Stress Doppler Echocardiography for Identification of Susceptibility to High Altitude Pulmonary Edema
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OBJECTIVE
This prospective single-blinded study was performed to quantitate noninvasive pulmonary artery systolic pressure (PASP) responses to prolonged acute hypoxia and normoxic exercise.

BACKGROUND
Hypoxia-induced excessive rise in pulmonary artery pressure is a key factor in high-altitude pulmonary edema (HAPE). We hypothesized that subjects susceptible to HAPE (HAPE-S) have increased pulmonary artery pressure response not only to hypoxia but also to exercise.

METHODS
PASP was estimated at 45, 90 and 240 min of hypoxia (FiO₂ = 12%) and during supine bicycle exercise in normoxia using Doppler-echocardiography in nine HAPE-S and in 11 control subjects.

RESULTS
In the control group, mean PASP increased from 26 ± 2 to 37 ± 4 mm Hg (ΔPASP 10.3 ± 2 mm Hg) after 90 min of hypoxia and from 27 ± 4 to 36 ± 3 mm Hg (ΔPASP 8 ± 2 mm Hg) during exercise. In contrast, all HAPE-S subjects revealed significantly greater increases (p = 0.002 vs. controls) in mean PASP both during hypoxia (from 28 ± 4 to 57 ± 10 mm Hg, ΔPASP 28.7 ± 6 mm Hg) and during exercise (from 28 ± 4 to 55 ± 11 mm Hg, ΔPASP 27 ± 8 mm Hg) than did control subjects. Stress echocardiography allowed discrimination between groups without overlap using a cut off PASP value of 45 mm Hg at work rates less than 150 W.

CONCLUSIONS
These data indicate that HAPE-S subjects may have abnormal pulmonary vascular responses not only to hypoxia but also to supine bicycle exercise under normoxic conditions. Thus, Doppler echocardiography during supine bicycle exercise or after 90 min of hypoxia may be useful noninvasive screening methods to identify subjects susceptible to HAPE. (J Am Coll Cardiol 2000;35:980–7) © 2000 by the American College of Cardiology

High-altitude pulmonary edema (HAPE) is a common disorder among mountaineers. Approximately 10% of unselected mountaineers develop HAPE within 24 h after a rapid ascent to 4,500 meters (1). Subjects with a history of HAPE had a recurrence rate of 60% with the same exposure (2). Mortality was estimated to be about 50% in Himalayan mountaineers when immediate treatment was not possible (3). Although HAPE can easily be prevented by slow ascent and effectively treated by rapid descent if recognized early, it remains the most common cause of death related to high altitude (4). Therefore, it would be of great value to improve the prevention of HAPE by identifying susceptible individuals through simple noninvasive tests and giving them appropriate advice on ascent rate or prescribing prophylactic medication (2).

Although pathophysiologic mechanisms leading to HAPE are not completely understood, it appears that an hypoxia-induced excessive rise in pulmonary artery pressure is a key factor as documented by invasive (5,6) and noninvasive (2,7,8) measurements during HAPE. Furthermore, invasive studies consistently showed that HAPE-susceptible (HAPE-S) subjects have an exaggerated hypoxic pulmonary vascular response during a brief hypoxic exposure at low altitude (9–11). Recent noninvasive studies using Doppler echocardiography to estimate pulmonary artery systolic pressure (PASP) during short exposure to hypoxia could, however, not sufficiently discriminate HAPE-S from non-susceptible individuals due to a considerable overlap between groups (12,13). We hypothesized that the lack of sufficient discrimination might be due to the fact that hypoxic exposure lasted only 15 min in these studies, because it was recently shown that the maximal pulmonary
artery pressure response in healthy humans requires at least 2 h of hypoxic exposure (14).

Furthermore, recent invasive studies documented that the rise of pulmonary artery pressure during exercise in normoxia is also greater in HAPE-S than in nonsusceptible individuals (10,15). Doppler echocardiography has been shown to accurately estimate PASP at rest (16), and during normoxic exercise in patients with chronic obstructive lung disease (17), mitral valve disease (18), congenital heart disease (19) and in patients with chronic congestive heart failure (20).

Therefore, the aim of this study was to examine whether HAPE-S subjects can be identified by their PASP response to normoxic supine bicycle exercise and to prolonged acute hypoxia using Doppler ultrasound.

