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# Effects of acute hypoxia and $CO_2$ inhalation on systemic and peripheral oxygen uptake and circulatory responses during moderate exercise

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**Summary.** The effect of acute hypoxia and $CO_2$ inhalation on leg blood flow (LBF), on leg vascular resistance (LVR) and on oxygen supply to and oxygen consumption in the exercising leg was studied in nine healthy male subjects during moderate one-leg exercise. Each subject exercised for 20 min on a cycle ergometer in four different conditions: normoxia, normoxia +2% $CO_2$, hypoxia corresponding to an altitude of 4000 m above sea level, and hypoxia +1.2% $CO_2$. Gas exchange, heart rate (HR), arterial blood pressure, and LBF were measured, and arterial and venous blood samples were analysed for $P_{CO_2}$, $P_{O_2}$, oxygen saturation, haematocrit and haemoglobin concentration. Systemic oxygen consumption was 1.83 $l \cdot min^{-1}$ (1.48—2.59) and was not affected by hypoxia or $CO_2$ inhalation in hypoxia. HR was unaffected by $CO_2$, but increased from 136 $beat \cdot min^{-1}$ (111—141) in normoxia to 155 (139—169) in hypoxia. LBF was 6.5 $l \cdot min^{-1}$ (5.4—7.6) in normoxia and increased significantly in hypoxia to 8.4 (5.9—10.1). LVR decreased significantly from 2.23 $kPa \cdot l^{-1} \cdot min$ (1.89—2.99) in normoxia to 1.89 (1.53—2.52) in hypoxia. The increase in LBF from normoxia to hypoxia correlated significantly with the decrease in LVR. When $CO_2$ was added in hypoxia a significant correlation was also found between the decrease in LBF and the increase in LVR. In normoxia, the addition of $CO_2$ caused a significant increase in mean blood pressure. Oxygen consumption in the exercising leg (leg $\dot{V}_{O_2}$) in normoxia was 0.97 $l \cdot min^{-1}$ (0.72—1.10), and was unaffected by hypoxia and $CO_2$. It is concluded that the $O_2$ supply to the exercising leg and its $\dot{V}_{O_2}$ are unaffected by hypoxia and $CO_2$. The increase in LBF in hypoxia is caused by a decrease in LVR. These changes can be counteracted by $CO_2$ inhalation. It is proposed that the regulatory mechanism behind these changes is that change in brain $P_{CO_2}$ causes change in the central regulation of vascular tonus in the muscles.

**Key words:** Moderate exercise — Hypoxia — $CO_2$ — Leg oxygen consumption — Leg blood flow — Leg vascular resistance

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## Introduction

During moderate exercise the acute cardiovascular response to decreased inspiratory oxygen pressure (hypoxic hypoxia) is characterized by an increased heart rate (HR) and cardiac output ($\dot{Q}$) (Asmussen and Nielsen 1955; Hartley et al. 1973; Klausen 1966; McManus et al. 1974; Pugh et al. 1964; Stenberg et al. 1966), and an unchanged systemic oxygen consumption ($\dot{V}_{O_2}$) compared to sea level (normoxia) (Hartley et al. 1973; Klausen 1969; Knuttgen and Saltin 1973; Lundin and Strøm 1947; McManus et al. 1974; Pugh et al. 1964; Stenberg et al. 1966). The blood flow to exercising skeletal muscles seems to be increased, as judged by a decreased arterio-femoral venous oxygen difference (Doll 1973; Hartley et al. 1973).

One aim of the present experiments was therefore to investigate the effect of acute hypoxia on leg blood flow (LBF), leg vascular resistance (LVR), and oxygen supply to and oxygen consumption (leg $\dot{V}_{O_2}$) in the exercising leg.

Another effect of acute hypoxia is pronounced hyperventilation during exercise. The effect of this hyperventilation is to decrease the $CO_2$ pres-

sure ($P_{CO_2}$) in blood and other body fluids. It is known from studies in animals and in man at rest that a decrease in $P_{CO_2}$ causes a decrease in blood flow to the brain (Kety and Schmidt 1946) and that changes in $P_{CO_2}$ influence blood flow to the skeletal muscles (Irving and Welch 1935; Kontos et al. 1965, 1968; Lennox and Gibbs 1932; Richardson et al. 1961).

