Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude

Yves Allemann, Martin Rotter, Damian Hutter, Ernst Lipp, Claudio Sartori, Urs Scherrer, and Christian Seiler. Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude. Am J Physiol Heart Circ Physiol 286: H856–H862, 2004. First published November 6, 2003; 10.1152/ajpheart.00518.2003.—In pulmonary hypertension right ventricular pressure overload leads to abnormal left ventricular (LV) diastolic function. Acute high-altitude exposure is associated with hypoxia-induced elevation of pulmonary artery pressure particularly in the setting of high-altitude pulmonary edema. Tissue Doppler imaging (TDI) allows assessment of LV diastolic function by direct measurements of myocardial velocities independently of cardiac preload. We hypothesized that in healthy mountaineers, hypoxia-induced pulmonary artery hypertension at high altitude is quantitatively related to LV diastolic function as assessed by conventional and TDI Doppler methods. Forty-one healthy subjects (30 men and 11 women; mean age 41 ± 12 yr) underwent transthoracic echocardiography at low altitude (550 m) and after a rapid ascent to high altitude (4,559 m). Measurements included the right ventricle to right atrial pressure gradient (∆P_{RV-RA}), transmitral early (E) and late (A) diastolic flow velocities and mitral annular early (E_{m}) and late (A_{m}) diastolic velocities obtained by TDI at four locations: septal, inferior, lateral, and anterior. At a high altitude, ∆P_{RV-RA} increased from 16 ± 7 to 44 ± 15 mmHg (P < 0.0001), whereas the transmitral E-to-A ratio (E/A ratio) was significantly lower (1.11 ± 0.27 vs. 1.41 ± 0.35; P < 0.0001) due to a significant increase of A from 52 ± 15 to 65 ± 16 cm/s (P = 0.0001). ∆P_{RV-RA} and transmitral E/A ratio were inversely correlated (r² = 0.16; P = 0.0002) for the whole spectrum of measured values (low and high altitude). Diastolic mitral annular motion interrogation showed similar findings for spatially averaged (four locations) as well as for the inferior and septal locations: A_{m} increased from low to high altitude (all P < 0.01); consequently, E_{m}/A_{m} ratio was lower at high versus low altitude (all P < 0.01). These intradividual changes were reflected interindividually by an inverse correlation between ∆P_{RV-RA} and E_{m}/A_{m} (all P < 0.006) and a positive association between E_{m}/A_{m} and A_{m} (all P < 0.0009). In conclusion, high-altitude exposure led to a two- to threefold increase in pulmonary artery pressure in healthy mountaineers. This acute increase in pulmonary artery pressure led to a change in LV diastolic function that was directly correlated with the severity of pulmonary hypertension. However, in contrast to patients suffering from some form of cardiopulmonary disease and pulmonary hypertension, in these healthy subjects, overt LV diastolic dysfunction was not observed because it was prevented by augmented atrial contraction. We propose the new concept of compensated diastolic (dys)function.

METHODS

Study Subjects and Design

Forty-one healthy (two with mild systemic hypertension) mountaineers (11 women and 30 men; age 41 ± 12 yr, range 25–63 yr) were included in the study. Among them, 18 (7 women and 11 men) had previously developed at least one episode of clinically and radiographically documented HAPE (HAPE-susceptible subjects). The 23 other subjects (4 women and 19 men) were known to be resistant to HAPE (HAPE-resistant subjects) during previous events of alpine-style climbing (21). The experimental protocol was approved by the institutional review board for human investigation at the Swiss Cardiovascular Center Bern, University Hospital, Bern, CH-3010; and Department of Internal Medicine, University Hospital, Lausanne CH-1000, Switzerland

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Centre Hospitalier Universitaire Vaudois, and all subjects provided written informed consent before the ascent to high altitude.

Study design. The study design consisted of an intra- as well as an interindividual comparison of LV diastolic function in relation to low versus high altitude (550 vs. 4,559 m above sea level) and relative to different Doppler-derived pulmonary artery pressures [i.e., systolic RV to right atrial (RA) pressure gradient (ΔPRV-RA)].

