Respiratory mechanics during exhaustive submaximal exercise at high altitude in healthy humans

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1. The present investigation was conducted to test the hypothesis that the respiratory system is stressed more during exhaustive exercise in chronic hypoxia than in normoxia.

2. Four healthy male subjects (aged 33–35 years) exercised on a cycle ergometer at 75% of the local maximum oxygen consumption ($\dot{V}_{O_2,max}$) until exhaustion, at sea level (SL) and after a 1 month stay at 5050 m (HA).

3. Airflow at the mouth ($\dot{V}$), oesophageal (P_o) and gastric (P_g) pressures were measured at rest, during exercise and recovery. Minute ventilation ($\dot{V}_E$), respiratory power ($\dot{W}_{resp}$), respiratory frequency (f) and transdiaphragmatic pressure (P_{di}) were calculated from the measured variables.

4. The subjects' mechanical power output of cycling at HA was 23·7% lower than at SL. In spite of this reduction, time to exhaustion at HA was 55·3% less than at SL. $\dot{V}_E$ increased slightly during exercise at SL, but showed a marked increase at HA, and at the end of exercise at HA was 47·3% higher than at SL.

5. Respiratory power increased more at HA than at SL (77·3% higher at the end of exercise) due to the increase in f needed to sustain the high $\dot{V}_E$.

6. Gastric pressure swings were negative at the end of HA exercise but always positive at SL. The $\bar{P}_{di}:\bar{P}_o$ ratio reached values below 1 at HA but never at SL.

7. These data seem to indicate that the respiratory system is stressed more during submaximal exercise at HA than at SL. We suggest that the exceedingly high $\dot{V}_E$ demand, requiring an excessive $\dot{W}_{resp}$, may lead to fatigue of the diaphragm.

The intensity of maximum exercise involving a large muscle mass that a subject can sustain is reduced at altitude. This reduction in maximum power output is greater the higher the altitude, and does not seem to be influenced much by acclimatization (Cerretelli, 1980; Ward, Milledge & West, 1990). In subjects acclimatized to high altitude, biopsies from the vastus lateralis muscle taken immediately after a progressive cycling test showed that, at exhaustion, the adenine nucleotide energy substrates were less depleted, less lactate had accumulated and less glycogen was degraded, whereas intramuscular pH was higher when compared with sea level conditions (Green, Sutton, Cymerman, Young & Houston, 1989).

A hypothesis to explain the reduction of classical biochemical signs of fatigue in the muscle after maximal exercise with large muscle groups at high altitude was proposed by Bigland-Ritchie & Vollestad (1988). According to these authors, at altitude a reduction in central drive to the locomotor muscles can possibly be induced by a maximally stressed respiratory system, and could limit exhaustive exercise with large muscle groups before their full potential is reached. The input for the brain leading to the cessation of exercise at altitude with large muscle groups before these reach their metabolic potential remains to be identified.

Hypoxia has been demonstrated to induce a reduction in endurance time while breathing against a high inspiratory resistance, with a faster shift of the high-to-low frequency ratio of the power spectrum of the diaphragm electromyogram with respect to normoxic conditions (Jardim, Farkas, Prefaut, Thomas, Macklem & Roussos, 1981). This suggests that during heavy exercise in hypoxic conditions inspiratory muscles may fail to generate the required respiratory pressures earlier than in normoxia. It is also noteworthy that heavy exercise in normoxic conditions may induce diaphragm fatigue in normal subjects

Table 1. Maximum oxygen consumption and maximum load during exercise at sea level and high altitude

	SL			HA		
	$\dot{V}_{O_2,max}$ (ml min^{-1})	$\dot{W}$ (W)	$\dot{W}_{75}$ (W)	$\dot{V}_{O_2,max}$ (ml min^{-1})	$\dot{W}$ (W)	$\dot{W}_{75}$ (W)
Subject 1	2560	180	135	1783	150	112
Subject 2	2810	180	135	1830	150	112
Subject 3	3738	300	225	2653	210	158
Subject 4	3024	240	180	1974	180	135
Mean	3033 ± 507*	225 ± 57	169 ± 43**	2060 ± 404*	173 ± 29	129 ± 22**

Mean values (± S.D.) for maximum oxygen consumption ($\dot{V}_{O_2,max}$), maximum load during incremental cycle-ergometer exercise ($\dot{W}$) and load during square wave ($\dot{W}_{75}$) at sea level (SL) and high altitude (HA) were measured for each subject. The statistical significance of the differences between SL and HA was tested for $\dot{V}_{O_2,max}$ and $\dot{W}_{75}$ by Student's t test for paired data. * $P < 0.001$, ** $P < 0.05$.

(Johnson, Babcock, Suman & Dempsey, 1993). Thus, it appears reasonable to expect respiratory muscle fatigue during heavy exhaustive exercise in chronic hypoxia.

On the basis of the hypothesis proposed by Bigland-Ritchie & Vollestad (1988), namely that a stressed ventilatory system would give feedback to the brain leading to the cessation of exercise, it should first be ascertained if the respiratory system is stressed more during exhaustive submaximal exercise at high altitude than at sea level. To this aim we subjected four healthy human males to an exhaustive submaximal endurance test on a cycle ergometer at sea level and at the end of a 1 month stay at 5050 m and compared the mechanics of breathing in the two conditions.

