Mechanisms and Drug Therapy of Pulmonary Hypertension at High Altitude

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Abstract

Scherrer, Urs, Yves Allemann, Emrush Rexhaj, Stefano F. Rimoldi, and Claudio Sartori. Mechanisms and drug therapy of pulmonary hypertension at high altitude. High Alt Med Biol 14:126–133, 2013.—Pulmonary vasoconstriction represents a physiological adaptive mechanism to high altitude. If exaggerated, however, it is associated with important morbidity and mortality. Recent mechanistic studies using short-term acute high altitude exposure have provided insight into the importance of defective vascular endothelial and respiratory epithelial nitric oxide (NO) synthesis, increased endothelin-1 bioavailability, and overactivation of the sympathetic nervous system in causing exaggerated hypoxic pulmonary hypertension in humans. Based on these studies, drugs that increase NO bioavailability, attenuate endothelin-1 induced pulmonary vasoconstriction, or prevent exaggerated sympathetic activation have been shown to be useful for the treatment/prevention of exaggerated pulmonary hypertension during acute short-term high altitude exposure. The mechanisms underpinning chronic pulmonary hypertension in high altitude dwellers are less well understood, but recent evidence suggests that they differ in some aspects from those involved in short-term adaptation to high altitude. These differences have consequences for the choice of the treatment for chronic pulmonary hypertension at high altitude. Finally, recent data indicate that fetal programming of pulmonary vascular dysfunction in offspring of preeclampsia and children generated by assisted reproductive technologies represents a novel and frequent cause of pulmonary hypertension at high altitude. In animal models of fetal programming of hypoxic pulmonary hypertension, epigenetic mechanisms play a role, and targeting of these mechanisms with drugs lowers pulmonary artery pressure. If epigenetic mechanisms also are operational in the fetal programming of pulmonary vascular dysfunction in humans, such drugs may become novel tools for the treatment of hypoxic pulmonary hypertension.

Key Words: chronic mountain sickness, fetal growth, high altitude pulmonary edema, free radicals

Introduction

Pulmonary artery vasoconstriction is a hallmark of the adaptation to hypoxia. It occurs very rapidly after exposure to hypoxia and is intended to reduce blood flow through poorly ventilated alveoli. When self-limited, this vasoconstriction helps to match alveolar perfusion to ventilation. It thereby decreases the shunt effect and attenuates systemic hypoxemia. When sustained, however, hypoxic pulmonary vasoconstriction and vascular remodeling may have detrimental consequences, such as exaggerated pulmonary hypertension, right ventricular hypertrophy and right heart failure, diseases that are associated with a high morbidity and mortality (Leon-Velarde et al, 2010; Penaloza and Arias-Stella, 2007; Ward et al., 1989).

Over the past 2 decades, studies using acute, short-term exposure to high altitude have greatly advanced our knowledge of the underlying mechanisms regulating pulmonary artery pressure at high altitude. More recently, studies in high-altitude dwellers have provided additional mechanistic insight into this issue and, most interestingly, pointed to potential differences in the mechanisms regulating pulmonary artery pressure during acute and chronic high-altitude exposure. Finally, very recent studies designed to unravel factors

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predisposing to exaggerated hypoxic pulmonary hypertension have demonstrated that fetal programming of pulmonary vascular dysfunction represents an important novel risk factor (Jayet et al., 2010; Redhaj et al., 2011). Based on this new knowledge, novel therapeutic strategies for the treatment and/or prevention of high-altitude-induced pulmonary hypertension have been developed. We will briefly review these issues.

