REVIEW ARTICLE

Clinical applications of QT/RR hysteresis assessment: A systematic review

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Background: QT/RR hysteresis (QT-hys) is an index of the time accommodation of ventricular repolarization to heart rate changes. This report comprehensively reviews studies addressing QT-hys as a biomarker of medical conditions.

Methods: This is a secondary analysis of data from a recent systematic review pertaining to methods of assessment of QT-hys. Articles included in the former review were filtered in order to select original articles investigating the association of QT-hys with medical conditions in humans.

Results: Nineteen articles fulfilled our inclusion criteria. Given the heterogeneity of the methods and investigated conditions, no pooled analysis of data could be implemented. QT-hys was mostly studied as a risk marker of severe arrhythmias, as a predictor of the long QT syndrome (LQTS) phenotypes and genotypes and as a marker of exercise-induced ischemia. An increased QT-hys appears to be implicated in arrhythmogenesis, although the evidence in this regard relies on few human studies. An augmented QT-hys was reported in the LQTS, predominantly in the LQT2 genotype, but conflicting results were obtained between studies using different methods of assessment. In addition, QT-hys appears to be a useful marker of stress-induced myocardial ischemia in patients suspected of coronary artery disease.

Conclusions: QT-hys evaluation has potential clinical utility in at least some clinical conditions. Further studies of the clinical validity of QT-hys assessment are warranted, particularly condition specific studies based on QT-hys evaluation methods that provide separate estimates of QT-hys and QT/RR dependency.

KEYWORDS

clinical, electrophysiology—long QT syndrome, clinical, electrophysiology—ventricular tachycardia, non invasive techniques—electrocardiography

1 | INTRODUCTION

Identifying patients at risk of arrhythmic events that could lead to sudden cardiac death is a persistent challenge in clinical practice. Multiple studies have addressed repolarization descriptors measured from the surface electrocardiogram (ECG) as potential biomarkers of arrhythmic risk (Monitillo et al., 2016; Pueyo, Martinez, & Laguna, 2009). Among those, one seemingly promising repolarization descriptor is the time of accommodation of the QT interval to heart rate changes, referred to as

QT/RR hysteresis or hysteresis lag (QT-hys) (Krahn, Klein, & Yee, 1997; Lau et al., 1988; Malik et al., 2008; Pueyo et al., 2003; Sarma et al., 1987).

The most obvious manifestation of QT-hys is the differential response of the QT interval during sequential heart rate acceleration and deceleration, during exercise and recovery for example. The QT/RR relationship during such events, is not the same during acceleration compared to deceleration, which creates a “hysteresis loop” in the graphic representation (Figure 1) (Sarma et al., 1987). Such loop is most likely explained by the time lag of QT adaptation to sudden changes of heart

rate. The QT interval adaptation following a sustained change in pacing rate, for instance, requires around 3 minutes to reach its steady-state in humans (Attwell, Cohen, & Eisner, 1981; Lau et al., 1988; Seed et al., 1987). This well-documented phenomenon is reproducible both on the surface ECG and at the cellular level. The lag of adaptation of action potential duration to sustained changes of pacing rate was observed several decades ago in animal studies (Carmeliet, 1955) and properly described in the intact human heart (Franz et al., 1988). Several methods exist for the quantification of individual profiles of QT-hys with no clear consensus on the method to use for clinical purposes. We therefore studied the various publications on the subject and summarized them in a recent systematic review aiming to display the reported methodologies and their associated pitfalls and technical hurdles (Gravel et al., 2017). In short, the dynamic QT/RR relationship could be divided into two distinct processes: the QT/RR dependency, i.e. how much the steady-state QT interval varies through the range of physiological RR intervals, and the QT/RR hysteresis, i.e. how fast the QT interval attains its steady-state following a sustained variation in RR interval. While studies of the QT/RR relationship have often confounded these two processes, recent studies suggest that QT/RR dependency and QT-hys are uncorrelated and likely represent distinct physiological mechanisms (Malik et al., 2008, 2013). This very principle is essential to understand the strengths and limitations of QT-hys assessment methods and their applicability to various clinical settings.

