

RESEARCH ARTICLE | Hypoxia

# Susceptibility to high-altitude pulmonary edema is associated with increased pulmonary arterial stiffness during exercise

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**Mulchrone A, Moulton H, Eldridge MW, Chesler NC.** Susceptibility to high-altitude pulmonary edema is associated with increased pulmonary arterial stiffness during exercise. *J Appl Physiol* 128: 514–522, 2020. First published December 19, 2019; doi:10.1152/jappphysiol.00153.2019.—High-altitude pulmonary edema (HAPE), a reversible form of capillary leak, is a common consequence of rapid ascension to high altitude and a major cause of death related to high-altitude exposure. Individuals with a prior history of HAPE are more susceptible to future episodes, but the underlying risk factors remain uncertain. Previous studies have shown that HAPE-susceptible subjects have an exaggerated pulmonary vasoreactivity to acute hypoxia, but incomplete data are available regarding their vascular response to exercise. To examine this, seven HAPE-susceptible subjects and nine control subjects (HAPE-resistant) were studied at rest and during incremental exercise at sea level and at 3,810 m altitude. Studies were conducted in both normoxic (inspired  $P_{O_2}$  = 148 Torr) and hypoxic (inspired  $P_{O_2}$  = 91 Torr) conditions at each location. Here, we report an expanded analysis of previously published data, including a distensible vessel model that showed that HAPE-susceptible subjects had significantly reduced small distal artery distensibility at sea level compared with HAPE-resistant control subjects [ $0.011 \pm 0.001$  vs.  $0.021 \pm 0.002$  mmHg<sup>-1</sup>;  $P < 0.001$ ]. Moreover, HAPE-susceptible subjects demonstrated constant distensibility over all conditions, suggesting that distal arteries are maximally distended at rest. Consistent with having increased distal artery stiffness, HAPE-susceptible subjects had greater increases in pulmonary artery pulse pressure with exercise, which suggests increased proximal artery stiffness. In summary, HAPE-susceptible subjects have exercise-induced increases in proximal artery stiffness and baseline increases in distal artery stiffness, suggesting increased pulsatile load on the right ventricle.

**NEW & NOTEWORTHY** In comparison to subjects who appear resistant to high-altitude pulmonary edema, those previously symptomatic show greater increases in large and small artery stiffness in response to exercise. These differences in arterial stiffness may be a risk factor for the development of high-altitude pulmonary edema or evidence that consequences of high-altitude pulmonary edema are long-lasting after return to sea level.

distensibility; effective arterial elastance; high-altitude pulmonary edema; pulse pressure; total arterial compliance

## INTRODUCTION

High-altitude pulmonary edema (HAPE) is a reversible form of noncardiogenic alveolar capillary membrane leak typically occurring in young, healthy individuals who ascend to altitudes over 2,000 m and engage in vigorous exercise. Although treatment can be as simple as rest, oxygen supplementation, or returning to low altitude (19, 23, 38), HAPE is one of the major causes of death related to high-altitude exposure (3, 29). HAPE is a multifactorial condition with both genetic and environmental contributors (3, 15, 26, 40). The rate of ascent, peak altitude reached, and preacclimatization are known to contribute to susceptibility, but one of the most important predictors may be having experienced a prior HAPE episode (15, 26).

Many hypotheses have been suggested to explain the underlying pathophysiological mechanisms behind HAPE, but the exact cause remains uncertain. One of the most supported theories suggests that it is initiated by uneven hypoxic vasoconstriction, with possible hypoxia-induced pulmonary venous constriction, causing increased microvascular pressures (8, 21). These elevated pressures cause interstitial leakage, and the result is a high-permeability form of edema (3, 35). However, alterations in the classic Starling forces alone do not account for the presence of plasma proteins, red blood cells, and proinflammatory cytokines found within the bronchoalveolar lavage fluid (18, 56, 57, 64).

To better explain the unexpected presence of these large molecules in the lavage fluid, West et al. proposed that HAPE is initiated by a mechanical stress failure of the pulmonary capillaries (69, 70) or some alteration in the selectivity of the alveolar-capillary barrier, and Swenson et al. demonstrated that inflammation occurs as a secondary consequence (64). Patz et al. hypothesized that the uneven hypoxic vasoconstriction could be the result of regionally heterogeneous distribution of ventilation and  $P_{O_2}$  within the lungs. However, further investigation revealed that HAPE-susceptible subjects had a more uniform distribution of ventilation, so Patz et al. then postulated that the mechanism behind HAPE resides within the pulmonary vasculature (46).

HAPE-susceptible individuals have increased pulmonary arterial pressures (PAP) in hypoxic conditions and an increased vasoreactivity to hypoxia (12, 21, 22), but incomplete data are available regarding their response to exercise. Some studies have demonstrated elevated PAP and increased pulmonary vascular resistance (PVR) in HAPE-susceptible subjects in response to light exercise in comparison to HAPE-resistant

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control subjects (11, 17, 28). However, Viswanathan et al. failed to demonstrate any abnormal response to exercise (66), and Hultgren et al. reported a slightly abnormal elevation in PAP in only one of five HAPE-susceptible subjects (24).

To better understand the differences in the pulmonary vasculature between HAPE-susceptible and HAPE-resistant subjects, we expanded the analysis of previously published data from seven HAPE-susceptible subjects and nine HAPE-resistant subjects under conditions of exercise, acute hypoxia, and hypobaria (11, 48) to focus on arterial stiffness and pulsatile pulmonary hemodynamics. We hypothesized that previous HAPE episodes are correlated with pulmonary artery (PA) stiffening during stress, which contributes to increased pulsatile loading of the right ventricle (RV).

