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Effect of Controlled Ventilation on Renal and Splanchnic Blood Flows during Severe Arterial Hypoxia (42366)

GEORGE J. CRYSTAL, TIMOTHY D. SAYE, AND MARIA T. B. BEDRAN DE CASTRO

Department of Physiology, University of Texas Health Science Center and Cardiovascular Research Center at Methodist Hospital, Dallas, Texas 75235, and Departments of Anesthesiology, University of Illinois College of Medicine, and Illinois Masonic Medical Center, Chicago, Illinois 60680

Abstract. The present study was undertaken to evaluate the extent that the lung inflation reflex attenuates vasoconstrictor responses in renal cortex and splanchnic beds during severe arterial hypoxia. Hypoxia was induced by inspiration of a 3–5% oxygen gas mixture in three groups of chloralose-anesthetized dogs: Group I, free breathing; Group II, controlled ventilation; Group III, free breathing with arterial PCO_2 held constant. Regional vascular conductances (VC) were calculated from regional blood flows measured with 15-μm radioactive microspheres. In Group I, hypoxia caused marked hyperventilation, which was accompanied by no significant change in VC in renal cortex, and by reductions in VC in spleen (−36%), pancreas (−56%), and duodenum (−28%). In Group II, hypoxia caused reduction in VC in renal cortex (−70%), and reductions in VC in spleen, pancreas, and duodenum similar to those in Group I. In Group III, hypoxia again caused marked hyperventilation, but reductions in VC in renal cortex, spleen, pancreas, and duodenum were similar to those in Group II. Results indicate that during severe arterial hypoxia activation of lung inflation reflex does not attenuate or reverse vasoconstriction in renal cortex, spleen, pancreas, and duodenum.

Mechanical hyperventilation has been demonstrated to cause peripheral vasodilation in a variety of vascular beds, including the renal and splanchnic beds (1, 2). This vasodilation is initiated by pulmonary stretch receptors and is the result of reduction in sympathetic tone. When hyperventilation occurs reflexly during selective activation of carotid bodies with nicotine or hypoxic blood (3, 4), or during moderate arterial hypoxia (5), the lung inflation reflex attenuates the sympathetic vasoconstrictor response in the renal and splanchnic beds caused by chemoreceptor stimulation. However, our recent finding (6) of similar reductions in renal and splanchnic vascular conductance during intravenous infusion of nicotine in free-breathing and artifically ventilated dogs demonstrates that the lung inflation reflex can be completely negated when opposed by sufficiently potent vasoconstrictor mechanisms. During intravenous nicotine, these vasoconstrictor mechanisms include high levels of sympathetic outflow secondary to stimulation of sympathetic ganglia, central nervous system, and arterial chemoreceptors, as well as elevated blood concentrations of vasopressin.

It remains uncertain to what extent the lung inflation reflex attenuates renal and splanchnic vasoconstriction during severe arterial hypoxia, when arterial PO_2 is lowered adequately (below 30 mm Hg) for direct stimulation of the central nervous system (7) to reinforce the increase in sympathetic outflow arising from the arterial chemoreceptors. Accordingly, the present study was conducted in which changes in renal and splanchnic blood flows and vascular conductances during severe arterial hypoxia were compared in free-breathing and artificially ventilated dogs.

Materials and Methods. Experiments were performed on adult mongrel dogs of either sex. The dogs were tranquilized with ketamine hydrochloride, 2 mg/kg iv (Ketalar; Parke, Davis & Co., Detroit, Mich.) before being anesthetized with α-chloralose, 100 mg/kg iv initially and supplemented as required to maintain a stable plane of anesthesia. Animals were intubated and catheters were inserted into (a) the thoracic aorta (via the right brachial artery) for measurement of mean aortic pressure, (b) the vena cava (via the left femoral vein) for measurement of central venous pressure, (c) the left ventricle (via the left femoral artery

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and aorta) for systemic injections of radioactive microspheres, and (d) the right femoral vein for intravenous injections. Respiratory activity was monitored with a pneumograph (Harvard Apparatus Company, Inc., South Natick, Mass.). Heparin, 500 U/kg iv (Elkins-Sinn, Inc., Cherry Hill, N.J.), was used as an anticoagulant. Blood pressures were measured with Statham pressure transducers, Model 23Db (Gould Inc., Oxnard, Calif.). A record of blood pressures and of respiratory activity was made with a Beckman recorder, Model R411 (Beckman Instruments, Inc., Schiller Park, Ill.).

