Impacts of Surgically Performed Renal Denervation on the Cardiovascular and Electrophysiological Variables in the Chronic Atrioventricular Block Dogs – Comparison With Those of Amiodarone Treatment –

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Background: In order to begin to precisely clarify the impact of renal denervation on the blood pressure, atrial fibrillation and ventricular tachyarrhythmias, in addition to proarrhythmic potential, its cardiovascular effects were assessed by using the chronic complete atrioventricular block dogs.

Methods and Results: Cardiohemodynamic and electrophysiological effects, together with neurohumoral factors and/or electrolytes, were assessed before and 4 weeks after either renal denervation (n=5) or amiodarone treatment (n=6). Amiodarone hydrochloride was given orally to the animals every day in a dose of 200 mg/day for the first 7 days followed by 100 mg/day for the following 21 days. The renal denervation decreased the systolic pressure, idioventricular rate, prolonged ventricular effective refractory period, and slightly suppressed the adrenergic tone and the renin-angiotensin-aldosterone system, but hardly affected the atrial effective refractory period and terminal repolarization period. Amiodarone prolonged the atrial effective refractory period, whereas no significant change was detected in the other variables.

Conclusions: Surgically performed renal denervation may possess the anti-ventricular tachyarrhythmic rather than anti-atrial fibrillatory potentials, and it also modestly decreased the blood pressure. Thus, currently obtained information may be used as guidance for better understanding the utility and limitation of renal denervation against various types of cardiovascular diseases. (Circ J 2016; 80: 1556–1563)

Key Words: Amiodarone; Atrial fibrillation; Effective refractory period; Hypertension; Renal denervation
Cardiovascular Effects of Renal Denervation

All experiments in this study were approved by Toho University Animal Care and User Committee (Nos. 13-53-152, 14-52-237) and performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of Toho University. All studies involving animals are reported in accordance with the ARRIVE guidelines for reporting experiments involving animals.

**Experimental Protocol**

The experimental protocol is summarized in Figure 1. More than 4 weeks after the onset of atrioventricular block, the dogs were divided into 2 groups; namely, renal denervation treatment (n=5) or amiodarone administration (n=6) groups. In the renal denervation group, the cardiohemodynamic and electrophysiological variables, together with neurohumoral factors and/or electrolytes, were assessed before and 28 days after the renal denervation. Meanwhile, in the amiodarone group, the same variables were measured before and 29 days after the start of amiodarone administration. Amiodarone hydrochloride was given orally to the dogs every day, in a dose of 200 mg per body/day for the first 7 days followed by 100 mg per body/day for the following 21 days.

**Production of the Chronic Atrioventricular Block Canine Model**

The catheter ablation technique of the atrioventricular node was used, as described previously. Furthermore, the combination of pulmonary vein isolation therapy and renal denervation was shown to reduce the recurrence of atrial fibrillation more than pulmonary vein isolation alone. However, information regarding the impact of renal denervation on the blood pressure, atrial fibrillation and ventricular tachyarrhythmias, in addition to proarrhythmic potential, remains limited.

In this study, we assessed the cardiohemodynamic and electrophysiological effects of renal denervation precisely by using the chronic complete atrioventricular block dogs. The animals have been reported to possess pathophysiology including severe hypertension, chronically compensated heart failure via the activation of sympathetic tones, and the stretch activating paradigm of atrium and ventricles, leading to fibrosis and conduction abnormalities that may promote the occurrence and maintenance of atrial fibrillation as well as ventricular tachyarrhythmias. Moreover, the incidence of sudden cardiac death in dogs with complete atrioventricular block was reported to be up to 40% within 6 months of diagnosis. We then totally removed the visible nerves in the area of the renal hilus by a using surgical technique in order to overcome one of the problems described in SYMPLICITY HTN-3 trial, and to reduce the risk of renal artery stenosis after renal denervation with a catheter. Finally, to better characterize the electrophysiological effects of renal denervation, we also assessed those of amiodarone as a reference, which is known to be efficacious for preventing the recurrence of atrial fibrillation as well as unstable ventricular tachyarrhythmias.

