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Phase I dynamics of cardiac output, systemic O_2 delivery, and lung O_2 uptake at exercise onset in men in acute normobaric hypoxia

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Lador F, Tam E, Azabji Kenfack M, Cautero M, Moia C, Morel DR, Capelli C, Ferretti G. Phase I dynamics of cardiac output, systemic O_2 delivery, and lung O_2 uptake at exercise onset in men in acute normobaric hypoxia. *Am J Physiol Regul Integr Comp Physiol* 295: R624–R632, 2008. First published May 21, 2008; doi:10.1152/ajpregu.00797.2007.—We tested the hypothesis that vagal withdrawal plays a role in the rapid (phase I) cardiopulmonary response to exercise. To this aim, in five men (24.6 ± 3.4 yr, 82.1 ± 13.7 kg, maximal aerobic power 330 ± 67 W), we determined beat-by-beat cardiac output ($\dot{Q}$), oxygen delivery ($\dot{Q}a_{O_2}$), and breath-by-breath lung oxygen uptake ($\dot{V}O_2$) at light exercise (50 and 100 W) in normoxia and acute hypoxia (fraction of inspired O_2 = 0.11), because the latter reduces resting vagal activity. We computed $\dot{Q}$ from stroke volume (Q_{st}, by model flow) and heart rate (f_H, electrocardiography), and $\dot{Q}a_{O_2}$ from $\dot{Q}$ and arterial O_2 concentration. Double exponentials were fitted to the data. In hypoxia compared with normoxia, steady-state f_H and $\dot{Q}$ were higher, and Q_{st} and $\dot{V}O_2$ were unchanged. $\dot{Q}a_{O_2}$ was unchanged at rest and lower at exercise. During transients, amplitude of phase I (A_1) for $\dot{V}O_2$ was unchanged. For f_H, $\dot{Q}$ and $\dot{Q}a_{O_2}$, A_1 was lower. Phase I time constant (τ_1) for $\dot{Q}a_{O_2}$ and $\dot{V}O_2$ was unchanged. The same was the case for $\dot{Q}$ at 100 W and for f_H at 50 W. Q_{st} kinetics were unaffected. In conclusion, the results do not fully support the hypothesis that vagal withdrawal determines phase I, because it was not completely suppressed. Although we can attribute the decrease in A_1 of f_H to a diminished degree of vagal withdrawal in hypoxia, this is not so for Q_{st}. Thus the dual origin of the phase I of $\dot{Q}$ and $\dot{Q}a_{O_2}$, neural (vagal) and mechanical (venous return increase by muscle pump action), would rather be confirmed.

cardiovascular response

ALTHOUGH OUR KNOWLEDGE of the central (neural) control of the cardiovascular system at the exercise steady state is quite well established (19, 42, 57), how the circulatory readjustments upon exercise onset occur and match the increase in pulmonary oxygen uptake ($\dot{V}O_2$) is less understood, as are the mechanisms underlying this matching. The kinetics of $\dot{V}O_2$ at exercise onset were seen for a long time as reflecting essentially the metabolic adaptations in the working muscles (15, 31, 33). Some authors, however, soon identified two components of the $\dot{V}O_2$ kinetics: *1*) a rapid, almost immediate phase (phase I) (5, 54, 55), which they attributed to an immediate increase in cardiac output ($\dot{Q}$) at exercise start; and *2*) a subsequent slower phase (phase II), to which they restricted the influence of muscle metabolic adjustments. The strongest support to this view came from the demonstration that the kinetics of $\dot{Q}$ (12, 13, 16, 60) and arterial O_2 flow ($\dot{Q}a_{O_2}$) (27) are very rapid.

The concept of a close correspondence between $\dot{V}O_2$ and muscle O_2 consumption was further undermined by the recent demonstration that, upon the onset of light exercise, the $\dot{V}O_2$ kinetics are faster than the kinetics of muscle O_2 consumption estimated from the monoexponential decrease in phosphocreatine concentration (7, 14, 43). This would imply dissociation of the kinetics of $\dot{V}O_2$ and muscle O_2 consumption, which should respond to different control mechanisms.

Our postulate is that the $\dot{V}O_2$ kinetics are dictated by the regulation of the systemic cardiovascular response to exercise, whereas the metabolic regulatory processes dictate only the kinetics of muscle O_2 consumption. In this context, Fagraeus and Linnarsson (18) proposed that the rapid heart rate (f_H) changes in exercise transients "are mediated through a withdrawal of vagal tone" (termed "vagal withdrawal" from this point), which can be defined as a quasi-immediate inhibition of vagal action on the sinus node at exercise start. In fact, they showed that the rapid phase of the f_H kinetics was cancelled out under vagal blockade, whereas β-adrenergic blockade with propranolol did not affect it. In this study, we tested the hypothesis that vagal withdrawal also plays a major role in determining phase I kinetics of $\dot{Q}$, $\dot{Q}a_{O_2}$, and $\dot{V}O_2$. If this is so, then in acute normobaric hypoxia, wherein reduced vagal activity (8, 26) and increased sympathetic activity at rest have been postulated (21, 26, 58, 59), phase I would be either absent or at least less intense compared with normoxia.

With this hypothesis in mind, the aim of this study was to perform simultaneous determinations of the phase I kinetics of f_H, $\dot{Q}$, $\dot{Q}a_{O_2}$, and $\dot{V}O_2$ upon exercise onset in normoxia and acute normobaric hypoxia. Such an experiment was never carried out in the past, to the best of our knowledge.

METHODS

Subjects. Five healthy, nonsmoking young male subjects took part in the experiments. They were 24.6 ± 3.4 yr old, 1.79 ± 0.09 m tall, and weighed 82.1 ± 13.7 kg. Their maximal O_2 consumption and maximal aerobic mechanical power in normoxia were 4.42 ± 0.62 l/min and 330 ± 67 W, respectively. The corresponding values in hypoxia were 3.41 ± 0.83 l/min and 255 ± 78 W, respectively. All

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subjects were preliminarily informed of all procedures and risks associated with the experimental testing. Informed consent was obtained from each volunteer, who was aware of his right to withdraw from the study at any time without jeopardy. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Comités d'Ethique des Hôpitaux Universitaires Genevois (Switzerland). The experiments were carried out at Geneva, Switzerland.

