Differential Response to Right and Left Ansae Subclaviae Stimulation of Early Afterdepolarizations and Ventricular Tachycardia Induced by Cesium in Dogs

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Early afterdepolarizations (EADs) are depolarizing potentials that occur before complete repolarization. They may be important in the acquired and possibly the idiopathic long QT syndrome and associated ventricular tachycardia (VT). The purpose of these experiments was to study in 20 open-chest dogs the effects of sympathetic stimulation on EADs and VT produced with cesium chloride (84 mg/kg i.v.) alone or combined with left (LAS), right (RAS), or bilateral (BAS) ansae subclaviae stimulation (2 Hz, 4 msec, 2 mA). We compared the EAD amplitude and area as a percentage of monophasic action potential amplitude and area, respectively, recorded simultaneously with contact electrodes from right (RV) and left ventricular (LV) endocardium and recorded the prevalence of VT induction during each intervention. Both LAS and BAS produced left ventricular EADs with larger amplitudes and areas than did RAS or cesium alone. BAS and LAS produced larger EADs recorded from the LV than from the RV. Cesium produced VT in six of 20 dogs, RAS in three of 20, BAS in 12 of 20, and LAS in 16 of 20. Norepinephrine (0.1–1.5 μg/kg/min) caused VT in all dogs by producing a dose-related increase in EAD amplitude that was similar in RV and LV, suggesting that the response of RV and LV EADs to catecholamine stimulation was not intrinsically different. During stimulation of left ansae subclaviae at increasing frequencies (1, 2, 4, and 6 Hz), EADs were significantly larger in LV than in RV at all stimulus frequencies, and the amplitude of EADs in both ventricles increased with increasing stimulus frequencies. Based on the increased LV amplitude and area of cesium chloride–induced EADs during LAS and BAS, with EAD amplitude dependent on the frequency of LAS but with an equal RV and LV EAD amplitude during norepinephrine infusion, it is possible that more norepinephrine released into the LV during LAS and BAS compared with RAS causes larger amplitude LV EADs that reach threshold to cause VT more often. Thus, quantitative differences between the effects of left and right stellate ganglia stimulation rather than qualitative differences or imbalance may account for the arrhythmogenic potential of the left stellate ganglion. (Circulation 1988;78:1241–1250)

Under certain conditions, the sympathetic nervous system can profoundly influence the electrophysiological properties of the heart and thereby the genesis of ventricular arrhythmias. In patients who have the idiopathic long QT syndrome, activities likely to result in increased sympathetic discharge, such as strong emotions or physical exertion, often precipitate syncope and sudden death due to paroxysmal ventricular tachyarrhythmias. The electrophysiological mechanism(s) responsible for the arrhythmias typical of the long QT syndrome, for example, torsades de pointes, is uncertain. However, it is possible that the prolonged time course for repolarization is due to afterdepolarizations that trigger these ventricular arrhythmias.

Data from several studies, as well as from clinical experience, implicate left stellate ganglion dominance, due to excessive left stellate activity or reduced right stellate activity or both, as a cause of
arrhythmias in patients with the idiopathic long QT syndrome. However, the validity of this hypothesis of “sympathetic imbalance” has never been proven conclusively even though it fits all the facts known about the long QT syndrome.

Cesium chloride, which prolongs the QT interval and initiates polymorphic ventricular tachycardia in dogs, induces early afterdepolarizations that can be recorded with a contact electrode. Early afterdepolarizations have also been detected by suction electrodes in animals and in patients. Although it is possible that early afterdepolarizations are important in the acquired long QT syndrome, for example, caused by quinidine, they may be important also in the idiopathic long QT syndrome. The constant prolonged QT interval may be due to early afterdepolarizations, augmented by sympathetic stimulation to produce arrhythmias. The recent demonstration of delayed afterdepolarizations in vivo by sympathetic stimulation implicates the latter in the genesis of some arrhythmias also.

