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Effect of exposure to compressed air and elevated oxygen levels on bone blood flow in the rabbit

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Davis TRC, Holloway IT, Pooley J. Effect of exposure to compressed air and elevated oxygen levels on bone blood flow in the rabbit. Undersea Biomed Res 1990; 17(3):201–211.—As the pathogenesis of dysbaric osteonecrosis is not fully understood, we investigated the effects of compressed air, decompression, and elevated oxygen levels on bone blood flow. Bone blood flow was measured in 4 groups of rabbits using the radioactive-labeled microsphere technique. In the Control and Oxygen groups it was measured at normal pressure (1 ATA) at the end of 4-h exposures to air and 100% oxygen, respectively. In the Pressure group it was measured "at pressure" at the end of a 4-h exposure to compressed air (3 ATA) and in the Decompression group it was measured after decompression following a 3.5-h exposure to compressed air (3 ATA). Femoral head blood flow was significantly lower ($P = 0.027$) in both the Pressure (7.5 ml · 100 g^{-1} · min^{-1}) and Decompression (7.1 ml · 100 g^{-1} · min^{-1}) groups than in the Control group (13.0 ml · 100 g^{-1} · min^{-1}). Moreover, the distribution of blood flow between the cortex and marrow of the humerus differed significantly ($P = 0.044$) between the Control and Pressure groups. No differences were found between the bone blood flow rates of the Control and Oxygen groups. It is concluded that femoral head blood flow is reduced by prolonged exposure to compressed air (without decompression) and that this is not solely an effect of the high partial pressure of oxygen.

dysbaric osteonecrosis
oxygen
bone blood flow
hyperbaric exposures

Dysbaric osteonecrosis is a type of avascular necrosis of bone and, as such, is caused by ischemia and subsequent infarction of bone (1). The disruption of bone blood flow is generally thought to occur as a result of nitrogen bubble formation during the decompression phase of a dive (2). The results of 2 animal experiments lend support to this hypothesis: rapid decompression reduces canine femoral head blood flow (3) and minipig femoral bone blood flow is reduced during safe decompressions (4).

However, two studies that measured bone blood flow "at pressure" (before decompression) have observed reductions in minipig (4) and rabbit (5) bone blood flow during 6- and 4-h exposures to compressed air (3 ATA): it is therefore possible that prolonged exposure to compressed air (without decompression) reduces bone blood

flow. It is suggested that these at pressure reductions in bone blood flow are due to oxygen toxicity which generates an intraosseous compartment syndrome (5). The proposed mechanism is that high oxygen tensions are toxic to bone marrow fat cells and cause them to swell. Within the fixed volume of the marrow cavity, fat cell swelling would cause an increase in intraosseous pressure. If this exceeded venous pressure, then bone blood flow would decrease and bone infarction could occur. This theory has similarities to theories regarding the pathogenesis of alcohol and steroid-induced osteonecrosis (6). However, although high partial pressures of oxygen may cause swelling of extra- and intramedullary fat cells (4, 7), the development of an intraosseous compartment syndrome has never been demonstrated.

The at pressure reductions in bone blood flow (4, 5) may not have been caused by a specific intraosseous mechanism. High partial pressures of oxygen cause arterial vasoconstriction (8) and reduce cerebral (9), coronary (10), and renal (11) blood flow. Studies in the rat suggest that at pressure reductions in organ blood flow are predominantly caused by the increased oxygen tension, although increased ambient pressure may also have an effect (12).

We investigated the effects of oxygen, compressed air, and decompression on the blood flow of bone and other organs of the rabbit. The aims of this study were:

1. To confirm that both prolonged exposure to compressed air and decompression reduce bone blood flow.
2. To investigate whether exposure to pure oxygen at atmospheric pressure reduces bone blood flow.
3. To observe whether changes in bone blood flow are accompanied by changes in the blood flows of other organs. If this were the case, it would suggest that the reduction in bone blood flow was the result of a nonspecific systemic mechanism.

METHODS AND MATERIALS

Adult female rabbits, aged 1.5–3 yr, with fused epiphyses and weighing between 4 and 5 kg were used in this study. Due to a shortage of such rabbits, three breeds (Californian, Half-lop, and New Zealand White) were used. The rabbits were allocated to a Control group, a Pressure group, a Decompression group, and an Oxygen group.

