Increased hepcidin levels in high-altitude pulmonary edema

Sandro Altamura,1 Peter Bärtsch,2 Christoph Dehnert,2 Marco Maggiorini,3 Günter Weiss,4 Igor Theurl,4 Martina U. Muckenthaler,1* and Heimo Mairbäurl2**

1Pediatric Oncology, Hematology & Immunology, University Hospital Heidelberg, Germany; 2Medical Clinic VII, Sports Medicine, University Hospital Heidelberg, Germany; 3Intensive Care Unit, Internal Medicine, University Hospital Zürich, Switzerland; and 4Department of Internal Medicine VI, Clinical Immunology and Infectious Diseases, Medical University of Innsbruck, Austria

Submitted 21 October 2014; accepted in final form 12 December 2014

Increased hepcidin levels in high-altitude pulmonary edema. J Appl Physiol 118: 292–298, 2015. First published December 18, 2014; doi:10.1152/japplphysiol.00940.2014.—Low iron availability enhances hypoxic pulmonary vasoconstriction (HPV). Considering that reduced serum iron is caused by increased erythropoiesis, insufficient reabsorption, or elevated hepcidin levels, one might speculate that exaggerated HPV in high-altitude pulmonary edema (HAPE) is related to low serum iron. To test this notion we measured serum iron and hepcidin in blood samples obtained in previously published studies at low altitude and during 2 days at 4,559 m (HA1, HA2) from controls, individuals with HAPE, and HAPE-susceptible individuals where prophylactic dexamethasone and tadalafil prevented HAPE. As reported, at 4,559 m pulmonary arterial pressure was increased in healthy volunteers but reached higher levels in HAPE. Serum iron levels were reduced in all groups at HA2. Hepcidin levels were reduced in all groups at HA1 and HA2 except in HAPE, where hepcidin was decreased at HA1 but unexpectedly high at HA2. Elevated hepcidin in HAPE correlated with increased IL-6 at HA2, suggesting that an inflammatory response related to HAPE contributes to increased hepcidin. Likewise, platelet-derived growth factor, a regulator of hepcidin, was increased at HA1 and HA2 in controls but not in HAPE, suggesting that hypoxia-controlled factors that regulate serum iron are inappropriately expressed in HAPE. In summary, we found that HAPE is associated with inappropriate expression of hepcidin without inducing expected changes in serum iron within 2 days at HA, likely due to too short time. Although hepcidin expression is uncoupled from serum iron availability and hypoxia in individuals developing HAPE, our findings indicate that serum iron is not related with exaggerated HPVs.

Iron; ferritin; hepcidin; erythropoiesis; pulmonary arterial hypertension; pulmonary edema

HYPOXIA STIMULATES ERYTHROPOIESIS to meet the demands of an increased oxygen transport capacity in hypoxia. The physiological hypoxic response is initiated by the stabilization of HIF-2α, a transcription factor that activates erythropoietin (EPO) synthesis in the kidney (8). EPO enhances erythrocyte production, a process requiring high amounts of iron. As a consequence, serum iron levels are decreased and iron absorption from the diet is increased in individuals at high altitude (HA) (7, 15).

Serum iron levels are regulated by the hepatic peptide hormone hepcidin that controls dietary iron uptake and iron release from intracellular stores (10). Hepcidin posttranslationally inhibits the expression of the iron exporter ferroportin to prevent iron release from duodenal enterocytes and macrophages that recycle iron from eliminated red blood cells. Hepcidin synthesis is increased by high serum iron and inflammatory cytokines and is decreased by hypoxia and erythropoietic activity (10, 18, 27). The decrease of hepcidin in hypoxia is mediated by the effects of hypoxia and erythropoietin on erythropoiesis and serves to increase iron availability for hemoglobin synthesis. Elevated levels of growth differentiation factor-15 (GDF-15) (28), twisted gastrulation (TWSG1) (29), and the platelet-derived growth factor (PDGF) (24) have been suggested as circulating factors decreasing hepcidin expression. Conversely, a decrease in serum iron subsequent to elevated hepcidin is caused by inflammatory cytokines such as IL-6 (10) and by increased bone morphogenetic protein signaling as in idiopathic pulmonary arterial hypertension, where it leads to iron deficiency (10, 19).

