Bosentan Decreases Pulmonary Vascular Resistance and Improves Exercise Capacity in Acute Hypoxia*

Vitalie Faoro, MSc, PhD; Saskia Boldingh, MSc; Mickael Moreels, MD; Sarah Martinez, MSc; Michel Lamotte, MSc; Philippe Unger, MD, PhD; Serge Brimioulle, MD, PhD; Sandrine Huez, MD, PhD; and Robert Naeije, MD, PhD

Background: **Altitude exposure is associated with mild pulmonary hypertension and decreased exercise capacity. We tested the hypothesis that pulmonary vascular resistance (PVR) contributes to decreased exercise capacity in hypoxic healthy subjects.**

Methods: **An incremental cycle ergometer cardiopulmonary exercise test and echocardiographic estimation of pulmonary artery pressure (Ppa) and cardiac output to calculate total PVR were performed in 11 healthy volunteers in normoxia and after 1 h of hypoxic breathing (12% O_2). The measurements were performed in a random order at 1-week intervals after the receiving either a placebo or bosentan, following a double-blind randomized crossover design. Bosentan was administered twice a day for 3 days, 62.5 mg on the first day and 125 mg on the next 2 days.**

Results: **Hypoxic breathing decreased the mean (± SE) pulse oximetric saturation (Spo_2) from 99 ± 1% to 3 ± 1% and increased the mean PVR from 5.6 ± 0.3 to 7.2 ± 0.5 mm Hg/L/min/m^2, together with a decrease in mean maximum O_2 uptake ($\dot{V}o_2max$) from 47 ± 2 to 35 ± 2 mL/kg/min. Bosentan had no effect on normoxic measurements and did not affect hypoxic Spo_2, but decreased PVR to 5.6 ± 0.3 mm Hg/L/min/m^2 ($p < 0.01$) and increased $\dot{V}o_2max$ to 39 ± 2 mL/kg/min ($p < 0.01$) in hypoxia. Bosentan therapy, on average, restored 30% of the hypoxia-induced decrease in $\dot{V}o_2max$. Bosentan-induced changes in Ppa and $\dot{V}o_2max$ were correlated ($p = 0.01$).**

Conclusions: **We conclude that hypoxic pulmonary hypertension partially limits exercise capacity in healthy subjects, and that bosentan therapy can prevent it.** ***(CHEST 2009; 135:1215–1222)***

Key words: altitude; echocardiography; exercise; exercise testing; pulmonary hypertension

Abbreviations: AT = anaerobic threshold; CPET = cardiopulmonary exercise test; ET = endothelin; FIo_2 = fraction of inspired oxygen; HR = heart rate; HRmax = maximum heart rate; mPpa = mean pulmonary artery pressure; Ppa = pulmonary artery pressure; Psa = systemic arterial pressure; PVR = pulmonary vascular resistance; Q = cardiac output; RER = respiratory exchange ratio; Spo_2 = pulse oximetric saturation; sPpa = systolic pulmonary artery pressure; $\dot{V}co_2$ = carbon dioxide output; $\dot{V}E$ = minute ventilation; $\dot{V}E$max = maximum minute ventilation; $\dot{V}o_2$ = oxygen uptake; $\dot{V}o_2$max = maximum oxygen uptake

High-altitude exposure has long been known to decrease aerobic exercise capacity. This is explained by a decrease in O_2 delivery to the tissues, due to decreases in both arterial O_2 content and in maximum cardiac output (Q).[1] Acclimatization is associated with a restoration of arterial O_2 content due to hyperventilation and increased hemoglobin content. However, exercise capacity remains decreased, which is at least partly related to a decrease in maximum Q.[1,2] The mechanisms of decreased maximum Q at high altitudes are not entirely clear.[3] A recently raised possibility is that of a limitation in right ventricular flow output by hypoxic pulmonary vasoconstriction. An improvement in exercise capacity together with a decrease in pulmonary artery pressure (Ppa) was indeed reported after the intake of sildenafil in hypoxic healthy volunteers.[4] However, these effects did not appear to be sustained and could be ascribed at least in part to an associated improvement in arterial oxygenation.[5]

We therefore investigated the effects of the endothelin (ET) A and ETB receptor blocker bosentan on

the pulmonary circulation and on exercise capacity in hypoxic healthy volunteers. Bosentan is an efficient therapy of pulmonary arterial hypertension[6] and decreases Ppa levels in healthy subjects after a rapid ascent to high altitude.[7] The drug is without effects on systemic BP, ventilation, or arterial oxygenation in acute hypoxic conditions.[7,8] Accordingly, the hypothesis tested in the present study was that a specific decrease in pulmonary vascular resistance (PVR) by the intake of bosentan would improve aerobic exercise capacity in healthy acutely hypoxic subjects.

Materials and Methods

Subjects

Eleven healthy volunteers (2 women and 9 men; age range, 20 to 45 years; mean age, 29 years; mean [± SD] height, 178 ± 10 cm; mean weight, 70 ± 11 kg) gave written informed consent to the study, which was approved by the Ethics Committee of the Erasme University Hospital. All the subjects were healthy and active, with an unremarkable medical history, and normal clinical examination and ECG findings. They had been prescreened to ensure good quality echocardiographic signals.

