Effect of Stellectomy and Vagotomy on Ventricular Refractoriness in Dogs

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SUMMARY The influence of tonic sympathetic and parasympathetic nervous system activity on ventricular refractoriness during ventricular fibrillation was studied in 13 mongrel dogs. Strength-interval curves were obtained from the apex of the right ventricular endocardium with a transvenous bipolar catheter. The effects of sympathetic activity were assessed by unilateral and bilateral stellate ganglia stimulation and of cardiac conduction system stimulation were obtained from the apex of the right ventricular endocardium with a transvenous bipolar catheter. The effects of sympathetic activity were assessed by unilateral and bilateral stellate ganglia stimulation and tonic vagal effects were studied by inducing cholinergic blockade with atropine (0.2 mg/kg) and by sectioning the cervical vagus bilaterally. Right stellectomy shifted the strength-interval curve 3-5 msec earlier (P < 0.005). In contrast, left stellectomy shifted the strength-interval curve 4-7 msec later (P < 0.001). Thus, right and left unilateral stellectomy produced opposite effects. However, when the contralateral ganglion was removed, right and left stellectomy produced qualitatively similar effects, increasing refractoriness. The net effect of bilateral stellectomy was to shift the strength-interval curve 8-10 msec later (P < 0.001) and this was primarily dependent on left stellectomy. Blockade of vagal efferent activity with atropine shifted the strength-interval curve 3-6 msec earlier (P = 0.001). Removal of vagal afferent activity by vagotomy during atropine blockade shifted the strength-interval curve 2-3 msec earlier (P = 0.03). It is concluded that both stellate ganglia exert qualitatively similar effects on cardiac refractoriness; however, the left ganglion dominates and unilateral right stellectomy produces a paradoxical decrease in refractoriness. The sympathetic effects are tonically antagonized by vagal activity.

IT HAS BEEN hypothesized that electrical asymmetry of the cardiac conducting system predisposes to reentrant arrhythmias leading to ventricular fibrillation. It is well established that stimulation of the midbrain reticular formation and of areas in the diencephalon and thalamus produces electrocardiographic changes and a diversity of arrhythmias. The rhythm disorders that result from central neural system stimulation may be related to inhomogeneities induced in cardiac excitability. Indeed, right- and left-sided sympathetic efferent outflow is distributed to different areas of the ventricular myocardium. Opposite sides of the brain, furthermore, exhibit different effects on the heart. Thus in the cat, right hypothalamic stimulation decreases T wave amplitude whereas a rise in amplitude attends stimulation of the contralateral side. In dogs, left stellate ganglion stimulation or right stellectomy prolongs the Q-T interval and T wave amplitude whereas right-sided stimulation or left stellectomy results in T wave inversion without affecting the Q-T duration. It also has been demonstrated that the stellate ganglia differ in their effects on ventricular vulnerability. Ablation of the left stellate ganglion reduces the prevalence of arrhythmias following coronary artery occlusion and raises the ventricular fibrillation threshold whereas an opposite effect results when the right ganglion is removed. In the intact animal sympathetic discharges probably do not occur independently of changes in parasympathetic nervous activity. Evidence is accumulating that the parasympathetic vagal system profoundly affects ventricular excitability. The effects of the vagus, however, are influenced substantially by the prevailing level of adrenergic tone.

These considerations have guided the modeling of the present investigation, the aim of which was to define the distinctive effects of the right and left stellate ganglia on ventricular excitability. The specific objectives were the following: (1) to determine the effect of tonic cardiac sympathetic outflow on ventricular excitability; (2) to evaluate the relative roles of right and left stellate ganglia; and (3) to assess the contribution of tonic vagal activity.

Methods

Thirteen mongrel dogs weighing 16-21 kg were anesthetized with intravenous α-chloralose, 100 mg/kg. A stabilization period of at least 20 minutes was allowed between anesthetic administration and experimental interventions. Artificial ventilation was instituted using a Harvard respirator that supplied room air via a cuffed endotracheal tube. A polyethylene catheter was inserted into a femoral artery for sampling arterial blood and for monitoring blood pressure. The respirator was adjusted to maintain arterial pH between 7.35 and 7.50 and PO2 at greater than 90 mm Hg. Rectal temperature was maintained at 37 ± 1°C with a thermal blanket. Systemic arterial pressure was monitored continuously with a Statham P23Db transducer. Mean pressures were obtained by electrically integrating the output of the transducer. Cervical vagosympathetic trunks were exposed bilaterally 2 cm below the level of the carotid bifurcation. Bilateral thoracotomies were performed in the 2nd intercostal space to expose the stellate ganglia. Drugs were administered via a femoral venous catheter.

