Effects of Cardiac Sympathetic Stimulation and Ablation on Canine Ventricular Anodal Strength-Interval Curves

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SUMMARY We studied the effects of cardiac sympathetic stimulation and ablation on characteristics of the anodal-strength-interval curve in 10 pentobarbital-anesthetized open-chest dogs. We gave special attention to the form and particularly the depth of early dips of the anodal-strength-interval curve. When the central connections of the cardiac sympathetic nerves were intact, left stellate stimulation decreased threshold for excitation during the dip only slightly (from 883 ± 442 μA to 774 ± 326 μA, P < 0.1). However, when left stellectomy and upper thoracic ganglionectionomy, stimulation of the cut ends of the ansa subclavia decreased the dip threshold from an average of 952 ± 321 μA to 707 ± 210 μA, P < 0.01. Dip thresholds in strength-interval curves determined 1.5 hours after ganglionectomy averaged 1164 ± 296 μA compared to an average dip threshold of 791 ± 269 μA in strength-interval curves measured immediately prior to stellectomy. This increase is statistically significant (P < 0.005). In addition to the effects of sympathetic tone on disparity of refractory period and ventricular fibrillation threshold, the effects of sympathetic tone on the form of the strength-interval curve may be another factor influencing vulnerability to arrhythmias and particularly in patients with abnormal autonomic tone.

INCREASED LEVELS of cardiac sympathetic tone lower fibrillation threshold and increase the incidence of arrhythmias in experimental animals under control conditions and in the setting of acute coronary artery occlusion. Both an increase in the disparity of ventricular recovery properties and enhancement of latent pacemaker activity occur with increased sympathetic tone and probably are factors that influence vulnerability to arrhythmias when sympathetic tone is high. Characteristics of the form of the anodal strength-interval curve also may play a role in modifying the incidence of arrhythmias. The time of the dip in the anodal strength-interval curve has been related to the vulnerable period, and the depth of the dip and supernormal period that follow basic driven beats and premature beats has been related to the type of arrhythmia that occurs in response to continuously available low intensity stimuli. The influence of cardiac sympathetic stimulation and ablation on the form of the anodal-strength interval curve has not been studied previously in detail and is the subject of this report. The results of our study show that sympathetic stimulation increases and stellectomy decreases the depth of the dip in the strength-interval curve.

Methods

Experiments were made on 10 pentobarbital-anesthetized open-chest mongrel dogs. The sinus node was crushed, a bipolar stimulating electrode was attached to the right atrial appendage, and the heart was driven at cycle lengths of 300-400 msec. The rate used was sufficiently fast that control of the rhythm could be maintained during sympathetic stimulation. The left stellate ganglion and ansa subclavia were isolated and a bipolar stimulating electrode was placed with the cathode proximal to the heart. In three dogs the central connections of the stellates were left intact, and in the other seven dogs observations were made before and after the left stellate ganglion and upper four or five thoracic ganglia were removed. The stellate ganglion or the cut ends of the ansa subclavia were stimulated with trains of pulses at 10 Hz, 2-4 msec in duration, and with intensities of 0.5-8 V. Effectiveness of stimulation was judged from changes in the T waveform in a vertical electrocardiogram (ECG) lead and from shortening of the refractory period during sympathetic stimulation. Anodal strength-interval curves were determined by methods similar to those reported by Cranefield et al. Anodal stimuli 2 msec in duration were delivered through an Ag-AgCl surface electrode 2.5 mm in diameter and embedded in a Teflon disk which was sutured to the anterior surface of the left ventricle in the area to which the left cardiac sympathetic nerves are distributed. The indifferent electrode was an Ag-AgCl disk implanted under the skin of the groin. Test stimuli were applied after every 2nd or 3rd atrial driving stimulus. Threshold for propagated excitation was measured at 5- to 10-msec intervals during late portions of the cardiac cycle and at 1- or 2-msec intervals during early portions of the cycle. The intensity of stimuli was increased by increments of 10 μA until a propagated response was induced. A constant current, digitally programmed stimulator with stimulus intensity accurate to ±0.5 μA was used for these experiments, and offset potentials were monitored with an ammeter. Strength-interval curves were determined alternately during control periods and during stellate stimulation, and a period of 5-10 minutes was allowed after sympathetic stimulation before control measurements were repeated. In previous studies in our laboratory we have...
found that refractory periods return to control values by this
time after stellate stimulation. Data were analyzed with the
paired t-test.

