Pulmonary artery pressure and cardiac function in children and adolescents after rapid ascent to 3,450 m

Yves Allemann,1,* Thomas Stuber,1,* Stefano F. de Marchi,1,* Emrush Rexhaj,1 Claudio Sartori,2 Urs Scherrer,1,3,* and Stefano F. Rimoldi1,*

1Department of Cardiology, Inselspital, University Hospital, Bern, Switzerland; 2Botnar Center for Extreme Medicine, Department of Internal Medicine, University Hospital, Lausanne, Switzerland, and 3Facultad de Ciencias, Departamento de Biología, Universidad de Tarapacá, Arica, Chile

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Allemann Y, Stuber T, de Marchi SF, Rexhaj E, Sartori C, Scherrer U, Rimoldi SF. Pulmonary artery pressure and cardiac function in children and adolescents after rapid ascent to 3,450 m. Am J Physiol Heart Circ Physiol 302: H2646–H2653, 2012. First published April 20, 2012; doi:10.1152/ajpheart.00053.2012.—High-altitude destinations are visited by increasing numbers of children and adolescents. High-altitude hypoxia triggers pulmonary hypertension that in turn may have adverse effects on cardiac function and may induce life-threatening high-altitude pulmonary edema (HAPE), but there are limited data in this young population. We, therefore, assessed in 118 nonacclimatized healthy children and adolescents (mean ± SD; age: 11 ± 2 yr; range: 6–16 yr) the effects of rapid ascent to high altitude on pulmonary artery pressure and right and left ventricular function by echocardiography. Pulmonary artery pressure was estimated by measuring the systolic right ventricular to right atrial pressure gradient. The echocardiography was performed at low altitude and 40 h after rapid ascent to 3,450 m. Pulmonary artery pressure was more than twofold higher at high than at low altitude (35 ± 11 vs. 16 ± 3 mmHg; \( P < 0.0001 \)), and there existed a wide variability of pulmonary artery pressure at high altitude with an estimated upper 95% limit of 52 mmHg. Moreover, pulmonary artery pressure and its altitude-induced increase were inversely related to age, resulting in an almost twofold larger increase in the 6- to 9- than in the 14- to 16-yr-old participants (24 ± 12 vs. 13 ± 8 mmHg; \( P = 0.004 \)). Even in children with the most severe altitude-induced pulmonary hypertension, right ventricular systolic function did not decrease, but increased, and none of the children developed HAPE. HAPE appears to be a rare event in this young population after rapid ascent to this altitude at which major tourist destinations are located.

high-altitude pulmonary edema; hypoxia; right ventricle; left ventricle; sympathetic activity

WITH THE DEVELOPMENT OF MODERN transportation systems high-altitude tourist destinations are visited by an increasing number of individuals including many children and adolescents. High altitude-associated hypoxia triggers a series of cardiovascular adjustments, with pulmonary vasoconstriction being the most important one (3, 35, 39). These adjustments, if exaggerated, may cause significant diseases such as life-threatening high-altitude pulmonary edema (HAPE) (20, 36). In adults, there is abundant evidence that an exaggerated increase of pulmonary artery pressure plays a key role in causing HAPE (3, 35–39), as evidenced by an invasive study demonstrating a threshold for pulmonary capillary pressure >19 mmHg for subjects subse-

quent to developing HAPE (20). For pulmonary artery pressure, a distinct threshold value has not been established, but echocardiographic estimates of systolic pulmonary artery pressure in mountaineers who will develop HAPE are typically >55 mmHg (3, 39). Surprisingly, in children and adolescents there is very little information on cardiovascular adjustments to acute high altitude exposure (26). A recent small study (17) suggests that the initial altitude-induced increase of pulmonary artery pressure is more pronounced in children than in their fathers. We speculated that if confirmed this exaggerated increase of pulmonary artery pressure could suggest that the risk of developing HAPE and acute right ventricular pressure overload may be greater in children than in adults.

We, therefore, assessed pulmonary artery pressure and right ventricular function in a large group of healthy nonacclimated children and adolescents 40 h after rapid ascent by train to 3,450 m.

