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REVIEW ARTICLE

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Categorization and theoretical comparison of quantitative methods for assessing QT/RR hysteresis

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Background: In the human electrocardiogram, there is a lag of adaptation of the QT interval to heart rate changes, usually termed QT/RR hysteresis (QT-hys). Subject-specific quantifiers of QT-hys have been proposed as potential biomarkers, but there is no consensus on the choice of the quantifier.

Methods: A comprehensive literature search was conducted to identify original articles reporting quantifiers of repolarization hysteresis from the surface ECG in humans.

Results: Sixty articles fulfilled our inclusion criteria. Reported biomarkers were grouped under four categories. A simple mathematical model of QT/RR loop was used to illustrate differences between the methods. Category I quantifiers use direct measurement of QT time course of adaptation. They are limited to conditions where RR intervals are under strict control. Category IIa and IIb quantifiers compare QT responses during consecutive heart rate acceleration and deceleration. They are relevant when a QT/RR loop is observed, typically during exercise and recovery, but are not robust to protocol variations. Category III quantifiers evaluate the optimum RR memory in dynamic QT/RR relationship modeling. They estimate an intrinsic memory parameter independent from the nature of RR changes, but their reliability remains to be confirmed when multiple memory parameters are estimated. Promising approaches include the differentiation of short-term and long-term memory and adaptive estimation of memory parameters.

Conclusion: Model-based approaches to QT-hys assessment appear to be the most versatile, as they allow separate quantification of QT/RR dependency and QT-hys, and can be applied to a wide range of experimental settings.

KEYWORDS
QT adaptation, QT hysteresis, quantitative ECG, repolarization

1 | INTRODUCTION

The QT interval on the human electrocardiogram (ECG) depends on heart rate. The simplest forms of rate correction of the QT interval assume a universal static relationship between QT and the immediately preceding RR interval (Bazett, 1920; Fridericia, 1920). It has been demonstrated more recently that the steady-state relationship between QT and RR intervals differs among healthy individuals (Malik et al., 2002). In addition, there is a lag of adaptation of QT to sudden changes in heart rate (Attwell, Cohen, & Eisner, 1981), meaning that the QT interval is influenced by the history of preceding RR intervals. As a result, QT intervals measured shortly after a sudden heart rate increase are longer than QT intervals measured at a similar heart rate while it is decreasing. This well-documented phenomenon, referred to

as QT/RR hysteresis (QT-hys) (Sarma et al., 1987), is observable both on the surface ECG and at the cellular level: The lag of adaptation of action potential duration (APD) to sustained changes in pacing rate was observed several decades ago in animal studies (Carmeliet, 1955) and properly described in the intact human heart (Franz et al., 1988).

While universal formulas accounting for RR history in QT/RR modeling have been proposed (Razak et al., 2011), it has been suggested that the profiles of QT-hys were highly individual (Malik, Hnatkova, Novotny, et al., 2008). The dynamic QT/RR relationship thus could be divided into two distinct processes, both appearing to be subject-specific: QT/RR dependency, that is, how much the steady-state QT interval varies through the range of physiological RR intervals; and QT/RR hysteresis (more precisely termed "hysteresis lag"), that is, how fast the QT interval attains its steady state following a sustained variation of RR intervals. While studies of the QT/RR relationship in humans have often merged these two processes, recent studies have suggested that QT/RR dependency and QT-hys are uncorrelated and likely represent distinct physiological mechanisms (Malik, Hnatkova, Novotny, et al., 2008; Malik et al., 2013).

Several methods of quantification of QT-hys have been proposed. Given the widespread use of rate-corrected QT interval measurement (QTc), notably in the evaluation of potentially QT prolonging drugs, individual QT-hys modeling has been used to increase the robustness of QT correction (Malik et al., 2009a). A recent study challenges this concept, suggesting that despite the wide variability of QT-hys profiles among humans, individual optimization of rate correction for hysteresis has little impact on QTc measurement (Malik et al., 2016). However, multiple studies have proposed that QT-hys descriptors may hold prognostic value, independent of QTc. Among other things, QT-hys has been suggested as a risk marker of arrhythmic death in survivors of myocardial infarction (Pueyo et al., 2004) and as a predictor of exercise-induced myocardial ischemia (Lauer et al., 2006; Zhang et al., 2014). QT-hys have also been shown to increase with age (Malik et al., 2013) and to differ between men and women (Malik et al., 2016). In continuity with an editorial pointing out multiple issues regarding QT-hys evaluation (Malik, 2014), the aim of this review was to comprehensively identify, categorize, and compare published quantifiers of QT-hys.

2 | SYSTEMATIC REVIEW

This review was conducted following the PRISMA statement (Moher et al., 2009). A systematic literature search was operated using the following search engines and databases: Web of Science (all databases), PubMed (MEDLINE), OvidSP (EMBASE), and EBSCOhost (CINAHL and SPORTDiscus). Journal articles written in English or French from inception to September 23, 2016, were searched in all database fields using the following query:

[qt OR "q-t" OR repolarization] AND [rr OR "r-r" OR rate OR "cycle length"] AND [hysteresis OR dynamic* OR lag OR memory OR adaptation] AND [heart OR cardiac OR ventricular OR ECG]

After removal of duplicates, articles were screened for inclusion based on title, on abstract and, if needed, on full text. References cited in included articles were systematically screened for inclusion. To be included, articles had to comply with the three following criteria:

1. Report original data acquired in human subjects.
2. Address the relationship between ventricular repolarization time and cardiac cycle length, measured from the surface ECG.
3. Report at least one quantifier of the lag in the aforementioned relationship.

