Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anthopleurin-A model of type-3 long QT syndrome

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Aims The effects of adrenergic activity and beta-blockade were studied in a canine experimental model of type-3 long QT syndrome (LQT3) induced by application of anthopleurin-A.

Methods and results Boluses of epinephrine at 0.5 and/or 1.0 µg/kg were administered before and after propranolol, 0.3 mg/kg, and the distribution of the ventricular repolarization and the development of polymorphic ventricular tachyarrhythmia (VA) were assessed. Using needle electrodes, transmural unipolar electrograms were recorded across the left ventricle (LV) and right ventricle (RV). Activation-recovery interval (ARI) was measured in each electrogram to estimate local repolarization during RV pacing at the cycle length of 750 ms after the creation of complete atrioventricular block. Before propranolol, epinephrine, 0.5 µg/kg, did not induce VA in any experiment. However, a dose of 1.0 µg/kg induced polymorphic VA following multiple premature ventricular complex (PVC) in four of six experiments. Epinephrine, 0.5 µg/kg, did not induce VA in any experiment. However, a dose of 1.0 µg/kg induced polymorphic VA following multiple premature ventricular complex (PVC) in four of six experiments. Epinephrine, 0.5 µg/kg, shortened ARI at all sites and lessened LV transmural ARI dispersion. Neither ARI nor its dispersion could be determined after 1.0 µg/kg of epinephrine because of the induction of PVC, polymorphic VA, or both. Propranolol (i) prevented epinephrine-induced PVC and polymorphic VA in all experiments, (ii) slightly prolonged ARI at all sites, along with a decrease in LV transmural ARI dispersion, and (iii) reversed the epinephrine-induced shortening of ARI.

Conclusion In this LQT3 model, an increase in adrenergic activity by epinephrine had dose-dependent, opposite effects on ventricular electrical stability. Since beta-adrenergic blockade suppressed epinephrine-induced PVC and polymorphic VA, it might be considered for supplemental therapy to suppress VA in patients presenting with LQT3.

KEYWORDS Type-3 long QT syndrome; Adrenergic activity; Beta-adrenergic blockade

Introduction The enhancement of adrenergic activity is arrhythmogenic,1–3 and beta-adrenergic blockade is antiarrhythmic4,5 in patients suffering from congenital type-1 (LQT1) or type-2 (LQT2) long QT syndrome (LQTS). The effects of adrenergic activity on ventricular arrhythmias (VA) in type-3 (LQT3) congenital LQTS, however, are poorly understood. While most adverse cardiac events in LQT3 occur at rest or during sleep, VA can, in some patients, develop during exercise or emotional stress.4,5 Experimental studies, using pharmacological models (arterially perfused ventricular myocardial wedges, sliced myocardium, or isolated myocardial cells),5–8 or genetically modified murine hearts,9,10 and a few clinical cases1–5 have examined the effects of adrenergic activity in congenital LQTS. However, these studies did not include analyses of intracardiac electrograms at multiple ventricular sites, and the basal autonomic tone was disrupted during the course of the experiments. Therefore, to further clarify the role of adrenergic activity in LQT3, we studied in vivo the effects of intravenous boluses of epinephrine administered before and after treatment with propranolol, in a whole heart model of LQT3 made by application of anthopleurin-A (AP-A),11,12 with special focus on the relationship between transmural dispersion of ventricular repolarization and epinephrine-induced polymorphic VA.