Regional organ blood flows were determined from tissue content of 15 ± 3-μm microspheres administered into the left ventricle. The microspheres were labeled with gamma-emitting radionuclides (^{46}Sc, ^{51}Co, ^{85}Sr, ^{113}Sn; New England Nuclear, Boston, Mass., and 3M Co., St. Paul, Minn.). Prior to injection, the microspheres were dispersed by agitation in an ultrasonic bath and with a vortex mixer. Approximately 10^6 microspheres were administered for each flow determination. These determinations had no detectable effect on monitored hemodynamic parameters. Upon injection of microspheres, duplicate reference samples of arterial blood were withdrawn from two different sites in the aorta at a constant rate (approximately 7.5 ml/min) for 2 min, so that regional blood flows could be computed (8). A difference of less than 10% of radioactivity in duplicate reference samples verified adequate mixing of microspheres in the left ventricular output.

After the final dose of microspheres, the dog was killed by intravenous injection of potassium chloride. The kidneys and portions of spleen, pancreas, duodenum, and liver were removed. Duplicate samples were cut from excised tissues, placed in vials, and weighed. Flow values for duplicate samples were averaged. The tissue samples and the reference arterial blood samples were analyzed for radioactivity in a gamma counter equipped with a multichannel analyzer (Packard Instrument Co., Downers Grove, Ill.). Isotope separation was accomplished by standard techniques of gamma spectroscopy with the aid of PDP/8E minicomputer (Digital Equipment Corp., Maynard, Miss.). Sufficient counts were accumulated from all samples to maintain counting errors less than 3%. All tissue samples contained at least 400 microspheres, which was sufficient for low error, high precision flow measurements (9).

Twenty-one dogs were divided into three equal groups. Those in Groups I and III breathed spontaneously through a low resistance valve system. Dogs of Group II were ventilated by a Harvard respirator after undergoing bilateral thoracotomy and skeletal muscle paralysis with succinylcholine, 1 mg/kg iv with supplementary injections when necessary (Anectine; Burroughs Wellcome Co., Research Park, N.C.), in order to prevent chemoreflex hyperventilation during hypoxia. Under control (normoxic) conditions, dogs inspired room air which was enriched with oxygen, if necessary, to maintain arterial PO_2 above 100 mm Hg. Any metabolic acidosis was corrected by intravenous infusion of 7.5% $NaHCO_3$. Values for monitored hemodynamic parameters and anaerobic samples of arterial blood were obtained. Subsequently, the blood samples were analyzed for PO_2, PCO_2, and pH with an Instrumentation Laboratory blood gas analyzer, Model 113 (Instrumentation Laboratory, Inc., Boston, Mass.) and for hematocrit by centrifugation. The first injection of microspheres was made to define the distribution of organ blood flows during control (normoxic) conditions. After control determinations, the dogs were made hypoxic by ventilating them with a low oxygen gas mixture. The free-breathing dogs of Group I were administered 4.6% oxygen in nitrogen, which, in addition to reducing arterial PO_2, also reduced arterial PCO_2 and increased arterial pH because of chemoreflex hyperventilation (see Results). The artificially ventilated, thoracotomized, and paralyzed dogs of Group II were administered 4.6% oxygen in nitrogen to induce systemic hypoxia in the absence of chemoreflex hyperventilation. Arterial PCO_2 and pH remained near control values in this group. The free-breathing dogs of Group III were adminstered hypoxic gas which contained carbon dioxide (5% oxygen–5% carbon dioxide in nitrogen), so that arterial PCO_2 and pH remained at control levels in spite of chemoreflex hyperventilation. In some dogs of Group III, it was necessary to add 2% oxygen–5% carbon dioxide in nitrogen to the hypoxic gas mixture in order to lower arterial PO_2 to

a level comparable with that in the dogs of Groups I and II. During hypoxia, microsphere injections were made and values for systemic hemodynamic parameters were obtained when monitored hemodynamic parameters attained steady state levels (usually 4–5 min after switching to low oxygen gas mixture). Animals were maintained on hypoxia for 2 min following injection of microspheres to permit collection of reference samples.

