EFFECTS OF HYPOXIC HYPOXIA AND CARBON MONOXIDE-INDUCED HYPOXIA ON THE CARDIOVASCULAR SYSTEM AND REGIONAL BLOOD FLOW OF THE ANESTHETIZED CAT

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ABSTRACT

The purpose of this study was to investigate the potential responses of the cardiovascular system and regional blood flow to hypoxic hypoxia (HH) and to carbon monoxide (CO)-induced hypoxia (COH). Ten anesthetized cats were studied under two normoxic (control: CONT) and two hypoxic conditions. Four types of radioactive microspheres were used to measure regional blood flow during CONT and two hypoxic conditions. During CONT the animal was ventilated with 22% O_2, 5% CO_2 and N_2 (room air). HH was induced by ventilating the cat for 15 min with 6-8% O_2, and COH by adding 0.1% CO to room air and reducing blood oxygen content to the same level as HH. Cardiac output and contractility significantly increased ($p<0.05$) during HH and COH but this increase was more pronounced during HH. There was a 22% increase in mean arterial blood pressure (Pa) without a significant change in total peripheral resistance (TPR) during HH. On the other hand, despite a 47% increase in cardiac output during COH, there was a 29% reduction in Pa which was due to peripheral vasodilation (TPR diminished by 45%). Analysis of regional blood flow (mL/min per 100g) showed that each organ acted differently. Coronary blood flow (80±7; CONT) increased during HH (678±153) and COH (584±106). Cerebral blood flow (30±4; CONT) was augmented during HH (86±7) and COH (124±14). Gracilis muscle, hepatic artery, renal, and small and large intestine blood flow did not change significantly during systemic hypoxia ($p>0.05$). Gastric blood flow (14±2; CONT) only increased during HH (22±4) but splenic blood flow (119±2; CONT) decreased with both HH (40±9) and COH (37±9). Regional blood flow of other segments measured showed a mixed response to HH and COH. In conclusion, it seems that: 1) systemic hypoxia would stimulate the heart to increase its output to maintain Pa and overcome the increased demand of some organs, and 2) the different responses of regional vascular beds to HH and COH may be due to various sensitivities of each organ to arterial blood oxygen tension and autonomic neuro-hormonal controls that have originated from stimulations of aortic and carotid chemoreceptors.

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INTRODUCTION

The cardiovascular system (CVS) transports oxygen to the tissues of an organism and removes carbon dioxide. The response of this system to acute hypoxic challenges and the role of arterial chemoreceptors [aortic (ab) and carotid bodies (cb)] in the CVS response to acute hypoxemia are subjects which were taken into consideration in this study. The assumption of this investigation is based on previous findings that ab and cb have different responses to normoxia and acute hypoxemia induced by HH and COH. That is, 1) both ab and cb fire sporadically or are almost silent during normoxia;[6] 2) the responses of ab and cb to decreased arterial oxygen tension are similar,[6,10,12] and finally 3) neural discharge of ab increases in response to decreased arterial oxygen content (CaO_2 such as during COH and anemia) even when PaO_2 is normal, whereas the cb does not.[6,10] This hypothesis, therefore, is based on the fact that lowering PaO_2 and CaO_2 concurrently by ventilating with low O_2 tension (HH) will increase neural discharge of both ab and cb. If the same cat is made hypoxic with COH (keeping PaO_2 at a normal level but decreasing CaO_2 to the same level as during HH), only ab will increase its neural discharge to the brainstem. Moreover, since during both hypoxic conditions, the central nervous system and the whole body are exposed to the same level of hypoxemia, the differences which might exist between the results of the two hypoxic conditions have to be due to the diversity of arterial chemoreceptor neural discharges to the brainstem.

MATERIAL AND METHODS

Experiments were carried out in 10 cats of either sex weighing 3-4 kg. They were anesthetized with an intraperitoneal injection of 30 mg/kg pentobarbitone. The right femoral vein was exposed and cannulated for intravenous infusion of fluids and drugs. The right femoral artery was cannulated for recording arterial blood pressure and taking samples for blood gas analysis. This cannula was advanced up to the descending aorta and connected to a P-23 Db Statham pressure transducer (USA) to record aortic systolic and diastolic pressures. Mean arterial blood pressure (Pa) was also recorded by electronically damping the arterial pressure traces. The left femoral venous cannula was advanced up into the right atrium to take blood samples during microsphere procedure. A temperature probe (Beckman USA) was placed rectally to make a record of body temperature and keep it at $37\pm1°C$ by a heating pad. During surgery a small drip of dextrose saline (20-30 mL/kg) was infused to feed the animal and prevent dehydration.