Measurements. $\dot{V}O_2$ was determined on a breath-by-breath basis. The time course of O_2 and CO_2 partial pressures throughout the respiratory cycles were continuously monitored with a mass spectrometer (Balzers Prisma, Balzers, Liechtenstein) calibrated against gas mixtures of known composition. The inspiratory and expiratory ventilations were measured by an ultrasonic flowmeter (Spiroson; Ecomedics, Duernten, Switzerland) calibrated with a 3-liter syringe. The alignment of traces was corrected for the time delay between the flowmeter and the mass spectrometer. Breath-by-breath $\dot{V}O_2$ and CO_2 output ($\dot{V}CO_2$) were then computed off-line by means of a modified version of Grønlund's algorithm (9). Software purposely written under the Labview developing environment (Labview 5.0; National Instruments, Austin, TX) was used. The characteristics and physiological implications of Grønlund's algorithm are widely discussed elsewhere (9, 11, 27).

f_H and arterial oxygen saturation (Sa_{O_2}) were continuously measured using electrocardiography (Elmed ETM 2000; Heiligenhaus, Germany) and fingertip infrared oximetry (Ohmeda 2350; Finapres, Englewood, CO), respectively. In hypoxia, Sa_{O_2} data were corrected for time delay between lungs and fingertip (30). Continuous recordings of arterial pulse pressure were obtained at a fingertip of the right arm by means of a noninvasive cuff pressure recorder (Portapres; FMS, Amsterdam, The Netherlands). Beat-by-beat mean arterial pressure (P) was computed as the integral mean of each pressure profile using the Beatscope software package (FMS).

The stroke volume of the heart (Q_{st}) was determined on a beat-by-beat basis by means of the model flow method (53), applied off-line to the pulse pressure profiles, again using the Beatscope software package. Beat-by-beat $\dot{Q}$ was computed as the product of single-beat Q_{st} times the corresponding single-beat f_H. Correction for the inaccuracy of the method was applied as previously described (2, 27, 50). To this purpose, steady-state $\dot{Q}$ values also were obtained by means of the open-circuit acetylene method (4) using a procedure that was previously described (27). Individual correction factors at rest and at each workload were calculated as previously described (27) and also applied during dynamic states with rapid changes in $\dot{Q}$ (51).

Exercise was carried out on an electrically braked cycle ergometer (Ergometrics 800-S; Ergoline, Bitz, Germany). The pedaling frequency was recorded, and its sudden increase at the exercise onset and decrease at the exercise offset were used as markers to identify precisely the start and the end of exercise. The electromechanical characteristics of the ergometer were such as to permit workload application in <50 ms. All the signals were digitalized in parallel by a 16-channel analog-to-digital converter (MP100; Biopac Systems, Goleta, CA) and stored on a computer. The acquisition rate was 100 Hz.

Blood hemoglobin concentration ([Hb]) was measured using a photometric technique (HemoCue, Ängelholm, Sweden) on 10-μl blood samples from a peripheral venous line inserted in the left forearm. Blood lactate concentration ($[La]_b$) was measured using an electroenzymatic method (Eppendorf EBIO 6666, Erlangen, Germany) on 20-μl blood samples from the same venous line. Arterial blood gas composition was measured with microelectrodes (Instrumentation Laboratory Synthesis 10, Lexington, MA) on 300-μl blood samples taken from an arterial catheter inserted in the left radial artery.

Protocol. Experiments were first performed in normoxia and then in acute normobaric hypoxia (fraction of inspired O_2, 0.11; inspired O_2 partial pressure, 80 mmHg). In hypoxia, inspired gas was administered from high-pressure gas cylinders via an 80-liter Douglas bag buffer. The fraction of inspired O_2 was monitored on the inspiratory line, close to the mouth. The gas flow from the cylinders was continuously adjusted to the subject's ventilation. Experiments in hypoxia were preceded by a 10-min period for gas store equilibration. The experimental protocol started with the performance of blood sampling and the measurement of acetylene $\dot{Q}$ at rest, and then 2 min of quiet resting recordings were allowed, after which the exercise at 50 W started, for a duration of 10 min. Arterial blood gas composition and $[La]_b$ were measured at *minute 5* and at the end of exercise. At *minute 7*, the measurement of $\dot{Q}$ with the acetylene technique was initiated. The 50-W exercise was followed by a 10-min recovery, during which $[La]_b$ was measured at *minutes 2*, *4*, and *6*, and arterial blood gas composition was determined at *minutes 5* and *10*. The 100-W exercise was then carried out, for a 10-min duration, and with the same timing of events as at 50 W. A 10-min recovery followed, with the same characteristics as the previous one. The overall duration of this protocol was about 60 min, during which [Hb] was systematically measured at 1-min intervals.

Each subject repeated this protocol four times, in both normoxia and hypoxia. At each repetition, the performance of blood sampling for [Hb] determination was shifted by 15 s, as previously described (27), to obtain, after superposition of the four tests, an overall description of the changes in [Hb] on a 15-s time basis.

Data treatment. The superimposed time course of [Hb] was smoothed by a four-sample mobile mean, to account for interrepetition variability, and interpolated by means of a 6th degree polynomial, as previously described (27). The continuous Sa_{O_2} traces from the four repetitions were temporally aligned and superimposed by means of an ensemble average procedure. The resulting overall Sa_{O_2} trace was then interpolated by means of a 6th degree polynomial. The resulting functions, describing the time course of [Hb] and Sa_{O_2}, were used to compute the time course of arterial O_2 concentration (Ca_{O_2}, ml/l) on an equivalent beat-by-beat time scale, established after the pulse pressure profile traces, as in a previous study (27).

The beat-by-beat f_H, Q_{st}, P, and $\dot{Q}$ values from the four repetitions of each subject were aligned temporally by setting the time of exercise start as *time 0* for the analysis of on kinetics. The data were then averaged on a beat-by-beat basis to obtain a single averaged, superimposed time series for each parameter and subject. Beat-by-beat $\dot{Q}a_{O_2}$ was then calculated as

$$\dot{Q}a_{O_2}(t) = \dot{Q}(t) \times Ca_{O_2}(t) \quad (1)$$

Beat-by-beat total peripheral resistance (R_p) was calculated by dividing each P value by the corresponding $\dot{Q}$ value, on the assumption that the pressure in the right atrium can be neglected as a determinant of peripheral resistance.

