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Short communication

Upright posture increases oxyhemoglobin saturation in Peruvian highlanders

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ABSTRACT

At high altitude, hypoxia amplifies oxyhemoglobin saturation (S_pO_2) swings with changes in respiratory mechanics. Our objective was to examine the effects of posture on S_pO_2 and determine predictors of postural S_pO_2 changes in highlanders.

50 native highlanders from Puno, Peru (3825 m) assumed supine and upright-seated postures, in rotating sequence, while undergoing continuous pulse-oximetry. We compared mean S_pO_2 in each posture with a paired *t*-test. We examined associations of BMI, age, sex and spirometry with postural S_pO_2 changes with mixed-effects linear regression.

In highlanders, S_pO_2 was 84% in the supine posture and was 1.0% ± 1.1 ($p < 0.0001$) greater in the upright-seated posture. Greater postural changes in S_pO_2 were associated with older age ($p = 0.01$ for interaction) but not with sex, BMI, FVC or FEV_1.

In highlanders, S_pO_2 is higher in the upright-seated compared to supine posture, especially with older age. Because we generally sleep flat, posture may contribute significantly to highlanders' hypoxemic burden during sleep. Postural intervention during sleep may mitigate nocturnal hypoxemia.

1. Introduction

Hypoxemia is a significant risk factor for cardiovascular morbidity and mortality. Worsening hypoxemia is an independent risk factor for cardiometabolic diseases in highlanders. Evidence suggests that hypoxia is a potent source of cardiovascular and metabolic stress. In healthy volunteers, for example, hypoxia activates the sympathetic nervous system. Acute hypoxia also increases blood glucose and insulin resistance and may account for increased risk of diabetes in hypoxic disease such as sleep apnea. In cross-sectional studies, hypoxic chronic obstructive pulmonary disease (COPD) patients are at increased risk for right-sided heart failure and cardiovascular disease compared to normoxic patients. Highlanders can develop chronic mountain sickness, which shares many common features with end stage COPD including right heart failure, and secondary erythrocytosis. Daytime hypoxemia is associated with several markers of cardiovascular risk including metabolic syndrome, elevated Hemoglobin A1c, and C-reactive protein. The nocturnal period can be an especially vulnerable window for worsening hypoxemia and cardiometabolic stress.

Nocturnal hypoxemia in this setting largely stems from well-recognized alterations in ventilatory mechanics and drive as neuromotor tone to respiratory muscles decreases during sleep (Douglas et al., 1982a, 1982b; Orem et al., 1974; Remmers et al., 1978). In supine subjects, gravitational displacement of upper airway structures, abdominal contents and leg fluid volume reduce pharyngeal patency (Boudewyns et al., 2000; Heinzer et al., 2006; Joosten et al., 2015; Kairaitis et al., 2009; Martin et al., 1995) and lung volume (Oksenberg et al., 2009; Squier et al., 2010; Thut et al., 1993). Concomitant decreases in resting lung volume (functional residual capacity [FRC]) lead to reductions in oxygen stores and worsening ventilation-perfusion (V/Q) mismatch (Hakala et al., 2000, 1995). Mechanical loads on the upper airway and respiratory system decrease substantially when subjects sleep on their side or in a semi-recumbent position (Neill et al., 1997; Owens et al., 2015; Penzel et al., 2001). Postural maneuvers can

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decrease the severity of nocturnal hypoxemia and oxyhemoglobin desaturations during sleep disordered breathing (SDB) episodes (Series et al., 1989; Soll et al., 2009; Szollosi et al., 2006). Thus, postural maneuvers could reverse nocturnal oxygenation disturbances in highlanders.

The current study explores a potentially novel, low-cost alternative for alleviating SDB and nocturnal hypoxemia in native highlanders. Our primary objective was to examine the effects of postural maneuvers on oxygenation during wakefulness in native highlanders. We hypothesized that S_pO_2 will improve in the upright sitting compared to supine posture in native highlanders.

2. Methods

2.1. Study setting and subjects

We recruited a convenience sample of healthy native highlanders from the high altitude arm of the CRONICAS cohort study in Puno, Peru (3,825 m above sea level). Briefly, CRONICAS is an ongoing study that focuses on non-communicable chronic diseases in four distinct Peruvian settings (Miranda et al., 2012).

2.2. Ethics approvals

The study was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, and Universidad Peruana Cayetano Heredia and A.B. PRISMA in Lima, Peru. Because of low literacy rates, field personnel explained the study to each participant before obtaining verbal informed assent in Spanish, Aymara or Quechua.

