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METHODS
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T Wave Amplitude Correction of QT Interval Variability for Improved Repolarization Lability Measurement

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Objectives: The inverse relationship between QT interval variability (QTV) and T wave amplitude potentially confounds QT variability assessment. We quantified the influence of the T wave amplitude on QTV in a comprehensive dataset and devised a correction formula.

Methods: Three ECG datasets of healthy subjects were analyzed to model the relationship between T wave amplitude and QTV. To derive a generally valid correction formula, linear regression analysis was used. The proposed correction formula was applied to patients enrolled in the Evaluation of Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE) to assess the prognostic significance of QTV for all-cause mortality in patients with non-ischemic dilated cardiomyopathy.

Results: A strong inverse relationship between T wave amplitude and QTV was demonstrated, both in healthy subjects ($R^2 = 0.68$, $p < 0.001$) and DEFINITE patients ($R^2 = 0.20$, $p < 0.001$). Applying the T wave amplitude correction to QTV achieved 2.5-times better group discrimination between patients enrolled in the DEFINITE study and healthy subjects. Kaplan-Meier estimator analysis showed that T wave amplitude corrected QTVi is inversely related to survival ($p < 0.01$) and a significant predictor of all-cause mortality.

Conclusion: We have proposed a simple correction formula for improved QTV assessment. Using this correction, predictive value of QTV for all-cause mortality in patients with non-ischemic cardiomyopathy has been demonstrated.

Keywords: ECG, QT interval variability, T wave amplitude, risk stratification, DEFINITE

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1. INTRODUCTION

Beat-to-beat fluctuations of ventricular repolarization are reflected in the QT interval variations of surface ECG. Several studies have shown promise in exploiting QT interval variability (QTV) for quantifying temporal repolarization lability (Baumert et al., 2016a) and associations between elevated QTV and cardiac mortality have been reported (Berger et al., 1997; Piccirillo et al., 2007).

However, measuring the rather subtle beat-to-beat changes in QT interval remains challenging. Novel techniques that utilize templates have been proposed and demonstrated robustness toward

FIGURE 1 | Relation between SDQT and T wave amplitude ($\overline{T}_{amp}$) in datasets of healthy subjects (ATHLETE, PTB and sTQT) and DEFINITE dataset is shown in (A). Linear regression analysis applied to logarithmized SDQT and logarithmized $\overline{T}_{amp}$ is plotted in **(B)**.

3.2. Influence of QT Interval Extraction Method

Comparing 2DSW with the template stretching algorithm shows similar results regarding the correlation and regression between SDQT and $\overline{T}_{amp}$ and between $\log_{10}(SDQT)$ and $\log_{10}(\overline{T}_{amp})$ (For details see **Table 2**).

Because the standard implementation of the template stretching method is limited to QT interval extraction and does not provide T wave amplitude values, T wave amplitudes extracted by 2DSW have been used for correction for the further analysis.

3.3. Between-Lead Comparisons of the Regression Coefficient

ECG lead dependent analysis showed similar regression slopes (m_c) for multichannel datasets: PTB: $m_{c,PTB} = -0.40 \pm 0.09$ [mean regression slopes of all leads where a significant relation was found (Student's t-test; $p < 0.05$)] and dataset TQT: $m_{c,QT} = -0.33 \pm 0.05$ (12 of 12 leads, where $p < 0.05$).

3.4. Influence of T Wave Amplitude Correction on QTV Assessment

3.4.1. Effect of Orthostatic Stress on QTV (ATHLETE Dataset)

The group average of $\overline{T}_{amp}$ [$p < 0.05$ (Student's t-test)] was significantly higher in the supine position ($398 \pm 182\ \mu V$) compared to standing ($290 \pm 150\ \mu V$). Conversely, SDQT was significantly lower in the supine position compared to standing ($5.88 \pm 2.23\ ms$ vs. $11.09 \pm 3.70\ ms$; $p < 0.001$). When correcting for T wave amplitude, cSDQT was significantly lower while lying compared to standing ($5.88 \pm 2.23\ ms$ vs. $11.09 \pm 3.70\ ms$; $p < 0.001$). No notable differences in QTV were observed in corrected vs. uncorrected data.

