality during the follow-up period was 4.8 %.*

We analyzed three-dimensional variability of the T-loop and QT interval variability on a single lead basis by employing three-dimensional signals adaptation and two-dimensional signal warping, respectively, to quantify VRV. To assess the predictive value of VRV parameters, Kaplan-Meier survival curves of baseline Holter ECGs were calculated. Significant parameters were further investigated for their correlations with patient-specific characteristics and between each other.

Our results showed significant association to survival ($P < 0.01$ *by the log-rank test) for T wave amplitude corrected QT interval variability index (cQTVi) on single lead basis. Low cQTVi group showed no mortality for the entire observation period. We found no associations between cQTVi groups and patient-specific parameters.*

Further investigations will focus on the comparison of risk stratification based on three-dimensional vectorcardiography and two-dimensional single lead ECG VRV parameters.

1. Introduction

Ventricular repolarization variability (VRV) has predictive value for mortality in patients with ischemic heart disease [1], where the mode of death is likely malignant ventricular arrhythmia [2]. However, the potential for risk stratification in patients with nonischemic cardiomyopathy remains unclear [2].

QT interval variations of the surface electrocardiogram (ECG) reflect beat-to-beat fluctuations of the ventricular repolarization. Several studies have shown that temporal VRV as indicated by an increased QT interval variability (QTV) is associated with cardiac mortality [2, 3]. However, measuring subtle beat-to-beat changes in QT interval remains challenging. Although novel QTV techniques have improved sensitivity and robustness [4, 5], conventional QTV measures still lack in insightful QTV description [2]. Alongside the improved QTV measurement, new techniques are able to capture VRV from vectorcardiography (VCG) [6] and thus offer new feature sets for the characterization of the ventricular repolarization.

In this study we investigate the predictive value of VRV for all-cause mortality in patients with nonischemic dilated cardiomyopathy. Therefore, we analyzed the Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE) to demonstrate (1) the applicability of new methods to characterize VRV using the VCG and (2) to investigate the predictive value of VRV parameters from VCG for risk stratification of all-cause mortality in

the DEFINITE study.

2. Material and Methods

2.1. Data Material

The Telemetric and Holter ECG Warehouse (THEW) data set E-HOL-03-0401-017 was used for analysis [7]. The data set comprises 393 recordings from 236 patients of the DEFINITE study (67 women, age 60 ± 14 years; 168 men, age: 58 ± 12 years; 1 record not specified). All patients had a left ventricular ejection fraction $< 36\%$ and were randomized to receiving standard medical therapy with or without an ICD (see Tab. 1). 24h-Holter 3-lead (Frank lead system) ECGs were performed at enrollment and after up to 5 years' follow-up with a sampling frequency of 500 Hz and an amplitude resolution of 1 μV [8]. The all-cause mortality during the follow-up period was 4.8%.

Table 1. Characteristics of DEFINITE patients used (THEW data) at baseline. Percentages are in normal brackets and ranges are in square brackets.

Characteristic		Therapy Standard	Therapy ICD
Patients		103 (44 %)	132 (56 %)
Sex	male	70 (30 %)	98 (42 %)
	female	33 (14 %)	34 (14 %)
Age, yr	mean	58.0 [22-80]	58.3 [26-82]
NYHA	I	25 (11 %)	41 (17 %)
	II	56 (24 %)	70 (30 %)
	III	22 (9 %)	21 (9 %)
LVEF, %	mean	21.8 [10-36]	20.6 [9-35]

2.2. VRV Quantification

We analyzed three-dimensional variability of the T loop and QT interval variability on a single lead basis by employing three-dimensional signals adaptation (3DSA) [6] and iterative two-dimensional signal warping (i2DSW) [5, 9], respectively, to quantify VRV.