## METHODS

A detailed description of this study's methods can be found in Eldridge et al. 1996 (11), in which hemodynamic pressure differences between the subject groups were reported, as well as a companion paper by Podolsky et al. that identified ventilation-perfusion mismatch (48). Therefore, the description of methods here is limited to details pertaining to the methods of data analysis. All procedures were approved by the Human Subject Committees at the University of California, San Diego and the University of California, San Francisco.

**Study population.** Sixteen healthy mountain climbers (with experience above 3,000 m) who engaged in regular, heavy exercise were recruited for this study. Seven of these subjects (6 men, 1 woman) reported having experienced HAPE at least once on previous trips to high altitude. The remaining nine subjects (all men) had made repeated trips to comparable altitudes without complication.

**Preliminary studies.** Each subject first underwent a preliminary exercise test on a stationary cycle ergometer. They were asked to exercise at incremental workloads to exhaustion in both normoxia and hypoxia [fraction of inspired O<sub>2</sub> (F<sub>I</sub>O<sub>2</sub>) = 0.125] to determine their maximal work rate in each condition. The subsequent exercise protocols were then performed at 35%, 65%, and 85% of that respective maximal work rate (P<sub>max</sub>), with a minimum of 30 min of rest between the two runs. Blood samples were collected at rest and during each exercise stage.

**Experimental design.** The experimental protocol was first carried out in San Diego, California, which is located approximately at sea level. The subjects inhaled ambient air for normoxia and dry 12.5% O<sub>2</sub> to achieve hypoxia. One month later, subjects were brought up to the University of California White Mountain Laboratory, located at an altitude of 3,810 m. At altitude, 33% dry O<sub>2</sub> was inhaled for normoxia and ambient air for hypoxia.

**Calculations.** Cardiac output (Q) was calculated from the Fick equation with the blood gas data:

$$Q = \dot{V}O_2(a-vCO_2) \quad (1)$$

where  $\dot{V}O_2$  is the measured oxygen uptake and a-vCO<sub>2</sub> is the difference in oxygen content between the arterial and mixed venous blood samples. Further explanation and assumptions are given in Podolsky et al. 1996 (48).

Distensibility of the pulmonary vasculature ( $\alpha$ ) was calculated with the governing equation from the distensible vessel model developed by Linehan et al. (32):

$$mPAP = \frac{[(1 + \alpha P_w)^5 + 5\alpha \cdot R_0 \cdot Q]^{1/5} - 1}{\alpha} \quad (2)$$

where mPAP is the mean pulmonary artery pressure, P<sub>w</sub> is the

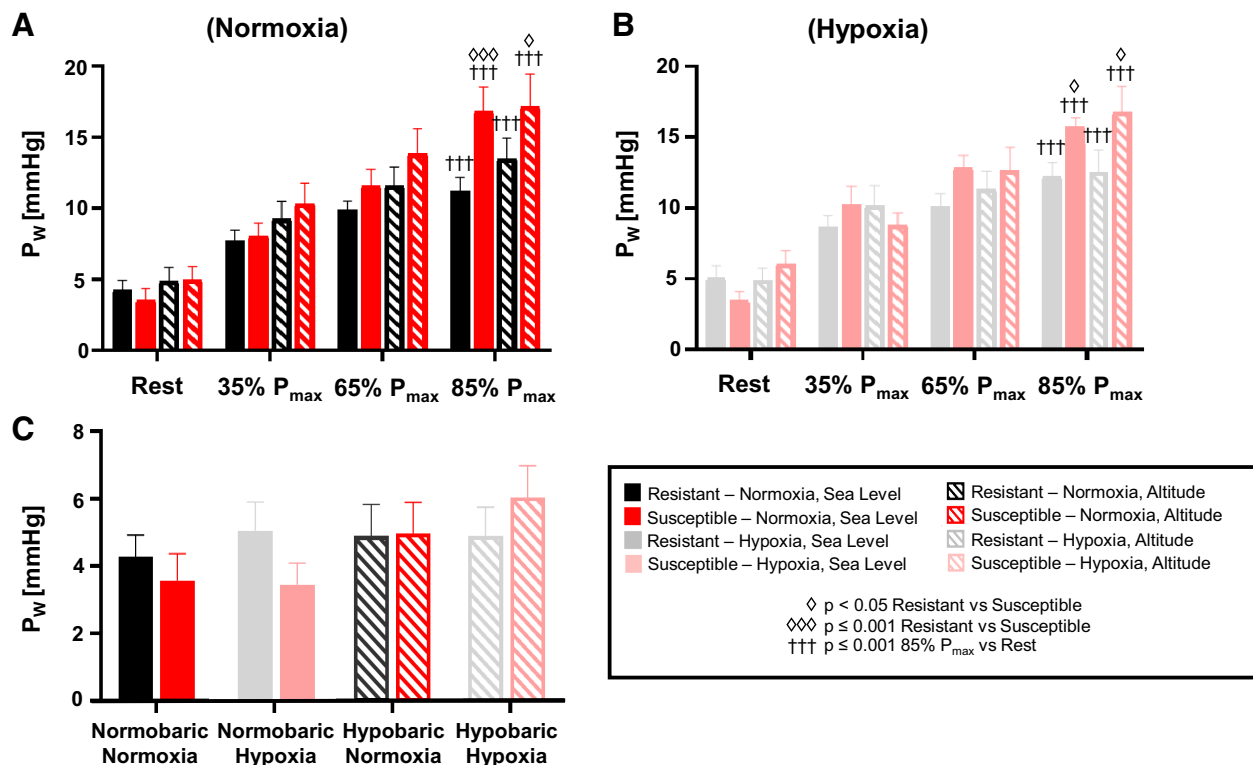


Fig. 1. A and B: pulmonary capillary wedge pressure (P<sub>w</sub>) estimates during exercise in normoxic conditions (A) and hypoxic conditions (B). P<sub>max</sub>, maximal work rate. C: an overview of the 4 resting states. Missing wedge pressures were estimated by a superimposed linear fit to the measured mean pulmonary artery pressure vs. P<sub>w</sub> data for each subject group per condition.