**Methods**

Experiments were performed with 11 male beagle dogs weighing approximately 10 kg. Animals were obtained through Kitayama Labes Co, Ltd (Nagano, Japan). The dogs were kept in individual cages on a 12-h light-dark (6:00–18:00, 18:00–6:00) cycle. The ventilation provided a total air exchange rate of 10–15 times per hour. The room temperature was maintained at 23±2°C, and relative humidity was 50±30%. Each dog was fed 200 g/day of standard diet (CD-5M; CLEA Japan, Inc, Tokyo, Japan), and was allowed free access to tap water.

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**Production of the Chronic Atrioventricular Block Canine Model**

The catheter ablation technique of the atrioventricular node was used, as described previously. The endpoint of this procedure was the development of the complete atrioventricular block, with an appearance of stable idioventricular-escaped rhythm. Proper care was taken in the treatment of the animals. The anatomical and electrophysiological remodeling has been shown to be completed within 4 weeks after the onset of complete atrioventricular block, and no further prolongation of the QT interval was reported to be detected thereafter.

**Renal Denervation for the Atrioventricular Block Dogs**

More than 4 weeks after the production of the atrioventricular block, the dogs were anesthetized with pentobarbital sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, the dogs were artificially ventilated with 100% oxygen by using a volume-limited ventilator (SN-408-3; Shinano, Japan). All experiments in this study were approved by Toho University Animal Care and User Committee (Nos. 13-53-152, 14-52-237) and performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of Toho University. All studies involving animals are reported in accordance with the ARRIVE guidelines for reporting experiments involving animals.
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vein to obtain MAP signals. A standard 6-French quad-polar electrodes catheter (Cordis-Webster, Inc, Baldwin Park, CA, USA) was positioned at the sinus nodal area of the right atrium through the right femoral vein to electrically pace and record the local electrogram. The signals were amplified with a DC preamplifier (model 300; EP Technologies, Inc). The duration of the MAP signals was measured as an interval, along a line horizontal to the diastolic baseline, from the MAP upstroke to the desired repolarization level. The interval (ms) at the 90% repolarization level was defined as MAP\(_{90}\), which could reflect the QT interval. The corrected MAP interval (MAP\(_{90}\)cF) was calculated by using Fridericia’s formula.\(^{32}\) The systemic blood pressure, ECG and MAP signals were monitored by using a polygraph system (RM-6000; Nihon-Kohden, Corporation, Tokyo, Japan) and analyzed by using a real-time fully automatic data analysis system (WinVAS3 ver 1.1R24v; Physio-Tech, Co, Ltd, Tokyo, Japan).

The heart was electrically driven by using a cardiac stimulator (SEC-3102; Nihon Kohden, Co) with the pacing electrodes of the combination catheter placed in the right ventricle or the

Manufacturing Co, Ltd, Tokyo, Japan). The tidal volume and respiratory rate were set at 20ml/kg and 15 strokes/min, respectively. Additional doses of pentobarbital sodium (3–6 mg/kg, i.v.) were given when necessary. Both kidneys were approached through bilateral retroperitoneal flank incisions, and were surgically denervated by removing the visible nerves in the area of the renal hilus, followed by stripping connective tissue around the renal arteries.\(^{31}\) After the surgical denervation, the incision sites were restored, and proper care was taken of the animals.

Measurement of the Cardiohemodynamic and Electrophysiological Variables

A clinically available indwelling needle was placed in the right femoral artery to measure the systemic blood pressure. The surface lead II ECG was obtained from the limb electrodes. A bidirectional steerable monophasic action potential (MAP) recording/pacing combination catheter (1675P; EP Technologies, Inc, Sunnyvale, CA, USA) was positioned at the endocardium of the right ventricle through the left femoral

