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Carotid sinus nerve stimulation; studies on the mechanism of the hypotensive response and possible therapeutic application

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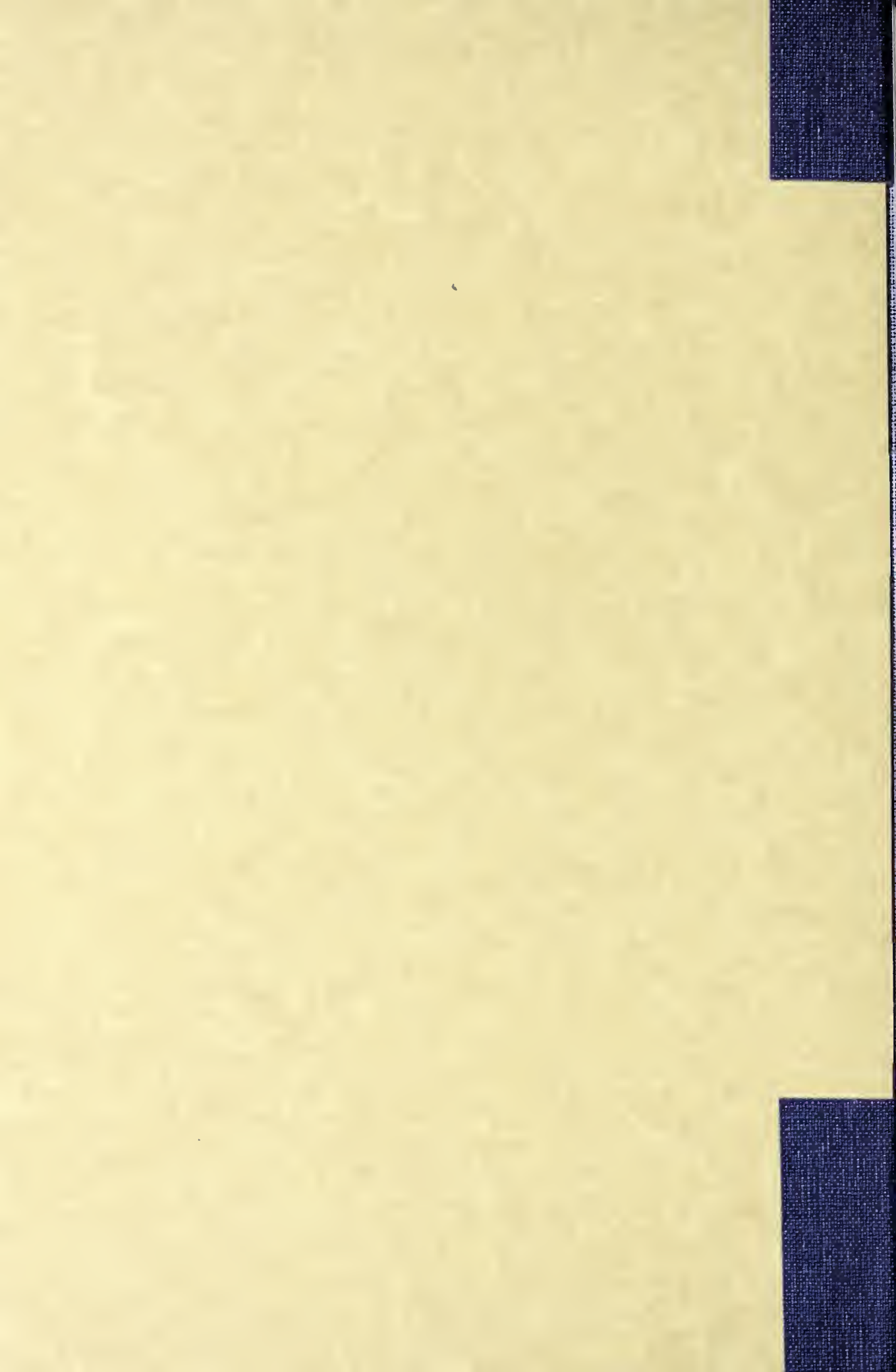
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CAROTID SINUS NERVE STIMULATION --
STUDIES ON THE MECHANISM OF THE HYPOTENSIVE RESPONSE
AND POSSIBLE THERAPEUTIC APPLICATION

by

John A. Drews

B.S. Duke University 1963

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INTRODUCTION

The first organized study and a description of the carotid sinus reflex was made by Hering in the 1920's.^{20,21} He elicited two separate cardiovascular responses -- bradycardia and systemic hypotension -- by stimulating the central end of the carotid sinus nerve, by tugging on the common carotid artery, and by stimulating the internal wall of the sinus region with a sound. Cutting the carotid sinus nerves not only abolished these responses, but caused systemic hypertension.

A decade later, Bronk and Stella recorded the discharge of impulses from the entire carotid sinus nerve as well as from single end-organs.^{7,8} They demonstrated the tonic activity of the carotid sinus nerve baroreceptors, delineated the range of pressures at which peak activity occurred, and noted the outburst of impulses synchronous with cardiac systole. They attributed this large outburst during systole to: (1) increased impulse frequency in individual fibers, and (2) activity of a greater number of end-organs during this part of the cycle. Ead and others later demonstrated the superiority of pulsatile flow over non-pulsatile flow in inducing reflex systemic hypotension.¹³ This reflex is altered or abolished, however, when the distensibility of the sinus wall is altered, through local administration of drugs, changes in sympathetic discharge to the arterial wall from the superior cervical ganglion, or alteration of the structure of the arterial wall itself.^{19,22,25,28,30}

Adaptation of the carotid baroreceptors to hypertensive levels

has been demonstrated by several workers.^{26,27,29} Kezdi found no significant difference between the blood pressure and pulse rate elevation of normotensive and hypertensive subjects following procaine block of the carotid sinus. Kubicek and others showed adaptation of all baroreceptors to transient neurogenic hypertension induced by deliberate stimulation of the splanchnic nerves in dogs. Following cessation of stimulation, the sudden drop in blood pressure accelerated the heart rate as the pressor reflex system attempted to maintain the previously elevated pressure. McCubbin and others demonstrated a rise in the threshold to stimulation and a shift upwards in the normal range of response of the carotid sinus nerves in renal hypertension.³³ The nerve activity in hypertensive dogs followed the normal pulsatile pattern of normotensive dogs, though at a higher level of blood pressure.

