Targeting the β-adrenergic receptor in the clinical management of congenital long QT syndrome

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The long QT syndrome (LQTS) is largely treated pharmacologically with β-blockers, despite the role of sympathetic activity in LQTS being poorly understood. Using the trigger–substrate model of cardiac arrhythmias in this review, we amalgamate current experimental and clinical data from both animal and human studies to explain the mechanism of adrenergic stimulation and blockade on LQT arrhythmic risk and hence assess the efficacy of β-adrenoceptor blockade in the management of LQTS. In LQTS1 and LQTS2, sympathetic stimulation increases arrhythmic risk by enhancing early afterdepolarizations and transmural dispersion of repolarization. β-Blockers successfully reduce cardiac events by reducing these triggers and substrates; however, these effects are less marked in LQTS2 compared with LQTS1. In LQTS3, clinical and experimental investigations of the effects of sympathetic stimulation and β-blocker use have produced contradictory findings, resulting in significant clinical uncertainty. We offer explanations for these contradicting results relating to study sample size, the dose of the β-blocker administered associated with its off-target Na+ channel effects, as well as the type of β-blocker used. We conclude that the antiarrhythmic efficacy of β-blockers is a genotype-specific phenomenon, and hence the use of β-blockers in clinical practice should be genotype dependent.

Keywords: long QT syndrome; arrhythmia; β-blockers

Preferred citation:
Saadeh, K., K. Shivkumar & K. Jeevaratnam. 2020. Targeting the β-adrenergic receptor in the clinical management of congenital long QT syndrome. In “MARROW,” ed. by M. Zaidi. Ann. N.Y. Acad. Sci. 1474: 27–46.

Introduction

Cardiac arrhythmias result from disruption in the orderly sequence of action potential (AP) activation and propagation through successive regions of the myocardium, causing failure of coordinated and effective cardiac contraction.1

Of arrhythmic syndromes associated with congenital ion channel abnormality, long QT syndrome (LQTS) is characterized by prolonged electrocardiographic (ECG) QT intervals attributable to elongated ventricular AP duration (APD).2 The LQTS has a prevalence of 1 in 2000 persons;3 it is associated with predisposition to the normally self-terminating episodic polymorphic ventricular tachycardia (VT) torsades de pointes (TdP), with the potential to degenerate into ventricular fibrillation (VF) and/or sudden cardiac death.2,4,5 LQTS patients also show atrial fibrillation (AF) more commonly than the remaining population,6 with up to one-third of LQTS patients developing self-terminating atrial arrhythmias under daily life conditions.7

doi: 10.1111/nyas.14425

Ann. N.Y. Acad. Sci. 1474 (2020) 27–46 © 2020 The Authors. Annals of the New York Academy of Sciences published by Wiley Periodicals LLC on behalf of New York Academy of Sciences

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Table 1. Channel mutations in LQTS1, LQTS2, and LQTS3 and the ionic currents affected

| LQTS  | Proportion of cases | Gene  | Channel | Physiological function | Current changes            |
|-------|---------------------|-------|---------|------------------------|----------------------------|
| LQTS1 | 49%                 | KCNQ1 | Kv7.1   | I_{Ks}: phase 3 slow activating component of the delayed rectifier potassium current during action potential repolarization | Decreased I_{Ks} |
| LQTS2 | 39%                 | HERG  | Kv11.1  | I_{Kr}: phase 3 rapidly activating component of the delayed rectifier potassium current during action potential repolarization | Decreased I_{Kr} |
| LQTS3 | 10%                 | SCN5A | Nav1.5  | I_{Na,L}: phase 0 depolarization of the action potential | Increased late current I_{Na-L} |

LQTS includes many subtypes associated with abnormalities in up to 16 genes.8 Table 1 summarizes the causative mutations and currents involved in LQTS1, LQTS2, and LQTS3. The three major LQTS genes KCNQ1, HERG, and SCN5A account for 49%, 39%, and 10% of LQTS cases, respectively.9 All three subtypes cause prolongation of the APD (shown in Fig. 1A). LQTS1 is associated with a loss-of-function mutation in KCNQ1, which encodes the Kv7.1 channel; the mutation results in decreased I_{Ks} current that is responsible for the slow activating component of the delayed rectifier potassium current during phase 3 repolarization of the cardiac AP (shown in Fig. 1B). LQTS2 is associated with a loss-of-function mutation in HERG encoding the Kv11.1 channel, and results in decreased I_{Kr} current that is responsible for the rapidly activating component of the delayed rectifier potassium current during phase 3 repolarization of the cardiac AP (shown in Fig. 1C). LQTS3 is associated with a gain-of-function mutation in SCN5A, which encodes the Nav1.5 channel; this results in increased late Na⁺ current, I_{Na-L}, as a consequence of impaired channel inactivation, with I_{Na} being responsible for phase 0 depolarization of the cardiac AP (shown in Fig. 1D).

The trigger substrate model of cardiac arrhythmias

Reentry arrhythmia occurs when an AP wave fails to extinguish and results in excitation of previously excited, but now recovered, regions. The trigger–substrate model explains reentrant arrhythmias as occurring following the application of a single trigger to an arrhythmic substrate.1,10 The trigger, typically an extrasystole, forms an area of refractoriness—a functional obstacle—around which the AP wave circulates. The substrate is formed of slowed conduction velocity, resulting in tissue ahead of the wave becoming excitable and transmural dispersion of repolarization (TDR) owing to heterogeneities in recovery from excitability; this results in a unidirectional conduction block preventing the wave from self-extinguishing.11,12 Thus, arrhythmias arise when both a trigger and a substrate occur simultaneously (shown in Fig. 2). Sympathetic activity is associated with an increased risk of arrhythmias, as adrenergic stimulation increases the risk of both arrhythmic triggers and substrate. Unfortunately, despite the term arrhythmic trigger being used in cellular physiology to mean abnormal wave formation, which develops a functional obstacle, it is also used in clinical papers to refer to an environmental event that precedes and predisposes to arrhythmias, for example, exercise. Thus, to avoid confusion, we will use trigger (in italics) to refer to the physiological organ-level phenomenon of abnormal depolarization, and trigger (no italics) to refer to the clinical setting of the patient.

Sympathetic stimulation promotes arrhythmogenesis via enhancing triggered activity and developing arrhythmic substrates

Sympathetic input to the myocardium acts mainly on β-adrenergic receptors, primarily β1 adrenergic
receptors (β1-AR) and, to a lesser extent, β2-AR, but also the α1-adrenergic receptor (α1-AR), in order to promote chronotrophic and inotropic effects. AR are G protein–coupled receptors (GPCRs) that activate an intracellular cascade acting on a variety of surface membrane ion channels and intracellular Ca^{2+} homeostasis proteins. β-AR are G_{αs} GPCRs that activate adenylate cyclase to increase intracellular cAMP levels and trigger the protein kinase A (PKA) phosphorylation cascade. α1-AR is a G_{αq} GPCR that activates PLC that then cleaves phosphatidylinositol, increasing IP_{3} that binds to IP_{3} receptor and diacylglycerol to initiate PKC phosphorylation changes. Together, these phosphorylation changes can increase triggered activity and cause the development of an arrhythmic substrate, hence increasing the risk of cardiac arrhythmias. Figure 3 summarizes AR signaling and its effects on arrhythmic triggers.

**β-Adrenergic receptors promote triggered activity**

Table 2 summarizes the effects of β1-AR stimulation on surface membrane currents and intracellular Ca^{2+} homeostasis in relation to triggered activity. Briefly, the β-AR–PKA cascade initially phosphorylates Na_{v}1.5 that is responsible for phase 0 depolarization, giving rise to the rapid inward current (I_{Na}) and leading to faster inactivation kinetics and augmentation of I_{Na} amplitude. Second, it phosphorylates the L-type Ca^{2+} channel.
Figure 2. Reentrant arrhythmia occurs when an action potential (AP) wave fails to extinguish and results in reexcitation of previously excited, but now recovered, regions. Abnormal wave formation via triggered beats causes a functional obstacle, a region of refractoriness, around which the AP wave circulates. This is the initiating event–arrhythmic trigger. Arrhythmic substrates maintain reentrant arrhythmia and include slowed conduction velocity (CV), resulting in tissue ahead of the wave being excitable, and transmural dispersion of repolarization (TDR), resulting in unidirectional conduction block preventing the wave from self-extinguishing.

channel Ca_{V}1.2 that is responsible for the plateau phase 2, leading to an increase in the inward depolarizing Ca^{2+} current (I_{Ca-L}) Ca^{2+} entry. In relation to pathology, reactivation of Ca^{2+} channels and an increase in I_{Ca-L} during phase 2 or 3, and made more likely by adrenergic modulation effects, will result in early afterdepolarizations (EADs) and hence an arrhythmic trigger. Third, β-AR exerts complex effects on HERG channels, which gives rise to the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) that contributes to AP plateau phase 2 and phase 3 repolarization, where adrenergic stimulation has been mainly shown to decrease (but also to increase) I_{Kr} (depending on stimulation conditions). Fourth, PKA phosphorylates K_{V}7.1, which gives rise to the slow activating component of the delayed rectifier potassium current (I_{Ks}) responsible for AP plateau phase 2 and phase 3 repolarization, leading to an increase in I_{Ks} and faster repolarization. Pathological disruption of the repolarization currents will promote triggered activity by reducing the repolarization current and offsetting delayed afterdepolarizations (DADs), hence increasing DAD amplitude and prolonging the AP associated with EADs. Fifth, β-AR stimulation has also been shown to increase Na^{+}–K^{+} pump activity associated with DADs through Na^{+}–Ca^{2+} exchanger (NCX) promotion. Finally, β-AR–PKA phosphorlates a variety of intracellular targets relating to Ca^{2+} homeostasis, including ryanodine receptor (RyR), thereby increasing sarcoplasmic reticulum (SR) Ca^{2+} release and phospholamban, which leads to disinhibition of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and increased Ca^{2+} recycling. This ultimately increases the magnitude of intracellular Ca^{2+} transients driving the depolarizing NCX activity, therefore promoting DADs.

