Impact of Altitude on Cardiopulmonary and Right Ventricular Hemodynamics During Exercise

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Conveniences of modern travel allow for an increasing number of people to sojourn to mountainous, high-altitude locations for work and/or pleasure. Travel to these types of locations places unique stressors on the human body and, more specifically, the cardiovascular and pulmonary systems since ambient oxygen content declines at altitude. The physiologic response to hypoxia is a highly dynamic process that begins immediately and continues to evolve from acute (hours to days) to chronic (days to weeks) time periods. Furthermore, sojourns to hypoxic locations frequently involve exercise, which places additional strain on the heart and lungs. The aim of this review is to emphasize clinically relevant physiologic responses that occur, both acutely and chronically, after travel to high-altitude locations.

INTRODUCTION

More than 100 million individuals travel to high-altitude environments per year for work or pleasure.[1–3] Reductions in the partial pressure of ambient oxygen initiate a cascade of physiologic responses, which place unique stressors on the cardiovascular and pulmonary systems. These stressors are accentuated by attempts to exercise. Information available on the effects of hypoxia on human physiology, both at rest and with exercise, is derived primarily from healthy individuals. Nevertheless, the prevalence of cardiovascular disease (~18 million), hypertension (~108 million), and heart failure (~6 million) in the United States is high, and many of these individuals, who have abnormal sea level (SL) hemodynamics, may experience much larger perturbations in cardiopulmonary and exercise hemodynamics than healthy populations. In this review, cardiac and pulmonary responses to hypoxia are emphasized, and exercise physiology at altitude is highlighted.

CARDIOVASCULAR, PULMONARY, AND RESPIRATORY RESPONSES TO HYPOXIA

The hemodynamic response to hypoxia is highly dynamic and evolves from acute (hours to days) to chronic (days to weeks) exposure. Acutely, the cardiovascular response to hypoxia is dominated by a marked increase in sympathetic nerve activity (SNA).[4–8] Microneurography studies of healthy humans have demonstrated that SNA increased from SL values of 27.1 ± 2.9 bursts/min to 36.4 ± 2.6, 39.1 ± 3.1, and 40.2 ± 4.2 bursts/min at 4000, 5000, and 6000 m, respectively.[7] This increase in sympathetic tone results from hypoxia-induced activation of peripheral chemoreceptors and acutely increases heart rate (HR), stroke volume (SV), cardiac output (Qc), and muscle blood flow compared with levels encountered at SL.[4,5] As the body adapts to hypoxia over several days to weeks, Qc falls in response to a decline in SV.[4–6,9] This reduction in SV occurs over the first several days of altitude exposure and stabilizes after ~1 week.[6,10,11]

Hypoxic pulmonary vasoconstriction leads to an acute increase in pulmonary arterial pressures (PAPs), which increase in proportion to altitude exposure.[12–16] In a study of healthy mountaineers, pulmonary artery systolic pressure, determined by echocardiography, increased from 22 ± 3 mm Hg at SL to 33 ± 6 mm Hg after 4 hours of exposure to a simulated height of 4500 m (fraction of inspired oxygen [FIO_2] = 0.12).[15] In another study involving invasive hemodynamic assessment by pulmonary arterial catheterization of healthy volunteers, mean PAP increased from 14 ± 1 mm Hg at a baseline altitude of 490 m to 22 ± 1 mm Hg after only 10 minutes of breathing hypoxic gas (FIO_2 = 0.12).[13] At more extreme altitudes, greater increases in PAP have been observed.[16] In Operation Everest 2, healthy volunteers experienced large increases in mean PAP from 15 ± 1 mm Hg to 34 ± 3 mm Hg over a 40-day simulated ascent to 8840 m (summit of Mount Everest), and pulmonary vascular resistance increased from 1.2 ± 0.1 to 4.3 ± 0.3 Woods units.[16]

Ventilation increases dramatically after hypoxic exposure. For example, among healthy males, resting minute ventilation increased from 7.1 ± 0.3 L/min at SL to 11.8 ± 0.5 L/min on the first day of exposure to 3110 m.[17] This increase in ventilation continues to rise over time with ongoing hypoxic exposure[18] and is relevant insomuch as a significant amount of oxygenated blood may be diverted to supply respiratory muscles to support the increased work of breathing, thereby causing a respiratory "steal" phenomenon which contributes to reductions in exercise capacity at altitude.[18,19]

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CARDIOPULMONARY HEMODYNAMICS OF EXERCISE AT HIGH ALTITUDE

One critical relationship in exercise physiology pertains to oxygen uptake (VO_2) and Qc, such that Qc increases ~6 L/min for every 1 L/min rise in VO_2.[20–22] During exercise at high altitude, this relationship between Qc and VO_2 is preserved.[23] However, maximal oxygen uptake (VO_2Max) declines in proportion to the altitude at which exercise is undertaken. Specifically, VO_2Max decreases by ~1% for every 100-m increase in altitude above 1500 m.[24–26] Ventilatory threshold, a marker of sustainable workload, occurs at HRs similar to SL but at lower workloads.[26,27]

