Evidence supportive of impaired myocardial blood flow reserve at high altitude in subjects developing high-altitude pulmonary edema

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Kaufmann BA, Bernheim AM, Kiencke S, Fischler M, Sklenar J, Mairbaurl H, Maggiorini M, Brunner-Rocca HP. Evidence supportive of impaired myocardial blood flow reserve at high altitude in subjects developing high-altitude pulmonary edema. Am J Physiol Heart Circ Physiol 294: H1651–H1657, 2008. First published February 29, 2008; doi:10.1152/ajpheart.00760.2007.—An exaggerated increase in pulmonary arterial pressure is the hallmark of high-altitude pulmonary edema (HAPE) and is associated with endothelial dysfunction of the pulmonary vasculature. Whether the myocardial circulation is affected as well is not known. The aim of this study was, therefore, to investigate whether myocardial blood flow reserve (MBFr) is altered in mountaineers developing HAPE. Healthy mountaineers taking part in a trial of prophylactic treatment of HAPE were examined at low (490 m) and high altitude (4,559 m). MBFr was derived from low mechanical index contrast echocardiography, performed at rest and during submaximal exercise. Among 24 subjects evaluated for MBFr, 9 were HAPE-susceptible individuals on prophylactic treatment with dexamethasone or tadalafil, 6 were HAPE-susceptible individuals on placebo, and 9 persons without HAPE susceptibility served as controls. At low altitude, MBFr did not differ between groups. At high altitude, MBFr increased significantly in HAPE-susceptible individuals on treatment (from 2.2 ± 0.8 at low to 2.9 ± 1.0 at high altitude, P = 0.04) and in control persons (from 1.9 ± 0.8 to 2.8 ± 1.0, P = 0.02), but not in HAPE-susceptible individuals on placebo (2.5 ± 0.3 and 2.0 ± 1.3 at low and high altitude, respectively, P > 0.1). The response to high altitude was significantly different between the two groups (P = 0.01). There was a significant inverse relation between the increase in the pressure gradient across the tricuspid valve and the change in myocardial blood flow reserve. HAPE-susceptible individuals not taking prophylactic treatment exhibited a reduced MBFr compared with either treated HAPE-susceptible individuals or healthy controls at high altitude.

hypoxia; exercise; echocardiography

HIGH-ALTITUDE PULMONARY EDEMA (HAPE) is a potentially fatal condition occurring in nonacclimatized individuals ascending rapidly to altitudes >2,500 m. In an unselected population, ~5–6% develop HAPE, usually within 2–3 days, if ascending rapidly to 4,500 m, whereas individuals with a history of HAPE have a 60% chance of recurrence (5). The pathophysiological hallmark of HAPE is an exaggerated hypoxic pulmonary vasoconstriction with an abnormal increase in pulmonary artery (2, 16, 24, 26) and capillary pressure (21). Transmural flow leakage (28, 29), irregular distribution of vasoconstriction with regional overperfusion, or venoconstriction (38) have been proposed as mechanisms, while inflammatory mechanisms do not seem to play a major role (37). Decreased concentrations of nitric oxide (NO) in exhaled air are found in HAPE-susceptible (HAPE-S) individuals exposed to hypoxia (37). Furthermore, if individuals with HAPE inhale NO at high altitude, pulmonary arterial pressure (PAP) is lowered and gas exchange improved to values seen in normal individuals (3, 27). These data suggest an endothelium-dependent reduced vasodilatory capacity in HAPE-S individuals, owing to a decreased bioavailability of NO and thus an exaggerated hypoxic vasoconstriction.

Systolic function of the left ventricle (LV) is normal in individuals exposed to high altitude, irrespective of HAPE susceptibility. Data on diastolic function are not uniform (1, 8, 19), with some suggesting the presence of borderline diastolic dysfunction. Recently, a reduced vasodilatory capacity of the systemic vasculature has been found in HAPE-S individuals when exposed to hypoxia (6). However, whether there is also a reduced vasodilation in the myocardial microcirculation similar to that in the pulmonary and systemic vasculature is not known. Such a reduced vasodilator capacity could potentially lead to a diastolic dysfunction and have implications in the pathogenesis of HAPE. Furthermore, the effect of HAPE prevention on myocardial blood flow (MBF) is not known. Therefore, the aim of the present study was to investigate whether a reduced vasodilation is present in the coronary circulation and whether medical prophylaxis of HAPE might influence myocardial microcirculation. Therefore, we measured MBF reserve (MBFr) with myocardial contrast echocardiography (MCE) at high altitude in HAPE-S individuals participating in a placebo-controlled, double-blind study for HAPE prevention and in resistant controls.