α1-Adrenergic receptors promote triggered activity
Table 2 summarizes the effects of α1-AR stimulation on surface membrane currents in relation to triggered activity. α1-AR activity contributes to the previously discussed generation of EADs and DADs. First, phosphorylation of the K_{V}4 channels, giving rise to the transient outward potassium current (I_{to}) responsible for the initial rapid repolarization phase 1 of the AP, reduces I_{to} and allows the plateau phase to occur at higher voltages, permitting an increase in APD and I_{Ca-L}, and thus is an important contributor to EADs. Second, α1-AR inhibits the inwardly rectifying potassium channels, reducing background potassium current (I_{K1}), hence importantly contributes to DADs by reducing the polarizing current, which normally offsets them. Finally, α1-AR has also been shown to increase Na^{+}–K^{+} pump activity, which accelerates the forward depolarizing mode of NCX and thereby contributes to the generation of DADs.

Overall, in healthy hearts, the increase in Ca^{2+} transients and depolarizing currents due to sympathetic stimulation are balanced by an increase in the repolarizing potassium currents. Imbalance in these mechanisms in LQTS hearts, for example, due to failure to increase repolarizing potassium currents in LQTS1 and LQTS2 or to a persistent increase in I_{Na-L}, prolonging repolarization in LQTS3, will predispose them to triggered activity during adrenergic stimulation.

Sympathetic stimulation promoting TDR arrhythmic substrate
In addition, sympathetic activity promotes the development of an arrhythmic substrate (shown in Fig. 4) owing to regional heterogeneities in sympathetic input and response, including base-to-apex and epicardial-to-endocardial gradients of those...
Figure 3. Sympathetic input to the myocardium acts on α1- and β1-adrenergic receptors (α1-AR and β1-AR). β1-AR is a G$_{as}$ GPCR that activates adenylate cyclase (AC), increasing intracellular cAMP levels and triggering the protein kinase A (PKA) phosphorylation cascade that acts on a variety of surface membrane ion channels and intracellular Ca$^{2+}$ homeostasis proteins. α1-AR is a G$_{q}$ GPCR that activates PLC that cleaves phosphatidylinositol increasing IP3, which then binds to the IP3 receptor and diacylglycerol (DAG), leading to a PKC phosphorylation cascade that acts on a variety of surface membrane ion channels. These changes increase the risk of early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) arrhythmic triggers.

Regional differences in sympathetic input can arise as a consequence of differences in sympathetic nerve distribution as well as β-1AdR and α1-AR density. Differences in response to sympathetic stimulation largely arise as a consequence of regional differences in expression levels and activity of membrane ion channels. These regional differences consequently result in TDRs, and hence an arrhythmic substrate. As a consequence of its effect of increasing arrhythmic triggers and substrate, sympathetic activity is associated with an increased incidence of cardiac arrhythmias. Thus, sympathetic β-adrenergic antagonism in inherited arrhythmic syndromes, especially LQTS, has been an important area of research, as it elucidates the arrhythmogenic mechanism in those syndromes and offers a therapeutic target.

Implications of cardiac sympathetic stimulation in LQTS is a genotype-specific phenomenon

Briefly, after the identification of the LQTS genes, clinical reports demonstrated genotype-specific environmental triggers relating to sympathetic or parasympathetic (vagal) activity. In 1995, Schwartz and colleagues provided an early account of the effect of increasing heart rate (HR), reflecting sympathetic activation, on the QT interval of seven LQTS3 and four LQTS2 patients. LQTS3 patients shortened their QT interval more than LQTS2 patients, and even more than healthy controls. Furthermore, Schwartz and colleagues reported cardiac events occurring more during rest or sleep for LQTS3 but during emotional or physical stress for LQTS2. These findings justified further clinical and experimental studies to investigate genotype-specific triggers.

These clinical triggers can be classified into three major types: (1) physical stress, or exercise, characterized by progressively increasing HR via sympathetic stimulation from both neural and circulating catecholamines; (2) emotional stress and abrupt arousals characterized by sudden sympathetic activity via neural catecholamines, whereby HR does not significantly rise and without permitting time for QT shortening to faster rates; and (3) rest, or sleep, characterized by slower HR, predominance of
Table 2. The main effects of adrenergic stimulation on ionic currents and arrhythmic triggers

| Channel | Current | Physiological role in the cardiac action potential/Ca\(^{2+}\) homeostasis | Adrenergic receptor | Effect | Associated pathological triggered activity |
|---------|---------|-------------------------------------------------|-------------------|--------|-----------------------------------|
| \(\text{Na}^+\text{v}1.5\) | \(I_{Na}\) | Phase 0 depolarization; inward Na\(^+\) current | \(\beta_1\)-AR | Faster kinetics and an increase in \(I_{Na}\) amplitude | EADs and DADs |
| \(\text{K}^+\text{v}4\) | \(I_{ko}\) | Phase 1: transient outward potassium current | \(\alpha_1\)-AR | Decrease in \(I_{ko}\) | EADs |
| \(\text{Ca}^+\text{v}1.2\) | \(I_{Ca-L}\) | Phase 2: inward Ca\(^{2+}\) current | \(\beta_1\)-AR | Increase in \(I_{Ca-L}\) | EADs |
| \(\text{K}^+\text{v}11.1\) | \(I_{Kr}\) | Phases 2–3: rapidly activating component of the delayed rectifier potassium current | \(\beta_1\)-AR | Condition-dependent decrease (main) or increase in \(I_{Kr}\) | EADs |
| \(\text{K}^+\text{r}\) | \(I_{K1}\) | Phase 4: inwardly rectifying background potassium current | \(\alpha_1\)-AR | Decrease in \(I_{K1}\) | DADs |
| \(\text{Na}^+\text{-K}^+\) pump | \(I_{Na-K}\) | Phase 4: maintains ionic gradients | \(\beta_1\)-AR and \(\alpha_1\)-AR | Increase in \(I_{Na-K}\) | DADs |
| SERCA | \(I_{up}\) | Recycles cytosolic Ca\(^{2+}\) into the SR | \(\beta_1\)-AR | Increase in \(I_{up}\) | DADs |
| RyR | \(I_{RyR}\) | Release of SR Ca\(^{2+}\) | \(\beta_1\)-AR | Increase in \(I_{RyR}\) | DADs |

parasympathetic vagal input, and hence the absence of significant catecholaminergic activity.

One study investigated the association of the aforementioned triggers with cardiac events in 371 LQTS1, 234 LQTS2, and 65 LQTS3 patients. In LQTS1, patients experienced 62% of cardiac events during exercise and only 3% during rest/sleep. Furthermore, 68% of lethal events occurred during exercise, suggesting that exercise/physical stress, and hence sympathetic activity, appears to be the predominant trigger. In LQTS2, patients experienced 43% of cardiac events during emotional stress, 13% during exercise, and 29% during rest/sleep. Interestingly, 49% of lethal cardiac events occurred during rest/sleep. However, sleep is not a homogenous state of vagal dominance. Periods of rapid eye movement (REM) sleep are associated with significant sympathetic activation that can trigger cardiac events. Despite auditory triggers being rare in LQTS1 and LQTS3, 26% of LQTS2 patients experienced them, with 64% reported to have occurred during sleep. Therefore, emotional stress and abrupt triggers during sleep (auditory stimuli) reflect sudden sympathetic activity that appears to be a predominant trigger in LQTS2 patients. The difference in triggers between LQTS1 and LQTS2 patients is recapitulated by other clinical reports, such as those finding that events in LQTS1 are associated with swimming (i.e., exercise), whereas events in LQTS2 are associated with auditory stimuli. Together, these findings implicate sympathetic activity as a trigger in both LQTS1 and LQTS2 but operating by different mechanisms. In LQTS1, sympathetic activity promotes arrhythmia during sustained activity, whereas in LQTS2 it promotes arrhythmia during sudden activity.

In LQTS3, patients experience 39% of cardiac events during rest/sleep and only 13% and 19% during exercise and emotional stress, respectively. Furthermore, 64% of lethal events occur during rest/sleep. This is consistent with previous reports, including those from a smaller study that found that symptomatic LQTS3 patients had cardiac events at rest or during sleep, with only one also during emotional stress. In a family with a high incidence of nocturnal sudden death, patients were characterized with sinus bradycardia and bradycardia-dependent QT prolongation, indicating a bradycardic mode of cardiac death. Therefore, in contrast to LQTS1 and LQTS2,
Figure 4. Sympathetic activity promotes the development of an arrhythmic substrate. This arises as a consequence of regional heterogeneities in sympathetic nerve distribution, adrenergic receptor density, and regional differences in expression levels and activity of membrane ion channels. Thus, sympathetic stimulation promotes transmural dispersion of repolarization (TDR), which allows the development of a unidirectional conduction block and, hence, the development of a substrate for reentry arrhythmia.

rest/sleep—reflecting a period of decreased cardiac sympathetic activity—appears to be the trigger in LQTS3 patients. Though this initially seems to suggest that sympathetic stimulation is protective, it is worth noting that cardiac events still occurred during periods of increased sympathetic activity, such as emotional stress and exercise.\(^\text{70,71}\) Furthermore, as previously discussed, sleep does not necessarily mean an absence of sympathetic activity.\(^\text{72}\)

**Molecular basis of the differential role of sympathetic stimulation in LQT subtypes**

The differential response of LQTS subtypes to sympathetic stimulation can be understood by considering the role of the mutated channel. In the healthy myocardium, sympathetic stimulation increases both inward depolarizing currents, for example \(I_{\text{Ca-L}}\) and \(I_{\text{NCX}}\), and outward repolarizing currents, for example \(I_{K_S}\), with the net outward current ensuring faster repolarization and shortened APD.

