Effect of Interaction of the Hypothalamus and the Carotid Sinus Mechanoreceptor System on Renal Hemodynamics in the Anesthetized Dog

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ABSTRACT

The purpose of this investigation was to show how the operating characteristics of the reflex having carotid sinus pressure as an input and renal pressure and flow as an output are modified by graded stimulation of the posterior hypothalamus. Consequently, the effects of graded stimulation of the posterior hypothalamus on renal hemodynamics were investigated in the anesthetized dog. The carotid sinuses were isolated and subjected to controlled pulsatile pressures. In general, discrete stimulation of the hypothalamus caused a frequency-dependent increase in renal impedance, and stimulation of the carotid sinus caused a decrease. Concomitant stimulation of the hypothalamus and the carotid sinuses had a significant, nonalgebraic effect on the d-c impedance (renal resistance) but no effect on renal impedance at high frequencies. Hypothalamic stimulation modified the sensitivity of renal resistance to carotid sinus pressure. This reflex sensitivity to hypothalamic stimulation passed through a single maximum. The estimated characteristic renal impedance varied inversely with carotid sinus pressure due to active vasomotor changes in renal vascular mechanical properties, rather than to passive effects of concomitant blood pressure changes.

KEY WORDS
carotid sinus reflex reflex operating levels
reflex sensitivity open-loop analysis characteristic impedance
renal artery elastic modulus renal artery impedance
from increases in peripheral vascular resistance and cardiac output (4).

Stimulation of the carotid sinus mechanoreceptors results in decreased sympathetic nerve activity to the heart and peripheral vascular beds such as the splanchnic, mesenteric, and renal. This usually causes peripheral vasodilatation and bradycardia and leads to a reduction in peripheral resistance and systemic blood pressure (5). These changes occur after inhibition of the vasomotor center by the carotid sinus mechanoreceptor inputs to the medulla. Djojosugito et al. (6) found that this reduction of sympathetic nerve activity to the heart is suppressed during posterior hypothalamic stimulation. However, they also found that cardiovascular mechanoreceptor influence on discharge in peripheral vasoconstrictor fibers was essentially unchanged by stimulation of the posterior hypothalamus. On the
other hand, Gebber and Snyder (7) found that carotid occlusion enhanced the pressor response evoked by hypothalamic stimulation, whereas carotid sinus nerve stimulation inhibited it.

The sympathetic vasmotor innervation to a blood vessel is one of the principal inputs determining cross-sectional area and, therefore, blood flow. Thus it is of paramount importance to an organism if the posterior hypothalamus can modify the operating characteristics of the carotid sinus reflex and thereby influence the control of peripheral blood flow by changing postganglionic sympathetic nerve activity. Hence, the purpose of this work was to clarify this important aspect of circulatory physiology. To determine the characteristics of the carotid sinus-hypothalamic-cardiovascular interactions, the effect of graded stimulation of the posterior hypothalamus on the operating characteristics of the carotid sinus reflex was studied in the dog. Carotid sinus pressure was used as the input and renal pressure and flow as output of the reflex.

The renal vascular bed was chosen as the end organ for the study of the carotid sinus reflex because of the importance of the kidney in control of systemic blood pressure by control of renin release (8) and regulation of body fluids (9). Furthermore, the general pattern of resistance changes secondary to mesencephalic pressor area stimulation is similar for the kidney, intestine, lower extremities, and overall systemic resistance (10). In most of the above-mentioned studies concerning hypothalamus-carotid sinus interaction, the hemodynamic consequence of any such interaction was usually ignored or considered to be a steady-state relationship. However, pressure and flow are oscillatory phenomena, and an accepted, meaningful way of expressing the pressure-flow relationships of a vascular bed uses the input-impedance concept (11), which involves the instantaneous, simultaneous measurement of blood pressure and flow at the input to a vascular bed or blood-vessel system. The input impedance is a measure of the opposition to total blood flow, both pulsatile and nonpulsatile; it also provides information about the physical characteristics of the blood vessels involved. Impedance is a frequency-dependent variable having an amplitude and a phase; the impedance amplitude at zero frequency is the commonly used frequency-independent resistance to d-c blood flow. Consequently, to describe the changes in renal hemodynamics as completely as possible, the renal input impedance was measured as the effector limb of the carotid sinus reflex.

Methods

Thirteen experiments were done on mongrel dogs of both sexes; of these, seven were considered technically satisfactory and were subsequently analyzed. The animals had an average weight of 22.6 ± 0.9 kg and were premedicated with morphine sulfate (2 mg/kg, im) and anesthetized with alpha chloralose (100 mg/kg, iv).