Several humoral factors appear to be involved in the carotid sinus reflex. A rise in the catecholamine level in the blood follows the reduction of pulse pressure in the carotid sinus.³⁴ The effect of common carotid artery occlusion on renal function, notably a natriuresis and a diuresis, is one of hormonal mediation.¹⁰ There is a complete dissociation of the pressor and saluretic responses; the saluresis is not merely a passive consequence of a renal or systemic hemodynamic change, but is due to the action of a humoral substance, probably produced in the posterior hypothalamus, on tubular sodium transport.¹¹

In 1964, Bilgutay and others, and Griffith and Schwartz, demon-

strated the feasibility of reversing hypertension by stimulating the carotid sinus nerves.^{6,18} For the first time, the therapeutic implications of carotid sinus nerve stimulation were recognized. Bilgutay and Lillehei described the application of this method of treating hypertension in two patients.⁴

The effect of the carotid sinus reflex on cardiac output has not been documented satisfactorily. Some investigators found no significant change in cardiac output after occlusion of the carotid artery, electrical stimulation of the nerve, or perfusion of the sinus.²⁴ Others found an increase, a decrease, or no change in cardiac output after eliciting the carotid sinus reflex.²³ Carlsten and others believed the decreased pulse amplitude noted in humans during carotid sinus nerve stimulation indicated a fall in cardiac output, and believed this to be due to a decrease in the stroke volume, secondary to a reduction in the venous return and elimination of the positive inotropic effect by reflex inhibition of sympathetic tone.^{1,9} Sarnoff and others showed that a decreased carotid sinus pressure increased the sympathetic activity to the heart and decreased the efferent vagal activity, causing augmented ventricular contractions.³⁶ Lindgren and Manning demonstrated, by maintaining constant the aortic pressure, that the decrease in cardiac force following stimulation of the carotid sinus nerve was not secondary to the decrease in systemic blood pressure.³¹

The present study was undertaken to attempt to corroborate some of the recent findings reported in the literature on the effect of

carotid sinus nerve stimulation, especially with regard to cardiac output, and to aid further evaluation of this technique for the treatment of hypertension.

METHOD

Three groups of dogs, weighing 13 to 17 kilograms, were used: seven normotensive, thirteen with acute hypertension induced by bilateral ligation of the common carotid arteries (see Figure 1),

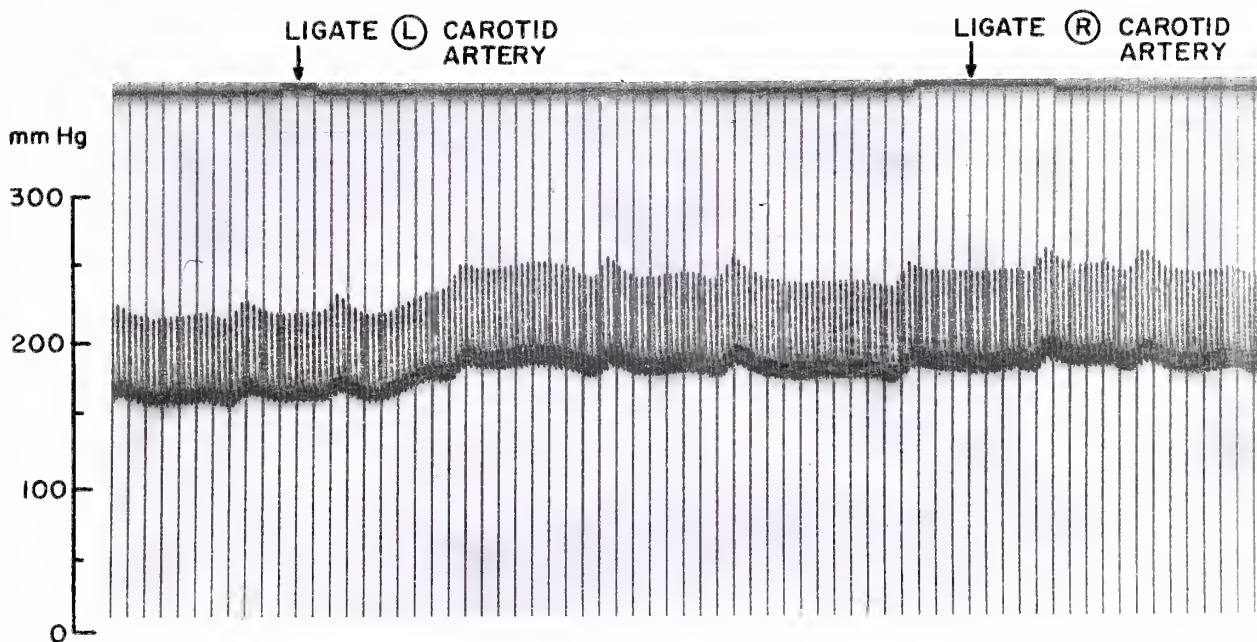


Figure 1. Bilateral common carotid artery ligation in normotensive dog inducing acute hypertension. (Vertical line = one sec.)

and eight with renal hypertension induced by intentional stenosis of the renal arteries bilaterally.^{16,17} The stenosis was verified by retrograde aortography after one week (see Figure 2), and bilateral



Figure 2. Aortogram demonstrating bilateral renal artery stenosis (arrows). Note post-stenotic dilatation and that right kidney in the dog is higher than the left.

renal function was documented by subsequent pyelogram (see Figure 3). In order to follow the development of the hypertension after constriction of the renal arteries, the dogs were trained to hold still while blood pressure readings were taken from a hind paw by means of



Figure 3. Pyelogram demonstrating intact renal function bilaterally in dog subjected to bilateral renal artery stenosis.

a newborn-type sphygmomanometer cuff. This indirect method of blood pressure determination was adequate for the purpose intended and was validated by comparison of its readings with direct readings from dogs under anesthesia. In the acute experiments, the anesthetic used was intravenous pentobarbital.

The operative approach to the sinus area was through a midline incision in the neck to allow exposure of both carotid sinus nerves.

The carotid bifurcations were isolated and the tissue mass within each bifurcation, including the carotid sinus nerve, was dissected free from the internal and external carotid arteries (see Figure 4).

