Neurogenic Control of Peripheral Resistance in Renal Hypertension

By Alberto C. Taquini, Jr., M.D.

It has been well established that there is a resetting of baroreceptor nerve activity in chronic experimental renal hypertension.1,2 This, together with the fact that pithing of the brain and spinal cord lowers the blood pressure of hypertensive animals to the same low values that are found in normal animals after pithing,3 and that it is possible to lower the blood pressure of rats with chronic hypertension by the use of yohimbine,4 suggests that neurogenic tone may play an important part in the mechanism of the increased peripheral resistance that accompanies hypertension.

The importance of neurogenic tone in hypertension is suggested also by the fact that it is possible to produce hypertension by a number of techniques which act on the nervous system; among these are hemidecortication,5 audiogenic stimulation,6 electrical stimulation of the central nervous system,7 cerebral ischemia,8 kaolin injections,9 and baroreceptor nerve section.10

In the present study, I present experiments that support the theory that experimental renal hypertension is neurogenically mediated. By this is meant that the mechanism responsible for the increased peripheral resistance that accompanies hypertension fails when neurogenic tone fails, or has been abolished.

This discussion is not meant to be a complete analysis of the mechanism of hypertension, since it would be unlikely that a single mechanism could account for a process as complex and interacting as that of the regulation of blood pressure. It would be even more unlikely that a neurogenic mechanism is the sole responsible factor in hypertension.

My first approach to this problem, stimulated by Dr. David F. Bohr, consisted of a study designed to evaluate the role of neurogenic tone in chronic renal hypertension in rats.11 It was supposed that if all of the increased resistance in hypertension were due to an elevated neurogenic vasoconstrictor tone, the arterial pressure of normotensive and hypertensive animals would fall to the same level after neurogenic control is eliminated by pithing.

Methods

Hypertension was produced by a figure-of-8 ligature around one kidney and a contralateral nephrectomy; two to 25 weeks later, 35 mg/kg pentobarbital was given intramuscularly and the animals were ventilated artificially with pure oxygen by means of a positive pressure pump at a pressure of 9 cm H2O. Femoral arterial pressure was recorded with a mercury manometer. To accomplish destruction of the brain and cord, a steel rod 3.9 mm in diameter was forced within seconds through the right orbital fossa and down the length of the spinal canal.

Results

Figure 1 shows a tracing of arterial pressure response to pithing in a normotensive and a hypertensive animal. Pithing brought about an initial abrupt rise in arterial pressure, presumably due to a massive sympathoadrenal discharge; this was followed immediately by a sharp drop to a very low pressure. It has been seen that the low blood pressure level is maintained for hours, provided adequate ventilation is maintained. Figures 2 and 3 represent the changes in blood pressure produced by pithing in 14 normotensive and in 16 hypertensive animals. The initial mean blood pressure for normal animals was 137 ± 18 mm Hg; after pithing it was 31 ± 4 mm Hg. In the hypertensive group, the blood pressure before pithing was 193 ± 25; after pithing it was 31 ± 4 mm Hg.
PERIPHERAL RESISTANCE IN RENAL HYPERTENSION

Representative blood pressure response to pithing in normal and renal hypertensive rats.

Pithing it fell to 31 ± 4 mm Hg. Figure 4 shows the blood pressures and the standard deviations after pithing for each group. There is no significant difference in pressure between the normotensive and the hypertensive animals.

These results suggest that pithing removes the cause of the increased blood pressure of the hypertensive animals. The possibility exists that after pithing the two groups may differ in cardiac output, in which case the change in pressure would not be necessarily an index of peripheral resistance. Moreover, the decrease in cardiac output by decreasing distending pressure could passively increase resistance in both groups, thereby masking pre-existing changes in resistance.

Our second study was designed to clarify this point. Simultaneous measurements of blood pressure and cardiac output were made before and after pithing in normotensive or renal hypertensive dogs. These animals were rendered hypertensive by partial occlusion of the renal artery and by contralateral nephrectomy 15 days later. These animals were used 9 to 62 days after the second operation.

Pithing was done after caudal laminectomy, followed by the cephalic passage of a 4 mm steel rod through the vertebral canal. Dogs under thiopental anesthesia and positive pressure respiration were used. Arterial pressure was recorded from the femoral artery. Cardiac output was determined by the Fick method.

The blood pressure changes following pithing in dogs are similar to those observed in rats (fig. 5). Marked individual variation in

FIGURE 1
Representative blood pressure response to pithing in normal and renal hypertensive rats.