METHODS

Study subjects and design. A total of 39 subjects were studied. Of these, 29 were mountaineers with a history of at least one episode of HAPE (termed HAPE-S; 4 women and 25 men), and 10 were control subjects (1 woman) without a history of HAPE. Two subjects developed acute mountain sickness (both HAPE-S on tadalafil), and another three subjects (all HAPE-S, two on placebo, one on tadalafil) developed HAPE before undergoing echocardiography at high altitude. In an additional 10 subjects (29%), the quality of the echocardiographic images was not sufficient for analysis of perfusion, based on the subjective assessment of the investigators analyzing the perfusion data.
The study population consisted of 24 subjects. The subjects not included in the study were heavier (78.1 ± 8.5 vs. 71.4 ± 10.7 kg, P = 0.05) and had a higher body mass index (25.9 ± 3.2 vs. 23.4 ± 3.0 kg/m², P = 0.02).

This study was performed as a nested project of a trial investigating the effect of the phosphodiesterase inhibitor tadalafil (Cialis, Lilly, 10 mg, 2 times/day) or dexamethasone (Fortecortin, Merck, 8 mg, 2 times/day) for HAPE prevention. Study medication was started on the day before ascent (20). Apart from medication intake, procedures in control subjects did not differ. None of the study subjects had any known cardiovascular risk factor. The study protocol was approved by the ethics committees of the involved institutions, and all participants gave written, informed consent.

Baseline measurements were performed in Zurich (490 m) 2–4 wk before the investigation at the high-altitude research laboratory at Capanna Regina Margherita, Italy (4,559 m). In Zurich, patients underwent clinical examination and, thereafter, bicycle exercise testing until exhaustion to assess the maximal exercise capacity. On the following day, Doppler echocardiography was performed at rest and during exercise, with the subject sitting on a bicycle ergometer in a semirecumbent position. During the exercise test, heart rate, arterial blood pressure (Task Force Monitor, CNSystems, Graz, Austria), and peripheral oxygen saturation were monitored. For echocardiographic image acquisition, the subjects were momentarily placed in a left lateral position. Stress echocardiographic data were recorded at a workload corresponding to 40% of the individual peak exercise capacity (in Watts).

The subjects ascended within 22 h from 1,130 to 4,559 m. First they ascended by cable car to an altitude of 3,200 m, from where they climbed −1.5 h to 3,600 m. After an overnight stay, they then climbed within an additional 4.5 h to 4,559-m altitude. Echocardiography was performed on the following day at rest and during bicycle ergometry at a workload corresponding to 70% of that at low altitude (i.e., 28% of individual peak exercise capacity in Watts at low altitude). Workload was reduced to compensate for the effects of high altitude based on previous experience (35).

HAPE was clinically suspected at the appearance of either dry cough, orthopnea, or pulmonary rales. A postero-anterior thorax radiograph was then taken using a mobile unit (TRS, Siemens, Stockholm, Sweden) with a fixed distance of 1.4 m at 95 kV and 3–6 mAs. Radiographs were scored retrospectively by a second radiologist blinded to other study results. HAPE was defined as previously reported (32).

Assessment of MBF. MBFr was assessed using MCE. The ultrasound contrast agent Sonovue (Bracco, Switzerland) was diluted 1:5 in 0.9% NaCl and infused intravenously. A constant infusion rate of 50–70 ml/h was maintained using a prototype mixing pump (Bracco, Switzerland). Contrast images were acquired on a Toshiba Aplio 80 (Toshiba, Japan) equipped with a 4-MHz transducer. The system was set to pulse inversion imaging mode at a mechanical index (MI) of 0.1 and 40-dB dynamic range. The compression level and postprocessing algorithms were adjusted for maximum linearity of the imaging. Images were acquired from the apical window. Infusion rate of the contrast agent was optimized as previously described (23, 34) to produce a dense, homogeneous LV cavity opacification, with shadowing limited only to the left atrial cavity. The focus of the ultrasound beam was set at the mitral valve level, and gain settings were optimized and held constant throughout the examination. Microbubbles in the myocardium were then destroyed by transmitting several high MI (of 1.4) frames followed by 10–15 s of continuous imaging at low MI to observe the contrast replenishment in the LV myocardium. Low- and high-altitude images at rest and during bicycle ergometer stress were each acquired in a single breath hold. Images were transferred to an offline computer for image processing using custom software (University of Virginia).