Reduced oxygen availability at HA causes pulmonary vasoconstriction and an increase in pulmonary arterial systolic pressure (sPAP) (11, 30). Interestingly, an increase in serum iron by infusion before exposure to hypoxia has been shown to blunt the increase in sPAP by hypoxia (23), indicating that iron-dependent processes play a role in hypoxic pulmonary vasoconstriction. A small percentage of otherwise healthy individuals experiences an exaggerated increase in sPAP upon ascent to HA or during exposure to normobaric hypoxia (for review, see Ref. 1) and an increased hydrostatic pressure in pulmonary capillaries (14). The high pressure causes leakage of water, plasma proteins, and even erythrocytes into the alveolar space (26), a state termed high-altitude pulmonary edema (HAPE). HAPE can be prevented by decreasing sPAP (2, 13).

Because low iron availability enhances the pulmonary vascular tone in hypoxia, we hypothesized that low serum iron in normoxia and at HA might contribute to the exaggerated hypoxic pulmonary arterial hypertension and HAPE. Low serum iron could be a consequence of increased hepcidin levels in HAPE.

To assess the relationship between iron status, hepcidin, and HAPE we analyzed blood samples obtained in recently published studies (5, 13) in the Capanna Regina Margherita (4,559 m). We show that upon ascent to HA, serum iron transiently increases, whereas we observe a drop after 48 h at HA. Hepcidin showed the expected decrease at HA in healthy controls and the HAPE-treatment groups. Interestingly, hepcidin values were increased significantly after 48 h at HA in HAPE. The increase in hepcidin in individuals with HAPE correlated with inappropriate expression of factors that control hepcidin levels. However, changes in serum iron at HA were...
uncoupled from hepcidin levels and did not correlate with sPAP and the occurrence of HAPE.

METHODS

Blood samples from two independent previously published studies on the pathophysiology and prevention of HAPE at the Capanna Regina Margherita (altitude 4,559 m) (5, 13) with similar design and ascent profile were analyzed. Baseline tests were performed in Zürich (490 m) or Heidelberg (110 m) several weeks before high-altitude exposure. Ascent started in Alagna Valsesia, Italy (1,100 m) by cable car to 3,200 m and continued by foot to the Capanna Gnfetti (3,600 m), where individuals spent one night. On the next morning, for 4 to 5 h, they continued to ascend by foot to the Capanna Regina Margherita (4,559 m) where they spent two nights without further physical activity.

Blood samples were collected by venipuncture in the pre-altitude test (low altitude, LA) and on the morning after the first (HA1) and after the second night (HA2) at 4,559 m, corresponding to ~18 and 42 h HA exposure, respectively. Blood samples were centrifuged, and plasma was frozen immediately in liquid nitrogen for transport and was stored at −80°C in Heidelberg until analyses.

Both studies included individuals with and without a history of HAPE (5, 13). In the study by Maggiorini and colleagues (13), subgroups of individuals with previous HAPE received prophylactic dexamethasone, tadalafil, or placebo in a randomized, placebo-controlled, double-blind manner. There was an additional control group of individuals not susceptible to HAPE (controls) that was not reported in the previous publication (13). Individuals participated after written informed consent, and studies were performed according to the Declaration of Helsinki and its current amendments and were approved by the Ethics Committees of the Medical Faculty of the Universities of Heidelberg (Heidelberg, Germany) and Zürich (Switzerland).

