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REGULATION OF PERFUSIVE O_2 TRANSPORT DURING EXERCISE IN HUMANS: EFFECTS OF CHANGES IN HAEMOGLOBIN CONCENTRATION

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SUMMARY

1. Recently it was suggested that submaximal cardiac output ($\dot{Q}$) could vary in response to changes in arterial O_2 concentration (C_{a,O_2}), so that arterial O_2 delivery ($\dot{Q}_{a,O_2} = \dot{Q} \times C_{a,O_2}$, in ml min^{-1}) is kept constant.

2. This hypothesis was tested on eight healthy male subjects, at rest and during exercise (50, 100 and 150 W) in three conditions: normaemia (N), after 6 weeks of endurance training (T), and 2 days after subsequent autologous blood reinfusion (P).

3. Measured variables were oxygen consumption ($\dot{V}_{O_2}$), by open circuit method, $\dot{Q}$, by a CO_2 rebreathing method, and haemoglobin concentration ([Hb]), by a photometric method. C_{a,O_2} was calculated as the product of [Hb], arterial O_2 saturation (0·97), and the O_2 binding coefficient.

4. [Hb] and thus C_{a,O_2} increased by 2·6% (T *vs.* N) and subsequently by further 5·8% (P *vs.* T). $\dot{V}_{O_2}$ and $\dot{Q}_{a,O_2}$ were linear functions of power ($\dot{w}$), both relationships being unaffected by changes in C_{a,O_2}. As a consequence, the linear $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ relationships were shifted downward as C_{a,O_2} increased.

5. The $\dot{V}_{O_2}$ *vs.* $\dot{w}$ and the $\dot{Q}_{a,O_2}$ *vs.* $\dot{w}$ relationships had the same slope. Therefore, the difference between $\dot{Q}_{a,O_2}$ ($\dot{w}$) and $\dot{V}_{O_2}$ ($\dot{w}$), equal to O_2 flow in mixed venous blood ($\dot{Q}_{v,O_2}$), was constant.

6. In conclusion, the tested hypothesis was supported by the present results. The observed constancy of $\dot{Q}_{v,O_2}$ suggested that $\dot{Q}_{v,O_2}$ may play a key role in regulating the cardiovascular response to exercise.

INTRODUCTION

The flow of O_2 through the respiratory system from ambient air to mitochondria is assumed to be driven by O_2 pressure gradients across a number of resistances in series (di Prampero & Ferretti, 1990). At each metabolic steady state, the O_2 flow ($\dot{V}_{O_2}$) across each resistance is equal, and it corresponds to the rate of O_2 consumption.

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With increasing exercise intensity, a progressively larger fraction of $\dot{V}_{O_2}$ is directed to the working muscles. This implies modulation of the parameters governing $\dot{V}_{O_2}$ at each step along the respiratory system.

With regard to the perfusive resistance to O_2 flow, $\dot{V}_{O_2}$ is the product of cardiac output ($\dot{Q}$) and the arterial–venous O_2 difference ($C_{a,O_2} - C_{v,O_2}$, where C_{a,O_2} and C_{v,O_2} are the O_2 concentrations in arterial and mixed venous blood, respectively). The remarkable constancy of the relationship between $\dot{Q}$ and $\dot{V}_{O_2}$ has become a classical notion (see e.g. Cerretelli & di Prampero, 1987). Admitted exceptions are the upward shift of the $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ line observed in acute hypoxia (Stenberg, Ekblom & Messin, 1966; Hughes, Clode, Edwards, Goodwin & Jones, 1968) and after moderate CO poisoning (Vogel & Gleser, 1972). These exceptions have been explained in terms of an 'error signal', related to reduced C_{a,O_2} influencing the control system of $\dot{Q}$ (Cerretelli & di Prampero, 1987).

Recently, the observation of a reduced $\dot{Q}$ at any submaximal work load in subjects acclimatized to altitude upon return to sea level (i.e. in a condition of increased C_{a,O_2}, see Ferretti, Boutellier, Pendergast, Moia, Minetti, Howald & di Prampero, 1990), has challenged the above concept of a constant, controlled $\dot{Q}$ as a function of $\dot{V}_{O_2}$. Those authors put forward a different hypothesis, suggesting that, at any submaximal work load, $\dot{Q}$ may be adjusted in response to changes in C_{a,O_2}, so that an adequate oxygen delivery ($\dot{Q}_{a,O_2}$), specific to each level of submaximal power output, is maintained.

