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Exercise training in chronic hypoxia has no effect on ventilatory muscle function in humans

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Abstract

At the highest altitude, aerobic work is limited by environmental oxygen availability. We therefore reasoned that the hyperpnea associated with endurance training at altitude should provide a strong stimulus for adaptation of the ventilatory muscles. We measured peak inspiratory muscle pressure-flow characteristics (inspiring through graded resistors) and maximum sustainable ventilation capacity in ten permanent residents of La Paz, Bolivia (3600 m) prior to and immediately following 6 weeks of incremental endurance training. Additionally, eight local residents did no training and functioned as controls for the capacity test. While V_{O_2}max measured in hypoxia increased by 19% (Favier et al., 1995b. J. Appl Physiol. 78, 2286–2293.), none of the tested ventilatory variables showed significant changes. The values for the group mean slopes of maximum inspiratory pressure-flow pairs (-10.5 vs. -9.8 cm $H_2O \cdot sec \cdot L^{-1}$, $P = 0.301$; before versus after training, respectively), maximum inspiratory pressure (112.1 ± 8.9 vs. 106.9 ± 8.6 cmH_2O, $P = 0.163$), peak inspiratory flow (9.8 ± 0.41 vs. 10.2 ± 0.55 $L \cdot sec^{-1}$, $P = 0.172$) and the maximum volitional volume in 12 sec (43.9 ± 2.4 vs. 45.6 ± 2.4 L in 12 sec, $P = 0.133$) were unchanged with exercise training. Likewise, maximal sustainable minute volume was not different between post-training and control subjects (177.4 ± 7.9 vs. 165.4 ± 8.4 $L \cdot min^{-1}$, $P = 0.141$). These data support the concept that endurance training fails to elicit functional adaptations in ventilatory muscles in humans, even when exercise is done in hypoxia.

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1. Introduction

Like all vertebrate skeletal muscles, the ventilatory muscles (VM) of humans can respond adaptively to strength and endurance training. In the laboratory, specific VM training protocols have resulted in significant improvements in peak inspiratory or expiratory pressure maxima and sustained ventilatory capacity tasks (Leith and Bradley, 1976; Morgan et al., 1987; Belman and Gaesser, 1988; Fairbarn et al., 1991). There is less evidence that functional or structural adaptations of VM occur as a consequence of increased ventilatory demands concomitant with whole-animal, chronic endurance training. While some studies on humans suggest that VM endurance can be improved with swimming or running exercises (Robinson and Kjeldgaard, 1982; Clanton et al., 1987) the results of various animal experiments are controversial. Several reports demonstrate increases in the activity of marker enzymes of oxidative metabolism in diaphragm of rats subjected to various types of endurance training (Powers et al., 1990, 1992a,b; Uribe et al., 1992). However, just as many studies were unable to detect changes in diaphragmatic oxidative capacity after endurance training in two species (Metzger and Fitts, 1986, rats; Fregosi et al., 1987, rats; Green et al., 1989, rats; Hoppeler et al., 1995, guinea pigs). Taken collectively, these studies demonstrate some functional phenotypic plasticity of the ventilatory muscles; however, the direct role of endurance-type training in eliciting this plasticity remains equivocal.

Aerobic performance and $\dot{V}_{O_2}$peak both decline monotonically above about 1500 m elevation. It is generally accepted that this decline is the consequence of reduced oxygen availability resulting in diminished arterial oxygen pressure and saturation during moderate and heavy work, hence the use of the term $\dot{V}_{O_2}$peak rather than $\dot{V}_{O_2}$max (Dempsey et al., 1977; Favier et al., 1995a) which is not compensated by increased cardiac output. We hypothesized that endurance training at altitude should provide a powerful ventilatory challenge and should therefore pose a critical test of VM functional plasticity in humans. To address this question, we measured VM power and endurance in a group of high altitude residents of La Paz, Bolivia (3600 m) prior to and immediately following an endurance training protocol designed to increase (see Favier et al., 1995b). Specifically, we tested the hypothesis that the static (isometric) and dynamic (miometric) properties of the human ventilatory muscles as defined by the slope of the maximum inspiratory pressure-flow curve (MIPF) through graded resistors, the maximum sustainable ventilatory capacity (MSVC) and the maximum 12 sec ventilation (MVV_{12}) will respond adaptively to 6 weeks of hypoxic endurance (cycle ergometry) training as they seem to following specific respiratory muscle training tasks (Leith and Bradley, 1976; O'Kroy and Coast 1993).

