Effect of hypoxia on vascular responses to the carotid baroreflex

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Pelletier, Conrad L., and John T. Shepherd. Effect of hypoxia on vascular responses to the carotid baroreflex. Am. J. Physiol. 228(1):331–336, 1975.—The effect of systemic hypoxia on the vascular responses to the carotid baroreflex was studied in anesthetized, vagotomized, artificially ventilated dogs. One hindlimb, kidney, gracilis muscle, and paw were perfused at constant flow, and neurograms were obtained from renal sympathetic fibers. Bilateral carotid occlusions were performed while the animal was breathing a mixture of air and O2 (mean arterial P02 = 106 mmHg) and again during ventilation with 10% O2 (P02 = 40 mmHg). With occlusion, the average increase in mean aortic pressure was 36 mmHg greater during hypoxia than during normoxia and the increase in renal perfusion pressure was 87 mmHg greater; the increase in hindlimb perfusion pressure was identical in both situations. Hypoxia did not change the reflex response of the paw to carotid occlusion and increased that of the muscle vessels by only 10%; the increase in renal sympathetic activity averaged 56 ± 10% more with hypoxia than with normoxia. When the carotid chemoreceptors were destroyed, the greater increase in aortic and renal pressure response to carotid occlusion during hypoxia as compared to normoxia was abolished. Thus systemic hypoxia markedly potentiates the reflex renal constriction caused by the baroreflex, and this effect is due to the carotid chemoreceptor afferent input.

carotid occlusion; chemoreceptors; hindlimb perfusion; kidney perfusion; muscle; paw; renal neurograms; peripheral resistance; sympathetic activity

ELIMINATION OF THE INHIBITORY influence of the arterial baroreceptors induces an increase in sympathetic nerve traffic to skeletal muscle and kidney. This increase is equivalent to electrical stimulation of the sympathetic nerves to the skeletal muscles at a frequency of eight impulses per second but at a frequency, at most, of only four impulses per second to the kidney. This indicates that withdrawal of baroreceptor restraint on the vasomotor center is followed by a lower firing rate in renal vasoconstrictor fibers than in those to skeletal muscle. This appears to result from a lower level of spontaneous activity in the renal neuron pools in the vasomotor center as compared to those governing the skeletal muscles (9, 11). However, in other circumstances, the response of the renal vessels to changes in baroreceptor activity can be greatly increased. In the cat, during hypoventilation or acidosis, the spontaneous activity in the renal vasomotor neurons evidently increases, so that the renal vasoconstriction in response to decreased baroreceptor activity is augmented (6, 9); in the rabbit, inter-

ruption of aortic or vagal nerve afferents during normoxia causes a relatively greater reflex constriction of muscle than of renal vessels, whereas during hypercapnia this is reversed (12, 13). Hypothalamic stimulation also modifies the sensitivity of renal resistance vessels to carotid sinus pressure (2); it increases renal sympathetic output at low pressure and displaces the point of complete inhibition at a higher pressure (15).

Thus it appears that the changes in renal resistance induced by the baroreflexes can be altered by other inputs converging or acting directly on the vasomotor neurons. In the current studies, the effect of hypoxia on the vascular responses to the carotid baroreflex was studied in order to examine the possibility that the carotid chemoreflex might affect the renal involvement in the baroreflex.

METHODS

Preparation

Dogs, 10–29 kg in body weight, were anesthetized with thiopental and chloralose (15 and 60 mg/kg, respectively) and artificially ventilated at 12–15 cycles/min. Additional chloralose (10 mg/kg) was administered hourly. Prior to cannulation of the blood vessels, gallamine and heparin (3 mg/kg each) were given intravenously and repeated hourly (1 mg/kg each). The two vagosympathetic trunks were cut in the neck.

In the control condition, the dogs were ventilated with a mixture of room air and O2. Systemic hypoxia was produced by ventilating the animals with 10% O2 in N2 for 2 min, after which the ventilation was returned to the control condition (normoxia reached after 2 min). Blood samples were taken during the control situations before and after hypoxia and at the end of 2 min of hypoxic ventilation for measurement of arterial blood gases and pH. In the normoxic condition, arterial P02 averaged 106 mmHg (range: 77–142 mmHg); after 2 min of hypoxic ventilation it averaged 40 mmHg (range: 32–47 mmHg). Arterial Pco2 was maintained normal throughout the experiment by adjusting the tidal volume and was the same during normoxia and hypoxia, averaging 32 mmHg (range: 25–38 mmHg). The pH of arterial blood was kept normal by infusing bicarbonate as needed and averaged 7.41 (range: 7.34–7.49) during normoxia and 7.41 (range: 7.35–7.53) during hypoxia.