2.3. Monitoring

Participants were fitted with recording devices, which included a pulse oximeter that generated a continuously array of values at 1 Hz sampling frequency (ApneaLink Plus with integrated NONIN Pulse Oximeter; ResMed, Ltd., San Diego, USA). The oximeter was placed on the right index finger to monitor oxyhemoglobin saturation (S_pO_2).

2.4. Study protocol

We conducted a cross-over experimental study of postural maneuvers on mean S_pO_2. The participant lay supine in bed or sat on a straight-backed chair at a 90° angle. Participants were instructed to remain still, quiet, and awake with their eyes open in both postures. During these maneuvers, pulse-oximetry was recorded continuously for 15 min in either posture. After 15 min, participants assumed the alternate posture and S_pO_2 was recorded continuously for another 15 min. The order of posture was predetermined according to consecutive enrollment. We systematically alternated posture order between subjects (e.g. even-numbered participants started in the supine posture and all odd-numbered upright).

2.5. Statistical analysis

Our primary outcome was change in S_pO_2 from the supine to upright-seated positions. Mean S_pO_2 was calculated from the average of the continuous S_pO_2 recording over the last 14 min in each posture so as to allow for signal stabilization after changing posture.

To test our primary hypothesis for postural differences in S_pO_2, we used a paired *t*-test to compare the mean S_pO_2 in supine and upright-seated postures. To identify factors that were associated with postural responses in S_pO_2, we performed *post-hoc* analyses in two stages. In the first stage, we developed separate models for each potential modifier of S_pO_2 responses to postural intervention. Specifically, mixed-effects linear regression was used to model S_pO_2 as a function of posture and its interaction with demographic (age and sex), anthropometric (BMI and waist circumference), and spirometric (forced vital capacity, FVC and the first second forced expiratory volume, FEV1) parameters. We incorporated both absolute and normalized (to height^2) spirometric values as predictors in modeling S_pO_2. In the second stage, we included BMI, sex and age as well as their interactions with posture in a multivariable mixed-effects linear regression model. To examine whether the order of exposure in each posture influenced the saturation, we modeled the order effect on saturation by including an interaction terms for posture and order in a mixed effects linear regression model. Analyses were performed with R (www.r-project.otg) and the LME4 package for linear mixed effects models.

Table 1
Subject Characteristics.

Characteristics		
N	50	
Sex = Male (n, (%))	20	(40.0)
Age [years], (Mean ± SD)	62.8	± 11.4
Weight [Kg], (Mean ± SD)	67.3	± 13.7
Height [m], (Mean ± SD)	1.6	± 0.1
BMI [Kg/m^2], (Mean ± SD)	27.7	± 4.6
Obese (n, (%))	13	(26.0)

SD: Standard Deviation. BMI (kg/m^2): Body mass index (kilograms/meters^2). Obese (%) ≥ 30.0 BMI.

3. Results

3.1. Participant characteristics

Participant characteristics are presented in Table 1. 50 subjects were recruited, of whom 40% were men. Subjects were 62.8 ± 11.4 years old and had a body-mass index (BMI) of 27.7 ± 4.6 kg/meters^2 (kg/m^2, mean ± SD).

3.2. Effect of posture on oxyhemoglobin saturation (S_pO_2)

A representative 30-minute pulse oximetry recording in a single subject illustrates the effect of posture on S_pO_2. In this recording, S_pO_2 decreased from a mean of 83% in the upright-seated posture to 79% in the supine posture (Fig. 1).

In the entire group, mean S_pO_2 was 84% in the supine posture and 85% in the upright-seated posture, with an average greater S_pO_2 of 1.0 ± 1.1% ($p < 0.0001$, Fig. 2, Left Panel). In 80% of subjects, S_pO_2 increased in the upright compared to supine posture (Fig. 2, Right Panel). The order of postural testing did not significantly influence the

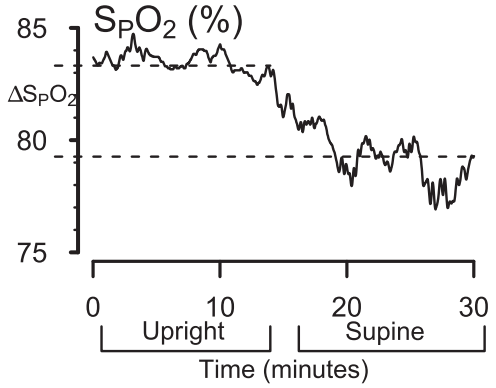

Fig. 1. Representative pulse oximetry recording in upright-seated and supine posture. Oxyhemoglobin Saturation (S_pO_2) vs. Time (minutes). Mean S_pO_2: 83% upright-seated, 79% supine (dashed lines). Change in Mean S_pO_2 (ΔS_pO_2): 4%.

