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Canine Renal Vascular Response to Bilateral Carotid Occlusion during Hypoxia[1] (42162)

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Abstract. Chloralose–urethane anesthetized dogs were utilized to determine if hypoxemic potentiation of the baroreceptor-mediated increase in renal sympathetic nerve activity (RSNA) results in sufficient renal vascular vasoconstriction to reduce renal blood flow (RBF) during bilateral carotid occlusion (BCO). Additionally, hypercapnia and mechanical ventilation were randomly combined with hypoxemia during BCO to determine if further augmentation of renal vasoconstriction could be accomplished. BCO resulted in a similar increase in blood pressure (renal perfusion pressure) in all periods. RBF was not reduced significantly by BCO during any period even though renal vascular resistance was significantly increased by BCO during each period. When hypoxemia was combined with hypercapnia and mechanical ventilation simultaneously, there was a greater percentage increase in renal resistance with BCO. During BCO, when renal perfusion pressure was returned to control values by suprarenal aortic constriction, RBF remained unchanged and renal resistance decreased to control values. These results indicate that the BCO-induced increase in RSNA is relatively moderate and, even when potentiated by hypoxemia, hypercapnia, and mechanical ventilation, is not sufficient to reduce RBF in the presence of an increase in blood pressure and renal autoregulation.

Bilateral carotid occlusion (BCO) and the baroreflex apparently have little effect on renal blood flow (RBF) (1–6) despite reflexive increases in renal sympathetic nerve activity (RSNA) (7–9). Presumably, the rise in arterial blood pressure (renal perfusion pressure, RPP) subsequent to BCO, along with renal vascular autoregulation, serves to maintain RBF (2, 3, 6, 10). Other central nervous stimuli which also increase RPP and RSNA, such as startle caused by a loud noise, result in a decrease in RBF (2). As shown by Gross and Kirchheim (2), the increase in RSNA with BCO is only 62%, while the increase in RSNA with startle is 500%. Therefore, the BCO-induced increase in RSNA is comparatively moderate and not sufficient to reduce RBF under these circumstances.

However, the baroreflex-mediated increase in RSNA has been shown to be potentiated by systemic hypoxia (8, 11). The increase in chemoreceptor afferent activity caused by hypoxemia acts on the motor neuron pool to facilitate the increase in RSNA when inhibition of the motor neuron pool is reduced by decreased baroreceptor afferent activity with BCO (12–16).

It has not been determined if the hypoxemic potentiation of the baroreceptor-mediated increase in RSNA results in sufficient renal vascular vasoconstriction to reduce RBF during BCO. Therefore, the purpose of the present study was to determine the RBF response to BCO during normoxia compared with the response during hypoxemia. Both hypercapnia and mechanical ventilation also have been shown to potentiate the cardiovascular effects of the chemoreceptor response to hypoxemia (17–20) and would be expected to augment the RSNA induced by BCO during hypoxemia. Thus, the RBF response to BCO was also evaluated during hypoxemia combined with hypercapnia and mechanical ventilation.

Materials and Methods. Eight mongrel dogs of either sex (20–25 kg) were anesthetized with chloralose (50 mg/kg) and urethane

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(500 mg/kg), with supplement anesthetic every half hour. Following intubation, the femoral artery was catheterized and the catheter tip advanced into the abdominal aorta to the level of the renal arteries. This catheter was used for the measurement of renal perfusion pressure (Statham P23db Transducer) and P_aO_2, P_aCO_2, and pH (IL 213 blood gas analyzer). A femoral vein catheter was placed for the administration of anesthetic or neuromuscular blocker when appropriate. A Swan–Ganz thermal dilution catheter was inserted into the jugular vein and advanced into the pulmonary artery for the measurement of cardiac output (Cardiomax II, Columbus Instruments). A left flank incision was performed and the renal artery approached retroperitoneally. After careful dissection to avoid damage of the renal nerves, an electromagnetic flow probe (Carolina Medical) was placed on the renal artery to obtain renal blood flow, and a Blalock adjustable clamp was placed around the aorta cranial to the origin of the renal arteries for the adjustment of renal perfusion pressure. Both carotid arteries were isolated in the neck and occluders applied loosely for bilateral carotid occlusion without manipulation of the arteries.

Cardiac output determinations were accomplished using room-temperature injectate. Injections were standardized by timing the injections to end-expiration (21), thereby reducing the variability.

Protocol. Sixty minutes following surgical preparation, the experimental protocol was initiated. With the animal spontaneously breathing room air, control measurements were made. BCO was then accomplished for 60 sec with hemodynamic measurements made at 30 sec. Renal perfusion pressure was then quickly reduced to control values and measurements of RPP and RBF made during the last 10 sec of BCO. All occlusions were released and the parameters permitted to return to control.

