Effects of hypercapnia and hypoxia on the cardiovascular system: vascular capacitance and aortic chemoreceptors

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ROTHE, CARL F., ROBERTO MAASS-MORENO, AND A. DEAN FLANAGAN. *Effects of hypercapnia and hypoxia on the cardiovascular system: vascular capacitance and aortic chemoreceptors.* Am. J. Physiol. 259 (Heart Circ. Physiol. 28): H932–H939, 1990.—Aortic chemoreceptor influences on vascular capacitance after changes in blood carbon dioxide and oxygen were studied in mongrel dogs anesthetized with methoxyflurane and nitrous oxide. The mean circulatory filling pressure (P_{mcf}), measured during transient cardiac fibrillation, provided a measure of capacitance vessel tone. Hypercapnia, hypoxia, and hypoxic hypercapnia significantly increased most variables, except that hypercapnia caused the total peripheral resistance (TPR) to decrease. Hypocapnia caused a significant decrease in mean systemic (P_{sa}) and pulmonary (P_{pa}) arterial blood pressures, cardiac output (CO), and central blood volume and an increase in TPR and heart rate. The changes in P_{mcf} on changing blood gas tensions could be described by the equation $\Delta P_{mcf} = -1.60 + 0.036(\text{arterial } P_{CO_2}) + 50.8/\text{arterial } P_{O_2}$. Thus a 10 mmHg increase in arterial P_{CO_2} caused a 0.36 mmHg increase in P_{mcf} with receptors intact. Cold block (2°C) of the cervical vagosympathetic trunks did not significantly influence the measured variables at control. During severe hypercapnia, vagal cooling caused a small but significant decrease in P_{mcf}, P_{sa}, P_{pa}, and CO but not TPR. During hypoxia, vagal cooling caused the P_{mcf}, P_{sa}, and TPR to decrease. We conclude that although hypercapnia or hypoxia acts reflexly to increase the capacitance vessel tone (an increase in P_{mcf}), the aortic and cardiopulmonary chemoreceptors with afferents in the vagi have only a small influence on the capacitance system, accounting for only ~25% of the total body response.

mean circulatory filling pressure; hypocapnia; vagal cold block; dog

ALTHOUGH HYPERCAPNIA AND HYPOXIA tend to increase capacitance vessel tone (3, 5, 6, 10, 13, 14, 16, 17, 29, 31–33), the magnitude of response and the location of the receptors for this control are not clear. We have found little direct (nonreflex) influence of hypoxia or hypercapnia on vascular capacitance, in contrast with the direct dilating effect on the resistance vessels (30).

Aortic chemoreceptor stimulation [using mixed venous blood or high arterial CO_2 tension (Pa_{CO_2}) and controlling respiration] increases cardiovascular system activity. Cardiac contractility (maximum dP/dt) and heart rate (HR) are increased (19), as is the total peripheral resistance (TPR) (6). Venoconstriction occurs, as deduced by an increase in reservoir volume of a perfusion system (6). The abdominal vascular capacitance is decreased and the abdominal vascular resistance is increased (13). However, cutaneous veins, as exemplified by the vascularly isolated saphenous vein, dilate when the aortic arch chemoreceptors are stimulated with cyanide (4).

Venoconstriction is induced by perfusing the head with high Pa_{CO_2} (12) or by cerebral ischemia (34). Perfusing the head with hypercapnic blood increases cardiac contractility (8, 15), as does a low Pa_{O_2} (8). Part of the increase in cardiac output (CO) induced by arterial hypoxia in awake sinoaortic-denervated dogs is from central chemoreceptors that reflexly decrease vascular capacitance (20).

Carotid body chemoreceptor stimulation, using low Pa_{CO_2}, high Pa_{CO_2}, or venous blood, and controlling ventilation, inhibits part of the circulatory system by decreasing HR (7, 19), cardiac contractility (8, 15, 19), and CO (7). However, TPR is increased by hypoxia (7). Furthermore, perfusing the carotid bodies with venous blood causes an increase in abdominal vascular resistance (using a constant perfusion) and a decrease in abdominal vascular capacitance (14). Stimulation of vascularly isolated carotid bodies perfused at constant pressure with hypercapnic blood caused a small decrease in systemic vascular volume when using a preparation involving a reservoir that held CO and central venous pressure constant (23). [If dogs breathe spontaneously, carotid body stimulation with hypoxic blood causes an increase in minute ventilation, HR, and CO and a decrease in TPR (7).] Daly and Scott (7) have speculated that hypoxia may induce venodilation via carotid body stimulation, but have also postulated that the increase in CO seen during perfusion of the carotid bodies with hypoxic blood in artificially ventilated dogs is largely due to venoconstriction.

In previous work, we examined the effects on vascular capacitance of total body (30, 31), central (head) (12), and carotid (23) chemoreceptor stimulation by hypercapnia, hypoxia, or hypoxic hypercapnia. We have also investigated the importance of cardiovascular reflexes on the capacitance vessels during blood gas changes (30). In this study, we determined the effects of various levels of hypercapnia and hypoxia on vascular capacitance and other cardiovascular variables before and after cold blocking the cervical vagosympathetic trunks to quantify the relative importance of the aortic chemoreceptors. We tested the hypothesis that cardiovascular responses to hypercapnia (with ventilation controlled) are linear, in contrast to the marked nonlinear response of the respi-

ratory system. We have reexamined whether hypocapnia reflexly depresses the cardiovascular system. Because stimulation of the chemoreceptors induces a marked increase in ventilation (7), which in turn reflexly influences the cardiovascular system, we used anesthetized and paralyzed animals that were mechanically ventilated to minimize these effects.

