Modulation of renal sympathetic innervation: recent insights beyond blood pressure control

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Modulation of renal sympathetic innervation:

Recent insights beyond blood pressure control

Short Title: Renal innervation and cardiac arrhythmias

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Abstract

Renal afferent and efferent sympathetic nerves are involved in the regulation of blood pressure and have a pathophysiological role in hypertension. Additionally, several conditions that frequently coexist with hypertension, such as heart failure, obstructive sleep apnea, atrial fibrillation, renal dysfunction, and metabolic syndrome demonstrate enhanced sympathetic activity. Renal denervation (RDN) is an approach to reduce renal and whole body sympathetic activation. Experimental models indicate that RDN has the potential to lower blood pressure and prevent cardio-renal remodeling in chronic diseases associated with enhanced sympathetic activation. Studies have shown that RDN can reduce blood pressure in drug-naïve hypertensive patients and in hypertensive patients under drug treatment. Beyond its effects on blood pressure, sympathetic modulation by RDN has been shown to have profound effects on cardiac electrophysiology and cardiac arrhythmogenesis. RDN can display antiarrhythmic effects in a variety of animal models for atrial fibrillation and ventricular arrhythmias. First non-randomized studies demonstrate that RDN may promote the maintenance of sinus rhythm following catheter ablation in patients with atrial fibrillation. Registry data point towards a beneficial effect of RDN to prevent ventricular arrhythmias in patients with heart failure and electrical storm. Further large randomized placebo-controlled trials are needed to confirm the antihypertensive and antiarrhythmic effects of RDN. Herein, we will review the current literature on antiarrhythmic effects of RDN with focus on atrial fibrillation and ventricular arrhythmias. We will discuss new insights from preclinical and clinical mechanistic studies and possible clinical implications of RDN.

Keywords: Renal denervation, atrial fibrillation, ventricular fibrillation, arrhythmias, sleep apnea.

Introduction

Renal sensory afferent and efferent nerves allow the bidirectional communication between the central nervous system and the kidney. Peripheral and central inputs alter efferent renal sympathetic nerve activity influencing the innervated structural and functional components of the kidney, including vessels, glomeruli, and tubuli.[1] The physiological efferent renal sympathetic nerve activity regulates renal blood flow, glomerular filtration rate, tubular sodium and water handling and stimulates renin release from the juxtaglomerular apparatus which regulates blood pressure and renal perfusion.[1,2] Under pathophysiological conditions, abnormal efferent renal sympathetic nerve activity can contribute to the associated abnormalities of renal function which, in turn, are of importance in the pathogenesis of several disease conditions like hypertension, renal disease and heart failure.[2] This efferent signaling is further regulated by afferent input from sensory renal chemo- and mechano-receptors in the kidney. Afferent fibers from the kidney travel along with the sympathetic nerves at the level of the kidney and then enter the dorsal roots and project to regions of the brainstem involved in cardiovascular control.[2-5] Therefore, the kidney represents a source of increased sympathetic activation under certain pathophysiological conditions, such as renal ischaemia, hypoxia, and intrinsic renal disease.[6-8] The density of peri-arterial renal sympathetic nerve fibers is lower in distal segments and dorsal locations when compared with proximal superior locations. There is a clear predominance of efferent nerve fibers, with decreasing density of afferent nerves from proximal to distal peri-arterial and renal parenchyma.[3]

These observations support the rationale to modulate autonomic innervation of the renal artery, arterioles and tubules in order to reduce norepinephrine spillover from the kidney and to influence sympathetically dependent pathophysiologies.[9-11] Renal denervation (RDN) substantially prevents progressive blood pressure rise and

associated renal injury and cardiac remodelling in animal models of hypertension[9,10] (**Figure 1**). Factors such as withdrawal of sympathetic nerve activity to the kidney and subsequent changes in fluid mobilisation and reduction in circulating angiotensin II, as well as removal of elevated afferent renal nerve activity as a consequence of a pathophysiological alteration in the kidney may contribute to the antihypertensive effects of RDN. Interestingly, selective destruction of afferent renal nerves had limited antihypertensive effects in hypertensive Dahl salt-sensitive rats.[12,13]

In non-randomized studies[14,15] and registries,[16] RDN reduced blood pressure and partially reversed cardiac hypertensive end-organ damage in patients with drug resistant hypertension.[17-19] A recent randomized sham controlled trial (SYMPLICITY HTN-3, ClinicalTrials.gov number, NCT01418261) could not confirm blood pressure reduction by RDN in drug resistant hypertensive patients.[20] However, in another published, randomized, sham controlled trial, RDN by a new ablation catheter reduced blood pressure in medication naïve hypertensive patients.[21] Several factors such as problems with assessment of renal denervation efficacy, variable experience of the proceduralists and the complex issues of patient drug compliance including improvement of drug adherence in initially poorly adherent patients (the Hawthorne effect), placebo effect and regression to the mean makes the interpretation of the results difficult.

