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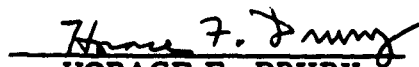
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ABSTRACT

The effect of induced hypoxia on body temperature regulation and cardiopulmonary function is assessed in anesthetized dogs under warm, neutral and cold environments. Hypoxia acts differently to heat conservation (shivering) and heat dissipation (thermal panting) mechanisms: the former is suppressed, while the latter is facilitated. It is also found that the suppression of shivering is partly due to the hypocapnia which is produced under hypoxia. The lethal threshold of acutely induced hypoxia is at the inspiratory O₂ level of approximately 3 per cent in the neutral and cold environments, whereas it is at 5 per cent in the warm environment. Under hypoxia, the total ventilation is increased two- to threefold. The alveolar ventilation, however, is augmented to a lesser degree with a progressive increase in physiological dead space. Contrary to respiration, the cardiac output is only slightly increased (less than 30 per cent over the control value) under hypoxia.

PUBLICATION REVIEW


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THE EFFECT OF INDUCED HYPOXIA ON THERMOREGULATION AND CARDIOPULMONARY FUNCTION

SECTION 1. INTRODUCTION

One of the prerequisites for the effective thermal equilibrium of the mammalian body is the adequate supply of oxygen for its biochemical process of oxidation. By artificially depriving oxygen supply from the body it is anticipated that some of the essential thermoregulatory mechanisms are disturbed and that the cardiopulmonary functions which bear direct relation to the gas transport are altered.

The purpose of the present investigation is to delineate the nature and the extent of such disturbances and alterations brought about by induced hypoxia under various thermal environments in the anesthetized animal.

Particular attention is given to the disturbance of body temperature regulatory mechanisms, such as central and peripheral temperatures, shivering and thermal panting. A critical assessment of the cardiorespiratory functions is made with special reference to the oxygen consumption, arterio-venous oxygen difference and cardiac output.

SECTION 2. SUMMARY

The effect of induced hypoxia on body temperature regulation and cardiopulmonary function is assessed in 55 anesthetized dogs under warm (45° C), neutral (25° C) and cold (5° C) environments. Hypoxia is produced by the rebreathing technique at the inspiratory O₂ levels of 9%, 7% and 5%, the corresponding arterial O₂ saturation being 45%, 37% and 25% respectively.

In the neutral series the core temperature falls from 38° to 35° C, and the peripheral temperature from 36° to 33° C under hypoxia. In the cold series the temperature changes are more prominent, the core temperature falling from 38° to 30° C and the peripheral temperature from 34° to 23° C. In the warm series both central and peripheral temperatures are elevated from 38° to 43° C.

The reduction of body temperature under hypoxia is mainly due to the suppression of shivering as reflected in the O_2 consumption and the electro-myogram. An attempt is made to elucidate further the mechanism of this suppression. It is concluded that it is partly due to the hypocapnia because the prevention of hypocapnia repeatedly restores the intensity of shivering to a certain extent. Nevertheless, it appears that there is also another unknown mechanism involved.

Contrary to the suppression of shivering, thermal panting is invariably facilitated by hypoxia. Since the available data suggest that sweating is also facilitated by hypoxia, it is concluded that hypoxia acts differently to heat conservation and heat dissipation mechanisms: the former is depressed while the latter is facilitated.

The relationship between the alveolar CO_2 level and shivering has been investigated. The shivering response to hypocapnia (produced by artificial hyperventilation) or hypercapnia (produced by CO_2 breathing) is not always consistent. Additional investigation in the future along this line is warranted.

The lethal threshold of acutely induced hypoxia in the lightly anesthetized dogs is at the inspiratory O_2 level of approximately 3 per cent in the neutral and the cold environments. However, the animals succumb to hypoxia at the higher inspiratory O_2 level of about 5 per cent in the warm environment indicating a lowered tolerance to hypoxia under heat stress.

The study of metabolic rate under hypoxia requires a careful interpretation. Since the O_2 consumption is not significantly altered under hypoxia despite the concomitant depression of shivering and body temperature, it is concluded that the true O_2 consumption during hypoxia is probably slightly higher than the control level (room-air breathing).

Hypoxia stimulates respiration causing two- to threefold increases in total ventilation. In consequence the alveolar PCO_2 is lowered and the arterial pH is elevated. The alveolar ventilation is also augmented but its rate of increase is of a lesser degree than that of the total ventilation. There is a progressive increase in physiological dead space in proportion to the severity of hypoxia.

During hypoxia the cardiac output is increased only slightly (up to 29 per cent of the control value) but due to the large variation within the same animal as well as among the different animals, the increase is not statistically significant. The heart rate and the systemic arterial blood pressure are elevated in hypoxia. The arteriovenous O_2 difference remains constant at the hypoxia levels of 9% and 7% O_2 . At 5% O_2 , however, it begins to fall. The ratio of the alveolar ventilation and the cardiac output in hypoxia is significantly higher in hypoxia than in room-air breathing.

SECTION 3. METHODS

Experiments were conducted on 55 mongrel dogs with body weights ranging from 12 to 27 kg. The dogs were anesthetized with 10 mg/kg nembutal and 175 mg/kg sodium barbital intravenously. Following anesthesia the animals were depilated and were placed on an animal board in the supine position. The tracheotomy was performed and the right femoral artery and vein were exposed through incision and dissection to allow introduction of an intravenous catheter (Kifa red catheter, o. d. 0.086 inches, i. d. 0.056 inches). Following heparinization the arterial catheter (150 cm in length) was inserted to the region of the descending aorta in the thorax. The venous catheter (145 cm in length) was inserted into the right ventricle as determined by the change of intra-cardiac pressure observed on the oscillograph (Visicorder). All surgical procedures were performed using aseptic technique to avoid possible contamination with pyrogens.

The body temperatures were continuously registered on a Honeywell automatic temperature recorder through copper-constantan thermocouples (30 gauge). The central temperature was measured in the esophagus (approximately 12 inches deep from the incisor) or in the rectum (approximately 2 inches deep). The peripheral temperatures were monitored at the forehead, chest, upper and lower forelegs, upper and lower hind legs and foot. From these peripheral temperatures the mean skin temperature was estimated by means of Burton's (1935) equation. To provide a known thermal stress to the animals a temperature chamber was used. It was made of plywood, measured approximately 3.0 x 3.5 x 8.0 feet and was insulated by Rockwool. The inside temperature of the chamber was maintained automatically at any desired level within $\pm 1^{\circ}\text{C}$ over the range of 0 to 50°C . Three thermal levels were used: neutral, cold and warm environments, where the chamber temperatures were maintained at 25° , 5° and 45°C , respectively, with a relative humidity of approximately 20% to 30%.

Hypoxia was induced by means of a rebreathing system, which is shown schematically in Figure 1. This system consisted of a spirometer (9 liter capacity), a canister for CO_2 absorption, a large carboy for mixing of expired air, a Beckman O_2 analyzer and another spirometer (4 liter capacity) for O_2 supply. As an animal rebreathed in the closed system, the partial pressure of O_2 in the system fell gradually as monitored continuously by the O_2 analyzer. When the PO_2 reached a desired level, the needle valve between the spirometers was opened introducing 100% O_2 into the system. Once an equilibrium between the metabolic rate and O_2 supply was reached, the spirometer tracing remained horizontal. With this system, shown in Figure 1, it was possible to sustain a hypoxic level within $\pm 3\text{ mm Hg}$ of PO_2 . The advantages of using this rebreathing system were that it was readily

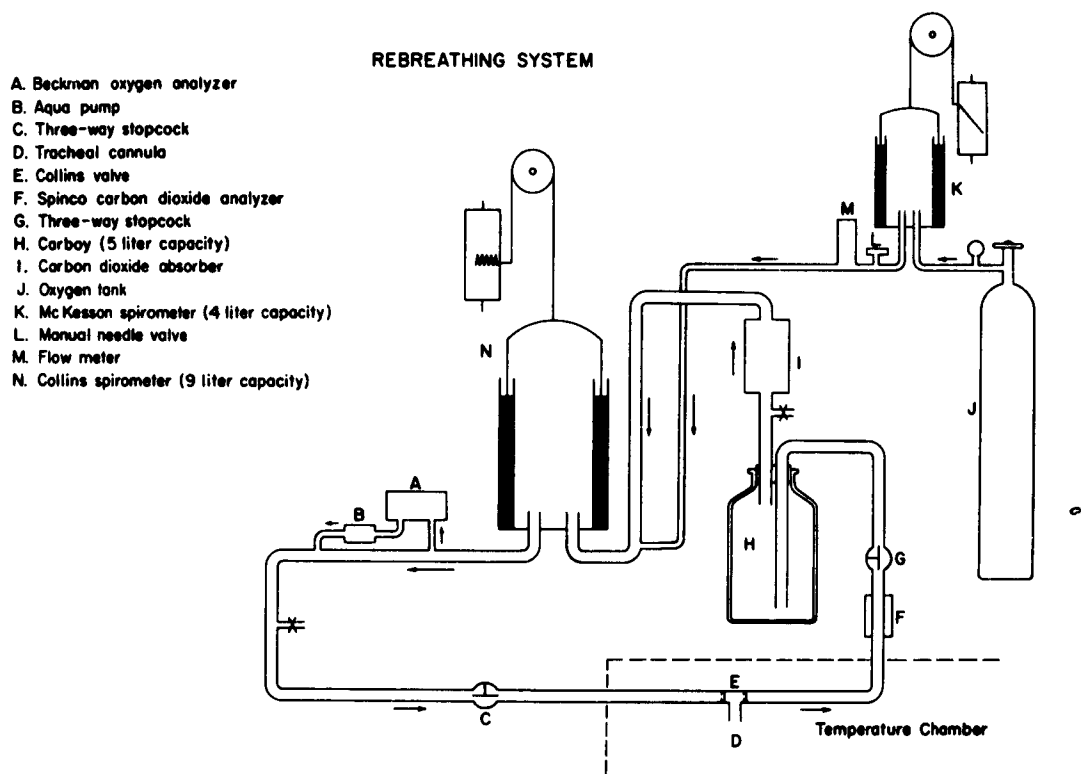


FIGURE 1. Rebreathing system

possible to reach any desired level of hypoxia, and it was much more economical than using commercial gas mixtures. The level of hypoxia (in terms of O_2 fraction in the inspiratory air) in the neutral series were 9%, 7% and 5%; in the cold series, 9% and 7%; and in the warm series, 9% or 7%. In the warm series the body temperature increased at such a rate that the observation was possible only at a single level of hypoxia. The duration of hypoxia in each hypoxia level was 30 minutes. Following this period, the measurements of respiration and the blood samples were taken.

In the time control studies (room air breathing) which were done in each series, the expired air was collected in a Douglas bag for three to five minutes at the end of the 35th, 80th, 125th and 170th minute. The content of the bag was determined by the Scholander gas analyzer, and total ventilation ($\dot{V}_E$), O_2 consumption ($\dot{V}_{O_2}$), CO_2 production ($\dot{V}_{CO_2}$), respiratory gas exchange ratio (RER) and the ventilatory equivalent for O_2 ($\dot{V}_{E_{O_2}}$) were computed. During the collection of expired gas, respiratory rate (f) was also counted. In the closed circuit of rebreathing, total ventilation was obtained from the tracings of the spirometer N, and O_2 consumption from the slopes of spirometer K. The continuous registration of expired CO_2 fraction is made on the oscillograph by means of infrared CO_2 analyzer (F in Figure 1). From the expired CO_2 fraction and the respiratory volume measurement, the CO_2 output was estimated. Occasionally both inspired and expired airs were sampled simultaneously from the side arms for chemical analyses. These analyses served as a valuable check for O_2 and CO_2 levels registered on Beckman O_2 and infrared CO_2 analyzers.

The blood pressures at the descending aorta and the right ventricle were recorded on the oscillograph employing strain gage transducers (Statham). The blood samples were taken simultaneously from the aorta and the right ventricle for the analyses of O_2 content, O_2 capacity, total CO_2 content and pH. The techniques of blood gas analyses have been described previously (Lim et al, 1958). The cardiac output was estimated by means of Fick's principle. Following all the measurements, the O_2 supply was shut off completely by closing the needle valve L. The PO_2 continued to fall to a lower level until the animal expired. The level of PO_2 at this moment was designated as the lethal level of hypoxia.

In the course of investigation it became apparent that shivering was influenced by the level of CO_2 in the inspiratory air. To elucidate further this aspect, additional studies were made: (A) In the rebreathing series, the effect of hypoxia on shivering was observed under the condition where the alveolar CO_2 tension was maintained normal or slightly above normal. This was achieved by partially by-passing the CO_2 absorber in the closed system so as to maintain a reasonably high CO_2 level in the inspiratory gas. (B) In the CO_2 series, the shivering animal was artificially hyperventilated with room air by means of a mechanical respirator. The purpose of this

hyperventilation was to observe the effect of lowered alveolar CO₂ on shivering. Conversely the shivering animal was given CO₂ mixture (5% to 6% CO₂ in air) to determine the effect of increased CO₂ level on shivering. The latter series was carried out employing an open circuit method. Throughout these studies on shivering, the electromyogram (Gilson's polygraph) was taken to quantitate the intensity of shivering. The description of the EMG technique employed has been published (Lim, 1960).

SECTION 4. RESULTS

Thermoregulatory Mechanisms

Alterations of Body Temperature. The thermal behaviors in hypoxia in three different environments (neutral, cold and warm) are tabulated in Table 1. The neutral series consists of 17 dogs, among which six dogs are for the time-control. The cold and warm series have nine animals each, among which four animals are for the time-control.

In the control group of neutral series, the central and peripheral temperatures are well maintained within normal ranges of 37.7° to 38.3° C, and 34.2° to 35.5° C, respectively. This is achieved primarily by means of the involuntary muscular contractions of shivering as observed in most of the animals in this series. However, as soon as hypoxia is imposed, the central temperature begins to fall gradually, as shown schematically in Figure 2. (The dots and crosses in the figure are the actual measurements and the lines represent the arithmetic means. These denotations also apply to the other figures in this report.) Thus, in the hypoxia group the core temperature falls from the initial level of 37.6° C to the final level of 34.9° C at the end of the experiment. The peripheral temperature seems to fall also with hypoxia but the difference between the control group at the end of the experiment is only slight (33.3° vs 34.4° C) and statistically insignificant ($t=1.25$, d. f. =15, $0.2 < p < 0.3$).

These trends of temperature change observed in the neutral series are more distinctly demonstrated in the cold environment. In the control group of the cold series the average central temperature falls from 37.8° to 35.5° C during the first 30 minutes and then is maintained at about 35° C throughout the rest of the experimental period by means of vigorous shivering. The peripheral temperature in this group also follows a similar pattern, falling from 34.8° to 29.4° C during the first 30 minutes and then being kept at this level throughout the rest of the time. Contrary to these, the thermal behaviors of the hypoxia group are characterized by the continuous decline of both central and peripheral temperatures as shown in Figure 3. In this group

Table 1. Alterations of body temperature during induced hypoxia

Neutral Series (n=17)

A: Hypoxia

Animal No.	air		9%		7%		5%	
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.
3	TC	36.9	36.7 (-0.2)	36.5	35.8 (-0.7)	-	-	35.4 (-0.9)
	TS	35.7	35.5 (-0.2)	35.2	34.7 (-0.5)	-	-	34.2 (-0.3)
5	TC	38.2	38.0 (-0.2)	37.5	36.9 (-0.6)	36.7	36.2 (-0.5)	35.9 (-0.6)
	TS	36.3	36.2 (-0.1)	35.8	34.9 (-0.9)	34.7	34.2 (-0.5)	33.8 (-0.6)
6	TC	36.7	36.4 (-0.3)	36.2	35.7 (-0.5)	35.6	35.0 (-0.6)	34.8 (-0.6)
	TS	35.5	34.9 (-0.6)	34.5	34.0 (-0.5)	33.6	33.1 (-0.5)	33.1 (-0.3)
7	TC	37.7	37.6 (-0.1)	37.1	36.5 (-0.6)	36.2	35.6 (-0.6)	35.2 (-0.4)
	TS	35.6	35.1 (-0.5)	34.6	34.2 (-0.4)	33.8	33.4 (-0.4)	33.2 (-0.2)
8	TC	38.0	37.7 (-0.3)	37.5	37.2 (-0.3)	37.0	36.6 (-0.4)	36.4 (-0.4)
	TS	37.0	36.9 (-0.1)	36.8	36.6 (-0.2)	36.5	36.1 (-0.4)	36.0 (-0.5)

Table 1 cont'd.

