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Vagal Reflexes Following an Exercise Stress Test: a Simple Clinical Tool for Gene-Specific Risk Stratification in the Long QT Syndrome

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Abstract

Objectives—To assess whether heart rate (HR) reduction following an exercise stress test (ExStrT), an easily quantifiable marker of vagal reflexes, might identify high and low risk long QT syndrome (LQTS) type 1 (LQT1) patients.

Background—Identification of LQTS patients more likely to be symptomatic remains elusive. We have previously shown that depressed baroreflex sensitivity (BRS), an established marker of reduced vagal reflexes, predicts low probability of symptoms among LQT1.

Methods—We studied 169 LQTS genotype-positive patients below age 50 who performed an ExStrT with the same protocol, on and off β-blockers including 47 South African LQT1 patients all harboring the KCNQ1-A341V mutation and 122 Italian LQTS patients with impaired (I_{Ks}−, LQT1, n=66) or normal (I_{Ks}+, 50 LQT2 and 6 LQT3) I_{Ks} current.

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Results—Despite similar maximal HR and workload, by the first minute after cessation of exercise the symptomatic patients in both $I_{Ks}-$ groups had a greater HR reduction compared to the asymptomatic (19±7 vs 13±5 and 27±10 vs 20±8 bpm, both p=0.009). By contrast, there was no difference between the $I_{Ks}+$ symptomatic and asymptomatic patients (23±9 vs 26±9 bpm, p=0.47). LQT1 patients in the upper tertile for HR reduction had a higher risk of being symptomatic (OR 3.28, 95% CI 1.3–8.3, p=0.012).

Conclusions—HR reduction following exercise identifies LQT1 patients at high or low arrhythmic risk, independently of β-blocker therapy, and contributes to risk stratification. Exercise training, which potentiates vagal reflexes, should be avoided by LQT1 patients.

Keywords

autonomic nervous system; exercise testing; genetics; long QT syndrome; sudden death

INTRODUCTION

During the last 40 years significant progress has been made in the understanding and management of the long QT syndrome (LQTS), the best known among arrhythmogenic channelopathies[1–3]. Its prevalence has been defined[4], effective therapies are available[2,3], a growing number of disease-causing genes has been identified[3], and complex genotypephenotype correlations are being elucidated[5,6]. However, it remains challenging to assess the probability of an asymptomatic patient to suffer cardiac events, such as syncope or cardiac arrest.

Recently, some common genetic variants have been associated with increased risk for life-threatening arrhythmias[7–9]; however, their role in clinical practice is uncertain. Similarly, markers of electrical instability such as the presence of T wave alternans[10] or notches on the T wave[11] or specific echocardiographic abnormalities[12–14] are often confined to patients with a QTc > 500 ms, an established risk factor[15].

Given the differential arrhythmic risk associated with different mutations, based on their intragenic location and on their specific functional effect on ionic currents[16], large populations are usually needed to draw meaningful conclusions for risk stratification but the confounding effect of individual mutations is difficult to assess. Founder populations[17], characterized by the presence of the same mutation in a relatively large number of individuals, offer the unique opportunity to identify factors, other than the primary mutation, able to influence phenotypic differences.

The availability of a well characterized South African (SA) LQT1 founder population segregating the malignant KCNQ1-A341V mutation[18,19], allowed us to demonstrate that the autonomic nervous system could act as an arrhythmia risk modifier in LQTS[20]. Specifically, we have shown that patients with relatively lower values of baroreflex sensitivity (BRS), measured by the phenylephrine method, were also at lower risk for life-threatening arrhythmias[20]. This suggests that when heart rate (HR) changes occur too rapidly, due to strong autonomic reflexes, there is a higher probability of being symptomatic. Unfortunately, the phenylephrine method to assess BRS is cumbersome[21] and this has prevented its widespread use for risk stratification in clinical practice.

We thought that a simpler parameter providing information similar to that of BRS might be equally useful in the risk stratification for LQT1 patients. The extent of the HR reduction at the end of an exercise stress test (ExStrT) is an easily quantifiable marker of reflex vagal activation[22–25] and here we have tested our hypothesis that it might perform as well as BRS

in the identification of those LQT1 patients more likely to be at risk for life-threatening arrhythmias.

METHODS

Study Population

The present study involved 169 LQTS genotype-positive patients from two distinct populations. One served as a discovery cohort and included 47 patients belonging to a large SA kindred harboring an identical LQT1-causing mutation in *KCNQ1* (A341V)[18–20]. The second (n=122) originated from our data base in Pavia, served as validation cohort, and included 66 LQT1, 50 LQT2 and 6 LQT3 patients. These latter patients (referred to as non-SA) were selected on the basis of having an available ExStrT performed in the same standardized conditions as those of the SA population to allow a proper comparison; accordingly, they had to be below age 50 and to have performed the ExStrT off β-blocker therapy. To avoid any selection bias, not a single subject with these characteristics was excluded. Our primary analysis focused on patients exercised off β-blocker therapy. Because of the clinical relevance of β-blocker therapy, most patients were studied also on therapy.

Clinical and genetic data were recorded on specifically designed forms including demographic information, personal and family history of disease, symptoms and therapy. Cardiac events were syncope or aborted cardiac arrest. Mutation carriers (MCs) were classified as either symptomatic or asymptomatic. Symptomatic MCs had experienced at least one cardiac event irrespective of therapy, whereas asymptomatic MCs had to be at least 15- years-old and without previous cardiac events in the absence of therapy.

From the SA population we included 44 MCs (34 with symptoms and 10 without) who had an available ExStrT test off β-blocker therapy and who were below 50 years; 3 patients were tested only on β-blocker therapy. The reason for excluding MCs above age 50, which corresponds to the 75th percentile of the age distribution, is due to the negative correlation existing between age and: 1) the maximal HR reached during ExStrT at the same workload, 2) vagal reflexes, and 3) BRS[21]. In this way we did control for age as a potentially confounding factor.

All subjects in the study were genetically confirmed LQTS patients; those with multiple independent, mutations[26,27] were excluded. All probands and family members provided written informed consent for clinical and genetic evaluations, as approved by the Ethical Review Boards of the Stellenbosch, Vanderbilt and Pavia University.

Basal ECG Evaluation

A baseline ECG in the absence of β-blocker therapy was recorded for 160 (44 SA and 116 non-SA) patients. Baseline HR, duration of the QT and RR intervals were measured in leads II and V3 from resting 12-lead ECGs and the mean between the two values was considered. The QT interval was corrected for HR by the Bazett's formula.

