# Repetitive and Brief Occlusion of Total Right Atrium Venous Blood Flow Improves Experimental Pulmonary Arterial Hypertension: a novel potential therapeutic strategy

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**Abstract**

Pulmonary arterial hypertension (PAH) is a vascular disorder associated with significant morbidity and mortality. The pathophysiology of PAH remains controversial, but the only currently available therapies for PAH are pharmacological pulmonary artery vasodilation, decreasing right ventricular (RV) afterload, and relieving symptoms. By now, there is no therapy being able to minimize vascular remodeling processes and thus to reverse or delay the natural history of the disease. It has been generally thought that reduction of RV preload was detrimental, which deteriorated the systemic hemodynamics. In the present study, however, we repetitively and briefly occluded (RBO) both superior vena cava and inferior vena cava by ligation (occlusion for less than 5 seconds then re-open for 30 seconds and repeated 5 cycles as one sequence, 1 sequence every 6 hours) to intermittently restrict RV preload, for continuous 24 hours, total 5 sequences, in the Sugen 5416 (VEGF receptor blocker) and hypoxia induced PAH rat models and we found this strategy was beneficial for lowering pulmonary vascular resistance (PVR).

## Main

Pulmonary arterial hypertension (PAH) is a vascular disorder associated with significant morbidity and mortality. The pathophysiology of PAH remains controversial, but the only currently available therapies for PAH are pharmacological pulmonary artery vasodilation, decreasing right ventricular (RV) afterload, and relieving symptoms. By now, there is no therapy being able to minimize vascular remodeling processes and thus to reverse or delay the natural history of the disease. It has been generally thought that reduction of RV preload was detrimental, which deteriorated the systemic hemodynamics. In the present study, however, we repetitively and briefly occluded (RBO) both superior vena cava and inferior vena cava by ligation (occlusion for less than 5 seconds then re-open for 30 seconds and repeated 5 cycles as one sequence, 1 sequence every 6 hours) to intermittently restrict RV preload, for continuous 24 hours, total 5 sequences, in the Sugen 5416 (VEGF receptor blocker) and hypoxia induced PAH rat models[1] and we found this strategy was beneficial for lowering pulmonary vascular resistance (PVR).

To assess the acute effects of RBO treatment, hemodynamic evaluation was performed after 1 hour rest following the 24-h-RBO treatment. In studies of acute effects of RBO in vivo, the mean peak RV systolic pressure (RVSP) was significantly lower in PAH+RBO group (39.1±1.1 mmHg, n=7) than in PAH+sham group (62.2±2.9 mmHg, n=5), see in Fig. 1A. In the PAH+RBO group, mean artery pressure (MAP) decreased significantly 14% (Fig. 1B) and cardiac output (CO) decreased significantly 4% (Fig. 1C) compared to the PAH+sham group. RBO treatment also decreased MAP and CO in control groups (CTL+RBO vs CTL+sham, Fig. 1B, C). PVR, calculated by dividing RVSP by CO, was acutely decreased about 35% in PAH+RBO group compared with PAH+sham group.

The estimation of PVR in vivo could be affected by many biological factors. To directly examine the acute effect of RBO on PVR in lungs, we isolated lungs and performed perfusion experiments[2] after RBO treatment finished in vivo. Lungs were perfused with a mixture of blood and physiological saline solution. Perfusion was maintained at a constant flow (0.04 $ml \cdot min^{-1} \cdot Kg^{-1}$) so that changes in arterial perfusion pressure reflected changes in total PVR. Mean pulmonary arterial pressure (PAP) in PAH+sham group (n=7) was 20.3±0.7 mmHg and was significantly reduced to 14.2±0.8 mmHg in PAH+RBO group (n=8, Fig. 1E). Thus the acute effects of RBO were structural dilation of pulmonary artery as PVR decreased in vivo and the dilation maintained after lungs isolated.

To test the long-term effect of once RBO treatment, we measured hemodynamics in vivo after 1 week refeeding following RBO treatment in independent groups. The mean peak RVSP in long-term PAH+RBO group (Long-PAH+RBO) deceased further (27.3±1.7 mmHg, n=7, Fig. 1A) than in the acute PAH+RBO. The acute reduction of MAP and CO in PAH+RBO group observed previously was largely reversed in Long-CTL+RBO and in Long-PAH+RBO group (Fig. 1B, C). Thus the calculated PVR in Long PAH+RBO was decreased further than in the acute effect PAH+RBO group.

To confirm that the PVR could be decreased further after RBO treatment followed by a one-week normal feeding, we measured the PAP in isolated lung perfusion experiment after PAH rats were