The purpose of this study was to test the causal role of right (RAS), left (LAS), and bilateral (BAS) ansae subclaviae stimulation in the genesis of ventricular tachyarrhythmias in dogs treated with cesium by determining the response of early afterdepolarizations and related arrhythmias to different combinations of sympathetic stimulation.

Materials and Methods

Surgical Preparations

Mongrel dogs of both sexes weighing 16–26 kg were anesthetized with sodium secobarbital (30 mg/kg i.v.) and artificially ventilated with room air by a constant volume respirator (Model 607, Harvard Apparatus, South Natick, Massachusetts). Catheters were placed in the femoral artery and veins to monitor arterial blood pressure (Statham transducer P-12 D6, Cleveland, Ohio) and to infuse drugs. After a median sternotomy, the heart was suspended in a pericardial cradle. An operating room table lamp was used to maintain epicardial temperature between 36° and 38° C, monitored by a Tele-Thermometer (Yellow Springs Instrument, Yellow Springs, Ohio). A plastic sheet covered the sternotomy to maintain temperature and minimize drying of the cardiac surface.

The ansae subclaviae were isolated where they exited from the stellate ganglia and were doubly ligated and transected to produce sympathetic neural decentralization. Shielded bipolar electrodes were placed on the right and left anterior and posterior ansae subclaviae to stimulate the efferent cardiac sympathetic nerves. Stimuli were square-wave pulses (2 Hz, 4 msec, 2 mA) delivered throughout a constant-current stimulus isolator and a Grass S88 stimulator (Quincy, Massachusetts). In one group of dogs, the frequency of ansae subclaviae stimulation was varied.

The region of the sinus node was crushed in all dogs. This does not alter autonomic innervation to the ventricle. Bipolar plunge electrodes, constructed with two Teflon-coated stainless steel wires threaded through a 21-gauge needle and bent at the tip to form a hook, were placed 5 mm apart in the right atrial appendage and in the left ventricle for bipolar electrogram recordings. A hook electrode for unipolar cathodal stimulation was placed in the right atrium. The anode was a circular metal disk inserted in abdominal muscles.

Monophasic Action Potential Recordings

Monophasic action potentials were recorded from the right and left ventricular endocardium with a 4F bipolar contact catheter with a silver–silver chloride distal electrode and a reference lead 5 mm away (Bard Electrophysiology, Billerica, Massachusetts). To minimize movement of the contact electrode catheter within the heart and to control its tip at a specific endocardial region, the electrode catheter was advanced through the lumen of an end-hole guiding catheter, and both were introduced through a 7F sheath with a one-way valve. The sheaths and catheter assemblies were introduced into the right and left ventricular cavities through the right internal jugular vein and the left common carotid artery, respectively. The tip of the right ventricular endocardial electrode was positioned in the anterior right ventricular wall, whereas the left ventricular electrode was placed at the anterior left ventricular apex. Both electrodes were monitored electrocardiographically for stability. Lead II, bipolar atrial and ventricular electrograms, and monophasic action potentials from the right and left ventricular endocardium were displayed simultaneously on storage oscilloscope (Model 5115, Tektronix, Beaverton, Oregon) and recorded on a strip chart recorder (VR-12, Electronics for Medicine, Pleasantville, New York) at paper speeds of 50 or 100 mm/sec. Signals were amplified and filtered at a frequency of 0.04–500 Hz. Baseline recordings were obtained after placement of the catheter electrode in a position that provided continuous monophasic action potential recordings of stable amplitude, smooth contour, and isopotential diastolic baselines from a single endocardial site for at least 5 minutes before each intervention (Figure 1).

We defined early afterdepolarizations as depolarizing afterpotentials that interrupted or delayed repolarization of the action potential. Data acceptable for monophasic action potential analysis were derived only from stable recordings, which were judged on the basis of 1) constant amplitude, morphology, and stable resting membrane potential at control; whether 20 or more consecutive monophasic action potentials were identical; 2) whether the amplitude of phase 2 exceeded 15 mV during control; 3) the absence of afterdepolarizations or any voltage deflections during phase 4; and 4) the appearance of an interruption in the smooth repolarization
contour during phase 3 of the monophasic action potential within 20–60 seconds of the cesium injection without a shift in catheter position.