During acute exposure to high altitude, exercise Qc may be higher than SL values in response to the aforementioned rise in sympathetic tone. However, as the body acclimates, exercise Qc typically declines compared with SL values.[23] Notably, this reduction in Qc is not a result of hypoxia-induced left ventricular (LV) dysfunction. In Operation Everest 2, it was found that SV was maintained for any given pulmonary capillary wedge pressure, indicating that LV contractility is preserved even up to extreme altitudes of 8400 m.[9] At any level of work, HR is higher at altitude than at SL, but maximal HRs achieved at altitude are lower than exercise at SL.[28] Stroke volume at all levels of exercise is reduced compared with values during exercise at the same workload at SL.[28]

Exercise PAP at altitude is higher than levels observed at SL and therefore may impact right ventricular (RV) function,[23] yet less is known about RV performance during exercise at altitude. The majority of studies evaluating cardiovascular function have incorporated echocardiography,[23,29–31] and it is unclear whether observed changes in noninvasive metrics of RV performance (eg, strain, tricuspid annular plane systolic excursion [TAPSE]) result from changes in loading conditions or are a reflection of overt dysfunction.[29] In one of these studies, RV longitudinal strain at 5050 m was reduced compared with SL values, but this decrement in strain was attributed to reductions in RV volumes.[29] In Operation Everest 2, which incorporated pulmonary arterial catheters, right atrial pressure (a surrogate marker of RV function) was reduced during rest and exercise at altitude, and based on this finding, it was concluded that RV function is preserved.[9,16] Nevertheless, in placebo controlled studies using either sildenafil[32] or bosentan,[33] pulmonary vasodilator administration with normobaric hypoxia resulted in a reduced PAP and pulmonary vascular resistance and was associated with an improved maximal exercise workload (FIO_2 = 0.10)(26) and a 30% increase in VO_2Max (FIO_2 = 0.12)(27).

Additionally, there are data to suggest that RV function may decline over time in response to chronic (eg, weeks) exposure to hypoxia.[29] Hypoxia-mediated augmentations in PAP lead to an increase in RV afterload.[6,34–40] In a study of healthy individuals, RV end-diastolic volume increased from 52 ± 12 to 61 ± 25 mL at SL to 5085 m, respectively, which coincided with increases in systolic PAP (13.1 ± 5.9 versus 26.6 ± 10.8 mm Hg).[37] In another study, TAPSE declined from 2.9 ± 0.3 to 2.3 ± 0.3 from SL to 5050 m.[29] Finally, pharmacologic reductions of PAP by administration of sildenafil led to an increase in LV SV.[39] In total, these data suggest that, as PAP (and hence, RV afterload) rises, RV contractility declines over time, and this reduction in RV function compromises LV SV. Further research incorporating invasive and comprehensive assessments of RV function—such as has recently been performed in patients with pulmonary arterial hypertension,[41] heart failure with preserved ejection fraction,[42] heart failure patients supported by LV assist devices,[43] and even healthy individuals exercising at SL[40]—is necessary to characterize the effects of acute and chronic altitude exposure on resting and exertional RV performance and how decrements in RV function may influence LV SV, Qc, and exercise capacity overall.

A minority of individuals experience subacute mountain sickness after several months' exposure to hypoxia at altitude. Subacute mountain sickness in humans has been compared to Brisket disease in cattle living above 3000 m, which was reported well over 100 years ago and presents as edema in the neck and chest.[6] In humans, this syndrome was described in soldiers who participated in vigorous exercises at altitudes of 5800–6700 m for up to 6 months.[44] These individuals had evidence of RV failure, including generalized edema, ascites, and pericardial effusion. On echocardiography, these soldiers displayed evidence of RV enlargement, which normalized on repeat assessment several weeks after return to low altitude.[44] Based on these types of observations, it has been proposed that this disease entity be termed "high-altitude right heart failure."[6,45]

CONCLUSIONS

Sojourns to mountainous locations lead to acute and chronic stressors on the cardiovascular and pulmonary systems. These stressors result primarily from reductions in ambient oxygen content, which acutely increases sympathetic tone through activation of peripheral chemoreceptors and increases PAP through hypoxic pulmonary vasoconstriction. Hypoxia-mediated increases in RV afterload (ie, PAP) may lead to RV enlargement and compromise resting and exertional RV performance. Overt RV failure appears to be quite rare and occurs after several months of exposure to altitudes above 5500 m. Compared to SL performance, exercise capacity declines linearly in proportion to the level of altitude.

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