So far, a large portion of studies addressing QT-hys assessment were designed with the sole aim of improving the reliability of the rate-corrected QT interval (QTc) measurement. However, some studies have proposed that individual QT-hys may be used as a biomarker of specific medical conditions, independent of QTc. The aim of the

current review is to comprehensively identify and summarize these reported clinical applications of QT-hys measurement.

2 | METHODS

This is a secondary analysis of data from our recently published systematic review pertaining to mathematical methods assessing QT-hys (Gravel et al., 2017). The detailed search methodology and results are specified in the original paper. In brief, databases were searched for articles written in English or French from inception to September 23, 2016, using search keywords and inclusion criteria designed to comprehensively identify original articles reporting a method of quantification of QT-hys in humans. The original review identified 60 articles which were filtered in the current review by applying the following criteria in order to select only articles reporting clinical applications of QT-hys assessment:

1. The article reports QT-hys measured among patients with a specific medical condition
2. The article reports statistical testing of QT-hys differences between patients and controls, between patients with different outcomes or testing of its correlation with markers of disease severity.

The following data were extracted from the selected articles: description and size of study groups, cause of RR variation during ECG acquisition, method of QT-hys measurement, descriptive statistics of QT-hys quantifiers and results of statistical testing. Reported methods of QT-hys measurements were grouped under three categories which are briefly described here and illustrated in Figures 1 and 2. A thorough description of categories was published in our former review.

FIGURE 1 Δ QT and loop area methods of QT/RR hysteresis quantification. Points A and B are steady-state QT/RR pairs observed at rest (A) and during exercise at fixed intensity (B). Δ QT is the absolute QT difference between exercise and recovery QT/RR curves at a predetermined reference RR interval or time-point of recovery (600 ms in the illustration). Loop area is the area between exercise and recovery QT/RR curves over a predetermined RR range

Δ QT (Figure 1) Estimates the difference (in ms) between QT intervals measured at a predetermined RR observed both during rate acceleration and deceleration, typically during exercise and recovery.

Loop area (Figure 1) Estimates the area (in ms^2) between QT/RR curves fitted separately for rate acceleration and deceleration, typically during exercise and recovery.

Optimal RR memory (Figure 2) Practically, the optimal RR memory is the mathematical equivalent of the duration of QT adaptation to a sustained step change in heart rate. It is independent from the QT/RR dependency. Mathematically, it estimates the lag in the individual QT/RR relationship modeled from recorded beat-to-beat QT and RR time series. In brief, a model is constructed as such as the QT intervals are predicted according to the preceding series of RR intervals. The optimal RR memory (in s or beat counts) represents the extent of previous RR history to include in the mathematical model in order to optimize beat-to-beat QT prediction (Gravel et al., 2017; Halamek et al., 2007; Jacquemet et al., 2011; Malik et al., 2008; Pueyo et al., 2004).

3 | RESULTS

Nineteen articles fulfilled our inclusion criteria. Among these, three studies examined QT-hys in relation to arrhythmic risk or clinical

FIGURE 2 Estimation of the optimal RR memory from a beat-to-beat QT and RR time series. The optimal RR memory is extracted from a dynamic model of QT time series prediction from the RR time series. The model accounts for the steady-state QT/RR dependency, described by the parameters of the function relating QT intervals to a weighted average of preceding RR intervals, and for the RR memory, described by the parameters of the weight function. The optimal RR memory is a parameter of the weight function that corresponds to the extent of previous RR history to include in the model to optimize beat-to-beat QT prediction

history of severe arrhythmia, seven investigated QT-hys in the long QT syndrome (LQTS), five in coronary artery disease (CAD) or associated risk factors, and four studied other clinical conditions, namely depression (Baumert et al., 2008) abnormal uterine perfusion in pregnancy (Baumert et al., 2010) anorexia (Padfield et al., 2016) and exposure to simulated microgravity (Bolea et al., 2013). Due to the heterogeneity of reviewed clinical conditions and measurement methods, we did not implement pooled analysis of the extracted data. Moreover, since the absolute QT-hys values are specific to the calculation methods and vary greatly among reviewed articles, we elected to report the presence and direction of significant QT-hys differences compared to control groups. Therefore, the QT-hys descriptive statistics reported in the original articles are not systematically reproduced in the current review.

4 | DISCUSSION

The included articles addressed QT-hys in three main clinical settings and will be discussed accordingly hereafter. The four included articles examining other conditions listed above typically reported QT-hys as a secondary variable and mostly obtained inconclusive results. These specific conditions will therefore not be discussed.