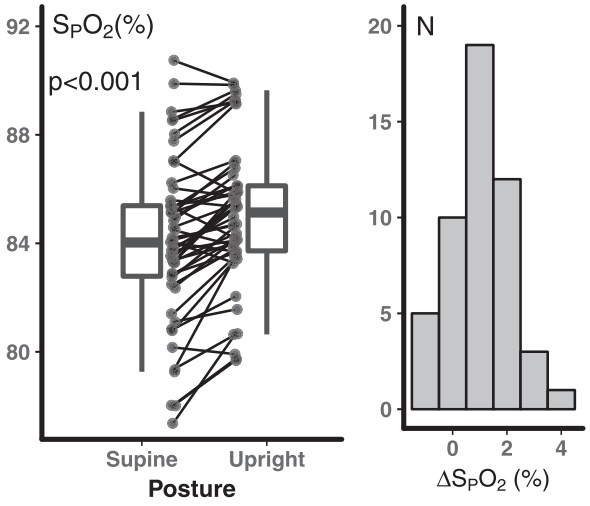

Fig. 2. Effect of posture on oxyhemoglobin saturation (n = 50). Left panel: The distribution of the mean oxyhemoglobin saturation (S_PO_2) in supine and upright postures are represented in a box-and-whisker plot (box boundaries: quartiles, whiskers: median ± 2.5 interquartile range) and individual subjects' lines. Change in mean S_PO_2 (upright – supine): 1.0 ± 1.1% (p < 0.001). Right panel: Histogram of S_PO_2 responses to postural maneuvers.

effect of posture on saturation (p for interaction = 0.49).

3.3. Predictors of in S_PO_2 and modifiers of postural responses

In unadjusted models of S_PO_2 responses to postural maneuvers (Table 2), we found that older age, female sex, elevated BMI and elevated waist circumference were associated with lower S_PO_2. Taller height and greater FVC and FEV_1, on the other hand, were associated elevated S_PO_2. Age was a significant modifier of S_PO_2 responses to postural maneuvers and each decade of age was associated with an additional 0.3% greater S_PO_2 in upright compared to supine posture (Fig. 3, Panel A, p for interaction = 0.01). In contrast, BMI (Fig. 3 Panel B, p = 0.31), waist circumference (p = 0.75), height (Fig. 3 Panel C, p = 0.11), sex (Fig. 3 Panel D, p = 0.11), $height^2$-normalized FVC (Fig. 3 Panel E, FVC, p = 0.16) $height^2$-normalized FEV1 s (Fig. 3 Panel F, p = 0.11) did not modify postural responses.

In a multivariable model of mean S_PO_2 (Table 3), older age, female sex and elevated BMI older age were associated with reductions in S_PO_2. Upright posture was associated with an increase in 1.25% increase in mean S_PO_2. Older age was associated with greater increases in S_PO_2 in the upright compared to supine posture (p = 0.008 for interaction with posture), independent of BMI and sex. Women had a higher saturation response between the supine and upright positions than men, although this difference was not statistically significant (p = 0.09 for interaction).

4. Discussion

In native Andean highlanders, we found that the upright-seated posture significantly improved oxyhemoglobin saturation. This postural maneuver increased S_PO_2 to a greater degree in older subjects. We also found a trend towards greater increases in S_PO_2 in women compared to men. In contrast, the response in S_PO_2 with postural maneuvers was not significantly associated with body-mass index (BMI), or pulmonary function.

