Prolonged Pressor Effects of Selective Stimulation of the Stellate Ganglion

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With both intensity and duration of individual current pulses maintained constant and at low values, frequencies were varied from \( \frac{1}{2} \) to 80/sec., and the stimulating current was applied to the stellate ganglion of the open chest dog. Whereas systolic and pulse pressures increased rapidly with the application of high frequency currents, the pressures were not long maintained even though the stimulation was continuous. With low frequency currents, systolic and pulse pressures rose more slowly but to higher levels which were sustained for periods of 5 to 11 hours. It is believed that neither cardiac acceleration nor systemic vasoconstriction contributed significantly to the pressor responses, but rather that augmentation of myocardial contraction and increased systolic ejection were the important causative factors.

AN ACTION of the sympathetic cardiac nerves which greatly augments the force of myocardial contraction has been amply demonstrated in the recent literature.1-4 This augmentor action is most prominent during stimulation of the left sympathetic trunk and its associated pathways, whereas excitation of the right trunk induces more prominent cardiac acceleration. A notable feature of the response to sympathetic nerve stimulation is the sustained elevation in pulse pressure which persists for some time following removal of the stimulating current.

This marked elevation in blood pressure induced by way of the cardiac innervation suggested the possibility that more prolonged stimulation may result in sustained elevations of blood pressure. Accordingly, it was decided to investigate the effects of continuous stimulation of the stellate ganglia of the dog lasting for a period of several hours.

**METHOD**

Using a unipolar stimulation technic and an American Electronics Model 104 square wave generator, controlled stimulating current pulses were delivered to the right or left stellate ganglia, or both, of the open chest dog by way of an insulated wire electrode. All experiments were carried out under pentobarbital anesthesia. Pulses having a duration of 5 to 10 msec., intensity of 0.5 to 4.5 V., and frequencies varying from 0.5 to 80/sec. were employed. All stimulations were monitored by a DuMont Cathode Ray Oscilloscope connected across the electrodes. Voltages reported are those read from the oscilloscope during stimulation. Carotid or femoral blood pressure and heart rate were recorded optically from segment capsules or by a Sanborn Electromanometer and Polyviso.

**RESULTS**

The adequacy of stimulating current pulses immediately became apparent as a very significant and sometimes limiting factor in determining the character of cardiovascular response to nerve stimulation. It is well known that current parameters different from those which stimulate somatic nerve fibers are required for excitation of autonomic nerves.5, 6 Nevertheless, much published work has paid too little attention to the precise control of the duration, intensity and frequency of stimulating current pulses in the evaluation of cardiovascular responses to electric stimulation. Using current pulses of 10 msec. duration and relatively high frequencies (20-80/sec.), it became evident that blood pressure responses may attain high peaks, but show relatively rapid decay even though the stimulating current was continuously applied (fig. 1). In these experiments the higher the frequency of current pulses, other parameters remaining constant, the shorter the period through which high pressures were maintained and the more rapidly the increased pulse pressure returned toward normal.

This relationship between frequency of stimulation and maintenance of significantly elevated blood pressures was examined by the...
application of an electrode to the left stellate ganglion with a gradual increase in frequency of stimulating current pulses from 0.5 to a maximum of 20/sec. Figure 2 illustrates the progressive elevation in blood pressure as frequency was progressively increased. With each increment in frequency from 0.5 to 8/sec., there was a significant elevation in systolic pressure which then reached a plateau at frequencies from 8 to 15/sec. No further increase in pressure was elicited and, in fact, progressive decay in systolic and pulse pressures appeared as the frequency was further increased to 20/sec. In order to determine whether this decay represented a real relationship to frequency, the stimulating current was switched instantaneously from 20 to 2/sec. (third row, fig. 2). There followed an immediate downward adjustment both in systolic and diastolic pressures with little or no alteration in pulse pressure. As stimulation continued then at 2/sec., pressures once again progressively increased until a maximum of 180/90 mm. Hg was sustained for a period of several hours.