Results

The effects of sympathetic stimulation on the form of
anodal strength-interval curves of one dog before and after
removal of the left stellate and upper thoracic ganglia are
shown in Figure 1. In this dog sympathetic stimulation
decreased the threshold for excitation during the dip both
before and after ganglionectomy. Prior to ganglionectomy,
sympathetic stimulation decreased the dip threshold to 530
\( \mu A \), 440 \( \mu A \) lower than control value. After stellectomy dip
threshold increased to 1,250 \( \mu A \), a value 280 \( \mu A \) above the
control dip threshold determined prior to ganglionectomy.
Stimulation of the cut ends of the ansa subclavia, after
ganglionectomy, decreased the dip threshold of this dog to
430 \( \mu A \). The earlier occurrence of the steep portion of the
strength-interval curves during stellate stimulation is a
reflection of the shortening of refractory period duration
associated with sympathetic stimulation.

During the course of our experiments, dip thresholds
changed during both control periods and periods of stellate
stimulation. In some dogs the tendency was for the control
dip threshold to increase and in others the tendency was for
dip threshold to decrease. Observations made during control
periods and during stellate stimulation therefore were
alternated and data were analyzed with the paired t-test. The
dip thresholds for one dog during repeated control periods
and periods of sympathetic stimulation are graphed in
Figure 2. The central connections of the stellate ganglia were
intact during these observations. During the course of the
experiment the dip threshold measured during control
periods decreased, but for each pair of observations sympa-
thetic stimulation decreased it further. Dip thresholds from
repeated measurements on another dog are graphed in
Figure 3. In this dog, prior to ganglionectomy, control dip
threshold was 20 \( \mu A \) lower than end-diastolic threshold, and
sympathetic stimulation increased dip threshold. After sur-
gical removal of the left stellate and upper thoracic ganglia
the dip threshold increased from the control value of 570 \( \mu A \)
to 750 \( \mu A \). Stimulation of the cut ends of the ansa subclavia
then decreased the dip threshold.

The effects of sympathetic stimulation on the form of the
strength-interval curve were studied before and after re-
moval of the left stellate ganglion and upper four or five
thoracic ganglia in seven dogs. In these dogs we observed the
effects of the ganglionectomy on the form of the strength-
interval curve in addition to studying the effects of sympa-
thetic stimulation on the form of the strength interval curve.
In three other dogs the central connections of the stellate
ganglia were left intact, and the effects of stellate stimula-
tion on the form of the strength-interval curve were observed
only under this condition. As shown in Figure 4, when data
for all dogs were analyzed the effects of sympathetic
stimulation on dip threshold were more pronounced after
ganglionectomy than they were when the central connections of the stellate ganglia were intact. The graph on the left of the figure summarizes measurements of dip thresholds during control periods and periods of sympathetic stimulation in dogs with the central connections of the stellate ganglia intact. The data shown are averages of dip thresholds in strength-interval curves determined for 10 dogs during 22 control periods and 22 periods of stellate stimulation. The average threshold of the dip during control observations was 883 ± 441 μA. The average threshold of the dip during stellate stimulation decreased to 774 ± 326 μA, P < 0.1. In the seven dogs in which left stellectomy and upper thoracic gangionectomy were performed, strength-interval curves were determined after this intervention during 13 control periods and 13 periods of sympathetic stimulation. These data are summarized on the right of Figure 4. After stellectomy dip thresholds during control periods averaged 952 ± 321 μA, and during sympathetic stimulation dip thresholds averaged 707 ± 210 μA, a statistically significant decrease at the P < 0.01 level.

