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Version: Version of Record

Link(s) to article on publisher's website:
http://dx.doi.org/doi:10.1016/j.ijcard.2019.01.098

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Proarrhythmic proclivity of left-stellate ganglion stimulation in a canine model of drug-induced long-QT syndrome type 1

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Abstract

Background: Left-stellate ganglion stimulation (LSGS) can modify regional dispersion of ventricular refractoriness, promote triggered activity, and reduce the threshold for ventricular fibrillation (VF). Sympathetic hyperactivity precipitates torsades de pointes (TdP) and VF in susceptible patients with long-QT syndrome type 1 (LQT1). We investigated the electromechanical effects of LSGS in a canine model of drug-induced LQT1, gaining novel arrhythmogenic insights.

Methods: In nine mongrel dogs, the left and right stellate ganglia were exposed for electrical stimulation. ECG, left- and right-ventricular endocardial monophasic action potentials (MAPs) and pressures (LVP, RVP) were recorded. The electromechanical window (EMW; Q to LVP at 90% relaxation minus QT interval) was calculated. LQT1 was mimicked by infusion of the KCNQ1/IKs blocker HMR1556.

Results: At baseline, LSGS and right-stellate ganglion stimulation (RSGS) caused similar heart-rate acceleration and QT shortening. Positive inotropic and lusitropic effects were more pronounced under LSGS than RSGS. IKs blockade prolonged QTc, triggered MAP-early afterdepolarizations (EADs) and rendered the EMW negative, but no ventricular tachyarrhythmias occurred. Superimposed LSGS exaggerated EMW negativity and evoked TdP in 5/9 dogs within 30 s. Preceding extrasystoles originated mostly from the outflow-tracts region. TdP deteriorated into therapy-refractory VF in 4/5 animals. RSGS did not provoke TdP/VF.

Conclusions: In this model of drug-induced LQT1, LSGS readily induced TdP and VF during repolarization prolongation and MAP-EAD generation, but only if EMW turned from positive to very negative. We postulate that altered mechano-electric coupling can exaggerate regional dispersion of refractoriness and facilitates ventricular ectopy.

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1. Introduction

Stimulation of the left (LSGS) and right stellate ganglion (RSGS) has generalized cardiovascular (i.e., heart-rate and blood-pressure rise) and localized myocardial effects. Marked differences in chronotropic, inotropic, lusitropic, and dromotropic effects exist among species, including humans [1,2]. LSGS mainly causes electrical activation of the left-ventricular (LV) inferior and lateral regions, whereas RSGS modulates predominantly the anterior sides of both ventricles [3]. Sympathetic hyperactivity and/or regionally dispersed sympathetic innervation impinge on these electrophysiological properties [1], potentially exaggerating dispersion of excitation and refractoriness. Augmented LSG activity facilitates triggered activity [4], shortens ventricular refractoriness [5], and reduces the threshold for ventricular fibrillation (VF) in normal and structurally-remodeled hearts [6,7].

Sympathetic-related ventricular tachyarrhythmias are a hallmark of the long-QT syndrome type 1 (LQT1), as arrhythmic events are mostly evoked during exercise and/or emotion (~90% of symptomatic LQT1 patients) [8]. Accordingly, beta-adrenergic receptor blockade is the mainstay of therapy, and left-cardiac sympathetic denervation should be considered in symptomatic patients when beta-blockade is not effective, not tolerated or contraindicated [9–11].

Previous studies in canine LQTS models addressed the effects of unilateral or bilateral stellate ganglion stimulation during cesium-chloride-induced QT prolongation [12] and d-sotalol-induced LQT2 [13]. In drug-induced LQT1, TdP was readily evoked by the beta-adrenergic agonist isoproterenol [14]. In the latter, exaggerated spatiotemporal dispersion of repolarization, substantial electromechanical heterogeneities...
Heart rate and QT interval were measured from an extremity lead (usually lead II), with a discernible T-wave ending and the longest QT interval. Heart-rate corrected QT (QTc) was calculated using van de Water's formula, QTc = QT – 0.047(RR-1000), which is superior to Bazett's in anesthetized dogs [20]. Tpeak–Tend was calculated as a marker of spatial dispersion of ventricular repolarization.