4.1 | Ventricular arrhythmia

While an association between the QT-hys phenomenon and the occurrence of ventricular arrhythmia is conceivable, only three studies fitting our inclusion criteria addressed QT-hys in direct relation to documented arrhythmia. Pueyo et al. (2004) examined QT-hys as a predictor of arrhythmic mortality in survivors of acute myocardial infarction (MI). The study was based on a large sample of 866 MI survivors including 44 cases of arrhythmic death during follow-up, recruited for a clinical trial evaluating the efficacy of amiodarone treatment (Julian et al., 1997). They presented a thorough analysis of repolarization dynamics, considering four different quantifiers of QT-hys and additional repolarization variables. The QT-hys quantifiers were all estimators of the optimal RR memory extracted from Holter recordings, although different calculation methods were used. In brief, QT-hys was estimated separately using the whole recording and using partial segments where abrupt rate changes were identified. QT-hys was estimated using both a continuous time approach (weights of preceding RR

intervals in the QT/RR dynamic model are a function of time) and a discrete time approach (weights of preceding RR intervals are a function of the number of cardiac cycles). QT-hys was compared between victims of arrhythmic death and survivors, separately in the placebo and amiodarone treated groups. While two of the four QT-hys variables did not discriminate victims of ventricular arrhythmia from survivors, two discrete time approach quantifiers were significantly increased in patients who succumbed to arrhythmic death (in essence, the QT interval needed more time to adapt to RR variations in victims). Quantifier λ , an index based on the whole ECG recording, was significantly increased in victims in the placebo group only, and quantifier M_{90} , an index based on ECG segments with abrupt RR change, was significantly increased in victims in the amiodarone group and with only borderline significance in the placebo group.

Using another method of optimal RR memory estimation, Trost (2008) determined QT-hys from Holter recordings obtained <24 hr preceding the onset of torsades de pointes in six patients, compared to healthy controls. An increased QT-hys was observed with the mean optimal RR memory being approximately twice as long in torsades de pointes patients compared to healthy subjects. This is in accordance with a recent report of QT-hys in three patients with documented torsades de pointes to be in the upper range of QT-hys relative to their control group (Minchole et al., 2015).

Chen & Trayanova (2012) measured QT-hys in 15 patients with documented ventricular tachycardia. QT-hys in the same patients was significantly increased when measured within the 10 minutes preceding ventricular tachycardia compared to 1 hr before the onset of ventricular tachycardia. However, their study is based on a sophisticated QT-hys index that may not be comparable to other optimal RR memory quantifiers discussed in the present review. This study is rather unique in that it suggests that QT-hys is acutely increased at the very moment of arrhythmia onset. Whereas the results from their analysis may not provide a predictor of the event, they would rather propose an electric mechanism precipitating the event.

Interestingly, an *in silico* study by Pueyo et al. (2010) addressing the mechanisms of QT-hys puts forward a linkage between increased QT-hys and the occurrence of early after-depolarizations. The experiment in simulated human ventricular cardiomyocytes demonstrated that partial inhibition of Na^+/K^+ pump current (I_{NaK}) simultaneously increased QT-hys and induced early after-depolarizations on pseudo ECG. Such mechanism would not only explain the increased arrhythmic risk in medical conditions associated with impaired QT-hys, but

would implicate that there is an acutely increased arrhythmic risk concurrent with the manifestation of QT-hys. However, the inducibility of early after-depolarizations could not be demonstrated by pharmacologic inhibition of I_{NaK} in isolated canine papillary muscle and the proposed mechanism thus requires further validation. A more recent investigation by the same research team expanded this finding, suggesting that spatial heterogeneity of the duration of action potential duration adaptation to rate changes was implicated in arrhythmogenesis (Bueno-Orovio et al., 2014).

Taken altogether, this evidence suggests that increased QT-hys may be associated with arrhythmogenesis. However, two of the three clinical reports in human subjects were based on very small sample sizes (6 to 15 subjects with documented ventricular arrhythmia) (Chen & Trayanova, 2012; Trost, 2008). The only report of a large series demonstrated a clear association between increased QT-hys and arrhythmic death (Pueyo et al., 2004). However, the results were divergent according to the different methods of QT-hys estimation used in this study. Nevertheless, results from simulation studies are promising, suggesting a potential link between increased QT-hys and initiation of ventricular arrhythmia.

