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Low Oxygen Delivery Produced by Anemia, Hypoxia, and Low Cardiac Output

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In pentobarbital-anesthetized dogs, oxygen delivery (DO_2) was measured by thermodilution cardiac output and cooximeter determined oxygen content, while oxygen consumption (VO_2) was measured independently by spirometry. Oxygen delivery was decreased by isovolemic dilutional anemia, breathing hypoxic gas mixtures, or cardiac tamponade to reduce cardiac output. Baseline VO_2 (cc/kg/min) for the three groups was 5.9 ± 0.7 (anemia), 5.4 ± 0.4 (hypoxia), and 5.6 ± 0.1 (low C.O.) (NS). A critical level of oxygen delivery (DO_{2crit}) was found at 9–10 cc/kg/min (anemia), 10–11 cc/kg/min (hypoxia), and 9–10 cc/kg/min (low C.O.) (NS.). Below this level, VO_2 fell (became supply dependent) and lactic acidosis occurred, regardless of the mechanism of impaired oxygen delivery.

INTRODUCTION

Mammalian studies have identified critically low levels of oxygen delivery (DO_2) below which total body oxygen consumption (VO_2) is dependent upon oxygen delivery and above which oxygen consumption is independent of oxygen delivery [1–5]. This critical level of oxygen delivery (DO_{2crit}) is much lower than the normal DO_2 for any species and is associated with lactatemia, acidosis, and hypotension.

In previous studies, the three components of oxygen delivery (hemoglobin, arterial oxygen content, and cardiac output) have not been manipulated independently. Also, in most studies, the same measured variable was used to calculate both oxygen delivery and oxygen consumption. Either cardiac output and blood oxygen content were measured and used to calculate oxygen consumption by the Fick relationship or oxygen consumption was measured and used similarly to calculate cardiac output in order to determine oxygen delivery. In few studies have the variables DO_2 and VO_2 been measured entirely independently [6, 7, 8].

In an earlier study, we controlled DO_2 and measured VO_2 independently in anesthetized dogs [7]. In the current study, using a canine model, the components of oxygen delivery were manipulated independently to determine if DO_{2crit} is dependent upon the component that is altered. In addition total body oxygen consumption was measured independently of oxygen delivery. Volumetric spirometry was used to measure oxygen consumption while oxygen delivery was calculated from thermodilution cardiac output and arterial oxygen content. In order to analyze the data in a statistically valid fashion, a method of interpolation was applied to the data set.

The hypothesis of this experiment is that DO_{2crit} is independent of the method by which DO_2 is reduced.

METHODS

Experimental Design.

(See Fig. 1) Mongrel dogs (15–20 kg) were fasted over night, anesthetized with pentobarbital (15 mg/kg), and ventilated with a volume ventilator to a pCO_2 of 30–45 mm Hg. FiO_2 was 0.3–0.5 except in the induced hypoxia group. Supplemental pentobarbital was given throughout the experiment to ablate the inner canthal reflex. Temperature was maintained at 37.5°C by external warming. A right groin dissection was performed for introduction of an 8 French arterial catheter for arterial blood sampling and systemic arterial blood pressure monitoring. An injectate catheter for cardiac output determination was positioned in the right atrium via the right femoral vein. A balloon-tipped pulmonary artery catheter with a thermistor was inserted through the right external jugular vein for measuring cardiac outputs. Position was confirmed by identifying the pulmonary artery pressure tracing that changed to a pulmonary capillary wedge pressure tracing with 1 ml air injected into the balloon. Additionally, the catheter was palpated in the pulmonary artery at autopsy.

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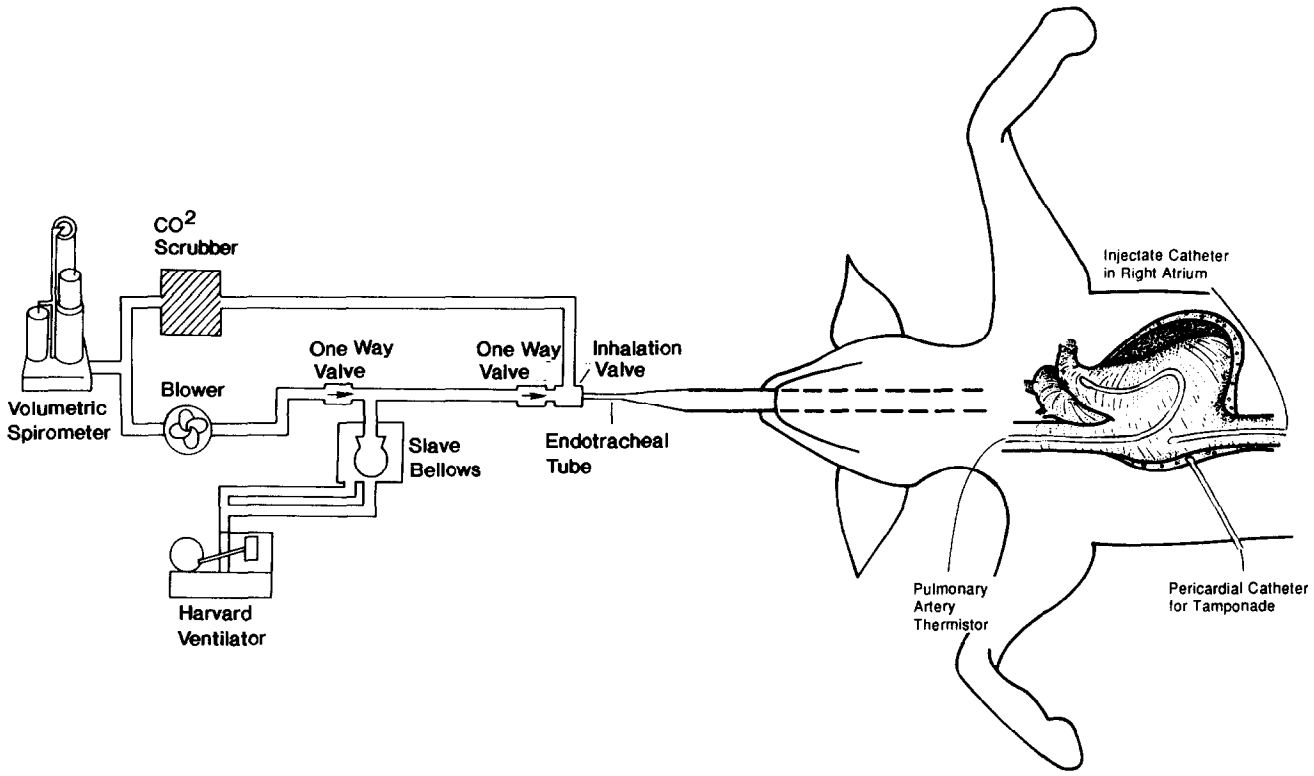