Beyond regulation of blood pressure, increased sympathetic activity is suggested to contribute to the progression of cardiac arrhythmias.[22] At the cellular level, norepinephrine, the neurotransmitter of the sympathetic nervous system, is released from postganglionic neurons in response to sympathetic stimuli activating cardiac beta-receptors. Subsequently, altered cardiac calcium handling and electrophysiology contribute to arrhythmogenic mechanisms including delayed afterdepolarization-related ectopic firing and reentry.[23,24] Sympathetic

hyperinnervation is reported in the atria of dogs following rapid atrial pacing[25] and increased sympathetic and vagal nerve discharges can be documented before the onset of atrial fibrillation (AF) in dogs with pacing-induced congestive heart failure.[26] Additionally, recent data have shown that sympathetic activation promotes the development of the arrhythmogenic substrate via neurohumoral mechanisms, such as the renin-angiotensin-aldosterone system, leading to the upregulation of profibrotic pathways in the atria.[23,24] Therefore, elevated sympathetic activity may contribute to both cardiac structural and electrical remodelling, thus predisposing to arrhythmia. Activation of the autonomic nervous system plays an important role in the initiation and the maintenance of AF, but may also be targeted for the maintenance of sinus rhythm. Beta-receptor blockade by metoprolol was effective in preventing recurrence of AF after successful cardioversion[27] and autonomic modulation by for example low-level baroreceptor stimulation can help to maintain sinus rhythm.[22,28]

These observations raise the question of whether modulation of the autonomic nervous system by targeting the renal sympathetic nerves might be an effective strategy to improve rhythm control in patients with cardiac arrhythmias. Herein, we will review the current literature on the antiarrhythmic effects of autonomic nervous system modulation through RDN, with particular focus on atrial fibrillation and ventricular arrhythmias. We will discuss new insight from preclinical and clinical mechanistic studies and possible clinical implications.

Modulation of renal sympathetic innervation by renal denervation

In small animal models, RDN can be performed by combined surgical and chemical approaches, which modulates both, efferent and afferent renal nerve activity.[9,11] Both kidneys are approached through medial laparotomy and the visible nerves in the area of the renal hilus are removed and approximately 2–4 mm of the adventitia from the renal artery is stripped. The area is then moistened with a phenol/ethanol (10-20%) solution for 10–15 minutes. Combined surgical and chemical RDN reduces kidney tissue norepinephrine levels by >90-95% in several animal models. The release of norepinephrine into the urine and renal venous blood, which is inducable by efferent sympathetic nerve stimulation, can be reduced by 80% after RDN in animal studies.[5,29] Previous studies on RDN in normotensive rats by a 10% phenol/ethanol solution suggest renal reinnervation within 9 weeks.[30] In obese spontaneously hypertensive rats, RDN by a 20% phenol/ethanol solution resulted in a more sustained reduction in blood pressure, renal sympathetic nerve density and renal norepinephrine tissue content (**Figure 1**).[9]

Additionally, RDN can prevent cardiac neural remodeling and nerve sprouting under pathophysiological conditions suggesting reduction of afferent nerve activity. In spontaneously hypertensive rats, RDN by a 20% phenol/ethanol solution resulted in a reduced expression of the norepinephrine transporter in the kidney and in the heart (**Figure 2**). In rats with ischemic heart failure, RDN preserves sympathetic nerve innervation in the ventricles, thus improving cardiac function,[31] while in goats and dogs with atrial fibrillation induced by atrial tachypacing, RDN achieved a significant reduction in atrial sympathetic nerve sprouting.[32-34]

Most of the brainstem regions involved in cardiovascular control receive input from the renal afferent fibers. Afferent signals arising from the renal sympathetic nerves are able to influence nerve activity of several ganglia including those innervating the heart (**Figure 3**). Studies suggest a direct link between renal sympathetic nerve activity and left stellate ganglion (LSG) activity.[35-36] Renal sympathetic nerve stimulation is associated with LSG neuronal activity and upregulates the level of LSG nerve growth factor expression.[36] Importantly, the stimulation procedure does not only activate the efferent sympathetic nerves but also the afferent fibers going from the kidney to the central nervous system. Additionally, the stimulation frequency used in these renal nerve activation studies are likely to impact renal hemodynamic or excretory renal function, which has not been characterized and studied sufficiently.

Besides modulation of circulating catecholamines and whole body sympathetic nerve activity, bilateral RDN caused significant central and peripheral sympathetic nerve remodeling, improved baroreflex sensetivity[37] and reduced stellate ganglion nerve activity in ambulatory dogs.[36] Catheter based RDN can also affect cardiac sympathetic activity. Selective RDN significantly reduces cardiac sympathetic overdrive assessed by 123I-MIBG scintigraphy.[39,40]

A catheter-based approach for RDN has been developed for human use. RDN can result in an up to 50% reduction of renal norepinephrine spillover measured with a radiochemical tracer methodology using 3H-norepinephrine in humans.[12,13] Additionally, firing of single sympathetic vasoconstrictor fibres (measured by single muscle sympathetic nerve activity), was reduced by 37%.[38] These findings indicate that sympathetic activation can be reduced by RDN beyond just the kidneys, suggesting a combined modulation of efferent and afferent signaling (**Figure 3**).

The first-generation devices used radiofrequency pulses emitted from a monopolar electrode positioned under fluoroscopic guidance in each of the renal arteries. The

latest generation devices are multi-electrode catheters allowing a more standardized and more intense ablation procedure.[41] During the development of RDN catheters, the ablation strategy changed from ablation limited on the main vessels to more extended ablation in the main and subsequent branch vessels.[41] This revised approach was associated with higher efficacy and lower variability in treatment effects in preclinical studies. Alternatively, ultrasound or chemical ablation are investigated in clinical studies.[41]

Despite great advantages in catheter techniques, there is no universally accepted measure by which the completeness of RDN can be properly assessed intraprocedurally. Although periprocedural changes in circulating norepinephrine or neuropeptide Y,[42] nerve stimulation-induced blood pressure changes[43,44] and anatomy guided lesion placement,[45] have been introduced to improve ablation outcome, a standardized protocol to directly measure renal sympathetic nerve activity in humans is still lacking. In sedated and unrestrained conscious rodent models, assessment and quantification of renal nerve activity is feasible.[46,47] The development of endovascular recording of renal nerve action potentials may provide a useful accessory tool to assess successful RDN. Innovation in this area will be crucial to predict and monitor the therapeutic value of RDN.[48]