**LQTS1**

In LQTS1, decreased \(I_{K_S}\) results in a scenario in which sympathetic stimulation still increases the depolarizing currents, but with a much weaker repolarizing current. Therefore, the APD will be paradoxically prolonged. This was demonstrated clinically both by exercise monitoring and epinephrine infusion. Clinical monitoring of LQTS1 patients during exercise demonstrated impaired HR response to exercise, reflected in prolonged QT due to extended ventricular repolarization time.\(^\text{73,76,77}\) Additionally, infusing patients with epinephrine resulted in a sustained prolonged QT interval.\(^\text{78,79}\) Experiments with
infusion of isoproterenol in canine left ventricle wedge preparations, arterially perfused with $I_{Kr}$ blocker chromanol 293B modeling LQTS1, persistently prolonged the QT interval and the APD in midmyocardial (M) cells.\textsuperscript{77,80} Thus, a sustained increase in the APD following adrenergic stimulation in LQTS1 will increase the risk of EADs, and therefore increase the risk of an arrhythmic trigger.

Furthermore, the previously discussed effect of adrenergic stimulation promoting TDR is potentiated in LQTS1 syndrome. Clinically, this was shown by prolonged ECG indicators of TDR, for example, $T_{peak-end}$ ($T_{cp-e}$), intervals, following exercise stress test\textsuperscript{81} or epinephrine administration in LQTS1 patients.\textsuperscript{77,82} Experimental investigation in the canine chromanol 293B pharmacological model of LQTS1 demonstrated that adrenergic stimulation prolongs APD in M cells, where $I_{Kr}$ is intrinsically weak but abbreviates APD in epicardial and endocardial cells, resulting in the persistent increase in TDR and possible induction of TdP.\textsuperscript{77,80} Thus, the sustained increase in TDR following adrenergic stimulation in LQTS1 allows the development of an arrhythmic substrate. Therefore, in LQTS1 patients, sympathetic stimulation results in a persistent increase in both arrhythmic trigger and substrate and, consequently, increases the risk of cardiac arrhythmias. This accounts for the previously discussed reports that LQTS1 patients are at an increased risk of cardiac events during sympathetic stimulation, hence providing the support for the use of $\beta$-blockers in the treatment of LQTS1.

**LQTS2**

In LQTS2, decreased $I_{Kr}$ results in a scenario in which sympathetic stimulation increases the depolarizing currents, but with a much weaker rapidly activating repolarizing current $I_{Kr}$. This results in the dominance of inward depolarizing currents, and hence prolonged APD. However, following a delay, the slower $I_{ks}$ is increased and thus the APD will shorten. Therefore, in response to sympathetic stimulation, there will be a transient prolongation of the APD, which then reverses and shortens. This was demonstrated clinically both by exercise monitoring and epinephrine infusion, where the QT interval initially prolonged but later shortened to control values.\textsuperscript{76,78,79} Experimental isoproterenol infusion in canine left ventricle wedge preparations, arterially perfused with $I_{Kr}$ blocker $\alpha$-sotalol modeling LQTS2, initially prolonged then abbreviated the QT interval and the APD in M cells.\textsuperscript{77} Similarly, the dofetilide pharmacological model of LQTS2 in guinea pig ventricular myocytes demonstrated that either exposure to isoproterenol or rapid pacing shortens the APD but only after an initial 3-min prolongation.\textsuperscript{83} Thus, a transient increase in the APD following adrenergic stimulation in LQTS2 will increase the risk of EADs and, therefore, an arrhythmic trigger.\textsuperscript{77,83}

Furthermore, the previously discussed effect of adrenergic stimulation promoting TDR has been reported in LQTS2. In the $\alpha$-sotalol canine pharmacological model, isoproterenol initially prolonged, then abbreviated, the APD of M cells but always shortened epicardial APD, transiently increasing TDR and the ability to induce TdP.\textsuperscript{77} A transient increase in TDR following adrenergic stimulation in LQTS2 allows the reversible development of an arrhythmic substrate. Therefore, in LQTS2, patients demonstrate that sympathetic stimulation results in a brief increase in both arrhythmic trigger and substrate and, consequently, transiently increases the risk of cardiac arrhythmias. This accounts for the previously discussed reports that LQTS2 patients are at an increased risk of cardiac events during sudden sympathetic stimulation, hence providing the support for the use of $\beta$-blockers in the treatment of LQTS2.

Nonetheless, these effects of sympathetic stimulation are less pronounced in LQTS2 than in LQTS1. Clinically, the characteristic ECG features of TDR increase more prominently during exercise in LQTS1 than in LQTS2 patients.\textsuperscript{81} Similarly, sympathetic stimulation with epinephrine produces a greater increase in TDR in LQTS1 than in LQTS2.\textsuperscript{84} This may explain why cardiac events during exercise, and hence sympathetic activity, are less common in LQTS2 than in LQTS1. In turn, this predicts that $\beta$-blockers would be less effective in LQTS2 than in LQTS1 patients.

**LQTS3**

In contrast to LQTS1 and LQTS2, in which clinical and experimental findings have been consistent, LQTS3 reflects a more complex situation. In LQTS3, delayed channel inactivation results in excessive $I_{Na-L}$, and hence prolonged APD. Increased $I_{Na-L}$ is associated with an increased risk of arrhythmias via a variety of mechanisms relating to increased EAD
and DAD triggers and TDR reentry substrate. The effects of adrenergic stimulation have been reported to influence both the fast and late components of the Na⁺ current. Despite the important role of I_{Na,L} in shaping the AP and contributing to arrhythmias, it remains a relatively poorly understood current, with the exact short- and long-term consequences of adrenergic stimulation remaining under investigation.

Because of this, reports investigating adrenergic effects on I_{Na,L} have offered different results. Studies in rabbit ventricular myocytes, for example, reported that adrenergic stimulation increases I_{Na,L} via both the PKA and CaMKII pathways. In other experiments, adrenergic stimulation enhanced inactivation of the Na⁺ channel, and hence reduced I_{Na,L}. Interestingly, however, in a number of different experiments, adrenergic stimulation has been shown to increase I_{Na,L}, hence effectively exacerbating the inactivation defect of the Na⁺1.5 channel. The effect of increased I_{Na,L} in LQTS3 on APD and arrhythmogenicity will depend on the interaction with the effects of adrenergic stimulation on other ion currents that contribute to repolarization and intracellular Ca²⁺ homeostasis. Interestingly, clinical reports reveal that in response to an increase in HR or epinephrine administration, the QT interval and APD are shortened to normal control values, or even abbreviated to values shorter than the controls.

Experimental investigation confirmed the clinical observations. In canine left ventricles wedge preparations, arterially perfused with ATX-II which augments I_{Na,L} modeling LQTS3, isoproterenol constantly shortened the QT interval and the APD in M cells, even to values below the control. Similarly, the anthopleurin pharmacological model of LQTS3 in guinea pig ventricular myocytes demonstrated that either exposure to isoproterenol or rapid pacing shortens the APD. In a murine LQTS3 model, isoproterenol shortened rate-corrected APD and suppressed arrhythmias. Together, these studies report a decrease in the APD following adrenergic stimulation in LQTS3, decreasing the risk of EADs and, therefore, of arrhythmic trigger.

Moreover, the previously discussed effect of adrenergic stimulation promoting TDR has not been reported in LQTS3. Interestingly, in experimental reports of canine left ventricle wedge preparations arterially perfused with I_{Na} modifier ATX-II modeling LQTS3, isoproterenol infusion shortens the APD in endocardial, M, and epicardial cells, and hence persistently decreases TDR and suppresses TdP. Similarly, in a Scn5a⁺/ΔKPQ murine model of LQTS3, dobutamine sympathetic stimulation reduced the incidence of repolarization alternans. Thus, decreased TDR following adrenergic stimulation in LQTS3 suppresses the development of an arrhythmic substrate. Therefore, clinical and experimental data appear to suggest that sympathetic stimulation results in a decrease in both arrhythmic trigger and substrate, and hence decreases the risk of cardiac arrhythmias.

However, some studies contradicting this conclusion have reported that sympathetic activity may be without effect, or may even be proarrhythmic. These discrepancies arise because of differences in the protocol of sympathetic stimulation and dose of pharmacological agonists. These reports showed a protective effect of sympathetic activity in response to a progressive increase in adrenergic stimulation. However, under a protocol of sudden accelerations in HR in a murine model of LQTS3, the APD was prolonged and caused EADs and triggered arrhythmias. Nonetheless, the same study found that isoproterenol infusion normalized the response to rate acceleration in vitro by preventing lengthening in APD, and suppressed arrhythmias upon premature stimulation in vivo—hence, demonstrating that differences in protocol produce different effects on APD and, consequently, on the risk of arrhythmic trigger. These results were further complimented by in vivo LQTS3 murine reports: following an increase in ventricular rate produced by dobutamine sympathetic stimulation, a delay in ventricular repolarization adaptation was reported. This may represent an increased arrhythmic risk by sympathetic stimulation following transient HR increase.

