Exaggerated Ventricular Arrhythmias and Myocardial Fatty Changes After Large Doses of Norepinephrine and Epinephrine in Unanesthetized Dogs

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ABSTRACT
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An intravenous infusion of a large dose (0.51 mg/kg) of norepinephrine sensitizes the heart to the action of catechol amines for a period of 2-4 days. During this period, small doses of either epinephrine or norepinephrine induce ventricular tachycardia. In dogs killed the day after infusion, frozen sections of the myocardium stained with Oil red O reveal fatty changes, the severity of which roughly parallels that of the induced tachycardias. Fatty changes were still present in the hearts of dogs killed the 3rd day after infusion, but were negligible 5 days after infusion. Similar, but less marked, cardiac effects were elicited by infusions of large doses of epinephrine.

DURING a study of amine induced ventricular arrhythmias, the observation was made that large doses of norepinephrine or epinephrine sensitize the ventricles of the heart in some dogs to small doses of either drug. This cardiac hyperirritability was similar to that occurring in dogs after coronary artery occlusion (1). The present paper describes a hypersensitivity of the heart to small doses of catechol amines which continues for 2-4 days after administration to normal dogs of large doses of either epinephrine or norepinephrine. The myocardial hyperirritability is correlated with histopathologic changes.

METHODS

Unanesthetized healthy mongrel dogs of both sexes weighing between 8 and 17 kg were studied. Injections and infusions were made into a saphenous vein through an indwelling polyethylene catheter. Femoral arterial pressure was recorded with a Statham P23D transducer connected to an indwelling polyethylene catheter inserted under local anesthesia. Arterial pressure and lead II electrocardiograms were recorded on a Grass multichannel oscillograph. Synthetic L-norepinephrine and L-epinephrine were administered as bitartrates (Levophed and Suprarenin). Responses to test doses of catechol amines were recorded on the oscillograph before and at varying intervals after infusions of norepinephrine, epinephrine or saline. Results are expressed as mean values ± standard error of the mean.

Test Doses. Equimolecular amounts of norepinephrine and epinephrine were used in the experiments. The small test doses were 0.95 µg/kg for norepinephrine and 1.03 µg/kg for epinephrine; the large test doses were 10 times as great. Each test dose was injected in a volume of 2 ml and flushed in with 2 ml saline. The total injection time was 10 seconds. Test doses were given 20 minutes apart. The electrocardiographic responses to test doses...
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Figure 1. A graphical summary of the cardiovascular effects seen in 10 unanesthetized dogs during and after continuous infusion into the saphenous vein of 0.51 mg/kg norepinephrine at a rate of 6.2 μg/kg/min for approximately 83 min. Each point is the mean of values obtained on the number of dogs indicated in the parentheses. One of the 10 dogs died during the night following the infusion.

were recorded continuously for 2 minutes after an injection. Six-second tracings were then recorded every 30 seconds until 5 minutes had elapsed. Total and ectopic heart rates for successive 30-second intervals were plotted as in figure 2. The highest ectopic rate in one of these successive 30-second intervals was designated as the maximum ectopic rate.

Infusions. Large doses of norepinephrine or epinephrine were usually administered by continuous infusion, using a Bowman pump. Each of 25 dogs received 0.51 mg/kg norepinephrine in 20 or 45 ml saline. Twenty-three of these dogs were infused at a rate of 6.2 μg/kg/min for approximately 83 minutes, and two dogs were infused at a rate of 2.1 μg/kg/min for 4 hours. Seven dogs received the equimolar infusion (0.55 mg/kg) of epinephrine in approximately 83 minutes. Fourteen dogs received 0.85-0.95 mg/kg norepinephrine infused during 83 minutes in a volume of 20 ml. Nine dogs received an infusion of 0.24 mg/kg epinephrine. Eleven control dogs received an infusion of 20 ml saline at a rate of 0.24 ml/min.

In two dogs, a total dose of 1.0 mg/kg norepinephrine was administered in six injections at 20-minute intervals.

Pathologic Studies. Most of the dogs were killed for pathologic study 1 or 2 days after infusion. Autopsies were also made on dogs that died as a result of the infusions. Tissues obtained at autopsy were fixed in 10% formalin buffered to pH 7.0. Routine paraffin sections were stained with hematoxylin and eosin. Frozen sections were stained for neutral fat with Oil red O.