Tracheotomy was accomplished through a midline incision to ventilate the animal artificially. The left fifth intercostal space was opened, the pericardium cut and catheters placed in the left atrium and the left ventricle. An electromagnetic flow probe (No. 5) was carefully placed around the root of the aorta and connected to a Carolina flowmeter (USA) to have a continuous measurement of cardiac output as reported earlier.[5,7] All recordings were performed on an eight channel Grass polygraph (USA).

Regional blood flow was measured by the standard technique of injecting microspheres into the left atrium under conditions described below. Four isotopes of 15μ diameter ($15\pm3\mu$) of carbonized microspheres (Sigma, USA) were used in each experiment. These isotopes were Scandium-46, Strontium-85, tin-113 and Cesium-141. One of these isotopes was chosen randomly, suspended in normal saline, subjected to ultrasonication for 20 minutes, removed from the sonicator and vigorously shaken for 30-50 seconds. 0.2 mL of this suspension (about 8×10^5 spheres) was drawn into a disposable syringe, diluted with 3 mL saline, shaken for one minute and injected into the left atrium over a 20 second period. Reference arterial blood samples were taken with a Harvard syringe pump at a constant flow (1.36 ± 0.2 mL/min) for a period of 120 seconds (30 seconds before and 90 seconds after injection) from the right arterial cannula. The radioactivity of the reference blood and tissue samples were counted at the

Table I. Blood oxygen, carbon dioxide, and hydrogen ion values during normoxia and 15 minutes of exposure to HH and COH (Mean±SE).

Situation	pHa	$PaCO_2$ mmHg	PaO_2 mmHg	CaO_2 mL%
CONT-1	7.430±0.019	32.5±1.7	129±13	15.8±1.7
HH	7.348±0.043	34.0±1.7	24±2*	6.6±0.6*
CONT-2	7.398±0.002	34.0±1.9	133±12	17.2±0.4
COH	7.339±0.027	34.2±1.9	147±13	6.9±0.8*

*= significantly different from control at $p<0.05$.

Table II. Arterial blood pressure, cardiac output, heart rate, left ventricular contractility and total peripheral resistance during normoxia and 15 minutes of exposure to HH and COH (Mean±SE).

Situation	Pa mmHg	C.O. mL/min	LVd/dt mmHg/s	HR B/min	TPR × 1000 (RU)
CONT-1	101 ±4	312 ±14	2475 ±195	185 ±11	323 ±52
HH	122 ±6*	499 ±46*	4315 ±305*	173 ±14	262 ±14
CONT-2	104 ±7	316 ±33	2325 ±280	176 ±14	329 ±21
COH	85 ±8*	462 ±37*	3625 ±245*	180 ±16	183* ±21

*= significantly different from control at $p<0.05$.

same time in a Well Gamma Counter (Packard Auto-Gamma Scintillation Spectrometer, USA). Counts were analyzed by the use of the equation shown below and described by Buckberg et al., Cobb et al., and Marcus et al.[3,4,8]

$$\dot{Q}_i = \frac{A_i}{A_r} \times \frac{Q_r}{W_t} \times 100$$

Q_i= tissue blood flow (mL/min per 100 g); Q_r= withdrawal rate of the reference blood sample (mL/min); A_i and A_r are total tissue and reference counts/min respectively; Wt= weight of the organ of interest in grams.

Experimental protocol

Having recovered for three hours after surgery, the cats were ventilated with 22% O_2, 5% CO_2 in nitrogen for 15 minutes. At the end of this period an arterial blood sample was taken and the first microsphere was injected into the left atrium; the results were considered as control group 1 (CONT-1). The cat was then challenged with 6-8% O_2, 5% CO_2 in N_2 for 15 minutes (HH), concomitantly lowering the O_2 content (CaO_2) and PaO_2 (Table I). After taking an arterial blood sample the second microsphere injection was performed and the results considered as HH (Table I). The animal was then allowed to recover for one hour on room air. At the end of this period the above procedure was repeated and the third microsphere injection was performed (CONT-2). The second hypoxic challenge was accomplished for 15 minutes by initially adding 2% CO to the breathing air for two minutes (reducing CaO_2 rapidly), then leaving the animal on 0.1% CO and lowering CaO_2 to the same level as HH while keeping PaO_2 normal (COH; Table I). At the end of this period the last arterial blood sample was taken and the fourth microsphere was injected.

Table III. Vascular conductance (mL/mmHg per min) during normoxia and after 15 minutes of exposure to HH or COH (Mean ± SE).