3.4.2. Predictive Value of QTV for All-Cause Mortality in Non-ischemic Cardiomyopathy (Definite Trial)

Linear regression analysis of $\log_{10}(SDQT)$ and $\log_{10}(\overline{T}_{amp})$ in patients with non-ischemic cardiomyopathy showed results similar to datasets of healthy subjects, but the coefficient of determination ($R^2 = 0.20$) was notably smaller than in healthy subjects. To compare QTV of healthy subjects to that of DEFINITE patients, the TQT dataset has been used. As QT recordings started approximately at 7 o'clock (07:08 ± 00:26 h), segments between 7 and 8 o'clock of the DEFINITE data have been used to minimize the influence of circadian rhythm (Schmidt et al., 2014a). Note that we could not take into account individual differences in circadian rhythmicity (i.e., chronotypes) and individual activities because no time resolved individual information on the patient state was available. A random lead selection was applied to the TQT dataset (12-Lead standard ECG) for comparison to the analyzed lead Z of the DEFINITE data. We found smaller $\overline{T}_{amp}$ in TQT ($74.35 \pm 58.30\ \mu V$) compared to DEFINITE ($187.18 \pm 158.05\ \mu V$). SDQT showed significant differences [$p < 0.005$ (Student's t-test)] between TQT ($13.46 \pm 8.81\ ms$) and DEFINITE ($16.73 \pm 10.41\ ms$). Similarly, cSDQT showed highly significant differences (TQT: $6.60 \pm 2.77\ ms$; DEFINITE: $12.47 \pm 7.36\ ms$; $p < 0.001$). However, Cohen's d calculated between both groups increased 2.5-times (from 0.31 to 0.80; **Figure 2**).

To assess the predictive value of QTV Kaplan-Meier survival curves were generated for trichotomized corrected QTVi (cQTVi) values (1 – lowest tertile, 2 – medium tertile, 3– highest tertile) of baseline Holter ECG. Results show significant

TABLE 2 | Results of correlation and regression analysis for all datasets and QT interval extraction algorithms.

	Dataset	QT interval extraction algorithm	Pearson correlation coefficient r		Linear regression slope m_c
			SDQT and $\overline{T}_{amp}$	$\log_{10}(SDQT)$ and $\log_{10}(\overline{T}_{amp})$	$\log_{10}(SDQT)$ and $\log_{10}(\overline{T}_{amp})$
Healthy	ALL	2DSW	0.537***	0.826***	−0.501***
		Template stretching	0.246***	0.738***	−0.454***
	ATHLETE	2DSW	0.471**	0.544***	−0.427***
		Template stretching	0.193	0.293*	−0.270*
	PTB	2DSW	0.338***	0.598***	−0.374***
		Template stretching	0.090**	0.531***	−0.393***
	TQT	2DSW	0.456***	0.584***	−0.293***
		Template stretching	0.159***	0.241***	−0.103***
	DEFINITE	2DSW	0.333***	0.449***	−0.354***

*Note that data set size differs (see **Table 1**) and therefore quantitative comparability of correlation coefficients is limited.*
**p < 0.05; **p < 0.01; ***p < 0.001;*
SDQT, standard deviation of QT intervals; $\overline{T}_{amp}$, median T wave amplitude.

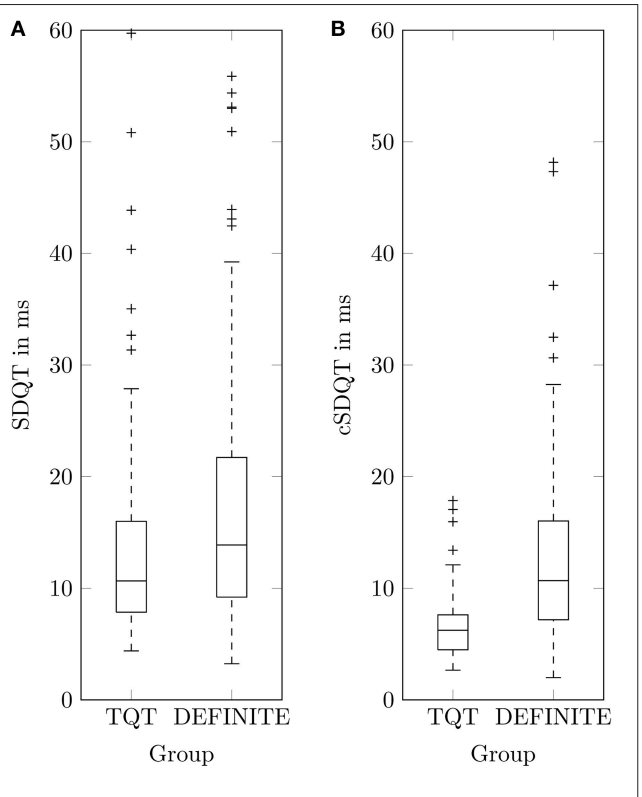

FIGURE 2 | Boxplots of QT standard deviation SDQT (A) and corrected QT standard deviation cSDQT (B) for healthy TQT dataset and patients with non-ischemic cardiomyopathy (DEFINITE).

association between survival and cQTVi ($p < 0.01$ by the log-rank test; **Figure 3**). At year one the rate of death was 0.0% in the low and the medium cQTVi group and 5.1% in the group with high cQTVi. After 2 years, it was 0.0% in the low cQTVi group, 1.9% in the medium cQTVi group and 8.9% in the group with high cQTVi. At the end of survival estimation (after 3 years) cQTVi was 0.0 in the low cQTVi group, 1.9% in the medium cQTVi group and 20.1% 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 ($p = 0.12$; **Figure 3**).

