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Proportional Assist Ventilation Reduces the Work of Breathing during Exercise at Moderate Altitude

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ABSTRACT

Kleinsasser, Axel, Achim Von Goedecke, Christoph Hoermann, Stephan Maier, Andreas Schaefer, Christian Keller, and Alex Loeckinger. Proportional assist ventilation reduces the work of breathing during exercise at moderate altitude. *High Alt. Med. Biol.* 5:420–428, 2004.—Reducing the work of breathing (WOB) during exercise and thus the oxygen required solely for ventilation may be an option to increase the oxygen available for nonventilatory physiological tasks at altitude. This study evaluated whether pressure support ventilation (PSV) and proportional assist ventilation (PAV) may partially reduce WOB during exercise at altitude. Seven volunteers breathing with either PSV or PAV or without support (control) were examined for WOB, inspiratory pressure time product (iPTP), and $\dot{V}_{O_2}$ before and during pedaling at 160 W for 4 min on an ergometer at an altitude of 2860 m, where barometric pressure and oxygen partial pressure are approximately 30% less than at sea level. PSV and PAV reduced WOB from 4.5 ± 0.9 $J/L^{-1}/min^{-1}$ during unsupported breathing to 3.7 ± 0.4 ($p < 0.05$) and 3.2 ± 0.7 ($p < 0.01$), respectively. iPTP was reduced during PAV (570 ± 151 cm $H_2O/sec/min^{-1}$, $p < 0.01$), but not during PSV (727 ± 116, $p = 0.58$) compared with unsupported ventilation during exercise (763 ± 90). During PSV and PAV breathing, higher arterial oxygen saturations (84 ± 2%, $p < 0.05$, and 86 ± 1%, $p < 0.01$, respectively) were observed compared with control (80 ± 3%), indicating that PSV and PAV attenuated hypoxemia during exercise at altitude. Total body $\dot{V}_{O_2}$, however, was not reduced during PSV or PAV. In conclusion, both PSV and PAV reduced the WOB during exercise at altitude, but only PAV reduces iPTP. Both modes reduce hypoxemia, which may be due to higher alveolar ventilation or decreased ventilation–perfusion heterogeneity compared to unsupported breathing.

Key Words: assisted ventilation; pressure time product; hemoglobin saturation; esophageal pressure measurement; pleural pressure

INTRODUCTION

We recently proposed the use of pressure support ventilation (PSV) at high altitude to compensate for low alveolar gas pressures and to reduce the work of breathing (WOB), leaving more oxygen for nonventilatory tasks (Kleinsasser and Loeckinger, 2002). However, our theoretical study only evaluated PSV, whereas a newer mode, proportional assist

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ventilation (PAV), was not examined. This study's aim was to compare PSV and PAV with respect to unloading WOB in volunteers during exercise at altitude.

PSV is the classic mode (Tyler and Grape, 1962) of noninvasive positive pressure ventilation traditionally used for intermittent ventilatory support and for weaning from mechanical ventilation (Ambrosino et al., 1992). In PSV, inspiration is supported by a preset level of pressure, which is provided after detection of an inspiratory effort of the subject. Mechanical inspiratory support is terminated by the decrease in gas flow at the end of the subject's inspiration. PSV may be understood as subject-triggered mechanical ventilation.

While in PSV inspiratory pressure support is constant, in PAV the inspiratory pressure support is *dynamically* adjusted. Pressure support in PAV is applied in linear proportion to the inspiratory flow and volume generated by the subject and based on preset proportionality factors (Younes, 1992). Compared to PSV, PAV is more efficient in reducing WOB (Grasso et al., 2000). PAV responds to flow and volume movements generated by the subject and amplifies airway pressure accordingly. Compared to PSV, PAV is adaptive. During heavy, exhaustive exercise, PAV may prevent diaphragmatic fatigue by reducing diaphragmatic work (Babcock et al., 1997), which may be based on competition between limb skeletal muscles and respiratory muscles (Wetter et al., 1999).

At altitude, respiratory minute volume (VE) is higher than at sea level to compensate for low barometric and inspiratory partial pressures of oxygen ($P_{I_{O_2}}$). Cibella and coworkers found that the oxygen cost of breathing is increased at altitude (Cibella et al., 1999), although air viscosity and resistance to gas flow in the respiratory system are less than at sea level. The purpose of this study was to examine whether PSV and PAV offset WOB. Neither PSV nor PAV were designed for exercise and high VEs at altitude. We hypothesized that both PSV and PAV might reduce the work of breathing and subsequently total body oxygen uptake ($\dot{V}_{O_2}$) during exercise at altitude.