Search results are summarized in Figure 1. A total of 65 articles were initially included in the review. Five articles were preliminary versions (published in conference proceedings) of more substantial studies published later by the same research groups and were excluded, leading to a final count of 60 articles.

The following data were extracted from the selected articles: cause of RR variation during ECG acquisition, description of the quantifier of QT-hys, subject demographics (sample size, age, sex, and medical condition), and descriptive statistics of QT-hys. The nature of the review was descriptive and did not allow pooled analysis of the extracted data.

3 | CATEGORIZATION OF REVIEWED METHODS

A wide variety of stressors have been used to provoke and measure QT-hys: atrial or ventricular pacing, gradual or burst exercise protocols, postural changes, tilt test, controlled breathing, face immersion in cold water, and selection of Holter segments with significant RR variation due to normal daily activity or occurrence of supraventricular tachycardia. Therefore, it appeared more relevant to categorize QT-hys descriptors according to the quantification techniques rather than the stressors. We defined four categories of QT-hys quantification methods based on their conceptual approach and experimental design:

Category I (six articles): QT-hys is computed without accounting for the concurrent RR sequence which is assumed to be experimentally controlled.

Category IIa (10 articles): QT-hys is computed from QT intervals measured at a predetermined RR interval observed during sequential rate increase and decrease through provocative testing.

Category IIb (seven articles): QT-hys is computed from QT intervals measured over a predetermined RR interval range observed during sequential rate increase and decrease through provocative testing.

Category III (34 articles): The QT interval is predicted by a parametric function of the effective RR interval expressed as a weighted sum of the history of preceding RR intervals. After parameter optimization, QT-hys is computed from the decay rate of these weights along time.

QT-hys quantifiers are accordingly listed in four tables and discussed hereafter. Three articles not fitting any of these categories are discussed

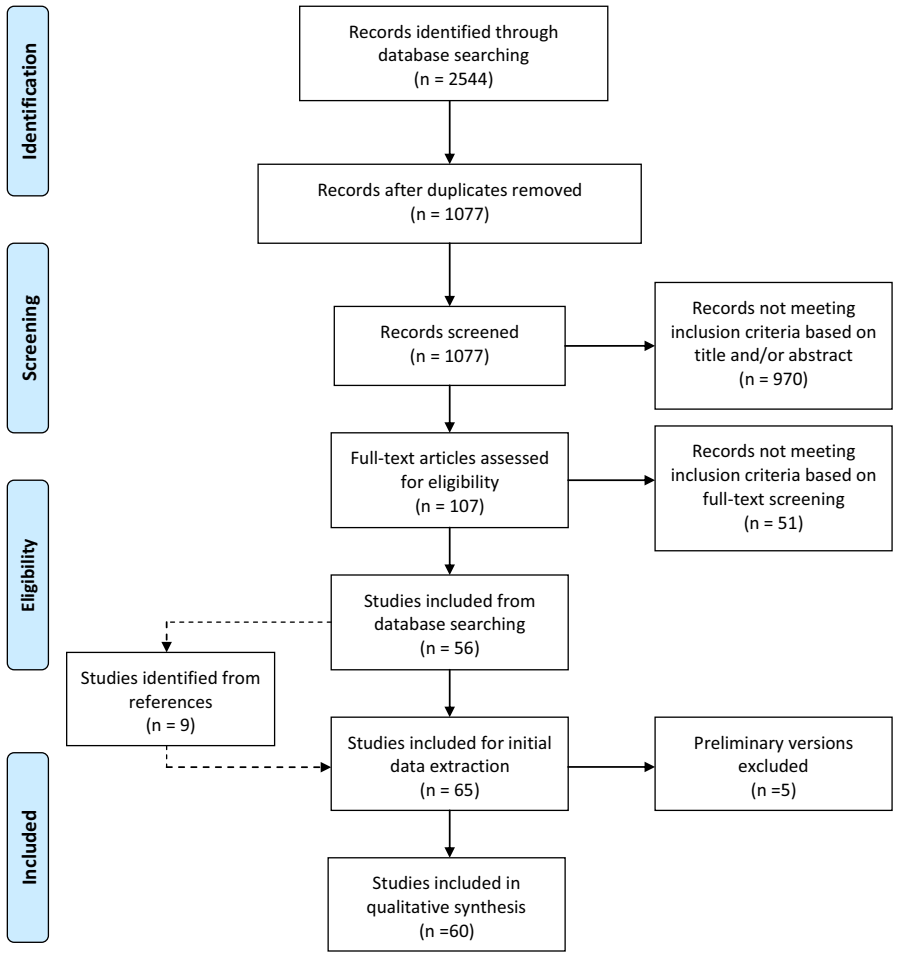


FIGURE 1 Flowchart of searching and filtering of articles

separately. When available, summary descriptive statistics of the individually assessed QT-hys are reported in the last column of Tables 1–4. Studies reporting strict application of a previously described method are listed together with the original article in the tables.

