Nonuniformity of cardiac excitability during the relatively refractory period is known to be an important factor in the induction of fibrillation. Any agency which increases the degree of asynchrony of excitability recovery in ventricular muscle might be expected to facilitate the induction of ventricular fibrillation. It has been demonstrated that ouabain or quinidine intoxication, administration of chloroform, myocardial ischemia, and hypothermia, agencies all known to facilitate the induction of ventricular fibrillation, increase temporal dispersion of excitability recovery in ventricular muscle. In the same study, it was shown that stimulation of the cardiac sympathetic nerves increases the temporal dispersion of excitability recovery, while administration of epinephrine or norepinephrine decreases it. If nonuniformity of recovery following excitation does indeed favor fractionation of impulses and turbulent impulse propagation, vulnerability of the ventricles to fibrillation during stimulation of the cardiac sympathetic nerves should be greater than that during administration of sympathomimetic amines.

The experiments described below were designed to compare effects of stimulation of the cardiac sympathetic nerves and intravenous administration of sympathomimetic amines on the ventricular multiple response or fibrillation threshold, diastolic threshold, duration and range of variation of the refractory period, and intraventricular conduction time. The possible role of hyperkalemia in mediating some of the effects of epinephrine was also investigated.

**Methods**

Experiments were performed on 30 mongrel dogs ranging in weight from 9 to 18 kg, anesthetized by intravenous injection of sodium pentobarbital, 35 mg/kg. Under artificial respiration, the chest was opened in the mid-line and the pericardium was opened widely to expose the anterior surface of the heart. Except in experiments involving stimulation of the cardiac sympathetic nerves, the heart was denervated by cutting both cervical vagi and extirpating the stellate and upper thoracic sympathetic ganglia on both sides, in order to reduce reflexly induced variations of autonomic nerve activity.

Details of the experimental technique are illustrated in figure 1. The stimulating and recording electrodes were small steel hooks. A variable interval generator was used to drive a Tektronix pulse generator (pulse generator A) and a Grass stimulator (pulse generator B) which, in turn, delivered rectangular pulses of variable interval, duration, and strength to the ventricles through the stimulating electrodes. After the S-A node had been inactivated by crushing, the ventricles were driven by stimuli delivered through bipolar electrodes near the pulmonary conus. These basic driving stimuli from pulse generator A were of 2 msec duration at twice the diastolic threshold, and at a rate sufficiently rapid to maintain control
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517 during stimulation of the cardiac sympathetic nerves or administration of sympathomimetic amines. One channel (A) of a dual beam oscilloscope was used to record the responses at the bipolar electrodes near the right ventricular apex. The other channel (B) was used to record the responses at a pair of test electrodes placed 8 mm apart and at a distance of 8 mm from the site of the basic driving stimuli. These bipolar electrodes could be switched from the recording channel to pulse generator B which delivered a test stimulus at selected intervals after the basic stimulus; the test stimulus artefact was then displayed on the calibrated oscilloscope channel B by means of a Tektronix current probe amplifier. The stimulus strength in ma was determined from the amplitude of the recorded pulse. The interval between the moment of activation and time of application of the test stimulus could be determined from the position of the stimulus pulse, relative to the previously determined moment of activation at that point on channel B.

The diastolic threshold was determined with a bipolar test stimulus of 10 msec duration delivered during late diastole. To determine vulnerability of the ventricle, a test stimulus of 10 msec duration was delivered during the vulnerable period of the cardiac cycle. The strength of the test stimulus was increased progressively in order to obtain the threshold for either multiple responses or fibrillation. Since the threshold for fibrillation is only slightly higher than that for multiple responses, attempts were made to induce only multiple responses in order to avoid the delay incurred by fibrillation and countershock defibrillation. After repeating the above procedure at several different intervals during the vulnerable period, the lowest threshold for multiple responses was chosen as the ventricular multiple response threshold (hereafter referred to as VMRT) which represents inverse of ventricular vulnerability. In the illustrations of the experimental results, the "fibrillation" threshold actually represents the value of VMRT in most instances.