Each rabbit was sedated with an intramuscular injection of fentanyl citrate (0.1125 $mg \cdot kg^{-1}$) and fluanisone (3 $mg \cdot kg^{-1}$) before its neck was shaved. The rabbits of the Oxygen group were placed in a small oxygen chamber. Those of the other 3 groups were put in transportation boxes and placed in the compression chamber. As this chamber had a pressure lock it was possible for personnel to enter it and prepare the rabbits for bone blood flow measurement without altering the chamber pressure.

The 4 groups of rabbits were subjected to different atmospheric conditions. The Control group breathed air at atmospheric pressure throughout the 4-h experiment while the Oxygen group breathed 100% oxygen at atmospheric pressure for 4 h. The Pressure group breathed compressed air at a pressure of 3 ATA (20 msw) for 4 h. The Decompression group was exposed to compressed air at 3 ATA (20 msw) for 3 h and 35 min and was then decompressed back to atmospheric pressure with 5-min stops at pressures of 6 and 3 msw: for the final 10 min of the experiment these rabbits breathed air at atmospheric pressure. The duration of the hyperbaric exposures of

the Pressure and Decompression groups was calculated, using respiratory exchange values (13, 14) to allow saturation of each rabbit.

One hour before the end of the 4-h experiment each rabbit was premedicated with an i.m. injection of fentanyl citrate (0.1125 mg · kg^{-1}) and fluanisone (3 mg · kg^{-1}). Twenty minutes later the marginal vein of the ear was cannulated and each rabbit was anesthetized (i.v. midazolam 2 mg · kg^{-1}). Anesthesia was then maintained by a constant i.v. infusion of fentanyl citrate (0.0375 mg · kg^{-1} · h^{-1}) and fluanisone (1 mg · kg^{-1} · h^{-1}). To premedicate the rabbits of the Oxygen group it was necessary to remove them from the oxygen chamber for a few seconds. After premedication they were returned to the oxygen chamber; 20 min later each rabbit was finally removed from the oxygen chamber and anesthetized. After induction of anesthesia, which took less than 2 min, these rabbits breathed 100% oxygen through a face mask until a tracheostomy had been created.

Each rabbit was laid supine on the operating table (for the Control, Pressure, and Decompression groups this was in the compression chamber) and an anterior midline neck incision was made. The platysma and subcutaneous fat were retracted, and the trachea and left carotid artery were exposed. A tracheostomy was performed and maintained with an endotracheal tube (Portex 3fg). Each rabbit was artificially ventilated (intermittent positive pressure ventilation) by a pediatric ventilator (J.F. Earley, Sheffield; settings: inspiratory time = 0.5 sec, expiratory time = 1 sec, flow rate in all groups = 5 liters · min^{-1}). The Oxygen group was ventilated with 100% oxygen, the Control group with air at atmospheric pressure, and the Pressure group with compressed air (3 ATA). The Decompression group was ventilated with air, which was maintained at a pressure equal to the compression chamber pressure throughout the experiment. Two arterial cannulae (Portex o.d. 1.02 mm) were then placed in the left carotid artery (15). The proximal cannula was passed in a retrograde direction into the aortic arch. The distal cannula was passed in an orthograde direction toward the circle of Willis, which is complete in the rabbit. Both cannulae were flushed through with 1 · 100 IU^{-1} heparin solution, and blood pressure was then monitored through the proximal cannula. These surgical procedures could be performed within 20–30 min, and blood flow was measured 40 min after the induction of anesthesia.

The radioactively labeled microsphere technique was used to measure bone and organ blood flow. Radioactively labeled 15-μm NENTRAC microspheres (New England Nuclear, Southampton) were used because they can be injected in sufficient numbers to measure regional bone blood flow (15–18) and have nonentrapment rates of less than 15% in the rabbit systemic circulation (16) and less than 1% in bone (19).