METHODS

Study population and design. We investigated 21 healthy male mountaineers whose susceptibility to HAPE was known because they had participated in previous studies at the Capanna Regina Margherita, ascending from 1,120 to 4,559 m within 22 h (2). During the study, one subject of the HAPE-S group had to be excluded due to inadequate Doppler signals. Therefore, the final study group consisted of 20 subjects. The HAPE-S group consisted of nine healthy male mountaineers (mean age 45 ± 8 years, weight 82 ± 9 kg, height 182 ± 8 cm) who have had at least one episode of pulmonary edema at an altitude of 4,559 m documented by chest roentgenogram within the last four years. The control group consisted of 11 male mountaineers (mean age 37 ± 11 years, weight 76 ± 7 kg, height 179 ± 6 cm) who did not develop HAPE with the same altitude exposure. Acute or chronic pulmonary and cardiac diseases were ruled out in all subjects.

The subjects were studied in Heidelberg, Germany, at an elevation of 100 m. All subjects were nonsmokers, natives of low altitude and had not resided above 2,000 m during two weeks before the examination. None of the subjects received any medication during the study period. On the first day, we performed stress-echocardiography under normoxic conditions. On the following day, PASP was measured during 4 h of exposure to normobaric hypoxia. In one subject of the control group, the study had to be terminated after 55 min of hypoxia because of nausea and discomfort. The Ethics Committee of the Medical Faculty of the University of Heidelberg approved the protocol of this study, and the subjects gave their written, informed consent before the study.

Echocardiography. Two-dimensional and Doppler echocardiographic recordings were obtained using 2.5-MHz duplex probes and conventional equipment (SSD-2200; Aloka, Tokyo, Japan) on two occasions: on the first day during stress-echocardiography; and on the second day during baseline in normoxia and at 45, 90 and 240 min of hypoxia (FiO2 = 12%). PASP was estimated from peak tricuspid regurgitation jet velocities according to the equation: PASP = 4 (V2 + 5 mm Hg, where V is the peak velocity (in m/s) of tricuspid valve regurgitant jet, and 5 mm Hg is the estimated right atrial pressure (16). The right ventricular (RV) and atrial areas were obtained in apical four-chamber views using planimetry as described by Bonmer et al. (21). Left ventricular (LV) volumes and ejection fractions (EFs) were calculated by the disc summation method (modified Simpson’s rule). Cardiac output was estimated from aortic outflow. Echocardiographic studies were performed by experienced cardiac sonographers (E.G., D.M.), who had no knowledge of the clinical data and classification of the subjects. Recordings were analyzed off-line in random order and in a blinded fashion.

Stress-echocardiography. Patients were examined on a variable load supine bicycle ergometer (model 8420; KHL Corp., Kirkland, Washington). The exercise table was tilted laterally by 20 to 30 degrees to the left. After obtaining two-dimensional and Doppler echocardiographic images at rest, exercise was started at an initial workload of 25 W. Workload was increased by 25 W every 2 min, and blood pressure and 12-lead electrocardiogram (ECG) were recorded. A 12-lead ECG and echocardiographic examinations were continuously recorded. Exercise was discontinued because of exhaustion (n = 1, workload of 175 W), hypertensive blood pressure (n = 1, workload of 175 W) or when reaching a work load level of 200 W (n = 18). All subjects reached 80% of the age-predicted heart rate.

Measurements during hypoxia. During the study, the subjects were supine and breathing a gas mixture of 12% oxygen and 88% nitrogen from a 30-liter reservoir bag over a face mask. This partial pressure of O2 in the inspired air corresponds to an altitude of 4,500 m. The fraction of inspired oxygen, minute ventilation, end-tidal oxygen and carbon dioxide concentrations were measured intermittently, while oxygen saturation and heart rate were recorded continuously using a fingertip pulse oximeter (Biox 3700; Ohmeda, Louisville, Colorado). Systemic arterial pressure and heart rate were measured with a Finapress blood pressure monitor (Ohmeda). Arterial blood was obtained before and at 90 min of hypoxic exposure by a Microsampler (Biomedical Industrade, Graz, Austria) from a radial artery and analyzed with a blood gas CO-oxymeter (model 845;
Bayer Diagnostics, Fernwald, Germany). Echocardiographic variables were obtained at rest and during hypoxia at 45, 90 and 240 min.

