Effects of Sympathetic Stimulation on Various Repolarization Indices in the Congenital Long QT Syndrome

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Abstract Sympathetic stimulation or catecholamines modulate ventricular repolarization and provoke ventricular tachyarrhythmias in a variety of heart diseases and conditions. Among those, the congenital form of long QT syndrome (LQTS) has long been known to be a Rosetta stone for sympathetic-related ventricular tachyarrhythmias. Recent experimental studies employing arterially-perfused ventricular wedge preparations as well as some clinical studies have greatly advanced our knowledge of the cellular mechanism of the T wave and the various repolarization indices in the ECG, as well as the effect of sympathetic stimulation on these repolarization indices under normal and long QT conditions. Differences in the time course of repolarization of the three predominant cell types, the epicardial, midmyocardial (M), and endocardial cells, across the ventricular wall give rise to voltage gradients responsible for the inscription of normal T waves as well as the manifestation of abnormal T waves in the congenital LQTS. The data from the wedge experiments suggest that the repolarization time of the longest M cell action potential determines the Q-Tend interval, while that of the epicardial action potential determines the Q-Tpeak interval. Therefore, Tpeak-end interval in the ECG may provide an index of transmural dispersion of repolarization (TDR). In this review article, sympathetic stimulation with isoproterenol or epinephrine infusion is demonstrated to modulate differentially these repolarization indices in the ECG as well as the action potentials of the three cells between the LQT1, LQT2, and LQT3 syndromes both experimentally and clinically, explaining the differences in the sensitivity of genotypes of congenital LQTS to sympathetic stimulation.

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Sympathetic stimulation or catecholamines have long been known to provoke ventricular tachyarrhythmias in a variety of conditions, such as acute ischemia and heart failure as well as in several organic heart diseases, such as old myocardial infarction and cardiomyopathy.¹ In addition, the congenital form of long QT syndrome (LQTS) has been appreciated to be a Rosetta stone for sympathetic-related ventricular tachyarrhythmias for many years, and some forms of congenital LQTS are exquisitely sensitive to sympathetic stimulation.²⁻⁷

Arrhythmogenicity produced by sympathetic stimulation is in part due to facilitation of conduction as well as triggered activity (e.g., early afterdepolarization and delayed afterdepolarization) or automaticity induced by sympathetic stimulation. Another important condition enhanced by sympathetic stimulation, which may provide a substrate for ventricular tachyarrhythmias, is heterogeneity of ventricular repolarization (refractoriness). Spatial (interventricular or apico-basal) heterogeneity of ventricular repolarization may exist and play a sig-

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nificant role in the generation of ventricular arrhythmias.⁸ Moreover, numerous studies over these last 10 years have highlighted the heterogeneity of ventricular repolarization across the ventricular wall (i.e., transmural heterogeneity) in the response of the diverse cell types to pharmacological agents and pathophysiological states.⁹⁻¹¹ The three different cell types across the ventricular wall, epicardial, midmyocardial (M), and endocardial cells, differ principally with respect to their repolarization characteristics. M cells are distinguished by the ability of their action potential to prolong more than those of epicardial and endocardial cells in response to a slowing of rate and/or in response to drugs with QT-prolonging actions.^{9,12,13} The repolarization characteristics of M cells have been described in a number of species, including humans.^{9,13-15} The ionic basis for these features has been unveiled and includes the presence of a smaller slowly activating delayed rectifier potassium current (I_{Ks}),¹⁴ a larger late sodium current (I_{Na}),¹⁶ and a larger electrogenic sodium-calcium exchange current (I_{Na-Ca})¹⁷ in the M region compared with those in the epicardial or endocardial cell.

In this review article, we present our recent experimental and clinical data to demonstrate the effects of sympathetic stimulation on various repolarization indices representing the spatial and transmural heterogeneity of repolarization under experimental long QT conditions and in patients with congenital LQTS.