FIGURE 2
Blood pressure changes in response to pithing in normal rats. Each point represents a single experiment. The thick midline represents the mean of 14 experiments; cross hatching shows standard deviation and the outer, horizontal lines, the range.
cardiac output are present prior to pithing; however, the mean values are approximately equal in normal and hypertensive dogs. Cardiac output fell in both normotensive and hypertensive animals after pithing; there is no significant difference between the mean value for the two groups (fig. 6).

Figure 7 gives pre- and postpithing peripheral resistance values. Peripheral resistance, higher in hypertensive animals in the control period, falls after pithing to approximately equal values in both groups. Obviously, the fall in peripheral resistance was greater in the hypertensive animals than in the normals.

The data show that both peripheral resistance and cardiac output fall after pithing; however, the peripheral resistance decreases, since the magnitude of the blood pressure fall is much greater than that of cardiac output. The similarity of the postpithing resistances of the hypertensives and normals leads to the conclusion that the elimination of neurogenic tone also eliminates the mechanisms that maintain the peripheral resistance at an elevated level in hypertension.

In the chronic stage of experimental renal hypertension, the pressoreceptors are reset; further, local application of norepinephrine to the adventitia of the carotid sinus results in a fall of the blood pressure to low values, which is similar for normotensives and for renal hypertensives.13

We thought it of interest to determine whether the hemodynamic pattern that follows the fall in pressure produced by the local...
application of norepinephrine to the carotid sinus was similar to that observed after pithing. Normal and renal hypertensive dogs were morphinized (1 mg/kg) and anesthetized with intravenous chloralose (100 mg/kg). Hypertension was produced in dogs by application of a ligature around the left renal artery, followed 15 days later by contralateral nephrectomy. Femoral blood pressure was measured by Statham strain gauges on a Sanborn recorder. Cardiac output was measured by the dye-dilution technique, using a cuvette densitometer. Both vagi were sectioned and 200 μg norepinephrine was injected into the adventitia of each carotid sinus. This was followed by a fall in both normal and renal hypertensive dogs similar to that seen after pithing (fig. 8). After the application of norepinephrine, the arterial pressure was 84 mm Hg for the normal and 64 mm Hg for the hypertensive animals (fig. 9). On application of norepinephrine to the carotid sinus, we were able to lower the blood pressure in normal and hypertensive animals to values of around 35 mm Hg.

Since effective nerve blockade abolishes the difference in peripheral resistance between normotensive and hypertensive dogs, we may conclude that the decrease in the cross section of the resistance vessels is due to: (a) an increase in catecholamine secretion at the nerve endings, or (b) hypersensitivity of the resistance vessels of hypertensive animals to normal amounts of catecholamines produced because of an increased force of contraction of the vascular smooth muscle or by an apparent increase in vascular reactivity due to an alteration in the wall/lumen ratio.

We have made a comparative study of the catecholamine content in various tissues of normotensive and hypertensive rats in an effort to obtain an index of sympathetic nervous system activity. This was based on the assumption that the tissue catecholamine content represents the rate of liberation. In
these animals, hypertension was produced by a figure-of-8 ligature on one kidney, followed
a week later by contralateral nephrectomy. The hypertensive animals were used 8 to 12
weeks after the second operation.

The tissue content of catecholamines was
similar in the two groups of animals (Fig. 10).
These results agree with observations that
blood or urine catecholamines in hypertensive
subjects are in the same range as that found
in normotensive individuals and with obser-
vations on chronic renal hypertensive dogs in
which no significant changes could be seen in
the urinary catecholamine excretion.

Conclusions
1. After pithing the spinal cord or after
administration of norepinephrine to the
carotid sinuses of dogs, there is a fall in blood
pressure to equally low values in normal and
renal hypertensive dogs and rats.

2. This is associated with a fall in cardiac
output in normotensive and hypertensive ani-
ments; however, the magnitude of the fall in
pressure is greater than that of the output; therefore, resistance also falls.

3. The magnitude of the fall in resistance is greater in hypertensive than in normotensive animals, whether the animals had been pithed or the inhibitory effect of their carotid sinuses had been activated. Resistance decreased to equal values in both groups.

4. Catecholamine secretion apparently does not increase in hypertensive rats. This conclusion is drawn upon the assumption that the content of catecholamines in the tissues at a given moment represents the rate of liberation.

Our studies support the theory that the neurogenic tone is necessary to account for the increased peripheral resistance that accompanies hypertension, and probably that normal amounts of catecholamines, acting on the vessels of hypertensive animals, bring about the increase in peripheral resistance.