In six of the animals ventilated by a respirator (Group II) differently labeled 50-μm microspheres were injected along with the 15-μm microspheres to measure regional organ blood flows during systemic hypoxia. Prior to injection, the different size microsphere suspensions were prepared as described above. Then the different sized spheres were combined in a syringe which was agitated vigorously with a vortex mixer to ensure thorough mixing just prior to injection. In five additional artificially ventilated dogs, regional distribution of 15- and 50-μm microspheres was compared under normoxic conditions.

The statistical significance of differences in effects of hypoxia for Groups I–III (free breathing, controlled ventilation, and free breathing with PCO_2 constant) was tested using a completely randomized analysis of variance and the Student–Newman–Keuls procedures (10). The Student t test (10) was used to test the effect of hypoxia within experimental groups and to test the difference in regional distributions of 15- and 50-μm microspheres.

Results. *Group I: Responses to systemic hypoxia in free-breathing dogs without correction of hypocapnia.* In this group, hypoxia was associated with marked reduction in arterial PO_2 to 16.9 ± 0.9 mm Hg, and hyperventilation (Fig. 1), which reduced arterial PCO_2 and increased arterial pH (Table I). These blood gas changes were accompanied by an increase in aortic pressure (+35%) and by no change in heart rate (Table I). Under these conditions, hypoxia had no significant effect on blood flow in renal cortex or splanchnic organs (Table II).

Regional blood flow is determined by the perfusion pressure gradient and by the regional vascular conductance (VC). Because systemic hypoxia caused changes in aortic and venous pressures, vasoactivity in regional circulations was assessed through changes in regional vascular conductance, which was calculated according to the equation

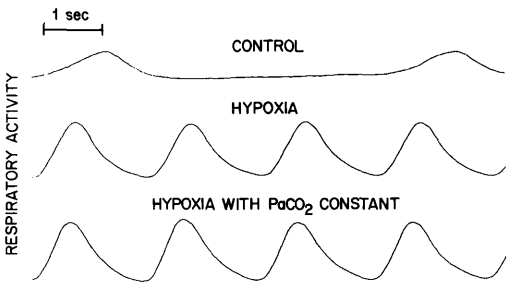

FIG. 1. Actual tracing from single dog demonstrating similarity of increase in respiratory activity during severe arterial hypoxia with and without constant arterial PCO_2.

$$VC = \text{blood flow}/(\text{mean aortic pressure} - \text{mean central venous pressure}).$$

Since central venous pressure rather than portal venous pressure was used to calculate conductance in pancreas, duodenum, and spleen, conductances in these vascular beds may be slightly underestimated.

In Group I, hypoxia caused reduction in vascular conductance in spleen (−36%), pancreas (−56%), and duodenum (−28%), but it did not affect vascular conductance in renal cortex or liver, i.e., hepatic artery bed (Fig. 2).

Group II: Responses to systemic hypoxia in dogs during controlled ventilation. In this group, hypoxia was associated with marked reduction in arterial PO_2 to 15.4 ± 2.2 mm Hg and with relatively constant arterial PCO_2 and pH (Table I). These blood gas responses were accompanied by an increase in aortic pressure (+35%) and by a decrease in heart rate (−43%) (Table I).

With ventilation controlled, hypoxia decreased blood flow in renal cortex (−65%), spleen (−47%), and pancreas (−72%), but it had no effect on blood flow in duodenum or liver (Table II). Controlled ventilation converted no change in vascular conductance in renal cortex during hypoxia into a marked decrease (−70%), while it did not affect reductions in vascular conductance in spleen, pancreas, and duodenum during hypoxia (Fig. 2). As in Group I, hypoxia had no effect on vascular conductance in liver (Fig. 2).

