Pulmonary hypertension in high-altitude chronic hypoxia: response to nifedipine


ABSTRACT: Permanent residents at high altitude may develop excessive polycythaemia (H-Hb) and pulmonary hypertension, which often leads to cardiac failure. Inhibitors of calcium channels have been shown to reverse pulmonary hypertension in respiratory diseases and in primary pulmonary hypertension, but their efficiency has not been evaluated in high-altitude-induced pulmonary hypertension.

Systolic pulmonary arterial pressure (Ppa) was studied by Doppler echocardiography, at rest and after sublingual nifedipine, in 31 asymptomatic residents at 3,600 m. Individuals were separated into two groups according to resting Ppa: a group with low Ppa (dp4.7 kPa, n=17) and a group with high Ppa (dp4.7 kPa, n=14). Individuals were also split into two groups according to haemoglobin (Hb) concentration: a normocyaemic (L-Hb) group ([Hb] <180 g·L-1, n=17) and a H-Hb group ([Hb] >180 g·L-1, n=14).

No significant difference in Ppa was observed between the L-Hb and H-Hb groups. There was no correlation between [Hb] and Ppa in two-thirds of the subjects. This response was correlated with higher levels of Ppa in two-thirds of the subjects. This response was correlated with higher levels of Ppa (p<0.001) and was inversely correlated with age in the L-Hb group (p<0.05).

Pulmonary vasoreactivity to nifedipine was independent of the degree of H-Hb.

Pulmonary hypertension secondary to chronic altitude hypoxia may be reversible, despite a possible remodelling of the pulmonary arterioles.


The vasoconstrictive effect of hypoxia upon pulmonary artery vessels is well known in most mammalian species, including humans. A pure form of hypoxic pulmonary artery hypertension can be seen in high-altitude residents. A loss of adaptation to chronic hypoxia, known as chronic mountain sickness (CMS), is observed in 5–10% of people sojourning above 3,000 m and is characterized by excessive polycythaemia (H-Hb), pulmonary hypertension and nonspecific neurological symptoms [1]. Ongoing pulmonary vasoconstriction leads to increased vascular resistance and pulmonary artery pressure (Ppa), which are probable maladaptive responses to high altitude since they result in minimal improvement in ventilation–perfusion matching and increased workload for the right ventricle.

In addition to vasoconstriction, chronic alveolar hypoxia is associated with structural changes in the media of terminal portions of pulmonary arterioles [2], such as smooth muscle cell proliferation, thickening of the media, proliferation and turgescence of endothelial cells. Recently, this vascular remodelling has been found in only a few residents at high altitude [3], but it is admitted that sustained hypoxia is able to increase muscularization of the small pulmonary vessels and to increase even further the pulmonary vascular resistance.

A reduction in Ppa, under hypoxic conditions, has been obtained by the calcium channel-blocker nifedipine in healthy humans exposed to acute normobaric hypoxia [4] or in subjects suffering from high-altitude pulmonary oedema in hypobaric hypoxia [5]. In other aetiologies of pulmonary hypertension, such as primary pulmonary hypertension [6] or secondary to obstructive pulmonary disease [7, 8], nifedipine and felodipine were efficient in decreasing Ppa. Calcium antagonists have also been shown to be efficient in experimental hypoxic pulmonary vasoconstriction [9, 10].

Reversal of hypoxic pulmonary hypertension with calcium channel-blockers has not been evaluated in a population chronically exposed to high altitude. Venesection has been used to treat CMS, but no modification of pulmonary haemodynamics has been reported.

The objectives of this study were to assess pulmonary hypertension in native residents at high-altitude by echocardiography, to analyse the relationship between Ppa and H-Hb, and to study the effect of acute administration of nifedipine on pulmonary pressure. In the presence of reversible vascular changes in altitude-induced pulmonary hypertension, a nifedipine-induced vasodilatation could be anticipated.