The magnitude of the early afterdepolarizations was calculated by two different methods. In one, the amplitude of the monophasic action potential was defined as the difference between phase 2 and the maximum diastolic potential during phase 4. The amplitude of the early afterdepolarizations was obtained in the same manner as for early afterdepolarizations obtained from transmembrane recordings and was defined as the potential difference between phase 4 and the first deviation from the smooth contour during phase 3 repolarization (Figure 2). The amplitude of the early afterdepolarizations was expressed as a percentage of monophasic action potential amplitude. In the second method, the area of the monophasic action potential and early afterdepolarization was measured. Lines were drawn to extend phase 3 of the action potential and the resting membrane potential until they intersected. The area enclosed by these two lines separated the monophasic action potential from the early afterdepolarization. The areas of monophasic action potential and early afterdepolarization were then obtained by planimetry. The area encompassed by the early afterdepolarization was expressed as a percentage of the area of the monophasic action potential.

Stability of the monophasic action potential recordings was tested during RAS, LAS, and BAS

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Simultaneous recordings of monophasic action potentials from right (RVMAP) and left (LVMAP) ventricles during control state. Tracings were obtained during atrial pacing (basic cycle length, 800 msec). Note the continuous MAP recordings of stable amplitude, smooth contour, and isopotential diastolic baselines. Paper speed was 50 mm/sec. Time lines at 1-second intervals. ECG, lead II during atrial pacing: RA, right atrial electrogram; LVEG, bipolar electrogram from epicardial left ventricle. 0, 0 mV; 5, 5 mV.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Monophasic action potential (MAP) recordings showing method for measuring the amplitude of MAP and early afterdepolarization (EAD). MAP amplitude was defined as the difference between phase 2 and phase 4. To measure the EAD, amplitude lines were drawn to extend phase 3 and phase 4 of the action potential until they intersected. EAD amplitude was defined as the difference between phase 4 and the first deviation from the smooth repolarization phase. Note the stability of MAP recording despite premature atrial complex during the repolarization of the second QRS complex (arrow). Artifacts (arrow heads) are due to ansae subclaviae stimulation.

(2Hz, 4 msec, 2 mA) in three additional dogs. Left ventricular pressure and dP/dt were recorded with a catheter-tipped pressure transducer (Millar, Houston, Texas) along with wall-motion changes with ultrasonic crystals implanted in the midwall of the left ventricular myocardium parallel to the minor axis of the heart at atrial pacing of cycle lengths of 800, 600, and 300 msec.

**QT Interval**

The QT interval was determined from electrocardiographic lead II. The QT duration was measured from the onset of the QRS complex to the point at which the line of maximal downslope of the T wave crosses the baseline at a paper speed of 50 mm/sec. The monophasic action potential duration was determined from the left ventricular monophasic action potential recording and was measured to 100% repolarization. The measurements were taken during atrial pacing at control state immediately before each intervention ("immediate control") and 3 minutes after intervention.
Experimental Protocol

Atrial pacing was performed at a basic cycle length of 800 msec throughout the experiment, with 2-msec rectangular cathodal stimuli at twice late diastolic threshold delivered from a programmable stimulator (STIM-1, Krannert Medical Engineering, Indianapolis, Indiana). Twenty dogs were treated with cesium chloride 84 mg/kg (i.v. bolus during 10 seconds) alone or combined with 20 seconds of LAS, RAS, or BAS (2 Hz, 4 msec, 2 mA). The order of ansae subclaviae stimulation was chosen randomly and performed at 30-minute intervals. Before each intervention, recordings during control state and during RAS, LAS, and BAS (without cesium injection) were taken. The measurements of monophasic action potentials and early afterdepolarizations recorded from left and right ventricular contact electrodes were taken as the average from three consecutive, paced beats 1–2 minutes after each cesium injection when the maximal effect of cesium occurred. An episode of ventricular tachycardia induction during an intervention was judged present if sustained monomorphic ventricular tachycardia, nonsustained ventricular tachycardia (less than 30 seconds duration), or torsades de pointes resulted within the first 3 minutes after cesium injection.