To estimate the ventricular refractory period and the degree of asynchrony of recovery of excitability at various points in ventricular muscle, three or four unipolar test electrodes were placed at a distance of 8 mm from the site of the basic driving electrodes. At each test point, the diastolic threshold was determined with a cathodal stimulus in a manner already described above, and the test stimulus was set at 1.5 times the diastolic threshold value. The refractory period duration was then estimated from the position of the earliest test stimulus which produced a propagated response recorded at the reference electrodes. The approximate duration of the refractory period at each of the test points was known, observations of the latest ineffective and the earliest effective stimulus could be recorded for all points within about 30 seconds. During stable conditions, repeated observations checked very closely. During periods of rapidly changing conditions, of course, time for duplicate observations was limited, but the values were recorded at intervals of one to two minutes (figs. 3 and 4). In the illustrations of the experimental results, the value of ventricular refractory period represents either the value obtained at one test point, or the average value when the test was made at three or four points. The degree of asynchrony of excitability was recorded as the range of variation of refractory periods measured at all test points. Intraventricular conduction time was determined by measuring the delay between the basic driving stimulus delivered at the conus and the response recorded at the reference electrodes near the right ventricular apex.

For observation of the effects of sympathetic nerve stimulation, preganglionic fibers of the left stellate ganglion were dissected and placed on bipolar shielded electrodes. The stellate and upper thoracic sympathetic ganglia were removed from the right side, and both vagus nerves were sectioned in the neck to prevent reflex activation during sympathetic stimulation. The stimuli applied to the sympathetic fibers were 2 msec pulses.
at a frequency of 10 per second, and at a voltage sufficient to increase the heart rate to about 1.5 times the control value. Mean arterial pressure was increased by about 20 mm Hg during stimulation. For comparison, solutions of L-epinephrine or L-norepinephrine were infused, via the external jugular vein, at rates from 2 to 3 μg/kg/min. Mean arterial pressure was increased by about 40 mm Hg during epinephrine infusion, and by about 60 mm Hg during norepinephrine infusion. In some experiments, a solution of potassium chloride was infused at rates from 2 to 6 mg/kg/min. The rapid time course of changes in the various parameters made it impossible to assess all measurements during a single course of nerve stimulation or infusion of drugs. It was, therefore, necessary to repeat another course of these experimental conditions to complete measurements of all parameters. In a few experiments, the celiac and mesenteric arteries were occluded and the hepatic hilus was clamped to prevent hyperkalemia during epinephrine infusion. Samples of the arterial blood were drawn from the carotid artery at various intervals during these experiments for determination of serum potassium concentrations by means of flame photometry.

**Results**

**COMPARISON OF EFFECTS OF STIMULATION OF LEFT STELLATE GANGLION AND ADMINISTRATION OF SYMPATHOMIMETIC AMINES**

Comparative effects of electrical stimulation of the left stellate ganglion and intravenous administration of epinephrine and norepinephrine on the VMRT are illustrated in figure 2. Sympathetic nerve stimulation decreased the threshold throughout the 15-minute period of stimulation, with the lowest value observed within 1.5 minutes after the start of stimulation. In contrast, norepinephrine and epinephrine, each administered at a rate of 2 μg/kg/min, produced an initial decrease in the threshold, followed by an increase which lasted until the infusion was stopped.

Similar results were consistently observed in all animals (table 1). Stellate stimulation decreased the VMRT by an average of 34% within an average of 2.6 min after the start of stimulation. The infusion of norepinephrine at rates of 2 to 3 μg/kg/min produced an initial decrease averaging 27% followed by an increase of 38%. Both the initial decrease and the later increase were statistically significant. Infusion of epinephrine at rates of 2 to 3 μg/kg/min produced results similar to those obtained with norepinephrine; the VMRT was initially decreased by 26%, and was subsequently elevated to 41% above control values.