**Mechanisms Underlying Hypoxic Pulmonary Hypertension During Acute Short-Term Adaptation to High Altitude**

The ambient hypoxia associated with high-altitude exposure invariably increases pulmonary artery pressure in healthy normal subjects. There is, however, considerable inter-individual variability in this response (Allemann et al., 2012; Rimoldi et al., 2010) that is markedly exaggerated in subjects with pulmonary vascular dysfunction, as illustrated by persons who are susceptible to high altitude pulmonary edema (HAPE) (Scherrer et al., 2010). For example, whereas after rapid ascent to 4559 m, average systolic pulmonary artery pressure in healthy HAPE-resistant mountaineers is around 35 to 40 mm Hg, in HAPE-prone subjects it increases to values between 55 and 80 mm Hg (Maggiorini et al., 2001; Sartori et al., 1997). It is important to note here that this pulmonary vascular dysfunction is not detectable under normoxic conditions, because pulmonary artery pressure consistently was found to be similar in HAPE-prone and HAPE-resistant subjects at low altitude. Studies comparing HAPE-prone and HAPE-resistant subjects at high altitude have provided important mechanistic insight into the regulation of pulmonary artery pressure during acute short-term hypoxia (Scherrer et al., 1999; 2010). These studies have shown that, in humans, both defective vasodilator and exaggerated activation of vasoconstrictor mechanisms contribute to exaggerated pulmonary hypertension at high altitude.

**Pulmonary vascular endothelial and respiratory epithelial nitric oxide**

Pulmonary endothelial nitric oxide (NO) plays an important role in the regulation of pulmonary vascular responsiveness hypoxia in animals and humans. In mice lacking the gene for endothelial NO synthesis (eNOS -/-) the hypoxic pulmonary artery pressure response is markedly exaggerated (Champion et al., 2002; Duplain et al., 1999). In healthy humans, inhibition of NO synthesis by L-N G-monomethyl-L-arginine (NMMA) infusion potentiates the pulmonary hypertension evoked by hypoxia, whereas NO inhibition attenuates this response (Blitzer et al., 1996). Studies in HAPE-prone subjects have provided evidence for the importance of pulmonary vascular endothelial and pulmonary alveolar epithelial NO synthesis in the regulation of pulmonary vascular responsiveness during acute short term high-altitude exposure. The evidence is as follows: NO, when administered by inhalation, lowers pulmonary artery pressure to a much larger extent in HAPE-susceptible subjects than in control subjects who never experienced HAPE (Scherrer et al. 1996), suggesting that defective pulmonary endothelial NO synthesis is one of the mechanisms contributing to exaggerated hypoxic pulmonary hypertension in humans. Consistent with this concept, eNOS polymorphisms associated with impaired vascular NO synthesis are found in HAPE-prone persons (Ahsan et al., 2004; Droma et al., 2002), whereas eNOS polymorphisms associated with increased NO synthesis are found in populations characterized by attenuated hypoxic pulmonary hypertension at high altitude (Droma et al, 2006).

NO produced by the respiratory epithelium also regulates pulmonary artery pressure in humans, as evidenced by invasive measurements of pulmonary artery pressure in normal subjects showing lower pulmonary artery pressure during nasal than during oral respiration (Settergren et al., 1998). Respiratory epithelial (but not pulmonary endothelial) NO synthesis can be assessed by measuring NO in the exhaled air (Cook et al., 2003; Sartori et al., 1999). At low altitude, short-term-hypoxia decreases exhaled NO in HAPE-prone, but not in control subjects (Busch et al., 2001). Most importantly, at high altitude, exhaled NO is lower in HAPE-prone than in HAPE-resistant subjects, and there exists an inverse relationship between pulmonary artery pressure and exhaled NO (Duplain et al., 2000).

Taken together, these findings indicate that during acute short-term high altitude exposure both defective pulmonary endothelial and respiratory epithelial NO synthesis contribute to exaggerated hypoxic pulmonary hypertension in humans. In line with this concept, inhibiting degradation of cyclic GMP by administration of a phosphodiesterase-5 inhibitor prevents exaggerated hypoxic pulmonary hypertension (and lung edema) in HAPE-prone subjects during acute high-altitude exposure (Maggiorini et al., 2006; 2010).

In addition to defective vasodilator mechanisms, exaggerated activation of vasoconstrictor mechanisms also contributes to exaggerated hypoxic pulmonary hypertension in humans.