MATERIALS AND METHODS

Study subjects and protocol. The study group consisted of 118 healthy Caucasian children and adolescents (mean age: 11 ± 2 yr; range: 6–16 yr; 55 girls and 63 boys; Table 1). All except 2 (who were living at 1,100 m) were living at altitudes <800 m. None of the children had slept at an altitude >1,500 m during the 2 mo preceding the study, and none was taking any medication at the time of the study. None of the participants had ever traveled to or slept at an altitude similar to the present study altitude. Twenty-four subjects had traveled/stayed at altitudes between 1,500 and 2,500 m in the past. All children were born at term (gestation 39.2 ± 1.9 wk) and had normal birth weight (3,351 ± 496 g). None of the children suffered from congenital heart disease. None of the children was born after a pregnancy complicated by preeclampsia or had suffered from transient perinatal hypoxia, problems predisposing to exaggerated hypoxic pulmonary hypertension (14, 33). The baseline examination was performed at the University Hospital in Bern, Switzerland (568 m). Within 4 wk after the low-altitude examination, the children ascended by a 2½-h train ride to the high-altitude research station Jungfraujoch, Switzerland at 3,450 m. Hemodynamic measurements at high altitude were performed in the morning of the second day (~40 h after arrival) after an overnight fast. In a representative subgroup of children (\( n = 25 \); mean age 12 ± 2 yr, 10 girls and 15 boys), measurements were also made 4–6 h and 18–20 h after arrival. All parents gave written informed consent. The protocol was approved by the institutional review boards on human investigation of the Universities of Lausanne and Bern, both in Switzerland, and was registered (Clinical Trials Gov Registration No. NCT00837642).

Echocardiographic exam. Echocardiographic recordings were obtained in the left lateral position using an Acuson Sequoia 512 ultrasound system (Acuson, Mountain View, CA), equipped with a 4V1c adult and a 7V3c pediatric transducer with an integrated color Doppler system (3.6 or 6.0 MHz for pulsed and 2.15 or 3.6 MHz for
Continuous-wave Doppler recording. Tricuspid regurgitation (continuous-wave Doppler), right ventricular two-dimensional clips, and tricuspid annular motion (pulsed-wave tissue Doppler) were acquired from an apical four-chamber view. Data were stored on DVD and analyzed offline by two investigators (S. F. Rimoldi, S. F. de Marchi) who were unaware of the subject identity and study site. Reported values represent the mean of at least three measurements.

Pulmonary artery pressure. To estimate systolic pulmonary artery pressure (PAP), we measured the peak systolic tricuspid regurgitation jet velocity in all possible views and calculated the right ventricular to right atrial pressure gradient using the highest jet velocity of the qualitatively best signal, as previously described (2, 14). These measurements represent the mean of at least three measurements.

Right ventricular function. End-systolic and -diastolic right ventricular areas were manually traced from a two-dimensional echocardiographic clip, and the right ventricular fractional area change was calculated. Right ventricular fractional area change correlates closely with MRI-derived right ventricular ejection fraction (19). The peak systolic velocity and early and late diastolic velocities of the lateral tricuspid annulus were assessed using pulse-wave tissue Doppler tracings (1, 23). Peak systolic velocity has a good sensitivity and specificity in predicting right ventricular dysfunction (43). Regional right ventricular strain and strain rate, a measure of systolic and diastolic functions, were calculated using speckle tracking technology (Syngo US Workplace v.3.1; Siemens Medical Solutions, Mountain View, CA, USA) as previously described (18). Briefly, two-dimensional clips of the right ventricle were acquired at high frame rates (100–140 frames/s) and subendocardial speckle motion during the cardiac cycle was tracked automatically after initial manual border tracing in end-diastole. Measurements were limited to the middle portion of the right ventricular free wall, because this portion is particularly prone to pulmonary hypertension-induced dysfunction (16, 21).