MATERIALS AND METHODS

Healthy random-source hounds (held 1 mo by the supplier and free of heartworm and internal and external parasites) weighing 18.3 ± 2.9 (SD) kg were anesthetized with methohexital sodium (Brevital, Lilly), 10 mg/kg iv. They were maintained with a combination of 50% N_2O-50% methoxyflurane (Metafane, Pitman-Moore). A piston-type respirator (Harvard Apparatus, model 613) provided controlled ventilation, with a tidal volume of 30 ml/kg, 15 breaths/min, and inspiration/expiration ratio of 1:3. The inhaled percentages of N_2O, O_2, CO_2, and N_2 were obtained by adjusting the respective flows for a total delivery of 10 l/min to the respirator; the excess was vented. Rotameter flowmeters (Matheson Gas Products, model 603 or 604) were used. The flowmeters were calibrated for the specific gases by timed collections in a spirometer. The rotameters were driven at 15 psi with the control valves downstream from the rotameter ball, so that the pressure and gas density around the rotameter ball were constant. The amount of methoxyflurane added to the respiratory gases was adjusted via the bypass valve in the anesthesia machine evaporating chamber (Snyder, New Philadelphia, OH, model SAAM with the CO_2 absorbing chamber empty). The exhaled gas from the dog and the overflow of gases were vented outside the building. Blood gases were measured with a blood-gas analysis machine (Corning, model 165). The expired CO_2 was sampled through a CO_2 meter (Beckman, model LD-2) and recorded. CO_2 tensions at control were adjusted by changing the CO_2 flow into the system, providing end tidal CO_2 of 4–5%.

The right external jugular vein was cannulated with a 30-cm long tube (0.25 in. OD) that contained a central venous pressure (P_{cv}) line, a fibrillating electrode, a Swan-Ganz catheter for pulmonary arterial pressure, and a dye injection line. The P_{cv} and dye injection lines were positioned at approximately the superior vena cava-right atrial junction; the Swan-Ganz catheter was floated into a pulmonary artery, and the fibrillating electrode was positioned in the right ventricle. The left brachial artery was cannulated for systemic arterial pressure (P_{sa}). The right brachial artery had a 1.2-mm ID 36-cm long catheter advanced to the aortic arch for blood sampling to determine CO and central blood volume (CBV) by a dye dilution technique. The end of the catheter was slightly bent so that it could be manipulated, while monitoring the pressure pulse, past various arterial branches and into the aorta. The catheter was then withdrawn so that the tip was in the vicinity of the aortic arch. Catheters were introduced through both the right and left femoral artery and vein to provide a means of shunting blood rapidly from the arterial to venous circulation during the mean circulatory filling pressure (P_{mcf}) maneuver.

Cooling the cervical vagi of the dogs to 6°C abolishes conduction in myelinated fibers (11, 18, 22) with virtually all nonmyelinated fibers being blocked at 3°C (11, 22). However, isolated or very low frequency pulses may be conducted at 0°C (11). Both cervical vagosympathetic trunks were carefully isolated and placed in J-shaped hollow stainless steel cuffs for cold blockade. The cuffs were 12 mm wide and 2 mm thick, with a 3 × 6 × 12-mm space for the nerves. A copper-constantan thermocouple (0.12-mm wire), cemented to the bottom of the cuff slot, was used to monitor the cuff temperature. Vagal blockade was induced by reducing the cuff temperature to ~2°C by pumping water from an ice-water reservoir at 500 ml/min through the cuffs. The vagi were reheated to ~39°C with 40°C water to reverse the blockade.

Giving heparin as a bolus of 500 U/kg after all surgery and at 1,000 U/h prevented blood coagulation. Body temperature (rectal) was maintained at 38.8 ± 0.6°C by warming the surgical table to 40°C and using heat lamps.

For CO and CBV measurements, blood was pumped at 15 ml/min with a roller-type pump from the arch of the aorta through a cuvette densitometer and CO unit (Waters DC-410 and TD-1) and returned via the jugular catheter. A pneumatic-driven dye injector was used to inject 0.500 ± 0.005 ml of 2.5 mg/ml indocyanine green (Cardio-Green, Hynson, Westcott, and Dunning). The output of both the injector timing signal and the dye-densitometer was filtered through identical four-pole Bessel filters (Analog Devices, model 730LT-1) set for a characteristic frequency of 5 Hz. The data were sampled at 10/s, using a digital acquisition system (Keithley DAS, series 500). CO and CBV were computed in a manner similar to that described previously (34). The area between the zero baseline and the dye concentration data was integrated for flow calculation. The mean transit time (MTT) computation was based on the same dye data and the integral of concentration × time. The correction for recirculation was based on the computation of the rate constant of the decaying dye concentration, which was assumed to be a monoexponential function. Pressures were monitored with strain gauge transducers (Statham-Gould P23 Db or P23 De) held in an aluminum block heated with water at 30 ± 0.2°C to prevent temperature drift. Catheters were continuously flushed with 0.9% sodium chloride solution, 0.05 ml/min (Gould Critiflow, model TA 40004). Data were recorded on two six-channel recorders (Beckman, Type R). Pressure data were filtered before analog-to-digital conversion with another set of four-pole Bessel filters set to a characteristic frequency of 0.18 Hz. Data were then printed at 0.1-min intervals, along with 1-min averages for subsequent data analysis.