This demonstrated relationship between frequency of stimulating current pulses and elevated systolic blood pressure suggested the continuous stimulation of the stellate ganglion at low frequencies. Figure 3 represents an experiment in which the left stellate ganglion was continuously stimulated at the rate of 3/sec. for a period of nearly 5 hours. Systolic pressure was elevated through values in excess of 240 mm. Hg, a level which was sustained for a period as long as the open chest preparation would permit without general cardiovascular deterioration. At intervals during the experiment, the current was turned off for periods of 2 to 4 min. in order to determine whether the blood pressure would return to normal levels (third row, fig. 3). In each instance the pressure did return toward normal until the stimulating current was returned at low frequen-
Prompt re-establishment of elevated pressures followed. Thus, from an initial normal pressure of 110/80 (upper left, fig. 3), there developed a hypertensive state marked by pressures of 240/120 when the experiment was terminated, nearly 5 hours later. No significant increase in heart rate occurred at any time during the experiment. With careful closure of the chest following application of the electrode, similar hypertensive states have been maintained for as long as 11 hours.

Cardiac acceleration plays little or no part in these pressor responses. Although diastolic pressures sometimes rise moderately during stimulation, it is the elevated systolic pressure which commands attention. Although much slower and more gradual in development, maximum systolic and pulse pressures were considerably higher in the present series of experiments than were observed during short periods of stimulation. This inotropic action of the sympathetic cardiac nerves is best explained as a result of a remarkable increase in the force of contraction of the ventricular musculature with a consequent elevation in the volume of systolic ejection. Since the pressure then remains elevated for the duration of stimulation, it follows that venous return must keep pace with elevated systolic ejection.

Continuous stimulation of the right stellate ganglion and associated cardiac nerves resulted in a somewhat similar but more variable response. Cardiac acceleration was more prominent as an early feature of the response, frequently superimposed upon a moderate elevation in systolic and pulse pressures. With long continued stimulation, the cardiac acceleration tended to decrease leaving the augmented systolic pressure response intact. Thus, although sustained hypertension was generally induced through continuous excitation of the right stellate, it was usually lesser in magnitude and more variable in duration.

Discussion

Thus, it has been established that experimental hypertension may be induced in the open chest dog by prolonged, continuous, low frequency stimulation of the cardiosympathetic nerves. Such results have been obtained in animals in which the vagi have been sectioned bilaterally and the sympathetic trunk has been cut immediately caudal to the stellate ganglion. Thus, the preparation was neurally isolated in such a way that direct excitation of the splanchnic vascular bed and the adrenal medulla was eliminated and reflex systemic vasoconstriction minimized. The augmentor action of the sympathetic innervation of the heart remained, therefore, as the main factor in the production of this type of experimentally induced hypertension.

The importance of carefully determining the appropriate stimulating current parameters to elicit cardiovascular responses to nerve stimulation is emphasized. It is well known that the normal impulse traffic in sympathetic nerves is less than 10/sec., probably approaching 2/sec. in most situations. Therefore, it seems only reasonable that one should employ relatively low frequency stimulation in order to mimic impulse traffic under experimental conditions such as those reported here. That such stimulation procedure does not excessively damage the nerve tissue is illustrated by the fact that the stimulation continues to be effective over long periods of time. On the other hand, the use of both long pulse duration and high current intensity is seriously damaging to nervous tissue.

Since the sympathetic innervation of the heart is normally functional in intact animals and known connections exist between the higher levels of the central nervous system and the sympathetic outflow to the heart, it seems possible that this mechanism may participate in the induction of neurogenic hypertension of emotional or psychic origin. Predominantly cardioaugmentor responses have been elicited by the electric stimulation of the brain stem through electrodes placed stereotaxically in the anterior medulla of both the cat and dog.