Just before injection of the microspheres, the tip of the proximal cannula was introduced into the left ventricle of the heart and its position was confirmed by observing the blood pressure trace. The distal cannula was then connected to the reference organ (modified syringe driver MS16A: Graseby Medical, Watford.); this is a constant withdrawal pump which withdraws blood from the distal cannula at a known constant rate (2.5 ml · min^{-1}). Using a stopwatch to control the timing of events, the reference organ was switched on. After it had run for 30 sec, approximately 1 million 15-μm-diameter, ^{153}Gd-labeled microspheres, which were suspended in 5 ml of normal saline, were injected into the left ventricle over a period of 60 sec. The central cannula was flushed through with 5 ml of normal saline in the subsequent 60 sec, and the reference organ was switched off after a further 60 sec had elapsed (total running time = 3.5 min). Great care was taken to prevent any air being

introduced into the circulation either during the insertion of the cannulae or the injection of the microspheres. It should be stressed that in the Pressure group the microspheres were injected while the rabbits were still at pressure (3 ATA).

After the microsphere injection, the central cannula was withdrawn from the left ventricle and the blood pressure was monitored for a few minutes. Each rabbit was then killed with an overdose of pentobarbitone sodium. The brain, heart, and kidneys and the femora, tibiae, humeri, scapulae, and innominate bones were removed and cleaned of attached tissues. Each sample and the reference organ were then weighed and their radioactivity in the principal photon energy of ^{153}Gd was measured. To measure regional bone blood flow the long bones were sectioned (Fig. 1) and, in all sections apart from the femoral and humeral heads, the cortical bone was separated from the marrow and trabecular bone. These regional bone samples were weighed and their radioactivity was measured. Blood flow was calculated using Eqs. *1* and *2* and then expressed as ml · 100^{-1} · min^{-1}. By measuring the radioactivity of special microsphere standards, which contained a known number of microspheres, the number of microspheres in each sample was calculated (Eq. *3*).

$$\text{Blood flow of sample} = \frac{\text{Radioactivity of sample} \times \text{Reference organ flow rate}}{\text{Radioactivity of ref organ}} \qquad (1)$$

$$\text{Reference organ flow rate} = \frac{\text{Wt of blood in reference organ}}{\text{Running time of ref organ} \times 1.05} \qquad (2)$$

(1.05 = specific gravity of blood)

$$\text{Microspheres in sample} = \frac{\text{Microspheres in standard} \times \text{Radioactivity of sample}}{\text{Radioactivity of standard}} \qquad (3)$$

Adequate mixing of the microspheres was confirmed by comparing the estimated blood flows of the right and left kidneys, cerebral hemispheres, and each whole bone

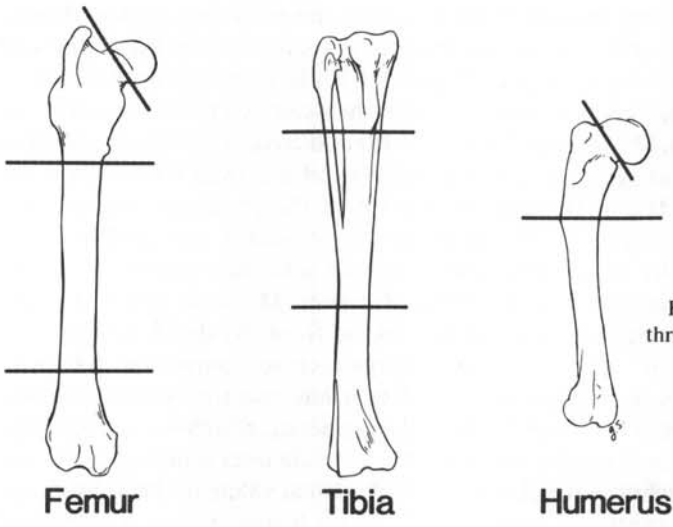

Fig 1. The lines of section of the three long bones.

(Table 1). All the soft tissue and whole bone samples contained more than 400 microspheres and each section of each long bone contained more than 100; 95% confidence levels for the estimates of blood flow are therefore at least 5% (20) and 10% (18), respectively.

To detect any relative changes between the blood flows of the bones and other organs, the ratios of renal, cerebral, and myocardial blood flows to the blood flow of each whole bone were calculated in each rabbit. Renal, myocardial, and cerebral blood flows were selected for comparison because all are reduced by exposure to high oxygen tensions (9–12).

Statistical analyses

As the blood flows of left and right paired organs of each rabbit are not independent variables, the flow rates of matching paired samples were averaged and the mean flow rates were used in the statistical analyses.