METHODS

Location

After obtaining institutional research board and ethic's committee approval and after written informed consent had been obtained from all seven volunteers, tests were carried out at the bottom of the Rettenbach glacier, Tirol, Austria, at an altitude of 2860 m (9383 ft). Experimental runs were performed in a facility provided by the local cable car company (Ötztaler Gletscherbahnen, Sölden, Austria).

Subjects and study protocol

Seven healthy, male, nonsmoking volunteers aged 35 to 38 yr were examined. The group consisted of two sedentary subjects and five recreational runners.

To avoid any acclimatization, the subjects were brought up to the testing facility from 560 m every morning and down from altitude after no more than two exercise runs per day. A minimum delay of 2 hr between individual exercise runs was stipulated. Baseline measurements were performed with the subjects sitting on the bicycle ergometer without pedaling.

Ventilator, PSV, and PAV settings

An Evita 4 ICU ventilator (Dräger, Lübeck, Germany) was used. For reasons of better comparability, all settings were chosen after pilot experimental runs with all subjects.

In studies comparing PSV with PAV, the inspiratory pressure time product (iPTP, see below) is typically used as the target variable to ensure that PSV and PAV provide equivalent support (Grasso et al., 2000). As WOB and iPTP were the key variables, we examined a different approach to find comparable settings. After finding the average VE and tidal volumes during exercise with unsupported breathing, the settings for PSV were determined. PSV was begun with an inspiratory pressure and gradually adjusted to achieve a tidal volume of 50 mL/kg [BTPS]. Settings for PAV were then determined using the runaway method as previously described (Patrick, et al., 1996). Briefly, volume assist was set to 5 cm H_2O/L and flow assist was set to 2 cm $H_2O/L^{-1}/sec^{-1}$. Leaving flow assist unchanged, volume assist was then increased by steps of 2 cm $H_2O/L^{-1}/sec^{-1}$ until runaway was observed. Runaway reflects overcompensation of resistance and elastance by the ventilator, and the subject actively needs to terminate inspiration. From the runaway point, volume assist was gradually reduced to achieve comparable VEs and tidal volumes as during PSV and unsupported breathing. With the Evita 4, flow and pressure changes are detected in the ventilator (expiratory limb), rather than at the mouth.

An 8F esophageal balloon catheter (Smart Cath, Allied Health Products, Riverside, CA) was inserted after applying topical anesthesia with 2% lidocaine to nares, nasal conchae, and pharynx. The catheter was advanced into the stomach until a positive waveform in the pressure reading could be observed. The catheter was then retracted 10 cm, and a sniff test was performed to verify the balloon's position in the lower third of the esophagus (Thomas et al., 1997). A flow transducer (Var Flex, Allied Health Products, Riverside, CA) was inserted between a high-flow mouthpiece and the Y-piece of the ventilator's circuit. Nose clips were used during testing.

Exercise tests lasted for a total of 9 min. After 3 min of unloaded pedaling, the workload was gradually increased over 2 min until 160 W at 90 revolutions/min was reached. Cadence was continuously monitored, and subjects were encouraged to pedal steadily. This workload was maintained over 4 min. During the fourth minute of pedaling at 160 W, inspiratory and expiratory samples were collected, and respiratory variables were recorded. Exercise measurements were performed using a mouthpiece with PSV, PAV, or unsupported breathing through the ventilator circuit in random order.

Variables recorded

Variables recorded included subject demographics, barometric pressure, change in esophageal pressure (δPes), WOB, iPTP, arterial hemoglobin saturation (SpO2, AS-3 CCU monitor, Datex, Helsinki, Finland), $\dot{V}_{O_2}$, VE, tidal volume, airway pressure, heart rate, and arterial blood pressure (sphygmomanometer, Datex AS-3). The Datex monitor periodically inflates the cuff just like the classic Dynamap device. A measurement lasts for approximately 1 min, and the value recorded during the fourth minute of exercise was recorded.