LV and RV MAP durations were measured at 90% repolarization (MAPD90). Beat-to-beat variability of repolarization was measured on LV and RV MAP recordings during 10 consecutive beats, in the absence of ventricular ectopy. Short-term variability was calculated as: STV = \( \sum_{n=1}^{N} |\text{MAPD}_{n-1} - \text{MAPD}_{n}| / (10 \times \text{SD}) \). Long-term variability as: \( \text{LTV} = \sum_{n=1}^{N} |\text{MAPD}_{n} - \text{MAPD}_{\text{mean}}| / (10 \times \text{SD}) \). Also, the occurrence of early afterdepolarizations (EADs) in MAPs, and EAD-preceding transient repolarization delays (i.e., when dVp/dt < 50% of baseline) were noted.

Ventricular peak systolic and end-diastolic pressure, duration of ventricular contraction at 90% relaxation (LVp90), and the dp/dtmax, dp/dtmin were measured. The EMW was calculated by subtracting the QT interval from the QLVP90. The pressure signals were carefully screened for (low-amplitude) aftercontractions [14]. At ventricular tachyarrhythmias occurred, we located the origin of the triggering premature ventricular complex (PVC) by analyzing the QRS morphology and the sequence of RV and LV MAP activation. The last supraventricular beat before TdP/VF was designated beat “0” with the preceding intervals being \( t_{1-0} \) (Online Fig. 2). These RR intervals were measured to determine the pause dependency of arrhythmia initiation, defined as \( t_{1-2} = t_{1-0} \). QT, EMW, and QLVP90 were compared between TdP–inducible and noninducible stimulations. Dogs were designated resistant to TdP/VF or inducible during SCS.

2.4. Statistical analysis

Data were measured in 10 consecutive beats, using the average for further statistical analysis. Pooled data were expressed as mean ± standard deviation. Normality was assessed for each dataset using the Shapiro–Wilk test. Differences of parameters in paired data were assessed using the paired-samples t-test and in the Wilcoxon signed rank test as appropriate. Intergroup comparison was performed using the Student's t-test or the Kruskal–Wallis test. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Stellate ganglion stimulation of the normal canine heart

Fig. 1 depicts representative examples of the cardiac effects of LSGS and RSGS at baseline. During LSGS, heart rate increased by 79% and the QT interval shortened by 23%, effectively reducing QTc from 290 ± 24 to 253 ± 13 ms (P = 0.0003; Online Table 1). LV and RV MAPD90 analysis did not reveal augmented interventricular or temporal (i.e., beat-to-beat) dispersion of repolarization. In both ventricles, inotropy increased significantly: LV peak systolic pressure by 37% and RVP by 157%, LV dp/dtmax increased by 394%, RV dp/dtmin decreased by 110%, indicating increased lusitropy, and effectively leading QLVP90 to shorten from 373 ± 65 to 214 ± 46 ms (−43%, P = 0.006; Online Table 1). Changes in diastolic LVP did not reach statistical significance. Due to preferential mechanical–systole over QT shortening, LV EMW decreased from 95 ± 53 to 51 ± 24 ms (P = 0.009, Fig. 2). RV inotropy and lusitropy also increased significantly (Online Table 1).

LSGS readily evoked a junctional or low–atrial tachycardia, overriding the LSGS-induced accelerated sinus rhythm within 6 ± 3 s (asterisks in Fig. 1). Occasionally, solitary RV/LV ectopic activity occurred during LSGS, but MAP–EADs, aftercontractions, or non–sustained ventricular tachyarrhythmias (NSVT) were not observed. In approximately one third of LSG stimulations a short–lived paradoxical heart–rate slowing was observed, which could be counteracted by atropine.

We observed an immediate and protracted (87 ± 41 s) vagal rebound following LSGS (Fig. 3) characterized by sinus bradycardia, ventricular ectopy, and episodes of idioventricular rhythm. The post–LSGS systolic LVP remained elevated during this vagal episode, and returned to steady–state values parallel with the restoration of sinus rhythm. Such vagal rebound was never observed after isoproterenol administration in the same experimental set–up [14].