For the present new analyses, we chose as controls (n = 20) those individuals from both studies who did not have a history of HAPE in previous stays at HA and who did not experience HAPE in these studies. We compared them with HAPE-susceptible individuals, who typically have an exaggerated increase in sPAP in hypoxia and who also developed HAPE in the course of these studies (HAPE; n = 11). We further analyzed samples from 19 additional HAPE-susceptible individuals who received prophylactic dexamethasone (n = 10) or tadalafil (n = 9) and did not develop HAPE to test whether these treatments affect iron status and hepcidin levels.

sPAP was determined by Doppler echocardiography as described earlier (5, 13). Blood gases and oxygen saturation were determined from blood samples collected by puncture of the radial artery. New analyses include blood iron status (serum iron, transferrin saturation, ferritin), erythropoietin, IL-6, and C-reactive protein (CRP) measured in plasma or serum prepared from venous blood using routine assays in the central laboratory of the University Hospital Heidelberg, Germany. Hepcidin serum levels were measured using the Hecpidin-25 bioactive competitive ELISA (DRG International, Marburg, Germany) following the manufacturer’s instructions. Serum PDGF levels were measured with commercially available ELISAs according to manufacturer’s instructions (Quantikine PDGF-BB Immunoassay, R&D Systems, Minneapolis, MN). Because of the unavailability of samples, not all parameters could be measured in all individuals.

Results are presented as mean values ± SD. Changes within groups and differences between groups were evaluated by analysis of variance. Tests for least squares differences** were used for pairwise comparisons. Student’s t-tests were used for comparisons between controls and HAPE. Level of significance was P ≤ 0.05.

RESULTS

The newly analyzed samples were collected in two independent previously published studies (5, 13) investigating the pathophysiology of HAPE and included individuals without a history of HAPE (controls), individuals susceptible to HAPE who experienced HAPE during the studies (HAPE), as well as HAPE-susceptible individuals receiving prophylactic dexamethasone or tadalafil and who did not develop HAPE (5, 13). Table 1 summarizes the mean values of sPAP and of parameters of blood oxygen transport from both previously published studies (5, 13) combined. It shows that sPAP was increased at high altitude (HA1) in controls (P < 0.001) but significantly more in HAPE (P < 0.001) and was kept at control levels by treatment with dexamethasone and tadalafil. Arterial PO2 and arterial oxygen saturation [PaO2 and SaO2, respectively, values were reported in the previously published studies (5, 13)] were significantly lower at HA in HAPE compared with controls, confirming earlier findings (5, 13). Serum erythropoietin (EPO), newly analyzed for this study, was strongly elevated at HA1 and HA2 in all groups (each group: P < 0.001). Hemoglobin and hematocrit values (were measured when obtaining the samples, but values have not been reported) among the different groups were slightly elevated at HA.

Serum iron levels (Fig. 1A) and transferrin saturation (Fig. 2A) showed a mild increase at HA1 in controls (P = 0.004) but no statistically significant change in the other groups (P values: HAPE: 0.046; dexamethasone: 0.229; tadalafil: 0.094). At HA2 there was a statistically significant decrease in serum iron (Fig. 1A) and transferrin saturation (Fig. 1B) relative to HA1 in all groups (P values <0.009). Transferrin levels remained unchanged (Fig. 2B). Ferritin, a marker for tissue iron levels (Fig. 2C) decreased at HA in the dexamethasone group only; it did not change in HAPE. In the tadalafil group there were two individuals with a ferritin >250 μg/l causing large scattering. When omitting these two individuals from the calculation, ferritin values were similar to the control group (not shown). There was no correlation between serum iron levels and sPAP at HA (R = 0.06; P = 0.656; Fig. 3A).

Figure 1B reveals that serum hepcidin was significantly decreased at HA1 in all groups. Although hepcidin remained low at HA2 in controls and dexamethasone or tadalafil-treated individuals, it shows a surprising increase in individuals who develop HAPE (HA1 vs. HA2: P = 0.036). Unexpectedly, hepcidin levels were uncoupled from alterations in serum iron levels at HA indicated by a lack of correlation (R = 0.001; P = 0.996; Fig. 3B). This suggests that either a 2-day period was not sufficient to observe the drop in serum iron in response to increased hepcidin levels or that additional factors may contribute to the regulation of systemic iron homeostasis at HA. It is further of note that the dexamethasone-treated group showed the lowest hepcidin values of all groups at HA.