MECHANORECEPTOR ACTIVATION

The isolated carotid sinuses were perfused at 37°C with an oxygenated physiological salt solution of the following composition in mm: NaH₂PO₄ 1.2, MgSO₄·7H₂O 1.2, CaCl₂ 2.5, NaHCO₃ 22.5, NaCl 121.3, K₂SO₄ 2.25, glucose 5.6. Figure 1 is a plan of the perfusion system. After saturation with 95% O₂-5% CO₂, the perfusion solution was drawn into two 200-ml syringes of a Harvard pump, model 2202; the pump provided the perfusion pressure. The solution was then passed through a plexiglass chamber with a flexible diaphragm in one wall into a heat exchanger, and finally, through subcutaneous tubing in the ventral chest wall of the dog (to compensate for post-heat-exchanger losses), into the common carotid arteries caudal to the superior thyroid arteries. The carotid sinuses were isolated...
by ligating all branches except the external carotid arteries, which were cannulated.

Mean carotid sinus pressure was controlled by varying the resistance of the drainage tubes from the right and left external carotid arteries and the rate of infusion from the Harvard pump. After the perfusion solution passed through the drainage tubes, it was discarded. Ligation of the common carotid arteries reduced cerebral blood flow. However, vertebral artery blood flow to the brainstem was intact. Furthermore, the fall in cerebral blood flow tended to increase the blood flow through the Circle of Willis to the forebrain.

The fluid in the jacket of the heat exchanger was circulated by a Haake circulator pump, and the isolated carotid sinus pressure was monitored through a catheter in the right or left superior thyroid artery.

While the carotid sinuses were being isolated, the left kidney was exposed retroperitoneally through a left flank incision. A Statham type P23Db strain-gauge manometers. The renal catheter was standardized using polyethylene tubing, 1.15 mm i.d. and 20 cm long. The other catheters were not standardized. The amplitude and phase characteristics of the catheter-manometer system were obtained from step-function responses by Hansen’s technique (13) and the method of Fry (14). The amplitude response was flat within 5% up to 20 Hz, with a phase shift of less than 2° at this frequency. No corrections were applied to the pressure data. At the end of each experiment, static calibration of each catheter-manometer system was carried out with a precision barometer (Hass Instrument Co.).

FLOW MEASUREMENTS

Volume-flow rates were measured with a gated sine wave electromagnetic flowmeter (Statham, model M4001). All blood-flow data were corrected for phase and amplitude distortion introduced by the flowmeter as has been described previously (15). Zero flow signals were obtained by mechanically occluding the renal artery proximal to the flow probe. At the termination of each experiment, the renal flow probe was calibrated in situ. The renal artery was cannulated distal to the flow probe with polyethylene tubing; the outflow end of the tubing was elevated to maintain contact between the artery and the flow probe. By varying the cross-sectional area of the outflow tube mechanically, several timed volumes were collected and flow rates determined.

HYPOTHALAMIC STIMULATION

Stimuli were applied to the pressor areas in the posterior portions of the hypothalamus, including the nucleus hypothalamicus dorsomedialis, nucleus hypothalamicus ventromedialis, and hypothalamus posterior. These areas were stimulated stereotaxically, according to the coordinates from the atlas of the dog’s brain by Lim, Liu, and Moffit (16), 20 mm rostral on the anteroposterior axis, 6–10 mm from the zero point of the dorsoventral axis, and 1–2 mm to either side of the medial line of the right-left axis.

The posterior hypothalamus was stimulated with a square-wave pulse generator (Tektronix), the output of which was passed through an isolation unit (Grass) to a unipolar stainless steel needle electrode having a diameter of 1.0 mm and insulated with Epoxylite except for 0.5 mm at the tip. An indifferent electrode was placed on the skull. Stimulation parameters were 1–5 v, 100 Hz, and 1 msec, for a duration of 15 seconds.

To avoid the cardiovascular effects secondary to centrally induced respiratory changes or muscular activity, the animals were curarized with gallamine triethiodide (3 mg/kg, Flaxedil). At the same time, a supplemental dose of alpha chloralose was given (25 mg/kg, iv); the animals were then artificially respired. After a delay of approximately 30 minutes to allow the transient effects of the drugs to dissipate, and with the carotid sinus reflex functioning at its closed-loop
operating point, i.e., with the carotid sinus pressure held equal to renal blood pressure, the hypothalamus was stimulated at 1 v. If no recognizable pressor response was obtained, the stimulation intensity was then increased in increments of 1 v until a recognizable pressor response was obtained; all other stimulation parameters remained constant throughout the experiment.