2. Materials and methods

This study was completed in conjunction with a study designed to examine the effects of endurance training on $\dot{V}_{O_2}$peak and skeletal muscle composition in high altitude natives. Data for oxygen uptake, power output and minute volume come from that study (Favier et al., 1995a,b). A group of 18 young men, residents of La Paz, Bolivia (3600 m) were assigned to either an endurance training (ET) or control (C) group. All subjects underwent a clinical check-up including ECG, those with a history of signs of cardiac disease were excluded from the study. Based on the results of pulmonary function tests, all subjects were classified as normal for high altitude residents as defined by Greksa (1986) (Table 1).

Table 1
Anthropometric and respiratory function data (with the standard error) of the trained and control subjects both at rest and at $\dot{V}_{O_2}$peak

Group	Age	Weight	Rest			Maximum $\dot{V}_{O_2}$			
	(years)	(kg)	Pa_{O_2} (Torr)	Pa_{CO_2} (Torr)	HR (min^{-1})	Pa_{O_2} (Torr)	Pa_{CO_2} (Torr)	HR (min^{-1})	Power (W)
Trained	24.2	61.1	57.3	29.0	78	59.8	24.5	189	214
SEM	0.5	1.3	0.7	0.4	3	1.6	0.6	3	11
Control	25.0	61.3	58.4	27.7	76	61.5	23.8	188	191
SEM	1.3	2.0	0.9	1.6	2	0.4	0.5	3	10

2.1. Maximum cycling oxygen uptake

$\dot{V}_{O_2}$peak for each subject was determined via cycle ergometry as previously described in Favier et al. (1995a). Subjects breathed through a Hans Rudolph (model 2700) two-way valve fitted with flappers. Expired air was collected in a Douglas bag which was subsequently quantified with a 120 L Tissot Spirometer. A sample of this air was dried and passed through CO_2 and O_2 analyzers. Group ET subjects then began an incremental endurance training program which consisted of cycling for 30 min/day, 5 day/week, for 6 week at an external power output ($\dot{W}_{max}$) initially set to elicit 70% of their individual $\dot{V}_{O_2}$peak values measured in ambient (hypoxic) conditions and subsequently adjusted to maintain a constant relative work intensity with regard to $\dot{V}_{O_2}$peak. This was accomplished by using a constant training heart rate; which was equal to approximately 85% of the maximum heart rate for each of the subjects; this heart rate was found to elicit 70% of $\dot{V}_{O_2}$peak (Favier et al., 1995a).

2.2. Ventilatory muscle profile: static measurements

Inspiratory pressure-flow values were determined for each subject after the technique of Agostoni and Fenn (1960). Peak inspiratory flow ($\dot{V}_I$max) and peak airway opening (mouth) pressure (P_{ao}) were simultaneously measured while the subjects performed maximal peak inspiratory flow manuevers through nine graded resistors (R1-R8: 20.9, 15.9, 12.9, 10.70, 8.50, 7.20, 5.81, 2.38 mm internal diameter and R9 near occlusion, that is a pinhole to prevent a Valsalva maneuver). Beginning lung volume was controlled during these maneuvers by starting at functional residual capacity (FRC). Flow was measured with a heated Rudolph pneumotachometer (Finucane et al., 1972; Turney and Blumenfeld, 1973) fitted with an Omega differential pressure transducer (model # PX170). Since pressure transducers are sensitive to temperature, we encapsulated the entire pressure transducer with liqui-foam to insure a thermal steady state. Constant excitation voltage was furnished to the transducer by a 12 V battery since the line voltage in La Paz was highly irregular. The pneumotachometer was calibrated with two shop vacuums assembled in series and a Matheson laminar flow element over the range of 0–800 $L \cdot min^{-1}$. Calibration was checked thrice daily with a 3 L volume syringe (W.E. Collins), over several flow velocities.