Effects of RDN on cardiac arrhythmias

Beyond hypertension and hypertensive end-organ damage, cardiac rhythm disorders, namely atrial fibrillation and ventricular arrhythmias, have been identified as a promising and emerging target of RDN.[49]

Atrial electrophysiological effects of renal denervation

Experimental data: RDN resulted in a reduction in heart rate and AV-conduction velocity in pigs.[50] In chloralose/urethane anasthetized pigs, neither atrial effective refractory period nor P-wave duration were influenced by acute RDN, thus excluding a direct impact of RDN on atrial refractoriness or atrial conduction during sinus rhythm.[50] Additionally, the sensitivity of ganglionated plexi was not modulated by RDN. In an AF pig model with rapid atrial pacing, RDN reduced the duration of pacing induced AF.[51] However, AF-induced electrical remodeling was not attenuated.[50] Reduced AV-conduction velocity was associated with lower ventricular heart rate during AF.[50]

In a goat model of persistent AF induced by atrial tachypacing,[32] RDN (**Figure 4)** reduced renal norepinephrine concentrations, blunted atrial neural remodeling and reduced AF complexity along with structural remodeling. Moreover, increased AF-inducibility, shortening and dispersion of atrial refractoriness as well as elevated plasma norepinephrine levels were almost completely prevented by RDN in animals subjected to stimulation of left stellate ganglion and rapid atrial pacing for three hours.[52,53]

In a pig model of obstructive sleep apnea (OSA), shortened atrial refractoriness[54,55] acutely induced by applied negative thoracic pressure was primarily mediated by combined sympathovagal activation, since it could be influenced by atropine, bilateral vagotomy or beta-receptor blockade.[54,56] Compared to beta-blocker treatment, RDN

resulted in more pronounced attenuation of the shortening in atrial refractoriness during OSA-maneuvers, which might explain the superior antiarrhythmic effect of RDN compared with beta-blocker therapy in this animal model.[55] Importantly, antiarrhythmic drugs such as amiodarone or sotalol displayed a considerably less pronounced antiarrhythmic effect compared to RDN in the same model.[55] In pigs undergoing repetitive OSA-maneuvers over 4 hours, RDN inhibited spontaneous atrial premature beats, and reduced the number AF-episodes as well as AF-duration.[56] The observed reduction in spontaneous atrial extrabeats by RDN may reduce the trigger for AF in OSA.[56] Additionally, RDN has been shown to reduce susceptibility to AF in a canine models of renal impairment, induced by embolization of small branches of the renal artery in the right kidney using gelatin sponge granules,[57] and tachycardiomyopathy, induced by ventricular tachypacing.[58] Taken together, these studies provide strong preclinical evidence towards an anti-arrhythmogenic effect of RDN.

Clinical data: RDN can reduce heart rate in patients with resistant hypertension.[59] In persistent AF, RDN can improve rate control,[60] which might improve clinical symptoms and outcomes in patients with AF. RDN has been shown to prevent or even reverse atrial remodelling determined by echocardiography[61] or by electroanatomical mapping.[62] In a small study of patients with symptomatic AF and resistant hypertension, the atrial antiarrhythmic effects of circumferential pulmonary vein isolation (PVI) combined with RDN were investigated.[63-65] Patients who received the combined procedures showed significant reductions in average systolic and diastolic blood pressure, whereas those in the PVI-only group did not show any significant improvement in blood pressure. Other electrophysiological parameters were not obviously changed by RDN. At one-year follow-up, 69% of patients who received both procedures maintained sinus rhythm, compared to 29% of those in the

PVI-only group.[63] In chronic kidney disease patients, the addition of RDN to pulmonary vein isolation reduced recurrence of paroxysmal atrial fibrillation.[66] In a case report, even RDN without PVI reduced blood pressure and attenuated paroxysmal AF-episodes, which were symptomatic and drug-resistant before RDN.[67] It remains unknown, whether sympathetic modulation of the autonomic nervous system by RDN can display antiarrhythmic effects in hypertensive AF patients independent from its blood pressure lowering effects. This important clinical and pathophysiological question should be addressed in a randomized sham controlled trial, where RDN is compared to aggressive and adopted up-titration of antihypertensive drugs in the control group.

Ventricular arrhythmias, heart failure and renal denervation

In dogs, 3 hours of renal sympathetic nerve stimulation increased LSG neuronal activity, and facilitated the incidence of ventricular arrhythmias during acute myocardial ischemia. Interestingly, the increase in ventricular arrhythmias could be attenuated by LSG ablation.[68] In different pig models with acute ischemia/reperfusion[66] (**Figure 5)** or with myocardial infarction induced by a permanent coronary occlusion,[70-72] RDN has been shown to reduce ventricular ectopic activity and ventricular fibrillation. Also in a dog model of heart failure induced by atrial tachycardiomyopathy induced by ventricular high-rate pacing, RDN attenuated the ventricular remodelling process.[73,74] The occurrence of spontaneous premature ventricular contractions and the subsequent ventricular dysfunction could be prevented by sympathetic modulation by the procedure.[75] Similarly, arrhythmogenic prolongation of ventricular repolarization (QT-interval) induced by simulated sleep apnea[76] or by cesium[77] could be attenuated by RDN.