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Methods

Surgical preparation

This study was approved by the Animal Studies Subcommittee of the Institutional Review Board, and complied with the guidelines of the United States National Institutes of Health for the Care and Use of Laboratory Animals. The experiments were performed in six beagles weighing between 10.0 and 13.0 kg, which were anesthetized with a 17.5 mg/kg i.v. bolus of sodium thiopental, followed by a 5.0 mg/kg/h infusion. They were intubated and artificially ventilated. Catheters were inserted into the femoral vein for administration of fluids and drugs, and into the femoral artery to monitor arterial blood pressure (ABP). The core temperatures were kept at 37 °C with a thermostatically controlled thermal blanket. The ABP and leads I, III, and aVF of the surface electrocardiogram were continuously monitored. The hearts were exposed via a midline sternotomy, and saline warmed to 37 °C was regularly applied to moisten the heart and prevent cooling of the epicardial surface. Upon completion of the experiments, the animals were sacrificed by electrical induction of ventricular fibrillation under general anaesthesia.

Recordings and pacing electrodes

Four 21-gauge, stainless steel, plunge needle electrodes were inserted in the basal region of the lateral left ventricular (LV) wall, where prominent M-cell-like activity has been described in the dog,13,14 and three plunge electrodes were inserted into the right ventricular (RV) free wall. Each LV needle had eight and each RV six polymide-coated tungsten wire electrodes, 50 μm in diameter, 1 mm apart, for the simultaneous transmural recording of unipolar electrograms, from epicardial (Epi), mid-myocardial and endocardial (Endo) sites, with the last electrode of unipolar electrograms, from epicardial (Epi), mid-myocardial and endocardial (Endo) sites, with the last electrode recorded the Epi and the first electrode the Endo electrogram. To simplify the analysis, the electrode that recorded the longest activation–recovery interval (ARI) between Epi and Endo was used as representative of the Mid ventricular layer.12,13 ARI values were measured between the minimum first derivative of the intrinsic deflection of the QRS and maximum first derivative of the T wave of the unipolar electrogram,15,16 and used to estimate the local repolarization. Previous studies have shown that ARIs derived from unipolar electrograms reasonably approximate the local effective refractory periods.15,16 Furthermore, excellent correlation of ARI and the effective refractory period have been reported in the AP-A model.17 Complete atrioventricular (AV) block was produced by radiofrequency catheter ablation of the AV node so as to control the heart rate, and the hearts were paced from bipolar silver wire electrodes inserted on the RV wall, using 2.0-ms pulses at twice the diastolic threshold delivered by a programmable cardiac stimulator (Model SEC-3102, Nihon Kohden Co. Tokyo, Japan).

Pharmacologic intervention

A 5 μg/kg i.v. bolus of AP-A (Protein Express Inc., Cincinnati, OH, USA) dissolved in sterile saline was administered, followed by a 0.15 μg/kg/min continuous infusion. Epinephrine (Daich Sankyo Co. Ltd, Tokyo, Japan), diluted to 10 μg/mL in sterile saline, was injected in 0.5 μg/kg or 1.0 μg/kg i.v. boluses. Propranolol (AstraZeneca K.K., Osaka, Japan) was administered intravenously in doses of 0.3 mg/kg.

Study protocol and data collection

After creation of a complete AV block, the hearts were paced at the cycle length of 600 ms from the RV during the preparatory period of the experiments. The following protocol was applied in all six experiments during RV pacing at the cycle length of 750 ms.

(i) Before insertion of the needle electrodes in the ventricles, a 1.0 μg/kg i.v. bolus of epinephrine was administered.

(ii) Thereafter, the needle electrodes were positioned in the heart and AP-A was administrated. Recordings of ARI and of its transmural dispersion were obtained before and 60 s after an i.v. bolus of epinephrine, 0.5 μg/kg.

(iii) After a 10 min interval, an additional 1.0 μg/kg i.v. bolus of epinephrine was administered.

(iv) After the administration of propranolol, 0.3 mg/kg, recordings of ARI and of its transmural dispersion were obtained before and 60 s after an i.v. bolus of epinephrine, 1.0 μg/kg.

Inducibility of VA was assessed in each step of the protocol. If polymorphic VA developed, its modes of onset were examined from the transmural ventricular electrograms. ARI and ARI dispersion were averaged over three consecutive cycles. The experimental protocol was completed within 3 h after the creation of AV block, ~2.0 h after the onset of AP-A administration.