Hence the second aim of this study was to investigate the effect of inhalation of small concentrations of $CO_2$ during moderate one-leg exercise in hypoxia, in order to clarify to what extent the physiological changes that take place in acute hypoxia are due to decreased $P_{CO_2}$ in blood and other body fluids. One-leg exercise was chosen, as it is known that hyperventilation is more pronounced during this type of exercise.

## Subjects and methods

Nine healthy male subjects age 26 years (24—29) height 184 cm (180—193), weight 79 kg (71—88) (median and range values), participated in this study, after their informed consent was obtained. The protocol was approved by the local ethical committee. None of the subjects were especially accustomed to bicycle exercise. The subjects exercised with the right leg on a modified Monark cycle ergometer at a moderate power output (110 W (84—140)) for 20 min. This test was repeated in exactly the same way four times, except that the fractional composition of the inspired air ($F_I$) was varied as follows: 1) normoxia, 2) normoxia +2% $CO_2$, 3) hypoxia ($F_IO_2=0.125$ corresponding to an altitude of about 4000 m above sea level) and 4) hypoxia +1.2% $CO_2$. The order of these four conditions was randomized, and the subjects were unaware of what gas mixture they inspired. The subjects performed the one-leg exercise procedure several times before the actual experiments in order to avoid the effects of adaptation. The four experiments were carried out on two days 14 days apart.

The subject was allowed a light breakfast before he reported to the laboratory at 7 a.m. Using the Seldinger technique, one catheter was inserted into the brachial artery and one 4F thermodilution catheter (Edwards Lab. 94 — 110 — 4F) and one 6F Teflon catheter for blood sampling were inserted into the right femoral vein. The tips of the two venous catheters were placed in the right iliac vein at the level of the right sacro-iliac joint under fluoroscopic control. The catheterizations were performed under local anaesthesia and no premedication was given.

The subject then rested in the supine position for 1 hour. Arterial and venous resting blood samples were drawn anaerobically before the subject was seated behind the ergometer in such a way that he could exercise with the right leg in a horizontal position. He rested in this position for 30 min, inspiring one of the gas mixtures from a 200 l Douglas bag, in which dry gas from a high pressure cylinder was moistened. After this equilibration period a new set of blood samples was obtained.

Thereafter the subject exercised for 20 min at the preset power output. Blood samples were taken after 2, 6, 12, and 20 min. Expired air was collected in two Douglas bags from the 15th to 19th min. During the same period LBF was measured. HR and arterial blood pressure (BP) were recorded continuously during the exercise period.

After this period of exercise the subject rested supine for 1 hour. Then he was prepared for the second 20 min exercise period of the day by a ½ h adaptation to the gas mixture in question.

*Measurements.* The blood samples were drawn simultaneously from the brachial artery and the iliac vein at rest and during the 20th min of exercise. The blood samples were analyzed for $P_{CO_2}$, $P_{O_2}$ (Radiometer microelectrode system), haematocrit, oxygen saturation ($S_{O_2}$) (Holmgren and Pernow 1959), and haemoglobin concentration.

HR was continuously recorded from one precordial lead and the intraarterial BP was recorded from the catheter in the brachial artery using a pressure transducer (Elema-Schönander EMT 35). Mean blood pressure (MBP) was calculated as the diastolic pressure plus one third of the pulse pressure. LBF was measured by thermodilution technique (Jorfeldt et al. 1978). A bolus of 4 ml 0.9% saline solution at 0° C was injected into the thermodilution catheter. The injection port was situated 10 cm from the tip of the catheter, where the thermistor was placed. LBF was calculated by a cardiac output computer (Edwards Lab. model 9510). LBF was measured from the 15th to the 19th min of exercise. The value used for LBF in each subject was the mean of five single determinations in each experimental situation. The coefficient of variation for the determined LBF values was 10%. LVR was calculated by dividing MBP by LBF, assuming that the pressure on the venous side was zero in all situations.

The composition of the inspired gas mixtures was analyzed by the Scholander technique, and the expired air collected in Douglas bags was analyzed by a Servomex paramagnetic $O_2$ analyzer for oxygen content ($F_EO_2$) and a Beckman LB-2 infrared $CO_2$ analyzer for carbon dioxide ($F_ECO_2$). Bag volumes were measured in a Tissot spirometer (Collins).