FIG. 1. Experimental diagram. Ventilator-respirometer measures VO_2; cardiac instrumentation.

A right subcostal incision was then performed and the spleen was removed. Splenectomy was performed to prevent splenic autotransfusion. A small area of pericardium was exposed through an incision in the right hemidiaphragm and an 8 French catheter was secured inside the pericardium by a purse string suture for the portion of the experiment requiring tamponade.

The animal was then attached to the ventilator respirometer (see below, measurement of VO_2) and sequential oxygen consumption measurements were performed over a 3–8 hr period during which oxygen delivery was manipulated as described below. Dogs were assigned to one of three experimental groups. In Group I seven dogs were made anemic with oxygenation and cardiac output constant. In group II five dogs were made hypoxic at constant hemoglobin and cardiac output. In Group III four dogs underwent cardiac tamponade by injection of isotonic saline into the pericardium to reduce cardiac output at constant oxygenation and hemoglobin.

Manipulation of Oxygen Delivery

Anemia. Whole blood was removed from Group I animals in 200-ml aliquots followed by crystalloid replacement to return pulmonary capillary wedge pressure to the baseline level. As the dogs became anemic and began to develop tachycardia and increased cardiac output, cardiac tamponade was used to restrict this compensatory response. Small aliquots of saline were injected into the pericardial catheter to maintain cardiac output at baseline levels. Oxygen consumption was measured at progressively lower levels of oxygen delivery as the dogs became more anemic. When very low levels of oxygen delivery were reached, below the critical level of oxygen delivery, oxygen consumption fell and hemodynamic instability occurred. To acquire more data points above and below the DO_{2crit}, some dogs were resuscitated with whole blood to raise their oxygen delivery and return their oxygen consumption to baseline. These animals were then bled further and data collection continued. As cardiac output fell at very low levels of DO_2, tamponade was released in an effort to keep the cardiac output at baseline levels. All animals eventually died of heart failure secondary to anemia and low DO_2.

Hypoxia. Animals were made hypoxic by adding nitrogen to the ventilator-respirometer to decrease the FiO_2 in the apparatus. FiO_2 was changed in 2% increments until very low levels of DO_2 were reached. Animals were returned to the original FiO_2 to confirm that baseline VO_2 had not changed when DO_2 was above DO_{2crit}. The lowest levels of oxygen delivery were investigated immediately prior to death from hypoxia. Cardiac tamponade was used to prevent the compensatory increase in cardiac output that occurs with hypoxia. As DO_2 was lowered by hypoxia, marked respiratory muscular activity was noted at very low DO_2 ($<DO_{2crit}$). When this phenomenon occurs the animal promptly dies, (unpublished observation) presumably as a result of in-

creased VO_2 from muscular activity and the fixed low level of oxygen delivery. In an effort to examine the lowest DO_2 induced by hypoxia, pancuronium bromide (3 mg) was given intravenously to the hypoxic animals prior to final reduction of DO_2 before death.

Low cardiac output. The pericardial catheter was used to create cardiac tamponade by progressive volume infusion. Animals were tamponaded until a desired cardiac output was obtained. Tamponade was then adjusted to maintain this cardiac output. The amount of tamponade was varied to acquire data points above and below the DO_{2crit} until the lowest levels of DO_2 caused instability and death.

Measurement of Oxygen Delivery

Cardiac output was measured using the thermodilution system described earlier. This system employed two catheters, one for injecting iced saline in the right atrium and one for measuring the temperature change in the pulmonary artery. This ensured that the injectate was mixed over the same anatomic distance in all animals regardless of the animal size. A Sorensen research cardiac output computer (Model 03950-00, Salt Lake City, UT) was used to calculate the cardiac output using a Stewart–Hamilton calibration factor of 0.442. Three to five measurements were made during each data set collection, using 5-ml injections of iced saline. The average was used in calculation of oxygen delivery. Arterial blood samples were taken with each data set and analyzed by a cooximeter, calibrated for canine blood (Instrumentation Laboratory Model 282, Lexington, MA). The instrument measured the oxyhemoglobin saturation and hemoglobin and then calculated the oxygen content using 1.39 ml O_2/g of hemoglobin as the oxygen-combining capacity of canine hemoglobin. Dissolved oxygen in plasma was calculated by measuring pO_2 with a blood gas analyzer (Radiometer ABL-30, Copenhagen, Denmark) and multiplying by the solubility coefficient of oxygen in plasma (0.003 ml O_2/dl plasma/mm Hg). The oxygen delivery per unit weight was calculated: DO_2 = (TDCO) (Hb-bound O_2 + dissolved O_2).