The animal was then randomly given one of three hypoxic gas mixtures to breathe, to represent hypoxia–hypocapnia (hypocapnia occurred as a result of spontaneous hyperventilation), hypoxia–eucapnia or hypoxia–hypercapnia. The hypoxic gas mixtures were accomplished by introducing N_2 into a mixing chamber on the inspiratory side of a unidirectional valve attached to the endotracheal tube. End-expired O_2 was monitored (Beckman OM-11) along with P_aO_2 to achieve the same level of hypoxemia in each case. When appropriate, CO_2 was added to the mixing chamber to achieve eucapnia or hypercapnia as monitored by end-expired CO_2 (Beckman LB-2) and P_aCO_2. The hypoxic gas mixture was delivered for 5 min prior to control measurements, followed by BCO as for the normoxic period.

Each of the three hypoxic periods was followed by a 10-min normoxic period with return of blood gases to normal. The final normoxic period included a repeat of the BCO maneuver.

The animals were then placed on a Harvard animal ventilator and blood gases normalized. Spontaneous ventilation was prevented by neuromuscular blockade with pancuronium bromide (0.1 mg/kg, supplemented with 0.01 mg/kg as needed). Following a normoxic period with BCO, a similar protocol to the spontaneously breathing protocol was accomplished. A hypoxic–hypocapnic period was not included as this would have necessitated hyperventilation with the ventilator, thus only hypoxia–eucapnia (eucapnia as a result of constant ventilation) and hypoxia–hypercapnia were utilized.

Statistical analysis. A repeated-measures analysis of variance with Duncan's post hoc test was used to compare means of each period and the means of the percentage change from control.

Results. Table I presents the arterial blood gases and pH. All hypoxic periods were at the same level of hypoxemia. Hypoxia–hypocapnia resulted in a significant decrease in P_aCO_2 and an increase in pH. All hypoxia–eucapnic periods had P_aCO_2 and pH values at control values; and all hypoxia–hypercapnia periods had a similar increase in P_aCO_2 with a decrease in pH.

Cardiac output, which averaged 3.7 ± 0.4 liter/min during normoxic control periods, was not significantly changed by BCO during any hypoxic period. Arterial blood pressure increased significantly with BCO and was increased by the same magnitude for all periods (Table II). Renal perfusion pressure was reduced to control values by suprarenal aortic constriction during BCO (Table II).

RBF was not statistically significantly dif-

TABLE I. ARTERIAL BLOOD GASES

	PaO_2	$PaCO_2$	pH
		Spontaneously breathing	
Normoxia	82 ± 2	45 ± 2	7.37 ± 0.02
Hypoxia–eucapnia	36 ± 1*	40 ± 2	7.40 ± 0.01
Hypoxia–hypercapnia	37 ± 2*	51 ± 2*	7.31 ± 0.02*
Hypoxia–hypocapnia	35 ± 2*	32 ± 2*	7.46 ± 0.02*
Normoxia	75 ± 4	40 ± 3	7.36 ± 0.03
		Mechanical ventilation	
Normoxia	86 ± 3	37 ± 1	7.40 ± 0.02
Hypoxia–eucapnia	31 ± 2*	36 ± 1	7.41 ± 0.01
Hypoxia–hypercapnia	35 ± 3*	48 ± 2*	7.29 ± 0.02*
Normoxia	76 ± 5	39 ± 2	7.35 ± 0.02

Note. Values are means ± SEM. P_aO_2, arterial O_2 partial pressure (Torr); P_aCO_2, arterial CO_2 partial pressure (Torr); pH, arterial pH.

* $P < 0.05$ compared to normoxia.

ferent during any period, including the return of renal perfusion pressure to control values during BCO (Table II). However, the P value for hypoxia–hypercania–spontaneously breathing and hypoxia-hypercapnia–mechanical ventilation was between 0.10 and 0.05 while all others were greater than 0.10 (Table II). When the percentage change in RBF with BCO was calculated, there was a significantly greater percentage change in RBF with BCO during hypoxia–hypercapnia–mechanical ventilation and borderline significance for hypoxia–hypercapnia–spontaneously breathing, (Table III), thus supporting the data trend.

BCO resulted in a significant increase in renal vascular resistance in each period (Table II). Renal resistance was returned to values not different from control when renal perfusion pressure was returned to control values (Table II). The greatest percentage change in renal resistance with BCO occurred with hypoxia–hypercapnia–mechanical ventilation (Table IV).