CELLULAR BASIS FOR INSCRIPTION OF THE T WAVE AND REPOLARIZATION INDICES

Antzelevitch et al. have developed an arterially-perfused canine ventricular wedge preparation in which the transmembrane activity from epicardial, M, and endocardial cells was simultaneously recorded together with a pseudoelectrocardiogram (ECG) along the same axis, permitting a correlation of transmembrane and ECG activity.^{10,18-29} Data from the arterially-perfused wedges demonstrate the cellular basis for the inscription of the electrocardiographic T wave and show that currents flowing down voltage gradients on either side of the M region underlie the T wave.¹⁹⁻²² The interplay between these opposing currents determines the height and width of the T wave as well as the morphology of the T wave (Fig. 1).²⁹ In the case of

Figure 1. Voltage gradients on either side of the M region contribute to the inscription of the electrocardiographic T wave. Top panel shows superimposed action potentials (AP), which are simultaneously recorded from endocardial (Endo), epicardial (Epi), and M cells of an arterially-perfused canine left ventricular wedge preparation. Middle panel shows ECG recorded across the wedge preparation. Bottom panel illustrates computed voltage differences between the Epi and the M cell action potentials (ΔV_{M-Epi}) and those between the M and the Endo cell action potential (ΔV_{Endo-M}). The T wave in the ECG begins when the plateau of the Epi cell action potential diverges from that of the M cell action potential. As the epicardium repolarizes, the voltage gradient between the Epi and the M cells continues to grow giving rise to the ascending limb of the T wave. The voltage gradient between the Epi and the M cells (ΔV_{M-Epi}) reaches a peak when the Epi cells are fully repolarized. Therefore, full repolarization of the Epi cells marks the peak of the T wave. On the other end of the ventricular wall, the plateau of the Endo cell action potential separates from that of the M cell action potential, generating an opposing voltage gradient (ΔV_{Endo-M}) that limits the amplitude of the T wave and contributes to the initial part of the descending limb of the T wave. The final part of repolarization occurs in the M region, and all the voltage gradients are extinguished when the longest M cells are fully repolarized—this marks the end of the T wave. Modified from reference 29 with permission.

a positive T wave, the action potential of epicardial cells is always the earliest to repolarize, while the repolarization of the M cell action potential is the

Figure 2. Cellular basis of abnormal T wave patterns in the LQT1, LQT2, and LQT3 syndromes. Upper traces (A - C) depict clinical electrocardiographic lead V5 obtained in patients with LQT1, LQT2, and LQT3 syndromes. Lower traces (D - I) depict transmembrane action potentials recorded simultaneously from endocardial (Endo), M, and epicardial (Epi) cells together with a transmural ECG at a BCL of 2000 msec in the three models of the arterially-perfused wedge preparations. In all the cases, the peak of the T wave in the ECG coincides with the repolarization of the Epi cell action potential, whereas the end of the T wave coincides with the repolarization of the M cell action potential. In all three models, pharmacologic interventions mimic the phenotypic appearance of the T wave. Modified from references 19 and 20 with permission.

last. Full repolarization of the epicardial action potential is coincident with the peak of the T wave, and repolarization of the M cell action potential coincides with the end of the T wave. The repolarization of the endocardial cells is usually between those of the epicardial and the M cells (Fig. 1).²⁹ Therefore, the repolarization time [activation time + action potential duration (APD)] of the longest M cell across the ventricular wall determines the duration of the QT interval in each ECG reflecting the potential of the wall.

The cellular basis for QT dispersion recorded from the body surface has long been a matter of debate. Heterogeneities of repolarization time of the M cells in the three-dimensional structure of

the ventricular myocardium (interventricular or apico-basal) may contribute to the QT dispersion.²³ However, this assumption is based on the hypothesis that the ECGs recorded from the body surface preserve the spatial distribution of action potentials along the surface of the heart. A recent simulation study suggested that regional heterogeneity of repolarization was not reflected by QT dispersion recorded from the body surface 12-lead or 64-lead ECG.³⁰ Further studies will be definitely needed to conclude the clinical implications of the QT dispersion.

On the other hand, transmural heterogeneity in repolarization time (transmural dispersion of repolarization: TDR) is likely to depict a more onerous

Figure 3. Differential effect of β -agonist, isoproterenol (Iso) on the QT interval and the action potentials in the LQT1, LQT2, and LQT3 models of the arterially-perfused wedge preparations. Superimposed action potentials recorded simultaneously from M and epicardial (Epi) cells are shown, together with a transmural ECG at a BCL of 2000 msec. A: In the LQT1 model (chromanol 293B), Iso dramatically prolongs the APD of the M cells (2 min) and maintains this as the effect approaches a steady state (10 min), whereas the Epi cell action potential is always abbreviated, resulting in a persistent increase in the QT interval and the transmural dispersion of repolarization (TDR). B: In the LQT2 model (d-sotalol), Iso initially prolongs (2 min) and then abbreviates the APD of the M cells to the control level (10 min), whereas the APD of the Epi

substrate for the development of ventricular arrhythmias, because they are more abrupt than those recorded along the surfaces of the heart. The time interval between the peak and the end of the T wave (Tpeak-end) provides an index of TDR, which may have the potential to be a valuable prognostic tool.^{10,19-22}

