Acute Changes in Pulmonary Artery Pressures Due to Exercise and Exposure to High Altitude Do Not Cause Left Ventricular Diastolic Dysfunction*

Alain M. Bernheim, MD; Stephanie Kiencke, MD; Manuel Fischler, MD; Lorenz Dorschner, MD; Johann Debrunner, MD; Heimo Mairbäurl, PhD; Marco Maggiorini, MD; and Hans Peter Brunner-La Rocca, MD

Background: **Altitude-induced pulmonary hypertension has been suggested to cause left ventricular (LV) diastolic dysfunction due to ventricular interaction. In this study, we evaluate the effects of exercise- and altitude-induced increase in pulmonary artery pressures on LV diastolic function in an interventional setting investigating high-altitude pulmonary edema (HAPE) prophylaxis.**

Methods: **Among 39 subjects, 29 were HAPE susceptible (HAPE-S) and 10 served as control subjects. HAPE-S subjects were randomly assigned to prophylactic tadalafil (10 mg), dexamethasone (8 mg), or placebo bid, starting 1 day before ascent. Doppler echocardiography at rest and during submaximal exercise was performed at low altitude (490 m) and high altitude (4,559 m). The ratio of early transmitral inflow peak velocity (E) to atrial transmitral inflow peak velocity (A), pulmonary venous flow parameters, and tissue velocity within the septal mitral annulus during early diastole (E') were used to assess LV diastolic properties. LV filling pressures were estimated by E/E'. Systolic right ventricular to atrial pressure gradients (RVPGs) were measured in order to estimate pulmonary artery pressures.**

Results: **At 490 m, E/A decreased similarly with exercise in HAPE-S and control subjects (HAPE-S, 1.5 ± 0.3 to 1.3 ± 0.3; control, 1.7 ± 0.4 to 1.3 ± 0.3; $p = 0.12$ between groups) [mean ± SD], whereas RVPG increased significantly more in HAPE-S subjects (20 ± 5 to 43 ± 9 mm Hg vs 18 ± 3 to 28 ± 3 mm Hg, $p < 0.001$). Changes in RVPG levels during exercise did not correlate with changes in E/A ($p > 0.1$). From 490 to 4,559 m, no correlations between changes in RVPG and changes in E/A or atrial reversal (both $p > 0.1$) were observed. Neither of the groups showed an increase in E/E' from 490 to 4,559 m.**

Conclusion: **Increased pulmonary artery pressure associated with exercise and acute exposure to 4,559 m appears not to cause LV diastolic dysfunction in healthy subjects. Therefore, ventricular interaction seems not to be of hemodynamic relevance in this setting.**

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Key words: acute pulmonary hypertension; healthy subjects; high altitude; left ventricular diastolic function

Abbreviations: A = atrial transmitral inflow peak velocity; AMS = acute mountain sickness; E = early transmitral inflow peak velocity; E' = tissue velocity within the septal mitral annulus during early diastole; HAPE = high altitude pulmonary edema; HAPE-S = high altitude pulmonary edema susceptible; LV = left ventricular/ventricle; LVEF = left ventricular ejection fraction; RVPG = systolic right ventricular to atrial pressure gradient

In various forms of pulmonary hypertension, an association between elevated pulmonary artery pressures and abnormal left ventricular (LV) diastolic function has been proposed.[1–3] Ventricular interaction with a shift of the septum toward the LV as a consequence of right ventricular pressure overload has been suggested as the primary cause of LV diastolic dysfunction.[4]

At high altitude, not only acute hypoxia-induced pulmonary hypertension but also changes of the transmitral inflow pattern suggestive of impaired LV diastolic function have been described.[5–7] In accordance to chronic right-sided pressure overload, ventricular interaction has been discussed as a cause for the observed alteration in LV diastolic function.[5,6] Recently, a new concept of compensated altitude-

induced diastolic dysfunction was proposed because changes in diastolic function at high altitude were mainly related to an increase in the atrial phase of LV filling.[6]

In high-altitude pulmonary edema-susceptible (HAPE-S) subjects, an abnormal pulmonary vascular response occurs not only at high altitude but also under normoxic conditions during submaximal levels of exercise. Concurrent data on LV diastolic function, however, are limited to evaluation of mitral inflow patterns recorded during exercise.[8]

Prophylactic administration of the phosphodiesterase inhibitor tadalafil or the corticosteroid dexamethasone has been shown to effectively reduce altitude-induced pulmonary hypertension and prevent high-altitude pulmonary edema (HAPE).[9] To date, assessment of LV diastolic function at high altitude has not been studied under the influence of HAPE prophylaxis.