Group III: Responses to systemic hypoxia

TABLE I. EFFECT OF SEVERE ARTERIAL HYPOXIA ON ARTERIAL BLOOD GASES AND SYSTEMIC HEMODYNAMIC PARAMETERS DURING FREE BREATHING (GROUP I), CONTROLLED VENTILATION (GROUP II), AND FREE BREATHING WITH ARTERIAL PCO_2 CONSTANT (GROUP III)

	Group I		Group II		Group III	
	Control	Hypoxia	Control	Hypoxia	Control	Hypoxia
PO_2 (mm Hg)	209 ± 30	16.9 ± 0.9*	171 ± 27	15.4 ± 2.2*	168 ± 20	16.7 ± 1.3*
PCO_2 (mm Hg)	40.4 ± 5.3	23.2 ± 3.5*	39.3 ± 1.8	35.4 ± 1.1*	38.1 ± 2.3	40.6 ± 1.9*
pH	7.39 ± 0.02	7.57 ± 0.04*	7.40 ± 0.01	7.42 ± 0.01	7.41 ± 0.01	7.38 ± 0.02
Hematocrit (%)	36.7 ± 4.4	43.2 ± 4.7*	37.4 ± 4.2	42.6 ± 4.3*	40.4 ± 3.9	43.3 ± 3.6*
Mean aortic pressure (mm Hg)	141 ± 9	191 ± 21*	114 ± 8	154 ± 10*	129 ± 8	161 ± 6*
Central venous pressure (mm Hg)	7.4 ± 1.0	8.4 ± 2.2	4.5 ± 1.4	10.1 ± 1.5*	4.0 ± 1.1	4.4 ± 0.9
Heart rate (beats/min)	149 ± 13	137 ± 22	151 ± 11	86 ± 12*	159 ± 13	68 ± 6*

Note. Values are means ± SE in seven dogs.
* $P < 0.05$, effect of hypoxia.

in free-breathing dogs with correction of hypocapnia. In this group, hypoxia was associated with marked reduction in arterial PO_2 to 16.7 ± 1.3 mm Hg, but with no remarkable change in arterial PO_2 or pH (Table I) in spite of pronounced hyperventilation. The magnitude of this hyperventilation was comparable to that in free-breathing dogs without correction of hypocapnia (Fig. 1). In Group III, hypoxia increased aortic pressure (+25%) and reduced heart rate (−57%) (Table I).

In Group III, hypoxia reduced blood flow in renal cortex (−52%), spleen (−60%), and pancreas (−70%), but it caused no change in blood flow in duodenum and liver (Table II). The blood flow responses in renal cortex, spleen, pancreas, and duodenum were associated with reductions in vascular conductance, which were similar to those under controlled ventilation (Fig. 2). In Group III, hypoxia had no effect on vascular conductance in liver (Fig. 2).

Comparison of blood flows measured with 15- and 50-μm microspheres. Table III presents ratios of regional blood flows measured with 15-μm microspheres to those measured with 50-μm microspheres under control conditions and during hypoxia. These data indicate that 15- and 50-μm microsphere blood flows were not significantly different except in liver during hypoxia when 15-μm flows were modestly higher.

Discussion. *Critique of microsphere method.* In the present study 15-μm radioactive microspheres were used to measure regional organ blood flows. Microspheres of this size were

TABLE II. EFFECT OF SEVERE ARTERIAL HYPOXIA ON BLOOD FLOW IN RENAL CORTEX AND SPLANCHNIC ORGANS DURING FREE BREATHING (GROUP I), CONTROLLED VENTILATION (GROUP II), AND FREE BREATHING WITH ARTERIAL PCO_2 CONSTANT (GROUP III)

