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Autonomic Control of Heart Rate and QT Interval Variability Influences Arrhythmic Risk in Long QT Syndrome Type 1

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ABSTRACT

BACKGROUND A puzzling feature of the long QT syndrome (LQTS) is that family members carrying the same mutation often have divergent symptoms and clinical outcomes.

OBJECTIVES This study tested the hypothesis that vagal and sympathetic control, as assessed by spectral analysis of spontaneous beat-to-beat variability of RR and QT intervals from standard 24-h electrocardiogram Holter recordings, could modulate the severity of LQTS type 1 (LQT1) in 46 members of a South-African LQT1 founder population carrying the clinically severe *KCNQ1* A341V mutation.

METHODS Nonmutation carriers (NMCs) (n = 14) were compared with mutation carriers (MCs) (n = 32), 22 with and 10 without major symptoms. We assessed the effect of circadian rhythm and beta-blocker therapy over traditional time and frequency domain RR and QT variability indexes.

RESULTS The asymptomatic MCs differed significantly from the symptomatic MCs and from NMCs in less vagal control of heart rate and more reactive sympathetic modulation of the QT interval, particularly during daytime when arrhythmia risk for patients with LQT1 is greatest.

CONCLUSIONS The present data identified an additional factor contributing to the differential arrhythmic risk among patients with LQT1 carrying the same mutation. A healthy autonomic control confers a high risk, whereas patients with higher sympathetic control of the QT interval and reduced vagal control of heart rate are at lower risk. This differential "autonomic make-up," likely under genetic control, will allow refinement of risk stratification within families with LQTS, leading to more targeted management. (J Am Coll Cardiol 2015;65:367–74) © 2015 by the American College of Cardiology Foundation.

Despite major progress in the understanding (1,2) and management (1,3,4) of congenital long QT syndrome (LQTS), several unsolved questions of high clinical relevance remain. One of the most puzzling, and most emotionally disquieting for the affected families, is represented by the unequal arrhythmic risk present among family members who carry the same disease-causing mutation. Foreseeing a benign or life-threatening outcome, even among genetically affected siblings,

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ABBREVIATIONS AND ACRONYMS

AMC = asymptomatic mutation carrier

BB = beta-blocker

HFa_{RR} = high-frequency power computed over the RR series and expressed in absolute units

LFa_{RTe} = low-frequency power computed over the RTe series and expressed in absolute units

LQT1 = long QT syndrome type 1

LQTS = long QT syndrome

MC = mutation carrier

NMC = nonmutation carrier

SMC = symptomatic mutation carrier

proves problematic for physicians caring for these patients.

Over the last decade, this challenge prompted numerous attempts to identify "modifier genes," genetic variants associated with a higher or lower arrhythmic risk (2,5). The current view holds that these modifiers include factors that either modify the underlying arrhythmogenic myocardial substrate or affect the probability and magnitude of arrhythmia-triggering events (2). The former include proteins that likely contribute to the balance of inward and outward currents operating during the cardiac action potential, and several of these have already been identified (6–10), and the latter include genes modulating differences in sympathetic and vagal responses (11–13).

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The present study aimed at expanding the understanding of the relationship between neural control and arrhythmic risk in LQTS. Two concepts, preliminary for the design of our study, were: 1) the focus should be on patients with LQTS type 1 (LQT1) because they are at risk specifically during sympathetic activation (14); and 2) these patients with LQT1 should all be from a single founder population and thus have the same mutation to avoid the phenotypic variability attributed to mutation heterogeneity. Founder populations represent the ideal human model to study modifier genes (6).

We previously showed that LQT1 asymptomatic mutation carriers (AMCs) were more likely to have a lower heart rate (11), lower baroreflex sensitivity (11), and smaller heart rate decrease at the end of an exercise stress test than symptomatic mutation carriers (SMCs) (12). The last 2 findings point to a protective effect of reduced vagal reflexes. A limitation of our studies is that although they provided novel data about vagal control in patients with LQTS, we had no specific information on the sympathetic control at the ventricular level.

