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Peripheral circulatory responses to acute hyperoxia

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Plewes JL, Farhi LE. Peripheral circulatory responses to acute hyperoxia. Undersea Biomed Res 1983; 10(2):123–129.—Acute hyperoxia (1 atm) in anesthetized dogs produced a 14% decrease in cardiac output relative to that observed with $F_{I_{O_2}} = 0.21$ and was associated with 7% decreases in heart rate and stroke volume. Changes in the distribution of peripheral blood flow during hyperoxia, as measured with radioactive labeled microspheres, included decreases in renal cortical flow (−20%), retinal blood flow (−27%), and blood flow to the caudate nucleus, mesencephalon, hippocampus, and cerebellum. Absolute blood flow to intestinal viscera, to respiratory and skeletal muscle, and to fat were unchanged. Simulation of these changes in cardiac output and distribution of blood flow using a digital computer model show a minimal change in the pattern of nitrogen gas elimination, with nitrogen partial pressures in the "slowest" body compartment within 1% of control by 60 min.

nitrogen washout
peripheral blood flow
hyperoxia

Denitrogenation by breathing pure oxygen before undergoing a decompression maneuver is intended to decrease the partial pressure of nitrogen in all tissue groups so that there will be insufficient inert gas present to produce bubbling. Changes in cardiac output, or in the absolute blood flow to different tissue groups of the body, will produce changes in the elimination of inert gases from those groups. There are a number of reports of small (10%–15%) but significant decreases in cardiac output during hyperoxia; similarly, there are reported decreases in cerebral (1) and renal blood flow (2) during hyperoxia. However, changes in blood flow to such "fast" groups, with relatively high blood flows per unit volume, will affect the initial profile of inert gas washout but not significantly affect the rate of denitrogenation in the groups of "slower" tissues such as muscle or fat. We have studied the effects of acute hyperoxia on cardiovascular dynamics and peripheral blood flow in order to determine whether changes occur in cardiac output, or in the absolute blood flow to different tissue groups, that would significantly affect the rate of body denitrogenation.

METHODS

Mongrel dogs of either sex weighing between 14 and 20 kg were used for this study. Each dog was anesthetized with thiopental sodium (30 mg/kg i.v.), intubated with a cuffed endotra-

cheal tube, and mechanically ventilated to produce Pa_{CO_2} of about 28 torr. Anesthesia was maintained with 1.2% halothane in the inspired gas mixture.

Catheters were inserted into a peripheral vein to allow infusion of i.v. maintenance fluids (Ringer's Lactate at 4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}) and drugs, and they were inserted into the descending aorta via the right femoral artery to allow measurement of systemic blood pressures and for withdrawal of reference samples of arterial blood during the period of microsphere injection. A Swan-Ganz (Edwards Laboratories, Santa Ana, CA) thermodilution catheter was inserted into the pulmonary artery via the external jugular vein in order to measure both cardiac output and pulmonary artery pressure. A #7F Cordis pigtailed catheter (Cordis Laboratories, Inc., Miami, FL) was placed with its tip in the left ventricle via the left femoral artery for measurement of left ventricular pressures and injection of microspheres.

After insertion of the catheters the animal was allowed to stabilize for about 90 min in order that anesthetic uptake would have stabilized. During this time the inspired gas mixture was room air with 1.2% halothane. Vascular pressures were measured with Statham strain gauge manometers (Statham Instruments, Oxnard, CA) and compared to a zero reference level opposite the level of the right atrium. Temperature was measured with a rectal thermometer and with the thermistor in the Swan-Ganz catheter.

At the end of this period, the cardiac output was measured by determining the mean thermodilution response to several serial injections of iced 5% glucose in water. Pressure data and blood gases (arterial and pulmonary arterial) were obtained during this time period. The first injection of radioactive labeled microspheres was made via the left ventricular catheter at this time to determine the distribution of peripheral blood flow. We used 15-μ polystyrene spheres (New England Nuclear, Boston, MA) labeled with one of ^{153}Gd, ^{103}Ru, ^{113}Sn, ^{95}Nb, or ^{46}Sc and suspended in a 0.9% NaCl solution containing 0.01% tween to prevent sphere aggregation. The spheres had been measured to determine true diameters (13.5 μm $\pm$ 2 μm SD) and variability, and to ensure the absence of nonspherical spheres. A sample of each type of sphere was counted to determine mean radioactivity levels in counts per minute. Approximately one million spheres were suspended in 10 ml of the dog's blood and injected into the left ventricle. From about 10 s before and for about 3 min after each injection blood was withdrawn continuously from the descending aorta at a constant rate to obtain a reference microsphere count in this "artificial organ" with known blood flow.