METHODS

Four healthy young human males (mean age, 34·2 years; range, 33–35 years) were studied during exercise at sea level (SL), and after a 28 day stay at 5050 m (HA), at a barometric pressure of ~410 Torr, in the Italian Pyramid laboratory 'Ardito Desio' in the high Khumbu Valley, close to the Mount Everest Base Camp in Nepal. None of the subjects was in athletic training: two subjects (1 and 2) had a sedentary life style, the other two were active on a recreational basis. For each subject, maximal oxygen consumption ($\dot{V}_{O_2,max}$) was measured by a standard open circuit method during an incremental cycle ergometer exercise both at SL and at HA; starting at 60 W, the power was increased by 30 W every 4 min until voluntary exhaustion. Two days later the subjects cycled at 75% of their power output corresponding to $\dot{V}_{O_2,max}$ until exhaustion. In Table 1 the individual and mean $\dot{V}_{O_2,max}$ values, the maximum load during incremental cycle ergometer exercise, and the load during the square-wave exercise are presented, both for SL and HA. The subjects were studied for 3 min at rest before exercise, during the whole exercise to exhaustion, and during the first 3 min of recovery. The following variables were measured: bidirectional airflow at the mouth ($\dot{V}$) by a mouthpiece and a calibrated pneumotachograph (Fleisch 3) connected to a differential pressure transducer (MP-45 Validyne, range ± 5 cmH_2O, Validyne, Northridge, CA, USA). The pneumotachograph was heated to prevent condensation. The added dead space of the mouthpiece–pneumotachograph system was 65 ml. Oesophageal pressure (P_o) and gastric pressure (P_g) were conventionally measured by two balloon-tipped catheters placed in the lower third of the oesophagus and in the stomach, respectively, connected to two calibrated differential pressure transducers (MP-45 Validyne, range ± 80 cmH_2O) referenced to atmospheric pressure. The gastric catheter was held in place by an inflated latex ballon obstructing the oesophageal–gastric junction, as currently used for recording diaphragm electromyogram data. The tubing placed on the reference side of both manometers was adjusted in length to balance the opposite sides of the transducer. The position of the oesophageal catheter was adjusted following the occlusion technique proposed by Baydur, Behrakis, Zin, Jaeger & Milic-Emili (1982). Transdiaphragmatic pressure (P_{di}) was calculated as the difference between P_g and P_o.

Maximum inspiratory pressures during airway occlusion were measured at rest before exercising while seated on the cycle ergometer, by a Müller manoeuvre at functional residual capacity, and maximum transdiaphragmatic pressure ($P_{di,max}$) was calculated.

All the analog signals were recorded on a 4-channel strip-chart recorder (Hewlett Packard 7754B) and on an 8-channel magnetic tape recorder (Hewlett Packard 3968A) for further play back and analysis.

Bidirectional airflow at the mouth, P_o and P_g signals were sampled at 10 ms intervals and, after analog-to-digital conversion, were stored in the mass memory of a computer (Digital Vax 8200, Digital Equipment Co., Maynard, MA, USA). A mean of 856 breaths for SL experiments and 568 breaths for HA experiments was analysed for each subject. From the calibrated $\dot{V}$, P_o and P_g signals the computer calculated breath-by-breath at body pressure and temperature when saturated with water vapour: tidal volume (V_T) by integration of inspiratory $\dot{V}$; inspiratory duration (T_I); expiratory duration (T_E); total duration of the respiratory cycle (T_{TOT}); respiratory frequency (f); minute ventilation ($\dot{V}_E$); mean inspiratory flow (V_T/T_I); duty cycle (T_I/T_{TOT}); P_o at end-expiration ($P_{o,ee}$); P_o at end-inspiration ($P_{o,ei}$); P_g at end-expiration ($P_{g,ee}$) and P_g at end-inspiration ($P_{g,ei}$). P_{di} at end-expiration and P_{di} at end-inspiration were calculated as the difference between the respective P_g and P_o values. The changes in pressure parameters (ΔP_o, ΔP_g and ΔP_{di}) were calculated as the pressure difference between end-inspiratory and end-expiratory absolute values. The ratio $\bar{P}_{di} : \bar{P}_o$ was calculated as the ratio between mean inspiratory P_{di} and mean inspiratory P_o

(calculated as the area under the curve of P_{di} and P_o inspiratory swings divided by T_I). The work of breathing (W) was calculated on the volume–pressure loops; power ($\dot{W}_{resp}$), as the product of W times f; the diaphragm tension–time index (TT_{di}) according to the formula: $TT_{di} = (\bar{P}_{di}/P_{di,max})(T_I/T_{TOT})$, where $\bar{P}_{di}$ is mean inspiratory P_{di}.

Since exercise duration differed with the individual and was shorter at HA, comparisons between different conditions were calculated for the mean values for individual variables computed at each 10% fraction of total exercise time. Sea level and HA measurements were kept separate and a mean value for resting as well as for each 10% fraction of exercise, was obtained. In addition, we calculated mean values (± S.D.) for resting and for each absolute minute of exercise, for both SL and HA, to evaluate better the changes in respiratory parameters during exercise under the two different conditions. P_o–P_g loops were plotted for single breaths during resting, exercise and recovery.

Student's t test for paired data was used to evaluate differences in endurance time under the two conditions. One-way analysis of variance (ANOVA) was used to test differences in the last 10% fraction of exercise at SL and HA. A linear regression analysis was performed on the relationships between the time of exercise from the fourth minute to the end of exercise as an independent variable and on $\dot{V}_E$, V_T, f and ΔP_{di} as dependent variables. Analysis of covariance (ANCOVA) was used to compare within each subject the slopes obtained at SL and HA. Results were considered significant for P values less than 0·05.

The study was approved by the Ev-K²-CNR Scientific Committee. All four subjects gave their written informed consent and all were familiar with laboratory experiments and respiratory manoeuvres.