Based on the conclusions arrived at in a previous study (27), the kinetics of $\dot{V}O_2$, $\dot{Q}$, and $\dot{Q}a_{O_2}$ were described by means of a two-phase model, whereby an exponential increase in flow (phase II) is preceded by a faster flow increase in the first seconds of exercise (phase I), which Barstow and Molé (5) also treated as an exponential. To compute the characteristic parameters of the exponential equations describing phase I, the four repetitions were interpolated to 1-s intervals (28) and then aligned temporally, as described above, and averaged to obtain a single superimposed time series (27). Since the tested hypothesis concerns specifically a phenomenon that takes place during phase I, in the results we report only the phase I parameters, neglecting the phase II parameters, to which the tested hypothesis does not pertain.

Statistics. Data are means and standard deviations of the values obtained for each parameter from the average superimposed files of each subject, to account for interindividual variability. The effects of exercise intensity and hypoxia on the investigated parameters were analyzed separately using a one-tailed *t*-test for paired observations. Bonferroni correction was then applied. The parameters of the models were estimated by utilizing a weighted nonlinear least squares proce-

dure (10), implemented under Labview (version 5.0; National Instruments, Austin TX). Initial guesses of the parameters of the model were entered after visual inspection of the data. The effects of exercise intensity and hypoxia on these values were investigated using a one-tailed *t*-test for paired observations. The results were considered significant if $P < 0.025$.

RESULTS

The [Hb], Sa_{O_2}, and Ca_{O_2} values at rest and at the exercise steady state are reported in Table 1, together with arterial blood pH, P_{O_2}, and P_{CO_2}. The Sa_{O_2} and Ca_{O_2} values in hypoxia were lower than the corresponding values in normoxia. Arterial blood pH was higher in hypoxia than in normoxia and was unaffected by the exercise intensity in both conditions. P_{O_2} and P_{CO_2} were both lower in hypoxia than in normoxia. In the latter, they did not vary at exercise. In hypoxia, P_{O_2} decreased during exercise ($P < 0.025$) and P_{CO_2} tended to decrease (not significant, NS). In normoxia, $[La]_b$ was 1.3 ± 0.3 mM at rest and did not change at exercise. In hypoxia, $[La]_b$ was 2.0 ± 0.5 mM at rest and 2.3 ± 0.5 mM at 50 W (NS). At 100 W, $[La]_b$ increased to 3.7 ± 1.3 mM at *minute 5* and 4.5 ± 1.7 mM at *minute 10*.

The mean values for $\dot{Q}$, f_H, Q_{st}, $\bar{P}$, R_p, $\dot{Q}a_{O_2}$, and $\dot{V}_{O_2}$, obtained at rest and at the exercise steady state at both powers, are reported in Table 2. At all metabolic powers, f_H was higher in hypoxia than in normoxia. Q_{st} was the same in hypoxia as in normoxia so that $\dot{Q}$ resulted systematically higher in hypoxia than in normoxia. At rest, $\bar{P}$ was lower in hypoxia than in normoxia, but this difference disappeared at exercise. As a consequence, systematically lower R_p values were found in hypoxia than in normoxia (NS at rest, $P < 0.025$ at 50 and 100 W). $\dot{Q}a_{O_2}$ was not significantly different from normoxia at rest. At 50 and 100 W, however, $\dot{Q}a_{O_2}$ turned out lower in hypoxia than in normoxia. $\dot{V}_{O_2}$ was the same in hypoxia as in normoxia.

The time courses of f_H, Q_{st}, $\dot{Q}$, $\bar{P}$, and R_p upon the onset of 50- and 100-W exercise are shown in Fig. 1. Beat-by-beat data collected in the 15 s that preceded and in the 45 s that followed the start of exercise are shown in Fig. 1, to draw attention to phase I events. In normoxia, a steady state for f_H appeared as soon as phase I was completed at 50 W, whereas a clear slower phase II increase was evident at 100 W. In hypoxia, the relative contribution of phase I to the f_H response was less than in normoxia. The time course of Q_{st} was the same in hypoxia as in normoxia. Thus the initial change of $\dot{Q}$ in hypoxia, compared with normoxia, followed essentially the same patterns as for f_H. The increase in $\bar{P}$ was modest and slow, in both normoxia and hypoxia. Conversely, R_p underwent a sudden dramatic decrease, the amplitude of which was smaller in hypoxia than in normoxia.

Table 1. *Oxygen, hemoglobin, and pH in arterial blood*

Workload	Rest	50 W	100 W
	Normoxia		
[Hb], g/l	147.4±10.0	149.8±9.7	153.4±10.6
Sa_{O_2}	0.965±0.007	0.965±0.004	0.956±0.012
Ca_{O_2}, ml/l	190.5±12.7	193.7±12.1	196.4±11.6
pH	7.41±0.01	7.42±0.01	7.41±0.01
Pa_{O_2}, mmHg	85.8±3.9	88.6±3.2	86.4±2.1
Pa_{CO_2}, mmHg	38.4±1.6	36.8±1.6	37.7±2.4
	Hypoxia		
[Hb], g/l	151.9±9.3	153.1±10.8	155.5±10.9
Sa_{O_2}	0.676±0.046*	0.608±0.055*	0.578±0.075*
Ca_{O_2}, ml/l	137.7±14.5*	121.5±34.9*	121.0±22.4*
pH	7.47±0.02*	7.48±0.02*	7.48±0.02*
Pa_{O_2}, mmHg	39.5±5.1*	35.2±3.3*	33.2±2.9*
Pa_{CO_2}, mmHg	31.7±2.2*	30.9±2.3*	27.9±1.9*

Values are means + SD of steady-state values. [Hb], blood hemoglobin concentration; Sa_{O_2}, arterial O_2 saturation; Ca_{O_2}, arterial O_2 concentration; Pa_{O_2}, arterial partial pressure of O_2; Pa_{CO_2}, arterial partial pressure of CO_2. *$P < 0.25$, significantly different from corresponding value in normoxia.

