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Chemoreceptor Responsiveness at Sea Level Does Not Predict the Pulmonary Pressure Response to High Altitude

Ryan L. Hoiland, BHK; Glen E. Foster, PhD; Joseph Donnelly, MBChB; Mike Stembridge, MSc; Chris K. Willie, PhD; Kurt J. Smith, MSc; Nia C. Lewis, PhD; Samuel J. E. Lucas, PhD; Jim D. Cotter, PhD; David J. Yeoman, BSc; Kate N. Thomas, BSc; Trevor A. Day, PhD; Mike M. Tymko, BHSc; Keith R. Burgess, MD; and Philip N. Ainslie, PhD

BACKGROUND: The hypoxic ventilatory response (HVR) at sea level (SL) is moderately predictive of the change in pulmonary artery systolic pressure (PASP) to acute normobaric hypoxia. However, because of progressive changes in the chemoreflex control of breathing and acid-base balance at high altitude (HA), HVR at SL may not predict PASP at HA. We hypothesized that resting oxygen saturation as measured by pulse oximetry (Spo_2) at HA would correlate better than HVR at SL with PASP at HA.

METHODS: In 20 participants at SL, we measured normobaric, isocapnic HVR ($L/min \cdot -\%Spo_2^{-1}$) and resting PASP using echocardiography. Both resting Spo_2 and PASP measures were repeated on day 2 (n = 10), days 4 to 8 (n = 12), and 2 to 3 weeks (n = 8) after arrival at 5,050 m. These data were also collected at 5,050 m in life-long HA residents (ie, Sherpa [n = 21]).

RESULTS: Compared with SL, Spo_2 decreased from 98.6% to 80.5% ($P < .001$), whereas PASP increased from 21.7 to 34.0 mm Hg ($P < .001$) after 2 to 3 weeks at 5,050 m. Isocapnic HVR at SL was not related to Spo_2 or PASP at any time point at 5,050 m (all $P > .05$). Sherpa had lower PASP ($P < .01$) than lowlanders on days 4 to 8 despite similar Spo_2. Upon correction for hematocrit, Sherpa PASP was not different from lowlanders at SL but was lower than lowlanders at all HA time points. At 5,050 m, although Spo_2 was not related to PASP in lowlanders at any point (all $R^2 \leq 0.05$, $P > .50$), there was a weak relationship in the Sherpa ($R^2 = 0.16$, $P = .07$).

CONCLUSIONS: We conclude that neither HVR at SL nor resting Spo_2 at HA correlates with elevations in PASP at HA.

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ABBREVIATIONS: AMS = acute mountain sickness; HA = high altitude; HAPE = high altitude pulmonary edema; HCT = hematocrit; HCVR = hypercapnic ventilatory response; HPV = hypoxic pulmonary vasoconstriction; HVR = hypoxic ventilatory response; PAP = pulmonary artery pressure; PASP = pulmonary artery systolic pressure; P_{ETCO_2} = partial pressure of end-tidal CO_2; P_{ETO_2} = partial pressure of end-tidal oxygen; PVR = pulmonary vascular resistance; SL = sea level; Spo_2 = oxygen saturation as measured by pulse oximetry; TRV = tricuspid regurgitation jet velocity; $\dot{V}_E$ = expired volume per unit time

AFFILIATIONS: From the Centre for Heart, Lung and Vascular Health (Messrs Hoiland, Smith, and Tymko and Drs Foster, Willie, Lewis, and Ainslie), School of Health and Exercise Sciences, University of British Columbia–Okanagan, Kelowna, BC, Canada; Division of Neurosurgery (Dr Donnelly), Department of Clinical Neuroscience, University of Cambridge, Cambridge, England; Department of Physiology (Drs Donnelly and Lucas and Ms Thomas) and School of Physical Education (Drs Lucas and Cotter), Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand; Cardiff School of Sport (Mr Stembridge), Cardiff Metropolitan University, Cardiff, Wales; School of Sport, Exercise and Rehabilitation Sciences (Dr Lucas), University of Birmingham, Birmingham, England; Department of Cardiology (Mr Yeoman), Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; Department of Biology (Dr Day), Faculty of Science and Technology, Mount Royal University, Calgary, AB, Canada; and Peninsula Sleep Laboratory (Dr Burgess) and Department of Medicine (Dr Burgess), University of Sydney, Sydney, NSW, Australia.

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The initial increase in ventilation in response to hypoxia (ie, hypoxic ventilatory response [HVR]) is highly variable.[1] In response to a decreased Po_2 at high altitude (HA), pulmonary artery pressure (PAP) increases primarily through hypoxic pulmonary vasoconstriction (HPV).[2] In some studies, a blunted HVR is characteristic of subjects susceptible to high altitude pulmonary edema (HAPE) who exhibit marked elevations in PAP.[3-9] The latter findings highlight a link between HVR and PAP at altitude.