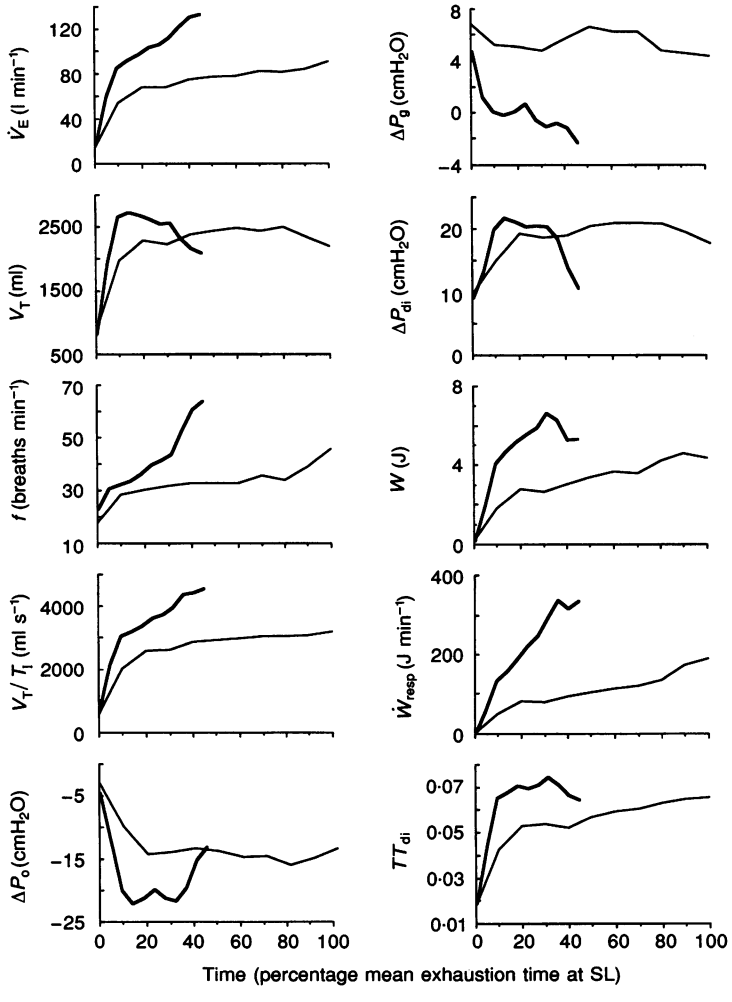

Figure 1. Mean overall values of the different variables relevant to all four subjects during resting (time = 0) and exercise

Exercise at SL is shown by the thin line and HA by the thick line. The values are expressed as means for resting and each 10% fraction of the total exercise time. On the x-axis time is expressed as percentage of exhaustion time at SL. $\dot{V}_E$, ventilation; V_T, tidal volume; f, respiratory frequency; V_T/T_I, mean inspiratory flow; ΔP_o, difference between end-inspiratory and end-expiratory oesophageal pressure; ΔP_g, difference between end-inspiratory and end-expiratory gastric pressure; ΔP_{di}, difference between end-inspiratory and end-expiratory transdiaphragmatic pressure; W, work of breathing; $\dot{W}_{resp}$, power; TT_{di}, diaphragm tension–time index.

Table 2. Endurance exercise times

	SL	HA
Subject 1	23′19″	9′03″
Subject 2	17′01″	11′41″
Subject 3	39′59″	16′51″
Subject 4	34′03″	16′51″
Mean ± S.D.	28′35″ ± 10′21″	12′43″ ± 3′16″

Endurance exercise times (in minutes and seconds) relevant to each subject during sea level (SL) and high altitude (HA) experiments. The difference between mean values was significant ($P < 0.04$; Student's t test for paired data).

RESULTS

Despite the 23·7% reduction in absolute power output at HA (Table 1), the endurance time decreased significantly ($P < 0.04$) by an average of 55·3% with respect to SL (Table 2). At sea level, all the subjects reported leg pain at exhaustion. Conversely, at high altitude the exercise interruption was due to dyspnoea and abdominal pain, which was similar for all four subjects.

In Fig. 1 the overall values (relevant to all four subjects) of the different measured or calculated variables during rest and exercise at SL and HA, are shown as means at each 10% fraction of total exercise time. On the x-axis, time is expressed as a percentage of the SL exercise exhaustion time. Table 3 shows the absolute overall mean values (± S.D. of the mean) relevant to the last 10% fraction of exercise at SL and HA. From Fig. 1 and Table 3 the following can be observed. (a) $\dot{V}_E$ increased slightly during exercise at SL, but the increase was more marked at HA. During the last 10% fraction of exercise, $\dot{V}_E$ was 91·2 l min^{-1} at SL and 134·3 l min^{-1} at HA (an addition of 47·3%). The increase in $\dot{V}_E$ during exercise was due to an initial increase in V_T at the beginning of exercise, while the successive progressive increase was due to an increase in f, both at SL and HA. At SL, V_T did not change during exercise after the initial increase, whereas it progressively decreased at HA, showing the least value at exhaustion. At HA, f was 40·7% higher at the end of exercise than SL. A large increase (42·8%) in $V_T : T_I$ was observed in the last fraction of exercise at HA, with respect to SL, due to the decrease of T_I. (b) The change in oesophageal pressure rapidly became more negative after the beginning of exercise at SL, then remaining quite stable until exhaustion. At HA, ΔP_o showed a sharp decrease toward more negative values, which were maintained during the middle part of exercise, then showed a marked shift towards less negative values before exhaustion. So, at the end of exercise at HA, ΔP_o was not significantly different from SL. No large differences were found in ΔP_{di} behaviour at SL and HA during the first fractions of exercise, whereas, before exhaustion at HA, ΔP_{di} showed a significant reduction such that at the last 10% fraction of exercise it was 39·3% less at HA than SL. Large differences were also found in the trend of ΔP_g during exercise: at SL the ΔP_g was stable and always showed positive values. Conversely, at HA it decreased progressively during the whole exercise reaching negative values at exhaustion. At the last exercise fraction ΔP_g was 4·37 cmH_2O at SL and −2·25 at HA. This difference in ΔP_g was found to be similar in all the subjects: in fact, at HA ΔP_g values were always lower than at SL. (c) Due to the negative ΔP_g values, at HA the $\bar{P}_{di} : \bar{P}_o$ ratio progressively decreased during exercise, being 18·7% less during the last fraction than at SL. Conversely, at SL it never decreased below 1. (d) The work of breathing was always higher at HA.