For the P_{mcf} determination, the dog was fibrillated for 12 s with a 3-V root mean square 60-Hz stimulus applied between the spring-tipped stainless steel guide wire that was inserted between the right atrium and the base of the right ventricle and an 18-gauge needle placed subcutaneously next to the sternum. The arterial-to-venous pumping at ~100 $ml \cdot min^{-1} \cdot kg^{-1}$ was maintained until the P_{sa} was less than ~10 mmHg. This generally required <3 s. During the P_{mcf} maneuver, P_{sa}, P_{cv}, and P_{pa} were

printed at 1-s intervals. The P_{mcf} was considered to be the P_{cv} at 7 s from the start of the fall in P_{sa} during fibrillation (29). The mean pulmonary filling pressure (P_{mpf}) was considered to be the mean pulmonary arterial pressure after 7 s of zero CO. Defibrillation was accomplished with a 150–250 W·s DC countershock (Electrodyne, model D-84-M).

After we checked that the level of methoxyflurane and nitrous oxide had been maintaining surgical anesthetic levels for at least 30 min, the dogs were paralyzed with 0.1 mg/kg vercuronium chloride (Norcuron, Organon) while maintaining the anesthesia. Paralysis was maintained by giving 0.05 mg/kg vecuronium at the beginning of each protocol section, or if there were signs of spontaneous respiratory activity during hypercapnia, or during the P_{mcf} maneuver.

Protocol. The basic protocol consisted of seven segments: *segment a*, a control period of 5 min; followed by 5 min of cold block of the vagi, *segment b*, and then rewarming the vagi for 5 min for a second control determination, *segment c*. At 15 min, the experimental gases were changed and at 21 min, *segment d*, experimental control values were obtained. At 25 min, *segment e*, the vagi were again cold blocked, followed at 31 min by warming and *segment f*, a second experimental control determination. At 35 min, the control gases were reinstated and then, after 6 min, *segment g*, a final control run. At the end of each of these seven segments CO and CBV were measured, and the 1-min average of the arterial blood pressure, central venous pressure, pulmonary arterial pressure, and HR were recorded. One minute after injection of the dye, the P_{mcf} maneuver was performed. Arterial blood gas samples were taken at 0, 12, 26, 32, and 40 min. At least 3 min was allowed for recovery from the P_{mcf} maneuver, and at least 6 min was allowed for the gas change effects to take place. [The increase in sympathetic nerve activity after a sudden change in Pa_{O_2} reaches a plateau by ~5 min (16).]

The basic protocol was repeated four times for different gas compositions, unless the experiment was terminated after two or three mixtures because of preparation deterioration. The control gas mixture consisted of 50% N_2O, 30% O_2, and 2.5 ± 0.5% CO_2, with the remainder N_2. The dogs were hyperventilated at a constant level (440 $ml \cdot min^{-1} \cdot kg^{-1}$) throughout the experiment. The experimental gas mixture to produce hypocapnia (*treatment 1*) was 30% O_2, 0% CO_2, 50% N_2O, and the remainder N_2. For the mild (*treatment 2*), medium (*treatment 3*), and high hypercapnia (*treatment 4*), the inspired CO_2 was 6.6 ± 0.8, 9.0 ± 0.8, and 11.2 ± 0.4%, respectively, plus 50% N_2O, 30% O_2 and the remainder N_2. Hypoxia (*treatment 5*) consisted of 10% O_2 and 2.5% CO_2, and for hypoxic hypercapnia (*treatment 6*) we used 10% O_2, 9% CO_2, 50% N_2O, and the remainder N_2. The treatments were applied in random order except for *treatment 6*, which was applied last because of the stress to the animal from 20 min of this mixture.

Responses to treatment were computed as the average of the two experimental treatment segments (*d* and *f*) minus average of the three control segments (*a*, *c*, and *g*), and were statistically analyzed with a paired-comparison Student's *t* test. The use of two experimental and three control values for the paired comparison corrected for between-animal variability and is statistically conservative. We did not use a repeated measures analysis of variance, because each dog received at most only four of the six experimental gas mixtures and because there were some missing data. The decision to make the reported comparisons was made a priori and therefore did not require a multicomparison approach. Significance was considered to be at $P \leq 0.05$. We also used regression equations to describe our results because they provided a pooled statistically best estimate of the response to various levels of Pa_{CO_2} and Pa_{O_2}. Regression analyses were computed with the Multivariate General Linear Hypothesis module of SYSTAT (Evanston, IL). Variabilities about means are given as SD.

RESULTS

Total body responses. The control values (average of *segments a* and *c*) of the variables measured are given in Table 1. Except for the high HR, the values are normal for resting dogs. The effects of the various gas mixtures on the different cardiovascular variables are summarized in Table 2. Both hypercapnia and hypoxia caused a significant increase in mean P_{mcf}. A multiple regression fit of the data (Table 3) provided the following equation to describe the changes in P_{mcf}: $\Delta P_{mcf} = -1.6 + 0.036\ Pa_{CO_2} + 50.8/Pa_{O_2}$, where ΔP_{mcf} is the change in mean circulatory filling pressure (in mmHg) calculated as the average of the two experimental periods (*segments d* and *f*) minus the average of the three control periods (*segments a*, *c*, and *g*). (The recovery P_{mcf} control value, *segment g*, was not significantly different from the initial control values for *treatments 1–3*, but was ~1 mmHg lower for *treatments 4–6*.) The standard deviation of the fit of data around the regression curve (square root of residual mean square, RMSE) was 0.70 mmHg. The equation predicts that a 10 mmHg increase in blood CO_2 tension produced on the average a 0.36 mmHg increase in P_{mcf} (Fig. 1). With hypoxic hypercapnia (Pa_{O_2} = 42.0 mmHg and Pa_{CO_2} = 70.8 mmHg) the P_{mcf} was predicted from this equation to increase 2.16 mmHg (Fig. 1), com-