Measurement of Oxygen Consumption

Closed circuit spirometry techniques were adapted to measure oxygen consumption. A volume ventilator compressed a slave bellows included in the closed circuit. Tidal volumes were delivered to the animals which then passively expired back into the circuit. Flow was directed through the circuit via one-way valves. The expired carbon dioxide was removed from the circuit by a calcium hydroxide scrubber. An in-line calibrated magnetic valve on the exhalation side of the circuit provided 5 cm of expiratory pressure. A volumetric spirometer attached to the circuit replaced oxygen consumed, directly measuring VO_2. The circuit was checked for leaks prior to the experiment and a leak-free circuit was confirmed at the end of the experiment by ventilating the animal after death and noting that no change in volume in the circuit occurred. Oxygen consumption, measured at atmospheric temperature and pressure, saturated was converted to standard temperature and pressure, dry, using standard tables based on the ideal behavior of atmospheric gases. Oxygen consumption was expressed as ccO_2 (STPD)/kg/min.

Atmospheric pressure was measured during each experiment using a mercury barometer.

Lactate Determination

Venous blood samples (3 ml) were drawn during data collection and immediately centrifuged. The serum was decanted and frozen. Lactate determinations were made using the ACA lactic acid method (DuPont Automatic Clinical Analyzer, Wilmington, DE). This method is a modification of the Marbach and Weil method and employs the enzymatic oxidation of lactate to pyruvate. The absorption of NADH produced in this reaction is measured using a 2 filter endpoint technique and is directly proportional to the lactate concentration.

Data Collection

Oxygen consumption was monitored at 1- to 3-min intervals depending upon the stability of animal. When oxygen consumption stabilized at a particular level of delivery, a data set was collected. Each data set consisted of the following: VO_2, cardiac output, hemoglobin, and hemoglobin saturation for arterial and venous blood, PaO_2, PVO_2, blood sample for lactate determination, systemic arterial blood pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure.

Statistical Analysis

Ideally, sufficient data points would be collected from each animal to determine the DO_{2crit} for each animal; however, each animal provides relatively few data points because of instability occurring below the DO_{2crit}. In addition, VO_2 was not measured at the same DO_2 in each animal. The methods allowed a series of VO_2 measurements over a range of DO_2 for each animal but we did not attempt to establish identical normalized DO_2 conditions for all animals in each group. Therefore, to compare animals to each other, and to establish a full range of DO_2/VO_2 values for each group, a method of interpolation of DO_2 and VO_2 was employed to determine a value for the critical level of delivery for each experimental group. Each group was stratified into DO_2 intervals of 1 ml/kg/min. Based on the observation that VO_2 is constant above a DO_2 of 14 cc/kg/min in anesthetized dogs with VO_2 below 6 cc/kg/min [7], the VO_2 values at DO_2 greater than 14 ml/kg/min were averaged to determine the baseline VO_2. For each animal, interpolated values of VO_2 and DO_2 were assigned to each 1 cc/kg/min DO_2

TABLE 1

Baseline Hemodynamic and Oxygenation Parameters in Anemic, Hypoxic, and Low C.O. Groups

Group	Anemia	Hypoxia	Low C.O.
n	7	5	4
wt (kg)	16.6 ± 1.2	18.2 ± 2.4	19.4 ± 0.9
t (°C)	37.5 ± 0.8	37.7 ± 0.6	37.6 ± 0.6
SBP (mm Hg)	186 ± 16	175 ± 32	173 ± 45
DBP (mm Hg)	111 ± 15	110 ± 13	95 ± 29
HR (min^{-1})	169 ± 24	183 ± 17	157 ± 49
PCWP (cmH_2O)	10 ± 3	9 ± 3	6 ± 3
TDCO (cc/kg/min)	172 ± 38	156 ± 38	141 ± 65
pH	7.38 ± 0.05	7.33 ± 0.05	7.34 ± 0.05
pCO_2	36 ± 5	40 ± 4	34 ± 4
pO_2	163 ± 118	122 ± 50	166 ± 125
Hb (g/dl)	13.7 ± 2.7	17.5 ± 3.1	14.5 ± 4.1
VO_2 (cc/kg/min)	5.9 ± 0.7	5.4 ± 0.7	5.6 ± 0.05
Lactate (mmole/liter)	1.8 ± 1.9	1.3 ± 0.7	2.6 ± 1.0

Note. Differences are not significant.

interval when no data points were measured in that interval. Interpolated values were determined by comparing the measured VO_2 values at the DO_2 interval higher and lower than the interval in question, and assigning the greater value of VO_2 to the interval. This method biases the interpolated values to not differ from baseline VO_2. Group average values of VO_2 were determined for each 1 cc/kg/min DO_2 interval using measured and interpolated values. In each group a 1 tailed paired *t* test was used to compare the VO_2 of each interval to the baseline VO_2. The critical level of oxygen delivery was defined as the highest DO_2 interval at which a significant decrease from baseline was seen at the $P < 0.05$ confidence level. The three groups were then compared using a one-tailed paired *t* test. The relationships between serum lactate and DO_2, and PvO_2 and DO_2, were similarly analyzed.