Study Protocol
Subjects were first studied at high altitude. The subjects ascended from 1,130 to 4,559 m above sea level within a period of <24 h. The ascent consisted of a transport by cable car to an altitude of 3,200 m, followed by a 1.5-h climb to an altitude of 3,611 m, where they spent the night in a hut. The next day, a 4- to 5-h climb took them to the high altitude research laboratory at Capanna Regina Margherita (4,559 m above sea level). The subjects then spent 2 days and 2 nights at this altitude, unless they developed HAPE and needed to be evacuated earlier. Body mass index, heart rate, systemic blood pressure, oxygen saturation, Doppler echocardiographic estimates of systolic pulmonary artery pressure, and LV diastolic function aside from conventional transthoracic Doppler echocardiographic measurements were performed 18 to 30 h after arrival at the Marginherita hut, or earlier if the subject had developed HAPE. Nine of the HAPE-susceptible subjects had pulmonary edema at the time of the determination of Doppler-derived pulmonary artery pressure. Within 6 mo after the study at high altitude, identical Doppler echocardiographic measurements were performed at low altitude (550 m). A total of 50 subjects was initially screened. Nine were excluded from the study because of technical difficulties in diastolic parameter acquisition, Doppler echocardiographic measurements were performed at low altitude (550 m). A total of 50 subjects was initially screened. Nine were excluded from the study because of technical difficulties in diastolic parameter acquisition, Doppler echocardiographic measurements were performed at low altitude (550 m).

Doppler Echocardiography
At high altitude, transthoracic Doppler echocardiographic recordings were obtained using a real-time phased array sector scanner (model Sonos 5000; Hewlett-Packard; Andover, MA) with an integrated color Doppler system and a transducer containing crystals for imaging at 2.5 to 4 MHz with second harmonic capabilities. For continuous and pulsed wave Doppler recordings including tissue Doppler imaging, the transducer emitted at 1.9 MHz. At low altitude, conventional transthoracic Doppler echocardiography was performed with the use of a Sequoia echocardiogram (model C 256, Acuson; Mountain View, CA) with a 3.5-MHz transducer including second harmonic and tissue Doppler imaging technology. At both altitudes, the subjects were examined identically in the supine, left lateral, or anterior tissue Doppler imaging position after an overnight fast. The subjects underwent conventional M-mode and two-dimensional echocardiography from a left parasternal and apical window. M-mode measurements of the LV were obtained during end systole and end diastole. Septal and posterior wall thickness and LV and left atrial cavity diameter were measured according to the leading edge method. LV mass was calculated according to the cube formula using end-diastolic values of septal and posterior wall thickness and LV cavity dimension. LV volume measurements for the calculation of LV ejection fraction were carried out in biplane projection from apical four- and two-chamber views. LV volumes were computed using the biapical Simpson rule.

After tricuspid valve regurgitation had been located by color Doppler imaging, the peak flow velocity of the tricuspid jet (VTR, m/s) was measured using continuous wave Doppler. To calculate ΔP (mmHg) between the RV and the RA, the following simplified Bernoulli equation was used: ΔP_{RV-RA} = 4V^2_{TR}. Because right atrial pressure cannot be measured noninvasively, pulmonary artery pressure was not calculated and the directly obtainable ΔP_{RV-RA} was employed for all analyses. Doppler-derived pressure gradients across the tricuspid valve have been shown to accurately estimate invasively determined pulmonary artery pressures at low (3, 5) as well as at high altitude (2).

LV diastolic function was assessed from the apical four-chamber view using transmitral and pulmonary venous Doppler flow velocity, and mitral annular motion velocity measurements (7, 18). The pulsed-wave sample volume of the conventional Doppler was placed at the tips of the mitral valve leaflets and 1 cm within the right upper pulmonary vein. The obtained variables included peak flow velocity (E, cm/s) and deceleration time (ms) of early diastolic transmitral filling, peak flow velocity (A, cm/s) of late diastolic transmitral filling, and isovolumetric relaxation time (in ms) as well as transmitral A wave duration (ms). Pulmonary venous flow parameters included peak systolic (cm/s), diastolic (cm/s), and reverse (cm/s) flow velocity as well as reverse flow duration at atrial contraction (in ms) (6). Mitral annular motion velocity (cm/s;Fig. 1) during early (Ea) and late (Am) diastole was determined using Doppler tissue imaging with the pulsed-wave sample volume placed at the septal, lateral, inferior, and anterior mitral annulus from the apical four- and two-chamber view, respectively. For data analysis, spatially averaged (the sum of septal plus inferior plus lateral plus anterior tissue Doppler velocities divided by 4) as well as local values were used (7). Septal early diastolic mitral annular motion velocities ≤8 cm/s have been documented to accurately detect impaired LV diastolic function independent of cardiac loading conditions (18).