4.2 | Long QT syndrome

LQTS was the most frequently investigated medical condition among the reviewed articles pertaining to QT-hys (Table 1). There indeed seems to be compelling fundamental and clinical rationale for such investigation since LQTS is caused by genetic mutations leading to malfunctioning of cardiac ion channels and to an increased risk of syncope and sudden death, often triggered by exercise or emotional arousal (Schwartz et al., 2001).

Krahn et al. (1997) were the first to demonstrate that exercise-induced QT-hys (or rather RT/RR hysteresis in this specific study) was increased in LQTS patients who were not genotyped. This was confirmed by three studies based on Δ QT measurements during exercise and recovery (Chattha et al., 2010; Gao et al., 2007; Krahn et al., 2002). However, the study by Wong et al. (2010) identified an increased QT-hys in LQT2 patients only, and not in LQT1. This is in accordance with Chattha et al. (2010) who obtained results of borderline significance suggesting that QT response during exercise and recovery may discriminate the LQT1 from the LQT2 genotype, LQT1 presenting longer QT-intervals during early recovery and LQT2 having larger QT-hys (Δ QT measured at 100 bpm). Chauhan et al. (2004), for their part, measured the QT/RR loop area during exercise and recovery. The study confirmed that QT-hys was increased in LQTS (ungenotyped). Accordingly, QT/RR loop areas estimated from a graded cycle ergometer protocol could discriminate LQTS from controls, while measurements made during a burst protocol at a fixed power output did not. In addition, the increased QT-hys during graded exercise and following recovery was observed in LQTS patients on and off beta-blockers alike. The latter finding, however, contradicted other studies which suggested QT-hys normalization under beta-blockers (Krahn et al., 2002; Wong et al., 2010).

To our knowledge, a single study investigated QT-hys in LQTS based on the estimation of the optimal RR memory in a dynamic QT/RR model (Halamek et al., 2012). In a relatively large sample of LQT1 patients, they reported a significantly decreased QT-hys in LQT1 patients compared to controls, seemingly contradicting aforementioned studies which reported either increased QT-hys in ungenotyped LQTS samples (most likely including a significant proportion of LQT1 patients) (Chauhan et al., 2004; Gao et al., 2007; Krahn et al., 1997; Krahn et al., 2002) or similar QT-hys in LQT1 and controls (Chattha et al., 2010; Wong et al., 2010). The decreased QT-hys in Halamek et al. was observed even in subjects with LQT1 genotype with normal resting QTc. In the same study, an increased QT/RR dependency (steeper steady-state QT/RR slope) was also associated with the LQT1 genotype.

In general, it is difficult to compare the results between various studies addressing QT response to stress testing. A large proportion of published data does not allow the differentiation between altered QT/RR dependency (steady-state QT/RR relationship) and altered QT-hys (time lag of QT accommodation to RR change). For instance, studies of the QT or corrected QT interval measured at a given time-point following a standardized stress (e.g. postural change, epinephrine infusion) are simply merging QT-hys and QT/RR dependency in a single estimator. For their part, studies based on the estimation of Δ QT or QT/RR loop area as described above (six of the seven reviewed studies addressing QT-hys in LQTS) are using an estimator of QT-hys that is to some degree influenced by QT/RR dependency, as previously demonstrated (Gravel et al., 2017). Therefore, a sufficiently powered study of QT response to RR change assessing the most frequent LQTS genotypes, and using a method that allows separate estimation of QT/RR dependency and QT-hys, appears necessary to validate the clinical usefulness of stress testing in LQTS.

Nevertheless, one scenario could nearly reconcile the divergent results reported among reviewed studies: increased QT-hys could be a characteristic of the LQT2 genotype, while the LQT1 genotype would present a normal or even decreased QT-hys. One must, however, seriously consider that none of the included studies estimated QT-hys as a risk marker of malignant arrhythmias or sudden death in LQTS, but rather as a way of predicting the presence of LQTS and the corresponding genotype from a simple stress test. Thus, further studies are needed to clarify the implications of the identified QT-hys alterations in the LQTS.