Using orthogonal ECG leads, a vector ECG was generated. Its loops are characterized by 3DSA. This adaptation takes place in different phases, the global and the local template adaptation. Templates of interest are first globally translated, scaled and rotated using statistical methods in the form of Procrustes analysis. In the global phase, the template is roughly adapted via Procruste's analysis in order to be subsequently adapted to the local morphology changes via a kernel ridge regression. To account for complex noise behavior encountered in quasi-periodic signals, 3DSA ensues to complete the framework with an adaptive noise model. VRV was evaluated by 3DSA using the two parameters mean-loop-length (MLL) and distance variability (DV) from the T loop. MML is calculated as the sum of the distances between adjacent points on a loop and DV contains a vector of distances between related points on the template loop and the matched template loop. Mean (DVmean) and standard deviation (DVsd) of DV were used. [6]

Single lead analysis was performed in pseudo-orthogonal lead bipolar Z because of the highest T wave amplitude and thus maximized signal-to-noise ratio [10]. By applying i2DSW we were able to account for subtle inhomogeneous shape variations of the ECG waveform in time and amplitude [5, 9]. i2DSW automatically generates a template beat with common features of interest (e.g. the PQ, QRS or QT intervals or amplitude related information) based on ensemble averaging of appropriate beats. To adapt the template, a 2D mesh of warping points is superimposed. By shifting warping points in time- and amplitude-direction and minimizing the Euclidean distance between template and the beat under consideration, the optimal template adaptation is calculated. From the adapted template, changes of annotated points can be tracked from beat to beat in time and amplitude. Next to the adapted template we used QT intervals and T wave amplitudes for further analysis. Automatic beat rejection [5] was applied to exclude noisy heart beats. We used standard QTV parameters including standard deviation of QT intervals (SDQT) and the QT interval variability index (QTVi) [11]. To consider the inverse relationship between QTV and T wave amplitude, we calculated the T wave amplitude-corrected QTV measures of SDQT (cSDQT) and QTVi (cQTVi) [10].

All parameters were calculated from 5-min epochs throughout the 24-h Holter ECGs. To characterize daily VRV we calculated the median, max quantile (highest 95 %) and min quantile (lowest 5 %).

2.3. Survival Analysis

To assess the predictive value of VRV parameters, Kaplan-Meier survival curves of baseline Holter ECGs were calculated for trichotomized median, min and max of SDQT, QTVi, cSDQT, cQTVi, MLLT, DVmean, and DVsd. Significant parameters were further investigated for their correlations with patient-specific characteristics to show their independent value. Furthermore, Spearman's correlation analysis was performed for a clearer understanding of the relationships between the analyzed parameters.

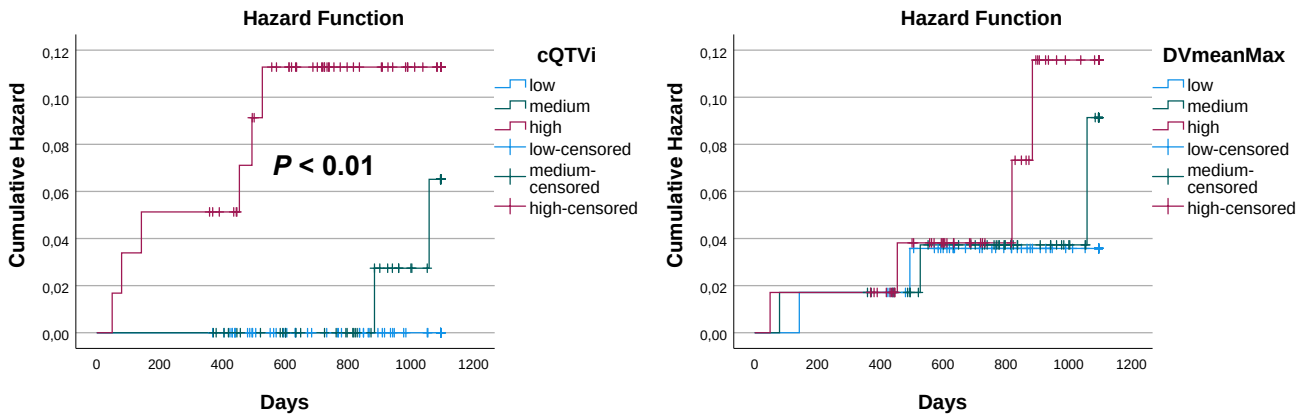

Figure 1. Hazard functions of Kaplan–Meier survival analysis; Estimated hazard of DEFINITE patients for trichotomized cQTVi (left) and trichotomized DVmeanMax (right) for 3 years. Last observations of a patient are marked in the curves with a cross (censored data).