End-systolic frames were selected and aligned manually. The first end-systolic frame after microbubble destruction was then used as a background frame and subtracted from contrast frames. Video intensities were linearized on a pixel-by-pixel basis by applying an exponential function that was an inverse to the known logarithmic function used by the ultrasound system during the imaging. A region of interest was manually placed on the midventricular septum, and linearized data from the region of interest were averaged and fitted to the exponential function:

\[
y = A[1 - e^{-\beta t}]
\]

where A is proportional to the microvascular myocardial blood volume, \(\beta\) is proportional to the MBF velocity, and, hence, the product of \(A \times \beta\) is proportional to the microvascular MBF (33). The A value measured at the midventricular septum was then normalized by division by the video-intensity value measured in a region of similar size placed in the adjacent ventricular cavity to compensate for differences in microbubble concentration (36) and thus render A and \(A \times \beta\) values that could be compared among subjects. Data on day-to-day variability of this technique have recently been published (15).

MBFr was then calculated as MBF at stress divided by MBF at rest. Investigators analyzing the perfusion data (B. A. Kaufmann, A. Bernheim) were blinded to study drug intake, HAPE susceptibility, and the subject’s clinical outcome. For interobserver variability, the investigators were blinded to the results of the other investigator’s analysis.

Doppler echocardiography. By continuous wave Doppler, the peak flow velocity of the trans-tricuspid regurgitant jet was measured for assessment of pressure gradients across the tricuspid valve as an estimate of systolic PAP. LV diastolic function was assessed in the apical four-chamber view. The sample volume of pulsed wave Doppler was placed at the tips of the mitral valve leaflets. The obtained values were peak flow velocity (cm/s) and deceleration time (ms) of the early diastolic filling (E), peak flow velocity (cm/s) of the late diastolic filling (A), and isovolumetric relaxation time. Tissue Doppler imaging was used for measuring tissue velocities at the basal septum to obtain the mitral annular motion velocity (E’, cm/s) during early diastole.

Statistical analysis. Statistical analysis was performed with a commercially available program (SPSS version 13.0). Values are reported as means ± SD, unless otherwise stated. Between-group comparisons were done using the Mann-Whitney U-test or Kruskal-Wallis H-test, as appropriate; within-group comparisons were done using the Wilcoxon test. For comparison between groups from low to high altitude, changes were calculated and then compared using the appropriate nonparametric test. A P value of 0.05 was considered to be statistically significant.

RESULTS

Study population. The baseline characteristics of the 24 subjects included in the study are presented in Table 1. Among the 24 subjects, 9 were HAPE-S individuals on prophylactic treatment with dexamethasone or tadalafil, 6 were HAPE-S individuals on placebo, and 9 persons without HAPE susceptibility served as controls. Five of these subjects (21%) eventually developed HAPE; all of them were known HAPE-S individuals receiving placebo (5 of 6 HAPE-S on placebo-developed HAPE). None of the control subjects and none of those either on dexamethasone or tadalafil in this study developed HAPE.

Hemodynamic parameters. Hemodynamic parameters are summarized in Table 1. Heart rates at rest were not different between groups, both at low and high altitude, whereas control subjects attained a slightly higher heart rate during exercise at
low altitude, and at high altitude there was a trend toward a higher heart rate during exercise in HAPE-S on placebo. Control subjects had a slightly lower blood pressure at rest at low altitude, but there were no blood pressure differences between groups at high altitude. The rate pressure product (RPP) showed a difference only during exercise at high altitude, which was due to a lower RPP in subjects with prophylactic treatment, while there was no difference between HAPE-S on placebo and controls. Arterial O2 saturations were not different between groups at low altitude. At high altitude, O2 saturations were significantly lower in HAPE-S on placebo compared with the other groups at rest. However, there were no differences in O2 saturations at high altitude during exercise, nor in the relative change of the O2 saturation caused by exercise at high altitude. The hematocrit was not different between the groups at both low and high altitude. HAPE-S were older than control subjects. Therefore, all analyses were repeated after adjustment for age, which did not influence the results (data not shown).