All animals were cared for under guidelines established by the University of Michigan Unit for Laboratory Animal Medicine.

RESULTS

Comparison of Anemic, Hypoxic, and Low Cardiac Output Groups

The initial hemodynamic and oxygenation measurements prior to manipulation for each group are given in Table 1. No significant differences among the groups were present at baseline. In the anemic group, the lowest level of hemoglobin obtained was 2.6 ± 0.5 g/dl. The lowest p_aO_2 achieved in the hypoxic group was 22 ± 4 mm Hg. Cardiac output was reduced to 34 ± 11 cc/kg/min in the low cardiac output group. To determine if the three groups were indeed separate, the influence of hemoglobin, arterial saturation, and cardiac output on the changes in oxygen delivery in each group was analyzed. Coefficients of correlation between the changes in each component of DO_2 and the changes in total DO_2 for each group are given in Table 2. Changes in DO_2 were due almost exclusively to the changes in SaO_2 in the "hypoxic group" ($r = 0.91$) and to CO in the "low cardiac output group" ($r = 0.98$). Changes in DO_2 correlated most highly with the changes in hemoglobin in the "anemic group" ($r = 0.78$).

DO_2 and VO_2 Relationships

The biphasic relationship between VO_2 and DO_2 is illustrated for the anemic, hypoxic, and low cardiac output group (Fig. 2). VO_2 values for every DO_2 interval were calculated using the method of interpolation. The statistical analysis used to determine the DO_{2crit} for each group is presented in Table 3. DO_{2crit} occurred in the 9–10 ml/kg/min interval for the anemic group, since above this interval VO_2 does not differ significantly from the baseline; at and below 9–10 ml/kg/min, VO_2 values are significantly below baseline. The DO_{2crit} for the hypoxic group occurred in the 10–11 cc/kg/min interval, although two lower DO_2 values had VO_2 values which did not differ significantly from baseline because of the large standard deviation in these intervals and the degrees of freedom imposed by the sample size. The DO_{2crit} for the low cardiac output group occurred in the 9–10 cc/kg/min interval.

The DO_2/VO_2 relationships of the three groups are compared in Table 4. The differences between interval VO_2 and baseline VO_2 were compared in each DO_2 interval. The analysis shows that the relationship between DO_2 and VO_2 is not statistically different between groups at the interval of the DO_{2crit} and all other DO_2 intervals, except the anemic and low cardiac output groups in the DO_2 12–13 cc/kg/min interval.

DO_2 and Serum Lactate Relationships

Serum lactate concentrations for the three groups are shown in Fig. 3. The biphasic relationships similar to that of VO_2 is readily apparent. The method of interpolation was applied to lactate levels at 1 cc/kg/min DO_2 intervals to determine the DO_2 level at which lactate

TABLE 2

Correlation Coefficients between Percentage Change in DO_2 in Sequential Measurements and Percentage Change in Component of DO_2 for Each Group of Experimental Animals

	DO_2:HB	DO_2:SaO_2	DO_2:C.O.
Anemic group	0.78	0.40	0.52
Hypoxic group	−0.34	0.91	0.11
Low C.O. group	−0.16	0.16	0.98