4.3 | Coronary artery disease and associated risk factors

Among the five articles addressing QT-hys in coronary artery disease (CAD) (Table 2), two studies of relatively large cohorts with suspected CAD suggest a clinical relevance to QT-hys assessment. Lauer et al. (2006). investigated patients with myocardial ischemia as assessed by rest and stress single photon emission computed tomography (SPECT) myocardial perfusion imaging. Patients were divided according to quartiles of the evaluated hysteresis index (based on QT-RR loop area during exercise and recovery). Accordingly, the likelihood of any ischemia or severe ischemia was significantly higher in the upper

TABLE 1 QT-hys investigated in the long QT syndrome

Reporting article	Category of QT-Hys quantifier	Cases	Control group	Findings
Krahn et al., 1997	Δ QT measured at three time points during recovery from symptom-limited treadmill test	LQTS patients (n = 14)	Unaffected family members (n = 9) Healthy subjects (n = 40)	↑ in LQTS compared to other groups (all indicators) = in unaffected family members versus CTRL (all indicators)
Krahn et al., 2002	Δ QT measured at six time points during recovery from symptom-limited treadmill test	LQTS patients (n = 14)	Healthy subjects (n = 10)	↑ in LQTS off betablockers versus CTRL and LQTS on betablockers (at 1 min of recovery and at six time points combined)
Chauhan et al., 2004	Loop area during graded or burst exercise and recovery	LQTS patients on beta-blockers (n = 21) LQTS patients off beta-blockers (n = 5)	Healthy subjects (n = 20)	↑ in both LQTS groups compared to controls (graded protocol) = across all groups (burst protocol)
Gao et al., 2007	Δ QT measured at four time points during recovery from symptom-limited treadmill test	Children with definite LQTS (n = 17) Children with uncertain LQTS (n = 16)	Healthy children (n = 18)	↑ in children with definite LQTS versus other groups (at 1, 2, and 4 min of recovery) = between all groups (at 6 min of recovery) = between children with uncertain LQTS and CTRL (all indicators)
Chattha et al., 2010	Δ QT at a heart rate of 100 bpm (cycle ergometer protocol)	LQT1 patients (n = 25) LQT2 patients (n = 25)	Healthy subjects (n = 25)	Δ QT at 100 bpm: 10.4 ± 8.5 ms in LQT1 33.9 ± 7.4 ms in LQT2 9.2 ± 4.0 ms in controls "Borderline significance between groups" (p = .06)
Wong et al., 2010	Δ QT 2 min into recovery from exercise	LQT1 patients (n = 50) LQT2 patients (n = 45)	Genotype-negative family members (n = 64)	↑ in LQT2 vs LQT1 and CTRL ↓ by beta-blockade in both LQT1 and LQT2
Halamek et al., 2012	Optimal RR memory based on segments of diurnal Holter ECG recordings	LQT1 patients on beta-blockers (n = 97) LQT1 patients off beta-blockers (n = 97)	Healthy controls (n = 154)	↓ in combined LQT1 versus CTRL ↓ in combined LQT1 patients with normal resting QTc (370 < QTc < 430) compared to CTRL with similar resting QTc = between LQT1 patients on and off beta-blockers

↑, increased QT-hys; ↓, decreased QT-hys; =, difference between groups is not significant, CTRL, control subjects; LQTS, long QT syndrome; LQT1/2, long QT syndrome of type 1/2; QTc, rate-corrected QT interval using a subject-specific correction formula.

quartile of QT-hys compared to the lower quartile. Interestingly, QT-hys was a predictor of any or severe ischemia, independent of other clinical variables including ST-segment changes, exercise capacity and heart rate recovery. In a subset of patients, QT-hys was also associated with the presence of CAD identified by coronary angiography. Zhang et al. (2014) conducted a similar study investigating the sensitivity and specificity of QT-hys measurement, based on QT-RR loop area as well, to detect angiographically proven CAD. The diagnostic accuracy of QT-hys was superior to that of the Duke treadmill score or conventional treadmill exercise test criteria. QT-hys also correlated with CAD severity based on the SYNTAX score. In multivariate analysis, QT-hys combined to treadmill exercise test criteria was an independent predictor of CAD, but not QT-hys alone.