CARDIAC TESTING

Electrical testing of the heart was accomplished by using an intracavitary lead system. The unit consists of a trans-
venous bipolar pacing catheter (Medtronic no. 5819, platinum electrodes with an interelectrode distance of 1.5 cm and a pole width of 3 mm) and an electrocardiogram (ECG) recording probe (Elecath semifloating probe no. 567). The catheter was passed through a jugular vein and positioned at the apex of the right ventricle under fluoroscopic control. The bipolar pacing catheter was used for both pacing and cardiac testing. The distal pole of the catheter was made cathodal. A Medtronic pacemaker was used to deliver rectangular pulses 2 msec in duration at 280-msec intervals. This rate (214 beats/min) was selected to overdrive spontaneous heart rate following vagotomy. The pacemaker current was adjusted to twice the mid-diastolic threshold. Testing impulses of 2-msec duration were delivered by using an electrically isolated Grass S44 square wave pulse generator and a Kepco operational power supply (type OPS-100) to generate constant current stimuli (2% accuracy). The output of the unit was calibrated with an oscilloscope current probe (Tektronix P6021). The generator was equipped with appropriate circuitry to inhibit the output of the pacemaker for 3-5 seconds after delivery of the test stimulus. The test was delivered after every 15th paced beat. 

Electrical testing of the heart was performed in the following manner: The timing of the test stimulus was set to occur in mid-electrical diastole. The intensity of the stimulus was increased in 0.1-mA steps (starting at 0.5 mA) until a single propagated response was evoked. The minimum current required to elicit a propagated response was taken as the mid-diastolic threshold. 

**Unilateral and Bilateral Stellectomy**

Stellate ganglionectomy was accomplished by removing the intact body of the stellate ganglia after having sectioned all its pre- and postganglionic fibers. The sequence of right and left stellectomy was randomized among the 10 dogs studied. Removal of the right ganglion was associated with distinct sinus bradycardia (20-40 beats/min. decrease); left stellectomy, however, produced no significant change in rate. In all cases, a rest period of 30 minutes was allowed after stellectomy to permit the effects of injury to subside. Strength-interval curves then were obtained to define the influence of unilateral stellectomy on ventricular excitability. The contralateral stellate ganglion was removed subsequently and, after a 30-minute recovery period, a final strength-interval curve was obtained.

**Cholinergic Blockade and Vagotomy**

The role of the parasympathetic nervous system in regulating ventricular excitability was studied in six dogs. The contribution of efferent vagal activity was investigated by inducing cholinergic blockade with the selectively muscarinic agent, atropine sulfate (0.2 mg/kg, iv, Lilly). Strength-interval curves were obtained just before and 25 minutes after administration of the drug. The influence of afferent vagal activity on ventricular excitability was explored by sectioning the vagosympathetic trunks while efferent vagal fiber activity was still under cholinergic blockade. Strength-interval curves were obtained 10-15 minutes after sectioning the vagni. This time interval was allowed to achieve a steady state following vagotomy.

In three additional dogs, atropine was administered after bilateral stellectomy and vagotomy to determine any effect this drug might exert on ventricular excitability aside from its anticholinergic action.

Statistical comparisons were made by multiple variance analysis. Data are expressed as means ± SE.