Neutral Series (n=17)

A: Hypoxia (cont.)

Animal No.	air		9%		7%		5%	
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.
10 TC	37.2	36.5 (-0.7)	36.2	35.5 (-0.7)	35.3	34.8 (-0.5)	34.7	34.0 (-0.7)
TS	35.9	35.0 (-0.9)	34.9	34.4 (-0.5)	34.3	33.5 (-0.8)	33.3	32.7 (-0.6)
12 TC	37.5	37.1 (-0.4)	36.6	36.1 (-0.5)	36.0	35.5 (-0.5)	35.4	34.6 (-0.8)
TS	35.5	34.4 (-1.1)	34.0	33.4 (-0.6)	33.1	32.8 (-0.3)	32.4	32.1 (-0.3)
13 TC	38.1	37.5 (-0.6)	37.2	36.5 (-0.7)	36.2	35.6 (-0.6)	35.3	34.9 (-0.4)
TS	36.9	35.7 (-1.2)	35.4	35.0 (-0.4)	34.9	34.5 (-0.4)	33.2	32.7 (-0.5)
14 TC	38.4	38.0 (-0.4)	37.8	37.4 (-0.4)	37.2	36.8 (-0.4)	36.6	36.0 (-0.6)
TS	37.5	36.9 (-0.6)	36.7	36.4 (-0.3)	36.3	35.8 (-0.5)	35.6	34.9 (-0.7)
15 TC	37.9	37.3 (-0.6)	37.0	36.5 (-0.5)	36.4	36.1 (-0.3)	35.9	35.2 (-0.7)
TS	35.1	34.3 (-0.8)	34.1	33.8 (-0.3)	33.7	33.2 (-0.5)	33.0	32.7 (-0.3)
16 TC	37.0	36.4 (-0.6)	36.1	35.6 (-0.5)	35.2	34.8 (-0.4)	34.7	34.1 (-0.6)
TS	35.3	34.7 (-0.6)	34.5	33.6 (-0.9)	33.6	33.2 (-0.4)	32.9	32.4 (-0.5)
$\bar{X}$ TC	37.6	37.2	36.9	36.3	36.2	35.7	35.5	34.9
TS	36.0	35.4	35.1	34.6	34.5	34.0	33.7	33.3

Table 1 cont'd

B: Time-control

Animal No.	air		air		air	
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.
25	TC 36.8 35.9	36.6 (-0.2) 35.1 (-0.8)	36.3 34.9	36.4 (+0.1) 34.9 (0.0)	36.7 35.2	37.2 (+0.5) 35.7 (+0.5)
26	TC 37.8 36.4	38.6 (+0.8) 35.9 (-0.5)	38.6 35.9	38.4 (-0.2) 34.8 (-1.1)	38.4 34.8	38.7 (+0.3) 34.3 (-0.5)
27	TC 38.7 34.6	38.5 (-0.2) 34.2 (-0.4)	38.5 34.2	38.2 (-0.3) 33.7 (-0.5)	38.2 33.7	38.2 (0.0) 33.4 (-0.3)
28	TC 37.6 36.7	37.2 (-0.4) 36.2 (-0.5)	37.2 36.2	36.4 (-0.8) 35.2 (-1.0)	36.4 35.2	36.7 (+0.3) 34.9 (-0.3)
29	TC 37.4 33.1	36.8 (-0.6) 33.5 (+0.4)	36.8 33.5	37.1 (+0.3) 32.3 (-1.2)	37.1 32.3	37.3 (+0.2) 29.8 (-2.5)
30	TC 38.2 36.2	38.7 (+0.5) 36.5 (+0.3)	38.7 36.5	39.4 (+0.7) 36.9 (+0.4)	39.4 36.9	40.1 (+0.7) 37.0 (+0.1)
$\bar{x}$	TC 37.8 35.5	37.7 35.2	37.7 35.2	37.7 34.6	37.7 34.7	38.0 34.2
					38.1 34.2	38.3 34.4

Table 1 cont'd

Cold Series (n=9)

A: Hypoxia

Animal No.	air		9%		7%		air	
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.
18 TC	37.0	35.0 (-2.0)	34.8	33.1 (-1.7)	32.7	30.8 (-1.9)	30.2	30.4 (+0.2)
TS	33.5	28.4 (-5.1)	28.0	26.4 (-1.6)	25.9	23.3 (-2.6)	22.8	22.9 (+0.1)
20 TC	38.0	36.6 (-1.4)	36.6	34.9 (-1.7)	34.3	32.2 (-2.1)	31.7	30.9 (-0.8)
TS	33.9	29.5 (-4.4)	29.7	27.3 (-2.4)	26.7	24.2 (-2.5)	23.7	24.4 (+0.7)
21 TC	36.8	35.0 (-1.8)	35.0	33.6 (-1.4)	32.8	31.0 (-1.8)	30.7	30.9 (+0.2)
TS	33.5	29.5 (-4.0)	29.1	27.0 (-2.1)	26.1	24.5 (-1.6)	24.1	24.0 (-0.1)
23 TC	37.0	35.3 (-1.7)	33.9	32.3 (-1.6)	32.8	29.8 (-3.0)	29.3	28.4 (-0.9)
TS	34.9	31.6 (-3.3)	30.7	28.1 (-2.6)	27.0	24.0 (-3.0)	23.4	22.9 (-0.5)
24 TC	37.0	35.4 (-1.6)	34.2	32.3 (-1.9)	31.1	28.9 (-2.2)	28.4	27.6 (-0.8)
TS	31.6	29.1 (-2.5)	26.5	24.5 (-2.0)	23.4	21.5 (-1.9)	21.0	20.4 (-0.6)
$\bar{X}$ TC	37.2	35.5	34.9	33.2	32.8	30.5	30.1	29.6
TS	33.5	29.6	28.8	26.7	25.8	23.5	23.0	22.9

Table 1 cont'd

B: Time-control

Animal No.	air		air		air		air	
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.
31 TC TS	36.9 34.7	34.8 (-2.1) 29.4 (-5.3)	34.8 29.4	35.4 (-0.6) 29.3 (-0.1)	35.4 29.3	36.8 (+1.4) 30.9 (+1.6)	36.8 30.9	37.6 (+0.8) 31.9 (+1.0)
33 TC TS	36.6 34.0	34.8 (-1.8) 28.8 (-5.2)	34.8 28.8	34.8 (0.0) 28.0 (-0.8)	34.8 28.0	36.0 (+1.2) 29.1 (+1.1)	36.0 29.1	36.8 (+0.8) 28.6 (-0.5)
34 TC TS	38.1 34.9	35.9 (-2.2) 30.4 (-4.5)	35.9 30.4	36.5 (+0.6) 30.8 (+0.4)	36.5 30.8	36.9 (+0.4) 31.3 (+0.5)	36.9 31.3	37.2 (+0.3) 31.7 (+0.4)
35 TC TS	39.6 35.5	36.3 (-3.3) 28.8 (-6.7)	36.3 28.8	34.6 (-1.7) 27.2 (-1.6)	34.6 27.2	34.2 (-0.4) 27.4 (+0.2)	34.2 27.4	33.4 (-0.8) 26.7 (-0.7)
$\bar{x}$ TC TS	37.8 34.8	35.5 29.4	35.5 29.4	35.3 28.8	35.3 28.8	36.0 29.7	36.0 29.7	36.3 29.7

Table 1 cont'd

Heat Series (n=9)									
Δ: Hypoxia									
Animal No.	air		9%		7%		air		
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	
40									
TC	38.8	40.6 (+1.8)	40.6	42.5 (+1.9)	-	-	-	-	
TS	38.9	40.9 (+2.0)	40.9	42.5 (+1.6)	-	-	-	-	
41									
TC	35.8	38.7 (+2.9)	38.7	41.5 (+2.8)	41.5	43.5 (+2.0)	43.5	44.3 (+0.8)	
TS	36.2	39.0 (+2.8)	39.0	41.5 (+2.5)	41.5	43.3 (+1.8)	43.3	44.2 (+0.9)	
42									
TC	36.8	39.2 (+2.4)	-	-	40.2	41.8 (+1.6)	42.2	43.3 (+1.1)	
TS	37.4	39.3 (+1.9)	-	-	40.4	42.0 (+1.6)	42.4	43.5 (+1.1)	
43									
TC	36.7	38.9 (+2.2)	-	-	39.8	41.6 (+1.8)	42.0	43.2 (+1.2)	
TS	37.5	39.3 (+1.8)	-	-	40.3	41.6 (+1.3)	42.0	43.2 (+1.2)	
44									
TC	37.2	38.7 (+1.5)	-	-	39.6	41.2 (+1.6)	41.6	43.2 (+1.6)	
TS	37.1	38.6 (+1.5)	-	-	39.7	41.0 (+1.3)	41.5	43.0 (+1.5)	

Table 1 cont'd

B. Time-control									
Animal No.	air		air		air		air		air
	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	0 min.	30 min.	
36 TC TS	37.8	40.0 (+2.2)	40.0	42.2 (+2.2)	42.2	43.4 (+1.2)	42.2	43.9 (+0.5)	43.4
	37.5	40.6 (+3.1)	40.6	42.2 (+1.6)	42.2	43.2 (+1.0)	42.2	43.6 (+0.4)	43.2
37 TC TS	37.8	39.5 (+1.7)	39.5	41.5 (+2.0)	41.5	42.4 (+0.9)	41.5	43.2 (+0.8)	42.4
	37.8	39.7 (+1.9)	39.7	41.6 (+1.9)	41.6	42.7 (+1.1)	41.6	43.3 (+0.6)	42.7
38 TC TS	36.9	39.1 (+2.2)	39.1	41.2 (+2.1)	41.2	42.2 (+1.0)	41.2	42.9 (+0.7)	42.2
	38.5	39.5 (+1.0)	39.5	41.7 (+2.2)	41.7	42.6 (+0.9)	41.7	43.5 (+0.9)	42.6
39 TC TS	38.7	39.9 (+1.2)	39.9	41.8 (+1.9)	41.8	43.1 (+1.3)	41.8	43.7 (+0.6)	43.1
	37.8	40.1 (+2.3)	40.1	42.1 (+2.0)	42.1	43.2 (+1.1)	42.1	43.7 (+0.5)	43.2
$\bar{x}$ TC TS	37.8	39.6	39.6	41.7	41.7	42.8	41.7	43.4	42.8
	37.9	40.0	40.0	41.9	41.9	42.9	41.9	43.5	42.9

NEUTRAL SERIES (n = 17)

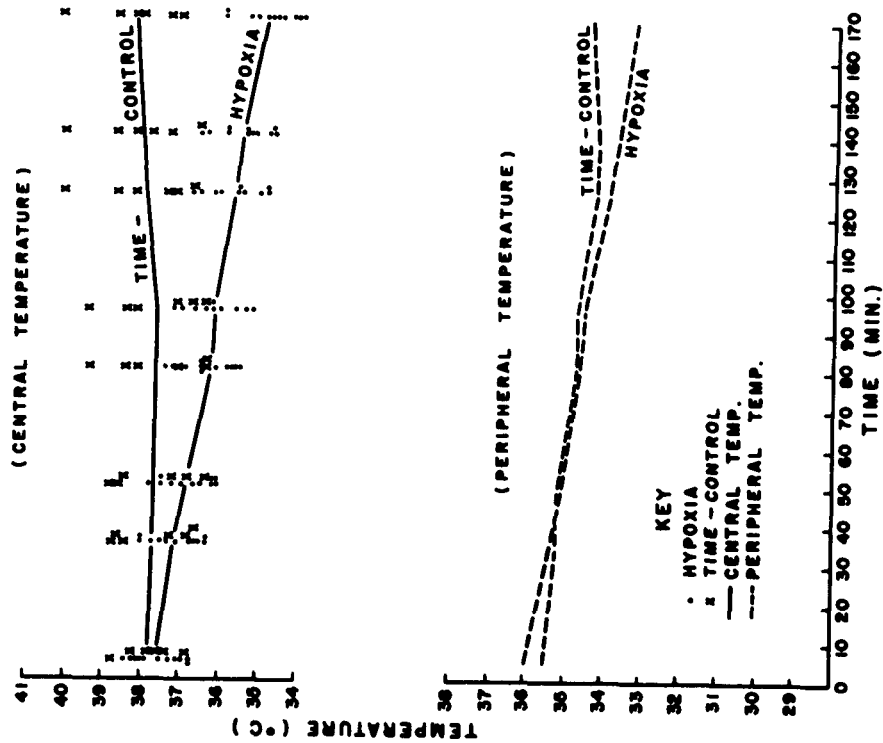


FIGURE 2. Effect of hypoxia on body temperature in neutral environment

COLD SERIES (n = 9)

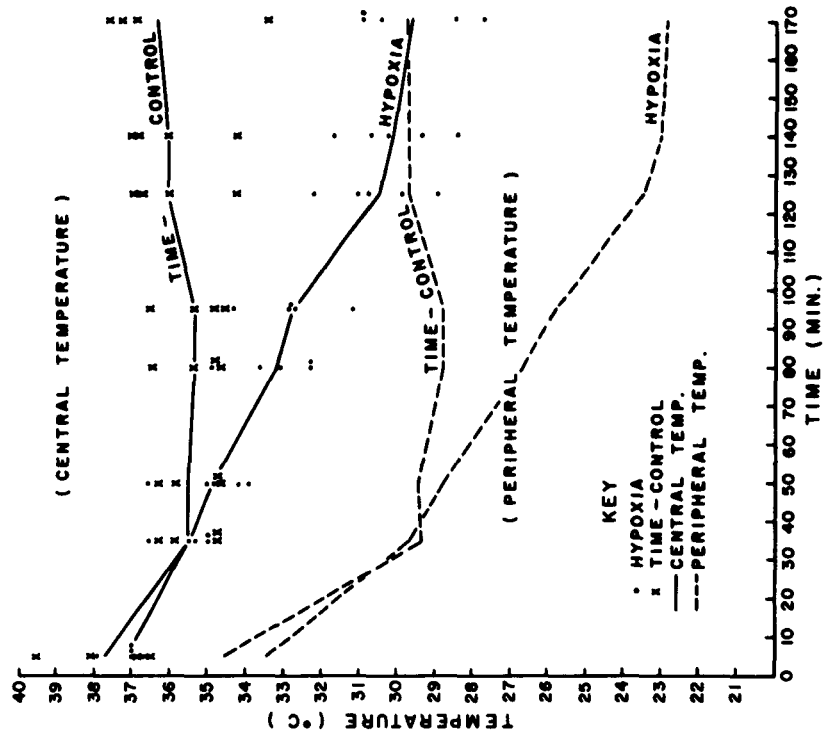


FIGURE 3. Effect of hypoxia on body temperature in cold environment

the core temperature falls from the original level of 37.2° to 29.6° C at the end of 170 minutes. The peripheral temperature also follows a similar pattern, falling from the original level of 33.5° C to a low level of 22.9° C at the end of the experimental period. These reductions of body temperature are related to the depression of shivering.