The different approaches are applied to a simple mathematical model of QT hysteresis (Figure 2) based on exponential RR variation during exercise and recovery, on linear QT/RR dependency based on Sagie et al. (1992), and on a hysteresis model with exponentially decaying weights. This model enables analytical calculation of QT-hys indices and allows the identification of inherent dependencies of quantifiers to variables of the recording protocol. It will be used as a guide for the discussion.

4 | DISCUSSION

4.1 | Category I: direct measurement of QT time course of adaptation

A simple method of QT-hys assessment is to measure the time needed for the QT interval to attain its steady state after initiation of a sustained RR change, or the time to reach 90% of QT total variation (Figure 2c). That approach typically led to values around 3 min (Table 1). Two studies also reported the time constant of the exponential fit of QT versus time after rate change (Lau et al., 1988; Seethala et al., 2011). The obtained values of 35–60 s correspond to a time to reach 90% of QT adaptation of approximately 80–140 s. Based on the observation of a biphasic QT response to rate change, which is a common finding in pacing studies both at the cellular level and on the surface ECG (Franz et al., 1988; Lau et al., 1988), Seethala et al. (2011) excluded the QT intervals measured during the initial fast QT response from their exponential curve fitting, thus providing a specific descriptor of the slow component of QT response.

Category I quantifiers describe the time course of QT adaptation following a provoked and sustained RR change, assumed to be controlled experimentally. As illustrated in the simple model (formula for H_{Lau} in Figure 2), slow RR kinetics (large τ_{RR}) lead to an overestimation of QT-hys using category I quantifiers. Under pacing however, τ_{RR} tends to zero and H_{Lau} effectively describes the time lag of QT accommodation. Appropriately, most studies listed in Table 1 investigated QT response during atrial or ventricular pacing. Besides the concerns of invasiveness, an issue of pacing studies is that they may not be representative of normal cardiac activity under autonomic control. It has been suggested that part of QT shortening during exercise is independent of ventricular rate and potentially explained by autonomic modulation (Rickards & Norman, 1981). Thus, while pacing studies are of primary importance to gain insights into the basic mechanisms of hysteresis, their clinical relevance is limited.

TABLE 1 Category I quantifiers: direct measurement of QT time course of adaptation

Reference	Method of RR variation	Description of QT-hys indexes	Range of QT-hys values
Attwell et al. (1981)	Right atrial pacing	Time to QT steady state after cessation of pacing at 180 bpm	~3 min
Seed et al. (1987)	Right atrial or right ventricular pacing (n = 4)	Time to QpTp steady state after rate change	>3 min
Lau et al. (1988)	Right ventricular pacing (n = 7)	1. Time for completing 25%, 50%, 75%, and 90% of QT adaptation after rate change 2. Time constant of the exponential fit of %QT adaptation vs time after rate change	1. 130–200 s (90% adaptation) 2. 50–60 s
Vainer et al. (1994)	Recovery from 1 min of rapid knee bending (n = 10) Atrial pacing (n = 3)	1. Time to maximal QT interval in the 5-min window following exercise 2. Time to QT steady state after pacing rate change	1. 192 ± 50 s 2. 132 ± 40 s
Grom et al. (2005)	Selected Holter segments surrounding episodes of AFib (n = 32) Atrial pacing (n = 20)	Time to restoration of baseline QTc after AFib conversion or rate change	1–5 min
Seethala et al. (2011)	Atrial pacing before and during dobutamine infusion (n = 10)	1. Time to QT steady state after rate change (based on linear fit of QT vs time), excluding the immediate response 2. Time constant of the exponential fit of QT adaptation vs time after rate change, excluding the immediate response	1. <300 s 2. 30–60 s

AFib, atrial fibrillation; QpTp, interval from peak of Q wave to peak of T wave; QTc, QT interval corrected for heart rate using Bazett's formula.

4.2 | Category II: comparison of QT response during RR shortening vs lengthening

QT-hys may be evaluated by comparing QT response at similar RR intervals during sequential heart rate acceleration and deceleration. Instead of estimating the time lag of QT adaptation to RR change, these methods measure the amplitude of the hysteresis loop (Figure 2d).

A first approach is to measure the difference of QT intervals (ΔQT) during heart rate increase and decrease at the same RR interval (H_{Krahn} in Figure 2d). All reviewed studies using this approach (Table 2) were based on exercise test data. There is no consensus about the reference RR interval to be considered for ΔQT measurement, some using predetermined reference RR intervals and others measuring ΔQT at predetermined timings during recovery from peak exercise. The mathematical model (Figure 2) shows that this measure depends on an extrinsic variable (τ_{RR}) which may hamper its reproducibility. In contrast to category I methods, this dependency does not disappear even if only abrupt RR variations are considered.