In nine participants at high, and six at low altitude, strain and strain rate could not be measured because of an insufficient echo window for right ventricular speckle tracking. To assess right ventricular afterload, right ventricular peak systolic wall stress (WSps, g/cm²) was estimated using the following formula: $WS_{ps} = 1.35 \times D \times \text{PAP} \times 4 \times T \left[1 + (T / D)\right]$, where D is the end-systolic right ventricular cavity diameter and T is the end-systolic right ventricular free wall thickness. D and T were measured from an apical four-chamber view (15). The intra- and interobserver coefficient of variation for strain was 8.4 and 10.8%, and for strain rate was 10.0 and 13.6%, respectively.

Left ventricular function. To assess systolic left ventricular function, left ventricular ejection fraction was calculated using the Teichholz and the modified biplane Simpson methods (25). Left ventricular diastolic function was assessed from the apical four-chamber view using transmitral Doppler flow velocity and mitral annular motion velocity measurements as previously described (1).

For the noninvasive estimation of left ventricular end-diastolic filling pressure, the ratio between the early diastolic transmural peak flow velocity (E) and the septal early diastolic peak velocity of the mitral annulus (E/EmEm), was calculated (E/EmEm).

Central venous pressure. Echocardiographic estimation of central venous pressure was performed by measuring the respiratory change of the diameter of the inferior vena cava in the subcostal view according to current guidelines (30).

Heart rate variability. To gain insight into underlying neural mechanisms of the regulation of heart rate and cardiac function, heart rate variability, a surrogate marker of cardiac sympathetic nervous system activity, was measured. Subjects were examined in the supine position in a calm environment breathing regularly at 0.25 Hz. After a variable period of familiarization of 10–20 min, a 5-min ECG was recorded at a sample rate of 1,024 Hz (Lifecard CF, Spacelabs Healthcare, Issaquah, WA). The recordings were analyzed on a workstation using the Pathfinder analyzer software (DelMar Reynolds Medical, Spacelabs Healthcare). A 5-min ECG segment free from ectopy and noise was selected before an RR-interval list was exported and analysed for heart rate variability (HRV Analysis Software, University of Kuopio, Finland, Vers. 1.1.) (24). Frequency domain analysis was performed using a Fast Fourier Transformation. Two frequency bands were considered: the low-frequency band (0.04–0.15 Hz) and the high-frequency band (0.15–0.4 Hz). Whereas the high-frequency heart rate fluctuations coincide with respiration, and therefore reflect vagal tone, the low-frequency fluctuations are predominantly of sympathetic origin (27). The magnitude of sympathetic activity was assessed by normalizing the area under the low-frequency spectral curve to the total area (after subtracting the very low-frequency component) and multiplying by 100 (27, 40).

Cardiac output, pulmonary vascular resistance, and arterial oxygen saturation. Cardiac output was determined by measuring the diameter of the left ventricular outflow tract and the time-velocity integral of its Doppler signal. The left ventricular outflow tract diameter was measured in the parasternal long axis view, and its surface was calculated assuming circular geometry. The stroke volume was calculated by multiplying the left ventricular outflow tract time velocity integral with the cross-sectional area. Cardiac output was then obtained by multiplying stroke volume with heart rate (25). We previously reported an intra- and interobserver variability of 10.7 ± 10.2 and 7.2 ± 4.0% for cardiac output measurements in

### Table 1. Clinical, echocardiographic, and electrocardiographic parameters at low and high altitude

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Altitude: 568 m (n = 118)</th>
<th>High Altitude: 3,450 m (n = 118)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm</td>
<td>150 ± 14</td>
<td>171 ± 18</td>
<td></td>
</tr>
<tr>
<td>Weight, cm</td>
<td>42.6 ± 13.7</td>
<td>45.0 ± 7.5</td>
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<tr>
<td>Body surface area, m²</td>
<td>1.33 ± 0.26</td>
<td>1.77 ± 0.21</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>71 ± 9</td>
<td>76 ± 10</td>
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<tr>
<td>SaO₂, %</td>
<td>97 ± 1</td>
<td>93 ± 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>113 ± 10</td>
<td>115 ± 15</td>
<td>0.45</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>69 ± 7</td>
<td>70 ± 8</td>
<td>0.30</td>
</tr>
<tr>
<td>Cardiac index, l/min-m²</td>
<td>2.7 ± 0.5</td>
<td>2.9 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>16 ± 3</td>
<td>16 ± 3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVRI, dyn·cm⁻⁵/m²</td>
<td>285 ± 93</td>
<td>478 ± 172</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HRVLF, %</td>
<td>43.6 ± 17.2</td>
<td>57.4 ± 21.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are means ± SD (95% confidence interval). BP, blood pressure; HRVLF, low-frequency component of heart rate variability; PAP, pulmonary artery pressure; PVRI, total pulmonary vascular resistance; SaO₂, arterial oxygen saturation.
children at high altitude (41). Cardiac index was obtained by dividing cardiac output by body surface area (m²). Total pulmonary vascular resistance (PVRTot; dyn·s·cm⁻¹) was calculated as follows: PVRTot = 80 × mean pulmonary artery pressure divided by cardiac output (25).