The purpose of the present study was to test the above hypothesis of C_{a,O_2}-related changes in $\dot{Q}$. To this end, C_{a,O_2} was varied by increasing haemoglobin concentration ([Hb]) by means of reinfusion of autologous red cells in subjects who had previously undergone endurance training. $\dot{V}_{O_2}$ and its cardiovascular determinants were measured at various submaximal work loads.

Preliminary reports of this study have previously been published (Ferretti, Kayser, Schena, Turner & Hoppeler, 1991; Ferretti, Kayser, Moia, Schena & Turner, 1991).

METHODS

Subjects

Eight young (age 25±6 years) male subjects participated in the study. The subjects had not previously engaged in regular endurance-type exercise. They were fully informed of the protocols as well as of the possible risks inherent to this study, and gave their informed consent. The study was approved by the Ethical Commission of the University of Bern.

All subjects were clinically healthy. They had a normal resting and exercise electrocardiogram. An echocardiographic examination, including 2-D M-mode and Doppler colour echocardiography, showed normal results.

Experimental design

Two units (~ 900 ml) of whole blood were withdrawn from each subject. Blood was taken following the criteria prescribed by the Blood Transfusion Service of the Swiss Red Cross. Red cells were glycerolized (low glycerol–high freezing rate technique), frozen in liquid nitrogen within the first day from donation, and stored in the vapour phase of liquid nitrogen (< 123 K).

Approximately two months were allowed in order to re-establish normal haemoglobin levels after blood withdrawal. During this period, the subjects were supplemented with iron (1 g day^{-1}). Subsequently, the first set of experiments (control tests in normaemia, N) was performed.

The subjects then underwent a 6 week duration endurance training, following the protocol described by others (Hoppeler, Howald, Conley, Lindstedt, Claassen, Vock & Weibel, 1985). In

short, they exercised for 30 min at a constant load on a bicycle ergometer five times a week. The initial work load was that attained at the 4 mM-lactate threshold during the experiments in normaemia. Heart rate (HR) was continuously measured. At the end of each training session the subjects were practically exhausted, and HR was about 90% of the maximal HR measured in normaemia. The workload was occasionally adjusted in order to obtain equivalent HR levels throughout the whole training period.

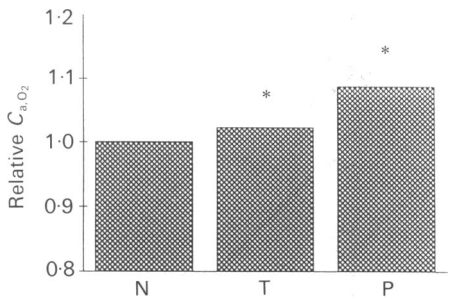

Fig. 1. Average arterial oxygen concentration (C_{a,O_2}) expressed relative to the value observed in normaemia (N), in the three tested conditions (T, post-training; P, polycythaemia). Asterisks indicate $P < 0{\cdot}05$ T *vs.* N and P *vs.* T.

At the end of the training period, the second set of experiments was carried out (post-training, T). Subsequently, the stored blood (2 units of packed red cells) was reinfused. Blood defreezing and reconstitution were carried out on the day of retransfusion. After 48 h, the final experimental session was performed (polycythaemia, P).

Exercise testing protocol

$\dot{V}_{O_2}$ was measured at rest and during cycloergometric exercise of 50, 100, and 150 W power outputs. At each work level, $\dot{V}_{O_2}$ was measured during the 5th min of continuous constant load exercise, i.e. when a steady state for pulmonary gas exchange was attained.

$\dot{Q}$ was measured in the course of the same test as for the assessment of $\dot{V}_{O_2}$. Three determinations of $\dot{Q}$ were carried out at rest and at each level of exercise. $\dot{Q}$ was measured at 1·5, 3 and 5 min from the onset of each load. The mean of the three $\dot{Q}$ measurements was retained as the $\dot{Q}$ value for that exercise level.

[Hb] was measured at rest, shortly before the start of exercise.

Measurements and calculations

$\dot{V}_{O_2}$ (l min^{-1}) was measured by standard open circuit method. Expired air was collected in Douglas bags, whose volume was then determined by means of a Singer dry gas meter (USA). Expired O_2 and CO_2 fractions were measured by gas analysers (Oxynos 1-C oxymeter, and LB-2 CO_2 meter, respectively, Leybold Haereus, Germany).

