Autonomic modulation of ventricular arrhythmia in cesium chloride–induced long QT syndrome

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ABSTRACT To evaluate autonomic influence on arrhythmogenesis in an animal preparation of triggered activity, we gave increasing doses of cesium chloride (0.125 to 5.0 mmol/kg iv) to 24 dogs distributed equally among four protocols of autonomic intervention: control, total denervation, β-blockade, and left stellate stimulation. All dogs underwent atrioventricular node ablation followed by ventricular pacing. A left ventricular endocardial monophasic action potential (MAP) catheter allowed for detection of “MAP early afterdepolarizations” (mEAD). mEAD amplitude was measured relative to MAP amplitude. Cesium chloride (CsCl) increased both MAP duration (132% after 0.125 mmol/kg to 188% after 1.0 mmol/kg; p < .001) and mEAD amplitude (20% after 0.125 mmol/kg to 49% after 1.0 mmol/kg; p < .001) in a dose-dependent fashion. All dogs exhibited ventricular ectopy at roughly equivalent doses (0.88 ± 0.5 mmol/kg). Cesium’s peak effect on MAP characteristics, sinus node automaticity, and systolic blood pressure coincided with the onset of sustained ventricular tachycardia (VT). Whereas control and denervated dogs developed VT after similar doses of CsCl (1.21 ± 0.1 vs 1.12 ± 0.14 mmol/kg; p = NS), none of the six β-blocked dogs developed sustained VT. Conversely, those dogs having undergone stellate stimulation developed VT after smaller doses (0.58 ± 0.34 mmol/kg; p < .001) and with earlier onset (12 vs 30 sec; p < .025). After 0.5 mmol/kg of CsCl, left stellate stimulation augmented relative mEAD amplitude compared with control (51% vs 38%; p < .001), whereas β-blockade had little effect (39% vs 38%; p = NS). Autonomic intervention as such can affect the arrhythmogenicity of CsCl and similarly alter MAP characteristics. Furthermore, as β-blockade can prevent sustained arrhythmia without eliminating mEADs, autonomic tone appears to modulate the expression of mEADs as sustained VT.


THE IDIOPATHIC long QT syndrome is complicated by polymorphic ventricular tachycardia (VT), the mechanism of which in unknown yet presumed to be triggered activity dependent on early afterdepolarizations.1–5 Current evidence implicates a central role for the sympathetic nervous system in this life-threatening arrhythmia.6 Stressful conditions known to increase sympathetic activity, such as violent emotions or exercise, appear to precipitate syncope and sudden death in patients with idiopathic long QT syndrome. β-Blockade and left high thoracic sympathectomy, on the other hand, exert an antiarrhythmic effect.5

In vitro, high concentrations of epinephrine applied to Purkinje fibers produce spontaneous activity arising from early afterdepolarizations.7 To study autonomic influence on triggered activity in vivo, we chose an animal preparation of polymorphic VT occurring in the setting of long QT interval produced by cesium chloride (CsCl).8 Cesium has been reported to induce release of catecholamines, both centrally and in the periphery.9 The VT produced by cesium in the intact dog is electrocardiographically similar to torsade de pointes and is caused by early afterdepolarizations that are bradycardia dependent.8

The phenomenon of early afterdepolarizations in the cesium induced long QT preparation, a central feature of the resultant triggered rhythms, appears detectable with a monophasic action potential (MAP) catheter.2 These “apparent afterdepolarizations” in MAP recordings are related temporally to the appearance of ventricular arrhythmias and have a coupling interval and amplitude nearly identical to the coupling interval and
take-off potential of associated ventricular premature
beats.2

The present studies correlated MAP recordings with
arrhythmic outcome in 24 dogs given increasing doses of
CsCl after autonomic intervention. We intended to
answer three questions: Does the autonomic nervous
system mediate or modulate induction of bradycardia
and VT by CsCl? Does this interaction influence MAP
characteristics, specifically delayed repolarization and
“apparent early afterdepolarizations”? Finally, can
clarification of an interaction between autonomic tone and
triggered activity add to an understanding of ar-
rhythmogenesis in this preparation?

Methods

After induction of anesthesia with 5 to 12 ml of intravenous
sodium thiamylal (5%), 24 mongrel dogs weighing 8 to 13 kg
were anesthetized with a combination of α-chloralose and ure-
thane (13.6 and 136 mg/kg im) and ventilated with room air.
A jugular or femoral vein was cannulated for administration of
drugs. A lead II surface electrocardiogram and arterial pressure
were monitored continuously, the latter through cannulation of
the carotid or femoral artery. In most experiments, expired CO2
was monitored (Datex exhaled gas analyzer) and rectal temper-
ature was maintained at 38° to 38.5°C with a thermally regulated
operating table.

After median sternotomy, the heart was supported in a peri-
cardial sling. Bipolar plunge electrodes consisting of Teflon-
coated silver wires exposed at the tip were placed in the right
atrial appendage and both ventricles to record reference elec-
rograms. An additional set placed in the right ventricle served
as bipolar pacing leads.