Bilateral occlusion of the common carotid arteries (BCO) was used to study the reflex responses to decreases in carotid...
baroreceptor activity. Each occlusion lasted 30-40 s and was not repeated until all pressures had returned to control level. The occlusion was done during the control condition, after 2 min of hypoxic ventilation, and 2 min after normoxic ventilation was resumed. To minimize the duration of systemic hypoxia, only one occlusion was done for each period of hypoxia, which was repeated an average of 4 times in each experiment, interrupted by intervals of at least 6 min of normoxia.

The left lumbar sympathetic trunk was cut at the level of L₂, and the rami at L₃, L₄, and L₅ were divided. A bipolar stimulating electrode was placed on the trunk between L₃ and L₄. Monophasic square-wave stimuli were given (Grass stimulator, model S-4) at 10 V, 5 ms duration, and frequencies from 1.0 to 12/s. Stimulation was maintained until the response of the hindlimb resistance vessels had reached a plateau. Between stimulations, hindlimb perfusion pressure was allowed to return to control level.

Measurements

All pressures were measured with strain-gauge transducers (Statham P23 De) and recorded on a Honeywell ultraviolet Visicorder (model 1508).

Aortic pressure. The pressure was measured in the aortic arch through a catheter inserted in the right brachial artery.

Constant-flow perfusion. The kidney, hindlimb, gracilis muscle, and paw were perfused at constant flow with roller pumps, using arterial blood taken from the iliac artery. Depulsators and heat exchangers were interposed in the perfusion lines, and the temperature of the blood was maintained at 37°C. Perfusion pressures were measured through the side arm of T connectors immediately upstream from the inflow cannula to each bed. The perfusion pressures of the hindlimb, gracilis muscle, and paw were adjusted to approximately mean aortic pressure at the beginning of the experiment (about 150 mmHg); the perfusion pressure of the kidney was set between 100 and 110 mmHg to avoid excessively high perfusion pressures being reached in the kidney during sympathetic nerve activation and a failure to return to control levels on cessation of stimulation. After the pressures were adjusted initially, they were left unchanged thereafter. The left renal artery was cannulated at its origin from the aorta. The renal blood flow was 3.2 ± 0.3 ml/min per g of tissue (mean ± SE).

The hindlimb was perfused via the left external iliac artery. To eliminate other sources of arterial inflow to the limb, all branches of the terminal aorta, the deep circumflex iliac artery, and the deep caudal epigastric artery were ligated. The left gracilis muscle was isolated from the remainder of the thigh, except for its neurovascular pedicle, and its artery was cannulated. The left paw was perfused via a cannula inserted in the cranial tibial artery 3-4 cm above the ankle, and all other arterial branches were tied at this level. Blood flows averaged 12 ml/min in the gracilis muscle and 33 ml/min in the paw. Satisfactory isolation of the vascular beds studied was indicated by a backflow pressure of 40 mmHg or less when the perfusion lines were occluded. Flow being constant, changes in perfusion pressure reflected changes in vascular resistance in each bed.

Renal neurograms. Efferent activity was recorded from multifiber preparations of sympathetic nerves to the left kidney. Through a lateral incision, the renal nerve was dissected retroperitoneally over a length of 2 cm with the use of a dissecting microscope. Fat and connective tissue were removed, the nerve was thinned, and its distal end was crushed. The remaining fibers were placed on a pair of platinum electrodes 3-4 mm apart. The whole preparation was immersed in mineral oil to prevent nerve fibers from drying. The nerve signals were amplified (AC preamplifier P511 and power supply RPS-107, Grass Instrument Co., Quincy, Mass.) and transformed into standard pulses. At the beginning of each experiment, the activity record was inspected to determine the noise level as judged by the background activity during the quiet periods between the bursts of impulses; a discriminator was then set to eliminate the noise from being counted. The impulse frequency was integrated by a rate meter. The response-time characteristics of the equipment permitted counting of signals at intervals of 0.25 ms.

Analysis of Data

Because the tests were repeated in the same dog, the responses to BCO during normoxia and those during hypoxia were averaged separately for each dog, and these averages were used to calculate the mean results for the group. All results were expressed as means ± SE. The Student paired t test was used for the statistical analysis of the data.