CELLULAR BASIS FOR PHENOTYPIC APPEARANCE OF THE LONG QT SYNDROME

The congenital LQTS is a hereditary disorder characterized by a prolonged QT interval in the ECG, commonly associated with an atypical polymorphic ventricular tachycardia known as torsade de pointes (TdP).¹⁻⁷ Genetic studies have shown that congenital LQTS is a primary electrical disease and can be subdivided into five genotypes distinguished so far by mutations in five different ion channel genes located on chromosomes 3, 7, 11, and 21.³¹⁻³⁴ Mutations in *KCNQ1* and *KCNE1* are responsible for defects in the I_{Ks} underlying the LQT1 and LQT5 forms of LQTS,^{35,36} while mutations in *HERG* and *KCNE2* result in defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for the LQT2 and LQT6.^{37,38} Mutations in *SCN5A* decrease the function of late I_{Na} responsible for LQT3.³²

Moss et al. demonstrated a correlation between the phenotypic appearance of abnormal T waves and the three genotypes of the congenital LQTS in 1995 (Fig. 2),³⁹ although exceptions were later shown to exist in all three genotypes.⁴⁰ The broad-based prolonged T waves are commonly observed in LQT1, low-amplitude T waves with a notched or bifurcated configuration are often seen in LQT2, and late-appearing T waves are specific in LQT3. Experimental studies employing the arterially-perfused wedge preparation have shown that differences in the time course of repolarization of the epicardial, M, and endocardial cells give rise to voltage gradients responsible for the manifestation of abnormal T waves in the three genotypes of the congenital LQTS (Fig. 2).^{19,20,22,24-28}

cells is always abbreviated, resulting in a transient increase in the QT interval and the TDR. C: In the LQT3 model (ATX-II), Iso always abbreviates the APD of both cells, resulting in a persistent decrease in the QT interval and the TDR. Modified from reference 27 with permission.

Figure 4. Composite data of the effect of isoproterenol (Iso) on the QT interval, the APD₉₀ of the M and the epicardial (Epi) cells and the transmural dispersion of repolarization (TDR) in the LQT1, LQT2, and LQT3 models of the wedge preparations. In the LQT1 model, Iso produces a persistent prolongation of the APD₉₀ of the M cells and of the QT interval (at both 2 and 10 min), whereas the APD₉₀ of the Epi cells is always abbreviated, resulting in a persistent increase in the QT interval and the TDR (A and B). In the LQT2 model, Iso initially prolongs (2 min) and then abbreviates the QT interval and the APD₉₀ of the M cells to the control level (10 min), whereas the APD₉₀ of the Epi cells is always abbreviated, resulting in a transient increase in the QT interval and the TDR (C and D). In the LQT3 model, Iso produces a persistent abbreviation of the QT interval and the APD₉₀ of both the M and Epi cells (at both 2 and 10 minutes), resulting in a persistent decrease in the QT interval and the TDR (E and F). *P < 0.0005 vs. Control; †P < 0.0005, ††P < 0.005, †††P < 0.05, vs. 293B, d-Sotalol (d-Sot) or ATX-II. From reference 27 with permission.

I_{Ks} block with chromanol 293B is used to mimic the LQT1 syndrome, and the β -adrenergic agonist, isoproterenol, is used to assess the influence of the β -adrenergic system.^{20,26-28} I_{Ks} block alone produces a homogeneous prolongation of repolarization of the three cell types. The addition of isoproterenol abbreviates the APD in the epicardial and

the endocardial cells, but not in the M cells. This results in a dramatic augmentation of TDR and gives rise to a broad-based T wave commonly seen in LQT1 patients (Figs. 2A and 2E).