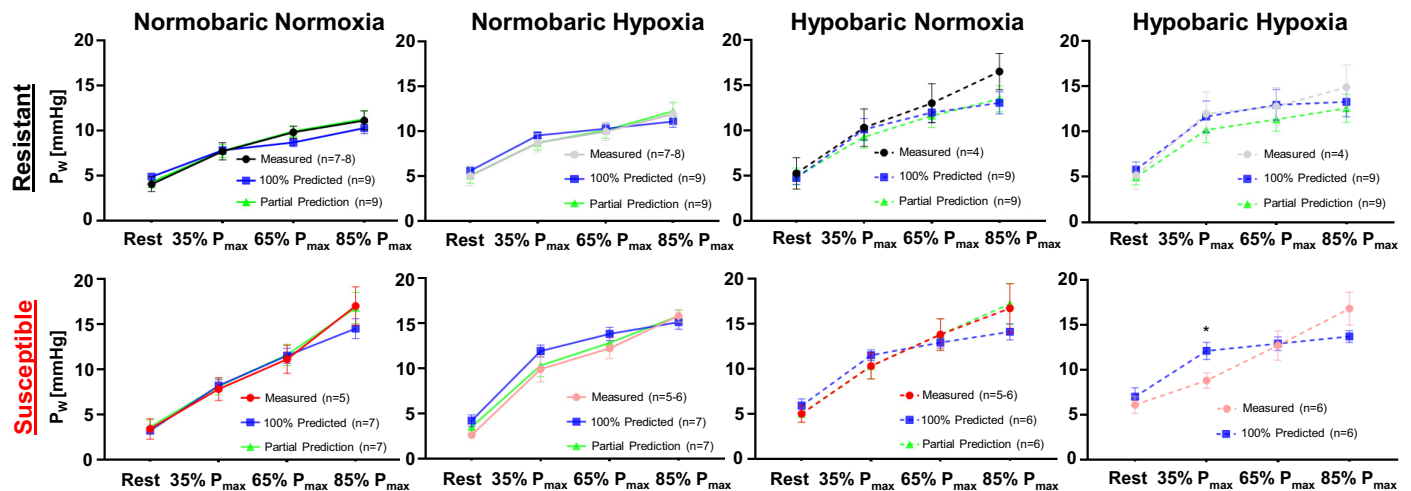


Fig. 2. Sensitivity analysis of pulmonary capillary wedge pressure ( $P_w$ ). Each graph contains the original data set with no estimated values, termed “measured.” Blue squares represent the data set with each data point estimated using the experimentally derived relationships in each subject group in each condition. Green triangles represent the data using the partial prediction, where only the missing wedge pressures were estimated.  $P_{max}$ , maximal work rate. \* $P < 0.05$  vs. measured.

pulmonary wedge pressure, and  $R_0$  is the total pulmonary vascular resistance at rest, calculated as (51):

$$R_0 = \frac{mPAP}{Q} \quad (3)$$

To account for changes in hydration during exercise and at altitude,  $R_0$  was normalized to changes in hematocrit (Hct), which was calcu-

lated from the centrifuged blood samples:

$$Hct = \frac{\text{length of red blood cell column}}{\text{length of whole blood column}} \times 100 \quad (4)$$

$\alpha$  was solved with the method of successive iterations, as described by Reeves et al. (51).

Initial safety concerns regarding the balloon occlusion necessary to obtain  $P_w$  during exercise at altitude prevented the acquisition of