The statistical analyses comprised a non-parametric test for paired samples (Wilcoxon), and a Spearman rank correlation test with a level of significance set at $p \leq 0.05$. Seven subjects exercised in all 4 experimental conditions, while two subjects only performed experiments in hypoxia and hypoxia +1.2% $CO_2$. Comparison of results from normoxia, normoxia +2% $CO_2$ and hypoxia is based on data from seven subjects, while the comparison betweens hypoxia and hypoxia +1.2% $CO_2$ is based on nine subjects.

## Results

Unless otherwise stated, the results are given as median values and ranges. Table 1 shows the blood samples values at rest, and Tables 2 and 3 show the results from the last minutes of exercise.

At rest the composition of the blood samples in normoxia was the same on the two experimental days. The arterial and venous $P_{CO_2}$, $P_{O_2}$ and $S_{O_2}$ decreased significantly with hypoxia. By adding $CO_2$ to the inspired air, arterial $CO_2$ ($P_aCO_2$) and venous $CO_2$ ($P_vCO_2$) increased significantly in hypoxia. Adding $CO_2$ in normoxia produced significant decreases in $P_vO_2$ $S_vO_2$% and $C_vO_2$.

**Table 1.** Arterial and venous blood values (medians and ranges) at rest, sitting

| Arterial | Normoxia | Normoxia +2% $CO_2$ | Hypoxia | Hypoxia +1.2% $CO_2$ |
|---|---|---|---|---|
| $PaCO_2$ (kPa) | 5.87 (4.94—6.53) | 5.74 (4.94—6.80) | 4.27* (3.47—4.80) | 5.20** (4.13—5.60) |
| $PaO_2$ (kPa) | 14.40 (13.20—16.67) | 17.21 (13.87—17.87) | 7.47* (5.34—9.34) | 8.00 (6.67—10.40) |
| $SaO_2$ (%) | 98.9 (98.1—99.8) | 99.2 (98.8—100.7) | 88.5* (69.1—98.3) | 86.8 (80.9—98.7) |
| Haematocrit | 40.7 (38.2—42.6) | 40.7 (36.3—43.1) | 41.7 (38.7—44.1) | 41.2 (37.2—43.1) |
| Haemoglobin $g \times dl^{-1}$ | 12.9 (11.9—13.8) | 13.3 (11.2—14.2) | 13.3 (12.2—14.5) | 13.2 (12.1—13.9) |
| $CaO_2$ (vol%) | 17.68 (16.02—19.05) | 18.34 (15.38—19.68) | 16.24 (12.10—19.35) | 15.54 (14.55—18.52) |
| *Venous* | | | | |
| $PvCO_2$ (kPa) | 6.27 (5.60—6.40) | 6.54 (5.60—7.20) | 5.34* (4.27—5.87) | 6.14* (4.40—6.54) |
| $PvO_2$ (kPa) | 6.67 (5.34—6.94) | 5.20** (4.00—6.40) | 4.13* (3.73—4.94) | 4.40 (3.60—5.20) |
| $SvO_2$ (%) | 73.9 (56.5—90.1) | 60.9** (47.6—81.2) | 48.9* (41.8—74.1) | 56.0 (48.7—80.2) |
| Haematocrit | 39.7 (38.2—42.1) | 41.2 (38.2—42.1) | 42.1 (38.7—44.1) | 40.7 (37.2—43.1) |
| Haemoglobin $g \times dl^{-1}$ | 12.8 (12.0—13.7) | 13.3 (11.7—14.4) | 13.2 (12.1—14.5) | 13.2 (12.2—15.0) |
| $CvO_2$ (vol%) | 13.64 (10.05—15.91) | 13.08** (8.14—15.12) | 9.96* (7.00—14.01) | 10.18 (8.26—15.38) |
| Leg (a-v)$O_2$ diff (ml/100 ml blood) | 4.12 (2.00—5.41) | 5.15** (3.22—8.22) | 5.10 (3.60—8.00) | 5.48 (2.54—7.05) |

1 kPa = 7.50 mm Hg
* Significant change from normoxia to hypoxia
** Significant change by addition of $CO_2$ in normoxia or in hypoxia