Summary
The increased peripheral resistance responsible for hypertension associated with unilateral renal ischemia and contralateral nephrectomy, is abolished after destruction by pithing of the central nervous system of dogs and rats, or after inactivation of the inhibitory carotid sinus reflex in dogs. The tissue catecholamine content of renal hypertensive rats was in the same range as in the normotensive animals. These results suggest that the increased peripheral resistance in hypertension is neurogenically mediated and that the increased resistance is due to an increased response of the resistance vessels to normal neurogenic stimulation.

Acknowledgment
I am grateful to Dr. Ruth McVaugh, Department of Physiology, University of Michigan, for her invaluable help in preparing this manuscript in English.

References
Discussion

Dr. Irvine H. Page, Cleveland: It is always nice to have the son of a distinguished father follow in his footsteps. Alberto Taquini, Sr., is an old and very cherished friend of mine and I think he should be proud of his son's performance. I am sure some of you are old enough to remember that the pithing experiment and its relationship to renal hypertension date back to William Dock. I have never found a satisfying explanation for them. When the experiment is done acutely it is difficult to interpret, if only because it is such a traumatic operation. I have done many such operations in cats and dogs, and I know for several hours after it that cardiovascular reactivity changes markedly. Whether so-called "blood pressure floors" mean much after so drastic a procedure, I am not sure.

You may recall that Frank Glenn and I did a series of experiments in the early thirties where the cord was cut at the level of C6 and the dogs carefully nursed. They had been made hypertensive before the cord section. For several weeks the blood pressure was normal, but with passage of months there was a progressive rise to hypertensive levels. In these chronic experiments, the nervous system did not seem essential to development of hypertension. As you will hear later, Dr. McCubbin and I have been interested in the degree to which the nervous system participates in experimental renal hypertension ever since Ogden made the distinction in mechanism between acute and chronic renal hypertension. Dr. McCubbin will tell you of the singular position endogenous norepinephrine seems to occupy and how tyramine can be used to bring it out. We have also been much impressed with the effective hypotensive action of ganglionic, a substance that seems to act on the nervous system by preventing the release of norepinephrine at the myoneural junction in reducing arterial pressure of both renal hypertensive dogs and patients.

As you know, studies of cardiovascular reactivity in hypertensive animals and patients to a whole battery of drugs have shown such divergent results that an objective analysis is impossible. McCubbin and I have been studying this problem for the past 30 years and still cannot be certain of our results in renal hypertension. So far, the only drug we have come upon that shows an increased response is tyramine. Doubtless there will be more. A pharmacological response pattern in experimental neurogenic hypertension was easy for us to demonstrate after we knew the right drugs.

This is all a very long-winded way of saying that I think the nervous system is here to stay in the mechanism of experimental renal hypertension, whether produced by a clamp on the renal artery or by a cellophane-induced holl around the parenchyma. Dr. Sibley W. Hoobler, Ann Arbor, Michigan: For me, the most important part of this presentation is the extension of Dr. Taquini's observations concerning the importance of nervous tone to the carotid sinus experiments. Some years ago, at the Prague Symposium on the Pathogenesis of Essential Hypertension, Dr. Heymans first showed dramatically the manner in which the elevated blood pressure of a chronic renal hypertensive dog can be brought to normal by injections around the carotid sinus region. He had not demonstrated that this reduction was in fact a decline in peripheral resistance; however, Dr. Taquini has clearly shown that the blood pressure in renal hypertension can be reduced to normal through a decline in total peripheral resistance. One must conclude then, that either the sympathetic nervous system is permissive to the development of renal hypertension, or that there is an elevated sympathetic neural tone in renal hypertension which is abrogated by certain manipulations around the carotid sinus or that injections of norepinephrine into the carotid sinus activate vasodilator efferent pathways which are normally inactive or underactive during the hypertension produced by renal clamping. It seems to me that these studies provide important further leads for the study of the pathogenesis of renal hypertension.
Dr. Milton Mendlowitz, New York: It has already been mentioned that pithing produces shock which may influence the results, and I should like to add that during such experiments, the level of the blood pressure may be determined more by such factors as intrinsic dilatation of the capillary circulation and aggregation of erythrocytes with obstruction within small blood vessels. The carotid sinus experiments, however, are more difficult to explain. We, too, like Dr. Page, have found no increase in responsiveness of blood vessels to catecholamines in human renal hypertension. The meaning of Dr. Taquini's experiments will therefore have to await more definitive data with respect to such factors as catecholamine pool size and nerve discharge.