All echocardiographies were performed by fully trained cardiologists from the same center (Y. Allemann, M. Rotter, D. Hutter, and E. Lipp) and the offline analysis was done by M. Rotter and D. Hutter.

Statistical Analysis
For comparison of continuous demographic and Doppler echocardiographic variables obtained in the same individual at low and high altitude, the paired, two-sided Student’s t-test was used. The χ2-test was used to compare intraindividual categorical variables between the two altitudes were compared with the use of a t-test. Linear regression analysis was carried out for the detection of statistically relevant interindividual correlations between Doppler tissue imaging values (dependent variable) and ΔPRV-RA (independent variable). Data are expressed as means ± SD. Statistical significance was defined at a P < 0.05.

RESULTS
Study Subjects’ Characteristics, Hemodynamic, and Echocardiographic Data
Body mass index, systolic and diastolic blood pressure, and LV mass index were comparable at low and high altitude (Table 1). At high altitude, oxygen saturation was significantly lower than at 550 m above sea level (Table 1). As expected, ΔPRV-RA was >50% lower at low than at high altitude (Table 1 and Fig. 2). The nine subjects that actually developed HAPE had ΔPRV-RA that was markedly higher than the one measured in subjects without HAPE (61 ± 11 mmHg compared with 40 ± 13 mmHg, P < 0.0001).

At low altitude, heart rate and LV ejection fraction were significantly lower than at high altitude (Table 1), and LV cavity diameter (47 ± 6 mm), septum (11 ± 2 mm), and posterior (10 ± 2 mm) wall thickness obtained at end diastole were normal.
Transmitral and Pulmonary Venous Doppler Flow Data

Intraindividual comparison. Table 2 shows that transmitral E-to-A ratio (E/A ratio) was markedly smaller at high altitude because of a significant increase in transmitral A wave velocity. Moreover, pulmonary venous diastolic flow velocity and pulmonary venous reversed A wave velocity were significantly decreased at high altitude. The shortening of the pulmonary venous reversed A wave duration at high altitude suggests that LV diastolic function was preserved at high altitude. In accordance, early diastolic transmitral flow velocity was not found to be 10 or more times greater than mitral annular motion velocity (another indicator of LV filling pressure >15 mmHg) in any of the subjects. Furthermore, absolute early diastolic mitral annular motion velocity ≤8 cm/s (a parameter of elevated LV filling pressure) was not detected in any of the study subjects at high altitude.

On the other hand, in 7 of 41 subjects, reversed pulmonary venous flow duration exceeded transmitral flow duration during atrial contraction, thus suggesting the presence of elevated LV filling pressure at high altitude in a minority of study subjects.

Fig. 1. Recording of septal mitral annular motion velocity using tissue Doppler imaging at low (A) and high (B) altitudes.
subjects. Five of those individuals developed HAPE, i.e., 5 of 9 subjects with HAPE manifested signs of elevated LV filling pressure according to pulmonary venous and transmitral flow data, whereas only 2 of 32 individuals without HAPE did so ($P < 0.05$). In absolute terms, compared with transmitral $A$ duration, pulmonary venous $A$ duration was longer by only 2 ms in individuals with HAPE and by 16 ms in the subjects without HAPE ($P = 0.08$).

**Interindividual comparison.** There was a significant inverse correlation between $\Delta P_{RV-RA}$ and transmitral $E/A$ ratio: $r^2 = 0.16$, $P = 0.0002$. No association was found between $\Delta P_{RV-RA}$ and isovolumetric relaxation time. Pulmonary venous reversed $A$ wave velocity was significantly related to $\Delta P_{RV-RA}$ ($r^2 = 0.16$, $P = 0.0006$) and there was an inverse correlation between pulmonary venous reversed $A$ wave duration and $\Delta P_{RV-RA}$ ($r^2 = 0.11$, $P = 0.004$).