TABLE 1. *Control values and influence of vagal cold block during administration of control gases*

Variable	Control	Block Effect*
CO_2, mmHg	38.8±2.8	
O_2, mmHg	145±21	
pH, mmHg	7.30±0.05	
P_{mcf}, mmHg	6.0±1.2	0.10±0.49
P_{mpf}, mmHg	7.2±1.4	0.11±0.71
P_{sa}, mmHg	95.2±8.2	−0.72±10.1
P_{pa}, mmHg	12.9±1.9	−0.01±0.66
P_{cv}, mmHg	2.1±1.0	0.001±0.46
CO, $ml \cdot min^{-1} \cdot kg^{-1}$	97.0±19.0	0.94±6.88
CBV, ml/kg	18.0±3.1	−0.14±1.29
TPR, $mmHg \cdot min \cdot kg \cdot ml^{-1}$	0.98±0.17	−0.005±0.088
HR, beats/min	167±22	0.7±4.8

Values are means ± SD; n = 46–52 observations from 15 dogs. * Change in variable value by cold blocking (<3°C) of both cervical vagi in comparison to average of control values determined before and after cold block. None of the variables were changed significantly by vagal block during normal blood gas tensions. See text for definitions.

TABLE 2. *Change of cardiovascular variables during experimental gases compared with control and changes induced by vagal block during experimental gases*

Treatment:	Hypocap *1*	Mild *2*	Moderate *3*	Severe *4*	Hypoxia *5*	HH *6*
n	8 to 10	8 to 10	8 to 10	8 to 9	8 to 9	5 to 6
Pa_{O_2}, mmHg	152±24	148±17	152±20	160±11	37.9±8.6	42.0±4.6
Pa_{CO_2}, mmHg	27±3.5	63.4±5.6	76.0±7.7	92.5±5.6	39.3±2.2	70.8±8.0
ΔP_{mcf}, mmHg	−0.24±0.38	0.67±0.55*	1.85±0.67‡	2.02±0.61‡	0.99±0.40‡	2.55±1.11†
Vagal block	0.08±0.37	0.38±0.71	−0.26±1.10	−0.43±0.87	−0.41±0.79	−0.95±1.12
ΔP_{mpf}, mmHg	−0.48±0.46*	1.47±1.26†	1.46±1.01†	1.99±0.47‡	1.28±0.62‡	1.83±0.98†
Vagal block	−0.08±0.45	0.04±1.18	−0.17±1.34	−0.32±0.88	−0.83±0.72*	−0.96±0.65*
ΔP_{sa}, mmHg	−3.6±3.1†	3.3±7.9	6.4±4.7†	6.5±8.0*	13.0±7.8†	24.2±23.7
Vagal block	0.8±6.6	5.1±6.5*	−1.8±18.0	−5.4±13.8	−1.2±10.7	−20.2±13.1*
ΔP_{pa}, mmHg	−0.4±0.5*	2.1±1.7†	2.7±1.1‡	3.4±1.2‡	6.9±2.9‡	11.1±4.7†
Vagal block	0.1±0.3	0.2±0.7	−0.5±1.5	−0.7±1.2	−0.1±1.2	−1.6±1.9
ΔP_{cv}, mmHg	0.06±0.28	0.04±0.54	0.38±0.40*	0.38±0.32*	−0.02±0.93	−0.44±1.0
Vagal block	−0.09±0.22	0.08±0.36	0.06±0.30	−0.29±0.38	−0.40±0.54	−0.12±0.78
ΔCO, $ml \cdot min^{-1} \cdot kg^{-1}$	−8.6±5.0†	16.6±17.1*	24.6±18.9†	29.2±12.7‡	15.6±10.7†	28.7±26.1*
Vagal block	1.0±3.1	0.2±6.1	−4.1±13.7	−3.8±4.9	6.7±8.7*	−5.5±11.3
ΔCBV, ml/kg	−1.34±0.75‡	1.10±1.28*	2.03±1.26†	2.82±1.65‡	−1.69±1.08†	−1.60±0.74†
Vagal block	0.08±1.07	−0.42±0.98	0.00±0.93	−0.34±1.34	−0.01±0.98	−1.02±0.61*
ΔTPR, $mmHg \cdot min \cdot kg \cdot ml^{-1}$	0.05±0.05*	−0.09±0.08†	−0.12±0.11*	−0.20±0.10‡	−0.04±0.12	−0.05±0.21
Vagal block	−0.01±0.06	0.04±0.04*	−0.0±0.10	−0.02±0.06	−0.07±0.09	−0.18±0.16*
ΔHR, beats/min	3.47±3.93†	−0.53±6.41	−2.48±7.58	1.75±9.92	6.18±4.57†	13.4±17.0
Vagal block	0.9±3.4	0.9±4.3	−0.8±9.9	0.4±7.2	2.4±4.2	5.2±20.7

Values are means ± SD; *n* = number of dogs receiving treatment. * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$ (by paired comparison; see text). HH, hypoxic hypercapnia. Control: Pa_{O_2} = 145 ± 21; Pa_{CO_2} = 38.8 ± 2.8 mmHg. See text for definitions and conditions for each treatment.