To attempt some standardization of individual sensitivity to hypothalamic stimulation, the minimum stimulation intensity evoking a pressor response at the closed-loop carotid sinus operating point was designated 1 v. The mean carotid sinus pressure was then raised to approximately 275 mm Hg, and the stroke of the sinusoidal pump adjusted to give a carotid sinus pulse pressure of approximately 50 mm Hg. When the renal pressure and flow reached a steady state, the hypothalamus was stimulated at 1 v. Following complete recovery from the pressor response, the posterior hypothalamic stimulation was repeated in increments of 1 v for a total of four intensity levels at each of six carotid sinus pressures decreasing from approximately 275 mm Hg in decrements of 50 mm Hg.

All transducer outputs, together with the output from the pulse generator, were fed into a multichannel analog tape recorder (Sangamo) and also displayed on an eight-channel oscillograph (Brush).

DATA ANALYSIS

Renal pressure and flow values were chosen for analysis in all control states and after hypothalamic stimulation at the point of the maximum pressor response. The procedure and criteria for tape edition and analog-to-digital conversion have been described (15).

The resulting digital tape was then used as an input to a digital computer program (IBM 360-75) which defined a cardiac cycle between points of end diastole, calibrated the resulting points, and performed a Fourier analysis on calibrated data. For each site chosen for analysis, five consecutive cardiac cycles were analyzed where possible. The renovascular input impedance, an expression of the opposition to the total blood flow at the input to the renal bed, was then calculated from the Fourier analysis of the renal pressure and flow curves (11).

For all the experiments analyzed, the control values of heart rate, renal pressure, flow, and impedance for each stimulation-intensity level were averaged for each of the six carotid sinus pressure levels. Peak response parameters at each level of equivalent stimulation intensity were then averaged for all experiments. Thus any control point is the average of about 140 cardiac cycles, and each response point is the average of approximately 35 cardiac cycles. Mean carotid sinus pressures were calculated directly from the analog record.

STATISTICAL METHODS

The data in the text and in the figures are expressed as the mean ± 1 SE, except where the error is very small or would cause confusion graphically. To evaluate the significance of the data, a factorial analysis and an analysis of variance were conducted according to standard procedures (17). A factorial experimental design provides information about the main effects of the factors considered and about their interactions. A two-factor, 6 by 5 factorial analysis was employed; the two factors were carotid sinus pressure and intensity of hypothalamic stimulation. The former was considered at six levels of pressures, the latter at five levels of intensity (10–14). Four, two-factor, 2 by 6 factorial analyses were performed on the original 6 by 5 matrix; each level of hypothalamic stimulation was compared with the control level, 10, at all six carotid sinus pressure levels.

The variables considered were heart rate, renal resistance, and renal impedance for the first four
RESULTS

EFFECTS OF CAROTID SINUS PRESSURE ON RENAL HEMODYNAMICS

Changing the carotid sinus pressure from 11.8 ± 4.1 mm Hg to 275.6 ± 1.4 mm Hg resulted in a decrease in renal resistance from 211.1 ± 30.3 × 10⁸ dyne sec cm⁻⁶ to 50.6 ± 3.9 × 10⁸ dyne sec cm⁻⁶ (curve I₀, Fig. 2). Over this range, renal blood flow increased from 78 ± 5.5 ml/min to 138 ± 4.5 ml/min (curve I₀, Fig. 3), whereas renal artery pressure fell from 157 ± 8 mm Hg to 85 ± 6 mm Hg (curve I₀, Fig. 4). Heart rate was depressed from a maximum of 214 ± 5.5 beats/min at a carotid sinus pressure of 79.1 ± 3.4 mm Hg to a minimum of 194 ± 4.8 beats/min at a carotid sinus pressure of 275.6 ± 1.4 mm Hg (curve I₀, Fig. 5).

For the six levels of carotid sinus pressure, the renal input impedance (11) represented a relatively high fraction of the renal resistance. This fraction varied from 20–50% over the carotid sinus pressure range considered, at harmonics with an acceptable signal to noise ratio and with frequencies within the response range of the system—in most cases, this included the first four or five harmonics. There was a progressive decrease in the magnitude of renal impedance with increasing frequency for all carotid sinus pressures, and, as the latter increased, there was a progressive decrease in magnitude at the harmonics shown in Figure 6. The phase angles also showed a progressive fall with frequency and were negative for all carotid sinus pressures (Fig. 6).

