



QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology

Mathias Baumert¹, Alberto Porta^{2,3}, Marc A. Vos⁴, Marek Malik^{5*}, Jean-Philippe Couderc⁶, Pablo Laguna⁷, Gianfranco Piccirillo⁸, Godfrey L. Smith⁹, Larisa G. Tereshchenko¹⁰, and Paul G.A. Volders¹¹

¹School of Electrical and Electronic Engineering, The University of Adelaide, Adelaide, SA, Australia; ²Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; ³Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, Milan, Italy; ⁴Department of Medical Physiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, The Netherlands; ⁵St Paul's Cardiac Electrophysiology, University of London, and National Heart and Lung Institute, Imperial College, Dovehouse Street, London SW3 6LY, UK; ⁶Heart Research Follow-Up Program, University of Rochester Medical Center, Rochester, NY, USA; ⁷Zaragoza University and CIBER-BBN, Zaragoza, Spain; ⁸Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Università 'La Sapienza' Rome, Rome, Italy; ⁹Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; ¹⁰Oregon Health and Science University, Knight Cardiovascular Institute, Portland, OR, USA; and ¹¹Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands

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This consensus guideline discusses the electrocardiographic phenomenon of beat-to-beat QT interval variability (QTV) on surface electrocardiograms. The text covers measurement principles, physiological basis, and clinical value of QTV. Technical considerations include QT interval measurement and the relation between QTV and heart rate variability. Research frontiers of QTV include understanding of QTV physiology, systematic evaluation of the link between QTV and direct measures of neural activity, modelling of the QTV dependence on the variability of other physiological variables, distinction between QTV and general T wave shape variability, and assessing of the QTV utility for guiding therapy. Increased QTV appears to be a risk marker of arrhythmic and cardiovascular death. It remains to be established whether it can guide therapy alone or in combination with other risk factors. QT interval variability has a possible role in non-invasive assessment of tonic sympathetic activity.

Keywords ECG • QT interval variability • Repolarization • Heart rate variability • Sympathetic activity • Autonomic nervous system

Introduction

In 2014, the European Heart Rhythm Association (EHRA) together with the ESC Working Group on Cardiac Cellular Electrophysiology charged the authors of this text with reviewing the topic of beat-to-beat QT interval variability (QTV) to provide a consensus guideline concerning its measurement, physiological background, and clinical utility. In addition to the review of the topic, the text provides recommendations highlighted in italics.

The RR interval measured from body surface ECG exhibits spontaneous beat-to-beat changes, usually termed heart rate (HR) variability (HRV), and related to sinus nodal autonomic control.¹ The QT interval also exhibits spontaneous beat-to-beat fluctuations, reflecting subtle temporal variations in ventricular depolarization and repolarization. These are termed QTV and usually monitored simultaneously with HRV. Under normal resting stable HR conditions, QTV is small (2–3 magnitudes smaller than HRV), with a standard deviation typically below 5 ms (*Figure 1*).² Assuming that ventricular

* Corresponding author and Chair of the Writing Committee. Fax: +44 20 8660 6031. E-mail address: marek.malik@btinternet.com

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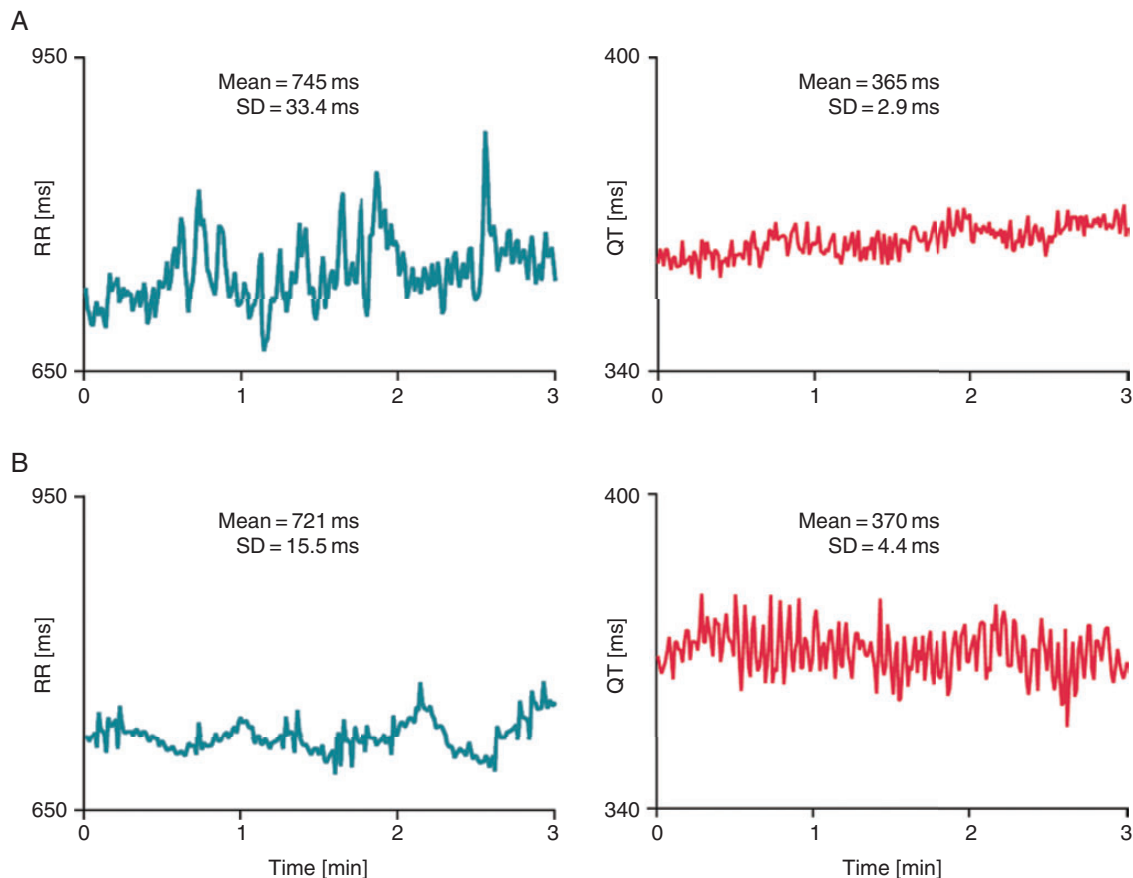


Figure 1 Example traces of RR (left) and QT intervals (right) of a normal subject (A) in comparison to a patient following MI (B), demonstrating augmented beat-to-beat QT variability after MI despite the reduction in HRV (unpublished data).

depolarization is much more stable compared with the beat-to-beat changes in repolarization duration, QTV is understood to measure the variability of ventricular repolarization duration. Despite some relation, QTV differs from T wave variability³ or alternans,⁴ which deal with beat-to-beat changes in the T-wave amplitude and morphology.

Methodology

Measurement principles

QT interval measurement

Under normal conditions, beat-to-beat QT interval changes are minimal, detectable by computerized high-resolution ECG. Accurate delineation of T wave end (T_{end}) is challenging, and most commercial systems measure the average, rate-corrected QT interval, and QT dynamicity, utilizing simple tangent and threshold methods.⁵ Although such techniques were used for QTV analysis,^{6–10} their accuracy appears insufficient and other QT delineations should be considered.¹¹

Dedicated QTV measurement techniques match complete or partial ECG waveforms with one or several templates, either user-defined or automatically computed. Since T_{end} in a given ECG lead

does not necessarily correspond to the true repolarization end, information beyond the lead-specific QT interval needs to be considered on scalar ECG.

In all consideration on QTV, it needs to be also recognized that measurement of the duration of the QT interval does not utilize the information within the T wave itself. Morphological beat-to-beat T wave changes that also represent repolarization variability should also be considered in repolarization variability analysis. Nevertheless, as this text deals solely with QTV, no further references to the morphological and other changes within the T wave are made.

The most commonly used algorithm matches the stretched or compressed ST-T segments of consecutive beats with a user-defined template, obtaining ST-T segment duration changes relative to the template duration.¹² The QRS interval is assumed constant. Naturally, this is not always fully accurate as rate-dependent changes in activation sequence also exist. Variation in the metrics used for template matching might thus also be erroneously interpreted as primary repolarization variation when in fact secondary variations due to the activation sequence modulations should also be considered. Time matching a template of the T wave descending part within consecutive beats together with beat-to-beat Q onset detection was also proposed.¹³ Recently, a matching algorithm based on two-

dimensional warping of the entire QT interval was introduced.¹⁴ Fiducial segment averaging is an alternative basic template matching approach.¹⁵ Operator's choice of the template duration appears to have a low impact on measurement reproducibility results¹⁶ and it has been reported that both inter- and intra-operator variability is low.¹⁷ Automated template generation may improve reproducibility.¹³

Using robust, (semi-)automated template matching techniques for QTV analysis is recommended.¹⁸

ECG lead and T wave amplitude

Temporal QT interval variations may differ between recording sites reflecting local repolarization signal heterogeneity, lead-specific respiration effects and noise (e.g. myopotentials).¹⁹ Short-term QTV analysis of 12-lead ECG suggests considerable inter-lead differences.²⁰ Short-term QTV from ambulatory ECG showed significant differences between the lateral and septal/anterior leads.²¹ Non-significant QTV difference between leads I, AVF, and V2 and moderate correlations were reported in patients undergoing electrophysiological study.²² Larger respiration-related cardiac axis movements were suggested in Z lead RT_{peak} measurements compared with X and Y leads.²³ The T wave amplitude may influence QTV (Figure 2). Leads with tall T waves and high signal-to-noise ratio typically yield lower QTV.^{2,20} Conversely, flat T waves decrease certainty of T_{end} determination, leading to increased variability. QT interval variability was inversely related to the T wave amplitude in some,^{18,20} but not in all studies.²⁴

Using simple measurement algorithms should be considered with caution. For instance, fluctuations in T wave amplitude, even in the setting of seemingly identical morphology, may lead to fluctuations in time of steepest T downstroke which in turn may lead to fluctuations in tangent method determination of T_{end} . Observed variation in T_{end} may then have little to do with repolarization variation.

The dominant singular value decomposition component of multi-lead ECG was proposed for QTV analysis.²⁵ Information on spatial repolarization heterogeneity may be gained by measuring QTV differences across leads.²² Regional pathology-driven differences in ventricular repolarization may be reflected in QTV differences across leads.¹⁹

In single-lead QTV analysis, lead II may be recommended allowing study-to-study comparisons.² Alternatively, QTV may be analysed in the lead with the tallest T wave. QT interval variability should be reported in relation to the T wave amplitude and noise levels. Multi-lead QTV analysis warrants further investigation.