4. DISCUSSION

In this study we have introduced a novel T wave amplitude correction formula for QTV analysis. Its potential for improving QTV assessment was demonstrated by using QTV as predictor for all-cause mortality in heart failure patients (DEFINITE; $p < 0.01$). Without correction, QTV prediction of all-cause mortality is not significant ($p = 0.12$). At the same time, expected effects of the sympathetic nervous system on QTV can be equally shown even after correction (ATHLETE). Both are considered important applications of QTV analysis (Baumert et al., 2016a).

In previous studies (Baumert et al., 2012; Hasan et al., 2012; Schmidt et al., 2014b) as well as the current one smaller T wave amplitudes have been shown to artificially increase QTV owing to the noise sensitivity of common QT interval extraction techniques. To minimize the influence of T wave amplitude, we propose a simple correction of QTV parameters for T wave amplitude. The correction was devised based on three datasets of healthy subjects that were independently acquired under different conditions, using different equipment, hence providing a representative sample of ECG recordings. Linear regression analyses of double log-transformed data have shown similar behavior in all three datasets that confirm the findings of Hasan et al. (2012). The choices of QT interval extraction algorithm and ECG lead have not shown any major effect on the relation between T wave amplitude and QTV.

To adjust common QTV metrics for T wave amplitude dependency, we introduced a correction formula that yields T wave amplitude corrected standard deviation of QT intervals (cSDQT), offering the possibility for QTV measurement that

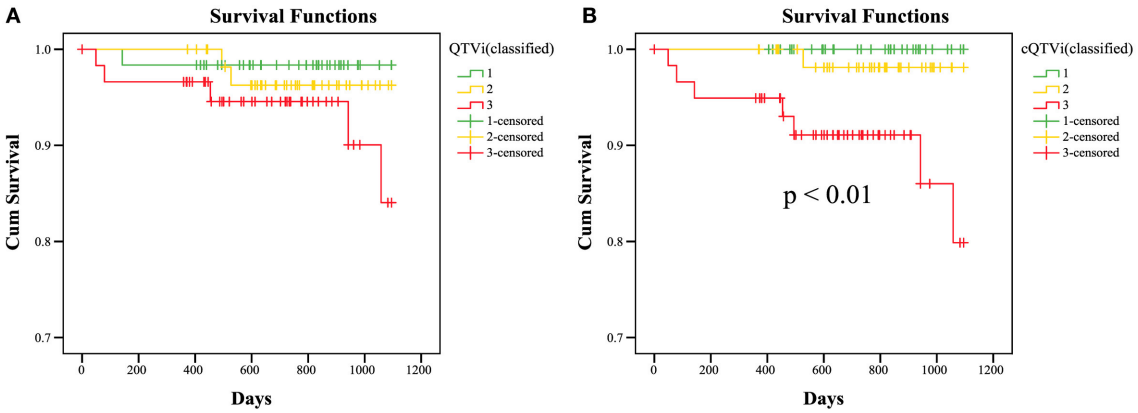

FIGURE 3 | KaplanMeier survival curves; Estimated survival of DEFINITE patients for QTVi (A) and cQTVi (B; classified in tertiles: 1 – lowest tertile, 2 – medium tertile, 3 – highest tertile) for 3 years. Last observations of a patient are marked in the curves with a cross (censored data).

is less sensitive to T waveform characteristics. Furthermore, by normalizing QTV to a specific T wave amplitude, comparisons of QTV between leads or groups of different T wave amplitudes become more meaningful. By adjusting the calculation of the frequently used QTVi metric accordingly, a more precise non-invasive measure of repolarization lability is obtained. Applying the correction formula to QTV measurements is straight forward; the only additional data needed is the median T wave amplitude. In this regard, the 2DSW algorithm, for example, offers the possibility to extract both, QT interval and T wave amplitude.