**Left ventricular diastolic filling.** Mitral inflow velocities were measured by pulsed-wave Doppler echocardiography at the tip of the mitral leaflets. Measurements were obtained at rest, at peak exercise and during prolonged hypoxia at time periods of 45, 90 and 240 min. Ratios of peak early (E) to late (A) diastolic filling velocities (E/A) were derived off-line from digitized mitral inflow tracings. An E/A ratio < 1.0 was considered abnormally low, consistent with impaired LV relaxation.

**Statistical methods.** Data in figures and tables are given as mean values ± SD. All reported values of PASP represent the mean of at least three measurements. Comparisons between groups at particular examinations were performed by Mann–Whitney–Wilcoxon test. The correlation between the PASP increase with hypoxia and normoxic exercise was calculated. Differences from baseline in estimated PASP, heart rates and cardiac output between both groups were assessed using the Mann–Whitney–Wilcoxon test. In all repeated measurements, Bonferroni correction was performed by multiplication of the p value with the number of comparisons. Any p values < 0.05 were considered statistically significant.

**RESULTS**

**Blood gas analysis and pulmonary vascular responses with hypoxia.** **BLOOD GAS ANALYSIS.** Arterial blood gases were not significantly different between the groups before and at 90 min of hypoxia (Table 1). There was, however, a trend to lower PaO₂ and SaO₂ values with hypoxia despite higher ventilation, as indicated by lower PaCO₂ and more pronounced alkalosis in HAPE-S as compared with control subjects. Heart rates and systemic arterial blood pressures did not change significantly in either group during hypoxia.

**PASP RESPONSE.** At baseline, mean PASP was similar in HAPE-S (28 ± 4 mm Hg) and in control subjects (26 ± 2 mm Hg, p = 0.36). During hypoxia, there was a two- to threefold greater increase in mean PASP in the HAPE-S compared with the control subjects. This increase was already evident within the first 45 min of hypoxia (ΔPASP 21 ± 5 mm Hg in HAPE-S vs. 4.5 ± 2 mm Hg in control subjects, p = 0.0012) and reached a maximum at 90 min (ΔPASP 28.7 ± 6 mm Hg in HAPE-S vs. 10.3 ± 2 mm Hg in control subjects, p = 0.0016). There was very little overlap in pulmonary artery pressures between the groups: two HAPE-S and one control subject attained a maximal PASP of 45 mm Hg. All other control subjects had maximal PASP values ≤ 40 mm Hg, and all other HAPE-S subjects had maximal PASP values ≥ 45 mm Hg (Fig. 1). In five HAPE-S subjects, the PASP increased to 60 to 70 mm Hg at 90 min of hypoxia. If 45 mm Hg is taken as an upper limit of normal hypoxic pulmonary vasoreactivity, the sensitivity of Doppler ultrasound identification of HAPE-S subjects was 55.5% to 99.7% (95% confidence interval). Specificity ranged from 40.0% to 97.2% (95% confidence interval).

**Cardiac and pulmonary vascular responses with normoxic exercise.** **EXERCISE CAPACITY AND CHANGES OF HEART RATE, CARDIAC OUTPUT AND RATE-PRESSURE PRODUCT DURING EXERCISE.** The groups did not differ significantly in age, body weight and height, mean work load, mean rate-pressure product, mean heart rate and percent of age-predicted heart rate at maximal exercise and at the measurement of maximal PASP (Table 2). At rest, both groups also had similar mean heart rates, cardiac output and blood pressures. Exercise capacity of all mountaineers was high, as documented by their high maximal workloads and rate-pressure products. The lowest maximal workload reached by one subject in each group was 175 W. All other subjects reached a workload of 200 W, the highest possible workload of the ergometer. Technically adequate

### Table 1. Arterial Blood Gas Data at Baseline and During Hypoxia

<table>
<thead>
<tr>
<th></th>
<th>HAPE-S</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, per min</td>
<td>60.6 ± 10</td>
<td>61.0 ± 8</td>
<td>0.15</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>88.7 ± 6</td>
<td>94.3 ± 8</td>
<td>0.10</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>42.3 ± 2</td>
<td>41.6 ± 6</td>
<td>0.56</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.40 ± 0.03</td>
<td>0.84</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>97.8 ± 1</td>
<td>98.5 ± 1</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>90-min Hypoxia 12% FiO₂</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, per min</td>
<td>65.0 ± 10</td>
<td>67.0 ± 10</td>
<td>0.31</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>37.6 ± 5</td>
<td>41.6 ± 6</td>
<td>0.23</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>34.4 ± 2</td>
<td>36.2 ± 2</td>
<td>0.10</td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.04</td>
<td>7.41 ± 0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>78.4 ± 6</td>
<td>82.6 ± 6</td>
<td>0.15</td>
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</tbody>
</table>