$\dot{Q}$ (l min^{-1}) was measured by a CO_2 rebreathing method (Farhi, Nesarajah, Olszowka, Metildi & Ellis, 1976). The evolution of the CO_2 fraction at the mouth during and immediately before the rebreathing manoeuvre was analysed by a mass spectrometer (Centronics 200 MGA, England), followed on an oscilloscope (M 6012, BBC Metrawatt, Germany), digitized and stored on discs. Tracings were subsequently elaborated by means of a computer (ALR 386/220, USA).

Heart rate was measured by cardiotachography (Baumann et Cie, Switzerland). [Hb] was measured by a standard photometric technique (Compur 1000, Bayer, Germany) on fingertip blood samples.

Arterial O_2 saturation (S_{a,O_2}) was not measured in this study and was assumed to be 0·97, as was reported for the same subjects during another exercise protocol in similar conditions (D. L. Turner,

TABLE 1. Mean values (±S.D.) of the measured and calculated variables, at rest and during exercise (50, 100 and 150 W), in the three tested conditions

	$\dot{V}_{O_2}$ (l min^{-1})	$\dot{Q}$ (l min^{-1})	HR (min^{-1})	SV (ml)	$(C_{a,O_2}-C_{v,O_2})$ (ml l^{-1})	$\dot{Q}_{a,O_2}$ (l min^{-1})	$O_{2,ext}$
Rest							
Normaemia	0·37±0·05	8·7±1·0	76±10	113±19	43·4±8·8	1·70±0·18	0·22±0·04
Training	0·35±0·05	7·2±1·4	69·5±5	106±17	50·8±14·1	1·43±0·29	0·25±0·07
Polycythaemia	0·40±0·05	6·8±1·6	71±9	96±15	59·4±8·4	1·45±0·31	0·28±0·04
P (ANOVA)	n.s.	0·01	0·01	n.s.	0·02	n.s.	n.s.
Bonferroni		N−P	N−T, N−P		N−P		
50 W							
Normaemia	1·30±0·15	14·7±1·7	112±15	134±12	89·1±12·2	2·87±0·34	0·46±0·05
Training	1·30±0·10	13·0±1·1	107±11	120±13	98·5±11·2	2·60±0·25	0·50±0·06
Polycythaemia	1·23±0·09	11·4±1·3	102±12	113±7	109·0±12·5	2·43±0·25	0·51±0·06
P (ANOVA)	n.s.	0·01	0·01	n.s.	0·001	n.s.	n.s.
Bonferroni		N−T, N−P	N−T, N−P		N−P		
100 W							
Normaemia	1·79±0·16	16·2±1·9	131±15	123±10	112·0±17·4	3·17±0·35	0·57±0·08
Training	1·81±0·13	15·9±1·0	121±12	130±11	112·0±12·0	3·17±0·20	0·57±0·07
Polycythaemia	1·76±0·12	14·8±0·9	116±13	129±14	119·5±11·1	3·14±0·18	0·56±0·06
P (ANOVA)	n.s.	0·04	0·001	n.s.	n.s.	n.s.	n.s.
Bonferroni		N−P	N−T, N−P				
150 W							
Normaemia	2·32±0·18	18·7±1·4	150±18	127±16	124·5±13·8	3·67±0·31	0·64±0·08
Training	2·32±0·13	17·7±1·4	137±16	129±17	129·9±14·8	3·55±0·31	0·66±0·08
Polycythaemia	2·34±0·07	16·4±1·9	131±13	126±17	144·5±18·5	3·48±0·38	0·68±0·09
P (ANOVA)	n.s.	0·02	0·001	n.s.	n.s.	n.s.	n.s.
Bonferroni		N−P	N−T, N−P				

Abbreviations: $\dot{V}_{O_2}$, oxygen flow; $\dot{Q}$, cardiac output; HR, heart rate; SV, stroke volume; $C_{a,O_2}-C_{v,O_2}$ = arterial–venous oxygen concentration difference; $\dot{Q}_{a,O_2}$, arterial oxygen delivery; $O_{2,ext}$, oxygen extraction coefficient; N, normaemia; T, post-training; P, polycythaemia.