Effects of Norepinephrine and Stimulus Frequency

In a separate group of six dogs, cesium chloride (84 mg/kg) was injected during a continuous norepinephrine infusion, and early afterdepolarizations from the right and left ventricles were measured. Four different norepinephrine solutions (0.1, 0.5, 1.0, and 1.5 μg/kg/min) were infused intravenously in random order at a rate of 1 ml/min for 5 minutes before cesium injection. The hearts were permitted to recover for 45 minutes between different norepinephrine infusions, and the process was repeated until all four norepinephrine doses were administered.

In 10 other dogs, early afterdepolarizations from the right and left ventricles were measured after cesium chloride injection (84 mg/kg) alone and with LAS at four different frequencies: 1, 2, 4, and 6 Hz. The order of stimulus frequency was chosen randomly and performed at 30-minute intervals.

Control Dogs

The amplitude of early afterdepolarization and the prevalence of ventricular tachyarrhythmia were monitored in eight dogs during four cesium chloride injections (84 mg/kg) at 30-minute intervals. No interventions were made in these animals to test the potential cumulative effects of repeated injections of cesium.

Data Analysis

Data are given as the mean ± SD. Mean values were compared with an analysis of variance for repeated measures. The amplitude of monophasic action potentials and early afterdepolarizations recorded from the right and left ventricles was compared by a paired t test. Multiple comparisons were made by the t test modified by Bonferroni’s method. χ² test for matched pairs was used to compare the frequency of ventricular tachyarrhythmia induction. A p value less than 0.05 was considered statistically significant.

Results

Effects on monophasic action potentials and early afterdepolarizations and ventricular tachyarrhythmias of ansae subclaviae stimulation during cesium injection. Control monophasic action potential amplitudes recorded from right and left ventricles in 20 dogs ranged from 15.8 to 39.6 mV (mean, 24.4 ± 6.3 mV). During the control state and during RAS, LAS, and BAS alone, no early or delayed afterdepolarizations were recorded. The mean amplitude of the cesium-induced early afterdepolarization recorded from the left ventricle during LAS (44.1 ± 7.5%) and during BAS (40.0 ± 8.7%) was significantly greater than the early afterdepolarization amplitude recorded during RAS (30.0 ± 13.8%) and during cesium injection without ansae subclaviae stimulation (29.1 ± 10.7%) (p < 0.05). LAS produced larger early afterdepolarizations recorded from the left ventricle than from the right ventricle (Figure 3). The magnitude of early afterdepolarizations determined by planimetricing the area of the monophasic action potential and early afterdepolarization correlated closely with the results obtained by measuring the amplitude of early afterdepolarization (Table 1). By area, LAS and BAS produced
larger afterdepolarizations than did RAS or cesium alone (p<0.05) and larger left than right ventricular early afterdepolarizations (p<0.01). Early afterdepolarization coupling intervals did not change measurably during RAS, LAS, and BAS at the same pacing cycle lengths. Figure 4 is a record of a representative monophasic action potential during each intervention in the same dog.

During 27 trials of ansae subclaviae stimulation in three dogs that did not receive cesium, small late-positive voltage deflections were recorded on 17 occasions. Atrial pacing failed to produce continuous capture on three occasions at cycle lengths of 800 msec and on two occasions at cycle lengths of 600 msec. The results from these five trials were discarded. In all of the 12 remaining trials, despite changes in cycle length, the magnitude of the voltage deflection remained constant, about 9% of the monophasic action potential, and its onset remained simultaneous with the onset of the period of isovolumic relaxation, 20–30 msec before the maximal negative dP/dt (Figure 5). We conclude that it was probably due to wall motion.