We next analyzed whether elevated levels of hepcidin in individuals with HAPE at HA2 can be explained by inappropriate expression of PDGF or IL-6, circulating factors known to control hepcidin levels. PDGF expression is increased under hypoxic conditions and downregulates hepcidin expression (24). As expected, PDGF levels in the serum were significantly increased at HA1 (P = 0.017) and HA2 (P = 0.002) in controls, whereas only a tendency was observed in the dexamethasone (P = 0.09) and tadalafil (P = 0.12) groups (Fig. 4A). Interestingly, there was no change in PDGF levels in individuals with HAPE (P = 0.60), suggesting that inappropriately low PDGF levels may contribute to high hepcidin expression in HAPE-susceptible individuals. The proinflammatory cytokine IL-6...
Iron, Hepcidin, and sPAP in HAPE • Altamura S et al.

Table 1. sPAP, PaO₂ and SaO₂, EPO, Hb, and Hct before and at HA1 and HA2 in HAPE-resistant (control), HAPE, and HAPE-susceptibles receiving prophylactic dexamethasone or tadalafil, measured in samples collected in studies by Dehnert et al. (5) and Maggiorini et al. (13)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HAPE</th>
<th>Dex.</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPAP, mmHg§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>21.4 ± 3.1</td>
<td>26.7 ± 3.4+</td>
<td>22.4 ± 4.4</td>
<td>25.3 ± 6.7</td>
</tr>
<tr>
<td>HA1</td>
<td>35.0 ± 6.5+</td>
<td>55.6 ± 9.8+</td>
<td>36.5 ± 8.7+</td>
<td>38.7 ± 4.7+</td>
</tr>
<tr>
<td>HA2</td>
<td>33.6 ± 6.5+</td>
<td>51.5 ± 15.7+†</td>
<td>42.1 ± 10.1+</td>
<td>37.3 ± 4.3+</td>
</tr>
<tr>
<td>PaO₂, mmHg§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>92.5 ± 9.1</td>
<td>93.2 ± 10.8</td>
<td>88.0 ± 10.3</td>
<td>83.3 ± 8.0</td>
</tr>
<tr>
<td>HA1</td>
<td>44.4 ± 3.4†</td>
<td>36.5 ± 4.2+</td>
<td>49.7 ± 7.3†</td>
<td>45.1 ± 10.0†</td>
</tr>
<tr>
<td>HA2</td>
<td>43.8 ± 4.4†</td>
<td>40.1 ± 2.3†</td>
<td>40.9 ± 2.5†</td>
<td>40.0 ± 2.0†</td>
</tr>
<tr>
<td>SaO₂, %§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>94.7 ± 9.4</td>
<td>96.1 ± 1.6</td>
<td>96.1 ± 1.9</td>
<td>95.8 ± 2.3</td>
</tr>
<tr>
<td>HA1</td>
<td>78.9 ± 4.4*</td>
<td>64.5 ± 9.5*</td>
<td>81.3 ± 6.3*</td>
<td>74.9 ± 9.3*</td>
</tr>
<tr>
<td>HA2</td>
<td>80.9 ± 3.9*</td>
<td>69.2 ± 6.0+</td>
<td>83.1 ± 6.0*</td>
<td>77.7 ± 3.8*</td>
</tr>
<tr>
<td>EPO, mU/ml</td>
<td>9.1 ± 2.4</td>
<td>6.4 ± 2.5</td>
<td>7.5 ± 3.3</td>
<td>11.0 ± 5.4</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>95.9 ± 55.4*</td>
<td>199.4 ± 144.6*</td>
<td>42.8 ± 23.1*‡</td>
<td>121.8 ± 39.9*</td>
</tr>
<tr>
<td>HA1</td>
<td>92.3 ± 94.9*</td>
<td>123.6 ± 21.6*</td>
<td>41.7 ± 36.2*</td>
<td>89.3 ± 27.6*</td>
</tr>
<tr>
<td>HA2</td>
<td>143.4 ± 9.1</td>
<td>137.6 ± 5.9</td>
<td>139.5 ± 7.1</td>
<td>142.9 ± 7.0</td>
</tr>
<tr>
<td>Hct, %</td>
<td>149.3 ± 10.4</td>
<td>137.0 ± 10.8†</td>
<td>137.6 ± 9.1†</td>
<td>138.9 ± 7.9†</td>
</tr>
<tr>
<td>HA1</td>
<td>149.8 ± 9.3*</td>
<td>144.2 ± 12.4</td>
<td>143.0 ± 11.8</td>
<td>139.4 ± 5.6</td>
</tr>
<tr>
<td>HA2</td>
<td>44.0 ± 2.1</td>
<td>42.5 ± 2.9</td>
<td>42.3 ± 2.0</td>
<td>43.3 ± 2.0</td>
</tr>
<tr>
<td>HA1</td>
<td>45.5 ± 2.5*</td>
<td>43.9 ± 3.8</td>
<td>43.1 ± 2.1*</td>
<td>43.1 ± 2.1</td>
</tr>
<tr>
<td>HA2</td>
<td>45.6 ± 2.1†</td>
<td>45.0 ± 3.7*</td>
<td>43.7 ± 3.5*</td>
<td>43.1 ± 1.5</td>
</tr>
</tbody>
</table>
| *Significantly different from prealtitude; †significantly different from controls; ‡significantly different from other groups (P < 0.05); §indicates that these values were reported in the previously published studies (5, 13).