Clinical data: In patients with heart failure with reduced ejection fraction, circulating norepinephrine concentrations predict mortality.[78] Interestingly, cardiac and renal norepinephrine (NE) spillover is increased in mild to moderate and severe chronic heart failure compared to healthy subjects, with the absolute renal norepinephrine spillover higher than the cardiac spillover suggesting that the kidney contributes more to total norepinephrine spillover than the heart in heart failure.[79,80]

A small case series has provided evidence that in patients with dilated cardiomyopathy and an electrical storm, RDN was able to reduce ICD shocks and ventricular ectopic activity.[81] These antiarrhythmic effects could be confirmed in several other case series[82,83] and in an international multicenter registry.[84] RDN may be most beneficial for patients with heart failure with recurrent, refractory arrhythmias that cannot tolerate maximal beta-blockade and are not eligible for antiarrhythmic catheter based ablation of ventricular tachycardia. Alternatively, RDN may also be used as an adjunct strategy in patients undergoing catheter ablation. In patients with heart failure, RDN reduced NT-proBNP and was safe without any adverse event deterioration of other indices of cardiac and renal function.[85] The role of autonomic modulation by RDN in patients with heart failure and ventricular arrhythmias need to be further investigated in randomized, sham controlled trials.

Conclusions

RDN is a promising and safe strategy to modulate the autonomic nervous system activity. Beyond its blood pressure lowering effects, animal models of atrial fibrillation have demonstrated favourable electrophysiological changes, reverse remodeling and potential antiarrhythmic effects of sympathetic modulation by RDN. Interestingly, adjunct RDN improved outcome of catheter ablation in atrial fibrillation patients in

small non-randomized clinical trials; these findings warrant further clinical trials. Additionally, animal experiments and early registry data also suggest promising ventricular antiarrhythmic effects by RDN in the setting of heart failure. Further studies are needed to investigate the antiarrhythmic effects of RDN.

Conflict of interest

DL, FM, PS and MB received research grants, speaker honoraria, and consultancy fees from Medtronic/Ardian, St. Jude, Boston Scientific, and Cordis. The other authors report no conflicts.

References

1. DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997;77:75-197.
2. Böhm M, Linz D, Ukena C, Esler M, Mahfoud F. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? Circ Res. 2014;115:400-409.
3. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64:635-643.
4. Stella A, Zanchetti A. Functional role of renal afferents. Physiol Rev. 1991;71:659-682.

5. Bradley T, Hjemdahl P. Influence of afferent renal nerve activity on contralateral renal overflow of noradrenaline and dopamine to plasma in the dog. Acta Physiol. Scand. 1986;128, 119–120.
6. Larsen R, Thorp A, Schlaich M. Regulation of the sympathetic nervous system by the kidney. Curr Opin Nephrol Hypertens. 2014;23:61-68.
7. Patel KP, Knuepfer MM. Effect of afferent renal nerve stimulation on blood pressure, heart rate and noradrenergic activity in conscious rats. J Auton Nerv Syst. 1986;17,121–130.
8. Rogenes PR. Single-unit and multiunit analyses of renorenal reflexes elicited by stimulation of renal chemoreceptors in the rat. J Auton Nerv Syst. 1982;6,143–156.
9. Linz D, Hohl M, Schütze J, Mahfoud F, Speer T, Linz B, Hübschle T, Juretschke HP, Dechend R, Geisel J, Rütten H, Böhm M. Progression of kidney injury and cardiac remodeling in obese spontaneously hypertensive rats: the role of renal sympathetic innervation. Am J Hypertens. 2015;28:256-265.
10. Mahfoud F, Moon LB, Pipenhagen CA, Jensen JA, Pathak A, Papademetriou V, Ewen S, Linz D, Böhm M. Catheter-based radio-frequency renal nerve denervation lowers blood pressure in obese hypertensive swine model. J Hypertens. 2016;34:1854-1862.
11. Hohl M, Linz D, Fries P, Müller A, Stroeder J, Urban D, Speer T, Geisel J, Hummel B, Laufs U, Schirmer SH, Böhm M, Mahfoud F. Modulation of the sympathetic nervous system by renal denervation prevents reduction of aortic distensibility in atherosclerosis prone ApoE-deficient rats. J Transl Med. 2016;14:167.

12. Foss JD, Fink GD, Osborn JW. Differential role of afferent and efferent renal nerves in the maintenance of early- and late-phase Dahl S hypertension. Am J Physiol Regul Integr Comp Physiol. 2016;310:R262-267.
13. Osborn JW, Foss JD. Renal Nerves and Long-Term Control of Arterial Pressure. Compr Physiol. 2017;7:263-320.
14. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373:1275–1281.
15. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M for the Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. Lancet. 2010;376:1903–1909.
16. Böhm M, Ukena C, Ewen S, Linz D, Zivanovic I, Hoppe U, Narkiewicz K, Ruilope L, Schlaich M, Negoita M, Schmieder R, Williams B, Zeymer U, Zirlik A, Mancia G, Mahfoud F; Global SYMPLICITY Registry Investigators. Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry. J Hypertens. 2016;34:2480-2486.
17. Linz D, Mancia G, Mahfoud F, Narkiewicz K, Ruilope L, Schlaich M, Kindermann I, Schmieder RE, Ewen S, Williams B, Böhm M; Global SYMPLICITY Registry Investigators. Renal artery denervation for treatment of patients with self-reported obstructive sleep apnea and resistant hypertension: results from the Global SYMPLICITY Registry. J Hypertens. 2017;35:148-153.
18. Mahfoud F, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, Fries P, Dreysse S, Wellnhofer E, Schneider G, Buecker A, Schneeweis C, Doltra A,

Schlaich MP, Esler MD, Fleck E, Böhm M, Kelle S. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. Eur Heart J. 2014;35:2224-2231.