**Ventricular Tachyarrhythmias**

The prevalence of ventricular tachyarrhythmias during LAS and BAS was significantly greater than during RAS and cesium alone (Table 2). Whenever a ventricular tachyarrhythmia developed, prominent early afterdepolarizations appeared in the monophasic action potential recording within 30 seconds of the cesium injection. Figure 6 demonstrates a

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**Table 1. Early Afterdepolarization Amplitude and Early Afterdepolarization Area**

<table>
<thead>
<tr>
<th>Early afterdepolarization</th>
<th>Cesium</th>
<th>RAS</th>
<th>BAS</th>
<th>LAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%) MAP</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
</tr>
<tr>
<td>Amplitude</td>
<td>29.7± 10.9</td>
<td>29.1± 10.7</td>
<td>26.3± 9.7</td>
<td>30.0± 13.8</td>
</tr>
<tr>
<td>Planimetry</td>
<td>13.2± 8.3</td>
<td>14.3± 6.0</td>
<td>13.7± 6.1</td>
<td>15.1± 6.6</td>
</tr>
<tr>
<td>r value</td>
<td>0.80</td>
<td>0.83</td>
<td>0.74</td>
<td>0.82</td>
</tr>
</tbody>
</table>

MAP, monophasic action potential amplitude; RAS, right ansae subclaviae stimulation; BAS, bilateral ansae subclaviae stimulation; LAS, left ansae subclaviae stimulation; RV, right ventricle; LV, left ventricle.
complete episode of a cesium-induced ventricular tachyarrhythmia during LAS. An early afterdepolarization developed 20 seconds after cesium injection and continued to increase in amplitude until the ventricular tachyarrhythmia was triggered. Left ansae subclaviae stimulation initiated early afterdepolarizations of greater amplitude from the left ventricle and a higher prevalence of ventricular tachycardia induction than did RAS (p<0.01).

Effects of Norepinephrine Infusion

In the dogs given norepinephrine infusions, the mean amplitude of early afterdepolarizations recorded in the right ventricle was not different from the mean amplitude of early afterdepolarizations recorded in the left ventricle (p<0.1). When the data are displayed as dose-response curves (Figure 7), both curves are almost parallel. Cesium injections during norepinephrine infusions caused ventricular tachyarrhythmia in all dogs. Before cesium injection, norepinephrine infusion did not produce early or delayed afterdepolarizations.

Effects of stimulus frequency. The amplitude of early afterdepolarizations was measured in 10 dogs from the right and left ventricles after cesium injection alone and with left ansae subclaviae stimulation at different frequencies. At all stimulus frequencies, the magnitudes of early afterdepolarizations were significantly greater in the left than in the right ventricle. In both ventricles, the amplitude of early afterdepolarizations increased with increasing stimulus frequencies, reaching a plateau at a frequency of 4–6 Hz. When the data are displayed as frequency-response curves (Figure 8), there is an upward shift of the left ventricular response curve compared with the right ventricular response curve, whereas both curves show a similar pattern, indicating a quantitative difference between them (p<0.001).

Effects of ansae subclaviae stimulation and cesium on QT interval and monophasic action potential duration. LAS, RAS, and BAS significantly shortened the monophasic action potential duration recorded in the left ventricle (p<0.05). The QT interval shortened significantly only after LAS and did not change after RAS and BAS. Cesium lengthened the QT interval and monophasic action potential duration (Table 3).