RGMS (n = 3, Fig. 1) caused comparable heart–rate accelerations (188 ± 55 bpm) as LSGS (in the absence of decentralization), without provoking supraventricular arrhythmias. Both QT and QTC intervals shortened significantly (by 29% and 18% respectively), but these were not different from the effects of LSGS. Endocardial MAPD90 decreased...
similarly in both ventricles (Online Table 1). RSGS-evoked positive inotropy was less prominent than during LSGS. Similarly, we observed only limited QLVP90 shortening upon RSGS, resulting in less EMW reduction than upon LSGS (Online Table 1).

3.2. Repolarization instability during IKs inhibition

Intravenous administration of HMR1556 prolonged QT and QTc to 373 ± 65 and 371 ± 61 ms, respectively (+21% and +20%; P = 0.002 and P = 0.007, Table 1). Heart rate decreased to 60 ± 11 bpm (P = 0.0003). Preferential LV over RV MAPD90 prolongation (335 ± 74 and 286 ± 50 ms; P < 0.0001) augmented interventricular dispersion of repolarization. This was paralleled by a more pronounced LV temporal dispersion of repolarization, with STV-MAPD90 increasing by 129% and LTV-MAPD90 by 173%. LV EADs emerged in four dogs at a wide range of cycle lengths; RV EADs in three dogs (Fig. 4). Upon IKs inhibition, the LV-peak systolic pressure and LV dP/dt max increased to 114 ± 19 mm Hg (+23%; P = 0.01) and 2373 ± 1159 mm Hg/s (+27%; P = 0.001). Despite a significant prolongation of the electrical systole, QLVP90 remained unaltered, providing an EMW negativity of −14 ± 69 ms (P = 0.001, Fig. 2). No sizeable aftercontractions or spontaneous ventricular arrhythmias occurred under these conditions.

3.3. Proarrhythmic proclivity of LSGS during drug-induced LQT1

Left-sided sympathetic stimulation during IKs inhibition led to QTc and APD90 shortening to 306 ± 44 ms and 225 ± 31 ms respectively (Table 1). A markedly decreased QLVP90 rendered the EMW negative (−61 ± 34 ms; P = 0.0004, Fig. 2). Beat-to-beat variability of repolarization duration increased and T-wave amplitudes reduced. Under these conditions, TdP/VF occurred in 5 of 9 dogs after 26 ± 6 s (Fig. 5). In most animals, once TdP initiated it rapidly degenerated into VF that did not respond to immediate and repeated electrical cardioversion, and was resistant to magnesium infusion. In one dog, a protracted vagal period with intermittent episodes of nonsustained VT was observed after termination of VF. RSGS was never torsadogenic.

In the dogs with inducible TdP/VF, pre-LSGS QT was significantly more prolonged and LV EMW more negative than in resistant animals: 440 ± 67 versus 344 ± 56 ms (P = 0.007) and −64 ± 87 versus 27 ± 40 ms (P = 0.04, respectively) (Fig. 6). EMW negativity was more pronounced in the final beats preceding TdP/VF (reaching −94 ± 31 ms at I), compared with the non-inducible group (−43 ± 25 ms; P = 0.002, Figs. 5 and 6). QLVP90 did not differ between these groups. QT prolongation was more exaggerated (282 ± 53 ms; P = 0.02) in the beats prior to TdP when compared to pre-NSVT (225 ± 21 ms) or solitary PVCs (229 ± 39 ms) in susceptible animals, and EMW was more negative −94 ± 31 ms prior to TdP/VF (P = 0.005) versus −23 ± 37 ms (pre-NSVT), and −38 ± 37 ms (pre-PVC).