ExStrT Evaluation

A multistage fatigue-limited ExStrT was performed on a bicycle ergometer in the upright position. The initial workload was 25 watt, with subsequent stepwise increments of 25 watt every 2 minutes at a pedaling rate of 60 rpm; peak workload was followed by at least a 5-minute cool-down period. Standard 12-lead ECG and blood pressure were recorded in pre-test condition (when there is already sympathetic activation), every minute during exercise, at peak exercise, and every minute during recovery. During the ExStrT, HR increases were measured at 1 ($HR_{1'ExStrT}$) and 2 ($HR_{2'ExStrT}$) minutes after the beginning and at the peak

exercise (HR_{MAX}). HR decreases during the recovery ("Rec") phase were calculated as the difference (Δ) in HR between the values recorded at the peak exercise (HR_{MAX}) and those recorded 1 ($HR_{1'rec}$) and 2 ($HR_{2'rec}$) minutes after termination of exercise.

BRS Measurements

As previously reported[20], BRS was determined by the phenylephrine method, relating a transient increase in blood pressure (20–30 mmHg) induced by bolus injections of phenylephrine (2–3 μg/kg) to the resultant lengthening of the RR interval[21]. The slope of a best-fit regression line defined BRS. Beat-to-beat RR interval and blood pressure were continuously recorded (FINAPRES, Ohmeda) and then digitally converted. Given the significant negative correlation between BRS and age, we focused our analysis on the second and third age quartiles (age 26 to 47 years)[20] in order to reliably assess BRS while controlling for the effect of age. BRS was determined only in the SA population because of the difficulty in obtaining phenylephrine in Italy at the time of the study.

Statistical analysis

Continuous variables are presented as mean ± SD and compared by Student's t test or one-way ANOVA for independent samples, with Bonferroni correction for multiple comparisons. Changes in ExStrT parameters mean values measured on β-blockers compared to wash out were evaluated by paired t test. Categorical variables were expressed as absolute and relative frequencies and compared by the Fisher's exact test. To determine the association of ΔHR_{max}-1' recovery with the occurrence of cardiac events in the population under study, this variable was dichotomized at the upper tertile of its distribution, and unadjusted ORs with 95%CI were estimated by logistic regression. The relationship of BRS with the reduced HR during the first minute of recovery after termination of exercise (ΔHR_{max}-1' recovery) was analyzed by non-parametric Spearman correlations. Receiver-operating characteristics (ROC) curves were constructed and the area under the curves (AUC) were used to determine the performance of both BRS and $\Delta HR_{max} - HR_{1'rec}$ tests in discriminating between MCs with and without cardiac events. A 2-sided p-value <0.05 was considered statistically significant. All analyses were performed with SPSS software (version 19).

RESULTS

Study Populations

Table 1 shows the study populations with their demographic and baseline ECG characteristics. Table 2 presents the individual mutations identified in the non-SA population, whereas all patients in the founder SA population share the same mutation (KCNQ1-A341V). In the non-SA population not a single mutation is over represented and carries therefore undue weight.

The SA and non-SA populations were comparable for gender and age at ExStrT, whereas significant differences were present in baseline QTc interval prolongation, with an expected longer QTc observed in the SA A341V group consistent with the established severity of this mutation[18,19].

We did assess the effect of β-blocker therapy on the ExStrT measurements because very often when LQTS patients are referred for consultation and risk stratification they are already on therapy. Accordingly, we did this by analyzing 104 LQTS patients (43 SA, 30 LQT1, 29 LQT2 and 2 LQT3) with an ExStrT performed on β-blockers. Fig. 1 illustrates how different numbers of patients, belonging to the various groups, were tested on and offβ-blockers.

For all the analyses involving the non SA-LQTS subgroup, as the 6 LQT3 patients had mean values and patterns very similar to those of the 50 LQT2 patients and as both these groups have a well preserved I_{Ks} current, we considered them together. Thus, we compared two groups identified as I_{Ks}+ (i.e. preserved I_{Ks}), which included the LQT2 and LQT3 patients, and as I_{Ks}− (i.e. impaired I_{Ks}) which included all the LQT1 patients, SA and non-SA.

HR during the ExStrT and arrhythmic risk

Table 3 compares the symptomatic and asymptomatic subjects for the relevant parameters measured at pre-specified times during ExStrT off β-blockers in 130 MCs aged <50 years. We present first the results off- and then the results on β-blocker therapy.

Off β-blockers- SA population—In the A341V SA population, HR_{max} (124±15 vs 128±18 bpm, p =0.55) and the maximum workload reached during ExStrT (129±42 vs 117±26 watt, p =0.41) were similar between symptomatic and asymptomatic MCs. However, a significant difference was observed in the HR decrease during the first minute of recovery from peak of exercise ($\Delta HR_{max}–HR_{1'rec}$). Between these two time points of the ExStrT, the symptomatic MCs reduced their HR significantly more than the asymptomatic MCs (19±7 vs 13±5 bpm, p=0.009). Furthermore, when dichotomized at 21 bpm, representing the upper tertile of its distribution, $\Delta HR_{max}–HR_{1'rec}$ carried a differential arrhythmic risk among the MCs (Fig. 2). Indeed, all patients with a reduction in HR > 21 bpm had previously suffered from cardiac events. Conversely, all 10 asymptomatic SA MCs had $\Delta HR_{max}–HR_{1'rec}$ values below this threshold (p=0.02).

To assess the potential importance and mechanistic significance of the rapidity of the HR reduction, the analyses were repeated focusing on the decrease in HR from peak exercise to the 2nd minute of recovery. There were no significant differences between symptomatic and asymptomatic MCs in $\Delta HR_{max}–HR_{2'rec}$ (33±11 vs 30±13 bpm, p=0.50). This suggests that the difference between symptomatic and asymptomatic depends on the rapidity of HR decrease, which is the direct consequence of the vagal activation occurring at the cessation of exercise[25].

Off β-blockers - Non-SA LQTS population—The same analyses were performed in 86 mutation-confirmed LQTS patients, aged < 50 years and off-β-blockers therapy (Table 3). While the $\Delta HR_{max} – HR_{1'rec}$ was not significantly different (23±9 vs 26±9 bpm, p=0.47) between symptomatic and asymptomatic LQT2/LQT3 patients (the I_{Ks}+ group), among the LQT1 patients (the I_{Ks}− group), this parameter showed the same pattern observed in the SA MCs. Indeed, the LQT1 patients with cardiac events had a significantly greater decrease in HR during the first minute of recovery from peak exercise than the asymptomatic MCs (27±10 vs 20±8 bpm, p=0.009), once again without significant differences in HR_{max} (141±18 vs 148±18 bpm, p=0.27) and in the maximum workload reached during the ExStrT (141±41 vs 147±49 watt, p=0.70). The validation in this independent cohort of 51 LQT1 non-A341V MCs of the finding observed in the SA A341V MCs clearly strengthens the clinical relevance of the $\Delta HR_{max}–HR_{1'rec}$ parameter in differentiating between symptomatic and asymptomatic LQT1 patients independently of their specific disease-causing mutation.