The statistical analyses were computed using SAS software (SAS Institute, North Carolina), which accommodates the use of unequal group sizes. The analysis of variance was used to detect significant differences between the 4 groups; the *P* values presented in this paper refer to this statistical test. If a significant difference was detected, Duncan's multiple range test was used to determine the minimum significant difference between group means.

RESULTS

The 4 groups of rabbits were well matched for age, weight, and breed. In 2 rabbits, 1 from the Pressure group and 1 from the Oxygen group, the experiment was not performed satisfactorily. These 2 animals have been excluded. After these 2 exclusions, there were 10 rabbits in the Control group, 7 in the Pressure group, 5 in the Decompression group, and 5 in the Oxygen group. Following the microsphere injection, a slight fall in blood pressure (no more than 5 mmHg) was frequently observed.

TABLE 1

REGRESSION COEFFICIENTS AND REGRESSION SLOPES OBTAINED BY COMPARISON OF THE BLOOD FLOWS OF LEFT AND RIGHT PAIRED ORGANS

	Regression Coefficient	Regression Slope	*P*
Kidney	0.989	0.95	<0.001
Cerebral hemispheres	0.924	0.73	<0.001
Femur	0.983	1.02	<0.001
Tibia	0.962	1.01	<0.001
Humerus	0.929	1.03	<0.001
Scapula	0.947	0.85	<0.001
Innominate	0.973	0.94	<0.001

The heart rates and mean blood pressures in each group were similar, as were arterial pH and P_{CO_2} (Table 2). In the Decompression group, heart rate and blood pressure remained stable during decompression and during the microsphere injection. However, 5–10 min after the estimation of blood flow, 2 of the rabbits became progressively hypotensive and developed fatal type II decompression sickness. These 2 rabbits were not excluded as their cardiovascular parameters remained stable during the blood flow estimations; furthermore, analysis of the organ blood flow rates of these 2 animals confirmed that they were not in cardiovascular shock at that time.

Organ blood flow

The mean organ blood flow rates of each group are shown in Table 3. Only myocardial blood flow differed significantly between the groups ($P = 0.01$: minimum significant difference between group means = 105 ml · 100 g^{-1} · min^{-1}). This was significantly lower in the Pressure group than in both the Control and Decompression groups and was lower in the Oxygen group than in the Decompression group.

Bone blood flow

The whole bone blood flow rates tended to be lower in the Pressure and Decompression groups than in the Control group (Table 3) but none of these differences achieved significance. The bone blood flow rates of the Oxygen and Control groups were similar (Table 3).

Study of the regional femoral bone blood flow also revealed that the flow rates of the Control group were generally greater than those of the Pressure and Decompression groups. These differences were more obvious in cortical bone than in the marrow (Table 4). However, only femoral head blood flow differed significantly between the

TABLE 2
MEAN PULSE RATE, BLOOD PRESSURE, AND ARTERIAL pH, P_{O_2}, AND P_{CO_2} OF THE 4 GROUPS[a]

	Control	Pressure	Decompression	Oxygen
Pulse, beats · min^{-1}	232 (30)	205 (37)	180 (38)	228 (30)
Blood pressure, mm Hg	70 (7)	67 (17)	62 (10)	71 (11)
pH	7.34 (0.09)	7.28 (0.11)	7.43 (0.03)	7.39 (0.11)
P_{O_2}	100 (35)	322 (31)	139 (51)	372 (91)
P_{CO_2}	34 (12)	34 (6)	30 (7)	31 (7)

[a]Standard deviations in parentheses.

TABLE 3

MEAN BLOOD FLOW RATES (ML · 100 G^{-1} · MIN^{-1}) OF THE 4 GROUPS OF RABBITS[a]

	Control	Pressure	Decompression	Oxygen
Heart[b]	214.0 (107)	102.0 (29)	275.0 (62)	162.0 (59)
Kidney	248.0 (67)	207.0 (75)	252.0 (70)	245.0 (36)
Brain	47.1 (18)	39.2 (7.1)	41.8 (10)	44.6 (7.1)
Femur	11.3 (3.4)	9.2 (2.0)	8.1 (4.1)	11.0 (3.4)
Tibia	7.2 (2.5)	5.9 (1.4)	4.8 (2.8)	6.9 (2.0)
Humerus	14.3 (4.3)	14.2 (3.9)	10.1 (4.5)	14.8 (5.0)
Innominate	12.2 (3.4)	9.6 (1.9)	8.5 (3.6)	12.1 (3.8)
Scapula	12.9 (3.9)	11.6 (2.9)	8.7 (2.7)	13.2 (2.9)

[a]Standard deviations in parentheses. [b]Significant difference between i) the Pressure and both the Control and Decompression groups; ii) the Oxygen and Decompression groups.

