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Original article

Beneficial Effects of Renal Denervation on Pulmonary Vascular Remodeling in Experimental Pulmonary Artery Hypertension

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ABSTRACT

Introduction and objectives: Activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system is closely associated with pulmonary arterial hypertension. We hypothesized that renal denervation decreases renin-angiotensin-aldosterone activity and inhibits the progression of pulmonary arterial hypertension.

Methods: Twenty-two beagles were randomized into 3 groups. The dogs' pulmonary dynamics were measured before and 8 weeks after injection of 0.1 mL/kg dimethylformamide (control dogs) or 2 mg/kg dehydromonocrotaline (pulmonary arterial hypertension and pulmonary arterial hypertension + renal denervation dogs). Eight weeks after injection, neurohormone levels and pulmonary tissue morphology were measured.

Results: Levels of plasma angiotensin II and endothelin-1 were significantly increased after 8 weeks in the pulmonary arterial hypertension dogs and were higher in the lung tissues of these dogs than in those of the control and renal denervation dogs (mean [standard deviation] angiotensin II: 65 [9.8] vs 38 [6.7], 46 [8.1]; endothelin-1: 96 [10.3] vs 54 [6.2], 67 [9.4]; $P < .01$). Dehydromonocrotaline increased the mean pulmonary arterial pressure (16 [3.4] mmHg vs 33 [7.3] mmHg; $P < .01$), and renal denervation prevented this increase. Pulmonary smooth muscle cell proliferation was higher in the pulmonary arterial hypertension dogs than in the control and pulmonary arterial hypertension + renal denervation dogs.

Conclusions: Renal denervation attenuates pulmonary vascular remodeling and decreases pulmonary arterial pressure in experimental pulmonary arterial hypertension. The effect of renal denervation may contribute to decreased neurohormone levels.

Efectos beneficiosos de la simpatectomía renal sobre el remodelado vascular pulmonar en la hipertensión arterial primaria experimental

Palabras clave:
Hipertensión arterial pulmonar
Inervación simpática renal
Ablación
Endotelina
Angiotensina II

RESUMEN

Introducción y objetivos: La activación tanto del sistema nervioso simpático como del sistema renina-angiotensina-aldosterona está estrechamente relacionada con la hipertensión arterial pulmonar. Nuestra hipótesis era que la simpatectomía renal reduce la actividad del sistema renina-angiotensina-aldosterona e inhibe la progresión de la hipertensión arterial pulmonar.

Métodos: Se asignó aleatoriamente a un total de 22 perros *beagle* a tres grupos de estudio. Se efectuaron determinaciones de la dinámica pulmonar de esos animales antes y 8 semanas después de la inyección de 0,1 ml/kg de dimetilformamida (perros de control) o de 2 mg/kg de deshidromonocrotalina (perros con hipertensión arterial pulmonar y perros con hipertensión arterial pulmonar + simpatectomía renal). Ocho semanas después de la inyección, se determinaron las concentraciones de neurohormonas y se evaluó la morfología del tejido pulmonar.

Resultados: Se observó un aumento significativo de la concentración de angiotensina II y endotelina-1 en plasma después de 8 semanas en los perros con hipertensión arterial pulmonar, y los valores obtenidos en los tejidos pulmonares de estos animales eran superiores a los de los perros del grupo de control y el grupo de simpatectomía renal (medias: angiotensina II, $65 \pm 9,8$ frente a $38 \pm 6,7$ y $46 \pm 8,1$; endotelina-1, $96 \pm 10,3$ frente a $54 \pm 6,2$ y $67 \pm 9,4$; $p < 0,01$). La deshidromonocrotalina aumentó la presión arterial pulmonar media ($16 \pm 3,4$ frente a $33 \pm 7,3$ mmHg; $p < 0,01$), y la simpatectomía renal evitó que se

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produjera este aumento. La proliferación celular del músculo liso pulmonar fue mayor en los perros con hipertensión arterial pulmonar que en los animales de los grupos de control y de hipertensión arterial pulmonar + simpatectomía renal.

Conclusiones: La simpatectomía renal atenúa el remodelado vascular pulmonar y reduce la presión arterial pulmonar en la hipertensión arterial pulmonar experimental. El efecto de la simpatectomía renal puede contribuir a reducir las concentraciones de neurohormonas.