Organ	CONT-1	HH	CONT-2	COH
Brain	0.30 ±0.04	0.72 ±0.05*	0.34 ±0.04	1.55 ±0.16*
Heart	0.11 ±0.01	0.76 ±0.08*	0.16 ±0.01	0.90 ±0.06*
Kidney	0.62 ±0.07	0.74 ±0.09	0.79 ±0.10	0.92 ±0.10
Liver (artery)	0.38 ±0.07	0.45 ±0.12	0.46 ±0.06	0.49 ±0.04
Small intestine	0.35 ±0.10	0.50 ±0.17	0.53 ±0.18	0.78 ±0.1*9
Large intestine	0.14 ±0.05	0.12 ±0.05	0.17 ±0.05	0.19 ±0.07
Spleen	0.15 ±0.05	0.04 ±0.01*	0.15 ±0.01	0.05 ±0.01*
Stomach	0.04 ±0.01	0.05 ±0.01	0.05 ±0.01	0.09 ±0.02
Splanchnic beds	1.11 ±0.16	1.23 ±0.17	1.40 ±0.22	1.62 ±0.25
Gracilis muscle	0.91 ±0.04	0.62 ±0.07*	0.68 ±0.08	0.58 ±0.06

*= significantly different from control at $p<0.05$

During the course of these trials all cardiovascular parameters presented in Table II were continuously recorded. At the end of the experiment the animal was sacrificed with an intravenous injection of 5 mL saturated KCl or pentobarbitone. For the measurement of regional blood flow each organ was taken out, cleaned, washed, weighed fresh, divided to small pieces and placed in counting

Table IV. Regional blood flow (mL/min/100g) after 15 minutes of exposure to HH and COH (values are expressed as mean±SE).

Organ	WT (gm)	CONT-1	HH	CONT-2	COH
Brain	29 ±1	30 ±4	86 ±6*	33 ±2	124 ±14*
Heart	14 ±1	81 ±7	678 ±153*	112 ±14	585 ±106*
Kidney	33 ±8	245 ±29	285 ±35	240 ±28	234 ±36
Liver (arterial)	115 ±17	40 ±12	54 ±19	46 ±14	40 ±10
Small intestine	106 ±7	42 ±8	51 ±18*	47 ±15	56 ±12
Large intestine	23 ±3	55 ±14	58 ±15	65 ±15	60 ±19
Spleen	12 ±4	119 ±20	41 ±14*	106 ±14	37 ±9*
Stomach	28 ±2	14 ±2	22 ±4	18 ±4	24 ±5
Gracilis muscle	31 ±3	2.2 ±0.2	3.7 ±1.2	2.3 ±0.3	1.6 ±0.4

*= significantly different from control at $p<0.05$

vials. The standards for the injected isotopes present in the samples including reference blood and organ samples were counted for one minute duration and regional blood flow was calculated.

Statistical analysis

One way analysis of variance and Duncan's new multiple range test was used at $p<0.05$ to obtain the statistical differences among the means of the parameters presented in the tables.

RESULTS

Blood gas values

The changes in arterial blood gas values, pHa, and CaO_2 during control and hypoxic conditions are presented in Table I. Arterial pCO_2 and pH (ranged from 32.5±1.7 to 34.2±1.9 mmHg and 7.339±0.027 to 7.430±0.019, respectively) were statistically the same throughout the course of the study. Exposure of the cat to HH reduced both PaO_2 and CaO_2 to about 30% of their control values, whereas COH exposure only reduced CaO_2 (Table I).

Cardiovascular reaction to HH and COH

Mean arterial bloodpressure (Pa), cardiac output (C.O.) and LVdp/dt (an index of left ventricular contractility) were elevated by 21, 60 and 175 percent, respectively, whereas there was a 22% decrease in calculated total peripheral resistance (TPR; Equation 2)* during HH (Table II). The observed data indicated that although during COH there was a concomitant reduction in Pa (20%) and TPR (45%), significant rises were still noticed in C.O. (46%) and LVdp/dt (60%). Changes in left and right atrial pressures are not presented here. This is so because their changes were minimal, rarely statistically significant, and probably

*Peripheral resistance (TPR) and vascular conductance were calculated by using equations 2 and 3, respectively.

Equation 2 $$TPR = \frac{Pa - PRA \,(mmHg)}{C.O. \,(mL/min)}$$

Equation 3 $$Vascular\ conductance = \frac{Q\,(mL/min)}{Pa - PRA\,(mmHg)}$$

never physiologically important. HR did not change either, undoubtedly influenced by pentobarbitone anesthesia, a vagolytic agent.