**Table 2.** Respiratory and circulatory values (medians and ranges) measured during the 15th—19th min of exercise

| | Normoxia | Normoxia +2% $CO_2$ | Hypoxia | Hypoxia +1.2% $CO_2$ |
|---|---|---|---|---|
| $\dot{V}_{E_{BTPS}}$ ($l \times min^{-1}$) | 48.27 (42.88—76.35) | 62.92** (46.46—88.41) | 73.86* (61.50—114.14) | 80.22 (65.47—102.85) |
| $\dot{V}_{O_2}$ ($l \times min^{-1}$) | 1.83 (1.48—2.59) | 1.74** (1.35—2.15) | 1.79 (1.48—2.60) | 1.78 (1.55—2.20) |
| HR (beats $\times min^{-1}$) | 136 (111—141) | 134 (109—144) | 155* (139—164) | 146 (119—162) |
| MBP (kPa) | 14.14 (12.80—16.27) | 15.60** (14.94—17.74) | 15.47 (12.67—16.14) | 15.47 (13.60—16.81) |
| LBF ($l \times min^{-1}$) | 6.5 (5.4—7.6) | 6.5 (4.8—7.2) | 8.4* (5.9—10.1) | 7.1 (5.7—9.3) |
| LVR ($kPa \times l^{-1} \times min$) | 2.23 (1.89—2.99) | 2.37** (2.20—2.97) | 1.89 (1.53—2.52) | 2.17 (1.69—2.71) |
| Leg $\dot{V}_{O_2}$ ($l \times min^{-1}$) | 0.97 (0.72—1.10) | 0.96 (0.60—1.03) | 0.89 (0.70—1.19) | 0.88 (0.75—1.20) |

1 kPa = 7.50 mm Hg
* Significant change from normoxia to hypoxia
** Significant change by addition of $CO_2$ in normoxia or hypoxia

**Table 3.** Arterial and venous blood values (medians and ranges) measured at the 20th min of exercise

| Arterial | Normoxia | Normoxia +2% $CO_2$ | Hypoxia | Hypoxia +1.2% $CO_2$ |
|---|---|---|---|---|
| $PaCO_2$ (kPa) | 5.20 (5.07—5.60) | 5.60** (5.34—6.54) | 3.87* (2.13—4.53) | 4.53** (4.27—5.07) |
| $PaO_2$ (kPa) | 13.47 (12.00—15.60) | 15.47** (14.81—17.34) | 6.40* (5.06—7.34) | 6.67* (6.14—7.34) |
| $SaO_2$ (%) | 98.1 (97.0—99.0) | 99.0** (98.2—100.0) | 79.0* (72.5—87.7) | 82.5** (80.0—88.4) |
| Haematocrit | 43.1 (41.2—45.1) | 42.1 (38.2—44.1) | 44.5* (41.7—46.6) | 44.1 (39.7—47.5) |
| Haemoglobin $g \times dl^{-1}$ | 14.0 (12.8—15.1) | 13.7 (12.5—14.5) | 14.0 (13.4—15.4) | 14.0 (13.0—15.4) |
| $CaO_2$ (vol%) | 19.11 (17.40—20.59) | 18.97 (17.10—20.03) | 16.30 (13.81—17.07) | 16.05 (14.79—18.47) |
| *Venous* | | | | |
| $PvCO_2$ (kPa) | 8.14 (7.60—8.40) | 8.80** (8.14—9.34) | 6.40* (5.74—7.47) | 7.34** (6.54—8.14) |
| $PvO_2$ (kPa) | 3.07 (1.87—3.33) | 3.07 (2.00—3.33) | 2.40* (2.00—2.67) | 2.53 (2.13—2.93) |
| $SvO_2$ (%) | 23.3 (18.8—37.3) | 24.4 (21.2—35.1) | 17.8* (12.0—19.4) | 17.8 (14.0—23.7) |
| Haematocrit | 44.1 (42.6—46.1) | 43.1 (38.7—45.1) | 44.6 (41.7—48.5) | 45.1 (40.2—48.0) |
| Haemoglobin $g \times dl^{-1}$ | 14.2 (13.1—15.3) | 14.0 (12.8—14.7) | 13.9 (13.5—15.6) | 14.2 (13.3—15.7) |
| $CvO_2$ (vol%) | 4.52 (4.00—7.06) | 4.65 (4.01—6.92) | 3.43* (2.59—3.91) | 3.51 (2.82—4.74) |
| Leg (a-v)$P_2$ diff. (ml/100 ml blood) | 14.35 (11.40—15.98) | 14.29 (12.10—15.02) | 12.82* (10.43—14.21) | 12.77 (11.22—13.73) |