19. Schirmer SH, Sayed MM, Reil JC, Ukena C, Linz D, Kindermann M, Laufs U, Mahfoud F, Böhm M. Improvements of left-ventricular hypertrophy and diastolic function following renal denervation - Effects beyond blood pressure and heart rate reduction. J Am Coll Cardiol. 2014;63:1916-1923.
20. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393-1401.
21. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp ASP, Watkinson AF, Schmieder RE, Schmid A, Choi JW, East C, Walton A, Hopper I, Cohen DL, Wilensky R, Lee DP, Ma A, Devireddy CM, Lea JP, Lurz PC, Fengler K, Davies J, Chapman N, Cohen SA, DeBruin V, Fahy M, Jones DE, Rothman M, Böhm M; SPYRAL HTN-OFF MED trial investigators*. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017. doi: 10.1016/S0140-6736(17)32281-X.
22. Linz D, Ukena C, Mahfoud F, Neuberger HR, Böhm M. Atrial autonomic innervation: a target for interventional antiarrhythmic therapy? J Am Coll Cardiol. 2014;63:215-224.

23. Linz D, van Hunnik A, Ukena C, Ewen S, Mahfoud F, Schirmer SH, Lenski M, Neuberger HR, Schotten U, Böhm M. Renal denervation: effects on atrial electrophysiology and arrhythmias. Clin Res Cardiol. 2014;103:765-774.
24. Ripplinger CM, Noujaim SF, Linz D. The nervous heart. Prog Biophys Mol Biol. 2016;120:199-209.
25. Jayachandran JV, Sih HJ, Winkle W, Zipes DP, Hutchins GD, Olgin JE. Atrial fibrillation produced by prolonged rapid atrial pacing is associated with heterogeneous changes in atrial sympathetic innervation. Circulation. 2000;101:1185–1191.
26. Ogawa M, Zhou S, Tan AY, Song J, Gholmieh G, Fishbein MC, Luo H, Siegel RJ, Karagueuzian HS, Chen LS, Lin SF, Chen PS. Left stellate ganglion and vagal nerve activity and cardiac arrhythmias in ambulatory dogs with pacing-induced congestive heart failure. J Am Coll Cardiol. 2007;50:335–343
27. Kühlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 2000;36:139-146.
28. Linz D, Hohl M, Khoshkish S, Mahfoud F, Ukena C, Neuberger HR, Wirth K, Böhm M. Low-Level But Not High-Level Baroreceptor Stimulation Inhibits Atrial Fibrillation in a Pig Model of Sleep Apnea. J Cardiovasc Electrophysiol. 2016;27:1086-1092.
29. Oliver JA, Pinto J, Sciacca RR, Cannon PJ. Basal norepinephrine overflow into the renal vein: effect of renal nerve stimulation. Am J Physiol. 1980;239:F371–F377.
30. Mulder J, Hökfelt T, Knuepfer MM, Kopp UC. Renal sensory and sympathetic nerves reinnervate the kidney in a similar time-dependent fashion after renal

denervation in rats. Am J Physiol Regul Integr Comp Physiol. 2013;304:R675-682.

31. Pinkham MI, Loftus MT, Amirapu S, Guild SJ, Quill G, Woodward WR, Habecker BA, Barrett CJ. Renal denervation in male rats with heart failure improves ventricular sympathetic nerve innervation and function. Am J Physiol Regul Integr Comp Physiol. 2017;312:R368-R379.
32. Linz D, van Hunnik A, Hohl M, Mahfoud F, Wolf M, Neuberger HR, Casadei B, Reilly SN, Verheule S, Böhm M, Schotten U. Catheter-based renal denervation reduces atrial nerve sprouting and complexity of atrial fibrillation in goats. Circ Arrhythm Electrophysiol. 2015;8:466-474.
33. Wang X, Zhao Q, Huang H, Tang Y, Xiao J, Dai Z, Yu S, Huang C. Effect of renal sympathetic denervation on atrial substrate remodeling in ambulatory canines with prolonged atrial pacing. PLoS One. 2013;8:e64611.
34. Huang B, Yu L, Scherlag BJ, Wang S, He B, Yang K, Liao K, Lu Z, He W, Zhang L, Po SS, Jiang H. Left renal nerves stimulation facilitates ischemia-induced ventricular arrhythmia by increasing nerve activity of left stellate ganglion. J Cardiovasc Electrophysiol. 2014;25:1249-1256.
35. Yu L, Huang B, Wang Z, Wang S, Wang M, Li X, Zhou L, Meng G, Yuan S, Zhou X, Jiang H. Impacts of Renal Sympathetic Activation on Atrial Fibrillation: The Potential Role of the Autonomic Cross Talk Between Kidney and Heart. J Am Heart Assoc. 2017;6.
36. Tsai WC, Chan YH, Chinda K, Chen Z, Patel J, Shen C, Zhao Y, Jiang Z, Yuan Y, Ye M, Chen LS, Riley AA, Persohn SA, Territo PR, Everett TH, Lin SF, Vinters HV, Fishbein MC, Chen PS. Effects of renal sympathetic denervation on the stellate ganglion and brain stem in dogs. Heart Rhythm. 2017;14:255-262.