RESULTS

Cardiovascular Effects During and After Infusion of Norepinephrine or Epinephrine. Figure 1 summarizes the cardiovascular effects elicited in 10 dogs during and after the infusion of 0.51 mg/kg norepinephrine over a period of approximately 83 minutes. The blood pressure was sustained during infusion substantially above control level, although most dogs showed some decline from the peak pressure. After the infusion, the blood pressure promptly fell below the preinfusion level. A fall in blood pressure after infusions of norepinephrine in various animal species has been reported by others (2-4).

Reflex cardiac slowing and some ectopic activity occurred during norepinephrine infusion (fig. 1), with most dogs showing one or more bursts of ventricular tachycardia. For several hours after infusion, the heart rate was invariably high.

Similar cardiovascular effects were seen during and after infusions of epinephrine.

The day after infusion of 0.51 mg/kg norepinephrine, the blood pressure was lower than before infusion, but the mean pressure
Responses to Test Doses Before and After Infusion. Figure 2 compares the arterial pressure and electrocardiographic response of a dog to the large test dose of norepinephrine before and the day after infusion of 0.51 mg/kg norepinephrine. The test dose produced cardiac slowing and only slight ectopic activity before infusion. It induced ventricular tachycardia lasting approximately 3 minutes the day after infusion. The peak diastolic pressure was higher the day after infusion than before infusion, probably because of the tachycardia.

The day after infusion, the mean arterial pressure was consistently below the preinjection level five minutes after the test dose (fig. 3). Thus in 12 dogs, the average mean arterial pressure 5 minutes after injection of the large test dose was 76.2 + 8.6 mm Hg, 41 mm below the average preinjection level. In contrast, in these same dogs before norepinephrine infusion and in the control dogs both before and the day after saline infusion, the mean pressure 5 minutes after injection of the large test dose was back to the preinjection level.

The two dogs which received 1.0 mg/kg norepinephrine in divided doses showed similar abnormal responses the next day.

Statistical Comparison of Responses to Test Doses Before and After Norepinephrine Infusion. Figure 4 compares the maximum ectopic rates induced by the small test dose in two groups of dogs before and the day after infusion. The 10 dogs in group A received saline infusions and the 21 dogs in group B received 0.51 mg/kg norepinephrine. Both groups showed similar electrocardiographic responses before infusion. The responses were not significantly changed for group A the day after infusion. However, in 14 of the 21 dogs in group B, the small test dose induced ventricular tachycardia the day after norepinephrine
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Fig. 3. A graphical summary of the arterial pressure responses to the large test dose (9.5 μg/kg) of norepinephrine in 12 unanesthetized dogs before and the day after infusion of 0.51 mg/kg (3 amole/kg) norepinephrine. Note that on the day after infusion, the arterial pressure 5 min. after injection of the test dose was significantly below the preinjection level.

infusion, with maximum ectopic rates ranging from 112/min. to 186/min. Three dogs responded with ventricular rhythms at rates of 40, 86 and 96 ectopic beats/min. The maximum ectopic rates induced in the dogs in group B the day after infusion differed significantly from the responses of the control dogs in group A (P < 0.001).

The mean maximum ectopic rate induced by the large test dose of norepinephrine in 21 dogs was 253 ± 13.4 ectopic beats/min. the day after infusion of 0.51 mg/kg norepinephrine, in contrast to 76.5 ± 11.6 ectopic beats/min. before infusion. Only 1 of the 21 dogs failed to respond with ventricular tachycardia to the large test dose the day after infusion. The other 20 dogs showed maximum ectopic beats ranging from 190 to 318/min. However, since an occasional supposedly normal dog will respond with ventricular tachycardia to the large test dose the day after infusion, the fast ectopic rates induced by the small test dose (fig. 4) are perhaps a more significant demonstration of cardiac hyperirritability.

The day after infusion, test doses of norepinephrine induce ventricular tachycardias which are faster than those induced by the equimolar test doses of epinephrine.

The dogs which received 0.55 mg/kg epinephrine did not show a significant change in their response to the small test dose of norepinephrine the day after infusion. However, the large dose of norepinephrine induced tachycardias with a mean maximum ectopic rate of 146.0 ± 36 the day after epinephrine infusion. Although epinephrine infusion caused a prolonged cardiac hyperirritability, it is less potent than norepinephrine.