TABLE 3. *Multiple regression coefficients of changes of cardiovascular variables as a function of Pa_{CO_2} and Pa_{O_2}*

	k_1	k_2	k_3	Multiple r^2	RMSE	*n*
ΔP_{mcf}	−1.60±0.37‡	+0.0360±0.0046‡	+50.8±12.2‡	0.594	0.70	47
ΔP_{sa}	−13.8±5.0†	+0.182±0.064†	+828±166‡	0.358	10.1	52
ΔP_{pa}	−5.2±1.0‡	+0.070±0.013‡	+400±34‡	0.744	2.1	52
ΔP_{cv}	+0.28±0.32	+0.001±0.004	−23±11*	0.121	0.6	46
ΔCO	−28.2±7.3‡	+0.58±0.09‡	+807±245†	0.476	14.7	50
ΔCBV	−1.78±0.63†	+0.055±0.008‡	−103±21‡	0.672	1.3	50
ΔTPR	+0.143±0.054*	−0.0034±0.0007‡	−0.96±1.83	0.348	0.11	50
ΔHR	−4.3±4.2	+0.023±0.054	+491±140‡	0.206	8.6	52

Values are means ± SE, derived from equation $\Delta variable = k_1 + k_2 \cdot Pa_{CO_2} + k_3/Pa_{O_2}$, *n* = no. of observations. Units of variables as in Table 1; Pa_{CO_2}, and Pa_{O_2} in mmHg. Changes computed as average of the 2 experimental periods minus the average of the 3 control periods. * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$ that coefficient different from zero. All analyses of variance significant ($P < 0.05$), except for ΔHR ($P = 0.063$). RMSE, Square root of residual mean square (standard deviation of the fit of data about the multiple regression line).

pared with the observed average of 2.55 ± 1.11 mmHg (Table 2). With eucapnic hypoxia (Pa_{O_2} = 38 mmHg and Pa_{CO_2} = 39 mmHg) the P_{mcf} increase was 1.15 mmHg compared with the observed average of 0.99 ± 0.40 mmHg.

Equations of the form $\Delta variable = k_1 + k_2 \cdot Pa_{CO_2} + k_3/Pa_{O_2}$ were fitted to the data for the other variables and are reported in Table 3. The coefficients provide numerical values for the sensitivity of these variables to changes in Pa_{CO_2} and Pa_{O_2}. [Because we used only two levels of Pa_{O_2}, the coefficients describing the effects of hypoxia on the various cardiovascular variables (Table 3) are uncertain.] The data suggest a positive linear effect of Pa_{CO_2} on P_{mcf}, P_{sa}, pulmonary arterial pressure (P_{pa}), CO, and CBV (Figs. 1 and 2), and a negative linear effect on TPR (Fig. 2).

Hypercapnia caused a significant increase in all variables except TPR [$TPR = (P_{sa} - P_{cv})/CO$], which decreased (Fig. 2), and HR, which did not change (Table 2). Hypocapnia (Pa_{CO_2} = 27 ± 3.5 mmHg) significantly decreased mean P_{sa}, mean P_{pa}, CO, and CBV. HR and TPR were increased. Thus, hypercapnia tended to elicit cardiovascular stimulation including an increase in vascular capacitance tone, while hypocapnia reduced cardiovascular activity.

Hypoxia caused a significant increase in all variables (Table 2, Figs. 1 and 2) except CBV, which was significantly decreased (Fig. 2); P_{cv} and TPR were not significantly changed by hypoxia. The influence of hypoxia plus hypercapnia was generally additive except for their influences on CBV and TPR (Figs. 1 and 2).

The data were also fitted to other equations. Using the change from Pa_{CO_2} instead of the actual experimental Pa_{CO_2} resulted in slightly lower coefficients of determination (multiple r^2) and had virtually no effect (<5%) on the Pa_{CO_2} coefficients. Adding a term for $(Pa_{CO_2})^2$ to test for nonlinearity did not significantly improve the fit. Including the reciprocal of the Pa_{O_2} term improved the fit, especially for P_{sa}, P_{pa}, CO, and HR. The Pa_{CO_2} coefficient for P_{mcf}, based on changes in Pa_{CO_2} with 30% inspired oxygen (*treatments 1–4*), was 0.0346 ± 0.0045 mmHg/mmHg ΔPa_{CO_2}.