If the renal vascular bed is considered to be analogous to a transmission line, then the characteristic renal impedance is the impedance in the absence of reflected waves. Characteristic impedance is determined by the dimensions and elastic properties of the main renal artery and an undetermined number of relatively large, branching generations beyond it whose dimensions are sufficient to allow pulsatile flow (18, 19). The characteristic impedance modulus was calculated, in most cases, by averaging the observed moduli.
Effects of posterior hypothalamic stimulation on the heart rate for six carotid sinus pressure levels. I₀—I₄ are the same as in Figure 2.

making the isolated carotid sinus pressure equal to the systemic blood pressure.

At this simulated closed-loop operating pressure, the minimal intensity of hypothalamic stimulation required to effect a recognizable pressor response, designated I₁, had an average value of 1.57 ± 0.20 v for seven experiments. All increments of intensity of hypothalamic stimulation were 1 v, therefore I₂ equaled 2.57 ± 0.20 v, I₃ 3.57 ± 0.20 v, and I₄ 4.57 ± 0.20 v. Frequency and duration of stimulation remained constant.

Following the cessation of hypothalamic stimulation, the typical pressor response gradually returned to control levels within a variable period; in the majority of cases, all
parameters had returned to control levels within 5 minutes. The variable prolongation of the pressor effect was attributed to the secondary release of humoral substances, mainly adrenal catecholamines (10). Consequently, evaluation of the responses was limited to the initial pattern during the 15 seconds of hypothalamic stimulation; these changes were regarded as purely neurogenic.

Hypothalamic stimulation resulted in an increase in heart rate and renal resistance as the intensity of stimulation was increased. There was also a progressive increase in the magnitude of renal impedance at the harmonics considered. These changes were not independent of carotid sinus pressure and are shown for hypothalamic stimulation levels I₁, I₂, and I₄ at the first four carotid sinus pressure levels in Figure 7.

Effects of the Interaction of the Carotid Sinus Mechanoreceptor System and the Hypothalamus on Renal Hemodynamics

Peak renal resistance at all hypothalamic stimulation-intensity levels decreased as the carotid sinus pressure increased. The absolute decrease became greater with decreasing intensity of stimulation; at high carotid sinus pressures, for stimulation levels I₁ and I₂, there was complete inhibition of the response (Fig. 2).

Similarly, a stimulation intensity of I₄ volts caused maximum depression of renal blood flow, maximum tachycardia, and increased blood pressure. There was a gradual reduction in these changes with decreasing intensity of stimulation and with increasing carotid sinus pressure (Fig. 3-5).

Figure 8 shows the effect on renal pressure and flow of increasing the intensity of hypothalamic stimulation while keeping the carotid sinus pressure constant. Figure 9 illustrates the effect on renal pressure and flow of decreasing the carotid sinus pressure while keeping the parameters of hypothalamic stimulation constant. The sensitivity of renal resistance to changes in carotid sinus pressure (21), expressed as the change in renal resistance/mm Hg carotid sinus pressure change, is shown in Figure 10 for five levels of intensity of hypothalamic stimulation.

The experimental situation required the examination of the effects of varying two
Effect of increasing the intensity of posterior hypothalamic stimulation from 2-5 \( \text{c} \) at constant frequency on renal pressure and flow. Carotid sinus pressure is kept constant at a mean of approximately 125 mm Hg and the pulse pressure is 50 mm Hg. Mean renal pressure and flow are also shown.

Factors, the intensity of posterior hypothalamic stimulation and the carotid sinus pressure, and each factor was considered at several levels. Either factor alone affected the cardiovascular system, but the two factors together interacted to produce cardiovascular effects which were not an algebraic summation of their individual effects. Therefore, to optimize experimental efficiency, the study was considered as a two-factor, 5 by 6 factorial experiment for seven replicates, combined with an analysis of variance.

The data, as considered in the factorial analysis, are represented diagrammatically in Figure 11 for renal resistance. Consideration of renal resistance at all levels revealed a highly significant interaction of the carotid sinus mechanoreceptor system and the hypothalamus \((P<0.0001)\). The effect of simultaneous stimulation of the carotid sinus mechanoreceptors and the hypothalamus showed that these factors did not significantly interact to affect heart rate. However, each factor alone had a significant effect \((P<0.001)\), and the two factors can be considered independent due to their lack of significant interaction. There was a significant interaction of the factors which affected renal impedance for the first and second harmonics \((P<0.001)\), but not for the third and fourth harmonics.

