Doppler assessment of hypoxic pulmonary vasoconstriction and susceptibility to high altitude pulmonary oedema

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Abstract

Background – Subjects with previous high altitude pulmonary oedema may have stronger than normal hypoxic pulmonary vasoconstriction. Susceptibility to high altitude pulmonary oedema may be detectable by echo Doppler assessment of the pulmonary vascular reactivity to breathing a hypoxic gas mixture at sea level.

Methods – The study included 20 healthy controls, seven subjects with a previous episode of high altitude pulmonary oedema, and nine who had successfully climbed to altitudes of 6000-8842 m during the 40th anniversary British expedition to Mount Everest. Echo Doppler measurements of pulmonary blood flow acceleration time (AT) and ejection time (ET), and of the peak velocity of the tricuspid regurgitation jet (TR), were obtained under normobaric conditions of normoxia (fraction of inspired oxygen, FiO2, 0-21), of hyperoxia (FiO2, 1-0), and of hypoxia (FiO2, 0-125).

Results – Hypoxia decreased AT/ET by mean (SE) 0.06 (0.01) in the control subjects, by 0.11 (0.01) in those susceptible to high altitude pulmonary oedema, and by 0.02 (0.02) in the successful high altitude climbers. Hypoxia increased TR in the three groups by 0.22 (0.06) (n=14), 0.56 (0-13) (n=5), and 0.18 (0-1) (n=7) m/s, respectively. However, AT/ET and/or TR measurements outside the normal range, defined as mean ± 2 SD of measurements obtained in the controls under hypoxia, were observed in only two of the subjects susceptible to high altitude pulmonary oedema and in five of the successful high altitude climbers.

Conclusions – Pulmonary vascular reactivity to hypoxia is enhanced in subjects with previous high altitude pulmonary oedema and decreased in successful high altitude climbers. However, echo Doppler estimates of hypoxic pulmonary vasoconstriction at sea level cannot reliably identify subjects susceptible to high altitude pulmonary oedema or successful high altitude climbers from a normal control population.

Keywords: Doppler, hypoxic pulmonary vasoconstriction, high altitude pulmonary oedema.
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Successful high altitude climbers.

The subjects with previous high altitude pulmonary oedema consisted of six men and one woman of mean (SD) age 43 (7) years (range 30–63), all of whom had successfully climbed to altitudes of 4000–8200 m. None showed symptoms of high altitude pulmonary oedema nor any change in spirometric indices during the climb.

MEASUREMENTS

The echo Doppler examinations were performed using a Hewlett-Packard SONOS 1000 ultrasound system with a combined 3-5 MHz two-dimensional imaging/Doppler transducer. Doppler recordings were obtained from the parasternal short axis or apical position with each subject lying with a slight left oblique rotation. Colour mode Doppler was used to superimpose the ultrasound beam on the flow-velocity axis to avoid any angle correction. The pulsed Doppler mode was used to study pulmonary flow velocity. The sample volume (size 3 x 3 mm) was located in the central part of the pulmonary trunk or in the right ventricular outflow tract, close to the valve. Acceleration time (AT) was defined as the interval between the onset of ejection and the peak flow velocity. Right ventricular ejection time (ET) was defined as the time between the onset of ejection to that of zero flow velocity. The maximum velocity of the tricuspid regurgitation jet (TR) was measured by continuous wave Doppler imaging. The echo Doppler examinations were recorded and cross-checked by the cardiologists of the Brussels and Glasgow teams.

Blood pressure was measured using an automated oscillometric device (Accutorm TA 1A, Datascope Corp, Paramus, New Jersey, USA). Heart rate was determined from a continuously monitored electrocardiographic lead. Arterial oxygen saturation (SaO2) was measured continuously by pulse oximetry (Hewlett-Packard or Ohmeda).