A second approach is to measure the area between QT/RR curves obtained separately during increasing and decreasing rates, thus estimating the average extent of the hysteresis loop (H_{Sarma} in Figure 2d). This generalizes the ΔQT method to a range of RR variation. Following the pioneering work of Arnold et al. (1982), several methods for quantifying QT/RR loop area (usually reported in ms^2) have been suggested, using different stress protocols and curve fitting techniques (Table 3). In the same way as the ΔQT method, the loop area method brings the problem of the choice of the reference RR range or reference timing of measurement. As the reference RR range affects the magnitude of the total loop area, it seems inappropriate to compare QT/RR loop areas among subjects with different ranges of RR variation in response to a stress protocol. To overcome this problem, some studies have used a fixed range of RR variation for the assessment of the loop area, for example, from minimum RR with a range of 150 ms (Pelchovitz et al., 2012; Sarma et al., 1987). Other studies have divided the measured loop area by the total magnitude of RR variation (ΔRR_{total} in Figure 2d), resulting in an index of QT-hys equivalent to the mean ΔQT over the observed RR range (Lauer et al., 2006; Zhang et al., 2014).

A limitation of these methods is that their QT-hys estimate may be influenced by the steepness of the QT/RR curve. At similar QT time lag and RR range, the steeper the QT/RR curve, the larger the loop area. A solution to this problem is to divide the loop area by the

TABLE 2 Category IIa quantifiers: difference between QT intervals observed at similar heart rates during RR shortening vs lengthening

Reference	Method of RR variation	Description of QT-hys indexes	Range of QT-hys values
Krahn et al. (1997) applied in: Wong et al. (2010)	Modified Bruce treadmill test (*n* = 63, including 14 LQTS patients)	1. Difference between RpTp at 1, 2, and 4 min of recovery from peak exercise and RpTp at similar heart rate (within 10 bpm) during gradual exercise. Also reported as percentage of baseline RpTp 2. Same as above, but correcting RpTp for heart rate (Bazett's formula)	1 min into recovery: 1. 43 ± 28 ms (LQTS) 11 ± 11 ms (controls) 2. 58 ± 31 ms (LQTS) 18 ± 15 ms (controls)
Swan, Toivonen, and Viitasalo (1998) applied in: Swan et al. (1999)	Graded cycle ergometer test (*n* = 38)	Tests within group differences of QT, QTp, and TpTe at predetermined heart rates during exercise and recovery	Significant QT and QTp hysteresis
Krahn et al. (2002)	Modified Bruce treadmill test (14 LQTS patients and 10 controls)	Difference between QTp measured at 30 s, 1, 2, 3, 4, and 5 min into recovery from peak exercise and QTp at identical heart rate during gradual exercise	1 min into recovery: 46 ± 19 ms (LQTS off beta-blockers) 25 ± 35 ms (LQTS on beta-blockers) 19 ± 11 ms (controls)
Chauhan et al. (2002)	Graded cycle ergometer test (*n* = 20)	Difference between exercise and recovery QTp/heart rate curves (quadratic fitting) computed for heart rates observed at 1 and 2 min into recovery from peak exercise	1 min into recovery: 20 ± 20 ms
Lewis and Short (2006)	Graded cycle ergometer test (*n* = 12)	Difference between QTp averaged in 10 consecutive windows of 1 min following peak exercise and QTp at corresponding RR interval during exercise	Maximal QT-hys among the 10 windows: 10–30 ms
Gao et al. (2007)	Modified Bruce treadmill test (17 LQTS patients, 16 with uncertain LQTS, 18 controls)	Difference between QT measured at 1, 2, 4, and 6 min into recovery from peak exercise and QT at identical heart rate during gradual exercise	1 min into recovery: 45 ± 11 ms (LQTS) 23 ± 9 ms (uncertain LQTS) 19 ± 10 ms (controls)
Chattha et al. (2010)	Burst exercise and graded cycle ergometer test (25 LQT1 patients, 25 LQT2, and 25 controls)	Difference between QT measured at 100 bpm during exercise and QT at same heart rate during recovery	10 ± 9 ms (LQT1) 34 ± 7 ms (LQT2) 9 ± 4 ms (controls)
Padfield et al. (2016)	Graded cycle ergometer test (*n* = 106)	Difference between QTc measured at 100 bpm during exercise and at similar heart rate during recovery	No evidence of significant QT-hys

LQTS, long QT syndrome; LQT1/LQT2, long QT syndrome of type 1/type 2; QTc, QT interval corrected for heart rate using Bazett's formula; QTp, interval from Q onset to peak of T wave; RpTp, interval from peak of R wave to peak of T wave; TpTe, interval from peak to end of T wave.

total rectangular area ($\Delta QT_{total} \cdot \Delta RR_{total}$). This approach proposed by Lauer et al. (2006) may help reduce the confounding effect of subject-specific QT/RR dependency. In the mathematical model (Figure 2d, H_{Sarma}) with linear QT/RR dependency, the normalization suppresses this effect. In the presence of QT/RR curvature (Malik et al., 2013) revealed by stress testing, however, the normalization would be approximate and residual dependency of QT-hys on QT/RR curve may remain. In any case, as with the first approach, the dependency in the extrinsic variable τ_{RR} remains (Figure 2). One can presume that τ_{RR} during provocative testing is mostly controlled by the stress protocol, for instance, by the steepness of exercise intensity variation and duration of exercise stages. However, it has been demonstrated that individual heart rate kinetics to a given stress level are variable among humans (Hettinga et al., 2014). It remains to be elucidated whether such variability is sufficient to undermine QT-hys estimates using the aforementioned methods during a fixed stress protocol.