Dr. David B. Gordon, Cleveland: In connection with your discussion of two alternative possibilities to account for the increase in peripheral resistance in the hypertensive animal, that is: (a) an increase in the secretion of catecholamines at the sympathetic nerve endings, or (b) an increased responsiveness of the resistance vessels to normal amounts of catecholamines released at these endings, I should like to call your attention to an important paper by Dr. Sol Rothman, of Southern California. Dr. Rothman reports his pharmacological attempts to differentiate between a high, normal, or low rate of catecholamine secretion by the nerves supplying the resistance vessels. This is done by measuring the responsiveness of the blood pressure to exogenous injection of norepinephrine. The results obtained show that as compared with the normal rabbit, the renal hypertensive rabbit exhibits an increased pressor response to injected norepinephrine. On the other hand, the cerebral hypertensive rabbit shows a diminished response as compared to the normal animal. These cerebral hypertensive rabbits were prepared by carotid artery ligation—a technique similar to, but not identical with, the method used by Dr. Wakerlin to prepare his chronic cerebral hypertensive dogs. The fact that the cerebral hypertensive rabbits have a decreased responsiveness to exogenous norepinephrine, is taken to mean that they already are secreting larger than normal amounts of norepinephrine at the sympathetic nerve endings to the resistance vessels and thus are on a part of the dose response curve at which additional amounts of norepinephrine are relatively ineffective. By similar reasoning, one may conclude that the renal hypertensive animal is not secreting larger than normal amounts of catecholamines, but is hyper-responsive to the amounts secreted. This conclusion is in full agreement with your own.

I should like to make one other small point in regard to terminology: Somehow the word neurogenic has come to be used to describe the mechanism of hypertension, renal or otherwise, when it has reached a stage which apparently cannot be accounted for by a humoral or renal pressor mechanism. From the above discussion, I think that it must be apparent that, at least sometimes, the nervous system need only be involved to the extent that it continue on at its normal rate of activity but the musculature of the blood vessel walls may be abnormally reactive. For such a situation, I should like to introduce a new word, or rather a new use of an old word—namely, myogenic. Let us speak of myogenic as well as of neurogenic phases of hypertension.

Dr. James Conaway, Ann Arbor, Michigan: I think that Dr. Taquini's results are interesting and provocative. There may, however, be a methodological explanation for them. Before coming to this, however, I should like to ask him to comment upon the difference in blood pressure he obtains after pithing and that obtained after large doses of reserpine or autonomie blocking drugs. Although we all appreciate that pharmacological blockade is never complete, it is extensive and we would not expect the pressure obtained after autonomie blockade, which is about 80 to 100 mm Hg in the conscious dog, to differ greatly from that obtained after pithing. This is of some importance, since it has been shown that there is a difference between normal and hypertensive animals in blood pressure after ganglion blockade. It seems possible that your inability to
show this difference between normals and hypertensives could be due to the very low blood pressures you obtained. In experiments measuring flow and pressure in the hindlimb of the dog, when the blood pressure is increased by intravenous noradrenaline, there is a distinct change in the pressure flow curve from that obtained in a denervated state (fig. 1). At the very low pressure of 30 mm Hg, or so, these two curves approximate so closely that it might be difficult to differentiate the one from the other. Similarly, in your preparation, the low blood pressure may prevent a registration of differences between normotensive and hypertensive. It might be possible, therefore, to demonstrate a difference if you were to reinfuse your dogs and restore the cardiac output to its normal level.

Dr. Maxwell Little, Winston-Salem, North Carolina: In view of some information that in renal hypertension the factors maintaining the elevated arterial pressure may differ between early and late hypertension, have you noticed any difference in the response to your procedures when applied during recently established hypertension as opposed to a more chronic renal hypertension?

Dr. Eugene Braunwald, Bethesda, Maryland: I believe you indicated that tissue catecholamine content may be an index of sympathetic activity and represent the rate of liberation of catecholamines. Further, you assume that since tissue catecholamine stores are not altered in hypertensive rats, there is no increase in catecholamine secretion in these animals. You then suggest that the elevated peripheral resistance in the hypertensive animals results from a normal quantity of the adrenergic neurotransmitter acting on the vessel wall. A very simple experiment makes me wonder about the validity of the basic assumption. If one stimulates a sympathetic nerve electrically and greatly augments the liberation of noradrenaline from the adrenergic nerve ending, there is no consistent change in the total catecholamine stores of the tissues innervated by the nerve. There are other examples to support the view that the total tissue catecholamine stores do not bear any relationship whatsoever to the sympathetic activity and to the rate of liberation of catecholamines. For this reason, I wonder if you could tell me on what specific experimental evidence you base the assumption that there is even a remote connection between the tissue catecholamine stores and the sympathetic activity and/or the liberation of catecholamines?