1 kPa = 7.50 mm Hg
* Significant change from normoxia to hypoxia
** Significant change by addition of $CO_2$ in normoxia or hypoxia

The calculated leg arterio-venous (a-v) oxygen difference increased significantly when $CO_2$ was added in normoxia. Assuming a constant leg $\dot{V}_{O_2}$ this implies a decrease in LBF in this situation.

During exercise $\dot{V}_E$BTPS increased significantly with hypoxia (Table 2). By adding 2% $CO_2$ to the inspired air $\dot{V}_E$BTPS increased significantly in normoxia, while in hypoxia +1.2% $CO_2$ $\dot{V}_E$BTPS was unchanged as compared to hypoxia. The increase in $\dot{V}_E$ from normoxia to hypoxia resulted in a significant decrease in $P_aCO_2$. $P_aCO_2$ incrased significantly by adding $CO_2$ in both normoxia and hypoxia. $\dot{V}_{O_2}$ was unchanged from normoxia to hypoxia and by adding $CO_2$ in hypoxia, but was decreased significantly by the addition of $CO_2$ in normoxia.

There was a significant increase in HR from normoxia to hypoxia. Adding $CO_2$ dit not change HR significantly (Fig. 1). The invidual HR values showed a decrease by adding $CO_2$ in hypoxia in 6 subjects, unchanged HR in 2 subjects, and only 1 subject showed an increased HR. Systolic BP (SBP) and diastolic BP (DBP) were similar in all 4 experimental exercise conditions (about 22.7 and 11.3 kPa), although SBP tended to increase when $CO_2$ was added to the inspired air both in normoxia and hypoxia (5 subjects showed an increased SBP in both situations). MBP increased significantly with addition of $CO_2$ in normoxia (Fig. 1).

LBF increased significantly from normoxia to hypoxia but did not change significantly when $CO_2$ was added (Fig. 1). Individual values showed, however, that 6 of the 9 subjects had a decrease in LBF when $CO_2$ was added in hypoxia, whereas the LBF was unchanged in 2 subjects and increased in 1.

LVR decreased from normoxia to hypoxia in 5 subjects, while it was unchanged in 1 subject and increased in 1 subject. Addition of $CO_2$ increased LVR significantly in normoxia (Fig. 1) while in




**Fig. 1.** Circulatory mean values from exercise in normoxia $+CO_2$ ($N^+$), hypoxia (H), and hypoxia$+CO_2$ ($H^+$). Values are expressed as percentages of the values obtained in normoxia. * significant change from normoxia to hypoxia. ** significant change from normoxia to normoxia$+CO_2$

hypoxia LVR increased in 7 subjects and decreased in 2.

The oxygen supply to the exercising muscles calculated by multiplying LBF and $O_2$ content in arterial blood ($C_aO_2$ Vol%) was the same in the four experimental conditions (about 1230 ml $O_2 \cdot min^{-1}$).

The leg (a-v)$O_2$ difference decreased significantly from normoxia to hypoxia, but was unaffected by $CO_2$ addition in either situation (Fig. 1). However, the leg $\dot{V}_{O_2}$ (calculated by use of Ficks principle) was not influenced by either hypoxia or the addition of $CO_2$ (Table 2). Leg $\dot{V}_{O_2}$ amounted in all situations to about 50% of systemic $\dot{V}_{O_2}$ (median values ranged between 48—49% (42—69%).

