Effect of Renal Denervation on Cardiac Function and Inflammatory Factors in Heart Failure After Myocardial Infarction

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Abstract: Heart failure (HF) affects around 100 million people and is a staggering burden for health care system worldwide. Rapid and sustained activation of inflammatory response is an important feature of HF after myocardial infarction. Sympathetic overactivation is also an important factor in the occurrence and progression of HF. The beneficial effect of renal denervation (RDN) has been demonstrated in HF. In the current study, we hypothesized that RDN improves cardiac function in HF canine models due to acute myocardial infarction (AMI) and reduced inflammation might be involved. Twenty-four beagles were randomized into the control (n = 8), HF (n = 8), and HF + RDN group (n = 8). The HF model after AMI was established by embolization the anterior descending distal artery with anhydrous ethanol in the HF and HF + RDN group. Bilateral renal artery ablation was performed in the HF + RDN group. Cardiac function, serum creatine kinase, creatine kinase-MB and NT-Pro BNP level, and expression of inflammation-related proteins in myocardial were examined. Because the paraventricular nucleus of the hypothalamus might be involved in inflammation-induced central neural excitation in HF and plays an important role in regulating extracellular fluid volume and sympathetic activity, expression of inflammation-related proteins in hypothalamus was also examined. AMI and post-AMI HF model was created successfully. Compared with the HF group, dogs in the HF + RDN group showed better cardiac function 4 weeks after AMI: lower left ventricular end-diastolic pressure, left ventricular end-diastolic dimension, and left ventricular end-systolic dimension and higher LEVF and left ventricular systolic pressure (P < 0.05 for all) were observed in the HF + RDN group. In addition, dogs in the HF + RDN group had slightly less ventricular fibrosis. Interestingly, RDN had lower expression of inflammation-related proteins including interleukin-6, tumor necrosis factors-α, nuclear factor κB, and monocyte chemotactic protein 1 (P < 0.05 for all) in both myocardial tissue and hypothalamus. RDN can improve cardiac function in dogs with HF after myocardial infarction. Our results suggested that RDN might affect cytokine-induced central neural excitation in HF and later affect sympathetic activity. Our results suggested a potential beneficial mechanism of RDN independent of mechanism involving renal afferent and efferent sympathetic nerves.

Key Words: heart failure, renal denervation, acute myocardial infarction, canine models, inflammatory factors

INTRODUCTION

Heart failure (HF) can develop secondary to various conditions including coronary heart disease, rheumatic heart disease, and hypertension. HF affects around 100 million people and is a staggering burden for health care system worldwide. Although treatments could improve HF symptoms, the prognosis remains poor; the 5 year survival rate of HF remains only 45.5%.1 Sympathetic overactivation is an important factor in the occurrence and onset of HF and is a contributing factor in accelerating disease progression and shortening survival time.2–4 Continuous sympathetic activation leads to apoptosis and necrosis of cardiomyocytes, which further affect myocardial contractility. Continuous sympathetic activation is an important cause of HF and sudden cardiac death.5–7 Studies have shown that spillover of both cardiac and renal norepinephrine increases HF.6,7 Inhibition of excessive activation of the sympathetic nervous system is a key to the treatment of HF.

Renal denervation (RDN) is a therapy that directly targets nerve traffic—renal artery. It not only decreases renal norepinephrine spillover but also decreases whole-body norepinephrine spillover.8 Initially, RDN was applied to treat drug refractory hypertension. However, studies have shown inconsistent results.9–13 Later as researchers discovered that RDN decreases the whole-body sympathetic tone, it has been used to treat other diseases involving sympathetic activation, including pulmonary hypertension,9,14 and arrhythmia.15 The beneficial effect of RDN has been demonstrated in HF.16,17 However, the underlying mechanism is unclear.

In recent years, studies have found that rapid and sustained activation of inflammatory response is an important feature of HF after myocardial infarction. Studies have shown that inflammation
in the heart can cause left ventricular remodeling and left ventricular dysfunction. In patients with HF with reduced ejection fraction and patients with preserved ejection fraction, correlation between increased serum proinflammatory cytokines and adverse clinical outcomes has been observed. Evidence suggested that RDN might affect immune cell activation and inflammation. The paraventricular nucleus (PVN) of the hypothalamus is a key brain region of the neuroendocrine activity and plays an important role in regulating extracellular fluid volume and sympathetic activity. A previous study has shown that inflammatory factors (such as tumor necrosis factors [TNF]-α and IL-1β) increase significantly in HF rats.