**Discussion**

Control of the circulation involves a complex system of regulatory feedback loops. The vascular mechanoreceptors of the carotid sinuses are a major input to the circulatory control system. The afferent nerve inputs to the central vasomotor centers from these and other vascular mechanoreceptors are determined by the intravascular blood pressure and by the viscoelastic properties of the receptor-containing vessel walls. This relationship has been extensively discussed by Peterson and co-workers (22-24). In turn, autonomic nervous system outputs controlling the mechanical properties of the blood vessels (vascular tone) are determined by the inputs from the vascular mechanoreceptors and by the interaction or intermodulation of the mechanoreceptor inputs with central inputs within the
Renal hemodynamics, rather than efferent sympathetic nerve activity, were selected as an effector function for studying the interplay of carotid sinus and hypothalamic influences on vascular control for several reasons: (1) It is difficult to estimate whole nerve activity from surface electrodes. (2) Blood flow is functionally more significant to the organism than sympathetic nerve activity. (3) Total peripheral resistance lumps peripheral bed characteristics, but the reaction of a particular bed to a change in sympathetic nerve activity depends on the hydraulic and morphological characteristics of the bed, i.e., the operating characteristics described by the transfer function relating nervous activity to hemodynamic changes. (4) Any central or peripheral differentiation may influence vasoconstrictor activity to functionally different organs (10). (5) If opposing signals such as vasoconstriction and vasodilatation are both contained in the same peripheral nerve, their individual significance as an index of input characteristics to an effector organ would obviously be reduced.

There are two methods of effecting a progressive increase in the cardiovascular pressor response to posterior hypothalamic stimulation at a given site: (1) by varying the frequency of stimulation at optimal intensities, and (2) by varying the intensity of stimulation at optimal frequencies. Each of the present experiments involved hypothalamic stimulation lasting approximately 360 seconds. For this duration of stimulation, the former method caused a significant loss of sensitivity, presumably due to damage to the stimulation site. Therefore, the latter method was used. In view of the possibility that some loss of sensitivity could still arise even with this method, the experiments were conducted so that the carotid sinus pressure was reduced from a high level in six decrements. Therefore, any loss of sensitivity would detract from the results and not complement them as it would if the carotid sinus pressure was increased from a low level.

Earlier studies on renal blood flow in anesthetized dogs suggest that a decrease in
carotid sinus pressure following common carotid occlusion does not initiate a sustained vasoconstriction of neurogenic origin (27–30). More recently, Gilmore (31), using an intact perfused kidney in the dog, concluded that the primary renal response to carotid occlusion was vasoconstriction mediated by the renal sympathetic nerves. Similarly, Balint and Chatel (32) reported a decrease in renal blood flow following bilateral common carotid compression; the cardiac output remained unchanged. They concluded that there had been active vasoconstriction of the renal vessels, because the change in renal resistance was more pronounced than the change in peripheral resistance. The work of Iriuchijima and Wilson (33) confirmed the findings of the latter two studies only when mean arterial blood pressure was held constant, thus presumably eliminating renal autoregulation. The work of Vatner et al. (34) suggested indirectly that renal arterial impedance was an inverse function of carotid sinus stimulation, since stimulation of the carotid sinus nerve in the intact, unanesthetized dog increased the size of the pulsations of renal blood flow, whereas the pulsations of aortic pressure changed very little.

The above studies were carried out on dogs with the vagi intact. In the present study the vagi were cut. This should potentiate the level of renal sympathetic nerve activity for a given carotid sinus pressure because it eliminates vasomotor center inhibition by the aortic arch mechanoreceptors. This deduction is consistent with the observed increase in renal flow with increasing carotid sinus pressure. It must be remembered that the responses observed are a function of the operating characteristics of the renal bed and its control loops. Direct comparison of data from independent studies has little meaning unless the state of the control loops is identical.
Recent work on the cat (6) suggests that hypothalamic defense-area stimulation suppresses carotid sinus mechanoreceptor inhibition of the heart but has little effect on the ability of the carotid sinuses to influence sympathetic vasoconstrictor nerve activity. Kylstra and Lisander (4) concluded that the above differentiated interaction resulted in a synergistic effect with respect to efficient cardiovascular performance in states of emergency, since the reflex inhibition of regional vasoconstrictor tone would enhance the ultimate aim of the cardiovascular system—the establishment of nutritional flow to the tissues. This effect would be potentiated by the increased cardiac neurogenic drive, causing an increased cardiac output.