Statistical analysis

Values are presented as the means ± SEM. Statistical comparisons of ARI and percent shortening of ARI by epinephrine among the Endo, Mid, and Epi ventricular layers were performed by analysis of variance (ANOVA) using the software of SPSS ver.14 (SPSS Inc., Chicago, IL, USA). The ARI and percent shortening of ARI difference between two of the three ventricular layers (Mid vs. Epi, Mid vs. Endo, and Endo vs. Epi) was assessed using Scheffe’s test. Student’s t-test was used to assess the effects of epinephrine or propranolol administration on ARI and transmural ARI dispersion. Alteration of ABP by the administration of epinephrine or propranolol was also analysed using Student’s t-test. A P-value < 0.05 was considered statistically significant.

Results

Epinephrine-induced ventricular arrhythmias

After the creation of AV block, experiments were performed during RV pacing at a cycle length of 750 ms. Before the administration of AP-A, a 1.0 μg/kg bolus of epinephrine induced multiple PVC in all six experiments, though no sustained polymorphic VA was observed. After the administration of AP-A, epinephrine, in a dose of 0.5 μg/kg, induced no sustained polymorphic VA in any experiment (Figure 1A), although a few PVC developed in one experiment. In contrast, when administered at a dose of 1.0 μg/kg, epinephrine induced multiple PVCs in all experiments, and sustained polymorphic VA triggered by the PVC was induced in four of the six experiments (Figure 1B). As
observed in previous studies. The onset of polymorphic VA seemed to be associated with the development of PVC which, as they propagated, caused delayed conduction or conduction block at the LV Mid and Endo sites, where the ARIs were recorded during baseline rhythm (Figure 2). These findings seemed to suggest that re-entry was a likely mechanism of the polymorphic VA, but this could not be demonstrated in this study because of the very low resolution of the analysis of ventricular activation and unipolar recording of the local electrogram. After the administration of propranolol, epinephrine, in a dose of 1.0 \( \mu g/\text{kg} \), induced neither PVC nor polymorphic VA. However, when administered in a dose of 1.0 \( \mu g/\text{kg} \), epinephrine induced two PVC, of which the second triggered sustained polymorphic VA (B). After treatment with propranolol, neither PVC nor polymorphic VA was induced by epinephrine, 1.0 \( \mu g/\text{kg} \). See text for additional details. Endo, endocardial site; Mid, mid-myocardial site; Epi, epicardial site.

![Figure 1](image1.jpg)

**Figure 1** Effects of intravenous administration of epinephrine before and after propranolol in a model of LQT3 created with AP-A. Leads I and III of the surface electrocardiogram and selected LV transmural unipolar electrograms. The heart rate was paced at the cycle length of 750 ms. At baseline (A), epinephrine, 0.5 \( \mu g/\text{kg} \), induced neither PVC nor polymorphic VA. However, when administered in a dose of 1.0 \( \mu g/\text{kg} \), epinephrine induced two PVC, of which the second triggered sustained polymorphic VA (B). After treatment with propranolol, neither PVC nor polymorphic VA was induced by epinephrine, 1.0 \( \mu g/\text{kg} \). See text for additional details. Endo, endocardial site; Mid, mid-myocardial site; Epi, epicardial site.

![Figure 2](image2.jpg)

**Figure 2** Initiation of polymorphic VA by the administration of epinephrine. Leads I and III of the surface electrocardiogram and selected transmural unipolar electrograms of the LV and RV. The heart rate was paced at the cycle length of 750 ms. When administered at a dose of 1.0 \( \mu g/\text{kg} \), epinephrine induced three consecutive premature ventricular complexes, of which the third triggered sustained polymorphic VA. The onset of polymorphic VA appeared associated with delayed conduction, functional conduction block, or both, at the LV Mid/Endo layer. The measured ARIs are shown with each intracardiac cycle, and calculated ARI dispersion (ARI-D) is present. ARIs could not be calculated for some of the beats because QRS complex superimposed on the preceding T wave. Abbreviations as in Figure 1.