Interestingly, an animal study supports the observed association in humans between myocardial ischemia and QT-hys. Starobin et al., (2007) modeled CAD by inducing graded coronary flow reductions in pigs, while simultaneously measuring the QT/RR loop area during gradual heart rate acceleration and deceleration controlled by pacing. The study confirmed that QT-hys correlated with the extent of coronary flow reduction and with markers of inflammation and myocyte injury, strongly suggesting that QT-hys measurement in this setting is a signature of recent myocardial ischemia. During ischemia, electrophysiological properties of cardiomyocytes are altered, leading to shortening of action potential duration through opening of the ATP sensitive potassium channels (Akar & Akar, 2007). While the above-mentioned articles observed an increased

TABLE 2 QT-hys investigated in coronary artery disease and associated risk factors

Reporting article	Category of QT-Hys quantifier	Cases	Control group	Findings
Ng et al., 1998	Loop area from maximal Bruce treadmill test	Patients with CAD (n = 28)	Healthy subjects (n = 14)	Different between CAD and CTRL (unspecified direction of difference)
Lauer et al., 2006	Loop area from symptom-limited treadmill test	Patients referred for exercise test (n = 260)	NA (correlational study)	Higher levels are associated with a greater likelihood of ischemia or severe ischemia (assessed by SPECT myocardial perfusion imaging)
Halamek et al., 2010	Optimal RR memory (2 models) during supine bicycling submaximal protocol	Hypertensive patients (n = 25)	Healthy subjects (n = 23)	↓ in hypertensive patients versus CTRL (Halamek's model) = between hypertensive patients and CTRL (Pueyo's model)
Pelchovitz et al., 2012	Loop area from submaximal cycle ergometer exercise and recovery ΔQT at minimum RR +50 ms	Patients with type 2 diabetes (n = 16) Patients with CAD and preserved LVEF (n = 71) Patients with CAD and depressed LVEF (n = 17)	Healthy subjects (n = 20)	= between groups (loop area) Comparison of ΔQT between groups are unreported
Zhang et al., 2014	Loop area from symptom-limited treadmill test	Patients with suspected CAD: Negative angiography (n = 61) Positive angiography (n = 77)	NA (correlational study)	↑ in patients with positive versus negative angiography Correlated with the severity of CAD (SYNTAX score) in patients with positive angiography Accuracy of QT-hys testing for CAD diagnosis is superior to the conventional treadmill exercise test criteria and to the Duke treadmill score

↑, increased QT-hys; ↓, decreased QT-hys; =, difference between groups is not significant; CAD, Coronary artery disease; CTRL, control subjects; LVEF, left ventricle ejection fraction; SPECT, single photon emission computed tomography.

QT/RR loop area concurrently with ischemia both in animals and humans, it is probable that such observation is not a consequence of an increased time lag of QT accommodation to RR changes, but rather of a relatively durable downward shift of the steady-state QT/RR curve following ischemia. In patients during stress testing, such event would cause a greater dissociation between the pre-ischemia exercise curve and the postischemia recovery curve. Although QT-hys measurement could not differentiate these two potential underlying mechanisms, the association with ischemia persists and QT-hys testing could nevertheless be useful in the diagnosis of CAD.

In contrast with these promising results, Pelchovitz et al. (2012) examined QT-hys in CAD patients, both with preserved and depressed left ventricular ejection fraction, in type 2 diabetes patients and in healthy controls, but failed to find significant QT-hys differences between groups. Finally, Halamek et al. (2010) compared hypertensive subjects to healthy controls where a decreased QT time lag was observed in hypertensive subjects compared to controls, only according to the authors' own quantification model, but not according to a model introduced by Pueyo et al. (2004).

We could only speculate about the reasons for these conflicting results, but one could suppose that discrepancies between study designs are involved. First, the studies with negative results were based

on small samples and could lack sufficient power to identify QT-hys impairments in CAD. Second, the exercise protocols in these same studies were submaximal and the exercise stress may have been insufficient to provoke QT-hys alterations in tested subjects. Third, the study by Halamek et al. (2010) tested hypertensive patients without known CAD, an apparently less severe condition compared to other studies. However, given the results of former studies, it remains unexpected that QT-hys in hypertensive patients is significantly decreased compared to control subjects in this report.