Bicycle ergometer and workload

A commercial ergometer (Cateye Ergocisor; EC 1200, Boulder, CO) was used. A work rate of 160 W was chosen because we found in pilot experiments that this workload results in VEs of approximately 70 L/min, which is below the maximum flow capacity of the ventilator used (150 L/min absolute flow for inspiration and expiration).

Respiratory mechanics, WOB, and iPTP measurements

An esophageal catheter (see above) and a flow transducer connected to a pulmonary mechanics computer (CP-100, BiCore, Irvine, CA) were used. All calculations were performed using the BiCore software. The software of the Bicore® monitor used in this experiment applies the Campbell (volume) loop (Campbell, 1958). This setup with Bicore® monitor and Campbell loop software has been validated versus the conventional setup to construct a Campbell loop and was found to be highly accurate (Blanch and Banner, 1994). WOB (J/L) was calculated by integrating Pes versus the volume loop. iPTP (cm $H_2O/sec/min^{-1}$) was obtained by integrating esophageal pressure and time for the duration of contraction over a 1-min interval (ATS/ERS, 2002). iPTP quantifies the subject's respiratory effort in overcoming isometric and volumetric opposing forces (Thomas et al., 1997). In particular, iPTP quantifies changes in inspiratory muscle effort over an observational period of 1 min. Technically, iPTP is calculated by integrating esophageal pressure and time for the duration of contraction over a 1-min interval (ATS/ERS, 2002), which has the units cm $H_2O/sec/min^{-1}$. iPTP is one of the best indicators of actual effort during the respiratory cycle and, together with VE and Pes, iPTP was shown to reflect changes in respiratory effort in cardiopulmonary exercise testing (Thomas et al., 1997). In WOB and iPTP calculations, δPes (swing in Pes) was used as a surrogate for changes in pleural pressure (Milic-Emily et al., 1964).

Oxygen uptake measurements

Oxygen uptake ($\dot{V}_{O_2}$) was assessed using the classic Douglas bag method (Douglas et al., 1913). Briefly, mixed expiratory gases were collected in a gas-tight weather balloon with a capacity of 100 L. Respiratory minute volume was thereafter measured by using a calibrated Wright Respirometer® (Ferraris, New York, NY). Mixed expiratory gas samples were collected from the center of the inflated balloon into gas-tight glass syringes. Inspiratory gas samples were collected from the inspiratory hose of the ventilator into gas-tight glass syringes. All samples were immediately analyzed using the gas sample option of a blood gas analyzer (Ciba Corning, Oberlin, OH). Body temperature was measured orally immediately after an experimental run.

Data analysis

A two-way analysis of variance for repeated measurements (ANOVA) was used. Significant differences were post hoc examined using the Newman–Keuls test. Significance was accepted at $p < 0.05$. Values are given as mean ± standard deviation (SD).

RESULTS

All subjects tolerated the experimental procedure well.

Barometric pressure

Barometric pressure during the experimental runs at 2860 m (9383 ft) was 534 ± 3 torr. The resulting inspiratory pressure of oxygen was 101 ± 1 torr (sea level: 149 torr).

Demographic data

There were no differences in age, height, weight, or body surface area. All experimental subjects lived in Innsbruck, Austria, at an altitude of 560 m (barometric pressure ≈ 713 torr).

WOB and iPTP measurements

Data are given in Figs. 1 and 2. In comparison to unsupported breathing during exercise WOB was reduced during PSV and PAV.

PAV resulted in less iPTP than PSV ($p < 0.05$) or unsupported breathing ($p < 0.01$). Comparing iPTP during PSV and unsupported breathing did not reveal any difference (Fig. 1).

δPes (Fig. 2), surrogate of pleural pressure, is the deflection of esophageal pressure during in- and expiration and indicative for the effort to breathe. The was no difference comparing δPes during unsupported breathing, PSV, and PAV.

Other respiratory variables

During exercise with either PSV, PAV, or without ventilatory support, there were no significant differences in VE (indexed to body weight, Fig. 2) and tidal volume (indexed to body weight, Fig. 2).

Mean airway pressure was higher during PAV ($p < 0.01$) and PSV ($p < 0.05$) compared to unsupported breathing (Fig. 2).

Respiratory rates were 22 ± 5 breaths per minute during unsupported breathing, 16 ± 4 during PSV, and 18 ± 6 during PAV. Differences were not significant.

Oxyhemoglobin saturation during control, PSV, and PAV

Data are presented in Fig. 1. In comparison to unsupported breathing during exercise, oxyhemoglobin saturation was increased during PSV or PAV breathing.