Changes in regional blood flow

Regional blood flow (mL/min per 100g) and calculated vascular conductance of organs weighing more than 10 grams are presented in Tables III and IV during normoxia, HH and COH. The significant reductions in cerebral vascular conductance during HH (59%) and COH (78%) augmented blood flow by 185% (HH) and 275% (COH), respectively. It is interesting to mention that the value of increased cerebral blood flow during COH was 68% greater than during HH. Coronary vasculature beds showed profound vasodilation (85% and 82%) with a concomitant increase in blood flow (730% and 422%) during HH and COH. In contrary to cerebral blood flow, the absolute values of increased coronary blood flow during HH were 27% greater than that of COH. The rise in conductance of gastric beds were less pronounced and hence there were modest increases in blood flow during HH (66%) and COH (40%). Vascular beds of the spleen were highly constricted and their blood flow decreased (HH 255% and COH 157%) significantly inasmuch as hepatic beds did not change their conductance and blood flow during both conditions of hypoxemia. At the same time dilation of blood vessels of the stomach and small intestine during HH brought on a significant increase (57% and 75% respectively) in their blood flow, whereas no changes in flow were observed during COH. Pooling the data of all these organs as a whole indicated that there were no significant changes in the vascular conductance and blood flow of splanchnic beds during HH and COH. Renal and gracilis muscle beds did not change their conductance statistically; therefore, they had constant blood flows during the study.

DISCUSSION

Cardiac responses to systemic hypoxia

Many factors influence the cardiovascular system (CVS) during systemic hypoxia. During HH not only are the direct influences of systemic hypoxia present, but also the combined increased neural impulses of ab and cb to the brainstem influences the CVS via the autonomic neuroendocrine system.[1,7,9,14] Whereas, during CO-induced systemic hypoxia, only ab stimulation is involved and cb is silent.[6,7,13] These different effects presumably are principally the result of quantitative differences in sympathetic impulses to the heart and the vasculature.[5,7,13,14] The outcome of these differences are provoking dissimilar levels of increased C.O. and LVdp/dt. What is produced quantitatively when only ab is stimulated is that the level of increased C.O. and LVdp/dt is less obviated as compared to combined stimulation of ab and cb during systemic hypoxia (46% vs.

60% and 56% vs. 75%, respectively; Table III). This is in spite of the fact that the decreased blood pressure which evokes a stimulatory baroreceptor reflex on the heart should have induced greater myocardial performance as concluded by Fitzgerald et al., Serani et al., and others.[7,13,14] As noted above, however, since heart rate was not significantly changed throughout the trials, this index apparently does not follow the chronotropic behavior of the heart as reported by Serani and Shirai et al.[13,14]

Vascular responses to systemic hypoxia

Although the combined stimulation of ab and cb (HH) could not diminish the direct local vasodilatory influences of low O_2 on vascular beds of sensitive organs such as the brain and coronary beds, the least reduction of peripheral resistance in general (3.23 ± 0.52 vs. 265 ± 14 RU) and higher elevation of cardiac output caused a meaningful increase in the arterial blood pressure (Table III). Actually the reflex chemoreceptor stimulation of both ab and cb during systemic hypoxia could induce arterial hypertension by increasing cardiac output more effectively, possibly by sympathetic constriction of venous beds and concomitant prevention of peripheral vasodilation to keep blood pressure elevated as stated by many investigators.[5,7,13,14] Combined stimulation of ab and cb during systemic hypoxia in the cat is able to increase cardiac output more extensively, as observed by King and his colleagues in the dog,[9] and perfuse susceptible organs like the brain and heart (Table IV) and at the same time overcome the direct dilatory effects of hypoxemia on peripheral vascular beds.

However, when ab alone has input into the brainstem and systemic hypoxia is still present, then the stimulation of the heart is not as great and peripheral vasodilation is so distinct that the CVS is not able to keep the arterial pressure at normal levels (Table III). This is so because the consequence of weak central sympathetic impulses to the CVS was an 18% reduction in Pa due to a 60% reduction of TPR during COH.

Vascular conductance and blood flow in specific organs

As noted above and recognized by others previously, acute systemic hypoxemia provokes vasodilation by direct local effects.[1,2,6,9] It is interesting to note that besides O_2 content and tension, all other blood gas variables presented in Table I are almost exactly the same during both hypoxic conditions. Albeit there appears to be opposing effects of combined stimulations of ab and cb upon the direct vasodilatory effects of hypoxemia on the vascular beds, it seems that each organ's response to hypoxemia is different (Table III). As shown in Table IV, cerebral and coronary blood flow have significantly increased ($p < 0.05$) during HH and COH. The kidney, large intestine, liver, stomach and skeletal muscles (e.g. gracilis muscle) are unique in that none of them changed their blood flow significantly.

Hence it seems these organs autoregulate themselves totally during acute systemic hypoxia independent of various chemoreceptor neural inputs to the brainstem. In contrast, the data suggest that maximum reduction in splenic blood flow is seen (65%) under the conditions of HH and COH.

In summary, under the conditions of acute systemic hypoxia with involvement of both arterial chemoreceptors, positive inotropic or sympathetic impulses to heat and the peripheral vasculature are more abundant than the involvement of aortic chemoreceptors alone. However, the responses of the brain, heart, kidney and splanchnic vascular beds (except the spleen) to systemic hypoxia seem to be affected very little by chemoreceptor inputs to the brain stem.

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