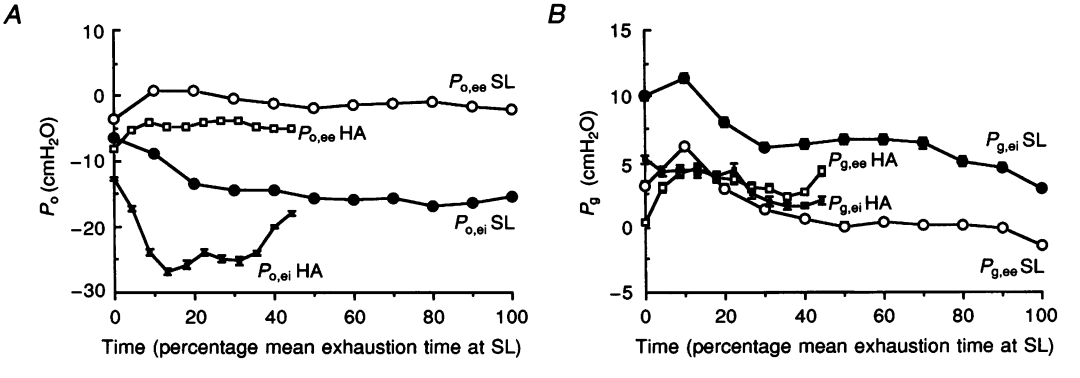

Figure 2. Values of oesophageal (P_o) and gastric pressures (P_g) at end-expiration (ee) and at end-inspiration (ei) during resting and exercise at sea level (SL) and at altitude (HA)

Each point represents the mean for all four subjects (± S.E.M.) for resting and each 10% fraction of exercise (when not visible, S.E.M. is within the limits of the graphic symbol). On the x-axis, time is expressed as fraction of the mean exhaustion time at sea level.

Table 3. Absolute overall mean values in the last 10% fraction of exercise at SL and HA

	SL	HA	*P* value	Δ(HA − SL)/SL (%)
$\dot{V}_E$ (l min^{-1})	91·2 ± 12·1	134·3 ± 12·0	0·0001	47·3
V_T (ml)	2204 ± 752	2109 ± 289	n.s.	−4·3
T_I (s)	0·66 ± 0·17	0·44 ± 0·05	0·0001	−33·3
T_E (s)	0·83 ± 0·36	0·49 ± 0·15	0·0001	−41·0
f (breaths min^{-1})	45·73 ± 13·95	64·33 ± 6·50	0·0001	40·7
V_T/T_I (ml s^{-1})	3202 ± 590	4574 ± 443	0·0001	42·8
ΔP_o (cmH_2O)	−13·34 ± 5·85	−12·98 ± 3·93	n.s.	2·7
ΔP_g (cmH_2O)	4·37 ± 4·12	−2·25 ± 3·88	0·0001	−151·5
ΔP_{di} (cmH_2O)	17·71 ± 6·44	10·74 ± 5·90	0·0001	−39·3
$\tilde{P}_{di}:\tilde{P}_o$	1·07 ± 0·16	0·87 ± 0·08	0·0001	−18·7
W (J)	4·36 ± 1·46	5·32 ± 1·82	0·0001	22·0
$\dot{W}_{resp}$ (J min^{-1})	189·6 ± 64·3	336·2 ± 98·9	0·0001	77·3
TT_{di}	0·066 ± 0·01	0·065 ± 0·01	n.s.	−1·4

SL and HA, mean values (± S.D.) obtained at sea level and high altitude, respectively. The statistical significance of the differences between SL and HA was calculated by one-way analysis of variance. Change was calculated as HA − SL, expressed as a percentage of SL value.

At the end of exercise it was 22·0% higher than at SL. Similarly, $\dot{W}_{resp}$ was higher at HA, being 77·3% higher at the end of exercise than at SL. (e) During exercise TT_{di} was higher at HA with respect to SL, and its behaviour was different. Only a slight increase in TT_{di} was seen throughout the entire exercise at SL, whereas at HA TT_{di} increased at the beginning of exercise, but decreased in the late phase of exercise and reached, before exhaustion, a value very close to that at SL (during the third 10% fraction the HA value was exceeding the SL value by 26·6%). This reduction in TT_{di} was not due to reduction in $T_I:T_{TOT}$; in fact, the duty cycle remained quite stable during the whole exercise both at SL and HA. In particular, $T_I:T_{TOT}$ was on average 0·47 ± 0·05 (S.D.) during the third 10% fraction of exercise at HA and 0·48 ± 0·05 during the last 10% fraction. At SL $T_I:T_{TOT}$ was 0·43 ± 0·06 and 0·46 ± 0·08, respectively.

In Table 4 values of the slopes of the linear relationships between $\dot{V}_E$, V_T, f and ΔP_{di}, as dependent variables, *versus* time, as an independent variable, are shown for each subject at SL and HA, from the 4th min of exercise to exhaustion.

Table 4. Slopes of the relationships between $\dot{V}_E$, V_T, f and ΔP_{di} *versus* time for each subject at sea level and high altitude, from the 4th minute of exercise to exhaustion

	SL	HA	*P*
Subject 1			
$\dot{V}_E$/time (l min^{-2})	1·34	9·21	< 0·0001
V_T/time (ml min^{-1})	13·20	−80·00	< 0·0001
f/time (breaths min^{-2})	0·35	5·41	< 0·0001
ΔP_{di}/time (cmH_2O min^{-1})	−0·07	−2·29	< 0·0001
Subject 2			
$\dot{V}_E$/time (l min^{-2})	2·29	4·42	< 0·0001
V_T/time (ml min^{-1})	−53·90	−69·60	n.s.
f/time (breaths min^{-2})	2·60	2·98	n.s.
ΔP_{di}/time (cmH_2O min^{-1})	−0·49	−1·04	< 0·0001
Subject 3			
$\dot{V}_E$/time (l min^{-2})	0·42	3·72	< 0·0001
V_T/time (ml min^{-1})	5·06	−65·90	< 0·0001
f/time (breaths min^{-2})	0·09	2·88	< 0·0001
ΔP_{di}/time (cmH_2O min^{-1})	−0·18	−1·89	< 0·0001
Subject 4			
$\dot{V}_E$/time (l min^{-2})	0·75	4·11	< 0·0001
V_T/time (ml min^{-1})	−3·53	−59·70	< 0·0001
f/time (breaths min^{-2})	0·57	3·25	< 0·0001
ΔP_{di}/time (cmH_2O min^{-1})	0·26	−0·61	< 0·0001

The statistical significance of the differences between sea level (SL) and high altitude (HA) slopes was calculated by the analysis of covariance.