In addition, brain tissue and myocardial TNF-α increase almost simultaneously in early HF, and TNF-α and IL-1β in the PVN region increase more markedly. Inhibition of TNF-α and nuclear factor κB (NF-κB) in the lateral ventricle reduce paraventricular nuclear inflammatory factor levels and significantly reduce the sympathetic nerve activity. Moreover, inhibiting inflammation in PVN was shown to decrease sympathetic activity and improve some hemodynamic and anatomic indicators of left ventricular function in HF rats. Thus, we hypothesized that RDN could (1) reduce inflammation in both myocardial tissue and hypothalamus and (2) later inhibit sympathetic activity and improve cardiac function and reduce fibrosis in HF. In the current study, we aimed to investigate the effects of RDN on HF due to acute myocardial infarction (AMI) in canine models.

**METHOD**

This study was performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The Animal Care Committee of Tianjin Medical University approved the study protocol.

**Animal Model**

Twenty-four healthy adult beagles (10 males and 14 females; weight 14–18 kg) were randomly divided into 3 groups: control group (n = 8), HF group (n = 8), and HF + RDN group (n = 8) (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCVP/A505). In the HF group and the HF + RDN group, the HF model after AMI was established by embolization the anterior descending artery with anhydrous ethanol similar to the previous study. The control group only underwent coronary angiography. Four weeks later, bilateral renal artery ablation was performed in the HF + RDN group. In the HF group, only renal artery angiography was performed. Four weeks after ablation, the animal was sacrificed, and myocardium, hypothalamus, and renal artery tissue were collected and analyzed.

**AMI Protocol**

Each beagle was anesthetized with sodium pentobarbital, intubated, and ventilated. Each beagle was connected with physiological instruments (Johnson and Johnson, Linden, NJ) and Mac-Lab Hemodynamics (GE Healthcare, Chicago, IL) to monitor heart rate, blood pressure, and other conditions before and after modeling. Coronary angiography was performed using the femoral route. The distal end of the left anterior descending artery was selected as the embolization site. The 6F JR4.0 guide catheter (Johnson and Johnson) was used for coronary angiography. The microcatheter was sent along the guide wire to the distal end of the anterior descending artery, and 0.2 mL of ethanol was slowly injected through the microcatheter, and 0.25 mL of saline was used to rinse the residual alcohol in the microcatheter. ST segment elevation of the anterior wall lead was observed on the ECG monitor (Fig. 1). After 10 minutes of observation, coronary angiography was performed again, and the distal embolization of the anterior descending artery was confirmed (Fig. 2).

**Renal Denervation**

Bilateral renal artery ablation was performed 4 weeks after successful HF modeling in the HF + RDN group. In brief, bilateral renal arteriography was performed using a 5F JR 4.0 catheter (Johnson and Johnson). A 6F ablation catheter was delivered to the bilateral renal arteries, and both sites were ablated for 90 seconds. Renal angiography was performed again after the end of ablation to determine whether renal artery stenosis occurred. The radiofrequency was set to be 43°C and 10 W, respectively. In the HF group, only renal arteriography was performed.

**Cardiac Function Monitoring**

Echocardiography was performed at baseline, before ablation, and 4 weeks after ablation using CX50 color...
Doppler (Philips, Amsterdam, the Netherlands). Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic pressure (LVEDP), and left ventricular systolic pressure (LVSP) were recorded. Three cardiac cycles were monitored, and the average was taken as the final result. All examinations were performed by the same examiner. A cardiac catheter using a 5F pigtail catheter (Johnson and Johnson) was performed to measure heart rate, LVEDP, and LVSP in each beagle.