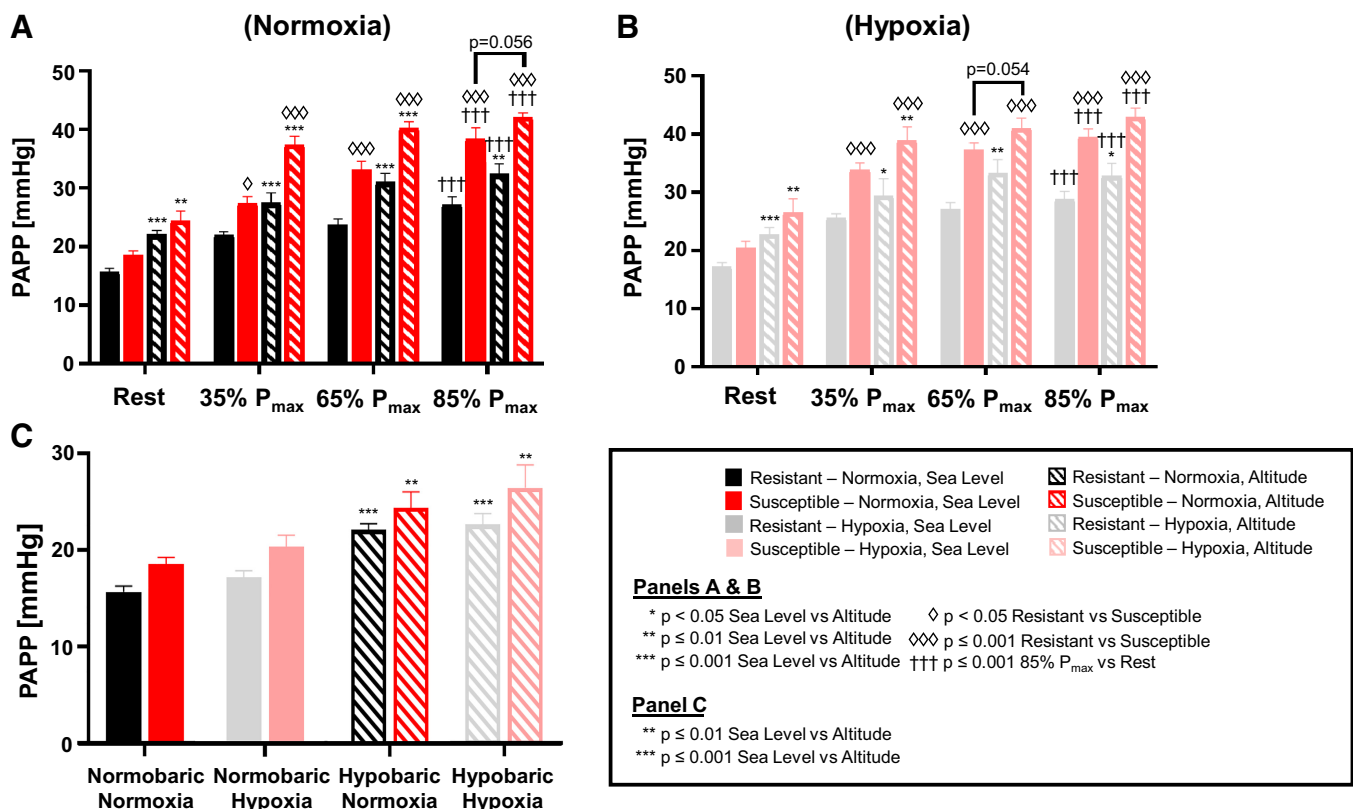


Fig. 3. A and B: estimated pulmonary artery pulse pressures (PAPP) during exercise in normoxic conditions (A) and hypoxic conditions (B) as estimated from the measured mean pulmonary artery pressure (Eq. 6).  $P_{max}$ , maximal work rate. C: an overview of the 4 resting states.

several wedge pressures, with 11 of the subjects missing some or all of the wedge pressures. However, there is a predictable relationship between mPAP and  $P_w$  that has been well accepted (73) and has been shown to be directly proportional to increases in Q (1, 31, 43, 44). We used this relationship to estimate the missing  $P_w$  values by superimposing a linear fit to the obtained mPAP vs.  $P_w$  data for each subject.

A predictable relationship also exists between the systolic pulmonary artery pressure (sPAP), the diastolic pulmonary artery pressure (dPAP), and the mPAP (6, 65). Since the pulmonary artery pulse pressure (PAPP) is defined as

$$PAPP = sPAP - dPAP \quad (5)$$

it follows that there also exists a linear relationship between PAPP and mPAP (52):

$$PAPP = 4.5 + 0.88(mPAP) \quad (6)$$

This relationship has been shown to hold true in both children and adults, as well as across a variety of disease states, exercise states, postures, and with administered vasodilators (6, 52, 65). This was then used to estimate the total arterial compliance (7, 13, 20, 36, 50):

$$\text{total arterial compliance} = \frac{SV}{PAPP} \quad (7)$$

where SV is the stroke volume. Finally, a modified version of the windkessel model was used to estimate the effective arterial elastance ( $E_a$ ), a measure of RV afterload that includes pulsatile loading in addition to steady loading (2):

$$E_a = \frac{mPAP - P_w}{SV} \quad (8)$$

**Statistical analysis.** A linear mixed-effects model with subject-specific random effects and repeated measures across exercise levels

was used to conduct the comparisons between treatment groups and other experimental conditions. Two- and three-way interaction effects between treatment group, altitude, and oxygen level were included in the model. Model adjusted mean values were calculated for each experimental condition. All data are reported as means  $\pm$  standard error. All  $P$  values are two sided, with  $P < 0.05$  being considered evidence of statistical significance.

## RESULTS

The hemodynamic response to exercise, acute hypoxia, and hypobaria was successfully measured in nine HAPE-resistant control subjects. Seven HAPE-susceptible subjects were analyzed at sea level, but one subject dropped out of the study after this phase, so only six subjects are included at altitude.

**Pulmonary pressures.** Figure 1 shows the mean  $P_w$  after the missing values were estimated from the superimposed linear fit. Overall, the average  $P_w$  increased with increasing exercise effort for both HAPE-resistant and HAPE-susceptible groups. The HAPE-susceptible group had an exaggerated response to exercise compared with the HAPE-resistant group. At 85% of their maximal power, HAPE-susceptible subjects had a 4.7-fold increase compared with rest ( $3.57 \pm 0.80$  vs.  $16.84 \pm 1.69$  mmHg;  $P < 0.001$ ), whereas HAPE-resistant subjects had a 2.6-fold increase ( $4.28 \pm 0.64$  v.  $11.27 \pm 0.95$  mmHg;  $P < 0.001$ ). No significant changes were observed with exposure to acute hypoxia or altitude in either group. Sensitivity analysis did not reveal statistical differences between the measured and predicted  $P_w$  values (Fig. 2). The pulmonary artery pulse pressure (PAPP) was also directly proportional to the exercise level; increased exercise effort resulted in higher PAPP, with