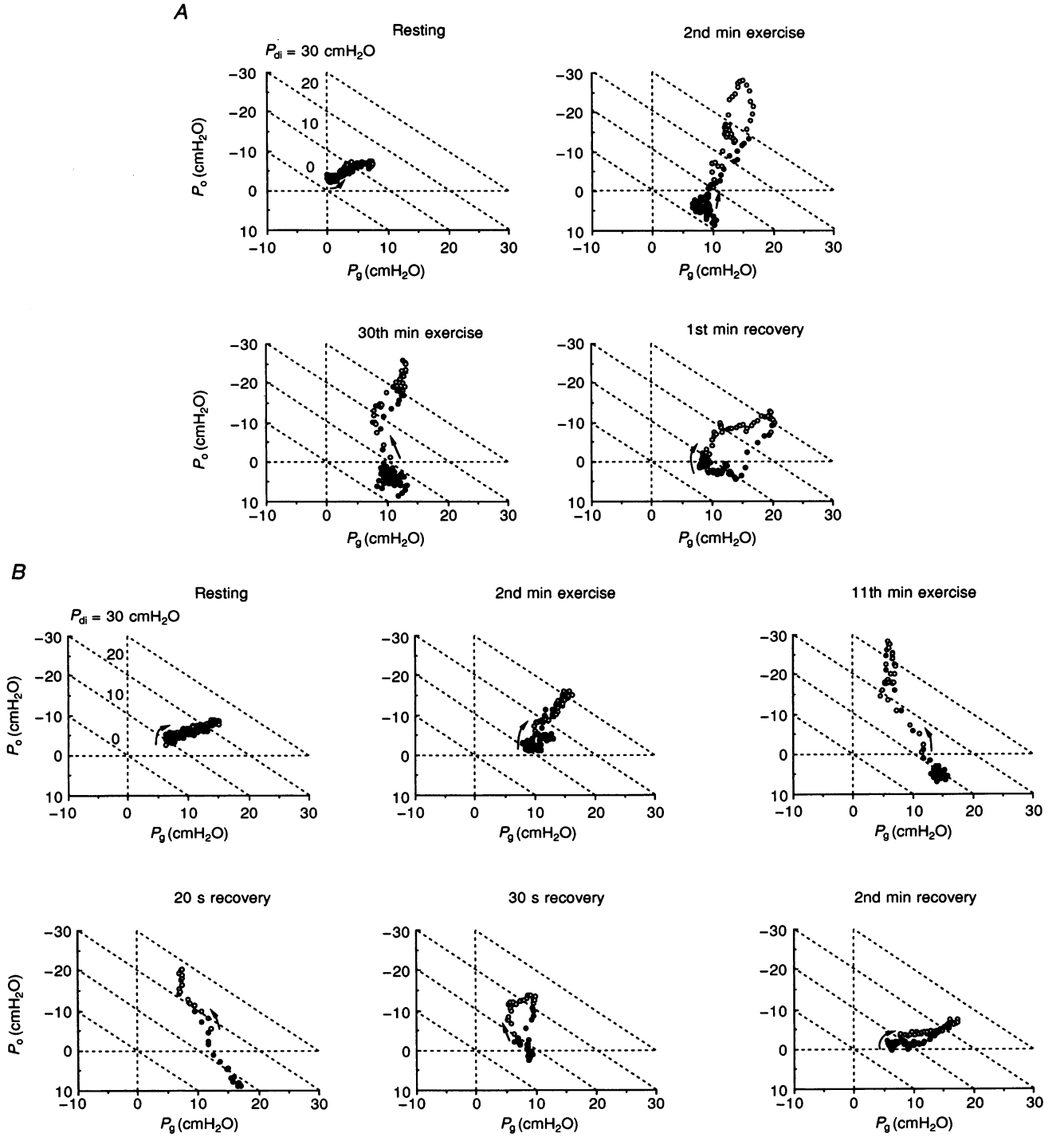

Figure 3. Oesophageal pressure *versus* gastric pressure loops

A, oesophageal pressure *versus* gastric pressure loops during sea level exercise for a representative subject 3 during resting and at different times of exercise and recovery. Raw P_o and P_g values were obtained from single breaths both for inspiration (○) and expiration (●). To simplify the picture, only the 50% of sampled data points are shown. Arrows indicate the beginning of inspiration. Isopleths for P_{di} are shown. *B*, oesophageal pressure *versus* gastric pressure loops during high altitude exercise for a representative subject 3 during resting and at different times of exercise and recovery. Details as in *A*.

In all the subjects, comparison between the two conditions resulted in significant differences (ANCOVA) in the slopes of each variable *versus* time of exercise, with the exception of V_T–time and f–time relationships in subject 2. At HA, $\dot{V}_E$ and f showed increased slopes, while V_T and ΔP_{dl} showed negative or more negative slopes.

In Fig. 2 the values of P_o and P_g at end-expiration and end-inspiration are shown during both SL and HA exercise. Oesophogeal pressure at end-expiration ($P_{o,ee}$), at SL, showed values slightly less negative with respect to HA during the course of exercise, always maintaining less negative and stable values with respect to resting values. Stable negative values of $P_{o,ei}$ were rapidly reached and maintained during the whole exercise. Consequently, quite stable P_o swings were maintained during the time course of the exercise at SL. At HA, $P_{o,ee}$ did not change significantly during exercise, following a behaviour similar to that at SL. Conversely, after a sharp decrease followed by a plateau, $P_{o,ei}$ showed an increase before exhaustion, causing a decrease in P_o swing. Consequently, in the last fraction of the exercise $P_{o,ei}$ values were similar in both conditions.

At SL, both $P_{g,ee}$ and $P_{g,ei}$ showed slight and parallel decreases during the exercise, producing only small changes in swings (ΔP_g in Fig. 1). At HA, the P_g pattern markedly changed: while $P_{g,ee}$ progressively increased toward more positive values, indicating greater activation of abdominal muscles, $P_{o,ei}$ slightly decreased reaching values below those for $P_{g,ee}$, thus resulting in negative ΔP_g (Fig. 1).