An initial delay in MAP repolarization was present throughout a broad range of RR cycle lengths during LSGS and IKs blockade, but
overt EADs did not occur (Fig. 4). Increased diastolic slopes suggesting delayed afterdepolarizations were also not observed. During this condition with fast-rate dependent electrical instability and mechano-electric heterogeneity, relatively short-coupled non-pause dependent PVCs occurred (Figs. 5–7). Macroscopic aftercontractions preceded TdP in one dog. The TdP/VF-triggering PVCs typically had an intermediate QRS axis, large QRS amplitudes, and their earliest endocardial activation at the RV MAP signal (in 4/5 dogs, Fig. 7), suggesting focal activation in the vicinity of the outflow-tracts region. In one animal, TdP initiation emerged from the inferior LV. TdP onset was non-pause dependent with \( I(-1) \) never exceeding \( I(-2) \). In some cases ventricular ectopy occurred prior to \( I(-2) \).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>HMR</th>
<th>P value</th>
<th>+ LSGS</th>
<th>P value</th>
<th>+ RSGS</th>
<th>P value</th>
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<tr>
<td>RR interval (ms)</td>
<td>680 ± 116</td>
<td>1026 ± 168</td>
<td>0.0002</td>
<td>481 ± 184</td>
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<td>407 ± 82</td>
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<td>Heart rate (bpm)</td>
<td>91 ± 17</td>
<td>60 ± 11</td>
<td>0.0003</td>
<td>142 ± 48</td>
<td>-0.0001</td>
<td>152 ± 30</td>
<td>0.01</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>280 ± 23</td>
<td>373 ± 65</td>
<td>0.002</td>
<td>260 ± 50</td>
<td>-0.0001</td>
<td>246 ± 37</td>
<td>0.005</td>
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<tr>
<td>QTc (ms)</td>
<td>308 ± 17</td>
<td>371 ± 61</td>
<td>0.007</td>
<td>306 ± 44</td>
<td>-0.0001</td>
<td>298 ± 34</td>
<td>0.003</td>
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<tr>
<td>Tp-Te (ms)</td>
<td>57 ± 27</td>
<td>92 ± 34</td>
<td>0.03</td>
<td>47 ± 16</td>
<td>-0.0001</td>
<td>44 ± 10</td>
<td>0.007</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
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<td></td>
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<tr>
<td>MAPD90 (ms)</td>
<td>238 ± 29</td>
<td>335 ± 74</td>
<td>0.001</td>
<td>225 ± 31</td>
<td>0.001</td>
<td>230 ± 58</td>
<td>0.14</td>
</tr>
<tr>
<td>MAP-STV</td>
<td>4.8 ± 1.6</td>
<td>6.4 ± 4.6</td>
<td>0.003</td>
<td>6.1 ± 5.9</td>
<td>0.08</td>
<td>6.9 ± 11</td>
<td>0.76</td>
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<tr>
<td>MAP-LTV</td>
<td>3.3 ± 1.5</td>
<td>9.0 ± 8.1</td>
<td>0.02</td>
<td>10.2 ± 10.0</td>
<td>0.42</td>
<td>7.3 ± 9.2</td>
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<tr>
<td>LVP syst. (mm Hg)</td>
<td>102 ± 24</td>
<td>114 ± 19</td>
<td>0.01</td>
<td>180 ± 22</td>
<td>-0.0001</td>
<td>150 ± 27</td>
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<td>LVP diast. (mm Hg)</td>
<td>12 ± 8</td>
<td>14 ± 8</td>
<td>0.003</td>
<td>5 ± 8</td>
<td>0.003</td>
<td>16 ± 14</td>
<td>0.35</td>
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<tr>
<td>dP/dtmax (mm Hg/s)</td>
<td>1734 ± 857</td>
<td>2373 ± 1159</td>
<td>0.001</td>
<td>9267 ± 3498</td>
<td>-0.0001</td>
<td>3556 ± 1615</td>
<td>0.02</td>
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<tr>
<td>dP/dtmin (mm Hg/s)</td>
<td>3127 ± 2634</td>
<td>4432 ± 3466</td>
<td>0.07</td>
<td>-8774 ± 7044</td>
<td>0.0004</td>
<td>-3025 ± 1063</td>
<td>0.04</td>
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<td>LVPd90 (ms)</td>
<td>360 ± 31</td>
<td>355 ± 34</td>
<td>0.86</td>
<td>198 ± 77</td>
<td>0.0002</td>
<td>248 ± 45</td>
<td>0.002</td>
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<td>EMW (ms)</td>
<td>79 ± 36</td>
<td>-14 ± 69</td>
<td>0.001</td>
<td>-61 ± 34</td>
<td>0.0004</td>
<td>11 ± 31</td>
<td>0.81</td>
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<td>Right ventricle</td>
<td></td>
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</tr>
<tr>
<td>MAPD90 (ms)</td>
<td>213 ± 21</td>
<td>286 ± 50</td>
<td>0.008</td>
<td>209 ± 52</td>
<td>-0.0001</td>
<td>204 ± 33</td>
<td>0.03</td>
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<td>RVP syst. (mm Hg)</td>
<td>25 ± 9</td>
<td>28 ± 8</td>
<td>0.03</td>
<td>64 ± 16</td>
<td>0.003</td>
<td>35 ± 4</td>
<td>0.0002</td>
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<tr>
<td>RVP diast. (mm Hg)</td>
<td>6 ± 4</td>
<td>8 ± 5</td>
<td>0.02</td>
<td>7 ± 5</td>
<td>0.05</td>
<td>6 ± 6</td>
<td>0.03</td>
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<tr>
<td>dP/dtmax (mm Hg/s)</td>
<td>610 ± 316</td>
<td>820 ± 641</td>
<td>0.13</td>
<td>4635 ± 1526</td>
<td>0.005</td>
<td>929 ± 309</td>
<td>0.03</td>
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<tr>
<td>dP/dtmin (mm Hg/s)</td>
<td>-266 ± 47</td>
<td>-329 ± 39</td>
<td>0.02</td>
<td>-3290 ± 4983</td>
<td>0.008</td>
<td>-483 ± 150</td>
<td>0.12</td>
</tr>
</tbody>
</table>

