The effect of amlodipine on respiratory and pulmonary vascular responses to hypoxia in mountaineers

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ABSTRACT: Calcium antagonists are known to reduce the incidence of high-altitude pulmonary oedema, but the mechanism is unclear. The aim of this study was to examine the effects of the calcium antagonist, amlodipine, on cardiac and respiratory responses in normoxia and hypoxia. Fourteen normal subjects aged 31±4 yrs who had climbed to altitudes of 5,000–7,500 m without problems were randomly assigned to a double-blind crossover trial of amlodipine versus placebo, using sea-level inspiratory hypoxia to simulate altitude. Doppler echocardiographic estimates of resting pulmonary haemodynamics and cycle ergometer test results of cardiorespiratory responses to exercise were recorded in normoxia and hypoxia.

It was found that, although hypoxic pulmonary vasoconstriction (HPV) was not significantly reduced by amlodipine, the effect of the drug on HPV was inversely related to the serum level of amlodipine. Amlodipine did not alter left ventricular function measured echocardiographically. During exercise, amlodipine increased breathlessness, measured using standard scales, in both normoxia and hypoxia but had no effect on ventilatory variables.

It was concluded that amlodipine has the potential to block hypoxic pulmonary vasoconstriction as evidenced by a drug concentration-related decrease in resting tricuspid regurgitation jet velocity without any change in resting myocardial contractility. However, with amlodipine, the subjects felt more breathless during exercise. The reasons for this increase in breathlessness are not clear.


Keywords: Calcium antagonists

echocardiography

exercise test

hypoxia

pulmonary vasoconstriction

High altitude pulmonary oedema (HAPO) is a potentially fatal altitude illness that may occur in healthy subjects at altitudes as low as 2,700 m. It is difficult to give a precise figure for the incidence of HAPO but Hackett and Rennie [1] showed that 2.5% of trekkers passing through Phereche (4,243 m) in the Khumbu region of Nepal suffered from HAPO. The cause of HAPO is not known [2], but it has been shown to be associated with excessive hypoxic pulmonary vasoconstriction (HPV) [3]. It has also been suggested that a decreased hypoxic ventilatory response (HVR) may, in part, be responsible. Studies of HVR at rest have produced conflicting results [4, 5]. In view of this uncertainty, some authors have chosen to examine HVR on exercise, taking the view that any abnormality would be amplified by making subjects exercise under hypoxic conditions. Once again, the results have been controversial. Hohenhaus et al. [6] suggested that subjects with a history of HAPO cannot be distinguished from those with a history of acute mountain sickness. Rathat et al. [7] maintain that comparison of the concomitant changes in ventilation, cardiac frequency and arterial oxygen saturation (SaO2) while subjects undergo exercise testing under hypoxic conditions distinguishes subjects at risk of severe mountain sickness from those resistant to the effects of altitude, but they have not studied subjects with HAPO. It is known that calcium antagonists, especially nifedipine, can be used to both treat and prevent HAPO. In a field study, Bartsch et al. [8] showed that, when subjects with a history of proven HAPO were subjected to altitude exposure, those on nifedipine did better than those on placebo. With these results in mind and the continuing controversy about the relevance of the cardiopulmonary responses to hypoxia to susceptibility to HAPO, it was decided to study the effects of a calcium antagonist on HPV and HVR under conditions of experimental hypoxia. It was reasoned that if HPV and HVR were important in the genesis of HAPO then calcium antagonists (which are known to be successful both in the prophylaxis and treatment of HAPO) should alter one or more of these variables. Amlodipine was chosen for study because it is known to have little negative inotropic activity at rest [9, 10] and hence may be advantageous to those in whom cardiac exercise performance is important, e.g. mountain climbers.