RESULTS

Carotid Sinus Pressure

In 6 of the 10 dogs referred to below, the changes in carotid sinus pressure with BCO were measured distal to the level of occlusion by a catheter inserted through the external carotid artery. Before occlusion, mean sinus pressure averaged 143 ± 7 mmHg during normoxia and
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144 ± 6 mmHg during hypoxia; mean pulse pressure was 30 and 29 mmHg and mean pulse frequency was 162 and 166/min, respectively. With BCO, carotid sinus pressure decreased to 75 ± 3 and 72 ± 4 mmHg, respectively, and then stabilized at 114 ± 5 and 115 ± 8 mmHg after approximately 15 s of occlusion.

Renal and Hindlimb Resistance Vessels

In 10 dogs, the left kidney and hindlimb were perfused simultaneously. Before BCO, mean aortic pressure was identical during normoxia and hypoxia (147 ± 6 mmHg). There was no significant change in the perfusion pressures in response to hypoxia (Fig. 1). With normoxia (mean arterial PO₂ = 107 mmHg), BCO caused a larger increase in hindlimb perfusion pressure than in kidney perfusion pressure. The reverse occurred when BCO was performed during hypoxia (mean arterial PO₂ = 41 mmHg). The increase in mean aortic pressure averaged 36 mmHg larger with hypoxia and the renal perfusion pressure increased 3 times more than during normoxia; the response in the hindlimb was the same in both conditions (Fig. 2).

In five of these dogs, the influence of the carotid chemoreceptors was eliminated by ligating the occipital arteries at their origin from the external carotid and by dissecting and removing the immediately adjacent tissue; BCO was repeated afterward and two or three tests with hypoxia were performed. Prior to occlusion, all pressures were similar during normoxia (mean arterial PO₂ = 117 mmHg) and hypoxia (mean arterial PO₂ = 38 mmHg). After the chemoreceptors were eliminated, the increases in aortic, renal, and hindlimb pressures caused by BCO during hypoxia did not differ in any of these dogs from those during normoxia (Figs. 1 and 2). No apparent damage to baroreceptor fibers or loss of reactivity occurred after surgical destruction of the chemoreceptors because the increases in aortic pressure and in hindlimb and renal perfusion pressures with BCO during normoxia were similar to those obtained prior to these manipulations, averaging 63, 61, and 39 mmHg, respectively (Fig. 2).

Maximal Lumbar Sympathetic Activation

In three dogs, the left lumbar sympathetic trunk was electrically stimulated at frequencies of 1.0–12 cycles/s. Stimulus-response curves were obtained during normoxia and systemic hypoxia, and the maximal increases in hindlimb perfusion pressure were compared to the maximal pressure achieved with BCO in the same dog (Fig. 3). There was no difference in the curves for stimulations performed under normoxic or hypoxic conditions. The maximal perfusion pressures with electrical stimulation were 25, 78, and 59 mmHg higher than the maximal hindlimb perfusion pressure achieved during BCO in each dog.

Muscle and Paw Resistance Vessels

In four dogs, the gracilis muscle and the paw were studied simultaneously. Before occlusion, mean aortic pressure averaged 137 ± 6 mmHg during normoxia (mean arterial PO₂ = 110 mmHg) and 142 ± 7 mmHg during hypoxia (mean arterial PO₂ = 35 mmHg). Hypoxia did not cause any change in perfusion pressure of the paw but it increased that of the muscle by an average of 9 mmHg (Fig. 4). With systemic hypoxia, the increase in aortic pressure due to BCO averaged 31 mmHg greater than during normoxia; the increase in muscle perfusion pressure was also significantly greater (P < 0.05), averaging 19 mmHg more, but the response in the paw did not change significantly. When computed as percentage of control pressure, the increase in perfusion pressure of the muscle with BCO was only 10% greater during hypoxia than
and short duration was used, and arterial $P_{CO_2}$ and $pH$ were maintained normal throughout the experiments. An arterial $P_{O_2}$ of 40 mmHg is known to activate the carotid chemoreceptors and cause a reflex vasoconstriction when the carotid bodies are selectively perfused in vagotomized dogs with the activity of the carotid baroreceptors maintained constant (14). In the present experiments, systemic hypoxia did not cause such circulatory changes with the carotid baroreceptors operative, although the $P_{O_2}$ averaged 40 mmHg at the time of carotid occlusion. It also has been found by others (3, 5), in the dog and the rabbit, that such a degree of systemic hypoxia does not change the limb or muscle vascular resistances. Presumably, this results from
the interaction of a number of excitatory and inhibitory effects of the hypoxia. With the hypoxia, there was no significant difference in mean aortic pressure, pulse pressure, and pulse frequency before the occlusion, as compared to normoxia, in 14 of the 20 animals studied. Likewise, the changes in carotid sinus pressure during occlusion were similar to those in normoxic conditions. However, in the six dogs in which renal sympathetic nerve activity was determined, there was a small but significant decrease in mean aortic pressure (from 135 ± 7 to 142 ± 6 mmHg) when the animals were made hypoxic.

