Renal Denervation Reduces Pulmonary Vascular Remodeling and Right Ventricular Diastolic Stiffness in Experimental Pulmonary Hypertension

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HIGHLIGHTS

- Neurohormonal dysfunction (increased sympathetic nervous system and renin angiotensin-aldosterone system) play an important role in pulmonary hypertension progression.
- In this proof-of-concept study we demonstrated in 2 pulmonary hypertension rat models that renal denervation therapy improved pulmonary vascular remodeling, lowered right ventricular afterload, and decreased right ventricular stiffness.
- Renal denervation effects may be associated with a suppression of the renin-angiotensin-aldosterone system.
SUMMARY

Neurohormonal overactivation plays an important role in pulmonary hypertension (PH). In this context, renal denervation, which aims to inhibit the neurohormonal systems, may be a promising adjunct therapy in PH. In this proof-of-concept study, we have demonstrated in 2 experimental models of PH that renal denervation delayed disease progression, reduced pulmonary vascular remodeling, lowered right ventricular afterload, and decreased right ventricular diastolic stiffness, most likely by suppression of the renin-angiotensin-aldosterone system. (J Am Coll Cardiol Basic Trans Science 2017;2:22-35) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

METHODS

All experiments were approved by the Institutional Animal Care and Use Committee of the VU University, Amsterdam, the Netherlands (FYS 13-05 and 14-10) and performed according to the Declaration of Helsinki conventions for the use and care of animals.

EXPERIMENTAL PH. In this study we investigated the effects of RD-therapy in 2 PH animal models: monocrotaline (MCT) and sugen 5416 combined with chronic hypoxia (SuHx) (4,22,23). PH status was confirmed by echocardiography at week 2 (MCT model) and week 6 (SuHx model); at this point animals were randomized to sham surgery or RD surgery. At end-of-study (week 6 for MCT; week 10 for SuHx, or when animals manifest signs of right heart failure), echocardiography and RV catheterization with pressure-volume analyses were performed. An overview flow of the study design can be found in Supplemental Figure S1A and S1B (4,13).

SURGICAL RD. Thirty minutes before anesthesia (isoflurane induction: 4.0% in 1:1 O₂/air mix; maintenance: 2.0% in 1:1 O₂/air mix), rats received an injection of analgesia (buprenorphine; 0.1 mg/kg subcutaneously). Bilateral flank incisions were performed and the kidneys were approached retroperitoneally. The renal arteries and veins were stripped from the adventitia. All visible renal nerve bundles
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