Inspiratory resistors (R1-R9) were inserted between two plexiglass tubes each 3.15 cm ID, 10.26 cm in length. Pressure ports (1.70 mm ID) were machined into the tube 5.12 cm distal and 5.14 cm proximal to the resistor but not penetrating into the airstream. W.E. Collins non-threaded respiratory hose couplers provided an airtight seal around the orifice. The pressure across the orifice was measured with an Omega differential pressure transducer (model # PX126) attached to the pressure ports via tygon tubing with care to keep the volume of tubing constant on both sides. The transducer was calibrated over the range of 0–94 cm of H_2O with a water-filled manometer. Signals resulting in delta pressures across the orifice

above 94 cm H_2O were estimated from a linear calibration curve ($R^2 = 0.9999$). Between each inspiratory trial, the transducer was opened to the atmosphere to check zero.

2.3. Ventilatory muscle profile: dynamic measurements

Maximum ventilatory volume in 12 sec (MVV_{12}) and maximum sustainable minute volume (MSMV) were measured on a rebreathing rig. At the start of the run, the subject expired to fill a 5 L Douglas, to function as a air reservoir. The inspirate passed through the pneumotachometer then into the subject past a Rudolph valve (model 2700). The flow signal was integrated to determine inspired volume. To avoid condensation build-up on the pneumotachometer screens, the expired air passed through a condensing coil built from wide bore Collins respiratory tubing submerged in an ice slurry to lower the dew point of the airstream below that of the pneumotachometer. Near the Douglas bag, a pump removed a sample of air from the air column to monitor CO_2 content in the system. The CO_2 concentration was maintained at $6 \pm 0.5\%$ (P_{CO_2} 27–32 Torr) by selectively directing the airflow through a column of barium hydroxide. The gas re-entered the airstream at the condensing coil. Douglas bag volume was held nearly constant with the addition of 100% O_2. All electronic signals were passed through an analog to digital converter then routed into a computer and stored on diskette for subsequent analysis.

2.4. Protocol

$\dot{V}_I$max maneuvers were initiated at relaxed end-expiratory lung volume while the subjects were standing. The order of orifice selection was sytematically randomized and subjects were unaware of the orifice diameter prior to each trial. We attempted to minimize pressure loaded fatigue, (McCool et al., 1992) by requiring 30 sec between each inspiratory trial.

MVV_{12} was measured while the subjects were seated and through the rebreathing rig described above. Subjects were given real-time visual cues of inspiratory volume and were verbally encouraged during the trial to move the maximum amount of air possible during the 12 sec. MSMV was determined from an incremental load hyperpnea test. Subjects were asked to match a target ventilation displayed on the computer screen. Following a brief warm-up period, initial minute volume was set at 72 $L \cdot min^{-1}$ and increased stepwise every 2 min by 12 $L \cdot min^{-1}$. The test was terminated when the subject could not match the target for 15 sec. Extreme verbal encouragement was provided by the investigators as the subjects approached the test termination criterion.

All tests were repeated over several days, always in the above sequence to control for learning effects. For statistical analyses, the best performance for each particular task was taken as the datum.

2.4.1. Statistical analysis

A t-test for paired variates was used to compare MIP, $\dot{V}_I$max, and MVV_{12} (Figs. 2 and 3) data before and after training. An unpaired t-test was used to compare the same dependent variables as well as MSMV (Fig. 3) between ET pre-training and the control subjects. All assumptions of the t-test were satisfied according to the D'Agostino-Pearson Omnibus K^2 test. The method of least squares was used to determine the regression line for the MIPF pairs. Parallelism of slope, variance around the regression line, and homogeneity of the Y-intercept were evaluated for ET pre- compared to post-training and between ET pre-training and 'control' with a single classification analysis of covariance. In all instances, the level of significance (α) was set at 0.05.

3. Results

Comparing ET pre-training and C, mean $\dot{V}_{O_2}$peak (2.42 ± 0.10 $L \cdot min^{-1}$ (mean $\pm$ 1 SEM) vs. 2.49 ± 0.13, $P = 0.70$), maximum exercise minute volume ($\dot{V}_E$max) (127.7 ± 5.4 $L \cdot min^{-1}$ vs. 132.1 ± 6.8, $P = 0.61$), and (173.0 ± 6.0 W vs. 191.3 ± 9.7, $P = 0.11$) were not different (via unpaired t-test). Following 6 weeks of cycle endurance training at 3600 m, $\dot{V}_{O_2}$peak and $\dot{W}_{max}$

both increased by 19%, $P < 0.05$, while $\dot{V}_E$max increased insignificantly by only 13% ($P = 0.17$, n.s.; all data from Favier et al., 1995a, Fig. 1).