H. Hoppeler, C. Noti, H. P. Gürtner, H. Gerber & G. Ferretti, unpublished observation). Arterial O_2 concentration (C_{a,O_2}, ml l^{-1}) was calculated as:

$$C_{a,O_2} = [Hb] \times S_{a,O_2} \times 1{\cdot}34, \quad (1)$$

where 1·34 is the physiological O_2 binding coefficient of haemoglobin. ($C_{a,O_2} - C_{v,O_2}$, ml l^{-1}) was calculated as the ratio of $\dot{V}_{O_2}$ to $\dot{Q}$. Arterial O_2 delivery ($\dot{Q}_{a,O_2}$, l min^{-1}) was calculated as the product of $\dot{Q}$ times C_{a,O_2}. The O_2 extraction coefficient ($O_{2,ext}$) was calculated as the ratio of $\dot{V}_{O_2}$ to $\dot{Q}_{a,O_2}$. $O_{2,ext}$ is also equal to $(C_{a,O_2} - C_{v,O_2})/C_{a,O_2}$. The stroke volume of the heart (in ml) was calculated as the ratio of $\dot{Q}$ to HR.

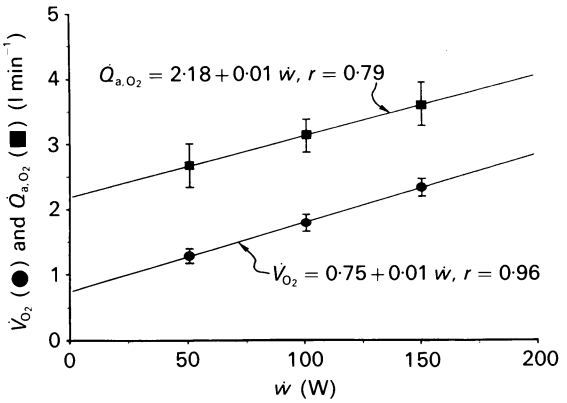

Fig. 2. Arterial oxygen delivery ($\dot{Q}_{a,O_2}$, l min^{-1}) and oxygen flow ($\dot{V}_{O_2}$, l min^{-1}) as a function of power output ($\dot{w}$). The points represent the mean values obtained at each work load. Bars indicate S.D. The two regression lines depicted by the equations given in the figure were calculated using all individual values regardless of the tested condition.

Statistics

Data are reported as means ± S.D. Changes in the various measured and calculated parameters in the three tested conditions (N, T and P) were assessed by ANOVA. A *post hoc* Bonferroni test was used to determine differences between pairs. When appropriate, differences between regression lines were assessed by ANOVA according to the methods of Kleinbaum, Kupper & Muller (1988). Normal distribution of errors was assumed. The results were considered significant if $P < 0{\cdot}05$.

RESULTS

Haemoglobin

During the training programme, [Hb] increased from 152 ± 6 (N) to 156 ± 6 (T) g l^{-1} ($P < 0{\cdot}05$). After autologous red cell reinfusion, [Hb] increased from 156 ± 6 (T) to 165 ± 8 (P) g l^{-1} ($P < 0{\cdot}05$). Relative changes in C_{a,O_2} are described in Fig. 1.

Submaximal exercise

The measured and calculated parameters are presented in Table 1. $\dot{V}_{O_2}$ and $\dot{Q}_{a,O_2}$ at each work load were unchanged in the three tested conditions. Hence the linear relationships between either $\dot{V}_{O_2}$ or $\dot{Q}_{a,O_2}$ and $\dot{w}$, shown in Fig. 2, were calculated regardless of the observed changes in C_{a,O_2} and therefore represent the overall set of

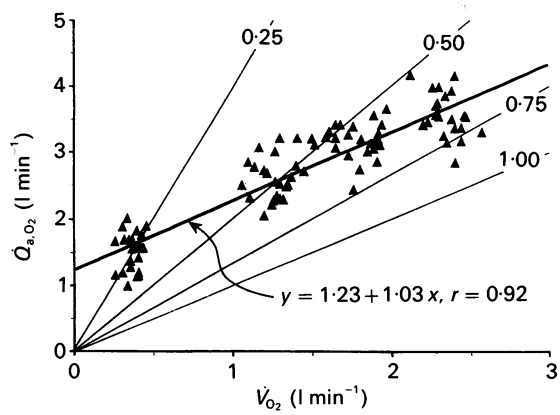

Fig. 3. Arterial oxygen delivery ($\dot{Q}_{a,O_2}$) as a function of oxygen flow ($\dot{V}_{O_2}$), for the overall set of data. The thick line is the regression line through all individual points. Thin lines are isopleths for oxygen extraction coefficient ($= \dot{V}_{O_2}/\dot{Q}_{a,O_2}$).