These findings are consistent with those of Gebber and Snyder (7) who demonstrated a suprabulbar system in the cat which inhibits the vagal inhibition induced by cardiovascular mechanoreceptor activation. During the hypothalamic stimulation, cardiovascular mechano-receptor modulation of central sympathetic outflow remained functionally intact. They also showed that norepinephrine reduces hypothalamus-induced sympathetic activity in the preganglionic splanchnic nerve, inferior cardiac branch of the stellate ganglion, and the external carotid branch of the superior cervical ganglion. These responses were enhanced by bilateral carotid occlusion or cardiovascular mechanoreceptor denervation; the latter lowered the threshold voltage of hypothalamic stimulation required to evoke a pressor response.

The study reported here demonstrates the effect of interaction between the posterior hypothalamus and the carotid sinus reflex on renal hemodynamics in the dog. The modulation of the carotid sinus reflex by the posterior hypothalamus was not linear and uniform, and it depended on the respective level of stimulation of the two sites. These results are consistent with a synaptic break in the descending hypothalamic pathways at which the cardiovascular mechanoreceptor afferents exert an inhibitory action. On the basis of these results, however, there is insufficient information to prove where in the central nervous system such an inhibition might take place.

Tuttle and McCleary (35) were able to inhibit the hypothalamic defense reaction by direct medullary stimulation, but they failed to elicit a defense response from the latter site, reducing the likelihood of any antidromic inhibition of hypothalamic efferents by the carotid sinuses. Trzebski et al. (36) considered the modulation of the electrical activity of medullary units secondary to the variation of carotid sinus pressure. They found that only a relatively small fraction (9%) of the total single medullary units tested exhibited direct alterations in electrical activity obviously associated with contralateral, ipsilateral, or bilateral carotid sinus receptor variation. Peiss is of the opinion that some fibers originating in the hypothalamus might bypass the medulla oblongata and descend directly to the lateral horn cells of the spinal cord (37). However, the likelihood of inhibition at the level of the lateral horn cells or ganglia is small, since there is little evidence for depressor fibers in the spinal cord (38).

In the present study, the renal resistance was expressed as a function of carotid sinus pressure for each intensity of hypothalamic stimulation and showed a maximum at a stimulation intensity of 12 (Fig. 10). Thus, there appeared to be an intensity of hypothalamic stimulation for a given frequency which optimized the sensitivity of renal resistance to carotid sinus mechanoreceptor stimulation. It is interesting that the optimum intensity of hypothalamic stimulation (I2) is in the same range as that found by Iizuka to be potentiated by subpressor doses of angiotensin infused into the vertebral circulation of the dog (39).

This optimal change of renal resistance following hypothalamic stimulation occurred at a carotid sinus pressure of approximately 170 mm Hg. Similarly, the renal impedance spectra seen at different carotid sinus pressures (Fig. 6) appeared to be distributed around a zone of maximum sensitivity at physiological pressures.
The significant effect of the interaction of the hypothalamus and the carotid sinuses on renal resistance is extended to the renal impedance at low frequencies but not at high frequencies (above the second harmonic). This result would be consistent with an interaction affecting the small renal vessels but not the larger renal vessels with diameters larger than those of arterioles. The absence of a significant effect on heart rate in the vagotomized dogs tends to confirm that the maintenance of tachycardia during hypothalamic stimulation is produced by inhibition of cardiovascular mechanoreceptor-induced vagal bradycardia (7).

For all carotid sinus pressures, the values of the renal input impedance represent a considerable fraction of the d-c impedance (20-50%). With the exception of the mesenteric artery, this is a larger fraction than is found in other vascular beds considered by Attinger (40). The change of renal impedance, in particular the characteristic impedance, as a function of carotid sinus pressure can reflexly influence the mechanical properties of the renal vasculature.

The modulation of postganglionic sympathetic nerve activity to the heart and peripheral vascular beds by the carotid sinus outputs is not in doubt (5). However, this modulation will produce changes in peripheral resistance and, therefore, systemic blood pressure. The question, therefore, arises as to whether the changes in renal characteristic impedance induced by carotid sinus pressure changes are due to active changes in the renal vasculature or to passive changes induced by an alteration in distending pressure secondary to a change in peripheral resistance or heart rate or both.

If the changes are vasomotor in origin, then they should be abolished by renal denervation, either anatomical or pharmacological. Relative to its size, the kidney in the dog receives profuse and widespread nerve inputs from T4 through L2 via the celiac plexus, the thoracic splanchnic nerves, and the intermesenteric nerves. Filaments from these nerves do not cluster intimately around the renal artery but approach the branches of this vessel in the kidney hilum. Consequently, true anatomical denervation, apart from total nephrectomy, was not considered feasible (41). The localized introduction of an α-receptor blocking drug to a nonisolated viscus is difficult to control, particularly for the length of time required to carry out carotid sinus pressure variation over the whole range considered in this experiment.