Discussion. It is well established that BCO increases RSNA (7, 8, 22–24). Additionally, hypoxemia, through chemoreceptor stimulation, has been shown to potentiate the increase in RSNA initiated by BCO (8, 11). Hypercapnia has been shown to potentiate the cardiovascular effects of the chemoreceptor response to hypoxemia (17, 19). Correspondingly, controlling ventilation with mechanical ventilation has been demonstrated to increase the cardiovascular effects of chemoreceptor stimulation by reducing the lung-inflation-induced cardiovascular effects, which are generally opposite to those induced by chemoreceptor stimulation (18, 20). Both hypercapnia and mechanical ventilation would thus be expected to further increase the RSNA initiated by BCO and potentiated by hypoxemia.

As indicated by the results of the present study, BCO did not result in a significant reduction in RBF during any period. Therefore, the increase in RSNA initiated by BCO and potentiated by hypoxemia, hypercapnia, or mechanical ventilation was not sufficient to decrease RBF under the conditions of the experiment. This was demonstrated further when renal perfusion pressure was returned to control values during each BCO. Under these circumstances, as renal perfusion pressure was reduced by suprarenal aortic constriction, a reduction of RBF should have occurred if significant RSNA was present. This did not occur in these experiments (Table II).

The influence of the aortic baroreceptors on renal vascular resistance during suprarenal aortic constriction must be considered. It is possible that a further increase in pressure in the aorta could have elicited an opposite response to that observed with BCO. However, if this were so, a reduction in heart rate should have occurred during aortic constriction. This did not occur. Recently, Gross *et al.* (3) evaluated suprarenal aortic constriction during BCO and the possible contribution of

TABLE II. RENAL PERFUSION PRESSURE (RPP), RENAL BLOOD FLOW (RBF), AND RENAL VASCULAR RESISTANCE (RR) RESPONSES TO CAROTID OCCLUSION (BCO), AND TO BCO WITH SUPRARENAL AORTIC CONSTRICTION (BCO–AC)

	RPP	RBF	RR
		Spontaneously breathing	
Normoxia			
Control	130 ± 3	343 ± 49	44 ± 7
BCO	180 ± 8*	336 ± 54	64 ± 11*
BCO–AC	130 ± 3	334 ± 52	46 ± 8
Hypoxia–eucapnia			
Control	139 ± 3	343 ± 59	49 ± 7
BCO	177 ± 7*	343 ± 59	62 ± 10*
BCO–AC	138 ± 4	347 ± 57	47 ± 7
Hypoxia–hypercapnia			
Control	139 ± 4	367 ± 60	45 ± 6
BCO	179 ± 5*	336 ± 66**	66 ± 12*
BCO–AC	139 ± 3	343 ± 64	48 ± 7
Hypoxia–hypocapnia			
Control	148 ± 3	354 ± 62	49 ± 7
BCO	195 ± 11*	344 ± 59	65 ± 9*
BCO–AC	147 ± 3	349 ± 59	48 ± 6
Normoxia			
Control	127 ± 5	285 ± 52	54 ± 9
BCO	171 ± 7*	275 ± 50	73 ± 10*
BCO–AC	127 ± 4	273 ± 46	54 ± 7
		Mechanical ventilation	
Normoxia			
Control	134 ± 5	266 ± 49	64 ± 12
BCO	182 ± 8*	266 ± 54	90 ± 19*
BCO–AC	136 ± 5	262 ± 52	67 ± 13
Hypoxia–eucapnia			
Control	146 ± 6	273 ± 72	85 ± 25
BCO	188 ± 10*	268 ± 68	112 ± 33*
BCO–AC	145 ± 6	267 ± 73	97 ± 34
Hypoxia–hypercapnia			
Control	142 ± 5	274 ± 75	78 ± 16
BCO	188 ± 7*	257 ± 83**	174 ± 71*
BCO–AC	141 ± 5	273 ± 78	83 ± 19
Normoxia			
Control	130 ± 4	283 ± 55	56 ± 8
BCO	159 ± 11*	275 ± 59	72 ± 11*
BCO–AC	130 ± 4	263 ± 49	60 ± 8

Note. Values are means ± SEM. RPP, mm Hg; RBF, ml/min; RR, (mm Hg/ml/min) · 100.
* $P < 0.05$ compared to control.
** $0.10 < P < 0.05$ compared to control.

the aortic baroreceptors. Based on the lack of heart rate changes and on the simultaneous measurement of pressures above and below the aortic constriction, they concluded that there was no significant contribution of the aortic baroreceptors under these circumstances. Thus, in the present study, the renal vascular changes observed following suprarenal aortic constriction were related to the change in renal perfusion pressure.

