

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

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Pulmonary hypertension in high-altitude chronic hypoxia: response to nifedipine. A.M. Antezana, G. Antezana, O. Aparicio, I. Noriega, F.L. Velarde, J-P. Richalet. ©ERS Journals Ltd 1998.

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 (P_{pa}) 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 P_{pa} : a group with low P_{pa} (≤ 4.7 kPa, $n=17$) and a group with high P_{pa} (>4.7 kPa, $n=14$). Individuals were also split into two groups according to haemoglobin (Hb) concentration: a normocythaemic (L-Hb) group ($[Hb] \leq 180$ g·L⁻¹, $n=17$) and a H-Hb group ($[Hb] >180$ g·L⁻¹, $n=14$).

No significant difference in P_{pa} was observed between the L-Hb and H-Hb groups. There was no correlation between $[Hb]$ and P_{pa} . Nifedipine induced a decrease of $>20\%$ in P_{pa} in two-thirds of the subjects. This response was correlated with higher levels of basal P_{pa} ($p<0.001$) 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.

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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 (P_{pa}), 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 P_{pa} , 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 P_{pa} . 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 P_{pa} 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 females, native residents of La Paz (3,500–4,100 m), Bolivia, were included in this non-randomized study. Asymptomatic subjects were recruited

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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 \pm 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.

Methods

The normal value of [Hb] at 3,600 m is 160 ± 20 g·L⁻¹ [11]. Subjects were included in the normocythaemic (L-Hb) group when [Hb] was $\delta 180$ 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 tricuspidian regurgitation in a four-chamber view [12] and right atrial pressure was estimated as 1.3 kPa. Normal P_{pa} at this altitude is 4.3 ± 0.40 kPa [13]. Patients were included in a low P_{pa} group (LP_{pa}) when P_{pa} was $\delta 4.7$ kPa, and in a high P_{pa} group (HP_{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 erythaema, cyanosis, dyspnoea, headache, chest pain, finger paresthesia, 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 HP_{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 \pm 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 normocythaemic 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 basal P_{pa} . No relationship was found between either P_{pa} and

Table 1. – Baseline cardiovascular findings in all subjects

| | L-Hb | H-Hb | LP_{pa} | HP_{pa} |
|------------------------------|---------------|-----------------|---------------|---------------|
| Subjects n | 14 | 17 | 17 | 14 |
| [Hb] g·L ⁻¹ | 173 ± 7 | $223 \pm 25^*$ | 198 ± 25 | 203 ± 40 |
| P_{pa} mmHg | 43 ± 11 | 42 ± 14 | 31 ± 5 | $51 \pm 13^+$ |
| fc beats·min ⁻¹ | 63 ± 11 | 68 ± 9 | 67 ± 14 | 63 ± 8 |
| SBP mmHg | 111 ± 13 | 121 ± 9 | 111 ± 12 | 113 ± 13 |
| DBP mmHg | 79 ± 9 | 85 ± 7 | 82 ± 8 | 80 ± 9 |
| Sa_{aO_2} % | 93 ± 2 | 94 ± 2 | 94 ± 2 | 93 ± 2 |
| AQRS ° | 110 ± 20 | 120 ± 10 | 110 ± 30 | 125 ± 30 |
| RVD mm | 21 ± 5 | $24 \pm 4^*$ | 23 ± 4 | 23 ± 6 |
| CO L·min ⁻¹ | 4.3 ± 0.8 | $5.3 \pm 1.2^*$ | 4.5 ± 0.7 | 4.9 ± 1.1 |

Values are mean \pm SD (n=31). L-Hb: normocythaemic group; H-Hb: polycythaemic group; LP_{pa} : low pulmonary artery pressure group; HP_{pa} : high pulmonary artery pressure group; Hb: haemoglobin; P_{pa} : systolic pulmonary artery pressure; fc : cardiac frequency; SBP and DBP: systolic and diastolic arterial blood pressure, respectively; Sa_{aO_2} : arterial oxygen saturation; AQRS: QRS electrical axis; RVD: right ventricular diameter; CO: cardiac output. *: $p < 0.01$ for L-Hb versus H-Hb; +: $p < 0.01$ for LP_{pa} versus HP_{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 $SE=10 \text{ cm}\cdot\text{s}^{-1}$. The right atrium was not enlarged on inspection in a four-chamber view and the largest diameter in any subject was $<40 \text{ mm}$. 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 $>200 \text{ g}\cdot\text{L}^{-1}$. 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} $\dot{S}5.3 \text{ kPa}$. 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

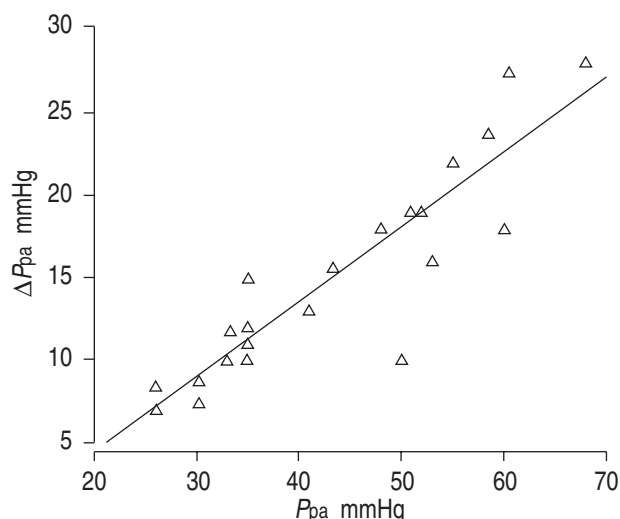


Fig. 1. – Significant correlation between basal systolic pulmonary artery pressure (P_{pa}) and the variation in P_{pa} induced by nifedipine treatment ($\dot{y}P_{pa}$), in absolute values ($y=0.452x - 4.691$, $r^2=0.827$, $p=0.0001$).

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

| | Subjects n | $\dot{y}P_{pa}$ mmHg | $\dot{y}P_{pa}$ % | $\dot{y}fc$ beats \cdot min $^{-1}$ | $\dot{y}CO$ L \cdot min $^{-1}$ | $\dot{y}SBP$ mmHg | $\dot{y}DBP$ mmHg |
|----------------------|---------------|-------------------------|----------------------|------------------------------------------|--------------------------------------|----------------------|----------------------|
| LP_{pa} responders | 11 | -10 ± 3 | -31 ± 5 | $+9\pm 7$ | $+1.0\pm 1.1$ | -14 ± 8 | -14 ± 8 |
| HP_{pa} responders | 12 | $-20\pm 5^{++}$ | -36 ± 7 | $+11\pm 7$ | $+0.6\pm 0.5^{++}$ | -13 ± 8 | $-9\pm 7^{++}$ |
| Nonresponders | 8 | $-2\pm 2^{**}$ | $-5\pm 5^{**}$ | $+9\pm 5$ | $+0.4\pm 0.3^*$ | $-23\pm 9^{**}$ | -9 ± 8 |

Values are mean \pm SD ($n=31$). \dot{y} : variation in each variable in response to nifedipine administration; P_{pa} : systolic pulmonary artery pressure; fc : 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 hypertension 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 excessive 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 anatomical 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 de-

monstrated 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 polycythaemia. Nifedipine was efficient in reducing pulmonary artery pressure and this effect was independent of the degree of polycythaemia. 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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