Values are means ± SD. Hemoglobin (Hb) and hematocrit (Hct) were measured in the respective studies but had not been reported. Erythropoietin (EPO) was analyzed newly for this study from samples stored frozen. sPAP, systolic pulmonary arterial pressure; PaO₂, arterial oxygen partial pressure; SaO₂, oxygen saturation; pre, before, HA1 and HA2, 18 and 42 h after arrival at high altitude (4,559); HAPE, high-altitude pulmonary edema; Dex., dexamethasone.

The physiological range and the occurrence of HAPE by individuals developing HAPE during a 2-day stay at 4,559 m. Significantly different at low and HA between controls and individuals developing HAPE during a 2-day stay at 4,559 m. These findings indicate that changes in serum iron levels within the physiological range and the occurrence of HAPE by day 2 of altitude exposure are not correlated.

DISCUSSION

Pulmonary arterial vasoconstriction is a hallmark of exposure to high altitude and normobaric hypoxia (4, 11, 21). Because infusion of iron or iron chelators blunts or aggravates hypoxic pulmonary vasoconstriction (23), respectively, it is conceivable that the disproportionate increase in systolic pulmonary arterial pressure in HAPE may be related to iron deficiency. Here we show that serum iron levels are not significantly different at low and HA between controls and individuals developing HAPE during a 2-day stay at 4,559 m. These findings indicate that changes in serum iron levels within the physiological range and the occurrence of HAPE by day 2 of altitude exposure are not correlated.

Serum iron and its regulation at high altitude. Iron is an essential element, because iron-containing proteins are involved in oxygen transport, electron transfer reactions, gene regulation, and cellular growth (3). However, excess unbound iron is potentially toxic because of its involvement in the formation of oxygen radicals as described by the Fenton reaction (9). Iron demand is increased during hypoxia mainly because of stimulated erythropoiesis. Additionally, iron is a critical cofactor for prolyl-hydroxylases that plays an important role for oxygen sensing. Low iron levels inhibit hypoxia-inducible factors (HIF)-prolyl hydroxylases in the presence of oxygen, resulting in increased HIF stability and transcription of erythropoietin and other HIF-dependent genes (25).

