Sleep apnoea and pulmonary hypertension in high-altitude dwellers: more than an association?

Urs Scherrer[1,2,3] and Samuel Verges[4,5]

Affiliations: [1]Dept of Cardiology, University Hospital Bern, Bern, Switzerland. [2]Dept of Clinical Research, University of Bern, Bern, Switzerland. [3]Departamento de Biología, Facultad de Ciencias, Universidad de Tarapacá, Arica, Chile. [4]Laboratoire HP2, Université Grenoble Alpes, Grenoble, France. [5]Unité 1042, Institut National de la Santé et de la Recherche Médicale (INSERM), Grenoble, France.

Correspondence: Urs Scherrer, Dept of Cardiology, University Hospital Bern, CH-3010 Bern, Switzerland. E-mail: urs.scherrer2@insel.ch

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Increased pulmonary arterial pressure (PAP) is a hallmark of high-altitude exposure and, if exaggerated, may be associated with morbidity and mortality. High altitude also alters nocturnal breathing and altered nocturnal respiration has recently been reported to be associated with altered pulmonary and systemic vascular function in Andean high-altitude dwellers [1], suggesting the possibility of a causal link. Consistent with this hypothesis, in this issue of the *European Respiratory Journal*, Latshang *et al.* [2] report an association between pulmonary hypertension and sleep apnoea in Kyrgyz highlanders which remains significant even when adjusting for several potentially confounding factors. The authors are to be commended for their interesting study, performed in a remote area in a so far little investigated high-altitude population; however, this study also leaves open some intriguing questions.

In Andean high-altitude dwellers, alterations in nocturnal breathing and oxygenation were found to be associated not only with pulmonary vascular dysfunction, resulting in increased PAP, but also with premature vascular ageing and increased arterial blood pressure in the systemic circulation [1]. It would, therefore, have been interesting to perform 24-h ambulatory blood-pressure measurements in order to investigate whether sleep-disordered breathing alters nocturnal blood-pressure regulation in Kyrgyz high-altitude dwellers. Recent observations at low altitude show that obstructive sleep apnoea (OSA) is associated with increased nocturnal blood pressure and an altered dipping pattern [3]. In Andean high-altitude dwellers, pulmonary hypertension and cardiovascular alterations in the systemic circulation associated with sleep-disordered breathing were reported to be more pronounced in the presence of a patent foramen ovale (PFO) [1]. This finding is consistent with previous reports demonstrating that a PFO facilitates pulmonary hypertension in subjects prone to high-altitude pulmonary edema (HAPE) [4] and predisposes Andean high-altitude dwellers to exaggerated exercise-induced pulmonary vasoconstriction and right ventricular dysfunction [5].

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Searching for the presence of a PFO by transoesophageal echocardiography, which is possible under field conditions, could have been not only of mechanistic but also of therapeutic importance in this high-altitude population living under remote conditions, among which classical treatment of sleep-disordered breathing with continuous positive airway pressure (CPAP) therapy might not be possible for technical reasons. Indeed, in analogy to recent observations in patients with sleep apnoea syndrome at low altitude [3], it appears possible that PFO closure may attenuate pulmonary (and systemic) hypertension and improve sleep-disordered breathing in Kyrgyz high-altitude dwellers.

A randomised prospective study testing the effects of treating sleep-disordered breathing on PAP will also be the only way to establish the existence (if any) of a causal link between the two entities. Participants with high-altitude pulmonary hypertension (HAPH) are markedly older and more obese than those without these problems and statistical analysis cannot entirely exclude confounding effects due to these two variables that are well established determinants of PAP. Prospective studies would also allow the determination of whether various mechanisms, such as negative pleural pressure swings associated with OSA events [6], impaired vasodilation related to defective pulmonary nitric oxide synthesis [7, 8] and increased oxidative stress [9], exaggerated vasoconstriction triggered by sympathetic hyperactivity [10, 11], or endothelin-1 synthesis [12] induced by nocturnal intermittent hypoxaemia, underlie the relationship between sleep apnoea and HAPH.