The greatest potentiation of BCO-induced RSNA should have occurred when hypoxemia, hypercapnia, and mechanical ventilation were combined, since all three increase the cardiovascular effect of chemoreceptor stimulation. While not dramatic, this concept

TABLE III. PERCENTAGE CHANGE IN RENAL BLOOD FLOW WITH CAROTID OCCLUSION

	Spontaneously breathing	Mechanical ventilation
Normoxia	−3 ± 2	−2 ± 4
Hypoxia–eucapnia	−1 ± 1	−2 ± 7
Hypoxia–hypercapina	−10 ± 5**	−13 ± 10*
Hypoxia–hypocapina	−2 ± 2	—
Normoxia	−1 ± 6	−5 ± 4

Note. Values are means ± SEM as percentage change from control.

* $P < 0.05$ compared to other means.

** $0.10 < P < 0.05$ compared to other means.

was supported by the trends in the data from the present study. While the mean values for RBF were not statistically altered by BCO, significance was approached in both the hypoxia–hypercapnia–spontaneously breathing and hypoxia–hypercapnia–mechanical ventilation periods. Supporting this trend, the percentage decrease in RBF was greatest during combined hypoxemia, hypercapnia, and mechanical ventilation (Table III). In addition, although renal vascular resistance increased with BCO in all periods, the largest percentage increase in resistance occurred during combined hypoxemia, hypercapnia, and mechanical ventilation (Table IV). These results would suggest that there was somewhat greater RSNA during this period.

BCO, under the conditions of this experiment and numerous previous investigations (1–3, 8), resulted in an increase in systemic blood pressure. This increase in pressure would tend to offset an increase in renal vascular resistance secondary to an increase in RSNA, thus tending to maintain RBF (3). Additionally, renal autoregulation (2, 3, 6, 10, 25) would also attempt to maintain RBF in response to this increase in pressure. It is clear from the present study that the renal vasculature is capable of autoregulatory behavior during BCO and in the presence of altered blood gases, since return of renal perfusion pressure to control values during BCO resulted in the appropriate renal vasodilation to maintain RBF (Table II).

In contrast to BCO, when vascularly isolated carotid sinuses have been perfused at reduced pressure (63 mm Hg), RBF was decreased when renal perfusion pressure was maintained at control values (22, 26, 27). BCO, while reducing pressure in the carotid sinus, does not reduce pressure to the extent anticipated due to collateral circulation. For example, Pelletier and Shepherd (8) measured carotid sinus pressure before and after BCO. Following BCO, carotid sinus pressure decreased from 145 to 75 mm Hg for the first 15 sec and then stabilized at 114 mm Hg. Hypoxemia did not change these values. Thus, because the pressure in the carotid sinuses during BCO is relatively moderate compared with those studies with isolated-perfused carotid sinuses, RSNA during BCO would be expected to be comparatively less (23, 24). Based on the results of the present study, potentiation of the RSNA with hypoxemia or hypercapnia must not quite raise the level of RSNA to compare with that achieved by lowering carotid sinus pressure to 63 mm Hg in the isolated-perfused carotid sinus, since returning renal perfusion pressure to control values in the present study did not result in a reduction of RBF.

In summary, BCO, while reducing carotid sinus pressure and eliciting a typical baroreflex, did not increase RSNA sufficiently to decrease RBF. Potentiation of this baroreflex-induced increase in RSNA with hypoxemia also did not reduce RBF. Only when the reflex was further potentiated by hypoxemia with hypercapnia during mechanical ventilation was there any indication of sufficient renal vasoconstriction to counter the increase in blood pressure and renal autoregulation. These results would be expected to be modified by the presence of systemic hypotension.

TABLE IV. PERCENTAGE CHANGE IN RENAL VASCULAR RESISTANCE WITH CAROTID OCCLUSION

	Spontaneously breathing	Mechanical ventilation
Normoxia	43 ± 5	40 ± 8
Hypoxia–eucapnia	27 ± 4	33 ± 14
Hypoxia–hypercapina	46 ± 11	105 ± 68*
Hypoxia–hypocapina	34 ± 6	—
Normoxia	39 ± 7	28 ± 3

Note. Values are means ± SEM as percentage change from control.

* $P < 0.05$ compared to other means.

Under those conditions, maximal baroreflex-induced increase in RSNA would be expected. RBF would then be expected to be reduced, especially in the presence of the systemic hypotension. Concurrent hypoxemia and hypercapnia during these circumstances might be expected to potentiate the RSNA and further reduce RBF.

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