When the decrement in HR during the first minute of recovery was calculated as percent reduction from HR at peak exercise $\{[(\Delta HR_{max}–HR_{1'rec})/HR_{max}]*100\}$, it was found to be similar (14±6%, 15±7%, and 16±6%, p=0.43) (Fig. 3A) in the SA, I_{Ks}− and I_{Ks}+ groups, respectively. However, when this decrease was related to the clinical status the differences, i.e. larger values among symptomatic than asymptomatic MCs, were fully confirmed in both discovery and validation cohorts of LQT1 patients (20±8 vs 13±5 %, p=0.002) but not at all among the patients with preserved I_{Ks} current (LQT2/3, 16±6 vs 16±6%)(Fig. 3B).

Based on the very similar behavior of the SA and non-SA LQT1 patients, they were merged in one group (I_{Ks}−) to facilitate comparisons. Given the differences in absolute HR levels between the SA and the non-SA populations, we focused on the percent change in HR. A cutoff value of 17%, corresponding to the upper tertile of the % $\Delta HR_{max}–HR_{1'rec}$ distribution, usefully differentiated between symptomatic and asymptomatic MCs of both genetic subgroups. Indeed, SA and non-SA I_{Ks}− MCs (LQT1) with a HR reduction during the 1' rec >17% of the HR_{max} had a significantly higher probability of having suffered cardiac events compared to those with a lower percent decrement (OR 3.28, 95% CI 1.3–8.3, p=0.012, Fig. 4). At the opposite end, HR reduction below the first tertile (11.5%) identified a significantly higher proportion (72%) of SA and non-SA LQT1 patients very likely to remain asymptomatic. The probability of having experienced cardiac events for MCs with a % $\Delta HR_{max}–HR_{1'rec}$ below 11.5% vs all those with a greater decrement corresponded to an OR of 0.24 (95% CI 0.09–0.61, p=0.003).

On β-blockers - SA population—Forty-three SA MCs (31 symptomatic and 12 asymptomatic) had an available ExStrT on β-blocker therapy. As expected, HR both at peak exercise and during the 1st minute of recovery was lower compared to that measured off βB (HR_{max}, from 125±16 to 110±16 bpm; $HR_{1'rec}$ from 108±17 to 88±16 bpm, p<0.001 for both tests). Nonetheless, the HR decrease during the first minute of recovery from peak exercise among SA patients on therapy preserved the meaningful pattern just reported in the off therapy condition and was significantly greater in symptomatic than in asymptomatic MCs (24±8 vs 17±5 bpm, respectively, p= 0.01).

On β-blockers- Non-SA LQTS population—As for the SA population, in 30 LQT1 patients (17 symptomatic and 13 asymptomatic) with an ExStrT on β-blocker therapy, the HR decrease during the first minute 11 of recovery from peak exercise was greater in symptomatic than in asymptomatic MCs (23±9 vs 16±6 bpm, respectively, p=0.03). By contrast, in the I_{Ks}+ subset (29 LQT2, 2 LQT3), the $\Delta HR_{max}–HR_{1'rec}$ on β-blocker therapy showed a totally different pattern, being greater in asymptomatic than in symptomatic subjects (24±7 bpm vs 19±6 bpm, p=0.03), thus confirming that the presence of a normal I_{Ks} prevents the phenomenon that we have observed for LQT1 patients.

Correlation between BRS and HR decrease during the first minute of recovery —We have previously shown that symptomatic LQT1 patients with the KCNQ1-A341V mutation have higher BRS values[20]. Here, we have demonstrated that they also have a greater HR reduction in the first minute of a recovery from exercise compared to the asymptomatic MCs. As both phenomena are due to increased vagal reflexes it seemed likely that they were correlated and that one could predict the other. To test this reasonable hypothesis we evaluated the correlation between BRS and HR decrease during the first minute of recovery from exercise.

This analysis was limited to SA MCs with BRS measurements available off BB therapy and we focused on the same MCs reported in the previous study[20] because of the need of controlling for the effect of age on BRS[21]. Accordingly, we plotted the BRS values of the 22 MCs aged 26–47 years against the $\Delta HR_{max}–HR_{1'rec}$ during the ExStrT and observed a strong positive correlation (r=0.64, p=0.001). A similar correlation was found also between BRS values and the percent HR reduction (r 0.69, p<0.001).

When the discriminatory power, i.e. the ability of a test to discriminate between patients with and without cardiac events, of both BRS and $\Delta HR_{max}–HR_{1'rec}$ were evaluated by the use of ROC curves, the Area Under the Curve (AUC) of both tests were very similar (0.77; 95% CI 0.57–0.97 vs.0.80; 95% CI 0.61–0.99). This analysis also showed that both

parameters performed moderately well (AUC >0.70) for the identification of those MCs at risk of life-threatening arrhythmias, thus implying that one could substitute for the other.

DISCUSSION

The present study provides the novel evidence that vagal reflexes, assessed by the extent of HR reduction in the first minute after cessation of an ExStrT, can contribute to identify patients at high or low risk for life-threatening arrhythmias. It also demonstrates that this relationship is gene-specific because it is valid only for LQT1 but not for LQT2 and LQT3 patients. Furthermore, and clinically relevant, the risk stratification value of HR reduction and its correlation with cardiac events is not affected by β-blocker therapy.

The underlying mechanism that explains why this is a gene-specific phenomenon is the presence or absence of a fully preserved I_{Ks} current, respectively characteristic of LQT2/LQT3 and of LQT1 patients. The possibility of using the HR changes produced by a tool as simple, inexpensive and easily available such as an ExStrT carries significant clinical implications, especially for risk stratification but also in the direction of previously unsuspected recommendation for gene-specific life-style management. It also helps to clarify the apparently complex relationship between the autonomic nervous system, mutations affecting or not affecting the I_{Ks} current, and propensity to potentially lethal arrhythmias.

Role of the ExStrT in LQTS

There has always been interest for the ExStrT in LQTS but, with few exceptions, most of the results in terms of risk stratification have been frustrating. Initially, it was performed to elicit arrhythmias as in real life with the idea of being then able to test different interventions to assess their therapeutic value, as it is routinely done for catecholaminergic polymorphic ventricular tachycardia (CPVT)[28]. However, at variance with CPVT, LQTS patients almost never develop arrhythmias during an ExStrT. Our interpretation has always been that probably LQTS patients with arrhythmias during exercise, and this feature is almost exclusively limited to LQT1 patients[6], do so because of a combination of physical exercise with some degree of “mental activation” or psychological stress as it occurs while running with fear or in a competitive setting. By contrast, an ExStrT performed in the reassuring hospital setting, does not elicit this compounded adrenergic activation.