Activation-recovery interval and transmural activation–recovery interval-dispersion

Before propranolol
After the administration of AP-A, a transmural ARI dispersion as long as 61 ± 4 ms was recorded through the LV during RV pacing at the cycle length of 750 ms (Figure 3, Tables 1 and 2). The transmural ARI dispersion across the RV wall was 18 ± 2 ms (Figure 4, Tables 1 and 2). Epinephrine at 0.5 \( \mu g/\text{kg} \) shortened ARI at all sites (Figures 3 and 4, Table 1). Since the magnitude of ARI shortening by epinephrine was greater \((P < 0.001)\) in the LV Mid (13.4 ± 1.2%) and Endo (13.1 ± 1.1%) layers than at the Epi sites (9.2 ± 0.9%), the transmural LV ARI dispersion was shortened to 34 ± 3 ms (Table 2). In the RV, the amount of epinephrine-induced ARI shortening was 8.0 ± 1.2% in Endo, 9.2 ± 1.3% in Mid, and 8.7 ± 1.1% in Epi (ns), and ARI dispersion in the RV was 14 ± 2 ms 60 s after administration of epinephrine (Table 2). After the injection of 1.0 \( \mu g/\text{kg} \) of epinephrine, the ARI distribution and transmural ARI dispersion could not be ascertained in either ventricle because of the development of multiple PVC, polymorphic VA, or both.

After propranolol
The intravenous administration of propranolol slightly prolonged ARI at all sites (Figures 3 and 4, Table 1). In the LV, the magnitude of ARI prolongation was smaller \((P < 0.001)\) (Table 1)
layers than in the Epi layer (10.4 ± 0.6%), and the transmural ARI dispersion was shortened to 37 ± 2 ms after propranolol (Figure 3, Table 2). The administration of propranolol reversed the epinephrine-induced shortening of ARI in both ventricles (Figures 3 and 4, Table 1) and, 60 s after 1.0 μg/kg of epinephrine, ARI dispersion was 35 ± 2 ms in the LV and 17 ± 2 ms in the RV (Table 2).

Discussion

Two main observations emerged from this study. First, in an experimental model of LQT3 created with AP-A, adrenergic stimulation had opposite effects on ventricular electrical stability depending on the dose of epinephrine administered intravenously. While 0.5 μg/kg resulted in homogeneous distribution of ventricular repolarization, without induction of sustained polymorphic VA, 1.0 μg/kg was pro-arrhythmic and caused sustained polymorphic VA triggered by PVC in 2/3 of the experiments. Second, propranolol prevented the development of epinephrine-induced polymorphic VA, along with inducing a mild decrease in transmural dispersion of ventricular repolarization during stable ventricular pacing. Although we did not measure the circulating concentration of AP-A, the AP-A model is considered a suitable surrogate for clinical LQT3 because the ventricular repolarization is reasonably prolonged and polymorphic VA spontaneously develops, especially during the slower heart rate and/or following short–long–short cardiac cycle or T wave alternans.11,12,19

Adrenergic stimulation in long QT syndrome

Adrenergic stimulation augments several currents in the ventricular myocytes, including IKS, ICa, the Ca2+-activated chloride current, and the Na+/Ca2+ exchange current.20–22

Table 1 Effects of epinephrine on left and right ventricular activation–recovery intervals at baseline and after the administration of propranolol in the endocardial (Endo), mid-myocardial (Mid), and epicardial (Epi) layers