Analysis of the spontaneous changes of the heart period and QT interval provides indexes that allow noninvasive inferences on the autonomic modulation directed to the sinus node and the ventricles (15–17). The power of the respiratory-related heart period changes in the high-frequency band (HF) (0.15 to 0.5 Hz) decreases with the vagal withdrawal progressively induced by graded head-up tilt (18–20). By contrast, the magnitude of fluctuations of the QT interval in the low-frequency band (LF; 0.04 to 0.15 Hz) positively correlates with the inclination of the tilt table (21,22), suggesting that QT variability and sympathetic control are directly linked (23,24). The combination of these 2 indexes (i.e., the HF power of heart period variability and the LF power of QT variability) provides a unique possibility to dissect vagal and sympathetic influences on the heart and to test whether different autonomic patterns might help distinguish AMCs and SMCs.

We tested this hypothesis in a well-characterized LQT1 South African founder population in which all the affected members carry *KCNQ1* A341V, one of the LQTS mutations with the most severe phenotype (25–27). This relatively common mutation (26) produces a 50% reduction in basal I_{Ks} current and in vitro severe reduction in cAMP responsiveness due to failure to phosphorylate *KCNQ1* at the N-terminal S27 (28).

METHODS

STUDY POPULATION AND PROTOCOL. The study population only included members of the 25 families constituting the South African LQT1 founder population carrying the *KCNQ1* A341V mutation (25–27). Holter recordings were performed in 46 of the family members, 32 MCs and 14 non-MCs (NMCs), who served as controls. The MCs were further subdivided into SMCs or AMCs according to having experienced or not, regardless of therapy, either syncope (fainting spells with transient but complete loss of consciousness) or aborted cardiac arrest requiring resuscitation. We defined AMC as an individual who had reached age 20 years without cardiac events while not being treated with beta-blocker (BB) therapy. The 3 groups were of similar age, with the median ranging between 35 and 39 years. All patients were studied off BB therapy (BBoff), and 28 of the 32 MCs (87.5%) were also studied on BB therapy (BBon), which was almost always propranolol. BBoff corresponded to a plasma concentration of propranolol <20 ng/ml. Patient selection depended mostly on the physical proximity of their residence to the Stellenbosch area in the Western Cape and on their willingness to visit the clinic a few times for the Holter recordings.

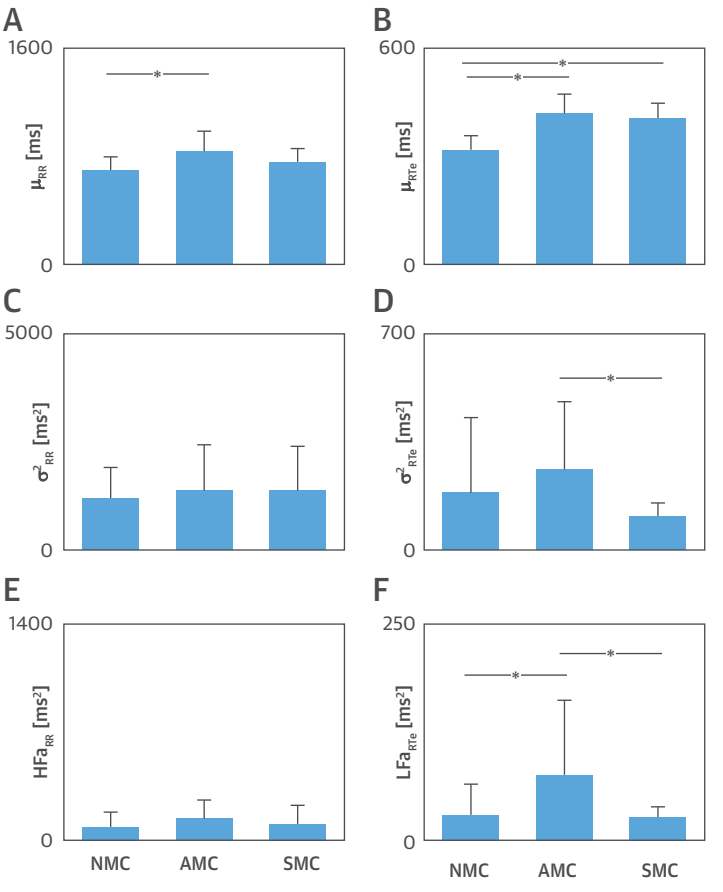
The study protocol consisted of the acquisition of 74 Holter recordings (12-lead 24-h; Mortara Instrument Inc., Milwaukee, Wisconsin). The sampling rate was 180 Hz. The analyses were carried out on lead II and were performed during daytime (2:00 PM to 6:00 PM) or nighttime (12:00 AM to 4:00 AM). The protocol adhered to the principles of the Declaration of Helsinki for medical research involving human subjects. All probands and family members provided written informed consent for clinical and genetic evaluations,