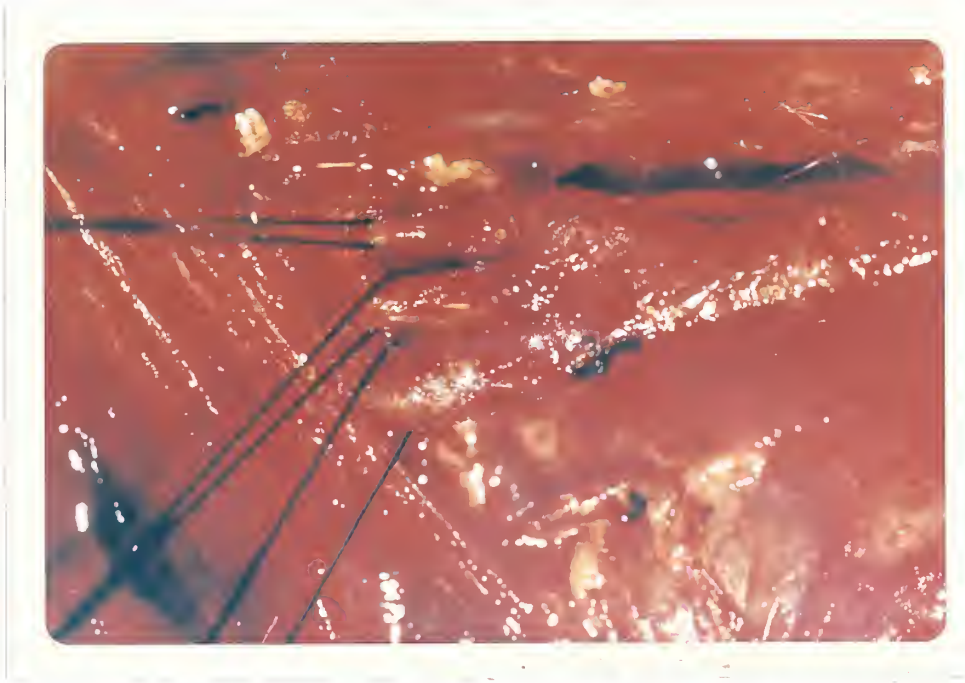


Figure 4. Dissection of the right carotid sinus region. Upper ligature around internal carotid artery, lower ligature around external carotid artery. Middle ligature around tissue within bifurcation, including the right carotid sinus nerve, all of which was enclosed by the stimulating electrode.

Microscopic section of this tissue mass revealed mostly fibrous tissue with the carotid sinus nerve at the periphery. This entire tissue mass was enclosed in the electrode, which was a bipolar, platinum one shielded with Silastic, similar to those used for phrenic nerve and bladder stimulation.^{2,15} (See Figures 5 and 6.) This technique was chosen for two reasons: (1) isolation of the carotid sinus nerve with preservation of full function proved to be techni-



Figure 5. Silastic-shielded, platinum, bipolar electrode used in carotid sinus nerve stimulation.

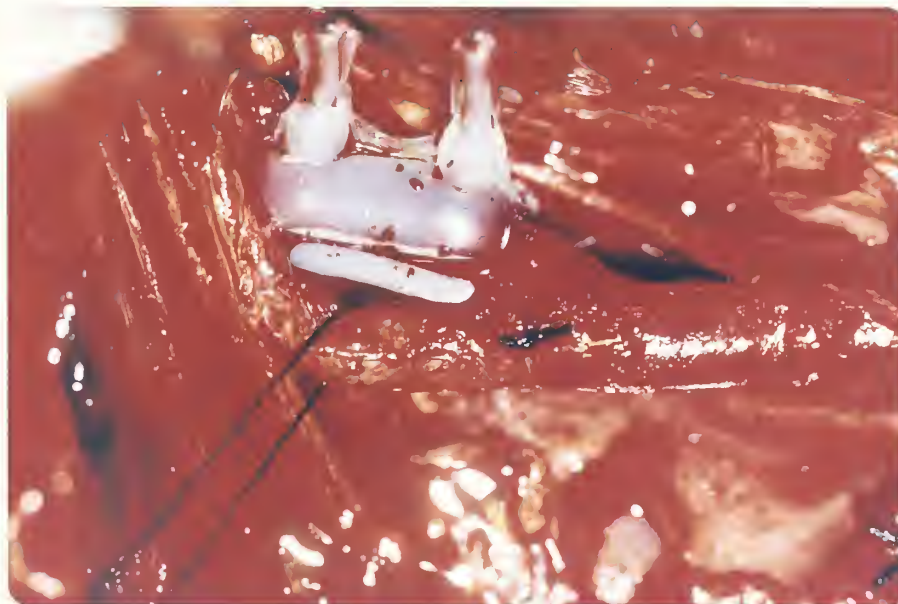


Figure 6. Carotid sinus nerve electrode in place.

cally difficult, and (2) maintenance of electrode contact with such a small structure is virtually impossible. With the method used these problems were eliminated, and a satisfactory response was obtained in nearly all cases.

The femoral artery was cannulated with polyethylene tubing and the blood pressure recorded through a transducer (Sanborn and Electronics for Medicine). Stimulation was provided by the Laboratory Stimulator, Model No. 104A, manufactured by American Electronics Laboratories. Initially, the carotid sinus nerves of normotensive and acutely hypertensive dogs were subjected to stimuli with a wide range of voltages, durations, and frequencies, to ascertain which conditions elicited the maximum response. Continuous stimulation was compared to 250 msec train - 350 msec delay stimulation. These selected conditions were then employed throughout the study. The responses to stimulation -- the changes in both systolic and diastolic blood pressure, and in the heart rate -- of the three groups were compared. Also, in the acutely hypertensive animals, the responses of each nerve singly and both nerves simultaneously were compared. In all cases, stimulation was maintained until a stable response was achieved, often as long as 30 to 45 seconds. A determination of the change in cardiac output before and during stimulation was made in all three groups of animals, utilizing the Fick principle. A Collins respirometer, delivering 100 per cent oxygen, was used to determine oxygen consumption. Mixed venous blood samples were taken through a catheter introduced into the pulmonary

artery under fluoroscopic guidance. Determinations of pO₂ and pH were made with a Beckman Physiological Gas Analyzer, Model 160, and a nomogram was consulted for the percentage oxygen saturation. Hemoglobin determinations were made with a Fisher hemophotometer. An A-V pressure monitor (Med-Science Electronics) was used to measure arterial and central venous pressure simultaneously. Calculation of total peripheral resistance was made from the following formula:

$$\text{Total Peripheral Resistance} = \frac{\text{aortic - caval pressure}}{\text{flow (ml/sec)}}$$