Serum iron levels are regulated by hepcidin, and both hypoxia and low serum iron availability suppress hepcidin expression, which allows iron reabsorption and release from macrophages (10). In fact, a decrease in plasma hepcidin levels was reported upon exposure to high altitude (7, 18, 27), which occurs well before the decrease of serum iron and ferritin levels (27). Our results confirm these findings by showing that hepcidin levels decrease although serum iron is mildly elevated (controls) or unchanged at HA1 (other groups) (Fig. 1, A and B). This supports the notion that the initial decrease in hepcidin upon ascent to HA is a consequence of hypoxia and increased erythropoietic activity and occurred independent of serum iron levels. With a prolonged stay at HA, serum iron levels decreased, suggesting that this may contribute to diminished hepcidin levels in addition to hypoxia. Low hepcidin levels allow for increased duodenal iron absorption and iron release from intracellular stores in macrophages and hepatocytes (10), which provides iron for hypoxia-induced erythropoiesis. This is in line with decreased serum iron after repeated applications of erythropoietin administration in normoxia (20), indicating that the likely explanation for decreased serum iron at HA2 is that release and reabsorption cannot match the increased re-

J Appl Physiol • doi:10.1152/japplphysiol.00940.2014 • www.jappl.org
quirement of erythropoiesis (7). Our results are in line with several other studies showing a decrease in serum iron levels at high altitude (7, 15, 18, 23), where the magnitude and time course of change differs likely because of different speed of ascent and the level of high altitude. We and others found no significant change in serum ferritin levels (15, 18, 23), indicating that iron stores were not depleted during the 2-day stay at high altitude. Similarly, ferritin was not decreased acutely but 3 to 4 days after treatment with erythropoietin in normoxia (20). By contrast, in another study at 4,559 m, ferritin was decreased already at HA1 in controls (7). We have no explanation for this discrepancy because both studies used similar ascent profiles.

Serum iron and sPAP. Smith and colleagues (23) showed that infusion of 200 mg of iron before exposure to normobaric, isocapnic hypoxia dramatically reduced the increase in sPAP in hypoxia relative to saline infusion, whereas infusion of the iron chelator desferrioxamine aggravated hypoxic pulmonary vasoconstriction. Likewise, iron infusion while exposed to HA also blunted the hypoxia-induced increase in sPAP (23). Based on their findings, one might expect a continuous increase in sPAP during the stay at HA because of the decrease in serum iron with prolonged exposure. However, sPAP was increased already shortly after arrival at HA, when serum iron was still high, and remained at this level despite a pronounced decrease in serum iron levels at HA2. Figure 3 shows this lack of correlation between sPAP and serum iron. It also shows that, regardless of serum iron levels, sPAP at HA was higher in most of those subjects who later developed HAPE compared with controls, although their serum iron was not different. Together this indicates that neither the physiological increase in sPAP nor the exaggerated pressure response in HAPE are related to differences in serum iron and that changes in serum iron within the physiological range seem not to affect sPAP.

It has to be noted that the magnitude of changes in serum iron during a stay at HA are much smaller than those achieved by Smith and colleagues (23). In their study, iron infusion increased transferrin saturation (TFS) to 100%, suggesting that unbound serum iron accumulates (21, 23). Unfortunately, serum iron and TFS were not reported in the desferrioxamine
We found pre-altitude TFS values within the physiological range between 20 and 35% and decreased levels at HA2 in all groups. Changes in TFS parallel serum iron because transferrin remained unchanged (Fig. 2). This result further supports the notion that changes in serum iron availability within the physiological range do not affect physiological hypoxic pulmonary arterial vasoconstriction and the exaggerated pressure response in HAPE-susceptible individuals.

High hepcidin levels in individuals with HAPE. An interesting observation of this study is the marked difference in serum hepcidin levels at HA1 and HA2. Values are from controls and HAPE at HA1 and HA2.

Fig. 3. Lack of correlation between serum iron levels and systolic pulmonary arterial pressure (sPAP; A) and between hepcidin and serum iron levels (B) but significant correlation between IL-6 and hepcidin (C) at high altitude (r = 0.77). Values are from controls and HAPE at HA1 and HA2.