4.3 | Category III: estimation of the optimum RR memory in the QT/RR relationship

The most recent and largest category of QT-hys quantifiers involves model-based estimation of memory parameters that describe the time lag between RR and QT changes. The QT interval is expressed as a function (QT/RR parametric curve) of the effective RR interval written as a linear combination (transfer function) of the history of RR intervals. The weight associated with each past RR interval depends on its time lag (Figure 2b). From the lag dependence of these weights, an intrinsic measure of QT-hys can be derived, typically the timescale of decay (Figure 2b) (Malik, Hnatkova, Novotny, et al., 2008; Pueyo et al., 2004) or the time to reach 90% of the cumulative weights (Halamek et al., 2007b; Pueyo et al., 2004). The weights can be a function of either continuous time (as in our mathematical model) or discrete time (number of beats). Whereas it has been shown that

TABLE 3 Category IIb quantifiers: area between QT/RR curves observed during RR shortening vs lengthening

Reference	Method of RR variation	Description of QT-hys indexes	Range of QT-hys values
Sarma et al. (1987)	Bruce treadmill test (n = 14)	QT/RR and QTp/RR loop areas measured between minimum RR and minimum RR + 150 ms	3709 ± 1676 ms^2 (QT) 3642 ± 1176 ms^2 (QTp)
Yamada et al. (1993)	Head-up tilt test (n = 14)	QT/RR loop area measured between points of intersection	7190 ± 4930 ms^2
Ng et al. (1998)	Bruce treadmill test (n = 42)	QT/RR loop area (unspecified method)	Significant QT-hys
Chauhan et al. (2004)	Burst exercise and graded cycle ergometer test (n = 21 LQTS patients on and 5 off beta-blockers, 20 controls)	QTp/RR loop area measured between points of intersection or for comparable RR	9371 ± 7859 ms^2 (LQTS on beta-blockers) 8921 ± 9074 ms^2 (LQTS off beta-blockers) 3176 ± 2994 ms^2 (controls)
Lauer et al. (2006)	Cornell treadmill test (n = 260)	QT/RR loop area measured between minimum RR and RR plateau at the end of recovery minus 10%, normalized for exercise performance and the extent of exercise-induced QT/RR total variation	253–375 (no unit)
Pelchovitz et al. (2012)	Graded submaximal cycle ergometer test (16 type-2 diabetes, 71 CAD with preserved LVEF, 17 with depressed LVEF, 20 controls)	1. QT/RR loop area measured between minimum RR and minimum RR +100 ms 2. Distance between exercise and recovery QT/RR curves (linear fit), measured at minimum RR +50 ms	1. 460 ± 841 ms^2 (type-2 diabetes) 675 ± 806 ms^2 (CAD) 689 ± 626 ms^2 (controls) 2. 4.6 ± 8.3 ms (type-2 diabetes) 6.6 ± 8.6 ms (CAD, LVEF+) 7.9 ± 5.6 ms (CAD, LVEF-) 6.8 ± 6.5 ms (controls)
Zhang et al. (2014)	Modified Bruce treadmill test (61 patients with negative and 77 with positive angiography)	1. QT/RR loop area measured between minimum RR +10% of total RR variation and minimum RR +90% of total RR variation 2. Loop area divided by RR variation range	1. 2357 ± 1335 ms2 (angio-) 7656 ± 3236 ms2 (angio+) 2. 8 ± 6 ms (angio-) 24 ± 13 ms (angio+)

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LQTS, long QT syndrome; QTp, interval from Q onset to the T peak of T wave.

the continuous-time approach led to slightly more reliable estimations of the rate-corrected QT interval (Malik, Hnatkova, Novotny, et al., 2008), solid evidence on a preferable method is still missing.

Most models are based on a limited number of parameters that are identified by minimizing the mean square prediction error of QT intervals from the RR time series. The QT/RR dependency parameters and the RR memory parameters are simultaneously optimized. The parametric models of QT/RR dependency were thoroughly studied (Malik, Hnatkova, Kowalski, et al., 2012). RR memory models with one parameter are typically exponentially decaying weights as in our mathematical model (Figure 2b). Such model was shown to have a better data fit than linearly decaying weights (Pueyo et al., 2004). Two-parameter models differentiate immediate QT response and long-term memory (Halamek et al., 2007b; Jacquemet et al., 2011). This is conceptually similar to the Cabasson model (Cabasson et al., 2012) which approximates the fast component of QT response to correspond to the immediate response of APD described by S1-S2 restitution curves, and adds an element of memory to explain slower QT changes. Indeed, the S1-S2 and dynamic restitution protocols are thought to respectively describe the fast and steady-state response of APD to rate change (Kalb et al., 2004). Models including more than two parameters have been proposed. Notably, in addition to the exponential model, Pueyo et al. (2003) reported a model in which every RR interval in a 5-min window preceding a QT interval is given an independent weight, without assumption of a fixed pattern of RR influence decay. Other memory models have included the history of past QT intervals (Chen & Trayanova, 2012), the short-term trend of RR variation (Hadley, Froelicher, Wang, et al., 2011), or the history of ECG derived respiration (Imam, Karmakar, Jelinek, et al., 2016). There are however some concerns about the robustness and reproducibility of estimating more than one memory parameter.

