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Exercise-Induced Pulmonary Artery Hypertension

A Rare Finding?

To the Editor: When exposed to hypoxia at high altitude without acclimatization, susceptible individuals may develop pulmonary edema. Although the mechanisms are not completely understood, a disproportionate hypoxia-induced rise in pulmonary artery pressure (PAP) is a key factor. Those susceptible to high altitude pulmonary edema (HAPE) also exhibit an excessive increase in PAP during physical exercise at normoxia (1). High altitude pulmonary edema susceptibility is believed to be harmless at normoxia. However, if exercise-induced pulmonary hypertension was present already at low-intensity exercise corresponding to daily activities and was associated with dilated right-sided cardiac chambers in predisposed subjects, HAPE susceptibility could be clinically relevant even under normoxic conditions. Since HAPE is prevalent in 6% to 10% of unselected individuals (2), exercise-induced pulmonary hypertension may be a largely underestimated problem. Therefore, we investigated the effect of low-intensity exercise on PAP at low altitude and its correlation to right-sided cardiac cavity dimensions in HAPE-susceptible subjects and control subjects.

Ten HAPE-susceptible mountaineers (age 33 ± 2 years, body surface area [BSA] 1.84 ± 0.18 m^2), participants of a HAPE prevention study (3), and 9 matched control subjects (age 32 ± 3 years, BSA 1.90 ± 0.07 m^2) were investigated at 500 m altitude. First, they performed a bicycle exercise test until exhaustion (maximal workload: HAPE-susceptible subjects 298 ± 74 W vs. 283 ± 31 W, p = 0.56; maximal heart rate 177 ± 5 beats/min vs. 175 ± 10 beats/min). The next day Doppler echocardiography was performed at rest. Dimensions of right-sided cardiac cavities and left atrium were determined using 2-dimensional recordings, adjusted to BSA. Left ventricular dimension was determined using M-mode recordings. Left ventricular ejection fraction was assessed by the monoplane area-length method and PAP from the systolic pressure gradient across the tricuspid valve (ΔpTR). Stroke volume was estimated from the time-velocity integral and the area of the left ventricular outflow tract. After resting examination, Doppler recordings were measured at low-intensity exercise (20% and 40% of maximal workload) on a supine bicycle ergometer. Recordings were analyzed off-line in duplicate by investigators blinded to other results (third in case of discrepant findings).

Results are expressed as mean ± standard deviation or frequencies. Unpaired *t* test or Mann-Whitney *U* test, and Pearson or Spearman rank correlations were used, as appropriate (version 14.0, SPSS Inc., Chicago, Illinois).

At rest, PAP was normal in all subjects (Fig. 1) (HAPE-susceptible subjects: ΔpTR 19 ± 4 mm Hg; control subjects: 17 ± 3 mm Hg, p = 0.47). The PAP increase during exercise was larger in HAPE-susceptible subjects (first step: increase in ΔpTR 12 ± 7 mm Hg vs. 7 ± 5 mm Hg, p = 0.08; second step: 23 ± 6 mm Hg vs. 11 ± 5 mm Hg, p < 0.001) (Fig. 1).

Both right ventricle and atrium were larger in HAPE-susceptible subjects. Thus, right ventricular end-diastolic diameter was 15% (20 ± 2 mm/m^2 vs. 17 ± 2 mm/m^2, p = 0.04) and area of the right atrium 24% larger (7.5 ± 1.5 cm^2/m^2 vs. 6.0 ± 0.8 cm^2/m^2, p = 0.02) than that seen in control subjects. Left ventricular end-diastolic diameter (26 ± 2 mm/m^2 vs. 25 ± 3 mm/m^2, p = 0.30), ejection fraction (rest: 61 ± 5% vs. 62 ± 3%; second step: 69 ± 4% vs. 68 ± 5%, both p > 0.5), and left atrial size (6.6 ± 1.1 cm^2/m^2 vs. 5.8 ± 1.2 cm^2/m^2, p = 0.14) did not differ significantly between groups. There was a correlation between right atrial area at rest and ΔpTR during the second step of exercise (r = 0.63, p = 0.005). A comparable correlation with right ventricular dimension was found (r = 0.45, p = 0.08).

Stroke volume was larger in HAPE-susceptible subjects at rest (86 ± 12 ml vs. 73 ± 13 ml, p = 0.04), but during exercise this difference was no longer significant (second step: 108 ± 19 ml vs. 98 ± 19 ml, p = 0.27).