Values are mean ± SE; HAPE-S = subjects susceptible to high-altitude pulmonary edema; PaO₂ = arterial O₂ partial pressure; PaCO₂ = arterial CO₂ partial pressure; SaO₂ = arterial oxygen saturation.
Tricuspid regurgitant jet velocity signals were obtained in 20 of 21 subjects (95%) at rest and during exercise. In one subject, no adequate signal was detectable.

**PASP changes during exercise.** Control subjects and HAPE-S subjects had similar PASP values at rest. During exercise, mean PASP increased to significantly higher levels (from $28 \pm 4$ to $55 \pm 11$ mm Hg, $\Delta$PASP $27 \pm 8$ mm Hg) in HAPE-S than in control subjects (from $27 \pm 4$ to $36 \pm 3$ mm Hg, $\Delta$PASP $8 \pm 2$ mm Hg, $p < 0.002$; Fig. 2). In 16 of 20 subjects (80%), adequate Doppler signals could be obtained through workloads of 125 W, corresponding to a heart rate of < 120 beats/min. At higher workloads with higher heart rates, Doppler signals became inadequate in these individuals. Only in four subjects could PASP be measured at a workload of 175 W and a heart rate of 198 b/min.

![Figure 1](image.png)

**Figure 1.** PASP response to prolonged hypoxia. Discrimination between controls and HAPE-S subjects by their PASP response to hypoxia estimated by Doppler-echocardiography. **HAPE-S**, subjects susceptible to high altitude pulmonary edema (n = 9); **CONTROLs**, control subjects (n = 11). The study was discontinued at 55 min of hypoxia in one control subject. No significant differences at rest between both groups ($p = 0.36$). *PASP in HAPE-S subjects compared with control subjects at 45 ($p = 0.0012$), 90 ($p = 0.0016$) and 240 ($p < 0.02$) min of hypoxia.

### Table 2. Mean Workload, Cardiac Output, Maximal Rate-Pressure Product, Mean Heart Rate and Percent of Age-predicted Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>HAPE-S</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>age, yrs</td>
<td>45 ± 8</td>
<td>37 ± 11</td>
<td>0.09</td>
</tr>
<tr>
<td>weight, kg</td>
<td>82 ± 9</td>
<td>76 ± 7</td>
<td>0.11</td>
</tr>
<tr>
<td>height, cm</td>
<td>182 ± 8</td>
<td>179 ± 6</td>
<td>0.44</td>
</tr>
<tr>
<td>At maximal exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>192 ± 13</td>
<td>198 ± 8</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiac output, liters/min</td>
<td>15.2 ± 13</td>
<td>14.4 ± 2</td>
<td>0.27</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg/min</td>
<td>32,812 ± 4,571</td>
<td>31,993 ± 5,646</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>154 ± 13</td>
<td>145 ± 15</td>
<td>0.16</td>
</tr>
<tr>
<td>Percent of age-predicted maximal heart rate, %</td>
<td>88 ± 10</td>
<td>72 ± 30</td>
<td>0.07</td>
</tr>
<tr>
<td>At maximal PASP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>117 ± 40</td>
<td>115 ± 39</td>
<td>0.93</td>
</tr>
<tr>
<td>Cardiac output, liters/min</td>
<td>8.7 ± 2</td>
<td>9.4 ± 1</td>
<td>0.32</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg × liters/min</td>
<td>21,421 ± 5,114</td>
<td>19,918 ± 4,663</td>
<td>0.51</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>118 ± 19</td>
<td>99 ± 35</td>
<td>0.15</td>
</tr>
<tr>
<td>Percent of age-predicted maximal heart rate, %</td>
<td>67 ± 10</td>
<td>60 ± 10</td>
<td>0.10</td>
</tr>
</tbody>
</table>
rate > 120 beats/min. Despite these technical limitations, both groups could be discriminated according to their PASP response at submaximal levels of exercise (25 to 125 W).