I_{Kr} block with d-sotalol is used to mimic the LQT2 syndrome and the most common acquired (drug-induced) form of the syndrome.^{19,25-28} Accen-

Figure 5. Differential dynamic response of the corrected QT (QTc) interval to sympathetic stimulation in patients with the LQT1, LQT2, and LQT3 syndromes. Each panel shows six precordial-lead ECGs under baseline conditions, at peak epinephrine effects, and under steady state conditions of epinephrine in patients with LQT1 (A), LQT2 (B), LQT3 (C) syndromes, and a control patient (D). A: The QTc interval is remarkably prolonged at the peak epinephrine effect (602 to 729 ms), and remains prolonged under steady-state conditions (673 ms) in the LQT1 patient. B: The QTc interval is also markedly prolonged at the peak epinephrine effect (549 to 706 ms) in the LQT2 patient, but is shortened above the baseline level under steady-state conditions (574 ms). C: In the LQT3 patient, the QTc interval is slightly prolonged at the peak epinephrine effect (544 to 577 ms) but much less than those in the LQT1 and LQT2 patients, and is shortened below the baseline level under steady-state conditions (509 ms). D: The QTc interval is slightly prolonged at the peak epinephrine effect (385 to 448 ms), and is shortened to the baseline level under steady-state conditions (379 ms) in the control patient. Modified from reference 46 with permission.

tuated I_{Kr} block with d-sotalol in the presence of hypokalemia produces a greater prolongation of the M cell APD and slowing of phase 3 of the action potential of all three cell types, resulting in a large TDR and a low amplitude T wave with a notched or bifurcated appearance similar to that commonly observed in LQT2 patients (Fig. 2B and 2G).

Augmentation of late I_{Na} with ATX-II, a sea anemone toxin, is used to mimic the LQT3 syndrome.^{19,24-28} ATX-II produces a greater prolongation of the APD in the M cells than that in the epicardial or the endocardial cells, thus causing a sharp rise in the TDR. The greater effect of ATX-II in prolonging the M cells is likely due to the pres-

ence of a larger late I_{Na} in the M cells. ATX-II also produces a marked delay in onset of the T wave, mainly as a result of the relatively large effect of ATX-II on the APD in the epicardial and the endocardial cells, consistent with the late-appearing T wave pattern (long isoelectric ST segment) specifically observed in LQT3 patients (Fig. 2C and 2I). Thus, the electrocardiographic T wave patterns described in the three LQTS models of wedge preparations are similar to those observed in patients with the three genotypes of congenital LQTS, although exceptions to these genotype-specific T wave morphologies are encountered in the wedge and the clinic.

DIFFERENTIAL EFFECTS OF SYMPATHETIC STIMULATION IN MODELS OF THE LONG QT SYNDROME

Recent clinical⁴¹⁻⁴⁴ and experimental^{20,27} studies have suggested differences in the sensitivity of the genotypes of congenital LQTS to sympathetic stimulation. Exercise-related events dominate the clinical picture in LQT1, while a sudden startle in the form of an auditory stimulus is the predominant trigger of cardiac events in LQT2. Sleep-related episodes are more common in LQT3. Data from the LQTS models using arterially-perfused wedges have advanced our knowledge of the differential cellular effect of sympathetic stimulation on repolarization in the three genotypes of the LQTS (Figs. 3 and 4).^{20,27}

In the LQT1 model (reduced I_{Ks}), chromanol 293B homogeneously prolongs the APD of the 3 cell types without increasing the TDR. However, the addition of β -adrenergic stimulation with isoproterenol prolongs the QT interval and the APD of M cells but abbreviates those of the epicardial and the endocardial cells, causing a persistent increase in the QT interval and the TDR (Figs. 3A, 4A, and 4B).²⁷ Beta-adrenergic stimulation is known to augment Ca^{2+} -activated I_{Ks} , an outward current, as well as inward currents including Ca^{2+} -activated chloride current ($I_{Cl(Ca)}$)⁴⁵ and I_{Na-Ca} . The response of the APD and of the QT interval to β -adrenergic stimulation largely depends on the balance of these three predominant currents. The presence of higher levels of I_{Ks} in the epicardial and the endocardial cells (even in the presence of chromanol 293B) accounts for the effect of the β -agonist to abbreviate the APD in these cells, while prolonga-