Table 2. *Steady-state values of cardiopulmonary parameters at rest and at exercise at 50 and 100 W*

Workload	Rest	50 W	100 W
	Normoxia		
$\dot{Q}$, l/min	6.84±0.20	12.06±0.30	14.88±0.38
f_H, min^{-1}	74.5±1.8	98.8±1.2	114.2±1.4
Q_{st}, ml	93.3±2.3	122.7±2.8	131.7±3.4
$\dot{Q}aO_2$, l/min	1.30±0.04	2.35±0.06	2.92±0.07
$\dot{V}_{O_2}$, l/min	0.54±0.06	1.45±0.06	1.79±0.03
$\bar{P}$, mmHg	90.1±1.7	101.3±1.3	104.3±2.5
R_p, mmHg·min·l^{-1}	13.77±0.51	8.66±0.28	7.28±0.28
	Hypoxia		
$\dot{Q}$, l/min	8.58±0.37*	15.32±0.37*	19.51±0.52*
f_H, min^{-1}	87.8±2.1*	121.6±1.6*	141.8±2.0*
Q_{st}, ml	97.3±3.4	126.1±2.6	136.8±3.5
$\dot{Q}aO_2$, l/min	1.30±0.05	1.99±0.05*	2.38±0.06*
$\dot{V}_{O_2}$, l/min	0.60±0.10	1.37±0.13	1.89±0.11
$\bar{P}$, mmHg	83.6±1.3*	95.2±1.7	101.7±1.4
R_p, mmHg·min·l^{-1}	10.84±0.53	6.64±0.21*	5.70±0.17*

Values are means + SD of single-beat values over 1 min at rest and exercise steady state. $\dot{Q}$, cardiac output; f_H, heart rate; Q_{st}, stroke volume; $\dot{Q}aO_2$, systemic O_2 delivery; $\dot{V}_{O_2}$, O_2 uptake; $\bar{P}$, mean arterial pressure; R_p, peripheral resistance. *$P < 0.025$, significantly different from corresponding value in normoxia.

The evolution of beat-by-beat f_H as a function of beat-by-beat $\bar{P}$ is shown in Fig. 2. For both normoxia and hypoxia, the resting values are located on the lower left side of the plot, and the exercise steady-state values are located on the upper right side. However, the resting values in hypoxia were displaced upward and leftward with respect to those in normoxia, as were the exercise values. In normoxia, at both workloads, the pattern of displacement of the baroreflex operational point from rest to exercise was dictated by the rapid increase in f_H, as demonstrated by the small number of points required to attain the cluster of the f_H and $\bar{P}$ values at exercise. Similar patterns were observed in hypoxia, although *1*) the size of the displacement of baroreflex operational point was larger than in normoxia, and *2*) the number of beats required to complete this displacement in hypoxia (within 30 and 60 beats at 50 and 100 W, respectively) was greater (slower increase) than in normoxia (within 20 and 45 beats at 50 and 100 W, respectively).

In normoxia, since Sa_{O_2} was unchanged, the evolution of Ca_{O_2} followed the changes in [Hb]. In hypoxia, Ca_{O_2} underwent larger changes than in normoxia, which were dictated not only by the changes in [Hb] but also by the decrease in Sa_{O_2} in the exercise transient. In hypoxia, a steady Ca_{O_2} level lower than at rest was attained within 2 min.

The time courses of $\dot{Q}a_{O_2}$ and $\dot{V}_{O_2}$ upon the onset of 50- and 100-W exercise are reported in Fig. 3. The rate of readjustment