Instead, the theoretical increase of renal characteristic impedance for a given increase in intravascular pressure alone was determined.

**SYMBOLS**

- \( Z_0 \) = Characteristic fluid impedance
- \( C_0 \) = Fluid phase velocity
- \( Z_f \) = Hydraulic fluid impedance
- \( \nu \) = Kinematic viscosity
- \( \gamma \) = Propagation constant
- \( E \) = Incremental elastic modulus
- \( \omega \) = Angular frequency
- \( \rho \) = Fluid density
- \( \alpha \) = Inner arterial radius
- \( \beta \) = Outer arterial radius
- \( \rho \) = Fluid viscosity
- \( T \) = Tangential tension
- \( P \) = Intravascular pressure
- \( j \) = \( \sqrt{-1} \)
- \( \omega \) = Angular frequency
- \( \alpha \) = Inner arterial radius
- \( \beta \) = Outer arterial radius

Hydraulic fluid impedance is related to characteristic impedance (42) by the equation

\[
Z_f = \frac{Z_0}{\gamma}
\]

The expression of Witzig (43) for fluid impedance is

\[
Z_f = \frac{j \omega \rho}{\pi \alpha^2 (1 - F_{10})},
\]

and the expression of Iberall (44) for the propagation constant is

\[
\gamma = \frac{j \omega}{C_0 (1 - F_{10})^2}.
\]

Then,

\[
Z_0 = \frac{j \omega \rho C_0 (1 - F_{10})}{\pi \alpha^2 (1 - F_{10})^2}.
\]

Lamb (45) derived an expression for the wave velocity in a fluid-filled elastic tube.
Theoretical characteristic impedance values based on the elastic properties and geometry of six canine renal arteries, expressed as a function of renal pressure. For each dog the impedance values are expressed as a ratio of the values at the initial renal pressure; the latter are in the range of 72 to 91 mm Hg. The quantity (1 - F₁₀) is given by

\( \frac{1}{F₁₀} = 1 - \frac{2I₁(z)}{Z₀(z)}, \)

where the nondimensional fluid parameter

\[ z = j \omega \rho / \nu, \]

At high frequencies \( F₁₀ \) was found to contribute less than 5% to the characteristic impedance of vessels of comparable mechanical properties (R. H. Cox, personal communication) and was neglected giving

\[ Z₀ = \left[ \frac{\rho}{\pi a^3} \times \frac{E(b^2 - a^2)}{3b^2 + a^2} \right], \]

The incremental tangential elastic modulus of the canine renal artery, in terms of its geometry, was derived for six vessels using the apparatus of Attinger (46) (R. J. Bagshaw and F. M. Attinger, unpublished observations). For each value of elastic modulus, the tangential tension developed in each renal artery was known, and the theoretical pressure inducing this tension at the inner aspect of the renal arterial wall was calculated using the relationship of Timoshenko (47), assuming zero pressure outside the vessel,

\[ T = \left[ \frac{a^2 P}{(b^2 - a^2)} \right] \times \left[ 1 + b^2 \right]. \]

Values for incremental renal elastic moduli, renal artery geometry, and theoretical characteristic impedance were calculated for renal pressures commencing in the range of 72 to 91 mm Hg for the six arteries. Impedance values at higher pressures were expressed as ratios of these initial values and then as a function of intrarenal pressure by a first order relationship (Fig. 12). This gave a theoretical characteristic renal impedance of 8.7 (±0.9) \( \times 10³ \) dyne sec cm⁻² at an initial pressure of 83 ± 6 mm Hg which increased by 10.9% as the pressure increased to 155 mm Hg. This compares with the experimental characteristic renal impedance of 12.7 (±1.1) \( \times 10³ \) dyne sec cm⁻² at a renal pressure of 85 ± 12 mm Hg which increased by 123% as the renal pressure increased an equivalent amount.

We, therefore, concluded that (1) in vivo, there is considerable renal artery tone, giving a high characteristic renal impedance, and (2) the changes in characteristic renal impedance resulting from changes in carotid sinus pressure are mainly due to active changes in arterial wall properties, presumably of neural origin. All values of characteristic impedance, both measured and theoretical, are consistent with the high ratios of renal collagen to elastin found by Fischer and Llaurado (48).

To the extent that the in vitro data for the renal artery mechanical properties are valid, it would appear that the renal impedance changes are relatively independent of the passive effects of changes in the blood pressure. This adds a corollary to the concept of the uncoupling of the heart from the periphery, since the mechanical properties of the renal artery, in addition to the transmission properties of the aorta, to the point of
origin of the renal artery, tend to isolate the heart from the periphery (49).