4 groups (P = 0.027: minimum significant difference between group means = 5.4 ml · 100 g^{-1} · min^{-1}). Femoral head blood flow was significantly lower in the Pressure and Decompression groups than in the Control and Oxygen groups. No significant differences were found in any of the regional blood flows of the tibia or humerus (Table 5). The regional bone blood flow rates of the Control and Oxygen groups were similar.

The percentage of each bone's total blood flow which perfused the cortical bone was calculated for the femur, tibia, and humerus (Table 6). For this analysis the femoral head and humeral head, where cortical bone cannot be separated from trabecular bone and marrow, were excluded. Although in all three bones the cortical contribution to total bone blood flow was lowest in the Pressure group, only the difference in humerus was significant (P = 0.044: minimum significant difference between group means = 10.5%). For this bone the difference between the Control and Pressure groups was significant. No differences were detected between these rates in the Control and Oxygen groups.

The ratios between cerebral, renal, and myocardial blood flow and each of the five whole bones showed an identical pattern. No significant differences were detected between the 4 groups for either the renal:bone or cerebral:bone blood flow ratios. For all five bones, the myocardial:bone ratio was significantly higher in the Decompression group (P = at least 0.01). As a significant difference between the femoral

TABLE 4

REGIONAL BLOOD FLOW RATES OF THE FEMUR (ML · 100 G^{-1} · MIN^{-1}) IN THE 4 GROUPS OF RABBITS[a]

Femur	Control	Pressure	Decompression	Oxygen
Head[b]	13.0	7.5	7.1	12.2
	(4.6)	(4.8)	(2.3)	(2.0)
Cortex	11.2	9.1	8.3	11.5
Upper metaphysis	(3.1)	(2.4)	(3.6)	(2.2)
Diaphysis	3.2	2.0	2.2	3.3
	(1.4)	(0.6)	(1.1)	(1.2)
Lower metaphysis	9.0	6.0	5.3	8.3
	(4.1)	(1.9)	(2.7)	(1.6)
Marrow	34.0	28.3	27.8	33.9
Upper metaphysis	(10)	(3.7)	(14)	(10)
Diaphysis	30.0	29.1	24.7	30.3
	(10)	(7.7)	(13)	(11)
Lower metaphysis	23.8	19.6	16.7	23.5
	(8.1)	(4.6)	(12)	(8.1)

[a]Standard deviations in parentheses. [b]Significant difference between the Control and Pressure groups and between the Control and Decompression groups.

head blood flows of the 4 groups had been demonstrated, the ratios of the blood flows of the three soft tissues and the femoral head were also analyzed: no significant differences were detected.

DISCUSSION

This experiment demonstrated significant differences between the myocardial and femoral head blood flows of the Control and Pressure groups. Based on the results of other studies, significant differences in cerebral (9), myocardial (10), and renal (11) blood flow should have been demonstrated between the Control group and both the Pressure and Oxygen groups. One possible reason for failing to detect such changes is that this experiment was rendered insensitive by the large interanimal variability in organ blood flow rates. This interanimal variability, which was no greater than that observed in a previous study (16), can be eliminated by monitoring bone blood flow in individual animals. Unfortunately this could not be done because continuing anesthesia causes a progressive decline in bone blood flow (21). Another possible explanation for the failure to detect differences in the organ blood flows of the Control and Oxygen groups is that, despite breathing 100% oxygen, the mean arterial P_{O_2} in the latter group was only 372 mmHg. This was almost certainly due to pulmonary shunting of blood (22), which is exacerbated by anesthesia and pulmonary atelectasis

TABLE 5

REGIONAL BLOOD FLOW RATES OF THE TIBIA AND HUMERUS (ML · 100 $G^{-1} \cdot MIN^{-1}$) IN THE 4 GROUPS OF RABBITS[a]