**Echocardiographic parameters.** Echocardiographic parameters are summarized in Table 2. The increase in PAP was significantly larger in HAPE-S during low-intensity exercise at low altitude (P < 0.001). At high altitude, increase in PAP was significantly larger in untreated HAPE-S. Comparing subjects developing HAPE (n = 5) and those not developing HAPE (n = 19), the increase in PAP from low to high altitude was particularly evident (change in pressure gradient tricuspid regurgitation: 33 ± 9 vs. 15 ± 9 mmHg, P < 0.001).

All subjects had a normal LV ejection fraction at rest at low altitude. LV ejection fraction increased significantly with exercise in all groups at low and high altitude, and there were no significant differences between the groups. Values for septal and inferolateral wall thickness were normal and not different between groups at low and high altitude. All assessed parameters of diastolic function (E velocity, A velocity, E/A ratio, E/E’ ratio, deceleration time, isovolumic relaxation time) were normal at rest at low altitude and did not differ significantly between the groups, despite differences in age.

**MBFr.** Examples of destruction replenishment sequences and the corresponding curves at high altitude are shown in Fig. 1. A, B, and A-B values from which MBFr were derived are shown in Table 3. At low altitude, there were no significant differences between the groups regarding MBFr (P > 0.1, Fig. 2). At high altitude, MBFr increased significantly (P <

### Table 1. Physiological characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>HAPE-S Placebo (n = 6)</th>
<th>HAPE-S On Treatment (n = 9)</th>
<th>Control Subjects (n = 9)</th>
<th>Significance Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>490 m</td>
<td>4,559 m</td>
<td>490 m</td>
<td>4,559 m</td>
</tr>
<tr>
<td>Age, yr</td>
<td>39 ± 7</td>
<td>45 ± 10</td>
<td>32 ± 4</td>
<td></td>
</tr>
<tr>
<td>Heart rate at rest, beats/min</td>
<td>63 ± 10</td>
<td>86 ± 12</td>
<td>63 ± 12</td>
<td>72 ± 18</td>
</tr>
<tr>
<td>Heart rate exercise*, beats/min</td>
<td>123 ± 15</td>
<td>141 ± 13</td>
<td>121 ± 12</td>
<td>123 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure at rest, mmHg</td>
<td>121 ± 11</td>
<td>132 ± 18</td>
<td>127 ± 13</td>
<td>124 ± 13</td>
</tr>
<tr>
<td>Diastolic blood pressure at rest, mmHg</td>
<td>78 ± 7</td>
<td>80 ± 13</td>
<td>85 ± 10</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure exercise, mmHg</td>
<td>153 ± 16</td>
<td>158 ± 21</td>
<td>163 ± 29</td>
<td>147 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure exercise, mmHg</td>
<td>95 ± 14</td>
<td>100 ± 20</td>
<td>97 ± 10</td>
<td>86 ± 13</td>
</tr>
<tr>
<td>RPP at rest, mmHg × beats/min</td>
<td>8,000 ±1,700</td>
<td>11,500 ±2,500</td>
<td>8,200 ±2,300</td>
<td>9,300 ±2,600</td>
</tr>
<tr>
<td>RPP exercise, mmHg × beats/min</td>
<td>18,000 ±2,800</td>
<td>21,500 ±2,200</td>
<td>19,300 ±4,400</td>
<td>18,600 ±3,000</td>
</tr>
<tr>
<td>O2 saturation at rest, %</td>
<td>96 ± 2</td>
<td>66 ± 11</td>
<td>96 ± 3</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>O2 saturation exercise, %</td>
<td>95 ± 1</td>
<td>61 ± 11</td>
<td>96 ± 2</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Relative change in O2 saturation, %</td>
<td>43 ± 5</td>
<td>44 ± 15</td>
<td>42 ± 2</td>
<td>42 ± 2</td>
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<tr>
<td>Hematocrit, %</td>
<td></td>
<td></td>
<td>43 ± 5</td>
<td>44 ± 15</td>
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</tbody>
</table>