STUDY PROTOCOL

Echo Doppler measurements were performed in triplicate when the subjects were in a steady state as evaluated by stable heart rate, blood pressure, and SaO2, for at least 10 minutes at each of the following fractions of inspired oxygen (Fio2): 1, 0-21, and 0-125. Gases were administered by a face mask in random order.

DATA ANALYSIS

All values are expressed as mean (SE). The effects of changes in Fio2 were evaluated using a three-factor repeated measure analysis of variance. When the F ratio of the analysis of variance reached a critical p<0.05 value, modified t tests with an adjustment for multiple comparisons were used to compare specific situations.

Results

BASELINE MEASUREMENTS BREATHING ROOM AIR

Compared with controls, subjects with a susceptibility to high altitude pulmonary oedema had an increased AT and ET and a decreased heart rate (p<0.05), while successful high alt-
Figure 1 Hypoxia-induced increases in maximum velocity of tricuspid regurgitation jets (TR) calculated as TR measured at an FIO₂ of 0-125 minus TR measured at an FIO₂ of 0-21 (delta TR) in normal controls, in subjects with previous high altitude pulmonary oedema (HAPO), and in successful high altitude climbers. Subjects with previous high altitude pulmonary oedema had an increased hypoxic response compared with the other groups.

Figure 2 Hypoxia-induced decreases in pulmonary blood flow acceleration time (AT) on right ventricular ejection time (ET) calculated as AT/ET at an FIO₂ of 0-21 minus AT/ET at an FIO₂ of 0-125 (delta AT/ET) in normal controls, in subjects with previous high altitude pulmonary oedema (HAPO), and in successful high altitude climbers. The hypoxic response was increased in subjects with previous high altitude pulmonary oedema and decreased in successful high altitude climbers.

Figure 3 Maximum velocity of tricuspid regurgitation jets (TR) in hypoxia in subjects with previous high altitude pulmonary oedema (HAPO) and in successful high altitude climbers. The shaded area represents limits of normal calculated from mean ± 2 SD of measurements in 14 controls. Two of five subjects with previous high altitude pulmonary oedema had greater than normal hypoxic TR, and four of seven high altitude climbers had lower than normal hypoxic TR.

Figure 4 Ratio of pulmonary blood flow acceleration time (AT) to right ventricular ejection time (ET) in hypoxia in subjects with previous high altitude pulmonary oedema (HAPO) and in successful high altitude climbers. The shaded area represents limits of normal calculated as mean ± 2 SD of measurements in 20 controls. None of the subjects with previous high altitude pulmonary oedema had normal, higher than normal, or lower than normal AT/ET.

The hypoxia-induced increase in TR was similar in controls and successful high altitude climbers, but was enhanced in subjects susceptible to high altitude pulmonary oedema compared with the two other groups (fig 1). The hypoxia-induced decrease in AT/ET was increased in subjects susceptible to high altitude pulmonary oedema compared with controls, and decreased in successful high altitude climbers (fig 2). Two of the five subjects susceptible to high altitude pulmonary oedema and three of the seven successful high altitude climbers in whom the measurements could be obtained had a TR outside the normal range (defined as mean ± 2 SD of the measurements).

and decreased Sao₂ and ET, but did not affect AT, AT/ET or TR (table).

HYPOXIA-INDUCED CHANGES IN PULMONARY HAEMODYNAMICS

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obtained in 14 of the normal controls) (fig 3). None of the subjects susceptible to high altitude pulmonary oedema and four of the successful high altitude climbers had an AT/ET value outside the normal range (defined as mean ± 2 SD of the measurements, obtained in the 20 controls) (fig 4).

Discussion
Our results suggest that the pulmonary vascular reactivity to hypoxia is reduced in subjects with previous high altitude pulmonary oedema and decreased in successful high altitude climbers. However, echo Doppler estimation of HPV at sea level cannot reliably identify subjects susceptible to high altitude pulmonary oedema, nor successful high altitude climbers, from a general control population.