Dr. Alberto C. Taquini, Jr., Buenos Aires: Thank you, Dr. Page. With respect to your comments on cardiovascular reactivity, we have observed that after pithing there is a potentiation of the pressor response to noradrenaline. Speaking of angiotensin, Dr. Helmer piths cats since he observes under this condition increased sensitivity to angiotensin. I am well aware of your work with Dr. Glenn in which you were able to show a progressive rise to hypertensive levels despite the fact that the dogs had the spinal cord sectioned. To explain this, I used your mosaic theory[2] which incidentally, I like very much, and said that in the absence of the neural component, other mechanisms that normally control blood pressure take over in order to maintain tissue perfusion pressure.

Regarding Dr. Mendlowitz' comment, our studies showed that pithing acts to decrease total peripheral resistance, thus relaxing the resistance vessels and not on the capillary site.

With respect to vascular reactivity, Bohr[4] has shown that arterioles (200 μ in diameter) from renal hypertensive rats have an
increased reactivity to catecholamines. These studies agree with recent work of Gordon in the aortas of hypertensive rats.

Dr. Conway, I think that the difference that exists between blood pressure after ganglion blockade and pithing indicates that pithing is more effective than drugs in removing neurogenic tone.

We have infused angiotensin (figs. 2 and 3) and norepinephrine in normal and hypertensive rats and pithed them during the infusion. Figure 2 represents a typical experiment of a rat infused with angiotensin. The same results were seen with the infusion of norepinephrine, as seen in the record—an infusion that elevates blood pressure around 30 mm Hg before pithing and is capable of producing a marked difference in pressure between the infusion and postinfusion period after pithing. In figure 3, it is possible to see the differences on the postpith blood pressure of normal, renal hypertensive, and angiotensin infused rats. In the latter group, the increase in mean blood pressure before pithing produced by angiotensin infusion was 15.9 mm Hg. As angiotensin has no effect on cardiac output, we can assume that changes in pressure represent changes in resistance; therefore, our preparation may detect changes in resistance in spite of the low blood pressure level. These studies will also indicate that postpithing blood pressure is not a fixed traumatic floor.

We have been doing a preliminary experiment (Taquini, A. C., Jr., Zuberbuhler, R. C., Kaumoan, A., and Taquini, A. C.: unpublished experiments) in normal and renal hypertensive dogs to observe changes in peripheral resistance before and after denervation of the isolated hind leg of both groups. We have observed an enormous variation of the pressure/flow curve from animal to animal which made difficult a comparative study, but apparently there was no difference in resistance between normal and hypertensives after denervation. These studies, if true, will confirm the observations of Laverty and Smirk, which showed that there was no difference in hind limb resistance among normal, renal hypertensive, and spontaneous hypertensive rats after the neurogenic tone was removed.

With respect to Dr. Little's question, we were unable to see any difference between chronic and the more acute forms of hyper-
tension. The rats were used 2 to 25 weeks after hypertension was produced; the dogs were used between 9 and 62 days. In our experiments with renin content, the acute phase lasted less than a week.8,9

I think there is good evidence against Dr. Braunwald’s comment about the lack of increase in tissue catecholamines after electrical nerve stimulation. It has been shown10 that after electrical stimulation of the cardiac sympathetic nerves, the myocardial content of norepinephrine increases 93%. Also, electrical stimulation results in an increased adrenal tissue content of catecholamines.11 With respect to Dr. Braunwald’s point on the lack of relationship between the tissue catecholamines and the sympathetic activity, it is well known that Cannon12 was the first to show the relationship between the sympathetic activity and the adrenergic nerves; it is also known that the sympathetic activity is mediated by norepinephrine,13,14 and that denervation produces a decrease in tissue catecholamines.15 All these results, together with the above-mentioned increase in tissue catecholamines after nerve stimulation, suggest that a correlation may exist between tissue catecholamines and sympathetic activity.

It has been shown that tissue catecholamines vary under different experimental conditions; it has been observed that after bilateral nephrectomy, which is known to produce experimental hypertension, the adrenal content of catecholamines increases; this has been used to suggest a possible role of catecholamines in hypertension.16 In spite of all this evidence, I still consider that tissue catecholamines are only an indirect index of the sympathetic activity; our investigation besides showing definite results, opens a new line of study on the role of the tissue catecholamines in hypertensive animals. Probably one of the preliminary steps is the study of the exchange of labeled norepinephrine in the tissues of normal and renal hypertensive animals.

References

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ALBERTO C. TAQUINI, JR.