<table>
<thead>
<tr>
<th>Activation-recovery intervals</th>
<th>Endo</th>
<th>Mid</th>
<th>Epi</th>
<th>P (Endo vs. Mid vs. Epi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before epinephrine</td>
<td>496 (4)</td>
<td>509 (4)</td>
<td>449 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After epinephrine</td>
<td>432 (7)</td>
<td>441 (8)</td>
<td>407 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (baseline vs. epinephrine)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>After propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before epinephrine</td>
<td>522 (4)</td>
<td>532 (4)</td>
<td>495 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After epinephrine</td>
<td>518 (4)</td>
<td>526 (3)</td>
<td>492 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (baseline vs. epinephrine)</td>
<td>0.062</td>
<td>0.012</td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before epinephrine</td>
<td>443 (4)</td>
<td>455 (4)</td>
<td>438 (3)</td>
<td>0.008</td>
</tr>
<tr>
<td>After epinephrine</td>
<td>407 (3)</td>
<td>413 (3)</td>
<td>399 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>P (baseline vs. epinephrine)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>After propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before epinephrine</td>
<td>475 (4)</td>
<td>486 (3)</td>
<td>469 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After epinephrine</td>
<td>474 (3)</td>
<td>482 (3)</td>
<td>465 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (baseline vs. epinephrine)</td>
<td>0.275</td>
<td>0.065</td>
<td>0.061</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SEM).
Adrenergic activity in LQT3

The response of ventricular repolarization to adrenergic stimulation in the normal heart largely depends on the shift in net outward current. An increase in the net outward repolarization current, due to a relatively large increase in $I_{Na}$ and $Ca^{2+}$-activated chloride currents compared to the $I_{Ca}$ and $Na^{+}/Ca^{2+}$ exchange currents, is thought to be responsible for the shortening of ventricular repolarization by adrenergic stimulation.20-22

Conversely, in LQT1 and LQT2, adrenergic stimulation has been reported to induce continuous or transient prolongations of the QT interval, and an increased dispersion of ventricular repolarization.6,6,23 These observations are closely related to the occurrence, in patients suffering from LQT1 and LQT2, of adverse cardiac events mostly associated with exercise, emotional stress, or both.1,4,5 In contrast to its effects in LQT1 and LQT2, adrenergic stimulation is considered less arrhythmogenic in LQT3, as most adverse cardiac events occur at rest or during sleep.1,4,5 Furthermore, in some experimental and clinical studies, adrenergic stimulation shortened the QT interval and lessened the dispersion of ventricular repolarization in LQT3.6,7,23 These beneficial effects of adrenergic stimulation in LQT3, where an enhanced inward $I_{Na}$ current is responsible for the prolongation of the QT interval, were attributed to an increase of the net outward current, mainly across normal $I_{Ks}$ channels.24,25 The results of this study, in a model of LQT3 created by AP-A, where ventricular ARI and transmural ARI dispersion were shortened by the administration of 0.5 $\mu$g/kg of epinephrine, are consistent with these previous observations.6,7,21 However, when administered a higher dose, epinephrine was pro-arrhythmic in the majority of the experiments. Since (i) 1.0 $\mu$g/kg is a relevant dose clinically, (ii) it did not cause inordinately severe hypertension, and (iii) similar PVC, but not polymorphic VA were induced by the same dose of epinephrine before the administration of AP-A, adrenergic activity exhibits opposite effects on ventricular electrical stability in the LQT3 model, depending on the intensity of stimulation. Furthermore, this observation is consistent with the incidence, in LQT3, of certain adverse cardiac events occurring in association with exercise or emotional stress.1,4,5

Table 2 Transmural dispersion of activity-recovery intervals before and after administration of epinephrine in the absence and presence of propranolol in the left and right ventricular walls

<table>
<thead>
<tr>
<th>ources</th>
<th>Before</th>
<th>After</th>
<th>P (Endo vs. Mid vs. Epi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td>Before</td>
<td>61 (4)</td>
<td>37 (2)</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>34 (3)</td>
<td>35 (2)</td>
</tr>
<tr>
<td></td>
<td>P (baseline vs. epinephrine)</td>
<td>&lt;0.001</td>
<td>0.205</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>Before</td>
<td>18 (2)</td>
<td>17 (1)</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>14 (2)</td>
<td>17 (2)</td>
</tr>
<tr>
<td></td>
<td>P (baseline vs. epinephrine)</td>
<td>0.148</td>
<td>0.905</td>
</tr>
</tbody>
</table>

Values are means (SEM).