as approved by the ethical review boards of the University of Stellenbosch, Vanderbilt University, and the University of Pavia.

VARIABILITY SERIES EXTRACTION AND DATA ANALYSIS. Electrocardiogram (ECG) recordings were pre-processed to limit broadband noise and cancel baseline wandering (29). Heart period was approximated as the temporal distance between 2 consecutive R-wave peaks (RR) on the ECG. The R-wave peak was detected using a derivative-threshold algorithm, and its occurrence was fixed using parabolic interpolation. The T-wave end was located according to a threshold on the absolute first derivative set as a fraction (i.e., 30%) of the absolute maximal first derivative value computed on the T-wave downslope (29). The temporal distance between R-wave peak and T-wave end (RTe) was taken as an approximation of QT interval automatically measured from the ECG recording (30). All R-wave peak detections were carefully checked. Erroneous identifications were corrected and missed beats were manually inserted. The cubic spline interpolation technique was applied over those RR and RTe values that were directly influenced by the occurrence of nonsinus beats. RR and RTe beat-to-beat series were extracted from 24-h Holter monitoring during daytime and nighttime. We considered frames of 250 cardiac beats. After the RR and RTe means (μ_{RR} and μ_{RTe}) were calculated, the RR and RTe series were linearly detrended. RR and RTe variances (σ^2_{RR} and σ^2_{RTe}) were calculated from detrended series.

Spectral analysis was performed via a parametric approach exploiting the autoregressive model (31). Briefly, the autoregressive model describes the beat-to-beat series in the time domain as a linear combination of p past samples weighted by constant coefficients plus a zero mean random white noise. The Levinson-Durbin recursion algorithm was used to estimate, directly from the data, the coefficients of the autoregressive model and the white noise variance. The number of coefficients, p, was chosen according to the Akaike figure of merit. Power spectral density was computed from the model coefficients and the white noise variance. The power spectral density was factorized into spectral components, the sum of which provides the entire power spectral density. A spectral component was labeled LF if its central frequency was in the LF band, and it was classified as HF if its central frequency was in the HF band (15). The LF and HF powers were defined as the sum of the powers of all LF and HF spectral components, respectively. We assessed the HF power over RR series (HFa_{RR}) as an index of vagal modulation (32,33) and the LF power of RTe series (LFa_{RTe}) as an index of sympathetic modulation (21,22). HFa_{RR} and LFa_{RTe} were expressed in absolute units (ms^2). All the considered indexes (i.e., μ_{RR}, μ_{RTe}, σ^2_{RR}, σ^2_{RTe}, HFa_{RR}, and LFa_{RTe}) were calculated for each frame. Analysis was iterated with 50% overlap over the entire period, thus resulting in a distribution of parameters. The median of the distribution was extracted for successive statistical analyses (34).