Figure 3 shows the changes in the P_o–P_g loops at SL and HA for a representative subject (subject 3) at rest, during exercise and recovery. At SL, during resting both P_o and P_g showed a normal pattern with increasing positive P_g and progressively more negative P_o during inspiration. During exercise P_g presented a slight decrease during early inspiration, with increasing values in late inspiration, maintaining this pattern until exhaustion. The resting pattern was promptly recovered after exhaustion (12 s after exercise cessation a fully increasing inspiratory P_g pattern was recorded; Fig. 3*A*). Conversely, during exercise at HA, the P_g pattern, which at rest was similar to SL, showed decreasing values during the whole inspiration, and this pattern was present beyond exhaustion. In fact, during the first 30 s of recovery, a fully decreasing inspiratory P_g was still maintained and it was restored only to the resting pattern after 90 s (Fig. 3*B*). Peak P_{dl} values were higher at SL.

Figure 4 shows the original P_o, P_g and $\dot{V}$ tracings at rest and at different times of exercise at HA for subject 3 (as Fig. 3): after a few minutes of exercise at HA, the normal positive inspiratory P_g changed in a double phase swing, characterized by a sudden decrease in early inspiration with a partial recovery during late inspiration and a new decrease at end inspiration. In a later phase of the exercise, the P_g swing showed a completely negative behaviour, without any increase during inspiration, while large expiratory peaks were developed.

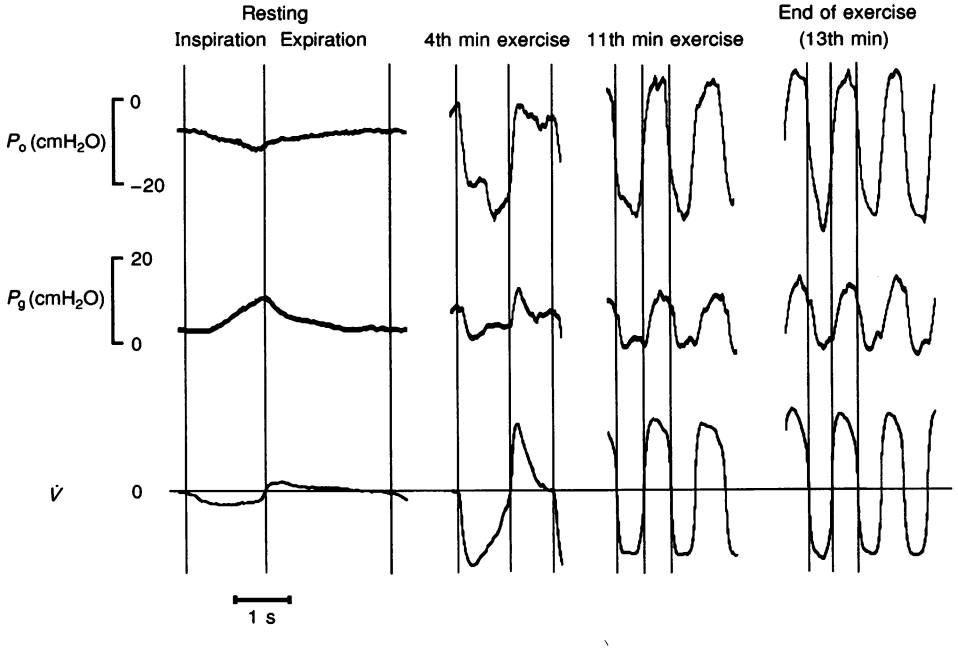

Figure 4. Original signals relevant to flow, gastric and oesophageal pressures, as recorded at high altitude

Oesophageal pressure (P_o), gastric pressure (P_g) and air flow at the mouth ($\dot{V}$) tracings relevant to resting, and at different times of exercise of subject 3 during the high altitude experiment.

A more detailed analysis of subject 4 is presented in Fig. 5, where V_T, $\dot{V}_E$, f and ΔP_o, are shown as means (± S.D.) for resting and for each absolute minute of exercise both for SL and HA, against absolute time. This representation gives a better overview of the differences between the two elevations. Moreover, in this subject a particular breathing pattern was evident during exercise at HA: after the first 11 min of a total of 17 min of HA exercise (indicated by the dashed lines), V_T showed a progressive decline. This decrease was followed by a sharp increase in f that was able to sustain the $\dot{V}_E$ increase until the 15th minute. After that, f reached a plateau and $\dot{V}_E$ started to decrease due to the progressive reduction of V_T. Subsequently, the exercise was interrupted. It is interesting that the V_T decrease was probably due to a reduction in neural activation (V_T/T_I) and in driving pressures (ΔP_o), and was associated with a reduction in ΔP_{di}. Conversely, a progressive ΔP_g decrease was evident just after the beginning of exercise.

DISCUSSION

The major finding of this study was the marked decrease in endurance time of exercise in chronic hypobaric hypoxia compared with normoxia (Table 2) despite the fact that in both conditions the power output was set at 75% of the local $\dot{V}_{O_2,max}$. In fact, at HA the subjects exercised at an absolute power output that was 23·7% lower than at SL. This result is in agreement with a recent report (Babcock, Johnson, Pegelow, Suman, Griffin & Dempsey, 1995) showing a 37% reduction in endurance time in acute hypoxia (inspired oxygen fraction $F_{I,O_2} = 0{\cdot}15$) with respect to normoxia during heavy exercise (85% of $\dot{V}_{O_2,max}$), even though, in this study, the same power output was used both in normoxic and in hypoxic conditions.

The shortening of exercise endurance time was associated with changes in ventilatory parameters and in thoraco-abdominal mechanics. Jardim *et al.* (1981) demonstrated that the endurance time was shorter by about 60% in subjects breathing through a high inspiratory resistance (at 80% of the maximal inspiratory mouth pressure) during acute hypoxia ($F_{I,O_2} = 0{\cdot}13$). This reduction was associated with a faster decrease in the high-to-low frequency ratio of the power spectrum of the diaphragm electromyogram with respect to normoxia, suggesting an earlier development of diaphragm fatigue while an equal inspiratory pressure was maintained against the resistance.