Values are means ± SD; n, no. of subjects. HAPE-S, high-altitude pulmonary edema-susceptible; RPP, rate pressure product; NS, not significant. *Response to high altitude different in HAPE-S on placebo vs. other groups: P < 0.05.
0.05) in control subjects and HAPE-S on treatment, whereas it remained unchanged in HAPE-S on placebo. The change in MBFr from low to high altitude significantly differed between HAPE-S on placebo and the other two groups ($P < 0.05$). The subjects ultimately developing HAPE showed no change in MBFr ($2.5 \pm 0.3$ to $2.0 \pm 0.3$, $P = 0.1$), whereas those not developing HAPE showed a highly significant increase ($2.1 \pm 0.8$ to $2.9 \pm 0.9$, $P = 0.001$). The response to high altitude significantly differed between the two groups ($P < 0.01$). No differences in the response to high altitude were observed between the two treatment groups and the control groups (controls $1.9 \pm 0.8$ to $2.8 \pm 1.0$; HAPE-S on tadalafil $2.0 \pm 0.2$ to $2.6 \pm 0.8$; and HAPE-S on dexamethasone $2.4 \pm 1.0$ to $3.1 \pm 1.1$).

Interobserver variability for determining MBFr was $21 \pm 16\%$. Importantly, the effects on MBFr in the different groups were observed by both investigators. In particular, results presented did not differ between the two investigators.

There was a significant negative correlation between the increase in PAP and the change in the MBFr from low to high altitude (Spearman $r = -0.48$, $P = 0.02$; Fig. 3). In particular, subjects developing HAPE showed a larger increase in PAP and a decrease in MBFr.

**Table 3.** $A$, $\beta$, and $A\cdot\beta$ values of the study population at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>HAPE-S Placebo ($n = 6$)</th>
<th>HAPE-S On Treatment ($n = 9$)</th>
<th>Control Subjects ($n = 9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>490 m 4.559 m</td>
<td>490 m 4.559 m</td>
<td>490 m 4.559 m</td>
</tr>
<tr>
<td>$A$ rest</td>
<td>$21 \pm 13$</td>
<td>$19 \pm 13$</td>
<td>$20 \pm 15$</td>
</tr>
<tr>
<td>$\beta$ rest</td>
<td>$0.30 \pm 0.06$</td>
<td>$0.30 \pm 0.11$</td>
<td>$0.30 \pm 0.15$</td>
</tr>
<tr>
<td>$A \cdot \beta$</td>
<td>$5.6 \pm 2.3$</td>
<td>$5.3 \pm 3.0$</td>
<td>$5.0 \pm 3.4$</td>
</tr>
<tr>
<td>$A$ exercise</td>
<td>$30 \pm 13$</td>
<td>$25 \pm 13$</td>
<td>$19 \pm 9$</td>
</tr>
<tr>
<td>$\beta$ exercise</td>
<td>$0.48 \pm 0.14$</td>
<td>$0.52 \pm 0.27$</td>
<td>$0.48 \pm 0.35$</td>
</tr>
<tr>
<td>$A \cdot \beta$</td>
<td>$13.9 \pm 5.5$</td>
<td>$12.0 \pm 9.2$</td>
<td>$8.7 \pm 5.3$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD; $n$, no. of subjects. $A$, myocardial blood volume; $\beta$, myocardial blood flow velocity; $A \cdot \beta$, myocardial blood flow.
Normalized $A \cdot \beta$ at rest at high altitude was not significantly different between groups ($8.0 \pm 8.1$ in HAPE-S on placebo, $5.3 \pm 3.1$ in HAPE-S on treatment, and $4.0 \pm 1.4$ in controls, $P = 0.4$).

Myocardial blood volume and flow velocity reserve. $A$ reserve and $\beta$ reserve did not differ significantly between the groups at low altitude. At high altitude, $A$ reserve did not change in any group compared with low altitude. Also, ultimate development of HAPE did not have an influence on $A$ reserve (Fig. 4). The $\beta$ reserve did not change ($\Delta$) from low to high altitude in control subjects and HAPE-S on treatment ($\Delta -0.4 \pm 1.2$). This was particularly evident in those ultimately developing HAPE, compared with those not developing HAPE, in whom $\beta$ reserve was lower (Fig. 4). The difference in $\beta$ reserve at high altitude between these two groups was of borderline statistical significance ($P = 0.053$).