**Endothelin-1**

Endothelin-1 (ET-1), the most potent vasoconstrictor factor synthesized by the pulmonary endothelium, regulates pulmonary artery pressure during high-altitude exposure. In normal humans, ET-1 plasma concentration increases at high altitude and ET-1 inhibitor administration attenuates hypoxic pulmonary hypertension (Modesti et al., 2006). In HAPE-prone subjects, the altitude-induced increase of ET-1 plasma concentration is exaggerated and there exists a direct relationship between the altitude-induced changes of ET-1 and pulmonary artery pressure (Sartori et al., 1999). Taken together, these data indicate that increased ET-1 synthesis and/or its decreased clearance contribute to exaggerated hypoxic pulmonary hypertension during acute altitude exposure in humans. In line with this concept, Bosentan attenuates hypoxic pulmonary vasoconstriction during acute high-altitude exposure in humans (Modesti et al., 2006; Kojonazarov et al., 2012). Finally, it appears possible that defective NO synthesis may facilitate exaggerated ET-1 synthesis, since NO inhibits ET-1 gene expression and synthesis in endothelial cells in vitro (Kourembanas et al., 1991; Rossi et al., 2001).

**Sympathetic nervous system**

Cardiovascular adjustments to hypoxia are mediated, at least in part, by the sympathetic nervous system (Krasney, 1994). In dogs, sympathetic activation facilitates hypoxic pulmonary vasoconstriction and alveolar fluid flooding (Chen, 1995). Studies in HAPE-susceptible humans indicate that hypoxia-induced sympathetic over-activity contributes to exaggerated pulmonary hypertension at high altitude.
Hypoxia, and greater pulmonary hypertension (Benumof et al., 1981). It remains to be shown whether in HAPE-prone subjects with large PFOs, its closure will attenuate exaggerated hypoxic pulmonary hypertension and, in turn, the prevalence of HAPE. Finally, in healthy adults, the prevalence of PFO is 20%–25% (Kerut et al., 2001). There is no information so far whether in this population, a PFO predisposes to exaggerated hypoxic pulmonary hypertension.

Other mechanisms

In experimental animal models, activation of the GTP-binding protein RhoA and its downstream target ROCK plays a role in the pathogenesis of pulmonary hypertension, as evidenced by attenuation of pulmonary hypertension by inhibition of the Rho/ROCK pathway (Antoniu, 2012; Raja, 2012). In line with these observations, preliminary data in humans suggest that the Rock inhibitor Fasudil reduces pulmonary artery pressure in patients with severe idiopathic pulmonary arterial hypertension (PAH) and high-altitude dwellers suffering from hypoxic pulmonary hypertension (Kojonazarov et al., 2012).

Recent work suggests that iron, possibly by acting through the hypoxia-inducible factor, may regulate hypoxic pulmonary artery responsiveness in humans, as evidenced by attenuation of this response by iron administration in healthy sea level residents and by exacerbation of pulmonary hypertension by bloodletting in patients suffering from chronic mountain sickness (Smith et al., 2009).

Conclusion

Based on these observations, we suggest that during acute short-term high-altitude exposure defective NO synthesis represents a central event in the pathogenesis of exaggerated pulmonary hypertension resulting in impaired pulmonary vasodilation and exaggerated activation of pulmonary vasoconstrictor mechanisms.

Mechanisms Underlying Chronic Hypoxic Pulmonary Hypertension in High-Altitude Dwellers

While the above-mentioned studies have provided new insight into the mechanisms involved in the cardio-pulmonary adjustments to short-term hypoxia, during the past decade, important progress has also been made in the understanding of pulmonary artery pressure regulation during long-term hypoxia (Scherrer et al., 1999; 2010). In the following, we will briefly summarize this new knowledge.

Comparison of high altitude adaptation in healthy Aymaras and Caucasians

Respiratory NO was found to be increased in Aymara and Tibetan high-altitude dwellers, compared with an American low-altitude population, and was suggested to protect against high-altitude pulmonary hypertension (Beall et al., 2001; Hoit et al., 2005). In a recent study, we directly compared pulmonary artery pressure and respiratory NO in large groups of Aymara and Caucasian children. While, as expected, pulmonary artery pressure was lower in Aymaras than in Caucasians, this difference was not related to increased respiratory NO synthesis, since it tended to be lower in Aymaras than in Caucasians (Stuber et al., 2008). In healthy Europeans, altitude-induced sympathetic overactivity was shown to persist for several weeks at high altitude (Hansen et al., 1999). In line with this concept, the alpha adrenergic antagonist phentolamine was found to be significantly more effective than nonspecific vasodilators or oxygen in lowering pulmonary artery pressure during acute high-altitude exposure (Hackett et al., 1992). Recent findings demonstrating that in HAPE-prone subjects, dexamethasone attenuates hypoxic pulmonary hypertension (and prevents lung edema) during acute high-altitude exposure provide additional evidence for the role of the sympathetic nervous system in this setting (Maggiorini et al., 2006). In healthy humans, dexamethasone prevents the central neural sympathetic activation induced by alcohol (Randin et al., 1995) and insulin (Scherrer et al., 1993), suggesting that it may attenuate hypoxia-induced pulmonary hypertension in HAPE-prone subjects by preventing hypoxia-induced sympathetic activation.