FIGURE 1 BBoff in NMCs, AMCs, and SMCs During Daytime

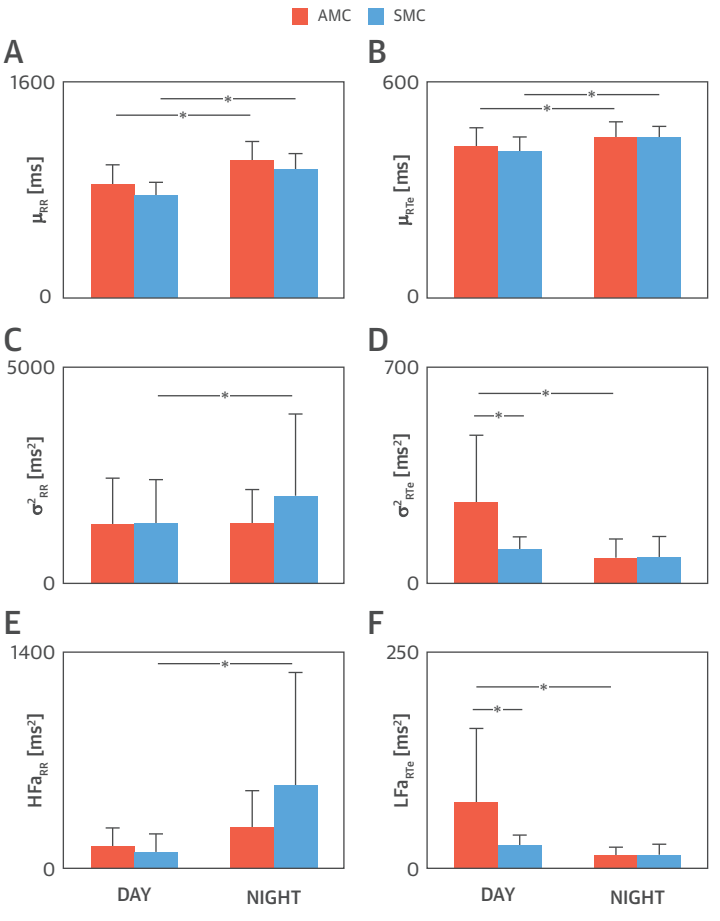


Bar graphs report the mean RR interval, μ_{RR} **(A)**, mean RTe interval, μ_{RTe} **(B)**, RR variance, σ^2_{RR} **(C)**, RTe variance, σ^2_{RTe} **(D)**, high-frequency power of the RR series expressed in absolute units, HFa_{RR} **(E)**, and low-frequency power of the RTe series expressed in absolute units, LFa_{RTe} **(F)** assessed off beta-blocker therapy (BBoff) in nonmutation carriers (NMCs), asymptomatic mutation carriers (AMCs), and symptomatic mutation carriers (SMCs) during the daytime (2:00 to 6:00 PM). Values are mean + SD. *$p < 0.05$.

STATISTICAL ANALYSIS. One-way analysis of variance (Dunnett test for multiple comparisons), or Kruskal-Wallis 1-way analysis of variance on ranks (Dunn test for multiple comparisons) when appropriate, was applied to check whether NMCs, AMCs, and SMCs could be distinguished based on the

considered parameters. Two-way repeated-measures analysis of variance (1-factor repetition, Holm-Sidak test for multiple comparisons) was performed to evaluate the significance of circadian rhythm of the time and frequency domain parameters in MCs (i.e., AMCs and SMCs were assessed during daytime and nighttime). Two-way repeated-measures analysis of variance (Holm-Sidak test for multiple comparisons) was performed to evaluate the significance of changes of time and frequency domain parameters induced by BB in MCs (i.e., AMCs and SMCs were assessed BBoff and BBon). If heterogeneity of variance was detected according to either the Bartlett test or, when appropriate, the Levene test, the data were log-transformed before the application of 1- or 2-way analysis of variance. Values are reported as mean ± SD. The statistical analysis was carried out using a commercial statistical program (Sigmastat, version 3.0.1, Systat Software, San Jose, California). A p value <0.05 was considered significant.

FIGURE 2 BBoff in AMCs and SMCs During Daytime and Nighttime



Grouped bar graphs report μ_{RR} **(A)**, μ_{RTe} **(B)**, σ^2_{RR} **(C)**, σ^2_{RTe} **(D)**, HFa_{RR} **(E)**, and LFa_{RTe} **(F)** assessed BBoff in AMCs **(salmon bars)** and SMCs **(blue bars)** during daytime and nighttime (12:00 to 4:00 AM). Values are mean + SD. *p < 0.05. Abbreviations as in Figure 1.