The interpretation of single-lead QTV studies needs also to reflect the fact that the QT interval in a given lead only measures the interval between the earliest depolarization and latest repolarization as projected onto the axis of that lead. There is no information contained in the measurement relating to localizing where along that axis the earliest depolarization or latest repolarization tissue resides.

RT_{peak} vs. QT_{end} measurement

Earlier studies and those using Holter ECGs utilized RT_{peak} interval to measure repolarization variability^{26–30} because of relatively easy automated detection and lesser susceptibility to broadband noise compared with RT_{end} measurements.²³ Comparison between RT_{peak} and RT_{end} variability suggests that HRV affects primarily the variability of the early T wave portion.²³ In normal subjects, QT_{peak} variability is significantly correlated with QT_{end} variability, but this correlation appears reduced in cardiovascular disease.³¹ Compared with RT_{end} , RT_{peak} interval is more sensitive to periodic noise.²³

T_{peak} is lead dependent and influenced by the cardiac axis movement. The descending T wave limb is believed to carry important information on repolarization heterogeneity. Therefore, QTV measurement without the exclusion of the $T_{peak} - T_{end}$ interval is recommended.

Rate correction of the QT interval and QT dynamicity

Most QTV studies have not considered HR correction, while some introduced only the QT interval dependence on the previous RR interval, assessed the QT–RR coupling in the frequency domain,^{26–28} or used generic rate correction formulae.³² More recent approaches account for the QT dependence of the sequence of preceding RR intervals³³ and additional influences (e.g. respiration).³⁴ As the QT–RR relationship varies among individuals, generic correction formulae may be problematic. Individual-specific correction formulae that also take into account hysteresis effects have been proposed to measure QT dynamicity,^{35,36} but a framework for

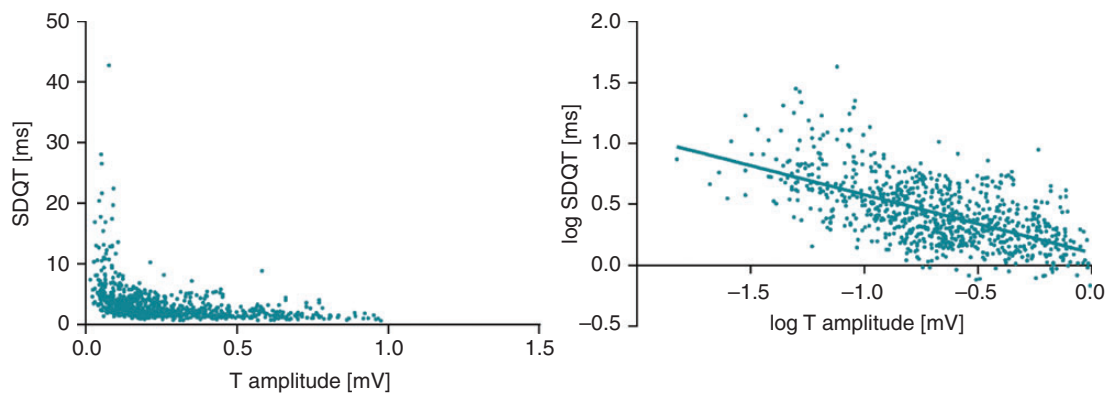


Figure 2 Inverse relation between T wave amplitude and QT variability. Data were obtained from 2-min, 12-lead ECG of 69 healthy subjects.²⁰

QTV analysis is lacking since separating rate-driven QTV from genuine fluctuations in QT interval is technically challenging. The most direct solution is to study QTV at constant HR. Since cardiac pacing is usually not feasible, several techniques have been proposed to achieve relative HR stability and to limit cardiac cycle dependency of QT changes during physiological conditions.³⁷ Strategies based on heart period binning, however, do not account for the beat-to-beat dynamical QT–RR relation (i.e. the dependence of the QT–RR relation on the history of the RR changes) and provide only static estimates of the QT–RR relationship, unless hysteresis is incorporated.³⁸ A method that combines the binning approach and instantaneous QT changes is under evaluation.³⁹

Until a thoroughly and independently validated method for separating QTV from HR is available, it can be recommended to report QTV uncorrected for HR together with HR (besides commonly used QTV–HRV ratios) and to study QTV under the stable HR conditions.

QT interval variability markers

Table 1 summarizes commonly used QTV measures. Most authors report standard deviation (SDQT) or variance of QTV (QTVar).^{8,13} QT interval variance normalized to the squared mean QT interval (QTVN)¹² and Poincaré plot-based, short-term variability have

also been reported.^{40,41} QT interval variability-to-HRV ratios are often calculated, the QT variability index (QTVi) being most popular (Table 1).^{12,39,42–47}

More recently, QTVi calculation based on the $T_{\text{peak}}-T_{\text{end}}$ interval has been suggested.⁴⁸ Other QTV-to-HRV ratios include the standard deviations of QT to RR intervals,⁸ the short-term variability of QT (STVQT) to that of RR (STVRR) ratio (VR) assessed from the Poincaré plots.⁴¹ Although the rationale of all these indexes is the same (i.e. normalizing QTV for HRV), the ratios differ, rendering cross-studies comparisons difficult. Importantly, physiological evidence of a general proportional relationship between QTV and HRV is lacking. Rather than separating genuine QTV from the HRV influence, these ratios are composite measures of partially correlated QTV and HRV variables.

Frequency domain analysis of QTV demonstrated oscillations related to respiratory rhythm and Traube–Hering–Mayer waves (Figure 3).^{26–28} Squared coherence quantifies QT–RR coupling as a function of frequency,^{12,26,29,49,50} demonstrating significant associations both in the low (LF, 0.04–0.15 Hz) and high frequencies (HF, 0.15–0.4 Hz) (Figure 4).¹ Thus, LF and HF rhythms in QTV are at least in part a reflection of QT rate adaptation.^{26,27,29} Transfer function analysis with HRV as input and QTV as output was utilized

Table 1 Commonly used variables of beat-to-beat QT interval variability

Variable	Units	Description
QT variability		
SDQT	ms	Standard deviation of QT intervals; $SDQT = \sqrt{\frac{1}{N} \sum (QT_n - QT_{\text{mean}})^2}$
QTVN	du	Normalized QT interval variance; $QTVN = \frac{SDQT^2}{QT_{\text{mean}}^2}$
STVQT	ms	Short-term QT interval variability; $STVQT = \sum \frac{ QT_{n+1} - QT_n }{N\sqrt{2}}$
LTVQT	ms	Long-term QT interval variability; $STVQT = \sum \frac{ QT_{n+1} - QT_{n-2} - 2QT_{\text{mean}} }{N\sqrt{2}}$
QT variability normalized to HRV		
QTVi	du	QT variability index; $QTVi = \log \frac{QTVN}{HRVN}$ or $QTVi = \log \frac{QTVN}{RRVN}$
VR	du	Variability ratio; $VR = \frac{STVQT}{STVRR}$
Frequency domain markers of QTV and QT–RR variability interactions		
QTV_{LF}	ms^2	Power of QTV assessed in LF band (from 0.04 to 0.15 Hz)
QTV_{HF}	ms^2	Power of QTV assessed in HF band (from 0.15 to 0.5 Hz)
$ H_{\text{qt-rr}} $	du	Transfer function gain from RRV to QTV; $ H_{\text{qt-rr}}(f) = \frac{ C_{\text{qt-rr}}(f) }{S_{\text{rr}}(f)}$
$\phi_{\text{qt-rr}}$	rad	Cross-spectrum phase from RRV to QTV; $\phi_{\text{qt-rr}}(f) = \text{phase of } C_{\text{qt-rr}}(f)$
$K_{(\text{qt-rr})^2}$	du	Squared coherence between RRV and QTV; $K_{(\text{qt-rr})^2}(f) = \frac{ C_{\text{qt-rr}}(f) ^2}{S_{\text{rr}}(f)S_{\text{qt}}(f)}$
Time domain QTV decomposition		
RR-related QTV	ms^2	QTV linearly related to RRV
RR-unrelated QTV	ms^2	QTV linearly independent of RRV
Normalized RR-related QTV	du	Percentage of QTV linearly related to RRV
Normalized RR-unrelated QTV	du	Percentage of QTV linearly independent of RRV

du, dimensionless units; LF, low frequency; HF, high frequency; N, number of beats; HRvar, variance of HR time series; RRvar, variance of RR time series; HRVN = $HRvar/HR_{\text{mean}}^2$; RRVN = $RRvar/RR_{\text{mean}}^2$; RRV, RR interval variability; S_{rr} , RRV power density spectrum; S_{qt} , QTV power density spectrum; $C_{\text{qt-rr}}$, cross-spectral power density between QTV and RRV.