Several potential mechanisms can explain the effects of posture on S_PO_2 in highlanders. First, posture-related changes in lung volume could account for postural responses to S_PO_2. In the supine posture, hydrostatic pressure from the abdominal compartment causes cephalad displacement of the diaphragm and a reduction in functional residual capacity (FRC). As FRC falls, airways close prematurely during normal tidal breathing and ventilation-perfusion (VQ) mismatch worsens accordingly, especially in dependent lung regions (Smith et al., 2010). Age-related changes in pulmonary mechanics can account for greater postural responses in S_PO_2 in the older compared to younger subjects in our study. The lung volume at which airways close (closing volume, CV) is also elevated in older persons (Ruff, 1974). As CV encroaches on FRC with increasing age, FRC will more likely fall below CV, resulting in greater reductions in arterial oxygen tension in the elderly (Craig et al., 1971). Obesity, however, did not impact postural changes in S_PO_2, suggesting that FRC changed similarly with postural maneuvers across the weight range. Our findings imply that age-related deterioration in lung function predominates over weight-related decreases in lung volume (Benedik et al., 2009) to augment S_PO_2 responses to postural maneuvers. Second, the effects of posture on S_PO_2 may be especially pronounced in highlanders, since baseline S_PO_2 lies on the steep portion of the oxyhemoglobin saturation curve where large changes in S_PO_2 with intervention are anticipated (Pham et al., 2017a). In healthy volunteers at low altitude, arterial oxygen tension may fall only a 3 mmHg, even when FRC falls below CV in the supine posture (Craig et al., 1971). If PaO_2 remains greater than 90 mmHg, this change in oxygen tension would result in less than a 1% reduction in oxyhemoglobin saturation (Severinghaus, 1966), and would account for an approximate 0.7% reduction (Ceylan et al., 2016) or no change in S_PO_2 whatsoever (Jones and Dean, 2004) between seated and supine postures.

Several compensatory mechanisms during wakefulness and sleep may influence postural responses in S_PO_2. To address this possibility, we examined data from a subset of participants who previously underwent nocturnal studies (n = 28). Of these, 19 did not have significant periodic breathing (defined by AHI ≥ 15/hr), 6 had predominantly

Table 2
Mixed Effects Linear Regression Models for Independent Predictors of S_PO_2 and Interactions with Upright Posture.

Predictor	Associations with Mean S_PO_2			Interaction of Predictor with Upright Posture		
	Mean (%)	95% CI (%)	P-value	Mean (%)	95% CI (%)	P-value for interaction
Age [years]	−0.09	(−0.15, −0.02)	0.02	0.03	(0.01, 0.06)	0.01
Female Sex	−1.64	(−3.18, −0.10)	0.04	0.44	(−0.18, 1.06)	0.11
BMI [kg/m^2]	−0.27	(−0.43, −0.11)	0.002	0.04	(−0.03, 0.10)	0.31
Waist Circumference [cm]	−0.07	(−0.13, −0.01)	0.04	0.00	(−0.02, 0.03)	0.75
Height [m]	0.11	(0.02, 0.20)	0.02	−3.03	(−6.66, 0.90)	0.11
FVC [L]	1.53	(0.79, 2.27)	< 0.001	−0.24	(−0.56, 0.09)	0.16
FEV1 [L]	2.05	(1.04, 3.06)	< 0.001	−0.36	(−0.8, 0.07)	0.11
Normalized FVC [L/m^2]	4.95	(2.71, 7.18)	< 0.001	−0.62	(−1.62, 0.39)	0.24
Normalized FEV_1 [L/m^2]	6.15	(3.17, 9.12)	< 0.001	−0.90	(−2.21, 0.41)	0.18

Mean S_PO_2: Mean oxyhemoglobin saturation by pulse oximetry over 14 min. **BMI [kg/m^2]:** Body mass index [kilograms/meters^{2}']. **FVC [L]:** Forced Vital Capacity [Liters]. **FEV1 [L]:** Forced expiratory volume in 1 s [Liters]. **Normalized FVC:** FVC/$Height^2$. **Normalized FEV1:** FEV1/$Height^2$. **CI:** Confidence interval. Each row represents the results of a single model examining independent and interactive effects of predictor variable with posture.