Additionally, the dose of sympathetic agonist administered may account for discrepancies between reports. In a canine experimental model of LQTS3 induced by anthopleurin-A, 0.5 μg/kg of epinephrine did not induce polymorphic ventricular tacharyrhythmia (PVA) and shortened the activation recovery interval at all sites and decreased TDR. By contrast, a dose of 1.0 μg/kg induced PVA, which demonstrates a dose-dependent opposite effect of sympathetic stimulation on arrhythmic tendency. This implicates the
magnitude of sympathetic activity in determining arrhythmic risk, such that it is not merely whether sympathetic activity is increased but the intensity of the stimulation that determines if it is pro- or antiarrhythmic. A computational model of LQTS3 (in mutant guinea pig ventricular myocytes) replicated the previous results finding that the effects of isoproterenol on EAD and TDR were dose and pacing protocol dependent.\textsuperscript{98} Therefore, both clinical and experimental evidence demonstrate that sympathetic activity plays a complex role in LQTS3.

It is important to treat experimental data with caution when considering generalizations to humans; animal models are limited by how similar their AP and ionic currents are to human counterparts. In this regard, many experiments use mouse models to study cardiac arrhythmias because of large structural and electrophysiological similarities to humans.\textsuperscript{99–103} For example, I\textsubscript{Na} plays the same physiological role in both mouse and humans, being responsible for the rapid depolarization phase of the AP\textsuperscript{102} and thus enabling the study of Na\textsuperscript{+} channel abnormalities, such as LQTS3.\textsuperscript{94–96,102} However, important differences exist, particularly regarding the less prominent Ca\textsuperscript{2+} current and different expression and role of potassium channels in repolarization.\textsuperscript{99,103} Considered together, this means mouse ventricular AP lacks the typical plateau phase present in human ventricular AP, as well as having a shorter APD.\textsuperscript{102–104} This may influence whether changes in I\textsubscript{Na-L}, I\textsubscript{Na}, and I\textsubscript{Kout} are pro or antiarrhythmic, and hence affect the interpretation of findings. Nonetheless, transgenic Scn5a\textsuperscript{+}/ΔKPQ mice that model LQTS3 have been shown to reflect the LQTS3 human phenotype, including prolonged APD, arrhythmic tendency, and ECG features.\textsuperscript{94–96,105} In summary, the effects of sympathetic stimulation are largely dependent on the clinical context and the experimental protocols used, which may influence the recommendation of use of β-blocker therapy in LQTS3 patients.

**β-Blockers are the primary treatment for LQT syndrome**

Currently, the predominant management strategy of LQTS is β-blocker use.\textsuperscript{106–108} Justification for this arose from previously discussed early findings that associated sympathetic stimulation with a proarrhythmic phenotype, and the observation that the majority of cardiac events occurred during sympathetic activity, for example, exercise. However, evaluation of the efficacy of β-blockers in LQTS management is significantly limited to retrospective studies due to their apparent clinical efficacy, and hence ethical implications preventing the performance of prospective, placebo-controlled, randomized studies.\textsuperscript{107} Furthermore, early studies lacked genotype profiling of patients, and hence examined β-blocker efficacy in LQTS without subtype specificity. Of those early studies, a large one was conducted on 233 LQTS patients who were symptomatic for syncope or cardiac arrest. For those patients not receiving antiadrenergic therapy, mortality 15 years after the first syncope was 60%, but for those on antiadrenergic therapy (β-blocker and/or left cardiac sympathetic denervation), mortality was 9%,\textsuperscript{109} hence, supporting the use of β-blockers. However, as discussed previously, sympathetic activity influences arrhythmic risk differently in different LQT subtypes. Thus, the efficacy of β-blockers should be investigated in a genotype-specific manner.

**β-Blocker therapy in LQTS1 and LQTS2**

Genotype-specific clinical studies initially involved small sample sizes, such as a study of 69 LQTS1 and 42 LQTS2 patients in which β-blockers were found to have a significant effect in reducing cardiac event rate in both groups of patients.\textsuperscript{110} Following these initial reports, larger clinical studies described the antiarrhythmic effects of β-blockers in both LQTS1 and LQTS2. For example, a study of 600 LQTS1 patients found that β-blockers were associated with a 79% reduction in the cumulative probability of first cardiac event,\textsuperscript{111} in another study of LQTS2 patients, β-blockers were associated with a 63% reduction in the cumulative probability of first cardiac event.\textsuperscript{112} Hence, the antiarrhythmic effect of β-blocker therapy was less in LQTS2 than in LQTS1 patients in the two studies. In yet another study, of 371 LQTS1 patients receiving β-blocker therapy 81% demonstrated recurrence-free survival, while 59% of 234 LQTS2 patients were recurrence free; nonetheless, the death rate was equally low in both patient groups (4%).\textsuperscript{113} β-Blocker therapy was shown to reduce the incidence of cardiac events from 47% to 10% in LQTS1, and to 23% in LQTS2 patients;\textsuperscript{113} and a recent meta-analysis found that β-blockers reduced the risk of cardiac events by...
71% in LQTS1 and 52% in LQTS1. Therefore, β-blocker therapy has been consistently associated with effective treatment of both LQTS1 and LQTS2 patients.

As previously discussed, sympathetic activity increases the risk of cardiac arrhythmias in LQTS1 and LQTS2 by increasing EADs and TDR. Thus, it is expected that the mechanism by which β-blockers exert their arrhythmic effects is by a reduction of incidence of EADs and TDRs. Indeed, clinical ECG monitoring of LQTS1 patients during exercise and recovery found that β-blockade reduced APD and hence EADs, measured as the QT interval; this study also found that β-blockade reduced TDR, measured as the T peak-to-end interval (Tp-e).

Additionally, propranolol suppressed the effect of epinephrine increasing TDR in LQTS1 and LQTS2 patients; this effect was greater in LQTS1 than in LQTS2 patients. Experimental pharmacological models of LQTS1 and LQTS2 induced by chromanol 293B and d-sotalol, respectively, demonstrated that propranolol prevented the development of TDR induced by isoproterenol, and suppressed the development of spontaneous and stimulation-induced Tp-e. Therefore, both clinical and experimental studies have demonstrated the effectiveness of β-blocker therapy in the management of LQTS1 and LQTS2 patients, with the therapy being more effective in LQTS1 than in LQTS2 patients. The evidence is consistent with a mechanism of action that involves a reduction in EADs and TDR, and hence a reduction in both arrhythmic trigger and substrate.

**β-Blocker therapy in LQTS3**

In contrast to LQTS1 and LQTS2, the use of β-blocker therapy in LQTS3 patients has been more controversial. In a study of 28 LQTS3 patients, β-blockers were found to have no significant effect on reducing cardiac event rate. Consistent with this finding, later studies reported minimal or no protective effects of β-blocker treatment. For example, 65 LQTS3 patients receiving β-blocker therapy had a lower percentage of patients with recurrence-free survival (50%) and a much higher death rate (17%) compared with LQTS1 and LQTS2 patients. Additionally, another study showed that β-blocker therapy reduced the incidence of cardiac event rate from 47% to just 32% in LQTS3 patients. And in a murine LQTS3 model, acute β-adrenoceptor blockade by esmolol or propranolol, or chronic blockade by propranolol in vivo, did not suppress arrhythmias. These studies are consistent with the conclusion that β-blocker therapy has no significant effect on reducing the risk of cardiac arrhythmias in LQTS3 patients.

On the other hand, other studies have described a proarrhythmic effect of β-blockers in LQTS3 patients. For example, in a family with a high incidence of nocturnal sudden death in combination with sinus bradycardia and bradycardia-dependent QT prolongation reflecting the LQTS3 phenotype, β-blocker therapy was contraindicated as it correlated with a bradyarrhythmic mode of cardiac death. Similarly, in LQTS3 patients with the ΔKPQ mutation, β-blockade correlated with slowed atrial, atrioventricular, and ventricular conduction. In a pharmacological model of LQTS3 induced by ATX-II, the propranolol reversed the protective effects of isoproterenol; propranolol prevented APD abbreviation and promoted the development of TDR. Similarly, in a murine LQTS3 model, β-blockade inhibited the beneficial effects of catecholamines, hence causing the prolongation of APD. Studies in a murine LQTS3 model also demonstrated that 1 µM propranolol not only failed to suppress VT but also increased TDR, hence promoting an arrhythmic substrate.