$\dot{V}_{O_2}$ measurements

Data are presented in Fig. 1. In comparison to unsupported breathing during exercise, $\dot{V}_{O_2}$ remained unchanged during either PSV and PAV breathing.

Heart rate and arterial blood pressure

Heart rate was not significantly different between groups (unsupported exercise: 159 ± 18 beats/min versus PSV 152 ± 15 versus PAV 152 ± 15).

Mean arterial pressure (MAP) was reduced from 162 ± 22 torr unsupported to 138 ± 17

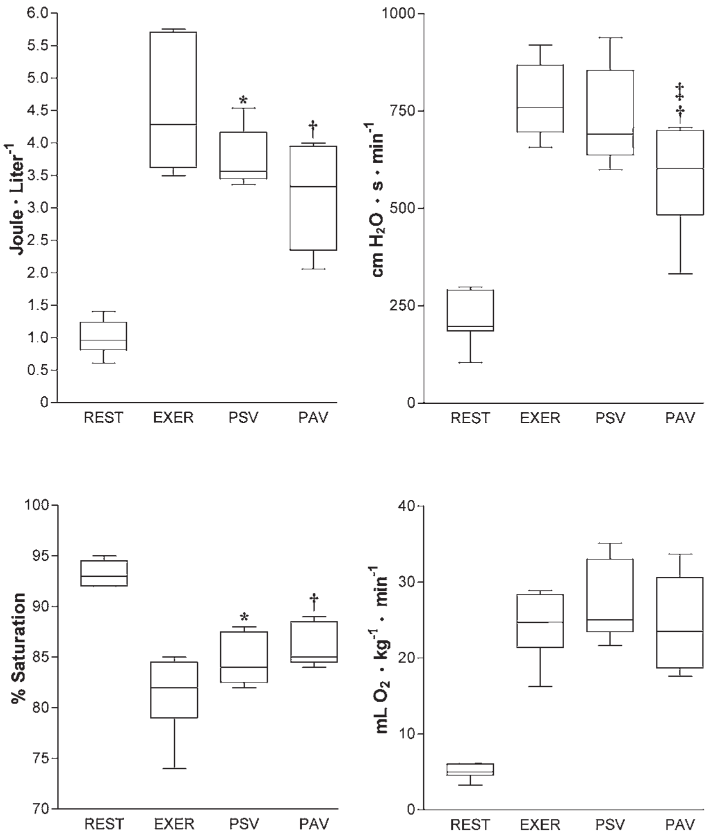

FIG. 1. Figure 1 displays work of breathing (upper left panel), iPTP or inspiratory pressure time product (upper right panel), hemoglobin saturation (lower left panel), and $\dot{V}_{O_2}$ or total body oxygen uptake (lower right panel). Abscissa of individual figures: REST, measurement sitting on the bicycle ergometer without pedaling; EXER, pedaling at 160 W without ventilatory support; PSV, pedaling at 160 W with pressure support ventilation; and PAV, pedaling at 160 W with proportional assist ventilation. Data are given as *five-number summary* (the classic box and whiskers plot), where the lowest horizontal line is the minimum value, the box's bottom line the 25th percentile, the horizontal line within the box the median value, the box's upper boundary the 75th percentile, and the top horizontal line the maximum value. If a line is not seen, it is because it is contained within the box's frame. *$p < 0.05$ and †$p < 0.01$ in comparison to EXER, and ‡$p < 0.05$ in comparison to PSV.

torr with PSV and 114 ± 24 during PAV ($p < 0.05$).

DISCUSSION

PSV and PAV are two augmented modes of breathing most commonly used to decrease a patient's work of breathing. In the present study, we examined whether augmented breathing may also be used in healthy subjects during exercise at altitude. Main findings were that PAV and PSV reduced WOB compared with unsupported breathing. Inspiratory iPTP was decreased during exercise with PAV, but not during exercise with PSV breathing. Compared to unsupported breathing, PSV and PAV breathing during exercise increased Sp_{O_2}. Total body $\dot{V}_{O_2}$ did not change during supported breathing.