When these measurements were complete, the inspired gas mixture was changed to 1.2% halothane in 100% oxygen ($F_{I_{O_2}} = 0.988$). After 45 min, another set of measurements were made. Following this, the $F_{I_{O_2}}$ was returned to 0.21 for 60 min, at the end of which another set of measurements were made. Then we returned $F_{I_{O_2}}$ to 0.988 for 45 min, at the end of which we repeated the measurements. Finally, we returned $F_{I_{O_2}}$ to 0.21, and after 60 min made the final set of measurements. We were thus able to obtain three complete sets of measurements at $F_{I_{O_2}} = 0.21$ and two complete sets with $F_{I_{O_2}} = 0.988$.

At the end of the experiment the animal was killed by i.v. injection of saturated KCl solution. The brain, heart, eyes, spinal cord, liver, kidneys, adrenals, and portions of the duodenum, ileum, colon, pancreas, spleen, adipose tissue, diaphragm, masseter, gastrocnemius, and biceps were removed and fixed in 10% formaldehyde for at least 4 days. At that time the organs were sectioned, weighed, and placed in plastic tubes for radioactive counting in an ND-60 (Nuclear Data, Inc., Schaumburg, IL) well-type gamma counter and multichannel analyzer. Tissue samples were counted long enough to ensure a minimum of 10,000 counts above background. We also could ensure from the radioactivity levels that the specimens contained a minimum of 400 spheres, in accordance with the suggestions of Heymann et al. (3) to minimize sampling errors.

Some organs were sectioned in detail to look for any intraorgan changes in the distribution of blood flow. The renal cortex was sectioned into four concentric layers, with layer 1 being outermost, and layer 4 being juxtamedullary. The brain was sectioned into numerous functional areas, including caudate nucleus, cerebellum, thalamus, hippocampus, pons, mesencephalon, and vermis.

From the "artificial organ" we were able to determine the amount (counts $\cdot$ min^{-1} $\cdot$ ml^{-1}) of arterial blood flow delivered during each of the injections. Regional flows were determined using the formula:

$$\text{tissue (Q)} = \frac{\text{no. of counts in sample per}}{\text{counts delivered per ml arterial blood}}$$

Tissues with low blood flows (fat, muscle) were measured by counting multiple larger samples. Total peripheral resistance and regional vascular resistances were calculated by dividing mean arterial blood pressure by blood flow in liters per minute assuming downstream venous pressure to be 10 torr.

Statistical analysis was performed using the nonparametric Wilcoxon signed-ranks test. Probability values of less than 0.02 were considered significant.

RESULTS

There were no statistically significant differences between the different groups of measurements taken at $FI_{O_2} = 0.21$, so that observations from all 7 animals were pooled. Similarly, the 2 groups of observations made at $FI_{O_2} = 1.0$ were not statistically different, and they also were pooled.

The average Pa_{O_2} on room air was 84 torr and increased to 603 torr on 100% oxygen ($P<0.02$). The Pv_{O_2} increased from 46 torr on room air to 63 torr on 100% oxygen ($P<0.02$), and Pa_{CO_2} remained at 28 torr in both conditions. There was a small increase in Pv_{CO_2}, from 33 torr to 35.4 torr ($P<0.02$). Arterial pH remained the same (7.42) in both conditions (Table 1).

Cardiac output decreased by 14% ($P<0.02$) during hyperoxia. This was associated with a 7% decrease in heart rate ($P<0.02$) but no change in mean arterial blood pressure. Changes in total peripheral resistance were not significant.

There were no significant changes measured in left ventricular end-diastolic pressure (LVEDP), mean pulmonary artery pressure, peak left ventricular dP/dt, hemoglobin concentration, or body temperature.

Renal cortical blood flow decreased by about 20% in all four layers during hyperoxia ($P<0.02$). Except for duodenum none of the other intra-abdominal organs showed significant changes in blood flow; these organs included liver, adrenal, spleen, pancreas, ileum, and colon (Table 2).

Total cerebral blood flow did not change significantly, although there were significant decreases in flow to caudate nucleus (-12%), cerebellum (-15%), mesencephalon (-20%), vermis (-11%), and hippocampus (-15%). Retinal blood flow decreased by 27% ($P<0.02$).

There were no changes in blood flow seen in skeletal muscle (triceps, gastrocnemius, masseter), diaphragm, or fat.