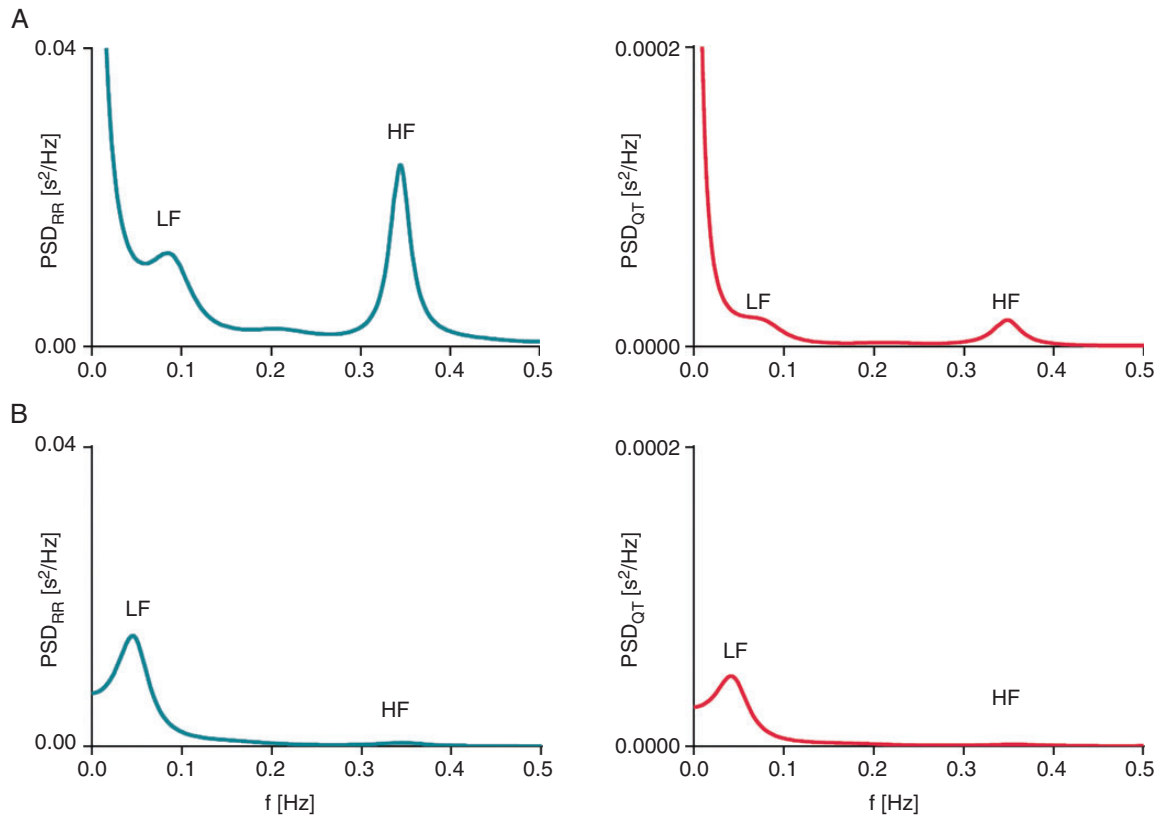


Figure 3 Power spectra density (PSD) of RR (left) and QT series (right) at rest in supine position (A) and during 90° head-up tilt (B) (unpublished data).

to estimate the gain and the phase of the QT–RR relation as a frequency function (Figure 4).^{26,28,29} More complex approaches of multivariate linear modelling and partial process decomposition quantify the amount of QTV driven by the variability of determinants (e.g. QTV driven by HRV, respiration).^{29,34} An example of this decomposition is shown in Figure 5. (See also Appendix A) More recently, non-linear dynamical systems and information theories have been adopted to quantify QTV (Appendix B).

Comparative studies identifying redundancies in QTV indices are needed. If composite measures are used, QTV and HRV should also be reported, including multivariable analyses to distinguish QTV and HRV contributions in a given clinical setting. Given the complexity and non-linearity of the QT–HRV relation, simple linear QTV–HRV relationships should be considered with caution. Frequency domain parameters have so far been insufficiently explored. Their further research in clinical settings is warranted.

Reproducibility studies

Short-term QTV measured randomly across 24-h ECG suggests better reproducibility compared with HRV, with a coefficient of variation (CV) of 0.22.²² Reproducibility analysis of QTV obtained from 24-h ECG on three different days showed a CV of SDQT < 0.14.⁸ A reproducibility study of short-term QTVi obtained during different days reported coefficients of variation of 0.18 in healthy

subjects and of 0.40 in end-stage renal disease patients.¹⁷ Month-to-month and year-to-year analysis of QTVi derived from short-term ECG in healthy subjects demonstrated coefficients of variation of 0.08 and 0.09, respectively.⁵¹ Comparison of short-term ECG recorded in the supine position vs. sitting resulted in a CV of 0.12.⁵¹ As QTV is affected by autonomic activity, temporal transition across autonomic states might adversely affect reproducibility in longer recordings.⁵² STVQT may therefore be better reproducible than QTvar.⁵³

Only few studies on QTV reproducibility are available. More focused research is needed.

Technical aspects influencing the QT interval variability markers

ECG acquisition requirements

ECG acquisition and pre-processing have not been standardized in QTV studies. Effects of filtering and digitizing require thorough investigation. A systematic comparison of sampling rates demonstrated that 500 Hz are sufficient while sampling rates of 200 Hz and below may artificially increase QTV values.⁵⁴ Theoretical investigation of digitization noise and simulation studies also suggests that 500 Hz is a sufficient sampling rate for QTV measurement.⁵⁵ High pass cut-off frequency of 0.05 Hz may be recommended. Using higher high pass cut-off frequencies, e.g. to reduce baseline wander, may

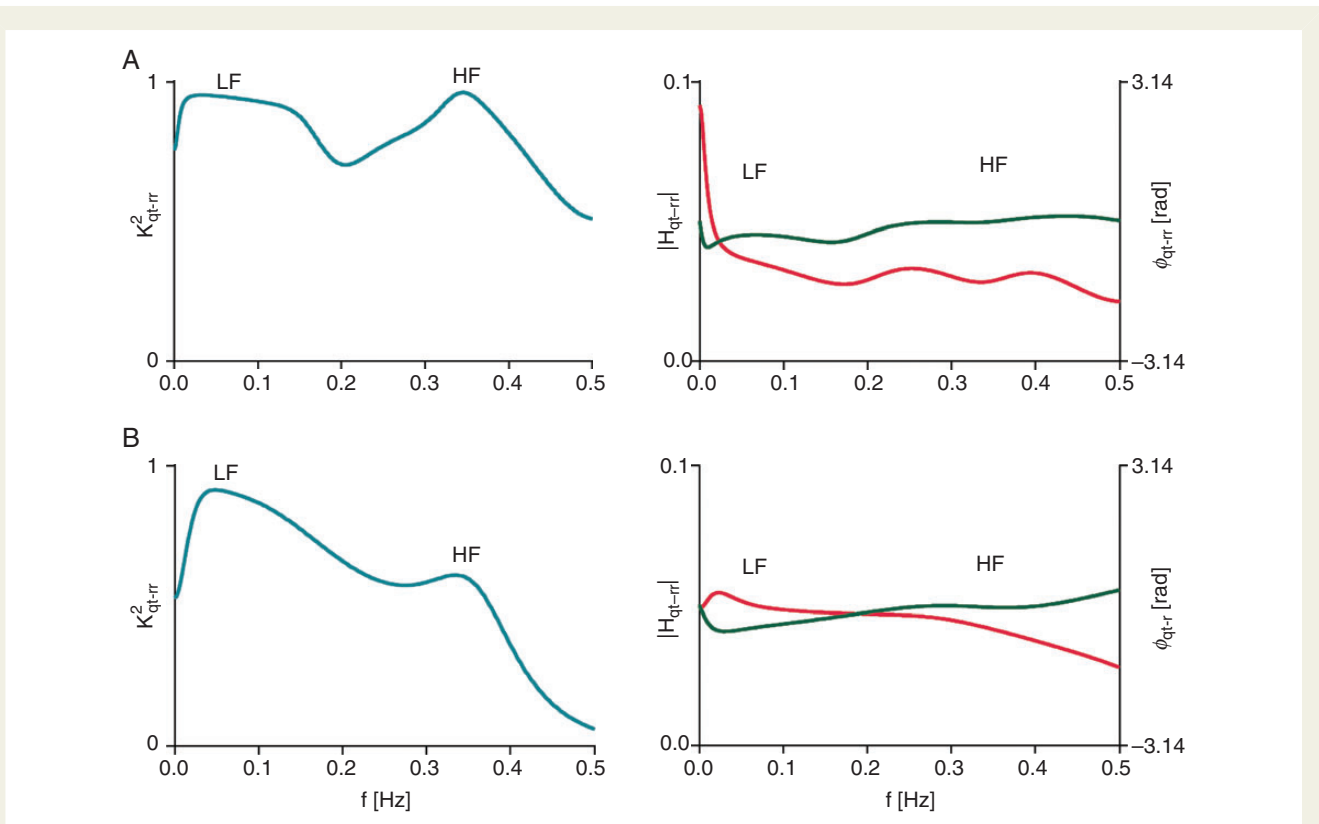


Figure 4 Left panels: squared coherence function between RR and QT series. Right panels: gain (red lines) and phase (green lines) of the transfer function from RR variability to QTV. The top row (A) shows results at rest in supine position and the bottom row (B) during 90° head-up tilt (unpublished data).

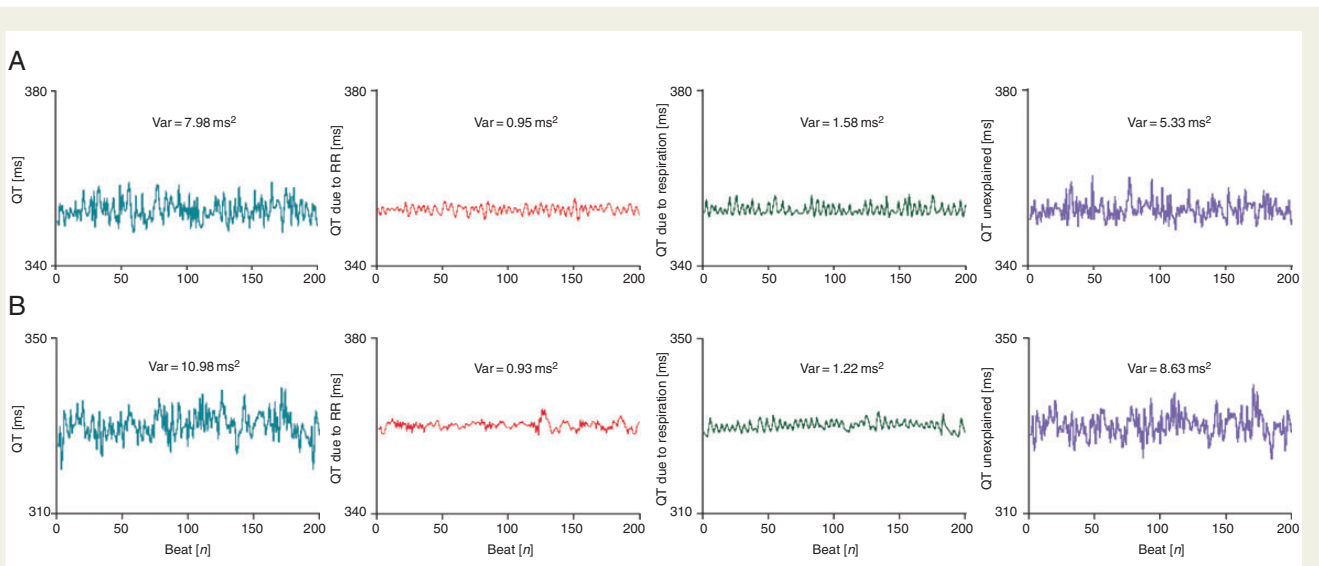


Figure 5 Decomposition of QTV into partial processes due to RR variability, respiration, and noise at rest (A) and during 90° head-up tilt (B) (unpublished data). Var, variance

significantly distort T morphology possibly if not likely affecting T_{end} measurement. Sufficiently fine gain resolution is needed to avoid the ‘staircase’ effect on the digitalized T waves.