3. Results and Discussion

Kaplan-Meier survival analysis shows significant association between survival and cQTVi ($P < 0.01$ by the log-rank test; Fig. 1). At year one the mortality was zero in the low and the medium cQTVi group and 5.0 % in the group with high cQTVi. After 2 years, it was 0.0 % in the low and the medium cQTVi group and 10.7 % in the group with high cQTVi. At the end of survival estimation (after 3 years) cQTVi was 0.0 % in the low cQTVi group, 6.3 % in the medium cQTVi group and 10.7 % in the group with high cQTVi. We found qualitatively similar results when using uncorrected QTVi, but the difference in survival across tertiles was not statistically significant ($P = 0.17$ by the log-rank test). Also, all other analyzed parameters have not been able to achieve significant prediction results. However, max of DVmean, extracted from the VCG, also shows qualitatively similar behavior for predicting mortality (see Fig. 1).

Table 2 shows the patient-specific characteristics of the trichotomized cQTVi. No relevant or even statistically significant differences were found between cQTVi groups with respect to sex, age, group of enrollment, NYHA class, and LVEF.

Results of the correlation analysis between the studied parameters are shown in Figure 2. We found medium effects ($|\rho| > 0.3$) between of DVmean and DVsd (median, min and max) and SDQT and QTVi (median and max). The largest effect ($|\rho| > 0.5$) is between max of SDQT and max of DVmean. Correlations between the VCG parameters and the single channel parameters are lower after T wave amplitude-correction.

Low cQTVi group showed zero mortality for the entire observation period. No associations were found between cQTVi groups and patient-specific parameters; therefore, this noninvasive parameter provides additional prognostic value for risk estimation. In the low cQTVi group, 36 patients received an ICD implantation (see Tab. 2). Since the risk of mortality is zero based on the survival analysis shown here, implantation implies additional risks for the patient.

Table 2. Patient characteristics according to trichotomized cQTVi for sex, age, group of enrollment , NYHA class, and LVEF at baseline. Ranges are shown in square brackets.

		cQTVi low	cQTVi median	cQTVi high
Sex	male	41	44	46
	female	18	15	15
Age, yr	mean	56.8 [26-82]	60.8 [27-80]	57.4 [22-81]
Group	Standard	23	27	29
	ICD	36	32	31
NYHA	I	18	14	16
	II	32	33	32
	III	9	12	12
LVEF, %	mean	20.8 [10-34]	22.0 [10-35]	20.0 [9-34]

4. Conclusion

In this study, we used two techniques to quantify VRV in VCG and on a single derivative basis. Our results show that Patients with non-ischemic cardiomyopathy and a high cQTVi have a significant higher all-cause mortality than patients with low cQTVi. Hence, cQTVi could contribute to a treatment decision, as in this group the implantation of an ICD could be avoided, thus reducing costs

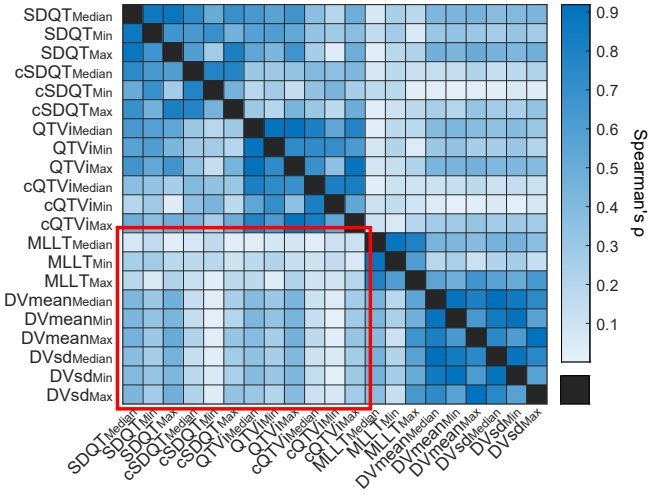

Figure 2. Correlation analysis between single lead ECG (SDQT, cSDQT, QTVi, cQTVi) and VCG (MLLT, DVmean, DVsd) VRV parameters (highlighted in red). Absolute values of Spearman's ρ are shown.

and risk for the patient. In upcoming treatment decision processes, VRV parameters may provide additional information besides established ones such as LVEF or NYHA class to enable improvement of patient survival. However, it should be noted the small number of deaths in the study investigated, and therefore further studies are needed.

Further investigations will focus on the comparison of risk stratification based on VCG and two-dimensional single lead ECG [12] VRV parameters.

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