Atrioventricular (AV) node ablation. To avoid variable
baseline heart rates after autonomic intervention and to facilitate
independent assessment of sinus and ventricular responses to
CsCl, all dogs underwent electrical ablation of the AV node
followed by continuous ventricular pacing. A standard No. 6F
quadripolar intracardiac recording catheter (USCI) with an inter-
electrode distance of 10 mm was introduced via the left carotid
artery into the aortic root. Guided by palpation, the catheter was
positioned posteriorly near the noncoronary cusp of the aortic
valve to obtain a His bundle electrogram. A bipolar signal
recorded from the distal and neighboring poles was amplified
and filtered at a band pass of 30 to 1000 Hz.

The anodal output (sink) paddle of a standard defibrillator
(Hewlett-Packard 78670A or Dallons) was placed underneath
the left ventricle, with the other paddle positioned on the pin
from the distal pole. Complete heart block was achieved by
delivery of 60 to 100 J in a single asynchronous DC shock. Only
one of 24 dogs developed ventricular fibrillation, which was
countershocked easily with 10 J. A second dog exhibited return
of AV conduction within 30 min and required a second shock
after repositioning of the catheter.

Continuous ventricular pacing at twice diastolic threshold and
600 msec cycle length was accomplished with a programmed
stimulator and constant-current source (Bloom). Hearts were
allowed 30 min to equilibrate before further manipulation.

MAP recordings. A bipolar catheter consisting of a silver-
and-silver chloride electrode and a reference lead 5 mm away29
was advanced via an apical left ventricular myostomy through the
full thickness of the myocardium to the underlying endocar-
dium. Catheter position was maintained with a 2.0 silk purse-
string suture and was readjusted before each recording to obtain

signals of maximal amplitude. MAP recordings were filtered
with a high pass of 100 Hz.

Amplified MAP signals, right atrial, right ventricular, and left
ventricular local electrograms, arterial pressure, lead II surface
electrocardiogram, and stimulus artifacts (from ventricular pac-
ing) were displayed on an oscilloscope (Tektronix or Electronics
for Medicine VR12). Signals were recorded simultaneously on
an electrostatic (Gould) or ink (Mingograph) paper recorder at
speeds of 25 to 50 mm/sec.

Recordings were taken starting at 10 sec before and continu-
ing for 90 sec after each injection. Twenty seconds after onset
of a sustained arrhythmia, the ventricular pacer was turned off.
Pacing resumed after spontaneous termination of an arrhythmia.

Autonomic intervention protocols. The 24 dogs were
distributed equally (six dogs each) among four protocols. Group
1 (control) received CsCl alone. Group 2 (denervation) first under-
went bilateral stellate ganglionectomy with bilateral cervical
truck vagotomy. Approximately 1 inch of vagus nerve was
removed bilaterally. Each stellate ganglion and its ansa subclavia
were removed entirely.

Group 3 (esmolol) first underwent bilateral cervical trunk
vagotomy and β-blockade with a continuous infusion of esmolol
(100 to 160 mg/kg/min iv). The infusion rate was titrated to
achieve 50% to 75% inhibition of the baseline heart rate’s
response to a test dose (0.5 μg/kg iv) of isoproterenol.11 A
moderately potent cardioselective β-blocker, esmolol has a rapid
distribution half-life (2 min) and a short elimination half-life (9
min). At the therapeutic dosages used, esmolol demonstrates no
intrinsc sympathomimetic activity in dogs nor any significant
membrane stabilizing activity.12 The pA2 for cardiac β-receptor
blockade is approximately 1/1000 the dose that produces direct
cardiac depression (pA2 being the negative log of antagonist
concentration producing an agonist dose ratio of 2).13

Group 4 (stellate stimulation) first underwent bilateral vagot-
omy and right stellate ganglionectomy. The left stellate ganglion
was then decentralized and its ansa subclavia nerve was carefully
isolated by blunt and sharp dissection. Bipolar stimulating elec-
rodes were placed around the ansa subclavia to deliver a 2 ms
csquare-wave pulse of 2 to 8 mA and 5 to 10 Hz from a stimulator
(Bloom). Stimulation was initiated 15 sec before and maintained
for 60 sec after each CsCl injection. Adequate stellate stimu-
lation was assessed as a 50% increase in systolic or pulse
pressure compared with baseline. Unilateral stimulation was
modeled after the clinical hypothesis that sympathetic imbalance
underlies the malignant arrhythmias in the idiopathic long QT
syndrome.6

“Tachycardia threshold dose.” To evaluate the effect of the
above autonomic interventions on arrhythmogenesis, increasing
doses of cesium were administered until a “threshold dose”
produced sustained VT. The latter was defined in this preparation
as lasting greater than 30 sec.14 CsCl was administered as a rapid
intravenous bolus (over several seconds) at 15 min intervals in
seven successively escalating doses: 0.125, 0.25, 0.5, 1.0, 1.25,
2.5, and 5.0 mmol/kg. Prior work has demonstrated that cumu-
lative doses of 1.0 to 1.5 mmol/kg frequently induce VT, higher
doses more often producing ventricular fibrillation.2, 8 The
seven doses chosen provided a broad range around 1.0 mmol/kg
to detect any change after autonomic intervention in cesium’s
tachycardia threshold dose. All animals developed ventricular
fibrillation, terminating the experiment, with or before the 5.0
mmol/kg injection.