Higher QTV has been previously reported in normal subjects in conditions of sympathetic activation such as standing, and hence it has been argued that high QTV is indicative of high sympathetic tone. Given that T wave amplitude during standing is smaller than in the supine position, previous observations might have at least in part been the result of the inverse T wave amplitude QTV relationship. Our results demonstrate for the first time that the difference in QTV observed between standing and lying is not solely caused by the reduction in T wave amplitude.

When exploring the T wave amplitude—QTV relationship in a clinical dataset of Holter ECG, we found a regression coefficient similar to that of healthy subjects but a smaller R^2. Pathologic cardiac repolarization in patients with non-ischemic cardiomyopathy might partly explain the increased variance in the dataset. When comparing QTV between patients enrolled in the DEFINITE study and healthy subjects, applying the T wave amplitude correction achieves 2.5-times better group discrimination by minimizing the inter-group variability of T wave amplitude influence. Kaplan-Meier estimator analysis showed that cQTVi is inversely related to survival. Patients with non-ischemic cardiomyopathy and a high cQTVi have a significant higher all-cause mortality than patients with low cQTVi. Importantly, QTV was only predictive of all-cause mortality after correcting for T wave amplitude.

Previous studies have repeatedly shown predictive value of QTV for mortality in patients with ischemic heart disease, where the mode of death is likely malignant ventricular arrhythmia (Baumert et al., 2016a), but its potential for risk stratification in patients with non-ischemic cardiomyopathy remains to be established.

In conclusion, all ECG datasets have shown a significant inverse relationship between T wave amplitude and QTV of similar characteristic. Exploiting this property, a simple correction formula has been proposed and improved QTV assessment for predicting all-cause mortality in patients with non-ischemic cardiomyopathy has been demonstrated.

5. LIMITATIONS

A potential limitation of the proposed correction formula is its dependence on the algorithm that is used to delineate the T wave. In principle, each algorithm might behave different as a function of T wave amplitude. To account for algorithm specific differences we did not rely on a single algorithm but invoked two algorithms for QT extraction. Both of them were previously shown to be very robust and appropriate for QTV measurement (Baumert et al., 2012; Schmidt et al., 2014b). The similar findings for both algorithm, not only qualitatively but also quantitatively, accounts for the general usability of the proposed correction.

Another potential limitation of the proposed algorithm is imposed by pathophysiologic alterations of T wave amplitude. QTV analysis is usually based on single ECG lead, representing the scalar projection of the cardiac electric vector on a particular point of the body surface. While in general those ECG leads are chosen that yield high T waves (Baumert et al., 2016a), e.g., lead II, and thereby a good signal-to-noise ratio, T wave axes may vary between individuals and hence may represent repolarization waves sub-optimally. This is particularly relevant in patients with cardiac myopathies where depolarization propagation and repolarization across the ventricular myocardium are highly individual. Hence, the predictive value of QTVi may partly lie in capturing differences in spatial axis-related patterns for the QRS and T waves. The T wave amplitude correction coefficient

introduced in this paper is agnostic to the source underlying the T wave amplitude change. Regarding the lead which actually has been used in this study, it should be noted that not a single one was used, i.e., in parts differing leads have been used for the different studies. This is mainly a consequence of our aim to invoke as comprehensive a data set as possible. Owing to the availability of data and the retrospective nature of our study, we could not restrict ourselves to use the same lead. However, extensive pretests showed that, from an algorithmic point of view, behavior is similar across leads. Even the normalization to a "standard" T wave amplitude, which comes along with the proposed method, contributes to such comparability.

Finally we have to mention a limitation, which is relevant for future studies on QTVi, normative values of QTVi and its extended use as marker for risk stratification. Though the primary aim of the proposed correction is to account for the influence of T wave amplitude on QT variability metrics, as stated before our algorithm also normalizes the resulting QTV to a reference T wave amplitude. In principle, such normalization is desirable, as it improves comparability of QTV measurements between subjects and across studies. However, it should be noted that two different definitions of QTVi exist: the original formula relates QTV to heart rate variability (Berger et al., 1997), while a later modification uses RR variability instead (Piccirillo et al., 2001), and has been used in this study. Both definitions are currently in use and the lack of consensus adds another layer of complexity to the comparability of QTVi measurements. Importantly, the amplitude correction proposed in this paper is independent from the definition of QTVi and resulted in similar improvements for either definition (results on using HRV for normalization are not shown).

AUTHOR CONTRIBUTIONS

MS processed ECG data, computed variability measures, conducted statistical analysis and drafted the manuscript. MB and SZ conducted statistical analysis and drafted the manuscript. HM drafted the manuscript. All authors have read and approved the final manuscript.

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