RESULTS

COMPARISON BETWEEN NMCs AND MCs. Figure 1 shows that although μ_{RR} was similar among SMCs and NMCs, it was longer in AMCs (Figure 1A). As expected, both AMCs and SMCs had longer μ_{RTe} than NMCs (Figure 1B). Analysis of RR variability revealed no significant differences between the 3 groups (Figures 1C and 1E). By contrast, analysis of RTe variability differentiated AMCs from SMCs: indeed, σ^2_{RTe} (Figure 1D) and LFa_{RTe} (Figure 1F) were greater in AMCs compared with SMCs. Importantly, the LFa_{RTe} of AMCs was significantly greater than that of NMCs (Figure 1F). Thus, AMCs appeared to have a sympathetically mediated greater variability of the QT interval.

CIRCADIAN RHYTHM OF AUTONOMIC ACTIVITY IN MCs. Figure 2A shows that μ_{RR} lengthened during nighttime in both AMCs and SMCs. During both daytime and nighttime, AMCs tended to have longer μ_{RR} than SMCs (Figure 2A). Also μ_{RTe} exhibited a circadian rhythmicity in MCs (Figure 2B). Although σ^2_{RR} increased during nighttime in SMCs, this value remained unchanged in AMCs (Figure 2C). Conversely, σ^2_{RTe} decreased during nighttime in AMCs, whereas it did not change in SMCs (Figure 2D). During daytime, σ^2_{RTe} was larger in AMCs than in SMCs, whereas no difference was observed during nighttime (Figure 2D). HFa_{RR} (Figure 2E) and LFa_{RTe} (Figure 2F) confirmed the differences observed in Figures 2C and 2D, respectively, and suggested a greater reactivity of the vagal control of heart rate in SMCs and of the sympathetic control of the QT interval in AMCs.

EFFECT OF BETA-BLOCKERS. Figure 3A shows that BB therapy lengthened μ_{RR} in both groups, but elongated μ_{RTe} only in SMCs (Figure 3B). Further, bradycardia induced by BBs was significantly greater in AMCs than in SMCs (Figure 3A). BB therapy significantly increased σ^2_{RR} in SMCs, whereas treatment did not affect this value in AMCs (Figure 3C). Conversely, BBs significantly decreased σ^2_{RTe} in AMCs, whereas treatment did not influence this parameter in SMCs (Figure 3D). The difference between σ^2_{RTe} in AMCs and SMCs observed in BBoff disappeared in BBon (Figure 3D). HFa_{RR} (Figure 3E) and LFa_{RTe} (Figure 3F) confirmed the differences observed in Figures 3C and 3D, respectively, and corroborated that, in

response to BBs, there was a larger reactivity of the vagal control of heart rate in SMCs and of the sympathetic control of QT interval in AMCs, as observed with the circadian changes.

