CHEST

Original Research

PULMONARY VASCULAR DISEASE

Atrial Septostomy Decreases Sympathetic Overactivity in Pulmonary Arterial Hypertension*

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Background: **We have reported previously that the sympathetic nervous system is activated in patients with pulmonary arterial hypertension (PAH), and that this is only partly explained by a decrease in arterial oxygenation. Possible causes for increased muscle sympathetic nerve activity (MSNA) in patients with PAH include right atrial distension and decreased cardiac output. Both may be improved by atrial septostomy, but this intervention also further decreases arterial oxygenation. In the present study, we wanted to investigate the effect of atrial septostomy on MSNA in patients with PAH.**

Methods: **We recorded BP, heart rate (HR), arterial O_2 saturation (Sao_2), and MSNA before and after atrial septostomy in PAH patients (mean [± SE] age, 48 ± 5 years) and in closely matched control subjects. Measurements were also performed after septostomy, while Sao_2 was brought to the preprocedure level by supplemental O_2 therapy.**

Results: **Compared to the control subjects (n = 10), the PAH patients (n = 11) had a lower mean BP (75 ± 2 vs 96 ± 3 mm Hg, respectively; $p < 0.001$), lower mean Sao_2 (92 ± 1% vs 97 ± 0%, respectively; $p < 0.001$), increased mean HR (84 ± 4 vs 68 ± 3 beats/min; $p < 0.01$), and markedly increased mean MSNA (76 ± 5 vs 29 ± 2 bursts per minute; $p < 0.001$). Atrial septostomy decreased mean Sao_2 (to 85 ± 2%; $p < 0.001$) and mean MSNA (to 69 ± 4 bursts per minute; $p < 0.01$), but did not affect HR or BP. Therapy with supplemental O_2 did not affect MSNA, BP, or HR. The decrease in MSNA was correlated to the decrease in right atrial pressure ($r = 0.62$; $p < 0.05$).**

Conclusions: **Atrial septostomy in PAH patients decreases sympathetic hyperactivity despite an associated decrease in arterial oxygenation, and this appears to be related to decreased right atrial distension.** ***(CHEST 2007; 131:1831–1837)***

Key words: atrial septostomy; muscle sympathetic nerve activity; pulmonary arterial hypertension

Abbreviations: BMI = body mass index; HR = heart rate; LAP = left atrial pressure; MBP = mean BP; MSNA = muscle sympathetic nerve activity; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; RAP = right atrial pressure; Sao_2 = arterial oxygen saturation

Heart failure is associated with activation of the sympathetic nervous system.[1,2] While activation is initially beneficial due to maintenance of tissue perfusion pressure and cardiac output, sympathetic overactivation aggravates heart failure by increasing the metabolic demand of the failing myocardium, decreasing myocardial oxygen supply, increasing sodium and water retention, decreasing skeletal muscle strength, decreasing the arrhythmogenic threshold, and inducing myocardial as well as systemic vascular remodeling.[3,4] Accordingly, in heart failure patients, sympathetic overactivity is associated with a poor prognosis, and β-adrenergic blocking agents improve the clinical state and survival.[5]

In 2004, we reported[6] that sympathetic nervous system activity, as assessed by peroneal nerve microneurography, is markedly increased in patients with pulmonary arterial hypertension (PAH), suggesting that the neurohumoral derangements reported in heart failure patients also occur in the particular

situation of right ventricular dysfunction due to increased afterload. In that study,[6] one fourth of the increased muscle sympathetic nerve activity (MSNA) was corrected by breathing supplemental O_2, suggesting minimal chemoreflex participation, in contrast with the lack of any effect of supplemental O_2 in patients with congestive heart failure.[7]

The mechanisms of sympathetic overactivity in heart failure patients are complex, and are believed to involve a decrease in cardiac output, atrial and ventricular wall stress, pulmonary arterial distension, decreased baroreflex sensitivity, increased muscle metaboreflex and chemoreflex sensitivity, and positive interactions with the endothelin and renin-angiotensin-aldosterone systems.[1–5,8,9] Some of these derangements may be corrected by an atrial septostomy in patients with advanced PAH and refractory right ventricular failure.[10] The procedure has been reported to improve clinical state, exercise capacity, and survival, as well as to decrease right atrial pressure (RAP) and to improve cardiac output, at the price, however, of a decrease in arterial oxygenation.[10]