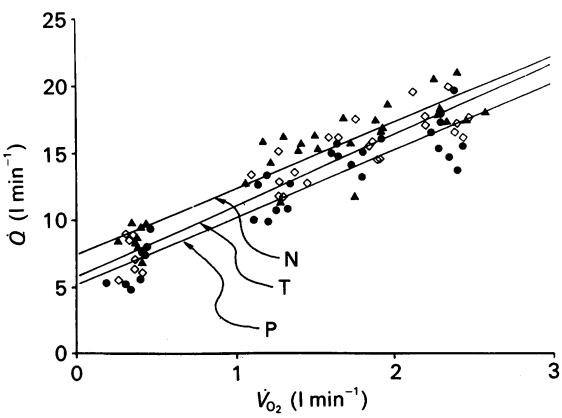

Fig. 4. Cardiac output ($\dot{Q}$, l min^{-1}) as a function of oxygen flow ($\dot{V}_{O_2}$, l min^{-1}) in normaemia (N, ▲), post-training (T, ◇) and in polycythaemia (P, ●). The three regression lines are described by the following equations: for N, $\dot{Q} = 7{\cdot}37 + 4{\cdot}99\ \dot{V}_{O_2}$ ($r = 0{\cdot}92$); for T, $\dot{Q} = 5{\cdot}79 + 5{\cdot}31\ \dot{V}_{O_2}$, $r = 0{\cdot}94$; for P, $\dot{Q} = 5{\cdot}14 + 5{\cdot}03\ \dot{V}_{O_2}$ ($r = 0{\cdot}93$). The three lines have the same slope, but different intercepts, the difference being significant between N and P ($P < 0{\cdot}05$).

data. The two lines of Fig. 2 are parallel. In Fig. 3, $\dot{Q}_{a,O_2}$ is plotted as a function of $\dot{V}_{O_2}$, regardless of the tested condition. The obtained linear relationship has a slope of 1·03. The regression line crosses isopleths of higher $O_{2,ext}$ as $\dot{V}_{O_2}$ increases.

Figure 4 shows the linear relationship between $\dot{Q}$ and $\dot{V}_{O_2}$. Three regression lines were drawn, corresponding to normaemia (N), post-training (T) and polycythaemia (P). Statistical analysis showed that the three regression lines have the same slope, but different intercepts, the difference being significant ($P < 0{\cdot}05$) for the N *vs.* P comparison. These results show a progressive decrease in $\dot{Q}$ as C_{a,O_2} increased. Furthermore, since $\dot{V}_{O_2}$ at any workload was invariant, the above data imply that changes in $\dot{Q}$ were compensated for by equivalent opposite change in $(C_{a,O_2} - C_{v,O_2})$.

Figure 5 shows that the HR *vs.* $\dot{V}_{O_2}$ relationship also tended to be shifted downward when moving from N to T and subsequently to P. As a consequence, at any work load, the stroke volume was similar in the three tested conditions (see Table 1).

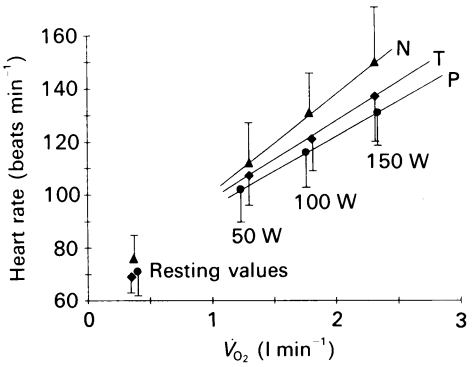

Fig. 5. Heart rate as a function of oxygen flow ($\dot{V}_{O_2}$). The points represent the mean values obtained at each work load in normaemia (N, ▲), post-training (T, ◇) and polycythaemia (P, ●). Bars indicate S.D. The regression lines through the individual points obtained during exercise in N, T and P are not statistically different.

