A patent foramen ovale (PFO) is present in approximately 25% of the general population, but a higher prevalence has been reported in disease states known to be associated with pulmonary hypertension such as chronic obstructive pulmonary disease and sleep apnea syndrome. These observations could suggest that under conditions associated with elevated pulmonary vascular and right-sided cardiac pressures, some foramen ovale may reopen, implying a functional rather than an anatomical closing of these foramen. A reopened foramen ovale may contribute to systemic arterial oxygen desaturation from right-to-left intracardiac shunting under any condition that results in a higher right than left atrial pressure. Exaggerated pulmonary hypertension is a hallmark of high-altitude pulmonary edema (HAPE) and plays an important role in its pathogenesis. Moreover, altitude-induced hypoxia is more pronounced in HAPE-susceptible than HAPE-resistant individuals prior to onset of edema. The underlying mechanisms are incompletely understood. In a preliminary report, Levine et al demonstrated right-to-left intracardiac shunting across a PFO in a patient with HAPE and suggested that in persons with PFO a vicious cycle may be operational at high altitude wherein hypoxic pulmonary hypertension initiates right-to-left shunting, which in turn aggravates hypoxemia.

We hypothesized that the frequency of PFO is greater in HAPE-susceptible than in HAPE-resistant individuals and, if so, may contribute to more severe hypoxemia at high altitude. To test this hypothesis, we searched for PFO by transesophageal echocardiography (TEE), estimated pulmonary artery pressure by Doppler echocardiography, and arterial oxygen saturation measured by pulse oximetry in HAPE-susceptible and HAPE-resistant participants at low (550 m) and high altitude (4559 m).

The frequency of PFO was more than 4 times higher in HAPE-susceptible than in HAPE-resistant participants, both at low altitude (56% vs 11%, P = .004; odds ratio [OR], 10.9 [95% confidence interval (CI), 1.9-64.0]) and high altitude (69% vs 16%, P = .001; OR, 11.7 [95% CI, 2.3-59.5]). At high altitude, mean (SD) arterial oxygen saturation prior to the onset of pulmonary edema was significantly lower in HAPE-susceptible participants than in the control group (73% [10%] vs 83% [7%], P = .001). Moreover, in the HAPE-susceptible group, participants with a large PFO had more severe arterial hypoxemia (65% [6%] vs 77% [8%], P = .02) than those with smaller or no PFO.

Patent foramen ovale was roughly 4 times more frequent in HAPE-susceptible mountaineers than in participants resistant to this condition. At high altitude, HAPE-susceptible participants with a large PFO had more severe hypoxemia. We speculate that at high altitude, a large PFO may contribute to exaggerated arterial hypoxemia and facilitate HAPE.

Methods

Study Design and Participants

Thirty-five healthy mountaineers were included in the study. Sixteen participants...

Context

Individuals susceptible to high-altitude pulmonary edema (HAPE) are characterized by exaggerated pulmonary hypertension and arterial hypoxemia at high altitude, but the underlying mechanism is incompletely understood. Anecdotal evidence suggests that shunting across a patent foramen ovale (PFO) may exacerbate hypoxemia in HAPE.

Objective

We hypothesized that PFO is more frequent in HAPE-susceptible individuals and may contribute to more severe arterial hypoxemia at high altitude.

Design, Setting, and Participants

Case-control study of 16 HAPE-susceptible participants and 19 mountaineers resistant to this condition (repeated climbing to peaks above 4000 m and no symptoms of HAPE).

Main Outcome Measures

Presence of PFO determined by transesophageal echocardiography, estimated pulmonary artery pressure by Doppler echocardiography, and arterial oxygen saturation measured by pulse oximetry in HAPE-susceptible and HAPE-resistant participants at low (550 m) and high altitude (4559 m).

Results

The frequency of PFO was more than 4 times higher in HAPE-susceptible than in HAPE-resistant participants, both at low altitude (56% vs 11%, P = .004; odds ratio [OR], 10.9 [95% confidence interval (CI), 1.9-64.0]) and high altitude (69% vs 16%, P = .001; OR, 11.7 [95% CI, 2.3-59.5]). At high altitude, mean (SD) arterial oxygen saturation prior to the onset of pulmonary edema was significantly lower in HAPE-susceptible participants than in the control group (73% [10%] vs 83% [7%], P = .001). Moreover, in the HAPE-susceptible group, participants with a large PFO had more severe arterial hypoxemia (65% [6%] vs 77% [8%], P = .02) than those with smaller or no PFO.