Mean pulmonary artery pressure (MPAP) was calculated as follows: MPAP = 0.61 × PAP + 2 (7). The intra- and interobserver coefficients of variation for PVRTot were 4.0 and 5.3%, respectively.

Transcutaneous arterial oxygen saturation was measured at a fingertip with a pulse oxymeter (OxiMax N-65, Nellcor, Pleasanton, CA).

Assessment of acute mountain sickness and HAPE. In the morning of the day of echocardiography, the presence of acute mountain sickness (AMS) was assessed with the Lake Louise Scoring System as previously described (5, 28). Briefly, for each of the five items (headache, gastrointestinal symptoms, fatigue, dizziness, and sleep disturbance), the participants noted a score between 0 and 3, with 0 indicating the absence of the symptom; 1, mild symptoms; 2, moderate symptoms; and 3, severe, incapacitating symptoms. Participants were considered suffering from AMS if they were experiencing headache and scored ≥3 on the self-assessment questionnaire. HAPE was assessed clinically in the morning after the first and second night spent at high altitude by asking for early symptoms (cough, breathlessness, and reduced performance during exercise).

Statistical analysis. Statistical analyses were performed using the GraphPad Prism 5 software package (GraphPad Software, San Diego CA). For comparisons of continuous variables between low and high altitude, a paired two-sided Student’s t-test was used. Relations between continuous variables were analyzed by linear regression analysis and the Pearson correlation coefficient.

Multiple regression analysis was performed on Statistica 7.0 (StatSoft, Tulsa, OK). To assess independent determinants of strain rate at high altitude, the variables found to be significant in univariate analyses or having a potential physiological relation to strain rate were entered in a stepwise multiple regression model. Only variables measured or calculated independently were entered. These included right ventricular peak systolic wall stress, heart rate, low-frequency heart rate variability, right ventricular fractional area change, arterial oxygen saturation, and cardiac index.

Results of the overall regression fittings were as follows: the intercept and standardized coefficients of the multiple regression equation (β), adjusted coefficient of determination (adjusted-r²), as well as ANOVA F and P values of the overall regression model. Only variables with significant nonzero slopes in the regression equation were considered independent predictors of strain rate. Residual analysis was performed, and satisfactory assumption testing was considered mandatory.

A P value <0.05 was considered to indicate statistical significance. Results are expressed as means ± SD.

RESULTS

Clinical and hemodynamic characteristics. During the 48 h at high altitude none of the participants developed symptoms or clinical signs of high-altitude pulmonary edema or acute cor pulmonale (Table 1). At the time of the echocardiographic examination, 7 of the 118 participants suffered from mild AMS (mean score: 3.6 ± 0.8; range: 3–5). Systolic and diastolic systemic blood pressure did not differ between low and high altitude. Arterial oxygen saturation was significantly lower (P < 0.0001), whereas heart rate and cardiac index were significantly higher at high altitude (both P < 0.0001).

Pulmonary artery pressure and vascular resistance. Tricuspid regurgitation could be detected and pulmonary artery pressure measured in all but five subjects at low (95%) and all but three subjects (97%) at high altitude (Table 1).