**Tissue Doppler Imaging Data**

**Intraindividual comparison.** The following pattern could be observed in diastolic mitral annular motion velocity for spatially averaged as well as septal and inferior but not lateral and anterior Doppler sample volume locations (Table 3): there was a nonsignificant trend to higher $E_m$ values at low than high altitude; $A_m$ values were significantly lower at low than at high altitude, and the ratio between early and late values ($E_m/A_m$) was significantly higher at low versus high altitude. In addition, averaged, septal, and inferior (Table 3) as well as lateral (83 ± 20 vs. 75 ± 11 ms; $P = 0.02$) and anterior (91 ± 24 vs. 81 ± 17 ms; $P = 0.01$) isovolumetric relaxation time obtained at the mitral annulus were significantly longer at low versus high altitude.

**Interindividual comparison.** The correlation among all the study subjects between $\Delta P_{RV-RA}$ and diastolic mitral annular motion parameters reflected the respective intraindividual changes observed at low versus high altitude: there was an inverse correlation between $\Delta P_{RV-RA}$ and inferior $E_m$ (Fig. 3); $\Delta P_{RV-RA}$ was directly associated with averaged (Fig. 4), inferior ($r^2 = 0.21$, $P < 0.0001$), and lateral ($r^2 = 0.09$, $P = 0.001$) $A_m$, and it was inversely correlated with the

**Table 2. Intraindividual comparison of transmitral and pulmonary venous Doppler flow data**

<table>
<thead>
<tr>
<th></th>
<th>550 m</th>
<th>4.559 m</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmitral $E$ wave, cm/s</td>
<td>71±17</td>
<td>70±15</td>
<td>0.74</td>
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<tr>
<td>Transmitral $A$ wave, cm/s</td>
<td>52±15</td>
<td>65±16</td>
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<td>Transmitral $E/A$</td>
<td>1.41±0.35</td>
<td>1.11±0.27</td>
<td>&lt;0.0001</td>
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<td>$E$ wave deceleration time, ms</td>
<td>165±37</td>
<td>152±51</td>
<td>0.25</td>
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<tr>
<td>Transmitral IVRT, ms</td>
<td>73±23</td>
<td>76±17</td>
<td>0.77</td>
</tr>
<tr>
<td>Transmitral $A$ duration, ms</td>
<td>139±28</td>
<td>129±22</td>
<td>0.24</td>
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<tr>
<td>Pulmonary venous systolic velocity, cm/s</td>
<td>51±16</td>
<td>52±15</td>
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<tr>
<td>Pulmonary venous diastolic velocity, cm/s</td>
<td>53±18</td>
<td>45±11</td>
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<tr>
<td>Pulmonary venous $A$ duration, ms</td>
<td>145±33</td>
<td>117±21</td>
<td>0.0002</td>
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<tr>
<td>Pulmonary venous $A$ velocity, cm/s</td>
<td>25±6</td>
<td>30±5</td>
<td>&lt;0.0001</td>
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</table>

Values are means ± SD; $n = 41$ subjects. $E$ wave, early wave; $A$ wave, late wave; $E/A$, early-to-late ratio; $A$ duration, transmitral minus pulmonary venous $A$ duration; IVRT, isovolumetric relaxation time.