Hepcidin increased significantly above pre-altitude values at HA2 (Fig. 1). The mechanism is not entirely clear. Expression of hepcidin is strongly stimulated by inflammatory cytokines such as IL-6 (16), which is elevated in HAPE (12) (Fig. 3). Interestingly, the decrease in hepcidin in HAPE at HA1 occurred despite elevated IL-6 and CRP levels, suggesting that at this time point signals that trigger the hypoxic hepcidin response dominate over inflammatory cues. In contrast, increased hepcidin in HAPE at HA2 correlates with elevated IL-6.

Another important regulator of hepcidin is PDGF (24). Here we show for the first time that PDGF expression is increased in

Fig. 4. Effects of exposure to high altitude, HAPE, and HAPE-prophylaxis on serum levels of the platelet-derived growth factor (PDGF; A), IL-6 (B), and C-reactive protein (CRP; C). Mean values ± SD of HAPE-resistant individuals (controls; n = 20), HAPE-susceptible individuals who also developed HAPE (n = 11), and HAPE-susceptible individuals receiving prophylactic dexamethasone (n = 10) or tadalafil (n = 9). *Significant change at high altitude; P ≤ 0.05. CRP values were previously only reported in (13). All other parameters were newly analyzed for this study from samples stored frozen.
controls at HA1 and HA2 (Fig. 4). Interestingly, in individuals with HAPE, who fail to suppress hepcidin, PDGF levels remain unaltered at high altitude. This suggests that PDGF contributes to diminished hepcidin levels in controls, whereas signals inducing PDGF at HA are suppressed in HAPE.

We further analyzed samples from HAPE-susceptible individuals, who received dexamethasone or taladafil for prevention of HAPE (13). Interestingly, both drugs, despite supposedly intervening at different sites to prevent HAPE, also prevented the increase in hepcidin at HA2 in HAPE-susceptible individuals. These results indicate that the atypical changes in PDGF and hepcidin appear to be related to the occurrence of HAPE but are not intrinsic to HAPE-susceptible individuals. Whether high hepcidin levels in individuals with HAPE target ferroportin-expressing pulmonary cell types, such as alveolar macrophages (17) or airway (6) or alveolar epithelial cells, to contribute to the pathophysiological consequences of the disease requires further investigation.

In summary, our results indicate that there is neither a pre-existing iron deficiency nor an abnormal decrease in serum iron levels at high altitude in individuals with HAPE that might explain the exaggerated increase in sPAP. Nevertheless, the blunt hypoxic pulmonary arterial vasoconstriction after infusion of iron (22, 23) implies a potential benefit of iron supplementation to prevent hypoxic pulmonary hypertension and HAPE, which needs to be carefully evaluated based on the potential toxicity of iron-induced ROS formation. Iron supplementation will also increase the erythropoietic response at high altitude. This study further opens the possibilities that a better understanding of the abnormal changes in regulators of serum iron levels, i.e., increase in hepcidin and lack of increase in PDGF in response to hypoxia in HAPE, might also further our insight into the pathophysiology of HAPE and that hepcidin may serve as a marker for HAPE-related pathologies.

ACKNOWLEDGMENTS

We thank Christiane Herth and Sonja Engelhardt, Medical Clinic VII, Sports Medicine, University of Heidelberg, for excellent technical assistance.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


In summary, our results indicate that there is neither a pre-existing iron deficiency nor an abnormal decrease in serum iron levels at high altitude in individuals with HAPE that might explain the exaggerated increase in sPAP. Nevertheless, the blunt hypoxic pulmonary arterial vasoconstriction after infusion of iron (22, 23) implies a potential benefit of iron supplementation to prevent hypoxic pulmonary hypertension and HAPE, which needs to be carefully evaluated based on the potential toxicity of iron-induced ROS formation. Iron supplementation will also increase the erythropoietic response at high altitude. This study further opens the possibilities that a better understanding of the abnormal changes in regulators of serum iron levels, i.e., increase in hepcidin and lack of increase in PDGF in response to hypoxia in HAPE, might also further our insight into the pathophysiology of HAPE and that hepcidin may serve as a marker for HAPE-related pathologies.

REFERENCES


J Appl Physiol • doi:10.1152/japplphysiol.00940.2014 • www.jappl.org