Intervals of 15 min were chosen to allow for resolution of
cesium’s arrhythmogenic effect.2, 8 Serum levels peak in less
than 2 min and greater than two-thirds of the drug is cleared
within 15 min.8 Intracellular levels, however, presumably accu-
mate at such frequent dosing intervals.

Data analysis. To assess sinus node response to CsCl, sequen-

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tial coupling intervals of atrial electrograms were digitized manually with a Hewlett-Packard 9836 computer system for the first three injections (0.125, 0.25, and 0.5 mmol/kg). The latter intervals, termed “sinus coupling intervals,” reflect the time between each successive atrial depolarization measured from our right atrial reference electrograms. Higher doses of CsCl were not evaluated since the resultant atrial rhythms were frequently chaotic.

Sinus coupling intervals for each injection were normalized relative to the cesium-free baseline (the latter expressed as 1.00). Prolongation of sinus coupling interval by cesium was then expressed as a percentage of that cesium-free baseline.

A similar sequential analysis of coupling intervals was carried out for left ventricular electrograms for those injections producing sustained VT. Those occasional ventricular coupling intervals involving interpolated paced beats (after onset of VT and before termination of pacing) were edited out to avoid artificial heterogeneity in the analysis of tachycardia cycle length.

Beat-to-beat sequential analysis of systolic blood pressure was likewise determined over time with the Hewlett-Packard 9836 system (resolution 2 mm Hg) for the first five injections (0.125, 0.25, 0.5, 1.0, and 1.25 mmol/kg). All animals succumbed to either the sixth (2.5 mmol/kg) or seventh (5.0 mmol/kg) injection.

MAP variables were measured at time of injection then at 5 sec intervals for the first 90 sec after each injection. Amplitude and duration were digitized manually with the Hewlett-Packard 9836 system, having a resolution of 0.02 mV and 1.0 msec. MAP amplitude was defined as the potential difference between the peak of the plateau (phase 2) and resting potential (phase 4). MAP duration was determined at 90% repolarization. Either a delay in repolarization accompanied by an inflection of phase 3 (figure 1, A) or true afterdepolarizations occurring during phase 2 or 3 of the MAP (figure 1, B, or C) were termed “MAP early afterdepolarizations” (mEADs).

As described for EADs in conventional transmembrane recordings, mEAD amplitude was defined and determined similarly. mEAD amplitude was expressed as percent of total MAP amplitude. MAP duration was expressed as percent of baseline duration.

Statistical analysis. The effect of CsCl on sinus coupling intervals, MAP variables, and systolic blood pressure manifested similar time courses, peaking at approximately 15 to 20 sec after injection. As such, these measurements were evaluated similarly by a mean and standard deviation of all measurements made over the interval between 15 and 60 sec after injection for the six dogs in each group. Means were calculated separately for each animal and then averaged to obtain a mean value for the group. Sixty seconds was chosen because stellate stimulation (group 4) had ended by that point.

Means for sinus coupling interval, MAP variables, or systolic blood pressure were compared simultaneously between groups and dosages by an analysis of variance with repeated measures. A p value of ≤ .05 was considered to indicate a significant difference. These mean values from the highest dose studied were compared between groups by a simple analysis of variance.

Mean tachycardia threshold dose, mean time of onset, and mean cycle length for the first run of sustained VT were each compared across the four groups by an analysis of variance. In group 4, mean cycle length excluded those values occurring after termination of stellate stimulation. A p value of ≤ .05 was considered to indicate a significant difference. Mean times of onset for the first versus second run of VT were compared within each group by a nonpaired t test.

Results

Sinus node automaticity. Ventricular arrhythmias produced by CsCl characteristically are heralded by marked sinus pauses, which augment the amplitude of bradyarrhythmia-dependent early afterdepolarizations. AV dissociation, a feature of the present experiments, allowed detection of prolonged sinus coupling intervals in the right atrial electrograms and surface electrocar-
diagram without the complication of retrograde atrial capture.

Figure 2 displays for all four groups the respective time course of prolongation of sinus coupling intervals after the first three doses of cesium. Each line represents a mean of time-aligned recordings from all six dogs in a group. The time course of cesium’s effect on sinus node automaticity appeared to be similar in all four groups. Peak effect occurred within 15 to 20 sec after injection. Within 15 min cesium’s effect had dissipated. As a result, by the onset of a subsequent injection, sinus coupling interval had returned to baseline.