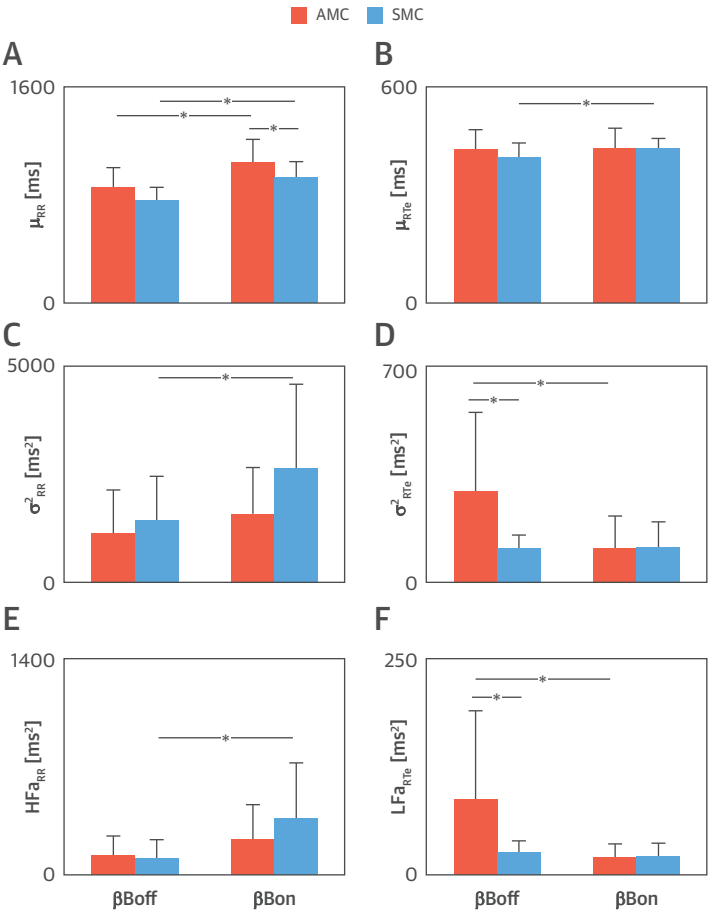
DISCUSSION

The present study significantly extends our previous work, which identified differences in autonomic responses, especially in vagal reflexes, between patients with LQT1 with and without cardiac events (11,12). The main novel finding here is the previously unsuspected fact that AMCs have a greater degree of sympathetic modulation directed to the ventricles than SMCs, and this is especially evident in daytime, when the arrhythmic risk for patients with LQT1 is higher (14). Contrary to common wisdom, this finding—which is directly associated with a higher variability of the QT interval—suggests that a greater sympathetic drive to the ventricles is a protective factor in LQT1. These new observations make an important contribution to our understanding of the physiological mechanisms underlying the otherwise puzzling phenomenon of patients carrying the same disease-causing mutation but with much lower arrhythmic risk (**Central Illustration**).

Additionally, we observed greater reactivity of the sympathetic control of the QT interval and lesser reactivity of the vagal regulation of heart rate in AMCs compared with SMCs. Indeed, markers of sympathetic modulation derived from QT interval variability in AMCs decreased during nighttime or on BB therapy, whereas they were unmodified in SMCs. Conversely, indexes of vagal modulation derived from RR variability in SMCs increased during nighttime or on BB therapy while remaining unchanged in AMCs. The present results are relevant to a better understanding of LQT1, offering a clue to a more sophisticated approach to risk stratification, and help dissect the mechanisms underlying the efficacy of therapeutic interventions.

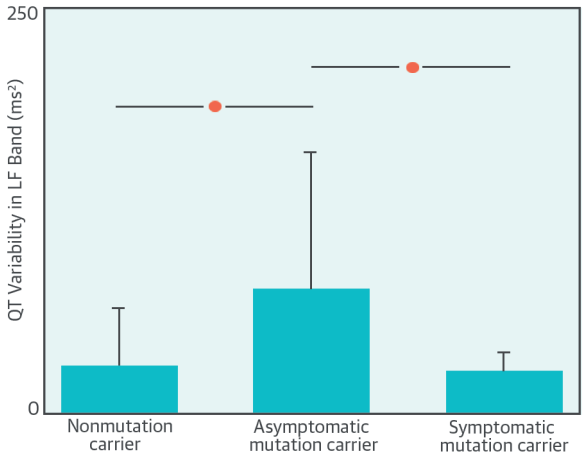
AUTONOMIC CONTROL OF HEART RATE. AMCs tended to have lower baseline heart rates, as reported previously (25), but the difference was significant only compared with NMCs. During daytime, time and frequency domain indexes derived from heart rate variability did not distinguish SMCs from AMCs. Circadian changes in heart rate were present in both the AMCs and SMCs, but nighttime RR variability was significantly greater only in the SMCs. In addition, the RR interval variability was greater in the SMCs than in the AMCs in response to BBs. Overall, the data pointed to greater vagally mediated RR control in SMCs, thus increasing the likelihood of abrupt changes in the RR interval that would produce a proarrhythmic effect in patients with LQT1. These data fit with and extend our previous observations (11,12). The extension is mainly the consequence of the evaluation of frequency domain heart rate variability parameters computed from 24-h Holter recordings in individuals both BBon and BBoff. We observed larger increases in heart rate variability power in the HF band, a widely recognized index of vagal modulation directed to the sinus node (15,18-20), during nighttime and under BB therapy in SMCs compared with AMCs. This supports the conclusion that SMCs show greater reactivity in the vagal control of heart rate compared with AMCs and that a sluggish vagal responsiveness to challenges is a protective factor in LQT1.