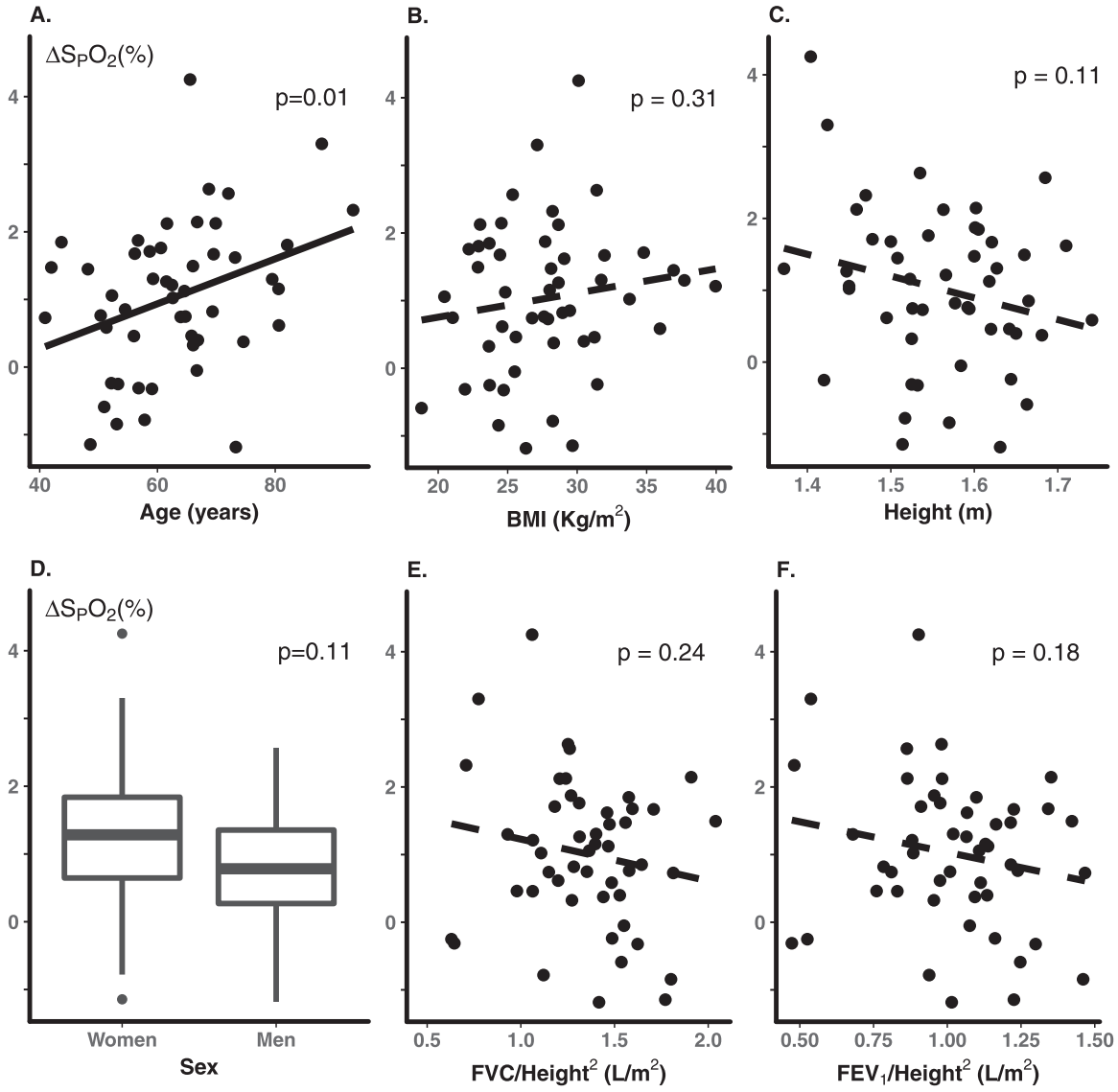

Fig. 3. Associations of demographics, anthropometrics, and pulmonary function tests with oxyhemoglobin saturation responses to upright posture.
The upright minus supine posture (ΔS_pO_2) as a function of sex (**Panel A**, box boundaries: quartiles; whiskers: median ± 2.5 interquartile range), age (**Panel B**), Body-mass index (BMI, kilograms/meters^2, **Panel C**), height (**Panel D**), forced vital capacity, normalized to height squared (FVC/Height^2, Liters/meter^2, **Panel E**) and forced expiratory volume in 1 s, normalized to height squared (FEV_1, Liters, **Panel F**). Solid (p for trend < 0.05) and dashed (p > 0.05) lines represent linear regression fit. P-values for interactions in mixed effects linear regression models are presented. Greater postural changes in S_pO_2 was significantly associated with older age (p for interaction = 0.01), but not sex, BMI, height, or spirometry.

Table 3
Multivariable Model of Mean Oxyhemoglobin Saturation.