IDENTIFICATION OF HAPE SUSCEPTIBILITY BY PASP CHANGES DURING EXERCISE. With respect to maximal PASP with exercise, there was no overlap between the groups (Fig. 3). HAPE-S and control subjects were not significantly different at rest (p = 0.28). All HAPE-S subjects revealed an exaggerated rise in PASP to levels ≥ 45 mm Hg during exercise. The increase of PASP in the control subjects was within the reported (22,23) normal range of ≤ 40 mm Hg. This increase of PASP during exercise correlated highly with that during 90 min of hypoxia in the examined subjects (r = 0.80, p < 0.001). Using a PASP of 45 mm Hg as a cut-off level, the sensitivity of PASP changes using stress Doppler echocardiography for identifying HAPE-S subjects was 71.5% to 100% (95% confidence interval). Specificity of this method ranged from 66.4% to 100% (95% confidence interval).

Left and right ventricular function during hypoxia and exercise. Mean LV (EFs) were normal at rest and increased in both groups significantly during exercise and within 240 min of hypoxia. Right ventricular end diastolic and end systolic areas were normal in all subjects and did not change significantly during exercise or hypoxia in both groups.

Changes of LV diastolic filling during hypoxia and exercise. Six of nine HAPE-S subjects revealed dyssynchronized septal motion and mitral inflow patterns of impaired LV relaxation (E/A < 1.0) during exercise and hypoxia. Impaired relaxation was documented only in one subject of the control group, who revealed hypertensive blood pressures at rest and during exercise. Therefore, E/A ratio was significantly lower in HAPE-S than in control subjects during maximal exercise and after 45 min of hypoxia (Fig. 4).

DISCUSSION

This study revealed a significantly greater increase in PASP during prolonged acute hypoxic exposure (90 to 240 min) and normoxic supine bicycle exercise in HAPE-S than in control subjects. There was no overlap of PASP during exercise between groups, while overlap of individual values was minimal with prolonged hypoxic exposure. Therefore, both stress Doppler echocardiography and Doppler echocardiography during prolonged hypoxia may be useful, noninvasive methods to identify HAPE-S subjects. However, stress Doppler echocardiography during normoxic exercise may be a superior method, because it is easier to perform, less time consuming and possibly more effective in discriminating between HAPE-S subjects and controls.

PASP changes during prolonged hypoxia. During hypoxia, PASP increased in all subjects. HAPE-S subjects had significantly greater increases in PASP during prolonged acute hypoxia than did controls. There was little overlap between the PASP values of the groups. The greater increase of PASP in HAPE-S subjects is consistent with measurements in previous studies using right heart catheterization (9,10,24) or Doppler echocardiography (11,12). However, there was a considerable overlap in pulmonary artery pressure between HAPE-S and control subjects when Doppler assessment was used (12,13). Hohenhaus et al. (14)
did not find significant differences in PASP of seven HAPE-S and control subjects during 10 min of hypoxia. The better discrimination between groups in our study is most likely due to the longer exposure of the subjects to hypoxia. Maximal PASP values was reached in our study population after 90 min of hypoxia. Whereas previous authors have assumed that a change in pulmonary vascular resistance occurs within minutes of exposure to hypoxia (25,26), a recent study has demonstrated that PASP reaches a maximum after 2 h of isocapnic hypoxia (14). This prolonged time course is in accordance with that observed in our study.

![Figure 3](image1.png)

Figure 3. PASP response to exercise. Discrimination between controls and HAPE-S subjects by their PASP response to exercise estimated by Doppler echocardiography. HAPE-S, subjects susceptible to high-altitude pulmonary edema (n = 9), CONTROLS, control subjects (n = 11). No significant differences at rest between both groups (p = 0.28). *Mean maximal PASP in controls (36 ± 3 mm Hg) vs. HAPE-S (55 ± 11 mm Hg) subjects, p < 0.002.