Summary

Employing a unipolar stimulation technic, the stellate ganglion was stimulated for periods up to 11 hours in the open chest dog. While maintaining both intensity and duration of
the stimulating current pulses constant, relatively high frequency (20 to 80/sec.) pulses induced prompt and sometimes profound elevations in systolic blood pressure. Alterations in diastolic pressure were very much less and sometimes entirely absent with a consequent significant increase in pulse pressure. With continuous application of the stimulating current for several minutes, both systolic and pulse pressures declined toward normal. With low frequency stimulation (1 to 3/sec.) however, pressures rose more slowly, to higher maximum levels, and remained elevated throughout the period of stimulation. Systolic pressures of 240 to 280 mm. Hg with pulse pressures in excess of 100 to 120 mm. Hg have been sustained for many hours (up to 11 hours in present preparations) of continuous stimulation. As the frequency was increased stepwise from 0.5 to 20/sec., a reversal in the pressor response occurred at frequencies between 8 and 15/sec. with both systolic and pulse pressures regressing from peak levels. This regression could then be halted and high pressures restored by suddenly switching back to low frequency stimulation. The source of elevated pressures is believed to be augmented force of myocardial contraction since heart rate was not a significant factor and systemic vasoconstriction was believed to be minimized by preliminary section of nerve pathways except those in the cardiac motor nerves.

**SUMMARY IN INTERLINGUA**

Per medio del technica a stimulation unipolar, le ganglion stellate esseva stimulate in le thorace aperte de canes durante periodos de usque a 11 horas. Durante que le intensitate e le duration del pulsos del currente stimulatori esseva mantenite a forma constante, pulsos a relativemente alte frequentias (20 a 80 per secunda) induceva un prompte e a vices considerabile elevation del pression de sanguine systolic. Le alterationes del pression diastolic esseva molto minus pronunciata. A vices illis esseva completamente absente, con un resultante augmento significative del pression pulsatil. Quando le currente stimulatori esseva applicate continuemente durante plure minutas, le pression systolic e le pression pulsatil decesceva verso le norma. Tamen, quando stimulos a basse frequentias (de 1 a 3 per secunda) esseva applicate, le pressiones acceesceva plus lentemente; illos attingeva plus alte nivellos; e illos remaneva altiati durante le integre periodo del stimulation. Pressiones systolic de 240 a 280 mm Hg con pressiones pulsatil de plus que 100 a 120 mm Hg esseva mantenite durante multe horas de stimulation continue. (In le experimentos del presente estudio durante usque a 11 horas.) Quando le frequentia esseva augmentate paso per paso ab 0,5 usque a 20 per secunda, un reversion del responda pressoral occurreva a frequentias de inter 8 e 15 per secunda, tanto le pression systolic como etiam le pression pulsatil regredeva ab lor nivellos maximal. Iste regression poteva esser arrestate e alte nivellos de pression pote esser restaurate per un retorno subitanee al stimulation a basse frequentias. Nos opinia que le origine del elevate pressiones debe esser cercate in un augmento del forta del contraction myocardial, proque le velocitate cardiac non esseva un factor significative e proque il pareva que le venoconstriction sistemica esseva reducite al minimo per le section preliminari del vias nerve con le exception del nervos cardiac motori.

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Impulses traveling over axons die out at their terminations on skeletal muscle. But, through operation of either an electric or humoral transmitter, a new impulse is generated at the end-plate which spreads through muscle fibers and excites them. It is now well established that curare prevents excitation of muscle over axons by preventing the development of the new impulses at the end-plates.

Since no differential tissue has been demonstrated between the juncture of specialized conducting and contracting cardiac muscle, it is generally assumed that the excitation wave is transmitted directly from one system to the other. For example, on this basis delay in passage of impulses over the atrioventricular node has generally been attributed to a slower rate of conduction. However, there has been a suspicion that a true synaptic delay may be involved.

In 1931 P. Rijlant (Arch. Internat. Physiol. 33: 418, 1931) reported that when contraction of atrial muscle was abolished by strychnine, impulses were still generated at the sinus region and conducted. Furthermore, the quiescent cardiac tissue still responded locally to direct excitation. He suggested that the effects could be explained, as in the case of a curarized skeletal muscle, by action of the drug on a junctional tissue. This junction was designated as “épaphé” rather than “synapse,” because of a lack of differentiation of the junctional tissue. Later it was found by his associates that curare, quinidine and aconitine have similar effects.

Recent studies indicate that the abolishment of cardiac contractions by hypothermia and anoxia can also be assigned to a similar interruption of excitation at junctional tissues.

Interest in “épaphé” block is not limited to conditions which lead to total block, but extends to those in which transmission and subsequent contractions are retarded and hence modify synchronicity of contraction. The possibility exists, for example, that difficulties in junctional transmission of impulses may play an essential role in flutter and fibrillation.

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