SCIENTIFIC LETTER

# Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension

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In pulmonary arterial hypertension (PAH) an increased pulmonary vascular resistance results in chronic pressure overload on the right ventricle and induces pathological right ventricular (RV) remodelling and RV failure. This causes limited exercise capacity, fatigue and increased mortality. Several treatment options have become available for PAH, and in patients given monotherapy, a second drug of a different class is given to improve symptoms and exercise capacity. Whether the addition of a second treatment reverses RV remodelling has not been described. In this study, the phosphodiesterase 5 inhibitor sildenafil was added to treatment with bosentan, an endothelin receptor antagonist. The objective of this study was to investigate whether the addition of sildenafil reverses RV remodelling and further improves RV function in patients with PAH treated with bosentan.

## METHODS

In 15 patients with PAH receiving bosentan for one year, sildenafil was added for three months. Sildenafil was started at 50 mg twice daily and increased to 50 mg thrice daily after four weeks. At the start of the study and again after one year of bosentan, right-heart catheterisation with vasoreactivity testing, cardiac magnetic resonance (CMR) and 6 min walk test (6MWT) were performed. N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined after one year of bosentan and after three months of combination therapy. After three months of combination therapy, the effects of the addition of sildenafil were evaluated with CMR, 6MWT and NT-proBNP. CMR was performed according to a previously described protocol and analysed by one observer blinded to clinical aspects of the study.[1] The 6MWT was performed according to American Thoracic Society guidelines.[2] Blood was analysed for NT-proBNP plasma concentrations (ECLIA, Roche Inc, Mannheim, Germany). Blood was sampled with the patients at rest within 24 h of CMR measurements. The institutional ethics review committee approved the study, and all patients gave informed consent.

Data are presented as mean (SD). Changes in parameters were analysed with analysis of variance for multiple assessment. Changes in NT-proBNP were analysed with the Wilcoxon signed rank test. Correlation coefficients were determined by linear regression analysis.

## RESULTS

Of the 15 patients, 12 were women, and the age was 45 (15) years. Causes of PAH were idiopathic PAH (nine patients), HIV (one patient), collagen vascular disease (three patients) and congenital systemic to pulmonary shunt (two patients). Thirteen patients were in New York Heart Association functional class III and two patients were in class II. Baseline pulmonary artery pressure was 54 (13) mm Hg and pulmonary vascular resistance was 866 (450) dyn·s·cm$^{-5}$. Side effects after addition of sildenafil were headache (one patient), heartburn (one patient) and epistaxis (one patient). None of the 15 patients had documented liver function abnormalities or changes in haematological or biochemical measurements. Table 1 summarises cardiac parameters assessed by CMR.

**Table 1** Changes in cardiac function, mass and volume in 15 patients with pulmonary arterial hypertension treated with bosentan for one year with sildenafil added for three months

| Variable | Baseline | 12 months bosentan | 12 months bosentan + 3 months combination |
|---|---|---|---|
| Cardiac index (l/min/m$^2$) | 2.0 (0.7) | 2.3 (0.6) | 2.8 (1.1)** |
| Stroke volume index (ml/m$^2$) | 30 (16) | 32 (14) | 36 (18) |
| RVEF (%) | 33 (16) | 39 (24) | 43 (19)* |
| LVEF (%) | 62 (22) | 70 (20) | 70 (20) |
| RV mass (g) | 87 (37) | 109 (36) | 101 (33)** |
| LV mass (g) | 129 (37) | 132 (28) | 133 (32) |
| RVEDV (ml) | 162 (34) | 174 (58) | 153 (28) |
| LVEDV (ml) | 83 (15) | 82 (27) | 86 (26) |
| RVEDV:LVEDV ratio | 2.1 (0.6) | 2.4 (0.9) | 2.0 (0.6)** |

Data are mean (SD).
*p<0.05; **p<0.01.
LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; RV, right ventricular; RVEDV, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction.

NT-proBNP decreased from 1269 ng/l (95% confidence interval (CI) 668 to 1869 ng/l) at 12 months of bosentan to 817 ng/l (95% CI 308 to 1326 ng/l) after sildenafil ($p = 0.007$). The decrease in NT proBNP was related to a decrease in RV dilatation ($R = 0.55$, $p = 0.035$), to a decrease in RV hypertrophy ($R = 0.61$, $p = 0.011$) and to an improvement in RV ejection fraction ($R = -0.62$, $p = 0.015$). The mean 6MWT increased from 399 (75) m at baseline to 429 (81) m after one year of bosentan and to 472 (91) m after the addition of sildenafil ($p < 0.01$). The improvement in 6MWT correlated with the improvements in RV function: cardiac index ($R = 0.71$, $p = 0.003$), RV stroke volume index ($R = 0.63$, $p = 0.012$) and RV ejection fraction ($R = 0.53$, $p = 0.043$). Improvement in 6MWT was not significantly related with decrease in RV dilatation and hypertrophy.

## DISCUSSION

RV mass was increased at the start of bosentan treatment and increased further after one year. After sildenafil was added,

**Abbreviations:** 6MWT, 6 min walk test; CMR, cardiac magnetic resonance; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RV, right ventricular

RV mass reduced significantly. In a recent comparison study between sildenafil and bosentan, RV mass did not change after three months of bosentan treatment, whereas sildenafil reduced RV mass.[3] Two mechanisms can explain the effects of sildenafil on RV mass. Firstly, RV mass decreases because the pulmonary vascular resistance decreases, resulting in less RV wall stress. The reduction in RV wall stress is also supported by the decrease in NT-proBNP after three months of sildenafil. Moreover, the reduction in NT-proBNP correlated with the reduction in RV dilatation and hypertrophy. Secondly, sildenafil may have an intrinsic effect on the heart. A recent animal study found that blocking the intrinsic catabolism of cyclic GMP with sildenafil suppresses chamber and myocyte hypertrophy and improves in vivo heart function.[4]

In patients with PAH, RV end diastolic volume is increased and left ventricular (LV) end diastolic volume is decreased, resulting in an increased RV:LV diastolic volume ratio. We observed a reduction in the RV:LV diastolic volume ratio after the addition of sildenafil, indicating improved LV function mediated by improved LV filling and interventricular interaction.

The improvement of 6MWT after one year of bosentan treatment was 30 m. Notably, the 6MWT improved a further 42 m in the following three months of bosentan and sildenafil combination therapy. These results confirm the finding of Hoeper *et al*[5] that addition of sildenafil can be effective in patients with PAH while they are receiving bosentan.

The side effects of the combination therapy were only minor, although our study population is too small to draw firm conclusions. Also, the study duration was too short to address safety of long-term combination therapy with bosentan and sildenafil. Three patients reported minor side effects; these patients' dosage of sildenafil was lowered to 25 mg thrice daily.

Although it may be tempting to conclude from our results that combination therapy is more effective than monotherapy, the study was not designed for this purpose. In the absence of a control group it remains unclear from our study whether the improvement in RV function is a result of combination therapy or due to the effects of sildenafil alone. Despite these limitations, our study showed that addition of sildenafil reversed RV dilatation and hypertrophy in patients already receiving treatment and that these positive effects on RV structure and function occurred in parallel with improvements in exercise capacity and NT-proBNP concentrations.

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