By the third dose (0.5 mmol/kg), marked sinus pauses shortly after injection were noted, most remarkably in the control group (figure 2, A). Only half of the control dogs, however, developed marked pauses, which when averaged accentuated the peaks in figure 2, A. Any suggestion of periodicity in the peaks is more an artifact of averaging, since in all cases the bradycardia was erratic. A trend toward irregular sinus discharges in all groups progressed with higher doses of cesium (1.0, 1.25, 2.5, and 5.0 mmol/kg) to a chaotic atrial rhythm with altered p wave axis (not shown).

Figure 3 summarizes differences among groups in the dose effect of CsCl on sinus node automaticity. Each data point represents a mean of values between 15 and 60 sec after injection for all six dogs in a group again for the first three doses. In group 1 (control), cesium depressed sinus node automaticity in a dose-dependent fashion. Cesium prolonged sinus coupling intervals by 32% compared with baseline after 0.125 mmol/kg, 68% after 0.25 mmol/kg, and 124% after 0.5 mmol/kg (p = .01). In the remaining three groups, however, cesium produced relatively less depression of automaticity. Maximum depression at 0.5 mmol/kg was 58% in group 2 (denervated), 34% in group 3 (esmolol), and 67% in group 4 (stellate) vs 124% in group 1 (p < .001).

As displayed in figure 3, no significant dose effect
FIGURE 3. Effect of dose of CsCl (mmol/kg) on mean sinus coupling interval. Each value represents a mean of sinus coupling intervals between 15 and 60 sec after injection derived from all six dogs in a group. Each line represents the first three doses for the labeled group. Coupling interval has been expressed as a percentage of the initial interval at onset of injection. Cesium depressed sinus node automaticity in all 4 groups; however, only in group 1 was a significant dose-dependent effect noted. mM = millimoles.

of CsCl on sinus node automaticity was seen in groups 2, 3, and 4. The latter dogs, unlike group 1, had undergone bilateral cervical vagotomy. Cesium nonetheless depressed sinus node automaticity directly in these dogs. Little effect on sinus rate was seen after termination of left stellate stimulation (group 4), presumably because the left ganglion provides minimal innervation to the sinus node.15

Induction of ventricular ectopy and tachycardia. CsCl produced VT in group 1 (control) at a relatively uniform dose (1.21 ± 0.1 mmol/kg). Brief ventricular ectopy occurred with lower doses. Bigeminy, a frequent arrhythmia after lower cesium doses (e.g., 0.5 mmol/kg) in our pilot experiments during normal sinus rhythm, was seen only rarely with our ventricularly paced dogs.

Although both polymorphic and uniform electrocardiographic morphologies were noted, the initial run of VT was more often uniform (figure 4, A). Transition to a less uniform morphology occurred occasionally after several minutes. Attempts to terminate the arrhythmia with brief (≤ 10 sec) overdrive pacing were, as might be expected,14 uniformly unsuccessful.

Figure 5 demonstrates differences among the four groups in mean tachycardia threshold doses. Although dogs from groups 1 (control) and 2 (denervated) first developed VT at similar doses (1.21 ± 0.01 vs 1.12 ± 0.14 mmol/kg; p = NS), none of the six dogs from group 3 (esmolol) developed sustained VT. Tachycardia threshold dose for the latter group is depicted in figure 5 by an open bar representing a highly increased threshold. Conversely, group 4 dogs (stellate) developed VT at significantly lower-than-control doses of CsCl: 0.58 ± 0.34 mmol/kg (cumulative: 1.04 ± 0.68 mmol/kg). These protocol-related differences in tachycardia threshold dose were highly significant (p < .001).

Group 3 dogs (esmolol) in response to escalating doses of cesium exhibited at most rare nonsustained VT (longest run, 7 ± 6 beats) after the 0.5 or 1.0 mmol/kg injection. Higher doses of cesium in these dogs resulted only in depressed contractility and altered conduction manifested as a widened QRS complex and eventually fine ventricular fibrillation. Although mean tachycardia threshold doses differed significantly among the four groups, the initial dose producing ventricular
ectopy was similar: 2.29 ± 0.65 mmol/kg in group 1 (control), 1.54 ± 0.52 mmol/kg in group 2 (denervated), 2.00 ± 1.84 mmol/kg in group 3 (esmolol), and 0.88 mmol/kg in group 4 (stellate stimulation) (p = NS).

Figure 6 displays the time course and mean cycle length of VT in the three groups exhibiting the arrhythmia. Each line represents a mean of time-aligned recordings from all six dogs in a group. Ventricularly paced at a cycle length of 600 msec, each heart, typically within 30 sec of cesium injection, developed ventricular tachycardia, the cycle length of which shortened progressively. The gradual shortening of cycle length occurred over several seconds in the majority of dogs. This acceleration until achieving a constant rate is classic for the "rhythm of development" of triggered foci.  