Materials and methods

Subjects

Thirty males and one female, native residents of La Paz (3,500–4,100 m), Bolivia, were included in this non-randomized study. Asymptomatic subjects were recruited
in the police department, whereas H-Hb patients were followed for a family history of H-Hb at the Instituto Boliviano de Biología de Altura (IBBA) in La Paz. All subjects were volunteers and provided informed consent before inclusion. This study was approved by the Ethics Committee of the University Mayor de San Andrés and the IBBA. All subjects were workers or students, aged 17–55 yrs (34±11, mean±SD) and were of mixed Indian and Spanish origins. All patients underwent functional evaluation before inclusion: physical examination, chest radiography, electrocardiography, echocardiography, transcutaneous oximetry and determination of haemoglobin (Hb) concentration. The exclusion criteria were any history of lung, cardiac or renal disease, allergies or drug consumption.

Study design

Subjects were included in various groups according to the value of their [Hb] and \( P_{pa} \). The acute effect of oral nifedipine on pulmonary circulation was evaluated by Doppler echocardiography.

Method

The normal value of [Hb] at 3,600 m is 160±20 g·L\(^{-1}\) [11]. Subjects were included in the normocytic (L-Hb) group when [Hb] was 180 g·L\(^{-1}\), and in the H-Hb group when [Hb] was >180 g·L\(^{-1}\).

Systolic \( P_{pa} \) was assessed by continuous Doppler (3 MHz probe, Advanced Technology Laboratory, Bothell, WA, USA), using Bernoulli’s formula on tricuspid regurgitation in a four-chamber view [12] and right atrial pressure was estimated as 1.3 kPa. Normal \( P_{pa} \) at this altitude is 3.4±0.14 kPa [13]. Patients were included in a low \( P_{pa} \) group (L\( P_{pa} \)) when \( P_{pa} \) was >4.7 kPa, and in a high \( P_{pa} \) group (H\( P_{pa} \)) when \( P_{pa} \) was >4.7 kPa.

Right ventricle wall thickness, septal motion, left ventricle diameters and regional contractility were measured in \( t_m \) (time motion) mode in a longitudinal parasternal axis and in a four-chamber view. Cardiac output was calculated by an indirect method using left ventricular volumes [14]. Systemic arterial pressure was measured using a sphygmomanometer.

Clinical symptoms and signs usually described in CMS were examined, i.e. cutaneous erythema, cyanosis, dyspnoea, headache, chest pain, finger paresis, intellectual fatigue, dizziness, inappetence, myalgia and atypical arthralgias. The determination of clinical cyanosis was blinded with regard to Hb levels. A CMS score based on the above symptoms and signs assigns a value of 1 to negative answers, a value of 2 when symptoms are sometimes present and a value of 3 when they are frequently present [15]. The odds ratio for this score was 1.57, the specificity was 0.91 and the negative predictive value was 0.86. A score of 11 means that none of these complaints were present.

Drug administration and criteria of efficiency

All included subjects were scheduled to attend for a second visit for a nifedipine test. Monitoring with cardiac Doppler and a clinical survey were performed during the 2 h after nifedipine administration. After a 30-minute supine resting period, all patients received a first dose of 10 mg nifedipine sublingually. A second dose of 10 mg nifedipine was administered when no significant variation in \( P_{pa} \) or systemic blood pressure was observed 30 min after the first dose. In the H\( P_{pa} \) group, a third dose could be administered if \( P_{pa} \) was unchanged and if systemic blood pressure was still within normal limits. Patients were considered as responders when a reduction of 20% in \( P_{pa} \) was observed within 2 h after of administration [6].

Statistical analysis

Results are presented as mean±SD. Changes in absolute values of \( P_{pa} \) with treatment were compared using the Student’s paired t-test (two-tailed). The difference between groups was considered significant when \( p<0.05 \). Relationships between variables were tested by simple linear regression. One-way analysis of variance (ANOVA) was used for multiple comparisons.

Results

Comparisons of normocytic and polycythaemic groups

H-Hb subjects were older than L-Hb subjects (40±10 and 28±11 yrs, respectively; \( p<0.01 \)). There was a positive correlation between age and [Hb] (\( p=0.01 \)) and between [Hb] and cardiac output (\( p=0.001 \)). \( P_{pa} \) was not significantly different between the two groups (table 1). No relationship was found between [Hb] and \( P_{pa} \). Resting cardiac frequency and blood pressure were similar, whereas cardiac output was higher in the H-Hb group (\( p<0.05 \)). There was a positive correlation between right ventricular diameter and cardiac output (\( p=0.01 \)) and between right ventricular diameter and [Hb] (\( p<0.05 \)).