37. Tsai WC, Chan YH, Chinda K, Lai WT, Lin SF, Chen PS. Renal sympathetic denervation decreases the incidence of atrial tachycardia and improves baroreflex sensitivity in ambulatory dogs. Heart Rhythm. 2014;11:236.
38. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension. 201;61:457–464.
39. Berukstis A, Vajauskas D, Gargalskaite U, Misonis N, Burneikaite G, Zakarkaite D, Miglinas M, Laucevicius A. Impact of renal sympathetic denervation on cardiac sympathetic nerve activity evaluated by cardiac MIBG imaging. EuroIntervention. 2016;11:1070-1076.
40. Donazzan L, Mahfoud F, Ewen S, Ukena C, Cremers B, Kirsch CM, Hellwig D, Eweiwi T, Ezziddin S, Esler M, Böhm M. Effects of catheter-based renal denervation on cardiac sympathetic activity and innervation in patients with resistant hypertension. Clin Res Cardiol. 2016;105:364-371.
41. Mahfoud F, Schmieder RE, Azizi M, Pathak A, Sievert H, Tsioufis C, Zeller T, Bertog S, Blankestijn PJ, Böhm M, Burnier M, Chatellier G, Durand Zaleski I, Ewen S, Grassi G, Joner M, Kjeldsen SE, Lobo MD, Lotan C, Felix Lüscher T, Parati G, Rossignol P, Ruilope L, Sharif F, van Leeuwen E, Volpe M, Windecker S, Witkowski A, Wijns W. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. Eur Heart J. 2017. doi: 10.1093/eurheartj/ehx215.
42. Dörr O, Ewen S, Liebetrau C, Möllmann H, Gaede L, Linz D, Hohl M, Troidl C, Bauer T, Böhm M, Hamm C, Mahfoud F, Nef H. Neuropeptide Y as an

indicator of successful alterations in sympathetic nervous activity after renal sympathetic denervation. Clin Res Cardiol. 2015;104:1064-1071.

43. de Jong MR, Adiyaman A, Gal P, Smit JJ, Delnoy PP, Heeg JE, van Hasselt BA, Lau EO, Persu A, Staessen JA, Ramdat Misier AR, Steinberg JS, Elvan A. Renal Nerve Stimulation-Induced Blood Pressure Changes Predict Ambulatory Blood Pressure Response After Renal Denervation. Hypertension. 2016;68:707-714.

44. Chinushi M, Suzuki K, Saitoh O, Furushima H, Iijima K, Izumi D, Sato A, Sugai M, Iwafuchi M. Electrical stimulation-based evaluation for functional modification of renal autonomic nerve activities induced by catheter ablation. Heart Rhythm. 2016;13:1707-1715.

45. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Böhm M, Melder RJ. Impact of Lesion Placement on Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation. J Am Coll Cardiol. 2015;66:1766-1775.

46. Stocker SD, Muntzel MS. Recording sympathetic nerve activity chronically in rats: surgery techniques, assessment of nerve activity, and quantification. Am J Physiol Heart Circ Physiol. 2013;305:H1407-1416.

47. Hamza SM, Hall JE. Direct recording of renal sympathetic nerve activity in unrestrained, conscious mice. Hypertension. 2012;60:856-864.

48. Barber-Chamoux N, Esler MD. Predictive factors for successful renal denervation: should we use them in clinical trials. Eur J Clin Invest. 2017. doi: 10.1111/eci.12792.

49. Linz D, Hunnik Av, Ukena C, Mahfoud F, Ewen S, Verheule S, Böhm M, Schotten U. Effects of renal denervation on atrial arrhythmogenesis. Future Cardiol. 2014;10:813-822.

50. Linz D, Mahfoud F, Schotten U, Ukena C, Hohl M, Neuberger HR, Wirth K, Böhm M. Renal sympathetic denervation provides ventricular rate control but does not prevent atrial electrical remodeling during atrial fibrillation. Hypertension. 2013;61:225–231.
51. Linz D, Mahfoud F, Schotten U, Ukena C, Neuberger HR, Wirth K, Böhm M. Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea. Hypertension. 2012;60:172–178.
52. Hou Y, Hu J, Po SS, Wang H, Zhang L, Zhang F, Wang K, Zhou Q. Catheter-based renal sympathetic denervation significantly inhibits atrial fibrillation induced by electrical stimulation of the left stellate ganglion and rapid atrial pacing. PLoS One. 2013;8:e78218.
53. Zhou Q, Zhou X, TuEr-Hong ZL, Wang H, Yin T, Li Y, Zhang L, Lu Y, Xing Q, Zhang J, Yang Y, Tang B. Renal sympathetic denervation suppresses atrial fibrillation induced by acute atrial ischemia/infarction through inhibition of cardiac sympathetic activity. Int J Cardiol. 2016;203:187-195.
54. Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. Heart Rhythm. 2011;8:1436-1443.
55. Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Combined blockade of early and late activated atrial potassium currents suppresses atrial fibrillation in a pig model of obstructive apnea. Heart Rhythm. 2011;8:1933-1939.
56. Linz D, Hohl M, Nickel A, Mahfoud F, Wagner M, Ewen S, Schotten U, Maack C, Wirth K, Böhm M. Effect of renal denervation on neurohumoral activation triggering atrial fibrillation in obstructive sleep apnea. Hypertension. 2013;62:767-774.