Figure 2. Effects of renal denervation and amiodarone on the blood pressure, sinoatrial rate (SAR), idioventricular rate (IVR) and duration of right ventricular monophasic action potential at 90% repolarization level (MAP\(_{90}\)) during idioventricular rhythm. These variables were obtained at pre-treatment control (Control) and at 4 weeks (4W) after the start of treatment. Effects of renal denervation (Left panel, n=5) and amiodarone (Right panel, n=6) on systolic blood pressure (SBP, circles), mean blood pressure (MBP, squares) and diastolic blood pressure (DBP, triangles) (A); those on SAR (squares) and IVR (circles) (B); and those on the MAP\(_{90}\) during idioventricular rhythm (MAP\(_{90}\)cF, circles) and MAP\(_{90}\) corrected by Fridericia’s formula (MAP\(_{90}\)cF, squares) (C). Data are presented as the mean±SEM. Closed symbols represent significant change from the respective pre-treatment control value by P<0.05.
reflecting phase 3 repolarization of the action potential, was calculated by the difference between the MAP$_{90}$ and VERP at the same site at each basic cycle length. These variables were obtained at the pre-treatment control (Control, circles) and at 4 weeks (4W, squares) after the start of treatment. Effects of renal denervation (Left panel, n=5) and amiodarone (Right panel, n=6) on the MAP$_{90}$ during the electrical pacing (A); those on the VERP and AERP during the electrical pacing (B); and those on the TRP (C). Data are presented as the mean±SEM. Closed symbols represent significant change from the pre-treatment control value by P<0.05.

**Figure 3.** Effects of renal denervation and amiodarone on the duration of right ventricular monophasic action potential at 90% repolarization level (MAP$_{90}$) during electrical pacing, the ventricular and atrial effective refractory period (VERP and AERP) during electrical pacing, and the terminal repolarization period (TRP; the difference between the MAP$_{90}$ and VERP at the same site at each basic cycle length). These variables were obtained at the pre-treatment control (Control, circles) and at 4 weeks (4W, squares) after the start of treatment. Effects of renal denervation (Left panel, n=5) and amiodarone (Right panel, n=6) on the MAP$_{90}$ during the electrical pacing (A); those on the VERP and AERP during the electrical pacing (B); and those on the TRP (C). Data are presented as the mean±SEM. Closed symbols represent significant change from the pre-treatment control value by P<0.05.
Co, Ltd, Osaka, Japan).

Statistical Analysis
Data are presented as the mean±SEM. The statistical significances within a variable were evaluated by using a paired t-test, and those of unpaired data between the groups were evaluated by using an unpaired t-test. A P value <0.05 was considered to be significant.

Results
No statistically significant difference was detected in the respective control values between the renal denervation group and amiodarone-treated group, except for the AERP at a basic pacing cycle length of 300 ms. All animals survived during the experimental period.

Effects on the Cardiohemodynamic and Electrophysiological Variables Under the Idioventricular Rhythm
The effects of renal denervation and amiodarone treatment on the blood pressure are summarized in Figure 2 (Top panels). The pre-treatment control values of the systolic, mean and diastolic pressure were 233±8, 126±12 and 93±10 mmHg in the renal denervation group, whereas they were 226±7, 144±5 and 106±5 mmHg in the amiodarone-treated group, respectively. Renal denervation significantly decreased the systolic pressure by 41 mmHg, whereas the mean and diastolic pressure tended to decrease; however, statistical significance was not detected. Amiodarone tended to decrease the systolic, mean and diastolic pressure, which did not achieve a statistical significance.

The effects of renal denervation and amiodarone treatment on the sinoatrial and idioventricular rate, MAP90 and MAPsecF during the idioventricular rhythm are summarized in Figure 2 (Middle and Bottom panels), and their pre-treatment control values were 146±9 bpm, 39±5 bpm, 285±19 ms and 243±14 in the renal denervation group, whereas they were 168±6 bpm, 55±3 bpm, 278±19 ms and 278±17 in the amiodarone-treated group, respectively. Renal denervation significantly decreased the idioventricular rate by 12 bpm, whereas the sinoatrial rate tended to decrease. The MAP90 and MAPsecF tended to increase. Meanwhile, amiodarone tended to decrease the sinoatrial and idioventricular rate. Both MAP90 and MAPsecF tended to increase.