In marked contrast to the neutral and cold series, the thermal behaviors in the warm environment show no appreciable difference between the control and hypoxia groups. As a matter of fact, the central and peripheral temperatures reach the same level of approximately 43° C at the end of 125 minutes in both groups. The thermal panting observed in the warm series seems to be independent of hypoxia as is shown below.

Suppression of Shivering and its Mechanism. The effect of hypoxia on shivering is illustrated by comparing the O_2 consumption in room-air breathing and hypoxia in Figures 4 and 5. In the control group of the neutral series the average O_2 consumption ranges from 119 cc/min to 195 cc/min, while in hypoxia it is from 88 cc/min to 102 cc/min, indicating the depressant effect of hypoxia on shivering in the latter. Such an influence of hypoxia on shivering is distinctly seen in the cold series. In this series the initial level of O_2 consumption is 227 cc/min (room-air breathing). This is greatly reduced to 147 cc/min with 7% O_2 and then further reduced to 70 cc/min with 5% O_2 . The fact that such depression of shivering is reversible is shown by the sharp rise of O_2 consumption to 284 cc/min when the animal is returned to room-air breathing (Figure 5). In the control group of this series there is a continual elevation of O_2 consumption due to shivering, its range being from 269 cc/min to 365 cc/min throughout the experimental period.

Hypoxia provokes hyperventilation leading to hypocapnia as shown by the reduced alveolar PCO_2 (Tables 2 and 3). In the neutral environment PCO_2 is reduced from the initial level of 41.9 mm Hg to 14.6 mm Hg at the end of the experiment, whereas in the cold environment PCO_2 is reduced from 43.4 mm Hg to 31.9 mm Hg with 7% O_2 . That the hypoxia produces hypocapnia is demonstrated by comparison of PCO_2 of the control group and that of the hypoxia group in both series. In the control group there is no significant deviation in PCO_2 despite moderate to vigorous shivering. Also notice the immediate recovery of PCO_2 on returning to the room air from hypoxia (7% O_2) in the cold series. The latter finding serves as additional evidence of hypocapnia induced by hypoxia.

In the elucidation of suppressor mechanism of shivering in hypoxia, a working hypothesis is advanced in which lowered PCO_2 is considered as a likely cause. To test this hypothesis the following two series of studies have been performed. The first comprises four animals in which the fall of the alveolar PCO_2 during hypoxia has been artificially prevented in the cold

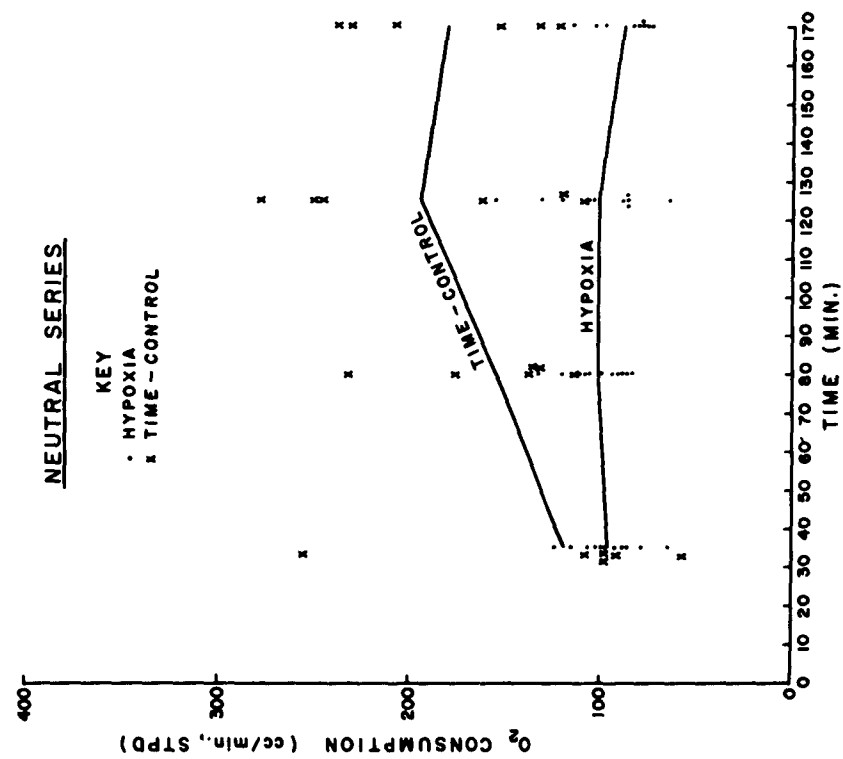


FIGURE 4. Influence of hypoxia on O₂ consumption in neutral environment

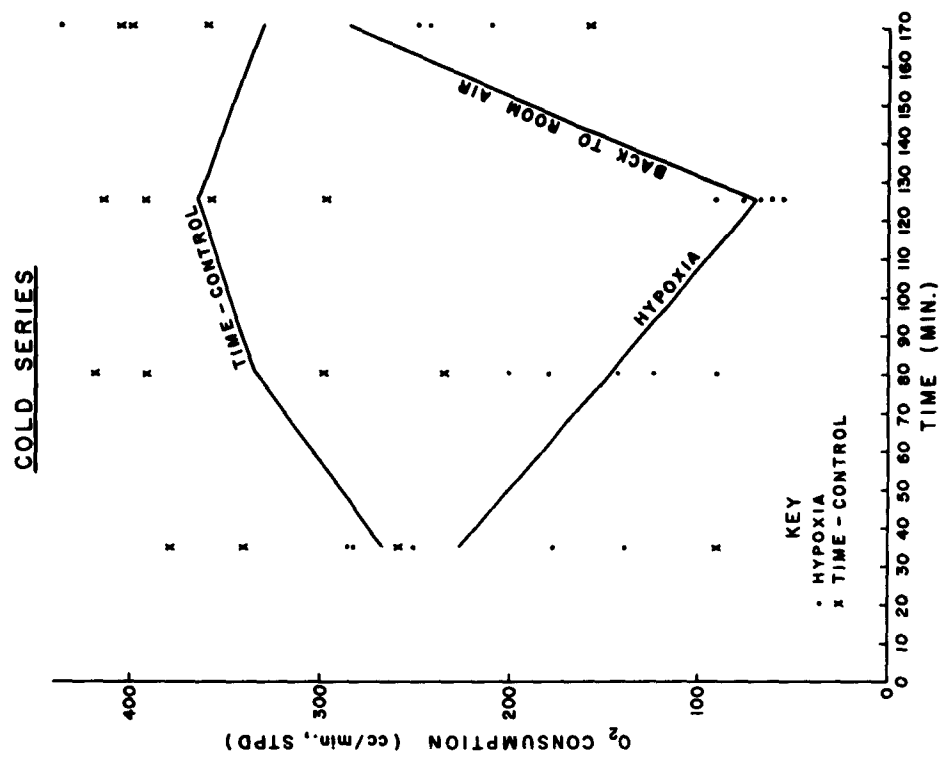


FIGURE 5. Influence of hypoxia on O₂ consumption in cold environment

Table 2. Pulmonary Ventilation during induced hypoxia

Animal No. and wt (kg)	Pre O ₂	FIO ₂ (%)	$\dot{V}_E$ (L/min) BIPS	f (breaths/min)	V _I (ml) BIPS	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	HER	pH	(CO ₂) P (mmHg)	P _{aCO₂} (mmHg)	$\dot{V}_A$ (L/min) BIPS	$\dot{V}_A/\dot{V}_E$
Neutral Series (n=17)													
A: Hypoxia													
No. 3 13.4	I	20.9	3.072	23.0	134	64	53	0.83	7.327	22.89	42.5	1.075	0.35
	II	9.0	6.645	44.0	151	94	70	0.74	7.472	19.12	25.9	2.334	0.35
	III	7.0	-	-	-	-	-	-	-	-	-	-	-
	IV	5.0	9.369	48.5	193	81	61	0.75	7.411	10.16	15.7	3.351	0.36
No. 5 12.3	I	20.9	3.748	32.0	117	86	73	0.85	7.326	18.37	34.2	1.842	0.49
	II	9.0	9.284	62.0	150	91	75	0.82	7.484	15.25	19.7	3.294	0.35
	III	7.0	6.847	69.5	99	86	63	0.73	7.490	13.26	17.2	3.154	0.46
	IV	5.0	12.618	60.0	210	79	68	0.86	7.583	10.58	11.2	5.240	0.42
No. 6 19.5	I	20.9	3.132	15.0	209	106	85	0.80	7.342	25.37	45.7	1.605	0.51
	II	9.0	8.605	88.0	98	120	103	0.86	7.501	21.02	26.7	3.332	0.39
	III	7.0	12.650	66.0	192	131	114	0.87	7.547	16.72	19.2	5.132	0.41
	IV	5.0	18.502	72.0	257	115	98	0.85	7.533	11.91	14.1	6.007	0.32
No. 7 15.0	I	20.9	3.437	18.2	189	88	69	0.78	7.310	25.02	48.3	1.233	0.36
	II	9.0	9.161	62.0	148	86	71	0.83	7.490	18.14	23.6	2.597	0.28
	III	7.0	15.348	80.5	191	86	75	0.87	7.451	12.90	18.3	3.543	0.23
	IV	5.0	-	-	-	-	-	-	-	-	-	-	-
No. 8 14.8	I	20.9	4.589	23.5	195	115	98	0.85	7.210	15.51	37.1	2.279	0.50
	II	9.0	15.124	77.0	196	132	153	1.16	7.339	11.40	20.7	6.394	0.42
	III	7.0	10.948	53.0	207	120	97	0.81	7.364	10.35	17.8	4.716	0.43
	IV	5.0	15.437	49.5	312	104	85	0.82	7.366	6.37	10.9	6.736	0.44

Table 2 cont'd.

Animal No. and Wt(kg)	Pre-treatment	F _I O ₂ (%)	$\dot{V}_E$ (L/min) BTPS	f (breaths/min)	V _T (ml) BTPS	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO ₂) P (mmHg)	P _a CO ₂ (mmHg)	$\dot{V}_A$ (L/min) BTPS	$\dot{V}_A/\dot{V}_E$
No. 10 17.5	I	20.9	2.690	16.0	168	99	70	0.71	7.314	22.67	43.4	1.392	0.52
	II	9.0	8.282	76.0	109	111	84	0.76	7.487	20.13	26.3	2.756	0.33
	III	7.0	11.505	92.0	125	104	93	0.89	7.508	18.59	23.2	3.459	0.30
	IV	5.0	8.542	58.0	147	83	74	0.89	7.356	11.62	20.3	3.146	0.37
No. 12 14.1	I	20.9	3.157	15.5	204	92	79	0.86	7.316	21.82	41.6	1.641	0.52
	II	9.0	7.705	53.0	145	100	91	0.91	7.454	18.72	26.4	2.978	0.39
	III	7.0	7.131	44.0	162	87	78	0.90	7.499	16.79	21.4	3.142	0.44
	IV	5.0	10.373	49.5	210	79	78	0.99	7.551	13.39	15.2	4.363	0.42
No. 13 13.9	I	20.9	3.111	15.0	207	97	79	0.81	7.333	21.68	39.8	1.714	0.55
	II	9.0	5.632	35.0	161	84	75	0.89	7.442	18.75	27.1	2.389	0.42
	III	7.0	7.736	60.0	129	63	57	0.90	7.486	16.71	21.9	2.243	0.29
	IV	5.0	-	-	-	-	-	-	-	-	-	-	-
No. 14 13.0	I	20.9	4.048	15.7	258	124	113	0.91	7.289	20.85	42.1	2.315	0.57
	II	9.0	9.066	51.0	178	108	129	1.19	7.386	14.75	24.1	4.635	0.51
	III	7.0	17.594	102.0	172	155	138	0.89	7.429	11.99	17.8	6.690	0.38
	IV	5.0	9.551	35.0	273	76	77	1.01	7.476	10.10	13.5	4.908	0.51
No. 15 25.0	I	20.9	3.134	13.2	237	102	80	0.78	7.363	22.59	38.8	1.779	0.57
	II	9.0	8.354	38.0	220	107	108	1.01	7.483	20.03	26.5	3.522	0.42
	III	7.0	11.932	53.5	223	106	99	0.93	7.567	14.11	15.5	5.523	0.46
	IV	5.0	18.935	69.0	274	98	97	0.99	7.593	12.06	12.5	6.713	0.35
No. 16 15.7	I	20.9	2.557	10.8	237	79	68	0.86	7.261	22.31	47.9	1.266	0.50
	II	9.0	8.255	54.5	151	88	94	1.07	7.449	19.37	27.6	2.944	0.36
	III	7.0	8.065	36.0	224	86	90	1.05	7.499	17.68	22.5	3.449	0.43
	IV	5.0	8.617	39.0	221	74	67	0.91	7.570	16.39	17.9	3.239	0.38
$\bar{x}$	I		3.334	18.0	196	96	79	0.82	7.308	21.73	41.9	1.649	0.49
	II		8.738	58.2	155	102	96	0.93	7.453	17.88	25.0	3.380	0.38
	III		10.976	65.7	172	102	90	0.88	7.484	14.91	19.5	4.105	0.38
	IV		12.438	53.4	233	88	78	0.90	7.493	11.40	14.6	4.856	0.40

Table 2 cont'd.

Animal No. and Wt (kg)	Pre- op No.	FIO ₂ (%)	$\dot{V}_E$ (L/min) BTPS	f (breaths /min)	V _T (ml) BTPS	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO ₂) P (mM/L)	P _{aCO₂} (mmHg)	$\dot{V}_A$ (L/min) BTPS	$\dot{V}_A/\dot{V}_E$
B. Time-control													
No. 25 18.9	I	20.9	2.759	16.5	167	99	70	0.71	7.331	23.71	43.8	1.379	0.50
	II	20.9	6.417	24.0	267	232	196	0.84	7.330	22.94	42.4	3.989	0.62
	III	20.9	6.909	24.5	282	250	187	0.75	7.352	22.09	38.9	4.149	0.60
	IV	20.9	6.943	26.0	267	238	183	0.77	7.378	21.01	35.0	4.512	0.65
No. 26 17.5	I	20.9	4.178	32.0	131	109	84	0.77	7.410	20.83	32.3	2.244	0.54
	II	20.9	5.099	29.0	176	138	107	0.78	7.378	19.81	33.0	2.798	0.55
	III	20.9	5.863	30.0	195	162	127	0.78	7.360	19.92	34.5	3.177	0.54
	IV	20.9	5.442	31.0	176	153	124	0.81	7.370	20.08	34.0	3.147	0.58
No. 27 15.9	I	20.9	4.782	49.0	98	91	74	0.81	7.307	19.20	37.3	1.713	0.36
	II	20.9	5.177	47.0	110	113	91	0.81	7.290	18.82	37.9	2.072	0.40
	III	20.9	5.634	45.0	125	120	98	0.82	7.304	18.11	35.4	2.389	0.42
	IV	20.9	5.866	49.0	120	122	99	0.81	7.265	17.59	37.4	2.284	0.39
No. 28 17.7	I	20.9	2.069	17.0	122	58	53	0.91	7.317	22.42	43.0	1.064	0.51
	II	20.9	5.100	23.0	222	137	122	0.89	7.317	20.53	39.3	2.679	0.53
	III	20.9	9.106	32.0	285	247	220	0.89	7.344	19.86	35.6	5.333	0.59
	IV	20.9	6.915	25.0	277	209	180	0.86	7.317	19.94	38.2	4.066	0.59

Table 2 cont'd.

