Carotid Sinus Participation in Experimental Renal Hypertension

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Using direct electroneurographic technics, it is shown that the carotid sinus baroreceptor reflexes adapt or reset to the higher pressure levels of chronic renal hypertension. They remain functional at the higher pressure level and thus act to maintain rather than to oppose it. This provides a satisfactory explanation for the presence of significant neurogenic vasoconstriction in chronic hypertension. Experiments on acutely hypertensive dogs indicate that the resetting process starts quite early but seems to lag behind the rise in arterial pressure.

THE buffer reflexes seem finally to have achieved a degree of recognition in the field of hypertension research. In view of their quite prominent controlling action on arterial pressure, it is a little surprising that this has taken so long and that more time has not been devoted to measuring their possible participation in renal hypertension, especially since it is becoming more and more clear that, whatever the initiating cause of renal hypertension, an extrarenal neurogenic mechanism seems to assume an important role in the chronic phase. This dual mechanism was suggested by Ogden in 1947 on the basis of experiments in collaboration with Sapirstein and other colleagues, in which yohimbine was used to estimate neurogenic vasoconstriction. Since then, numerous studies employing adrenergic or ganglion blocking agents or surgical procedures have all indicated near normal or even increased neurogenic vasoconstriction in chronic renal hypertension. This, of course, implies that the buffer reflexes are not exerting a satisfactory inhibitory effect on vasomotor centers. That is, they are not acting maximally to prevent the hypertension, unlike their action in acute chemically induced hypertension when, at comparable pressure levels, baroreceptor stimulation is maximum, leading to nearly complete inhibition of sympathetic vasoconstrictor discharge. Additionally, von Möller showed that pressure over the carotid sinus in hypertensive man caused a fall in systemic pressure. Kerz showed in hypertensive man, and Makin in renal hypertensive dogs, that adrenaline or noradrenaline injected into the adventitia of the carotid sinus caused a fall in systemic arterial pressure. These agents produce a contraction of the sinus wall leading to baroreceptor stimulation beyond that normally provoked by the existing hypertensive pressure levels. It was apparent, therefore, that the pressure levels of severe chronic hypertension were not sufficient alone to cause maximum baroreceptor stimulation.

We have tested directly, using electroneurographic technics, to determine whether some form of adaptation or resetting occurs at the baroreceptor level and, if so, to attempt to learn something of the possible mechanisms involved as well as the time required.5 I shall use the term resetting henceforth for want of a better one.

Despite the indirect evidence that some form of resetting does occur, we were, nevertheless, somewhat surprised to find the pattern of carotid sinus activity intermittent and apparently normal in chronically hypertensive dogs because we had become so accus-

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Supported in part by a grant from the American Heart Association.

*I am indebted to Drs. I. H. Page and J. H. Green for their collaboration in many of the studies on which this paper is based.
tomed to seeing the steady, continuous nerve activity when arterial pressure is raised chemically in a normal dog. An example of the maximum response is shown in figure 1. In contrast with this pattern of nerve activity at increased pressure levels in a normal dog, figure 2 shows the seemingly normal, intermittent activity of carotid sinus and aortic baroreceptors exposed to the very high pressure levels of chronic renal hypertension.

We felt, however, that this simple observation of an apparently normal pattern of baroreceptor activity might be misleading, since, as is apparent from figure 1, the more important stimulus to baroreceptors is pulse pressure, rather than mean pressure, and it is well known that pulse pressure is increased in chronic renal hypertension. It was conceivable that the wider pulse pressure alone could have accounted for the normal pattern of nerve activity, and that any so-called resetting could depend upon this hemodynamic change. We attempted, therefore, to determine the threshold response and the range of response in normal and chronic renal hypertensive dogs through application of steady pressures and then a standard, reproducible pulse form within the carotid sinus after tying off all of its vascular branches. In this manner, responses to standard pressure stimuli in any one preparation could be compared with those of any other. Arbitrarily selected steady pressures of 60, 120, and 240 mm. Hg consistently demonstrated a difference between normal and chronically hypertensive dogs (fig. 3). The normotensive preparations invariably showed nerve activity at 120 mm.

**Fig. 1.** Endosinus pressure measured from a cannulated external carotid artery shown at top of each trace; carotid sinus nerve activity shown beneath. Breaks in top reference line at 1 second intervals. Recording technic same in following figures. Top trace, control; middle, during infusion neosynephrine; bottom, recovery. Normal dog.
FIG. 2 Top. Carotid sinus nerve activity in dog with chronic renal hypertension (top trace) and aortic depressor nerve activity from another hypertensive dog (bottom trace). (Reprinted from Circulation Research 4: 206, 1956.)

Fig. 3 Bottom. Carotid sinus nerve activity with different steady endosinus pressures in normotensive (A) and hypertensive (B) dogs.

Hg and most at 60 mm. Hg, but 8 hypertensive dogs failed to show any activity at 60 mm. Hg, and only 2 showed activity at 120 mm. Hg.

This difference in baroreceptor response between normotensive and chronic hypertensive dogs was more striking when a standard, artificial pulse of 50 mm. Hg which took the form of a sine wave was superimposed upon these same steady pressures. Response in the hypertensive animals differed consistently from that in the normotensive ones (fig. 4). At a mean pressure of 60 mm. Hg, nerve activity was intermittent and synchronous
with rise in pressure in the normotensive, but absent in the hypertensive preparation; at 120 mm. Hg intermittent activity was seen in both; at 240 mm. Hg mean pressure with a pressure wave of 50 mm. Hg, firing was continuous in the normotensive dogs but still intermittent in the hypertensive animals. Thus, both groups of experiments seem to bear out the hypothesis that the buffer reflexes are indeed reset to act at a higher pressure level in chronic renal hypertension.