Serum Biomarker Measurement

Venous blood was taken at baseline and 6 hours after AMI modeling from each beagle. Serum creatine kinase (CK) and CK-MB were measured by a whole-blood biochemical analyzer (SIEMENS, Tarrytown, NY). NT-ProBNP was measured according to the instruction of the NT-ProBNP enzyme linked immunosorbent assay (ELISA) kit (ab193712; Abcam, Cambridge, MA) at baseline, before ablation, and 4 weeks after ablation. The serum C-reactive protein (CRP) level was measured according to the instruction of the CRP ELISA kit (ab99995; Abcam) before ablation and 4 weeks after ablation. Changes in serum creatinine levels and blood urea nitrogen (BUN) were measured according to the instructions for the creatinine ELISA kit (Abcam). All serum biomarkers data were measured without missing for animals under follow-up. Data were missing for 1 dog in the HF group and 1 dog in the HF + RDN group before RDN and at 4 weeks after RDN.

Tissue Analysis

Four weeks after the ablation, the heart, bilateral kidney, and hypothalamus were collected. The left ventricular fibrosis level was assessed by Masson staining. The interstitial collagen volume fraction was calculated as the area occupied by connective tissue divided by the sum of the areas of connective tissue and cardiac muscle cells. Intramural vessels, perivascular collagen, endocardium, and trabeculae were excluded from this particular analysis. We used 3 slides from each animal and examined 5 areas per slide to calculate the interstitial collagen volume fraction. Western blotting was used to measure the expression of inflammation-related protein including antibodies of interleukin-6 (IL-6), TNF-α, NF-κB, and monocyte chemotactic protein 1 (MCP-1). Hematoxylin and eosin staining was used to measure injury to the renal artery and nerve.

Statistical Analysis

Continuous data were shown as mean ± SD if following normal distribution and median (interquartile range) if not. Categorical data were expressed as number (percentage). Repeated measures analysis of variance was used to compare data measured at baseline, before ablation (ie, 4 weeks after AMI modeling), and 4 weeks after ablation. Post-hoc analysis was performed using the least significant difference method. For non-normal data, the Mann–Whitney rank test was used. A 2-sided P < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS v17 software (IBM Corp).

RESULTS

One dog in the HF group died 4 weeks after the ablation. One dog in the HF + RDN group died 1 day after AMI modeling and the rest underwent RDN successfully.
Cardiac Function

Baseline body weight, heart rate, LVEDD, LVESD, LVEF, LVEDP, and LVSP were measured in each group. As shown in Table 1, there was no significant difference in baseline cardiac function among the 3 groups (P > 0.05 for all).

Before RDN, there was no significant difference in the heart rate among the 3 groups (P > 0.05, Table 2). Compared with baseline, LVEDD, LVESD, and LVEF decreased significantly in the HF and the HF + RDN group (P < 0.05 for all) and were significantly higher than those in the control group (P < 0.05 for all). By contrast, LVSP and LVEDP decreased significantly in both the HF and the HF + RDN group and were lower than those in the control group (P < 0.05 for all). There was no significant difference in cardiac function between the HF group and the HF + RDN group (P > 0.05).

Four weeks after RDN, in the HF + RDN group, LVEDD, LVESD, and LVEF decreased significantly, whereas LVEF and LVSP increased significantly compared with those before RDN (P < 0.05, Table 3). In the HF and HF + RDN group, LVEDP, LVEDD, and LVESD were significantly higher than those in the control group (P < 0.05). The LVSP in the HF group was significantly lower than that in the control group (P < 0.05). Compared with the HF group, LVEDD, LVESD, and LVEF were significantly lower, whereas LVEF and LVSP were higher in the HF + RDN group (P < 0.05 for all). Overall, improved cardiac function was observed in the HF + RDN group.

Comparison of CK and CK-MB Levels

Baseline serum CK levels were not significantly different among the 3 groups: serum CK levels were 76.6 ± 52.8 U/L in the control group, 83.5 ± 35.9 U/L in the HF group, and 87.9 ± 42.1 U/L in the HF + RDN group, respectively (P > 0.05, Fig. 3). Six hours after AMI modeling, serum CK levels in the HF and HF + RDN group increased significantly to 1024.0 ± 147.9 and 947.7 ± 105.4 U/L, respectively. CK levels in the HF and HF + RDN group were significantly higher than that in the control group. A similar pattern was observed in serum CK-MB levels (Fig. 4).