The effects of sympathetic nerve stimulation upon the VMRT, diastolic excitability, duration and temporal dispersion of the refractory period, and intraventricular conduction time in a representative experiment are shown in figure 3. In this experiment, the ventricular refractory period was shortened, temporal dispersion of refractory periods was increased,

<table>
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<tr>
<th>Experimental conditions</th>
<th>Number of experiments</th>
<th>VMRT* ma</th>
<th>VMRT* ma</th>
<th>Decrease (—) or increase (+) in VMRT</th>
<th>Time after start of experimental condition* min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left stellate stimulation</td>
<td>6</td>
<td>18.3 ± 6.3</td>
<td>12.0 ± 5.8</td>
<td>—34</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>Norepinephrine 2 to 3 μg/kg/min</td>
<td>5</td>
<td>18.0 ± 6.9</td>
<td>13.2 ± 7.0</td>
<td>—27</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Epinephrine 2 to 3 μg/kg/min</td>
<td>10</td>
<td>18.0 ± 6.4</td>
<td>11.8 ± 5.9</td>
<td>—26</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Norepinephrine during ligation of hepatic hilus</td>
<td>5</td>
<td>15.6 ± 5.6</td>
<td>11.0 ± 5.0</td>
<td>—29</td>
<td>1.2 ± 0.8</td>
</tr>
<tr>
<td>Epinephrine 2 to 3 μg/kg/min</td>
<td>5</td>
<td>15.6 ± 5.6</td>
<td>20.8 ± 7.0</td>
<td>+33</td>
<td>6.9 ± 1.4</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.
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EXPERIMENT 1-11-63

FIGURE 3

Effects of left stellate stimulation on various properties of the ventricle.

and the VMRT was decreased during the entire course of stellate stimulation. The time of the lowest VMRT was coincident with the time of the maximum temporal dispersion of refractory periods at about two minutes after the start of stimulation. There was a relatively close temporal relationship between changes in the diastolic threshold and the VMRT. Intraventricular conduction time was decreased only slightly during the initial period of stellate stimulation.

The effects of intravenous administration of epinephrine in another experiment are shown in figure 4. The VMRT was decreased within two minutes after the start of infusion. Subsequently, the VMRT was increased and remained elevated during the rest of the infusion period. The time of the lowest VMRT coincided with the time of increased temporal dispersion of refractory periods when the ventricular refractory period was rapidly shortening. The VMRT was subsequently elevated while the mean ventricular refractory period was stabilized at the lower level and temporal dispersion of refractory periods was decreased. In this experiment, alteration of the diastolic threshold roughly paralleled the VMRT. Intraventricular conduction time decreased to a minimum at about five minutes after the start of infusion, and it then gradually increased above the control value. Norepinephrine, infused at rates of 2 to 3 \( \mu g/kg/min \), yielded results similar to those obtained with epinephrine, except that intraventricular conduction time was not significantly changed.

EFFECTS OF CHANGES IN SERUM POTASSIUM CONCENTRATION

Because epinephrine causes a liberation of potassium from the liver, and because the resulting hyperkalemia has been shown to be responsible for the decreased intraventricular...
It was important to determine to what extent the effects of infusions of epinephrine upon the VMRT and other cardiac properties were due to an indirect action mediated by potassium. This possibility was tested by (1) relating serum potassium levels to changes in the various cardiac properties, (2) assessing the effects of sympathomimetic amines during occlusion of the hepatic hilus, and (3) recording the effects of hyperkalemia induced by infusion of potassium chloride solutions.

The time course of changes in serum potassium concentration relative to the other alterations induced by epinephrine infusion is illustrated in figure 5. During infusion of epinephrine, there was a rise in serum potassium concentration from the control level of 4.6 mEq/liter to 6.8 mEq/liter shortly after the start of infusion, followed by a return to a level slightly above the control while the infusion was continued. Changes in intraventricular conduction time were roughly opposite to changes in serum potassium concentration; the time of the briefest intraventricular conduction time was coincident with the time of the highest potassium concentration. The VMRT was decreased while the refractory period was diminishing within two minutes after the start of infusion, and it was increased above control values when the refractory period became stabilized at the lower level. In this experiment, the diastolic threshold remained below control values at a time when

FIGURE 6
Effects of l-epinephrine infused at a rate 2 μg/kg/min for 12 minutes, on various properties of the ventricle and on serum potassium concentration in an animal in which the hepatic hilus was occluded.