**Results**

**EFFECTS OF UNILATERAL STELECTOMY**

This was examined in 10 vagotomized dogs (Fig. 1). In five dogs right stellectomy shifted the strength-interval curve 3-5 msec earlier. In none of the dogs was the strength-interval curve shifted later. The mid-diastolic threshold was unaltered. Right stellectomy decreased heart rate from 179 ± 8 to 150 ± 9 beats/min (P < 0.05) and decreased mean arterial blood pressure from 138 ± 8 to 130 ± 4 mm Hg. Left stellectomy shifted the strength-interval curve 4-7 msec later (P < 0.001). In no experiment was the strength-interval curve shifted earlier. The mid-diastolic threshold was unaffected. Left stellectomy reduced heart rate from 176 ± 10 to 175 ± 8 beats/min

**Figure 1** Effect of unilateral stellectomy on the endocardial strength-interval curve in vagotomized dogs. Right stellectomy in six dogs (panel A) shifted the strength-interval curve 3-5 msec earlier; left stellectomy in five dogs (panel B) produced an opposite effect of moving the strength-interval curve 4-7 msec later. Values are expressed as mean ± SEM.
and decreased mean arterial pressure from 139 ± 5 to 125 ± 7 mm Hg.

**EFFECT OF BILATERAL STELLECTOMY**

In the 10 dogs studied, bilateral stellectomy shifted the strength-interval curve 8-10 msec later (P < 0.0001) (Fig. 2). This figure, 8-10 msec, is the result of the net difference of the usually opposite effect of right and left stellectomy. Mid-diastolic threshold increased from 1.09 ± 0.7 mA to 1.27 ± 0.2; this change was not statistically significant (P = 0.07). Bilateral stellectomy decreased heart rate by 33 ± 13 beats/min (P < 0.001) and mean arterial blood pressure by 25 ± 6 mm Hg (P < 0.001).

The relative contribution of right and left stellate ganglia to the change produced by bilateral stellectomy was assessed by examining the effect on refractoriness produced by right- or left-sided stellectomy not only before but also after the ablation of the contralateral ganglion. In five dogs in which the left stellate ganglion had been previously removed, right stellectomy shifted the strength-interval curve 3-6 msec later (P < 0.001) (Fig. 3A). The direction of this shift was opposite to that observed when right stellectomy was performed in dogs with an intact left stellate ganglion (Fig. 1A). Left stellectomy following removal of the right ganglion shifted the strength-interval curve 10-14 msec later (P < 0.0005) (Fig. 3B). This effect did not differ qualitatively from that observed in dogs with unilateral left stellectomy (Fig. 1B). The relative contributions of right and left stellate ganglia in shifting the strength-interval curve later were 28% and 72%, respectively, of the change observed after bilateral stellectomy.

**EFFECT OF CHOLINERGIC BLOCKADE AND VAGOTOMY**

The influence of vagal efferent and afferent activity on ventricular excitability was investigated in six dogs with the sympathetic outflow intact. Blockade of vagal efferent fibers with atropine shifted the strength-interval curve 3-6 msec earlier (P = 0.001) (Fig. 4). This effect was accompanied by an increase in heart rate of 37 ± 5 beats/min (P < 0.001) and a slight decrease (5 ± 14 mm Hg) in mean arterial blood pressure. To determine the possible role of vagal afferents in modulating ventricular excitability following atropinization, the vagi were sectioned bilaterally. Vagotomy produced a moderate, but statistically significant 2- to 3-msec shift (P = 0.03) of the strength-interval curve earlier (Fig. 4). This was accompanied by a minor decrease in heart rate of 4 ± 6 beats/min and an increase in blood pressure of 10 ± 8 mm Hg. The mid-diastolic threshold was not altered by atropinization or vagotomy.

The effect of atropine administration after bilateral stellectomy and vagotomy were investigated in three dogs. In these denervated dogs atropine was without effect on the strength-interval curve or the mid-diastolic threshold.

