Baroceptor Function in Chronic Renal Hypertension

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The results of these experiments indicate that the carotid and aortic baroceptor mechanisms are reset to the hypertensive pressure levels of animals with chronic perinephritic hypertension. Thus, seemingly, the buffer reflexes tend to maintain, rather than prevent, the chronic phase of renal hypertension and are, presumably, an important component in the mechanism of chronic renal hypertension.

Experimental renal hypertension is initiated by a humoral mechanism; thereafter, etiology is less clear. Abundant evidence indicates, however, that there is a significant neurogenic component of the chronic phase of renal hypertension.

Normally, the buffer reflexes are an important nervous mechanism regulating arterial pressure; it is important, therefore, to determine their functional status in chronic renal hypertension. The fact that considerable neurogenic vasoconstriction exists in the chronic phase of renal hypertension implies that the buffer reflexes are not exerting a satisfactory inhibitory effect on the vasomotor centers; it can further be inferred either that this inhibitory effect is being blocked centrally or that some form of adaptation of baroceptors has occurred. To investigate these possibilities, we have measured baroceptor function by means of electroneurograms and the carotid occlusion response in normotensive and chronically hypertensive dogs.

Methods

Adult mongrel dogs were used in all experiments. Hypertension was produced by the cellophane perinephritis method of Page; animals were not used until hypertension of 200 or more mm Hg had been present for at least 6 weeks.

The Carotid Occlusion Response Before and After Appearance of Renal Hypertension. One carotid sinus nerve and both aortic depressor nerves were cut. The carotid artery of the remaining innervated sinus was then explanted in a tube of skin low in the neck. After 3–4 weeks, when healing was complete, a needle connected by tubing to a Hg manometer was inserted into the femoral artery, and arterial pressure recorded on a smoked drum. The explanted artery was occluded between the fingers and the effect on blood pressure determined. Measurements were repeated at weekly intervals before and during renal hypertension. Anesthesia or sedation was not required.

Buffer Nerve Activity of Chronic Renal Hypertensive Dogs. Using pentobarbital anesthesia, multifiber preparations of the carotid sinus and aortic nerves of normal dogs and dogs with hypertension of at least 6 weeks duration were placed on saline-wick electrodes connected to capacity-coupled amplifiers and neurograms recorded on cathode-ray tubes simultaneously with arterial pressure measured from a cannulated external carotid artery by an electromanometer designed by J. H. Green.

Carotid Sinus Nerve Activity in Response to a Standard Pressure Stimulus. Using pentobarbital anesthesia, all branches of the carotid bifurcation were tied and the external carotid artery was cannulated for recording of endosinus pressure.

A T-tube was placed in the homolateral common carotid artery so that the sinus could be subjected to the animal's own arterial pressure or, for short periods, to a sine wave pressure produced by a system consisting of saline filled pressure bottle and motor driven syringe connected in parallel. The tight-sinus preparation prevented saline from entering the carotid artery and only the animal's own blood was in contact with the sinus. Pressures were measured by a Green manometer, were recorded simultaneously on cathode-ray tubes. A bypass from the cannula in the external carotid artery to an external jugular vein permitted frequent flushing of the sinus with fresh blood.
given mean pressure, the stroke of the piston of the syringe was increased slowly and at a standard rate from zero to maximum. The resultant endosinus pressure took the form of a mean pressure on which was superimposed a sine wave which increased slowly and progressively in magnitude without change in either rate or mean pressure. In this way a family of pulsatile pressure curves with associated baroceptor activity was obtained. Corresponding portions of the pressure curves from different experiments were compared.

RESULTS

Carotid Occlusion Response Before and During Chronic Renal Hypertension. Occlusion of the explanted carotid artery leading to the one intact baroceptor area caused sharp and sustained rise in mean arterial pressure in each of four normotensive dogs. Since the resting arterial pressures were normal, or nearly so, it is assumed that the remaining one baroceptor area was able effectively to assume the moderator function of all four areas. The dogs showed no evidence of being disturbed by the procedure or by the pressor responses; anesthesia or sedation was not necessary. With release of the carotid artery, arterial pressure promptly returned to, or near to, the control level. Repetitive responses of approximately the same amplitude could be obtained during any one measurement and responses were remarkably similar from week to week.

Figure 1 is composed of representative recordings of the carotid occlusion response before and during renal hypertension in one experiment; figure 2 shows in graphic form the data from another. It will be noted that as mean arterial pressure rose, the carotid occlusion response tended to increase slightly over a period of months until the maximum hypertension was obtained. Comparable results were obtained in all four experiments; they indicate that baroceptor mechanisms remain functional with appearance of renal hypertension.