**DISCUSSION**

The main finding of the present study is that HAPE-S individuals on placebo exhibit a reduced MBFr compared with either treated HAPE-S individuals or healthy controls at high altitude.

MBF during rest and exercise is regulated by mechanical and metabolic vasodilatory factors. Important mechanical factors are the pressure gradient and the resistance across the myocardial microvasculature. The resistance is determined by the anatomy of the coronary vasculature and by blood viscosity (4). There are a number of factors thought to be involved in local control of MBF, including adenosine, ATP-sensitive potassium channels, and NO (7, 11, 14). In addition, sympathetic nervous system activation during exercise has been shown to contribute to exercise vasodilation, independent of its effect on local vasodilators (30).

Myocardial edema caused by pulmonary hypertension has been implicated in LV dysfunction in experimental studies (12). In our study, the myocardial thickness was not different at low or high altitude and between groups, and thus there was no evidence of myocardial edema as a cause of reduced flow reserve. Also, while blood pressure at rest at low altitude was slightly lower in control subjects, there were no differences in blood pressure during exercise at low altitude and during rest and exercise at high altitude. Right atrial pressures were not measured in this trial. However, we did not find Doppler-echocardiographic evidence (e.g., reduced variability of vena cava inferior during the breathing cycle) for increased right atrial pressure (data not shown), which is compatible with previous invasive data (18). It seems, therefore, unlikely that a reduction in coronary driving pressure was responsible for the reduced MBFr in HAPE-S on placebo. Similarly, there were no significant differences in hematocrit between groups, arguing against differences in blood viscosity between groups as an explanation for the differences in MBFr (25).

An important consideration when comparing blood flow reserve between different subjects is the metabolic demand at rest and during exercise. The RPP as an indicator of cardiac metabolic demand was comparable between groups, both at rest and during exercise at low and high altitude. There was only a small difference during exercise at high altitude, owing to a lower RPP in HAPE-S on prophylactic treatment, whereas the response in HAPE-S and controls was similar. Of note, the RPP during exercise at high altitude were not significantly different from exercise values at low altitude, indicating that
reducing the exercise workload at high altitude to 28% of the maximally attained workload (in Watts) as opposed to the exercise level of 40% of maximum used at low altitude was indeed justified.

Oxygen saturation significantly differed between groups at rest at high altitude. Given the almost complete oxygen extraction in the myocardium, this could cause differences in resting blood flow between groups. However, when comparing normalized $A\beta$ at rest at high altitude, there were no statistically significant differences, albeit with a trend to higher values for HAPE-S on placebo. In addition, both oxygen saturation values during exercise and the relative changes from rest to exercise did not significantly differ between groups. Thus, while we cannot exclude some contribution of higher blood flow at rest in HAPE-S on placebo to the reduced MBFr in this group, our data indicate that this does not fully explain the differences we found in MBFr.

In our study, we used MCE to assess MBFr for two reasons. First, MCE is the only known technique capable of rendering data on MBFr in a bedside manner, and thus the only technique that can reasonably be applied at high altitude. Second, MCE has the unique property to yield data not only on MBFr, but also on its individual components, myocardial blood volume, and blood flow velocity. In the normal myocardial microcirculation, the increase in blood flow during exercise is governed mainly by a decrease in resistance in the resistance arterioles and the capillary bed (10, 17). Capillary resistance can only decrease through recruitment of previously nonperfused capillaries during exercise on response to increased cellular oxygen requirements. In MCE, changes in the number of functioning capillaries will translate into a change in the $A$ value representing myocardial blood volume. Conversely, the resistance arterioles rely on an intact endothelial and smooth muscle function to lower resistance. Decreasing the resistance in arterioles results in an increase in MBF velocity represented by the $\beta$ value in MCE. Our results indicate that the $A$ reserve is not reduced in HAPE-S individuals on placebo developing pulmonary edema. Therefore, capillary recruitment during exercise does not seem to be affected in these individuals. In contrast, reduced $\beta$ reserve was the main trigger for reduced MBFr in HAPE-S individuals on placebo, particularly those developing HAPE. Thus, the reduced MBFr appears to be caused by a lesser decrease in arteriolar resistance rather than a lack of capillary recruitment during exercise, suggesting a reduced vasodilatory capacity in the coronary microcirculation.