Finally, studies in experimental animals and humans indicate that central neural NO buffers sympathetic outflow (Owlya et al., 1997; Sartori et al., 2005). This observation could be consistent with the hypothesis that defective NO synthesis could lead to exaggerated pulmonary hypertension by the combination of loss of NO-induced vasodilatation, and facilitation of ET-1- and sympathetically-mediated vasoconstriction.

Oxidative stress

In fetal lambs, ductus arteriosus ligation-induced pulmonary hypertension is associated with oxidative stress, and superoxide scavengers potentiate the vascular relaxation induced by exogenous NO in this model (Brennan et al., 2003). In rats, the antioxidant N-acetylcysteine attenuates hypoxia-induced stimulation of pulmonary phosphatidylcholine hydroperoxide synthesis, pulmonary hypertension, and right ventricular hypertrophy (Hoshikawa et al., 2001). Finally, in humans, acute short-term hypoxia stimulates oxidative stress (Joanny et al., 2001). Recent data suggest that increased oxidative stress also may contribute to reduced pulmonary NO synthesis and exaggerated pulmonary hypertension in HAPE-prone persons (Bailey et al., 2010).
and Sander, 2003). It is not known whether a similar phenomenon exists in populations born and permanently living at high altitude.

**Reentry HAPE (edema pulmonar de reentrada), a marker of sustained pulmonary hypertension in high altitude dwellers**

In the surroundings of La Paz, Bolivia (3600 m), millions of people have to deal permanently with lack of oxygen in the inspired air due to high altitude. Some of these high-altitude dwellers suffer from a very particular form of high-altitude pulmonary edema that occurs when they return from a sojourn at low altitude, the so-called “edema pulmonar de reentrada” or reentry HAPE. The underlying mechanism is not known. Since classical HAPE is characterized by exaggerated pulmonary hypertension (see above), we speculated that if a similar dysfunction of the pulmonary blood vessels exists in re-entry-HAPE-prone subjects, they will display sustained pulmonary hypertension at high altitude. This is exactly what we found. Re-entry-HAPE-prone subjects had markedly higher pulmonary artery pressure than control subjects who never experienced this problem (Thalmann et al., 2005). These important findings indicate that a history of reentry HAPE allows identification of high-altitude dwellers suffering from chronic pulmonary hypertension.

Observations in persons with Trisomy 21 are consistent with this concept. Circumstantial evidence suggests that children with Down syndrome are at risk for HAPE (Durmovicz, 2001) and re-entry HAPE (Scherrer 2006). We hypothesized that Down syndrome predisposes to pulmonary hypertension at high altitude. In line with this speculation, we found that pulmonary artery pressure in young Bolivian high-altitude natives with Down syndrome (without any associated cardiac malformation) was markedly higher than in control subjects. The underlying mechanism is not known yet. Interestingly, increased generation of hydrogen peroxide and hydroxyl radicals related to the extra gene for superoxide dismutase located on chromosome 21 leads to excessive oxidative stress (Carratelli et al., 2001) that contributes to the central neural and ocular manifestations of Trisomy 21 (Bras et al., 1989; de Haan et al., 2003; Iannello et al., 1999). Preliminary data suggest that it may also contribute to hypoxic pulmonary hypertension, since the antioxidant vitamin C decreased pulmonary artery pressure in children with Trisomy 21 living at high altitude, whereas it had no detectable effect in control children (Scherrer et al., 2010).

