Systolic Hypertension and Subendocardial Hemorrhages Produced by Electrical Stimulation of the Stellate Ganglion

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It is generally assumed that the basis for chronically elevated blood pressure lies primarily, if not entirely, in elevated peripheral resistance; yet, a certain group of hypertensive patients appears to have increased cardiac output and normal peripheral resistance.¹ In these patients, systolic pressure is elevated considerably more than diastolic,² resulting in remarkably large pulse pressure. It has been shown that severe experimental systolic hypertension may be induced acutely in the dog by electrical stimulation of the sympathetic nerves to the heart.³ Although diastolic pressure generally rises in these animals, it rises less than systolic, it is not consistently associated with tachycardia, and its genesis remains essentially unexplained. The elevation in systolic pressure is related to increased myocardial contraction resulting in increased systolic ejection.

Comparable acute pressor responses have been elicited in the cat by stimulation in the hypothalamus,⁴ and the response may be eliminated by stellectomy. The possibility, therefore, that certain cases of systolic hypertension, particularly those known to have a neurogenic origin, may be cardiogenic and initiated through the intervention of the hypothalamus and associated sympathetic cardiac nerves prompted the present studies.

Postmortem examination of hearts of animals sustaining prolonged stellate stimulation revealed a distinctive pattern of subendocardial hemorrhages, remarkably similar to those observed during hemorrhagic hypotension.⁵⁻⁶ The similarity was initially puzzling, since hemodynamic events in these two procedures are so different, the former being marked by high blood-pressure levels and the latter by hypotension. However, excessive excitation of sympathetic terminations in the myocardium undoubtedly occur in both procedures. Watts and others⁸⁻¹⁴ have recently shown that arterial epinephrine levels rise sharply during hemorrhagic hypotension. Maling and others¹⁵⁻¹⁸ have observed subendocardial hemorrhages following infusion of relatively large quantities of epinephrine and norepinephrine, while similar lesions have been reported by Wartman et al.¹⁹ following occlusion of the main coronary arterial supply to the left ventricle.

The occurrence of such subendocardial lesions implicates the sympathetic cardiac nerves and perhaps the catecholamine levels in the myocardium. Their obvious significance required careful study of the circumstances in which they appear during direct stellate stimulation.

Methods

The stellate ganglia of nembutalized (32 mg./Kg.) dogs were electrically stimulated continuously for periods ranging from 3 to 12 hours. In some animals the chest remained open, but in the majority it was closed and negative intrathoracic pressure restored after the unipolar electrode had been applied to the stellate through a rib-spreading approach. The parameters of stimulation included pulses of either 2.0- or 5.0-msec. duration and 3.0 to 5.9 volts as read directly from a cathode-ray oscilloscope across the stimulating electrodes. Frequency of stimulation was systematically varied as indicated in table 1. Pressure pulses were recorded from Statham P23Db transducers on an
STIMULATION OF STELLATE

Blood pressure responses to electrical stimulation of the left stellate ganglion at frequencies of 1 per second (A), 3 per second (B), and 10 per second (C). The data represent averages from 10 experiments for A, 10 for B, and 10 for C. Other parameters were 5.0-msec. pulse duration, and intensity of 3.0 volts. Each stimulation procedure was preceded by control recordings for 15 to 45 minutes; these control pressures were averaged as the initial values for each set of curves. The stimulator was then turned on and stimulation was continuous throughout the remainder of each experiment.

Results

In 10 animals, the left stellate ganglion was continuously stimulated at a frequency of one per second for several hours (fig. 1A). Blood pressure increased gradually over the first 10 to 15 minutes and was characterized by a moderate but well-sustained elevation in pulse pressure. This response tended to be maintained as long as stimulation was continued. Heart rate sometimes accelerated, but this was a less consistent response than the increase in pulse pressure. In some animals the vagi were sectioned, while in others they were left intact; but this procedure appeared to have no consistent influence on the terminal pressures attained nor upon the incidence of endocardial lesions. In only one of these 10 animals were subendocardial hemorrhages induced (table 1), although small adherent clots were sometimes associated with the valve leaflets.