At low altitude, pulmonary artery pressure was within normal limits (<24 mmHg) (22) in all participants (16 ± 3 mmHg; range 10 to 23 mmHg; Fig. 1) and there existed a significant positive relationship between age and pulmonary artery pressure (r = 0.25; P = 0.008; Fig. 2A). Pulmonary artery pressure was similar in female and male participants (17 ± 3 vs. 17 ± 3 mmHg; P = 0.24).

At high altitude, pulmonary artery pressure was more than twofold higher than at low altitude (35 ± 11 vs. 16 ± 3 mmHg; P < 0.0001; Fig. 1) and there existed a wide variability with an estimated upper 95% limit of 52 mmHg. Pulmonary artery pressure and its altitude-induced increase was comparable in boys and girls (36 ± 11 vs. 35 ± 12 mmHg; P = 0.65; and 19 ± 12 vs. 19 ± 12 mmHg; P = 0.84, respectively). Moreover, pulmonary artery pressure was similar 4–6, 18–20, and 40 h after arrival at high altitude (35 ± 10, 34 ± 12, and 34 ± 13 mmHg, respectively; P = 0.65).

Pulmonary artery pressure (r = −0.27; P = 0.004; Fig. 2B) and its altitude-induced increase (r = −0.33; P < 0.001) were inversely related to age, resulting in an almost twofold larger increase in the 6- to 9-yr-old than in the 14- to 16-yr-old participants (24 ± 12 vs. 13 ± 8 mmHg, P = 0.004). Moreover, pulmonary artery pressure was inversely related to arterial oxygen saturation (r = −0.32; P = 0.003) and positively related to heart rate (r = 0.31; P = 0.0007).

Right ventricular function and heart rate variability. Right ventricular end-diastolic area was slightly albeit significantly smaller at high than at low altitude (17.3 ± 4.0 vs. 18.8 ± 4.3 cm²; P < 0.01); there was a significant negative relationship between heart rate and diastolic surface area of the right ventricle at high altitude (r = −0.31; P < 0.0001). Strain rate and peak systolic tissue Doppler velocity of the lateral tricuspid annulus increased significantly (P < 0.001) at high altitude, whereas right ventricular fractional area and strain remained unchanged (Table 2). At high altitude, there was a significant positive relationship among strain rate and pulmonary artery pressure (r = 0.61; P < 0.0001), pulmonary vascular resistance (r = 0.30; P = 0.0018), and peak systolic right ventricu-
and low-frequency heart rate variability (r = 0.30; P < 0.0001), septal ADTI (r = 0.30; P < 0.0001), and lateral ADTI (r = 0.15; P = 0.03), whereas negative relationships existed between pulmonary artery pressure and transmitral E wave (r = -0.37; P < 0.0001), transmitral E/A ratio (r = -0.51; P < 0.0001), septal EDTI/ADTI ratio (r = -0.25; P < 0.0001) and lateral EDTI/ADTI ratio (r = -0.23; P < 0.0001). There was a significant positive relationship between heart rate and mitral E/A ratio (r = -0.30; P < 0.01) but not between heart rate and septal EDTI/ADTI ratio (r = -0.12; P = 0.19).

The E/EDTI ratio, a proxy of left ventricular end-diastolic filling pressure, while normal at both altitudes, was slightly albeit significantly lower at high altitude (Table 2).

Right atrial pressure. At high altitude, the mean diameter of the inferior vena cava decreased significantly from 1.3 ± 0.3 to 1.0 ± 0.4 cm (P < 0.01), whereas the respiratory change of the diameter was comparable at both altitudes (47 ± 9 vs. 47 ± 10%; P = 0.91).

**DISCUSSION**

Here, we report for the first time pulmonary artery pressure and cardiac function adjustments to rapid high-altitude exposure in a large group of healthy, nonacclimatized children and adolescents aged between 7 and 16 yr. The main finding was that in these healthy young subjects, rapid ascent to 3,450 m induced a roughly twofold increase of average systolic pulmonary artery pressure that was inversely related with the age. This increase of pulmonary artery pressure was associated with a concomitant stimulation of right ventricular contractility and preserved or even increased longitudinal systolic right ventricular function. Moreover, at high altitude, left ventricular ejection fraction increased slightly. None of these young nonacclimatized subjects developed clinical signs of acute right heart failure or HAPE. These findings suggest that in nonacclimatized children and adolescents with no previous high-altitude experience rapid ascent to an altitude at which major tourist destinations are located is relatively safe.