Yet, more recent, larger scale studies have found a significant antiarrhythmic effect of β-blocker therapy in LQTS3 patients. In a study with 111 LQTS3 patients treated with β-blockers, females had an 83% reduction in cardiac events, and yet no significant effect in males; this was explained by the low number of arrhythmic events in males, which prevented a conclusive finding. Nonetheless, there was no detrimental effect of β-blockers, as was previously reported. Similar results were reported by a later study involving 237 LQTS3 patients, which found a trend toward significant benefit of β-blockers in reducing cardiac events in LQTS3 females, but not in LQTS3 males. And one of the largest studies conducted involving 4480 person-years demonstrated the efficacy of the β-blocker nadolol in preventing life-threatening events in all of the three major LQTS genotypes. Additionally, rapid sympathetic activity has been implicated as a trigger in some LQTS3 patients, as discussed previously, which supports the use of β-blockers, as they would prevent such triggers.
during sudden sympathetic surges.\textsuperscript{95} Finally, in a canine LQTS3 pharmacological model, propranolol reversed the epinephrine-induced increase in TDR and prevented premature ventricular complexes and polymorphic VT induced by epinephrine;\textsuperscript{97} and carbachol induced VT and VF in a murine LQTS3 model that were prevented by pretreatment with propranolol, demonstrating its antiarrhythmic effect.\textsuperscript{124}

**Clarification of the contradictory findings in LQTS3**

Potential explanations for the contradicting findings include study sample size, the dose of the β-blocker administered relating to its off-target Na\textsuperscript{+} channel effects, and the type of β-blocker used.

**Sample size**

The relatively small sample size of the early clinical studies, which reported no beneficial effect of propranolol in LQTS3, has been criticized.\textsuperscript{114,121,124} These studies likely lack the statistical power necessary to detect a significant difference. More recent reports contain larger sample sizes and report an antiarrhythmic effect of β-blockers.

**β-Blocker dose and Na\textsuperscript{+} channel effects**

In a murine LQTS3 model, VT triggering following programmed electrical stimulation was modulated in a dose-dependent manner by propranolol.\textsuperscript{125} These effects were correlated with the effects of propranolol on TDR such that the concentration that suppressed VT triggering was associated with decreased TDR, and vice versa.\textsuperscript{125} In a similar canine model, under moderately high concentrations, propranolol increased TDR; however, with even higher concentrations associated with further Na\textsuperscript{+} channel inhibition, these effects were reversed, decreasing TDR. These findings are further supported by the computational model of LQTS3 mentioned above (in mutant guinea pig ventricular myocytes).\textsuperscript{98} This study found that at low concentrations, propranolol reversed the beneficial effects of β-adrenoceptor activation and had proarrhythmic effects; at higher concentrations, however, propranolol had antiarrhythmic effects. Consistently, clinical data have shown that 40% of patients with ventricular arrhythmias responsive to propranolol receive doses significantly higher than those required for β-adrenoceptor blockade (>150 ng/mL).\textsuperscript{126}

A physiological explanation for the paradoxical effects of propranolol\textsuperscript{125,127} is summarized in Figure 5. Independent of β-adrenoceptor blockade, propranolol has Na\textsuperscript{+} channel blocking effects.\textsuperscript{128,129} Thus, propranolol acting on the myocardium will block the Na\textsubscript{v}1.5 channel causing a decrease in the amplitude of phase 0 depolarization of the AP, as well as a decrease in the Na\textsuperscript{+} window/late Na\textsuperscript{+} current. Therefore, in the endocardium, these effects will cause an abbreviation in the APD.\textsuperscript{125,127} However, in the epicardium, while these effects do occur, the outcome is modulated by the presence of a dominant transient outward current (I\textsubscript{to}), which will open at more negative potentials and efflux of K\textsuperscript{+} will hyperpolarize the membrane. Though this would likely shift the membrane potential below the activation range of I\textsubscript{Ca} and hence decrease the number of open Ca\textsuperscript{2+} channels, relevant Ca\textsuperscript{2+} channels have already been activated during phase 0 depolarization. Furthermore, as a consequence of membrane hyperpolarization, the electrical gradient of the Ca\textsuperscript{2+} ions across the membrane is increased. This means that open Ca\textsuperscript{2+} channels will conduct more ions; I\textsubscript{to} will rapidly inactivate reducing the outward current giving rise to a delayed net inward current, I\textsubscript{Ca}; and the delay in I\textsubscript{Ca} would, in turn, delay activation of outward repolarizing components, hence resulting in a prolongation of the epicardial APD.\textsuperscript{74,76} This demonstrates the contrasting effects of propranolol on the endocardium and epicardium, resulting in increased TDR and thus a proarhythmic phenotype via promoting spatial heterogeneity in the form of transmural gradients.\textsuperscript{125,127} Nonetheless, at a higher critical threshold of propranolol concentration, the Na\textsuperscript{+} channel block in the epicardium will be sufficient to reduce phase 0 depolarization to even greater extent. As a consequence, with the shift of potentials negative to the activation threshold of I\textsubscript{Ca}, the outward currents would overwhelm any activated inward current, preventing the previously discussed proarhythmic sequence of electrical changes and, hence, exerting antiarrhythmic effects.\textsuperscript{125,127}

This demonstrates that the antiarrhythmic properties of propranolol are achieved at higher concentrations. However, the optimal dose of propranolol in LQTS3 has not been investigated clinically. Furthermore, the optimal antiarrhythmic dose in humans may be of such a high concentration that its use is not clinically feasible.\textsuperscript{125}
Figure 5. Potential physiological mechanisms for the paradoxical effects of propranolol through its \( \text{Na}^+ \text{V}1.5 \) blocking effects. (A) In the endocardium this will abbreviate the APD. In the epicardium, the dominant transient outward current (\( I_{\text{to}} \)) will open at more negative potentials, hyperpolarizing the membrane. Though fewer \( \text{Ca}^{2+} \) channels will open, sufficient \( \text{Ca}^{2+} \) channels have already activated during phase 0 depolarization. \( I_{\text{to}} \) will rapidly inactivate giving rise to a delayed net inward current, \( I_{\text{Ca}} \). In turn, this delays the activation of outward repolarizing components, hence prolonging the epicardial APD. Thus, spatial heterogeneity of transmural gradients develops, leading to a proarrhythmic phenotype. (B) At a higher critical threshold of propranolol concentration, \( \text{Na}^+ \text{V}1.5 \) block in the epicardium will reduce phase 0 depolarization to even greater extent, shifting the potential negative to the activation threshold of \( I_{\text{Ca}} \). The outward currents overwhelm any activated inward current, preventing the previous proarrhythmic sequence and hence exert antiarrhythmic effects.

\( \beta \)-Blocker type: compliance, long-term use, and \( \text{Na}^+ \) channel block

Different \( \beta \)-blockers have different efficacies in LQTS. Initially, this phenomenon was reported in LQTS1 and LQTS2 patients;\(^{130,131} \) one study reported that, among LQTS1 patients, atenolol was associated with a significant reduction in the risk of cardiac events, whereas nadolol was not. On the other hand, in LQTS2 patients, nadolol was associated with a significant reduction in the risk of cardiac events.\(^{130} \) However, a later study with a larger sample size partially contradicted these findings;\(^{131} \) the study compared the efficacy of atenolol, metoprolol, propranolol, and nadolol in reducing the risk of first cardiac event and reported that in LQTS1, all of the \( \beta \)-blockers were associated with a similar reduction of risk. Nonetheless, the results for LQTS2 patients were consistent, finding that only nadolol had a significant effect in reducing the risk of cardiac events.\(^{131} \) Other
studies reported the superior efficacy of the nonspecific β-blockers nadolol and propranolol, over selective blockers, such as metoprolol and atenolol. Similarly, a recent study with a population including LQTS3 patients found that nadolol was associated with a significant 62% reduction in the risk of life-threatening arrhythmic events. This was not the case for propranolol or selective β-blockers (i.e., metoprolol, atenolol, bisoprolol, carvedilol, and nebivolol).

Compliance. Regarding the reported differences in efficacy between the nonselective β-blockers nadolol and propranolol, they may be explained by differences in drug compliance. Noncompliance has been reported as an important factor underlying β-blocker therapy failures. For example, in 216 LQTS1 patients, 67% of patients who suffered cardiac arrest were noncompliant. And there have been no studies comparing the compliance of different β-blockers in LQTS patients. However, based on pharmacokinetic knowledge, previous reports predict a higher compliance for nadolol than propranolol. For example, propranolol is highly lipophilic, allowing it to cross the blood–brain barrier (BBB) and reach concentrations within the cerebrospinal fluid similar to that in free plasma concentration. By contrast, nadolol is significantly less lipophilic and hence does not cross the BBB. Therefore, propranolol is associated with more central nervous system side effects and potentially lower compliance than nadolol. This may account for previous reports of nadolol as more effective than propranolol in the treatment of LQT, or that propranolol is ineffective.

Long-term effects: receptor sensitization and electrical remodeling. The superior efficacy of nonselective β-blockers may be explained by the effects of selective blockers on receptor sensitization. The myocardium expresses β1, β2, and β3 adrenoceptors at proportions of 70–80%, 20–30%, and <2%, respectively. However, the functional expression of receptors has been reported to change both as a consequence of a variety of pathological conditions, such as heart failure, and of pharmacological interventions, such as selective β1-receptor blockers. Thus, selective β1-adrenoceptor blockers will result in increased functional expression and activity of β2-adrenoceptors that, acting via the Gαs subunit, will result in downstream positive inotropic and chronic effects similar to those generated by β1-adrenoceptor activation. Therefore, β2-adrenoceptors sensitization as a result of selective β1-adrenoceptor blocker use will compromise the ability of the β-blocker to prevent cardiac arrhythmias. 

In addition to changes in receptor expression and sensitization, the long-term β-blocker use has been associated with electrical remodeling of the myocardium. These changes have been reported to be antiarrhythmic in some rhythm disturbances, such as AF. Electrical remodeling arising from chronic β-blocker use primarily involves a decrease in the potassium repolarization currents, including functional decreases in the transient outward (Ito) and inward rectifier (Ikr) potassium currents. This causes prolonged repolarization and increases APD.