	Group I		Group II		Group III	
	Control	Hypoxia	Control	Hypoxia	Control	Hypoxia
Renal cortex	603 ± 73	666 ± 101	616 ± 37	216 ± 66*	527 ± 73	252 ± 90*
Spleen	204 ± 33	178 ± 45	139 ± 27	73 ± 18*	134 ± 36	54 ± 17*
Pancreas	46 ± 6	29 ± 10	47 ± 12	13 ± 2*	27 ± 5	8 ± 3*
Duodenum	75 ± 20	61 ± 9	61 ± 15	44 ± 5	48 ± 15	34 ± 5
Liver (hepatic A.)	44 ± 10	61 ± 8	16 ± 8	19 ± 6	47 ± 11	50 ± 13

Note. Value are means ± SE in seven dogs. Flows = ml/min/100 g.
* $P < 0.05$, effect of hypoxia.

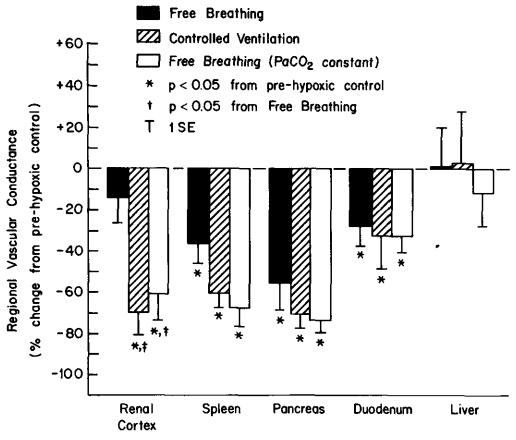

FIG. 2. Effect of severe arterial hyoxia on vascular conductance in renal cortex and splanchnic beds during free breathing, controlled ventilation, and free breathing with arterial PO_2 constant.

chosen because they had demonstrated no significant shunting in regional beds under control conditions (11), and because the regional distribution of larger spheres is distorted by rheological properties which differ from those of red blood cells (12). Because information on shunting in renal cortex and splanchnic beds during hypoxia was lacking, we evaluated shunting of 15-μm microspheres in these vascular beds during systemic hypoxia by comparing their distribution to that of 50-μm microspheres, which have been observed to undergo complete entrapment during their first circulation (13). Our data indicate no significant difference in the distributions of 15- and 50-μm microspheres in renal cortex, spleen, pancreas, and duodenum under both control and hypoxic conditions. Since shunting of 15-μm microspheres was not apparent in the splanchnic beds, it is likely that the moderately greater presence of 15-μm microspheres in liver was not due to their deivery via the portal system but due to anatomical pecularities of the hepatic circulation which hindered delivery of the 50-μm microspheres.

Effects of hypoxia. The major finding of the present study is that chemoreflex activation of lung inflation reflex does not attenuate or reverse vasoconstrictor responses in the renal cortex and splanchnic vascular beds during severe arterial hypoxia.

The marked vasoconstriction in spleen, pancreas, and duodenum during hypoxia in the free-breathing dogs of Group I is noteworthy because it occurred in the presence of three opposing vasodilator mechanisms: (a) the lung inflation reflex (inferred from increased chest expansion and arterial hypocapnia), (b) the local influence of very low arterial PO_2 (14), and (c) increased intravascular distending pressure. This implies very high levels of sympathetic vasoconstrictor nerve activity despite buffering by the arterial baroreceptors in response to arterial hypertension.

The absence of vasoconstriction in the renal cortex during hypoxia in Group I is not apparenty due to more pronounced local dilation by hypoxia, since previous studies have demonstrated that the renal bed, in contrast to the splanchnic beds, has minimal sensitivity to the direct effects of hypoxia (14). On the other hand, it is likely due to lesser reflex activation of the sympathetic vasoconstrictor nerves to the renal bed, because of a higher threshold for neurons in the central nervous system controlling its sympathetic outflow (15). The strong tendency of the renal bed to autoregulate its blood flow (16) may have also impaired renal vasoconstriction during systemic hypoxia in Group I.