Control Dogs

In eight control dogs in which early afterdepolarizations and ventricular tachyarrhythmias were induced by four repeated doses of cesium with no other interventions, the magnitude of early afterdepolarizations amplitude did not change significantly in the right (p=0.68) and left (p=0.78) ventricles. The distribution of ventricular tachyarrhythmias over time was not significantly related to the time from initial injection or to the total amount of cesium because the incidence of ventricular tachyarrhythmias at the second and third injections was greater than that at the end of the series of injections (Table 4).
Discussion

The results of this study indicate that in dogs treated with cesium, BAS and LAS produce larger early afterdepolarizations in the left than in the right ventricle. In addition, LAS and BAS produce larger left ventricular early afterdepolarizations than does RAS or cesium alone. Also, LAS and BAS cause an increased prevalence of ventricular tachycardia compared with RAS in dogs treated with cesium. Increasing the frequency of LAS increases the left ventricular early afterdepolarization amplitude during cesium injection. However, norepinephrine infusion produces a dose-related increase in early afterdepolarization amplitude that is similar in both the right and left ventricles. It is likely that when early afterdepolarizations reach a critical amplitude during sympathetic stimulation, ventricular tachycardia ensues.

Relevance of the Model

Previous studies have shown that cesium given in vivo induces early afterdepolarizations, QT prolongation, and ventricular tachyarrhythmias that often resemble torsades de pointes and may be due to triggered activity.\textsuperscript{3-5} Magnesium suppresses both the early afterdepolarizations and ventricular tachyarrhythmias.\textsuperscript{20} These responses of the canine heart to cesium exhibit features resembling aspects of both the acquired and idiopathic long QT syndromes with torsades de pointes. Suppression by magnesium resembles the response of the acquired long QT syndrome. Because there exists no other animal model yielding such similarities to the clinical syndromes, it seemed reasonable to test the effects of sympathetic stimulation in cesium-treated dogs. Although catecholamines have been shown to cause delayed afterdepolarizations and triggered activity in a variety of experimental preparations, such as the coronary sinus in vitro,\textsuperscript{21} sympathetic neural stimulation uncommonly provokes ventricular tachyarrhythmias in the normal dog heart\textsuperscript{17,22} and could be used to test concepts of "sympathetic imbalance," ascribed to patients with the congenital long QT syndrome. Recently, Priori et al\textsuperscript{16} demonstrated delayed afterdepolarizations in vivo during stellate ganglion stimulation.

The role of sympathetic stimulation in patients with acquired long QT syndrome is multifactorial.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Monophasic action potential recording of development of an early afterdepolarization in the left ventricle preceding the onset of nonsustained ventricular tachycardia. An early afterdepolarization developed 20 seconds after cesium injection and continued to increase in amplitude until the ventricular tachyarrhythmia was triggered. LAS, left ansae subclaviae stimulation; ECG, lead II during atrial pacing; RA, right atrial electrogram; MAP, monophasic action potential from right (RV) and left (LV) ventricles; LVEG, bipolar electrogram from epicardial left ventricle.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Plot of dose-response curve. Early afterdepolarization (EAD) amplitude (y axis) in response to varying concentrations of norepinephrine (NE, x axis) during cesium injection is shown for left (LV) and right (RV) ventricles.}
\end{figure}
Isoproterenol-induced increase in heart rate (held constant in this study) would be expected to decrease early afterdepolarization amplitude and the prevalence of ventricular tachyarrhythmias, whereas direct catecholamine effects might increase early afterdepolarization amplitude (by increasing the slow inward current, among other effects) and increase the prevalence of ventricular tachyarrhythmias. Whether the cesium model more closely resembles the acquired or the idiopathic long QT syndrome remains to be established, and the results from the present study must not be ascribed prematurely to clinical situations. Similarly, it is not clear whether early afterdepolarizations are more relevant to the acquired long QT syndrome and delayed afterdepolarizations to the idiopathic long QT syndrome.16,23

Concept of “Sympathetic Imbalance”

Yanowitz et al7 demonstrated that left stellate ganglion stimulation and right stellate ganglion interruption prolonged the QT interval, whereas left stellate ganglion interruption and right stellate ganglion stimulation shortened it. However, the QT interval was measured in only one electrocardiographic lead and increased by 10–90 msec (mean, 46 msec) 1–5 minutes after termination of the stimulation. They explained the QT interval prolongation by “unmasking” previously cancelled repolarization forces. Several years later, Abildskov24 showed that the QT prolongation produced during left stellate ganglion stimulation was very evanescent, lasting at most several minutes. Left stellate ganglion stimulation exceeding 2 minutes always shortened the QT interval. In the present study, the monophasic action potential duration was always shorter than the QT interval (i.e., providing no evidence of cancelled repolarization forces), and both shortened during LAS (Table 3).