= expressed in P.R.U.
(peripheral resistance units)

Three dogs with renal hypertension were equipped with chronic stimulation units -- two with direct-wire stimulators and one with a radio-frequency induction unit.¹⁴

RESULTS

The average rise in blood pressure in the thirteen animals subjected to bilateral common carotid artery ligation was 40/22. Bilateral vagotomy would have elevated the blood pressure more, but would have abolished a part of the reflex mechanism under study. In eight animals subjected to bilateral constriction of the renal arteries, the average rise in blood pressure was 42/25. In six other animals subjected to the same procedure, there was no detectable change in blood pressure; consequently, these animals were not included in the study.



The maximum fall in blood pressure having no adverse effect on the animals' cardiac or respiratory status was that which resulted from four volts, 80 cps, and 0.5 msec pulse duration (see Figures 7

I VOLTAGE COMPARISONS

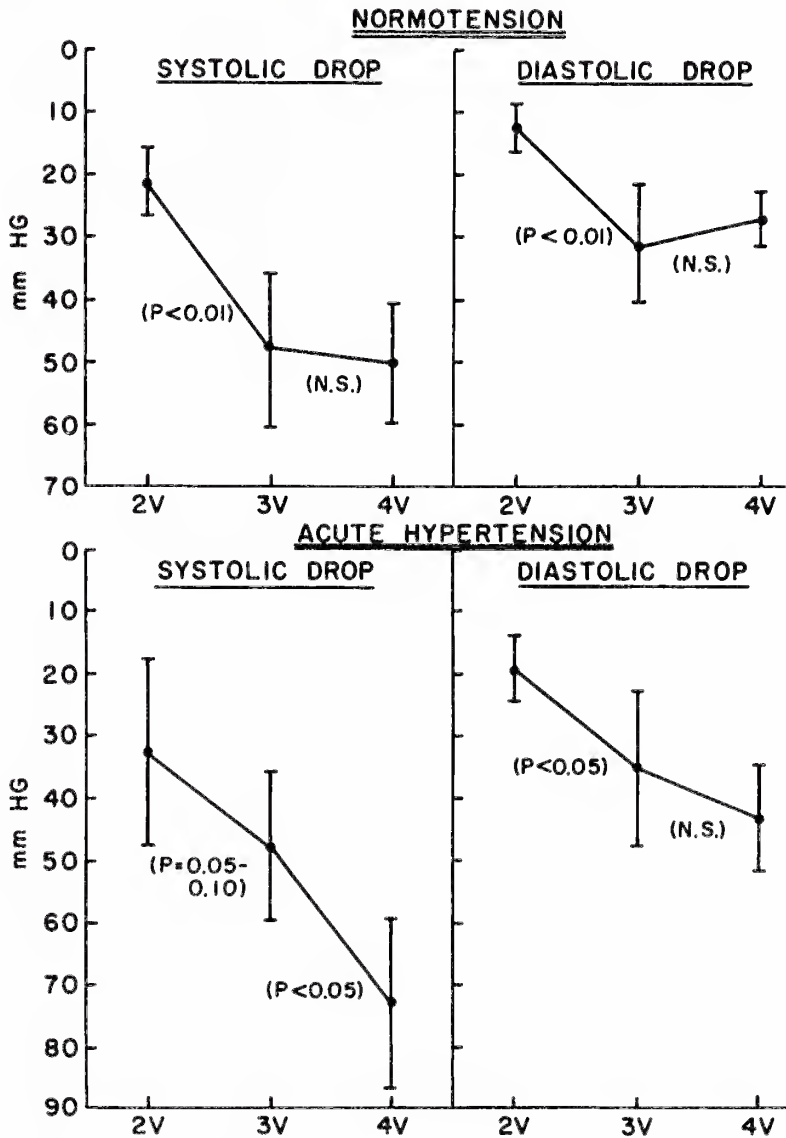


Figure 7. Comparison of voltages. All single nerve stimulations at 80 cps and 0.5 msec duration. (Vertical line = mean ± 2 SD)

and 8). Continuous stimulation was neither superior nor inferior

II FREQUENCY CURVE

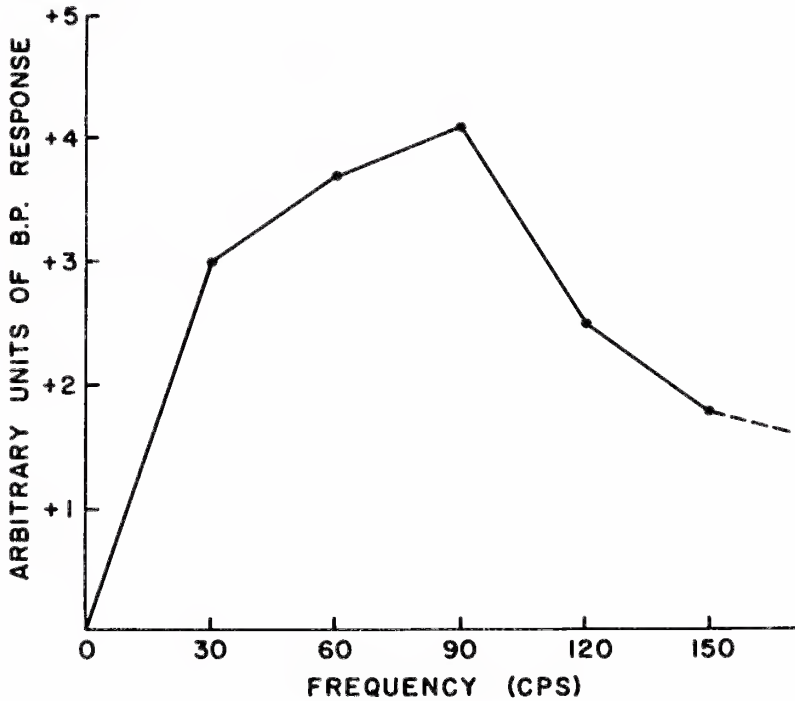


Figure 8. Comparison of frequencies. All single nerve stimulations. From this purely qualitative evaluation, 80 cps was chosen arbitrarily to be used in all subsequent studies.