Conclusions

Patent foramen ovale was roughly 4 times more frequent in HAPE-susceptible mountaineers than in participants resistant to this condition. At high altitude, HAPE-susceptible participants with a large PFO had more severe hypoxemia. We speculate that at high altitude, a large PFO may contribute to exaggerated arterial hypoxemia and facilitate HAPE.
(10 men and 6 women, mean [SD] age, 43 [12] years) had previously developed at least 1 episode of clinically and radio-
graphically documented HAPE (HAPE-susceptible [HAPE-S] group). The remain-
ing 19 participants (17 men, 2 women, mean [SD] age, 39 [12] years) were known to be resistant to HAPE (repeated alpine-
style climbing to peaks above 4000 m without symptoms of pulmonary edema;
HAPE-resistant [HAPE-R] group). The study was approved by the institutional
review board on human investigation of the University Hospital of Lausanne, and
all participants provided written informed consent.

Accompanied by a professional moun-
tain guide, the participants ascended in
groups of 2 to 4 from 1130 m to 4559 m
within 24 hours. The ascent consisted of
a transport by cable car to an altitude of
3200 m; a 1 1/2 hour climb to an altitude
of 3611 m, where the participants stayed
overnight; and on the next day, a 4- to
5-hour climb to the high-altitude re-
search laboratory at Capanna Regina
Margherita (4559 m). The participants
then spent 2 days and 2 nights at this hut. Transthoracic echocardiography (TTE)
in combination with contrast TEE was

Table 1. Participant Characteristics at High and Low Altitude*

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Abbreviations: AMS score, Lake Louise acute mountain sickness scoring system (range of possible scores 0-24, with higher scores indicating more severe disease); PFO, patent foramen ovale; Δ RV-RA, systolic right ventricular to right atrial pressure gradient; SaO2, arterial oxygen saturation; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography. Ellipses indicate gradient could not be measured because there was no tricuspid regurgitation.

*Time to echo is the time interval between arrival at 4559 m and echocardiography at high altitude. The echo time interval is the time interval between the echocardiographic studies at high and low altitude.
†Spontaneous right-to-left shunt.
performed during the first full day (TABLE 1) spent at the hut. None of the participants was receiving oxygen or taking any medications before the echocardiographic studies. Arterial oxygen saturation was assessed with a finger pulse oximeter. All measurements were repeated at low altitude (550 m) within 6 months after the high-altitude study.

At high altitude, posteroanterior chest radiographs were obtained for all participants, either at the time when symptoms of HAPE first occurred or before descent. The radiographs were analyzed according to previously described criteria by a radiologist who was unaware of the participants’ clinical history.

**Doppler Echocardiography**

Transthoracic echocardiography and TEE were performed with a real-time, phased array sector scanner (model Sonos 5000, Hewlett-Packard, Andover, Mass, and Siemens Acuson Sequoia C256, Mountain View, Calif) with an integrated color Doppler system and a transducer-containing crystal set for imaging (3.5 MHz, 7 MHz for the TEE omniplane probe) and for continuous-wave Doppler recording (1.9 MHz). The recordings were stored on videotape for offline analysis by 2 investigators who were unaware of the participants’ clinical history.

Transesophageal echocardiography in combination with injection of 2 mL of echo contrast medium (ad hoc sonicated mixture of 0.2 mL air plus 1.8 mL plasma expander [Physiogel, Pharmacy of the University Hospital, Inselspital, Bern, Switzerland]) into the right antecubital vein and the Valsalva maneuver were used for the search for PFO in at least 2 orthogonal image planes. The contrast bolus injection was given

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**Figure.** Detection of Patent Foramen Ovale Using Contrast Transesophageal Echocardiography (TEE)

A, Illustration of the position of the TEE transducer and plane of the long axis TEE view. B, TEE long axis view before injection of echo contrast. Arrowhead indicates region of the patent foramen ovale. C, Same view as in B during contrast injection. The right atrium is filled with contrast bubbles, and a small cloud of bubbles crosses the patent foramen ovale from the right atrium to the left atrium (arrowhead). (See video at http://jama.com/cgi/content/full/296/24/2954/DC1.)
at the start of the strain phase of the Val-
salva maneuver. The maneuver was con-
sidered successful when immediately af-
fter the release of the strain phase (lasting
5 to 10 seconds) a leftward deviation of
the interatrial septum in the fossa ovalis
region related to short right atrial pre-
load and pressure increase was ob-
served. The diagnosis of PFO required
the crossing of bubbles from the right
to the left atrium (FIGURE) within 4
heart beats following the release of the
strain (see video at http://jama.
.com/cgi/content/full/296/24/2954/
DC1).

