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The emerging role of PDE5 inhibition in heart failure

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Background

Heart failure (HF) is frequently associated with dysregulation of nitric oxide-mediated vascular tone. In HF patients with left ventricular systolic dysfunction (LVSD), right ventricular (RV) performance is an important determinant of exercise capacity and prognosis. Abnormal regulation of pulmonary vascular tone in these patients can lead to an increase in RV afterload and diminished function at rest and with exercise. The increased pulmonary vasomotor tone in HF patients is responsive to nitric oxide (NO), as administration of inhaled NO to patients with LVSD reduces pulmonary vascular resistance (PVR) and increases cardiac index (CI). As these beneficial effects of inhaled NO persist only briefly after cessation of its administration technically challenging to administercontinuously to ambulatory patients, the hydrolysis of its second messenger in vascular smooth muscle cells, cGMP, is an alternative target for pharmacologic augmentation through inhibition of phosphodiesterases (PDEs) responsible for its catabolism. Selective inhibition of Type 5 PDE, the predominant PDE isoform responsible for hydrolysis of cGMP in the lungs has been shown to lower resting PVR and pulmonary capillary wedge pressure (PCWP) and increase CI without causing systemichypotension in LVSD patients

Methods and results

Thirteen patients with New York Heart Association class III HF underwent assessment of right heart hemodynamics, gas exchange, and first-pass radionuclide ventriculography at rest and with cycle ergometry before and 60 minutes after administration of 50 mg of the oral PDE5 inhibitor sildenafil. Sildenafil reduced resting pulmonary arterial pressure, systemic vascular resistance (SVR), and PVR, and increased resting and exercise CI ($P < 0.05$ for all) without altering mean arterial pressure, heart rate, or PCWP. Sildenafil reduced exercise pulmonary arterial pressure, PVR, and PVR/SVR ratio (Figure 1), which indicate a selective pulmonary vasodilator effect with exercise. Peak V_{O_2} increased (15 ± 9%) and ventilatory response to CO_2 output (V_E/V_{CO_2} slope) decreased (16 ± 5%) after sildenafil treatment. Improvements in right heart hemodynamics and exercise capacity were confined to patients with secondary pulmonary hypertension (rest pulmonary arterial pressure > 25 mm Hg).

Conclusion

The present study shows that in patients with systolic HF, PDE5 inhibition with sildenafil improves peak V_{O_2} reduces V_E/V_{CO_2} slope, and acts as a selective pulmonary vasodilator during rest and exercise in patients with HF and pulmonary hypertension The results of a recently completed placebo-controlled study of chronic PDE5 inhibitor administration to HF patients with LVSD will be discussed.

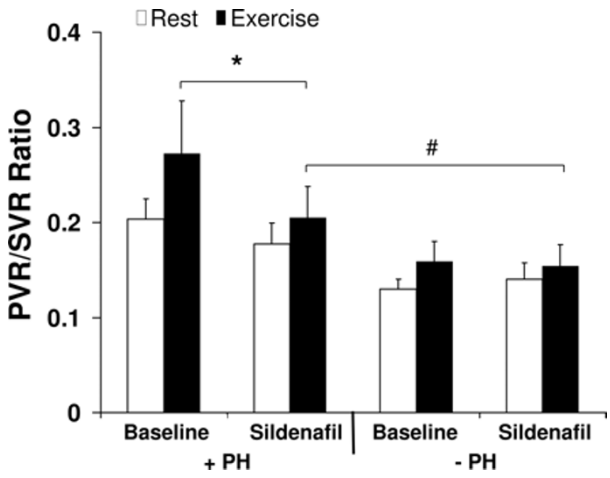

Figure 1
Effect of sildenafil on the ratio of PVR to SVR. *$P < 0.05$ for comparisons between baseline and sildenafil. #$P < 0.05$ for between-group comparison of patients in the +PH and -PH groups.

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