Effect of Adrenergic Blockade. Two mg/kg of Dibenzyline was injected intravenously 1 hour before infusion of 0.85 mg/kg norepinephrine in three dogs and before the infusion of the equimolar amount of epinephrine in one dog. Arterial pressure did not rise significantly and ectopic beats did not occur during the infusions. The next day the large test dose of norepinephrine did not induce ventricular tachycardias. The dogs which received 0.55 mg/kg epinephrine did not show a significant change in their response to the small test dose of norepinephrine the day after infusion of 0.51 mg/kg norepinephrine. Thus a cumulative intravenous dose of 15 mg/kg quinidine was required in one dog to block tachycardias induced by the large test dose of norepinephrine. In two dogs, cumulative doses of 80 mg/kg procaine amide failed to block completely the arrhythmias induced by this same test dose of norepinephrine, although their severity was reduced.

Effect of Quinidine and Procaine Amide. Antiarrhythmic drugs did not readily block the tachycardias induced by test doses of epinephrine the day after infusion of 0.51 mg/kg norepinephrine. Thus a cumulative intravenous dose of 15 mg/kg quinidine was required in one dog to block tachycardias induced by the large test dose of norepinephrine. In two dogs, cumulative doses of 80 mg/kg procaine amide failed to block completely the arrhythmias induced by this same test dose of norepinephrine, although their severity was reduced.

Duration of Cardiac Hyperirritability. The
responses to test doses of norepinephrine continued to be exaggerated for 2-4 days after an infusion of 0.51 mg/kg norepinephrine (fig. 5). The tachycardias induced by the large test dose of norepinephrine were almost as fast on the 2nd day after infusion as on the 1st day. One of the eight dogs tested 2 days after infusion died from ventricular fibrillation induced by the large test dose.

Post-Mortem Findings. All dogs survived at least 3 hours after an infusion. Eight of the thirteen dogs which died within 20 hours showed massive pulmonary edema with abundant frothy fluid in the tracheobronchial tree. Pulmonary edema was absent in the dogs which were killed.

Gross examination of the hearts of dogs infused with catechol amines usually revealed subendocardial hemorrhages involving particularly the papillary muscles and the apical half of the left ventricle and the anterior wall of the right ventricle. A few petechial hemorrhages were often noted in the mitral leaflets and the ventricular epicardium. The tips of the papillary muscles of the left ventricle were pale. The hemorrhages tended to be most severe in the animals that died and in those dogs that received the larger dose of catechol amines. Occasional hemorrhages were also seen involving the pleura, the peritoneum, and mucosa of the urinary bladder and gastrointestinal tract.

Fig. 4. Maximum ectopic rates induced by the small test dose (0.95 μg/kg) of norepinephrine before and the day after infusion of 20 ml saline in the 10 dogs of group A, and before and the day after infusion of 0.51 mg/kg norepinephrine in the 21 dogs of group B.

Fig. 5. Duration of cardiac hyperirritability in unanesthetized dogs after an infusion of 0.51 mg/kg norepinephrine. The points represent the mean maximum ectopic rates induced by the small and large test doses (0.95 and 9.5 μg/kg) of norepinephrine before and from 1 to 5 days after infusion.

No significant gross cardiac changes were seen in the control dogs which had been infused with saline.

Fatty Changes in the Myocardium. The hearts of dogs that died within 20 hours or were killed the day after infusion of a large dose of a catechol amine showed widespread fatty changes (table 1). Frozen sections re-
vealed patchy areas scattered throughout the ventricular myocardium in which the myocardial fibers were laden with minute droplets staining like neutral fat with Oil red O (fig. 6B). The auricular myocardium was usually less severely involved. For grading purposes, frozen sections of each heart were made from a comparable area at the base of the left ventricular border between the papillary muscles. Sections were graded with respect to fatty changes as mild (1+), moderate (2+), or severe (3+). The amount of fat in the fibers as well as the size of the areas involved were considered in the grading. In some very severe cases, nearly all the muscle fibers were heavily laden with fat droplets. Sections were graded negative (−) when few or no muscle fibers were laden with fat (fig. 6A).

The severity of the fatty changes in the hearts of dogs killed the day after infusion roughly paralleled the severity of the tachycardias induced by the test doses. There were exceptions, however, where the induced tachycardias were mild despite 3+ fatty changes and where severe tachycardias corresponded to 1+ or 2+ fatty changes. Marked fatty changes were present in the heart of one dog which died approximately 6 hours after infusion of 0.85 mg/kg norepinephrine, showing that fatty changes developed fairly rapidly. The duration of the fatty changes roughly paralleled the duration of the cardiac hyperirritability. Dogs killed 2 and 3 days after infusion of 0.51 mg/kg norepinephrine showed moderate (2+) fatty changes.

