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Bosentan for mild pulmonary vascular disease in Asd patients (the BOMPA trial): a double-blind, randomized controlled, pilot trial ☆,☆☆

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Using bicycle stress echocardiography, pulmonary vascular resistance can be estimated by linear regression analysis of pressure-flow plots. Previously, we have shown that patients who underwent atrial septal defect (ASD) closure at older age (>34 years of age) – although having normal pulmonary artery pressures (PAP) at rest – have an increased dynamic pulmonary vascular resistance (dPVR) as assessed using bicycle stress echocardiography [1]. Increased dPVR seems to be related with exercise intolerance and persistence of tricuspid valve regurgitation (TR) after ASD closure [2]. Both increased dPVR and persistent TR may lead to future complications, such as atrial fibrillation. We hypothesized that disease targeting therapy, such as endothelin receptor antagonists, decreases dPVR in patients who underwent late ASD closure. The purpose of this pilot trial (ClinicalTrials.gov NCT 01218607) was to evaluate the effect of bosentan on dPVR. Ten patients who underwent ASD closure (2 surgical, 8 percutaneous) after the age of 34 years at least six months before study enrolment were included in the study (inclusion from January 2011 to September 2012). They were randomized (1:1 design and double blinded) into group A, treated with bosentan and group B, treated with placebo. Bosentan was initiated at a dose of 62.5 mg bid, which was uptitrated after one month to 125 mg bid. The patients were prospectively followed for 16 weeks. All the patients underwent a bicycle stress echocardiography at inclusion, after one month, and at the end of the study. At each time point, dPVR was calculated as reported earlier [1]. Briefly, exercise echocardiography was performed on a semisupine ergometer (Easystress, Ecogito Medical sprl, Liège, Belgium). The protocol started at 25 W with an increment of 25 W every 2 min until the maximum tolerated load. dPVR was derived from a linear approximation using linear regression analysis from PAP pressure-flow plots. A single observer performed the analyses. In all patients, liver function tests were followed for safety. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. SPSS (Version 20, SPSS, Chicago, IL) was used for statistical analysis. Continuous data are reported as mean and standard deviation (SD). Comparative statistics (paired and un-paired) were performed where applicable. For each group, an analysis of covariance (ANCOVA) was performed to evaluate whether the slope of the PAP pressure-flow plots changed during the

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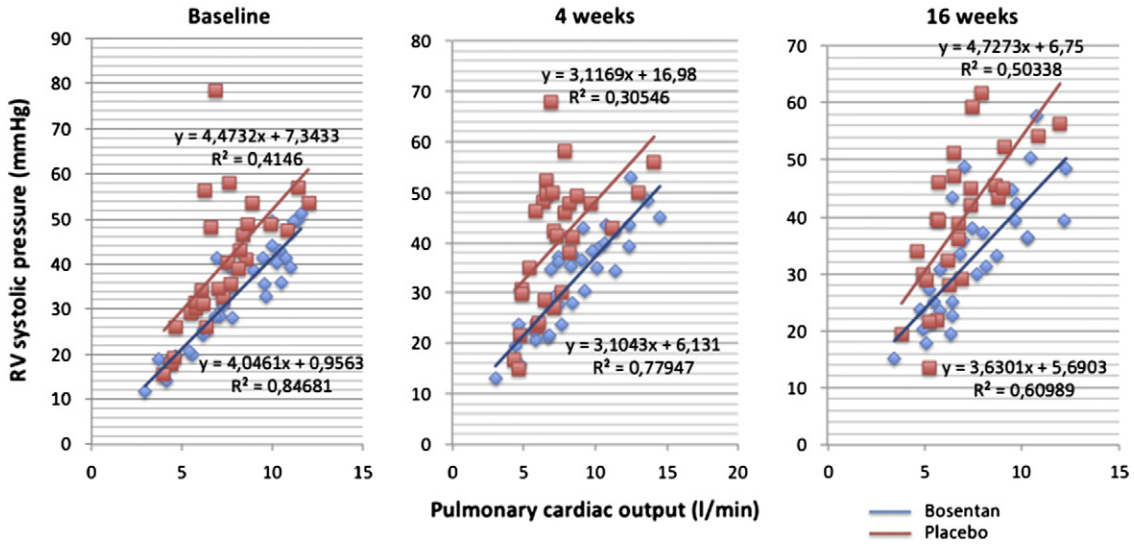

Fig. 1. Pressure-flow plots for bosentan and placebo treated patients at different time points (baseline, 4 weeks, 16 weeks). Results of the linear regression analyses are indicated in all graphics. The slope at each type point is represented by the β variable of the linear regression.

study period. All tests were two-sided and a p value <0.05 was considered to be statistically significant.

The study cohort consisted of one male and 9 females, mean age 55 ± 12 years. Mean body weight and length were 70 ± 13 kg and 163 ± 9 cm, respectively. At inclusion, the maximal workload and heart rate during the bicycle stress echocardiography for the patients in group A were 100 ± 18 W and 111 ± 17 bpm, respectively. In group B, at inclusion, the maximal workload and heart rate were 105 ± 21 W and 123 ± 29 bpm, respectively. Mean systolic PAP at rest was 19 ± 5 mm Hg and 23 ± 8 mm Hg ($p = 0.35$) for group A and B, respectively. Left ventricular parameters were normal for all patients. At 16 weeks, the maximal workload and heart rate for the patients in group A were 100 ± 18 W and 115 ± 22 bpm, respectively. In group B, the maximal workload and heart rate were 102 ± 13 W and 120 ± 21 bpm, respectively. Mean systolic PAP at rest was 20 ± 3 mm Hg and 23 ± 7 mm Hg ($p = 0.37$) for group A and B, respectively. All variables as discussed above and measured at week 4 and 16 weeks were similar to those of baseline. The evolution of the slopes of both study arms at each time point is depicted in Fig. 1. ANCOVA analysis showed that the slope from the PAP pressure-flow plots significantly changed over time in group A ($F = 4.3$, $p = 0.017$), whereas the slope did not change in group B ($F = 0.1$, $p = 0.90$). None of the patients experienced intolerance and liver function tests remained normal in all.

This study indicated that treatment with bosentan for 16 weeks in patients who underwent late ASD closure decreased dPVR. Bosentan was well tolerated and no adverse effects were observed. A longstanding volume overload of the pulmonary circulation through a left-to-right shunt may cause pulmonary vascular lesions eventually leading to increased PAP and even pulmonary arterial hypertension (PAH). Although shunt closure may normalize resting PAP in most patients [3], we recently documented that despite having normal PAP at rest, dPVR may be increased during exercise suggesting the presence of minimal pulmonary vascular damage (PVD) [1]. The importance of minimal PVD is currently not known, but may be related to morphometric changes in the right heart, such as persistence of TR after ASD closure [2]. Possibly, increased dPVR may be a precursor of PAH and a useful screening tool for early detection of PAH. Finally, our trial showed that bosentan decreased dPVR, which supports the hypothesis that increased dPVR is an expression of minimal PVD. Bosentan was chosen because of its beneficial effect on pulmonary vascular resistance in patients with congenital heart disease PAH [4]. Our major limitation was the low number of patients so that the study was underpowered for comparative statistics.

Larger trials are needed to determine the predictive value of dPVR and whether modifying dPVR would change predefined clinical outcome.

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