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Effects of 0.4N KCl solution, infused at a rate of 0.76 cc/min (2.2 mg/kg/min) for 12 minutes, on various properties of the ventricle and on serum potassium concentration.

The VMRT had increased significantly above the initial level. The time course of the alterations of VMRT was not related to the time course of serum potassium changes.

The effects of epinephrine infusion during occlusion of the hepatic hilus are illustrated in figure 6. This procedure prevented any significant effect of epinephrine on serum potassium concentration and on intraventricular conduction time, but it failed to prevent the effects of epinephrine on diastolic threshold, VMRT, and refractory period. Average results of epinephrine infusion, with and without access to the liver, are listed in table 1. Infusion of epinephrine during ligation of the hepatic hilus decreased the VMRT from the control value by an average of 29% shortly after the beginning of the infusion, and increased it by 33% at a later stage. Neither serum potassium nor intraventricular conduction time changed significantly in these five experiments.

In four experiments potassium chloride was infused intravenously to mimic the hyperkalemia caused by epinephrine. In the experiment shown in figure 7, serum potassium concentration gradually increased from the control level of 5.0 mEq/liter to 7.5 mEq/liter during the infusion. The increase in serum potassium concentration was accompanied by a reduction of intraventricular conduction time, but neither the ventricular refractory period nor the VMRT changed significantly. There was a slight decrease in the diastolic threshold for the first three minutes of infusion, followed by a subsequent increase.

Effects of 0.8N KCl solution, infused at a rate of 0.76 cc/min (5.1 mg/kg/min) for 16 minutes, on various properties of the ventricle and on serum potassium concentration.
which lasted until the infusion was stopped.

In the experiment shown in figure 8, a higher concentration of potassium chloride, infused for 16 minutes, caused a gradual increase in serum potassium concentration up to a level of 11.0 mEq/liter. Intraventricular conduction time was decreased until serum potassium concentration reached the level of 9.3 mEq/liter; at higher concentrations, intraventricular conduction was markedly depressed. The curve representing changes in the diastolic threshold was also biphasic, i.e., an initial decrease followed by an increase above the control value. The ventricular refractory period was slightly decreased initially, but it increased when serum potassium concentration exceeded 10.3 mEq/liter. The VMRT, initially unchanged, diminished progressively as conduction time and refractory period increased.

Discussion

The induction of fibrillation of the heart is facilitated when, as nonuniformity of the myocardium with respect to refractory period duration is increased, re-entry and irregular fractionation of a premature wave front are favored. The likelihood of development of such irregular activity is presumably enhanced by increased resting excitability, decreased refractory period duration, decreased conduction velocity, and increased automaticity. Adrenergic facilitation of the induction of fibrillation has been attributed to increased automaticity, decreased diastolic threshold, and decreased refractory period duration. However, the possible role of nonuniformity of recovery of excitability during increased adrenergic activity has not been previously tested.

Recently it was demonstrated that stimulation of the cardiac sympathetic nerves increases the range of variation of the refractory period in ventricular muscle, whereas administration of sympathomimetic amines reduces the dispersion of excitability recovery. Accordingly, it might be expected that the likelihood of ventricular fibrillation would be increased by stimulation of the cardiac sympathetic nerves and reduced by administration of sympathomimetic amines. It has been previously reported that administration of sympathomimetic amines increases the ventricular fibrillation threshold.

In the present study it was found that the VMRT was decreased during continuous stimulation of the cardiac sympathetic nerves, with the lowest fibrillation threshold obtained during the initial period of stimulation (fig. 3). The VMRT was increased during continuous infusion of sympathomimetic amines, following an initial brief decrease (fig. 4). The present study also demonstrates a close relationship between temporal dispersion of refractory periods and the VMRT; i.e., the curves representing changes in these two properties were roughly mirror images. The ventricles were more vulnerable to fibrillation when asynchrony of recovery of excitability was increased.