The size of the PFO was graded semi-
quantitatively according to the maximum
number of bubbles crossing into the left
atrium, using a score of 0 to 3: score 1, less
than 6 bubbles; score 2, 6 to 20 bubbles;
score 3, more than 20 bubbles.13,14 At high
altitude, TEE could not be performed in
9 participants, so contrast TTE was per-
fomed instead (Table 1). At low altitude,
2 participants (Table 1) refused TEE. We
did not encounter any complication in per-
forming TEE.

Systolic pulmonary artery pressure
was determined by TTE.15 After tricus-
pid regurgitation had been localized with
Doppler color flow imaging, the peak
flow velocity of the tricuspid jet ($v_{TR}$)
was measured using continuous-wave
Doppler and the pressure gradient be-
tween the right ventricle and the right
atrium was calculated using the modi-
fied Bernoulli equation: $\Delta p_{RV-RA} = 4 (v_{TR})^2$
($\Delta p$, pressure difference; RV, right ven-
tricle; RA, right atrium).2 All reported val-
ues represent the mean of at least 3 mea-
surements.

Statistics
Statistical analysis using SAS version 8.2
(SAS Institute Inc, Cary, NC) was per-
formed with paired and unpaired $t$ tests
for the comparisons within and be-
tween the groups, and the $\chi^2$ and Fisher
exact tests for nonparametric variables
(presence or absence of a PFO and
HAPE). The McNemar test was used for
paired comparisons of nonparametric
variables (presence or absence of a PFO
at low vs high altitude). For compari-
sions between HAPE-S participants with
large PFOs and HAPE-S participants with
small or no PFOs, the Wilcoxon rank-
sum test was used. Relations between
variables were analyzed by calculating
Pearson product-moment correlation co-
efficients or analysis of variance fac-
torial analysis, as appropriate. Statistical
significance was defined at a $P$ value of
<.05. Data are expressed as mean (SD).

RESULTS
At low altitude, the systolic tricuspi-
cusp blood pressure gradient and the arte-
rial oxygen saturation were normal and
comparable in the 2 groups, whereas the
frequency of PFO was 5 times higher in
HAPE-S than in HAPE-R participants
(56% vs 11%, $P = .004$, TABLE 2).

At high altitude, as expected, the sys-
tolic tricuspid blood pressure gradient
was significantly higher in HAPE-S par-
ticipants than in HAPE-R participants
(11%); however, none of the 19 HAPE-R
participants ($P < .001$, Table 1, Table 2)
developed HAPE. Patent foramen ovale
was more than 4 times more frequent
(69% vs 16%, $P = .001$, Table 2), and the
arterial oxygen saturation was signifi-
cantly lower (Table 2) in HAPE-S than in
HAPE-R participants. All compari-
sons made with the $t$ tests remained sig-
ificant after Bonferroni correction.

At high altitude, in 4 of the 5 HAPE-S
participants with large PFOs (Table 1),
we observed spontaneous right-to-left
shunting across the foramen ovale. More-
over, the 5 HAPE-S participants with
large PFOs had more severe arterial hy-
poxemia (mean [SD] arterial oxygen
saturation, 65% [6%] vs 77% [8%],
$P = .02$) and a non–statistically signifi-
ciant higher frequency of HAPE (4/5 vs
4/11, $P = .11$) than those with no (n = 5)
grade 1 (n = 2) or 2 (n = 4) PFOs, even
though the systolic right ventricular to
to atrial pressure gradient (55 [9] vs 57 [13]
mm Hg, $P = .68$) was similar in the 2 sub-
groups.

For the entire study population, there
existed a significant inverse relation-
ship between arterial oxygen satura-
tion and PFO size ($P = .002$), as well as
oxygen saturation and the systolic right
ventricular to atrial pressure gradient
($r = -0.57, P < .001$). There was no sig-
nificant relationship between PFO size
and the pressure gradient ($P = .68$).