Comparisons of groups with low and high pulmonary pressure

Age was similar in both groups (33±11 and 34±11 yrs, respectively). There was no relation between age and baseline \( P_{pa} \). No relationship was found between either \( P_{pa} \) and

| Table 1. – Baseline cardiovascular findings in all subjects |
|----------------|----------|-----------|----------|----------|
|                | L-Hb     | H-Hb      | L\( P_{pa} \) | H\( P_{pa} \) |
| Subjects n     | 14       | 17        | 17        | 14        |
| [Hb] g·L\(^{-1}\) | 173±7    | 223±25*   | 198±25   | 203±40   |
| \( P_{pa} \) mmHg | 43±11    | 42±14     | 31±5     | 51±13*   |
| \( f_c \) beats-min\(^{-1}\) | 63±11    | 68±9      | 67±14    | 63±8     |
| S\( a_0 \) % | 93±2     | 94±2      | 94±2     | 93±2     |
| A\( QRS \) | 110±20   | 120±10    | 110±30   | 125±30   |
| RVD mm | 21±5     | 24±4*     | 23±4     | 23±6     |
| CO L-min\(^{-1}\) | 4.3±0.8  | 5.3±1.2*  | 4.5±0.7  | 4.9±1.1  |

Values are mean±SD (n=31). L-Hb: normocytic group; H-Hb: polycythaemic group; L\( P_{pa} \): low pulmonary artery pressure group; H\( P_{pa} \): high pulmonary artery pressure group; Hb: haemoglobin; \( P_{pa} \): systolic pulmonary artery pressure; \( f_c \): cardiac frequency; S\( a_0 \): systemic arterial blood pressure, respectively; A\( QRS \): QRS electrical axis; RVD: right ventricular diameter; CO: cardiac output. *: \( p<0.01 \) for L-Hb versus H-Hb; <: \( p<0.01 \) for L\( P_{pa} \) versus H\( P_{pa} \).
cardiac output or $P_{pa}$ and systemic blood pressure. Cardiac frequency was similar in both groups, as were the other parameters shown in table 1.

**Echocardiography**

The measurement of peak velocity of tricuspid regurgitation, used for calculating $P_{pa}$, was performed by two observers and the correlation between the two measures was $r=0.80$ and $s=10$ cm·s$^{-1}$. The right atrium was not enlarged on inspection in a four-chamber view and the largest diameter in any subject was <40 mm. No leftward displacement of the interventricular septum was observed. Left ventricular contractility and wall kinetics were normal in all subjects. No right-to-left shunting was evidenced with pulsed Doppler.

**Chronic mountain sickness symptoms**

A score of $14±2$ was found in the L-Hb group and $16±2$ in the H-Hb group (nonsignificant). The score was correlated with [Hb] ($p=0.02$) and was not correlated with age. The score did not differ between LP$_{pa}$ and HP$_{pa}$ groups: $15±3$ and $16±2$, respectively. No relationship was found between symptoms and any haemodynamic parameter. L-Hb subjects with normal P$_{pa}$ did not complain of exertional dyspnoea. Dyspnoea was present in eight out of 17 patients with H-Hb, mainly when [Hb] was >200 g·L$^{-1}$. Half of the patients with pulmonary hypertension described exertional dyspnoea, as did five out of the 17 subjects with LP$_{pa}$. Cyanosis of the lips was observed in 12 out of 17 H-Hb, and in eight out of 14 L-Hb subjects ($p<0.05$). Cyanosis was present in 10 out of 14 HP$_{pa}$ patients and in six out of 17 LP$_{pa}$ subjects. Headache was frequent in H-Hb patients (nine out of 17), and seldom present in L-Hb subjects (three out of 14). ($p<0.05$).