In order to evaluate the contribution of the lung inflation reflex to hypoxia-induced vasomotor changes in the renal and splanchnic beds, we initially compared vasomotor responses in the free-breathing dogs of Group I to those in dogs whose ventilation was controlled. Controlling ventilation during hypoxia caused emergence of vasoconstriction in renal cortex, although it did not alter vasoconstrictor

TABLE III. RATIO OF REGIONAL BLOOD FLOW MEASURED WITH 15-μm MICROSPHERES TO THAT MEASURED WITH 50-μm MICROSPHERES

	Control (n = 5)	Hypoxia (n = 6)
Renal cortex	0.98 ± 0.03	0.99 ± 0.05
Spleen	1.02 ± 0.03	1.14 ± 0.09
Pancreas	1.06 ± 0.03	0.99 ± 0.06
Duodenum	0.88 ± 0.08	0.95 ± 0.07
Liver	1.16 ± 0.12	1.14 ± 0.05*

Note. Ratio of 1.0 indicates equal distribution of 15- and 50-μm microspheres

* $P < 0.05$, difference between distributions of 15- and 50-μm microspheres.

responses in spleen, pancreas, and duodenum. Our findings under controlled ventilation are consistent with past reports of widespread regional vasoconstriction during selective, hypoxic stimulation of carotid bodies in artificially ventilated dogs (4, 15). However, they are in sharp contrast to the report of Adachi *et al.* (17) which indicated that comparable arterial hypoxia in dogs under controlled ventilation caused vasodilation in pancreas and duodenum, and it had no net vasomotor effect in renal cortex and spleen. This discrepancy has several possible explanations. First, Adachi *et al.* used pentobarbital anesthesia, which has been demonstrated to cause significantly greater depression of chemoreceptor pathways than does α-chloralose (18). Second, in contrast to the present study, artificially ventilated dogs in the study of Adachi *et al.* were not thoracotomized and paralyzed. Inasmuch as Kontos *et al.* (19) showed that artificial ventilation without skeletal muscle paralysis was inadequate to prevent hyperventilation during hypoxia, inhibition of chemoreflex vasoconstriction by the lung inflation reflex cannot be discounted in the study of Adachi *et al.* Although we found that stimulatory input to the sympathetic nerves was sufficient to override inhibitory input from the pulmonary stretch receptors, this may not have been the case in the study of Adachi *et al.* when chemoreceptor pathways were depressed by pentobarbital anesthesia. Augmented lung inflation may also explain why Adachi *et al.* observed tachycardia during severe hypoxia in artificially ventilated dogs, whereas we and others (19) demonstrated bradycardia. Finally, because Adachi *et al.* extended hypoxia for 20 min more time was available for autoregulatory escape from the influence on the sympathetic vasoconstrictor nerves (20).

In addition to augmenting lung inflation, chemoreflex hyperventilation caused hypocapnic alkalosis in Group I which would be expected to influence regional vasomotor responses. Although hypocapnic alkalosis has been shown to cause local vasoconstriction (14), it has also been shown to reduce activity of arterial chemoreceptors (21) and to blunt sympathetic outflow (22). Thus, the role of hypocapnic alkalosis in dogs of Group I depended on the balance between these competing vasomotor mechanisms. To assess the effect of chemoreflex hyperventilation without the complicating influence of hypocapnic alkalosis, studies were conducted in free breathing dogs whose arterial PCO_2, and thus also pH, were held near control during hypoxia (Group III).

Despite significant chemoreflex hyperventilation, hypoxia with hypocapnia corrected caused vasoconstrictor responses in the renal cortex and splanchnic beds of Group III which were similar to those in dogs whose ventilation was controlled. This implies no important influence of the lung inflation reflex. Apparently, during severe arterial hypoxia stimulatory input from the arterial chemoreceptors and the central nervous system was sufficient to override inhibitory input from the pulmonary stretch receptors in control of sympathetic vasoconstrictor nerve discharge to the renal cortex and splanchnic organs.

The lack of significant reduction in vascular conductance in the hepatic bed during activation of the chemoreflex vasoconstrictor pathway may reflect autoregulatory responses to reduced portal blood flow because of vasoconstriction in other regions of the splanchnic bed. Such reciprocal vasomotor changes in the portal and hepatic circulations are well documented (22).

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