Experimental Design

Each subject underwent an echocardiographic examination in a semirecumbent position, at rest and at a moderated level of exercise to increase Q, so as to define PVR by the measurement of Ppa at several levels of flow, and an incremental maximum cycle ergometer cardiopulmonary exercise test (CPET) at a fraction of inspired oxygen (F_{IO_2}) of 0.21 (while breathing room air) or at an F_{IO_2} of 0.12 (while breathing from a premixed tank of O_2 in nitrogen). The subjects were equipped with tightly fitted facial masks in all experimental conditions. The facial mask was open to the atmosphere in normoxia and connected to the low O_2 tank with an interposed Douglas bag in hypoxia. The echocardiographic examinations and CPET were performed consecutively after the intake of bosentan, 62.5 mg bid followed by 125 mg bid for 2 days, or a placebo according to a double-blind, randomized, placebo-controlled crossover design. The sequence of F_{IO_2} 0.21 and 0.12 measurements was also randomized. The echocardiographic measurements were started 1 h after the subjects had been equipped with a face mask and were breathing either room air or the hypoxic gas mixture. The hypoxic breathing was not interrupted between the echocardiographic and CPET measurements. The average duration of the echocardiographic measurements was 20 min. The average duration of the CPET was 10 to 12 min. Therefore, the total duration of hypoxic exposure was approximately 90 min.

The dose of bosentan had been decided on the basis of the upper range of doses recommended for the treatment of pulmonary hypertension,[6] and it had previously been shown[7] to decrease hypoxic pulmonary hypertension in healthy volunteers. The F_{IO_2} of 0.12 was selected as being associated with a safe and near maximal hypoxic pulmonary vasoconstriction.[4,5,9,10]

Thus, every subject underwent a total of four sequences of echocardiographic examinations and CPET. Each of these sequences was performed at least 7 days apart, with the subjects in a resting state with stable systemic arterial pressure (Psa) and heart rate (HR). The subjects were requested to drink 1.5 L of water within the hour preceding the echocardiographic examination to optimize the Doppler signals. The echocardiographic examinations and CPET were performed under constant clinical supervision and monitoring of the ECG and O_2 saturation, with measurements of Psa made at regular intervals.

Clinical Measurements

Psa was measured by sphygmomanometry, with mean pressure calculated as diastolic pressure + one third pulse pressure. A three-lead ECG was used to measure HR. Pulse oximetric saturation (Spo_2) was measured by an earlobe pulse oximeter (Pulsox-3i; Konica Minolta Sensing; Osaka, Japan). The device was tested and calibrated following the manufacturer's recommendations. Particular attention was paid to the quality of the signal, especially during exercise, because it is known that the accuracy and precision of pulse oximetry at exercise may be decreased by local perfusion.[11]

Echocardiography

Echocardiography was performed using a portable ultrasound system equipped with a 2.5-MHz probe (Cypress; Acuson/Siemens; Erlangen, Germany). Recordings were stored on optical disks and analyzed by two independent blinded cardiologists experienced in echocardiography. Q was estimated from left ventricular outflow tract cross-sectional area and pulsed Doppler velocity-time integral measurements.[12] Systolic Ppa (sPpa) was estimated from a transtricuspid gradient calculated from the maximum velocity of continuous Doppler tricuspid regurgitation, with 5 mm Hg assigned to right atrial pressure.[10,13] Mean Ppa (mPpa) was calculated as 0.6 × sPpa + 2.[14] PVR was calculated as mPpa/Q.

Exercise echocardiography was performed on a supine ergometer (model 900 EL; Ergoline; Bitz, Germany), as previously described.[10] The exercise table was tilted laterally by 20 to 30 degrees to the left. After obtaining Doppler echocardiographic images at rest, exercise was started at an initial workload of 20 W. Workload was increased by 20 W every 2 min. Three to five pressure-flow coordinates were recorded in every subject, at levels of exercise below the anaerobic threshold (AT), and therefore without excessive increase in ventilation and/or discomfort to allow for optimal quality echocardiographic measure-

*From the Department of Physiology (Drs. Faoro and Naeije, and Ms. Martinez), Faculty of Medicine, Free University of Brussels, Belgium; VU University Medical Center (Ms. Boldingh), Amsterdam, the Netherlands; and the Departments of Cardiology (Drs. Moreels, Unger, and Huez, and Mr. Lamotte), and Intensive Care (Dr. Brimioulle), Erasme University Hospital, Brussels, Belgium.
Supported by the Foundation of Cardiac Surgery and by the Fonds de la Recherche Scientifique Médicale (grant No. 3.4551.05), Belgium. Dr. Huez was a fellow of the Fonds National de la Recherche Scientifique, Brussels, Belgium.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received September 13, 2008; revision accepted November 8, 2008.

Correspondence to: Robert Naeije, MD, PhD, Department of Physiology, Erasme Campus CP 604, 808 Lennik Rd, B-1070 Brussels, Belgium; e-mail: rnaeije@ulb.ac.be
DOI: 10.1378/chest.08-2222