The aim of this study was to examine the effects of amlodipine on cardiac and respiratory responses in both normoxia and hypoxia, using Doppler echocardiographic estimates of pulmonary haemodynamics at rest, and measurements of cardiopulmonary function during submaximal exercise while simultaneously measuring breathlessness using standard scores.
Methods

Subjects

Fourteen healthy male mountain climbers (aged 31±4 yrs) who were regular exercisers gave informed consent to participate in this study approved by the local ethics committee. Females were excluded because of possible teratogenic risks. The subjects completed a medical questionnaire and underwent examination, and routine blood tests before being considered fit to enter the study. Subjects were excluded if: 1) there was any evidence of cardiac, pulmonary, renal or liver disease; 2) they were taking any drug that could interact with amlodipine; and 3) they had recently been at high altitude.

Study design

This was a double-blind randomized cross-over study in which the subjects took amlodipine 10 mg-day⁻¹ (the maximum recommended dose) or identical placebo for 3 weeks and then took the alternate preparation for a further 3 weeks. These 3-week periods were essential because amlodipine is taken up widely by body tissues and has a very long half-life; thus plasma levels take ≥1 week to stabilize and elimination requires a similar period.

The schedule used was as follows. 1) Week 0: drug or placebo commenced. 2) Week 3: exercise test at 30% of maximum oxygen consumption (30% VO₂,max) in both normoxia and hypoxia inspiratory oxygen fraction (FI,O₂) 0.125), Doppler echocardiographic estimation of pulmonary haemodynamics, measurement of plasma amlodipine levels, and crossover from drug to placebo or vice versa. 3) Week 6: repeat exercise test in normoxia and hypoxia (FI,O₂, 0.125), Doppler echocardiographic estimation of pulmonary haemodynamics, and measurement of plasma amlodipine levels.

The studies described were all undertaken in laboratories at the University of Glasgow and the Western Infirmary in Glasgow (sea level). HPV was measured by means of Doppler echocardiography (while the subjects breathed 11.5% O₂) using a technique described by the authors’ group in a previous study (see below) [3]. The effects of hypoxia on exercise-induced cardiorespiratory responses: cardiac frequency, minute ventilation (V'E), oxygen consumption (VO₂), carbon dioxide production (VO₂CO₂) and SₐO₂ were examined while the subjects breathed 12.5% O₂.

Hypoxic pulmonary vasoconstriction

HPV was determined noninvasively from Doppler echocardiographic estimates of the maximum velocity of the tricuspid regurgitation (TR) jet and the relationship between right ventricular acceleration (AT, period between start of flow and peak flow in the pulmonary trunk) and ejection time (ET, period between beginning and end of flow) in normoxia and then in hypoxia (11.5% O₂). Examinations were performed with each subject in a semi-reclining position rotated to the left. Recordings were made using a combined 2.5-MHz two-dimensional imaging/Doppler transducer in the parasternal or short-axis position (Acuson 128x P/JOca; Acuson, Mountain View CA, USA). Colour Doppler was used to superimpose the ultrasound beam on the flow velocity axis in order to avoid angle correction. Pulsed wave Doppler was used to measure pulmonary flow velocity (AT and ET). The sample volume was located in the central part of the pulmonary trunk or in the right ventricular outflow tract close to the pulmonary valve. The maximum velocity of the TR jet was measured using continuous wave Doppler imaging. The TR jet velocity is proportional to the right atrial/right ventricular pressure difference (RA-RV) and this proportion is given by the Bernoulli equation:

\[ RA – RV = 4V², \]

where V is the velocity of the TR jet.

If the right atrial pressure is estimated clinically from the jugular venous pressure and added to this value then an estimate of systolic pulmonary artery pressure is obtained. To avoid such calculations, it was decided to use the previously published approach [3] and present the data as the TR jet velocity, which does not require any correction factors.

Subjects were examined breathing room air and then 11.5% O₂, SₐO₂ was monitored continually (Ohmeda Boulder, CO, USA) Doppler echocardiographic measurements were performed in triplicate 5 min after the introduction of hypoxia. The SₐO₂ at the time of successful Doppler measurements was noted.

Left ventricular end diastolic diameters (LVEDDs) and left ventricular end systolic diameters (LVESDs) were recorded in normoxia to measure fractional shortening (LVESD/LVEDD). This measurement was made at rest in normoxia both on and off amlodipine in order to assess the effects of the drug on left ventricular function.