The focus then shifted to ECG changes during or at cessation of an ExStrT. We called attention to the diagnostic value of certain striking repolarization changes occurring within the first few minutes after cessation of exercise[11], such as the appearance of notched or biphasic T waves, and we still use these changes to increase our clinical suspicion of LQTS. However, most of the investigators focused on QT interval changes at the end of an ExStrT, as we have recently reviewed[29]. The differences in the degree of QT prolongation after cessation of exercise seem to help differentiating between LQT1 and LQT2/3[30] but a relationship with a differential susceptibility to cardiac events has not been demonstrated. Recently, the interesting concept has been proposed that sudden standing from the supine position may produce differential QT changes between LQTS patients and unaffected individuals[31]. Even though actual exercise is not involved, this maneuver calls into question brisk autonomic changes as it happens with an ExStrT.

The role of the autonomic nervous system

Among cardiologists there is a rather widespread tendency to overlook the fact that the autonomic nervous system has two components, sympathetic and vagal, and to think primarily in terms of the sympathetic nervous system. The knowledge that sympathetic

activation often plays a critical role in initiating life-threatening arrhythmias in LQTS goes back to the initial reports of 50 years ago and is nothing new. What was new was the realization that sympathetic activation has different effects according to genes involved[5,6]. This important and apparently puzzling phenomenon is largely, but not entirely, explained by the critical role of I_{Ks} in shortening the QT interval during HR increases as a direct result of sympathetic activation[32,33]. Patients with mutations affecting I_{Ks}, i.e. the LQT1 patients (I_{Ks}−, in this manuscript), being unable to appropriately shorten their QT interval when HR increases, are at high arrhythmic risk whenever sympathetic activity increases. Conversely, for the specific condition of exercise which involves progressive increase in sympathetic activity, this is not the case for the LQT2 and LQT3 patients who have a well preserved I_{Ks} (I_{Ks}+, in this manuscript). What had almost completely escaped attention was the potential impact of vagal activation in LQTS patients, not to mention a gene-specific effect. The only suggestion in this regard came by our own 2008 study[20] in which we proposed that lowerthan- normal vagal reflexes might have been protective for LQT1 patients, at variance of what happens among post-myocardial infarction patients[34]. The present study demonstrates the previously unforeseen value for risk stratification of vagal reflexes determined by the HR changes occurring in the first minute following cessation of exercise. This prognostic information is gene-specific, as it applies only to LQT1 but not to LQT2 and LQT3 patients. These results may also contribute to explain the puzzling observation that swimming is the main trigger for cardiac events in LQT1 patients[6]. Indeed, swimming in cold water implies the synergistic combination of vagal activation superimposed on a condition of adrenergic activation, and in patients with an impaired I_{Ks} powerful vagal reflexes are more likely to elicit EADs and life-threatening arrhythmias.

The propensity for higher or lower vagal reflexes is largely determined at genetic level[35], even though this remains so far a mostly uncharted territory. As this aspect of genetic control is totally independent of LQTS-related mutations one would expect similar HR decreases at cessation of exercise for the 3 genotypes under study here. Indeed, Fig. 3A shows that the percent reduction in HR is almost identical between I_{Ks}− and I_{Ks}+ patients, taken all together independently of their symptoms. Obviously, each of these groups comprises several different individuals and each of them has his/her individual HR response, which will reflect the combination of genetic and non-genetic factors such as physical training. Thus, the overall HR reductions will be similar among different LQTS groups as expected but, within patients with an impaired I_{Ks}, they may cluster differently according to the risk for cardiac arrhythmias. As a matter of fact, Fig. 3B shows very clearly that I_{Ks}− patients with cardiac events, never mind whether SA carriers of the A341V mutation or Italian LQT1 patients with all sorts of different mutations, have significantly greater HR reductions markers of enhanced vagal reflexes.

The significance of this finding is now clear. For patients with a preserved I_{Ks} function, such as LQT2 and LQT3, whatever happens in terms of HR changes at cessation of exercise does not matter in terms of their arrhythmic risk. By striking contrast, for patients with an impaired I_{Ks} function, the LQT1 patients, the association between their disease-causing mutation and the propensity toward powerful vagal reflexes may have life-threatening consequences.

Clinical Implications

The present results carry two precise and distinct sets of clinical implications. One concerns risk stratification, the other suggests novel recommendations for gene-specific management.

An ExStrT should be performed in every LQTS patient. In LQT2 and LQT3 patients attention will focus primarily on T wave and QT interval changes[11,29,30], whereas in LQT1 patients the careful clinician will also quantify the HR reduction at 1 minute after cessation

of exercise. According to the value observed, he/she will know whether the patient is at high- or low-risk for life-threatening arrhythmias and will tailor therapy accordingly, more or less aggressively.

The present data also imply the necessity of new considerations to be made when dealing with an LQT1 patient. So far, one simply had to proscribe competitive sports, using an extra word of caution for swimming[3,36]. We need to do more now, as the physiology underlying the present results cannot be ignored. As we have shown that powerful vagal reflexes are detrimental for LQT1 patients, action should follow. Genetic propensity cannot be altered but vagal reflexes are also modulated by specific behaviors. It is common knowledge that exercise training increases vagal activity and potentiates vagal reflexes. Given the evidence just presented of a strong correlation between the heart decrease at the first minute after cessation of exercise and BRS, it is highly relevant here the fact we have previously demonstrated, experimentally and clinically, that exercise training increases BRS and thereby potentiates vagal reflexes[37,38]. It follows that LQT1 patients who do not participate in competitive sports but continue to perform significant exercise on a regular basis are unconsciously increasing their vagal reflexes and making more likely the occurrence of dangerous arrhythmias. While pleasant play and occasional non-competitive sport activity should always be allowed, also because of its positive psychological counterpart, more serious and regular activity resulting in exercise training should be discouraged on the basis of the present study.

Limitations

The present data suggest, but do not prove, that the analysis of heart rate reduction immediately post-exercise can identify among asymptomatic subjects those more likely to develop cardiac symptoms in absence of therapy. This will require a rather large prospective study.

The limited sample size, direct consequence of the need to avoid the influence of age on autonomic responses, has precluded the analysis of potentially confounding variables.