In 13 animals, the left stellate ganglion was stimulated as in the above series, except that the frequency was three to five per second (fig. 2). Photographic of the left ventricular endocardium, removed immediately following three and a half hours of electrical stimulation (10/sec., 5 msec., 3.0 volts) of the left stellate ganglion. Fresh hemorrhages were distributed along the papillary muscles, the trabeculae carneae, and over the septal wall, extending outward to involve the endocardium beneath the mitral valve.
Table 1

Incidence of Subendocardial Hemorrhage

<table>
<thead>
<tr>
<th>Stimulation pulse &amp; sec., 3.0 volts</th>
<th>Number of animals</th>
<th>Left ventricle No.</th>
<th>Per cent</th>
<th>Right ventricle No.</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left stellate 1/sec.</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left stellate 3/sec.</td>
<td>13</td>
<td>11</td>
<td>85</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Left stellate 10/sec.</td>
<td>20</td>
<td>18</td>
<td>90</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Right stellate 10/sec.</td>
<td>17</td>
<td>2</td>
<td>12</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

1B). The pressor response was generally more profound in that both systolic- and pulse-pressure changes were significantly greater. The augmented pressure pulses and elevated levels of blood pressure were well sustained for the early portions of the stimulation period, but sometimes deteriorated after several hours of stimulation. Diastolic-pressure elevations were occasionally superimposed upon augmented pulse pressures. In this group of 13 animals, 11 showed definite subendocardial hemorrhages (table 1). The hemorrhages consisted of macroscopic hemorrhagic streaks along the longitudinal surface of the trabeculae carneae and the papillary muscles of the left ventricle. In one animal, similar lesions appeared in the right ventricle.

In a group of 20 animals, the left stellate ganglion was stimulated at a frequency of 10/sec. (fig. 1C). The cardiac response was prompt (starting within two to three seconds) and more pronounced than in either of the earlier groups. Again the response was primarily augmentor, sometimes resulting in an increase in pulse pressure of as much as 80 mm Hg. In some animals the pressure pulse remained augmented for many hours, but generally the initial augmentation deteriorated more rapidly than in the earlier experiments and was marked by a decline in amplitude of the pressure pulse superimposed on falling systolic- and diastolic-pressure levels. The hearts of 18 of the 20 animals showed multiple small or frequently massive subendocardial hemorrhages in the left ventricle (fig. 2). They were distributed along the long axis of the trabeculae carneae and the papillary muscles, with the most common site at the point of attachment of the chordae tendineae to the papillary muscles. Between, and deep to the hemorrhages, the endocardium was generally normal in appearance, thus producing a series of dark, congested islets or long, narrow, and darkly discolored striations extending along the main outflow channel of the left ventricle. Massive hemorrhage over the middle third of the septal wall, sometimes with extension to the posterior wall, occasionally obliterated all normal appearance. Microscopic examination revealed the lesions to be recent hemorrhages in the interstitial tissue beneath the endocardium. No myocardial necrosis and no neutrophilic infiltration was present. However, all hearts examined in this initial group were removed from animals sacrificed immediately after stimulation. Studies are currently being made to determine whether these pathological changes are progressive with time. Only rarely was the lesion found in the right ventricle (4 of the 20), and it never became severe in this chamber. It was not observed in the atrial endocardium. (We have induced similar lesions both in the right ventricle and in the atrial walls by intravenous infusion of epinephrine.) In only two hearts from this group were lesions completely absent.

In contrast with the results above, responses to comparable (10 per second) electrical stimulation of the right stellate ganglion included marked cardiac acceleration with considerably less augmentation in pulse pressure. At postmortem examination, small but definite lesions were detected in the left ventricles of two, and in the right ventricles of four animals (table 1). The lesion appeared in the right ventricle in the same number of experiments regardless of whether the left or right stellate ganglion was stimulated.