Studies investigating the effect of low T wave amplitude on QTV and establishing the minimum gain resolution (in relation to T wave amplitudes) are needed.

Recording duration

Most QTV studies have used short-term ECG, typically 256–512 s durations or 256–512 beats, adopting the time frame recommended for short-term HRV analysis.¹ QT-RR hysteresis may introduce transient changes. Caution is thus warranted when inferring stationarity of short-term QTV based on seemingly stationary HR. To deal with this issue, detrending of QT time series has been proposed.¹² QT interval variability over longer durations, capturing diurnal or circadian cycles, has also been reported. However, in most cases, recordings were divided into short relatively noise-free segments and analysed separately.^{7,8,10,56,57,58} Longer recordings have been frequently utilized for non-linear analyses.⁵⁹

There is little data to guide time frame choices for QTV analyses. Systematic investigations are needed.

Effects of ECG artefacts

Template matching techniques deal with broadband noise better than traditional QT measurement techniques.¹⁸ However, they are susceptible to low frequency noise with periods similar to template duration.² Baseline wander may add further noise to QTV measurement,^{2,18,23} but its influence depends largely on methods for its removal. ECG amplitude modulation and spatial rotation due to respiratory cardiac axis movement is another source of measurement noise.²³ Its effect on QTV was reported to be small,¹⁸ but significant when axis movement is considered.⁶⁰ A minimum signal-to-noise ratio of 15 dB was found necessary for QTV analysis.⁶¹

Quantitative procedures should be specifically designed to evaluate and reduce the effect of ECG artefacts on the QTV computation.

Unless a study nature dictates different conditions, QTV investigations should include (but not necessarily be restricted to) measurements made in ECGs recorded in supine position so that different reports can be compared.

Ectopic beats

Ectopic beats are excluded in studies of repolarization instability following regular ventricular conduction.²² As premature ventricular

contraction itself may trigger ventricular tachycardia/fibrillation (VT/VF), inclusion of ectopic beats in the overall QTV assessment has been proposed.⁶² Recently, QTV before and after premature ventricular contraction was found to predict non-sustained VT in chronic heart failure (CHF) and an increased VT/VF risk.⁶³ Post-ectopic QT patterns may be linked to baroreflex response.⁶⁴

Ectopic and subsequent beats should be excluded from QTV assessment. The QT response to ectopic beats may be analysed separately and deserves further investigation.

Technical recommendation

QT interval variability (with no HR correction) should be measured over the entire QT interval in lead II or in the lead with the tallest T wave using high-resolution ECGs recorded at >500 Hz at steady HR. Studies are required to compare (i) consistency across available QTV measurement algorithms and metrics, (ii) reproducibility, and (iii) recording duration.

Physiological basis of QT interval variability

QT–heart rate relationship

In resting conditions, HRV is a major physiological source of QTV.⁶⁵ The QT interval is linked to HR through the cellular dependency of action potential duration (APD) on cycle length.⁶⁶ The QT response to RR changes comprises rapid and slow processes^{67,68,69,70} resulting in significant hysteresis effects.⁷¹ Figure 6 illustrates the QT interval response to different rates of cardiac pacing and demonstrates residual QTV. The relation between QT interval and HR follows individual-specific, well-reproducible curvatures.⁷² Basic physiological manoeuvres such as orthostatic challenge reveal acceleration-/deceleration-dependent hysteresis of the QT interval response to HR.⁷³ Cardiac pacing sequences may also affect the QT–RR relationship.⁷⁴ Although the QT–RR relation is crucial to QTV, the dynamical response of QT to RR changes under spontaneous conditions remains largely unknown.

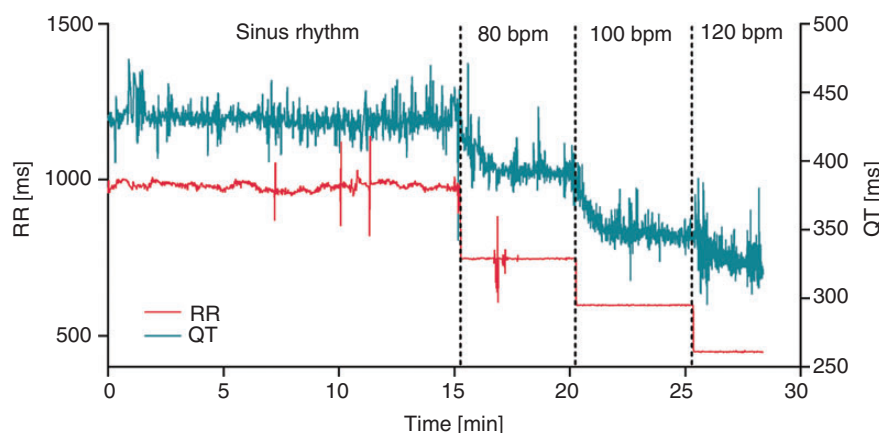


Figure 6 Example traces of RR (in red) and QT intervals (in green) in a patient during spontaneous sinus rhythm and during right atrial pacing at different rates, illustrating the rate adaption of the QT interval and residual QT variability in the absence of RR interval variability (unpublished data).

Further studies of the effects of the QT–HR relationship on QTV are needed, both in stationary and in non-stationary HR conditions. Until the effect of HR changes is better understood, QTV should be evaluated at steady HR.

Cellular mechanisms

Variation in QT duration at a constant RR interval is caused by beat-to-beat variability of the overall ventricular repolarization (BVR). Two factors potentially alter repolarization on a beat-to-beat basis: (i) variation in ventricular activation pattern and/or conduction velocity and (ii) variation in ventricular APD. To date, research has focused on mechanisms underlying variation in the duration and morphology of myocardial repolarization, as evidenced by monophasic action potential recordings from the ventricular surface/endocardium, transmembrane recordings from transmural ventricular wedge preparations, and microelectrode recordings from single isolated myocytes.^{75,76,77,78,79}

APD is determined by the magnitude and time course of voltage- and time-dependent ionic currents. The primary outward currents are carried by K^+ ions through distinct channel types, the rapidly and slowly activating delayed-rectifier potassium channels (I_{Kr} and I_{Ks}), and the transient outward (I_{to}), and inward rectifier potassium channels (I_{K1}). Inward currents, in particular the late Na^+ current (I_{NaLate}) and Ca^{2+} current ($I_{Ca,L}$), also determine the APD. In addition to this, there are ionic currents modulated by intracellular Ca^{2+} , including the Ca^{2+} -activated Cl^- current ($I_{Cl,Ca}$), $I_{Ca,L}$ and Na^+/Ca^{2+} exchanger (NCX), which allows beat-to-beat changes of intracellular Ca^{2+} to contribute to BVR. Myocardial metabolic status can also indirectly influence APD rapidly via ion channels controlled by metabolites, e.g. the ATP-sensitive K^+ channel (K_{ATP}) or by extracellular conditions, e.g. K^+ and H^+ concentration changes that result from changes in tissue perfusion. While unstable tissue perfusion characteristics may contribute to BVR, this has not been demonstrated experimentally.

The situation is further complicated by the direct and rapid modulation of APD via restitution in which a shortened diastolic interval limits the reactivation of inward currents and the inactivation of outward currents, thereby decreasing the proceeding APD. The shape and slope of this relationship critically affect the stability of APD. If the relationship between diastolic interval and the next APD has a shallow slope of <1 , minor perturbations of diastolic interval cause only a transient APD variation before the steady state is restored. Theoretically, with the slope of this relationship >1 , a sustained beat-to-beat APD variation occurs. However, the resulting pattern is stable APD alternans;⁸⁰ hence, a monophasic dependence of APD on diastolic interval cannot alone explain BVR. However, more complex (e.g. bi- and tri-phasic) relationships have been reported,⁸¹ predicting complex relationships between APD and RR interval that could contribute to BVR. A recent study⁷⁷ investigated APD, APD alternans, and BVR in canine ventricular myocytes, and found that alternans and BVR are clearly different in their dependency on rate and their connection to mechanical alternans, indicating distinct ionic mechanisms. At slow pacing rates, the potassium current I_{Ks} stabilizes BVR, despite minimal changes in APD. β -Adrenergic stimulation of I_{Ks} rescues from excessive repolarization instability and the generation of early after depolarizations. These data also show that under specific conditions it is

possible to dissociate APD and BVR, e.g. during I_{Ks} blockade combined with β -adrenergic stimulation (with or without intracellular Ca^{2+} buffering). Spontaneous release of Ca^{2+} from the sarcoplasmic reticulum during diastole can influence the subsequent APD through decreasing the inactivation time course of $I_{Ca,L}$, resulting in a longer APD.⁷⁶ The spontaneous Ca^{2+} release event is known to be a variable process on a beat-to-beat basis and therefore under conditions of excessive sarcoplasmic reticulum Ca^{2+} loads, the variable process of spontaneous diastolic Ca^{2+} release provides a mechanism for BVR at the single myocyte level.⁷⁶ However, it is unclear whether this mechanism can operate at the multicellular level where events in a single cell have negligible effect due to electrical coupling in the syncytium. In theory, the random nature of diastolic Ca^{2+} release will operate both temporally and spatially, and thus, the overall effect on ventricular APD will be minimized and would not be expected to generate BVR. On the other hand, recent reports suggest that spontaneous Ca^{2+} release in one cell can trigger release in adjacent cells.⁸² Therefore, under conditions of increased sarcoplasmic reticulum Ca^{2+} load, significant regions of myocardium may experience co-ordinated waves of spontaneous diastolic Ca^{2+} release⁸³ and therefore prolonged APD of the subsequent beat. This remains to be demonstrated experimentally. The link between intracellular Ca^{2+} and BVR is further supported by the evidence from *in vivo* studies that increased sympathetic activity, which raises intracellular Ca^{2+} levels, is associated with increased QTV. In an *in vivo* dog model of long QT1 syndrome,⁸⁴ QTV and BVR of the left ventricular monophasic APD were increased just prior to torsades de pointes. This repolarization instability was always accompanied by sizeable systolic after contractions, which also suggests a role of Ca^{2+} and/or mechanically evoked arrhythmogenesis. Isolated heart work indicated that local activation of β -adrenergic receptors can cause sufficient Ca^{2+} overload within a discrete area to trigger a ventricular ectopic beat.⁷⁹

*Although the cellular basis is not fully understood, the current evidence suggests that spontaneous sarcoplasmic reticulum Ca^{2+} release is a likely cellular mechanism for BVR and subsequent QTV. More generally, it is recognized that although single myocyte BVR is clearly not the sole contributor to *in vivo* QTV, insights into the ionic mechanisms of BVR are crucial for the understanding of BVR at the whole organ level.*

Stochastic ion channel properties

Isolated myocytes display intrinsic beat-to-beat APD variability proportional to APD duration that increases when blocking $I_{Ca,L}$ and I_{to} .⁸⁵ Stochastic fluctuations in I_{Ks} gating property have been shown to cause significant beat-to-beat APD variability in isolated cells.⁸⁶ Stochastic gating of I_{Na} , $I_{Ca,L}$, and I_{Kr} currents has also been implicated in APD variability.^{87,88} In the tissue, however, inter-cellular electrotonic interactions reduce the effect of stochastic gating.⁸⁹ Conditions with reduced repolarization reserve and gap junction decoupling may augment the effect of stochastic ion channel gating.