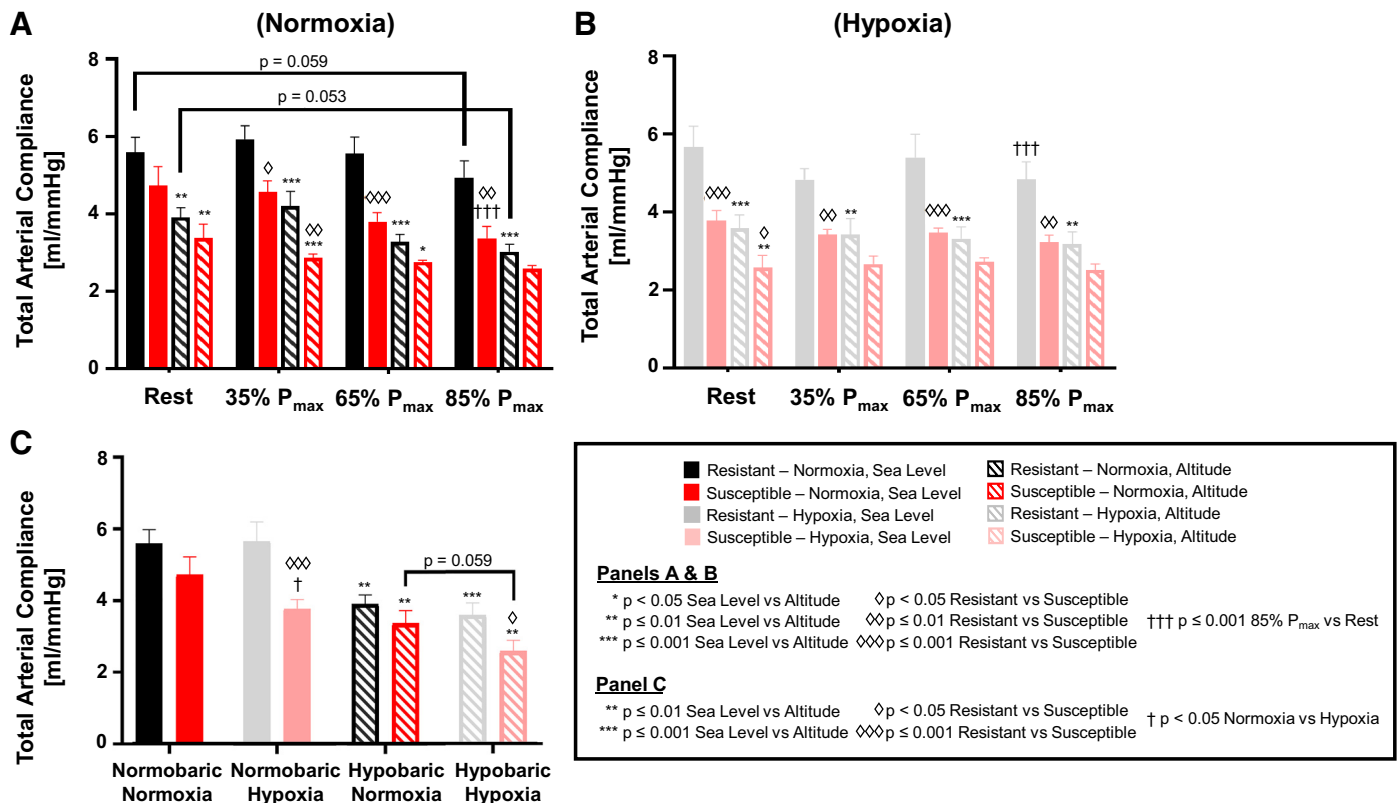


Fig. 4. A and B: total arterial compliance during exercise in normoxic conditions (A) and hypoxic conditions (B) as estimated from stroke volume/pulmonary artery pulse pressure (Eq. 7). P<sub>max</sub>, maximal work rate. C: an overview of the 4 resting states.

HAPE-susceptible subjects having significantly higher PAPP than HAPE-resistant subjects at every stage and condition apart from rest (Fig. 3). Both groups showed an increased pressure response when brought to high altitude, but no statistical differences were measured between normoxic and hypoxic conditions (Fig. 3C).

**RV afterload.** The total arterial compliance decreased in hypobaric conditions for both HAPE-resistant and HAPE-susceptible groups (Fig. 4). However, once again the HAPE-susceptible subjects had an exaggerated response. They showed further decreases when exposed to hypoxia both at sea level ( $4.73 \pm 0.49$  vs.  $3.78 \pm 0.26$  mL/mmHg;  $P < 0.05$ ) and at altitude ( $3.37 \pm 0.36$  vs.  $2.58 \pm 0.31$  mL/mmHg;  $P < 0.01$ ). In contrast, the HAPE-resistant group had little to no change with exposure to hypoxia at sea level ( $5.59 \pm 0.39$  vs.  $5.67 \pm 0.53$  mL/mmHg;  $P > 0.05$ ) or at altitude ( $3.91 \pm 0.25$  vs.  $3.59 \pm 0.34$  mL/mmHg;  $P > 0.05$ ).

The trends of increased pulmonary vascular resistance [see Eldridge et al. 1996 (11)] and the reduction in the total arterial compliance resulted in a 46% increase in  $E_a$  (Fig. 5) in HAPE-susceptible subjects compared with HAPE-resistant control subjects ( $0.10 \pm 0.01$  vs.  $0.15 \pm 0.02$  mmHg/mL;  $P = 0.076$ ). The heightened hypoxic response observed in the arterial compliance of HAPE-susceptible subjects was reflected as a 31% increase in  $E_a$  at sea level ( $0.15 \pm 0.02$  vs.  $0.20 \pm 0.02$  mmHg/mL;  $P = 0.064$ ). No change was observed in the HAPE-resistant control subjects with exposure to hypoxia ( $0.10 \pm 0.01$  vs.  $0.11 \pm 0.01$  mmHg/mL;  $P > 0.05$ ).

**Distensibility.** As described above, a distensible vessel model was used to calculate distal, small artery distensibility from a fit to the multipoint pulmonary vascular pressure-flow relationship (Fig. 6). Overall, HAPE-susceptible subjects had

reduced distensibility compared with HAPE resistant subjects, even at sea level ( $0.011 \pm 0.001$  vs.  $0.021 \pm 0.002$  mmHg<sup>-1</sup>;  $P < 0.001$ ). Interestingly, the HAPE-susceptible subjects appeared to be operating at, or very near, their maximal distensibility. Both exposure to acute hypoxia and several days at high altitude failed to elicit any significant changes, unlike the HAPE-resistant subjects. Sensitivity analysis did not reveal statistical differences comparing the subjects who had a full data set (requiring no estimation) with the data set compiled with the estimated values (Fig. 7).