**Pulmonary hypertension in chronic mountain sickness**

Chronic mountain sickness (CMS) is a major public health problem in Andean high-altitude populations. It is characterized by exaggerated hypoxemia and erythrocytosis and often associated with pulmonary hypertension (Monge, 1942). While pulmonary hypertension in CMS is usually quite mild, it is a leading cause of morbidity and mortality in these patients (Leon-Velarde et al., 2010; Penaloa and Arias-Stella, 2007). Since increased pulmonary artery pressure at rest and hypoxia are well known to potentiate exercise-induced pulmonary hypertension, we speculated that light to moderate exercise commonly associated with daily activities causes exaggerated pulmonary hypertension in patients with CMS. In line with this hypothesis, mild bicycle exercise (50 W) induced a >3 times larger increase of pulmonary artery pressure in patients with CMS than in control subjects (Stuber et al., 2010). Thus, pulmonary artery pressure measurements at rest greatly underestimate pulmonary artery pressure during light exercise in patients with CMS (and probably also in high-altitude dwellers with other forms of pulmonary hypertension). This marked pulmonary hypertension during daily activity may explain why this problem is a major cause of morbidity and mortality in these patients. Parenthetically, this exaggerated exercise-induced pulmonary hypertension not only is expected to lead to right heart failure in the long term, but causes interstitial fluid accumulation, exaggerated hypoxemia and exercise intolerance already now (Pratali et al., 2012).

**Oxidative stress in healthy high-altitude dwellers and patients with CMS**

As discussed above, oxidative stress facilitates pulmonary vasoconstriction during short-term hypoxia. In a recent study, we demonstrated a persistent increase of oxidative stress in healthy Aymara high-altitude dwellers (Bailey et al., 2013). This increase was of similar magnitude as the one evoked by acute short-term hypoxia in healthy lowlanders. Surprisingly, however, this increased oxidative stress that, when evoked acutely by short-term hypoxia in lowlanders, induces vascular dysfunction, failed to exert any detectable effect on vascular function in healthy highlanders. In patients with CMS, oxidative/nitrosative stress is markedly exaggerated, since it is of similar magnitude as the one evoked by maximal exercise in lowlanders. Moreover, it was associated with decreased NO plasma concentration and systemic and pulmonary vascular dysfunction in patients with CMS. It remains to be seen whether administration of antioxidants has beneficial effects on vascular function and pulmonary hypertension in patients with CMS.

While the studies presented so far have provided important new insight into the short- and long-term adaptation of the pulmonary circulation to hypoxia in humans, recent studies capitalizing on the fact that high-altitude exposure facilitates the detection of pulmonary vascular dysfunction at an early stage have led to the detection of fetal programming as a major novel mechanism predisposing to hypoxic pulmonary hypertension in humans.

**Fetal Programming of Pulmonary Vascular Dysfunction, a Major Novel Mechanism Predisposing to Exaggerated Hypoxic Pulmonary Hypertension**

**Perinatal hypoxia**

There is abundant evidence from epidemiological studies that adverse events in utero predispose to premature cardiovascular and metabolic disease in adulthood (Barker, 1999). More recently, direct evidence has been provided that pathological events during early life predispose to hypoxic pulmonary hypertension in animals and humans. In normal rats, exposure to hypoxia during the first days of life predisposes to exaggerated hypoxic pulmonary hypertension later in life (Hakim and Mortola, 1990). In humans, pulmonary artery pressure at high altitude (4559 m) in young healthy adults who had suffered from transient hypoxic pulmonary hypertension during the first week of life was much higher than in healthy control subjects (Sartori et al., 1999). These data represented the first demonstration in humans that a pathologic...
insult to the pulmonary circulation early in life leaves a persistent imprint that predisposes to a pathologic response later in life.

**Preeclampsia**

Preeclampsia is the most frequent complication of pregnancy. In the mother suffering from this problem, circulating vasculotoxic factors produced by the diseased placenta induce vascular dysfunction and arterial hypertension. We speculated that some of these factors may cross the placental barrier and alter the regulation of vascular function in the fetus, predisposing to a pathological response later in life. To test this hypothesis, we measured pulmonary artery pressure (and assessed systemic vascular function) in offspring of mothers with preeclampsia born and permanently living at high altitude (3600 m). We found that pulmonary artery pressure was roughly 30 percent higher in offspring of mothers with preeclampsia compared with control subjects living at the same altitude (Jayet et al., 2010). Augmented oxidative stress may represent an underlying mechanism since thiobarbituric acid-reactive substances plasma concentration was increased in offspring of preeclampsia. The preeclampsia-induced pulmonary vascular dysfunction has clinical consequences already at a young age, as evidenced by pulmonary hypertension in roughly a third of these offspring of preeclampsia living at high altitude (Jayet et al., 2010). Since preeclampsia is complicating up to 8% of pregnancies (Steegers et al., 2010), these new findings suggest that an important part of pulmonary hypertension in high altitude dwellers may be related to this problem.