**Pharmacological response to nifedipine**

Most of the subjects (n=21) received 20 mg nifedipine. Low systemic blood pressure did not allow the dose to be increased in seven subjects. A third dose of nifedipine was given to three patients with $P_{pa}$ $55.3$ kPa. Nifedipine was mostly well tolerated, with transient headache and facial flush in five individuals, without sustained arterial hypotension. The systemic response to nifedipine was similar in L-Hb and H-Hb groups, with significant decreases in systolic and diastolic blood pressure ($p<0.001$) and significant increases in cardiac frequency ($p<0.001$) and cardiac output ($p<0.05$). Table 2 shows the cardiovascular changes in the 23 responders to nifedipine and in the eight nonresponders. $P_{pa}$ decreased in both the LP$_{pa}$ and HP$_{pa}$ groups ($p<0.05$). This reduction correlated with the basal values of $P_{pa}$ (fig. 1) but not with the variation in systolic or diastolic blood pressure, cardiac output or cardiac frequency. The reduction in $P_{pa}$ was inversely correlated with age in the L-Hb group (r=0.6, $p<0.05$). The nifedipine-induced increase in cardiac output and decrease in diastolic blood pressure were greater in the LP$_{pa}$ than the HP$_{pa}$ group ($p<0.05$).

The only female included (18 yrs old) showed mild H-Hb and mild pulmonary hypertension and responded to nifedipine.

**Nonresponders.**

$P_{pa}$ did not change in eight subjects, after 20 mg nifedipine in five of them and after 30 mg in the other three. Six of these subjects had normal $P_{pa}$ and the other two had a slightly higher $P_{pa}$. Three subjects were L-Hb and the other five were H-Hb. Nonresponders were older ($p<0.01$) and showed higher systolic and diastolic blood pressure ($p<0.01$). A greater reduction in systolic blood pressure after nifedipine was found in these subjects (table 2).

**Table 2. – Cardiocirculatory changes after nifedipine administration**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$\Delta P_{pa}$ mmHg</th>
<th>$\Delta P_{pa}$ %</th>
<th>$\Delta f_C$ beats·min$^{-1}$</th>
<th>$\Delta CO$ L·min$^{-1}$</th>
<th>$\Delta SBP$ mmHg</th>
<th>$\Delta DBP$ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP$_{pa}$ responders</td>
<td>11</td>
<td>-10±3</td>
<td>-31±5</td>
<td>+9±7</td>
<td>+1.0±1.1</td>
<td>-14±8</td>
</tr>
<tr>
<td>HP$_{pa}$ responders</td>
<td>12</td>
<td>-20±5**</td>
<td>-36±7</td>
<td>+11±7</td>
<td>+0.6±0.5</td>
<td>-13±8</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>8</td>
<td>-24±2**</td>
<td>-5±5**</td>
<td>+9±5</td>
<td>+0.4±0.3*</td>
<td>-23±9**</td>
</tr>
</tbody>
</table>

Values are means (n=31). $\Delta$: variation in each variable in response to nifedipine administration; $P_{pa}$: systolic pulmonary artery pressure; $f_C$: cardiac frequency; $CO$: cardiac output; $SBP$ and $DBP$: systolic and diastolic arterial blood pressure, respectively; LP$_{pa}$: low pulmonary artery pressure group; HP$_{pa}$: high pulmonary artery pressure group. *: $p<0.05$, **: $p<0.001$, for nonresponders versus responders; ±: $p<0.001$ for LP$_{pa}$ responders versus HP$_{pa}$ responders.
Discussion

Moderate to mild pulmonary hypertension was found in 14 out of 31 residents at high altitude in this nonrandomized study at 3,600 m. Unexpectedly, $P_{pa}$ did not increase with age. The lack of relationship between pulmonary by-pertension and H-Hb in this population is a new finding. Nifedipine was efficient in decreasing $P_{pa}$ by 34% in two thirds of the subjects. No symptom or sign usually described in CMS correlated with pulmonary hypertension.

The low $P_{pa}$ found in some individuals indicates a good adaptive mechanism to chronic hypoxia and minimal pulmonary vasoconstriction in healthy individuals, as observed in normal Tibetans at 3,658 m [16]. Various conditions were observed in this study: subjects with high levels of $P_{pa}$ without H-Hb, and patients with excessive H-Hb with no pulmonary hypertension. One explanation could be the inter-individual variability in pulmonary vasoreactivity, such as in normal subjects at sea level or in patients with chronic obstructive pulmonary disease.