Effects on MAP90, VERP, AERP and TRP During Electrical Pacing
The effects of renal denervation and amiodarone treatment on the MAP90 during electrical pacing are summarized in Figure 3 (Top panels). The pre-treatment control values of the MAP90 at a pacing cycle length of 300, 400, 500, 600, 750 and 1,000 ms were 189±6, 217±9, 240±12, 258±13, 273±17 and 285±19 ms in the renal denervation group, whereas those in the amiodarone-treated group were 194±9, 221±12, 239±12, 259±15, 273±16 and 282±18 ms, respectively. Both renal denervation and amiodarone treatment tended to prolong the MAP90, whereas the extent of the prolongation of MAP90 was more in the renal denervation group compared with that in the amiodarone-treated group; however, these changes did not achieve the statistical significance.

The typical traces of the MAP during the assessment of the VERP before and 4 weeks after the renal denervation (Control) are depicted in Figure 4. The effects of renal denervation and amiodarone treatment on the VERP are summarized in Figure 3 (Middle panels). The pre-treatment control values of the VERP at a basic pacing cycle length of 300, 400, 500, 600, 750 and 1,000 ms were 213±6, 229±7, 243±10, 249±9, 255±10 and 259±13 ms in the renal denervation group, whereas those in the amiodarone-treated group were 200±7, 218±8, 228±8, 233±8, 236±8 and 233±8 ms, respectively. Renal denervation significantly prolonged the VERP except for that at a basic pacing cycle length of 300 ms, whereas amiodarone hardly affected them.
The effects of renal denervation and amiodarone treatment on the AERP are summarized in Figure 3 (Middle panels). The pre-treatment control values of the AERP at a basic pacing cycle length of 200 and 300 ms were 124±10 and 137±6 ms in the renal denervation group, whereas those in the amiodarone-treated group were 113±4 and 123±3 ms, respectively. Renal denervation hardly affected the AERP at a basic pacing cycle length of 200 or 300 ms. In contrast, amiodarone significantly prolonged the AERP at a basic pacing cycle length of 300 ms by 21 ms, whereas no significant change was detected in the AERP at a basic cycle length of 200 ms.

The effects of renal denervation and amiodarone treatment on the TRP are summarized in Figure 3 (Bottom panels). The pre-treatment control values of the TRP at a basic pacing cycle length of 300, 400, 500, 600, 750 and 1,000 ms were −24±6, −12±5, −3±2, 9±7, 18±10 and 26±15 ms in the renal denervation group, whereas those in the amiodarone-treated group were −8±5, −3±8, 13±5, 29±8, 41±9 and 51±11 ms, respectively. Renal denervation tended to shorten the TRP at a basic pacing cycle length of 400, 500, 600 and 750 ms, whereas the reverse was true for it at a basic pacing cycle length of 300 and 1,000 ms. In contrast, amiodarone treatment tended to prolong the TRP at each basic pacing cycle length.

Effects on the Neurohumoral Factors, Electrolytes, Cr and the Plasma Amiodarone Concentration

The effects of renal denervation and amiodarone treatment on the neurohumoral factors including adrenaline, noradrenaline, dopamine, angiotensin II, aldosterone and plasma renin activity are summarized in Table 1. Renal denervation significantly decreased the plasma renin activity, whereas the other factors tended to decrease, and this did not achieve the statistical significance. In contrast, amiodarone tended to decrease each factor, which did not achieve statistical significance. The effects of renal denervation on the concentrations of electrolytes and Cr are summarized in Table 2. Renal denervation hardly affected plasma Na⁺, Cl⁻, K⁺ and Cr concentrations. The plasma amiodarone concentration was 385±41 ng/ml at 4 weeks after the start of administration.