	Control	Pressure	Decompression	Oxygen
Tibia				
Cortex	8.9	6.1	5.2	9.2
Upper metaphysis	(4.0)	(2.2)	(2.3)	(2.5)
Diaphysis	2.0	1.7	1.7	2.4
	(0.7)	(0.6)	(0.8)	(1.1)
Lower metaphysis	3.7	2.4	2.2	3.3
	(2.3)	(1.0)	(1.0)	(0.9)
Marrow	23.9	22.7	17.3	23.4
Upper metaphysis	(8.4)	(4.2)	(14)	(10.7)
Remainder	16.7	18.2	15.7	16.5
	(5.5)	(2.7)	(10)	(5.2)
Humerus				
Head	21.7	18.5	14.0	21.0
	(6.8)	(8.6)	(6.2)	(5.8)
Cortex	10.7	7.6	7.3	10.3
Upper half	(6.8)	(8.6)	(6.2)	(2.7)
Lower half	6.3	4.8	4.7	6.6
	(1.9)	(1.9)	(3.2)	(1.7)
Marrow	37.9	36.9	28.6	40.5
Upper half	(15)	(7.2)	(16)	(18)
Lower half	35.7	40.4	27.6	38.7
	(15)	(5.5)	(10)	(15)

[a]Standard deviations in parentheses. No significant difference between the groups.

(a common complication of breathing pure oxygen). However, it should be noted that the arterial P_{O_2} levels of the Pressure and Oxygen groups were similar.

Femoral head blood flow was significantly lower in both the Pressure and Decompression groups than in the Control group; this suggests that prolonged exposure to compressed air reduces femoral head blood flow. No differences were detected between the bone blood flow rates of the Pressure and Decompression groups, and it is concluded that this decompression schedule did not effect bone blood flow. The relevance of these findings to the etiology of dysbaric osteonecrosis is uncertain, especially as this condition has never been produced in the rabbit. It cannot be concluded that exposure to compressed air is more important than the subsequent decompression in the pathogenesis of this condition. However, any reduction in bone blood flow, whether specific or nonspecific to bone, will prolong the time taken for

TABLE 6
CORTICAL CONTRIBUTION TO THE TOTAL BONE BLOOD FLOW OF EACH LONG BONE EXPRESSED AS A PERCENTAGE[a]

Bone	Control	Pressure	Decompression	Oxygen
Femur	37.9 (8.9)	29.8 (7.1)	32.7 (5.8)	34.8 (10.2)
Tibia	49.9 (10.7)	38.8 (5.9)	44.9 (9.2)	47.6 (14.6)
Humerus[b]	38.2 (8.8)	26.1 (3.2)	35.2 (6.2)	36.1 (12.8)

[a]Standard deviations in parentheses. [b]Significant difference between Control and Pressure groups.

removal of excess nitrogen from bone (23). This may predispose to intraosseous gas bubble formation during decompression, and possibly to dysbaric osteonecrosis.

The findings of this study seem similar to those of 2 other experiments which measured rabbit bone blood flow at pressure (4, 5). However, both concluded that compressed air reduced femoral bone marrow blood flow. In the present study no differences were observed in femoral bone marrow blood flow, and the results for the humerus suggest that compressed air caused a relative reduction in cortical bone blood flow. The reason for these differences is unknown but may have been caused by the different experimental designs.

This study has failed to provide evidence in support of the hypothesis that oxygen toxicity produces an intraosseous compartment syndrome and is the cause of at pressure reductions in bone blood flow. The bone blood flow rates of the Oxygen and Control groups were remarkably similar; therefore the changes observed in the Pressure group cannot be attributed solely to the high partial pressure of oxygen. Moreover, analysis of the soft tissue:bone blood flow ratios of the Control and Pressure groups provided no evidence that the effect of compressed air on femoral head blood flow was caused by a mechanism specific to bone.

In conclusion, it is inferred from the results of this study that exposure to compressed air may reduce the blood flow of the femoral head and cause a redistribution of the blood flow in the humerus. As both these locations are commonly involved in dysbaric osteonecrosis (24) it is possible that this finding may be of relevance to the etiology of that condition.

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