MIPF through graded resistors was analyzed via linear regression methods (Agostoni and Penn, 1960; Topulos et al., 1987; McCool et al., 1992) with the pre-training MIPF group mean slope equal to -10.5 compared with the control MIPF group mean slope of -12.1 $cmH_2O \cdot sec \cdot L^{-1}$(Fig. 2). The variance around the regression lines between ET and C was homogeneous ($P = 0.311$) and the regression lines shared a common slope ($P = 0.272$). Following training, ET's MIPF group mean slope equalled -9.8 $cmH_2O \cdot sec \cdot L^{-1}$. Comparing pre- to post-training MIPF group mean slopes, the variance was homogenous ($P = 0.257$) and the regression lines shared a common slope ($P = 0.301$).

Pre-training ET and C group mean MIP applied to a nearly occluded orifice (MIP) were similar (112.1 ± 8.9 vs. 129.7 ± 7.6, $P = 0.0798$). In ET, MIP did not change following training (112.1 ± 8.9 vs. 106.9 ± 8.6, $P = 0.163$).

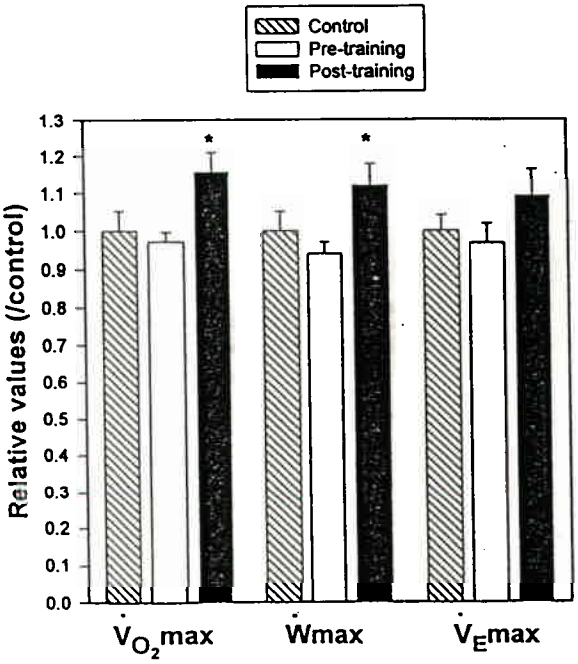

Fig. 1. Maximum oxygen uptake ($\dot{V}_{O_2}$peak) and peak work output at $\dot{V}_{O_2}$max ($\dot{W}$max) are shown before (empty bars) and after (filler bars) training relative to a second (control) group of untrainned individuals (hatched bars). Both $\dot{V}_{O_2}$max and $\dot{W}$max increased significantly by about 19% following training, while the 13% increase in $\dot{V}_E$max was not statistically significant.

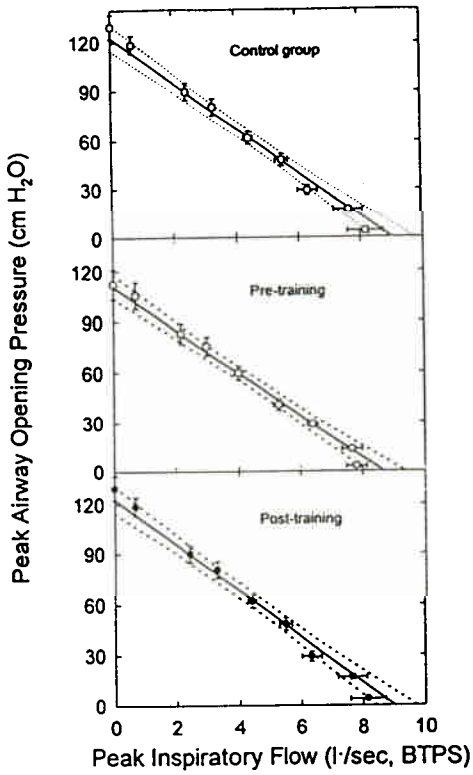

Fig. 2. Pressure at the mouth (airway opening) is plotted as a function of peak inspiratory flow for subjects breathing through graded resistors. Group mean slopes for maximum inspiratory pressure-flow (MIPF) pairs was not significantly different from pre- (open circles) to post- (closed circles) training, nor was it different from a set of control individuals (squares). For an individual orifice, MIPF data are represented as pooled means with variance (SEM) represented in both axes.