![Figure 4](image2.png)

Figure 4. Impaired LV relaxation in HAPE-S subjects during exercise and prolonged hypoxia assessed from mitral inflow velocities. Both exercise and prolonged hypoxia decreased E/A ratios to levels < 1.0 in six of nine patients susceptible to HAPE but in only one control patient; p = 0.01 at peak exercise, and at **45, ***90 and ****240 min of hypoxia.
Stress Doppler echocardiography. To the best of our knowledge, this is the first report of stress echocardiography as a method to identify HAPE-S subjects. Our results are in accordance with previous studies that observed an increase of PASP during normoxic exercise in HAPE-S subjects assessed by right heart catheterization (10,11,15). Kawashima et al. (10) measured a greater than twofold increase in mean pulmonary artery pressure in five HAPE-S compared with five control subjects during normoxic supine low-level exercise of 25 to 50 W. Eldridge et al. (15) found a twofold greater increase of mean pulmonary artery pressure during heavy upright exercise in individuals with a history of HAPE compared with controls, similar to our findings. Janosi et al. (22) documented invasively an upper limit of PASP during supine bicycle exercise of 38 mm Hg in subjects aged 15 to 50 years. Therefore, in our study, 40 mm Hg was taken as an upper limit of normal PASP. In none of our control subjects did PASP exceed 40 mm Hg during exercise.

The fact that exercise in normoxia and supine position as well as hypoxia cause an abnormal increase in pulmonary artery pressure in HAPE-S subjects suggests that they have an intrinsic heightened vasoreactivity of the pulmonary circulation. This hypothesis is supported by the observation that there is a strong correlation between the PASP increase with 90 min of hypoxia and with normoxic exercise. Reduced vascular cross-sectional area due to smaller and less distensible lungs may also contribute to this vasoreactivity because smaller vital capacity (13,15,24,27) and lower functional residual capacity as well as lower maximal CO diffusing capacity (27) have been found in HAPE-S individuals.

Left ventricular function. There was evidence for developing diastolic dysfunction during stress and hypoxia in subjects susceptible to HAPE. Six of the subjects in this group revealed mitral inflow patterns consistent with impaired relaxation and septal dyscoordination during hypoxia and exercise. In contrast, these patterns were detected in only one control subject with systemic arterial hypertension. The exact mechanism of this observation is not clear, because hemodynamic factors directly influencing mitral inflow such as left ventricular filling pressure, left atrial pressure and operating chamber compliance were not controlled in this study. However, it may be speculated that the acute rise of PASP during hypoxia, associated with dyscoordinated septal movement, mechanically impedes mitral inflow, as suggested by Ritter et al. (28). Direct alterations of active myocardial relaxation are unlikely because hypoxic conditions were similar for both groups, but reduced E/A patterns developed predominantly in the group susceptible to HAPE. Heart rate and blood pressures were similar in both groups and are unlikely to account for the observed impairment of early diastolic filling in HAPE-S.

Systolic left ventricular dysfunction has been demonstrated in chronic pulmonary hypertension secondary to chronic pulmonary diseases (29). However, in our study, the systolic LV function improved rather than decreased both during hypoxia and exercise in all subjects. This is in accordance with the findings of Suarez et al. (30), who echocardiographically documented a significant increase in LV EF in healthy subjects during exercise at a simulated altitude of 8,840 m. This improvement was associated with elevated circulating catecholamines reflecting enhanced sympathetic activity.

Study limitations. In previous studies, the investigators could measure PASP in about 40% to 85% of subjects, although echocardiographic contrast agents were used to enhance the Doppler signal and to improve accuracy of the investigation (13,17,20). In our study, we had only a small dropout rate (5%) due to insufficient Doppler signals. This might be due to differences in study population and ultrasound equipment used in our study. Whereas others examined patients with heart disease, our study population consisted of healthy, athletic subjects. Furthermore, there exist only few data on PASP measurements on stress Doppler echocardiography, and since then, a new generation of echocardiographic machines have been developed with a marked improvement of Doppler functions. Measurements by stress echocardiography may be further limited by the fact that PASP cannot be estimated by Doppler ultrasound in all subjects, especially at high levels of exercise with heart rates >120 beats/min. In our study, PASP were obtained up to a heart rate of 120/min. Because PASP rises considerably at the beginning of exercise, a good discrimination between both groups was seen within the first stages of exercise.

Clinical implications. HAPE-S subjects revealed a greater increase in estimated PASP during supine bicycle exercise at 50 to 125 W workload than nonsusceptible subjects without overlap of individual values. Differences of PASP during hypoxia are most prominent with minimal overlap between HAPE-S and control subjects after 90 min of exposure. Therefore, stress Doppler echocardiography during supine bicycle exercise or prolonged hypoxia may be a useful, widely available screening method for this life-threatening disorder. It needs, however, to be validated in a larger group of subjects before it can be recommended for clinical practice.

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