A significant advantage of model-based QT-hys quantifiers over other methods is that, along with the estimation of the lag of QT accommodation to RR change, they provide separate descriptors of the QT/RR steady-state dependency. In theory, and as illustrated in our simplified model, QT-hys quantifiers of other categories could even be extracted from the dynamic QT/RR model under certain assumptions. Another advantage is that they only require a sufficiently broad range of RR intervals regardless of the protocol design. In particular, the method is applicable to recordings at rest. The model may however be application-dependent; that is, under different recording conditions (rest, tilt test, exercise), different models may be needed to provide optimum QT prediction.

It is generally assumed that RR memory is time-invariant, that is, that it is fixed for a given individual, independent of the cause and pattern of heart rate change. This may be reasonable in near-resting

TABLE 4 Category III quantifiers: optimum RR memory in QT/RR dynamic modeling

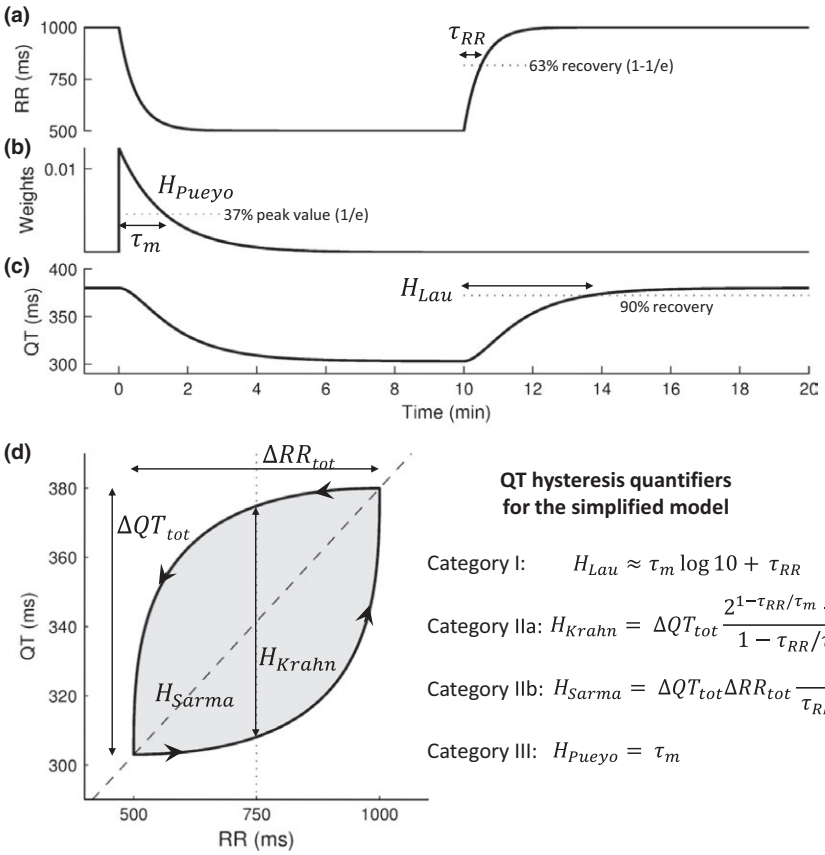
Reference	Method of RR variation	Description of QT/RR model	QT-hys quantifiers derived from the model	Range of QT-hys values
Raeder et al. (1995)	Controlled irregular breathing (n = 14)	RT is a linear combination of the history of RR	Duration of RT impulse response to RR change as observed on the cross-correlogram between RR and RT	2.9–4.7 s (supine) 1.3–1.6 s (standing) 4.8–8.1 s (standing with beta-blockade)
Dajani et al. (2003)	Selected segments of 24-h Holter (n = 6)	QT is predicted from the M preceding RR intervals using an artificial neural network	Optimal time delay in the model	4 min (estimated in one patient)
Pueyo et al. (2003, 2004) applied in: Baumert et al. (2008, 2010), Bolea et al. (2013), Malik, Hnatkova, Schmidt, et al. (2008), Malik et al. (2009a,b), Minchole et al. (2011, 2014, 2015), Ramirez et al. (2012), Smetana et al. (2004)	24-h Holter (462 MI survivors with depressed LVEF on amiodarone treatment and 404 on placebo)	QT/RR dependency: Best individual fit among 10 a priori selected regression models (two parameters) RR memory: two models 1. N-parameter model where N is the number of beats in preceding 5-min window 2. 1 parameter (exponential)	1. Duration of preceding RR sequence covering 90% of the cumulative sum of weights (derived from the N-parameter model) 2. Time constant of the exponential fit of the above-mentioned cumulative sum of weights 3. Equivalent to 1, computed only for ECG segments containing abrupt rate changes 4. Equivalent to 3, expressed in beat counts	1. 146 ± 37 s (amiodarone) 136 ± 32 s (placebo) 2. 46 ± 8 beats (amiodarone) 49 ± 8 beats (placebo) 3. 144 ± 39 s (amiodarone) 134 ± 32 s (placebo) 4. 150 ± 39 beats (amiodarone) 158 ± 37 beats (placebo)
Halamek et al. (2007b) applied in: Halamek et al. (2007a, 2010, 2011, 2012)	Supine rest/ tilt test/constant load cycling (n = 19)	QT/RR dependency: linear RR memory: two parameters describing the fast and slow components of QT response	Number of beats to reach 90% of QT variation following RR change	86 ± 28 beats (supine rest) 91 ± 31 beats (tilt test, breathing at 0,1 Hz) 78 ± 20 beats (tilt test, breathing at 0,33 Hz) 142 ± 35 beats (cycling) 104 ± 40 beats (combined measurements)
Pueyo et al. (2008)	Controlled postural maneuvering (n = 33)	QT/RR dependency: polynomial RR memory: adaptive estimation of the transfer function describing hysteresis	Equivalent to 1 in Pueyo et al., 2004) (described above), computable at each instant of the recording, and expressed in beat counts	Time varying (approximate range: 30–100 beats)
Trost (2008)	24-hour Holter (six patients with documented TdP, 36 controls)	QT/RR dependency: two parameters describing the static relation between 1/QT and 1/RR RR memory: Autoregressive moving-average transfer function	Number of beats to reach 99,5% of QT variation following RR change	415 ± 21 beats (controls) 1001 ± 41 beats (patients with TdP)
Malik, Hnatkova, Novotny et al. (2008) applied in: Malik et al. (2013, 2016), Malik, Hnatkova, et al. (2012), Malik, van Gelderen (2012), Hnatkova et al. (2010, 2014), Jacquemet et al (2014), Ramirez et al. (2014)	Daytime ECG ≥13 h (n = 40)	QT/RR dependency: Best individual fit among 10 a priori selected regression models (two parameters) RR memory: one parameter (exponential model). The weights of the RR intervals are separately plotted against continuous time (time-based approach) and discrete time (interval-based approach)	1. Adapted from 2 in Pueyo et al. (2004) (described above), expressed as a decay rate instead of a time constant, using the interval-based approach 2. Same as above, using the time-based approach	1. 4.7 ± 0.6 2. 5.0 ± 0.7