PAV and WOB during exercise

PAV has been used in a number of studies on respiratory muscle work to decrease WOB at sea level (Harms et al., 1997, 1998, 2000; Wetter et al., 1999). WOB during submaximal exercise makes only small demands for $\dot{V}_{O_2}$ (Harms et al., 1998), while during maximal exercise up to 14% to 16% of the cardiac output is directed to the respiratory muscles (Harms et al., 1998). Our findings are compatible with those of Harms et al. at sea level, as the 160 W used in our study performed at altitude was a

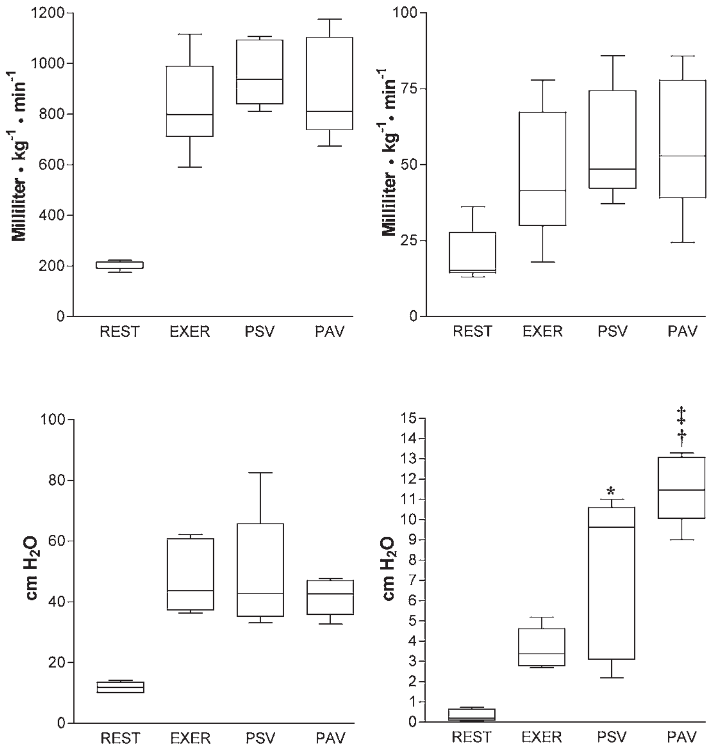

FIG. 2. Figure 2 displays respiratory minute volume indexed to body weight expressed as BTPS (VE, upper left panel), expiratory tidal volume [BTPS] (upper right panel), esophageal pressure as a measure of pleural pressure (lower left panel), and mean airway pressure (lower right panel). For a description of entries, see Fig. 1 caption.

relatively modest workload, and we did not find any changes in $\dot{V}_{O_2}$.

Increases in WOB during maximal but not during submaximal exercise decreased leg blood flow (Harms et al., 1997; Wetter et al., 1999). Unloading WOB during exercise at sea level may reduce $\dot{V}_{O_2}$ and reduce the rate of change in perceptions of respiratory and limb discomfort throughout the duration of exercise (Harms et al., 2000). Yet again this may also apply at altitude when WOB is unloaded using PAV.

PAV, WOB, and exercise tolerance

Our findings are consistent with a number of studies where PAV was used to unload WOB (Harms et al., 1997, 1998, 2000; Wetter et al., 1999). Unloading WOB increased leg blood flow and leg $\dot{V}_{O_2}$ during maximal exercise (Harms et al., 1997), but not during submaximal exercise (Wetter et al., 1999). In our study, where subjects exercised at submaximal workloads, $\dot{V}_{O_2}$ did not change when WOB was unloaded with PAV. We also speculate that unloading WOB with PAV may have increased exercise tolerance as observed by Harms and co-workers (Harms et al., 2000), as all our subjects reported that exercising felt easiest during PAV breathing.

PAV, but not PSV, reduced iPTP during exercise at altitude

In PAV, pressure is applied by the ventilator in proportion to the patient-generated volume and flow (Younes, 1992). Therefore, there is automatic synchrony between the patient's effort and the ventilatory cycle (Giannouli et al., 1999). Put differently, PAV amplifies airway pressure as a function of effort, whereas this variable is fixed in PSV. As inspiratory efforts naturally are vigorous during exercise, higher airway pressures were achieved during PAV (Fig. 2), as this mode provides amplification rather than constant support.

Breathing efforts are reflected in δPes, which mirrors the deflection in pleural pressure. In our experiment, there was a trend toward a smaller δPes during PAV than during PSV, indicating less breathing effort during PAV (Fig. 2).