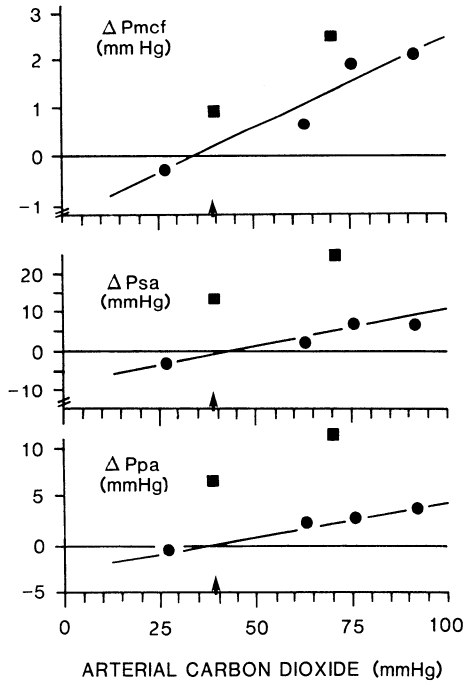

FIG. 1. Regression lines and mean data (Table 2) for changes in mean circulatory filling pressure (P_{mcf}), mean systemic arterial pressure (P_{sa}), and mean pulmonary arterial pressure (P_{pa}) from changes in blood CO_2 with receptors intact. Data are from average of 2 determinations during experimental gas administration (*segments d* and *f*) minus average of 3 determinations during control and recovery periods (*segments a*, *c* and *g*). Equations and coefficients for lines are from Table 3. ●, mean values for *treatments 1–4* (blood CO_2 change) at Pa_{O_2} of 153 mmHg. ■, mean values for *treatment 5* (hypoxia, Pa_{O_2} = 38 mmHg) and *treatment 6* (hypoxic hypercapnia, Pa_{O_2} = 42 mmHg and Pa_{CO_2} = 71 mmHg); see Table 2.

Aortic chemoreceptors. Cold blocking the vagi had no significant effect on any of the measured variables during the control periods, or for most variables during the treatments evaluated separately (Tables 1 and 2). The statistical test was a paired comparison of the vagal block observation to the average of the two values (before and after) control or experimental gas values. During hypoxia, vagal cold block reduced P_{mpf} and increased CO ($P = 0.049$). During hypoxic hypercapnia, P_{mpf}, P_{sa}, CBV, and TPR were significantly decreased by vagal block (Table 2).

To evaluate more carefully the effect of cold blocking the vagal afferent nerves, we fitted regression equations to the response to vagal cold block to the six treatment gas mixtures for each of the major variables to obtain a pooled best-fit estimate. The equation was of the same form as those in Table 3. The response value was the value during vagal cold block (*segment e*) minus the average of the pre- and postblock (*segments d* and *f*) values during the experimental gases. The coefficients (k_2) for Pa_{CO_2} were significantly different from zero ($P < 0.05$) for P_{mcf}, P_{sa}, P_{pa}, and CO (Table 4). The P_{cv}, CBV, TPR, and HR values were not changed. The coefficients for the reciprocal of Pa_{O_2} influences on the variables by vagal cooling were significant ($P < 0.05$) for P_{mcf}, P_{sa}, and TPR but were not significant for P_{pa}, CO, P_{cv}, CBV, or HR. In all cases, however, the coefficients of determination (r^2) were small (<0.25). These equations (Table 4) predicted that during hypoxic hypercapnia, vagal cooling would decrease P_{mcf} by 0.68 mmHg, compared with the 0.96 ± 0.65 mmHg decrease that we found, and would decrease P_{sa} 10.4 mmHg, compared with the 20.2 ± 13.1 mmHg decrease observed (Table 2, *treatment 6*). Cooling the vagi (aortic chemoreceptors blockade) had no significant effect on the TPR during hypercapnia, but with hypoxic hypercapnia the TPR was decreased (*treatment 6*, Tables 2 and 4).

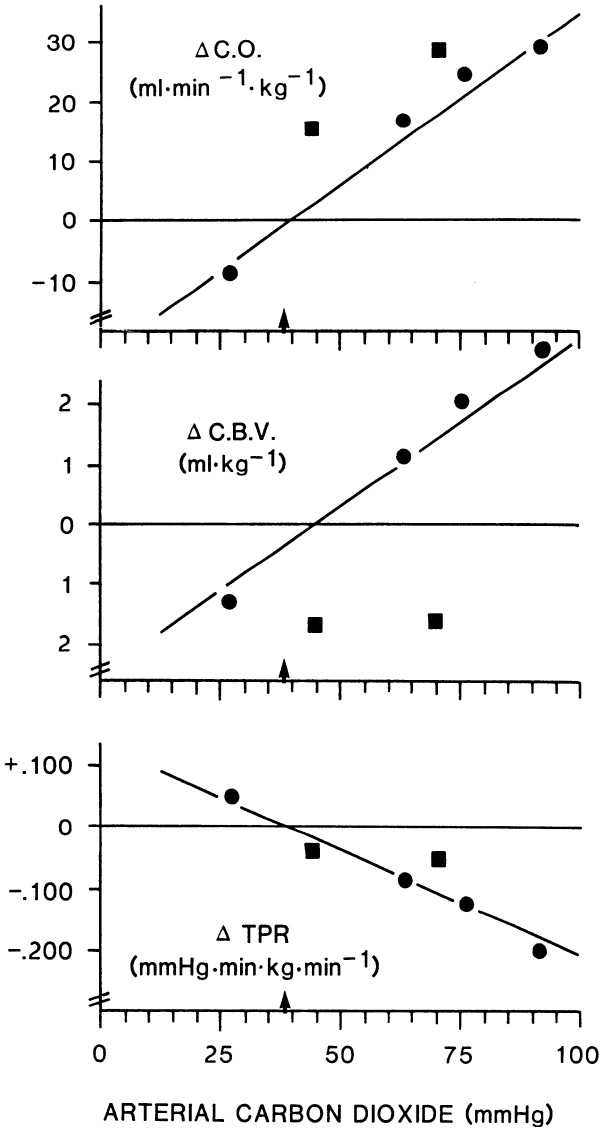

FIG. 2. Regression lines for changes in cardiac output (CO), central blood volume (CBV), and total peripheral resistance (TPR) with receptors intact (details as for Fig. 1).