**Table 3. Intraindividual comparison of tissue Doppler imaging data**

<table>
<thead>
<tr>
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<th>550 m</th>
<th>4.559 m</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>Averaged mitral annular motion velocity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Averaged $E_m$, cm/s</td>
<td>14.9±3.0</td>
<td>14.7±2.2</td>
<td>0.50</td>
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<tr>
<td>Averaged $A_m$, cm/s</td>
<td>11.0±2.7</td>
<td>13.8±3.0</td>
<td>0.01</td>
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<tr>
<td>Averaged $E_m/A_m$</td>
<td>1.50±0.56</td>
<td>1.14±0.29</td>
<td>0.01</td>
</tr>
<tr>
<td>Averaged isovolumetric relaxation time, ms</td>
<td>87±17</td>
<td>78±10</td>
<td>0.002</td>
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<tr>
<td>Septal mitral annular motion velocity</td>
<td></td>
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<tr>
<td>$E_m$, septal, cm/s</td>
<td>12.4±2.8</td>
<td>11.8±2.4</td>
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<td>$A_m$, septal, cm/s</td>
<td>10.6±2.3</td>
<td>14.0±3.4</td>
<td>&lt;0.0001</td>
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<td>$E_m/A_m$, septal</td>
<td>1.26±0.50</td>
<td>0.88±0.30</td>
<td>&lt;0.0001</td>
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<td>Isovolumetric relaxation time septal, ms</td>
<td>89±22</td>
<td>80±17</td>
<td>0.005</td>
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<td>Inferior mitral annular motion velocity</td>
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<tr>
<td>$E_m$, inferior, cm/s</td>
<td>14.9±3.7</td>
<td>13.8±3.6</td>
<td>0.10</td>
</tr>
<tr>
<td>$A_m$, inferior, cm/s</td>
<td>11.2±3.1</td>
<td>14.2±4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>$E_m/A_m$, inferior</td>
<td>1.46±0.6</td>
<td>1.09±0.55</td>
<td>0.008</td>
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<tr>
<td>Isovolumetric relaxation time inferior, ms</td>
<td>88±21</td>
<td>76±17</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 41$ subjects. $E_m$, mitral annular motion velocity during early diastole; $A_m$, mitral annular motion velocity during late diastole.
ratio of spatially averaged (Fig. 4), inferior (Fig. 3), septal ($r^2 = 0.16, P = 0.0003$), and lateral ($r^2 = 0.08, P = 0.02$) early and late mitral annular motion velocity.

**DISCUSSION**

As expected, acute high altitude exposure led to a two- to threefold increase in pulmonary artery pressure in healthy mountaineers. This acute increase in pulmonary artery pressure led to a change in LV diastolic function, which was directly correlated with the severity of pulmonary hypertension. However, in contrast to patients suffering from some form of preexisting cardiopulmonary disease and pulmonary hypertension, in these healthy subjects, overt LV diastolic dysfunction was not observed because it was prevented by augmented atrial contraction. We propose the new concept of compensated diastolic (dys)function.

**Pulmonary Hypertension and LV Diastolic Dysfunction**

At first sight, the transmitral flow patterns observed at high altitude might suggest LV relaxation abnormality, because early to late transmitral flow velocity ratio was decreased. A similar pattern of transmitral inflow has been described in a small small study (8 subjects) in which the ascent to Mount Everest was simulated in a hypobaric chamber (4). However, in contrast to studies performed in patients with primary pulmonary hypertension (11), among subjects following single lung transplantation (23) or in patients after pulmonary thromboendarterectomy (15), the decreased $EA$ ratio in our study was not due to diminished early diastolic filling flow velocity but exclusively to accelerated atrial contraction flow velocity. This observation suggests that atrial contraction was sufficient to prevent diastolic dysfunction (impaired relaxation) in our healthy subjects, but because transmitral filling velocities are load dependent, this interpretation may be prone to error (14).

In patients with cardiopulmonary disease, two other markers of LV diastolic dysfunction in pulmonary hypertension, prolonged isovolumetric relaxation time and an extended $E$ wave deceleration time (15), have been repeatedly found. In contrast, in our healthy subjects, these two variables remained unchanged at high altitude or even showed a trend to be shortened. Early (22) as well as recent studies (13) on the impact of pulmonary hypertension in patients with cardiopulmonary disease, suggest that LV diastolic dysfunction is a consequence of chronic septal distortion with subsequent myocardial remodel-

Fig. 3. Correlations between transtricuspid regurgitant pressure gradients and early ($E_m$, top) and late ($A_m$, middle) diastolic mitral annular motion velocities (vertical axes; cm/s) obtained by tissue Doppler imaging at the inferior annulus as well as their ratio (bottom).