There was an additional difference in baroceptor response between the hypertensive and normotensive groups. When endosinus pressure falls to a certain quite low level, the sinus wall tends to collapse inward, and since

**Fig. 4** Top. Carotid sinus nerve activity with standard endosinus pressure wave form at different mean pressures in normotensive (A) and hypertensive (B) dogs. (Reprinted from Circulation Research 4: 205, 1956.)

**Fig. 5** Bottom. Carotid sinus nerve activity in chronic renal hypertensive dog showing 'collapse firing' at trough of sine pressure wave at mean pressure of 60 mm. Hg.
baroceptors are really distortion receptors, this distortion of the wall causes increased baroceptor activity. This so-called "collapse-firing" was not observed in the group of normotensive dogs at the lowest pressure level used, but it did appear in more than half of the hypertensive preparations. An example of this "collapse-firing" in a chronic renal hypertensive dog can be seen in figure 5. Note that nerve activity accompanies a fall rather than rise in pressure at a mean pressure of 60 mm. Hg. This would seem to be a further indication that the range of response is shifted upward in chronic hypertension, that this low pressure level is more unphysiologic for the hypertensive than for the normotensive animal.

The mechanism of the resetting process is still unknown. Most of the evidence suggests it to be a passive change. It may depend upon some structural alteration causing a change in elasticity and distensibility of the sinus wall or the baroceptor nerve endings themselves may be altered. The process may be simply the passive effect of sustained increase in arterial pressure alone, or it may be facilitated by a circulating humoral agent. Kezdi\(^6\) has shown in dogs that the sympathetic innervation of the carotid sinus can markedly influence baroceptor response, and this mechanism might play a role.

One definite possibility for the mechanism of the resetting process can be guessed at from figure 6. Bronk and Stella\(^7\) showed some years ago that different baroceptor nerve endings have different thresholds of response. In figure 6 are shown the different thresholds of 2 baroceptor fibers from the carotid sinus nerve of a normal dog. At this raised pressure level due to infusion of neosynephrine, one fiber is firing not steadily, but nearly so, whereas the other fiber shows less response—firing only briefly with each pulse. With severe sustained hypertension, it is conceiv-able that the fiber showing nearly continuous activity, along with others having a low threshold of response, might become inactive, possibly due to fatigue, leaving only those nerve endings responding to the higher pressures. This would, of course, result in an apparently normal electroneurogram.

It is possible to say that the resetting process is not accomplished in a few hours. We have infused angiotonin or other pressor agent for 6 hours or more without modifying the pattern of nerve activity. While the resetting process is not quick enough to be measured in a few hours, it must nevertheless start relatively soon after a renal stimulus to hypertension. This is apparent from the response to a ganglion or adrenergic blocking agent during the hypertension that often follows within 1 to 3 days after application of a Goldblatt clamp. It is well documented that the hypotensive response is less than normal and may be quite minor, but the fact that there is any fall indicates a significant degree of neurogenic vasoconstriction; if the buffer reflexes were acting maximally to prevent the rise in pressure, there would be no hypotensive response to the blocking agent, as during relatively brief infusions of angio-tonin or other pressor agent. On the other hand, the smaller than usual falls in pressure in response to a blocking agent indicate that the resetting process lags behind the rise in pressure, the buffer reflexes acting only partially to inhibit it. Our initial experiments on acute renal hypertensive dogs, using the standard sine pressure wave stimulus as be-
fore, also indicate that some degree of resetting occurs early.

The results obtained during the hypertension that follows 1 to 3 days after application of a Goldblatt clamp were not as consistent or as regular as in the series of chronically hypertensive dogs. Resetting occurred to variable degrees and at variable speeds, ranging from being relatively complete to almost entirely absent after 1 to 2 days of hypertension. Figure 7 represents a rather typical early partial resetting. This initial partial resetting is often not clear from neurograms using the intact circulation. Nerve activity may appear much like that in the normal dog during infusion of a pressor agent.

The resetting process seems to continue to lag behind the progressive rise in arterial pressure for some time, and may never be entirely complete as estimated from the response to carotid occlusion. This response is, of course, enhanced in normal dogs if arterial pressure is increased; there should be no increase in renal hypertension if resetting is complete. We measured the occlusion response repetitively by compressing Van Leer-sum loops in unanesthetized dogs during the slow rise in arterial pressure that follows wrapping the kidneys with cellophane, and found somewhat greater responses even several months after arterial pressure had reached hypertensive levels.

To summarize, the often postulated re-set of the nervous system in chronic renal hypertension does occur, at least as regards the threshold and range of response of the baroreceptor reflexes. They remain functional at the higher pressure level and act to maintain rather than to oppose it. This provides a satisfactory explanation for the significant
neurogenic vasoconstriction in chronic hypertension, and provides support for the hypothesis offered by Ogden that experimental renal hypertension depends first on a renal and then predominantly on an extrarenal neurogenic mechanism. A further implication is that prolonged hypertension from any cause would tend to be self-sustaining.

Resetting may, of course, occur at several levels and it is apparent that this is but one facet in the mechanism of renal hypertension. It starts quite early but seems to lag behind the rise in arterial pressure, and probably is never entirely complete. It does not seem to be irreversible; return to normotensive levels of operation must occur in those instances where arterial pressure returns to normal after removal of a diseased kidney, and the same process might account for the tendency of some patients to maintain normal or nearly normal pressures after completion of suitably prolonged antihypertensive treatment.

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Circulation. 1958;17:791-797
doi: 10.1161/01.CIR.17.4.791

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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