Buffer Nerve Activity in Chronic Renal Hypertensive Dogs. Recordings were made from multifiber preparations of the carotid sinus and aortic nerves of dogs with chronic renal hypertension. Quite unlike the nearly continuous impulse traffic present when arterial pressure is raised to hypertensive levels in normal animals, nerve activity was intermittent in dogs with severe renal hypertension; it was synchronous with cardiac systole and resembled that in dogs with normal arterial pressures. Steady firing did not occur even when arterial pressure was raised another 50-60

![Figure 1](http://circres.ahajournals.org/)

**Fig. 1.** Carotid occlusion response before and at intervals during renal hypertension. No anesthesia. Period of occlusion indicated by signal marker. Scale at left in mm. Hg. Time marks: one minute.
mm Hg by injection of noradrenaline or angiotonin. Figure 3 illustrates the apparently normal pattern of activity in both carotid sinus and aortic nerves in severe chronic renal hypertension.

Because of the markedly different pulse pressures and pulse wave contours between different dogs and between normal and renal hypertensive dogs, it was felt that accurate comparison of nerve activity would only be possible if the pressure stimulus was the same; this necessitated the third group of experiments.

**Carotid Sinus Nerve Activity in Response to a Standard Pressure Stimulus in Normotensive and Chronic Renal Hypertensive Dogs.** A standard pressure in the form of a sine wave was induced within one carotid sinus of 6 normotensive dogs and of 6 dogs with renal hypertension (200 or more mm Hg.) of 6, 8, 12, 13, 19 and 20 weeks duration respectively while recording sinus nerve activity electrically. For purposes of comparison, a pressure wave of 50 mm Hg (trough to crest) applied at mean pressures of

60, 120 and 240 mm Hg was chosen arbitrarily. The pressure limits were thus 35–85, 95–145 and 215–265 respectively.

As illustrated in figure 4, the difference in response between normotensive and renal hypertensive dogs was striking. 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 dog but still intermittent in the hypertensive animal. Similar differences between normotensive and hypertensive animals were obtained in all experiments; one hypertensive dog failed to show nerve activity even at 120 mm Hg. In addition, it was noted in 4 of the 6 hypertensive animals that at the 60 mm Hg level of mean pressure, bursts of nerve activity did appear but accompanied the fall in endosinus pressure rather than the rise as in normotensive animals. Figure 5 shows an example of this; it is believed to be due to distortion of the carotid sinus wall by abnormally low endosinus pressures (Landgren). In this case the pressure range was abnormally low for the hypertensive but not for the normotensive dogs, providing additional evidence.
 Fig. 4. Neurograms from multifiber preparation of carotid sinus nerve of (A) normotensive and (B) hypertensive dog during standard endosinus pressure stimulus. See text for description. Breaks in top reference line at 1 sec. intervals.

that the normal range of response has been shifted upwards in the hypertensive animals. The nerve activity displayed on records from normotensive and hypertensive dogs also showed differences when endosinus pressure was held steady at different levels. At 60 and 120 mm. Hg, nerve activity was displayed by 5 of the 6 normotensive, but by none of the hypertensive animals. However, at a steady pressure of 240 mm. Hg, nerve activity was present in the hypertensive as well as in the normotensive animals.
INTERPRETATION

The fact that a pressor response to carotid occlusion persists in chronic renal hypertension is evidence that the baroceptor mechanism continues to operate in keeping the pressure down; without this mechanism pressure would be much higher. Further, baroceptor mechanisms continue their buffering action to maintain arterial pressure at hypertensive levels whenever there is any tendency for blood pressure to fall. Carotid occlusion in our experiments simulated such a fall of blood pressure as far as the carotid sinus is concerned; the blood pressure elevation obtained demonstrates the mechanisms that would operate in the whole animal if arterial pressure should fall.

The observation that in hypertensive dogs baroceptors fire intermittently at supernormal pressure levels, which induce continuous firing in normotensive animals, would seem to indicate that the regulating mechanism has been set to buffer arterial pressure at a higher level. This resetting of the carotid sinus mechanism was shown not to be the result of changes in the form and magnitude of pressure pulses; artificial pressure variations of standard magnitude and different levels of steady pressure demonstrated clearly the different thresholds of baroceptor response of normal and hypertensive dogs.