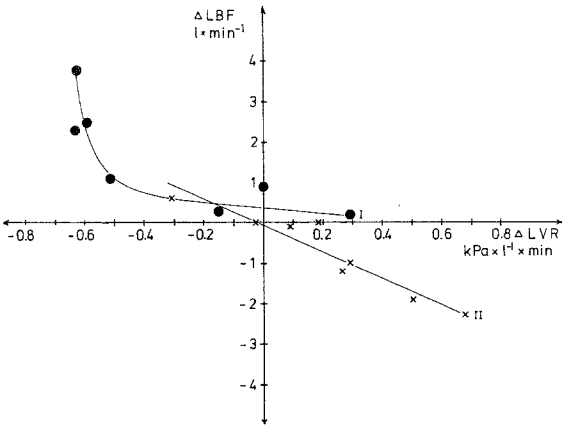


**Fig. 2.** Changes in LBF in relation to changes in LVR. Individual values. ● = changes from normoxia to hypoxia. $x$ = changes from hypoxia to hypoxia + $CO_2$

## Discussion

The experiments have shown that during moderate exercise the systemic $\dot{V}_{O_2}$, the $O_2$ supply to the exercising leg and the leg $\dot{V}_{O_2}$ were all unaffected by acute hypoxia corresponding to an altitude of 4000 m, and further unaffected by the addition of $CO_2$ in hypoxia. The unchanged systemic $\dot{V}_{O_2}$ from normoxia to hypoxia fits nicely with many other experiments (Hartley et al. 1973; Klausen 1969; Knuttgen and Saltin 1973; Ludin and Strøm 1947; McManus et al. 1974; Pugh et al. 1964; Stenberg et al. 1966), whereas there has only been indirect evidence that the $O_2$ supply to and the $O_2$ consumption in exercising human leg-muscles are unaffected by hypoxia (Hartley and Landowne 1973).

The finding that about 50% of the systemic $\dot{V}_{O_2}$ is used in the exercising leg, and the relationship of LBF to systemic $\dot{V}_{O_2}$ in normoxia are in accordance with previous studies in human subjects performing one-leg exercise in normoxia (Klausen et al. 1982).

As the $O_2$ content in arterial blood was decreased in hypoxia, the unchanged oxygen supply to the leg was maintained by a significant increase in LBF from 6.4 $l \cdot min^{-1}$ in normoxia to 8.4 $l \cdot min^{-1}$ in hypoxia. This increase in LBF in hypoxia correlates, significantly with the decrease in LVR from normoxia to hypoxia (Fig. 2). The latter can be explained by a dilatation of the arterioles in the working muscles. Since the decrease in LVR occurred concomitantly with decreases in $P_{O_2}$ and $P_{CO_2}$ in arterial and venous blood the vasodilatation can be due to a decrease in one or both of these two gases. Figure 3 illustrates the effects of these changes. It is well established that decreased $P_{O_2}$ in the muscles may cause vasodilatation (Guyton et al. 1964; Gömöri et al. 1959). The centrally mediated effect of decreased $P_aO_2$ in the brain of animals at rest is an increase in sympathetic vasoconstrictor activity to the skeletal muscles (Gregor and Janig 1977), and hence an increase in peripheral resistance (Downing et al. 1963). A local decrease in $P_{CO_2}$ causes vasoconstriction (Kontos et al. 1965) and an increase in $P_{CO_2}$ causes vasodilatation (Kontos et a. 1968; Richardson et al. 1961; Wendling et al. 1977) whereas an increase in $P_aCO_2$ in the brain results in increased activity in the vasoconstrictor neurones to the muscles (Downing et al. 1963; Gregor and Janig 1977). Thus the enhanced dilatation in hypoxia, found in 6 of 7 subjects in the present experiments, cannot be explained by the centrally mediated effect of the decrease in $P_aO_2$. Further, there is a positive, significant correlation between $P_aO_2$ in hypoxia and the decrease in LVR from normoxia to hypoxia, i.e. the subject with the lowest $P_aO_2$ has the smallest decrease in LVR

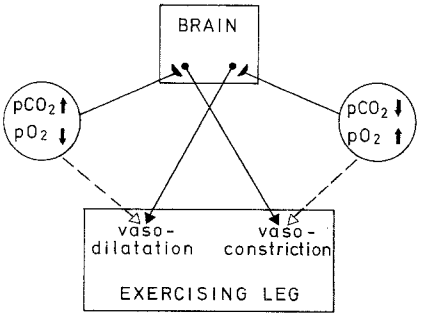


**Fig. 3.** Schematic presentation of the effects of increase (↑) or decrase (↓) in pressure of $CO_2$ ($P_{CO_2}$) or $O_2$ ($P_{O_2}$) on the resistance vessels in the exercising leg. - - - - - →: local effect, and ——→: centrally mediated effect of the two gases