Experimental evidence and computer simulations are needed to explore stochastic ion channel gating effects on QTV in body surface ECG.

Autonomic nervous system

The autonomous nervous system affects cardiac repolarization variability at cellular, tissue, and organ levels. β -Adrenoceptor stimulation during I_{Ks} block has been shown to increase variability of

cellular repolarization of canine myocytes.⁷⁷ Transmural differences in APD affect T wave morphology⁹⁰ and may be altered through β -adrenergic activation.⁹¹ The same applies to other intramyocardial gradients. Heterogeneous distribution of β -adrenoceptors, regional arborization of sympathetic nerves,^{92,93} and differential cardiac sympathetic control⁶⁶ may contribute to spatial APD heterogeneity across the ventricles during high-sympathetic activity. Vagal nerve activity may alter ventricular APD directly via the ACh-activated K^+ current⁹⁴ or indirectly through accentuated antagonistic effects on the sympathetic nerve, pre- and post-synaptically.⁹⁵

Postural provocations in man have been shown to increase various measures of QTV and QTVi in the majority,^{16,49,54,96,97} but not in all studies.⁹⁸ Inconsistencies might have resulted from age-related QTVi increases.⁹⁷ Similarly, hypoxia-induced sympatho-excitation increased QTVi and QTVN.⁹⁹ Spectral analyses of QTV during mental stress test during atrial pacing,¹⁰⁰ interview stress, and exercise¹⁰¹ all suggest an increase in LF oscillations during sympathetic activation. QT variability index was also shown to increase during exercise,^{102,103,104} while QTVN showed inconsistent increase.¹⁰³ Sympathetic activation by caffeine resulted in higher QTVi during REM sleep.¹⁰⁵ Pharmacological β -adrenoceptor activation consistently increases QTV,^{16,99,106,107} while β -adrenoceptor block has shown no effect on QTV during rest,^{98,106} but a reduction during atrial pacing in patients with structurally normal hearts.⁹ Ambulatory RT_{peak} analysis has shown a reduction in variability after β -adrenoceptor block.²⁶ Pharmacological α_1 -adrenergic receptor activation did not affect QTVi or QTVN.⁹⁹ Comparing QTV with direct measures of cardiac sympathetic activity, cardiac norepinephrine spillover showed no correlation during rest.¹⁰⁸ Similarly, QTVi was correlated with electrodermal activity during exercise, but not during rest,¹⁰² and QTVi was not correlated with cardiac sympathetic nerve activity in healthy dogs.¹⁰⁹ This all suggests QTV increase due to sympathetic activation in normal subjects. At rest, sympathetic outflow to the heart may be insufficient to elicit QTV.

Investigations of the relation between absolute levels of sympathetic activity (tone) and QTV in healthy subjects are encouraged to establish whether changes of QTV quantify absolute sympathetic activity directed to the heart. A clinical protocol of QTV assessment may include an orthostatic challenge. Simultaneous recording of surface ECG and intra-cardiac electrograms may elucidate the QTV proportion linked to sympathetic innervation heterogeneity. The relation between sympathetic activity and QTV in pathological cardiac substrate requires further investigation.

Respiration

Respiration may influence QTV through respiratory sinus arrhythmia,¹¹⁰ APD modulation of ventricular myocytes,¹¹¹ mechano-electrical feedback to changes in ventricular loading¹¹² and by measurement artefacts in single leads due to cardiac axis rotation.⁶⁰ Respiration also affects T wave amplitude with likely implications on simple algorithms of QT measurement.

Most studies on the effect of respiration on repolarization variability have been performed using the RT_{peak} interval, which may not be extrapolated to QTV. Spectral analysis of RT_{peak} variability in patients with structurally normal ventricles during sinus rhythm demonstrated HF oscillations in QTV directly related to HRV since no significant direct QTV influence of respiration was observed during fixed atrial pacing and autonomic blockade.³⁰ Another study of

RT_{peak} variability during fixed atrial pacing suggested small respiratory-related changes due to cardiac axis rotation,²⁷ consistent with the use of a spatially derived respiration-compensated lead for QTV assessment.⁶⁰ A small direct, HR-unrelated effect of respiration on QTV was detected during spontaneous breathing with graded head-up tilt, independent of the orthostatic challenge.^{23,34} Data suggest that the HR-unrelated contribution to respiratory-related RT_{peak} variability is negligible.

Metronomic breathing at various rates showed no difference in QT variance in normal subjects in the supine position and during standing compared with free breathing¹⁶ or in CHF patients.⁹⁷ However, increased power and gain in the HF band of the RR– RT_{peak} sequence was observed in normal subjects during metronomic breathing compared with free breathing.^{7,29}

QT interval variability measurement during spontaneous breathing is recommended if basic time domain metrics are considered. Metronomic breathing may be preferable for frequency domain analyses. Derived ECG leads compensated for cardiac axis rotation warrant further investigation.

Other factors influencing QT interval variability in normal subjects

Circadian influences

In normal subjects, QTV appears to be lower during night time compared with day time,^{8,10,26,113,114,115} supporting the QTV link with cardiac autonomic tone.^{116,117} Lower recordings noise during night as well as lower HR might also play a role.

Age

Data on QTV age dependency are inconclusive. SDQT obtained in ambulatory ECG^{91,94} and short-term ECG²⁰ were reported comparable between younger and older adults, while other studies found reduced¹¹⁸ or increased⁹⁸ QTV. QT variance obtained from ambulatory ECG was not different between children and adults,¹¹⁹ while short-term QT variance was found increased in children,⁵⁶ but comparable across children of different ages.¹²⁰ Most,^{97,118,120,121,122} but not all,⁵⁶ studies report the QTV/HRV ratio to increase with age, which may primarily be a reflection of the well-known age-related HRV reduction.

Sex

Ambulatory and pre-exercise ECG studies have shown no sex differences in absolute QTV^{59,115,121} with one exception.⁴⁸ Two additional reports showed increased VR¹²¹ and altered QT-RR dynamics in women.⁵⁹ Lead-specific short-term SDQT in 12-lead ECG suggests higher QTV in some leads in women.²⁰ Larger studies involving short-term ECG of >100 subjects demonstrated increased SDQT, QTVN, and QTVi in women.^{52,123} There is thus some evidence of a small sex effect, perhaps partly explainable by differences in autonomic modulation.¹²⁴

Pharmaceuticals

Only singular studies exist on drug effects. QT variability index in ambulatory ECG in normal subjects was increased by pemoline (dopaminergic) but unaltered by fluoxetine (selective serotonin reuptake inhibitor).¹²⁵ Yohimbine decreased QTVi while clonidine had no effect.¹²⁶ Oestrogen replacement therapy did not affect

QTV measures.¹²⁷ Sotalol infusion increased QTVi,^{128,129} but propranolol and amiodarone had no effect,^{98,128} whereas grapefruit,¹²⁸ sildenafil,¹³⁰ and sevoflurane increased QTVi, the latter in children.¹³¹

QTc duration

Few studies have investigated the relationship between QTc and QTV. Short-term variability of QT was not correlated with QTc (Bazett formula) in normal subjects.¹³² Similarly, QTVi showed no correlation with QT duration.¹³³ In normal subjects, RMSDQT was not correlated with QTc (Bazett and Fridericia formulae).¹³⁴ SDQT measured in 24-h ECG showed only moderate correlation with QTc.⁸ Thus, substantial correlation between QTV and QTc is unlikely, although little data are available and the generic rate correction formulae may have produced unreliable results.

Circadian effects, age, and sex should be considered when conducting QTV studies. The effects of drugs are poorly investigated, and focused investigations are needed. The relation between QTV and QTc warrants further studies.

Clinical value of QT interval variability assessment

General findings

QT interval variability has been studied in a wide range of clinical settings (Figure 7). Based on meta-analysis of 45 and 23 studies, respectively, involving 1954 and 1190 normal adults, average values of QTVi and SDQT during rest are -1.6 and 3.3 ms, possibly somewhat elevated in infants and children. A substantial number of studies of patients with primarily ischaemic heart disease (1850 patients) demonstrate consistently higher QTVi values, with a weighted average of -0.6 . SDQT values obtained from 404 patients show a similar picture, with a weighted average of 7.3 ms. Collated data from patients with other cardiac diseases show a less distinct increase in QTVi and SDQT. QT variability index values of patients with long QT syndromes (LQTS) are similar to the upper end of normal subjects, although this might be different in probands and in asymptomatic carriers. QT variability index values of patients with mental disorders largely overlap with normal values, while QTVi values in patients with diabetes and autonomic neuropathy spread widely across studies.

Further meta-analyses of existing studies combined with the analysis of large ECG databases are needed to establish normal QTV values.