**Figure 1** RV transmural electrograms. The display is as in Figure 2. At baseline (A), ARI at the Mid site is slightly longer than at the Epi and Endo sites, and ARI dispersion (ARI-D) is 26–29 ms. ARI was mildly shortened by epinephrine, 0.5 $\mu$g/kg (B). Propranolol prolonged ARI homogeneously (C) and ARI dispersion was 22–24 ms. The effects of epinephrine on the ARI distribution was reversed by propranolol (D). Abbreviations as in Figure 1.

Beta-adrenergic blockade in LQT3

Since VA in LQT3 are often bradycardia-dependent, beta-adrenergic blockade might be less effective or even harmful in this syndrome, as a slow heart rate can promote a more heterogeneous distribution of ventricular repolarization and facilitate the induction of triggered beats due to early after-depolarization.26-28 However, supplemental treatment with a beta-adrenergic blocker has the potential to limit the incidence of VA episodes if bradycardia is prevented by a pacemaker or an implantable cardioverter defibrillator.10 Previous studies using pharmacological models of an arterially perfused LV wedge, sliced myocardium, or ventricular cells have shown that beta-adrenergic blockade had little or no effect on the QT interval in several types of LQTS.6-8 However, in this study, propranolol prolonged ARI at all sites, although the ARI prolongation was mild. The difference between the previous studies and ours might be partially explained by the effect of basal autonomic nerve activity. In this study, basal adrenergic activity appears to have augmented the net outward current more than the net inward current, and thus shortened the ARI to some degree. Propranolol might counteract the adrenergic effects and prolong ARI in the ventricle. Similar results in the QT interval have been observed in patients with LQT3 treated with a beta-adrenergic blocker.4 However, Head et al.9 showed that the local electrogram duration was increased by propranolol in genetically modified Langendorff-perfused murine hearts modelling LQT3. They also reported that neither isoprenaline nor propranolol had any effect on the arrhythmogenecity in their genetically modified model of LQT3. Therefore, although the precise mechanisms are still uncertain, the effects of adrenergic stimulation in
ventricular repolarization and/or occurrence of polymorphic VA were non-uniform in different models of LQT3.

**Epinephrine-induced polymorphic ventricular tachyarrhythmia**

Triggered premature activity originating from the Purkinje network or subendocardium and heterogeneity of ventricular repolarization are the two key factors in the initiation and perpetuation of polymorphic VA in LQTS. As observed in previous studies with this AP-A model, in this study epinephrine-induced polymorphic VA appeared to be preceded by delayed conduction or functional conduction block of the premature wave front at LV Mid and Endo sites (Figure 2). Since polymorphic VA developed soon after the administration of epinephrine, the distribution of ventricular repolarization at that time point might not have been sufficiently homogeneous as the result of epinephrine. Indeed, distribution of the transmural ventricular repolarization was heterogeneous at the initiation of polymorphic VA, as shown in Figure 2. In our previous studies of the AP-A model of LQT3, large transmural dispersion of ventricular repolarization was not observed in canine hearts before the administration of AP-A.

Epinephrine usually shortens the cardiac cycle length and such changes in cardiac cycle can profoundly affect the QT segment of patients with LQTS. Nuyens et al. reported that pacing-induced sudden acceleration in the heart rate or premature beats caused transient lengthening of the action potential with early afterdepolarization, and triggered arrhythmia in a genetically modified mice model of LQT3. However, in their study, such paradoxical prolongation of the ventricular repolarization was not observed when the heart rate was progressively accelerated by the administration of propranolol. In this study, the cardiac cycle was fixed by RV pacing after the creation of the AV block.