## DISCUSSION

High-altitude pulmonary edema (HAPE) was first identified and documented by postmortem examination in 1891 and continues to be the focus of many investigations as the pathogenesis and underlying risk factors remain uncertain. Over the years, many mechanisms have been proposed to explain this disease. Increased pulmonary pressures is a hallmark of HAPE, but Scherrer et al. demonstrated that exaggerated pulmonary hypertension alone is not sufficient to trigger HAPE (54). Uneven hypoxic vasoconstriction is the most commonly proposed mechanism, possibly mediated by an abnormal production of nitric oxide, a potent vasodilator synthesized by endothelial cells. HAPE-susceptible subjects have been shown to have lower exhaled nitric oxide levels compared with HAPE-resistant subjects in hypoxia (5) and at altitude (9), and inhaled nitric oxide has been shown to induce larger decreases in PA pressures when given to HAPE-susceptible subjects, which suggests possible endothelial dysfunction and defective nitric oxide synthesis in HAPE-susceptible subjects (55). Known differences are not limited to the relaxation factors. HAPE-

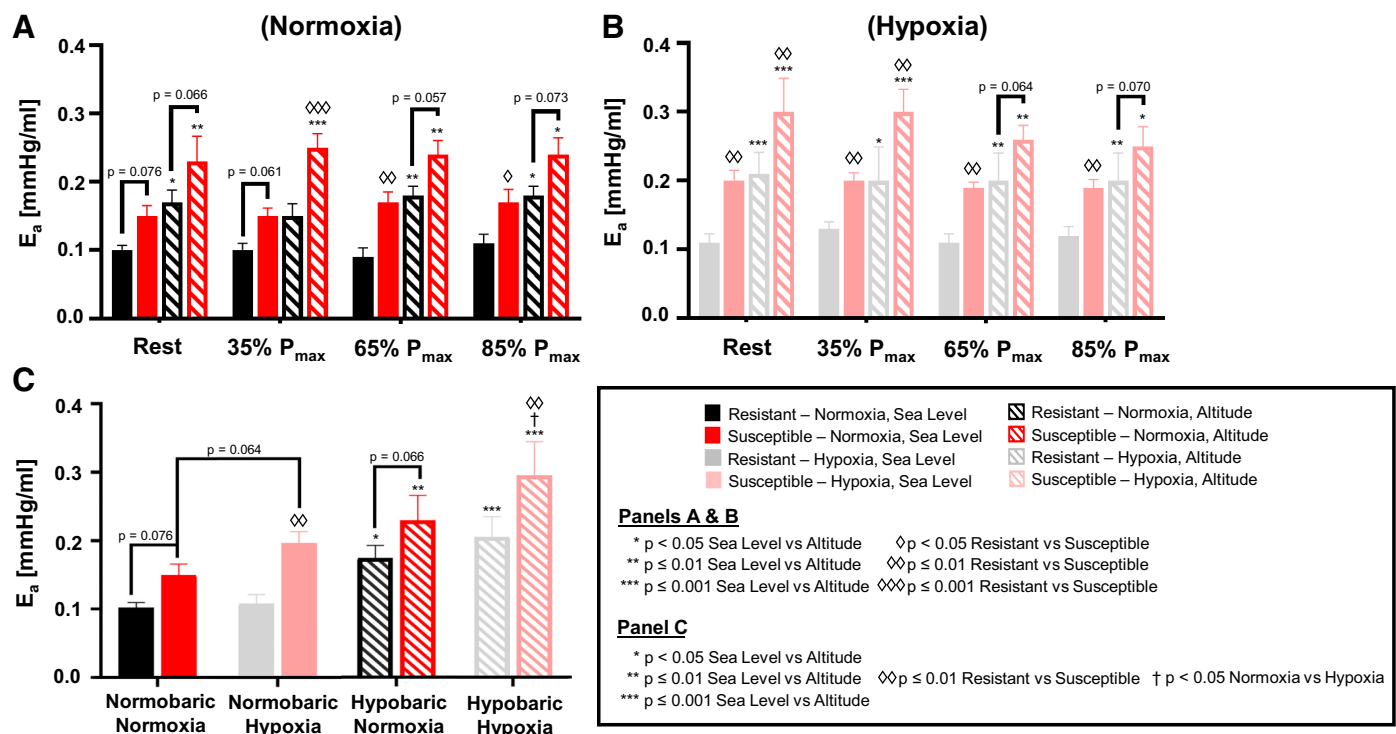


Fig. 5. A and B: effective arterial elastance ( $E_a$ ), a measure of right ventricle afterload, during exercise in normoxic conditions (A) and hypoxic conditions (B) as calculated from a modified version of the windkessel model (Eq. 8). C: an overview of the 4 resting rates.