to train-delay stimulation. Stimuli greater than four volts caused some reaction of adjacent nerves and muscles and, in some instances, caused a transient asystole with marked hyperventilation at the initiation of stimulation. A pulse duration greater than 0.5 msec (with a stimulus intensity of four volts) produced a similar effect. Representative tracings of the response to carotid sinus nerve stimu-

lation are shown in Figures 9 and 10. The tracing in Figure 9 is

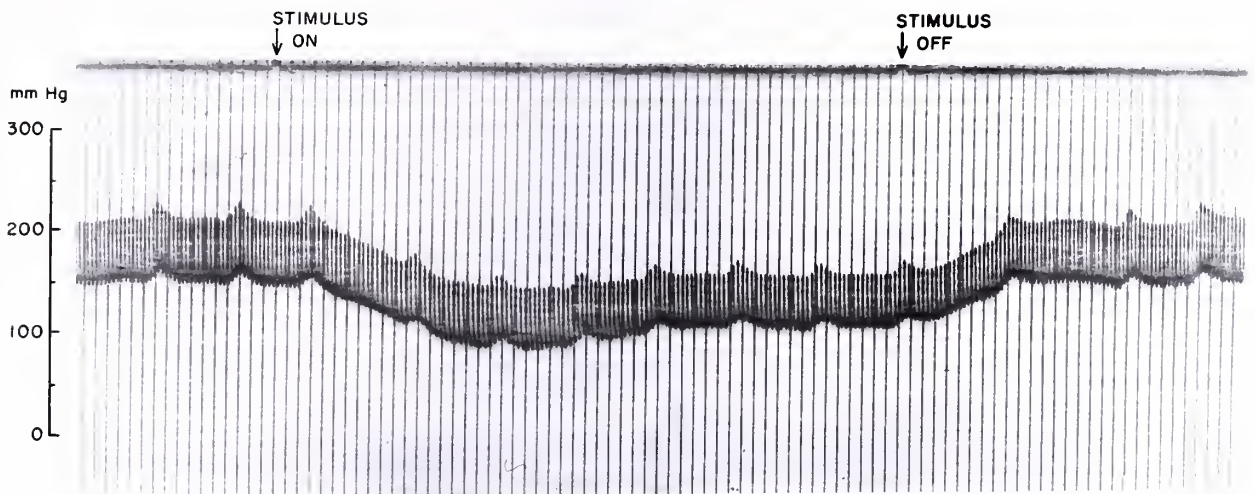


Figure 9. Typical blood pressure and heart rate response. Stimulation of right carotid sinus nerve of normotensive dog with four volts, 80 cps, and 0.5 msec duration. Note the initial transient dip and later stabilization of response. Close examination will reveal a decrease in heart rate during stimulation. (Vertical line = one second)

typical in that it illustrates the transient dip and later stabilization of the blood pressure. The tracing in Figure 10 is less typical but shows a more marked depression of blood pressure. Both tracings are recordings from normotensive animals. It was observed that the response to stimulation differed slightly from animal to

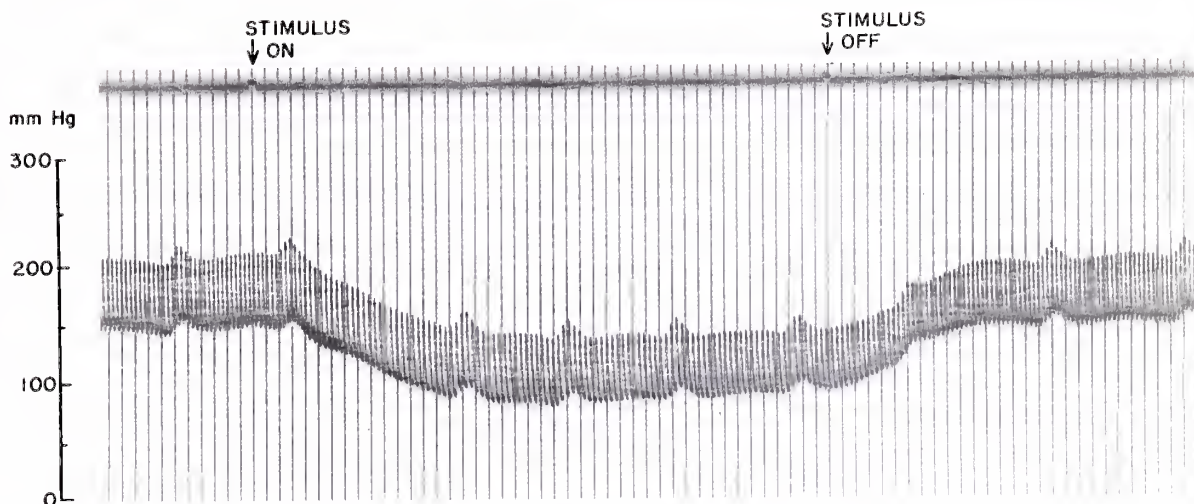


Figure 10. Blood pressure and heart rate response to stimulation of right carotid sinus nerve of normotensive dog with four volts, 80 cps, and 0.5 msec duration. (Vertical line = one second)

animal. Thus, thresholds of response varied from 0.5 to 1.5 volts, while some animals had maximal cardiovascular response at 3.0 to 3.5 volts, rather than at 4.0 volts.