Animal studies have clearly demonstrated that higher peripheral chemoreceptor responsiveness attenuates HPV.[10,11] For example, following mechanical ventilation of the lungs with 100% N_2, stimulation of the carotid chemoreceptors through arterial hypoxemia reduces pulmonary vascular resistance (PVR) in cats and dogs.[12,13] This neural modulation of PAP in hypoxia has been studied recently in humans by interpolating the pulmonary artery systolic pressure (PASP) response to hypoxia at an oxygen saturation as measured by pulse oximetry (Spo_2) of 85%.[14] Between-individual variability in HVR (indicative of peripheral chemoreceptor responsiveness) at sea level (SL) was moderately correlated ($R^2 = 0.38$) with PASP in normobaric hypoxia.[14] This finding is consistent with the aforementioned reports linking HVR to HAPE susceptibility and HAPE to excessive HPV. Furthermore, individuals with a blunted HVR will consequently have a lower PAO_2 and, thus, a greater stimulus to HPV at any given altitude.[14] However, the issue with extrapolating variability in HVR at SL to predict changes in PAP at HA is that in addition to acid-base adjustments, HVR represents a reflex arc with three components—afferent input, central integration, and efferent output[15]—all of which are likely changing, resulting in an overall change in HVR at HA.[16,17] Because of the myriad physiologic changes at HA related to HVR[18-20] and HPV,[21] we hypothesized that resting Spo_2 at HA would correlate better than variability in HVR at SL to PASP at HA (ie, by virtue of Spo_2 reflecting PAO_2 and, hence, HPV). We also reasoned that long-term adaptation to HA, as seen in the Sherpa, would result in a higher resting Spo_2 and lower PASP than that of lowlanders at HA.

Materials and Methods

Study Participants and Design

All experimental procedures and protocols were approved by the Clinical Research Ethics Board at the University of British Columbia, University of Otago, and the Nepal Health Medical Research Council and conformed to the Declaration of Helsinki (UBC IRB#: H11-03287). Twenty white lowlanders aged 34 ± 7 years (five women) and 21 Nepalese male highland Sherpa aged 31 ± 13 years provided informed consent and volunteered to participate in the study. One to 2 months prior to departure, white participants underwent a transthoracic echocardiographic assessment at or close to SL (see the Transthoracic Echocardiography section for details) and then again at day 2 (n = 10, from 2008), between days 4 to 8 (5.2 ± 0.8 [further referred to as day 5], n = 12, 10 from 2008, two from 2012), and between 2 and 3 weeks (16 ± 0.7 days, n = 8, from 2012) after arrival at the Ev-K2-CNR Pyramid Research Laboratory (Lobuche, Khumbu region, Nepal; 5,050 m) in the absence of acute mountain sickness (AMS) symptoms. Sherpa were assessed at 5,050 m only. All participants were free from respiratory and cardiovascular disease and were not taking prescription medications. The native Sherpa participants originated from and were residents of the Khumbu Valley at an altitude > 3,000 m and self-identified to be of Sherpa ethnicity. None of the Sherpa had traveled < 2,800 m for at least 6 months prior to testing. Height, body mass, BP, and Spo_2 were recorded prior to each transthoracic echocardiographic assessment (see the Transthoracic Echocardiography section for details). Peripheral and central chemoreflex sensitivities were also assessed on a different day at SL (see the Chemoreflex Testing section for details). Prior to each experiment, participants abstained from exercise and alcohol for 24 h and caffeine for 12 h.

In different participants, SL data were collected in February 2008 (n = 10) in Dunedin, New Zealand (at approximately 10 m) and in April 2012 (n = 10) in Kelowna, British Columbia, Canada (at an altitude of 344 m). The HA experiments were completed over 2 weeks (2008) and 3 weeks (2012) at the Ev-K2-CNR Pyramid Research Laboratory, in April to May of 2008 (New Zealand group) and 2012 (Canada group). After travel to Nepal and 7 nights in Kathmandu (approximately 1,400 m), participants flew to Lukla (2,800 m) and began an 8- to 11-day ascent to the Pyramid Research Laboratory (5,050 m). A cautious ascent profile was adopted, with ≤ 700 m net gain per day and at least 2 days with no net change in altitude. Participants were given a low oral dose of acetazolamide (125 mg) bid as an AMS prophylactic.[22] Acetazolamide was discontinued at approximately 4,300 m (Pheriche, Nepal) at least 1 day before ascending to the laboratory to allow sufficient time (≥ 48 h) for the drug to clear participants' systems prior to the first data collection session at 5,050 m.[23,24] Previously, pretreatment of acetazolamide resulted in an almost negligible difference of PASP (approximately 2 mm Hg; no statistical analyses were performed) 48 h after final drug treatment compared with individuals who received placebo treatment.[25] Although unlikely to alter the findings, we were unable to rule out the possibility of persistent physiologic sequelae secondary to acetazolamide treatment during day 2 testing. Participants spent 1 to 3 days at Pheriche before the final ascent. Expedition members participating in this study had a minimum of 48 h between this

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CORRESPONDENCE TO: Ryan L. Hoiland, BHK, Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia–Okanagan, 3333 University Way, Kelowna, BC, V1V 1V7, Canada; e-mail: ryanleohoiland@gmail.com

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