Pulmonary hypertension may be present in HAPE-susceptible subjects under normoxic conditions already during low-intensity exercise corresponding to daily activities. Since HAPE susceptibility is prevalent in up to 10% of the general population (2), exercise-induced pulmonary hypertension may be more common than previously thought. Therefore, it is tempting to speculate that exercise-induced pulmonary hypertension may be largely underestimated and clinically relevant. This hypothesis is supported by the structural alterations of right-sided cardiac cavities found in HAPE-susceptible subjects at rest. However, whether HAPE susceptibility may eventually be associated with the development of symptomatic (exercise-induced) pulmonary hypertension remains speculative.

Previously, excessively high pulmonary pressures were found during exercise in young, highly conditioned athletes, but not in healthy active young men (4), which was attributed to higher stroke volume in the former group. In our study, stroke volume was larger in HAPE-susceptible subjects at rest, but this difference vanished during exercise. Therefore, hyperdynamic response to exercise cannot explain the excessive increase in PAP in HAPE-susceptible subjects during stress testing. Additionally, exercise capacity did not differ between the 2 groups.

Based on the definition of exercise-induced pulmonary hypertension (i.e., invasively measured mean PAP ≥30 mm Hg) and previous limited results from an echocardiographic study in comparable subjects (1), systolic PAP of 45 mm Hg and, assuming a right atrial pressure of 5 mm Hg, ΔpTR of 40 mm Hg may be adopted as cutoff value for definition of exercise-induced pulmonary hypertension. All our control subjects were far below this cutoff, whereas 6 of 10 HAPE-susceptible subjects fulfilled this criterion already at low-intensity exercise. Interestingly, the 5 individuals with the largest right atria belonged to this subgroup.

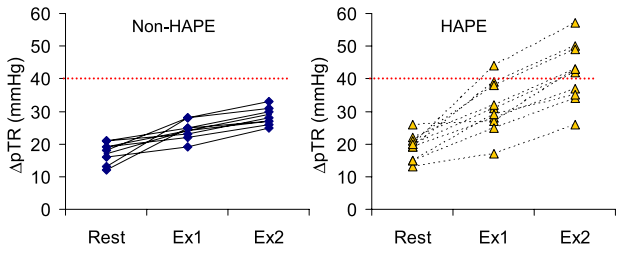

Figure 1 **Individual Response of ΔpTR**

Individual response of pressure gradient across tricuspid valve (ΔpTR) at low altitude from rest to low-intensity exercise (Ex1 = 20% and Ex2 = 40%, respectively, of previously tested maximal exercise capacity) in high altitude pulmonary edema (HAPE)-susceptible subjects **(right)** compared with control subjects (non-HAPE). **Red dotted lines** indicate approximate upper limit of normal during exercise.

Diagnosis of pulmonary hypertension is often delayed because of nonspecific symptoms (5), which may be even more so regarding exercise-induced pulmonary hypertension. Therefore, PAP measurement during exercise may be helpful in subjects with unexplained dyspnea on exertion, some of which are considered to have diastolic heart failure. High altitude pulmonary edema shows that it is not mandatory to have a significantly elevated left-sided filling pressure to develop pulmonary edema, but that alterations within the pulmonary vasculature can be the causative factor (6). Pulmonary vascular hyperreagibility in response to hypoxia (i.e., HAPE susceptibility) may also explain why some patients with pulmonary diseases develop pulmonary hypertension whereas others do not. In patients with chronic hypoxia, HAPE susceptibility might facilitate pulmonary vasoconstriction.

Since this study does not address pathogenetic issues, we are unable to shed further light on the underlying cause of HAPE susceptibility. Importantly, this study provides preliminary results only. The small number of subjects included contains some risk of a false-positive finding. Furthermore, whether some of the HAPE-susceptible subjects presented will actually develop clinical signs of pulmonary hypertension remains speculative. A long-term follow-up study is necessary to address this question.

Nevertheless, the relatively high prevalence of HAPE susceptibility and the fact that more than half of the HAPE-susceptible subjects developed pulmonary hypertension at a workload corresponding to daily activities with structural changes indicating right-sided cardiac pressure overload highlight the need for more frequent consideration of exercise-induced pulmonary hypertension as potential cause of exertional dyspnea.

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Letters to the Editor

Left Atrial Dimension in Stress Echocardiography

We read with interest the recent study by Bangalore et al. (1) evaluating the prognostic significance of left atrial (LA) enlargement in patients undergoing stress echocardiography. The authors demonstrate that left atrial dimension provides incremental prognostic significance in patients referred for stress echocardiography, irrespective of the presence of inducible ischemia. Although we applaud the authors for highlighting the importance of left atrial enlargement in this patient population, there are several methodologic concerns which profoundly limit the applicability of their findings to clinical practice.

First, the use of M-mode linear dimension to measure left atrial volume is inaccurate and varies widely among individual readers (2). We have previously shown that left atrial volume is most