Animal No. and wt (kg)	Sex	F _{IO2} (%)	$\dot{V}_E$ (L/min) BTFS	f (breaths/min)	V _T (ml)	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO ₂) P (mmHg)	P _{aCO2} (mmHg)	$\dot{V}_A$ (L/min) BTFS	$\dot{V}_A/\dot{V}_E$
B. Time-control (cont.)													
No. 29 14.8	I	20.9	3.562	23.5	152	99	79	0.80	7.381	23.08	38.2	1.787	0.50
	II	20.9	6.948	42.0	165	177	153	0.86	7.385	21.22	34.7	3.802	0.55
	III	20.9	3.749	22.0	170	109	87	0.80	7.369	20.80	35.3	2.126	0.57
	IV	20.9	4.593	22.0	209	133	108	0.81	7.360	20.15	34.9	2.674	0.58
No. 30 15.9	I	20.9	9.595	59.0	163	256	204	0.80	7.363	19.02	32.7	5.387	0.56
	II	20.9	5.566	52.8	105	133	96	0.72	7.347	19.24	34.3	2.415	0.43
	III	20.9	11.986	70.0	171	279	221	0.79	7.366	19.20	31.4	6.080	0.51
	IV	20.9	10.143	62.8	162	231	176	0.76	7.357	18.43	32.1	4.730	0.47
$\bar{x}$	I		4.491	32.8	139	119	94	0.80	7.352	21.38	37.9	2.262	0.50
	II		5.718	36.3	174	155	128	0.82	7.341	20.43	36.9	2.959	0.51
	III		7.208	37.3	205	195	157	0.81	7.353	20.00	35.2	3.876	0.54
	IV		6.650	36.0	202	181	145	0.80	7.341	19.53	35.3	3.569	0.54

Table 2 cont'd.

Animal No. and wt(kg)	$\bar{P}_{aO_2}$	F_{IO_2} (%)	$\dot{V}_E$ (L/min) BTPS	f (breaths/min)	V_T (ml)	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO_2) P (mmHg)	P_{aCO_2} (mmHg)	$\dot{V}_A$ (L/min) BTPS	$\dot{V}_A/\dot{V}_E$
Cold Series (n=9)													
A: Hypoxia													
No. 18 16.6	I II III IV	20.9 9.0 7.0 20.9	5.579 8.577 5.430 11.391	24.5 36.5 24.5 32.0	228 235 222 356	139 143 77 242	109 126 73 202	0.78 0.88 0.95 0.83	7.253 7.346 7.384 7.242	21.11 18.53 18.56 18.33	46.1 33.1 30.5 41.0	2.040 3.285 2.066 4.252	0.37 0.38 0.38 0.37
No. 20 13.6	I II III IV	20.9 9.0 7.0 20.9	5.250 9.231 4.412 8.134	21.0 47.0 28.0 20.0	250 196 158 407	177 179 67 248	133 121 47 172	0.75 0.68 0.70 0.69	7.251 7.371 7.346 7.193	19.20 16.04 16.42 18.91	42.1 27.1 29.3 46.9	2.726 3.853 1.384 3.165	0.52 0.42 0.31 0.39
No. 21 17.7	I II III IV	20.9 9.0 7.0 20.9	6.794 8.026 4.631 11.864	22.0 34.0 25.0 23.0	309 236 185 516	282 200 91 436	212 148 87 323	0.75 0.74 0.96 0.74	7.265 7.384 7.392 7.239	22.67 20.49 19.66 21.61	48.2 33.7 31.7 48.7	3.796 3.790 2.368 5.724	0.56 0.47 0.51 0.48
No. 23 16.1	I II III IV	20.9 9.0 7.0 20.9	9.498 7.790 4.227 7.853	26.0 38.0 23.0 24.0	365 205 184 327	285 124 55 209	227 106 46 139	0.80 0.85 0.84 0.67	7.285 7.406 7.388 7.214	20.85 19.24 18.58 19.29	42.5 30.1 30.3 45.7	4.609 3.039 1.310 2.625	0.49 0.39 0.31 0.33
No. 24 14.8	I II III IV	20.9 9.0 7.0 20.9	13.798 7.358 6.094 6.153	23.5 55.0 53.0 20.0	587 134 115 308	251 91 61 -	247 77 56 116	0.98 0.85 0.92 -	7.154 7.227 7.168 7.076	14.18 14.73 14.35 16.16	38.2 34.0 37.6 51.3	5.580 1.954 1.285 1.951	0.40 0.27 0.21 0.32
$\bar{x}$	I II III IV		8.184 8.196 4.959 9.079	23.4 42.1 30.7 23.8	348 201 173 383	227 147 70 284	186 116 62 190	0.81 0.80 0.87 0.73	7.242 7.347 7.336 7.193	19.60 17.81 17.51 18.86	43.4 31.6 31.9 46.7	3.750 3.184 1.683 3.543	0.47 0.39 0.34 0.38

Table 2 cont'd.

Animal No. and wt (kg)	$\bar{P}_{\text{O}_2}$ mmHg	$\text{F}_{\text{I O}_2}$ (%)	$\dot{V}_{\text{E}}$ (L/min) BTPS	f (breaths /min)	V_{T} (ml) BTPS	$\dot{V}_{\text{O}_2}$ (ml/min) STPD	$\dot{V}_{\text{CO}_2}$ (ml/min) STPD	RER	pH	(CO ₂) P (mmHg)	P_{aCO_2} (mmHg)	$\dot{V}_{\text{A}}$ (L/min) BTPS	$\dot{V}_{\text{A}}/\dot{V}_{\text{E}}$
B. Time-control													
No. 31 17.3	I	20.9	11.596	37.3	311	379	300	0.79	7.360	22.92	39.7	6.530	0.56
	II	20.9	8.027	31.3	256	298	216	0.72	7.349	22.50	40.0	4.665	0.58
	III	20.9	10.247	45.3	226	391	289	0.74	7.366	22.88	39.1	6.377	0.62
	IV	20.9	9.300	41.3	225	359	294	0.82	7.377	22.04	36.7	6.908	0.74
No. 33 15.9	I	20.9	4.932	10.0	493	259	199	0.77	7.269	24.79	52.3	3.284	0.67
	II	20.9	8.663	14.3	606	418	322	0.77	7.265	24.61	52.4	5.307	0.61
	III	20.9	10.231	19.0	538	413	352	0.85	7.280	22.67	46.7	6.512	0.64
	IV	20.9	7.865	14.0	562	404	317	0.78	7.239	23.85	53.7	5.093	0.65
No. 34 14.8	I	20.9	10.172	30.6	332	340	269	0.79	7.309	22.45	43.4	5.347	0.53
	II	20.9	11.097	34.3	324	390	302	0.77	7.297	22.31	44.3	5.887	0.53
	III	20.9	10.040	32.3	311	357	262	0.73	7.320	21.47	40.5	5.582	0.56
	IV	20.9	11.726	35.3	332	399	302	0.76	7.310	20.98	40.5	6.435	0.55
No. 35 14.1	I	20.9	2.809	13.4	210	91	67	0.74	7.283	22.21	45.4	1.273	0.45
	II	20.9	7.424	33.3	223	234	177	0.76	7.258	19.34	41.8	3.657	0.49
	III	20.9	13.052	63.3	206	297	241	0.81	7.271	19.29	40.5	5.132	0.39
	IV	20.9	5.707	33.3	171	157	115	0.73	7.248	21.00	46.4	2.141	0.38
$\bar{x}$	I		7.377	22.8	337	267	209	0.77	7.305	23.09	45.2	4.109	0.55
	II		8.803	28.3	352	335	254	0.76	7.292	22.19	44.6	4.879	0.55
	III		10.893	40.0	320	365	286	0.78	7.309	21.58	41.7	5.901	0.55
	IV		8.650	31.0	323	330	257	0.77	7.294	21.97	44.3	5.144	0.58

Table 2 cont'd.

Animal No. and Wt(kg)	Pos. No.	F _{IO2} (%)	$\dot{V}_E$ (L/min) BTPS	f (breaths /min)	V _T (ml) BTPS	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO ₂) P (mM/L)	P _{aCO2} (mmHg)	$\dot{V}_A$ (L/min) BTPS	$\dot{V}_A/\dot{V}_E$	T _C (°C)
Heat Series (n=9)														
A: Hypoxia														
No. 40 11.8	I	20.9	21.438	240	89	123	128	1.04	7.481	20.75	27.5	4.014	0.19	40.6
	II	9.0	51.468	165	312	204	314	1.54	7.739	9.97	7.4	36.619	0.71	42.5
No. 41 14.1	I	20.9	9.971	78	128	125	122	0.98	7.409	23.65	36.7	2.867	0.29	38.7
	II	9.0	52.367	132	397	170	272	1.60	7.654	12.19	11.0	21.340	0.41	41.5
No. 42 15.0	I	20.9	3.944	11	359	106	97	0.92	7.376	23.26	38.9	2.152	0.55	39.1
	II	7.0	51.024	112	456	228	280	1.23	7.717	11.20	8.7	27.648	0.54	41.8
	III	20.9	48.372	139	348	272	245	0.90	7.583	10.88	11.5	18.370	0.38	43.3
No. 43 14.5	I	20.9	3.646	18	203	105	83	0.79	7.357	27.47	47.9	1.497	0.41	38.9
	II	7.0	47.855	145	330	198	225	1.14	7.784	15.64	10.5	18.458	0.39	41.5
	III	20.9	44.044	125	352	214	204	0.95	7.786	13.08	8.8	20.097	0.46	43.1
No. 44 12.7	I	20.9	6.536	29	225	111	103	0.93	7.367	21.18	36.1	2.460	0.38	38.7
	II	7.0	42.847	148	290	122	189	1.55	7.684	13.48	11.4	14.308	0.33	41.3
	III	20.9	52.907	175	302	185	199	1.08	7.686	11.91	10.0	17.122	0.32	43.2
$\bar{x}$	I		9.107	75	201	114	107	0.93	7.398	23.26	37.40	2.598	0.36	39.2
	II		49.112	140	357	184	256	1.41	7.716	12.50	9.81	23.675	0.48	41.7
	III		48.440	146	334	224	216	0.98	7.685	11.96	10.10	18.530	0.39	43.2

Table 2 cont'd.

Animal No. and Wt (kg)	$\bar{P}_{iO_2}$	$\bar{F}_{iO_2}$ (%)	$\bar{V}_E$ (L/min) BTPS	f (breaths/min)	V_T (ml) BTPS	$\dot{V}O_2$ (ml/min) STPD	$\dot{V}CO_2$ (ml/min) STPD	RER	pH	(CO_2) P (mmHg)	$\bar{P}_{aCO_2}$ (mmHg)	$\bar{V}_A$ (L/min) BTPS	$\bar{V}_A/\bar{V}_E$	T_c ($^{\circ}C$)
B. Time-control														
No. 36 15.7	I	20.9	25.332	290	87	197	164	0.83	7.322	21.17	39.8	3.557	0.14	40.1
	II	20.9	32.705	285	115	197	171	0.87	7.459	16.65	23.2	6.364	0.19	42.4
	III	20.9	39.476	194	203	225	177	0.79	7.464	11.98	16.5	9.258	0.23	43.5
	IV	20.9	33.464	148	226	220	199	0.90	7.389	10.21	16.6	10.364	0.31	44.1
No. 37 14.1	I	20.9	6.402	49	131	119	96	0.81	7.402	21.44	33.8	2.450	0.38	39.5
	II	20.9	32.152	220	146	173	152	0.88	7.654	16.39	20.7	6.340	0.20	41.6
	III	20.9	32.173	172	187	178	137	0.77	7.709	12.17	9.7	12.214	0.38	42.4
	IV	20.9	31.330	158	198	167	144	0.86	7.618	11.28	11.0	11.308	0.36	43.2
No. 38 14.1	I	20.9	5.540	14	396	180	150	0.83	7.368	23.47	39.9	3.244	0.59	39.1
	II	20.9	40.360	280	144	177	121	0.68	7.621	17.24	16.7	6.249	0.15	41.4
	III	20.9	33.246	224	148	159	163	1.03	7.621	15.66	15.2	9.273	0.28	42.2
	IV	20.9	38.976	200	195	178	175	0.98	7.631	11.85	11.3	13.413	0.34	42.9
No. 39 16.4	I	20.9	13.064	90	145	165	149	0.90	7.406	21.68	33.9	3.790	0.29	39.9
	II	20.9	35.401	256	138	191	139	0.73	7.494	18.83	24.3	4.943	0.14	41.7
	III	20.9	32.587	208	157	198	158	0.80	7.510	15.40	19.2	7.120	0.22	42.9
	IV	20.9	37.071	160	232	198	170	0.86	7.451	13.53	19.2	7.657	0.21	43.5
$\bar{x}$	I		12.585	111	190	165	140	0.84	7.375	21.94	36.86	3.260	0.35	39.7
	II		35.155	260	136	185	146	0.79	7.557	17.28	21.22	5.974	0.17	41.8
	III		34.371	200	174	190	159	0.85	7.576	13.80	15.13	9.466	0.28	42.8
	IV		35.210	167	213	191	172	0.90	7.522	11.72	14.50	10.686	0.31	43.4

Abbreviations:

$\bar{P}_{iO_2}$, $\bar{V}_E$, f, V_T , $\dot{V}O_2$, $\dot{V}CO_2$, RER, pH, (CO_2)P, $\bar{P}_{aCO_2}$, $\bar{V}_A$, $\bar{V}_A/\bar{V}_E$ and T_c represent inspiratory O_2 fraction, total ventilation, respiratory rate, tidal volume, O_2 intake, CO_2 output, respiratory exchange ratio, hydrogen concentration, plasma CO_2 content, arterial CO_2 tension, alveolar ventilation, the ratio of alveolar to total ventilation and the core temperature respectively.