Several approaches based on echo Doppler technology have been developed for the non-invasive evaluation of pulmonary hypertension. Among these, the calculation of a transtricuspid pressure gradient based on the maximum velocity of tricuspid regurgitation jets and time to peak velocity measured on a pulmonary flow-velocity curve have proved most useful clinically. Tricuspid regurgitation jets are recovered in 70–90% of patients and have been found to correlate well with systolic right ventricular pressure measured at right heart catheterisation with correlation coefficients from 0.87 to 0.97. The recovery rate of TR in subjects without pulmonary hypertension is lower at about 70%,21 as in the present study. Pulmonary flow-velocity curves are recovered in 70–91% of patients, and AT and AT has been found to correlate highly with invasive measurements of mean pulmonary artery pressure with correlation coefficients from −0.65 to −0.85. Since AT decreases when heart rate increases, it is understandable that these correlations are improved by adding a correction for heart rate – for example, by dividing AT by ET. In the present study pulmonary flow-velocity curves could be recovered in all subjects at every value of Fio2.

Based on linear or curvilinear best fits of multipoint plots of TR, AT, or AT/ET versus simultaneous invasive determinations of pulmonary artery pressure or pulmonary vascular resistance, several equations have been proposed for the conversion of the Doppler measurements into pressures or resistances. In spite of the above mentioned good correlations, the predictive value of these equations on an individual basis is relatively poor. This is explained by the many assumptions upon which conversions of Doppler measurements to pressures or resistances are based. The conversion of TR to a systolic pulmonary artery pressure rests on the use of a simplified form of the Bernoulli equation and the clinical evaluation of right atrial pressure. The shape of a pulmonary flow-velocity curve is hypoxic pulmonary vasoconstriction influenced not only by pressure, but by a dynamic interplay between volume flow, resistance, elastance, and wave reflections. We therefore report the actual Doppler data instead of less reliable derived pressures or calculated resistances.

Doppler flow-velocity patterns may be very sensitive to sample location. Acceleration time and, eventually, AT/ET can be significantly shortened when sampling is done within the pulmonary trunk only a little further away from the pulmonary valve or closer to the posterior pulmonary wall. A careful review of our recordings showed that this was the most likely explanation for the shorter AT and wider scattering of AT/ET in the successful high altitude climbers. This limits any comparison of absolute values of AT and AT/ET between the subjects studied in Glasgow and in Brussels. Small differences in the sampling site probably account for the very low AT/ET values reported in normal subjects close to sea level in other studies. Indices of pulmonary flow-velocity curves are dependent on the examiner, even when, as in the present study, care is taken to use exactly the same method.

Breathing 100% oxygen has almost no effect on normal pulmonary artery pressure or vascular resistance. It is not surprising, therefore, that hypoxia had no effect on TR in any of our three study groups, nor on AT or AT/ET in the normal control subjects and those susceptible to high altitude pulmonary oedema. However, 100% oxygen increased AT and AT/ET in the successful high altitude climbers. An increase in AT may have persisted after correction for the decrease in heart rate has been reported in normal volunteers studied at Tucson at an altitude of about 1000 m. This may be explained by release of a slight degree of HPV at this altitude. In our study oxygen reduced the heart rate in the normal controls and in the subjects susceptible to high altitude pulmonary oedema, but not significantly in the high altitude climbers. Alternatively, the sampling site closer to the posterior wall of the pulmonary artery in the high altitude climbers may have made the flow-velocity curves more sensitive to changes in pulmonary vascular impedance.

Oxygen-induced increases in AT and in AT/ET in this group could thus be accounted for by subtle decreases in pulmonary vascular elastance and/or reflected waves, which may conceivably occur in the absence of actual changes in pulmonary vascular resistance.