Figure 6. Line charts of dynamic changes of the corrected QT (QTc) interval in the LQT1, LQT2, LQT3 syndromes, and control patients shown in Figure 5. The QTc interval is prolonged markedly at the peak epinephrine effect and remains prolonged under steady-state conditions in the LQT1 patient. The QTc interval is also markedly prolonged at the peak epinephrine effect, but is shortened above the baseline level under steady-state conditions in the LQT2 patient. The QTc interval is much less prolonged at the peak epinephrine effect in the LQT3 patient than those in either LQT1 or LQT2 patient, and is shortened below the baseline level under steady-state conditions. The QTc interval is also slightly prolonged at peak of epinephrine, and is shortened to the baseline level at steady-state conditions in the control patient. From reference 46 with permission.

tion of the APD in the M cells is due to much smaller I_{Ks} levels at which inward currents predominate. Persistent increases in the TDR as well as in the QT interval are concordant with the high sensitivity of patients with the LQT1 syndrome to sympathetic stimulation.⁴¹⁻⁴⁴

In the LQT2 model (reduced I_{Kr}), isoproterenol initially prolongs (2 min) and then abbreviates the QT interval and the APD of the M cells to the control level (10 min), whereas the APD of the epicardial and the endocardial cells is always abbreviated, resulting in a transient increase in the QT interval and the TDR (Figs. 3B, 4C, and 4D).²⁷ Transient prolongation of the M cell APD is possibly due to a more rapid increase of inward currents ($I_{Cl(Ca)}$, I_{Na-Ca}) than that of I_{Ks} . In contrast, the constant abbreviation of the APD of the epicardial and the endocardial cells is most likely due to the higher levels of I_{Ks} in these cell types. The transient nature of repolarization changes following an in-

A. Baseline (LQT1) **B. Epinephrine (LQT1)** **C. Baseline (LQT2)** **D. Epinephrine (LQT2)**

Figure 7. Differential effects of sympathetic stimulation on repolarization indices in patients with the LQT1 and LQT2 syndromes. Electrocardiographic lead H4 (I4) of body surface potential mapping is shown, which corresponds to lead V5 (V6) of the standard 12-lead ECG under baseline conditions (A and C) and during epinephrine infusion (B and D) in patients with LQT1 and LQT2 syndromes. Under the baseline conditions, the corrected Q-Tend interval (QTce; 603 ms, 518 ms) and the corrected Q-Tpeak interval (QTcp; 482 ms, 414 ms) are prolonged, and the corrected Tpeak-end (Tcp-e; 121 ms, 104 ms) is increased in both LQT1 and LQT2 patients (A and C). Epinephrine produces a significant prolongation in the QTce (712 ms, 618 ms), but a mild prolongation in the QTcp (520 ms, 494 ms), resulting in a significant increase in the Tcp-e (192 ms, 124 ms); these changes are more pronounced in the LQT1 (B) than the LQT2 (D) patients. Modified from reference 47 with permission.

crease in sympathetic activity may explain why cardiac events in LQT2 generally occur following a startle, especially in a state of sleep (alarm clock, telephone bell or ambulance siren, etc).⁴³

In the LQT3 model (increased late I_{Na}), isoproterenol produces a persistent abbreviation of the QT interval and the APD of the three cell types, resulting in a persistent decrease in the QT interval and the TDR (Figs. 3C, 4E, and 4F).²⁷ These effects of β -adrenergic stimulation are likely due to an increase of I_{Ks} as well as a reduction of the electrogenic I_{Na-Ca} , and are concordant with the observation that cardiac events are often observed at rest or during sleep when sympathetic tone is expected to be low in LQT3 patients.^{41,44}

DIFFERENTIAL DYNAMIC RESPONSE OF QT INTERVAL TO SYMPATHETIC STIMULATION IN PATIENTS WITH THE LONG QT SYNDROME

The differential response of the QT interval to sympathetic stimulation has been demonstrated in the clinic. Noda et al. have recently compared the influence of sympathetic stimulation with epinephrine infusion on continuous corrected QT (QTc) intervals between patients with LQT1, LQT2, and LQT3 syndromes.⁴⁶ Twelve-lead ECG is continuously recorded before and after bolus injection (0.1 μ g/kg) of epinephrine followed by continuous in-