The time from injection to onset of VT (latency) indicates when the ectopic cycle length shortened beyond the uniform paced cycle length (overtaking the paced rhythm). Latency, depicted in figure 6 by vertical arrows, differed significantly among groups: 30 ± 15 sec in group 1 (control), 24 ± 5 sec in group 2 (dener vated), and 12 ± 3 sec in group 4 (stellate) (p < .025). There were small but statistically significant differences as well in mean tachycardia cycle length: 332 ± 16 msec in group 1, 360 ± 59 msec in group 2, and 350 ± 89 msec in group 4 (p < .001). Nearly all tachycardias resolved spontaneously within 15 min, which is consistent with prior reports on the duration of cesium's arrhythmogenic effect.  

**FIGURE 5.** Mean first dose of CsCl (mmol/kg) within each group to produce sustained VT, i.e., "tachycardia threshold dose." The ordinate expresses dose as a cumulative sum. Each bar represents the mean for the group as labeled, standard deviation being displayed as a vertical line. Since no animal in group 3 (esmolol) developed sustained VT, the highest dose tolerated before onset of ventricular fibrillation is presented as an open bar, representing an increased "tachycardia threshold." Although groups 1 and 2 developed VT at similar doses, the decreased threshold in group 4 and increased threshold in group 3 were highly significant. mM = millimoles.

**FIGURE 6.** Ventricular coupling intervals during the first 90 sec after injection of the first dose of CsCl producing sustained VT, i.e., "tachycardia threshold dose." Values represent means of time-aligned recordings from all six dogs in a group. Since group 3 (esmolol) did not exhibit sustained ventricular VT, only group 1 (A), group 2 (B), and group 4 (C) are presented. Dots represent the standard errors for each mean value. Vertical arrows represent mean time of onset of tachycardia. Ventricularly paced at a cycle length of 600 msec, each heart, typically within 30 sec of cesium injection, developed VT, the cycle length of which progressively shortened over several seconds. Mean tachycardia threshold dose for each group is noted in the upper right-hand corner. The open arrow in panel C represents termination of stellate stimulation in group 4. mM = millimoles.
After the initial occurrence of VT, subsequent higher doses of CsCl usually produced VT or fibrillation. In all groups the morphology of the second run of tachycardia was less uniform (figure 4, B) compared with the initial occurrence (figure 4, A). Time of onset of the second occurrence was earlier and differed significantly among protocols: 22 ± 5 sec in group 1, 17 ± 2 sec in group 2, and 9 ± 10 sec in group 4 (p < .05). In certain animals from group 4 the second run of tachycardia occurred in the 15 sec window after resumption of stellate stimulation yet before injection of cesium.

Coarse ventricular fibrillation occurred in our control dogs at a relatively predictable cumulative dose, typically, as reported earlier, after the QRS complex had widened and in the setting of a marked fall in systolic pressure. All four groups developed ventricular fibrillation at similar cumulative doses: 8.96 ± 2.6 mmol/kg in group 1, 6.46 ± 2.0 mmol/kg in group 2, 8.13 ± 2.7 mmol/kg in group 3, and 6.67 ± 3.4 mmol/kg in group 4 (p = NS).

MAP characteristics. Figures 7 and 8 show the time course and extent of cesium’s effect on MAP duration and mEAD amplitude, respectively. The time course of alterations in MAP recordings mirrored that seen with cesium’s effect on sinus (figure 2) and ventricular (figure 6) coupling intervals: peaking within 20 sec after injection and largely subsiding by 15 min.

As suggested by figures 7 and 8, the dose-dependent effect of cesium chloride on MAP characteristics appeared similar in all four groups, unlike cesium’s effect on sinus node automaticity (figure 3). Figure 9 summarizes from figures 7 and 8 the similarities among groups in relative degree of prolongation of MAP duration or augmentation of mEAD amplitude with increasing doses of CsCl. Each data point represents a mean of values between 15 and 60 sec after injection for two to six dogs in a protocol. Onset of VT prevented accurate assessment of MAP characteristics, reducing the number of dogs available for analysis. Before the onset of tachycardia, successive doses of CsCl prolonged MAP duration in a dose-dependent fashion in group 1 dogs: 132% at 0.125 mmol/kg to 188% at 1.0 mmol/kg.

FIGURE 7. Time course and extent of prolongation of MAP duration, with increasing doses of CsCl (mmol/kg) in all four protocols: A, group 1 (control), B, group 2 (denervation), C, group 3 (esmolol), and D, group 4 (stellate stimulation). MAP duration is expressed as a percentage of initial duration at onset of injection. Each curve represents a mean of two to six dogs in a group for that dose as labeled in the top right panel; onset of VT prevented accurate assessment of MAP duration, reducing the number of dogs available for analysis. The first three to four doses of CsCl, specifically those before the tachycardia threshold dose, are presented. Cesium prolonged MAP duration in a significant dose-dependent fashion in all groups. mM = millimoles.
FIGURE 8. Time course and extent of augmentation of mEAD amplitude with increasing doses of CsCl (mmol/kg) in all four protocols: A, group 1 (control), B, group 2 (denervated), C, group 3 (esmolol), and D, group 4 (stellate stimulation). mEAD amplitude is expressed as a percentage of total MAP amplitude. Each curve represents a mean of two to six dogs in a group for that dose as labeled in the top right panel; onset of VT prevented accurate assessment of mEAD amplitude, reducing the number of dogs available for analysis. The first three to four doses of CsCl, specifically those before the tachycardia threshold dose, are presented. Cesium increased relative mEAD amplitude in a significant dose-dependent fashion in all groups. mM = millimoles.