On the other hand, Ica-L was not changed in amplitude, single channel kinetics, or expression. However, chronic β-blockade in mice was associated with impaired intracellular Ca+2 transients. Chronic β-blocker use in LQTS, unlike AF, is likely to be proarrhythmic, as they contribute to further prolonging of the APD, and hence arrhythmic triggers. Nonetheless, the long-term consequences of β-blockade on ion channel remodeling in the abnormal LQTs heart, and how that will influence the arrhythmic phenotype, has not been investigated and offers an important area for future research.

Na+ channel block. Comparison between different β-blockers is further complicated by different abilities to block the Na+ channel, which, as discussed previously, is an important aspect of their antiarrhythmic effects, especially in LQTS3. Of the β-blockers, propranolol exhibits the greatest Na+ blocking effect. One study using whole-cell patch clamp recordings reported that propranolol, but not nadolol, had Na+ blocking effects. Another study found that propranolol reduces both the peak and late Na+ currents and causes a hyperpolarizing shift in both the activation and steady state curves of the Na+ channel. On the other hand, nadolol reduces the peak but not the late Na+ current, and causes a hyperpolarizing shift in the activation and steady state curves of the Na+ channel. The difference in channel blocking effect may be due to the lipophilic structure of propranolol allowing it to move through the
membrane toward the blocking site. Thus, despite propranolol having greater Na\(^+\) channel inhibition, nadolol has been found to be more effective. This may be due to the previously discussed findings that Na\(^+\) channel inhibition is not necessarily antiarrhythmic but, under certain concentrations, proarrhythmic by increasing TDR. Therefore, it could be that nadolol avoids these proarrhythmic changes and is, hence, more effective than propranolol at clinically relevant concentrations.

Conclusions

The antiarrhythmic efficacy of β-blockers is a genotype-specific phenomenon, and therefore the use of β-blockers in clinical practice should be genotype dependent. In LQTS1 and LQTS2, cardiac events most commonly occur during periods of increased sympathetic activity, which increases arrhythmic triggers, EADs, and substrate, TDR. Treatment with β-blockers is successful in reducing cardiac events via reducing arrhythmic triggers and substrates, thus supporting the use of β-blockers in the treatment of LQTS1 and LQTS2. LQTS3 represents a more complex situation both with respect to clinical reports and physiological mechanisms. In LQTS3, cardiac events most commonly occur during periods typically associated with decreased sympathetic activity suggesting a protective role, but some still occurred during periods of increased activity. Investigations into the effects of sympathetic stimulation on arrhythmic triggers and substrate and the use of β-blockers produced contradictory results.

We offer insight to explain this by tying together disparate data. It becomes clear that understanding LQTS3 requires further research. Clinical studies with larger sample sizes and that control both for the type of β-blocker and concentration should clarify the optimal therapeutic protocol in LQTS3. If results are consistent with nadolol being the most effective at preventing arrhythmias in LQTS3, the mechanisms behind this could be investigated. We offer three testable hypotheses for nadolol being the drug of choice. First, nadolol’s non-selectivity prevents the sensitization of other β-adrenoceptors as occurs in selective β-blockers, and hence offers maximal antiadrenergic effect. Second, a study comparing the compliance of nadolol to propranolol in LQTS3 may show nadolol having higher compliance due to fewer side effects. Third, under clinically relevant concentrations, nadolol may shorten the APD of epicardial and endocardial LQTS3 cells, hence reducing TDRs in addition to suppressing EADs.

Acknowledgments

BioRender.com was used in the creation of Figures 3 and 5.

Competing interests

The authors declare no competing interests.

References

1. Huang, C.L., L. Wu, K. Jeewaratnam, et al. 2020. Update on antiarrhythmic drug pharmacology. J. Cardiovasc. Electrophysiol. 31: 579–592.
2. Crotti, L., G. Celano, F. Dagrati, et al. 2008. Congenital long QT syndrome. Orphanet. J. Rare Dis. 3: 18.
3. Schwartz, P.J., M. Stramba-Badiale, L. Crotti, et al. 2009. Prevalence of the congenital long-QT syndrome. Circulation 120: 1761–1767.
4. Chadda, K.R., K. Jeewaratnam, M. Lei, et al. 2017. Sodium channel biophysics, late sodium current and genetic arrhythmogenic syndromes. Pflugers Arch. 469: 629–641.
5. Meyer, J.S., A. Mehdirad, B.I. Salem, et al. 2003. Sudden arrhythmia death syndrome: importance of the long QT syndrome. Am. Fam. Phys. 68: 483–488.
6. Johnson, J.N., D.J. Tester, J. Perry, et al. 2008. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. Heart Rhythm 5: 704–709.
7. Zellerhoff, S., R. Pistulli, G. Mönnig, et al. 2009. Atrial arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. J. Cardiovasc. Electrophysiol. 20: 401–407.
8. Baskar, S. & P.F. Aziz. 2015. Genotype–phenotype correlation in long QT syndrome. Glob. Cardiol. Sci. Pract. 2015: 26.
9. Napolitano, C., S.G. Priori, P.J. Schwartz, et al. 2005. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 294: 2975–2980.
10. Martin, C.A., G.D. Matthews & C.L. Huang. 2012. Sudden cardiac death and inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease. Heart 98: 536–543.
11. Kleber, A.G. & Y. Rudy. 2004. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol. Rev. 84: 431–488.
12. Kalin, A., J. Usher-Smith, V.J. Jones, et al. 2010. Cardiac arrhythmia: a simple conceptual framework. Trends Cardiovasc. Med. 20: 103–107.
13. Gordan, R., J.K. Gwathmey & L.H. Xie. 2015. Autonomic and endocrine control of cardiovascular function. World J. Cardiol. 7: 204–214.
14. Behar, J., A. Ganesan, J. Zhang, et al. 2016. The autonomic nervous system regulates the heart rate through...
cAMP-PKA dependent and independent coupled-clock pacemaker cell mechanisms. *Front. Physiol.* 7: 419.
15. Bers, D.M. 2002. Cardiac excitation–contraction coupling. *Nature* 415: 198–205.
16. Gardner, R.T., C.M. Ripplinger, R.C. Myles, et al. 2016. Molecular mechanisms of sympathetic remodeling and arrhythmias. *Circ. Arrhythm. Electrophysiol.* 9: e001359.
17. Pogwizd, S.M. & D.M. Bers. 2004. Cellular basis of triggered arrhythmias in heart failure. *Trends Cardiovasc. Med.* 14: 61–66.
18. Sperelakis, N., Z. Xiong, G. Haddad, et al. 1994. Regulation of slow calcium channels of myocardial cells and vascular smooth muscle cells by cyclic nucleotides and phosphorylation. *Mol. Cell. Biochem.* 140: 103–117.
19. O’Connell, T.D., B.C. Jensen, A.J. Baker, et al. 2014. Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance. *Pharmacol. Rev.* 66: 308–333.
20. Rubart, M. & D.P. Zipes. 2005. Mechanisms of sudden cardiac death. *J. Clin. Invest.* 115: 2305–2315.
21. Zipes, D.P. & M. Rubart. 2006. Neural modulation of cardiac arrhythmias and sudden cardiac death. *Heart Rhythm* 3: 108–113.
22. Pogwizd, S.M., K. Schlothauer, L. Li, et al. 2001. Arrhythmogenesis and contractile dysfunction in heart failure: roles of sodium–calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. *Circ. Res.* 88: 1159–1167.
23. Haffaker, R., S.T. Lamp, J.N. Weiss, et al. 2004. Intracellular calcium cycling, early afterdepolarizations, and reentry in simulated long QT syndrome. *Heart Rhythm* 1: 441–448.
24. Shen, M.J. & D.P. Zipes. 2014. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ. Res.* 114: 1004–1021.
25. Chandra, R., V.S. Chauhan, C.F. Starmer, et al. 1999. Beta-adrenergic action on wild-type and KPQ mutant human cardiac Na+ channels: shift in gating but no change in Ca2+/Na+ selectivity. *Cardiovasc. Res.* 42: 490–502.
26. Schreibmayer, W., B. Frohnmwieser, N. Dascal, et al. 1994. Beta-adrenergic modulation of currents produced by rat cardiac Na+ channels expressed in *Xenopus laevis* oocytes. *Recept. Channels* 2: 339–350.
27. Frohnmwieser, B., L.Q. Chen, W. Schreibmayer, et al. 1997. Modulation of the human cardiac sodium channel alpha-subunit by cAMP-dependent protein kinase and the responsible sequence domain. *J. Physiol.* 498(Pt. 2): 309–318.
28. Ono, K., H.A. Fozzard & D.A. Hanck. 1993. Mechanism of cAMP-dependent modulation of cardiac sodium channel current kinetics. *Circ. Res.* 72: 807–815.
29. Shibata, E.F., T.L. Brown, Z.W. Washburn, et al. 2006. Autonomic regulation of voltage-gated cardiac ion channels. *J. Cardiovasc. Electrophysiol.* 17(Suppl. 1): S34–S42.
30. Palygin, O.A., J.M. Pettus & E.F. Shibata. 2008. Regulation of caveolar cardiac sodium current by a single Gsalpha histidine residue. *Am. J. Physiol. Heart Circ. Physiol.* 294: H1693–H1699.
mice lacking the p75 neurotrophin receptor. *Am. J. Physiol. Heart Circ. Physiol.* **298**: H1652–H1660.