DISCUSSION

The central hemodynamic changes seen in these experiments consisted of a 14% decrease in cardiac output, associated with 7% decreases in both heart rate and stroke volume. These

TABLE 1
MEASURED CARDIORESPIRATORY VARIABLES*

Variable	Air	Hyperoxia	*P*
Total Peripheral Resistance (torr ··liter^{-1} ··min)	26.34 ± 2.01	32.91 ± 3.15	NS
Cardiac Output (ml/min)	3129 ± 179	2699 ± 155	$P<0.02$
Heart Rate (beats/min)	99 ± 4	92 ± 4	$P<0.02$
Left ventricular end-diastolic pressure (torr)	6.7 ± 1.1	7.4 ± 1.3	NS
Mean Pulmonary Arterial Pressure (torr)	13.0 ± 1.1	13.0 ± 1.2	NS
Mean Arterial Pressure (torr)	90.0 ± 5.5	94.4 ± 6.0	NS
Peak LV dP/d*t* (torr/s)	1663 ± 76	1596 ± 67	NS
Body Temperature (°C)	36.7 ± 0.2	36.9 ± 0.1	NS
Pa_{O_2} (torr)	84.2 ± 2.5	603 ± 10.0	$P<0.02$
Pv_{O_2} (torr)	46.4 ± 1.2	63.1 ± 3.1	$P<0.02$
Pa_{CO_2} (torr)	27.9 ± 1.0	27.9 ± 0.7	NS
Pv_{CO_2} (torr)	33.1 ± 0.7	35.4 ± 0.8	$P<0.02$
pH	7.42 ± 0.02	7.42 ± 0.02	NS
Hemoglobin (g %)	13.7 ± 0.7	13.9 ± 0.7	NS

*Mean ± 1 SEM. For all variables $n = 14$.

changes are of similar magnitude to those reported in humans by Andersen and Hillestad (4), who saw a 12% decline in cardiac output associated with 5% decreases in stroke volume and heart rate. The reasons for these changes are not obvious. We saw no changes in preload as estimated by LVEDP, in left ventricular peak dP/d*t*, or in afterload as estimated by mean arterial pressure, leading us to conclude that no changes in left ventricular contractility occurred.

During acute hyperoxia, oxygen transport, calculated as the product of cardiac output and arteriovenous (A-V) oxygen difference, remained quite constant. If we assume a normal oxygen dissociation curve for dog blood (5) and a physical solubility of oxygen in blood of 0.003 ml · 100 ml^{-1} blood · torr^{-1} (6), the A-V O_2 difference on room air was 18.2 − 14.8 = 3.4 ml O_2/100 ml blood, while during hyperoxia it was 20.6 − 16.8 = 3.8 ml O_2/100 ml blood. Combined with the observed cardiac outputs, the oxygen delivery was 106 ml/min on room air, and 103 ml/min during hyperoxia.

TABLE 2
MEASURED TISSUE BLOOD FLOWS*

Tissue	Air	Hyperoxia	P
Renal Cortex (outer)	6.11 ± 0.57	5.08 ± 0.42	$P<0.02$
Adrenal	1.69 ± 0.23	1.26 ± 0.17	NS
Liver	0.27 ± 0.06	0.23 ± 0.05	NS
Duodenum	0.59 ± 0.10	0.49 ± 0.13	$P<0.02$
Ileum	0.55 ± 0.11	0.50 ± 0.11	NS
Total Cerebral Flow	0.52 ± 0.05	0.43 ± 0.05	NS
Hypothalamus	0.42 ± 0.04	0.31 ± 0.03	$P<0.02$
Caudate Nucleus	0.75 ± 0.11	0.66 ± 0.11	$P<0.02$
Cerebellum	0.39 ± 0.04	0.33 ± 0.03	$P<0.02$
Spinal Cord	0.14 ± 0.02	0.12 ± 0.01	NS
Retina	2.20 ± 0.16	1.60 ± 0.19	$P<0.02$
Diaphragm	0.036 ± 0.005	0.030 ± 0.004	NS
Fat	0.011 ± 0.0026	0.011 ± 0.003	NS
Renal Cortex (juxtamedullary)	4.98 ± 0.33	3.70 ± 0.36	$P<0.02$
Spleen	1.86 ± 0.36	1.40 ± 0.23	NS
Pancreas	0.19 ± 0.02	0.16 ± 0.02	NS
Caecum	0.57 ± 0.07	0.47 ± 0.06	NS
Pons	0.28 ± 0.02	0.23 ± 0.02	NS
Mesencephalon	0.41 ± 0.04	0.33 ± 0.03	$P<0.02$
Vermis	0.45 ± 0.04	0.40 ± 0.04	$P<0.02$
Thalamus	0.50 ± 0.07	0.42 ± 0.06	NS
Hippocampus	0.40 ± 0.04	0.34 ± 0.03	$P<0.02$
Triceps	0.033 ± 0.002	0.029 ± 0.003	NS

*In ml · g^{-1} · min^{-1}. Values are given as means, ± 1 SEM. For all tissues $n = 14$.