The thresholds used for [Hb] and for $P_{pa}$ may have influenced the results. In young individuals, an [Hb] of 170–180 g L$^{-1}$ may be considered abnormal. Conversely, an iron deficit, which was not assessed here, could explain the relatively low [Hb] in some subjects. The threshold of 4.7 kPa for $P_{pa}$ was chosen according to previous invasive studies at the same altitude [13, 17] and according to local experience with cardiac Doppler in healthy subjects (unpublished data). However, individuals with 5.3 kPa $P_{pa}$ were not very different from those with 4.7 or 4.0 kPa, but were considered as hypertensive for this altitude. The right atrial pressure was calculated as at sea level (1.3 kPa) and this probably resulted in an underestimation of $P_{pa}$. The large age range may have influenced the results, but an analysis within smaller groups did not modify the results.

The reduction in $P_{pa}$ by nifedipine in this nonrandomized study provides an argument against a fixed component of pulmonary hypertension. This response was positively correlated with basal $P_{pa}$ and was independent of other haemodynamic parameters. Responsiveness inversely correlated with age in the L-Hb subjects. The successful re-versibility of pulmonary hypertension in some residents at high altitude brought to sea level is also consistent with the lack of irreversible intimal fibrosis [2]. A subgroup of H-Hb subjects with high cardiac output did not show ex-cessive pulmonary hypertension; this could be explained by their ability to decrease pulmonary vascular resistance in response to large increases in pulmonary blood flow [18]. The other subgroup of H-Hb subjects with pulmonary hypertension but low cardiac output may have elevated basal pulmonary vascular resistance, due either to anat-omical remodelling or to greater vasoconstriction. Nevertheless, these subjects responded to nifedipine, suggesting a true vasodilatation. This response was probably also secondary to a recruitment of pulmonary vessels.

Short-term correction of hypoxia by oxygen inhalation, in a similar population, showed no effects on $P_{pa}$ at rest, but decreased the exercise-induced increment [19], suggesting the presence of pulmonary vasoconstriction during exercise and, thus, a dynamic regulation of pulmonary vascular resistance. Moreover, the fall in pulmonary vascular resistance during unilateral pulmonary occlusion demonstrated the ability of pulmonary vessels to passively distend in chronic hypoxia [17].

A reduction in $P_{pa}$ could limit the evolution of fixed vascular changes, as verapamil and nifedipine have been shown experimentally to inhibit the pressor response to acute intermittent hypoxia in rats and reverse the right ventricular hypertrophy and the medial thickening of pulmonary arterioles [10]. The reactivity of pulmonary vessels at high altitude might depend on the intensity of the vascular remodelling [2, 3], but also on the endothelium-dependent pulmonary vasodilation, which has been found to be impaired in experimental chronic hypoxia [20]. Indirect evidence of endothelial dysfunction has also been shown in humans exposed to acute hypoxia [21, 22].

The evaluation of $P_{pa}$ in individuals residing at high altitude should be performed more systematically since the incidence of respiratory diseases in this population is elevated, and in particular, since symptoms are serious and appear late in the evolution of disease. Pulmonary vascular changes may be present regardless of [Hb], as shown in experimental chronic hypoxia [23, 24]. Iron deficit should also be assessed, particularly regarding pseudonormal [Hb]. Patients with high altitude pulmonary hypertension, with or without excessive H-Hb, could benefit from a therapy using vasodilators when descent to a lower altitude is unfeasible. Calcium channel-blockers could be beneficial in this condition, but their efficacy should first be demonstrated during longer periods and should not lead to a deterioration in the ventilation-perfusion relationships or impair the hypoxic regulation of the pulmonary circulation, as observed in chronic obstructive pulmonary disease [8].

In conclusion, mild pulmonary hypertension in high-altitude residents was not linked to the degree of polycythemia. Nifedipine was efficient in reducing pulmonary artery pressure and this effect was independent of the degree of polycythemia. Pulmonary hypertension induced by chronic high altitude hypoxia could be partially reversible despite vascular remodelling. The prognostic implications of using vasodilators in this form of pulmonary hypertension are unknown, but the evolution towards cardiac failure could be prevented.

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References


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