Comparison of the three groups of animals showed the hypertensive animals (both acute and renal) to have significantly greater falls in systolic and diastolic blood pressure and in heart rate (see Figure 11). Though the difference in blood pressure response

III COMPARISON OF GROUPS

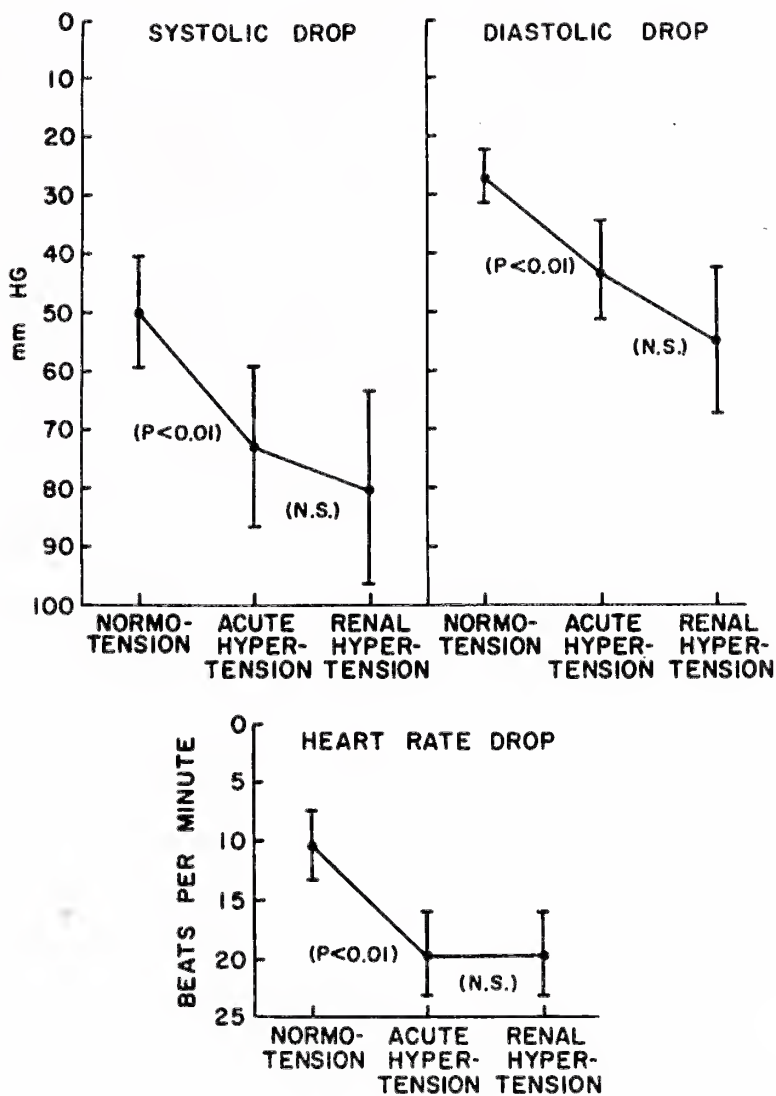


Figure 11. Comparison of groups. All single nerve stimulations with four volts, 80 cps, and 0.5 msec duration. (Vertical line = mean \pm 2 SD)

from stimulation of the right carotid sinus nerve as compared to the left, or from stimulation of both nerves simultaneously, was not

significant (see Figure 12), a suggestion of greater response from the right-sided stimulation provided the basis for the selection

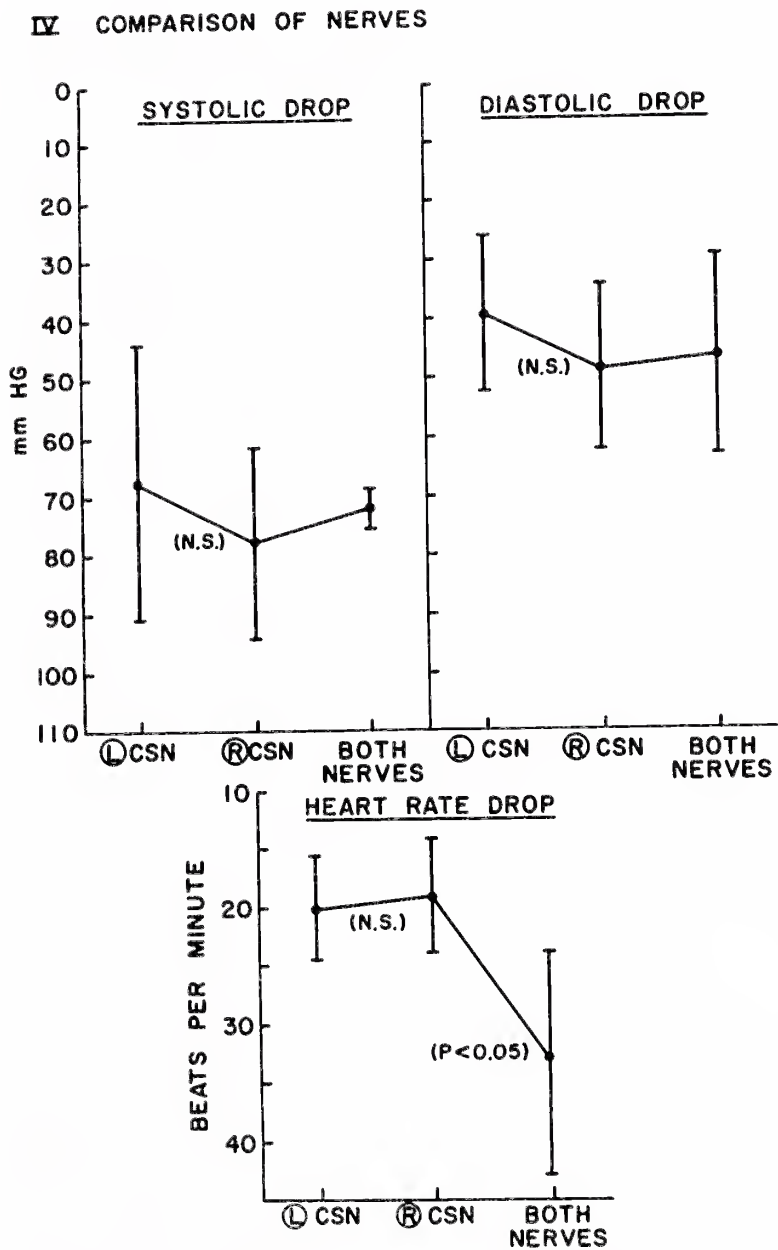


Figure 12. Comparison of nerves. Stimulation in acutely hypertensive animals with four volts, 80 cps, and 0.5 msec duration. (Vertical line = mean \pm 2 SD)

of the right carotid sinus nerve in the animals to be subjected to long-term stimulation. The fall in the heart rate was greatest when both nerves were stimulated simultaneously (Figure 12).