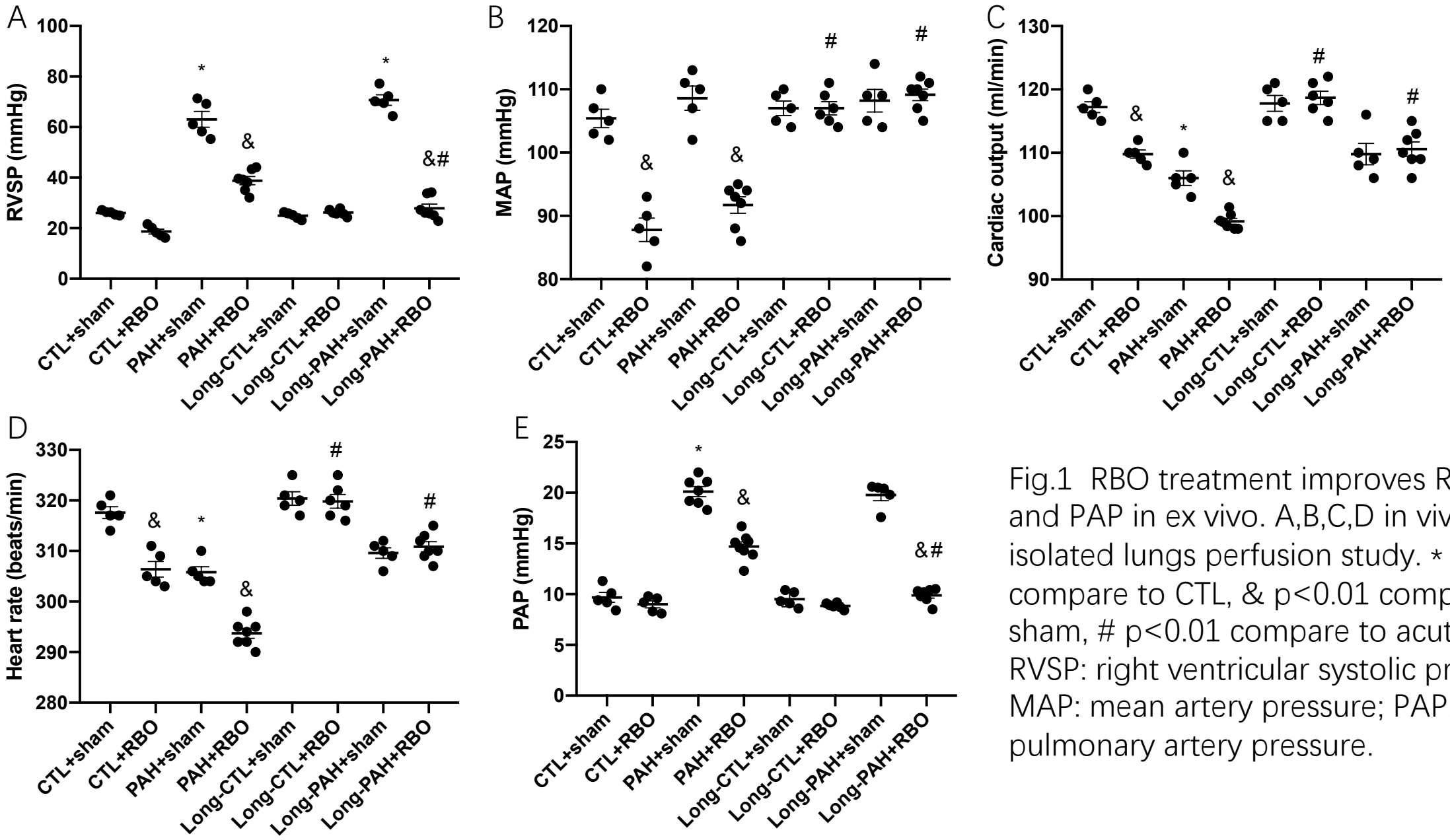


Fig.1 RBO treatment improves RVSP in vivo and PAP in ex vivo. A,B,C,D in vivo study, E isolated lungs perfusion study. * $p<0.01$ compare to CTL, & $p<0.01$ compare to sham, # $p<0.01$ compare to acute group. RVSP: right ventricular systolic pressure; MAP: mean artery pressure; PAP: pulmonary artery pressure.

treated by 1 week normal feeding following the RBO treatment. PAP in Long-PAH+RBO group was 9.7±0.8 mmHg (n=7, Fig. 1E), which was significantly lower than in Long-PAH+sham group and lower than the acute effect in the PAH+RBO group. Therefore, we confirmed that additional beneficial effects were observed after a period of normal feeding, including further decrease in PVR.

This is the first report of RBO treatment research for PAH. In present study, we found that intermittent reduction of RV preload by RBO treatment could reduce PVR and RVSP acutely which improved PAH. The side effect of RBO treatment was acute reduction of systemic MAP and CO. However, RBO followed by a one-week normal feeding period, the MAP and CO could recover and PVR decreased further. The restriction or reduction of RV preload might be previously thought as an adverse intervention by medicine for PAH because of the possible systemic hemodynamic deterioration. However, in present study, we briefly and repetitively restricted the RV preload using a non-medicine approach which provided a positive result on PAH therapy. The systemic hemodynamic adverse effects of RBO treatment were acceptable and reversable. The acute reduction of PVR by RBO treatment may be mediated by vasodilation and the beneficial effect maintained at least 1 week after RBO treatment. The mechanism of maintained pulmonary artery dilation by RBO treatment is not clear, and the study with respect to the effects of RBO in a longer time observation and on a big animal model is carrying on. The effect of RBO treatment on systemic hypertension is also under investigation. We only name this mechanism as a hypo-load induced vasodilation phenomenon.

[1] K. Abe *et al.*, “Formation of plexiform lesions in experimental severe pulmonary arterial hypertension,” *Circulation*, vol. 121, no. 25, pp. 2747–2754, Jun. 2010, doi: 10.1161/CIRCULATIONAHA.109.927681.

[2] E. Cadogan, N. Hopkins, S. Giles, J. G. Bannigan, J. Moynihan, and P. McLoughlin, “Enhanced expression of inducible nitric oxide synthase without vasodilator effect in chronically infected lungs,” *Am. J. Physiol.*, vol. 277, no. 3, pp. L616-627, 1999, doi: 10.1152/ajplung.1999.277.3.L616.