Conclusion

Powerful vagal reflexes, assessed by the degree of HR reduction in the first minute after cessation of exercise, are associated with increased risk for arrhythmic cardiac events for the LQTS patients with mutations affecting the I_{Ks} current (LQT1). This phenomenon is not true for patients with a preserved I_{Ks} (LQT2 and LQT3), thus indicating its gene-specific nature. Its quantification during the performance of an ExStrT allows to refine risk stratification for LQT1 patients. Another important practical implication is that exercise training, which potentiates vagal reflexes, is contraindicated for LQT1 patients.

The association between genetically-mediated propensity for powerful vagal reflexes and the presence of mutations causing LQTS is a random event which would have probably no consequences for LQT2 and LQT3 patients whereas it could significantly increase the risk of potentially lethal arrhythmias for LQT1 patients, and represent the play of chance.

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ABBREVIATIONS

AUC	Area Under the Curve
BRS	baroreflex sensitivity
CPVT	catecholaminergic polymorphic ventricular tachycardia
ExStrT	exercise stress test
HR	heart rate
LQTS	long QT Syndrome
MCs	mutation carriers
QTc	QT interval corrected for heart rate
SA	south African

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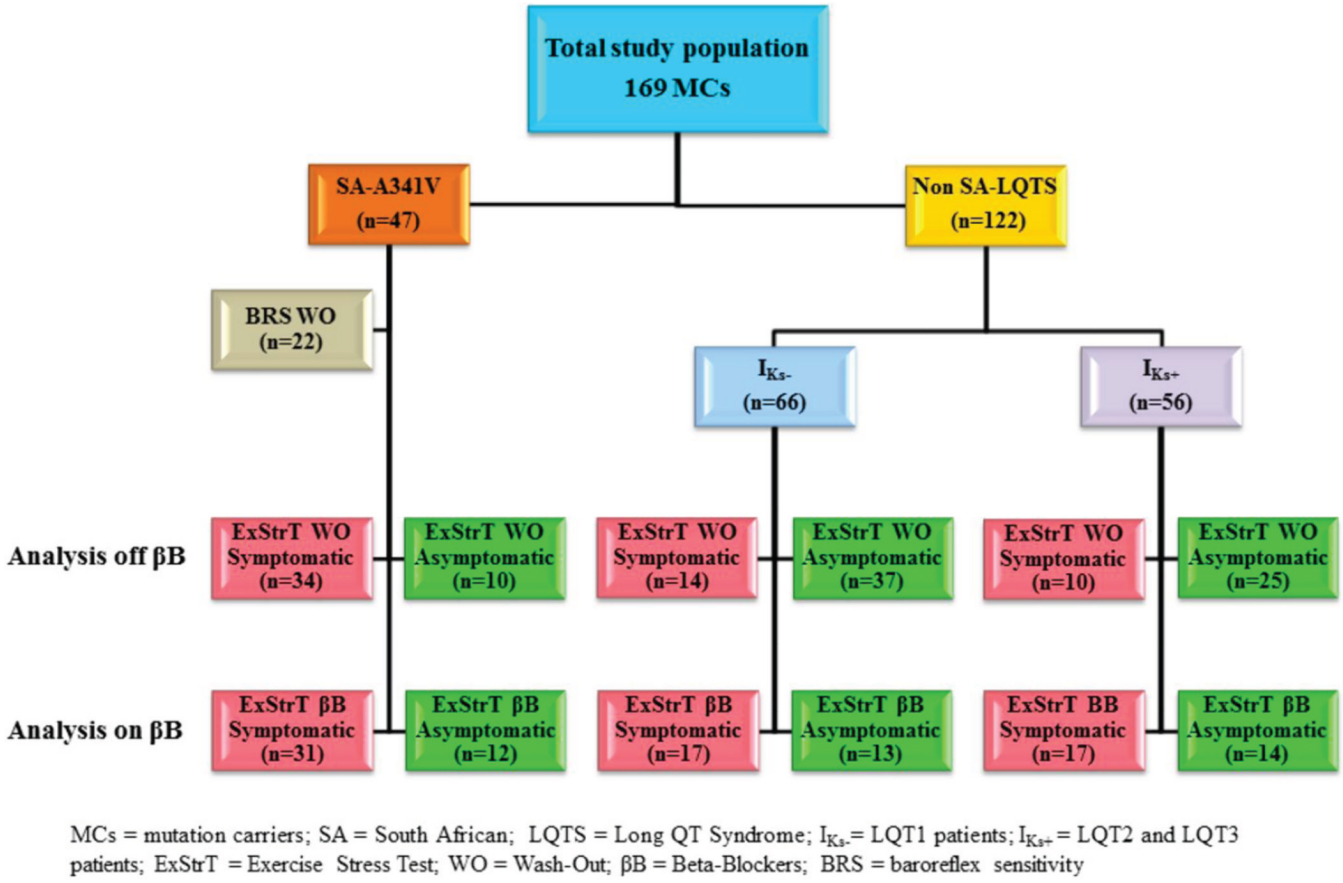

MCs = mutation carriers; SA = South African; LQTS = Long QT Syndrome; I_{Ks-} = LQT1 patients; I_{Ks+} = LQT2 and LQT3 patients; ExStrT = Exercise Stress Test; WO = Wash-Out; βB = Beta-Blockers; BRS = baroreflex sensitivity

Figure 1. Study Population

Outline of the study population.