Comparison of NT-ProBNP Levels

At baseline, serum NT-ProBNP levels were 106.70 ± 20.60 pg/mL in the control group, 122.70 ± 18.34 pg/mL in the HF group, and 126.65 ± 16.41 pg/mL in the HF + RDN group, respectively. There was no significant difference among the 3 groups (P > 0.05, Fig. 5). Before RDN, the serum NT-proBNP concentration were significantly higher in the HF and HF + RDN group than the control group (P < 0.05 for both), whereas no significance difference was observed in the HF group and the HF + RDN group. Four weeks after RDN, the serum NT-ProBNP levels were 121.46 ± 23.87 pg/mL in the control group, 1969.40 ± 136.78 pg/mL in the HF group, and 1056.00 ± 166.35 pg/mL in the HF + RDN group, respectively. Serum NT-ProBNP levels were lower in the HF + RDN group than the HF group (P < 0.05).

Comparison of Serum CRP

The baseline serum CRP levels were 159.84 ± 14.15 pg/mL in the control group, 164.23 ± 24.38 pg/mL in the HF group, and 161.32 ± 22.56 pg/mL in the HF + RDN group, respectively. There was no significant difference among the 3 groups (P > 0.05, Fig. 6). Before RDN, serum CRP levels in the HF group and HF + RDN group were slightly higher than that in the control group (P < 0.05 for both). At 4 weeks after RDN, the serum CRP level in the HF + RDN group decreased significantly compared with before RDN and was significantly lower than those in both the HF group and the control group (P < 0.05 for all).

TABLE 3. Comparison of Cardiac Function Indexes 4 Weeks After RDN

|                  | Control Group (n = 8) | HF Group (n = 8) | HF + RDN Group (n = 7) |
|------------------|-----------------------|-----------------|------------------------|
| HR, per min      | 81.63 ± 17.08         | 90.57 ± 8.42    | 84.00 ± 16.00          |
| LVEDD, mm        | 28.68 ± 1.47          | 38.37 ± 1.62*   | 34.59 ± 2.46*†         |
| LVESD, mm        | 22.35 ± 0.88          | 32.49 ± 3.70*   | 26.69 ± 3.35*†         |
| LVEF, %          | 56.79 ± 1.60          | 36.49 ± 2.92*   | 43.93 ± 2.20*†         |
| LVEDP, mm Hg     | 8.38 ± 2.50           | 23.57 ± 5.22*   | 12.86 ± 2.73*†         |
| LVSP, mm Hg      | 117.69 ± 10.06        | 94.10 ± 6.01*   | 110.21 ± 12.15†        |

*P < 0.05 compared with the control group.
†P < 0.05 compared with the HF group.

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Ventricular Tissue Fibrosis
To assess the level of fibrosis in ventricular samples, Masson staining was performed (Fig. 7). No obvious pathological change was observed in the control group. In the HF group, significant amount of interstitial collagen was observed. In addition, a small amount of inflammatory cell infiltration was observed. In the HF + RDN group, some fibrotic change was observed. The collagen volume fraction in the control group was 2.8% ± 0.4%, 5.7% ± 0.5% in the HF group, and 5.0% ± 0.3% in the HF + RDN group. The collagen volume fraction seemed lower in the HF + RDN group compared with that in the HF group, but the difference was not significant. Compared with the HF group, the area occupied by connective tissue in the HF + RDN group was significantly lower, and cardiac cells were arranged more neatly.

Inflammation-Related Protein Expression in Myocardial Tissue
Compared with the control group, the expression of antibodies of IL-6, TNF-α, NF-κB, and MCP-1 in the myocardial tissue was higher in the HF and HF + RDN group (P < 0.05 for all, Fig. 8). In addition, compared with the HF group, expression of the above proteins was downregulated in the HF + RDN group (P < 0.05 for all).

Inflammation-Related Protein Expression in the Hypothalamus
Compared with the control group, the expression of antibodies of IL-6, TNF-α, NF-κB, and MCP-1 in the hypothalamus were upregulated in the HF group and the HF + RDN group (P < 0.05 for all, Fig. 9). Compared with the HF group, the expression of the above protein was downregulated in the HF + RDN group (P < 0.05 for all).