FIGURE 3 BBoff and BBon in AMCs and SMCs During Daytime



Grouped bar graphs report μ_{RR} **(A)**, μ_{RTe} **(B)**, σ^2_{RR} **(C)**, σ^2_{RTe} **(D)**, HFa_{RR} **(E)**, and LFa_{RTe} **(F)** assessed BBoff and on beta-blocker therapy (BBon) in AMCs **(salmon bars)** and SMCs **(blue bars)** during the daytime. Values are mean + SD. *$p < 0.05$. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Differences in Autonomic Control in Patients With LQT1 Account for Divergent Arrhythmic Risk



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Asymptomatic patients with long QT syndrome type 1 (LQT1) have higher than normal sympathetic control of the QT interval as assessed by the power of QT variability in the low-frequency (LF) band, whereas the autonomic responses of symptomatic individuals with LQT1 and healthy controls are similar.

AUTONOMIC CONTROL OF THE QT INTERVAL. The data on the RTe interval, an accurate proxy for the QT interval, provide unexpected and novel insights regarding the autonomic control of ventricular repolarization in patients with LQT1. Indeed, the analysis of RTe variability demonstrated significant differences between AMCs and SMCs. Both the overall magnitude of RTe variability and its portion in the LF band were greater in AMCs. Because these indexes can be used as markers of sympathetic modulation directed to the ventricles (16,17,21–24), our finding supports the conclusion that AMCs have a greater degree of sympathetic control. It is most intriguing that this greater sympathetic control of ventricular repolarization differentiates the AMCs not only from the SMCs but also from the NMCs. This observation indicates that the group with abnormal autonomic responses is not, as one might have thought, the one with cardiac events but rather the asymptomatic group. We had reached an almost identical conclusion when examining baroreflex sensitivity, a very different but equally important autonomic parameter (11).

A greater degree of sympathetic control of ventricular repolarization implies a greater ability to adapt QT duration to rapid changes of the RR interval. This factor proves key to survival when heart rate increases rapidly and the QT interval must shorten appropriately to avoid the R-on-T phenomenon because when depolarization encroaches the vulnerable period of the T-wave, ventricular fibrillation likely occurs. This general concept is especially important for survival in patients with LQT1, given their impairment of the I_{Ks} current that is essential for the control of repolarization during heart rate increases.

This finding and the related analysis permit the following interpretation of what underlies the individual and hitherto mysterious propensity to be or not be a symptomatic patient with LQT1. We already demonstrated that the *KCNQ1* A341V mutation is a highly malignant one, with 80% of the MCs suffering major cardiac events (26). If a carrier of this mutation has a "normal" autonomic control, he/she will very likely develop life-threatening arrhythmias. The possibility of reducing this risk depends on either "external" protection, such as that afforded by the effective antiadrenergic therapies available (3), or "internal" protection, such as a spontaneous or genetically mediated autonomic modulation characterized by reduced vagal control of heart rate (11,12) associated with enhanced sympathetic control of ventricular repolarization, as we demonstrated here. This is why the AMCs are different, in terms of autonomic control, not only from the SMCs but also from the NMCs.

The effect of BB therapy, assessed by internal control analysis, also provided interesting data. As expected, the RR interval increased significantly in both groups, but once again, the more interesting finding came from the analysis of RTe variability. The magnitude of the RTe changes was significantly reduced in the AMCs, whereas it was unmodified in the SMCs, largely because it was already very low.