Cardiorespiratory responses to hypoxia during exercise

Assessments at 30% of maximum oxygen consumption—cardiac frequency, arterial oxygen saturation, minute ventilation, oxygen consumption and carbon dioxide production. Subjects were tested at the same time of day and were asked to report to the laboratory having fasted for 3 h and having undertaken no strenuous activity in the previous 48 h. In order to establish the work-rate achieved at 30% VO₂,max, subjects performed maximal and sub-maximal exercise tests on a cycle ergometer (Monark 818-cycle ergometer; Monark Varberg, Sweden) while V'E, oxygen consumption (VO₂) and CO₂ production (VO₂CO₂) were determined by means of expired gas collection in a Douglas bag. Expired gas was analysed for O₂ (Servomex 570A; Servomex, Crawley, UK) and CO₂ (Morgan 801B; Morgan, Rainham, UK). Analysers were calibrated using standard procedures before each test; expired gas volume was measured using a Parkinson Cowan dry gas meter (Cranlea, Birmingham, UK) calibrated against a Tissot spirometer (Collins, Brantree, MA, USA). Standard formulae were used to calculate VO₂ and VO₂CO₂.

The work-rate at which the subjects achieved a VO₂ of 30% VO₂,max was recorded and used for all subsequent tests.

Subjects exercised in both normoxia and hypoxia (12.5% O₂) at the work-rate achieved at 30% VO₂,max in normoxia. It was decided to use 12.5% rather than 11.5%
O₂, (used for resting Doppler) because, during pilot studies, some subjects suffered excessive hypoxaemia (\(\text{SaO}_2\ <70\%\)). Before the test, the subjects rested on the cycle ergometer for 5 min. Cardiac frequency (Sport Tester™ PE3000 heart rate monitor; Polar Electro, Kempele, Finland) and blood pressure (BP) (standard mercury sphygmomanometer) were recorded in the last min of the 5-min period. \(\text{SaO}_2\) was recorded every minute.

The subjects then cycled for 10 min. Steady state (variation of measured variables <10%) was achieved for \(V’O_2\) in the last 2 min. If this was not the case, the test was repeated. Cardiac frequency was recorded every 2 min and BP every 2nd min. Systemic BP and breathlessness scores were recorded every 2 min. \(\text{SaO}_2\) was recorded every minute and expired air was collected in the 9th and 10th min of exercise, so that \(V’E\), \(V’O_2\) and \(V’CO_2\) could be determined.

Assessments at 30% of maximum oxygen consumption—breathlessness. Breathlessness was measured using symptom scales, which have been shown to be reproducible and sensitive to change in a range of subject groups [11–13]. The visual analogue scale (VAS) consisted of a horizontal line. At the left-hand side of the scale was the word "none" and at the far right the phrase "very severe". Scores of 0–100 were obtained from the VAS. The subjects were unaware of the numbers used to score their responses. The Borg CR10 scale consisted of a vertical scale labelled 0–10 with verbal descriptors at various numbers on the scale. During each test, symptom scales were administered at 1.5 min and every 2 min thereafter using a computer-assisted scale. During the tests, the subjects were asked to respond to the scales when they appeared on a television monitor. The subjects were asked to quantify their sensation of breathlessness by referring to their common experience of "an uncomfortable awareness of breathing".

Statistical analysis

The data from the Doppler echocardiographic were obtained in triplicate and the mean used in calculations. The ventilatory exercise data obtained in minutes 9 and 10 were accepted and averaged if minute-to-minute variation was <10%. If not, the test was repeated. Two sample t-tests and repeated measures analysis of variance were employed to investigate possible differences between amloidipine and placebo. Some variables, e.g. \(V’E\) and \(V’O_2\) are directly influenced by body weight.

Results

Pulmonary haemodynamics

Normoxia. Amlodipine had no significant effect on the TR jet velocity, AT, ET or AT/ET or \(\text{SaO}_2\) measured during echocardiography. There was no change in LVEDD or LVESD and thus no change in fractional shortening while taking amloidipine (table 1), suggesting that left ventricular function was not disturbed by amloidipine in normoxia.

