Journal of Cardiovascular Magnetic Resonance (2005) **7,** 853–854

ISSN: 1097-6647 print / 1532-429X online
DOI: 10.1080/10976640500295540

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CASE REPORT

Functional and metabolic recovery of the right ventricle during Bosentan therapy in idiopathic pulmonary arterial hypertension

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An impaired high-energy phosphate metabolism might play a critical role in the pathogenesis of right ventricular (RV) failure due to chronic pulmonary arterial hypertension (PAH). 31P-NMR spectroscopy is well established for measurements of high-energy phosphate metabolites in various left ventricular heart diseases, however, mainly for technical and sensitivity reasons, its successful transfer for measurements in the RV is currently missing. In the present study, the usefulness of this non-invasive approach is not only shown in RV failure due to PAH but also tested during subsequent therapy.

Key Words: Pulmonary hypertension; Magnetic resonance spectroscopy; Right ventricular function; Myocardial metabolism

A 54-year-old man presented with a 3-month history of rapidly progressive dyspnea with exercise. After extensive diagnostic work-up, including ventilation-perfusion scanning, computed tomography of the chest, left and right heart catheterization, Doppler echocardiography, exercise and lung function tests as well as laboratory tests including vasculitis-associated antibodies and HIV, the diagnosis of idiopathic pulmonary arterial hypertension (PAH) was made. The patient was in functional NYHA class III–IV, the mean pulmonary arterial pressure was 65 mmHg, and the 6-min walk distance (6-MWD) was 280 m. The patient was started on chronic medical therapy including diuretics and anticoagulation and was a non-responder to acute vasodilatator challenge. MR imaging revealed a massively dilated and hypertrophied right ventricle (RV mass 105 g) (Fig. 1) with a markedly reduced ejection fraction (EF) of 16% and a reduced cardiac output (CO) of 3.2 L/min. RV stroke volume was 46 mL. Treatment with the endothelin-receptor antagonist Bosentan was started at a dose of 62.5 mg twice a day and the dose was increased to 125 mg twice a day after 4 weeks.

Since it has been shown previously in numerous models of heart failure and in clinical heart failure that the failing left ventricle is characterized by changes in myocardial energetics, including a depletion of phosphocreatine (PCr), it is hypothesized that impaired energetics play a critical role in

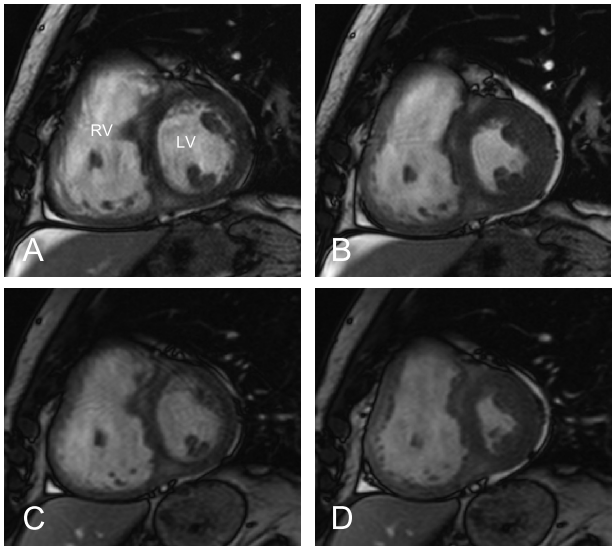

Figure 1. End-diastolic (A) and end-systolic (B) short axis views before and 6 month after treatment with Bosentan (C and D). Note the significant enlargement of the right ventricle (RV) and the thickening of its free wall. Compared to pre-treatment, end-diastolic RV volume decreased from 237 mL to 179 mL under Bosentan therapy, and stroke volume increased from 44 mL to 77 mL. MR imaging was performed on a 1.5-T clinical scanner using an ECG-triggered 2D cine true FISP sequence (FOV 400 × 400 mm^2, 10 contagious slices, slice thickness 8 mm).