62. Yagishita, D., R.W. Chui, K. Yamakawa, *et al.* 2015. Sympathetic nerve stimulation, not circulating norepinephrine, modulates T-peak to T-end interval by increasing global dispersion of repolarization. *Circ. Arrhythm. Electrophysiol.* **8**: 174–185.

63. Franciosi, S., F.K.G. Perry, T.M. Roston, *et al.* 2017. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. *Auton. Neurosci.* **205**: 1–11.

64. Antzelevitch, C., S. Sicouri, S.H. Litovsky, *et al.* 1991. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. *Circ. Res.* **69**: 1427–1449.

65. Nääbauer, M., D.J. Beuckelmann, P. Uberfuhr, *et al.* 1996. Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. *Circulation* **93**: 168–177.

66. Brunet, S., F. Aimond, H. Li, *et al.* 2004. Heterogeneous expression of repolarizing, voltage-gated K$^+$ currents in adult mouse ventricles. *J. Physiol.* **559**: 103–120.

67. Mantravadi, R., B. Gabris, T. Liu, *et al.* 2007. Autonomic nerve stimulation reverses ventricular repolarization sequence in rabbit hearts. *Circ. Res.* **100**: e72–e80.

68. Antzelevitch, C., G.X. Yan & W. Shimizu. 1999. Transmural dispersion of repolarization and arrhythmogenicity: the Brugada syndrome versus the long QT syndrome. *J. Electrocardiol.* **32**(Suppl.): 158–165.

69. Baker, L.C., B. London, B.R. Choi, *et al.* 2000. Enhanced dispersion of repolarization and refractoriness in transgenic mouse hearts promotes reentrant ventricular tachycardia. *Circ. Res.* **86**: 396–407.

70. Schwartz, P.J., S.G. Priori, E.H. Locati, *et al.* 1995. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na$^+$ channel blockade and to increases in heart rate. Implications for gene-specific therapy. *Circulation* **92**: 3381–3386.

71. Schwartz, P.J., S.G. Priori, C. Spazzolini, *et al.* 2001. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* **103**: 89–95.

72. Somers, V.K., M.E. Dyken, A.L. Mark, *et al.* 1993. Sympathetic-nerve activity during sleep in normal subjects. *N. Engl. J. Med.* **328**: 303–307.

73. Moss, A.J., J.L. Robinson, L. Gessman, *et al.* 1999. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *Am. J. Cardiol.* **84**: 876–879.

74. Wilde, A.A., R.J. Jongbloed, P.A. Doevendans, *et al.* 1999. Auditory stimuli as a trigger for arrhythmic events differentiating HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J. Am. Coll. Cardiol.* **33**: 327–332.

75. van den Berg, M.P., A.A. Wilde, T.J.W. Viersma, *et al.* 2001. Possible bradycardic mode of death and successful pacemaker treatment in a large family with features of long
QT syndrome type 3 and Brugada syndrome. *J. Cardiovasc. Electrophysiol.* **12**: 630–636.

76. Swan, H., M. Vittasalo, K. Piippo, et al. 1999. Sinus node function and ventricular repolarization during exercise stress test in long QT syndrome patients with KvLQT1 and HERG potassium channel defects. *J. Am. Coll. Cardiol.* **34**: 823–829.

77. Shimizu, W. & C. Antzelevitch. 2000. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J. Am. Coll. Cardiol.* **35**: 778–786.

78. Noda, T., H. Takaki, T. Kurita, et al. 2002. Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur. Heart J.* **23**: 975–983.

79. Ackerman, M.J., A. Khositseth, D.J. Tester, et al. 2002. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin. Proc.* **77**: 413–421.

80. Shimizu, W. & C. Antzelevitch. 1998. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* **98**: 2314–2322.

81. Takenaka, K., T. Ai, W. Shimizu, et al. 2003. Exercise stress test amplifies genotype–phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation* **107**: 838–844.

82. Shimizu, W., T. Noda, H. Takaki, et al. 2003. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *J. Am. Coll. Cardiol.* **41**: 633–642.

83. Priori, S.G., C. Napolitano, F. Cantù, et al. 1996. Differential response to Na⁺ channel blockade, beta-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. *Circ. Res.* **78**: 1009–1015.

84. Tanabe, Y., M. Inagaki, T. Kurita, et al. 2001. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J. Am. Coll. Cardiol.* **37**: 911–919.

85. Zaza, A., L. Belardinelli & J.C. Shroyock. 2008. Pathophysiology and pharmacology of the cardiac "late sodium current." *Pharmacol. Ther.* **119**: 326–339.

86. Antzelevitch, C., V. Nesterenko, J.C. Shroyock, et al. 2014. The role of late I Na in development of cardiac arrhythmias. *Handb. Exp. Pharmacol.* **221**: 137–168.

87. Belardinelli, L., J.C. Shroyck & H. Fraser. 2006. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart* **92**(Suppl. 4): iv6–iv14.

88. Belardinelli, L., W.R. Giles, S. Rajamani, et al. 2015. Cardiac late Na⁺ current: proarrhythmic effects, roles in long QT syndromes, and pathological relationship to CaMKII and oxidative stress. *Heart Rhythm* **12**: 440–448.

89. Hegyi, B., T. Bányász, L.T. Izu, et al. 2018. B-adrenergic regulation of late Na⁺. *J. Mol. Cell. Cardiol.* **123**: 168–179.

90. Hegyi, B., S. Morotti, C. Liu, et al. 2019. Enhanced depolarization drive in failing rabbit ventricular myocytes: calcium-dependent and β-adrenergic effects on late sodium, L-type calcium, and sodium–calcium exchange currents. *Circ. Arrhythm. Electrophysiol.* **12**: e007061.

91. Tsurugi, T., T. Nagatomo, H. Abe, et al. 2009. Differential modulation of late sodium current by protein kinase A in R1623Q mutant of LQT3. *Life Sci.* **84**: 380–387.

92. Tateyama, M., I. Rivolta, C.E. Clancy, et al. 2003. Modulation of cardiac sodium channel gating by protein kinase A can be altered by disease-linked mutation. *J. Biol. Chem.* **278**: 46718–46726.

93. Fabritz, L., D. Danke, M. Emmerich, et al. 2010. Autonomic modulation and antiarrhythmic therapy in a model of long QT syndrome type 3. *Cardiovasc. Res.* **87**: 60–72.

94. Chadda, K.R., S. Ahmad, H. Valli, et al. 2017. The effects of ageing and adrenergic challenge on electrocardiographic phenotypes in a murine model of long QT syndrome type 3. *Sci. Rep.* **7**: 11070.

95. Nuyens, D., M. Stengl, S. Dugarmaa, et al. 2001. Abrupt rate accelerations or premature beats cause life-threatening arrhythmias in mice with long-QT3 syndrome. *Nat. Med.* **7**: 1021–1027.

96. Head, C.E., R. Balasubramaniam, G. Thomas, et al. 2005. Paced electrogram fractionation analysis of arrhythmogenic tendency in DeltaKPQ Scn5a mice. *J. Cardiovasc. Electrophysiol.* **16**: 1329–1340.

97. Chinushi, M., D. Izumi, K. Iijima, et al. 2008. Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anphopleurin—a model of type-3 long QT syndrome. *Europace* **10**: 249–255.

98. Ahrens-Nicklas, R.C., C.E. Clancy & D.J. Christini. 2009. Re-evaluating the efficacy of beta-adrenergic agonists and antagonists in long QT-3 syndrome through computational modelling. *Cardiovasc. Res.* **82**: 439–447.

99. Nerbønne, J.M. 2004. Studying cardiac arrhythmias in the mouse—a reasonable model for probing mechanisms? *Trends Cardiovasc. Med.* **14**: 83–93.

100. Choy, L., J.M. Yeo, V. Tse, et al. 2016. Cardiac disease and arrhythmogenesis: mechanistic insights from mouse models. *Int. J. Cardiol. Heart Vasc.* **12**: 1–10.

101. Huang, C.L. 2017. Murine electrophysiological models of cardiac arrhythmogenesis. *Physiol. Rev.* **97**: 283–409.

102. Sabir, I.N., M.J. Killeen, A.A. Grace, et al. 2002. Correlation of adrenergic stimulation onelectrocardiographic phenotypes in a murine model of long QT3 syndrome. *Circulation* **105**: 249–255.

103. Clauss, S., C. Beyer, D. Schüttler, et al. 2019. Animal models of arrhythmia: classic electrophysiology to genetically modified large animals. *Nat. Rev. Cardiol.* **16**: 457–475.

104. Danik, S., C. Cabo, C. Chiello, et al. 2002. Abrupt rate accelerations or premature beats cause life-threatening arrhythmias in mice with long-QT3 syndrome. *Nat. Med.* **7**: 1021–1027.

105. Fabritz, L., P. Kirchhof, M.R. Franz, et al. 2003. Effect of pacing and mexiletine on dispersion of repolarization and...
arrhythmias in DeltaKPQ SCN5A (long QT3) mice. *Circ. Res.* 57: 1085–1093.

106. Moss, A.J. 1998. Management of patients with the hereditary long QT syndrome. *J. Cardiovasc. Electrophysiol.* 9: 668–674.

107. Priori, S.G., E. Aliot, C. Blomstrom-Lundqvist, et al. 2001. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur. Heart J.* 22: 1374–1450.