Similarly, it appears that oxygen delivery to all tissues remains relatively constant. Although there were significant decreases in blood flow to some tissues, the increase in arterial oxygen content associated with hyperoxia means that even with significant falls in flow, oxygen extraction may be maintained by increased extraction without lowering capillary P_{O_2} below that existing during room air breathing. For example, retinal blood flow decreased by 27%. If we assumed retinal A-V O_2 difference to be 3.4 ml O_2/100 ml blood (the same as the overall body A-V O_2 difference), then with the 27% decrease in flow observed during hyperoxia, this extraction would have to increase to 4.66 ml O_2 · 100 ml^{-1} blood · min^{-1}. This would lower retinal capillary O_2 content to 15.9 ml O_2/100 ml blood, a level higher than the 14.8 ml O_2/100 ml calculated to be present in venous blood during room air breathing.

The anesthetic used was halothane, a volatile halogenated hydrocarbon that has been shown to cause both myocardial depression and peripheral vasodilatation (7, 8). For this reason, anesthetic uptake was allowed to proceed for at least 2 h to approach completion, so that the peripheral and central effects would have stabilized. As shown by the results, the peripheral vascular beds remained responsive, since changes in flows between room air and 100% oxygen

were reversible upon return to room air. Similarly, the depression in cardiac output during hyperoxia was reversible. The possibility remains that these responses were of a different order of magnitude than would be seen in the conscious animal.

Although total peripheral resistance did not change significantly, there were changes in specific organ beds. Renal vascular resistance increased by about 20%, resulting in significant decreases in renal cortical blood flow. These results confirm those of Rennie and Knox (2), who observed progressive decreases in renal blood flow as dogs breathed 100% oxygen at 1–4 atm.

Cerebral blood flow remained constant, but there were major increases in intracerebral vascular resistances, resulting in decreases of 12%–20% in blood flow to caudate nucleus, mesencephalon, hippocampus, vermis, and cerebellum.

The decrease in retinal blood flow confirms the observations of Dollery et al. (9), who observed significant retinal vessel constriction in adults exposed to 1 and 2 atm of oxygen. This response seems to serve no purpose, but it may prevent exposure of the sensitive retinal tissue to the damaging effects of hyperoxia. This may be of importance in patients or workers in hyperoxic conditions, since bilateral permanent blindness secondary to chronic hyperoxia has been reported (10).

A digital computer model was used to simulate nitrogen washout and assess the effects of the observed changes in cardiac output and peripheral blood flow on the pattern and rate of nitrogen elimination from the body during breathing of pure oxygen. Standard values for cardiac output, minute ventilation, tissue volumes, tissue blood flows, and tissue solubilities for nitrogen were used initially, and then values for cardiac output and tissue blood flows were changed to duplicate the changes seen during hyperoxia. The depression in cardiac output seen during hyperoxia causes a generalized slowing of inert gas washout, especially during the first 10–15 min of the washout. However, because absolute blood flow to the fat and muscle compartments did not change during hyperoxia, only minimal changes occur in the calculated profile of nitrogen washout from these slower compartments. In fact, nitrogen partial pressure in the slowest compartment (fat) is within 1% of control levels after 60 min of washout, and so we may conclude that the changes in cardiac output and peripheral blood flow during hyperoxia will not significantly delay the rate of nitrogen elimination.

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Plewes JL, Farhi LE. Réponses circulatoires périphériques à l'hyperoxie aigue. Undersea Biomed Res 1983; 10(2):123–129.—L'hyperoxie aigue (1 atm) chez le chien anesthésié a produit une diminution de 14% du débit cardiaque relativement à la valeur obtenue avec une $F_{I_{O_2}} = 0.21$. Cet effet était associé avec une chute de 7% de la fréquence cardiaque et du volume systolique. Les changements dans la distribution de la circulation périphérique durant la période d'hyperoxie, tels que mesurés avec des microsphères marquées radioactives, ont inclu des diminutions du débit sanguin dans le cortex renal (−20%), la rétine (−27%), ainsi que le mésencéphale, l'hippocampe, le cervelet et le noyau caudé. Le débit sanguin absolu n'a pas changé dans les viscères intestinales, le tissus adipeux, de même que dans les muscles respiratoires et squelettiques. La simulation des effets de l'hyperoxie sur le débit cardiaque et la distribution du débit sanguin avec un modèle d'ordinateur digital a montré un changement minime dans le mode d'élimination de l'azote. Ceci est supporté par le fait que les pressions partielles de l'azote dans le compartiment tissulaire corporel le "plus lent" demeura à moins de 1% de la valeur témoin après 60 minutes de simulation.

lavage à l'azote
débit sanguin périphérique
hyperoxie

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