In the seven dogs in which stellectomy and upper thoracic gangionectomy were performed, the effect of this intervention on dip threshold also was evaluated and data are summarized in Figure 5. The dip thresholds in the strength-interval curves of these dogs, immediately prior to left stellate and upper thoracic gangionectomy, averaged 791 ± 269 μA, and dip thresholds in strength-interval curves determined 1-1½ hours after gangionectomy increased to an average value of 1164 ± 296 μA, a statistically significant increase at the P < 0.005 level.

The effects of sympathetic stimulation and stellectomy on end-diastolic threshold also were observed. Diastolic threshold sometimes increased and sometimes decreased as a result of these interventions. When the central connections of the stellates were intact, sympathetic stimulation had no significant effect on end-diastolic threshold. Similarly, ganglionectomy itself had no significant effect on end-diastolic threshold. After left stellectomy and upper thoracic ganglionectomy diastolic threshold increased slightly during sympathetic stimulation by an average of 35 ± 75 μA, P < 0.15.

Discussion

In contrast to cathodal strength-interval curves, anodal strength-interval curves frequently have a deep dip early in the cardiac cycle. Threshold for excitation during the dip may be lower than the threshold for excitation during earlier or later intervals of the cardiac cycle and sometimes is lower than end-diastolic threshold. The timing of the dip has been related to the vulnerable period, and its depth to the type of
arrhythmia that occurs in response to very low intensity, continuously available stimuli. In some dogs threshold for excitation during the dip or supernormal period is lower after regular driven atrial responses than it is after premature ventricular depolarizations. These dogs exhibit ventricular bigeminy in response to continuously available stimuli. For other dogs the anodal strength-interval curves after both basic driven complexes and premature complexes smoothly decrease to end-diastolic threshold; these dogs develop occasional premature complexes or slow ventricular tachycardia in response to trains of low intensity stimuli. Still others show deep dips in the strength-interval curves that follow both basic driven complexes and premature complexes, and in these dogs accelerating ventricular tachycardia and ventricular fibrillation occur in response to low intensity stimuli.

All of the factors that influence the form of strength-interval curves have not yet been defined. Differences in form of the curves have been reported with changes in acid-base balance, electrolyte balance, or in the level of pentobarbital anesthesia, and it is likely that there are additional factors that also affect the form of the strength-interval curve. Some of the variability in control measurements observed during the course of experiments in this study could have been due in part to factors not under direct experimental control, or perhaps to cumulative effects of sympathetic stimulation or ablation. To minimize the effects of these factors on the results as much as possible, measurements of strength-interval curves during control periods were alternated with measurements made during sympathetic stimulation and data were analyzed with the paired t-test.

Because of the time required to determine the form of the strength-interval curve in as much detail as is reported here, in each experiment measurements were made at only one site in the distribution of the left cardiac sympathetic nerves. Effects at other sites were not evaluated. It would not be surprising, however, if, with stimulation of long duration, comparable changes occurred at sites within and outside of the distribution of the stimulated nerves because of the effects of circulating catecholamines. The effects of right sympathetic stimulation were not studied because of the greater difficulty in controlling heart rate during stimulation of right, as compared to left, cardiac sympathetic nerves.

In addition to effects of the sympathetic nerves on the anodal dip, variability in other characteristics of excitability are associated with manipulation of autonomic tone. Hoffman et al. noted that early during infusion of epinephrine and norepinephrine the ventricular fibrillation threshold fell to almost the same level as threshold for single ventricular responses. These investigators, and later Han et al., noted that the effect of catecholamine infusion on fibrillation threshold was bimodal. Fibrillation threshold fell soon after starting an infusion of catecholamines, but after the infusion had continued for 10-30 minutes fibrillation threshold increased. Brooks et al. found that with sympathetic stimulation there was a minimal decrease in diastolic threshold soon after the onset of stimulation which later during stimulation was reversed to result in a slight increase in diastolic threshold above control values. This sequence of changes in diastolic threshold also occurred when epinephrine or norepinephrine was infused, and it was related to changes in serum potassium levels. Vassalle and Carpenter, using microelectrode techniques, found a difference in the effect of norepinephrine on resting membrane potential of Purkinje fibers that depended on the presence or absence of sodium in the perfusion medium. When added to Tyrode's solution, norepinephrine decreased Purkinje fiber resting potential, but if choline was substituted for sodium in the perfusion medium, norepinephrine increased resting membrane potential.