4.4 | Summary

It emerges from our review that QT-hys has potential clinical utility in at least some clinical conditions. The most promising results were obtained in relation to severe arrhythmia, to stress-induced myocardial ischemia, and in the LQTS. It seems unlikely that a single mechanism explains the increased QT-hys reported in these very diverse clinical scenarios. As suggested in a recent article, it is plausible that QT-hys is in fact explained by both electrophysiological properties of ventricular cells and rate-independent influence of cardiac autonomic modulation on ventricular repolarization (Swenne et al., 2015). Further studies remain necessary to gain a better understanding of the fundamental mechanisms of QT-hys,

especially studies addressing the lag of QT accommodation to pacing-induced rate changes during pharmacological autonomic manipulations in humans.

Our review also points out that it remains unknown if QT-hys is a time invariant individual characteristic that could be lastingly impaired in response to aging and disease, or a marker of time-varying and short-lived conditions that are involved in the initiation of an arrhythmic event. While QT-hys appears to be increased concurrently with exercise-induced myocardial ischemia (Lauer et al., 2006; Zhang et al., 2014) or in the minutes preceding onset of torsades de pointes (Chen & Trayanova, 2012); QT-hys from long ECG recordings (such as 24 hr Holter) is impaired in some conditions (Halamek et al., 2012; Malik et al., 2013; Pueyo et al., 2004), implying that QT-hys could be durably altered. Condition-specific studies using repeated or adaptive QT-hys assessment from continuous ECG recordings would be beneficial to clarify this question.

The present review highlights a common methodologic issue in clinical applications of QT-hys: while it was demonstrated that QT/RR steady-state dependency and QT-hys are distinct processes, the Δ QT and QT/RR loop area methods cannot entirely distinguish one from the other. This may explain inconsistent results across reviewed studies using different QT-hys assessment methods. The advantages of model-based QT-hys estimation are clear in this regard. QT-hys evaluation from dynamic QT/RR models is a more general approach, and under certain assumptions, the Δ QT and loop area estimators could also be extracted from such models.

4.5 | Future directions

The mere fact that QT-hys was reported as a predictor of arrhythmic events and myocardial ischemia justifies further investigations of the clinical validity and utility of QT-hys evaluation. In particular, the results obtained in limited samples of patients with documented ventricular arrhythmia (Chen & Trayanova, 2012; Trost, 2008) and in simulation studies (Bueno-Orovio et al., 2014; Pueyo et al., 2010) suggest an implication of QT-hys in arrhythmia onset. In addition to basic studies addressing the implication of hysteresis in arrhythmia onset, it appears necessary that more longitudinal studies are conducted in large samples, for instance in myocardial infarction and heart failure, in order to validate the use of QT-hys as a marker of arrhythmic risk.

Another promising application of QT-hys evaluation is its integration to conventional exercise testing, which appears to increase the accuracy of CAD prediction (Lauer et al., 2006; Zhang et al., 2014). The next step would be larger studies addressing the reliability of QT-hys measurement in this context and defining threshold values to identify patients who would benefit from more invasive testing for CAD diagnosis.

4.6 | Clinical applicability

It is reasonable to believe that QT-hys estimation, upon appropriate validation of its clinical validity, could be integrated in clinical practice

in the future. An obvious advantage is that QT-hys can be estimated using equipment and noninvasive tests that are already operating in regular practice. The main requirement pertaining to the general adoption of the recommended "optimal RR memory" methods is that they necessitate continuous beat-to-beat QT and RR measurements and thus cannot rely on manual ECG measurements. However, automated QT delineation techniques are now providing appropriately precise measurements from the resting ECG with limited human involvement (Couderc et al., 2011). It is believable that user-friendly analytical algorithms applicable with similar accuracy to Holter recordings, short term loop recorders, and exercise ECG, will soon be developed.

5 | CONCLUSION

Available studies suggest that QT-hys is implicated in arrhythmogenesis and that it is impaired in the LQTS, predominantly in the LQT2 genotype. In addition, QT-hys could be a useful marker of exercise-induced myocardial ischemia in patients suspected of CAD. QT-hys impairment most likely relies on various mechanisms that have different degrees of involvement according to clinical settings. Further studies of the clinical validity of QT-hys assessment are warranted, particularly condition specific studies based on QT-hys evaluation methods that provide separate estimates of QT-hys and QT/RR dependency.

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