Renal Artery HE Staining
HE staining was performed on renal artery and examined under microscopy (Fig. 10). In the control group and HF group, the vessel wall structure was intact with smooth intima. The medial membrane consisted of multiple layers of annular smooth muscle. The outer membrane nerve fibers were continuous without defects. In the HF + RDN group, the lumen was intact, but the axon of the adventitia was missing, and the nerve fibers were destroyed.

Comparison of Renal Function
At baseline, the serum creatinine levels were 56.23 ± 11.73 μmol/L in the control group, 58.57 ± 13.68 μmol/L in the HF group, and 61.35 ± 18.68 μmol/L in the HF + RDN group, respectively. There was no significant difference among the groups (P > 0.05, Fig. 11). Before RDN, there was no significant difference in serum creatinine among the groups (P > 0.05). At 4 weeks after RDN, the creatinine levels were 53.78 ± 5.78 μmol/L in the control group, 78.64 ± 6.26 μmol/L in the HF group, and 63.59 ± 11.48 μmol/L in the HF + RDN group, respectively. Compared with the control group, the serum creatinine level was significantly higher in the HF group (P < 0.05), whereas no significant difference was observed between the HF + RDN group and the control group. No kidney function deterioration was observed in the HF + RDN group. A similar trend of BUN levels was observed. No significant difference in baseline BUN levels were observed among the 3 groups.
(9.91 ± 2.0 mmol/L in the control group, 9.69 ± 1.7 mmol/L in the HF group, and 10.08 ± 1.8 mmol/L in the HF + RDN group). At 4 weeks after RDN, the BUN level increased significantly in the HF group (15.8 ± 2.2 mmol/L, \( P < 0.05 \) compared with the baseline), whereas the BUN levels in the control group and the HF + RDN group remained stable (10.31 ± 2.1 mmol/L in the control group and 10.9 ± 2.1 mmol/L in the HF + RDN group; \( P > 0.05 \) for both).

DISCUSSION

In this study, we successfully established a canine model of AMI and post-AMI HF. ECG change, elevation in CK and CK-MB, and elevation in NT-ProBNP were observed in both HF and HF + RDN groups. We demonstrated that RDN was performed successfully in the HF + RDN group. In addition, RDN was able to reserve cardiac function deterioration caused by AMI. RDN reduced levels of cytokines and other proinflammatory factors in myocardial tissue and in the hypothalamus. No impact on kidney function was observed, and actually RDN might have beneficial effect on renal function in HF. In summary, RDN has beneficial effect on HF and affecting cytokine-induced central neural excitation might be one of the underlying mechanisms.

In our work, cardiac function deteriorated after AMI modeling. Four weeks after AMI, RDN significantly improved cardiac function with lower LVEDD, LVESD, and LVEDP and higher levels of LVEF and LVSP. Lower level of NT-ProBNP and less cardiac fibrosis were also observed. The beneficial effect of RDN was consistent with the literature. In experimental studies of rats HF models after MI, RDN results in better cardiac function, better cardiac remodeling, better hemodynamics, downregulation of angiotensin AT1 receptors mediating maladaptive responses, and less fibrosis.\(^{10,31}\) In clinical trials, the Renal Artery Denervation in Chronic Heart Failure (REACH-Pilot) study showed that RDN was associated with improved symptoms and exercise capacity.\(^{32}\) Several other clinical studies demonstrated RDN improves HF symptoms and left ventricular function and less hormonal activation at mid-term follow-up.\(^{16,17,33}\) In patients with HF with preserved ejection fraction, RDN is also associated with improvement of surrogate endpoints.\(^{34}\) The past literature suggested that RDN affects sympathetic activation involving renal afferent and efferent sympathetic nerves, reduces renal and total body norepinephrine spillover, and thus has a positive impact on HF symptoms and outcomes. Sympathetic overactivity has an important role in HF. Systemic vasoconstriction and venous tone augment induced by norepinephrine aim to maintain the systemic blood pressure and increase preload. At the same time, norepinephrine reduces renal blood flow and increases renin release. In patients with HF, the cardiac spillover of norepinephrine increases, which is associated with central noradrenergic neurons activation.\(^{3}\) Norepinephrine has a

FIGURE 7. Masson staining of myocardial tissue (magnification ×400) in the control group (A), the HF group (B), and the HF + RDN group (C), the blue stands for fibrosis and collagen volume fraction (D). Five areas per slide and 3 slides from each animal were examined. No obvious pathological change was observed in the control group. In the HF group, significant amount of interstitial collagen was observed. In addition, a small amount of inflammatory cell infiltration was observed. In the HF + RDN group, some fibrotic change was observed. No significant difference in collagen volume fraction was observed between the HF and HF + RDN group. Ns, not statistically significant.