The A-V valves (especially the mitral) were the site of damage in a number of the higher-frequency (10/sec.) stimulations, both in the left- and right-stellate experiments. Whereas adherent clots were commonly observed in the control group, they were rarely massive and usually not subendocardial. Vischer and...
Henschel reported that subendothelial-valve lesions occurred only rarely in young dogs, but with increasing frequency in older animals. In our stimulated animals, the endocardium at the base of the valve was frequently involved and sometimes represented the major gross pathological change observed. Darkly colored and severely congested ridges marked the basal borders of the valve leaflets as a result of the subendocardial hemorrhages.

Discussion

Our earlier report of a significant relationship between stimulation frequency and a sustained pressor response related to the direct inotropic action of the sympathetic cardiac nerves is confirmed. Not only does the pressor response deteriorate during short periods of stimulation with frequencies of 20 to 80 per second, but frequently in prolonged stimulation experiments using frequencies of 10 per second or less. However, the fact that a pressor response similar to that observed in systolic hypertension may be induced and sustained by continuous, low-frequency (1 to 3/sec.) stimulation seems important. It is reported that the rate of preganglionic impulse flow in the dog seldom exceeds six to eight per second, and the normal rate is closer to one or two per second.21,22 The excitation of all, or nearly all, of the fibers under our stimulating electrodes certainly elicited an abnormally large number of impulses in the cardiac nerves and resulted in a relatively massive impingement upon the cardiac terminations. Whether systolic hypertension can be permanently established by longer periods of stimulation and whether diastolic-pressure elevations ultimately supervene remain to be investigated.

There is evidence that in a major fraction of patients with essential hypertension, the initiating factors are neurogenic and the efferent pathways consist of the hypothalamus and its sympathetic outflows.23 Direct neural connections to the heart, as well as to the blood vessels, have been conclusively demonstrated.24 If cardiomotor pathways are predominant in a given patient, elevated cardiac output and systolic hypertension may result. If vasomotor pathways are primary, elevated peripheral resistance and diastolic hypertension may occur. It is conceivable that various combinations of these may obtain, and also that a progressive transfer from one type to the other may occur with time.

An alternative explanation of the increased pulse pressure in systolic hypertension is related to a possible decrease in large-vessel distensibility. It is conceivable that the same stimulation which elicits an increased impulse flow in the cardiac nerves simultaneously activates sympathetic fibers ending in smooth-muscle elements of the aortic arch. Such an influence may, in fact, contribute to the increased pulse pressure.

The progressive deterioration from maximal levels of blood pressure, particularly noted during higher-frequency stimulation, was presumably related to inability of the cardiac sympathetic nerves to continuously produce norepinephrine in sufficient quantities. Although there was variation in the time of onset of this deterioration in different animals, it occurred in nearly all animals stimulated at 10 per second, in some of those stimulated at 3 per second, and in a few after prolonged stimulation at 1 per second.

In these experiments, prominent subendocardial hemorrhages were induced by electrical stimulation of the stellate ganglion, and this represents, to our knowledge, the first report on such lesions resulting from direct activation of the cardiac sympathetic nerves. Similar lesions produced in other experimental and pathological states known to implicate this system suggest the possibility of a common origin. The lesions observed in the present study were elicited by stimulation periods lasting five to six hours but in many experiments, severe lesions have been observed following only a few stimulations (6 to 10) of relatively short duration (15 to 30 seconds each).

Raab has reviewed the literature describing the identification of norepinephrine as the neurotransmitter at sympathetic terminations in the myocardium. He also emphasizes the
fact that heart muscle possesses a specific ability to absorb circulating catecholamines and to accumulate them in active form. Relatively large quantities are released locally during prolonged excitation of the cardiac sympathetic. Thus, a common factor appears in many of those procedures which produce subendocardial hemorrhages, that is, elevated levels of catecholamines. Watts et al. have demonstrated that arterial-blood epinephrine increased from a control value of 0.94 \( \mu g./L. \) to a maximum 29.0 \( \mu g./L. \) after a hemorrhage of 40 ml./Kg. Unfortunately, these authors did not report autopsy findings in their experiments. Poole and Watts were able to induce shock in dogs by the infusion of 3.4 \( \mu g./Kg./min. \) of epinephrine in confirmation of the earlier studies of Freeman et al. Again, autopsy findings were not reported. The infusion levels of Maling and Highman (2.1 to 6.2 \( \mu g./Kg./min. \)), which produced pathological changes in the myocardium, were in a comparable range.