Latshang *et al.* [2] report PAP estimations by echocardiography using three different methods and overall the data appear concordant. Interestingly, however, the right-ventricular to right-atrial pressure gradient estimations in healthy Kyrgyz participants are markedly lower (*i.e.* far below the 99% CI interval) than those reported in a recent meta-analysis [13] both at low altitude (14 mmHg *versus* 18.4 mmHg) and at high altitude (19 mmHg *versus* 25.5 mmHg). Does this mean that Kyrgyz are particularly well protected against HAPH? Probably not, since, in sharp contrast to this hypothesis, there appears to be an unexpectedly high prevalence of HAPH in (apparently healthy?) Kyrgyz high-altitude dwellers. Even though the way participants were recruited is not exactly clear, of the 127 highlanders agreeing to participate, roughly 30% (36 of 127) suffered from pulmonary hypertension, a prevalence that is orders of magnitude above the estimated prevalence (<1%) of this problem in other high-altitude populations reported in the meta-analysis by Soria *et al.* [13]. What is the explanation? Could there exist in this rural population an unexpectedly high prevalence of fetal/perinatal complications predisposing the offspring to HAPH [14, 15]? There is an urgent need for further studies of PAP in the Kyrgyz population to elucidate this contradiction. Estimations of PAP based on the right-ventricular to right-atrial pressure gradient have been most widely used in recent publications [13] and have been validated against invasive measurements [16]. To compare PAP in different high-altitude populations, it will be important to define a standard technique (and normal values) for its echocardiographic estimation in high altitude studies at a future expert consensus meeting.

Interestingly, daytime arterial oxygen saturation in participants with HAPH was also lower than in healthy controls but it was not associated with vascular dysfunction. Does this mean that daytime hypoxia does not play a role in causing pulmonary hypertension? Data in Andean high-altitude dwellers indicate that alterations of systemic vascular function become detectable when daytime arterial oxygen saturation at rest is <90% [17]. Moreover, it should be noted that in high-altitude dwellers, increased resting PAP predisposes to exaggerated pulmonary hypertension, pulmonary fluid accumulation and arterial hypoxaemia during the moderate levels of exercise expected to be commonly associated with daily activity [18]. Thus, measurements at rest may underestimate the prevailing daytime arterial oxygen desaturation and it appears possible that, in addition to nocturnal intermittent hypoxia related to sleep apnoea, daytime hypoxaemia may also contribute to pulmonary hypertension in Kyrgyz high-altitude dwellers.

Another surprising finding in Kyrgyz high-altitude dwellers with HAPH is the observation of an increased apnoea–hypopnea index mainly of obstructive rather than central origin. This is in contrast to the type of sleep disturbances generally encountered at high altitude, *i.e.* mostly Cheyne-stokes breathing and central sleep apnoea [19]. The obstructive origin renders it unlikely that the sleep disturbances in patients with HAPH are related to pulmonary hypertension, since this problem would be expected to promote central sleep apnoea [20]. Thus, other causes need to be considered. It is well known that increased body mass index (BMI) and ageing are factors which increase the prevalence of OSA at low altitude [6]. The observation that HAPH positive Kyrgyz high-altitude dwellers had a higher BMI and were older than their HAPH negative counterparts raises the question of the role of these factors in the association between pulmonary hypertension and sleep apnoea reported by Latshang *et al.* [2].

Is sleep-disordered breathing at high altitude always bad? The answer is probably no. While sleep disturbances in lowlanders arriving at high altitude were traditionally seen as a sign of poor acclimatisation, recent observations indicate that in lowlanders acutely exposed to high altitude, sleep-disordered breathing may protect against acute mountain sickness (AMS), as evidenced by more severe central apnoea/hypopnea in lowlanders resistant to AMS than in those who are susceptible to this problem [21]. Similarly, the role of

sleep-disordered breathing in the pathogenesis of chronic mountain sickness and the development of cardiovascular dysfunctions in highlanders needs to be further elucidated [22]. Last, but not least, the problem of treatment for pulmonary hypertension and sleep apnoea in these high altitude populations often living in remote areas needs to be addressed, considering both pharmacological interventions (*e.g.* phosphodiesterase inhibitors or acetazolamide) and non-pharmacological interventions (*e.g.* CPAP or added dead space).

Latshang *et al.* [2] are to be commended for their study, which provides important new observations regarding PAP and sleep-disordered breathing in Kyrgyz highlanders. Clearly more research is needed in this specific high-altitude population to better characterise the cardiopulmonary and respiratory phenotypes, their potential interactions, and their underpinning mechanisms. Most importantly, similar studies in other distinct high-altitude populations are needed (using standardised measurement techniques to be defined by an expert consensus meeting) with the aim of unravelling potential differences in these adaptations and interactions between specific populations. The insight gained by such studies will also be of potential interest for the understanding and treatment of patients living at sea level.

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