Despite the known regional distribution of right and left sympathetic fibers17,25–27 it is hard to explain permanent QT prolongation in patients by the transient changes in QT interval found in dogs. Because patients with the idiopathic long QT syndrome characteristically develop arrhythmias during periods of increased adrenergic activity, it is necessary to postulate that left stellate activity increases more than does right stellate activity to create sympathetic imbalance.2,9 The heart rate increase accompanying such activity should suppress early afterdepolarizations, whereas the direct adrenergic effects on the slow inward current, for example, might increase early afterdepolarization amplitude. In contrast, both adrenergic stimulation and heart-rate increase (within limits) might be expected to increase the amplitude of delayed afterdepolarizations,16 raising the potential importance of delayed afterdepolarizations.

Data on the effect of left stellate stimulation in human subjects are conflicting. One study showed a prolongation9 of the QT interval, whereas another with only two patients indicated no change.28 Left stellate ganglion interruption has been used as successful therapy for many8,29 but not all30 patients with the long QT syndrome and ventricular tachyarrhythmias. Left stellate ganglion interruption has also been shown to reduce sudden death in patients after anterior myocardial infarction.31 Thus, although the greater arrhythmogenic role ascribed to the left stellate ganglion compared with the right stellate ganglion seems reasonably conclusive, it is less certain that the long QT syndrome and related ventricular arrhythmias result from imbalance of left and right sympathetic effects.

Table 3. QT and Monophasic Action Potential Duration During Sympathetic Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LAS</th>
<th>Control</th>
<th>RAS</th>
<th>Control</th>
<th>BAS</th>
<th>Control</th>
<th>Cesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT interval (msec)</td>
<td>359 ± 36</td>
<td>346 ± 44</td>
<td>362 ± 36</td>
<td>359 ± 49</td>
<td>355 ± 40</td>
<td>347 ± 54</td>
<td>364 ± 35</td>
<td>440 ± 64</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>MAP duration (msec)</td>
<td>277 ± 29</td>
<td>262 ± 31</td>
<td>277 ± 32</td>
<td>266 ± 24</td>
<td>280 ± 33</td>
<td>263 ± 25</td>
<td>278 ± 30</td>
<td>383 ± 43</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
<td>0.05</td>
<td></td>
<td>0.05</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

LAS, left ansae subclaviae stimulation; RAS, right ansae subclaviae stimulation; BAS, bilateral ansae subclaviae stimulation; MAP, monophasic action potential; Cesium, cesium stimulation.
TABLE 4. Early Afterdepolarization Amplitude and Prevalence of Ventricular Tachycardia During Repeated Doses of Cesium at 30-Minute Intervals

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAD amplitude (% MAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>27.8±7.0</td>
<td>30.6±10.2</td>
<td>24.8±5.5</td>
<td>28.2±7.7</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>33.1±5.5</td>
<td>38.7±9.7</td>
<td>36.7±8.7</td>
<td>33.7±9.1</td>
</tr>
<tr>
<td>VT incidence</td>
<td>2/8 (25%)</td>
<td>4/8 (50%)</td>
<td>4/8 (50%)</td>
<td>3/8 (37.5%)</td>
</tr>
</tbody>
</table>

EAD, early afterdepolarization; MAP, monophasic action potential amplitude; VT, ventricular tachycardia.