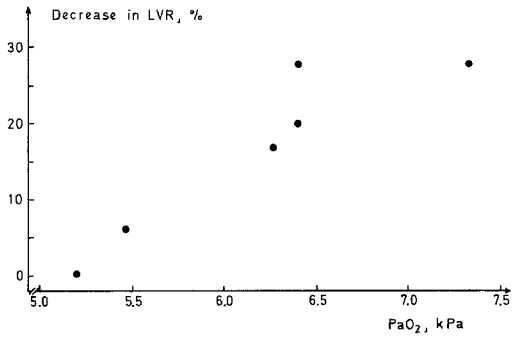


**Fig. 4.** Decrease in LVR during exercise in hypoxia as compared to normoxia, in relation to $P_aO_2$ in hypoxia. Individual values

(Fig. 4), which is the opposite of what would be expected from the local, peripheral effect of $P_{O_2}$. This last observation seems to indicate that a decrease in $P_aO_2$ leads to a centrally mediated vasoconstriction in working skeletal muscles. The further dilatation of the arterioles in the working muscles in hypoxia may be due to the central effect of the decreased $P_aCO_2$ and/or local effects of hormones and metabolites other than $CO_2$. It may further be stressed that this eventual local production of metabolites is not brought about by hypoxia in the working muscles since, as mentioned earlier the greatest dilatation is seen in the subject having the highest $P_aO_2$.

The influence of $P_aCO_2$ on the regulation of blood flow to exercising muscles gains further support from the finding that the addition of $CO_2$ to the inspired air in hypoxia counteracts the changes in hypoxia, and a significant correlation is found between the decrease in LBF and the increase in LVR (Fig. 2). These results are in line with Black and Roddie (1958), who found that an increased blood flow through the resting human arm in hypoxia caused by a decreased vascular resistance disappeared when 10% $CO_2$ was added to the inspired air.

The addition of $CO_2$ in normoxia increased LVR significantly, but no correlation was found between this increase and the change in LBF. On the other hand a significant increase was found in MBP. At rest the effects seems to be a decrease in LBF since the leg (a-v) $O_2$ difference increased significantly.

HR was increased from normoxia to hypoxia but was unaffected by the addition of $CO_2$ in normoxia and hypoxia. This is in line with previous experiments, where it has been observed that the addition of $CO_2$ to inspired air during exercise did not affect HR (Graham et al. 1980, 1982; Rizzo et al. 1976). Thus the increased HR in hypoxia seems not to be caused by a decrease in $P_aCO_2$, but rather by a decrease in $P_aO_2$ which increases sympathetic activity.

To conclude, the changes seen during moderate exercise going from normoxia to hypoxia was an increase in HR primarily caused by a decrease in $P_{O_2}$. Further it is suggested that the vasoconstrictor activity going to the arterioles in the working muscles is decreased because of a decrease in $P_aCO_2$ in the brain. LBF was increased because of a decrease in LVR. This decrease in LVR in hypoxia can be counteracted by adding $CO_2$ to the inspired air. The effect of the increase in LBF from normoxia to hypoxia was a sufficient $O_2$ supply to the exercising muscles, resulting in an unchanged leg $\dot{V}_{O_2}$.

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## References

Asmussen E, Nielsen M (1955) The cardiac output in rest and work at low and high oxygen pressure. Acta Physiol Scand 35:176—186

Black JE, Roddie JC (1958) Forearm vascular resistance during hypoxia. J Physiol 143:226—235

Doll E (1973) Oxygen pressure and content in the blood during physical exercise and hypoxia. In: Keul (ed) Limiting factors of physical Performance; Georg Thieme Publishers, Stuttgart, pp 201—211

Downing SE, Mitchell JH, Wallace AG (1963) Cardiovascular responses to ischemia, hypoxia and hypercapnia of the central nervous system. Am J Physiol 204:881—887

Graham T, Wilson BA, Sample M, van Dijk J, Bonen A (1980) The effects of hypercapnia on metabolic responses to progressive exhaustive work. Med Sci Sports Exercise 12:278—284

Graham T, Wilson BA, Sample M, van Dijk J, Goslin B (1982) The effects of hypercapnia on the metabolic response to steady-state exercise. Med Sci Sports Exercise 14:286—291