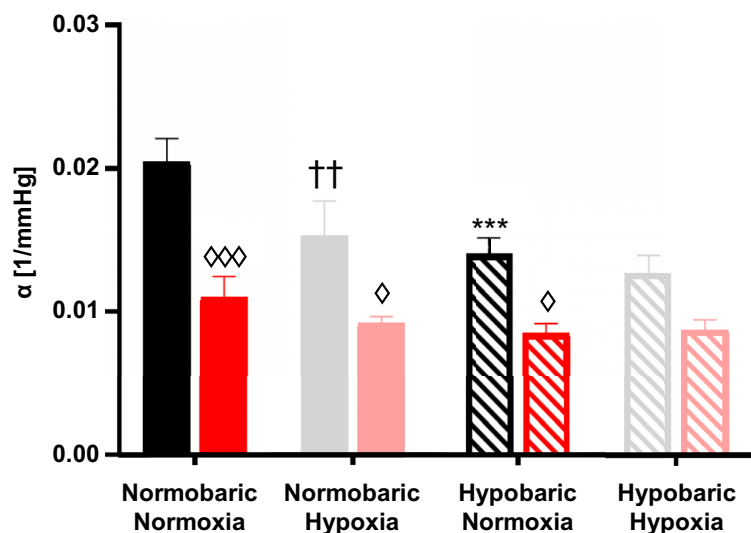
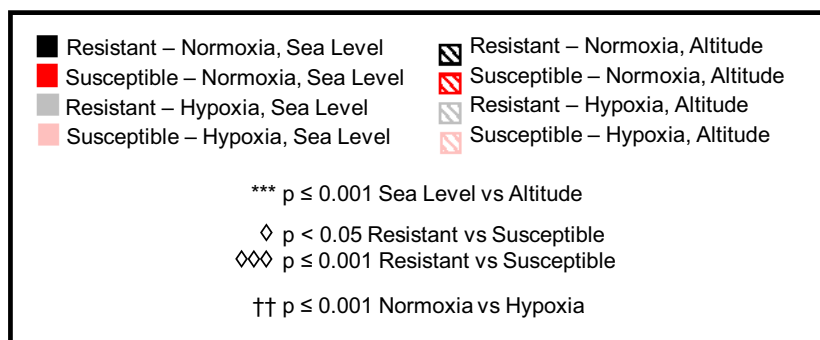


Fig. 6. Distensibility ( $\alpha$ ) calculated with the method of successive iterations (Eq. 2).

susceptible subjects have also been shown to have increased sympathetic activity and increased vasoconstrictors such as angiotensin II and endothelin I (53, 54). Here, we investigated another potential component to this puzzle, pulmonary vascular distensibility.

Our analysis demonstrates for the first time that HAPE-susceptible subjects have significantly reduced distensibility compared with HAPE-resistant control subjects even in normoxic, sea level conditions. Although the study was not designed to answer the question of the causality of HAPE, the striking differences in distensibility between the HAPE-susceptible and HAPE-resistant subjects suggest that either 1) reduced distensibility is a risk factor for the development of HAPE or 2) the current belief that HAPE can be completely reversed within several days (14, 16, 34, 45, 63) is flawed and there are potential life-long consequences. This could provide an explanation as to why previous HAPE episodes increase risk for the development of future ones.

Here we show that HAPE-susceptible subjects had an almost 50% decrease in  $\alpha$ , suggesting they have stiffened small, distal pulmonary arteries. The HAPE-susceptible subjects also had heightened increases in PAPP with exercise, which likely reflects proximal artery stiffening, independent of the distal vasculature (68). Contrary to several other studies that have failed to show changes with exercise at sea level in HAPE-susceptible subjects (24, 66), we observed exercise-induced stiffening in both the proximal and distal pulmonary arteries. No differences in PAPP were observed at rest between the HAPE-susceptible and HAPE-resistant subjects. The combina-

tion of these findings indicates that HAPE-susceptible subjects have an impaired ability to vasodilate in response to increased blood flow.

Increased pulmonary pulsatile load is associated with increased risk of RV failure in other types of pulmonary vascular disease (30, 41, 67); however, the chronic impact of this increased pulsatile loading on RV function remains to be studied in HAPE. It would be of interest to serially study HAPE-susceptible subjects with exercise cardiac magnetic resonance imaging methods. Based on our findings, we anticipate that HAPE-susceptible subjects are at increased risk of right heart dysfunction due to the chronic effects of decreased pulmonary vascular distensibility.

These data also demonstrate a significant hypobaric effect. It has been previously documented that exposure to high altitude causes increased pulmonary artery pressures (24, 27, 35, 60, 61), but here we also found decreased total arterial compliance, increased  $E_a$ , and decreased  $\alpha$ . Furthermore, there was a significant effect of hypobaric hypoxia in HAPE-susceptible subjects. When exposed to hypobaric hypoxia, HAPE-susceptible subjects had further decreases in total arterial compliance and further increases in  $E_a$  compared with hypobaric normoxia. This trend was not observed in the HAPE-resistant subjects.

A factor not frequently considered in the pathogenesis of HAPE is sex, even though uncontrolled retrospective analyses of cases in ski resorts suggest that postpubescent and premenopausal women may be protected from the development of the disease (25, 59) and occurrence rates in prepubescent children are identical between the sexes (10). Sex differences in the