Predictor Variable	Beta	95% CI	P-value
Upright Posture	1.25	(0.88, 1.62)	< 0.001
Age [years]	−0.10	(−0.16, −0.04)	0.002
Female Sex	−1.82	(−3.31, −0.51)	0.01
BMI [kg/m^2]	−0.26	(−0.4, −0.10)	< 0.001
Age : Upright Posture	0.04	(0.01, 0.06)	0.008
Female Sex : Upright Posture	0.52	(−0.05, 1.09)	0.09
BMI : Upright Posture	0.03	(−0.03, 1.10)	0.29

Mean S_pO_2: Mean oxyhemoglobin saturation by pulse oximetry over 14 min. **Beta**: Difference or Change in Mean S_pO_2 (%) per unit change in Predictor. **BMI [kg/m^2]:** Body mass index [kilograms/meters^2]. **CI:** Confidence Interval.

obstructive sleep apnea (AHI ≥ 15/hr and > 50% obstructive in etiology) and 3 had predominantly central sleep apnea (CSA) (AHI ≥ 15/hr and > 50% central in etiology). Indeed, the 3 subjects who had CSA had a lower S_pO_2 in the supine position and greater increases in S_pO_2 with upright posture. These findings suggest that central sleep apnea may be a response to hypoxemia at night and that postural therapy may improve intermittent hypoxemia in highlanders with CSA. Because of the small sample size of this analysis, however, additional studies are necessary to confirm the effects of postural maneuvers on nocturnal periodic breathing in high altitude residents.

Our findings demonstrate that recumbency can worsen oxygenation in highlanders. Since most individuals sleep flat, our findings suggest that recumbency can also worsen hypoxemia, at night. In fact, the prevalence and severity of SDB in highlanders greatly exceeds that of age-, weight- and BMI-matched lowlanders (Pham et al., 2017a). In the CRONICAS cohort, sustained nocturnal hypoxemia has been associated with excessive erythrocytosis, a recognized marker for the development of chronic mountain sickness in Andean populations (Pham et al., 2017b). Recent evidence has also linked intermittent nocturnal hypoxemia with glucose intolerance and markers of cardiovascular risk, including elevated hemoglobin A1C in Andean highlanders (Pham

et al., 2017b). The current study indicates that postural intervention has the potential to improve nocturnal oxygen profiles in highlanders, which may decrease susceptibility and/or progression of cardiometabolic outcomes (Drager et al., 2010, 2005; Gami et al., 2005; Marin et al., 2005, 1998; Marshall et al., 2008; Nieto et al., 2000; Peppard et al., 2000; Punjabi et al., 2004, 2003, 2002; Yaggi et al., 2005; Young et al., 2008).

There are several limitations worth considering when interpreting the results of this study. First, our study included a relatively small sample size (n = 50). Despite the number of subjects, we determined that postural maneuvers induced significant, albeit modest changes in S_PO_2. Second, although we piloted this intervention during wakefulness, we recognize that our intervention was intended to improve oxygenation during sleep. The effects of recumbency, however, may be even more pronounced during sleep, where ventilation, lung volume and pharyngeal patency decrease with concomitant apneas, oxyhemoglobin desaturations and arousals (Ainslie et al., 2013; Dempsey, 2005; Edwards et al., 2014; Weil, 1985). Fourth, upright posture can affect blood flow distribution. Perfusion to vital organs including the brain could be reduced, as a result. Improvements in oxygen delivery resulting from higher blood oxygen content could be attenuated, as a result. Finally, we acknowledge that people are unlikely to sleep completely upright, but we designed our protocol to detect responses to acute postural changes under tightly controlled conditions. Effects of more modest postural changes, however, on oxygenation over extended periods during sleep remain largely unexplored.

5. Conclusions

Our study has important implications for public health in highland populations around the world. Findings in this study and others suggest that oxygenation can improve if people lie in a semi-recumbent rather than flat posture (Hakala et al., 2000; Series et al., 1989; Soll et al., 2009; Szollosi et al., 2006). Although postural responses in S_PO_2 were relatively modest, this intervention can nonetheless mitigate cumulative exposure to hypoxemia over prolonged nocturnal periods, and thereby decrease overall risk and/or progression of cardiometabolic diseases (Soll et al., 2009; Szollosi et al., 2006). Thus, postural therapy could potentially have considerable impact on the development and progression of chronic cardiometabolic diseases, and may confer greater benefits in older individuals. Further work is still required to demonstrate effects of postural maneuvers during sleep and its applicability in low-resource highland settings and even in hypoxemic lowlanders (with underlying cardiopulmonary disease).

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