Fig. 4. Top: correlation between transtricuspid regurgitant pressure gradients obtained by tissue Doppler imaging at four annular locations (septal, inferior, lateral, and anterior sites; cm/s). Bottom: correlation between transtricuspid regurgitant pressure gradient and the ratio of early to late diastolic mitral annular motion velocity ($EA_m$) obtained by tissue Doppler imaging at the same four annular locations.
ling (increased septal wall thickness and reduced diastolic LV cavity diameter) and reduced LV compliance. The present finding of a shortened pulmonary venous flow reversal which was mostly terminated faster than the transmitral A wave further supports the concept that in these healthy subjects, acute pulmonary hypertension changed the pattern of LV diastolic filling, but that LV diastolic dysfunction was prevented by augmented left atrial contraction.

This interpretation is strengthened by tissue Doppler analysis of mitral annular motion within as well as among the study subjects. Mitral annular motion velocity measurements were performed for the first time in this particular setting, and they provide a unique opportunity to study the influence of spatially diverse influences of RV pressure overload on LV diastolic function. Considering a rather global perspective of LV diastolic function by focusing on spatially averaged mitral annular motion variables, the generally agreed on threshold of early diastolic velocity <8 cm/s defining LV diastolic dysfunction (18) was not reached in a single study individual at high altitude. However, at or close to the site where RV pressure overload due to pulmonary hypertension acted on, i.e., the septal or inferior mitral annulus, early diastolic velocity tended to decrease form low to high altitude, and at high altitude early diastolic velocity tended to be lower in the subjects with the most elevated pulmonary artery pressures.

Clinical Implications: Mechanisms Relating Altered LV Filling to HAPE

With regard to clinical consequences, it is important to distinguish between compensated and decompensated high altitude-induced changes in LV diastolic function because the former versus the latter is not reflected by increased LV filling pressure >15 mmHg. Pathophysiologically, elevated LV filling pressure represents the primary driving force eventually leading to clinical events such as dyspnea on exertion, orthopnea, dysnea at rest, and pulmonary edema. Thus two questions may be raised. First, on the basis of previous invasive studies, which have validated the Doppler variables for this purpose (10), do any of the noninvasively obtained Doppler parameters at high altitude indicate elevated LV filling pressure? Second, were the subjects suffering HAPE markedly different from those without regarding their LV diastolic function parameters?

With regard to the first question, absolute early diastolic mitral annular motion velocity <8 cm/s was not detected at high altitude, and early diastolic transmirtal flow velocity was not found to be 10 or more times greater than mitral annular motion velocity in any of the subjects. Thus these two parameters did not provide evidence for elevated LV filling pressure in healthy subjects at high altitude.

With regard to the second question, reversed pulmonary venous flow duration did exceed transmirtal flow duration during atrial contraction in 7 of 41 cases, thus suggesting the presence of elevated LV filling pressure at high altitude in a minority of study subjects. Five of those individuals developed HAPE, i.e., 5 of 9 subjects with HAPE manifested signs of elevated LV filling pressure according to pulmonary venous and transmirtal flow data, whereas only 2 of 32 individuals without HAPE did so. Moreover, in absolute terms, compared with transmitral A duration, pulmonary venous A duration at high altitude was shorter by only 2 ms in individuals with HAPE and by 16 ms in the subjects without HAPE. A shift of the interventricular septum toward the left ventricle as a direct consequence of acute hypoxia-induced pulmonary hypertension and consecutive right ventricular pressure overload is the hypothesized mechanism responsible for the elevated LV filling pressure. Because HAPE is thought to be caused by a hydrostatic-induced permeability leak of the pulmonary endothelial-epithelial barrier (9), it is tempting to speculate that some subjects with HAPE represent an exception to the rule of compensated diastolic function, and that pulmonary edema may result from the impossibility of augmented left atrial contraction to compensate for RV and LV pressure overload. Indeed, the concept of decompensated LV filling manifesting as elevated LV diastolic and pulmonary capillary pressures triggering HAPE in a minority of our study subjects would fit well with a recent study by Magniirini et al. (12), who found a pulmonary capillary pressure >19 mmHg to be the critical threshold for clinically manifest HAPE.

REFERENCES