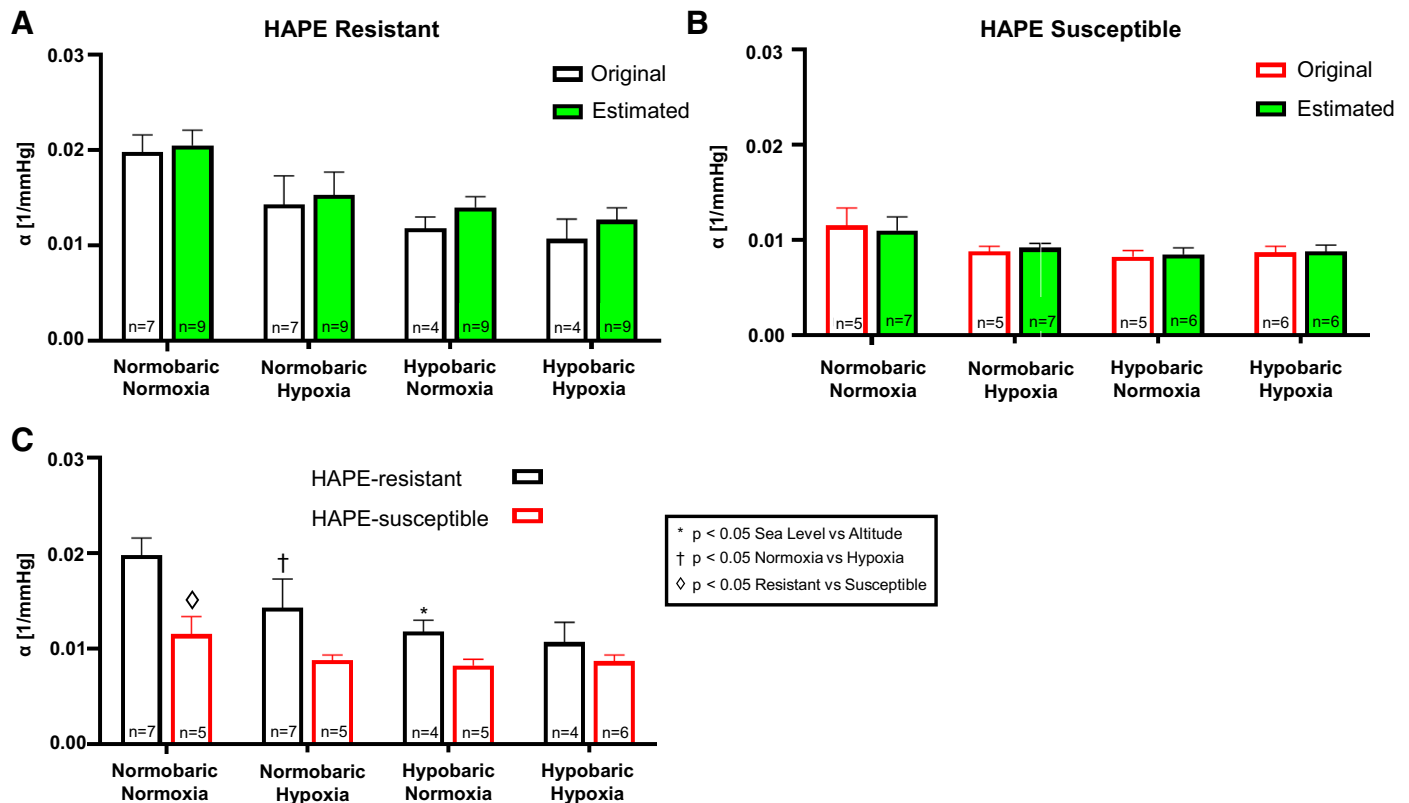


Fig. 7. Sensitivity analysis of distensibility ( $\alpha$ ), comparing the full data sets that contained no estimated values (termed “original”) to the combined data set after data imputation was used to approximate any missing pulmonary capillary wedge pressures (termed “estimated”). *A*: the data for the high-altitude pulmonary edema (HAPE)-resistant subjects. *B*: the data for the HAPE-susceptible subjects. *C*: comparison of HAPE-resistant and HAPE-susceptible subjects using only the subjects with complete data sets.

pulmonary vasculature in response to acute and chronic hypoxia have been well documented in animal studies (4, 39, 47, 49, 58, 71, 72), and it is noteworthy to mention that healthy adult women of reproductive age have more distensible pulmonary circulations than age-matched healthy adult men (1, 33, 42). Therefore, it seems possible that estrogen plays a protective role and should be further investigated.

Our findings of HAPE-susceptible subjects having decreased compliance and decreased distensibility compared with HAPE-resistant control subjects in all conditions suggests that impaired vasodilation is a feature of HAPE. Reduced distensibility has been shown to be a predictor of mortality in patients with heart failure and a potential target for vasodilator therapy for patients with pulmonary hypertension (37). It could also prove to be a target for the development of future treatments of HAPE.

Limitations of this study include altered acclimatization periods at altitude for two subjects. Subjects were typically studied 40–44 h after arriving to altitude, whereas one subject was studied at 36 h and one at 60 h. Another limitation was the unobtainable  $P_w$  pressures for several of the subjects, as well as no directly measured pulse pressures, which required us to compute pulse pressures based on established systolic-diastolic-mean PA pressure relationships that are well established in other conditions and diseases but unknown in the context of HAPE. Sensitivity analysis of  $P_w$  and  $\alpha$  did not highlight any notable differences, but this analysis was not possible for the pulse pressures. HAPE-susceptible subjects were also identi-

fied in retrospect, so further investigation is needed to determine whether these are inherent differences that result in increased susceptibility or whether they occur subsequent to the HAPE episode.

In conclusion, HAPE-susceptible subjects have increased proximal and distal pulmonary arterial stiffening in response to exercise, as well as an exaggerated hypoxic response leading to decreased total arterial compliance and increased effective arterial elastance. HAPE remains a multifactorial condition with no singular identifying mechanism or mutation able to account for all clinically observed features. Here, we identify another metric of interest in describing HAPE. Reduced distensibility could either be a potential risk factor for the development of HAPE or evidence that consequences of HAPE are long-lasting after return to sea level. It is possible that HAPE causes irreversible damage to the lungs themselves, which could account for the reduced distensibility and the well-documented reduction in lung volumes found in HAPE-susceptible subjects (11, 62). Further investigation is needed to address whether these changes occur prior or subsequent to HAPE development and the consequences of chronically increased pulsatile load on the right ventricle.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

M.W.E. conceived and designed research; M.W.E. performed experiments; A.M. and H.M. analyzed data; A.M. and N.C.C. interpreted results of experiments; A.M. prepared figures; A.M. drafted manuscript; A.M., M.W.E., and N.C.C. edited and revised manuscript; A.M., H.M., M.W.E., and N.C.C. approved final version of manuscript.

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