The exact underlying mechanism is not known yet, but data in offspring of restrictive diet pregnancy in mice, an experimental animal model mimicking preeclampsia in humans, suggest that epigenetic mechanisms play a role. In this model pulmonary DNA methylation was altered and associated with pulmonary endothelial dysfunction and exaggerated hypoxia-induced pulmonary hypertension and right ventricular hypertrophy (Rexhaj et al., 2011). Administration of histone deacetylase inhibitors to offspring of restrictive diet pregnancy normalized pulmonary DNA methylation and vascular function, demonstrating for the first time that fetal programming of pulmonary vascular dysfunction is related to an epigenetic mechanism (Rexhaj et al., 2011). It is tempting

### Table 1. Causes and Management of Pulmonary Hypertension During Short-Term High-Altitude Exposure

<table>
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<tr>
<th>Condition</th>
<th>Mechanism representing potential therapeutic target</th>
<th>Prevention</th>
<th>Treatment</th>
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<tbody>
<tr>
<td></td>
<td>Exaggerated sympathetic nerve activity [Duplain et al, 1999]</td>
<td>Dexamethasone</td>
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<td></td>
<td>Increased endothelin-1 bioavailability [Sartori et al, 1999]</td>
<td>[Maggiorini et al, 2006]</td>
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<td></td>
<td>PFO [Allemann et al, 2006]</td>
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<tr>
<td>Trisomy 21</td>
<td>Increased oxidative stress (related to gene dosage)</td>
<td></td>
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<tr>
<td>[Durmowicz, 2011]</td>
<td>Epigenetic</td>
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<td>ART [Scherrer et al, 2012]</td>
<td>Epigenetic</td>
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<tr>
<td>Perinatal hypoxia</td>
<td>Epigenetic ?</td>
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<tr>
<td>[Sartori et al, 1999]</td>
<td>Epigenetic</td>
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<tr>
<td>Preeclampsia ?</td>
<td>Epigenetic</td>
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### Table 2. Causes and Management of Pulmonary Hypertension in High-Altitude Dwellers

<table>
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<tr>
<th>Condition</th>
<th>Mechanism representing potential therapeutic target</th>
<th>Prevention</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>Exaggerated ET-1 synthesis ?</td>
<td>Bosentan [Kojonazorov et al; Pham et al, 2012]</td>
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<tr>
<td>Chronic mountain sickness</td>
<td>Increased oxidative stress (genetic) [Bailey et al, 2013]</td>
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<td></td>
<td>Exaggerated hypoxemia related to impaired hypoxic ventilatory response (genetic) [Monge, 1942]</td>
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<td>Reentry HAPE susceptibility</td>
<td>Sustained pulmonary hypertension [Thalmann et al., 2005] (epigenetic ?)</td>
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<td>Trisomy 21</td>
<td>Increased oxidative stress related to gene dosage [Scherrer et al, 2010]</td>
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<td>Preeclampsia</td>
<td>Increased oxidative stress (epigenetic) [Jay et al, 2010]</td>
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<td>ART ?</td>
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<td>Perinatal hypoxia ?</td>
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to speculate that similar mechanisms are operational in pre-eclampsia-induced vascular dysfunction in humans and that pharmacological targeting of these mechanisms offers novel possibilities to prevent/treat hypoxic pulmonary hypertension.

**Assisted reproductive technology**

Assisted reproductive technology (ART) has allowed millions of infertile couples to have children. ART involves the manipulation of embryos at early stages of their development when they may be particularly vulnerable to environmental influences that may induce epigenetic changes. We speculated that ART induces epigenetic changes resulting in altered cardiovascular function. In line with this speculation, we found that in addition to systemic vascular dysfunction, pulmonary artery pressure during acute high-altitude exposure was roughly 30% higher in ART than in control children (Scherrer et al., 2012). This vascular dysfunction appears to be related to the ART procedure per se, and data in ART mice suggest that epigenetic mechanisms play a role. We predict that a similar mechanism also is operational in humans and may become a target to prevent/treat hypoxic pulmonary hypertension in the ART population. The number of ART children is rapidly increasing worldwide and they now make up for 2%–4% of the births in developed countries. Given this evolution, ART represents a novel and increasingly important risk factor for exaggerated pulmonary hypertension at high altitude.