Table 3. Hemodynamic characteristics during induced hypoxia

Animal No. O ₂ capacity (vol.%)	Position	FI _{O2} (%)	CaO ₂ (vol.%)	CvO ₂ (vol.%)	(a-v)O ₂ Vol.%	Q̇ (L/min)	f (beats/min)	V _s (ml)	P _{sa} (mmHg)	ṡA/Q̇
Neutral Series (n=17)										
A: Hypoxia										
No. 3 22.83	I	20.9	17.13	14.35	2.78	2.302	160	14.4	160/109	0.47
	II	9.0	8.34	5.49	2.85	3.298	176	18.7	184/130	0.71
	III	7.0	-	-	-	-	-	-	-	-
	IV	5.0	3.71	1.28	2.43	3.333	160	20.8	155/102	1.01
No. 5 18.54	I	20.9	16.36	12.24	4.12	2.087	195	10.7	177/132	0.88
	II	9.0	9.89	5.86	4.03	2.258	203	11.1	182/138	1.46
	III	7.0	6.30	2.10	4.20	2.048	199	10.3	182/136	1.54
	IV	5.0	6.19	2.48	3.71	2.129	194	11.0	162/119	2.46
No. 6 18.24	I	20.9	14.15	10.79	3.36	3.155	107	29.5	168/122	0.51
	II	9.0	8.14	5.49	2.65	4.528	188	24.1	190/142	0.74
	III	7.0	8.32	5.27	3.05	4.295	182	23.6	166/118	1.19
	IV	5.0	5.36	2.12	3.24	3.549	158	22.5	140/95	1.89
No. 7 19.62	I	20.9	15.31	9.24	6.07	1.450	164	8.8	178/128	0.85
	II	9.0	8.25	2.81	5.44	1.581	222	7.1	202/140	1.64
	III	7.0	6.36	1.36	5.00	1.720	188	9.1	142/97	2.06
	IV	5.0	-	-	-	-	-	-	-	-
No. 8 17.03	I	20.9	12.50	9.83	2.67	4.307	179	24.1	172/120	0.53
	II	9.0	6.81	3.81	3.00	4.400	197	22.3	201/141	1.45
	III	7.0	6.37	2.38	3.99	3.008	192	15.7	193/135	1.57
	IV	5.0	3.33	0.90	2.43	4.280	185	23.1	169/113	1.57
No. 10 19.10	I	20.9	16.79	12.87	3.92	2.526	139	18.2	171/131	0.55
	II	9.0	7.12	3.60	3.52	3.153	171	18.4	206/152	0.87
	III	7.0	4.97	1.76	3.21	3.240	168	19.3	177/127	1.07
	IV	5.0	2.45	0.39	2.06	4.029	110	36.6	151/92	0.78

Table 3 cont'd.

Animal No.	$\bar{P}_{aO_2}$	$\bar{F}_{IO_2}$ (%)	$\bar{C}_{aO_2}$ (vol.%)	$\bar{C}_{vO_2}$ (vol.%)	(a-v) $\bar{O}_2$ Vol.%	$\bar{Q}$ (l/min)	$\bar{f}$ (beats/min)	$\bar{V}_s$ (ml)	$\bar{P}_{aa}$ (mmHg)	$\bar{V}_A/\bar{Q}$
Neutral Series (n=17) A: Hypoxia (cont.)										
No. 12	I	20.9	16.69	12.71	3.98	2.312	140	16.5	164/124	0.68
21.20	II	9.0	7.75	3.94	3.81	2.625	160	16.4	164/127	1.13
	III	7.0	6.49	2.38	4.11	2.117	160	13.2	154/120	1.48
	IV	5.0	4.32	1.54	2.78	2.842	160	17.8	145/101	1.56
No. 13	I	20.9	17.42	14.29	3.13	3.099	180	17.2	176/125	0.55
19.22	II	9.0	7.61	4.44	3.17	2.650	196	13.5	180/131	0.90
	III	7.0	5.69	2.32	3.37	1.869	167	11.2	160/119	1.20
	IV	5.0	-	-	-	-	-	-	-	-
No. 14	I	20.9	16.63	12.22	4.41	2.812	180	15.6	165/112	0.82
18.70	II	9.0	9.94	5.56	4.38	2.466	186	13.3	186/135	1.88
	III	7.0	9.82	5.35	4.47	3.468	186	18.6	165/118	1.93
	IV	5.0	6.07	2.13	3.94	1.929	150	12.9	154/110	2.54
No. 15	I	20.9	17.46	13.76	3.70	2.757	160	17.2	163/112	0.65
21.09	II	9.0	12.00	9.12	2.88	3.715	180	20.6	176/118	0.95
	III	7.0	10.60	6.74	3.86	2.746	173	15.9	160/115	2.01
	IV	5.0	8.48	5.11	3.37	2.908	168	17.3	163/112	2.31
No. 16	I	20.9	17.24	13.76	3.48	2.270	144	15.8	158/121	0.56
22.66	II	9.0	11.38	7.02	4.36	2.018	192	10.5	159/132	1.46
	III	7.0	8.66	4.44	4.22	2.038	180	11.3	156/127	1.69
	IV	5.0	4.17	2.89	1.28	5.781	180	32.1	149/119	0.56
$\bar{X}$	I		16.15	12.37	3.78	2.643	159	17.1	168/121	0.64
	II		8.84	5.19	3.64	2.972	190	16.0	185/135	1.20
	III		7.36	3.41	3.95	2.655	180	14.8	166/121	1.57
	IV		4.90	2.09	2.81	3.420	163	21.6	154/107	1.61

Table 3 cont'd. Animal No. O₂ capacity (vol.%)

B. Time-control											
No. 25	I	20.9	16.76	10.50	6.26	1.581	130	12.2	174/128	0.87	
18.75	II	20.9 <td>14.13<td>7.95<td>6.18<td>3.754<td>173</td><td>21.7<td>174/122<td>1.06</td></td></td></td></td></td></td>	14.13 <td>7.95<td>6.18<td>3.754<td>173</td><td>21.7<td>174/122<td>1.06</td></td></td></td></td></td>	7.95 <td>6.18<td>3.754<td>173</td><td>21.7<td>174/122<td>1.06</td></td></td></td></td>	6.18 <td>3.754<td>173</td><td>21.7<td>174/122<td>1.06</td></td></td></td>	3.754 <td>173</td> <td>21.7<td>174/122<td>1.06</td></td></td>	173	21.7 <td>174/122<td>1.06</td></td>	174/122 <td>1.06</td>	1.06	
	III	20.9 <td>16.68<td>6.91<td>9.77<td>2.559<td>184</td><td>13.9<td>179/122<td>1.62</td></td></td></td></td></td></td>	16.68 <td>6.91<td>9.77<td>2.559<td>184</td><td>13.9<td>179/122<td>1.62</td></td></td></td></td></td>	6.91 <td>9.77<td>2.559<td>184</td><td>13.9<td>179/122<td>1.62</td></td></td></td></td>	9.77 <td>2.559<td>184</td><td>13.9<td>179/122<td>1.62</td></td></td></td>	2.559 <td>184</td> <td>13.9<td>179/122<td>1.62</td></td></td>	184	13.9 <td>179/122<td>1.62</td></td>	179/122 <td>1.62</td>	1.62	
	IV	20.9 <td>17.04<td>7.14<td>9.90<td>2.404<td>202</td><td>11.9<td>188/132<td>1.88</td></td></td></td></td></td></td>	17.04 <td>7.14<td>9.90<td>2.404<td>202</td><td>11.9<td>188/132<td>1.88</td></td></td></td></td></td>	7.14 <td>9.90<td>2.404<td>202</td><td>11.9<td>188/132<td>1.88</td></td></td></td></td>	9.90 <td>2.404<td>202</td><td>11.9<td>188/132<td>1.88</td></td></td></td>	2.404 <td>202</td> <td>11.9<td>188/132<td>1.88</td></td></td>	202	11.9 <td>188/132<td>1.88</td></td>	188/132 <td>1.88</td>	1.88	
	No. 26	I	20.9 <td>25.08<td>14.33<td>10.75<td>204</td><td>5.0<td>120/97<td>2.21</td></td></td></td></td></td>	25.08 <td>14.33<td>10.75<td>204</td><td>5.0<td>120/97<td>2.21</td></td></td></td></td>	14.33 <td>10.75<td>204</td><td>5.0<td>120/97<td>2.21</td></td></td></td>	10.75 <td>204</td> <td>5.0<td>120/97<td>2.21</td></td></td>	204	5.0 <td>120/97<td>2.21</td></td>	120/97 <td>2.21</td>	2.21	
26.16	II	20.9 <td>23.89<td>12.37<td>11.52<td>1.198<td>218</td><td>5.5<td>122/97<td>2.34</td></td></td></td></td></td></td>	23.89 <td>12.37<td>11.52<td>1.198<td>218</td><td>5.5<td>122/97<td>2.34</td></td></td></td></td></td>	12.37 <td>11.52<td>1.198<td>218</td><td>5.5<td>122/97<td>2.34</td></td></td></td></td>	11.52 <td>1.198<td>218</td><td>5.5<td>122/97<td>2.34</td></td></td></td>	1.198 <td>218</td> <td>5.5<td>122/97<td>2.34</td></td></td>	218	5.5 <td>122/97<td>2.34</td></td>	122/97 <td>2.34</td>	2.34	
	III	20.9 <td>24.21<td>11.39<td>12.82<td>1.264<td>226</td><td>5.6<td>126/95<td>2.52</td></td></td></td></td></td></td>	24.21 <td>11.39<td>12.82<td>1.264<td>226</td><td>5.6<td>126/95<td>2.52</td></td></td></td></td></td>	11.39 <td>12.82<td>1.264<td>226</td><td>5.6<td>126/95<td>2.52</td></td></td></td></td>	12.82 <td>1.264<td>226</td><td>5.6<td>126/95<td>2.52</td></td></td></td>	1.264 <td>226</td> <td>5.6<td>126/95<td>2.52</td></td></td>	226	5.6 <td>126/95<td>2.52</td></td>	126/95 <td>2.52</td>	2.52	
	IV	20.9 <td>22.82<td>9.96<td>12.86<td>1.190<td>224</td><td>5.3<td>128/100<td>2.64</td></td></td></td></td></td></td>	22.82 <td>9.96<td>12.86<td>1.190<td>224</td><td>5.3<td>128/100<td>2.64</td></td></td></td></td></td>	9.96 <td>12.86<td>1.190<td>224</td><td>5.3<td>128/100<td>2.64</td></td></td></td></td>	12.86 <td>1.190<td>224</td><td>5.3<td>128/100<td>2.64</td></td></td></td>	1.190 <td>224</td> <td>5.3<td>128/100<td>2.64</td></td></td>	224	5.3 <td>128/100<td>2.64</td></td>	128/100 <td>2.64</td>	2.64	
	No. 27	I	20.9 <td>22.50<td>11.85<td>10.65<td>190</td><td>4.5<td>124/90<td>2.01</td></td></td></td></td></td>	22.50 <td>11.85<td>10.65<td>190</td><td>4.5<td>124/90<td>2.01</td></td></td></td></td>	11.85 <td>10.65<td>190</td><td>4.5<td>124/90<td>2.01</td></td></td></td>	10.65 <td>190</td> <td>4.5<td>124/90<td>2.01</td></td></td>	190	4.5 <td>124/90<td>2.01</td></td>	124/90 <td>2.01</td>	2.01	
25.14	II	20.9 <td>21.83<td>10.91<td>10.92<td>1.035<td>204</td><td>5.1<td>122/87<td>2.00</td></td></td></td></td></td></td>	21.83 <td>10.91<td>10.92<td>1.035<td>204</td><td>5.1<td>122/87<td>2.00</td></td></td></td></td></td>	10.91 <td>10.92<td>1.035<td>204</td><td>5.1<td>122/87<td>2.00</td></td></td></td></td>	10.92 <td>1.035<td>204</td><td>5.1<td>122/87<td>2.00</td></td></td></td>	1.035 <td>204</td> <td>5.1<td>122/87<td>2.00</td></td></td>	204	5.1 <td>122/87<td>2.00</td></td>	122/87 <td>2.00</td>	2.00	
	III	20.9 <td>21.91<td>9.43<td>12.48<td>0.962<td>212</td><td>4.5<td>126/90<td>2.48</td></td></td></td></td></td></td>	21.91 <td>9.43<td>12.48<td>0.962<td>212</td><td>4.5<td>126/90<td>2.48</td></td></td></td></td></td>	9.43 <td>12.48<td>0.962<td>212</td><td>4.5<td>126/90<td>2.48</td></td></td></td></td>	12.48 <td>0.962<td>212</td><td>4.5<td>126/90<td>2.48</td></td></td></td>	0.962 <td>212</td> <td>4.5<td>126/90<td>2.48</td></td></td>	212	4.5 <td>126/90<td>2.48</td></td>	126/90 <td>2.48</td>	2.48	
	IV	20.9 <td>21.13<td>8.29<td>12.84<td>0.950<td>218</td><td>4.4<td>120/86<td>2.40</td></td></td></td></td></td></td>	21.13 <td>8.29<td>12.84<td>0.950<td>218</td><td>4.4<td>120/86<td>2.40</td></td></td></td></td></td>	8.29 <td>12.84<td>0.950<td>218</td><td>4.4<td>120/86<td>2.40</td></td></td></td></td>	12.84 <td>0.950<td>218</td><td>4.4<td>120/86<td>2.40</td></td></td></td>	0.950 <td>218</td> <td>4.4<td>120/86<td>2.40</td></td></td>	218	4.4 <td>120/86<td>2.40</td></td>	120/86 <td>2.40</td>	2.40	
	No. 28	I	20.9 <td>17.94<td>15.01<td>2.93<td>180</td><td>11.0<td>168/116<td>0.54</td></td></td></td></td></td>	17.94 <td>15.01<td>2.93<td>180</td><td>11.0<td>168/116<td>0.54</td></td></td></td></td>	15.01 <td>2.93<td>180</td><td>11.0<td>168/116<td>0.54</td></td></td></td>	2.93 <td>180</td> <td>11.0<td>168/116<td>0.54</td></td></td>	180	11.0 <td>168/116<td>0.54</td></td>	168/116 <td>0.54</td>	0.54	
20.69	II	20.9 <td>18.34<td>14.51<td>3.83<td>3.577<td>192</td><td>18.6<td>176/126<td>0.75</td></td></td></td></td></td></td>	18.34 <td>14.51<td>3.83<td>3.577<td>192</td><td>18.6<td>176/126<td>0.75</td></td></td></td></td></td>	14.51 <td>3.83<td>3.577<td>192</td><td>18.6<td>176/126<td>0.75</td></td></td></td></td>	3.83 <td>3.577<td>192</td><td>18.6<td>176/126<td>0.75</td></td></td></td>	3.577 <td>192</td> <td>18.6<td>176/126<td>0.75</td></td></td>	192	18.6 <td>176/126<td>0.75</td></td>	176/126 <td>0.75</td>	0.75	
	III	20.9 <td>18.06<td>11.57<td>6.49<td>3.806<td>204</td><td>18.7<td>174/127<td>1.40</td></td></td></td></td></td></td>	18.06 <td>11.57<td>6.49<td>3.806<td>204</td><td>18.7<td>174/127<td>1.40</td></td></td></td></td></td>	11.57 <td>6.49<td>3.806<td>204</td><td>18.7<td>174/127<td>1.40</td></td></td></td></td>	6.49 <td>3.806<td>204</td><td>18.7<td>174/127<td>1.40</td></td></td></td>	3.806 <td>204</td> <td>18.7<td>174/127<td>1.40</td></td></td>	204	18.7 <td>174/127<td>1.40</td></td>	174/127 <td>1.40</td>	1.40	
	IV	20.9 <td>17.72<td>10.98<td>6.74<td>3.101<td>196</td><td>15.8<td>162/117<td>1.31</td></td></td></td></td></td></td>	17.72 <td>10.98<td>6.74<td>3.101<td>196</td><td>15.8<td>162/117<td>1.31</td></td></td></td></td></td>	10.98 <td>6.74<td>3.101<td>196</td><td>15.8<td>162/117<td>1.31</td></td></td></td></td>	6.74 <td>3.101<td>196</td><td>15.8<td>162/117<td>1.31</td></td></td></td>	3.101 <td>196</td> <td>15.8<td>162/117<td>1.31</td></td></td>	196	15.8 <td>162/117<td>1.31</td></td>	162/117 <td>1.31</td>	1.31	
	No. 29	I	20.9 <td>17.93<td>9.96<td>7.97<td>141</td><td>8.8<td>174/135<td>1.44</td></td></td></td></td></td>	17.93 <td>9.96<td>7.97<td>141</td><td>8.8<td>174/135<td>1.44</td></td></td></td></td>	9.96 <td>7.97<td>141</td><td>8.8<td>174/135<td>1.44</td></td></td></td>	7.97 <td>141</td> <td>8.8<td>174/135<td>1.44</td></td></td>	141	8.8 <td>174/135<td>1.44</td></td>	174/135 <td>1.44</td>	1.44	
18.96	II	20.9 <td>18.51<td>7.48<td>11.03<td>1.605<td>152</td><td>10.6<td>174/130<td>2.37</td></td></td></td></td></td></td>	18.51 <td>7.48<td>11.03<td>1.605<td>152</td><td>10.6<td>174/130<td>2.37</td></td></td></td></td></td>	7.48 <td>11.03<td>1.605<td>152</td><td>10.6<td>174/130<td>2.37</td></td></td></td></td>	11.03 <td>1.605<td>152</td><td>10.6<td>174/130<td>2.37</td></td></td></td>	1.605 <td>152</td> <td>10.6<td>174/130<td>2.37</td></td></td>	152	10.6 <td>174/130<td>2.37</td></td>	174/130 <td>2.37</td>	2.37	
	III	20.9 <td>16.95<td>7.40<td>9.55<td>1.141<td>154</td><td>7.4<td>165/127<td>1.86</td></td></td></td></td></td></td>	16.95 <td>7.40<td>9.55<td>1.141<td>154</td><td>7.4<td>165/127<td>1.86</td></td></td></td></td></td>	7.40 <td>9.55<td>1.141<td>154</td><td>7.4<td>165/127<td>1.86</td></td></td></td></td>	9.55 <td>1.141<td>154</td><td>7.4<td>165/127<td>1.86</td></td></td></td>	1.141 <td>154</td> <td>7.4<td>165/127<td>1.86</td></td></td>	154	7.4 <td>165/127<td>1.86</td></td>	165/127 <td>1.86</td>	1.86	
	IV	20.9 <td>17.56<td>6.53<td>11.03<td>1.206<td>180</td><td>6.7<td>178/124<td>2.22</td></td></td></td></td></td></td>	17.56 <td>6.53<td>11.03<td>1.206<td>180</td><td>6.7<td>178/124<td>2.22</td></td></td></td></td></td>	6.53 <td>11.03<td>1.206<td>180</td><td>6.7<td>178/124<td>2.22</td></td></td></td></td>	11.03 <td>1.206<td>180</td><td>6.7<td>178/124<td>2.22</td></td></td></td>	1.206 <td>180</td> <td>6.7<td>178/124<td>2.22</td></td></td>	180	6.7 <td>178/124<td>2.22</td></td>	178/124 <td>2.22</td>	2.22	
	No. 30	I	20.9 <td>15.22<td>9.18<td>6.04<td>224</td><td>18.9<td>160/110<td>1.27</td></td></td></td></td></td>	15.22 <td>9.18<td>6.04<td>224</td><td>18.9<td>160/110<td>1.27</td></td></td></td></td>	9.18 <td>6.04<td>224</td><td>18.9<td>160/110<td>1.27</td></td></td></td>	6.04 <td>224</td> <td>18.9<td>160/110<td>1.27</td></td></td>	224	18.9 <td>160/110<td>1.27</td></td>	160/110 <td>1.27</td>	1.27	
17.43	II	20.9 <td>14.72<td>10.73<td>3.99<td>3.333<td>204</td><td>16.3<td>158/113<td>0.72</td></td></td></td></td></td></td>	14.72 <td>10.73<td>3.99<td>3.333<td>204</td><td>16.3<td>158/113<td>0.72</td></td></td></td></td></td>	10.73 <td>3.99<td>3.333<td>204</td><td>16.3<td>158/113<td>0.72</td></td></td></td></td>	3.99 <td>3.333<td>204</td><td>16.3<td>158/113<td>0.72</td></td></td></td>	3.333 <td>204</td> <td>16.3<td>158/113<td>0.72</td></td></td>	204	16.3 <td>158/113<td>0.72</td></td>	158/113 <td>0.72</td>	0.72	
	III	20.9 <td>15.01<td>8.03<td>6.98<td>3.997<td>218</td><td>18.3<td>152/109<td>1.52</td></td></td></td></td></td></td>	15.01 <td>8.03<td>6.98<td>3.997<td>218</td><td>18.3<td>152/109<td>1.52</td></td></td></td></td></td>	8.03 <td>6.98<td>3.997<td>218</td><td>18.3<td>152/109<td>1.52</td></td></td></td></td>	6.98 <td>3.997<td>218</td><td>18.3<td>152/109<td>1.52</td></td></td></td>	3.997 <td>218</td> <td>18.3<td>152/109<td>1.52</td></td></td>	218	18.3 <td>152/109<td>1.52</td></td>	152/109 <td>1.52</td>	1.52	
	IV	20.9 <td>15.39<td>8.63<td>6.76<td>3.417<td>220</td><td>15.5<td>150/105<td>1.38</td></td></td></td></td></td></td>	15.39 <td>8.63<td>6.76<td>3.417<td>220</td><td>15.5<td>150/105<td>1.38</td></td></td></td></td></td>	8.63 <td>6.76<td>3.417<td>220</td><td>15.5<td>150/105<td>1.38</td></td></td></td></td>	6.76 <td>3.417<td>220</td><td>15.5<td>150/105<td>1.38</td></td></td></td>	3.417 <td>220</td> <td>15.5<td>150/105<td>1.38</td></td></td>	220	15.5 <td>150/105<td>1.38</td></td>	150/105 <td>1.38</td>	1.38	
	$\bar{x}$	I		19.24 <td>11.81<td>7.43<td>178</td><td>10.1<td>153/113<td>1.39</td></td></td></td></td>	11.81 <td>7.43<td>178</td><td>10.1<td>153/113<td>1.39</td></td></td></td>	7.43 <td>178</td> <td>10.1<td>153/113<td>1.39</td></td></td>	178	10.1 <td>153/113<td>1.39</td></td>	153/113 <td>1.39</td>	1.39	
	II		18.57 <td>10.66<td>7.91<td>2417<td>191</td><td>13.0<td>154/113<td>1.54</td></td></td></td></td></td>	10.66 <td>7.91<td>2417<td>191</td><td>13.0<td>154/113<td>1.54</td></td></td></td></td>	7.91 <td>2417<td>191</td><td>13.0<td>154/113<td>1.54</td></td></td></td>	2417 <td>191</td> <td>13.0<td>154/113<td>1.54</td></td></td>	191	13.0 <td>154/113<td>1.54</td></td>	154/113 <td>1.54</td>	1.54	
	III		18.80 <td>9.12</td> <td>9.68<td>2.288<td>200</td><td>11.4<td>154/112<td>1.90</td></td></td></td></td>	9.12	9.68 <td>2.288<td>200</td><td>11.4<td>154/112<td>1.90</td></td></td></td>	2.288 <td>200</td> <td>11.4<td>154/112<td>1.90</td></td></td>	200	11.4 <td>154/112<td>1.90</td></td>	154/112 <td>1.90</td>	1.90	
	IV		18.61 <td>8.59<td>10.02<td>2.045<td>207</td><td>9.9<td>154/111<td>1.97</td></td></td></td></td></td>	8.59 <td>10.02<td>2.045<td>207</td><td>9.9<td>154/111<td>1.97</td></td></td></td></td>	10.02 <td>2.045<td>207</td><td>9.9<td>154/111<td>1.97</td></td></td></td>	2.045 <td>207</td> <td>9.9<td>154/111<td>1.97</td></td></td>	207	9.9 <td>154/111<td>1.97</td></td>	154/111 <td>1.97</td>	1.97	