Furthermore, exercise-induced hyperventilation at SL has been shown previously to induce respiratory muscle fatigue sometimes, both in terms of $P_{di,max}$ reduction after heavy exercise in marathon runners (Loke, Mahler & Virgulto, 1982) as well as after cycle ergometer exercise at 80% of $\dot{V}_{O_2,max}$ (Bye, Esau, Walley, Macklem & Pardy, 1984). Also, Johnson *et al.* (1993) showed that heavy exercise (not less than 85% of $\dot{V}_{O_2,max}$) sustained until exhaustion, produces a reduction in P_{di} measured during bilateral transcutaneous supramaximal phrenic nerve stimulation.

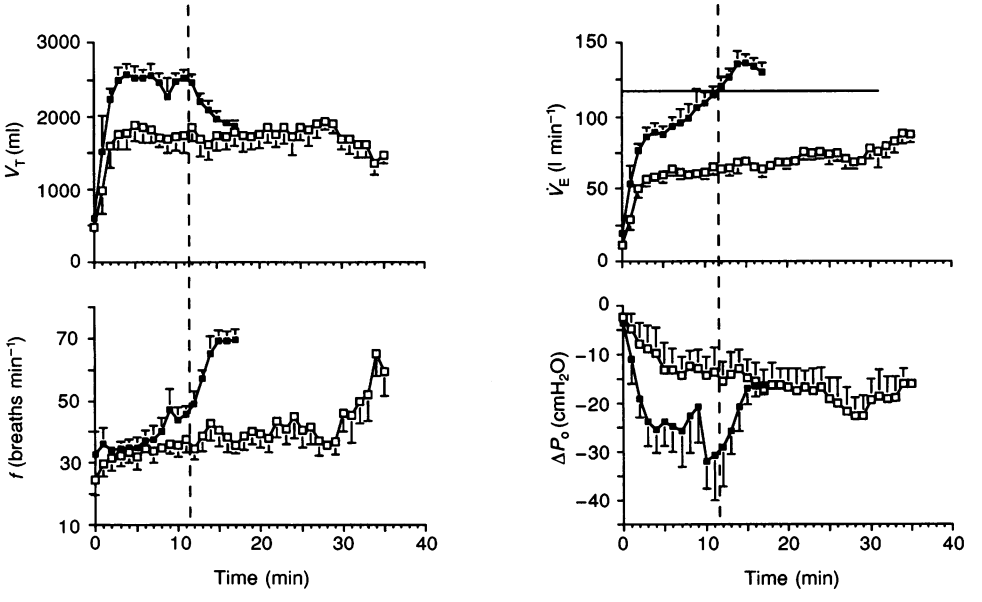

Figure 5. Mean values calculated for resting and each minute of exercise relevant to subject 4 during sea level and high altitude experiments

Time shown on the x-axis is expressed in absolute terms (minutes). Error bars are S.D. Vertical dashed lines depict the time of the exercise at which the V_T starts to decrease, at a $\dot{V}_E$ of ~120 l min^{-1}. Results from sea level, □; high altitude, ■.

In the present study, during exhaustive exercise at 75% of $\dot{V}_{O_2,max}$ until exhaustion at HA, $\dot{V}_E$ did not show a plateau in any of the subjects: it continuously increased reaching a mean value of 134·2 l min^{-1} during the last fraction of exercise on the basis of an increase in f, while V_T decreased. In contrast, the rate of increase of $\dot{V}_E$ was less at SL, leading to an average maximal $\dot{V}_E$ of 91·2 l min^{-1}. The marked increase in f at HA was responsible for a large increase in $\dot{W}_{resp}$ which was on average 77·4% higher at HA with respect to SL during the last 10% fraction of exercise. The high levels of $\dot{V}_E$ and $\dot{W}_{resp}$ reached before exhaustion at HA probably required an increased fraction of whole-body $\dot{V}_{O_2,max}$ as suggested by Aaron, Seow, Johnson & Dempsey (1992). So at HA, despite the lower mechanical power output on the cycle ergometer, the respiratory system attained such high powers that its energy demand possibly outgrew its energy supply. It is of interest that subject 4 (Fig. 5) showed marked changes in his ventilatory pattern when reaching a $\dot{V}_E$ of 120 l min^{-1} (corresponding to a $\dot{W}_{resp}$ increase of about 85 times with respect to resting value). Bye *et al.* (1984), suggested that, during exercise in room air, the development of inspiratory muscle fatigue is also possible at TT_{di} values lower than those (0·15–0·18) reported by Bellemare & Grassino (1982). The high flow rate observed during exercise will probably force the inspiratory muscles to work along a disadvantageous part of the force–velocity relationship. In our study V_T/T_I, an index of neural drive, increased continuously during exercise both at SL and HA. As can be seen in Fig. 6, the relationship between TT_{di} and V_T/T_I was linear and identical in both conditions, except for the last phase of exercise at HA, when, notwithstanding the continuous increase in neural drive (as suggested by the increase in V_T/T_I), a drop in the TT_{di} occurred.

Hypoxia may increase local lactate concentration with respect to normoxia (Jardim *et al.* 1981) enhancing the anaerobic metabolism and shifting blood flow to the locomotor muscles. We, therefore, speculate that at HA a reduced oxygen content of arterial blood could limit the oxygen uptake of the respiratory muscles forcing them to use anaerobic energy substrates for sustaining the necessary energy for the higher power output, thus possibly resulting in the development of metabolic fatigue.