QT interval variability in clinical populations

Cardiac patients

QT variability index appears useful for ECG-based screening of patients with coronary artery disease (CAD), left ventricular (LV) hypertrophy, and/or LV systolic dysfunction.¹³⁶

Coronary artery disease, myocardial infarction, and ischaemic cardiomyopathy. SDQT was significantly increased in CAD without prior myocardial infarction (MI).²⁴ Ambulatory ECG demonstrated increased QTVN and QTVi during acute ischaemia.¹³⁷ Decoupling of QTV from HRV was observed during

induced ischaemia.¹³⁸ During acute ST-segment elevation, positive troponin T was associated with increased SDQT.¹³⁹

Twelve-lead ECG of patients with recent MI showed increased SDQT in six leads.¹⁴⁰ QT variability index in leads corresponding to the infarct site were correlated with indices of LV dysfunction.¹⁹ The RR-independent component of QTV appeared increased¹⁴¹ and RT_{end} complexity increased,¹⁴² the latter being more pronounced in LV dysfunction. Data from patients with implanted cardioverter defibrillator (ICD), CAD, and ischaemic cardiomyopathy (ICM)-related CHF suggest an inverse relation between QTVi and LV ejection fraction (LVEF).^{48,105,143,144} Post-MI patients with low LVEF showed increased high frequency variability in RT_{end} time series compared with MI patients with LVEF $> 40\%$ and CAD patients, despite comparable high-frequency HRV power, arguing for respiratory modulation of venous return and LV filling and changes in mechano-electrical coupling.⁵⁰ Age appears to have no influence on QTVi in CHF,^{97,143} but its influence could be blurred by the impact of other factors accompanying the development of CHF.

Post-MI patients on β -blocker therapy were reported to have smaller SDQT in ambulatory ECG than patients on no β -blockers, with values similar to normal subjects while HR was comparable.¹¹⁴ One-year β -blocker treatment of ICM-related CHF lowered QTVi.¹⁴⁵ Magnesium sulphate reduced QTVi in ICM-related CHF patients, and the change in serum magnesium was inversely correlated with QTVi.¹⁴⁶ Sotalol and grapefruit tended to increase QTVi in ICM-related CHF patients, while amiodarone had no effect.¹²⁸ In ICM-related CHF, atorvastatin therapy reduced SDQT.¹⁴⁷ In mild ICM-related CHF, sildenafil increased QTVi.¹²⁹ In decompensated CHF, mostly due to CAD, the Ca²⁺ sensitizer levosimendan did not increase ambulatory SDQT, despite increasing non-sustained VT.¹⁴⁸ In primarily ICM-related CHF, ibutilide did not affect QTVi during sinus rhythm, but increased it during random atrial pacing.¹⁴⁹

The QTV response to acute autonomic stimuli appears blurred in cardiac patients. In CHF, QTVi was increased, but the response to head-up tilt was impaired^{97,150} and acute β -blockade showed no QTV effect.¹⁰⁶ In post-MI patients, anger recall test did not affect QTVi during β -blockade.¹⁴⁴ In a canine model, however, increased QTVi was observed with high sympathetic nerve activity after experimentally inducing heart failure,¹⁰⁹ mirroring circadian autonomic changes.¹⁵¹ Circadian variation in QTVi and QTVN and an inverse correlation between QTVN and serum potassium were shown in CHF patients.¹⁵² Exercise increased QTVi in patients with ICD and documented CAD.¹⁰⁴

CABG appears to acutely increase¹⁵³ and later reduce QTVi.¹⁵⁴ Similarly, SDQT increase was shown after cardiac surgery.¹³⁵ In patients with structural heart disease and cardiac resynchronization therapy, reverse electrical remodelling was associated with QTVN reduction and coherence increase.¹⁵⁵ Reduction in STVQT was observed in cardiac patients following a rehabilitation programme.¹⁵⁶

Hypertension and left ventricular hypertrophy. Increased QTVi was seen in nocturnal blood pressure (BP) non-dippers,¹⁵⁷ pre-hypertension,¹⁵⁸ and hypertension.^{158–160} QT variability index correlated with systolic BP¹⁵⁸ and inversely correlated with nocturnal BP reduction.¹⁵⁷ Similarly, QTVN correlated with resting systolic BP and cardiac norepinephrine spillover.¹⁶⁰ In

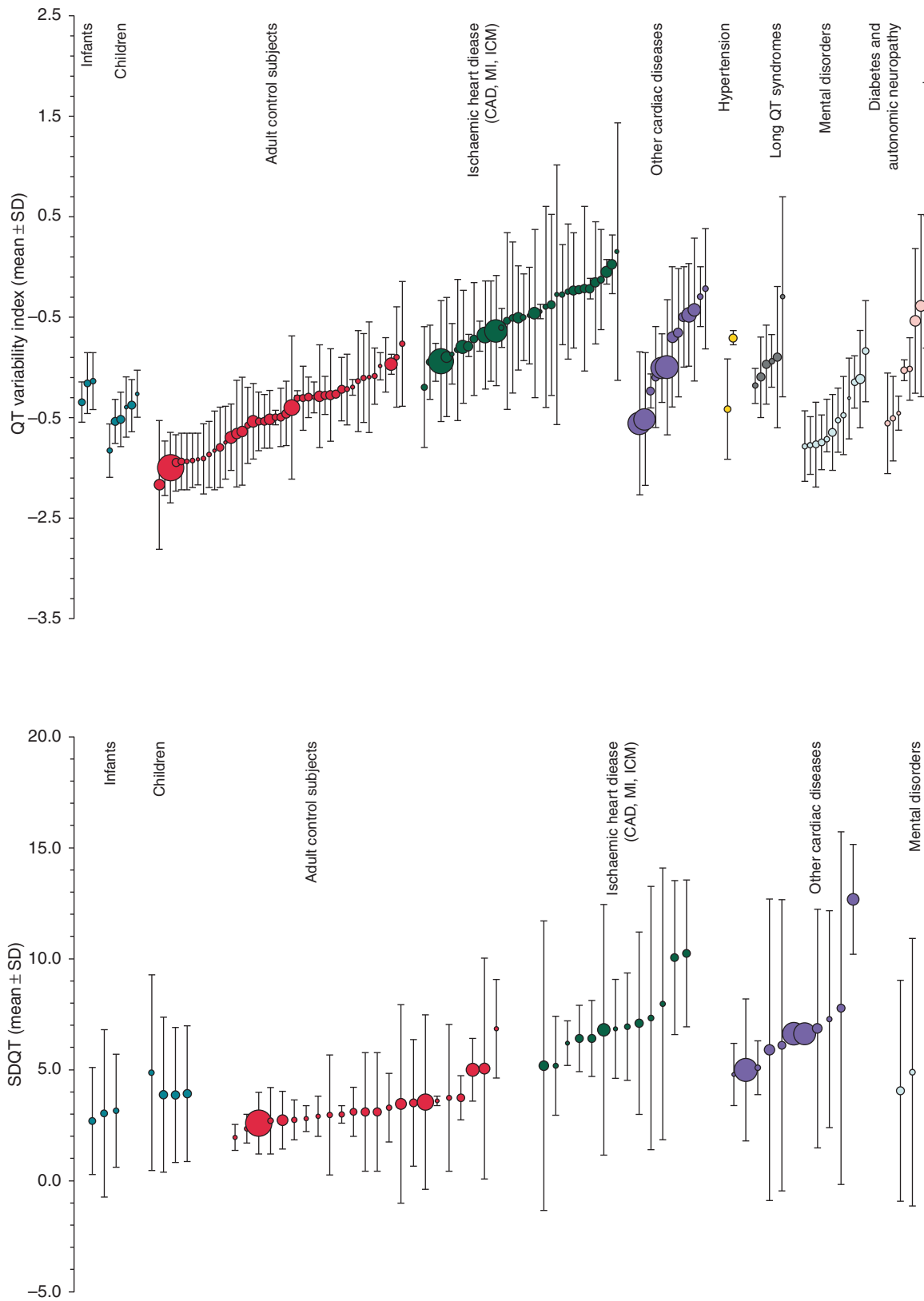


Figure 7 Reported values of QTVi (top) and SDQT (bottom). Data are presented as mean and standard deviations. The size of the circle indicates sample size. (Two studies were excluded due to reported methodical differences in the QT interval extraction that lead to very small SDQT values.)^{50,135}

hypertensive patients, the degree of hypertrophy correlated with QT_{Vi}.¹⁵⁹ SDQT also correlated with LV mass after renal transplantation.¹⁶¹ In normal adults, QT_{Vi} was correlated with cardiac output, e.g. stroke volume index and acceleration index.¹⁶²

Hypertrophic cardiomyopathy and myotonic dystrophy. QT variability index was increased and coherence reduced in hypertrophic cardiomyopathy (HCM) caused by a β -myosin heavy chain mutation.¹⁶³ SDQT from ambulatory ECG was also increased in HCM.¹⁶⁴ The QTV part unexplained by HRV was useful for screening of HCM patients.¹⁶⁵ Further, QT_{Vi} was increased in myotonic dystrophy Type 1.¹⁶⁶ In primarily non-ICM, QT_{Vi} was unrelated to LVEF,¹² but related to the late gadolinium enhancement in cardiac magnetic resonance imaging, a marker of disease severity and arrhythmic risk.¹⁶⁷

Long QT syndromes. Increased QTV has been repeatedly reported in mixed LQTS cohorts of patients with different mutations,^{132–134,168,169} suggestive of a link between QTV and reduced repolarization reserve. Cohorts that included Type 2 (and Type 3) mutations showed consistently increased QT_{Vi},^{133,168} root mean square of QT interval differences,¹³⁴ and STVQT.¹⁶⁸ In LQTS Type 1, QTV changes appear less pronounced; intermediate STVQT increases,¹⁶⁸ and no differences in QT_{Vi}¹³⁴ were reported. In LQT1 patients, QTV levels seem to be associated with arrhythmic risk.¹⁷⁰ Increases in QTV in LQT1 may be evident only after sympathetic stimulation.¹⁷¹ Measures of QTV were weakly correlated with QT_c interval duration at baseline^{133,134} or after sympathetic stimulation¹⁷¹ or with uncorrected QT duration.^{132,168} In patients with drug-induced LQTS, documented TdP was associated with increased STVQT in the absence of QT prolongation.¹⁷²

Other cardiac conditions. In paroxysmal atrial fibrillation (AF), VR was reduced in AF periods compared with sinus rhythm.¹⁷³ QT_{Vi} but not QT_{var} was increased in amyloidosis of familial Mediterranean fever.¹⁷⁴ In Brugada syndrome, sodium channel blockade increased already elevated SDQT in the right precordial leads.¹⁷⁵ QT variability index was increased in children with acute Kawasaki disease and correlated with temperature and C-reactive protein.¹⁷⁶ Bariatric surgery reduced QT_{Vi} in morbidly obese subjects.¹⁷⁷

Clinically relevant information may be derived from QTV in cardiac patients, despite unfavourable signal-to-noise ratios and measurement difficulties. Large QTV datasets from cardiac patients with different pathologies should be collected to explore relationships with clinical markers, clinical endpoints, and underlying mechanisms.