Hypoxia. TR jet velocity in hypoxia was increased. Amlodipine did not significantly reduce HPV, but the effect of the drug was directly related to the serum level of amloidipine (\(r^2=-0.831, p<0.01\)) (table 1, fig. 1). There were no significant differences in AT, ET or AT/ET.

Cardiorespiratory response to exercise in normoxia and hypoxia at rest and during exercise

Rest. The resting cardiac frequency in hypoxia was significantly raised by amloidipine (\(p<0.0007\); table 2), but \(\text{SaO}_2\) and mean BP were not significantly changed.

Exercise. There was no significant difference in \(V’O_2\) between the four parts of the study: exercise in normoxia or hypoxia, in the presence of amloidipine or placebo, i.e. \(V’O_2\) was constant for a given work-rate as would be expected.

Exercise in normoxia. Cardiac frequency was significantly elevated by amloidipine (\(p=0.003\), as was the breathlessness score using both scales (VAS, \(p=0.0165\); Borg, \(p=0.0365\)). There were no significant differences for BP, \(\text{SaO}_2\), \(V’E\) or \(V’CO_2\) between placebo and amloidipine.

| Table 1. – Doppler echocardiographic responses to amloidipine and placebo at rest in normoxia and hypoxia |
|-----------------|-----------------|-----------------|
| Placebo | Amlodipine | p-value |
| TR jet velocity in hypoxia m⁻¹ | 2.4+0.99 | 2.4+0.24 | 0.47 |
| AT/ET in hypoxia | 0.35+0.07 | 0.36+0.05 | 0.50 |
| \(\text{SaO}_2\) in hypoxia % | 79+6.6 | 78+8.4 | 0.39 |
| \(\Delta TR\) jet velocity m⁻¹ | 0.44+0.25 | 0.38+0.46 | 0.36 |
| \(\Delta AT/ET\) | 0.04+0.09 | 0.03+0.06 | 0.28 |

Data are expressed as mean±sd (n=13) and were measured at sea level under conditions of normoxia and inspiratory hypoxia (inspiratory oxygen fraction=0.115). The arterial oxygen saturation (\(\text{SaO}_2\)) in hypoxia was measured at the time of successful Doppler echocardiographic measurements. No significant differences were found in any variable due to amloidipine in either normoxia or hypoxia. TR: tricuspid regurgitation; AT: acceleration time; ET: ejection time; \(\Delta\) difference between measurements made in air and inspiratory hypoxia.

Fig. 1. – The relationship between tricuspid regurgitation (TR) jet velocity and serum amloidipine level when measured under conditions of normoxia (○) and hypoxia (■, inspiratory oxygen fraction 0.115). There was a significant correlation between serum levels of the drug and TR jet velocity in hypoxia (\(R^2=-0.831, p<0.01\)).
The perception of breathlessness was significantly increased by amlodipine (p = 0.017). Amlodipine had no effect on \(S_a\text{O}_2\). The ratio of the change in cardiac frequency attributable to a change in \(S_a\text{O}_2\) i.e. the difference between the measurements obtained in normoxia and hypoxia (as described by Rathat et al. [7]), was significantly increased by amlodipine (p = 0.017). Amlodipine had no effect on \(S_a\text{O}_2\). The perception of breathlessness was significantly increased by amlodipine on both scales (VAS, p = 0.038; Borg, p = 0.0156). Mean systemic BP was significantly reduced by amlodipine (p = 0.02). There were no significant differences for the other measurements, i.e. cardiac frequency, \(V'E\), \(V'O_2\) and \(\Delta V'E/\Delta S_a\text{O}_2\) (the difference between these measurements taken in normoxia and hypoxia). As described by Rathat et al. [7].