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Table 1: Fatty Changes in Myocardium of Dogs Which Either Died Within 20 Hours or Were Killed the Day After Infusion of a Large Dose of a Catechol Amine

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>No. of Dogs</th>
<th>Myocardial Fatty Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>μg/kg</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.51</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>0.85</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.55</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>0.02</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 ml</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Died within 20 hr. of infusion.

Fig. 6. Frozen sections stained for neutral fat with Oil red O. Fat droplets appear black. A. Myocardium of a dog killed the day after an infusion of 20 ml saline shows no significant fatty changes. B. Similar section from a dog killed the day after an infusion of 0.51 mg/kg norepinephrine shows marked (3+) fatty changes. Magnification X 300.

Three dogs killed 5 days after infusion showed fatty changes in only a few small patches of myocardium.

The control dogs infused with saline showed negligible (−) or slight (1+) fatty changes, with only one among the 11 showing moderate (2+) myocardial fatty changes.

Myocardial fatty changes were negligible in three and slight in one of the four dogs which received Dibenzyline 1 hour before infusion of a catechol amine.

Other Cardiac Findings. Some hearts showed a slight to severe valvulitis. The anterior mitral leaflet was most frequently and severely involved. Mitral hemorrhages were noted frequently and foci of necrosis occasionally. There were occasional hemorrhagic extravasations and small foci of inflammation and necrosis in the myocardium. Occasionally, some scattered myocardial fibers were laden with basophilic granules staining like calcium. A few dogs showed focal fatty or hyaline changes in the media of some small arteries and occasionally a perivascular infiltration by neutrophils. Similar nonfatty changes in the vessels and in the myocardium have been reported in dogs given single or multiple intravenous injections of large doses of epinephrine (6).

DISCUSSION

Cardiac hyperirritability persists for 2-4 days after a single infusion of a large dose of a catechol amine. During this period, ventricular
tachycardias are induced by test doses of norepinephrine or epinephrine which normally produce only slight ectopic activity. The tachycardias resemble those produced by the same test doses in conscious dogs for a period of almost 12 days following coronary artery occlusion (1). The mild 'spontaneous' ectopic activity which occurred in approximately 50% of the dogs the day after an infusion of the 0.5 mg/kg norepinephrine may also be compared to the more severe spontaneous ectopic activity which is consistently seen during the first few days following ligation of the anterior descending coronary artery in dogs (7).

Frozen sections stained with Oil red O revealed fatty changes in patchy areas of the myocardium of dogs given large infusions of catechol amines. Such changes are not apparent in routine paraffin sections stained with hematoxylin and eosin. The severity and duration of these fatty changes roughly paralleled the severity and duration of the period of hyperirritability. Dibenzyline administration before norepinephrine infusion prevented both the severe fatty changes and the induced tachycardias. In dogs after coronary artery ligation, fatty changes develop in the zone around the infarct within six hours and persist for about 14 days, as reported by Wartman et al. (8) and confirmed in this laboratory. This 2-week period of significant fatty changes within and around the infarct roughly corresponds to the period of cardiac hyperirritability (1). These findings suggest that fatty myocardial fibers are associated with cardiac hyperirritability. However, the fatty changes in the myocardium after infusions of catechol amines did not always parallel in severity the induced tachycardias. Perhaps, the location of the fatty patches in the myocardium, the severity of possible damage to the Purkinje conduction system and to neurons within the heart or some metabolic disturbance induced by the catechol amines may have a role.

The cause of the myocardial fatty changes induced by the catechol amines is not known. The fatty changes along the border of myocardial infarcts may be caused by ischemia resulting from partial but inadequate restoration of blood flow to this area by collateral blood vessels. Fatty changes following infusions of catechol amines may also be the result of a relative ischemia due to increased oxygen consumption of the myocardium associated with the increased work of the heart. Perhaps, coronary vasoconstriction may also contribute to the ischemia. This interpretation is supported by the fact that significant fatty changes did not develop in the hearts of those dogs in which vasoconstriction and a rise in arterial pressure during infusion were prevented by the prior administration of Dibenzyline.

The induced tachycardias (figs. 2 and 4) and the abnormal arterial pressure responses (fig. 3) suggest that the heart is damaged. The fat droplets in the myocardial fibers are a manifestation of damage and suggest an altered lipid metabolism. However, it is possible that other metabolic changes, less readily demonstrable at present, are involved in the cardiac hyperirritability.

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REFERENCES