$\dot{V}_I$max prior to training in ET was not different compared to the control group (9.8 ± 0.41 vs. 10.2 ± 0.71 $L \cdot sec^{-1}$, BTPS, $P = 0.296$). Six weeks of endurance training had no significant effect on $\dot{V}_I$max (9.8 ± 0.41 vs. 10.2 ± 0.55 $L \cdot sec^{-1}$, $P = 0.172$).

MVV_{12} was not significantly different between ET prior to training and C or after endurance training (43.9 ± 2.4 vs. 47.6 ± 2.6 L in 12 sec, BTPS, $P = 0.154$; post-training 45.6 ± 2.4 L in 12 sec, $P = 0.133$) respectively (Fig. 3). MSMV achieved during a progressive load hyperpnea test

was similar in ET post-training and C (177.4 ± 7.9 vs. 165.5 ± 7.1 L·min^{-1}, BTPS, $P = 0.141$).

4. Discussion

Our hypothesis predicted that endurance training at high altitude should provoke detectable functional adaptations of the ventilatory muscles. However, this study failed to demonstrate this result. Peak inspiratory pressures, flows, and MSVC, were not different before versus after nor comparing post-training values with those of control, untrained, subjects.

As a measure of inspiratory VM strength, we used a one-shot 'maximal' inspiratory flow maneuver through nine graded resistors controlling for initial lung volume (and therefore presumably initial sarcomere length). By having subjects inspire through graded resistors, we were observing the force-length-velocity behavior of the inspiratory muscles acting in synergy to produce inspiratory pressure and flow while changing the inspiratory load (McCool et al., 1992). Thus the slope of the MIPF through graded resistors provides a quantitative measure for the analysis of the (collective) pressure generating potential of the inspiratory muscles. Following 6 weeks of endurance training, the slope of the MIPF curve was not significantly different from pre-training values.

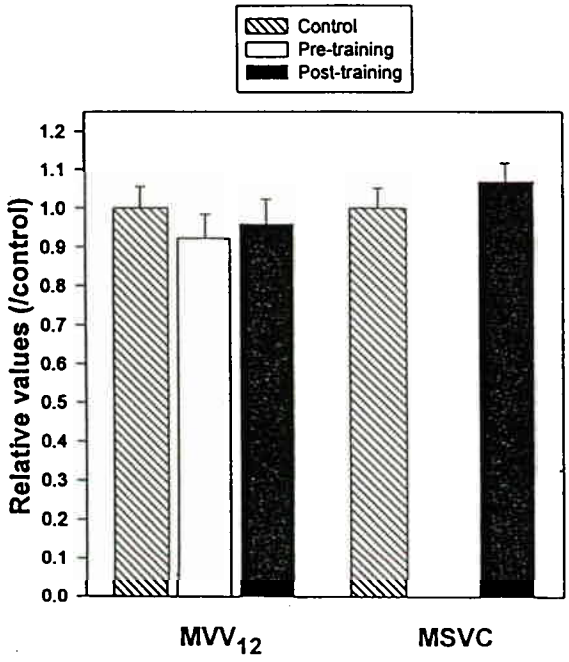

Fig. 3. Peak voluntary ventilation both in 12 sec (MVV_{12}) and sustained (MSVC) are shown before (empty bars) and after (filler bars) training relative to a second (control) group of untrainned individuals (hatched bars). Note that the MSVC was not measured per training. Neither of these variables was different as a function of trining or comparing the two groups of subjects.

One problem of published studies on VM endurance is the quantification of an unambiguous test-termination point. There appears to be no apparent standardized protocol to measure endurance capacity of breathing and the apparent lack of a universally accepted protocol among researchers studying VM endurance capacity complicates direct comparisons across studies. Techniques vary from using fractions of the MVV_{12} to set ventilatory targets (Belman and Gaesser, 1988), percentage of maximum mouth pressures (Clanton et al., 1987), and maximum ventilation for a pre-determined time varying from 1 to 15 min (Belman and Kendragon, 1982; O'Kroy and Coast, 1993; for a review see also Carter and Coast, 1993). Initially, we intended to evaluate VM endurance using a time-to-limitation criterion with a ventilatory target set at 65% of each subjects MVV_{12}. However, during the pre-training data collection, we found that the within group variance was unacceptably large and that inter-test reliability was poor. Therefore, we recruited eight sedentary subjects of similar age, weight, life history (i.e. high altitude residents) to function as an additional control group. Between data collection periods, we designed and tested a fixed incremental load hyperpnea test (maximal sustainable minute volume; MSMV), in effect, a ventilatory muscle $\dot{V}_{O_2}$peak test, which provided a clearly defined and highly reproducible end. While we did not pattern our protocol from any particular source, Martin and Stager (1981) used a progressive step ventilatory test consisting of four minute steps at 30 L·min^{-1} per step to evaluate ventilatory muscle endurance capacity. The major advantage of the MSMV is that it provides a defined end point from which to evaluate VM's capacity for sustained work.