**Therapeutic effects of propranolol in this LQT3 model**

In this study, inhibition of triggered PVC and a decrease in LV transmural ARI dispersion might have been responsible for the suppression of the epinephrine-induced polymorphic VA by propranolol. The former is suggested to be the more important factor, since epinephrine did not trigger any PVC after the administration of propranolol.

The results of this study support the therapeutic effects of propranolol against arrhythmias in LQT3 syndrome during ventricular pacing at a cycle length of 750 ms. However, the basal pacing rate might determine the effects of epinephrine or propranolol in this model. A slow heart rate seemed to accentuate the heterogeneous distribution of ventricular repolarization and facilitate the induction of PVC by epinephrine. On the other hand, a faster pacing rate should attenuate the heterogeneity of ventricular repolarization and decrease the number of triggered PVC. A relatively short diastolic interval during more rapid pacing potentially influences the myocardial ionic currents (including Iks and other currents) and modifies the restitution curve of the ventricular repolarization. It has been reported that characteristics of the restitution curve are associated with the occurrence of VA in LQT2 and LQT3 models. Therefore, the effects of epinephrine or propranolol (or both) on the distribution of ventricular repolarization and development of VA may need to be studied in several different ranges of basic pacing cycle length.

**Clinical implications**

Beta-adrenergic blockade effectively suppressed the epinephrine-induced PVC and polymorphic VA in this LQT3 model. Therefore, beta-adrenergic blockers have potential in small doses as supplemental therapy to suppress episodes of VA in patients suffering from LQT3, preferably combined with a pacemaker or an implantable cardioverter defibrillator to prevent marked bradycardia.

**Study limitations**

A first limitation of this study was the limited number of needle electrodes used and myocardial areas explored, which might have underestimated the heterogeneity of ventricular repolarization and/or occurrence of polymorphic VA. The steepest repolarization gradients between the surface of the epicardium and the deep subepicardium are difficult to detect with unipolar electrograms that begin at a depth of 0.5 mm. Furthermore, the source of triggered premature activity and mechanism of the epinephrine-induced polymorphic VA were not identified because of the low resolution of the local electrograms. However, it is likely that the electrophysiological mechanisms of polymorphic VA in this study were the same as those previously observed by detailed mapping in the same experimental model. Second, epinephrine augments both beta- and alpha-adrenergic activity, and the role played by beta- vs. alpha-adrenergic activation with respect to the ARI distribution and polymorphic VA was not examined separately. However, in clinical cases, sympathetic nervous activity enhances both alpha- and beta-adrenergic tones, although beta-adrenergic blockers, instead of alpha- and beta-adrenergic blockers together, have been used as a first-line medical treatment of congenital LQTS. Third, complete data from control experiments without AP-A is important to support the results of this study, but these were not performed here. Nevertheless, it seems to be reasonable to think that multiple PVCs and heterogeneous ventricular repolarization are two key factors in the induction of polymorphic VA by epinephrine (1.0 μg/kg) in this model because similar PVCs, but not polymorphic VA, were induced by the same dose of epinephrine before the administration of AP-A. Finally, the animals were anesthetized with thiopental, which might antagonize the increase in late Na+ current by AP-A.

**Conclusions**

Epinephrine was demonstrated to have bidirectional effects on ventricular electrical stability, depending on its dosage, in an AP-A model of LQT3. Small doses of epinephrine resulted in homogeneous distribution of the ventricular repolarization, whereas a larger dose induced sustained polymorphic VA. Propranolol prevented the induction of epinephrine-induced polymorphic VA without increasing the heterogeneity of ventricular repolarization during fixed ventricular pacing.

**Conflict of interest:** none declared.
References