STV indicates short-term variability; LTV, long-term variability; MAPD90, monophasic action potential duration at 90% repolarization; LVP, left-ventricular pressure; QLV90, time from QRS onset to 90% LV pressure normalization; EMW, electromechanical window.

Fig. 3. Vagal rebound post-LSGS at baseline. Upon termination of LSGS, and during a protracted positive inotropic response (upper panel), sinus and junctional bradycardia, ventricular extrasystoles and idioventricular rhythm occurred, indicating a vagal response by a baroreflex loop and/or sympathetic withdrawal. The lower ECG traces A, B, C, and D are ECG examples at different stages of the vagal rebound. LVP indicates left-ventricular pressure.

Fig. 4. Top, LV MAPs and first derivative (dV/dt) of MAP signal. After HMR1556, EADs followed after an initial delay in repolarization (arrowheads). Upon concomitant LSGS at 10–15 Hz, frank EAD upstrokes were absent but a discernable delay in repolarization (arrows) remained present, contributing to MAPD90 prolongation. Bottom, rate dependency of MAPD90 at baseline (square), during HMR1556 (circle) and simultaneous LSGS (triangle). Black symbols: EAD present; gray symbols: initial delay in repolarization. LSGS indicates left-stellate ganglion stimulation; APD90, action potential duration at 90% repolarization; CL, cycle length.
4. Discussion

This is the first study to demonstrate the proarrhythmic consequences of LSGS in an in-vivo model of drug-induced LQT1 \cite{14} in which autonomic reflexes, neurocardiac transmission and cardiac electromechanical coupling are only mildly influenced by the applied anesthesia. In-vivo \textit{I}_{\text{Ks}} blockage prolonged ventricular repolarization duration and augmented spatial and temporal repolarization dispersion, recapitulating LQT1 aspects. Only with concomitant LSGS did TdP occur, despite global repolarization shortening. Arrhythmia initiation was always fast-rate (non-pause) dependent \cite{22,23}, with the majority...
of triggering beats originating in the vicinity of the outflow-tracts region. This is consistent with the site of TdP onset in the majority of LQTS patients [24].

In this model of drug-induced LQT1, the finding of LSGS-induced repolarization shortening suggests that intense sympathetic stimulation can enhance residual \( I_{Ks} \) despite pharmacological inhibition. Other cesium-chloride-induced LQTS models with sympathetic stimulation led to similar results [12,25]. Inotropic and particularly lusitropic influences were dominant during left-sided stimulation. Therefore, mechanical systole shortened, and in the face of regional repolarization prolongation by \( I_{Ks} \) inhibition alone, superimposed LSGS exaggerated EMW disparity (Fig. 2), especially just prior to TdP. In most susceptible dogs with drug-induced LQT1 and LSGS, TdP rapidly deteriorated into defibrillation-resistant VF. Pronounced EMW negativity related to torsadogenesis has also been observed during beta-adrenergic stimulation in experimental LQT1 [17] and in clinical studies on symptomatic patients with genetically-confirmed LQTS [15,26]. This suggests that LSGS imposes regional electromechanical heterogeneities that facilitate arrhythmia during \( I_{Ks} \) inhibition/loss of function. In the present experiments, macroscopic aftercontractions were infrequently observed, but we speculate that the local myocardial effects of LSGS could have produced low-amplitude aftercontractile events (below the radar of global intracavitary pressure) with similar arrhythmogenic significance during EMW negativity. Future studies could focus on examining mechanoelectric triggers of arrhythmia in LQTS.