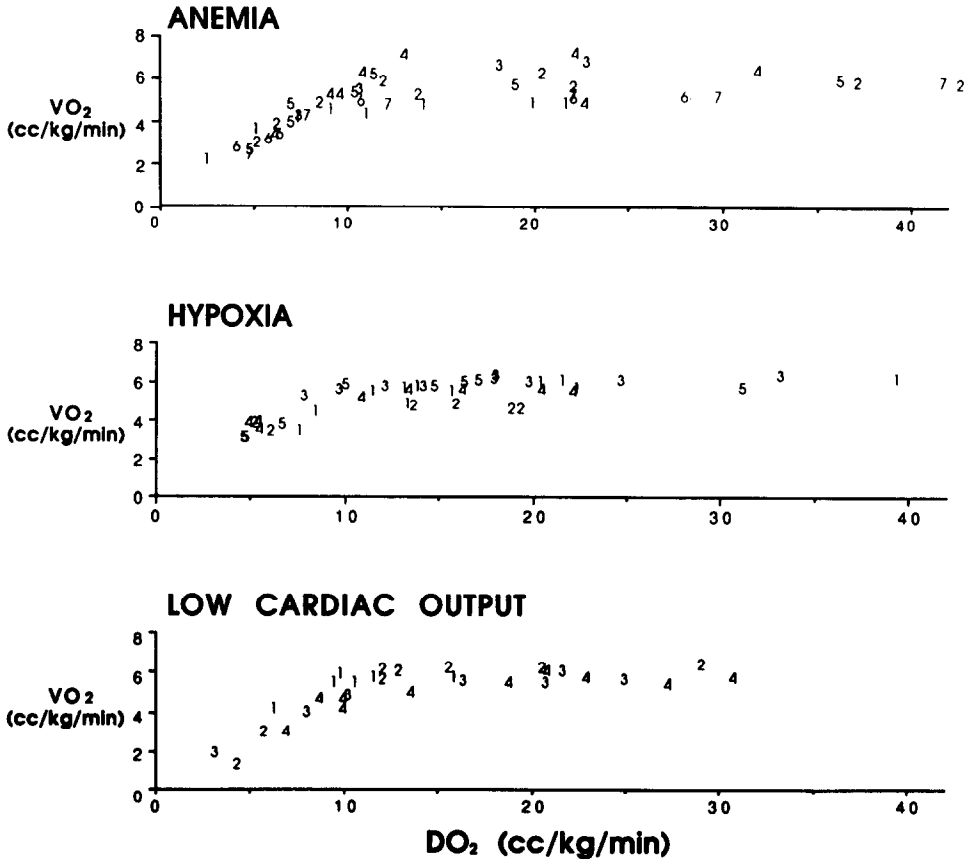

FIG. 2. VO_2 vs DO_2 in anemic hypoxic and low C.O. groups; numbers correspond to individual animals.

increased above baseline. Again the DO_2 levels at which lactate rises significantly above baseline are 9–10, 10–11, and 9–10 cc/kg/min for anemic, hypoxic, and low cardiac output groups, respectively. The levels do not differ significantly when the groups are compared.

DO_2 PvO_2 Relationships

The partial pressure of oxygen in pulmonary arterial blood for the three groups is shown in Fig. 4. Statistical analysis employed after interpolation demonstrated no difference between the anemic and low cardiac output group at any interval. The hypoxic group had a significantly lower PvO_2 at every DO_2 interval, including the DO_{2crit}.

Thermodilution Cardiac Output vs Fick Calculation of Cardiac Output from VO_2

The thermodilution cardiac output determination for each data collection was compared to the cardiac output calculated from the oxygen consumption and arterial and venous oxygen contents (Fick method). Analysis of variance revealed a correlation coefficient of .93. The thermodilution cardiac output averaged 19% higher than the Fick calculation.

DISCUSSION

The relationship between oxygen delivery and oxygen consumption in mammalian models is bimodal. Oxygen consumption is independent of delivery above a critical level of delivery, while below the critical level of oxygen delivery, oxygen consumption becomes dependent upon delivery. Adams *et al.* observed a critical value of oxygen delivery in the rat of 23 cc/kg/min, with a baseline VO_2 of 17.9 cc/kg/min [2]. Below this value oxygen consumption was apparently linearly dependent upon oxygen delivery. Their methods involve the measurement of oxygen consumption and the calculation of oxygen delivery using the Fick relationship. The critical value was well below the normal range of oxygen delivery in the rat.

Critical levels of oxygen delivery have been determined in other animal models. Oxygen consumption fell and acidosis developed in fetal lambs below fetal oxygen delivery rates of 13.4 cc/kg/min in one study and 12–15 cc/kg/min in another with baseline VO_2 calculated by the Fick method at 7–8 cc/kg/min [4, 5].

Using independently measured oxygen delivery (thermodilution cardiac output, arterial oxygen content calculated from pO_2, and hemoglobin) and VO_2 (mixed expired gas analysis), Pepe and Culver found DO_{2crit} of 13.0

TABLE 3

Determination of DO_{2crit}: Comparison of VO_2 at Successive DO_2 Intervals with Baseline VO_2 for Anemic, Hypoxic, and Low C.O. Animals

DO_2 interval	Mean difference between interval and baseline VO_2	Significance
Anemia		
3–4	−2.2 ± 1.00	$P < 0.05$
4–5	−2.1 ± 1.07	$P < 0.05$
5–6	−1.9 ± 0.91	$P < 0.05$
6–7	−0.9 ± 0.49	$P < 0.05$
7–8	−0.8 ± 0.56	$P < 0.05$
8–9	−0.6 ± 0.56	$P < 0.05$
9–10	−0.4 ± 0.26	$P < 0.05$
10–11	−0.06 ± 0.34	NS
11–12	−0.04 ± 0.34	NS
12–13	0.06 ± 0.18	NS
13–14	−0.04 ± 0.40	NS
Hypoxia		
4–5	−1.8 ± 1.01	$P < 0.05$
5–6	−2.0 ± 0.44	$P < 0.05$
6–7	−0.9 ± 0.94	NS
7–8	−0.7 ± 0.73	NS
8–9	−0.3 ± 0.26	$P < 0.05$
9–10	−0.3 ± 0.26	$P < 0.05$
10–11	−0.2 ± 0.19	$P < 0.05$
11–12	−0.1 ± 0.17	NS
12–13	−0.1 ± 0.17	NS
13–14	−0.1 ± 0.17	NS
Low C.O.		
5–6	−2.2 ± 0.95	$P < 0.05$
6–7	−1.3 ± 1.04	$P < 0.05$
7–8	−0.9 ± 0.62	$P < 0.05$
8–9	−0.6 ± 0.30	$P < 0.05$
9–10	−0.6 ± 0.46	$P < 0.05$
10–11	−0.3 ± 0.30	NS
11–12	−0.3 ± 0.32	NS
12–13	−0.2 ± 0.29	NS
13–14	0.00 ± 0	NS

cc/kg/min and VO_2 of 5.5–8.0 cc/kg/min in dogs [6]. When DO_2 was decreased by PEEP, by venous inflow occlusion (both resulting in decreased cardiac output) or by oleic acid lung injury (resulting in hypoxia) the DO_{2crit} values were not significantly different. In our previous study using another technique of independent measurements of DO_2 and VO_2, we found the DO_{2crit} in anesthetized dogs with a baseline VO_2 of 5.8 cc/kg/min to be 8.0 [7].