The hypoxia-induced increases in TR and decreases in AT/ET were greater in subjects with previous high altitude pulmonary oedema than controls, in keeping with the hypothesis that susceptibility to high altitude pulmonary oedema is somehow linked to enhanced HPV. These data agree with some, but not all, previous invasive haemodynamic studies in subjects susceptible to high altitude pulmonary oedema challenged acutely with an Fio2 of 0.12–0.15 in normobaric conditions. In one study five men with previous high altitude pulmonary oedema had abnormally high pulmonary artery pressures when a rapid ascent to 3100 m was combined with prolonged exercise. Volunteers, when tested at sea level only one had an enhanced hypoxic pulmonary vasoconstriction response. Furthermore, acute relief of hypoxia at high altitude did not restore pulmonary vascular resistance to normal, suggesting that some factor other than hypoxia...
accounted for the excessive pulmonary hypertension supposedly responsible for pulmonary oedema formation at high altitude. One of the two subjects with high altitude pulmonary oedema reported by Penazola and Sime was subsequently investigated at sea level and showed a normal increase in pulmonary artery pressures in response to a hypoxic challenge. In another study 44 Indian soldiers with previous high altitude pulmonary oedema had their hypoxic pulmonary pressor response compared with that of 51 soldiers who had also been on duty in the Himalayan regions at altitudes of 3000–6000 m but without evidence of high altitude pulmonary oedema. Susceptibility to high altitude pulmonary oedema was associated with a slightly enhanced hypoxic pulmonary pressor response but the overlap between the groups was considerable and the difference of dubious significance. Seven children with previous high altitude pulmonary oedema showed an increase in mean pulmonary artery pressure from 22 to 56 mm Hg breathing a FIO₂ of 0.16, compared with a rise from 17 to 19 mm Hg in six controls. However, five of these children with previous high altitude pulmonary oedema resided at Leadville (3060 m) until the day before the hypoxic testing in Denver (1600 m), so these results are difficult to compare with those of studies performed on adults at sea level. Interestingly, the controls had a surprisingly small hypoxic pressor response. A greater normobaric hypoxia-induced increase in pulmonary artery pressures has been reported in five men with previous high altitude pulmonary oedema at altitudes around 3000 m compared with five controls who had climbed above this altitude without any symptoms of high altitude pulmonary oedema. The same was found in eight subjects with previous high altitude pulmonary oedema compared with six successful climbers at altitudes around 3000 m. However, normal normobaric hypoxic pulmonary pressor responses have been reported in two subjects with previous high altitude pulmonary oedema compared with a normal unselected control population.

The magnitude of HPV varies considerably from one species to another and, within a species, from one individual to another. The limits of normal human HPV are defined using right heart catheterisation studies performed in 32 healthy volunteers aged 21–42 years (mean 25), it is apparent that most previously reported subjects with a susceptibility to high altitude pulmonary oedema actually had a normal normobaric HPV. In the present study only two of the subjects with previous high altitude pulmonary oedema had a TR above normal in hypoxia, and none had a lower than normal AT/ET in hypoxia. However, differences in hypoxic responses were more important with a minimal overlap between subjects susceptible to high altitude pulmonary oedema and successful high altitude climbers. This is in keeping with previous invasive studies in which subjects susceptible to high altitude pulmonary oedema have been compared with successful high altitude climbers or dwellers.

Interestingly, participants in the 40th anniversary British expedition to Mount Everest who successfully reached extremely high altitudes had a blunted hypoxic pulmonary pressor response. Very small or absent HPV has been reported previously in some, but not all, subjects who went without problem to altitudes of 3000–4000 m. It may be that a blunted HPV is needed for a successful climb to the summit of Mount Everest. Native Tibetans, probably the world’s highest and longest dwelling high altitude population, have minimal hypoxic pulmonary hypertension. Native high altitude cattle present with structural and functional adaptations leading to decreased pulmonary vascular reactivity to hypoxia. A decreased HPV might protect against high altitude pulmonary oedema and perhaps is associated with yet other unknown characteristics essential for a successful acute, as well as chronic, adaptation to altitudes.

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