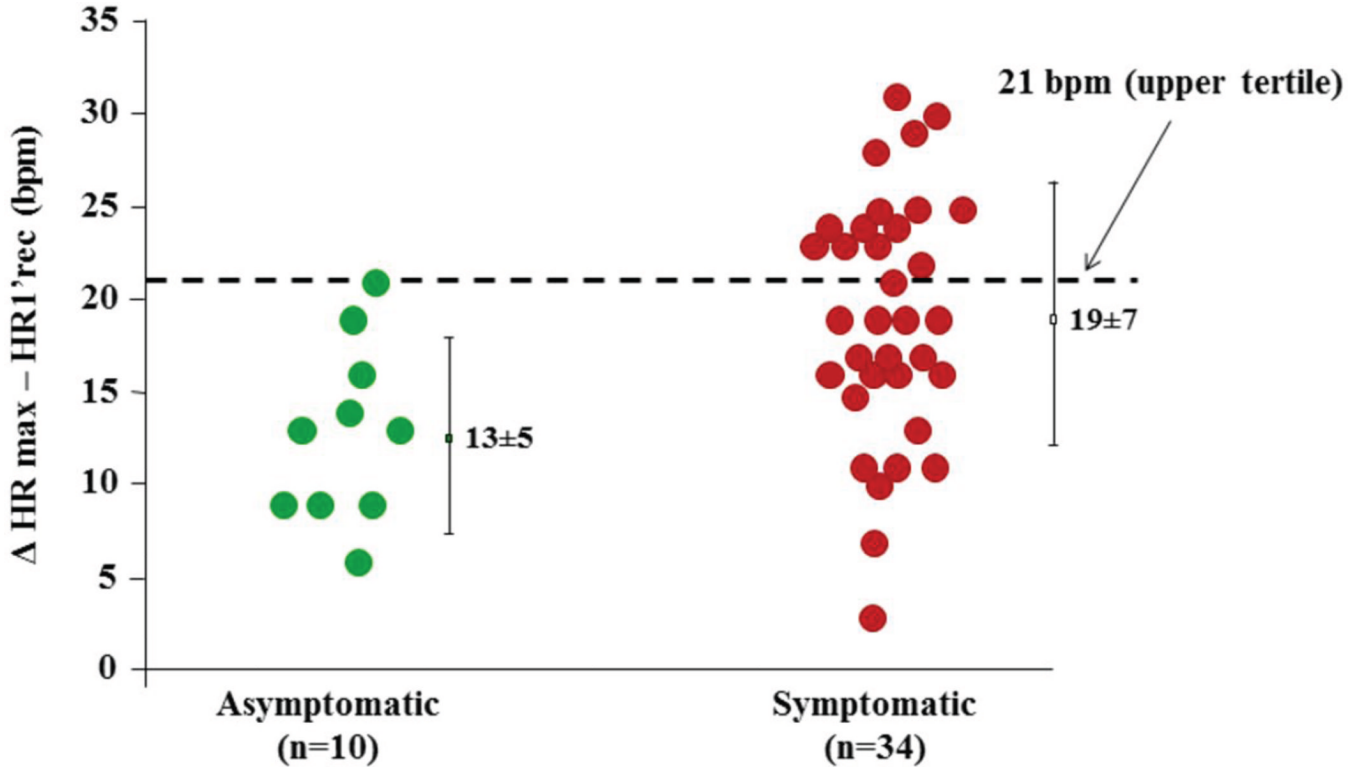

Figure 2. Post-exercise HR changes in the SA-LQT1 patients

HR reduction from peak exercise to the first minute after cessation of exercise in the 44 SA patients off beta-blockers. The horizontal line at 21 bpm represents the upper tertile for the entire SA population (n=44), and values above this cut-off are associated with an increased risk for cardiac events.

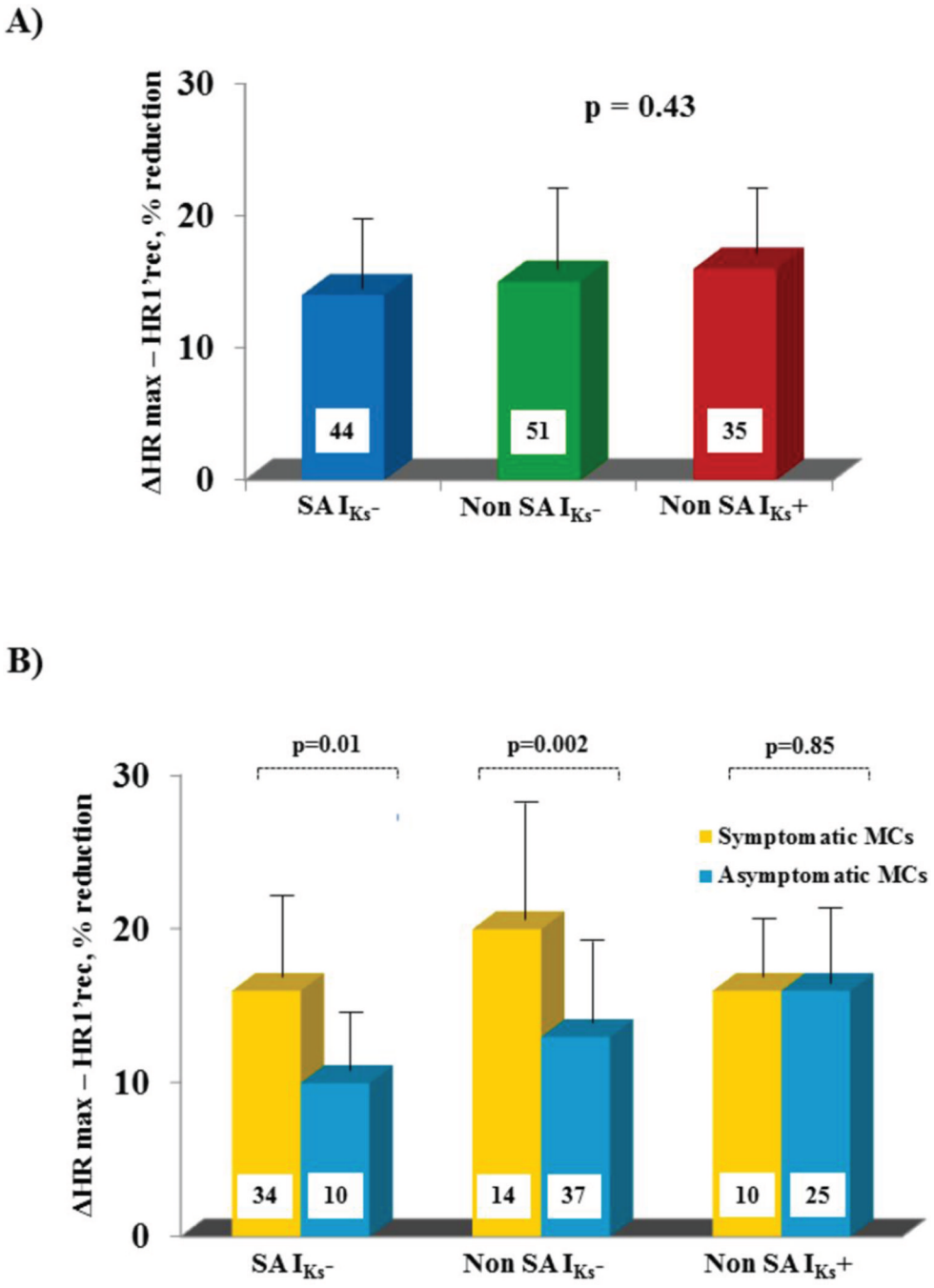

Figure 3. Post-exercise percent HR changes in the three study subgroups

HR reduction from peak exercise to the first minute after cessation of exercise. Figure 3A shows this reduction in the three groups (SA LQT1, Non-SA LQT1, and Non-SA LQT2 and LQT3) irrespective of cardiac symptoms. Figure 3B shows this reduction within the symptomatic and the asymptomatic patients. Note the lack of difference among the patients with preserved I_{Ks} current.