In studying the effect on cardiac output of carotid sinus nerve stimulation, three consecutive output determinations were made, two under normal conditions and one during stimulation of a single nerve. Normal deviations were then compared to deviations during stimulation. In most cases, a significant fall in cardiac output during carotid sinus nerve stimulation was shown (see Figure 13). Although some of the individual studies were only marginally significant, it is important to note that the cardiac output fell in 35 out of 36 separate determinations. Along with this fall in cardiac output, there was a significant fall in total peripheral resistance (see Figure 14).

The two dogs with renal hypertension having direct-wire stimulators survived for two days and one week, respectively, with functioning units producing significant hypotensive responses. Complications requiring sacrifice of these animals were mainly those of extensive wound infection. Long-term stimulation was attempted only in the dog with the radio-frequency unit. The unit remained functioning for over five weeks, eliciting a significant hypotensive response. In the sixth week, when a response was no longer obtained, roentgenographic examination revealed a broken electrode wire. An attempt at inserting a new electrode at re-operation failed, although the carotid sinus nerve was still completely functional.

V CARDIAC OUTPUT

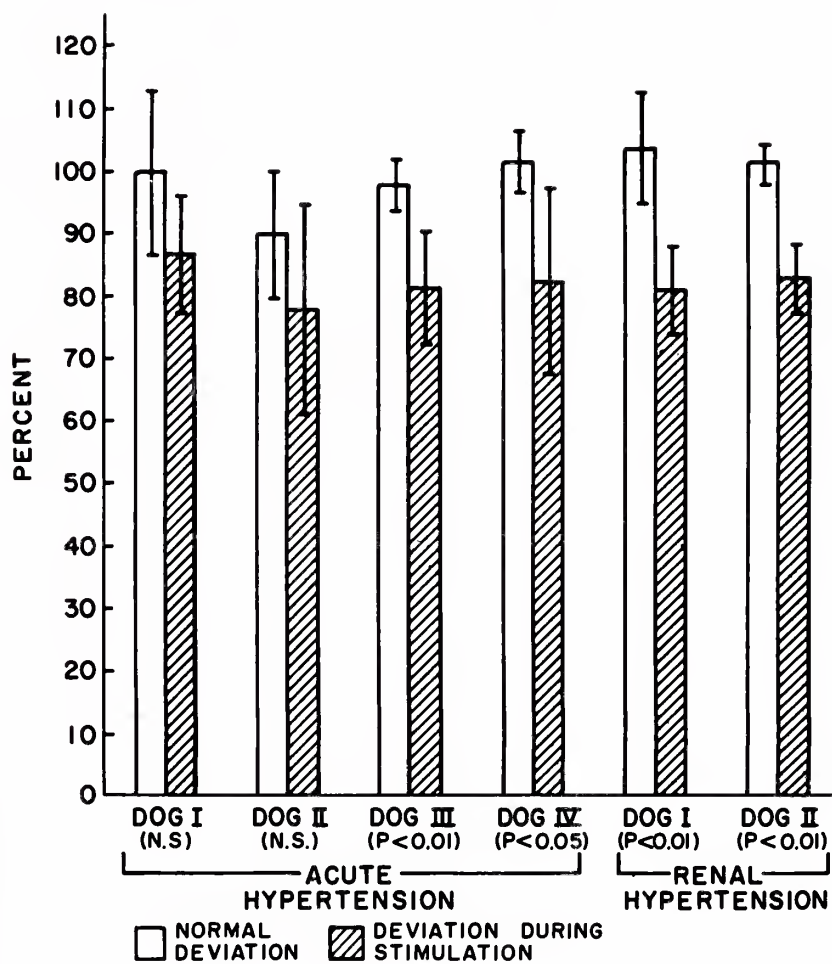


Figure 13. Determinations of cardiac output. All single nerve stimulations with four volts, 80 cps, and 0.5 msec duration. Similar results were obtained in a group of normotensive dogs. (Vertical line = mean \pm 2 SD)

VI TOTAL PERIPHERAL RESISTANCE

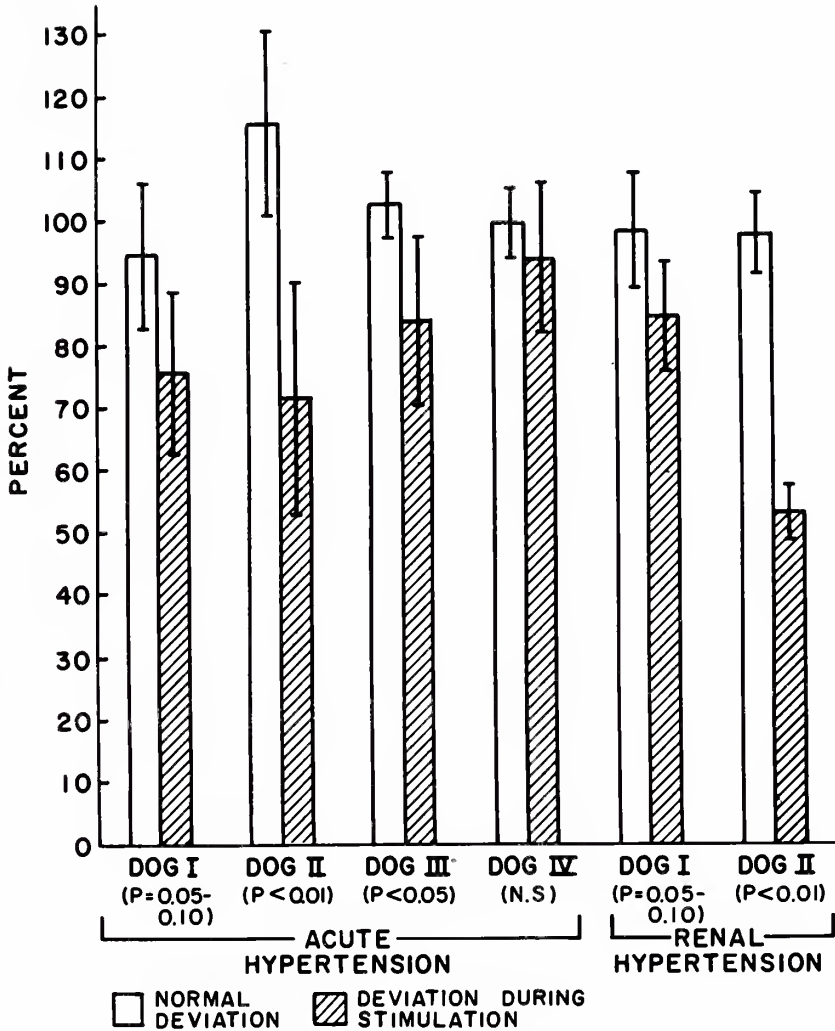


Figure 14. Determinations of total peripheral resistance. All single nerve stimulations with four volts, 80 cps, and 0.5 msec duration. Similar results were obtained in a group of normotensive dogs. (Vertical line = mean \pm 2 SD)