The endurance capacity of the VM might be expected to vary as a dependent function of aerobic training. In fact, following 3 months of swim training, Clanton et al. (1987) observed a significant increase in inspiratory muscle endurance nearly equal to that observed in a group of swimmers who underwent the same swim training but in addition performed inspiratory muscle training. Likewise, Robinson and Kjeldgaard (1982) linked a 16% increase in ventilatory muscle endurance to a similar increase in running performance following training in a group of previously sedentary humans. Neither of these studies reported $\dot{V}_{O_2}$max before and after training. Moreover, in Clanton's case, swimmers specialty (sprint versus endurance) was not reported making it difficult to judge the magnitude of the training effect. Therefore, swim- or run-training performed at sufficient intensities may improve the structural and functional capacity of the chest wall muscles.

Powers et al. (1990, 1992a,b) and Uribe et al. (1992) have reported increases in aerobic marker enzymes in the costal but not crural region of rat diaphragm following various intensities of chronic endurance training. In contrast, no significant effect on muscle mitochondrial content and capillarity in costal diaphragm was observed in growing Guinea pigs trained by endurance running for 6 weeks (Hoppeler et al., 1995). Likewise, a number of earlier studies failed at demonstrating training effects on the diaphragm induced by whole body exercise (Metzger and Fitts, 1986; Fregosi et al., 1987; Green et al., 1989). The latter studies merged the costal and crural portions of the diaphragm into a single biochemical assay while the former studies sampled these regions separately. There is some evidence obtained from stimulation experiments on dogs that costal and crural portions of the diaphragm might perform different functions (De Troyer et al., 1981). However, little seems to be known about the in vivo recruitment pattern and use of the costal and crural regions of the diaphragm. It has been hypothesized that exercise intensity must be very high indeed to induce structural adaptations in diaphragm (Powers et al., 1992a; Uribe et al., 1992). In this context one must consider that mitochondrial content and capillary supply of the diaphragm (both crural and costal) in a considerable number of mammalian species analyzed consistently surpasses that of locomotor muscles by far (diaphragm being second only to the heart with respect to these characteristics; Hoppeler et al., 1981; Conley et al., 1987). This could indicate that it may be difficult to further increase muscle structural determinants of endurance in a respiratory muscle by whole body exercise. Taken together, animal experimentation shows inconsistent results with regard to structural and biochemical adaptations of the diaphragm as a consequence of whole body endurance training. There is ample evidence however, that the diaphragm is extremely well equipped to perform continuous work.

The fact that in this study none of the ventilatory parameters changed following 6 weeks of endurance training, contrasts to several studies in which appropriately chosen specific ventilatory muscle training does increase inspiratory and expiratory pressure maxima as well as sustained ventilation capacity tasks. However, as noted above, evidence for ventilatory muscle adaptation following whole-animal endurance training is equivocal. Since O_2 availability limits work capacity at altitude, we felt that a chronic endurance training protocol in hypoxia would provide a strong signal to observe potential coupling of VM performance and peak aerobic capacity. Therefore, we chose to test our hypothesis that VM power and endurance are coupled to the downstream demand for O_2 in La Paz, Bolivia (3600 m) following a cycle ergometry endurance training bout designed to increase. Despite the fact that $\dot{V}_{O_2}$peak did increase, that increase was not accompanied by significant changes in any of our measures of ventilatory muscle performance.

Thus, our results suggest accepting the null hypothesis that VM power and endurance do not track increases in $\dot{V}_{O_2}$peak even when exercise training is carried out in severe environmental hypoxia. We have to conclude that sufficient VM structural and functional capacity was present prior to the endurance training bout to accommodate a 19% increase in $\dot{V}_{O_2}$peak. In other words, this implies that the maintenance of apparently 'excess ventilatory muscle capacity'.

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