Regarding the behaviour of respiratory pressures, we found more negative slopes of the ΔP_{di} *versus* time relationship during exercise (Table 4) at HA than at SL, indicating a progressive reduction in ΔP_{di} during the course of exercise. Similar results, expressed in terms of a reduction in end-inspiratory P_{di} at the end of exercise, were found by Bye *et al.* (1984) as a consequence of exercise hyperventilation and interpreted as evidence of a fatiguing diaphragm: this suggests the possibility that the pressure changes we observed at HA were due to diaphragm fatigue. This hypothesis is supported by the reduction found in ΔP_{di}, due to a progressive reduction of P_g contribution to P_{di} during exercise at HA, as shown by the $\tilde{P}_{di}:\tilde{P}_o$ ratio below 1 in the last fraction of exercise at HA (Table 3). Moreover, of interest is the P_g pattern during exercise at HA: ΔP_g decreases during the exercise due to the progressive reduction in $P_{g,ei}$. The observed $P_{g,ee}$ increase (evident just after the beginning of exercise; Fig. 2) is to be related to expiratory muscle recruitment. Conversely, no evidence of increase in $P_{g,ee}$ was seen during exercise at SL. We suppose that gastric pressure during inspiration, may present decreasing values due to the sudden relaxation of abdominal expiratory muscles at the beginning of inspiration, following their recruitment during the previous expiration. The lack of P_g increase at the beginning of inspiration produces a decreased P_{di}: this may be observed in Fig. 4, where at the 4th and 11th minutes an initial rapid drop in P_o at the start of inspiration matches a rapid drop of P_g. This first phase of inspiration may be considered as almost 'passive' and due to the abdominal muscle de-recruitment helping the downward movement of the diaphragm. A second drop in P_o is 'active' and is due to diaphragm contraction and is accompanied by P_g increase. At HA the ribcage muscles become very active in sustaining the diaphragm action: this may increase the reduction of P_g from end-expiration to end-inspiration, while at SL $P_{g,ei}$ is always higher than $P_{g,ee}$ (Fig. 2). It must be observed that P_g showed clearly negative values at HA before exhaustion, when the P_o swings were decreasing. Consequently, the complete negativity of P_g during inspiration may be due to an inability of the diaphragm to sustain, at the high respiratory rate reached before exhaustion (higher than 60 breaths min^{-1} in all subjects), the required power output. In these conditions, the diaphragm appeared to play a less

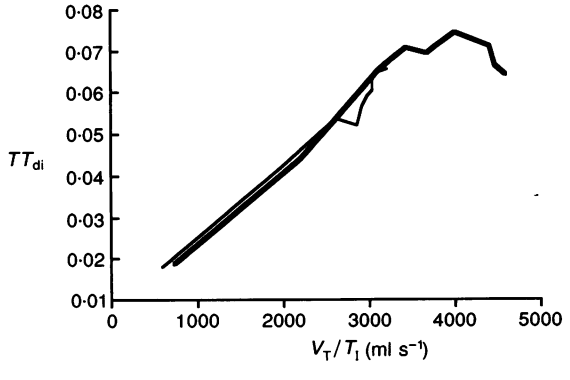

Figure 6. Relationship between diaphragm tension–time index and mean inspiratory flow
The diaphragm tension–time index (TT_{di}) and mean inspiratory flow (V_T/T_I, ml s^{-1}) relevant to pooled data (mean for each 10% of exercise time and for all the subjects) for sea level (SL, thin line) and high altitude (HA, thick line) experiments are shown.

active role in generating pressure, as demonstrated by the increase in the P_o necessary to maintain a useful stable P_{di}. The diaphragm probably decreased its relative role in respiratory work with a progressive recruitment of inspiratory ribcage muscles. This is supported by the observation that P_o *versus* P_g loops (Fig. 3*A* and *B*) during exercise at SL always had more positive P_g values at end-inspiration, even just before exhaustion, with an immediate return to the resting pattern after exhaustion. Conversely, during exercise at HA only decreasing inspiratory P_g values were found, and this pattern was maintained during the whole first minute of recovery after exhaustion. In fact, time was needed to return to the pre-exercise resting pattern. The P_g tracings recorded after recovery always restored a pattern with positive inspiratory swings. This decrease in inspiratory P_g was responsible for the decrease in the $\bar{P}_{di}:\bar{P}_o$ ratio evident during exercise at HA. Since ΔP_{di} was maintained at a stable value during the middle part of exercise at HA, we argue that an increase in P_o was needed to compensate for the decreasing P_g. It is noteworthy that the same reduction in $\bar{P}_{di}:\bar{P}_o$ ratio was also found by Johnson *et al.* (1993), with increasing P_o and stable P_{di} during the course of heavy exercise (85 and 95% of $V_{O_2,max}$) in normoxia. Using the technique of the bilateral, transcutaneous, supramaximal phrenic nerve stimulation, these authors found that the changes in thoraco-abdominal mechanics were correlated to the development of diaphragm fatigue. Furthermore, the decrease in stimulated P_{di} was correlated with the level of respiratory work. Our results, obtained during exercise at 75% of $V_{O_2,max}$ in chronic hypoxia are very similar, in terms of the $\dot{V}_E$ attained at the end of exercise, to those of Johnson *et al.* (1993) during exercise at 95% of $V_{O_2,max}$ in normoxic conditions. The respiratory power output appears to be higher among our subjects, which is probably due to the higher f reached at HA. Our data are also consistent with those of Babcock *et al.* (1995), showing that heavy exercise in acute hypoxia induces an earlier development of diaphragm fatigue with respect to normoxia. The progressive reduction in V_T we observed during exercise at HA may also be related to the development of respiratory muscle fatigue. In fact, it has been demonstrated that the induction of fatigue (electromyographically or mechanically) in the respiratory muscles by inspiratory resistive loading is able to bring about a marked decrease in V_T (Gallagher, Im Hof & Younes, 1985).

It is of interest that the $P_{o,ee}$ trend during exercise did not show important changes from SL to HA. The slight change to less negative values from rest to exercise observed in both conditions suggests end-expiratory volume changes below relaxation volume. The small difference in $P_{o,ee}$ between the two conditions together with the much lower $P_{o,ei}$ at HA during the exercise bout suggests higher operational lung volumes at altitude, but the observed pressures are not compatible with dynamic hyperinflation in either condition.

In conclusion, chronic hypoxia reduces the endurance time during submaximal exercise at the same relative load (75% of $V_{O_2,max}$) compared with normoxia. In this condition the contribution of the diaphragm to the respiratory work is reduced. It appears that the respiratory system is stressed more during submaximal exercise at HA than at SL. We suggest that this leads to fatigue of the diaphragm, caused by an exceedingly high $\dot{V}_E$ demand requiring an excessive $\dot{W}_{resp}$ to be sustained by the respiratory muscles. It remains to be shown that the respiratory muscles are a limiting factor in endurance during exercise with large muscle groups at altitude, but they certainly are a plausible candidate.

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