In studying low oxygen delivery states produced by anemia and hypoxia, Cain used mixed expired gas analysis to measure VO_2 and calculated cardiac output from the VO_2 and arterial-venous oxygen content difference [1]. He found the critical level of oxygen delivery to be 9.8 cc/kg/min in paralyzed, anesthetized dogs with a VO_2 of 6.2–6.4 cc/kg/min. DO_{2crit} was determined by linear regression of VO_2 values which were pooled from several experiments. There was no difference in the DO_{2crit} found in the anemic or hypoxic group. The conclusion drawn was that the ability of tissues to extract oxygen is dependent upon the absolute quantity of oxygen delivered to the tissues and not on the pO_2 within the tissue itself. At DO_{2crit} anemic animals had significantly higher mixed venous oxygen tension than the hypoxic animals (45 vs 17 ml mm Hg, respectively).

Simmons *et al.* studied the blood lactate levels in dogs subjected to hypoxia and low cardiac output states [9]. They failed to lower the oxygen delivery to the DO_{2crit} level in their "reduced cardiac output" group. It is not surprising that increased lactate was not found in this group. In their hypoxic group in which the oxygen delivery did fall to the levels of DO_{2crit}, elevated lactate was found ($DO_2 < 10$ cc/kg/min).

Lister has studied oxygen delivery and consumption in conscious lambs at varying postnatal ages. In a study in which oxygen delivery was lowered by decreasing cardiac output, critical levels of oxygen delivery of 11.0 cc/kg/min were found in lambs four weeks of age [10]. Using a similar preparation oxygen delivery was decreased by hypoxia in a group of chronically instrumented lambs

TABLE 4

Comparison of DO_2:VO_2 Relationship among Anemic, Hypoxic, and Low C.O. Groups

DO_2 Interval	Anemia	Hypoxia	Significance
4–5	−2.1 ± 1.14	−1.8 ± 1.01	NS
5–6	−1.9 ± 0.83	−2.0 ± 0.19	NS
6–7	−1.0 ± 0.24	−0.9 ± 0.89	NS
7–8	−0.9 ± 0.31	−0.7 ± 0.53	NS
8–9	−0.7 ± 0.31	−0.3 ± 0.67	NS
9–10	−0.4 ± 0.66	−0.3 ± 0.67	NS
10–11	−0.6 ± 0.12	−0.2 ± 0.04	NS
11–12	−0.4 ± 0.12	−0.1 ± 0.28	NS
12–13	−0.6 ± 0.33	−0.1 ± 0.30	NS
13–14	−0.4 ± 0.16	−0.1 ± 0.30	NS
	Hypoxia	Low C.O.	Significance
4–5	−1.8 ± 1.01	−2.5 ± 1.28	NS
5–6	−2.0 ± 0.19	−2.2 ± 0.91	NS
6–7	−0.9 ± 0.89	−1.3 ± 1.1	NS
7–8	−0.7 ± 0.53	−0.9 ± 0.39	NS
8–9	−0.3 ± 0.67	−0.9 ± 0.89	NS
9–10	−0.3 ± 0.67	−0.6 ± 0.21	NS
10–11	−0.2 ± 0.04	−0.3 ± 0.87	NS
11–12	−0.1 ± 0.03	−0.3 ± 0.10	NS
12–13	−0.1 ± 0.03	−0.2 ± 0.83	NS
	Anemia	Low C.O.	Significance
4–5	−2.1 ± 1.14	−2.5 ± 1.28	NS
5–6	−1.9 ± 0.83	−2.2 ± 0.9	NS
6–7	−1.0 ± 0.24	−1.3 ± 1.08	NS
7–8	−0.9 ± 0.31	−0.9 ± 0.39	NS
8–9	−0.7 ± 0.31	−0.6 ± 0.89	NS
9–10	−0.4 ± 0.66	−0.6 ± 0.21	NS
10–11	−0.6 ± 0.12	−0.3 ± 0.87	NS
11–12	−0.4 ± 0.12	−0.3 ± 0.10	NS
12–13	0.6 ± 0.03	−0.2 ± 0.82	$P < 0.05$