At low altitude, all participants had normal pulmonary artery pressure (right ventricular to right atrial pressure gradient <24 mmHg) (22) that, in accordance with a previous report (22), was directly related to age. Acute high-altitude exposure, as expected, consistently increased pulmonary artery pressure in these young healthy participants. Interestingly, this altitude-induced increase of pulmonary artery pressure was consider-

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Fig. 2. Relationship between PAP and age in 118 healthy children and adolescents at low altitude (A) and 40 h after rapid ascent by train to high altitude (B).

![Graph showing relationship between PAP and age](image-url)
ably more marked in children than in adolescents, suggesting that pulmonary vascular responsiveness to hypoxia decreases during this period. The average systolic pulmonary artery pressure during acute high-altitude exposure in the present study was roughly 5 mmHg higher than the one measured in healthy well-adapted Caucasian children and adolescents of comparable age permanently living at a similar altitude (41, 42), thereby providing an estimate of the capacity of adaptation to chronic hypoxia of the pulmonary circulation in Caucasians of this age group.

In these young participants, acute high-altitude exposure induced significant sympathetic activation as shown by the increase of low-frequency heart rate variability and tachycardia. This sympathetic activation was directly correlated with altitude-induced pulmonary hypertension, suggesting that it may represent an underlying mechanism. In line with this concept, sympathetic activation has been found to contribute to hypoxic pulmonary hypertension in adults (9, 10). An interesting finding was the brisker hypoxic pulmonary vascular response in children than in adolescents. The inverse relationship between age and low-frequency variability of heart rate could be consistent with the hypothesis that augmented sympathetic activation contributes to the brisker pulmonary vascular response to hypoxia in young children. Moreover, pulmonary endothelial and respiratory epithelial nitric oxide also play a role in the regulation of the pulmonary vascular responses to hypoxia (39). Interestingly, there is evidence that pulmonary nitric oxide synthesis may be decreased in children compared with adolescents (38). It is tempting to speculate that in the present study, this problem may also have contributed to the greater hypoxic pulmonary vascular responsiveness in children than in adolescents. Finally, the present finding of a less marked hypoxic pulmonary vascular responsiveness in adolescents than in children could be consistent with the observation that in children living at high altitude, the incidence of reentry HAPE decreases when they get older (38).

Despite an altitude-induced increase of pulmonary artery pressure that in some participants was of similar magnitude as the one observed in HAPE-prone adults (3, 20, 39), none of these young subjects developed HAPE or right heart failure, suggesting that after rapid ascent to this altitude these complications are relatively rare in a healthy population of this age group. The observation that despite marked pulmonary hypertension none of the subjects developed HAPE is consistent with a previous report (33) in adolescents having suffered from transient perinatal hypoxia who displayed exaggerated hypoxic pulmonary hypertension in the same range and who did also not develop HAPE while staying at 4,556 m. In adults, there is evidence that exaggerated pulmonary hypertension may not be sufficient to trigger HAPE and that defective alveolar fluid clearance contributes to this problem (32, 34). In line with this concept, respiratory transepithelial sodium and water transport was found to be normal in adolescents having suffered from transient perinatal hypoxia (32). It is tempting to speculate that in the present study, intact alveolar fluid clearance may have prevented HAPE in children with exaggerated hypoxic pulmonary hypertension. A previous small study (17) suggested that after rapid ascent to this altitude the increase of pulmonary artery pressure was maximal a few h after arrival.