p < .001 (figure 9, A). Cesium increased as well the relative amplitude of mEADs in a similar dose-dependent fashion in group 1: 20% at 0.125 mmol/kg to 49% at 1.0 mmol/kg; p < .001 (figure 9, B). The change in MAP duration seemed largely accounted for by the increase in mEAD amplitude.

All four curves in figure 9 exhibit a similar slope, suggesting the effect of CsCl dose on MAP characteristics far outweighed any effect of protocol when considering the first three injections. Evaluating mean MAP characteristics from these three injections in an analysis of variance with repeated measures revealed that dose effect of cesium on MAP duration or mEAD amplitude did not differ significantly across groups. However, some splay in the curves from figure 9, B, occurred with higher doses. For the highest of these doses (0.5 mmol/kg), that injection more likely to produce ectopy, a small but highly statistically significant difference in mean mEAD amplitude was noted between groups. Mean mEAD amplitude between 15 and 60 sec after 0.5 mmol/kg was 39% in group 1 (control), 49% in group 2 (denervated), 41% in group 3 (esmolol), and 51% in group 4 (stellate) (p < .001).

Such group-related differences were not noted with mean MAP duration: 172% in group 1, 173% in group 2, 179% in group 3, and 179% in group 4 (p = NS). Higher doses of cesium could not be compared between groups, since all dogs in group 4 had developed sustained VT by the fourth (1.0 mmol/kg) injection.

Although differing autonomic interventions had a significant effect on arrhythmic outcome (figure 5), this was accompanied by only minor changes in MAP characteristics (figure 9, B). Of note, sizable mEADs (figure 8, C) in group 3 (esmolol) occurred in the absence of sustained VT.

Low membrane potential early afterdepolarizations. Damiano and Rosen\textsuperscript{14} described two types of early afterdepolarizations produced by CsCl in vitro: (1) a high membrane potential EAD interrupting phase 3 and (2) a low membrane potential EAD interrupting phase...
2. High membrane potential EADs occurred with hypokalemia and induced triggered action potentials, whereas low membrane potential EADs produced by cesium occurred with normokalemia and were not associated with triggered activity.\textsuperscript{14} mEADs in the present experiments, as substantiated by earlier work,\textsuperscript{2} act like the first variety of EADs in vitro. A potential in vivo correlate of the second variety (low membrane potential) EAD was detected in the present experiments (figure 1, C) only with higher doses of cesium (greater than 1.25 mmol/kg) and, as such, more than 1 hr after initial injections. The occurrence and appearance of this second type of EAD did not exhibit any apparent differences among groups.

**Hypertensive response to cesium.** CsCl has previously been reported to acutely increase systolic blood pressure.\textsuperscript{8, 9, 17} Figure 10 displays for all four groups the respective time course and extent of increase in systolic pressure after increasing doses of cesium. Similar to cesium’s effect on sinus (figure 2) and ventricular (figure 6) coupling intervals or on MAP characteristics (figures 7 and 8), systolic blood pressure peaked within 20 sec and returned toward baseline within 15 min after injection. As might be expected with differing autonomic intervention, baseline systolic blood pressures differed among groups.

Figure 11 summarizes from figure 10 the significant dose-dependent fashion in which systolic blood pressure rose in all four groups. There were nonetheless differences among groups in the degree of hypertensive response partly because of differing initial pressures. By analysis of variance for the highest dose (1.25 mmol/kg), differences in mean systolic pressure among groups were statistically significant: 224 ± 32 mm Hg in group 1, 176 ± 36 mm Hg in group 2, 150 ± 44 mm Hg in group 3, and 191 ± 39 mm Hg in group 4 (p < .001).

**Discussion**

The present studies have shown that (1) autonomic intervention can affect the arrhythmogenicity of CsCl, (2) this autonomic effect is associated with relatively small but statistically significant changes in mEAD amplitude, and (3) cesium exerts a dose-dependent, chronologically similar effect on sinus node automaticity, mEAD amplitude, and systolic blood pressure, all of which peak with the onset of VT.

**Dose-dependence of cesium’s effect.** The time course of cesium’s effect on repolarization (figures 7 and 8) and arrhythmogenicity suggest that extracellular rather than intracellular levels of cesium trigger ventricular arrhythmia in this preparation. With a serum half-life of approximately 5 min,\textsuperscript{8} most of the ion is cleared from the blood within 15 min after injection. MAP characteristics concurrently return to baseline over this interval (figures 7 and 8). Intracellular levels remain at steady state, however, for greater than 30 min\textsuperscript{8} and presumably accumulate with subsequent injections. Ventricular fibrillation, which occurred in all dogs at roughly equivalent doses, is most likely a manifestation of toxic intracellular cesium levels.