57. Liang Z, Shi XM, Liu LF, Chen XP, Shan ZL, Lin K, Li J, Chen FK, Li YG, Guo HY, Wang YT. Renal denervation suppresses atrial fibrillation in a model of renal impairment. PLoS One. 2015;10:e0124123.
58. Wang X, Zhao Q, Deng H, Wang X, Guo Z, Dai Z, Xiao J, Wan P, Huang C. Effects of renal sympathetic denervation on the atrial electrophysiology in dogs with pacing-induced heart failure. Pacing Clin Electrophysiol. 2014;37:1357-1366
59. Ukena C, Mahfoud F, Spies A, Kindermann I, Linz D, Cremers B, Laufs U, Neuberger HR, Böhm M. Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. Int J Cardiol. 2013;167:2846–2851.
60. Qiu M, Shan Q, Chen C, Geng J, Guo J, Zhou X, Qian W, Tang L, Yin Y. Renal sympathetic denervation improves rate control in patients with symptomatic persistent atrial fibrillation and hypertension. Acta Cardiol. 2016;71:67-73.
61. Schirmer SH, Sayed MM, Reil JC, Lavall D, Ukena C, Linz D, Mahfoud F, Böhm M. Atrial Remodeling Following Catheter-Based Renal Denervation Occurs in a Blood Pressure- and Heart Rate-Independent Manner. JACC Cardiovasc Interv. 2015;8:972-980.
62. McLellan AJ, Schlaich MP, Taylor AJ, Prabhu S, Hering D, Hammond L, Marusic P, Duval J, Sata Y, Ellims A, Esler M, Peter K, Shaw J, Walton A, Kalman JM, Kistler PM. Reverse cardiac remodeling after renal denervation: Atrial electrophysiologic and structural changes associated with blood pressure lowering. Heart Rhythm. 2015;12:982-990.
63. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of

pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol. 2012;60:1163-1170.

64. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Bayramova S, Losik D, Baranova V, Karaskov A, Steinberg JS. Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: early experience. Heart Rhythm. 2014;11:1131-1138.

65. Romanov A, Pokushalov E, Ponomarev D, Strelnikov A, Shabanov V, Losik D, Karaskov A, Steinberg JS. Pulmonary vein isolation with concomitant renal artery denervation is associated with reduction of both arterial blood pressure and atrial fibrillation burden: data from implantable cardiac monitor. Cardiovasc Ther. 2017;35.

66. Kiuchi MG, Chen S, E Silva GR, Rodrigues Paz LM, Kiuchi T, de Paula Filho AG, Lima Souto GL. The addition of renal sympathetic denervation to pulmonary vein isolation reduces recurrence of paroxysmal atrial fibrillation in chronic kidney disease patients. J Interv Card Electrophysiol. 2017;48:215-222.

67. Vollmann D, Sossalla S, Schroeter MR, Zabel M. Renal artery ablation instead of pulmonary vein ablation in a hypertensive patient with symptomatic, drug-resistant, persistent atrial fibrillation. Clin Res Cardiol. 2013;102:315-318.

68. Huang B, Yu L, Scherlag BJ, Wang S, He B, Yang K, Liao K, Lu Z, He W, Zhang L, Po SS, Jiang H. Left renal nerves stimulation facilitates ischemia-induced ventricular arrhythmia by increasing nerve activity of left stellate ganglion. J Cardiovasc Electrophysiol. 2014;25:1249-1256.

69. Linz D, Wirth K, Ukena C, Mahfoud F, Pöss J, Linz B, Böhm M, Neuberger HR. Renal denervation suppresses ventricular arrhythmias during acute

ventricular ischemia in pigs. Heart Rhythm. Heart Rhythm. 2013;10:1525-1530.

70. Huang B, Yu L, He B, Lu Z, Wang S, He W, Yang K, Liao K, Zhang L, Jiang H. Renal sympathetic denervation modulates ventricular electrophysiology and has a protective effect on ischaemia-induced ventricular arrhythmia. Exp Physiol. 2014;99:1467-1477.

71. Jackson N, Gizurarson S, Azam MA, King B, Ramadeen A, Zamiri N, Porta-Sánchez A, Al-Hesayen A, Graham J, Kusha M, Massé S, Lai PF, Parker J, John R, Kiehl TR, Nair GK, Dorian P, Nanthakumar K. Effects of Renal Artery Denervation on Ventricular Arrhythmias in a Postinfarct Model. Circ Cardiovasc Interv. 2017;10:e004172.

72. Chang S-N, Chang S-H, Yu CC, et al. Renal denervation decreases susceptibility to arrhythmogenic cardiac alternans and ventricular arrhythmia in a rat model of post–myocardial infarction heart failure. J Am Coll Cardiol Basic Trans Science 2017;2:184–193.

73. Guo Z, Zhao Q, Deng H, Tang Y, Wang X, Dai Z, Xiao J, Wan P, Wang X, Huang H, Huang C. Renal sympathetic denervation attenuates the ventricular substrate and electrophysiological remodeling in dogs with pacing-induced heart failure. Int J Cardiol. 2014;175:185-186.

74. Dai Z, Yu S, Zhao Q, Meng Y, He H, Tang Y, Wang X, Xiao J, Wang X, Huang C. Renal sympathetic denervation suppresses ventricular substrate remodelling in a canine high-rate pacing model. EuroIntervention. 2014;10:392-399.

75. Yamada S, Lo LW, Chou YH, Lin WL, Chang SL, Lin YJ, Liu SH, Cheng WH, Tsai TY, Chen SA. Beneficial Effect of Renal Denervation on Ventricular Premature Complex Induced Cardiomyopathy. J Am Heart Assoc. 2017;6.