Table 3 cont'd.

Animal No. O ₂ capacity (vol.%)	Pos H ₂ O ₂	FLO ₂ (%)	CaO ₂ (vol.%)	CO ₂ (vol.%)	(a-v)O ₂ Vol. %	Q̇ (L/min)	f (beats /min)	V _E (ml)	P _{sa} (mmHg)	V̇A/Q̇
Cold Series (n=9) A: Hypoxia										
No. 18	I	20.9	16.35	10.01	6.34	2.192	186	11.8	178/136	0.93
19.00	II	9.0	8.34	3.21	5.13	2.788	180	15.5	173/131	1.18
	III	7.0	8.55	2.06	6.49	1.186	138	8.6	162/126	1.74
	IV	20.9	20.03	6.25	13.78	1.756	132	13.3	143/86	2.42
No. 20	I	20.9	14.95	8.48	6.47	2.736	210	13.0	198/150	1.00
16.43	II	9.0	8.01	2.96	5.05	3.545	210	16.9	198/160	1.09
	III	7.0	4.62	1.24	3.38	1.982	132	15.0	162/121	0.70
	IV	20.9	15.56	6.66	8.90	2.787	156	17.9	158/104	1.14
No. 21	I	20.9	18.45	12.07	6.38	4.420	198	22.3	198/119	0.86
21.18	II	9.0	7.30	3.08	4.22	4.739	186	25.5	192/126	0.80
	III	7.0	5.39	2.16	3.23	2.817	144	19.6	170/112	0.84
	IV	20.9	20.14	10.45	9.69	4.499	138	32.6	159/94	1.27
No. 23	I	20.9	16.59	9.16	7.43	3.836	180	21.3	162/110	1.20
17.64	II	9.0	7.43	3.16	4.27	2.904	172	16.9	162/120	1.05
	III	7.0	5.17	2.03	3.14	1.752	128	13.7	130/97	0.75
	IV	20.9	17.67	9.10	8.57	2.439	124	19.7	116/80	1.08
No. 24	I	20.9	22.07	9.63	12.44	2.018	177	11.4	172/132	2.77
20.25	II	9.0	8.66	3.10	5.56	1.637	156	10.5	163/126	1.19
	III	7.0	4.70	1.49	3.21	1.900	114	16.7	136/96	0.68
	IV	20.9	18.17	9.96	8.21	-	92	-	117/68	-
$\bar{x}$	I		17.68	9.87	7.81	3.040	190	16.0	182/129	1.35
	II		7.95	3.10	4.85	3.123	181	17.1	178/129	1.06
	III		5.69	1.80	3.89	1.927	131	14.7	152/110	0.94
	IV		18.31	8.48	9.83	2.870	128	20.9	139/86	1.48

Table 3 cont'd.

Animal No. O ₂ capacity (vol.%)	Position	F _I O ₂ (%)	C _a O ₂ (vol.%)	C _v O ₂ (vol.%)	(a-v) _O 2 Vol. %	Q̇ (L/min)	f (beats/min)	V _S (ml)	P _{sa} (mmHg)	V _A /Q̇
B. Time-control										
No. 31 20.80	I	20.9	19.93	12.99	6.94	5.461	188	29.0	194/132	1.20
	II	20.9	19.20	11.80	7.40	4.027	191	21.1	197/135	1.16
	III	20.9	18.32	9.84	8.48	4.611	198	23.3	185/131	1.38
	IV	20.9	17.04	8.80	8.24	4.357	196	22.2	190/137	1.59
No. 33 21.97	I	20.9	21.04	11.12	9.92	2.611	142	18.4	162/110	1.26
	II	20.9	20.91	9.30	11.61	3.600	148	24.3	164/113	1.47
	III	20.9	20.65	9.46	11.19	3.691	156	23.7	169/112	1.76
	IV	20.9	18.71	8.32	10.39	3.888	158	24.6	162/105	1.31
No. 34 24.90	I	20.9	22.37	11.37	11.00	3.091	148	20.9	183/120	1.73
	II	20.9	20.94	10.17	10.77	3.621	168	21.6	190/125	1.63
	III	20.9	20.61	9.90	10.71	3.333	176	18.9	187/124	1.67
	IV	20.9	20.14	8.92	11.22	3.556	184	19.3	186/124	1.81
No. 35 19.98	I	20.9	18.54	12.11	6.43	1.415	200	7.1	140/115	0.90
	II	20.9	19.29	7.49	11.80	1.983	196	10.1	129/75	1.84
	III	20.9	17.66	5.62	12.04	2.467	200	12.3	140/80	2.08
	IV	20.9	17.85	6.27	11.58	1.356	166	8.2	130/80	1.58
$\bar{x}$	I		20.47	11.90	8.57	3.145	170	18.9	170/119	1.27
	II		20.09	9.69	10.40	3.308	176	19.3	170/112	1.53
	III		19.31	8.71	10.61	3.526	183	19.6	170/112	1.72
	IV		18.44	8.08	10.36	3.289	176	18.6	167/112	1.57

Table 3 cont'd.

Animal No. O ₂ capacity (vol.%)	Period	F _I O ₂ (%)	C _a O ₂ (vol.%)	C _v O ₂ (vol.%)	(a-v)O ₂ Vol. %	Q̇ (L/min)	f (beats/min)	V _g (ml)	P _{sa} (mmHg)	V̇A/Q̇
Heat Series (n=9) A. Hypoxia										
No. 40 22.79	I	20.9	20.30	14.24	6.06	2.030	148	13.7	190/125	1.98
	II	9.0	17.52	11.32	6.20	3.290	160	20.6	194/130	11.13
No. 41 22.53	I	20.9	20.33	16.46	3.87	3.230	208	15.5	200/142	0.89
	II	9.0	10.86	5.37	5.49	3.100	196	15.8	206/128	6.88
No. 42 24.35	I	20.9	17.81	12.80	5.01	2.116	126	16.8	186/125	1.02
	II	7.0	10.04	4.96	5.08	4.488	234	19.2	192/122	6.16
	III	20.9	22.57	14.18	8.39	3.242	216	15.0	166/114	5.67
No. 43 25.04	I	20.9	18.32	13.42	4.90	2.143	144	14.9	168/120	0.70
	II	7.0	13.43	7.80	5.63	3.517	188	18.7	173/111	5.25
	III	20.9	25.50	17.82	7.68	2.786	204	13.7	163/108	7.21
No. 44 20.75	I	20.9	17.76	14.17	3.59	3.092	156	19.8	182/125	0.80
	II	7.0	6.92	3.02	3.90	3.128	172	18.2	150/94	4.57
	III	20.9	18.54	12.34	6.20	2.984	186	16.0	138/78	5.74
$\bar{X}$	I	20.9	18.90	14.22	4.69	2.522	156	16.1	185/127	1.08
	II	9.0 or 7.0	11.75	6.49	5.26	3.505	194	18.5	183/117	6.80
	III	20.9	22.20	14.78	7.42	3.004	202	14.9	156/100	6.21

Table 3 cont'd.