Thus, the circumstantial evidence relating catecholamine levels in the blood to severe subendocardial hemorrhagic lesions in animals sustaining excessive excitation of the cardiac sympathetic innervation appears striking and warrants further careful study. The appearance of subendocardial lesions in a majority of animals stimulated at frequencies of 3 and 10/sec. and the absence of lesions with stimulation at 1/sec. strengthen the correlation between frequency of excitation, the local concentration of catecholamines, and occurrence of the lesion.

Smith and Tomlinson state that hemorrhages limited to the subendocardial tissues of the left ventricle are commonly associated with intracranial lesions (in man), but are only rarely encountered in other pathological states. They found that the hemorrhages were most frequent in cases with a sudden rise in intracranial pressure and associated vagal action. Our observations in the experimental animal suggest they are associated more specifically with excessive sympathetic activity, a finding compatible with the functional disturbances associated with intracranial lesions.

A satisfactory explanation of the pathological changes induced by sympathetic procedures is not available. It is conceivable that they represent an artifact associated with the use of heparin; but if this were true, we should expect them to have similar incidence in all procedures, since heparin was employed in our entire series. We have also observed them in experiments in which heparin was not used. The statement that they are caused by anoxia may be relevant, but is certainly inadequate. The lesions are located specifically in the subendocardial layers and are distributed longitudinally along the papillary muscles and adjacent tissues. Perhaps careful anatomical studies of the length and structure of the capillary beds in these areas would provide significant information. It is possible that erythrocytes which travel through these channels may be subjected to the greatest compression during systole and, therefore, may be the most likely to be completely deprived of their available oxygen before reaching all the cells which they supply. The internal surface of the ventricles is extremely irregular due to the trabeculae carneae and the papillary muscles. One can visualize mechanical damage to these surfaces resulting from prolonged and forceful contractions of these muscular structures. Gauer mentions such "self-inflicted mechanical damage" in the nearly empty heart which is beating forcefully under the influence of epinephrine.

It has been suggested that sympathetic nerve stimulation augments the metabolic demands of the myocardium and that epinephrine increases \( O_2 \) consumption. Raab maintains the latter is out of proportion to the increased coronary flow and, therefore, induces a relative tissue anoxia. Eckstein et al. postulated that perhaps during nerve stimulation the endocardial surfaces meet and muscular contraction continues much as a "tightly clenched fist," with correspondingly high oxygen requirement.

Most of our stimulations have been applied to the left stellate ganglion, since this procedure has been shown to elicit more profound augmentation of the pressure pulse. Whereas...
endocardial lesions were regularly found in the left ventricle following stimulation (3/sec., 10/sec.), they were only rarely observed in the right ventricle. We are not prepared to discuss this striking difference at the present writing, but it may be related to the distribution of sympathetic postganglionic nerves in the myocardium, to differences in mechanical and hemodynamic factors in the two ventricles, or to differences in distribution of blood vessels to the ventricular muscles.

Summary
During prolonged electrical stimulation of the stellate ganglion in the dog, blood pressure, and more specifically systolic pressure, is significantly elevated. The amount of augmentation in pulse pressure is related to the frequency of stimulation, as is the duration of the sustained pressor response. Postmortem examination of the hearts revealed a distinctive pattern of subendocardial hemorrhages distributed along the long axis of the papillary muscles and the trabeculae carneae. They also frequently marked the endocardium at the base of the mitral valve. These lesions appeared in the left ventricle in 29 of 33 animals in which the left stellate ganglion was stimulated at a frequency of three to ten per second. They were found in only five instances in the right ventricles of these animals. The incidence of lesions in the ventricular wall was low during stimulation of the right stellate ganglion, although the mitral valve became involved in about 50 per cent of the animals. The similarity of the lesions to those induced during hemorrhagic hypotension, elevated intracranial pressures, and infusion of large quantities of the catecholamines suggests the possibility of a similar etiology. A satisfactory explanation of the lesion, however, is not yet available.

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