Manipulation of the right stellate ganglion causes contractile and electrophysiological changes in the anterior portion of the canine heart, primarily the right ventricle and a part of the anterior left ventricle. Left stellate ganglion stimulation results in similar changes on the posterior surface of the ventricles. The effects of left stellate stimulation also overlap the anterior distribution of right stellate effects. Thus, it would seem that the left stellate ganglion innervates most of the ventricular myocardium, or at least a much larger amount of the ventricle than does the right stellate ganglion. Further, norepinephrine content is greater in the left than in the right ventricle. Finally, left stellate ganglion stimulation results in a greater overflow of norepinephrine in coronary sinus blood than does right stellate ganglion stimulation. These data suggest the conclusion that the left stellate ganglion exerts a qualitatively greater adrenergic influence on the ventricles than does the right stellate ganglion. This factor, which results in more ventricular mass being affected because of more norepinephrine being released, rather than qualitative differences between stellate ganglia or left and right stellate imbalance, may be the basis for the arrhythmogenic potential of the left stellate ganglion. It also may account for the beneficial effects after surgical interruption of the left stellate ganglion. We hypothesize that patients with the idiopathic long QT syndrome have a primary myocardial membrane defect in repolarization, for example, involving an outward potassium current, that creates early afterdepolarizations and the long QTU interval. Sympathetic stimulation, primarily left, could periodically increase the amplitude of the early afterdepolarization to reach threshold and produce ventricular tachyarrhythmias. Surgical interruption of the left stellate ganglion could eliminate the arrhythmias without consistently shortening the QTU interval because the early afterdepolarization would still be present, only subthreshold.

Mechanisms in the Present Study

Interventions that delay repolarization may result in early afterdepolarizations. Cesium causes early afterdepolarizations presumably by blocking an outward $K^+$ repolarizing current. As mentioned earlier, catecholamine effects are multifactorial but, in this study with heart rate held constant, early afterdepolarization magnitude increased during LAS and BAS to the point when ventricular tachycardia occurred. However, monophasic action potential duration that was increased by cesium was decreased during sympathetic stimulation.

Before norepinephrine infusion or ansae subclaviae stimulation, early afterdepolarization amplitude was the same in both ventricles. During norepinephrine infusion, early afterdepolarization amplitude increased equivalently in both ventricles. These findings suggest that there was nothing unique in the response of the left and right ventricles to cesium or to catecholamine stimulation. Although it is now clear that the left ventricular epicardium exhibits an early outward current not present in the endocardium, whether that current is also in the right ventricle is not known. Considering all these observations, it seems reasonable to postulate that ansae subclaviae stimulation increases early afterdepolarization amplitude through the effects of $\beta$-receptor and possibly $\alpha$-receptor stimulation. The larger early afterdepolarization amplitude in the left ventricle during LAS or BAS may simply reflect more norepinephrine released and more myocardium affected. The fact that left stellate ganglion interruption reduces the incidence of syncope and sudden death in some patients with the long QT syndrome in whom $\beta$-adrenergic receptor blocking drugs are unsuccessful underscores the potential role of $\alpha$-receptor stimulation.

Consideration of the Model

An extracellular contact electrode for monitoring the transmembrane potential is imprecise but does provide an estimation of intracellular events. One cannot assume that the early afterdepolarization recorded is the particular early afterdepolarization responsible for the ventricular tachyarrhythmia. Yet, it is likely that the events recorded at any position along the endocardium represent other areas of heart tissue, including the site of the ectopic focus, during interventions affecting the entire heart homogeneously, that is, intravenous cesium or norepinephrine infusions. However, because of the distribution of right and left stellate ganglion innervation, electrophysiological findings at the recording sites during neural stimulation may not necessarily reflect changes in the rest of the ventricle. Because the amplitude and area of the early afterdepolarization vary from dog to dog and between interventions in the same dog because of catheter shift, these values were
determined as a percentage of the corresponding monophasic action potential. Finally, the conclusion that early afterdepolarizations caused the ventricular tachyarrhythmia is based on circumstantial evidence. However, successful modulation of early afterdepolarization amplitude with an appropriate increase or decrease in the incidence of ventricular tachycardia helps to establish causality.

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References
35. Isenberg G: Cardiac Purkinje fibers: Cesium as a tool to block inward rectifying potassium currents. Pflegers Arch 1976;365:99–106

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