Baroceptor and Sympathetic Activity in Experimental Renal Hypertension in the Dog

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Response to tetrathylammonium chloride was studied in normal and renal hypertensive dogs in which the carotid sinus was isolated and intrasinal pressure was maintained by a pump. Normal, chronic, and acute renal hypertensive animals differed in their response at different intrasinal pressure levels and indicated resetting of the baroceptors in the chronic hypertensive phase but not in the acute phase. This resetting may play a role in the maintenance of chronic renal hypertension.

There is ample evidence that experimental renal hypertension goes through an early acute phase before the prolonged chronic phase becomes established. A change in the basic mechanism of hypertension between the 2 phases seems to be well established. However, whether the problem is an increased circulating pressor substance or the failure of the kidney to remove a pressor substance is still not settled. Further questions await clarification. Why do baroceptors fail to respond to elevated blood pressure? Does increased sympathetic activity participate in the maintenance of renal hypertension?

Sympathetic outflow in renal hypertension has been tested by many investigators using ganglionic blocking drugs or centrally acting agents which depress sympathetic vasomotor centers. It has been suggested that there is no increase of the sympathetic vascular tone in the chronic phase of experimental renal hypertension. On the contrary, others believe in an increased sympathetic discharge. Recent evidence indicates that some of the paradoxical findings with ganglionic blocking drugs are due to modification of the sinoaortic buffering mechanism.

It seems puzzling at first that blocking of sympathetic transmission by tetrathylammonium chloride (TEAC) can occasionally result in blood pressure elevation rather than reduction and that an originally depressor response to this agent may become pressor when given during infusion of a pressor substance. This well known reversal of the TEAC response following constant norepinephrine infusion in the anesthetized dog is shown in figure 1. If on the other hand the carotid sinus is completely isolated from the systemic circulation, and intrasinal pressure is maintained by a pump (the aortic depressor nerves are cut), TEAC will decrease blood pressure both before and during norepinephrine infusion. In the intact anesthetized animal, norepinephrine hypertension stimulates the baroceptors which in turn decrease sympathetic outflow. Thus, not much is left to be blocked by TEAC. However, TEAC also blocks the parasympathetic ganglia thus preventing bradycardia and causing a further pressure increase. When the baroceptors are excluded from the systemic circulation by a method to be described, they do not depress sympathetic outflow during norepinephrine infusion and TEAC will decrease blood pressure. In view of this modifying effect of the baroceptors, the response to TEAC in normal and renal hypertensive dogs following bypass of the carotid sinus was studied.

Method

Dogs were anesthetized by chloralose, 100 mg. per Kg. of body weight. Chloralose was chosen because this drug does not depress central reflex
mechanisms and leaves the buffer reflexes relatively intact. In a few of the experiments pentobarbital was used. The experimental method is shown in figure 2. Two pieces of an isolated vein were everted. One end of each was tied and the other end cannulated. This gave a very distensible balloon. Both carotid sinuses were isolated and as many of the distal branches as possible were tied without damaging the nerve. The sinus end of the common carotid artery was cannulated so that the balloon was inside the carotid sinus area. The system was filled with water at body temperature and connected to a pump producing pulsatile pressure. In some of the earlier experiments static pressure was applied using a pressure bottle. The central end of the left common carotid artery was cannulated by advancing a plastic tube into the aorta for injection of drugs directly into the arterial system. The left depressor nerve and the right vagus trunk were cut.

Direct femoral artery pressures and pressures in the carotid sinus region were recorded on a drum with an electric paper recorder. Before cannulating the sinus, a test dose of 5 mg per Kg. TEAC was given. TEAC response was then tested at different intrasinusal and femoral artery pressure levels. The test was started with high intrasinusal and low femoral artery pressures in which case a gradually increasing TEAC response was expected as the intrasinusal pressure was reduced. Twenty to 25 minutes elapsed between TEAC injections to allow restoration of the blood pressure to the starting level. Altogether 4 to 6 injections were given.

RESULTS

Renal hypertensive dogs were prepared by cellophane encapsulation of 1 kidney and removal of the contralateral kidney. The responses of a normal dog are seen in figure 3. With high intrasinusal pressure and low sympathetic outflow, there is minimal TEAC response. As the pressure is lowered in the sinus and femoral artery pressure increases, the response to TEAC also increases indicating increasing sympathetic outflow which reaches its maximum at 0 intrasinusal pressure. Subsequent cutting of the carotid sinus nerves usually still increased the response, since complete 0 pressure can probably not be achieved in the sinus. The average of all the responses in 8 normotensive dogs is represented in figure 4. Sympathetic outflow, as

![Figure 1. Tetraethylammonium chloride (TEAC) response in an anesthetized dog before and after norepinephrine infusion. A, intact carotid sinus; B, intracarotid pressure maintained by a pump independently from the systemic circulation. Direct femoral artery pressure. Straight line in B is intrasinusal pressure. T, TEAC; 5 mg. per Kg. N and N, 1-norepinephrine, 0.6 mEq. per minute, N, 0.5 mEq. per minute. St. N, stop norepinephrine. Note pressure increase to TEAC following norepinephrine before bypass of the carotid sinus, and decrease afterwards.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.24.2.786?journalCode=circ)
FIG. 2. Experimental method. Pulsatile pressure produced by the pump can be seen in the right lower corner. Pressure level was controlled by changing resistance by a screw on the output side of the tubing.