Our results demonstrate that moderate hypoxia markedly increases the reflex response of the kidney to the baroreflex, while that of the extremity is unchanged. When the two major components of the extremity were separately investigated, it was found that hypoxia did not affect the reflex responses of the cutaneous resistance vessels and increased only slightly those of the muscle vessels. Because of the shift in control perfusion pressure of the latter during hypoxia, it is not possible to determine whether the 10% increase in the response was due to increased neurogenic activity or to the change in vessel wall tension consequent to hypoxia. At any rate, the difference in the response is at most modest and would support the results obtained with the perfusion of the whole hindlimb— that the response of this vascular bed to the baroreflex is affected little or not at all by hypoxia. The local effect of the lack of oxygen on the vascular smooth muscle of the limb could not have prevented the increase in the constrictor response because the vascular responses to electrical stimulation of the lumbar sympathetic chain were similar during normoxia and hypoxia. With electrical stimulation, the hindlimb perfusion pressure could be increased by 25–78 mmHg above that achieved by carotid occlusion, indicating that further vasoconstriction was possible.

In contrast, the constrictor response of the kidney to carotid occlusion was markedly potentiated by systemic hypoxia, increasing by approximately threefold. This increase occurred from the same control value as that present during normoxia. The increase in sympathetic nerve activity to the kidney caused by carotid occlusion was also markedly enhanced during hypoxia, confirming that the potentiation of the response was neurogenic. On release of bilateral carotid occlusion, the sympathetic nerve activity decreased abruptly to zero, both during normoxia and hypoxia. This suggests that the effect of hypoxia was mediated through the same pool of central neurons as those affected by the carotid baroreceptors.

The systemic hypertension resulting from the carotid occlusions was always greater with hypoxia than during normoxia (by 31–36 mmHg). It has been shown that the cardiac output is little affected by the carotid baroreflex (4). Thus, the hypertension would be due mostly to changes in peripheral resistance, and the larger response during hypoxia could reflect the enhancement of the renal vasoconstriction; however, it is possible that other vascular beds behave similarly to the kidney.

Elimination of the carotid chemoreceptors did not affect the reflex responses to carotid occlusion during normoxia, indicating that this procedure caused no apparent damage to the baroreceptor fibers and that the carotid chemoreceptors did not contribute to the reflex response to bilateral carotid occlusion. During hypoxia, the potentiation of the renal and aortic pressure responses to carotid occlusion was abolished. Our experiments do not remove the possibility that oxygen deprivation might affect directly the cerebral or spinal neurons to alter their level of spontaneous activity, as suggested by other authors (1, 6), but, at the level of hypoxia used in the present study, such a central action did not seem to occur, because after the carotid bodies were destroyed all the hemodynamic changes in response to bilateral carotid occlusion were similar during normoxia and hypoxia.

Thus, the potentiation of the renal responses to the carotid baroreflex would appear to be due to the carotid chemoreceptors. Similarly, Grillhorn et al. (7) have shown that the blood pressure increase in response to hypothalamic stimulation was greater with anoxia and that this was due to theafferent activity from the sinoaortic chemoreceptors.

Our results support the hypothesis that the intrinsic level of activity of the neurons governing the renal circulation is normally low (9, 11). Stimulation of the carotid chemoreceptors would result in an increase in activity that would not become manifest until these neurons were released from the restraint exerted by the carotid baroreceptors. When the latter occurs, there is a much larger increase in sympathetic outflow to the kidney than there is in the absence of chemoreceptor stimulation. This would also account for Korner’s findings (10) that, in arterial hypoxia, the increase in renal resistance is evoked through the combination of chemoreceptor and baroreceptor input, while sustained renal vasoconstriction cannot be obtained from the latter alone. Hypothalamic stimulation (2, 15), stimulation of afferent fibers from somatic muscles (8), C02 (13), or acaposis (9) would exert a similar excitatory action on this neuron pool. In contrast, the neurons controlling the resistance vessels of the extremities appear to discharge at a near-maximal level when released from the inhibitory effect of the baroreceptors, and little further increase would be expected by addition of another excitatory afferent input.

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