Animal No. O ₂ capacity (vol.%)	P _{O₂} arterial	F _I O ₂ (%)	C _a O ₂ (vol.%)	C _v O ₂ (vol.%)	(a-v)O ₂ Vol.%	$\dot{Q}$ (L/min)	f (beats/min)	V _s (ml)	$\bar{P}_{sa}$ (mmHg)	$\dot{V}_A/\dot{Q}$
B. Time-control										
No. 36 22.47	I	20.9	19.87	14.25	5.62	3.505	184	19.0	158/117	1.01
	II	20.9	20.46	13.20	7.26	2.713	240	11.3	150/100	2.35
	III	20.9	20.94	12.76	8.18	2.751	202	13.6	148/103	3.37
	IV	20.9	20.12	9.71	10.41	2.113	234	9.0	110/72	4.90
No. 37 19.80	I	20.9	16.72	12.59	4.13	2.881	200	14.4	170/134	0.85
	II	20.9	17.22	10.83	6.39	2.707	210	12.9	160/124	2.34
	III	20.9	18.27	11.97	6.30	2.825	192	14.7	152/115	4.32
	IV	20.9	18.29	12.20	6.09	2.742	186	14.7	158/116	4.12
No. 38 19.98	I	20.9	16.82	12.95	3.87	4.651	156	29.8	204/144	0.70
	II	20.9	17.03	10.07	6.96	2.543	144	17.7	213/151	2.46
	III	20.9	18.86	11.89	6.97	2.281	156	14.6	206/149	4.07
	IV	20.9	20.04	11.89	8.15	2.184	180	12.1	190/130	6.14
No. 39 20.24	I	20.9	18.72	14.49	4.23	3.901	144	27.1	164/110	0.97
	II	20.9	17.71	11.15	6.56	2.912	124	23.5	185/118	1.70
	III	20.9	18.56	12.39	6.17	3.209	148	21.7	152/100	2.22
	IV	20.9	18.29	13.41	4.88	4.057	188	21.6	146/92	1.89
$\bar{x}$	I	20.9	18.03	13.57	4.46	3.735	171	22.6	174/126	0.88
	II	20.9	18.11	11.31	6.79	2.719	180	16.4	177/123	2.21
	III	20.9	19.16	12.25	6.91	2.767	175	16.2	165/117	3.50
	IV	20.9	19.19	11.80	7.38	2.774	197	14.4	151/103	4.26

Abbreviations: F_IO₂, C_aO₂, C_vO₂, (a-v)O₂, $\dot{Q}$, f, V_s, $\bar{P}_{sa}$, and $\dot{V}_A/\dot{Q}$ represent inspiratory O₂ fraction, arterial O₂ content, mixed venous O₂ content, arteriovenous O₂ difference, cardiac output, heart rate, stroke volume, systemic arterial pressure and ventilation-perfusion ratio, respectively.

environment by the partial rebreathing technique as described in the section on Methods. Should the reduction of P_{CO_2} be the sole mechanism of suppression of shivering during hypoxia, then the maintenance of P_{CO_2} at or near the control level would prevent such a suppression of shivering.

The data on the rebreathing series are summarized in Table 4. Comparison of these data with those presented in Table 2 (cold series with hypoxia) shows that at the end of the second period of the experiment (i. e. 80th minute) the mean alveolar P_{CO_2} are 38.5 mm Hg in the rebreathing series and 31.6 mm Hg in the cold series, the difference in P_{CO_2} being almost 7 mm Hg. Under these circumstances, in confirmation of our hypothesis, the intensity of shivering in two series shows a considerable difference as reflected in the O_2 consumption. In the rebreathing series the initial level of O_2 consumption is 210 ml/min and it rises to 253 ml/min under either 9% or 7% O_2 (Table 4). On the other hand the O_2 consumption is reduced from the initial level of 227 ml/min to 147 ml/min in the cold series under 9% O_2 (Table 2). In the statistical analysis, the difference in O_2 consumption during the first period (35th minute) and the second period (80th minute) in the cold series and the rebreathing series is compared in groups as shown in Table 5. It is clear statistically that there is a significant difference in O_2 consumption between the rebreathing series (C) and the cold series (hypoxia) (B), while the difference between the rebreathing series (C) and the cold series (time-control) (A) is not determinable.

Although it is now established that the hypocapnia is definitely a factor in suppression of shivering, further analysis of Table 4 and other related data suggest that the suppression of shivering in hypoxia cannot be attributed solely to the hypocapnia. The evidence for the latter conclusion is exemplified in the shivering responses seen in animals No. 47 and No. 48 (Table 4) under transitions from hypoxia (9%) to the air and back to hypoxia (7%). If the hypocapnia were the sole mechanism of suppression of shivering, then the intensity of shivering as reflected in the O_2 consumption in the rebreathing series should be maintained at a high level, as it is in the cold series with room-air breathing. As shown in Table 4, it is not the case in both animals because the return to the air from 9% O_2 tends to increase O_2 consumption and, conversely, the imposition of 7% O_2 is followed by a moderate reduction of O_2 consumption.

The partially restored shivering during the rebreathing series is also observed in the electromyograms taken during the shivering. Figure 6 illustrates the pattern of muscle potentials under three different conditions; namely, the cold series (control), the rebreathing series and the cold series (hypoxia). It may be seen that in the cold series (control) the intensity of muscle potentials is consistently large while in the cold series (hypoxia) it is gradually suppressed, and that the muscle potentials are only partially restored in the rebreathing series. In Figure 6 the tracing A represents the

Table 4. Partial-rebreathing series (cold environment)

Animal No. and Wt. (kg)	Period	F _{IO2} (%)	$\dot{V}_E$ (L/min) BTPS	f (breaths /min)	V _T (ml) BTPS	$\dot{V}_{O_2}$ (ml/min) STPD	$\dot{V}_{CO_2}$ (ml/min) STPD	RER	pH	(CO ₂) _P (mM/L)	P _{aCO2} (mmHg)	T _C (°C)	T _S (°C)
No. 47 14.5	I	20.9	10.315	56.0	184	223	174	0.78	7.288	19.62	39.7	36.4	25.7
	II	9.0	25.303	75.0	337	319	234	0.73	7.333	18.06	33.1	35.2	24.0
	III	20.9	22.358	69.0	324	495	450	0.91	7.248	17.78	39.3	34.2	23.2
	IV	7.0	26.102	72.0	363	249	77	0.31	7.272	19.65	41.2	33.2	21.8
No. 48 14.5	I	20.9	10.671	36.5	292	284	241	0.85	7.365	21.58	37.0	37.0	25.4
	II	9.0	26.630	61.0	437	324	118	0.36	7.385	21.08	34.5	35.1	24.1
	III	20.9	12.236	36.0	340	353	272	0.77	7.338	20.32	36.9	35.0	23.7
	IV	7.0	26.976	61.0	442	208	121	0.58	7.306	21.55	41.9	33.5	21.0
No. 49 13.6	I	20.9	7.739	41.0	189	185	133	0.72	7.297	21.80	43.3	33.5	25.7
	II	9.0	12.253	46.0	266	154	105	0.68	7.311	20.95	40.4	30.5	24.7
No. 51 12.5	I	20.9	5.057	18.0	281	148	108	0.73	7.286	21.64	44.0	34.0	29.9
	II	7.0	20.964	39.0	538	216	135	0.63	7.253	20.97	45.8	30.8	27.8
$\bar{x}$	I	20.9	8.445	37.9	237	210	164	0.77	7.309	21.16	41.0	35.2	26.7
	II	9.0 or 7.0	21.287	55.3	395	253	148	0.60	7.321	20.27	38.5	32.9	25.2

Table 5. A Statistical Analysis (O₂ consumption in the cold series and the rebreathing series)

A		B		C	
Cold Series (time-control)		Cold Series (hypoxia)		Re-breathing Series	
Animal No.	$\dot{V}O_2$ (ml)	Animal No.	$\dot{V}O_2$ (ml)	Animal No.	$\dot{V}O_2$ (ml)
31	-81	18	+4	47	+96
33	+159	20	+2	48	+40
34	+50	21	-82	49	-31
35	+143	23	-161	51	+68
		24	-160		
$\Sigma X^2 = 54,791$ $\bar{X} = +68$ $\frac{(\Sigma X)^2}{n} = 18,360$		$\Sigma X^2 = 58,265$ $\bar{X} = -79$ $\frac{(\Sigma X)^2}{n} = 31,522$		$\Sigma X^2 = 16,401$ $\bar{X} = +43$ $\frac{(\Sigma X)^2}{n} = 7,482$	
		B vs C ---- t = 2.60*		d.f. = 7 0.01 < p < 0.05	
		A vs C ---- t = 0.42		d.f. = 6 0.5 < p	

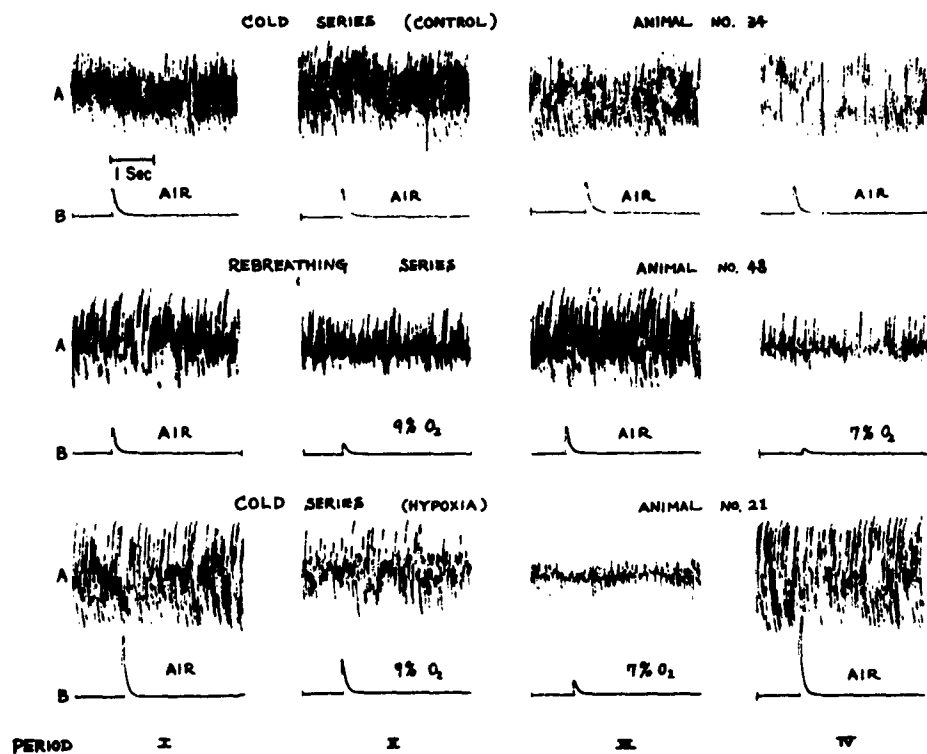


FIGURE 6. Effect of CO₂ on shivering

actual muscle potentials and the tracing B represents the integral potential (10 second). Strictly speaking, the amplitude of tracings between different animals are not comparable because the sensitivity of the amplifier is not always the same among the animals.

In an attempt to elucidate further the effect of CO_2 on shivering, a study is made in which the animal is given CO_2 mixture and/or is hyperventilated artificially by a respirator in the cold environment (CO_2 series). The breathing of CO_2 mixture (6.0% to 6.5% CO_2 in the air) elevates the alveolar PCO_2 while the artificial hyperventilation lowers it. Under these conditions, if there is a correlation between the intensity of shivering and PCO_2 , it will serve as an added evidence for arguing a close relationship between the two.

The data on four animals of CO_2 series are summarized in Table 6. The CO_2 inhalation which raises the alveolar PCO_2 to 48 to 55 mm Hg does not always facilitate the shivering as reflected in the O_2 consumption. In fact, the O_2 consumption is reduced in two animals (No. 52 and No. 55) following 15 minutes of CO_2 inhalation while it is elevated in the remaining two animals (No. 53 and No. 54). Likewise, the hypocapnia produced by the artificial hyperventilation does not show any definitive pattern of influence on shivering. In both animal No. 54 and No. 55 the alveolar PCO_2 is lowered to 18 mm Hg, yet in No. 54 the shivering is suppressed while in No. 55 it is facilitated as shown in the O_2 consumption. It is apparent from the above data that further study is needed in the future to clarify the role of CO_2 on shivering.

Facilitation of Thermal Panting. Although shivering (heat conservation mechanism) is suppressed by hypoxia to a marked degree, the similar suppressor action of hypoxia does not apply in the case of thermal panting (heat dissipation mechanism). As shown in the data on the heat series (Table 2), hypoxia facilitates thermal panting despite the accompanying hypocapnia. After 80 minutes in the warm environment (period II), the hypoxia group has an average total ventilation of 49.112 L/min, whereas in the control group it reaches an average of 35.155 L/min. A statistical evaluation reveals a highly significant difference in total ventilation between the two groups ($t=5.43$, d.f.=7, $p<0.001$). It is also obvious from the data that there is a definite difference in the respiratory pattern between the two groups; namely, in the hypoxia group the respiration is deep and its rate does not exceed 150/min, while in the control group breathing is shallow and more rapid. The facilitation of thermal panting is further indicated in other respiratory parameters. In the hypoxia group the respiratory exchange ratio and pH are higher, and the alveolar PCO_2 is lower than the control group. However, there is no significant difference between the two groups in core temperature during equivalent periods.

Table 6. CO₂ series (cold environment)

Animal No. and Wt. (kg)	Breathing	Time (min)	$\dot{V}_E$ (L/min) BTPS	f (breaths /min)	V _T (ml) BTPS	$\dot{V}_{O_2}$ (ml/min) STPD	pH	(CO ₂) _P (mM/L)	P _{CO₂} (mmHg)
No. 52 15.9	Spontaneous CO ₂ inhalation Respirator	20	10.522	53	199	256	7.339	20.94	37.9
		15	17.594	72	244	206	7.218	23.35	54.9
		42	40.418	64	632	240	7.376	21.12	35.3
No. 53 19.0	Spontaneous CO ₂ inhalation	25	7.479	18	416	112	7.310	19.05	36.8
		9	14.828	23	645	184	7.160	20.32	54.0
No. 54 15.0	Spontaneous CO ₂ inhalation Respirator	30	14.857	74	201	324	7.351	19.82	26.2
		11	32.296	86	376	567	7.239	21.31	48.0
		21	30.772	56	550	289	7.493	14.09	18.2
No. 55 27.2	Spontaneous Respirator CO ₂ inhalation	23	13.582	25	543	472	7.391	23.38	37.5
		20	48.242	64	754	587	7.562	16.41	18.1
		15	38.910	52	748	388	7.274	23.43	48.7

Note: CO₂ mixture contains 6.0 - 6.5% CO₂ in air

Cardiorespiratory Functions

Respiration. The ventilatory response to hypoxia in three different environmental temperatures is summarized in Table 2. In the neutral environment, hypoxia increases the total ventilation from its initial level of 3.334 L/min (room-air breathing) to 8.738 L/min, 10.976 L/min, and 12.438 L/min with 9%, 7% and 5% O₂, respectively (160%, 230% and 270% increases over the control value). These increases are brought about primarily by an increased respiratory rate and a secondary elevation of the tidal volume. Interestingly enough, there is no significant difference in O₂ consumption at all three levels of hypoxia. Thus, the ventilatory equivalent for O₂ is raised and the respiratory exchange ratio tends to be increased. The alveolar P_{CO₂} shows a marked reduction along with the depletion of plasma CO₂ content. The arterial pH is shifted from 7.3 to approximately 7.5 at the end of the experiment. Although the alveolar ventilation, as reflected in the CO₂ clearance, is also increased, its rate of increase is not enough to maintain the same rate of increase in total ventilation. Therefore, the ratio of alveolar to total ventilation is invariably reduced at all three levels of hypoxia.

The respiratory response to hypoxia in the cold and in the heat are of a somewhat different nature from that in the neutral environment. In the cold the total ventilation is almost the same under 9% O₂ as under room-air breathing, while it is decisively depressed under 7% O₂. There is also a progressive reduction of metabolic rate due to the suppression of shivering. Contrary to these findings, the total ventilation is enhanced to a marked degree in the warm environment. This is achieved by an altered respiratory pattern of a deep and slower type of breathing. In consequence, the alveolar ventilation is greatly improved and the ratio of the alveolar to total ventilation is elevated. The ventilatory response to the combined stresses of heat and hypoxia is of a considerable magnitude, suggesting a maximal mobilization of the respiratory apparatus. The five animals having an average body weight of 13.6 kg revealed a mean total ventilation of 49 L/min after having been given 9% or 7% O₂. This is approximately 3.6 L/min of ventilation per kg of body weight. In a normal man of an average body weight of 75 kg, the maximum breathing capacity is approximately 170 L/min, which has the ratio of 2.2 L/min of ventilation per kg of body weight. Since the maximum breathing capacity is known to be the largest amount of ventilatory response attainable, the greater magnitude of respiratory response observed under the combined stresses of heat and hypoxia deserves attention in future investigation.