To provide more detailed information on LV diastolic function in the presence of acute pulmonary hypertension and to evaluate potential consequences of therapeutic intervention, we investigated HAPE-S subjects randomized to tadalafil, dexamethasone, or placebo, and control subjects without a history of HAPE. Subjects were assessed by Doppler echocardiography at rest and during submaximal exercise, at low as well as at high altitude.

Materials and Methods

Study Population

Thirty-nine healthy mountaineers participated in the study. Twenty-nine subjects (4 women) had a history of at least one documented episode of HAPE.[9] The other 10 subjects (2 women) without history of a HAPE served as control subjects. The study was approved by the institutional ethical boards of the University Hospitals Zurich and Heidelberg. Subjects gave written informed consent to participate in the study.

*From the Division of Cardiology (Drs. Bernheim, Kiencke, and Brunner-La Rocca), University Hospital, Basel, Switzerland; the Intensive Care Unit (Drs. Fischler, Dorschner, Debrunner, and Maggiorini), Department of Internal Medicine, University Hospital, Zurich, Switzerland; and the Department of Sports Medicine (Dr. Mairbäurl), University Hospital, Heidelberg, Germany.
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Correspondence to: Alain M. Bernheim, MD, Division of Cardiology, University Hospital, Petersgraben 4, 4031 Basel, Switzerland; e-mail: bernheima@uhbs.ch.
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Study Design

Baseline measurements were performed at 490 m 2 to 4 weeks prior to the investigation at 4,559 m. At 490 m, subjects underwent clinical examination and bicycle exercise testing until exhaustion to assess the individual peak exercise capacity (mean ± SD, 270 ± 55 W). The following day, Doppler echocardiography was performed.

HAPE-S subjects were then randomized in a double-blind fashion to placebo, tadalafil, or dexamethasone. Details on design of the study have been previously published.[9] At 4,559 m, Doppler echocardiography was performed in the morning of the day after arrival.

Severe acute mountain sickness (AMS) requiring symptomatic treatment developed a few hours after arrival at 4,559 m in two participants receiving tadalafil. As a consequence, these two subjects were withdrawn from the previously published HAPE prevention analysis after initiation of treatment for AMS. Data of these two subjects served for analysis of a best-case scenario (neither of the two participants with HAPE) and a worst-case scenario (both with HAPE), whereas they were not considered for the evaluation of the systolic pulmonary artery pressure response to high altitude.[9] One of these two subjects had to descend prematurely, whereas the other remained at 4,559 m and underwent echocardiography after an overnight stay. Since the primary aim of the present study was to evaluate the effect of elevated pulmonary artery pressure on LV diastolic function rather than to compare the two prophylactic medications, we opted to include the data of this subject in the analysis.

Echocardiography at Rest and During Exercise

Doppler echocardiography was performed with an integrated color Doppler system using a 4.0-MHz transducer (Toshiba Aplio 80; Toshiba; Tokyo, Japan). In the apical four-chamber view, transmitral inflow velocity (*ie*, peak early transmitral inflow peak velocity [E] and atrial transmitral inflow peak velocity [A]), isovolemic relaxation time, and pulmonary venous flow parameters were obtained as previously described.[10] Color-coded Doppler tissue imaging was used to assess peak tissue velocity within the septal mitral annulus during early diastole (E'). LV ejection fraction (LVEF) was calculated using the single-plane area length method. Systolic right ventricular to atrial pressure gradient (RVPG) was calculated from the gradient across the tricuspid valve using the modified Bernoulli equation. Tricuspid regurgitation velocity was obtained from the right ventricular inflow or the apical four-chamber view. The regurgitant jet was first located by color Doppler, and the peak velocity was then measured using continuous-wave Doppler. If neither of these views revealed a representative continuous-wave Doppler signal, we additionally used a foreshortened four-chamber view.

After obtaining all recordings at rest, subjects started cycling on an ergometer in semirecumbent left-lateral position at a workload corresponding to 40% (mean, 108 ± 22 W) of individual peak exercise capacity. Apart from pulmonary venous flow, all Doppler echocardiographic parameters were reassessed during exercise. Study participants cycled for 2 min before echocardiographic recording was started. After this time period, two-dimensional recordings were first obtained. Doppler measurements where then recorded after 3 min of cycling. This protocol at an exercise level below the anaerobic threshold was chosen in order to warrant steady-state condition at the time of Doppler assessment. At 4,559 m, 70% of the workload (*ie*, 28% [mean, 76 ± 15 W] of the maximal performance at low altitude) was chosen using the same time intervals. The exercise level was reduced to compensate for the effects of high altitude on physical capacity.[11]

At rest, RVPG was obtainable in all subjects, at 490 m as well