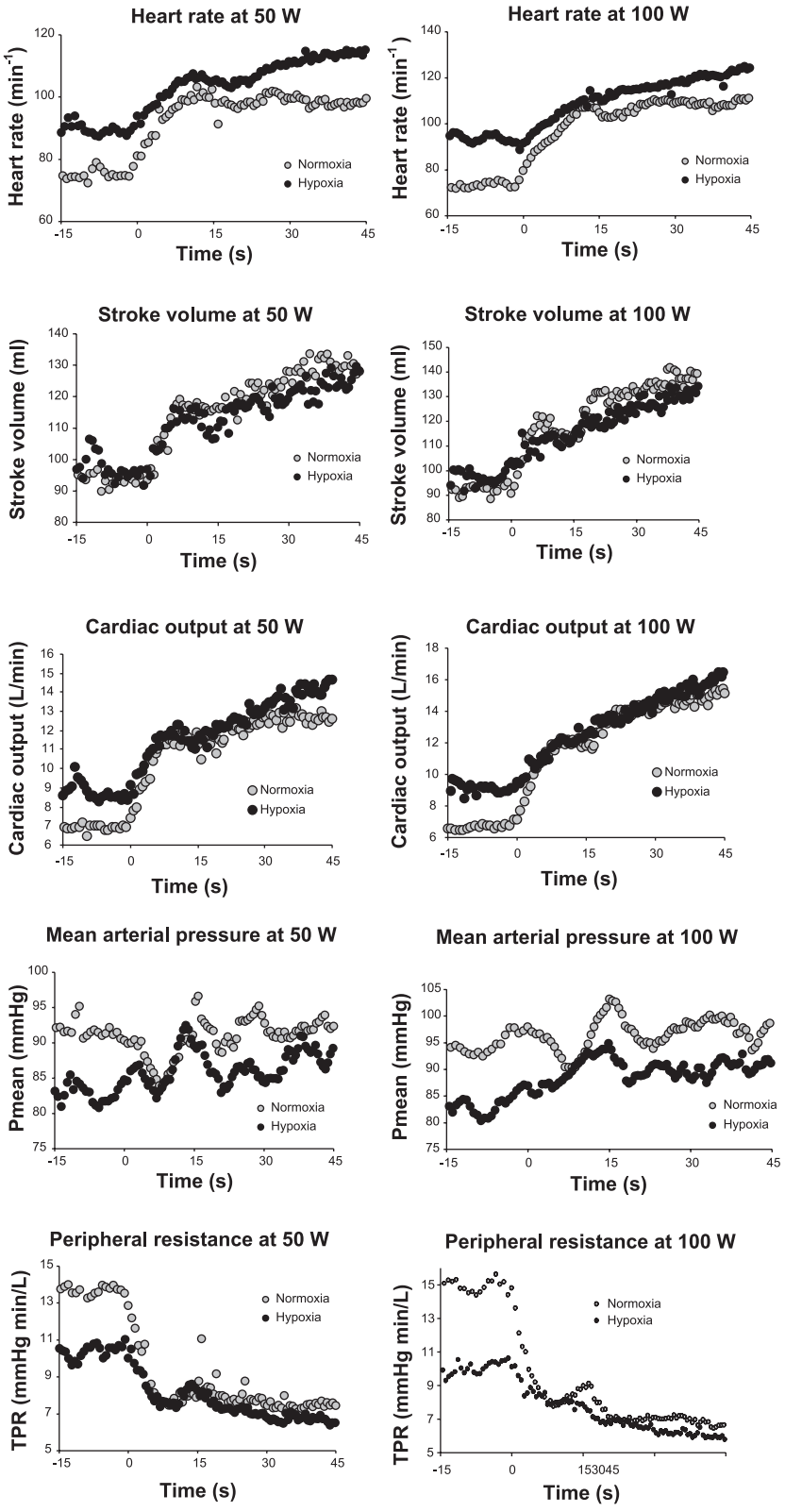

Fig. 1. Time course of investigated cardiovascular parameters upon the onset of exercise at 50 and 100 W in normoxia and hypoxia. Values are shown for heart rate, stroke volume, cardiac output, mean arterial pressure, and total peripheral resistance (TPR). Each value is the mean of the averaged superimposed values of all subjects. *Time 0* corresponds to the start of exercise.

of $\dot{V}O_2$ followed the same trend in hypoxia as in normoxia. In normoxia, it was slower than that of $\dot{Q}a_{O_2}$. This difference disappeared in hypoxia, because the rate of readjustment of $\dot{Q}a_{O_2}$ was slower in hypoxia than in normoxia.

The characteristic parameters describing the $\dot{Q}$, $\dot{Q}a_{O_2}$, $\dot{V}O_2$, and f_H kinetics during phase I are presented in Table 3. For $\dot{V}O_2$, amplitude of phase I (A_1) was the same in hypoxia as in normoxia. For $\dot{Q}$ and $\dot{Q}a_{O_2}$, A_1 was significantly lower in

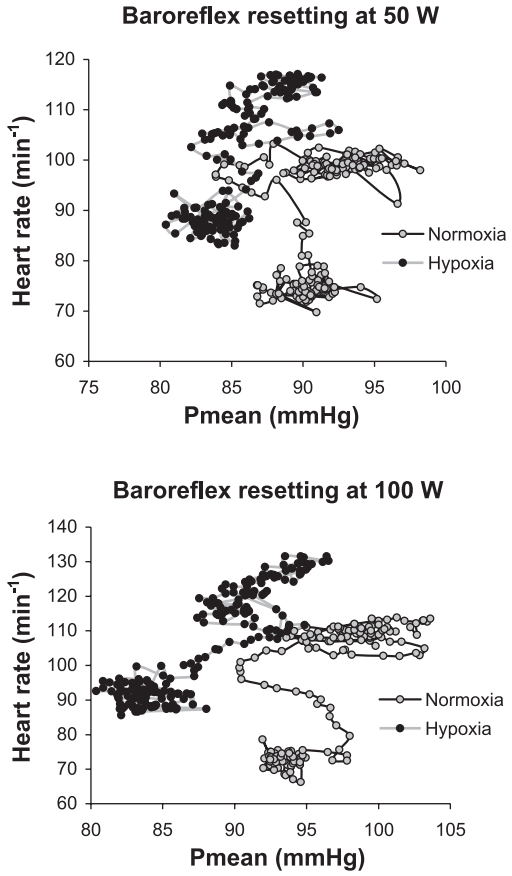

Fig. 2. Beat-by-beat heart rate as a function of the corresponding beat-by-beat mean arterial pressure (Pmean) upon the onset of exercise at 50 and 100 W in normoxia and hypoxia. The resting values are located on at *bottom left*; the exercise steady-state values are at *top right*. The resting values in hypoxia are displaced upward and leftward with respect to the corresponding values in normoxia. The pattern of displacement of the heart rate vs. Pmean operational range from rest to exercise is completed, at 50 W, within 20 and 30 beats, and at 100 W, within 45 and 60 beats, in normoxia and hypoxia, respectively.

hypoxia than in normoxia. In both normoxia and hypoxia, A_1 was the same at 100 W as at 50 W. For $\dot{Q}a_{O_2}$ and $\dot{V}O_2$, τ_1 was unaffected by hypoxia. For $\dot{Q}$, τ_1 was shorter in hypoxia than in normoxia at 50 W but not at 100 W. For f_H, A_1 was lower in hypoxia than in normoxia at 50 W but not at 100 W. In normoxia, A_1 was the same at 50 W as at 100 W, as it was in hypoxia. τ_1 was higher in hypoxia than in normoxia at 100 W but not at 50 W. In hypoxia, τ_1 was significantly greater at 100 W than at 50 W.

DISCUSSION

This study was carried out to test the hypothesis that vagal withdrawal determines the phase I kinetics of $\dot{Q}$, $\dot{Q}a_{O_2}$, and $\dot{V}O_2$ at exercise onset. This hypothesis implies that phase I would be either absent or eventually less intense compared with normoxia. The main finding of this study is that the amplitude of the phase I (A_1) of the kinetics of $\dot{Q}$ and $\dot{Q}a_{O_2}$ at exercise onset was smaller in acute normobaric hypoxia, wherein reduced vagal activity (8, 26) and increased sympathetic activity at rest have been postulated (21, 26, 58, 59), than in normoxia, whereas its time constant τ_1 was unchanged. No differences appeared concerning the phase I of $\dot{V}O_2$ kinetics. In hypoxia, the reductions in A_1 are coherent with the concept of a lesser effect of postulated vagal withdrawal at exercise onset.

Steady-state data. The increased sympathetic activity to the heart in acute hypoxia (21, 22, 44, 45), perhaps through peripheral chemoreceptor stimulation (22), may be sufficient to explain the higher f_H in hypoxia than in normoxia, both at rest and at any given work level. Since Q_{st} is unaffected by acute hypoxia, the increase in f_H entails a corresponding increase in $\dot{Q}$, as already demonstrated in several studies (1, 23, 49). The present data (see Table 2) are in full agreement with this picture.