The Lethal Level of Hypoxia. At the end of the experiment the O₂ supply to the animal is shut off completely to determine the level of hypoxia at which the animal's respiration ceases. The terminal O₂ fraction of the inspiratory gas, which is read from the O₂ analyzer, is summarized in Table 7.

Table 7. Lethal threshold of hypoxia

Neutral Series				Cold Series				Heat Series			
Hypoxia		Control		Hypoxia		Control		Hypoxia		Control	
Animal No.	FI _{O2}	Animal No.	FI _{O2}	Animal No.	FI _{O2}	Animal No.	FI _{O2}	Animal No.	FI _{O2}	Animal No.	FI _{O2}
No. 3	3.7	No. 25	4.1	No. 18	2.4	No. 31	2.4	No. 42	6.1	No. 36	7.3
No. 5	3.5	No. 26	3.2	No. 20	2.7	No. 33	2.8	No. 43	3.9	No. 37	4.5
No. 6	2.8	No. 27	2.8	No. 21	2.0	No. 34	3.9	No. 44	4.8	No. 38	3.9
No. 7	5.3	No. 28	3.4	No. 23	3.3	No. 35	4.0			No. 39	4.7
No. 8	3.2	No. 29	2.5	No. 24	5.2						
No. 10	3.8	No. 30	4.9								
No. 12	3.0										
No. 13	4.9										
No. 14	2.5										
No. 15	2.4										
No. 16	2.4										
$\bar{x}$	3.4		3.5		3.1		3.3		4.9		5.1

Although there is a considerable difference in the lethal threshold among animals even in the same series, it is apparent that the average lethal hypoxic level in the lightly anesthetized dogs is at the vicinity of 3 per cent of the inspiratory O₂ fraction. This corresponds to approximately 20 mm Hg of the O₂ tension. (The elevation of Albuquerque, New Mexico = 5,300 ft. The average barometric pressure = 630 mm Hg.)

It is also apparent from the table that there is no significant difference in the lethal threshold between the neutral and cold series. However, it is indicated that the animals of the heat series succumb to hypoxia at a higher level of inspiratory O₂, which is approximately 5% of O₂ (PO₂ = 32 mm Hg), suggesting the lowered tolerance to hypoxia under the heat stress.

Hemodynamics. The results on the cardiac output, the systemic arterial blood pressure and other related cardiovascular measurements in each animal are shown in detail in Table 3. The cardiac output during the first period (room-air breathing) of the neutral group (hypoxia series) averaged 2.643 L/min in 11 animals. It was 2.972 L/min, 2.655 L/min and 3.420 L/min following 9%, 7% and 5% O₂ and these values represent approximately 12%, 0.5% and 29% increases over the value observed during the first period, respectively. Due to the relatively large variation observed among individual measurements, the statistical analysis of the cardiac output revealed no significant difference between each period. The results in the cold series under hypoxia show a similar result except for the third period (7% O₂) where the cardiac output is markedly reduced. This reduction is apparently due to the animal's inability to tolerate this level of hypoxia in the cold environment. Note also that not only the cardiac output but also the O₂ consumption and pulmonary ventilation are markedly depressed during the same period in the cold series (see Table 2). Contrary to the findings in the neutral and cold series, the cardiac output showed a marked elevation in the heat series under hypoxia. The control value in this series during the first period (room-air breathing) was 2.522 L/min and it was significantly increased to 3.505 L/min (39% increase) at 9% or 7% O₂ level ($t=2.67$, d.f. =8, $0.02 < p < 0.05$). Obviously the return to the air following hypoxia brought the cardiac output back close to the control level.

The alterations in the heart rate and the stroke volume indicate that the heart rate is significantly increased under 9% and 7% O₂ while it returns to the control level at 5% O₂. The concomitant changes in the stroke volume are the reductions under 9% and 7% O₂ and no change under 5% O₂. Such opposite trends between cardiac frequency and amplitude tend to maintain the cardiac output relatively constant throughout the hypoxia periods in the neutral series. However this does not apply in the cold or heat series as shown in Table 3. In the cold series the heart rate tends to decrease at 9% O₂ while the stroke volume tends to increase. At 7% O₂ the heart rate is

markedly depressed along with the stroke volume. In the heat series both the heart rate and the stroke volume show a tendency to increase.

The systemic arterial pressure in the neutral series under hypoxia shows a diphasic alteration. Under 9% O₂ it is increased mildly only to return to the control level at 7% O₂, and then under 5% O₂ it is decreased below the control level. The pulse pressure remains almost the same throughout all the levels of hypoxia. In the cold with hypoxia there is a progressive reduction of both systolic and diastolic pressures with other signs of generalized depression. The blood pressure remains relatively constant in the heat series under hypoxia except at the third period where the blood pressure tends to fall at the core temperature above 43° C.

In the neutral series the arteriovenous O₂ difference remains remarkably unchanged under hypoxia until the inspiratory O₂ fraction reaches 5 per cent where it is reduced to 2.8 vol. % on the average. One of the interesting observations in relation to the arteriovenous O₂ difference is that the shivering activity extracts a large amount of O₂ from the muscles causing a marked reduction of the O₂ content of the mixed venous blood. This fact is reflected in the large increase of the arteriovenous O₂ difference in the control groups of the neutral and cold series. In the latter groups it reaches almost 10 vol. % of O₂.

As a rough estimate of the pulmonary ventilation and blood flow, a ratio of the alveolar ventilation and the cardiac output ($\dot{V}_A/\dot{Q}$) is estimated. As shown in Table 3, this ratio ranges from 1.4 to 2.0 in the control group of the neutral series. Under the hypoxia of 9%, 7% and 5% O₂, the ratio is maintained at a mean value of 1.2 to 1.6. On the other hand, the ratio tends to fall in the cold series whereas it is markedly elevated to 6.8 in the heat series under hypoxia.

SECTION 5. DISCUSSION

Our finding of marked reductions of both central and peripheral temperatures under hypoxia in the cold confirms numerous observations made by others in the past. The principal cause of such reduction is the suppression of heat conservation mechanism (shivering) by hypoxia rather than the facilitation of heat loss mechanism (vasodilatation). As a matter of fact, the patterns of temperature drop of the central and peripheral areas are almost identical (see Figure 2), indicating no unusual involvement of vasomotor activities under hypoxia. The elevation of peripheral temperature (facilitation of heat loss mechanism) during hypoxia as observed by Kottke et al (1948) in man and in animals could not be confirmed in the present investigation.

Although the suppression of shivering in hypoxia has been repeatedly observed by others, the mechanism of this suppression has never been clearly elucidated. As demonstrated in the rebreathing series of this study, the hypocapnia produced by the hyperventilation under hypoxia appears to be one of the suppressive mechanisms. Such a close relationship between shivering and respiration strongly suggests that either the efferent pathways of shivering, originating from the hypothalamus, pass through the respiratory centers in the medulla or there are intimate neural connections between the respiratory centers and the efferent pathways of shivering.

A further attempt to establish a relationship between the intensity of shivering and inspiratory CO₂ level was unsuccessful, as shown in the CO₂ series of this investigation. A review of literature in this regard reveals conflicting results among different authors. Hensel (1949) has reported a facilitation of shivering by inhibition of 3% CO₂ in the air in three normal subjects. The experiment was conducted in a weather chamber whose temperature was kept at 10° C. The duration of CO₂ inhalation was short, lasting for one minute in most cases. Within 10 to 15 seconds of CO₂ inhalation, shivering became vigorous as registered on an electromyograph. When the subject was returned to air breathing, the intensity of shivering diminished. Contrary to these data, von Euler and Soderberg (1958) have observed the inhibition of shivering in the anesthetized cat during spontaneous breathing or artificial respiration when 6.5% of CO₂ in O₂ was given. Similarly, Miller et al (1955) have reported the inhibition of shivering during inhalation of 1% to 5% CO₂ with an increased feeling of warmth in man. Further investigation in the future along this line is definitely warranted to clarify the relationship between shivering and respiration.

The facilitation of thermal panting (heat loss mechanism) under hypoxia is certainly an interesting phenomenon particularly in view of the opposite effect of hypoxia on shivering (heat conservation mechanism). In good agreement with our findings, McCutchan and Taylor (1954) reported facilitation of sweating under hypoxia in man. In a pressure chamber where air temperature was maintained at 60° C with a vapor pressure of 21 to 23 mm Hg, four healthy subjects were tested for the effect of altitude on body temperature, perspiration and heart rate. At the chamber pressures of 568 mm Hg (equivalent to 8,000 feet) and 379 mm Hg (equivalent to 18,000 feet) the perspiration rates rose from 293 gm/m²/hr of control value (sea level) to 328 gm/m²/hr, respectively.

For the interpretation of our data it is necessary to review briefly the anatomical relationship between the neural components for thermoregulation and respiration. For all practical purposes it may be stated that the heat dissipation center is located at the anterior hypothalamus and that the heat conservation center is at the posterior hypothalamus. These thermoregulatory centers have a connection, at least functionally as it is observed in our

experiment, with the respiratory centers in the medulla oblongata where the predominant stimulus is the blood CO_2 level. On the other hand, the hypoxic drive originates from the carotid and aortic bodies and is linked reflexly with the medullary respiratory centers. The physiological response we observed is the result of interplay between the hypothalamus, the medulla and the chemoreceptors in the thorax. Our findings and the data in the literature suggest that the heat conservation mechanism and the heat dissipation mechanism are influenced by hypoxia in a different manner. The former (shivering) is suppressed while the latter (thermal panting or sweating) is facilitated. One of the interpretations of such physiological response is that the efferent potentials from the heat dissipation center (anterior hypothalamus) is powerful enough to overcome the inhibitory effect of hypocapnia at the medulla and is further potentiated by the reflex drive of hypoxia from the carotid and aortic bodies. Contrary to this, the efferent potentials from the heat conservation center (posterior hypothalamus) are not strong enough to overcome the inhibitory effect of hypocapnia. Interestingly enough, such a postulate of differentiation of efferent central drives of heat gain and heat loss mechanisms is in good conformity with our previous observation, in which the predominance of central mechanism over the peripheral mechanism in thermal panting and the reverse relationship in shivering are demonstrated (Lim, 1960).

The O_2 uptake during hypoxia has been reported variously in the past. Some believe that it is somewhat augmented; others feel that there is no alteration; while still others consider that it is mildly reduced. There are two factors which must be taken into account in the evaluation of O_2 consumption in hypoxia — the alteration of body temperature and the duration of hypoxia. Under hypoxia the body temperature tends to fall in the anesthetized animals, even in the ordinary neutral environment, reducing the metabolic rate. Secondly, there is a temporary reduction of O_2 uptake for about 10 to 20 minutes immediately following exposure to hypoxia. This is due to the reduction of total oxyhemoglobin and tissue oxygen level to a new level, which serves as a temporary oxygen source thus reducing the O_2 uptake from the lungs.

According to Hemingway and Nahas (1952) the O_2 consumption fell early in the hypoxic period (8% to 16% O_2 in N_2 for one hour) but rose to above prehypoxic values later in the period in four unanesthetized trained dogs in both cold (12°C) and warm (24°C) environments. The rectal temperature fell almost at the same rate in both environments for breathing mixtures of 20.9%, 16% and 8% O_2 . Pichotka et al (1955) reported a reduction of O_2 consumption under hypoxia (8% O_2 for 100 minutes) below prehypoxic level in guinea pigs, with a fall of rectal temperature to a vicinity of 34° to 35°C . Similarly, Cross and his associates (1955) observed a reduction of O_2 consumption in new-born infants in response to hypoxia. Stroud and Rahn (1953) reported practically no change in O_2 consumption before and after hypoxia

(109 ml/min vs. 114 ml/min) (8% O₂ in N₂ for 10 to 15 minutes) in 16 nembutalized dogs. No account of the body temperature was given in the paper. Lewis and Gorlin (1952) observed increased O₂ consumption in nine anesthetized dogs (Morphine-Urethane-Chloralose) breathing 10% O₂ for 4 minutes to 8 hours. Again, nothing is mentioned about the alteration of the body temperature.

Our observation on O₂ consumption during hypoxia in the neutral series showed no marked change, with a gradual reduction of core temperature from 37.5° to 35.0° C (Table 2). Therefore, it is possible that if the body temperature were maintained constant, the O₂ consumption in hypoxia might have been significantly higher than the prehypoxic level. In this connection it is interesting to note Pugh's contention that adult homeotherms tend to increase their O₂ consumption in hypoxia, presumably because of the extra metabolism involved in the greater respiratory effort engendered by chemoreceptor stimulation (Pugh, 1957). One more point regarding the respiratory gas exchange in hypoxia is that CO₂ output during hypoxia may not return to normal for 30 to 40 minutes, as observed in man by Rahn and Otis (1947). Apparently it is also the case in our experiment, because the respiratory exchange ratio (RER) is significantly elevated in the neutral series at less than 5% level throughout the period of 9%, 7% and 5% O₂ inhalation.

The authors are unable to locate the literature concerning the effect of hypoxia on the alveolar and dead space ventilation. As demonstrated in this study (see Table 2), there is a consistent pattern of relationship between the alveolar and total ventilation in hypoxia. In the neutral environment hypoxia causes increases in both alveolar and total ventilation, but the ratios of increase in each measurement are not the same: the rate of increase in the alveolar ventilation is much slower than that of the total ventilation, indicating an increased dead space ventilation. Thus, the ratio between the alveolar to total ventilation is below 40 per cent in hypoxia while it is above 50 per cent in the control. When the physiological dead space is computed it also shows an increase from 94 ml (air) to 142 ml (5% O₂) on the average. The mechanism of increase of physiological dead space in hypoxia is probably due to the altered relationship of ventilation-perfusion. As shown in Table 3, the cardiac output remains virtually constant during hypoxia as compared to the normal level while the alveolar ventilation is increased. It appears that the lungs are over-ventilated and normally perfused during hypoxia.

There is a large amount of literature (Korner, 1959; Fishman, 1961) concerning the effect of hypoxia on hemodynamics. A critical review of these papers reveals that: (1) Cardiac output is unchanged or increased only slightly, if at all; (2) in most cases the heart rate is increased; (3) the stroke volume is either slightly reduced, unchanged or very mildly increased; and (4) the systemic arterial blood pressure tends to increase. Our data do not

show any statistically significant change in the cardiac output before and during hypoxia in all levels of hypoxia, i. e. 9%, 7% and 5% O₂, although numerically there is a trend of gradual increase up to approximately 30 per cent. However, due to the large variations inherent in the estimation of the cardiac output, the alterations less than 30 per cent cannot be stated as significant with certainty.

When the level of hypoxia is expressed as the percentage of O₂ in the blood, the control level of the arterial O₂ saturation ranges from 81% to 94% in all the series involved in our study. Such a mild reduction in the arterial O₂ saturation is almost unavoidable when the animal is anesthetized at the surgical stage. Upon imposition of hypoxia with 9%, 7% and 5% O₂, the corresponding O₂ saturation was reduced to 45%, 37% and 25%, respectively, in the systemic artery and to 26%, 17% and 11%, respectively, in the mixed venous blood.

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