DISCUSSION

Constancy of Q_{a,O_2} at each submaximal work load

At the steady state of constant-load submaximal exercise, the $\dot{V}_{O_2}$ *vs.* $\dot{w}$ relationship was identical in N, T and P, and therefore independent of the training condition and of the induced haematological changes (see Fig. 2). Steady-state O_2 flow, which is equal to O_2 consumption (metabolic power output), is primarily set by the mechanical work rate. Therefore, O_2 flow can be taken as an independent parameter. All other variables defining the functional relations within the respiratory system should then be adjusted in order to maintain the appropriate $\dot{V}_{O_2}$ at any work rate and/or metabolic rate.

Figure 2 shows that $\dot{Q}_{a,O_2}$ was also independent of the manipulations carried out in the present study, increasing linearly as a function of power. This implies that, at each submaximal work load, $\dot{Q}_{a,O_2}$ was invariant. Since $\dot{Q}_{a,O_2}$ is the product of $\dot{Q}$ and C_{a,O_2}, any change in C_{a,O_2} must have been compensated for by inverse proportional changes in $\dot{Q}$. As a consequence, the relationship between $\dot{Q}$ and C_{a,O_2} at any $\dot{V}_{O_2}$ (or $\dot{Q}_{a,O_2}$) level can be described by an equilateral hyperbola. Four equilateral hyperbolas, calculated from the mean values of $\dot{Q}_{a,O_2}$ obtained at rest and at each tested work load, are drawn in Fig. 6. The individual measured $\dot{Q}$ *vs.* C_{a,O_2} data cluster well around the corresponding theoretical hyperbola. Figure 6 may explain the different $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ relationships shown in Fig. 4. Indeed, it appears from Fig. 4 and Table 1, that $\dot{Q}$ was lower in those conditions in which C_{a,O_2} was increased. The different $\dot{Q}$ values at any work load seem to have resulted from changes in HR (Fig. 5) rather than in stroke volume.

Figures 4 and 6 provide support against the hypothesis of a constant $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ relationship (Cerretelli & di Prampero, 1987). They are consistent with the opposite changes in the $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ relationship reported to occur in acute hypoxia (Stenberg *et al.* 1966; Kontos, Levasseur, Richardson, Manck & Patterson, 1967; Hughes *et al.*

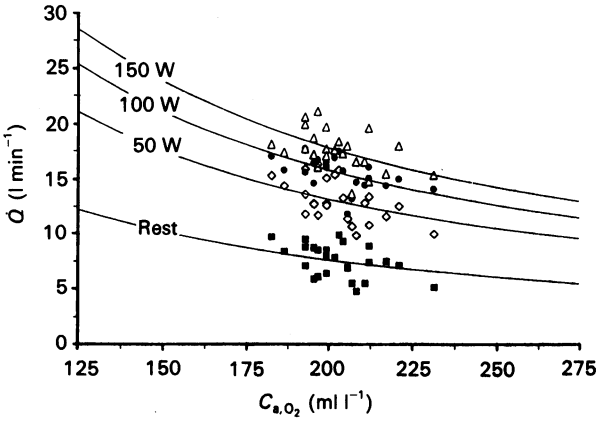

Fig. 6. Cardiac output ($\dot{Q}$) as a function of arterial oxygen concentration (C_{a,O_2}). Four equilateral hyperbolas are drawn corresponding to the mean values of arterial oxygen delivery ($\dot{Q}_{a,O_2} = \dot{Q}C_{a,O_2}$) obtained at rest and each tested work load. The individual data (■, at rest; ◇, at 50 W; ●, 100 W; △ 150 W) appear to cluster well around the corresponding $\dot{Q}_{a,O_2}$ hyperbola.

1968; Hartley, Vogel & Landowne, 1973) and in acute normoxia (Ferretti *et al.* 1990; Ferretti, 1990). They are also compatible with the finding that submaximal $\dot{Q}$ is higher in acute anaemia than in normaemia, as observed both in humans (Freedson, 1981; Celsing, Nyström, Pihlstedt, Werner & Ekblom, 1986; Woodson, Wills & Lenfant, 1978) and in dogs (Richardson & Guyton, 1959).