Received 6 May 2005; accepted 8 August 2005.
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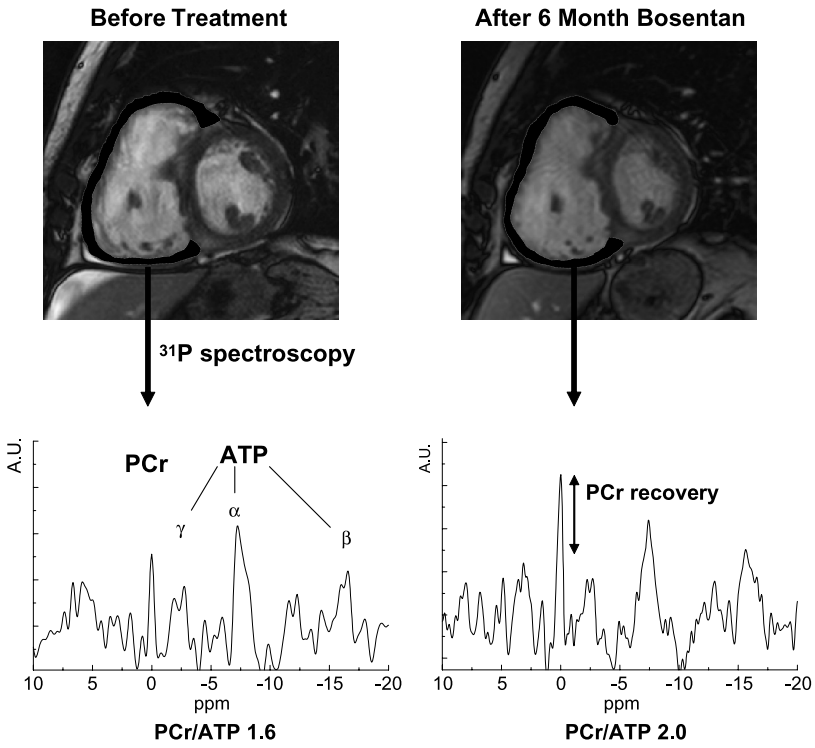

Figure 2. ^{31}P-spectral localization with optimum point spread function (SLOOP) spectra obtained from the right ventricle before and 6 months after Bosentan treatment. The shaded area denotes the compartment of the spatial response function giving rise to the RV ^{31}P-spectra. Note the significant increase of the PCr peak (arrow) relative to the ATP peaks during treatment. The ^{31}P-NMR spectroscopic measurements were performed on the same 1.5-T scanner using the SLOOP technique with a commercially available, double resonant ^{31}P/^{1}H-surface coil. ^{31}P-spectroscopic parameters were: automatic phase-sensitive map-shim, 3D chemical shift imaging sequence (double-oblique orientation, FOV 400 × 400 × 320 mm^3, 16 × 16 × 8 phase encoding steps, nuclear Overhauser enhancement, 45° flip angle in the right ventricle, standard T_1-values, curve fitting using ''AMARES''). ppm = parts per million; A.U. = arbitrary units; PCr = phosphocreatine; γ-, α-, and β-phosphate of ATP.

the failing RV as well. Clinical ^{31}P-NMR spectroscopy has proven its potential to non-invasively assess the steady-state concentrations of the high-energy phosphate metabolites in the left ventricle in numerous disease states in the past. However, due to technical and sensitivity reasons, the successful application of ^{31}P-NMR spectroscopy to characterize the energy metabolism of the right ventricle in the human heart is missing so far. Because of continuous improvements in the spectroscopic techniques (i.e., SLOOP-technique for anatomic shaped localization) (Fig. 2), it is now possible to reliably assess myocardial high-energy phosphate content also in the human right ventricle (RV). Therefore, ^{31}P-MR spectroscopy of the RV was performed in the present patient to evaluate RV energetics at baseline and after 6 month of Bosentan therapy.

During Bosentan therapy, the patient improved rapidly to NYHA class II, and the 6-MWD increased to 448 m. Whereas RV mass remained elevated (103 g) after 6 month of therapy, RV stroke volume (77 ml), CO (6.5 l/min) and EF (30%) doubled.

The phosphocreatine-to-adenosintriphosphate ratio (PCr/ATP) of the RV, an indicator of its energetic state, showed a substantial increase from 1.6 at baseline to 2.0 during Bosentan treatment (Fig. 2).

This example demonstrates the potential of magnetic resonance to non-invasively monitor not only the functional but also the metabolic recovery of the right ventricle during chronic vasodilator therapy for pulmonary hypertension. With the help of this powerful biophysical tool, it will be possible in the future not only to assess the energy metabolism of the RV in various disease states but also to monitor the relative changes during disease progression or to quantify the regression during therapy. This will not only help to better understand the underlying pathogenesis of the various diseases but also to tailor the available therapeutic options in the future.