In large datasets, the presence or absence of measurable QRS variations should also be investigated so that primary and secondary QTV sources can be distinguished.

Non-cardiac diseases

Mental disorders. Increased short-term QT_{Vi} in panic disorder (PD) was repeatedly reported.^{54,126,178,179} Increased QT_{Vi} and QT_{var} were also observed in children with anxiety disorders.¹⁸⁰ Sympathetic changes appear to cause these changes. The α_2 -adrenergic antagonist yohimbine increased anxiety as well as QT_{Vi}, whereas α_2 -adrenergic agonist clonidine reduced QT_{Vi} in PD.¹²⁶ QT interval variability response to β_1 - and β_2 -activation with isoprotenerol was pronounced in PD compared with normal subjects.¹⁷⁹ However, no correlations were observed between

resting cardiac norepinephrine spillover and QT_{Vi}.¹⁰⁸ Treatment with tricyclic antidepressant nortriptyline increased QT_{Vi} in PD, whereas selective serotonin reuptake inhibitors had no effect.^{108,181} Holter ECG analysis suggests increased QT_{Vi} in PD during night time.¹¹³ QT variability index and QTVN were also increased in major depressive disorder.^{54,182} Short-term antidepressant treatment with serotonin and noradrenaline reuptake inhibitors tended to increase QT_{Vi}.¹⁸² Correlation analyses between anxiety and depression scores and QT_{Vi} provided inconclusive results; positive,⁵⁴ negative,¹⁰⁸ and no correlations¹⁸² were reported in major depressive disorder and PD. In normal subjects, correlations between QT_{Vi} and anxiety scores were reported.⁹⁸ In patients with recent MI, depression was associated with increased QT_{Vi} while QTVN was not different.¹⁸³

Increased QT_{Vi} was also shown during the first episode of neuroleptic-naïve psychosis.¹⁸⁴ QT variability index and QTVN were increased in acute schizophrenia and QT_{Vi} correlated with the degree of hallucinations and delusions.¹⁸⁵ Increased QT_{Vi} was also observed in unaffected first-degree relatives.¹⁸⁶ Antipsychotic treatment with olanzapine did not normalize QT_{Vi}.¹⁸⁷

Increased QT_{Vi} correlating with serum potassium was reported in anorexia nervosa.¹⁸⁸ Treated anorexia nervosa with restored weight and normal serum electrolytes showed normal QT_{Vi}.¹⁸⁹

QT variability index was also found increased in alcoholics after acute alcohol withdrawal, but was normal in abstained alcoholics.¹⁹⁰ Cocaine increased QT_{Vi} in a dose-dependent relationship.¹⁹¹

Diabetes mellitus, autonomic neuropathy, spinal cord injury, and renal failure. In Type 2 diabetes mellitus, increased QT_{Vi} correlated with the degree of cardiovascular autonomic neuropathy,^{192,193} and cardiac sympathetic dysinnervation correlated with QTVN during orthostatic activation.¹⁹³ In chronic renal failure, diabetes was associated with increased QT_{Vi}.¹⁹⁴ In dilated cardiomyopathy, however, QT_{Vi} was not different between diabetic and non-diabetic patients.¹⁹⁵

In familial dysautonomia, QT_{Vi} was reported significantly increased,²⁵ unchanged,¹⁹⁶ or decreased;¹⁹⁷ while QTV unrelated to HRV was reported to be increased^{25,197} or unaltered.¹⁹⁶

Increased QT_{Vi} was reported in spinal cord injury above T5 and T6.^{198,199} While one study showed increased $T_{peak}-T_{end}$ variability,¹⁹⁸ another study showed no difference in QTVN.¹⁹⁹ Among spinal cord injury men, hypogonadism was associated with increased QT_{Vi},²⁰⁰ which reduced after testosterone replacement therapy²⁰⁰ that reduced coherence.²⁰¹

QT interval variability changes in non-cardiac patients are likely linked to autonomic and central nervous system effects. The pathways of QTV regulation should be investigated together with investigations of whether QTV could be used as a general marker of autonomic physiology and derangement.

Likely clinical value

QT interval variability was repeatedly advocated for guiding ICD therapy. Risk stratification studies that report hazard ratios are summarized in Table 2. Analysis of prospectively collected short-term ECG in MADIT II demonstrated both QT_{Vi} and QTVN predicting appropriate VT/MF shocks.⁴⁴ Sex-specific analysis showed predictive value of intracardiac QTVN and QT_{Vi} for men, but not women, in

Table 2 Hazard ratios of clinical studies on risk prediction based on QTV metrics

	Study population	N	Follow-up (event rate)	Variables	Endpoint	HR (95% CI)
Tereshchenko et al. ²⁰²	Structural heart disease, ICD (EF 33 ± 12%)	298	16 ± 8 months 17.4%	Highest QTVi quartile (≥0.114)	ICD shock for VT/VF	4.18 (1.40–12.46)
Dobson et al. ²⁰³ GISSI-HF	CHF, NYHA II–IV 180 patients EF ≤ 35% 88 patients EF > 35%	268	47 months (median) Total mortality 20% CV death 16%	QTVi (continuous) Highest QTVi quartile (more than -0.84)	Total mortality CV death Total mortality CV death	4.4 (1.91–10.1) 4 (1.8–8.8) 2 (1.1–3.6) 2.1 (1.1–3.8)
Haigney et al. ⁴⁴ MADIT II	History of MI and EF ≤ 30%	463	21 ± 12 months 22.4%	Highest QTVi quartile (more than -0.52) Highest QTVN quartile (>0.257)	ICD shock for VT/VF ICD shock for VT/VF	1.8 (1.09–2.95) 2.18 (1.34–3.55)
Piccirillo et al. ⁴⁵	CHF due to post-ischaemic CM, 35 < EF < 40 (37 ± 1%) NYHA I	396	60 months total mortality 11% SCD 6%	>80th QTVi percentile (more than or equal to -0.47) QTVi (continuous) >80th QTVN percentile (≥0.24) QTVN (continuous)	Total mortality SCD Total mortality SCD Total mortality SCD	2.4 (1.2–4.9) 4.6 (1.5–13.4) 2.6 (1.3–5.2) 2.9 (1.3–6.5) 1.5 (0.4–5.3) (n.s.) 0.4 (0.07–1.8) (n.s.) 0.1 (0.0–1.8) (n.s.) 0.8 (1.0–14) (n.s.)
Perkiomaki et al. ²⁰⁴	Consecutive patients with decreased LV function and ICD	47	26 ± 8 months 17% death 34% ICD shock/death	0.1 of ApEn of RT _{peak}	ICD shock/ death	3.36 (1.28–8.83)
Segerson et al. ²⁰⁵	Acute MI, EF 47 ± 9%	678	63 months (mean) 19.7%	RT _{peak} : DI scatter standard error	Death/documentated ventr. arrhythmia	2.5 (1.4–4.0)
Jensen et al. ²⁰⁴	Acute MI (EF 48 [24,60])	311	36 months 22.5%	0.1 of SDQT/SDNN	Total mortality	1.9 (1.5–2.4)
Sredniawa et al. ²⁰⁷	ICD patients implanted according to ESC guidelines	155	22 ± 12 months 11% major arrhythmic cardiac event	SDQT 1 ms increase in Holter ECG	Major arrhythmic cardiac event	1.08 (1.05–1.08)
Tereshchenko et al. ⁴⁶ MUSIC	CHF with ischaemic or non-ischaemic CM NYHA II–III 279 patients EF ≤ 35% 254 patients EF > 35%	533	44 months (median) 23.5% Total mortality 3.8% non-cardiac death 9.9% non-sudden CD 9.8% SCD	Highest QTVi quartile (more than -1.19) QTVN	CV death Non-cardiac death Non-sudden CD SCD CV death Non-cardiac death Non-sudden CD SCD	1.67 (1.14–2.47) n.s. 2.91 (1.69–5.01) n.s. n.s. n.s. n.s. n.s.
Oosterhoff et al. ⁴¹ (Data set from Tereshchenko et al. ²⁰²)	Structural heart disease, ICD	233	26 ± 15 months 21%	Highest quartile STV ratio (>0.88) +highest QTVi quartile (>0.14)	ICD shock for VT/VF or SCD	1.8 (1.0–3.4) 2.4 (1.3–4.3)
Vrtovec et al. ¹⁹⁵	DCM, NYHA II–III, EF < 40%	132	12 months 6% CHF death 7.6% SCD	Highest QTVi quartile (no numbers)	CHF death SCD	1.06 (1.03–1.41) 1.07 (1.02–1.42)

HR, hazard ratio of multivariate models; EF, ejection fraction; NYHA, New York Heart Association class; SCD, sudden cardiac death; CHF, chronic heart failure; CV, cardiovascular; MI, myocardial infarction; DCM, dilated cardiomyopathy.

whom reduced coherence was predictive.⁴⁷ Predictive value of QTVi and VR for appropriate VT/VF shock was also demonstrated in a large study of patients with structural heart disease, impaired LV function, and implanted ICD.^{41,202} QT variability index was higher in patients on Class III antiarrhythmics, but carried independent risk after drug effect adjustment.²⁰⁸ However, a smaller study in ICD patients with structural heart disease showed no significant intracardiac QTV increase in patients subsequently experiencing VT/VF.²⁰⁹ Increased QTVi predicted VT and sudden cardiac death (SCD) in patients undergoing electrophysiological study.⁴² In patients with a VT/VF history who also underwent electrophysiological study, QTVi was not predictive of ICD discharge, primarily caused by VT but not VF.²¹⁰ In patients with ICD implanted for SCD prevention, increased SDQT in ambulatory ECG was associated with major arrhythmic events.²⁰⁷

Retrospective analysis of the MUSIC study that enrolled patients with NYHA Classes II–III showed predictive value of QTVi for cardiovascular mortality but not for SCD.⁴⁶ However, increased QTVi predicted SCD in patients with dilated cardiomyopathy with NYHA Class II–III and LVEF < 40%.¹⁹⁵ QTVi predicted total and cardiovascular mortality in ambulatory ECG of the GISSI-HF trial that investigated a heterogeneous group of NYHA Class II–IV CHF patients with LVEF > 35%.²⁰³ Prospective analysis of asymptomatic CHF patients with ICM showed the predictive value of QTVi, but not QTVN for SCD and total mortality.⁴⁵ STVQT was found increased in patients with non-ischaemic CHF and VT history.⁴⁰ The complexity of QT intervals was increased in ICD patients with decreased LV function who died or experienced ICD shock.²⁰⁴ QT interval variability obtained from ambulatory ECG of acute MI patients were also shown to predict mortality.^{205,206} In patients with old MI, QTVi was increased in patients with documented VT/VF.⁴³

In organic heart disease, no significant differences in QTVi were observed in patients with and without a VT history.²¹¹ RT interval spectra in ambulatory ECG were predictive of SCD in HCM.²¹²

In survivors of unexplained cardiac arrest, QTVi and coherence measured during rest and epinephrine challenge were not significantly different from first-degree relatives of SCD victims.²¹³

Despite the evidence of the association between mortality and QTV, individual short- or long-term risk prediction for VT/VF appears to be challenging with commonly used measures.^{214,215} Sophisticated analysis of joint RR and QT dynamics seems to allow detecting repolarization instability preceding malignant ventricular arrhythmia in patients with acute MI.²¹⁶

Prospective studies on the predictive value of QTV are needed as part of a multivariate risk stratification procedure in different well-defined populations.

