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Asymmetric dimethylarginine (ADMA) predicts altitude-associated hypoxic pulmonary arterial hypertension

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Prolonged exposure to altitude-associated chronic hypoxia (CH) may cause high altitude pulmonary hypertension (HAPH). Chronic intermittent hypobaric hypoxia (CIH) occurs in individuals who commute between sea level and high altitude. CIH is associated with repetitive acute hypoxic acclimatization and conveys the long-term risk of HAPH. As nitric oxide (NO) is an important regulator of systemic and pulmonary vascular tone and asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthesis that increases in hypoxia, we aimed to investigate whether ADMA predicts the incidence of HAPH among Chilean frontiers personnel exposed to six months of CIH.

We performed a prospective study of 123 healthy male subjects who were subjected to CIH (5 days at appr. 3,550 m, followed by 2 days at sea level) for six months. ADMA, SDMA, L-arginine, arterial oxygen saturation, systemic arterial blood pressure, and haematocrit were measured at baseline and at months 1, 4, and 6 at high altitude. Acclimatization to high altitude was determined using the Lake Louise Score and the presence of acute mountain sickness (AMS). Echocardiography was performed after six months of CIH in a subgroup of 43 individuals with either good (n = 23) or poor (n = 20) aclimatization to altitude, respectively. Logistic regression was used to assess the association of biomarkers with HAPH.

100 study participants aged 18.3 ± 1.3 years with complete data sets were included in the final analysis. Arterial oxygen saturation decreased upon the first ascent to altitude and plateaued at about 90% during the further course of the study. Haematocrit increased to about 47% after one month and remained stable thereafter. ADMA continuously increased and SDMA decreased during the study course, whilst L-arginine levels showed no distinct pattern. The incidence of AMS and the Lake Louise Score were high after the first ascent (53 and 3.1 ± 2.4, respectively) and at one month of CIH (47 and 3.0 ± 2.6, respectively), but decreased to 20 and 1.4 ± 2.0 at month 6, respectively (both p < 0.001 for trend). In echocardiography, 18 participants (42%) showed a mean pulmonary arterial pressure (mPAP) greater than 25 mm Hg (mean ± SD, 30.4 ± 3.9 mm Hg), out of which 9 (21%) were classified as HAPH (mPAP = 30 mm Hg; mean ± SD, 33.9 ± 2.2 mm Hg). Baseline ADMA, but not SDMA, was significantly associated with mPAP at month 6 in univariate logistic regression analysis (R = 0.413; p = 0.007). In ROC analysis, a cut-off for baseline ADMA of 0.665 µmol/l was determined as the optimal cut-off level to predict HAPH (mPAP > 30 mm Hg) with a sensitivity of 100% and a specificity of 63.6%.

ADMA concentration increases during long-term CIH. It is an independent predictive biomarker for the incidence of HAPH. SDMA concentration decreases during CIH and shows no association with HAPH. Our data support a role of impaired NO-mediated pulmonary vasodilation in the pathogenesis of high altitude pulmonary hypertension.
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