Table 2. Right and left ventricular echocardiographic parameters at low and high altitude

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Altitude: 568 m (n = 109)</th>
<th>High Altitude: 3,450 m (n = 109)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Right ventricular function</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Strain, %</td>
<td>27.5 ± 5.6</td>
<td>26.5 ± 5.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Strain rate, s⁻¹</td>
<td>2.04 ± 0.45</td>
<td>2.25 ± 0.53</td>
<td>0.0009</td>
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<tr>
<td>Fractional area change, %</td>
<td>44 ± 7</td>
<td>43 ± 9</td>
<td>0.45</td>
</tr>
<tr>
<td>S&lt;sub&gt;DTL&lt;/sub&gt;, cm/s</td>
<td>14.5 ± 2.0</td>
<td>15.7 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;DTI&lt;/sub&gt; tricuspidal, cm/s</td>
<td>16.6 ± 2.6</td>
<td>17.4 ± 2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>A&lt;sub&gt;DTI&lt;/sub&gt; tricuspidal, cm/s</td>
<td>8.8 ± 1.5</td>
<td>11.3 ± 2.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>E&lt;sub&gt;DTI&lt;/sub&gt;/A&lt;sub&gt;DTI&lt;/sub&gt;</td>
<td>1.9 ± 0.4</td>
<td>1.6 ± 0.3</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Left ventricular function</strong></td>
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<td></td>
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<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEF (Teichholz), %</td>
<td>64.0 ± 4.2</td>
<td>65.2 ± 4.8</td>
<td>0.02</td>
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<tr>
<td>LVEF (Simpson), %</td>
<td>64.3 ± 3.6</td>
<td>65.5 ± 4.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Transmitral E wave, cm/s</td>
<td>89 ± 12</td>
<td>76 ± 12</td>
<td>&lt;0.0001</td>
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<tr>
<td>Transmitral A wave, cm/s</td>
<td>44 ± 9</td>
<td>53 ± 10</td>
<td>&lt;0.0001</td>
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<tr>
<td>Transmitral E/A</td>
<td>2.1 ± 0.4</td>
<td>1.5 ± 0.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>E-wave deceleration time, ms</td>
<td>146 ± 14</td>
<td>150 ± 23</td>
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<tr>
<td>Transmitral IVRT , ms</td>
<td>74 ± 8</td>
<td>69 ± 9</td>
<td>&lt;0.0001</td>
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<tr>
<td>E&lt;sub&gt;DTI&lt;/sub&gt; septal, cm/s,</td>
<td>13.9 ± 2.6</td>
<td>14.3 ± 2.3</td>
<td>0.20</td>
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<td>A&lt;sub&gt;DTI&lt;/sub&gt; septal, cm/s,</td>
<td>7.1 ± 1.3</td>
<td>8.3 ± 1.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>E&lt;sub&gt;DTI&lt;/sub&gt;/A&lt;sub&gt;DTI&lt;/sub&gt; septal</td>
<td>2.0 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>E&lt;sub&gt;DTI&lt;/sub&gt; lateral, cm/s</td>
<td>21.7 ± 3.2</td>
<td>21.0 ± 2.9</td>
<td>0.19</td>
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<td>A&lt;sub&gt;DTI&lt;/sub&gt; lateral, cm/s</td>
<td>9.7 ± 1.8</td>
<td>10.6 ± 2.1</td>
<td>&lt;0.0001</td>
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<td>E&lt;sub&gt;DTI&lt;/sub&gt;/A&lt;sub&gt;DTI&lt;/sub&gt; lateral</td>
<td>2.8 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>&lt;0.0001</td>
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<td>Estimation of LVEDP</td>
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<tr>
<td>E/E&lt;sub&gt;DTI&lt;/sub&gt; septal</td>
<td>6.5 ± 1.5</td>
<td>5.4 ± 1.1</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Data are means ± SD. A, late (transmitral) peak flow velocity; E, early (transmitral) peak flow velocity; DTI, Doppler tissue imagining; IVRT, isovolumetric relaxation time; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; S<sub>DTL</sub>, peak systolic velocity of the lateral tricuspid annulus.

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Cardiovascular Function in Children at High Altitude

Study, peak systolic right ventricular wall stress was an independent predictor of strain rate in children at high altitude. In contrast, in a previous short-time (90 min) hypoxic chamber study with a simulated altitude of ~4,500 m that increased pulmonary artery pressure similarly as in the present study (35 ± 6 mmHg), strain rate did not change significantly in healthy adults (12). This difference may be related to weak sympathetic activation by such short-term hypoxia in healthy adults (9) or to differences in right ventricular responsiveness to hypoxia between children and adults.