Cesium’s dose-dependent prolongation of phase 3 (figure 9, A) is consistent with prior work demonstrating cesium’s direct inhibition of potassium and non-
This "pacemaker" current, $i_p$, is a hyperpolarizing-activated current demonstrable in both sinoatrial node and Purkinje fibers, which is blocked in vitro by cesium at millimolar concentrations.9

The importance of circulating cesium and its dose-dependent effect suggest a surface membrane rather than intracellular action. The uniformity of dose producing sustained VT (figure 5) in our control dogs (aided by uniformity of heart rate) suggests that tachycardia occurs only after a threshold afterdepolarization is attained.

Mean tachycardia threshold dose in our control dogs (figure 5) was higher than in prior studies.6,8 The difference presumably lies in our method of dosing (every 15 min) and in our continuous ventricular pacing at shorter cycle lengths.8 In addition, pacing avoided any "proarrhythmic" effect of marked sinus pauses.

Injections exceeding the tachycardia threshold dose produced VT with earlier onset, shorter cycle length and less uniform morphology (figure 4). This suggests the possibility of multiple foci. Cesium has been shown in vitro to affect the myocardium and conduction system diffusely.8,14 Therefore, more than one site may concurrently reach a threshold level of prolonged repolarization. Multiple foci could account for the torsade picture often seen with this preparation and is consonant with prior theories regarding the mechanism of torsade des pointes.20

**Autonomic effect.** As displayed in figure 5, autonomic intervention exerts a highly significant effect on cesium’s arrhythmogenic potential as gauged by the tachycardia threshold dose. $\beta$-Blockade proved remarkably protective: no group 3 dogs developed sustained VT. Unilateral (left) stellate stimulation was provocative: group 4 dogs developed sustained VT at lower-than-control doses. In the latter group 15 min after the tachycardia threshold dose (by which point cesium’s arrhythmogenic effect would have subsided) merely resuming stellate stimulation in certain dogs reinitiated ventricular tachycardia. Although autonomic intervention significantly affected tachycardia threshold dose, all groups developed ventricular ectopy and eventually ventricular fibrillation at similar doses.
means were calculated separately for each animal in order to obtain a mean value for the group. CsCl dose is presented as a cumulative sum. Cesium increased systolic blood pressure in a dose-dependent fashion in all groups, although initial pressures and degree of significance varied. mM = millimoles.

Intact stellate ganglia and vagus nerves were not essential for sustained VT in this preparation. Total denervation (protocol 2) produced no significant effect on arrhythmogenic potential (figure 5). The latter finding implicates circulating catecholamines as the more crucial component of the autonomic nervous system in arrhythmogenesis.

Changes in cesium’s arrhythmogenic potential (figure 5) coincided with small but statistically significant changes in relative mEAD amplitude (figure 9, B). Left stellate stimulation (protocol 4) augmented mEAD amplitude. Esmolol with vagotomy (protocol 3), however, resulted in no significant effect on mEAD amplitude. Total denervation actually increased mEAD amplitude somewhat. These larger mEADs corresponded with a trend toward a lower tachycardia threshold dose in group 2 (figure 5). The larger mEADs in group 2 suggest a protective role of the vagus nerve. Prior work has shown that the activity of triggered foci in the coronary sinus can be abruptly terminated by the local application of acetylcholine, a property consistent with such foci being the cause of some of the atrial tachycardias that can be interrupted by vagal maneuvers.16

The influence of autonomic intervention on MAP characteristics was far overshadowed by the influence of dose of CsCl. Our most remarkable finding was that of large mEADs in group 3 in the absence of sustained arrhythmia. The implication is that the effect of circulating catecholamines on the amplitude of mEADs produced by cesium is relatively minor. Stellate stimulation, although highly provocative, produced only a small increase in mEAD amplitude. Sympathetic stimulation nonetheless markedly shortened latency (figure 6). Esmolol, on the other hand, significantly delayed the onset of peak mEAD amplitude (figure 8, C).

It should be emphasized that onset of sustained VT in our studies prevented further analysis of mEAD amplitude. Doses higher than 0.5 mmol/kg could not be compared between all four groups in terms of MAP characteristics (figure 9), since all group 4 dogs had exceeded their relatively low tachycardia threshold doses. Because higher doses of cesium typically produced more severe arrhythmia (shorter cycle length, earlier onset), the influence of autonomic intervention on MAP characteristics might have been more pronounced at these higher doses.