Discussion

The cardiovascular effects of renal denervation treatment (n=5) on the chronic atrioventricular block canine model were compared with those of chronically administered amiodarone (n=6). All animals survived for 4 weeks of the experimental period, suggesting that renal denervation or amiodarone may not possess the risks for inducing torsade de pointes via QT-interval prolongation, because the model has been used for detecting the drug-induced QT-interval prolongation and the onset of torsade de pointes.14,37 The result of amiodarone was in accordance with a previous report.38

Drug Dose in the Present Study

The dose of amiodarone was determined according to clinically recommended doses in Japan (interview form from the manufacturer; Sanofi K.K., April 2014, version 8) and previous experimental reports.39,40 In a previous clinical study, in which amiodarone was orally administered to patients in a dose of 400 mg/day for the first 14 days followed by 200 mg/day for 23 weeks, the plasma amiodarone concentration was 755±154 ng/ml.41 In this study, the plasma amiodarone concentration was 385±41 ng/ml at 4 weeks after the start of administration, indicating that our concentration was approximately half of that in the previous clinical study. There are 2 reports describing the cardiovascular effects of amiodarone at similar concentrations to the one used in this study. One study was an animal study with mongrel dogs (n=20), reporting that oral administration of amiodarone in a dose of 15 mg/kg/day for 28±2 days provided a plasma concentration of 400±76 ng/ml (n=10), which did not alter the cardiac output, ventricular contractile force or total peripheral resistance when compared with the control group (n=10).42 The other study was a clinical study, showing that the efficacy of amiodarone was confirmed in patients with supraventricular arrhythmias at a concentration of 319±70 ng/ml.41

Table 1. Effects of Renal Denervation and Amiodarone Treatment on Neurohumoral Factors

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<th>Renal denervation</th>
<th>Amiodarone</th>
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<td></td>
<td>Control 4 W</td>
<td>Control 4 W</td>
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<tr>
<td>Adrenaline (pg/ml)</td>
<td>210±161</td>
<td>88±69</td>
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<tr>
<td>Noradrenaline (pg/ml)</td>
<td>262±76</td>
<td>185±62</td>
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<tr>
<td>Dopamine (pg/ml)</td>
<td>22±7</td>
<td>17±4</td>
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<tr>
<td>Angiotensin II (pg/ml)</td>
<td>56±25</td>
<td>35±12</td>
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<tr>
<td>Aldosterone (pg/ml)</td>
<td>349±173</td>
<td>60±10</td>
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<td>Plasma renin activity (ng/ml/h)</td>
<td>9±3</td>
<td>5±2*</td>
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Data are presented as the mean±SEM. *P<0.05 compared with the pre-treatment control value (Control). 4 W, 4 weeks after the renal denervation or start of amiodarone administration; NA, not available.

Table 2. Effects of Renal Denervation on the Concentrations of the Electrolytes and Cr

<table>
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<tr>
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<th>Renal denervation</th>
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<tr>
<td></td>
<td>Control 4 W</td>
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<tr>
<td>Na⁺ (mEq/L)</td>
<td>150±0</td>
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<tr>
<td>Cl⁻ (mEq/L)</td>
<td>108±1</td>
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<tr>
<td>K⁺ (mEq/L)</td>
<td>3.8±0.1</td>
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<td>Cr (mg/dl)</td>
<td>0.7±0.0</td>
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Data are presented as the mean±SEM. Pre-treatment control value (Control). 4 W, 4 weeks after the renal denervation; Cr, creatinine.
As shown in Figure 2 (Top and Middle panels), renal denervation significantly decreased the systolic pressure and idioventricular rate in this study, which was not induced by amiodarone. In our chronic atrioventricular block canine model, the systolic pressure largely depends on the cardiac output, which is partly determined by the idioventricular rate, suggesting that the decrease of the systolic pressure in this study may be caused by the suppression of the idioventricular rhythm. Such decrease of systolic pressure would not be expected in patients with normal sinus rhythm, because the effects of bradycardia on the cardiac output may be much smaller in these patients than those in the atrioventricular block model. In contrast, the diastolic pressure tended to decrease, which did not achieve statistical significance. Because the diastolic pressure is determined by the total peripheral resistance, renal denervation may hardly affect the resistant vessels enough to decrease the diastolic pressure. Thus, the hypothetic effects of renal denervation might not be so efficacious against resistant hypertension, as reported in the results of the SYMPLICITY HTN-3 trial, however, further investigation is required to confirm this hypothesis.