Finally, systolic right ventricular function and strain rate are also preload dependent. It appears, however, unlikely that changes in contractility at high altitude were related to the Frank-Starling mechanism in this study, because echocardiographic estimation of central venous pressure did not reveal pathologic findings and only 11 of the 118 participants developed moderate tricuspidal regurgitation at high altitude. In line with this observation, in a previous invasive study, we found little variability of the central venous pressure after acute high-altitude exposure in adults, with all values remaining <10 mmHg even in those with very large increases in pulmonary artery pressure (2). Moreover, right ventricular end-diastolic areas were smaller at high compared with low altitude. Taken together, our findings suggest that in young healthy subjects the right ventricle is able to maintain stroke volume in the presence of an acute increase in afterload by increasing contractility through homeometric autoregulation (31, 44) while the Frank-Starling (or heterometric) mechanism does not play an important role.

Left ventricular systolic function was normal and slightly increased at high compared with low altitude. This finding is in accordance with previous studies in healthy adults (1, 4, 11). The acute increase in pulmonary artery pressure during high-altitude exposure induced a change in left ventricular diastolic function, which, as previously described in adults (1), was directly correlated with the severity of pulmonary hypertension. The decrease in transmitial early to late peak flow velocity ratio and tissue Doppler E/DtA ratio was mainly due to increased atrial contraction. These changes were not associated with an augmented left ventricular end-diastolic filling pressure, which remained normal at high altitude. Collectively, these findings show that the hemodynamic adaptation of the left ventricle to acute high-altitude exposure is very similar in healthy children and adults and they confirm that left ventricular dysfunction does not contribute to hypoxic pulmonary hypertension.

**Limitations.** We used noninvasive methods to assess pulmonary artery pressure and cardiac function in these studies. These methods are less precise than invasive measurements that for ethical reasons cannot be used in this healthy young population. In adults, HAPE typically develops 36 to 72 h after arrival at high altitude. Adults who will develop HAPE >48 h after arrival (the time point the children left the high altitude research laboratory) already feel sick at this time point. In the present study, none of the children showed any premonitory signs of HAPE and arterial oxygen saturation was >83% in all children at the time of descent, suggesting that it is very unlikely that one of them would have developed HAPE when staying longer at this altitude.

The fact that our study is mainly descriptive and does not investigate mechanisms is related to the problem that ethical approval for studies investigating mechanisms in healthy chil-

**Fig. 3.** Relationship between peak systolic right ventricular (RV) wall stress and strain rate (A) and between low-frequency heart rate variability (HRVLF) and strain rate (B) in 109 healthy children and adolescents 40 h after rapid ascent by train to high altitude (3,450 m).
Children is extremely difficult to obtain. We cannot exclude the possibility that the increase in heart rate may be confounding the interpretation of the data, insofar as rate related indexes of function (i.e., strain rate, annual velocity) but not force related indexes (i.e., strain, fractional area shortening), increased with exposure to high altitude.

Conclusions. This study represents the largest reported assessments of pulmonary artery pressure and right and left ventricular function adaptation to acute high-altitude exposure in healthy children and adolescents. Detection of tricuspid regurgitation and estimation of pulmonary artery pressure was possible in the vast majority (~95%) of these healthy young population. Rapid ascent to an altitude at which major tourist destinations (i.e., Lhasa, Cuzco, and La Paz) are located (3,450 m) induced a roughly twofold increase of mean systolic pulmonary artery pressure that was inversely related with the age, resulting in a roughly twofold larger altitude-induced increase of pulmonary artery pressure in young children than in adolescents. We observed a wide variation of pulmonary artery pressure at high altitude in these young healthy subjects (95% confidence interval, 22–52 mmHg). This increase of pulmonary artery pressure was associated with concomitant stimulation of right ventricular contractility resulting in preserved systolic right ventricular function, preserved systolic left ventricular function, end-diastolic pressure, and stroke volume in all subjects. Taken together with the observation that none of the children developed HAPE and that consistent with previous reports (5, 28) the prevalence of AMS was low, these findings suggest that acute exposure of this unacclimatized young population to this altitude is relatively safe.

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