Future outlook

Methodical considerations

While dedicated computer programs for QTV measurement are readily available, the current level QTV measurement standardization is insufficient. Data acquisition requirements, minimum signal-to-noise levels, recording duration, pre-processing modalities, and beat and artefact rejection techniques require further investigation. A more systematic application of advanced signal

processing tools capable of dealing with non-linearities and transients is necessary to improve QTV reproducibility and to derive more insightful QTV descriptors. In addition, systematic studies should explore the link between QTV and variability of the T wave morphology (of the entire T wave) as well as the signal beyond the T wave end.

Physiological determinants

The physiological basis of QTV is currently insufficiently explored. The QTV response to HR changes with respect to amplitude and direction of HR variation requires further investigation. Studying QT dynamics around the individual-specific QT-RR curvature in experimental and electrophysiological studies may provide additional insight. Although evidence suggests that QTV may be useful for quantifying relative changes in sympathetic ventricular outflow during states of heightened activity, it remains to be established whether QTV indices can be used to infer absolute values of sympathetic activity in normal subjects or whether QTV magnitude correlates with changes of sympathetic activity only. Future investigations should differentiate neural control directed to the sinus node from that directed to ventricles and research how this regulation contributes to the coupling/decoupling between HRV and QTV. The relation between cellular APD variability and body surface QTV also requires further studies.

Clinical applications

The pathophysiology of increased QTV is poorly understood, although reduced repolarization reserve, causing more variable regulation responses, may play a role. The relation between autonomic dysfunction and QTV in cardiac patients is not well established. The main clinical use of QTV may lie in SCD risk stratification. Although several studies have demonstrated independent predictive value of QTV, most of the evidence is based on retrospective data analysis. Prospective trials are needed to prove the usefulness of QTV. Cut-off values or hazard ratios need to be defined before QTV can become an integral part of decision-making. Established clinical risk markers may be combined to increase predictability. Advanced measurement modalities such as composite multi-lead QTV assessment or response to premature ventricular contractions may advance clinical utility.

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Appendix A: Linear time-invariant QT interval variability modelling

Linear time-invariant classes of models are applied to the qt series derived from the original QT series after mean removal. When the aim is spectral analysis, the qt series is usually modelled as an autoregressive process,^{27,34,61} i.e. the current qt value is described as a sum of previous qt values weighted with constant coefficients plus a noise term, representing the unpredictable part of qt dynamics (n_{qt}) and described as a white process:

$$qt(i) = \tilde{A}_{qt-qt}(z) \cdot qt(i) + n_{qt}(i),$$

where $\tilde{A}_{qt-qt}(z) = a_{1,qt-qt} \cdot z^{-1} + \dots + a_{n,qt-qt} \cdot z^{-n}$ is an all-zero polynomial of order n and z^{-1} represents the one-step delay operator in the z -domain. The power density spectrum can then be obtained as follows:

$$PSD_{qt}(f) = T\lambda_{qt}^2 \left| \frac{1}{1 - \tilde{A}_{qt-qt}(z)} \right|_{z=e^{2\pi jf}}^2,$$

where T is the mean heart period and λ_{qt}^2 is variance of the zero-mean white noise n_{qt} . Non-parametric approaches based on Fourier transform for the estimation of power spectral density have been utilized as well especially in the first pioneering studies.²⁶

More complex linear models have been exploited to describe the dependence of qt on previous rr intervals and other physiological influences such as the direct effect of respiration (resp).³⁴ For example,

$$qt(i) = \tilde{A}_{qt-qt}(z) \cdot qt(i) + B_{qt-rr}(z) \cdot rr(i) + B_{qt-resp}(z) \cdot resp(i) + \varepsilon_{qt}(i),$$

where $B_{qt-rr}(z) = b_{0,qt-rr} + b_{1,qt-rr} \cdot z^{-1} + \dots + b_{n,qt-rr} \cdot z^{-n}$ accounts for the action of current and previous rr values on qt, $B_{qt-resp}(z) = b_{0,qt-resp} + b_{1,qt-resp} \cdot z^{-1} + \dots + b_{n,qt-resp} \cdot z^{-n}$ accounts for the influence of current and past resp samples on qt and ε_{qt} is the noise affecting qt dynamics.

Based on the model structure the qt-rr cross-spectrum, $C_{qt-rr}(f)$, and the power spectra of rr and qt series, $S_{qt}(f)$ and $S_{rr}(f)$, can be estimated and the squared coherence can be computed as

$$K_{qt-rr}^2(f) = \frac{|C_{qt-rr}(f)|^2}{S_{qt}(f) \cdot S_{rr}(f)}$$

and the transfer function as

$$H_{qt-rr}(f) = \frac{C_{qt-rr}(f)}{S_{rr}(f)}.$$

Simpler model structures, such as the bivariate linear model with white residuals,^{26,28,29,49} and non-parametric techniques^{26,28,29} were also used. Examples of rr and qt series, $S_{qt}(f)$ and $S_{rr}(f)$ power spectra, squared coherence function between qt and rr series, $K_{qt-rr}^2(f)$, and transfer function modulus, $|H_{qt-rr}(f)|$, are shown in Figures 3 and 4.

Although these modelling approaches can be utilized to estimate QT-RR transfer function, and squared coherence, they have been proposed with the main purpose to decompose QTV variability into partial contributions due to the exogenous sources (Figure 5). Thus, this multivariate linear modelling approach separates the fraction of QTV that is independent from RR and to quantify the genuine QTV.^{28,29,34} Residual variance in QTV, not accounted for by these models, implicates factors other than RR in QTV generation.^{34,61} The total of unexplained QTV also depends on the approximation of the QT interval. The approximation of the QT interval by RT_{peak} led to smaller fractions of QTV

independent of RR variability compared with RT_{end} .²³ Overall RT_{peak} variance is also smaller than that of RT_{end} .²³ The part of QTV that is unrelated to RR changes occurs primarily in the very low frequency range, whereas the LF and HF oscillations are primarily driven by RR.²⁹ Among other factors, a part of RR-unrelated QTV depends on the autonomic state³⁴ and also modulates the QT-RR coupling strength.⁴⁹ Since the fraction of QTV unrelated to RR variations was shown to increase during graded head-up tilt (Figure 5), it may be under sympathetic control.³⁴ Uncoupling between QTV and RR variability at the respiratory rate was also observed during graded head-up tilt (Figure 4). This may be caused by the reduction in respiratory sinus arrhythmia due to vagal withdrawal and/or progressively more complex respiratory effects on QTV.⁴⁹

Linear multivariate modelling, estimating the transfer function suggests that autonomic activity modulates gain and phase of QT-RR coupling.²⁹ Graded head-up tilt increased gain in the LF band and augmented phase delay (Figure 4), while controlled breathing increased gain in the HF band and attenuated phase delay.²⁹ QT-RR gain functions derived from multivariate linear models and accounting for exogenous sources are less affected by noise sources than gain estimates obtained with more traditional methods.²⁹

Reduced ability of linear models to interpret QTV dynamics and its relation to HRV may result from autonomically induced wave morphology changes,²¹⁷ the linear coupling decrease due to increasingly non-linear QT-RR relationship, the underlying cardiac pathology,²¹⁸ or the presence of response with different time constants to RR variations. For example, the fraction of QTV depending on HRV was found decreased in post-MI patients.²¹⁸ In some studies, the linear dependences were non-linearly transformed to account for possible non-linear relations.⁷⁰

Appendix B: Non-linear QT interval variability analysis

Linear modelling may be insufficient to describe the interplay between cardiac cycles and QT interval. While techniques specifically designed for static measurement of the rate-corrected QT interval^{219,220} capture slow trends in QT interval well, they tend to underestimate beat-to-beat fluctuations. On the other hand, techniques commonly used to model beat-to-beat variability (e.g. autoregressive models as discussed above), approximate HF and LF oscillations closely but may not capture slow trends well, as reflected in the lack of squared coherence in the very low frequency range of QTV.²⁹ Using linear models with separate estimates of the rapid and slow component of QT rate-adaptation, close approximations of QTV were achieved in normal subjects during rest and exercise.⁶⁵

Several techniques from non-linear systems and information theory have been used to capture non-linear QTV dynamics. Multi-scale entropy and detrended fluctuation analyses showed significant differences in the beat-to-beat dynamics of QT intervals compared with RR intervals.^{204,221,222} Sample and approximate entropies were found to be higher in QT than in RR time series.^{204,221-223} QT interval time series lack the scale invariance that is typical of RR time series.²²¹ Further, point-wise correlation dimension was higher in QT time series than in RR time series.²²⁴ Largest Lyapunov exponent and embedding dimension²²⁵ were also utilized to quantify QTV complexity. Cross-conditional entropy measuring the amount of information carried by QT changes given RR variations²¹⁹ (i.e. the genuine information carried by QTV) and joint symbolic dynamics^{59,118} are among other techniques that have been proposed to capture non-linear features in the QT-RR relation. Recently, recurrence quantification and multi-fractal analyses have been proposed as further tools to explore QT interval dynamics.^{226,227}

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