FIGURE 8. Expression of inflammation-related proteins (antibodies to IL-6, TNF-\( \alpha \), NF-\( \kappa \)B, and MCP-1) in myocardial tissue. Three samples from each animal (8 in the control group, 7 from the HF group, and 7 from the HF + RDN group) were analyzed. \#\( P < 0.05 \) when compared with the control group. \*\( P < 0.05 \) when compared with the HF group. No significant differences were observed among other group comparisons.
direct toxic effect on cardiomyocytes by calcium overload and results in synthetic activity decrease and left ventricular hypertrophy. In our work, we observed RDN was also associated with marked decrease in proinflammatory cytokines in cardiac tissue. In line with our results, Dörr et al showed that RDN reduces serum IL-6, high-sensitive C-reactive protein (hsCRP), and matrix metalloproteinases. Xiao et al found that RDN prevents immune cell activation and renal inflammation in rats. In 42 patients with hypertension, RDN reduces monocyte activation and levels of inflammatory markers including IL-12 and TNF-α. It is known that chronic HF is associated with circulating inflammatory cytokines, and inflammation is an important contributor to clinical deterioration or progression of HF. All together, these evidence suggested that RDN might prevent exacerbation of inflammation and lead to beneficial effect in HF treatment.

Our results that RDN reduces proinflammatory cytokines in hypothalamus are intriguing. The hypothalamic PVN is a key regulator of neuroendocrine activity and plays an important role in regulating extracellular fluid volume and sympathetic activity. Previous studies have shown that in PVN, inflammatory factors (such as TNF-α and IL-1β) significantly increased in HF. Kang et al found that TNF-α was almost synchronously increased in brain tissue and myocardial tissue in early HF, and the increase in TNF-α and IL-1β were more prominent in PVN. Administering TNF-α and NF-κB inhibitors to lateral ventricle reduces the inflammatory factor level in the PVC and significantly reduces sympathetic activity. Inhibiting inflammation in PVN was shown to decrease sympathetic activity and improve some hemodynamic and anatomic indicators of left ventricular function in HF rats. These results indicate that inflammation factors in PVN may play important roles in the central regulation of HF. In our work, RDN decreases the expression of inflammatory protein in hypothalamus, which suggested that RDN might affect cytokine-induced central neural excitation with HF and later affect sympathetic activity. This might be mechanism independent of involving renal afferent and efferent sympathetic nerves.

There are some limitations in this study. First, the sample size is small, and the follow-up period is short. We were not able to assess the long-term effect of RDN in the HF model. Second, in our study, there might be variation of the anterior descending artery in each dog; the actual infarction size might be different. However, we did not observe marked difference during heart tissue collection.

In summary, RDN can improve cardiac function in dogs with HF after myocardial infarction. Our results suggested that RDN might affect cytokine-induced central

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**FIGURE 9.** Expression of inflammation-related proteins (antibodies of IL-6, TNF-α, NF-κB, and MCP-1) in the hypothalamus. Three samples from each animal (8 in the control group, 7 from the HF group, and 7 from the HF + RDN group) were analyzed. *P < 0.05 when compared with the control group. #P < 0.05 when compared with the HF group. No significant differences were observed among other group comparisons.

**FIGURE 10.** HE staining of the renal artery. Three samples from each animal (8 in the control group, 7 from the HF group, and 7 from the HF + RDN group) were analyzed. The vessel wall structure was intact in the control group (A, magnification ×40). The inner layer was smooth (B, magnification ×100), and the medial layer consisted of multiple layers of annular smooth muscle in the HF group (C, magnification ×400). In the HF + RDN group, the lumen was intact (D, magnification ×40), but the axon of the adventitia was missing and the nerve fibers were destroyed (E, magnification ×100 and F, magnification ×400).
neural excitation in HF and later affect sympathetic activity. Our results suggested a potential beneficial mechanism independent of involving renal afferent and efferent sympathetic nerves.

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