Figure 8. Composite data of differences of repolarization indices before and after epinephrine infusion in the mean corrected Q-Tend interval (QTce) (A), the mean corrected Q-Tpeak interval (QTcp) (B), and the mean corrected Tpeak-end interval (Tcp-e) (C), which are averaged among 87 leads, as well as the maximum (max) QTce (D), the minimum (min) QTce (E), and the dispersion of the QTce (QTce-D) (F) in the 13 LQT1, 6 LQT2, and 7 control patients. The prolongations in the mean QTce with epinephrine are largest in LQT1 patients, intermediate in LQT2 patients, and are not significant in control patients (A), whereas the changes in the mean QTcp are no different between the three groups (B). As a consequence, the increases in the Tcp-e are largest in LQT1 patients, intermediate in LQT2 patients, and are not significant in control patients (C). The prolongations in the max QTce with epinephrine are largest in LQT1 patients, intermediate in LQT2 patients, and are not significant in control patients (D), whereas the changes in the min QTce were no different between LQT1 and LQT2 patients, but significantly larger than those in control patients (E). As a consequence, the increases in the QTce-D are larger in LQT1 patients than those in LQT2 and control patients (F). Modified from reference 47 with permission.

fusion (0.1 $\mu\text{g/kg/min}$), and the QTc intervals of all beats are measured semiautomatically. The dynamic response of the QTc interval to epinephrine is clearly different between the three genotypes (Figs. 5 and 6).⁴⁶ In the LQT1 patients, the QTc is prolonged remarkably as the RR interval is maximally decreased (at peak epinephrine effect), and remains prolonged under steady state conditions of epinephrine (Figs. 5A and 6). Epinephrine also prolongs the QTc interval dramatically at peak epinephrine effect in LQT2 patients, but shortens it above the baseline levels under steady state condi-

tions (Figs. 5B and 6). In LQT3 patients, the QTc prolongation at peak epinephrine effect is much less than those in the LQT1 and LQT2 patients, and the QTc interval is shortened below the baseline levels under steady-state conditions (Figs. 5C and 6). In control patients, the QTc interval is slightly prolonged at peak epinephrine effect, and is shortened to the baseline levels under steady-state conditions (Figs. 5D and 6). Overall, these clinical data are consistent with the experimental data using wedge,^{20,27} and may explain why the trigger of cardiac events differs between the three genotypes

of congenital LQTS. The discrepancy of the QTc response at peak epinephrine effect between the LQT3 patients and the experimental LQT3 models can be explained by the use of Bazett's formula for rate correction as well as the different levels of sympathetic (β -adrenergic) stimulation and of augmented late I_{Na} between patients and experimental models.

DIFFERENTIAL EFFECTS OF SYMPATHETIC STIMULATION ON REPOLARIZATION INDICES IN PATIENTS WITH LONG QT SYNDROME

Although the differential response of dynamic QT interval to sympathetic stimulation has been clearly demonstrated in the clinical study by Noda et al.,⁴⁶ the QT response to sympathetic stimulation is not necessarily congruent with the arrhythmogenesis modified by sympathetic stimulation in patients with congenital LQTS. Tanabe et al. have recorded 87-lead body surface ECGs before and after epinephrine infusion and evaluated the effects of sympathetic stimulation on several repolarization indices representing transmural and spatial dispersion of repolarization in patients with LQT1 and LQT2 syndromes (Figs. 7 and 8).⁴⁷ In their study, the corrected Q-Tend interval (QTce), the corrected Q-Tpeak interval (QTcp), and the corrected Tpeak-end (Tc peak-end; QTce minus QTcp) as an index of TDR were measured automatically from all 87-lead ECGs, and averaged among all 87 leads. As an index of spatial dispersion of repolarization, the dispersion of the QTce (QTce-D) is defined as the interval between the maximum QTce and the minimum QTce among the 87 leads. Epinephrine significantly increases the mean QTce but not the mean QTcp, resulting in a significant increase in the mean Tc peak-end in both LQT1 and LQT2 patients; these changes are more pronounced in LQT1 than LQT2 patients (Figs. 7, 8A, 8B, and 8C).⁴⁷ Epinephrine also increases the maximum QTce but not the minimum QTce, producing a significant increase in the QTce-D in both LQT1 and LQT2 patients, and once again these are larger in LQT1 than LQT2 patients (Figs. 8D, 8E, and 8F).⁴⁷ The data by Tanabe et al. suggest that sympathetic stimulation produces a greater increase in both the transmural and spacial dispersion of repolarization in patients with LQT1 syndrome than LQT2 syndrome, and may further explain why

LQT1 patients are more sensitive to sympathetic stimulation.

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