The mechanisms concerned in resetting of baroceptor reflexes remain unknown. Possibilities that require more study are (1) that the natural distensibility of the carotid sinus has become altered, (2) that some of the lower threshold fibers have become inactivated, or (3) that all afferents have undergone a process of adaptation. Since the term "adaptation" has come to have a somewhat specialized meaning, emphasis should be placed on a change of threshold rather than incapacity to respond to continuing excitation. The buffer mechanism continues to operate to stabilize pressure but at hypertensive levels.

While the factors that determine such a resetting of baroceptors remain unknown, these experiments offer an explanation as to why experimental renal hypertension persists indefinitely after it is no longer possible to find significant quantities of renin or angiotensin in the blood. It may also explain why nephrectomy has been found to lower pressure in the acute stage of renal hypertension but not in the chronic, both in animals and in man. It would explain many pharmacologic data indicating an important degree of neurogenic vasoconstriction in chronic renal hypertension and its relative absence in the acute or malignant phase—resetting of the buffer mechanism not yet having developed. If hypertension due to any cause were allowed to persist long enough for resetting to occur, the buffer reflexes might be expected to maintain the hypertensive level though the original stimulus had disappeared. If true, this might be a factor in the occasional hypertension that persists after toxemia of pregnancy or removal of a pheochromocytoma.

SUMMARY

Baroceptor function has been measured from electroneurograms and the carotid occlusion response in normotensive and in chronic renal hypertensive dogs.

Neurograms of the carotid sinus and aortic depressor nerves of renal hypertensive dogs, contrasting with those of normal animals, showed intermittent activity at supernormal pressure levels which was synchronous with cardiac systole.

Carotid sinus baroceptors showed a striking difference in threshold response in hypertensive, as compared with normotensive animals,
when they were subjected to different levels of steady pressure or to a standard pulsatile pressure at different mean levels. Baroceptor discharge commenced at higher pressure levels in the hypertensive animals and, unlike that in normotensive dogs, was not steady at severely hypertensive pressure levels. Additionally, nerve activity due to distortion of the carotid sinus wall that appears at very low endosinus pressures occurred at higher pressure levels in the hypertensive than in the normotensive dogs.

Thus, baroceptor mechanisms appear to be reset at the higher pressure levels of dogs with chronic perinephritic hypertension. Their ability to buffer changes in arterial pressure remains; consequently, they would tend to maintain, rather than inhibit, the chronic phase of renal hypertension. The carotid occlusion response, measured repetitively before and during renal hypertension in unanesthetized animals, persisted and was slightly augmented during hypertension, suggesting that resetting of baroceptor mechanisms lags slightly behind the slow rise in pressure to hypertensive levels.

**REFERENCES**


**SUMMARIO IN INTERLINGUA**

Le function baroceptori esseva mesurate ab electroneurogrammas e ab le responsa al occlusion carotide in canes normotensive e in canes con chronic hypertension renal.

Neurogrammas del sinus carotide e del nervos depressori aortic, obtenite ab canes con hypertension renal, mostrava, in contrasto con illos obtenite ab canes normal, un activitate intermittente a nivellos supranormal de pression, synchrono con le systole cardiac.

Baroceptores de sinus carotide monstrava un frappante differentia del responsa liminal in canes hypertensive comparate con canes normotensive quando illos esseva subjicite a diferente nivellos de pression constante o a un pulsatile pression standard de diferente nivellos median. Le discarga baroceptori comenciava a plus alte nivellos de pression in canes hypertensive. In tal animales, in contrasto con observationes in canes normotensive, le discarga baroceptori non esseva constante a nivellos de pression severmente hypertensive. In plus, le activitate nervose, le qual es debite al distorsion del pariete del sinus carotide occurrente a bassissime pressiones endosinusal, se manifestava a plus alte nivellos de pression in canes hypertensive que in canes normotensive.

Assi il pare que mechanismos baroceptori se re-estabili al plus alte nivellos de pression in canes con chronic hypertension perinephritic. Lor capacitate a tamponar alterationes de pression arterial non se perde. Ergo on pote supponer que illos tende a mantener plus tosto que a inhibit le phase chronic de hypertension renal. Le responsa a occlusion carotide, mesurate repetitemente ante e durante hypertension renal in animales non-anesthesiate, se monstrava persistente e esseva levemente augmentate durante le hypertension. Isto pareva indicar que le restablimento del mechanismos baroceptori se retarda levemente post le lente augmento del pression verso nivellos hypertensive.
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