In the present study it was found that the VMRT was decreased during continuous stimulation of the cardiac sympathetic nerves, with the lowest fibrillation threshold obtained during the initial period of stimulation (fig. 3). The VMRT was increased during continuous infusion of sympathomimetic amines, following an initial brief decrease (fig. 4). The present study also demonstrates a close relationship between temporal dispersion of refractory periods and the VMRT; i.e., the curves representing changes in these two properties were roughly mirror images. The ventricles were more vulnerable to fibrillation when asynchrony of recovery of excitability was increased.

Increased temporal dispersion of refractory periods and the increased likelihood of fibrillation during stimulation of the cardiac sympathetic nerves may be a consequence of nonuniform distribution of the adrenergic mediator throughout the myocardium. The results here are similar to those reported for the effects of vagal stimulation on atrial refractory periods, but the range of variation induced in the ventricles by adrenergic stimulation is lesser in degree. It can be assumed, as in the study just cited, that myocardial fibers immediately adjacent to the effector nerve endings are exposed to relatively higher concentrations of the mediator, while fibers remote from the endings are exposed to lesser concentrations. Regardless of how densely the nerve endings are distributed in the myocardium, some degree of inhomogeneous distribution of the mediator may be expected. While it is also possible that the sensitivity of various fibers to the mediator is not uniform, this possibility seems unlikely in view of the effects of infusion of epinephrine. During the first two or three minutes of intravenous infusion of epinephrine, or norepinephrine, increased dispersion of refractory periods was regularly
observed. After this initial stage, however, when a uniform distribution of the infused material would be expected, asynchrony of excitability recovery was diminished. It seems likely, therefore, that the observed difference between the effects of nerve stimulation and intravenous infusion of adrenergic mediators upon the VMRT can be ascribed to differences in temporal dispersion of refractory periods, attributable, in turn, to differences in the distribution of the active agents.

Since increased potassium concentration is known to exert effects upon various properties of the cardiac muscle,\textsuperscript{16-17} it was necessary to determine whether the effects of epinephrine upon vulnerability were the result of the associated changes in serum potassium concentration. In the present study, changes in serum potassium concentration induced by infusion of epinephrine could not be temporally related to the changes in ventricular refractory period and VMRT (fig. 5). Epinephrine infused during ligation of the hepatic hilar prevented significant changes in serum potassium concentration and intraventricular conduction time, but it failed to prevent typical changes in the ventricular refractory period and VMRT; i.e., the VMRT was initially decreased when the refractory period was rapidly shortening, and it was increased when the refractory period was stabilized at the lower level (fig. 6). Infusion of norepinephrine, an agent known to have only a slight hyperkalemic effect,\textsuperscript{10} produced very slight changes in intraventricular conduction time, but it produced typical changes in the ventricular refractory period and VMRT. These results lead to the conclusion that the observed changes in the ventricular refractory period and VMRT resulting from infusion of epinephrine cannot be attributed to hyperkalemia and accompanying changes in intraventricular conduction. This was further supported by the finding that similar levels of hyperkalemia induced by infusion of potassium chloride failed to produce any significant changes in the ventricular refractory period and VMRT (fig. 7).

**Summary**

Effects of stimulation of the cardiac sympathetic nerves and intravenous administration of sympathomimetic amines on the multiple response or fibrillation threshold (VMRT) and on other properties of the dog ventricles were compared. Stimulation of the cardiac sympathetic nerves decreased the VMRT. Administration of sympathomimetic amines caused a brief decrease in the VMRT followed by a sustained increase. Temporal dispersion of recovery of excitability and the degree of ventricular vulnerability were closely related; the ventricle was more vulnerable to fibrillation when the dispersion was increased. The hyperkalemic effect of epinephrine was not responsible for the observed changes in ventricular vulnerability.

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