A larger sympathetic activity, if directed to peripheral vessels as well, might also imply peripheral vasoconstriction and, hence, a greater R_p in hypoxia than in normoxia. However, this was not so in the present study, since R_p (Table 2) was lower in hypoxia than in normoxia, whether at rest or at the two investigated workloads, because a higher $\dot{Q}$ was associated with an unchanged $\bar{P}$. R_p was rarely looked at in hypoxia in the past, yet it was possible to compute it from some studies (1, 23, 49). The obtained data are coherent with those of the present study. Moreover, increased peripheral sympathetic activation in hypoxia, though providing a potent peripheral vasoconstriction stimulus, is not accompanied by increased leg vascular resistance at rest, which was rather found to be reduced compared with normoxia (22).

This apparent contradiction may be explained by admitting either of these three hypotheses : *1*) hypoxemia reduces the sensitivity and increases the activation threshold of vascular sympathetic receptors (sympatholysis); *2*) hypoxemia superimposes a vasodilating stimulus in peripheral circulation; or *3*) the intensity and quality of sympathetic output may differ among various target organs in hypoxia. The first hypothesis was recently contradicted by the demonstration that the vascular response to tyramine is not reduced in hypoxia (56). The two other hypotheses were supported by the observation of β_2-mediated vasodilatation in resting skeletal muscle in hypoxia due to increased adrenaline release (52). Peripheral O_2 sensing mechanisms may be implied in this effect. For instance, according to Stamler et al. (48), the conformation of the reduced hemoglobin determines the rise of nitric oxide (NO) in blood with consequent vasodilatation. In contradiction to this, however, Weisbrod et al. (52) failed to show a reduction of peripheral hypoxic vasodilatation after NO synthase blockade. Other Sa_{O_2}-related mechanisms were postulated, which would imply ATP-mediated vasodilatation (32). A clear picture of the events that lead to decreased R_p is still far from being established.

Phase I kinetics. The hypothesis that vagal withdrawal determines phase I relies essentially on observations made on f_H upon exercise onset in normoxia, the kinetics of which were similar in this and previous studies (6, 18, 37, 46). In fact, the fast component of f_H kinetics *1*) was cancelled out under vagal blockade (18) and *2*) was not found in heart transplant recipients, whose hearts are denervated (3, 20, 40). To extend this hypothesis to explain phase I kinetics of $\dot{Q}$, $\dot{Q}a_{O_2}$, and $\dot{V}O_2$, we should be able to demonstrate that when vagal tone is attenuated, as is the case in acute normobaric hypoxia (26), the phase I should either be reduced or disappear for all these parameters. Indeed, hypoxia reduced A_1 significantly, for $\dot{Q}$ and $\dot{Q}a_{O_2}$ (Table 3) at both 50 and 100 W and for f_H at 50 W, but did not extinguish it. On the other hand, hypoxia acted very little on τ_1,

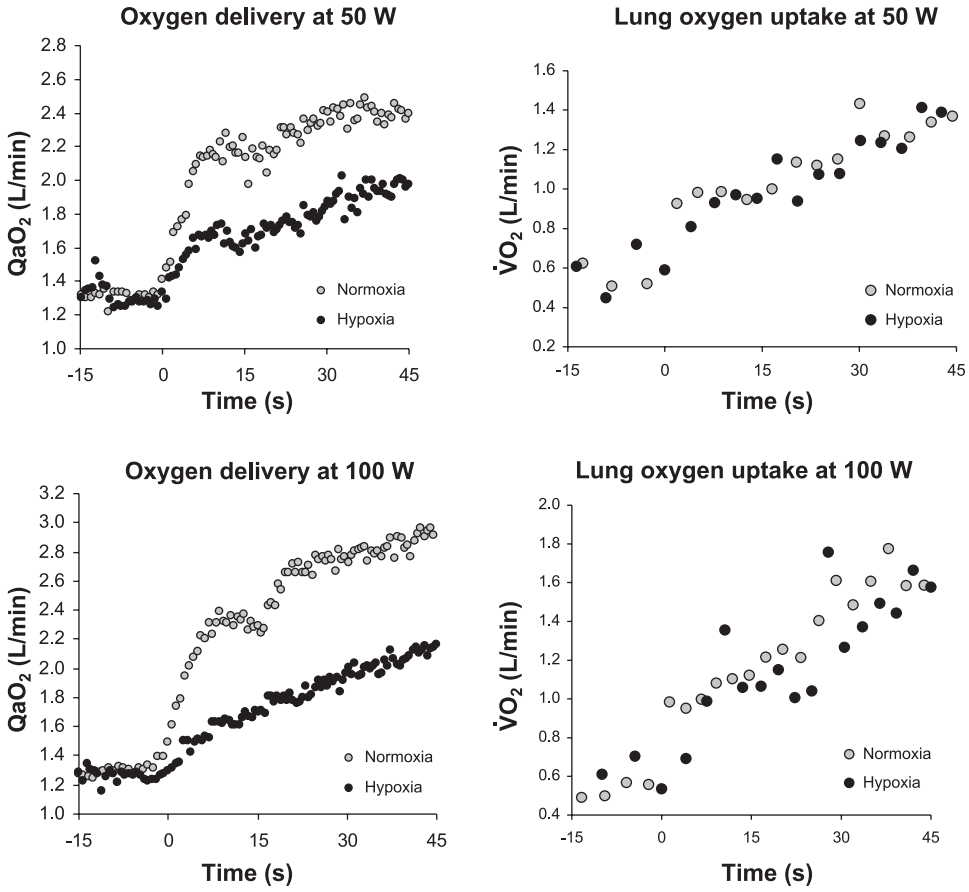

Fig. 3. Time course of arterial O_2 flow (oxygen delivery, $\dot{Q}a_{O_2}$) and lung O_2 uptake ($\dot{V}O_2$) upon the onset of exercise at 50 and 100 W in normoxia and hypoxia. Each value is the mean of the averaged superimposed values of all subjects. *Time 0* corresponds to the start of exercise.

whose very low values were essentially invariant; we noticed only a reduction at 50 W for $\dot{Q}$ and an increase at 100 W for f_H. This would mean that *1*) the τ_1 values in hypoxia also are compatible with a very rapid neural phenomenon, vagal withdrawal, as originally proposed by Fagraeus and Linnarsson (18) for normoxia; *2*) vagal withdrawal has a smaller amplitude in hypoxia than in normoxia because of lesser vagal activation in the former; and *3*) the patterns in the time domain of vagal withdrawal at exercise onset are fixed and invariant.