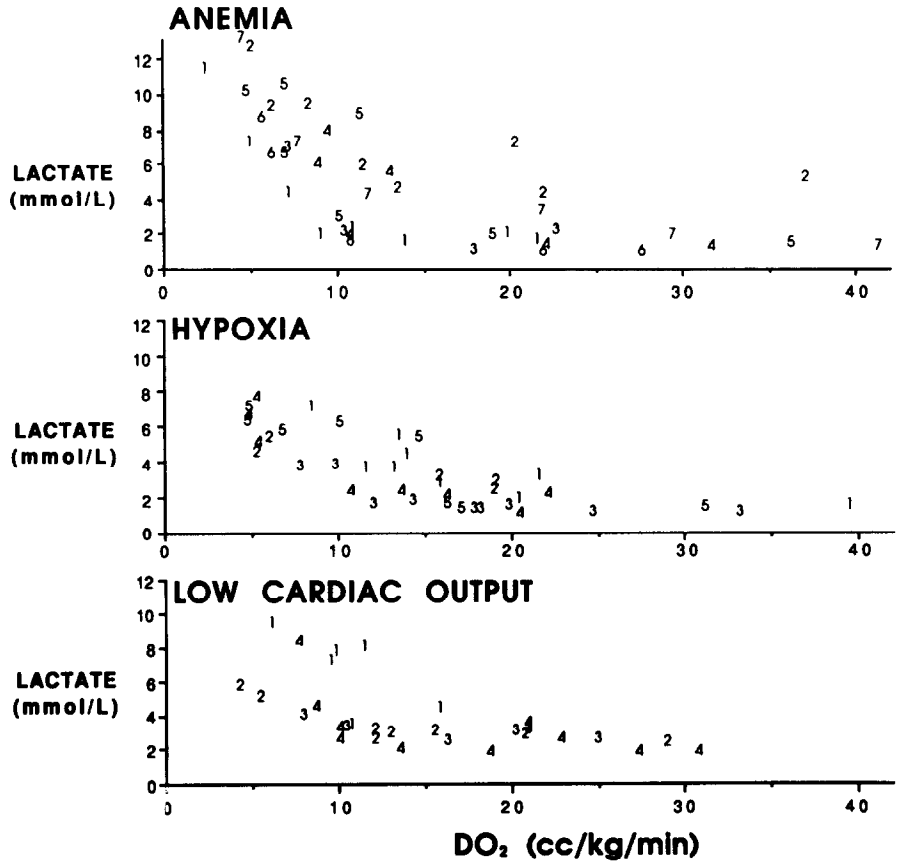

FIG. 3. Lactate vs DO_2 in anemic hypoxic and low C.O. groups; numbers correspond to individual animals.

[11]. The critical level of oxygen delivery at age 25–40 days was found to be 10.2 cc/kg/min. This further supports the finding that the limitation in tissue utilization of oxygen is dependent upon the total delivery of oxygen to the tissue and not upon the method in which delivery is limited.

The current study failed to demonstrate differences in the DO_{2crit} when the components of oxygen delivery were independently varied. The implication of these findings is that the absolute level of whole body oxygen delivery is of greater importance than the particular value of hemoglobin, arterial pO_2, or cardiac output in preventing delivery dependence and lactic acidosis ("shock"). The experimental animals developed lactic acidosis and hypotension below the DO_{2crit} regardless of how the low delivery state was achieved. There was no absolute hemoglobin value, pO_2 value, or level of cardiac output that was of itself detrimental. There are obvious practical limits to these findings determined by rheology, the oxygen-carrying capacity of blood, and the limits of cardiac performance. (1) Hemoglobin cannot be increased indefinitely to compensate for hypoxia and low cardiac output. (2) If hemoglobin is saturated with oxygen, dissolved oxygen can only increase the arterial oxygen content slightly in anemia and low flow states. (3) Cardiac output can only compensate to a point for hypoxia and anemia.

Further evidence that the DO_{2crit} has the same physiologic implication in anemic, hypoxic, and low cardiac output states comes from analysis of serum lactate concentrations. In these previously healthy animals, increased lactate production occurred concurrently with supply-dependent oxygen delivery. Lactate production increased at delivery levels lower than the DO_{2crit} and did not differ significantly among the groups. This "anaerobic threshold" or "shock state" is defined by the DO_2 and not by an absolute level of hemoglobin, pO_2, or cardiac output. The implication in clinical physiology is that DO_{2crit} is a physiologic definition of nonseptic shock.

In the current study whole body oxygen consumption, oxygen delivery, and lactate were measured. Reduction in the components of oxygen delivery may have different effects on different organs. This does not imply that all tissues and organs respond identically to decreased total body oxygen delivery. The effect of manipulating the components of oxygen delivery on individual organ blood flow and function requires further investigation.

Methods

Closed circuit spirometry was used to directly measure whole body VO_2, and thermal dilution cardiac output was used to calculate DO_2. The technique of closed cir-