**Discussion**

The consistent lengthening in refractory period duration resulting from bilateral stellectomy in vagotomized dogs suggests that the sympathetic nervous system exerts a tonic effect on ventricular refractoriness. These results are in accord with the findings of Yanowitz et al. and are consonant with the well documented observation that cardiac sympathetic nerve stimulation decreases ventricular refractoriness whether achieved by electrical stimulation or by psychological stress. It is pertinent that the magnitude of prolongation in refractoriness following bilateral
ventricular vulnerability during autonomic neural stimulation on ventricular vulnerability to fibrillation is threshold resulting from stellate ganglion stimulation is not dependent on heart rate acceleration. Changes in those maintained at rates of 60 beats/min following induction of complete atrioventricular block. Likewise, it has been shown that the decrease in ventricular fibrillation induction of complete atrioventricular block. This can be inferred from a number of other investigations. For example, the effect of posterior hypothalamic stimulation on ventricular vulnerability to fibrillation is unaltered in animals paced at a rate of 180 beats/min and in those maintained at rates of 60 beats/min following induction of complete atrioventricular block. Likewise, it has been shown that the decrease in ventricular fibrillation threshold resulting from stellate ganglion stimulation is not dependent on heart rate acceleration. Changes in ventricular vulnerability during autonomic neural stimulation are related to concomitant and similar shifts in strength-interval curve.

UNILATERAL STELECTOMY

Unilateral right and left stellectomy produced opposite effects on ventricular refractoriness; whereas the former procedure decreased refractoriness, the latter resulted in an increase. This finding might have suggested that the two stellate ganglia exert different effects on ventricular electrical properties. Several observations argue that this is not the case. First, in the present study we found that when the contralateral ganglion is removed first, either right or left stellectomy shifts the strength-interval curve in the same direction. Second, electrical stimulation of either the right or left stellate ganglion produces quantitatively similar changes in ventricular refractoriness (Verrier and Lown, unpublished observation) and in ventricular vulnerability.

The quantitative dominance of the left stellate ganglion may account for the paradoxical results of unilateral stellectomy on ventricular refractoriness. When one stellate ganglion is ablated, ensuing reduction in systemic arterial pressure decreases carotid sinus baroreceptor activity which thereupon results in increased sympathetic activity through the contralateral ganglion. Thus, unilateral stellectomy, while suppressing sympathetic activity on the ipsilateral side, may increase it on the contralateral side. The net change in ventricular refractoriness will depend on the net difference of the two opposing influences. In the case of right stellectomy, the increase in refractoriness produced by removal of this ganglion would be counteracted by the greater decrease in refractoriness resulting from enhanced activity of the more dominant left stellate ganglion. The result of isolated right stellectomy therefore would be manifested as a decrease in refractoriness. In contrast, when the left stellate is removed, the increased activity of the right is insufficient to compensate for the absence of the tonic discharge of the left ganglion; the consequence is an increase in cardiac refractoriness.

Recently, it has been demonstrated that left stellectomy, as was to be expected, increased the ventricular fibrillation threshold and suppressed the arrhythmias. When the right stellate ganglion was blocked or ablated, an opposite effect resulted; namely, an increase in prevalence of serious arrhythmias and a lowering in the threshold for ventricular fibrillation. The present findings are consistent with these observations. An imbalance in activity of the two sides of the sympathetic nervous system has been postulated as a basis for ventricular fibrillation among patients with the long Q-T syndrome.

VAGAL ACTION

Electrical stimulation of the peripheral cut ends of the vagi significantly increases ventricular refractoriness. The present finding that suppression of vagal efferent activity with atropine decreased refractoriness is consistent with this observation. The magnitude of the effect following cholinergic blockade suggests an important tonic influence of vagal efferent activity on ventricular refractoriness.
riness. The possibility that atropine action was mediated through extracholinergic mechanisms appears unlikely since the drug was without effect on ventricular refractoriness in vagotomized dogs.

The level of ventricular refractoriness appears to be modulated by afferent vagal activity as well. This was examined by studying strength-interval curves in atropinized dogs before and after vagotomy. When vagal afferent activity was interrupted, a moderate but statistically significant decrease in ventricular refractoriness was observed. This finding suggests that tonic activity in both afferent and efferent fibers in the vagi is involved in the regulation of ventricular refractoriness. The vagi, as do the sympathetic nerves, contain afferent fibers which originate from the cardiopulmonary region and have a tonic effect on sympathetic outflow. This is supported by the findings that significant increases in pressure and heart rate are produced by vagotomy in atropinized animals. Moreover, direct electrical stimulation of vagal afferent fibers also has been shown to decrease cardiac sympathetic efferent fiber activity. Thus, in the context of the present study, vagal afferent activity would tend to reduce cardiac sympathetic efferent discharge and thereby sustain ventricular refractoriness at an elevated level.

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