TABLE 1 Distinguishing Features of LQT1 AMCs

Reference	Distinguishing Features
Previous studies	Lower heart rate than SMCs (11)
	Smaller post-exercise heart rate reduction than SMCs (12)
	Lower baroreflex sensitivity than SMCs (11)
Present study	Lower heart rate than SMCs
	Lower increase in heart rate variability during nighttime than SMCs
	Lower increase in heart rate variability in response to BBs than SMCs
	Greater QT variability than both SMCs and NMCs
	Greater decrease in QT variability during nighttime than SMCs
	Greater decrease in QT variability in response to BBs than SMCs

AMCs = asymptomatic mutation carriers; BB = beta-blocker; LQT1 = long QT syndrome type 1; SMCs = symptomatic mutation carriers.

The reduction of RTe variability in the AMCs could raise concerns at first glance, but this is just one more case in medicine of an apparently negative side effect of therapy overshadowed by a more powerful protective effect; a classic example of this is the coronary vasoconstrictor effect of BBs being overcome by the reduction in oxygen consumption secondary to the heart rate reduction. For these AMCs, the loss in RTe variability is more than compensated by the RR increase and, above all, by the prevention of the arrhythmogenic effects of norepinephrine release. Analogously, the RR lengthening can compensate for the decrease of the RTe variability observed at nighttime in AMCs in the absence of BB therapy.

Furthermore, the observed decrease of RTe variability during the nighttime and in response to BB therapy in AMCs suggests a more important reactivity of the sympathetic control to challenges in AMCs compared with SMCs that again can be taken as an indication of the more flexible regulation of the QT interval in AMCs than in SMCs.

Finally, an important question for the understanding of the concepts underlying these observations and for their clinical translation: Is the propensity for different autonomic responses an independent, genetically controlled variable in respect to the presence/absence of the disease-causing mutation? For this to be true, it would be necessary that both patterns of autonomic responsiveness be present in both MCs and NMCs. This has indeed already been demonstrated by the fact that although baroreflex sensitivity differs significantly between SMCs and AMCs, the distribution of baroreflex responses is the same between MCs and NMCs (11). This proves that the coexistence between disease-causing mutations with autonomic responses that are divergent and carrying opposite influences on outcome is due to chance.

CLINICAL IMPLICATIONS. Even though good clinical management requires that all carriers of an LQTS-causing mutation who have a prolonged QT interval be treated with BBs (3), the ability to stratify patients based on arrhythmic risk would allow a more targeted therapeutic strategy. When the findings from the present study are integrated with those from our 2 previous analyses of autonomic parameters (11,12), a single coherent picture emerges.

Patients with LQT1 can, rather confidently, be stratified at low arrhythmic risk if they have a relatively low heart rate at rest, a relatively low baroreflex sensitivity, a sluggish heart rate reduction at the end of an exercise stress test, and, as shown here, active sympathetic control of ventricular repolarization and reduced vagal control of heart rate (Table 1). The converse is true for those with the opposite pattern, who can justifiably be regarded as at high risk.

STUDY LIMITATIONS. The conclusions of the study are based on indirect noninvasive indexes of vagal and sympathetic modulations. Future studies should test them against direct measures of the autonomic function.

CONCLUSIONS

We have learned a lot about the differential arrhythmic risk related to the characteristics of the specific mutations and their interaction with more common genetic variants. In this study, the data identified an additional factor contributing to the differential arrhythmic risk among patients with LQT1 carrying the same mutation. The combination of the individual genetic make-up (with the knowledge of the electrophysiological actions of the LQTS-causing mutations through their impact on ionic currents) and clinically quantifiable parameters describing autonomic function (as derived from routine 24-h Holter recordings) will significantly refine our clinical decision making for the benefit of our patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Members of families with long QT syndrome type 1 with the same mutation have disparate symptoms and clinical outcomes. Asymptomatic patients often have greater than normal sympathetically mediated variations in QT interval but less reactive vagal control of heart rate, whereas the autonomic responses of individuals at high risk are similar to those of normal controls.

TRANSLATIONAL OUTLOOK: Variations in autonomic control characteristics may help explain why patients with the same mutation may face divergent arrhythmic risk, but further studies are needed to translate these observations into targeted strategies for clinical management.

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