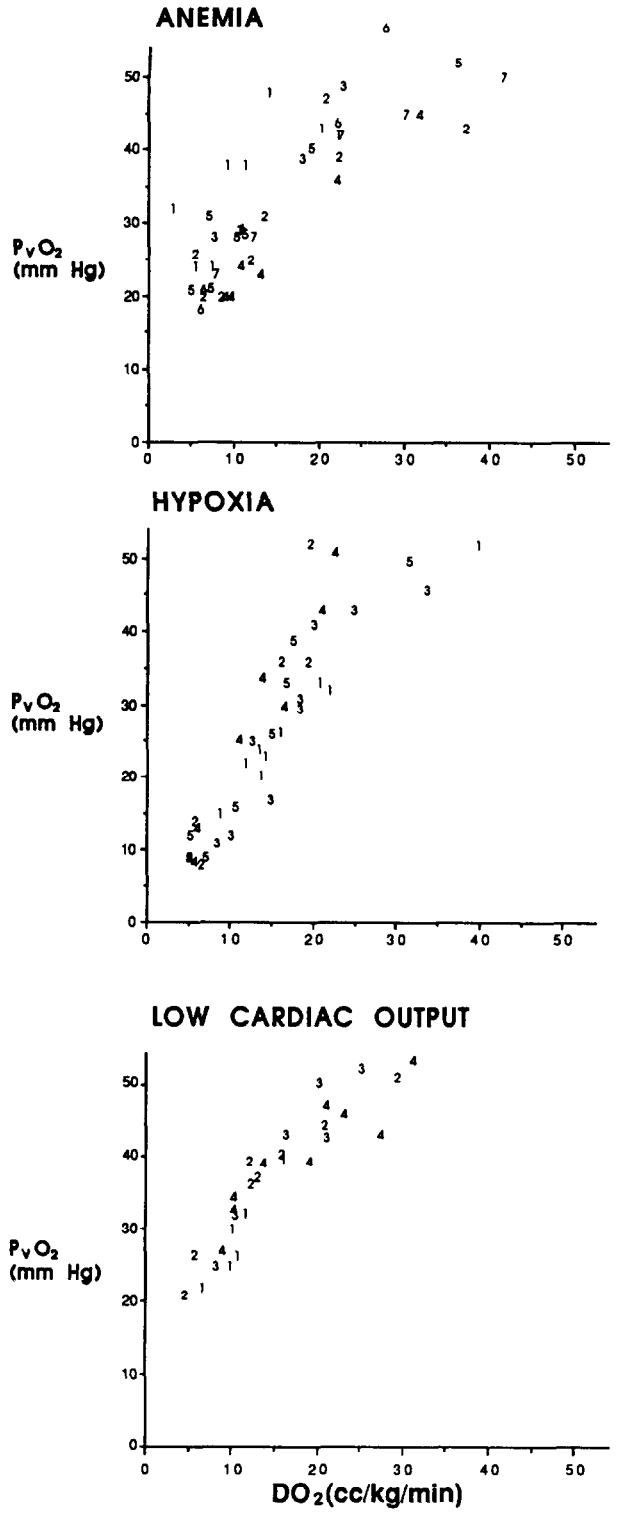

FIG. 4. PvO_2 vs DO_2 in anemic hypoxia and low C.O. group; numbers correspond to individual animals.

cuit spirometry is very accurate; however, it does depend upon a steady state VO_2 over the measurement interval. At the lowest levels of oxygen delivery animal deterioration limited the time over which replicate VO_2 measurements could be made, increasing the likelihood of error. The thermal dilution cardiac output determination is subject to numerous errors [12]. Standardization of technique will result in reproducible results. The possibility of systematic error with thermal dilution cardiac outputs is real. The thermal dilution cardiac output (TDCO) was consistently 19% higher than the Fick calculated cardiac output without obvious explanation. The r value of 0.93 shows close correlation between the two, however. We have used TDCO to calculate DO_2 for methodologic reasons as noted above. It is clear that our results would be similar if we had calculated DO_2 from the Fick VO_2 accepting the mathematical coupling involved. The only difference would be a lowering of the DO_2 values.

Ideally studies of VO_2 and DO_2 should avoid all pharmacologic agents that affect these variables. Anesthetic agents have been used in most previous studies reported. The light pentobarbital anesthesia used in this experiment may affect both cardiac output as well as whole body oxygen consumption. Pharmacologic paralysis was avoided as much as possible; however, strong reflexes stimulating marked muscular activity at the lowest levels of DO_2 induced by hypoxia necessitated paralysis under these circumstances.

Were the Groups Really Separate?

Normal compensatory mechanisms respond to falling levels of oxygen delivery. The most common is an increase in cardiac output seen initially in response to anemia and hypoxia. The response may not be seen if anemia is accompanied by hypovolemia or if insufficient cardiac reserve is present. At the extremes of hypoxia, cardiac output will also fall. Splenectomy was used to prevent reflex splenic autotransfusion that occurs in canines. Cardiac tamponade was a simple method of restricting cardiac output when necessary. The analysis presented in Table 2 indicated that the desired result was largely achieved but it is clear that low cardiac output was partially responsible for the decrease in DO_2 in the "anemic" group.

Statistical Analysis

Previous studies have determined DO_{2crit} by adaptations of curve-fitting techniques. These adaptations have been as simple as the best visual guess [4]. Others have used the intersection of regression lines below the DO_{2crit} with regression lines above the DO_{2crit} [1, 3, 6, 10, 11]. Polynomial curve-fitting techniques using computer analysis likewise generate numerical values for "inflection points" [13]. Using the method of interpolation, the VO_2 for any given DO_2 interval is assigned a value for each experimental animal. A mean and standard deviation are then calculated for that interval allowing a valid statistical comparison to other DO_2 intervals. This method seeks an inflection point by asking the

question, "Does the VO_2 value for this interval differ significantly from the VO_2 value assigned as the baseline?" The method assumes that the baseline VO_2 is delivery independent. The DO_{2crit} generated by this method can be compared in a valid statistical fashion with one another. The results are likewise dependent upon the size of the DO_2 interval. In this case the interval of 1 cc/kg/min was chosen because smaller intervals did not change the results. It is of note that when curve-fitting techniques are applied to the pooled data from all experiments the conclusions would be unchanged as can be seen from Figure 2. The method of interpolation allows these conclusions to be reached in a more statistically valid fashion.

CONCLUSIONS

In anesthetized dogs, oxygen delivery (DO_2) and oxygen consumption (VO_2) was measured by independent methods. The resting VO_2 was 5.4–5.9 cc/kg/min. When oxygen delivery was decreased by anemia, hypoxia, or cardiac tamponade, a critical level of oxygen delivery (DO_{2crit}) was found at approximately 10 cc/kg/min in all three groups. Lactic acidosis, and decreased (supply dependent) VO_2 occurred when the DO_2, baseline VO_2 ratio was below 1.8:1, regardless of the mechanism of impaired oxygen delivery.

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