DISCUSSION

Hypercapnia and hypoxia stimulate the cardiovascular system. With intact central and carotid chemoreceptors, on cooling the vagi and thus aortic chemoreceptors, P_{mcf}, P_{sa}, P_{pa}, and CO are decreased significantly in proportion to the level of Pa_{CO_2}, thereby providing evidence of a stimulatory signal from cardiopulmonary receptors, in particular the aortic chemoreceptors.

Cooling the vagi not only interrupts nerve traffic from the aortic chemoreceptors but also blocks nerve activity from aortic pressoreceptors, pulmonary stretch recep-

TABLE 4. *Multiple regression coefficients of changes of cardiovascular variables as a function of arterial carbon dioxide and oxygen tensions in response to vagal blockade*

Variable	k_1	k_2	k_3	Multiple r^2	RMSE	n
ΔP_{mcf}, mmHg	+0.82±0.42	−0.011±0.005*	−30±14*	0.13	0.84	48
ΔP_{sa}, mmHg	+14.8±6.0*	−0.190±0.076*	−493±202*	0.16	12.5	53
ΔP_{pa}, mmHg	+1.4±0.56†	−0.022±0.007†	−33±19	0.18	1.1	53
ΔCO, ml·min^{-1}·kg^{-1}	+6.7±4.7	−0.143±0.060*	+109±159	0.13	9.8	53
ΔTPR, mmHg·min·kg·ml^{-1}	+0.092±0.044*	−0.0009±0.0006	−5.9±1.5‡	0.24	0.092	53

Values are means ± SE. Equation used to calculate values was $\Delta\text{variable} = k_1 + k_2 \cdot Pa_{CO_2} + k_3/Pa_{O_2}$. * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P < 0.001$ that coefficient different from zero. All analyses of variance significant ($P < 0.05$). There were no significant changes in ΔP_{cv}, ΔCBV, or ΔHR during vagal blockade. RMSE, square root of residual mean square: standard deviation of the fit of the data about the multiple regression line.

tors, possibly other thoracic and cardiac receptors, and parasympathetic (afferent) nerve activity to the heart. With the control HR of 167 beats/min, a consequence of methoxyflurane and nitrous oxide anesthesia, little vagal tone was present and so vagal cooling had no effect on HR.

The response of the aortic chemoreceptors to hypercapnia and hypoxia may be modified by other reflexes. McCoy at al. (25) found that the reflex pressor (>20 mmHg) response to static skeletal muscle contraction reduced the discharge of aortic chemoreceptors of cats by 53%. Blood flow to the receptors, as well as changes in blood gas tensions, is an important determinant of chemoreceptor response (26). The aortic baroreceptors and thoracic stretch receptors, when stimulated, tend to attenuate sympathetic nervous system outflow, and thus would tend to attenuate the influence of aortic chemoreceptor activity. Reflex interactions are exceedingly complex (1, 10).

Our methods do not preclude the possibility that the influence of the aortic chemoreceptors was partly negated by concomitant aortic pressoreceptor activity under control conditions, as well as during severe chemoreceptor stimulation. Because the effect of vagal cold block on P_{mcf} and CO was so small, even during hypoxic hypercapnia, we did not attempt to isolate the aortic arch vascularly and denervate the aortic pressoreceptors.

Hypercapnia. Our study supports the suggestion of Daly et al. (6) that hypercapnic stimulation of aortic arch chemoreceptors of dogs leads to venoconstriction and increased P_{sa}. In another study (30), we also found that during hypercapnia (Pa_{CO_2} = 72 ± 3 mmHg) with intact reflexes, P_{mcf} and CO increased while TPR decreased. In that study, the net effect of increased CO and decreased TPR led to no significant change in P_{sa}, as was also reported by Shigemi (32). In the current study, there was a small increase in P_{sa} with increasing degrees of hypercapnia (Fig. 1). Blocking cardiovascular reflexes with hexamethonium and atropine does not modify the magnitude of decrease in TPR in response to hypercapnia (30). With general hypercapnia, the increase in P_{mcf} was associated with an increase in CBV and CO, suggesting that the venoconstriction acted to increase cardiac filling and so increased CO.

Hypoxia. With general hypoxia and receptors intact, the increased P_{mcf} and CO occurred in conjunction with a marked decrease in CBV. This suggests that increased CO was caused by a significant increase in cardiac contractility (9). The 30% increase in CO was associated with a 53% increase in P_{pa} and a 9% decrease in CBV. Others have also reported that hypoxic stimulation of the aortic body chemoreceptors acts to increase CO (2). Because P_{mcf} was increased, the decrease in CBV was more likely related to a direct or reflex stimulation of pulmonary vascular smooth muscle than to a reduction in cardiopulmonary blood volume from peripheral vasodilation. Hypoxia also has a direct depressing effect on the heart.

The changes in TPR were small and inconsistent during hypoxia (Tables 2 and 3; Fig. 2), in contrast to the vasodilation (reduced TPR, Fig. 2) induced by hypercapnia with or without intact sympathetic pathways (30). In our other study (30), the reduced TPR seen during hypoxia with reflexes blocked was maintained at the control levels when the reflexes were intact. In the current study, vagal cooling had little influence on TPR during hypercapnia, but during hypoxic hypercapnia it decreased (Table 2). In conscious dogs, Rose et al. (28) reported a 38% decrease in TPR during hypoxic hypercapnia (Pa_{O_2} = 34 mmHg, Pa_{CO_2} = 55 mmHg).