Exercise in hypoxia. The ratio of the change in (Δ) cardiac frequency to \(\Delta S_a\text{O}_2\) i.e. the difference between the measurements obtained in normoxia and hypoxia (as described by Rathat et al. [7]), was significantly increased by amlodipine (p = 0.017). Amlodipine had no effect on \(S_a\text{O}_2\). The perception of breathlessness was significantly increased by amlodipine on both scales (VAS, p = 0.038; Borg, p = 0.0156). Mean systemic BP was significantly reduced by amlodipine (p = 0.02). There were no significant differences for the other measurements, i.e. cardiac frequency, \(V'E\), \(V'O_2\) and \(\Delta V'E/\Delta S_a\text{O}_2\) (the difference between these measurements taken in normoxia and hypoxia), as described by Rathat et al. [7].

Table 2. – Cardiorespiratory responses to exercise in normoxia and hypoxia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Amlodipine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>/fC beats-min(^{-1})</td>
<td>Normoxia</td>
<td>62±15</td>
<td>68±14</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>62±15</td>
<td>68±14</td>
</tr>
<tr>
<td>Mean BP</td>
<td>Normoxia</td>
<td>98±11</td>
<td>96±11</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>99±11</td>
<td>96±12</td>
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Data are presented as the mean±SD (n=14) and were measured at rest at sea level under conditions of normoxia (breathing room air) and inspiratory hypoxia (inspiratory oxygen fraction= 0.115). Cardiac frequency (/fC) in hypoxia was increased by amlodipine but there were no changes in other variables.

(table 3). Furthermore, when calculations were made of placebo/dose differences for the ventilatory variables (\(V'E\), \(V'O_2\), \(V'CO_2\)) and they were correlated with drug concentration, no significant differences were found.

Exercise in hypoxia. The ratio of the change in (Δ) cardiac frequency to \(\Delta S_a\text{O}_2\) i.e. the difference between the measurements obtained in normoxia and hypoxia (as described by Rathat et al. [7]), was significantly increased by amlodipine (p = 0.017). Amlodipine had no effect on \(S_a\text{O}_2\). The perception of breathlessness was significantly increased by amlodipine on both scales (VAS, p = 0.038; Borg, p = 0.0156). Mean systemic BP was significantly reduced by amlodipine (p = 0.02). There were no significant differences for the other measurements, i.e. cardiac frequency, \(V'E\), \(V'O_2\) and \(\Delta V'E/\Delta S_a\text{O}_2\) (the difference between these measurements taken in normoxia and hypoxia), as described by Rathat et al. [7].

Table 3. – Cardiorespiratory responses to exercise in normoxia and hypoxia

<table>
<thead>
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<th>Condition</th>
<th>Placebo</th>
<th>Amlodipine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>/fC beats-min(^{-1})</td>
<td>Normoxia</td>
<td>95±15</td>
<td>102±15</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>102±8</td>
<td>102±8</td>
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<tr>
<td>Mean BP</td>
<td>Normoxia</td>
<td>102±9.5</td>
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<td></td>
<td>Hypoxia</td>
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<td>25.3±7.1</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>0.9±0.2</td>
<td>1.0±0.2</td>
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<td></td>
<td>Hypoxia</td>
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<td></td>
<td>Hypoxia</td>
<td>69±6.3</td>
<td>70±13.3</td>
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<td></td>
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<td>0.275±0.23</td>
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<td>0.475±0.61</td>
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<td>0.21±0.25</td>
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<td>Hypoxia</td>
<td>0.74±0.49</td>
<td>1.39±0.85</td>
</tr>
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</table>

Data are presented as the mean±SD (n=14) and were measured at rest at sea level under conditions of normoxia (breathing room air) and inspiratory hypoxia (inspiratory oxygen fraction= 0.115). Cardiac frequency (/fC) in hypoxia was increased by amlodipine but there were no changes in other variables.

Changes related to drug level

In view of the apparent effect amlodipine had on exercise in normoxia and hypoxia, the effect of drug level on Doppler echocardiography and exercise variables was investigated.

Doppler echocardiography. There was a significant relationship between drug level and TR jet velocity under hypoxic conditions, implying a dose/response effect (fig. 1).

Exercise. No correlation was shown between drug levels and the following variables: \(V'E\), \(V'O_2\) and \(V'CO_2\); nor were the placebo/drug differences for these variables related to drug level.