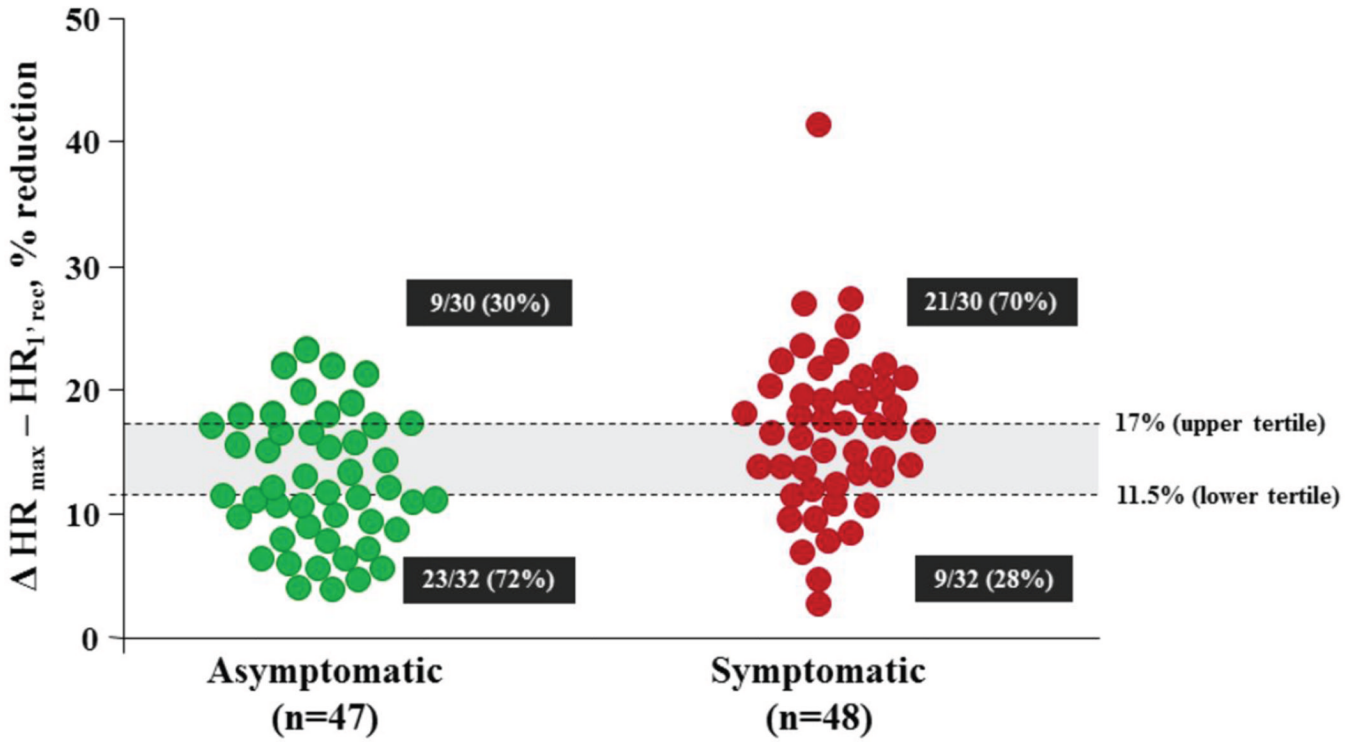

Figure 4. Post-exercise HR changes in symptomatic and asymptomatic LQTS patients

Percent reduction in HR from peak exercise to the first minute after cessation of exercise in the SA and Non-SA LQT1 patients (I_{Ks}−) according to presence or absence of symptoms. The horizontal lines at 17% and 11.5% represent the upper and the lower tertiles of the entire LQT1 population (n=95). The odds ratios for the risk of cardiac events are respectively 3.28 and 0.24.

Table 1

Baseline clinical and electrocardiographic features in the entire study population.

	LQT1 -A341V SA $I_{Ks}-$ (n=47)	**LQT1 non-SA $I_{Ks}-$ (n=66)**	**LQT2/3 $I_{Ks}+$ (n=56)**	**p-value**
Female gender, n(%)	31(66)	41(62)	32(57)	0.65
Age,yrs (mean±SD)	30±10	29±11	33±10	0.12
QTc, ms (mean±SD)	487±43 *	455±48	460±54	0.003
Basal heart rate (bpm), (mean ±SD)	69±11	69±13	66±13	0.35

* $p < 0.05$ vs both $I_{Ks}-$ and $I_{Ks}+$ groups from post-hoc Bonferroni test for multiple comparisons.

Table 2

Individual mutations identified in the non-SA population

GENE	REGION	NUCLEOTIDE CHANGE	MUTATION	MUTATIONTYPE	LOCATION	No. of Patients	No. of Families
KCNQ1	Exon 1	172G>C	A58P	Missense	N-term	2	1
KCNQ1	Exon 1	319C>T	Q107X	Nonsense	N-term	1	1
KCNQ1	Exon 1	332A>G	Y111C	Missense	N-term	2	2
KCNQ1	Exon 2	409C>T	L137F	Missense	S1	2	2
KCNQ1	Exon 3	444T>G	Y148X	Nonsense	S2	2	1
KCNQ1	Exon 3	569G>A	R190Q	Missense	S2-S3	2	1
KCNQ1	Exon 3	568C>T	R190W	Missense	S2-S3	6	5
KCNQ1	Exon 4	612C>G	I204M	Missense	S3	1	1
KCNQ1	Exon 5	691C>T	R231C	Missense	S4	6	2
KCNQ1	Exon 5	760G>C	V254L	Missense	S4-S5	1	1
KCNQ1	Exon 5	760G>A	V254M	Missense	S4–S5	1	1
KCNQ1	Exon 5	775C>T	R259C	Missense	S4–S5	2	2
KCNQ1	Intron 5	G781-2G	IVS5-2A/G	Splicing	S5-pore	4	3
KCNQ1	Intron 5	G781-1A	IVS5-1G/A	Splicing	S5-pore	2	1
KCNQ1	Exon 6	839T>A	V280E	Missense	S5	1	1
KCNQ1	Exon 6	904G>A	A302T	Missense	Pore	1	1
KCNQ1	Exon 6	914G>C	W305S	Missense	Pore	3	2
KCNQ1	Exon 7	940G>A	G314S	Missense	Pore	4	1
KCNQ1	Exon 7	943T>A	Y315N	Missense	Pore	2	1
KCNQ1	Exon 7	973 G>C	G325R	Missense	pore-S 6	1	1
KCNQ1	Exon 7	1022C>T	A341V	Missense	S6	47	1 Founder
KCNQ1	Exon 7	1032G>A	A344	Splicing	S6	1	1
KCNQ1	Exon 8	1075_1086del	359-362delQRQ K	Deletion	C-term	1	1
KCNQ1	Exon 8	1097G>A	R366Q	Missense	C-term	2	2
KCNQ1	Exon 8	1101G>T	Q367H	Missense	C-term	1	1
KCNQ1	Exon 8	1115C>A	A372D	Missense	C-term	3	2