**Prevention and Treatment of Pulmonary Hypertension During Acute Short-Term High Altitude Exposure (Table 1)**

We will limit our discussion to the use of drugs in this situation (for other nonpharmacological interventions that are useful, we refer to recent reviews of this topic: Luks et al., 2010; Maggiorini, 2010).

For both the prevention and the treatment of exaggerated pulmonary hypertension during acute high altitude exposure, the calcium antagonist nifedipine remains a cheap, effective, and well-documented choice (Hackett et al., 1992; Oelz et al., 1992). More recent data suggest that increasing NO availability by administration of a phosphodiesterase-5 inhibitor may represent an equipotent alternative (Maggiorini et al., 2006). Besides the fact that this treatment is considerably more expensive, aggravation of acute mountain sickness may represent a problem (Maggiorini et al., 2010). While endothelin antagonists are effective for the treatment of pulmonary hypertension at low altitude and attenuate altitude-induced pulmonary hypertension in normal subjects (Faoro et al., 1992), more recent data suggest that increasing NO availability will have beneficial effects on pulmonary hypertension during acute high-altitude exposure. Patients with CMS also display pulmonary hypertension associated with increased oxidative stress (persons with Trisomy 21, re-entry prone subjects), antioxidant administration for a few weeks may lower pulmonary artery pressure. Patients with CMS also display pulmonary hypertension associated with increased oxidative stress (Pratali et al., 2012). It is not known yet whether antioxidants will have beneficial effects on pulmonary hypertension in this important group of patients. Preliminary results suggest that acetazolamide administration may lower vascular resistance, but not pulmonary artery pressure, in patients with CMS (Richalet et al., 2008).

Finally, recent data demonstrate that preeclampsia and ART represent novel important risk factors for pulmonary hypertension at high altitude. It is likely that this problem is related, at least in part, to epigenetic mechanisms. In experimental animals with fetal programming of hypoxic pulmonary hypertension, drugs interfering with epigenetic mechanisms have been shown to lower pulmonary artery pressure. Such drugs may also offer novel possibilities for the treatment of hypoxic pulmonary hypertension related to fetal programming in humans.

**Drug Therapy of Chronic Hypoxic Pulmonary Hypertension in High-Altitude Dwellers (Table 2)**

Only few studies have examined the effects of drug therapy of pulmonary hypertension at high altitude. Bosentan has been reported to decrease pulmonary artery pressure in high-altitude dwellers (Kojonazarov et al., 2012; Pham et al., 2012). Preliminary evidence suggests that in high-altitude dwellers who display pulmonary hypertension associated with increased oxidative stress (persons with Trisomy 21, re-entry prone subjects), antioxidant administration for a few weeks may lower pulmonary artery pressure. Patients with CMS also display pulmonary hypertension associated with increased oxidative stress (Pratali et al., 2012). It is not known yet whether antioxidants will have beneficial effects on pulmonary hypertension in this important group of patients. Preliminary results suggest that acetazolamide administration may lower vascular resistance, but not pulmonary artery pressure, in patients with CMS (Richalet et al., 2008).

Finally, recent data demonstrate that preeclampsia and ART represent novel important risk factors for pulmonary hypertension at high altitude. It is likely that this problem is related, at least in part, to epigenetic mechanisms. In experimental animals with fetal programming of hypoxic pulmonary hypertension, drugs interfering with epigenetic mechanisms have been shown to lower pulmonary artery pressure. Such drugs may also offer novel possibilities for the treatment of hypoxic pulmonary hypertension related to fetal programming in humans.

**Acknowledgments**

The authors’ research has been supported by the Swiss National Science Foundation, the Placide Nicod Foundation, the Novartis Foundation, the Eagle Foundation and the Lee- naards Foundation.

**Author Disclosure Statement**

No competing financial interests exist.

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Received January 9, 2013;
accepted in final form February 20, 2013