Hypocapnia. The reduction in cardiovascular function by hypocapnia that we found is consistent with the studies of Prys-Roberts et al. (27) using halothane anesthetized humans. They, too, found that hypocapnia reduced CO and hypercapnia increased it. This study confirms the utility of using 5% CO_2 in oxygen during artificial respiration, and suggests that vascular capacitance is increased by hypocapnia.

Linearity. In our study, the cardiovascular responses to hypercapnia, with all receptor systems intact, were remarkably linear. In conscious sheep, however, Matalon et al. (24) reported a nonlinear CO response to hypercapnia. At a Pa_{CO_2} of 58 mmHg they found no significant change in CO (+10%), but at 75 mmHg CO was increased 48%. In contrast to the nonlinear response of the carotid and aortic chemoreceptors to hypoxia, both chemoreceptors show a linear response to increasing Pa_{CO_2} (21). The carotid chemoreceptors in the cat appear to have a threshold at a Pa_{CO_2} of ~20 mmHg, however (21).

The CO was increased by both hypoxia and hypercapnia, and the effects appeared to be additive (Fig. 2). When only the aortic body chemoreceptors were stimulated, Daly et al. (6) reported that high Pa_{O_2} (>100 mmHg) blocked the reflex effects of hypercapnia. In our study, with a Pa_{O_2} of 150 mmHg, the cardiovascular stimulatory effects of increasing the blood CO_2 were seen in all variables except P_{cv}, HR, and TPR.

Partition of receptor sites. A sensitivity of ~0.045

mmHg ΔP_{mcf}/mmHg ΔPa_{CO_2} seems to be a reasonable overall estimate for dogs with receptors intact. In this study, with all receptors intact, the sensitivity of P_{mcf} to changes in Pa_{CO_2} was 0.0360 ± 0.0046 mmHg/mmHg (Table 3, coefficient k_2). In our earlier study (31), with intact receptors, an increase of arterial Pa_{CO_2} from a control of 32 ± 8 mmHg to 114 ± 9 mmHg caused the P_{mcf} to increase from 6.0 ± 1.9 mmHg to 11.6 ± 4.4 mmHg, giving a sensitivity factor of 0.068 mmHg ΔP_{mcf}/mmHg ΔPa_{CO_2}. In another study designed to test the effect of cardiovascular reflex blockade (30), a 33 mmHg increase in Pa_{CO_2} caused a 1.4 mmHg increase in P_{mcf} when the reflexes were intact, giving a sensitivity of 0.042 mmHg per mmHg ΔPa_{CO_2}. A weighted average from these studies is 0.045.

It is now possible to tentatively partition the relative importance of the various receptor sites. In the current study, the blockade of aortic chemoreceptors during hypercapnia resulted in 0.011 ± 0.005 mmHg ΔP_{mcf}/mmHg ΔPa_{CO_2} (k_2, Table 4). When only the head is perfused with hypercapnic blood (12), the Pa_{CO_2} sensitivity coefficient for P_{mcf} was 0.014, confirming that part of the vascular capacitance response to hypercapnia is from receptors in the brain. In another study in our laboratory (23), using constant CO, a venous return reservoir, and perfusing the vascularly isolated carotid sinuses, we found that hypercapnic blood in the carotid sinuses caused the dog's volume to decrease 0.041 ml/kg per mmHg ΔPa_{CO_2}. With an assumed vascular compliance of 2 $ml \cdot mmHg^{-1} \cdot kg^{-1}$, the sensitivity coefficient of P_{mcf} to Pa_{CO_2} would be 0.020 mmHg ΔP_{mcf}/mmHg ΔPa_{CO_2}. The sum of the Pa_{CO_2} sensitivities from carotid (0.020), head (0.014), and aortic (0.011) receptors is 0.045. The influences of the various receptors may not be additive (1). However, the weighted average of the total body P_{mcf} responses from our laboratory was also 0.045. We therefore suggest that ~45% of the response to changes in Pa_{CO_2} is via carotid chemoreceptors [100(0.020/0.045)], 30% from receptors in the brain, and 25% from the aortic chemoreceptors. Hoka et al. (16) concluded that 60% of the response to severe hypoxia is via peripheral chemoreceptors. Methodological problems and high variability preclude a firm partitioning.

Summary. Our studies support the concept that hypercapnia elicits venoconstriction and that there are several sensing sites. Furthermore, they strengthen the concept that the cardiovascular system function is controlled not only by changes in HR, cardiac contractility, and TPR, but also by changes in vascular capacitance. From the data of this study, we make the following conclusions. *1*) Aortic chemoreceptors (with afferents in the vagi), when stimulated by hypercapnia, significantly increase P_{mcf}, P_{sa}, P_{pa}, and CO, but not TPR. *2*) With all receptors intact, the response of the capacitance system to changes in Pa_{CO_2} is linear (Fig. 1). *3*) Hypocapnia causes some depression of the cardiovascular system (Figs. 1 and 2). *4*) The effects of hypercapnia plus hypoxia on the cardiovascular system are additive, except for changes in CBV and TPR (Fig. 2). *5*) Changes in overall capacitance vessel tone do not necessarily parallel changes in overall vascular resistance tone. *6*) From our studies of the effects of Pa_{CO_2} on vascular capacitance, we suggest that the carotid chemoreceptors contribute 45%, receptors in the head 30%, and the aortic chemoreceptors 25% of the total.

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