GENE	REGION	NUCLEOTIDE CHANGE	MUTATION	MUTATIONTYPE	LOCATION	No. of Patients	No. of Families
KCNQ1	Exon 12	1541T>C	I514T	Missense	C-term	1	1
KCNQ1	Exon 13	1615G>T	R539W	Deletion	C-term	1	1
KCNQ1	Exon 14	1709C>T	P570L	Missense	C-term	1	1
KCNQ1	Exon 14	1717T>C	F573L	Missense	C-term	1	1
KCNQ1	Exon 14	1725_1728del	S575+15X	Deletion	C-term	2	1
KCNQ1	Exon 15	1772G>T	R591L	Missense	C-term	3	1
KCNQ1	Exon 15	1781G>A	R594Q	Missense	C-term	1	1
KCNQ1	Exon 16	1799C>T	T600M	Missense	C-term	1	1
KCNQ1	Exon 16	1893insC	P631+19X	Insertion	C-term	1	1
KCNH2	Exon 1	65T>A	F22Y	Missense	N-term	1	1
KCNH2	Exon 2	148G>T	E50X	Nonsense	PAS	1	1
KCNH2	Exon 2	174G>C	E58D	Missense	PAS	1	1
KCNH2	Exon 2	215C>G	P72R	Missense	N-term	1	1
KCNH2	Exon 3	442C>T	R148W	Missense	N-term	1	1
KCNH2	Exon4	526C>T	R176W	Missense	N-term	4	2
KCNH2	Exon 5	1096C>T	R366X	Nonsense	N-term	3	1
KCNH2	Exon 6	1283delC	Y427+5X	Frame shift	S1–S2	4	1
KCNH2	Exon 6	1283C>A	S428X	Nonsense	S1-S2	1	1
KCNH2	Exon 6	1468G>C	A490P	Missense	S2–S3	3	1
KCNH2	Exon 6	1490G>T	W497L	Missense	S3	1	1
KCNH2	Exon 7	1700T>C	I567T	Missense	S5	1	1
KCNH2	Exon 7	1747A>G	I583V	Missense	S5-pore	3	1
KCNH2	Exon 7	1810G>A	G604S	Missense	S5-pore	1	1
KCNH2	Exon 7	1877G>C	G626A	Missense	Pore	1	1
KCNH2	Exon 7	1898A>G	N633S	Missense	pore-S6	1	1
KCNH2	Exon 7	1912_1914del	638delK	In-frame del	pore-S6	4	1
KCNH2	Exon 8	1979C>T	S660L	Missense	C-term	1	1
KCNH2	Intron 9	2399-28G	IVS9-28A/G	Splicing	C-term	2	1

GENE	REGION	NUCLEOTIDE CHANGE	MUTATION	MUTATIONTYPE	LOCATION	No. of Patients	No. of Families
KCNH2	Exon 9	223 0C>T	R744X	Nonsense	C-term	1	1
KCNH2	Exon 10	2453C>T	S818L	Missense	C-term	1	1
KCNH2	Exon 10	2467C>T	R823W	Missense	C-term	1	1
KCNH2	Exon 10	2521G>C	V841L	Missense	C-term	1	1
KCNH2	Exon 11	2616delC	P872+4X	Frame shift	C-term	1	1
KCNH2	Exon 12	2775_2776ins G	G925+13X	Frame shift	C-term	1	1
KCNH2	Exon 12	2780G>A	W927X	Nonsense	C-term	3	2
KCNH2	Exon 12	2932G>T	E978X	Nonsense	C-term	1	1
KCNH2	Exon 13	3100delC	P1034+22X	Frame shift	C-term	1	1
KCNH2	Exon 13	3128A>G	D1043G	Nonsense	C-term	1	1
KCNH2	Exon 13	3139C>T	R1047C	Missense	C-term	1	1
KCNH2	Exon 14	3254_3255del	P1084+32X	Frame shift	C-term	1	1
KCNH2	Exon 15	3347C>T	A1116V	Missense	C-term	1	1
SCN5A	Exon 6	647C>T	S216L	Missense	DI-S3/S4	1	1
SCN5A	Exon 10	1231G>A	V411M	Missense	DI-S6	1	1
SCN5A	Exon 26	4501C>G	L1501V	Missense	DIII-DIV	2	1
SCN5A	Exon 28	5272A>G	I1758V	Missense	DIV-S6	1	1
SCN5A	Exon 28	5350G>A	E1784K	Missense	C-term	1	1

Table 3

Absolute HR and HR Changes (Δ) during ExStrT in washout in the entire study population, according to genetic and clinical status

	Symptomatic MCs (n=58)	Asymptomatic MCs (n=72)	p-value
$HR_{Pre\text{-}Test}$			
SA	78±13	77±11	0.78
$I_{Ks}-$	73±11	76±14	0.60
$I_{Ks}+$	72±15	71±12	0.96
HR_{max}			
SA	124±15	128±18	0.55
$I_{Ks}-$	141±18	148±18	0.27
$I_{Ks}+$	147±24	157±18	0.18
$HR_{1'rec}$			
SA	105±17	115±20	0.14
$I_{Ks}-$	114±21	128±18	0.023
$I_{Ks}+$	123±24	131±16	0.28
$HR_{2'rec}$			
SA	91±15	98±19	0.29
$I_{Ks}-$	100±16	110±17	0.08
$I_{Ks}+$	113±21	113±18	0.94
$\Delta\ HR_{max}–HR_{1'rec}$			
SA	19±7	13±5	0.009
$I_{Ks}-$	27±10	20±8	0.009
$I_{Ks}+$	23±9	26±9	0.47
$\Delta\ HR_{max}–HR_{2'rec}$			
SA	33±11	30±13	0.50
$I_{Ks}-$	41±9	37±10	0.23
$I_{Ks}+$	37±14	42±13	0.37
Maximum workload (watt)			
SA	129±42	117±26	0.41
$I_{Ks}-$	141±41	147±49	0.70
$I_{Ks}+$	105±26	167±56	0.002

All HR are expresses as beats per minute (bpm)