4.1. Proarrhythmic proclivity of LSGS during \( I_{Ks} \) inhibition

The present findings confirm the arrhythmogenic role of left-sided cardiac sympathetic hyperactivity in a clinically-relevant LQT1 model. Sympathetically-induced TdP/VF was markedly resistant to defibrillation attempts. Sympathetic hyperactivity, releasing norepinephrine locally at the myocardial nerve endings, accentuates heterogeneity in ventricular repolarization under these conditions, and favors reentrant excitation, whereas circulating catecholamines or infused (nor)epinephrine act more uniformly [27]. These differences are accompanied by a considerably larger positive inotropic (but similar chronotropic) response upon LSGS followed by a protracted vagal rebound. This vagal accentuation could be explained by the sudden sympathetic withdrawal and/or by baroreflex activation in response to the elevated arterial pressures. Supported by the observation of a prominent vagal rebound in the rare case of successful cardioversion of VF, our results suggest that reflex vagal activation may have promoted the LQT1-related TdP to deteriorate into VF. Vagal nerve stimulation operates mainly by antagonizing cardiac sympathetic activity, but it also increases ventricular dispersion of repolarization, as demonstrated in the setting of drug-induced LQT2 [28]. Moreover, when applied during induced VF in pigs or sheep, vagal nerve stimulation increases the variability of the dominant VF frequency, potentially sustaining the arrhythmia [29].

The triggers for life-threatening events in most LQT1 patients are either physical (75%) or emotional stress (15%) while rest/sleep accounts for only 10% [8]. One third of patients have events during swimming [8]. These arrhythmias are effectively prevented in most LQT1 patients by beta-blockade or by left-cardiac sympathetic denervation [9,30]. On the other hand, strong vagal reflexes have been implicated in high-risk LQT1 patients [31,32], and cold-water submersion and swimming, a genotype-specific trigger, provokes powerful co-stimulation of both sympathetic and parasympathetic limbs, at least in the first instances [33]. Our experimental results do not allow firm conclusions on the contribution of vagal stimulation to ventricular proarrrhythmia in LQTS, but they lend indirect support to the concept of "autonomic conflict" [34], which indicates that a more convoluted vago-sympathetic interaction can facilitate ventricular tachyarrhythmia.

4.2. Limitations

The present study involved a relatively small number of animals, which was driven by ethical considerations. However, the differences in results obtained in paired analysis or group comparisons were so profound that they readily reached statistical significance.

The use of an anesthesia model always brings into question the cardiovascular and autonomic effects of anesthesia, especially when dealing with autonomic interventions. In the present study, we minimized potentially confounding effects [16,17] by the choice of anesthetics.

5. Conclusions

For the first time in an in vivo model of drug-induced LQT1, we demonstrate the arrhythmogenic potency of LSGS to induce TdP and VF during repolarization prolongation, MAP-EADs generation, exaggerated spatiotemporal dispersion of repolarization, and EMW negativity. LSGS always rendered the EMW more negative prior to arrhythmia induction, which suggests that altered mecano-electric coupling is somehow involved in the proarrhythmic proclivity. Triggering PVCs most often emerged from the LV and RV outflow-tract regions. Our results offer novel mechanistic understanding of LQT1-related arrhythmogenesis and strengthen the rationale for left-cardiac sympathetic denervation in the prevention of life-threatening arrhythmias in several cardiac disorders, ranging from channelopathies [10] to structural heart diseases [10,11].

Funding

P.G.A.V. was supported by a Vidi grant from the Netherlands Organization for Scientific Research (ZonMW 91710365).

Conflict of interest

None declared by all authors.

Acknowledgements

The authors wish to thank Roel L.H.M.G. Spåtjens BSc, Maastricht University Medical Center, The Netherlands for excellent graphical support, and Antonio Zaza, MD, University of Milano Bicocca, Italy for fruitful discussions on neurocardiac physiology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.098.

References