Effects on the Electrophysiological Variables of the Ventricle
In previous studies using the chronic atrioventricular block canine model, the slow component of the delayed rectifier potassium current (IKs) was downregulated in the left and right ventricles, and the expression of the calcium-channel mRNA was hardly affected in the left ventricle, making the ventricle very sensitive to the drug that can increase the inward currents and/or decrease the outward currents. As shown in Figure 2 (Bottom panels) and Figure 3, amiodarone tended to increase the MAPo and MAPscF, but hardly affected the VERP. The lack of significant effects on the MAPo, MAPscF and VERP suggests that amiodarone can equally inhibit the inward and outward currents in the chronic atrioventricular block heart. Moreover, amiodarone hardly affected the TRP, explaining that chronic administration of amiodarone did not induce torsade de points in the present and previous studies using the chronic atrioventricular block canine model. In contrast, renal denervation also tended to increase the MAPo and MAPscF, but significantly prolonged the VERP, indicating that renal denervation inhibited the outward currents more than the inward currents in this model. In a previous study using pigs with acute myocardial infarction, the occurrence of premature ventricular beats and ventricular fibrillation was decreased by renal denervation as well as by the administration of a β-blocker. Thus, inhibition of IKs and IKc may be plausible to explain the hypothesis described above. Moreover, the extent of prolongation of the VERP at a slower pacing cycle length was greater than that at a faster length. A similar trend was observed for the MAPo. Thus, caution is required for the patients with bradycardia to prevent treatment-induced excessive repolarization delay. Furthermore, renal denervation tended to shorten the TRP at a basic cycle length of 400–750 ms, which was not observed with amiodarone treatment. Importantly, the negative TRP was observed at a basic cycle length of 300–500 ms, indicating the presence of post-repolarization refractoriness, which reflects antiarrhythmic activity. These results suggest that renal denervation may possess a more favorable electrophysiological profile as an antiarrhythmic intervention for ventricular tachyarrhythmias than amiodarone.

Effects on the Electrophysiological Variable in Atrium
The chronic atrioventricular block canine model has been reported to possess the structural and electrophysiological remodeling that may promote the occurrence and maintenance of atrial fibrillation. In this study, amiodarone prolonged the AERP, which supports the clinical efficacy of amiodarone in preventing the recurrence of atrial fibrillation. In contrast, renal denervation was reported to reduce the duration of rapid pacing-induced atrial fibrillation in the pig, by which the AERP and P-wave duration were hardly affected. Moreover, the combination of pulmonary vein isolation therapy and renal denervation has been clinically reported to reduce the recurrence of atrial fibrillation more than pulmonary vein isolation alone. However, in this study, renal denervation hardly affected the AERP, indicating that the treatment might not be so effective to suppress and/or prevent atrial fibrillation compared with amiodarone.

Effects on the Neurohumoral Factors, Electrolytes and Cr Levels
As shown in Table 1, renal denervation as well as amiodarone tended to decrease the neurohumoral factors, reflecting the adrenergic tone and renin-angiotensin-aldosterone system. Moreover, as shown in Table 2, renal denervation slightly decreased the plasma Na⁺ and Cr levels, but increased the K⁺ level, confirming the modest inhibition of the renin-angiotensin-aldosterone system.

Conclusion
Surgically performed renal denervation modestly decreased the blood pressure, might induce treatment-induced excessive ventricular repolarization delay, and can slightly inhibit the adrenergic tone and the renin-angiotensin-aldosterone system, but it may also possess the anti-ventricular tachyarrhythmic rather than anti-atrial fibrillatory potentials. Thus, currently obtained information may be used as guidance for better understanding the utility and limitation of renal denervation against various types of cardiovascular diseases.

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Disclosures
The authors declare that there are no conflicts of interest.

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