Gregor M, Janig W (1977) Effects of systemic hypoxia and hypercapnia on cutaneous and muscle vasoconstrictor neurones to the cats hindlimb. Pflügers Arch 368:71—81

Guyton AC, Ross JM, Carrier O, Walker JR (1964) Evidence for tissue oxygen demand as the major factor causing autoregulation. [Suppl I] Circ Res vol. XIV and XV

Gömöri PA, Kovach GB, Takacs L, Foldi M, Szabo GY, Nagy Z, Wiltner W, Kallay K (1959) The regulation of cardiac output in hypoxia. Acta Med Acad Sci (Hung) 16:93—98

Hartley LH, Vogel JA, Landowne M (1973) Central, femoral and brachial circulation during exercise in hypoxia. J Appl Physiol 34:87—90

Holmgren A, Pernow B (1959) Spectrophotometric measurements of oxygen saturation of blood in the determination of cardiac output. A comparison with the van Slyke method. Scan J Clin Lab Invest 11:143—149

Irving L, Welch MS (1935) The effect of the composition of the inspired air on the circulation through the brain. Department of Physiology, University of Toronto

Jorfeldt L, Juhlin-Dannfelt A, Pernow B, Wassen E (1978) Determination of human leg blood flow: a thermodilution technique based on femoral venous bolus injection. Clin Sci Mol Med 54:517—523

Kety SS, Schmidt CF (1946) The effects of active and passive hyperventilation on cerebral blood flow, oxygen consumption, cardiac output and blood pressure of normal young men. J Clin Invest 25:107—119

Kittle CG, Aoki H, Brown Jr EB (1965) The role of pH and $CO_2$ in the distribution of blood flow. Surgery 57:139—154

Klausen K (1966) Cardiac output in man in rest and work during and after acclimatization to 3800 m. J Appl Physiol 21:609—616

Klausen K (1969) Exercise under hypoxic conditions. Med Sci Sport 1:43—49

Klausen K, Secher NH, Clausen JP, Hartling O, Trap-Jensen J (1982) Central and regional circulatory adaptations to one-leg training. J Appl Physiol 52:976—983

Knuttgen H, Saltin B (1973) Oxygen uptake, muscle high-energy phosphats and lactate in exercise under acute hypoxic conditions in man. Acta Physiol Scand 87:368—376

Kontos HA, Page Mauck Jr H, Richardson DW, Patterson Jr JL (1965) Circulatory responses to hypocapnia in the anesthetized dog. Am J Physiol 208:139—143

Kontos HA, Richardson DW, Patterson Jr JL (1968) Roles of hypercapnia and acidosis in the vasodilator response to hypercapnia acidosis. Am J Physiol 215:1406—1408

Lennox WG, Gibbs EL (1932) The blood flow in the brain and leg of man and the changes induced by alteration of blood gases. J Clin Invest 11:1155—1177

Lundin G, Strøm G (1947) The concentration of blood lactic acid in man during muscular work in relation to the partial pressure of oxygen of inspired air. Acta Physiol Scand 13:253—266

McManus BM, Horvath SM, Baldnan N, Miller JC (1974) Metabolic and cardiorespiratory responses to longterm work under hypoxic conditions. J Appl Physiol 36:177—183

Pugh LGCE, Gill MB, Lahiri S, Milledge JS, Ward MP, West JB (1964) Muscular exercise at great altitudes. J Appl Physiol 19:431—440

Richardson DW, Wasserman AJ, Patterson Jr JL (1961) General and regional circulatory response to change in blood pH and Carbon dioxide tension. J Clin Invest 40:31—43

Rizzo A, Gimenez M, Horsky P, Saunier C (1976) Influence d'une atmosphere de $CO_2$ a 4% sur le comportement metabolique a l'exercise d'hommes jeunes. Bull Eur Physiopathol Respir 12:209—219

Stenberg J, Ekblom B, Messin R (1966) Hemodynamic response to work at simulated altitude, 4000 m. J Appl Physiol 21:1589—1594

Wendling MG, Eckstein JW, Abboud FM (1977) Cardiovascular responses to carbon dioxide before and after beta-adrenergic blockade. J Appl Physiol 22:223—226

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