The hypothesis put forward in the Introduction is thus strengthened by the present results. At any submaximal work load, $\dot{Q}_{a,O_2}$ seems to be regulated, such that $\dot{Q}$ is adjusted in response to changes in C_{a,O_2}, so as to maintain a constant $\dot{Q}_{a,O_2}$ at any given $\dot{V}_{O_2}$

Constancy of oxygen flow in mixed venous blood

As shown in Fig. 3, a linear relationship was found between $\dot{Q}_{a,O_2}$ and $\dot{V}_{O_2}$. Each point of that relationship lies on an origin-irradiating isopleth for $O_{2,ext}$ ($= \dot{V}_{O_2}/\dot{Q}_{a,O_2}$). The $\dot{Q}_{a,O_2}$ *vs.* $\dot{V}_{O_2}$ line has a positive intercept, reflecting the higher $\dot{Q}_{a,O_2}$ than $\dot{V}_{O_2}$ at any work load. Therefore, as the exercise intensity increases, involving a progressively greater active muscle mass, the $\dot{Q}_{a,O_2}$ *vs.* $\dot{V}_{O_2}$ relationship crosses isopleths of progressively higher $O_{2,ext}$. Indeed, this also appears to be the case for the data of $O_{2,ext}$ presented in Table 1.

The $\dot{Q}_{a,O_2}$ vs. $\dot{V}_{O_2}$ line is obviously parallel to an $O_{2,ext}$ isopleth, which corresponds to the maximal theoretical O_2 extraction coefficient. This is the $O_{2,ext}$ that could be achieved if $\dot{Q}_{a,O_2}$ and $\dot{V}_{O_2}$ were equal to infinity. The line is thus parallel to the isopleth

corresponding to an $O_{2,ext}$ of 1, whereby the slope ($\Delta\dot{Q}_{a,O_2}/\Delta\dot{V}_{O_2}$) of the line at stake is to be 1. This is indeed the case for the regression line through the individual experimental points from which Fig. 3 has been obtained (slope of 1·03, which is statistically not different from 1).

Figure 3 was constructed from Fig. 2 by transposition of the $\dot{V}_{O_2}$ ordinate. The slope of the line in Fig. 3 is equal to the ratio of the slopes of the two lines in Fig. 2 ($\Delta\dot{Q}_{a,O_2}/\Delta\dot{w}$ and $\Delta\dot{V}_{O_2}/\Delta\dot{w}$, respectively, where $\dot{w}$ is power). Therefore, if the slope of the $\dot{Q}_{a,O_2}$ *vs.* $\dot{V}_{O_2}$ relationship is 1, then the functions relating $\dot{Q}_{a,O_2}$ or $\dot{V}_{O_2}$ to power must be parallel. Indeed, this is what can be seen from the statistical comparison of the two regression lines plotted in Fig. 2 (different intercepts, $P < 0{\cdot}001$; slopes not different, $P > 0{\cdot}50$).

This finding implies that the difference between the two functions in Fig. 2 is a constant:

$$\dot{Q}_{a,O_2}(\dot{w}) - \dot{V}_{O_2}(\dot{w}) = K. \tag{2}$$

Developing eqn (1) yields:

$$\dot{Q}(\dot{w})\,C_{a,O_2} - \dot{Q}(\dot{w})\,(C_{a,O_2} - C_{v,O_2})\,(\dot{w}) = K. \tag{3}$$

whose resolution is:

$$\dot{Q}(\dot{w})\,C_{v,O_2}(\dot{w}) = K. \tag{4}$$

Equation (4) shows that the product of $\dot{Q}$ and C_{v,O_2}, i.e. the O_2 flow in mixed venous blood ($\dot{Q}_{v,O_2}$), is a constant, whatever the exercise level. This would suggest that $\dot{Q}_{v,O_2}$ may play a key role in determining the cardiovascular response to exercise. If this is the case, an O_2 flow sensor must be located in the right heart or on the arterial side of pulmonary circulation.

Conclusions

This study provides further evidence against the classical notion of a constant $\dot{Q}$ *vs.* $\dot{V}_{O_2}$ relationship. At any work load, cardiac output appears to be inversely proportional to arterial O_2 delivery, adequate to each metabolic level, as suggested by the tested hypothesis. The relationship between O_2 delivery and O_2 flow has a slope equal to 1. Hence, the functions relating arterial O_2 delivery and O_2 flow to power have equal slopes. As a consequence, the difference between these two functions, corresponding to the O_2 flow in mixed venous blood, is a constant. This finding suggests that the O_2 flow in mixed venous blood may play a key role in the regulation of the cardiovascular response to exercise.

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