COMMENT
We found that at both low and high
altitude, PFO was 4 to 5 times more fre-

### Table 2. Frequency of Patent Foramen Ovale (PFO) and High-Altitude Pulmonary Edema (HAPE), and Tricuspid Pressure Gradient and Arterial Oxygen Saturation in HAPE-Susceptible and HAPE-Resistant Participants at Low and High Altitude

<table>
<thead>
<tr>
<th>Frequency of PFO, No. (%)</th>
<th>HAPE-Susceptible Participants (n = 16)</th>
<th>HAPE-Resistant Participants (n = 19)</th>
<th>$P$ Value (Odds Ratio [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 550 m</td>
<td>9/16 (56)</td>
<td>2/19 (11)</td>
<td>.004 (10.9 [1.9-64.0])*</td>
</tr>
<tr>
<td>At 4559 m</td>
<td>11/16 (69)</td>
<td>3/19 (16)</td>
<td>.001 (11.7 [2.3-59.5])*</td>
</tr>
<tr>
<td>$P$ value (550 vs 4559 m)†</td>
<td>.16</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Frequency of HAPE, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4559 m</td>
<td>8/16 (50)</td>
<td>0/19 (0)</td>
<td>.001*</td>
</tr>
<tr>
<td>RV-RA gradient, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 550 m</td>
<td>17 (9)</td>
<td>16 (10)</td>
<td>.84‡</td>
</tr>
<tr>
<td>At 4559 m</td>
<td>57 (12)</td>
<td>36 (10)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>$P$ value (550 vs 4559 m)§</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>SaO₂, mean (SD), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 550 m</td>
<td>98 (1)</td>
<td>99 (1)</td>
<td>.33‡</td>
</tr>
<tr>
<td>At 4559 m</td>
<td>73 (10)</td>
<td>83 (7)</td>
<td>.001†</td>
</tr>
<tr>
<td>$P$ value (550 vs 4559 m)§</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RV-RA gradient, systolic right ventricle to right atrial pressure gradient; SaO₂, arterial oxygen saturation.

*McNemar test.
†Unpaired $t$ test.
‡Paired $t$ test.
quent in HAPE-S participants than in mountaineers resistant to this condition. At high altitude, the greater frequency of PFO was associated with a lower arterial oxygen saturation and a higher systolic pulmonary artery pressure. Moreover, in the HAPE-S group, the size of the PFO was directly related with arterial hypoxemia, and there existed a non-statistically significant higher occurrence of actual HAPE in this subgroup.

The greater frequency of PFO in HAPE-S participants at low altitude was an unexpected finding and could suggest that, together with exaggerated hypoxic pulmonary hypertension and defective alveolar fluid clearance, PFO may represent an additional constitutioanl anomaly associated with HAPE susceptibility. Alternatively, in HAPE-S participants, previous episodes of exaggerated pulmonary hypertension during high-altitude exposure may have resulted in the persistent reopening of a previously closed foramen ovale. Consistent with this latter hypothesis, in other clinical conditions associated with pulmonary hypertension, a comparatively high prevalence of PFO has been reported.  

HAPE-susceptible individuals are characterized by exaggerated altitude-induced hypoxemia that has been attributed to relative hypoventilation, an augmented alveolo-arterial oxygen gradient, or intrapulmonary or intracardiac right-to-left shunting. With regard to the latter hypothesis, a small study had suggested that intracardiac shunting across a PFO may exacerbate hypoxemia in HAPE. The current observation at high altitude of spontaneous right-to-left shunting in some HAPE-S participants with large PFOs and more pronounced arterial hypoxemia than in those with small or no PFOs suggests that the size, rather than its mere presence, may be clinically relevant in this setting. Observations made in divers with decompression illness and patients with platypnea-orthodeoxia are in line with this hypothesis.

These observations could suggest that right-to-left shunting across a large PFO may play a role in the pathogenesis of HAPE. A report of a 36-year-old man who developed symptoms of HAPE each time he returned to high altitude could be consistent with this hypothesis. In this patient, cardiac catheterization revealed an atrial septal defect with left-to-right shunting at rest, but a marked increase in pulmonary artery pressure and inversion of the shunt during a hypoxic challenge. After surgical closure of the atrial septal defect and treatment with a calcium channel blocker, the patient remained free of symptoms on subsequent visits to the same altitude. It is important to note, however, that this report does not establish causality between right-to-left shunting and HAPE, and a great deal of additional work is needed before closure of PFO to prevent HAPE may be considered.

Author Contributions: Dr Alleman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Scherrer and Seiler contributed equally to this work.

Study concept and design: Alleman, Lipp, Duplain, Egli, Cook.

Analysis and interpretation of data: Alleman, Lipp, Duplain, Egli, Cook.

Statistical analysis: Alleman, Lipp, Duplain, Egli, Cook.

Obtained funding: Duplain, Egli, Cook.

Administrative, technical, or material support: Duplain, Cook.

Critical revision of the manuscript: Duplain, Egli, Cook.

Data collection: Duplain, Egli, Cook.

Financial Disclosures: None reported.

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REFERENCES