It is possible that the effects of sympathetic stimulation on dip threshold also are bimodal, and this may account for some of the differences in magnitude of effect observed in the experiments reported here. With present techniques it takes at least 10 minutes to measure threshold to excitation at short enough intervals in the cardiac cycle to carefully define the form of the strength-interval curve. It therefore was not possible in these experiments to determine the time course of changes in characteristics of the strength-interval curve during sympathetic stimulation. Measurements started 2-3 minutes after the onset of stimulation and continuing during the additional 10-15 minutes required to complete the measurements did, however, demonstrate that the depth of the dip in the strength-interval curve increased during sympathetic stimulation. In addition it was demonstrated that 1-1.5 hours after removal of the cardiac sympathetic the depth of the dip in the strength-interval curve had decreased. Brooks et al. postulated that there is the equivalent of an anodal source of stimulation at the border between ischemic and nonischemic tissue and that this might be responsible for initiating arrhythmias. The data from the study reported here indicate that during brief portions of the cardiac cycle, comparable anodal sources may be present between areas of myocardial tissue that are affected unevenly by sympathetic tone. The results suggest that, in addition to the effects of sympathetic stimulation on disparity of refractory periods and enhancement of latent pacemaker activity, the increased depth of the dip in the strength-interval curve observed during sympathetic stimulation may be an additional factor influencing vulnerability to arrhythmias when sympathetic tone is high and particularly in patients with some forms of central nervous system disease or early in the course of acute myocardial infarction. The results also suggest the decreased depth of the dip that occurs after stellectomy may be one of the factors responsible for decreasing arrhythmias in patients treated with sympathetic blocking agents.

References

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SUMMARY The tail artery of the spontaneously hypertensive rat (SHR) (Carworth Farms), excised rapidly and immersed immediately in cold (2°C) Li-substituted physiologic salt solution (LiPSS), was developed to follow the passive downhill and active uphill phases of ionic movement across the vascular smooth muscle cell. The exchange was found to be fully reversibly offset by increased Na+ pumping activity, so that cell Na+ is slack, the leakiness of the cell membrane in the SHR is more than negligible in the control (Carworth Farms normotensive) (CFN). In the incubated artery at 37°C, when the vascular smooth muscle cell is contracting. Most recently, Jones and Hart have observed that the passive permeability of the cell to Na, or hindered its efflux. We pointed out that attempts by the cell to compensate would be reflected in an increase in the capacity of the cell to extrude Na. In recent years it has become technically feasible to examine these propositions experimentally, and the answers have been gratifyingly unambiguous.

Observations based on two entirely dissimilar methods have recently established that the passive permeability of the vascular smooth muscle cell is characteristically increased in salt-dependent forms of experimental hypertension. Jones, using isotope techniques, demonstrated that the rate of Na+ turnover is increased in aortic tissue from the spontaneously hypertensive rat (SHR). We have observed with ion exchange methods that the Na+-Li+ exchange is increased in established deoxycorticosterone acetate (DOCA) hypertension, but not in hypertension produced by renal artery constriction. Most recently, Jones and Hart have observed increased cation turnover rates in DOCA hypertension. It follows directly from these observations that, in these circumstances, the increased cation movement occurs in the absence of increased Na+ permeability, and is consistent with the sodium pump hypothesis. However, a mechanism for the increased Na+ pumping activity remains to be elucidated. It is possible that the increased Na+ turnover is due to increased Na+ transport protein synthesis, increased Na+ transport protein activity, or increased Na+ transport protein turnover.

Some years ago, in reviewing the effects of ions on vascular smooth muscle, we proposed that sustained hypertensive states would be produced by agents that either increased the permeability of the cell to Na, or hindered its efflux. We pointed out that attempts by the cell to compensate would be reflected in an increase in the capacity of the cell to extrude Na. In recent years it has become technically feasible to examine these propositions experimentally, and the answers have been gratifyingly unambiguous.

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