We hypothesized that septostomy would decrease sympathetic nervous system overactivity in PAH patients if the beneficial effects of the improved cardiac hemodynamics could compensate for the shunt-induced, hypoxemia-associated chemoreflex activation. We, therefore, measured MSNA before and after septostomy in patients with advanced PAH and correlated the results to changes in right ventricular filling pressures, cardiac output, and arterial O_2 saturation (Sa_{O_2}), with and without the correction of hypoxemia with supplemental O_2. The results suggest that increased right ventricular filling pressures contribute to sympathetic overactivity in PAH patients.

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Materials and Methods

Patients

Eleven patients with PAH (5 men and 6 women; mean [± SE] age, 48 ± 5 years; body mass index [BMI], 22 ± 1 kg/m^2) gave informed consent to participate in the study, which was approved by the Ethics Committee of Erasme Hospital. The patients had been scheduled to undergo atrial septostomy because of clinical deterioration despite optimal medical therapy. In two patients, atrial septostomy was being performed for the second time due to suspected atrial septal defect closure (the delays from the first atrial septostomy were 2 and 4 years). PAH was idiopathic in six patients, familial in two patients, associated with the previous intake of fenfluramine in two patients, and associated with a corrected ventricular septal defect in one patient. Specific therapies included beraprost (n = 2), epoprostenol (n = 2), treprostinil (n = 5), calcium channel blockers (n = 3), sildenafil (n = 1), and endothelin receptor blockers (*ie*, bosentan [n = 5], ambrisentan [n = 1], sitaxsentan [n = 2]). Conventional therapies included diuretics (*ie*, bumetanide [n = 4], furosemide [n = 6], spironolactone [n = 8], and hydrochlorothiazide [n = 1]), and anticoagulants. Therapy with anticoagulants was withdrawn 48 h before patients underwent atrial septostomy. All medications were kept unchanged during the study, except for therapy with diuretics, which was stopped or reduced in nine of the patients after they underwent atrial septostomy. All of the patients presented with advanced PAH, with New York Heart Association functional classes IV (n = 6) or III (n = 5), a mean 6-min walk distance of 376 ± 29 m, a mean Borg dyspnea score of 5.7 ± 0.5, and clinical signs of right heart failure, including turgescent jugular veins (n = 10), marked hepatomegaly (n = 6), and edema of the lower extremities (n = 4). Two patients presented with repetitive episodes of syncope.

Control Subjects

Ten healthy persons matched for age (mean age, 48 ± 2 years), BMI (mean BMI, 23 ± 1 kg/m^2), and gender (5 were women) served as control subjects. All of them had normal clinical examination findings. None was receiving any medication.

Atrial Septostomy and Invasive Hemodynamic Determinations

A Swan-Ganz pulmonary artery catheter was inserted in nine patients via a femoral vein for the measurement of RAP, pulmonary artery pressure (PAP), pulmonary artery occlusion pressure, and mixed venous O_2 saturation. Sa_{O_2} and mixed venous blood O_2 saturation were measured by oximetry before and after patients underwent atrial septostomy. In two patients, it was impossible to place a Swan-Ganz catheter beyond the right atrium. In one of these patients, a Cournand catheter was placed to determine PAP. Left atrial pressure (LAP) was measured before and after the procedure using a pigtail fluid-filled catheter positioned across the interatrial septum. In one patient, we did not measure LAP before the atrial septostomy. In this patient, we used pulmonary artery occlusion pressure as a surrogate measure of LAP.

Atrial septostomy was performed as previously reported.[11] A balloon catheter was passed across the septum through the sheath on a guidewire. The sheath was withdrawn to the right atrium, and the balloon was inflated until the waist was abolished under fluoroscopic control. Serial measurements were made of Sa_{O_2} and PAP. To obtain the measurements, the balloon was withdrawn into the sheath. The procedure was repeated with increasing balloon sizes until a septal defect was created ensuring a 10% fall in Sa_{O_2}. The maximum sizes of the balloons used were as