Abbreviations

Ang II: angiotensin II
DHMC: dehydromonocrotaline
ET-1: endothelin-1
PAH: pulmonary arterial hypertension
RSD: renal sympathetic denervation

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a fatal disease characterized by excessive pulmonary vascular remodeling that leads to elevated pressure in the pulmonary vascular system and in the right side of the heart.[1] Although the pathogenesis of PAH remains incompletely understood, previous studies have implicated the increased activity of the sympathetic nerve system and the renin–angiotensin–aldosterone system.[2,3] It has been suggested that increased sympathetic nerve activation could contribute to the alveolar hyperventilation observed in patients with PAH.[4,5] The increased plasma levels of renin and angiotensin II (Ang II) have been closely associated with PAH progression and prognosis.[6] Numerous treatments have been proven to be useful in decreasing PAH, but no treatment has long-term effects.[7,8]

Previous studies have confirmed that a significant reduction in renal noradrenaline spillover and blood pressure can be achieved after catheter-based renal sympathetic denervation (RSD).[9,10] Our previous study demonstrated that plasma Ang II concentrations were attenuated after RSD.[11,12] It is unknown whether RSD has an impact on the other neurohormones and the progression of PAH. Therefore, in the present study, we examined the impact of RSD on pulmonary vascular remodeling and neurohormones in experimental PAH.

METHODS

Preparation of the Animal Model

Twenty-two beagles of either sex, with a mean (standard deviation) weight of 13.5 (2.4) kg, were used in the present study. This study conformed to the current *Guide for the care and use of laboratory animals*, published by the National Institutes of Health (no. 85-23, revised in 1996). The study protocol was approved by the Ethics Committee of Wuhan University. Animal handling was performed according to the Wuhan Directive for Animal Research.

An intramuscular injection of 25 mg/kg ketamine sulfate was administered before pentobarbital sodium premedication. All the dogs were administered pentobarbital sodium (30 mg/kg intravenously), intubated, and ventilated with room air supplemented with oxygen by a respirator (MAO01746, Harvard Apparatus; Holliston, Montana, United States). Continuous electrocardiogram monitoring was performed using leads I, II and III. Group 1 consisted of 7 dogs that received 0.1 mL/kg dimethylformamide. Group 2 comprised 8 dogs that received dehydromonocrotaline (DHMC). Group 3 comprised 7 dogs that received DHMC and renal artery ablation. Group 1 was assigned to the control group (to exclude the effect of dimethylformamide on PAH, we used dimethylformamide as control), group 2 to the PAH group, and group 3 to the PAH + RSD group.

Dehydromonocrotaline was artificially synthesized as described by Mattocks et al.[13] The purity of the DHMC was determined by high-performance liquid chromatography.[14] Dehydromonocrotaline was dissolved in 0.1 mL/kg dimethylformamide just before injection.

Study Protocol

After stable anesthesia was obtained, all the beagles were injected with 1000 U heparin and hemostatic sheaths were inserted into their right femoral veins. Under X-ray fluoroscopy guidance, a 6-Fr Swan-Ganz pulmonary artery catheter (Edwards Lifesciences; Irvine, California, United States) filled with heparinized saline was inserted through the vein. The catheter was connected to both a pressure transducer and a Vigilance monitoring system. The pulmonary artery catheter was delivered through the right atria and ventricle into the small pulmonary artery. Then, the catheter was withdrawn, and measurements were taken of the pulmonary capillary wedge pressure, pulmonary arterial systolic pressure, pulmonary artery mean pressure, right ventricular systolic pressure, and right ventricular mean pressure. Cardiac output was measured using the continuous thermodilution method with the Vigilance monitoring system. We calculated the pulmonary vascular resistance according to the formula (pulmonary vascular resistance = 80 × [pulmonary artery mean pressure – pulmonary capillary wedge pressure]/cardiac output). After the baseline hemodynamic measurements, PAH and PAH + RSD beagles were injected with 2 mg/kg DHMC, and the control beagles were injected with 0.1 mL/kg dimethylformamide via a Swan-Ganz pulmonary artery catheter inserted into the right atria. In the PAH + RSD group, after the baseline hemodynamic measurements, the procedure of RSD was performed as in a previous study.[15] Then, all the beagles were allowed to recover for 8 weeks. After 8 weeks, all hemodynamic measurements were repeated in the 3 groups.

Echocardiography

Transthoracic 2-dimensional and Doppler echocardiography were performed in all the animals (IE33, S5-1, PHILIPS; The Netherlands) at baseline and again after 8 weeks. Standard 2-dimensional short-and long-parasternal views and 4-, 2-, and 3-chamber apical views were obtained. The left atrial dimension,