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Research Article

Renal denervation significantly attenuates cardiorenal fibrosis in rats with sustained pressure overload

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Abstract

To investigate the effects of renal denervation (RDN) on comprehensive cardiac and renal fibrosis in cardiomyopathy. Five weeks after successful transverse aortic constriction (TAC)–induced cardiomyopathy model building, Sprague-Dawley rats were randomly assigned to three groups: (1) RDN, (2) sham, and (3) losartan. Sham TAC rats served as control group. Compared with control, TAC groups showed a significant decrease in left ventricle ejection fraction and increase in ventricular septum thickness and left atrium diameter on echocardiography after 5 weeks. At 10 weeks post-TAC, venous blood samples were collected for fibrosis biochemical assay. Heart and kidney samples were also harvested for fibrosis pathophysiological detection. Cardiac and renal fibrosis quantity results showed that, compared with sham group, collagen volume fraction was significantly decreased in RDN group more than in losartan group. Biochemical parameters such as tumor necrosis factor α, aldosterone, and B-type natriuretic peptide levels as well as biomarkers for fibrosis such as procollagen type I N-terminal propeptide and procollagen type III N-terminal propeptide concentrations were significantly decreased in RDN group in comparison with sham. In addition, compared with sham group, left ventricle tissue protein expression of transforming growth factor-β1 and angiotensin II type I receptor was downregulated, and angiotensin-converting enzyme 2 was upregulated in RDN but not in losartan group. RDN significantly attenuates cardiac and renal fibrosis in cardiomyopathy. Differing from losartan, which only has angiotensin II type I receptor inhibition effects, RDN comprehensively suppresses cardiac and renal fibrogenesis through multiple pathways. J Am Soc Hypertens 2016;10(7):587–596. © 2016 American Society of Hypertension. All rights reserved.

Keywords: Cardiomyopathy; cardiac remodeling; pressure overload; renal sympathetic denervation.

Introduction

Heart failure (HF) is associated with a high morbidity and mortality, leading to a substantial societal burden, and the continued aging of population has exacerbated the problem. The failing heart is characterized by complicated tissue remodeling, of which cardiac fibrosis is the key component. Cardiac fibrosis, which is associated with various cardiac disorders and defined as excessive deposition of extracellular matrix in the heart,[1] strengthens myocardial stiffness in pressure-overload hypertrophy and diminishes ventricular filling and emptying rates.[2] In addition to causing cardiac dysfunction, cardiac fibrosis also leads to increased risks for life-threatening arrhythmia and cardiac sudden death.[3]

HF is accompanied by activation of the sympathetic nerve system (SNS) and rennin angiotensin aldosterone system (RAAS), which is also responsible for renal fibrosis.[3] Meanwhile, renal dysfunction resulting from renal fibrosis worsens clinical prognoses of HF patients.[4]

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Prevention against cardiorenal fibrosis is essential to HF treatment. However, for patients with poor adherence or response to medications, pharmaceutical therapy cannot effectively protect against cardiorenal fibrosis. Therefore, efforts are continually made to develop novel strategies to better prevent cardiac and renal fibrosis in HF, in turn, improve the life qualities and prognoses of these patients.

Renal denervation (RDN), an approach originally designed to treat resistant hypertension, has been shown to improve left ventricular hypertrophy and diastolic function.[5] We reported recently that RDN blocked activation of SNS and RAAS and improved cardiac dysfunction in rats with chronic left ventricle (LV) pressure overload.[6] However, effects of RDN on comprehensive cardiorenal fibrosis in cardiomyopathy have not been investigated yet. Hence, we designed this study to evaluate and compare effects of RDN with losartan on cardiorenal fibrosis in rats with cardiomyopathy induced by transverse aortic constriction (TAC).

Methods

Ethics Statement

All experiment procedures were approved by the Ethics Committee of Nanjing Medical University. The use and care of animals were complied with institutional guidelines.

Animals and Protocols

Forty 6-week-old Sprague-Dawley rats (200–220 g) were provided by Nanjing Medical University Laboratory Animal Center. After being housed in cages for 1 week for adaption period, 35 rats underwent TAC procedure, whereas 5 rats in control group underwent sham TAC. Five weeks after TAC, 18 survival TAC rats were randomly divided into three groups: RDN ($n = 6$), sham ($n = 6$), and losartan ($n = 6$). The rats in losartan group were fed orally with 15 $mg \cdot kg^{-1}$ day^{-1} losartan (Tocris) for another 5 weeks. The dosing regimen of losartan was based on previous published studies.[7] Echocardiography was performed at baseline (week 0), week 5, and week 10 post-TAC.

Transverse Aortic Constriction

TAC was performed in rats as previously described.[8] Briefly, the rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (60 mg/kg) until they lost the pedal withdrawal reflex. Then, with the tracheal intubation and respiratory support, a thoracotomy was performed at the second intercostal space, and the transverse aortic arch was ligated around a bent 20-gauge needle. Then, the needle was removed immediately. Rats in control group underwent the same procedures without aortic arch ligation.

Renal Denervation

Bilateral RDN or sham operation was performed in rats at week 5 of TAC. The procedures were performed as previously described.[6] Briefly, visible nerves, connective tissue, and fat around the renal arteries were stripped or severed. Then, the renal arteries were quickly painted with 20% phenol in absolute ethanol. Finally, renal arteries were washed with physiological saline. The control, sham, and losartan groups underwent the same procedures, but the renal vessels and nerves were kept intact.

Echocardiography

We used a Vevo2100 (VisualSonics, Canada) system equipped with a MS-250, 16.0-21.0 MHZ imaging transducer for echocardiography. Rats were anesthetized with isoflurane in the process.

Histological Analysis

At 10 weeks post-TAC, all rats were killed with an overdose of pentobarbital sodium (200 mg/kg iv.). The heart and kidney samples were harvested immediately. The left atrium (LA) tissue was separated from the heart and was fixed with 4% paraformaldehyde and then embedded in paraffin. The ventricle was cut transversely into two portions. One of the ventricle specimens was embedded in paraffin, and the other part comprising apex was stored at −80°C. For bilateral kidneys, the procedures were the same. Sections cut from paraffin blocks were stained with Masson's trichrome. We randomly selected five sections per sample and five microscopic fields (×400) per section for analysis. In LA, LV samples, we assessed interstitial fibrosis; in kidney, we evaluated glomerular fibrosis. The percent area of fibrosis was determined by the ratio of the blue fibrosis area to the total area. Collagen volume fraction (CVF, expressed by the percentage of the fibrosis area) was used to evaluate the extents of fibrosis by the Image-Pro Plus 6.0 software, as described previously.[9] The cross-sectional area of cardiomyocytes was quantitatively analyzed by morphometry in hematoxylin and eosin–stained sections.

Enzyme-Linked Immunosorbent Assay

Venous blood samples were collected at 10 weeks post-TAC. We obtained plasma by centrifuging whole blood at 4°C (3000 rpm × 10 minutes), and the plasma sample was stored at −80°C until enzyme-linked immunosorbent assay testing. Kidney samples were homogenized in phosphate-buffered saline followed by centrifugation at 3000 rpm for 10 minutes. The supernatant of homogenized kidney was collected to measure the content of tissue norepinephrine. Plasma B-type natriuretic peptide (BNP), norepinephrine, angiotensin II (Ang II), angiotensin (1-7)

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