108. Giudicessi, J.R. & M.J. Ackerman. 2013. Genotype- and phenotype-guided management of congenital long QT syndrome. *Curr. Probl. Cardiol.* 38: 417–455.

109. Schwartz, P.J. 1985. Idiopathic long QT syndrome: progress and questions. *Am. Heart J.* 109: 399–411.

110. Moss, A.J., W. Zareba, W.J. Hall, et al. 2000. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 101: 616–623.

111. Moss, A.J., W. Shimizu, A.A. Wilde, et al. 2007. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 115: 2481–2489.

112. Shimizu, W., A.J. Moss, A.A. Wilde, et al. 2009. Genotype–phenotype aspects of type 2 long QT syndrome. *J. Am. Coll. Cardiol.* 54: 2052–2062.

113. Priori, S.G., C. Napolitano, P.J. Schwartz, et al. 2004. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 292: 1341–1344.

114. Ahn, J., H.J. Kim, J.I. Choi, et al. 2017. Effectiveness of beta-blockers depending on the genotype of congenital long-QT syndrome: a meta-analysis. *PLoS One* 12: e0185680.

115. Villain, E., I. Denjoy, J.M. Lupoglazoff, et al. 2004. Low incidence of cardiac events with beta-blockers in children with long QT syndrome. *Eur. Heart J.* 25: 1405–1411.

116. Vincent, G.M., P.J. Schwartz, I. Denjoy, et al. 2009. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment “failures”. *Circulation* 119: 215–221.

117. Koponen, M., A. Marjamaa, A. Hiippala, et al. 2015. Follow-up of 316 molecularly defined pediatric long-QT syndrome patients: clinical course, treatments, and side effects. *Circ. Arrhythm. Electrophysiol.* 8: 815–823.

118. Gemma, L.W., G.M. Ward, M.M. Dettmer, et al. 2011. B-blockers protect against dispersion of repolarization during exercise in congenital long-QT syndrome type 1. *J. Cardiovasc. Electrophysiol.* 22: 1141–1146.

119. Shimizu, W., Y. Tanabe, T. Aiba, et al. 2002. Differential effects of beta-blockade on dispersion of repolarization in the absence and presence of sympathetic stimulation between the LQT1 and LQT2 forms of congenital long QT syndrome. *J. Am. Coll. Cardiol.* 39: 1984–1991.

120. Zareba, W., M.N. Sattari, S. Rosero, et al. 2001. Altered atrial, atrioventricular, and ventricular conduction in patients with the long QT syndrome caused by the DeltaKPQ SCN5A sodium channel gene mutation. *Am. J. Cardiol.* 88: 1311–1314.

121. Wilde, A.A., A.J. Moss, E.S. Kaufman, et al. 2016. Clinical aspects of type 3 long-QT syndrome: an International Multicenter Study. *Circulation* 134: 872–882.

122. Kutufa, V., U.A. Daimee, S. McNitt, et al. 2018. Clinical aspects of the three major genetic forms of long QT syndrome (LQT1, LQT2, LQT3). *Ann. Noninvasive Electrocardiol.* 23: e12537.

123. Mazzanti, A., R. Maragna, G. Vacanti, et al. 2018. Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome. *J. Am. Coll. Cardiol.* 71: 1663–1671.

124. Calvillo, L., C. Spazzolini, E. Vullo, et al. 2014. Propranolol prevents life-threatening arrhythmias in LQT3 transgenic mice: implications for the clinical management of LQT3 patients. *Heart Rhythm* 11: 126–132.

125. Thomas, G., M.J. Killeen, A.A. Grace, et al. 2008. Pharmacological separation of early afterdepolarizations from arrhythmogenic substrate in DeltaKPQ Scn5a murine hearts modelling human long QT 3 syndrome. *Acta Physiol (Oxf.)* 192: 505–517.

126. Duff, H.J., D.M. Roden, L. Brorson, et al. 1983. Electrophysiological actions of high plasma concentrations of propranolol in human subjects. *J. Am. Coll. Cardiol.* 2: 1134–1140.

127. Krishnan, S.C. & C. Antzelevitch. 1991. Sodium channel block produces opposite electrophysiological effects in canine ventricular epicardium and endocardium. *Circ. Res.* 69: 277–291.

128. Raouls, D.O. & J.K. Baker. 1979. Relationship of nonspecific antiarrhythmic and negative inotropic activity with physicochemical parameters of propranolol analogues. *J. Med. Chem.* 22: 81–86.

129. Matthews, J.C. & J.K. Baker. 1982. Effects of propranolol and a number of its analogues on sodium channels. *Biochim. Pharmacol.* 31: 1681–1685.

130. Goldenberg, I., J. Bradley, A. Moss, et al. 2010. Beta-blocker efficacy in high-risk patients with the congenital long-QT syndrome types 1 and 2: implications for patient management. *J. Cardiovasc. Electrophysiol.* 21: 893–901.

131. Abu-Zaitone, A., D.R. Peterson, B. Polonsky, et al. 2014. Efficacy of different beta-blockers in the treatment of long QT syndrome. *J. Am. Coll. Cardiol.* 64: 1352–1358.

132. Dorostkar, P.C., M. Eldar, B. Belhassen, et al. 1999. Long-term follow-up of patients with long-QT syndrome treated with beta-blockers and continuous pacing. *Circulation* 100: 2431–2436.

133. Chatrath, R., C.M. Bell & M.J. Ackerman. 2004. Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. *Pediatr. Cardiol.* 25: 459–465.

134. Chockalingam, P., L. Crotti, G. Girardengo, et al. 2012. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. *J. Am. Coll. Cardiol.* 60: 2092–2099.

135. Grace, A.A. & G.D.K. Matthews. 2018. Phenotypic landscape and risk management in long QT syndrome: nudging forward. *J. Am. Coll. Cardiol.* 71: 1672–1675.

136. Riddell, J.G., D.W. Harron & R.G. Shanks. 1987. Clinical pharmacokinetic of beta-adrenoceptor antagonists. *An update.* *Clin. Pharmacokinet.* 12: 305–320.

137. Neil-Dwyer, G., J. Bartlett, J. McAlinsh, et al. 1981. Beta-adrenoceptor blockers and the blood–brain barrier. *Br. J. Clin. Pharmacol.* 11: 549–553.
138. Bristow, M.R., R. Ginsburg, V. Umans, et al. 1986. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circ. Res. 59: 297–309.

139. Hall, J.A., A.J. Kaumann & M.J. Brown. 1990. Selective beta 1-adrenoceptor blockade enhances positive inotropic responses to endogenous catecholamines mediated through beta 2-adrenoceptors in human atrial myocardium. Circ. Res. 66: 1610–1623.

140. Hall, J.A., M.C. Petch & M.J. Brown. 1991. In vivo demonstration of cardiac beta 2-adrenoceptor sensitization by beta 1-antagonist treatment. Circ. Res. 69: 959–964.

141. Hall, J.A., A. Ferro, J.E. Dickerson, et al. 1993. Beta adrenoreceptor subtype cross regulation in the human heart. Br. Heart J. 69: 332–337.

142. Kharche, S.R., T. Stary, M.A. Colman, et al. 2014. Effects of human atrial ionic remodelling by β-blocker therapy on mechanisms of atrial fibrillation: a computer simulation. Europace 16: 1524–1533.

143. Workman, A.J., K.A. Kane, J.A. Russell, et al. 2003. Chronic beta-adrenoceptor blockade and human atrial cell electrophysiology: evidence of pharmacological remodelling. Cardiovasc. Res. 58: 518–525.

144. Workman, A.J. 2010. Cardiac adrenergic control and atrial fibrillation. Naunyn Schmiedebergs Arch. Pharmacol. 381: 235–249.

145. Marshall, G.E., J.A. Russell, J.O. Tellez, et al. 2012. Remodelling of human atrial K+ currents but not ion channel expression by chronic β-blockade. Pflugers Arch. 463: 537–548.

146. Raine, A.E. & E.M. Vaughan Williams. 1981. Adaptation to prolonged beta-blockade of rabbit atrial, purkinje, and ventricular potentials, and of papillary muscle contraction. Time-course of development of and recovery from adaptation. Circ. Res. 48: 804–812.

147. Redpath, C.J., A.C. Rankin, K.A. Kane, et al. 2006. Anti-adrenergic effects of endothelin on human atrial action potentials are potentially anti-arrhythmic. J. Mol. Cell. Cardiol. 40: 717–724.

148. Grammer, J.B., X. Zeng, R.F. Bosch, et al. 2001. Atrial L-type Ca2+-channel, beta-adrenoceptor, and 5-hydroxytryptamine type 4 receptor mRNAs in human atrial fibrillation. Basic Res. Cardiol. 96: 82–90.

149. Bartholomeu, J.B., A.S. Vanzelli, N.P. Rolim, et al. 2008. Intracellular mechanisms of specific beta-adrenoceptor antagonists involved in improved cardiac function and survival in a genetic model of heart failure. J. Mol. Cell. Cardiol. 45: 240–249.

150. Wang, D.W., A.M. Mistry, K.M. Kahlig, et al. 2010. Propranolol blocks cardiac and neuronal voltage-gated sodium channels. Front. Pharmacol. 1: 144.

151. Besana, A., D.W. Wang, A.L. George, et al. 2012. Nadolol block of Nav1.5 does not explain its efficacy in the long QT syndrome. J. Cardiovasc. Pharmacol. 59: 249–253.