Discussion

Pulmonary haemodynamics

Amlodipine had no effect on TR jet velocity, \(\Delta TR\) jet velocity, AT, ET, AT/ET or resting \(S_a\text{O}_2\) during the hypoxic challenge. Hypoxia caused only small increases in TR jet velocity. This finding is not entirely surprising since the 14 subjects were mountain climbers who had repeatedly ascended to altitudes of 5,000–7,500m without any episodes of acute mountain sickness or HAPO and, in the experience of the authors and others, would not be expected to have markedly abnormal pulmonary pressor responses to hypoxia. However, although amlodipine did not significantly reduce HPV, there was an inverse relationship between drug level and TR jet velocity in hypoxia, suggesting that the drug had an effect on HPV. There was no concomitant decrease in AT/ET. One possible explanation is the greater variability in AT/ET, as previously described by Hohenhaus et al. [6]. Another explanation is an amlodipine-induced increase in cardiac frequency with a concomitant fall in stroke volume (AT/ET compensates for cardiac frequency), but amlodipine did not appear to affect cardiac frequency in hypoxia. There was no demonstrable impairment of myocardial action in normoxia at rest, as shown by the unchanged measurements of left ventricular shortening, which is consistent with previous studies [9, 10]; thus so it is unlikely that negative inotropic activity was responsible for the dose-dependent fall in TR jet velocity.

Breathlessness and cardiorespiratory responses to exercise

Amlodipine significantly increased the subjects’ perception of breathlessness on both scales in exercise in normoxia and hypoxia. The two scales were used to eliminate any difficulty or misgivings the subjects might have had in using a VAS or category ratio scale (Borg CR10). The fact that an increase in breathlessness was seen using both scales indicates that the changes were real, but they are difficult to explain.

There was no change in \(V'O_2\) in all sections of the exercise tests, i.e. normoxia/hypoxia, amlodipine/placebo, and so the same physical work was performed in each test,
and, as J.S. Haldane pointed out, $V'\text{O}_2$ should remain unchanged regardless of whether work is carried out at sea level or at altitude. The fact that a consistent $V'\text{O}_2$ was measured for a given work-rate under all conditions suggests that the present results were reliable. Changes in $V'\text{O}_2$ due to amlodipine would not be expected, but neither did amlodipine result in changes in $V'E$, $V'\text{CO}_2$ or $S_a\text{O}_2$. Cardiac frequency was increased by amlodipine in normoxia. It is possible that amlodipine decreased cardiac function in hypoxia (not measured). Another possibility is so called cardiodynamic dyspnoea, in which an increase in blood flow decreases ventilation/perfusion ratios and results in a chemoreflex-derived increase in ventilation. However, amlodipine did not effect cardiac frequency in hypoxia and there was no increase in ventilation despite the increase in breathlessness seen in both normoxia and hypoxia. The present results suggest that the drug caused this effect by an action unrelated to its effect on haemodynamics. It is possible that amlodipine decreased cardiac function in hypoxia but, to the authors' knowledge, this effect is not a recognized feature of calcium antagonists.

The effect of amlodipine on the derived variables proposed by Rathat et al. [7] as discriminatory markers of susceptibility to mountain sickness were examined. Rathat et al. [7] showed that the changes in ratios of cardiac frequency and ventilation to arterial oxygen saturation caused by hypoxia while exercising at a submaximal work-rate are abnormally high in those subjects with susceptibility to "severe mountain sickness". It was reasoned that, if this were so, calcium antagonists, which are known to prevent high-altitude pulmonary oedema, might influence these ratios. No change was found in the ventilatory response to hypoxic exercise but there was an increase in the cardiac frequency response to hypoxic exercise. This was due to an increase in cardiac frequency without a change in arterial oxygen saturation, which would imply an increase in susceptibility to hypoxia in amlodipine-treated subjects. This would appear unlikely given what is known about calcium antagonists [14]. Whether this increase in cardiac frequency response is of benefit to mountaineers is debatable.

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**References**