(Continues)

TABLE 4 (Continued)

Reference	Method of RR variation	Description of QT/RR model	QT-hys quantifiers derived from the model	Range of QT-hys values
Hadley et al. (2011)	Treadmill test: (*n* = 1959 for model development, *n* = 5 for validation)	QT/RR dependency: quadratic fit RR memory: three parameters. The effective RR (exponential model) is determined from the predicted RR which accounts for both long-term RR history and local trend	Number of beats to reach 50% of QT variation following RR change	From near 0 to over 100 beats
Jacquemet et al. (2011)	Tilt test (*n* = 12) Atrial pacing (*n* = 1)	QT/RR dependency: best individual fit among 8 a priori selected regression models (three parameters) RR memory: two parameters describing the fast and slow components of QT response	Number of beats to reach 90% of QT variation following RR change	100 ± 20 beats (pacing) 43–117 beats (tilt test)
Chen and Trayanova (2012)	10-min ECG segments recorded before VT onset (*n* = 15)	QT is predicted from both preceding QT and RR intervals. 2M-parameter model where M is the extent of QT and RR history	Extent of activation history (in beat counts) to include in the model to reach a mean square error <5 ms^2 in QT prediction	38 ± 9 beats immediately before VT 32 ± 8 beats 1 hr before VT

LVEF, left ventricle ejection fraction; MI, myocardial infarction; TdP, torsades de pointes; VT, ventricular tachycardia.



QT hysteresis quantifiers for the simplified model

Category I: $H_{Lau} \approx \tau_m \log 10 + \tau_{RR}$

Category IIa: $H_{Krahn} = \Delta QT_{tot} \frac{2^{1-\tau_{RR}/\tau_m} - 1}{1 - \tau_{RR}/\tau_m}$

Category IIb: $H_{Sarma} = \Delta QT_{tot} \Delta RR_{tot} \frac{\tau_m}{\tau_{RR} + \tau_m}$

Category III: $H_{Pueyo} = \tau_m$

FIGURE 2 A simple mathematical model of QT/RR hysteresis. (a) The RR interval time course follows two exponential curves with time constant τ_{RR} corresponding to exercise and recovery. (b) The effective RR interval is a linear combination of preceding RR intervals with exponentially decaying weights with time constant τ_m. (c) The QT interval is computed as a linear function of the effective RR (Sagie et al. QT/RR relation). (d) Resulting QT/RR loop. The arrows indicate time evolution. The dashed line is the static QT/RR curve. Analytical formulas for the main QT-hys quantifiers in the context of this simple model are shown on the right-hand side. Calculation details are available upon request to the corresponding author

conditions. Repeated QT-hys assessment from separate long ECG recordings in the same subjects indicated that QT-hys (derived from a one-parameter model of RR memory) was stable in individuals and variable between subjects (Malik, Hnatkova, Novotny, et al., 2008). To our knowledge, this study was the only investigation of the repeatability of QT-hys measurement. The stability of other QT-hys quantifiers (category I–II and category III quantifiers derived from other models) remains to be demonstrated, as well as the stability of QT-hys estimation from short ECG recordings or in the presence of wide and sudden RR variations. Adaptive parameter estimation (Pueyo et al., 2008) may enable tracking the evolution of memory parameters, but the developments are still at the proof-of-concept stage.