VE, RR, and tidal volume were not different in comparison to breathing with PSV or unsupported breathing, suggesting that during PAV less effort was needed for the same amount of ventilation (Fig. 2). Accordingly, iPTP was reduced during PAV, but not during PSV, when compared with unsupported breathing (iPTP, Fig. 1).

$\dot{V}_{O_2}$ was not decreased during PAV despite a considerable reduction in iPTP

Unloading work and iPTP did not alter total body $\dot{V}_{O_2}$ in our experiment. In comparison to unsupported breathing, PAV reduced iPTP by approximately 25% (570 ± 151 versus 763 ± 90 cm $H_2O/sec/min^{-1}$, $p < 0.01$). Aaron and coworkers found that the oxygen cost of ventilation during maximum exercise averages 10 ± 0.7% of maximum $\dot{V}_{O_2}$ (Aaron et al., 1992). The subjects in this experiment were not doing maximal exercise. In fact, it was the relatively modest level of exercise that made it difficult to pick up what was presumably a reduced V_{O_2} during PSV or PAV breathing.

Mechanism for higher hemoglobin saturation during PSV and PAV breathing

Hemoglobin saturation was higher during PSV and PAV at a constant work rate, indicating less hypoxemia during augmented breathing.

Increased mean airway pressures during PSV and PAV (Fig. 2) may have led to higher alveolar pressures, which, given that everything else remained unchanged, increase the arterial partial pressure of oxygen and thus hemoglobin saturation.

Increased airway pressures may have improved all-over alveolar ventilation by recruitment of alveoli, which also contributes to a better arterial oxygenation, as this decreases heterogeneity of ventilation and perfusion.

VEs respiratory rate and tidal volumes were comparable between groups; hence, better alveolar ventilation during PSV and PAV breathing appears unlikely. By the same token, relative hyperventilation with lower alveolar partial pressures of carbon dioxide and the resulting higher alveolar pressures of oxygen can be ruled out.

But, also, an increase in lung volume may have played a role in improving hemoglobin saturation. δPes during inspiration, reflecting inspiratory effort, does not change with PSV or PAV. The integrated values of iPTP go down with application of the support pressures during PAV breathing (Fig. 1, upper right panel). This suggests that PAV and probably also PSV do not allow expiration to return lung volume to FRC. Thus the effect of this device is to increase mean lung volume during PAV and to a lesser extent during PSV. This volume increase distends airways, thus reducing airway resistance, and also opens more alveoli and/or improves uniformity of ventilation to poorly ventilated alveoli, explaining the rise in saturation. The reduced airway resistance may have resulted in reduced WOB during PSV and PAV breathing, as displayed in Fig. 1, upper left panel.

Arterial pressure during augmented ventilation

Surprisingly, MAP was lower during exercise with PAV compared with PSV or exercise with unsupported breathing. As with positive end-expiratory pressure (PEEP), positive airway pressures during augmented breathing may decrease cardiac stroke volume by increasing intrathoracic pressure and thereby decreasing preload (Gunn and Pinsky, 2001). This in turn decreases cardiac output (Frank–Starling relationship) and consequently arterial blood pressure.

Possible applications of PAV at altitude

Augmented breathing resulted in better arterial oxygenation. Increased arterial oxygenation may be an advantage for critically aerobic organs and tissues like myocardium, gut, kidney, or the central nervous system during exercise at altitude.

During severe exercise at high altitude, PAV may be used to reduce ventilation and therefore to keep it further below the critical value. Critical ventilation is reached when the oxygen gained by breathing is equal or less than the oxygen required for the work of breathing (Otis, 1954). Furthermore, all subjects agreed that exercise felt easier when breathing PAV.

Study limitations

First, it must be noted that an ICU ventilator is not designed for VEs in the range of 60 to 70 L/min. However, study design was adapted not to exceed the maximum flow capacity of the ventilator. Second, this experiment was carried out at moderate altitude; however, equal benefits can be extrapolated for the use of PAV at higher altitudes. It would be particularly interesting to test whether PAV during maximum exercise reduces $\dot{V}_{O_2}$ at very high altitude.

Conclusions

PSV and PAV decrease the work of breathing during exercise at altitude. Only PAV decreased iPTP. Neither PSV nor PAV decreased $\dot{V}_{O_2}$; however, arterial hemoglobin saturations were higher during both modes, indicating less hypoxemia during assisted breathing.

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