Role of mEADs. Prior work has strongly suggested that mEADs induced by cesium play an important role in the genesis of ventricular ectopic activity.2 In the present studies the existence of marked mEADs in the absence of sustained VT brings into question the role of mEADs in arrhythmogenesis in this preparation. The focus of the present studies was not to prove that afterdepolarizations recorded from an MAP catheter represent the same phenomenon as that represented by afterdepolarizations in conventional transmembrane recordings from isolated preparations exposed to CsCl. Nonetheless similarities among our groups in both the dose of cesium producing ventricular ectopy and the relative size of mEADs (figure 9, B) is consistent with the latter representing the source of initiating beats for a sustained tachycardia.

The above observations suggest that the autonomic nervous system, although weakly affecting the amplitude of mEADs, also modulates their expression as sustained VT. While mEADs might lead to initiating beats of a tachycardia, different factors, such as variations in autonomic tone, may be required to sustain the arrhythmia. This concept is supported by those group 4 dogs that exhibited a second occurrence of tachycardia after resumption of stellate stimulation but before the next injection of cesium. This phenomenon of autonomic modulation echoes a clinical hypothesis raised by Schwartz6 that a basic intracardiac abnormality in patients with long QT syndrome, possibly in the control of intracellular potassium, decreases the electrical stability of the heart and makes the myocardium more vulnerable to the effects of sympathetic discharge.

Role of sinus pauses. The bradycardia induced by
cesium is not crucial to arrhythmogenesis in this preparation, as proved in these studies wherein AV dissociation masked any effect of sinus pauses. Sinus pauses may nonetheless facilitate development of sustained VT in unblocked dogs by augmenting the amplitude of bradycardia-dependent EADs.

As suggested in figure 3, there are two components to cesium’s effect on sinus node automaticity: first a direct component presumably via suppression of the pacemaker current $i_r$, seen in all groups and unrelated to dose, and second a dose-dependent, vagally mediated component seen only in group 1 (control). The latter component may be partially mediated via baroreceptor reflexes. According to recent work in vitro, CsCl (5 mM) nearly fully abolishes $i_r$ in sinoatrial node cells. This block of the “pacemaker” channel is voltage dependent and resembles cesium’s affect on $i_r$ in Purkinje fibers.

Cesium depresses normal automaticity along the entire conduction system (sinus node, His-Purkinje, and ventricle) as a prologue to the onset of triggered activity. As with the ion’s effect on MAP characteristics, the time course of cesium’s depression on sinus node automaticity implicates extracellular rather than intracellular cesium.

Role of hypertensive response. The high systolic pressures achieved in these studies may have resulted from released catecholamines and/or a direct effect of cesium on myocardial contractility. Peak systolic pressure achieved in our control dogs (group 1) after the 1.0 or 1.25 mmol/kg injection was significantly higher than that in prior studies, possibly enhanced by our continuous pacing.

The rather high levels of afterload occurring in the present studies (figures 10 and 11) are analogous to those achieved with short-term aortic or pulmonary arterial constriction, which via contraction-excitation feedback produces EADs and regular coupled extrasystoles. EADs also occur in Purkinje fibers subjected to stretch alone or in hypertrophied myocardium resulting from chronic hypertension.

Contraction-excitation feedback could be inferred when changes in mechanical stress or strain precede or cause changes in membrane potential. Such feedback can appear either as a transient depolarization or as a prolongation of action potential, according to the type and timing of the mechanical change producing it. That the abrupt changes in afterload (systolic blood pressure) in the present experiments precede or at least are coincident with changes in mEAD amplitude raises the possibility that contraction-excitation feedback contributes to arrhythmogenesis in the CsCl preparation.

In the case of delayed afterdepolarizations, most and perhaps all of the factors that change amplitude, e.g., rate or catecholamines, have a similar effect on contractility.

**Toward understanding a mechanism.** Similar time courses of cesium’s effect on sinus node automaticity, blood pressure, MAP characteristics, and onset of VT suggest a mechanism that involves not only EADs but also interactions between sinus rate and systolic pressure, all three in turn modulated by the autonomic nervous system. This modulation appears to occur primarily by way of circulating catecholamines.

EADs are central to the development of ventricular ectopy, which can lead to sustained VT. Although the autonomic nervous system indirectly affects EAD amplitude via slowing sinus rates or increasing systolic pressure, there appears as well a direct effect on mEAD amplitude from the sympathetic nervous system and possibly also to a lesser extent from the vagus. Our findings indicate that the strongest influence of the sympathetic system on the production of sustained VT is in modulation of the expression of mEADs as sustained VT.

**Clinical relevance.** Whereas in this animal preparation cesium created EADs within normal myocardium, in patients with the idiopathic long QT syndrome EADs may already exist as a result of a basic intracardiac abnormality in the control of intracellular potassium. Autonomic intervention modulated cesium’s effect on mEADs as well as the ultimate production of sustained ventricular arrhythmia. In man this autonomic modulation may occur similarly; that is, increased sympathetic output may augment existing EADs and facilitate their expression as malignant ventricular arrhythmias. Antagonism of these effects by a β-blocker might account for the latter’s protective effect. Although cesium’s direct effect overshadowed autonomic influence on mEAD amplitude, in man the influence of autonomic tone would be paramount.

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