4.4 | Other methods

Three documented approaches to QT-hys evaluation did not fit under our categories. Cammarota & Curione (2012) investigated the time delay between the occurrence of the minimum RR interval and the minimum RT interval during a graded maximal exercise test and subsequent recovery. The estimated RR-RT lag in healthy subjects was approximately 19 s or 50 beats. In our mathematical model (Figure 2), in the case where the RR interval time series features a peak with exponential decay (time constant: τ_{RR}) on both sides, the RR-RT lag is calculated to be $\tau_{RR}\,\tau_m/(\tau_m - \tau_{RR}) \cdot \log((\tau_m + \tau_{RR})/2\tau_{RR})$. If the time constant of RR variation is τ_{RR} = 12 s, a RR-RT lag of 19 s is obtained provided that the memory time constant τ_m = 80 s, which seems reasonable, but illustrates the difficulty to interpret this measure as a QT-hys index.

Two other studies suggested methods closely related to the ΔQT between exercise and recovery. Toivonen, Helenius, and Viitasalo (1997) measured QT intervals during the relatively small rate increase observed in the first 30 s following awakening of subjects on alarm call and compared them to QT intervals measured at similar heart rates during stable conditions. Kannankeril, Harris, Norris, et al. (2008) compared QT intervals measured during the third minute of each stage of a graded exercise test to QT intervals measured at similar heart rate during the first minute of the same stage, therefore investigating QT-hys within an exercise stage. The two latter methods are inherently restricted to describe hysteresis during relatively short and small RR variations, which may decrease their signal-to-noise ratio (ΔQT-to-QT natural variability ratio). While both methods successfully detected the presence of hysteresis, they seem unlikely to be able to differentiate the extent of hysteresis between subjects.

4.5 | Perspectives

As mentioned above, it remains to be clarified whether individual QT-hys can be assumed as time-invariant. It has been advocated that QT-hys may differ between RR increase and decrease (Halamek, Jurak, Villa, et al., 2007a; Lau et al., 1988) or according to the method of RR variation (Halamek et al., 2007b) and that the extent of QT-hys may be positively correlated with the rate of RR change (Pueyo et al., 2008). The influence of such variables on QT-hys estimates remains to be examined to determine whether QT-hys measurement can be robust to variations of measurement conditions and between-subject variation of RR response to provocative testing.

In fact, the very mechanisms underlying QT-hys are yet to be elucidated. Monophasic APD in the human ventricular muscle has been shown to require up to several minutes to adapt to a sudden change in pacing rate (Franz et al., 1988), which suggests that QT-hys is mostly governed by the intrinsic electrophysiological properties of ventricular cells. This is consistent with a report of computer simulations suggesting that QT-hys is driven by intracellular sodium concentration and Na^+/K^+ pump dynamics (Pueyo et al., 2010). However, other studies have suggested that QT-hys may be related to cardiac autonomic modulation (Malik et al., 2013; Pelchovitz et al., 2012). As mentioned in a recent review article (Swenne, 2015), it is plausible that QT-hys is in fact driven by both electrophysiological properties of heart cells and cardiac autonomic modulation. More insights into these mechanisms will be needed to determine the significance of QT-hys.

It is conceivable that QT-hys quantifiers may eventually be used as clinical biomarkers of cardiac diseases. Among reviewed studies, the most promising results in this respect were obtained in certain variants of the long QT syndrome (Chattha et al., 2010; Chauhan et al., 2004; Gao, Fang, Chiu-Man, et al., 2007; Halamek et al., 2012; Krahn, Klein, & Yee, 1997; Krahn et al., 2002; Wong et al., 2010), in coronary artery disease (Lauer et al., 2006; Zhang et al., 2014), and in relation to arrhythmic risk (Pueyo et al., 2004; Trost, 2008). However, given the lack of consensus between studies and the heterogeneity of their methods, further studies are warranted so as to establish the clinical relevance of QT-hys assessment. In particular, future studies of QT-hys as a clinical biomarker must differentiate QT-hys from steady-state QT/RR dependency. Additionally, the question to be answered for a particular clinical condition may be better addressed by one mathematical model, whereas another model may lead to a better estimate to predict an outcome in a different clinical condition.

4.6 | Conclusion

There is no consensus on an optimal method of QT/RR hysteresis quantification in the literature. Our critical review advocates for the use of model-based estimation of memory (category III quantifiers). Such method appears to be the most versatile approach to QT-hys assessment, as it allows separate quantification of QT/RR dependency and QT-hys, and can be applied to a wider range of experimental settings. QT-hys models with one memory parameter (exponential weights) are recommended as they have been thoroughly validated. Nevertheless, a rigorous application-specific comparison of all methods would be desirable.

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