FIG. 3. TEAC response in a normal dog at different intrasinusal pressure levels. A, before bypass of the carotid sinus. 1 and 2, response to rt and lt; 3 and 4, to both common carotid occlusion; 5–8, blood pressure response to TEAC at decreasing levels of intrasinusal pressures (upper straight line).

tested by TEAC response, is completely controlled by the carotid sinus and depends on the intrasinusal pressure.

Seven chronic renal hypertensive dogs showed similar response patterns with the exception that the whole level was shifted up-
ward (fig. 5). When intrasinusal pressure is equal to the hypertensive level previously present in the dog, the femoral artery pressure is also close to this level, indicating equilibrium between intrasinusal pressure, carotid sinus discharge, and sympathetic outflow, such as is present before bypass of the sinus.

As soon as the pressure is decreased in the sinus below the hypertensive level but still above normal blood pressure values, there is gradual increase in response to TEAC indicating increased peripheral sympathetic outflow. In figure 6 the 2 graphs are superimposed. At equilibrium between intrasinusal and peripheral blood pressure, TEAC response is the same in normal and chronic hypertensive dogs. This equilibrium is at a higher blood pressure level in the latter. The "floor level" following sympathetic block is also significantly higher in hypertensives as compared to normal animals even following maximal intrasinusal pressure and additional TEAC.

Acute renal hypertension, tested within 2 weeks of the development of hypertension, seems to react differently. TEAC decreased the blood pressure in acute renal hyperten-

**Fig. 4.** Response pattern to TEAC in 8 normotensive dogs at different intrasinusal pressure levels. Height of vertical line indicates blood pressure depression after administration of TEAC at the femoral artery and carotid sinus pressure indicated. Equilibrium between intrasinusal and femoral artery pressures is marked by the interrupted line.

**Fig. 5.** Response pattern to TEAC in 7 chronic renal hypertensive dogs at different intrasinusal pressure levels. Notations as in figure 4.

sion by the same degree as in normals only when intrasinusal pressure was lowered to the prehypertensive level (fig. 7). At the hypertensive intrasinusal pressure level the response to TEAC was much decreased, indicating buffering of the sympathetic outflow by the baroceptors.

A slight upward slope is present in both normal and hypertensive animals when the activity of the sinus is gradually increased and sympathetic outflow is blocked only by TEAC (fig. 6). This upward slope may be due to the relatively small dose of TEAC (5 mg. per Kg.) which was probably not sufficient to block completely all the ganglia during the great showers of sympathetic discharge. That it is probably not due to decreased sensitivity to TEAC is suggested by the fact that the slope was also present in the few experiments where testing was started at 0 intrasinusal pressure. In one chronic renal hypertensive dog subsequent pithing lowered the blood pressure to the same level as was achieved by high intrasinusal pressure plus TEAC block.

**DISCUSSION**

Sympathetic discharge is controlled by the buffer mechanism which in turn is regulated by the intra-arterial pressure itself. The interpretation of the response to vasoactive and ganglionic blocking drugs is complicated in
the presence of the regulatory mechanism since the activity of the baroceptors and the sympathetic outflow varies with the fluctuation of humoral factors participating in the maintenance of the blood pressure. Vasoactive and ganglionic blocking drugs such as TEAC will only adequately measure the sympathetic vasomotor tone in the presence of actively responding baroceptors.

In chronic renal hypertension, sympathetic outflow is not significantly different from normal since at the elevated blood pressure the baroceptors reached an equilibrium and sympathetic discharge is at a normal rate. This equilibrium is achieved by resetting of the buffer system at the higher blood pressure level. The carotid sinus fires at a normal rate at the hypertensive level, as was shown by McCubbin and co-workers.8 This resetting is probably not central but in the receptors itself or in the barosensitive arterial walls. This is suggested by the fact that disruption of all buffer nerves leads to permanent hypertension and permanently high sympathetic outflow. Adaptation of the centers to the loss of a buffer mechanism would result in a slow decrease in blood pressure which apparently does not occur.

It seems evident from these experiments that resetting of the baroceptor plays a role in the maintenance of chronic renal hyper-

tension since it counteracts any decrease of the blood pressure below the hypertensive level. However, further observations are necessary to determine whether this mechanism is effective in resisting a decrease of blood pressure over a period of time.

In the acute phase of experimental renal hypertension, resetting of the baroceptors is not yet established. Hypertension is apparently caused by a great increase of circulating pressor substances and is incompletely buffered by the baroceptors, which are only partially effective in reducing the elevated blood pressure. Sympathetic outflow is decreased as can be shown by the TEAC response pattern.

The residual vasoconstriction represented by the different “floor” levels in normal and chronic renal hypertensives following sympathetic blockade must be humoral in origin. This higher floor level is due to either increased circulating pressor substances or increased sensitivity to normal amounts of pressor substances. Both elevation of pressor substances and increased sensitivity to angiotensin and norepinephrine in chronic renal hypertension has been shown by others.9 The nature of the increased sensitivity to pressor substances and the relation to the resetting of the baroceptors remains to be shown.
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Circulation. 1958;17:785-790
doi: 10.1161/01.CIR.17.4.785

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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