Table 3. *Kinetics of systemic O_2 delivery, O_2 uptake, and cardiac output within the two-phase model*

	50 W		100 W	
	A_1, l/min	τ_1, s	A_1, l/min	τ_1, s
$\dot{Q}$				
Normoxia	4.57±0.61	3.14±1.91	5.24±1.26	3.39±1.66
Hypoxia	2.52±0.90*	1.57±0.64*	3.71±1.75*	5.75±4.09§
$\dot{Q}aO_2$				
Normoxia	0.70±0.07	2.81±1.43	0.72±0.19	2.38±1.81
Hypoxia	0.38±0.16*	2.20±0.86	0.36±0.08*	3.22±1.61
$\dot{V}O_2$				
Normoxia	0.39±0.14	0.55±0.58	0.52±0.11	1.56±1.68
Hypoxia	0.35±0.07	2.36±0.59	0.45±0.17	3.14±0.68
f_H				
Normoxia	22.44±3.00	2.82±1.31	22.92±9.45	2.64±2.11
Hypoxia	14.50±5.59*	2.08±1.88	20.72±13.29	4.46±2.26*§

Data are means ± SD. A_1, amplitude of phase I change; τ_1, time constant of phase I. *$P < 0.025$, significantly different from corresponding value in normoxia. §$P < 0.025$, significantly different from corresponding value at 50 W.

However, the occurrence of phase I in hypoxia with a smaller amplitude, instead of a full suppression of it, may imply that *1*) hypoxia did not fully suppress vagal activity at rest so that some degree of vagal withdrawal still took place at exercise onset, or *2*) other mechanisms than vagal withdrawal participate in phase I. The former may indeed be the case for f_H. The latter is suggested by the apparent lack of changes in the Q_{st} kinetics in hypoxia with respect to normoxia (Fig. 1). In the absence of a clear predetermined model for the Q_{st} kinetics, whereby we refrained from fitting parameters through Q_{st} data, we evaluated the contribution of Q_{st} to $\dot{Q}$ A_1, as follows. Since $\dot{Q}$ is the product of f_H times Q_{st}, the absolute $\dot{Q}$ value at the peak of phase I is equal to

$$\dot{Q} + \Delta\dot{Q} = (f_H + \Delta f_H) \times (Q_{st} + \Delta Q_{st}) \quad (2)$$

where $\dot{Q}$, f_H, and Q_{st} are the resting values and $\Delta\dot{Q}$, Δf_H, and ΔQ_{st} are the corresponding increments during phase I, namely, the respective A_1 values. Solution of this equation for ΔQ_{st} thus provides an estimate of the Q_{st} amplitude during phase I that is necessary to sustain the observed increase in $\dot{Q}$. At 50 W, ΔQ_{st} was 23.9 ± 10.5 and 14.7 ± 7.1 ml in normoxia and hypoxia, respectively. The corresponding ΔQ_{st} values at 100 W were 33.1 ± 9.3 and 24.2 ± 21.2 ml. At both powers, although affected by a large scatter, ΔQ_{st} did not differ in hypoxia from normoxia ($P > 0.1$ in both cases), suggesting that, contrary to f_H, the alleged amplitude of Q_{st} in phase I may not vary in hypoxia with respect to normoxia. This being the case, then *1*) if indeed the reduction of the A_1 of f_H in hypoxia is due to lesser vagal withdrawal, then the same should be the case for

the reduction of the A_1 of $\dot{Q}$; and *2*) the Q_{st} changes during an exercise transient are independent of mechanisms related to vagal withdrawal. Concerning the latter, in supine posture, a condition in which central blood volume is increased (24, 29, 47), phase I of $\dot{Q}$ is not evident (25, 29), although resting vagal activation is greater supine than upright (25, 38). A higher central blood volume would reduce the amount of blood suddenly displaced from the periphery to the heart by muscle pump action, and thus the size of the immediate increase in venous return, thus preventing an efficient Frank-Starling mechanism. In the present study exercise was carried out in upright posture only, so it is likely that the increase in venous return due to muscle pump action would be the same in hypoxia as in normoxia, whence equivalent Q_{st} kinetics.

In both normoxia and hypoxia, the τ_1 of $\dot{V}O_2$ kinetics was extremely rapid and functionally instantaneous, indicating a practically immediate upward translation of $\dot{V}O_2$ that appears since the first breath. The τ_1 of $\dot{V}O_2$ did not differ between powers and can be considered equal to those of $\dot{Q}$ and $\dot{Q}a_{O_2}$ (Table 3), given that the minimal functional time window in which $\dot{V}O_2$ can be determined is one breathing cycle. This suggests that the phase I changes in $\dot{V}O_2$ are imposed by the corresponding phase I changes in $\dot{Q}$. Because of a delay between muscle O_2 consumption and $\dot{V}O_2$, we can assume that during the first seconds of exercise, arterial-venous O_2 difference (Ca_{O_2}-Cv_{O_2}) remains equal to that at rest (5). On this basis, the Fick principle allows a prediction of the expected $\dot{V}O_2$ increase in phase I as a consequence of the observed $\dot{Q}$ increase. In normoxia, A_1 of $\dot{Q}$ was on average 4.57 l/min (see Table 3). For an average resting Ca_{O_2}-Cv_{O_2} of 79 ml/l, we would expect an immediate $\dot{V}O_2$ increase upon exercise start of 0.36 l/min, compared with a measured A_1 of $\dot{V}O_2$ of 0.39 l/min (Table 3). By analogy, in hypoxia, A_1 of $\dot{Q}$ was on average 2.52 l/min (Table 3), and the resting Ca_{O_2}-Cv_{O_2} was 70 ml/l. Thus the expected $\dot{V}O_2$ increase would be 0.18 l/min, compared with a measured A_1 of $\dot{V}O_2$ of 0.35 l/min (Table 3). Despite this sizeable discrepancy, the two values are not significantly different, probably because of the relatively large coefficient of variation of the data in hypoxia. Nevertheless, the results of this analysis suggest that A_1 of $\dot{V}O_2$ may be a direct consequence of the rapid $\dot{Q}$ increase during phase I, in agreement with the so-called cardiodynamic hypothesis of lung $\dot{V}O_2$ transients (55).