DISCUSSION

It is clear from these experiments that those animals with a higher blood pressure initially (hypertensives) have a greater fall in blood pressure during carotid sinus nerve stimulation. The blood pressure is reduced not just to a normotensive level, but still further, to a "maximum response" level. This explains the significant difference between the blood pressure fall of the normotensive animals and that of the hypertensive animals -- the "maximum response" level is reached in both, but the hypertensive animals have started at a higher level. Any alteration of the blood pressure upwards (renal hypertension, acute hypertension, carotid sinus nerve section) produces such a situation in the experimental animal.

Carotid sinus nerve section is a special condition and may be considered in conjunction with the examination of the initial transient dip in blood pressure during carotid sinus nerve stimulation before later stabilization of the response (Figure 9). Stimulation of one carotid sinus nerve (with all baroreceptors intact) causes a fall in blood pressure with a concomitant decrease in impulses from all other pressoreceptors because of the low blood pressure. This in turn causes a slight increase in arteriolar and venomotor tone with a slight increase in blood pressure and stabilization. Thus, if one major baroreceptor organ is eliminated (as in single carotid sinus nerve section), not only is the initial blood pressure higher, but much of the mechanism for the recovery or stabilization phase is lost, which contributes to the decrease in blood pressure

under these conditions.

It has been mentioned that stimulation of only one carotid sinus nerve was preferable in order to prevent damaging both nerves with bilateral electrodes, which could produce even worse hypertension.⁴ As this study shows, stimulation of a single nerve is able to reverse the hypertension and is technically easier. Furthermore, bilateral stimulation causes a marked bradycardia. The reason for this is obscure, but could be explained if this part of the reflex is controlled exclusively by the carotid sinus baroreceptors with no influence exerted by the other pressoreceptors (unlike the peripheral part of the reflex). Consequently, during stimulation of a single nerve, both the blood pressure and heart rate undergo recovery to some extent, while in bilateral stimulation, only the blood pressure recovers slightly, with the heart rate remaining significantly depressed. As regards the latter, when one carotid sinus nerve was stimulated, a fall in heart rate occurred before a fall in blood pressure, and this part of the reflex was more variable from animal to animal, the stimulation sometimes producing asystole, sometimes a gradual drop in the heart rate.

Because of the decrease in both the total peripheral resistance and the cardiac output that results from carotid sinus nerve stimulation, the effectiveness and advisability of this method as a means of reversing hypertension can be seriously questioned. This appears to be especially true in regard to renal hypertension. Although a fall in blood pressure would result, there might also be changes in

renal blood flow and a compromise of renal function. These would certainly be undesirable consequences, especially if renal disease and renal hypertension were already present. In essential hypertension, where the renal blood flow is decreased by excessive vasoconstriction, stimulation of the carotid sinus nerve would probably be most helpful, but in the presence of ischemic renal disease the possibility of aggravating the ischemia is of real concern. Finally, if salt retention and anti-diuresis occur during stimulation (the reverse of the observed saluresis and diuresis following bilateral common carotid artery occlusion), the use of diuretics would be indicated in conjunction with carotid sinus nerve stimulation in the treatment of hypertension. Further studies on renal blood flow, renal function, and pressure-flow relationships during carotid sinus nerve stimulation should answer these questions.

Clinical application of carotid sinus nerve stimulation, in the light of the present observations and questions raised, should only be attempted under the most carefully controlled conditions: (1) single nerve stimulation should be employed, using the right carotid sinus nerve; (2) stimulation should be attempted only in patients who have proven essential hypertension, with no renal involvement; (3) the use of diuretics should be employed in conjunction with carotid sinus nerve stimulation, with more specific anti-hypertensive agents held in reserve; and (4) the stimulating unit employed should be a radio-frequency induction unit, because this type allows the "maximum response" level to be approached gradually through adjust-

ment made during and after implantation, and, because of the external location of the controls, permits easy adjustment in the event of a change in the threshold to stimulation.

A crucial question in the therapeutic application of carotid sinus nerve stimulation in any form of hypertension is whether or not the observed adaptation, or resetting, of the pressoreceptors will remain, even during the induced hypotension. If so, and if the pathogenetic process of the hypertension continues, it is conceivable that the blood pressure would then gradually rise to the previous hypertensive level. The potential danger in such a circumstance is obvious. If stimulation were to be suddenly discontinued, the blood pressure could then rise even further, rapidly, and with fatal consequences. The answer to this question will come with clinical trials, and only then will the efficacy of carotid sinus nerve stimulation in the treatment of hypertension be known for certain.

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SUMMARY

Carotid sinus nerve stimulation, through direct wires from an attached power source or by radio-frequency induction, was studied in dogs which were normotensive, dogs with acute hypertension from bilateral carotid artery ligation, and dogs with chronic hypertension from created stenosis of the renal arteries. The blood pressure and heart rate were reduced to a greater extent in the hypertensive animals as compared to those who were normotensive. There was no significant difference between the response of the blood pressure to stimulation applied to each nerve singly or to both nerves simultaneously, but there was a suggestion that the response to right nerve stimulation was greater. The heart rate dropped considerably more when both nerves were stimulated simultaneously.

The cardiac output and total peripheral resistance also fell significantly during carotid sinus nerve stimulation in all three groups of animals. As renal blood flow is probably diminished during carotid sinus nerve stimulation, great caution must be exercised in using this method of reducing blood pressure in patients with renal disease.

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