Several studies have suggested a reduced availability of NO as the underlying mechanism for the exaggerated pulmonary vasoconstriction in response to hypoxia in HAPE-S individuals (9, 13, 29). However, studies examining the physiological control of coronary blood flow during exercise performed in animals have failed to establish a clear role for NO in exercise-induced coronary vasodilation (31). In fact, the exact mechanism leading to an increase in blood flow in the myocardial circulation during exercise remains largely unknown. However, the mechanisms for microcirculatory blood flow regulation at high altitude may well differ from animal studies during normoxia used for the definition of the role of NO in coronary vasodilation. Additionally, in our study, HAPE-S treated with either dexamethasone or the phosphodiesterase-5 inhibitor tadalafil, agents known to influence either the production of NO in the pulmonary vasculature (dexamethasone), or to amplify the effect of NO by inhibiting the breakdown of cGMP (tadalafil) (22, 37), prevented the decrease in MBFr in the untreated HAPE-S. It is thus possible that, in the specific pathological situation of HAPE, a decreased availability of NO in the myocardium may limit MBFr, but further studies are needed to provide definitive evidence for this concept.

MBFr at high altitude has not been measured in normal individuals before, but there is one study using positron emission tomography to determine MBFr in normal subjects during hypoxia, corresponding to an altitude of 4,500 m for $<1$ h. In that study, similar to our results, an increase in MBFr was noted during hypoxia (35). The fact that this is not the case in HAPE-S individuals on placebo is in line with a recent study (6) showing reduced endothelial function in the systemic circulation in HAPE-S individuals by measuring forearm blood flow in response to acetylcholine during 4 h of hypoxia. The present study extends the findings of that study to a physiological setting, where the increase in blood flow is not produced by a pharmacological intervention, but by exercise at high altitude. Furthermore, we show that reduced vasodilator capacity may be present not just acutely, but also after exposure to high altitude for 24 h.

Diastolic LV function has been examined at high altitude in HAPE-S and HAPE-resistant subjects in two studies (1, 8). Some changes in diastolic function with an increase in atrial contraction were observed, leading to a new concept of compensated diastolic dysfunction. However, as previously reported, we found no correlation between changes in diastolic function and changes in PAPs from low to high altitude, implying that the two entities may be largely unrelated (8). In addition, we found no relationship between alterations in MBFr and LV diastolic function at rest. However, further studies should determine whether a hemodynamically relevant diastolic dysfunction may occur during exercise in a subset of mountaineers actually developing HAPE and a reduced MBFr.

**Limitations.** Some limitations have to be taken into consideration when interpreting this study. First, all HAPE-S study subjects were taking part in a trial testing whether the phosphodiesterase-5 inhibitor tadalafil, a selective pulmonary vasodilator, and dexamethasone prevent HAPE (20). Both drugs effectively reduced the incidence of HAPE, and thus a relatively small number of subjects eventually developing HAPE were included in this study. Nevertheless, we found a significant effect of altitude and subsequent development of HAPE on MBFr. Importantly, prevention of HAPE by these drugs also prevented reduction in MBFr, with no differences between the two drugs. Second, we cannot exclude an influence of the altered hemodynamics at high altitude on MBFr. However, the fact that an increase in MBFr at high altitude was seen in those not developing HAPE, despite an increase in PAP, argues against altered hemodynamics as the main reason for our findings. Third, the exercise workload at high altitude was reduced by 30% with respect to the workload at low altitude to account for an expected reduced maximal exercise capacity, which was based on previous findings. A separately conducted maximal exercise test showed that this assumption was adequate (maximal workload $258 \pm 60$ W at low altitude vs. $180 \pm 46$ W at high altitude). Finally, a considerable number of subjects were excluded from analysis due to insufficient image quality. The decision to exclude subjects from the analysis was taken by the two investigators blinded to all other
data, and thus the introduction of a bias in the study population seems unlikely. However, it should be noted that the excluded subjects were, on average, slightly heavier, with higher body mass index, than the subjects ultimately included in the study.

Conclusions. In conclusion, our data indicate that HAPE-S individuals on placebo show reduced exercise-induced MBFr compared with normal individuals when exposed to hypoxia at high altitude. This reduction may be prevented by treatment with either dexamethasone or sildenafil. Because HAPE susceptibility is relatively common in the general population, these findings might have implications, not only for subjects exposed to high altitude, but also in those with other causes of hypoxia.

REFERENCES