Baroreflex resetting. At rest in normoxia, $\bar{P}$ was 90 mmHg and f_H was 74.5 min^{-1}. Let us assume that these values set the operating point of the average baroreflex curve of present subjects and that the operating point of resting subjects in normoxia corresponds to the centering point of the baroreflex curve (42). Assume also that the maximal gain and the operating range of the baroreflex curve are as previously reported (36). On this basis, we can construct a resting baroreflex response curve for the present subjects, which is reported in Fig. 4. If we then add the average resting value observed in hypoxia to that curve, we can see that the subjects operated in hypoxia on the same baroreflex curve as in normoxia, with a displacement of the operating point along the curve toward the threshold. This is a result of the decrease in $\bar{P}$ induced by peripheral vasodilation, to which the subjects responded with an increase in f_H, supporting the notion that peripheral vascular changes play a significant role in the baroreflex response of resting humans (17, 35). If indeed hypoxemia induces vasodilation in peripheral circulation via β_2-sympathetic stimulation, then we can propose a role for peripheral chemoreflexes in the displacement of the baroreflex operating point in hypoxia.

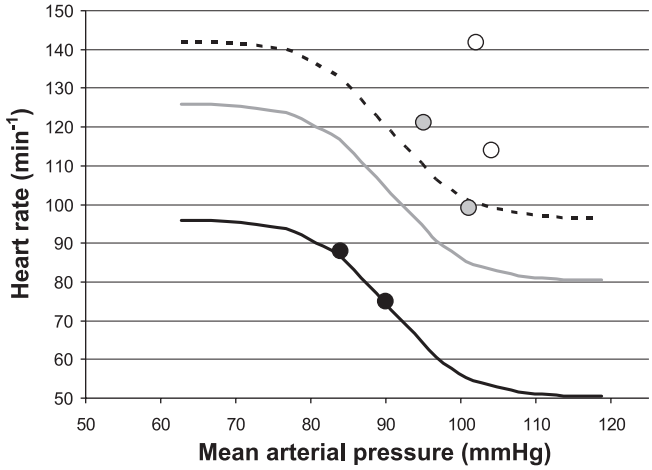

Fig. 4. Baroreflex response curve at rest and exercise steady state. Heart rate (f_H) as a function of mean arterial pressure ($\bar{P}$). Theoretical baroreflex curves are shown for rest (solid curve), exercise at 50 W (shaded curve), and exercise at 100 W (dashed curve). The curve at rest was constructed using the present mean resting values of $\bar{P}$ to define the baroreflex operating point and assuming *1*) that the operating point of resting subjects in normoxia corresponds to the center point (42) and *2*) that the maximal gain and the operating range of the baroreflex curve are as previously reported (36). The two curves at exercise were built by shifting the former upward by an amount equal to the average reported in previous studies (34, 35, 39, 41), assuming that the gain and operating ranges do not change at exercise steady state. The average steady-state values observed at rest (solid circles), exercise at 50 W (shaded circles), and exercise at 100 W (open circles) in normoxia and hypoxia are also indicated. At rest, the point in hypoxia is displaced upward and leftward, on the corresponding theoretical baroreflex curve. At exercise, the points do not lie on the corresponding theoretical baroreflex curve but are further displaced upward and rightward.

Exercise displaces the baroreflex curve upward and rightward, without changes in gain [baroreflex resetting (42)]. This phenomenon is part of the rapid cardiovascular response upon exercise start. Baroreflex resetting includes a fast phase (Fig. 2), completed within a few heartbeats, within the duration of phase I, which goes on in parallel with the rapid changes in R_p that take place at exercise start. However, the dynamics of baroreflex resetting implied a larger number of heartbeats in hypoxia than in normoxia. If vagal withdrawal sets phase I of f_H, then it will also contribute to the rapid upward shift of the baroreflex curve, but its role in baroreflex resetting will be less important in hypoxia than in normoxia.

Figure 4 also reports baroreflex curves for 50- and 100-W exercises, which are shifted upward as much as described in previous studies (34, 35, 39, 41). When the 50- and 100-W steady-state $\bar{P}$ and f_H values were added to Fig. 4, they were further displaced upward and rightward with respect to the predicted exercise baroreflex curve, suggesting that in the present study, baroreflex resetting was somewhat more intense than previously reported. Moreover, at both 50 and 100 W, the segment relating the experimental point in normoxia to the experimental point in hypoxia had a greater slope than the expected baroreflex gain, suggesting that the latter experimental point may lie on a different baroreflex curve than the former in both cases. A 50-W exercise provides a higher power relative to the maximum in hypoxia

than in normoxia because of the decrease in maximal O_2 uptake in hypoxia, whereby implying a greater role of the chemical component of the exercise pressor reflex (42). Yet we cannot distinguish the relative roles of central command or of the exercise pressor reflex in determining baroreflex resetting from the present data (42).

Conclusions. We conclude that in hypoxia, with respect to normoxia, *1*) phase I is not completely suppressed for f_H, although the A_1 for f_H is decreased, likely because the degree of vagal withdrawal is less; *2*) since phase I is partly maintained, arterial baroreflex resetting continues to be very rapid, taking place essentially within phase I; *3*) ΔQ_{st} is unchanged, because the increase in venous return due to muscle pump action is unchanged; *4*) the coupling of a decreased A_1 for f_H with an unchanged ΔQ_{st} would produce the observed decrease in A_1 of $\dot{Q}$; and *5*) the same factors that determine the phase I of $\dot{Q}$ are also responsible for the phase I of $\dot{V}_{O_2}$. Thus the present results provide only partial support to the hypothesis that vagal withdrawal determines the phase I kinetics of cardiovascular O_2 flow and lung O_2 uptake, because the suppression of phase I was incomplete. Although we can attribute the decrease in A_1 of f_H to a diminished degree of vagal withdrawal in hypoxia, this is not so for Q_{st}. Under these circumstances, the dual origin of the phase I of $\dot{Q}$ and $\dot{Q}a_{O_2}$, neural (vagal) and mechanical (increase in venous return by muscle pump action), would rather be confirmed.

GRANTS

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