It is not certain that the cardiovascular pressor response to hypothalamic stimulation represents a physiological response; it does, however, closely simulate the response observed during muscular exercise (50). It should be mentioned that several investigators have concluded that there is little involvement of suprabulbar mechanisms in the cardiovascular mechanoreceptor reflexes. Their conclusions are based on the lack of significant change in the resting arterial blood pressure after decerebration and the reflexly evoked blood pressure and heart rate changes following mechanoreceptor stimulation (51). However, the above findings are neither necessary nor sufficient to prove the lack of interaction of suprabulbar mechanisms and the mechanoreceptor system; also, contradictory evidence about the involvement of suprabulbar mechanisms has been found in decerebrate animals in other studies (52).

If the response to posterior hypothalamic stimulation approximates a physiological response, then the animal has the ability to parametrically vary the operating characteristics of the cardiovascular reflex with carotid sinus pressure as an input and activity of sympathetic nerves to the kidney as an output.

For example, if we postulate an initial level of hypothalamic sympathetic outflow to the peripheral vasculature in response to a stressful situation, then the carotid sinus reflex closed-loop operating point will be shifted to a higher pressure. At this new operating point, the carotid sinus pressure will inhibit the activity of sympathetic nerves to the kidney to a degree dependent on the sensitivity of the reflex at the new operating level, thus tending to maintain renal flow.

There is considerable evidence that renin release, and hence angiotensin formation, in man and dog depends on the level of sympathetic activity to the renal bed (53-55), as well as on a drop in the input pressure to the kidney (56). The effects of changes in the level of activity of sympathetic nerves to the kidney could be indirect in that an increased sympathetic input may reduce glomerular pressures. If, in spite of the interaction of the hypothalamus and the carotid sinus mechanoreceptor system at the postulated higher level, the activity of sympathetic nerves to the kidney rose sufficiently to initiate the release of renin, then angiotensin would subsequently be formed in the circulation from the renin substrate.

Iizuka has shown that a subpressor amount of angiotensin will potentiate the cardiovascular effects of posterior hypothalamic stimulation at low intensities; at the same time, it has no effect on the cardiovascular changes induced by medullary stimulation, carotid occlusion, or supramedullary stimulation at high intensities (39).

Thus, the angiotensin formed, as postulated above, could potentiate the existing hypothalamic sympathetic output; this would again raise the carotid sinus reflex closed-loop operating point and result in an increased reflex sensitivity at the higher operating level, thus tending to reduce the activity of sympathetic nerves to the kidney to a level below that causing the release of renin. Eventually, the system would become optimized at some hypothalamic sympathetic output level analogous to $I_o$ in Figure 10 in the sense that there would be optimum inhibition of activity of sympathetic nerves to the kidney and maximal renal flow for the degree of compensation by the animal.

Concomitant with these peripheral changes, the intense neurogenic drive to the heart would be relatively unopposed by the carotid sinuses and would result in a greater cardiac output (6). Any further increase in hypothalamic activity would shift the carotid sinus operating characteristics to a level at which the ability to inhibit activity of sympathetic nerves to the kidney, and hence to maintain renal flow, was greatly diminished.

In conclusion, modulation of the carotid sinus reflex by posterior hypothalamic stimulation, independent of vagally mediated heart rate changes, has been demonstrated with respect to renal hemodynamics. The renal
artery input impedance represented a significant fraction of the d-c impedance for all levels of stimulation of the carotid sinus mechanoreceptors and the posterior hypothalamus.

In general, an increase in the level of stimulation to the hypothalamus or a decrease to the carotid sinus mechanoreceptors resulted in an increase in renal impedance at all frequencies observed. Simultaneous stimulation of the hypothalamus and carotid sinus mechanoreceptors affects the renal resistance but not the high-frequency renal impedance. Thus, hypothalamic stimulation modified the carotid sinus reflex by shifting the reflex operating pressure and the renal resistance at that pressure. A level of hypothalamic stimulation was found which resulted in a maximum sensitivity of renal resistance to carotid sinus pressure.

There was a significant inverse relationship between carotid sinus pressure and the characteristic renal vascular impedance; it was concluded that the mechanical properties of the relatively large, as well as the small, renal arteries are modified by the carotid sinus reflex. Furthermore, the above relationship appeared to be independent of the passive effects of concomitant pressures changes.

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Effect of Interaction of the Hypothalamus and the Carotid Sinus Mechanoreceptor System on Renal Hemodynamics in the Anesthetized Dog
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