76. Linz D, Denner A, Illing S, Hohl M, Ukena C, Mahfoud F, Ewen S, Reil JC, Wirth K, Böhm M. Impact of obstructive and central apneas on ventricular repolarisation: lessons learned from studies in man and pigs. Clin Res Cardiol. 2016;105:639-647.
77. Yu L, Huang B, Zhou X, Wang S, Wang Z, Wang M, Li X, Zhou L, Meng G, Yuan S, Wang Y, Jiang H. Renal sympathetic stimulation and ablation affect ventricular arrhythmia by modulating autonomic activity in a cesium-induced long QT canine model. Heart Rhythm. 2017;14:912-919.
78. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311:819-823.
79. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation. 1986;73:615-621.
80. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur Heart J. 2005;26:906-913.
81. Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, Sobotka PA, Gawaz M, Böhm M. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. Clin Res Cardiol. 2012;101:63-67.
82. Armaganijan LV, Staico R, Moreira DA, Lopes RD, Medeiros PT, Habib R, Melo Neto J, Katz M, Armaganijan D, Sousa AG, Mahfoud F, Abizaid A. 6-Month Outcomes in Patients With Implantable Cardioverter-Defibrillators Undergoing Renal Sympathetic Denervation for the Treatment of Refractory Ventricular Arrhythmias. JACC Cardiovasc Interv. 2015;8:984-990.

83. Remo BF, Preminger M, Bradfield J, Mittal S, Boyle N, Gupta A, Shivkumar K, Steinberg JS, Dickfeld T. Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy. Heart Rhythm. 2014;11:541-546.

84. Ukena C, Mahfoud F, Ewen S, Bollmann A, Hindricks G, Hoffmann BA, Linz D, Musat D, Pavlicek V, Scholz E, Thomas D, Willems S, Böhm M, Steinberg JS. Renal denervation for treatment of ventricular arrhythmias: data from an International Multicenter Registry. Clin Res Cardiol. 2016;105:873-879.

85. Hopper I, Gronda E, Hoppe UC, Rundqvist B, Marwick TH, Shetty S, Hayward C, Lambert T, Hering D, Esler M, Schlaich M, Walton A, Airoldi F, Brandt MC, Cohen SA, Reiters P, Krum H. Sympathetic Response and Outcomes Following Renal Denervation in Patients With Chronic Heart Failure: 12-Month Outcomes From the SymplicityHF Feasibility Study. J Card Fail. 2017. doi: 10.1016/j.cardfail.2017.06.004.

Figures

Figure 1: Effects of renal denervation (RDN) on blood pressure, renal catecholamine levels and renal and cardiac interstitial fibrosis in spontaneously hypertensive obese rats (SHR-ob). (A) Mean arterial blood pressure measured by telemetry in control rats (Ctrs), SHRs-ob, and SHRs-ob + renal sympathetic denervation (SHRs-ob + RDN) during 100 days after RDN performed at the age of 34 weeks. (B) Immunohistochemical renal tyrosin hydroxylase staining and (C) renal norepinephrine tissue content at the age of 48 weeks. (D) Interstitial left ventricular (LV) and (E) kidney fibrosis with representative histological images. (Adopted from Linz et al., Am J Hypertens. 2015. (9)).

Figure 2: (A) Representative image during a chemical renal denervation (RDN) procedure in a spontaneously hypertensive rat. Both kidneys were surgically denervated by cutting all visible nerves in the area of the renal hilus and by stripping approximately 2–4 mm of the adventitia from the renal artery. The area was then moistened with a phenol/ethanol solution for 10–15 minutes using a brush. (B) Representative Western Blot to quantify protein expression of norepinephrine transporter (NET) in kidney and heart tissue of sham-denervated spontaneously hypertensive rat and of RDN spontaneously hypertensive rats.

Figure 3: Effects of renal denervation (RDN) on efferent and afferent signaling of the kidney. (Norepinephrine, NE; muscle sympathetic nerve activity, MSNA; Left stellate ganglion, LSG).

Figure 4: Effects of renal denervation (RDN) compared to sham intervention (Sham) in goats with atrial fibrillation induced by an implanted pace maker. (A) Representative X-ray images of the kidney. Locations of ablation delivery are indicated by superimposed small black points in the vessels. (B) Renal tissue norepinephrine concentrations in the left (white bars) and right (black bars) kidney determined after the sacrifice experiments. (C) Representative perivascular tyrosine hydroxylase (TH) staining (brown twigs) of cardiac sympathetic nerves in SHAM and RDN goats with 6 weeks AF (magnification, 1000×). (D) Quantification of TH-positive (indicating sympathetic nerve structures) fraction of the perivascular area in the anterior left atrium (LAant), posterior left atrium (LApost) and right atrium (RA). (E) Quantification of AF-complexity: Representative spatial and temporal distribution of AF activation pattern during one AF cycle length of the right and left atrium in SHAM (top) and RDN (bottom) goats with 6 weeks. Isochronal maps: time between isochrones 10 ms, red earliest, blue latest activation. (Adopted from Linz et al., Circ Arrhythm Electrophysiol. 2015. (32)).

Figure 5: Effects of renal denervation (RDN) on ventricular fibrillation (VF) in a pig model for ventricular ischemia and reperfusion. (A) Representative view on the left ventricular during ischemia reperfusion experiments. Atrial electrophysiology was recorded by an epicardial catheter. (B) Incidence of VF during ischemia and the reperfusion phase in RDN-treated compared to SHAM-treated pigs. (C) Representative hemodynamics and electrocardiographic (ECG) tracings during 20 minutes of left anterior descending coronary artery ligation followed by reperfusion in a SHAM-treated and a RDN-treated animal. (Adopted from Linz et al., Heart Rhythm. 2013. (69)).

Figure 1

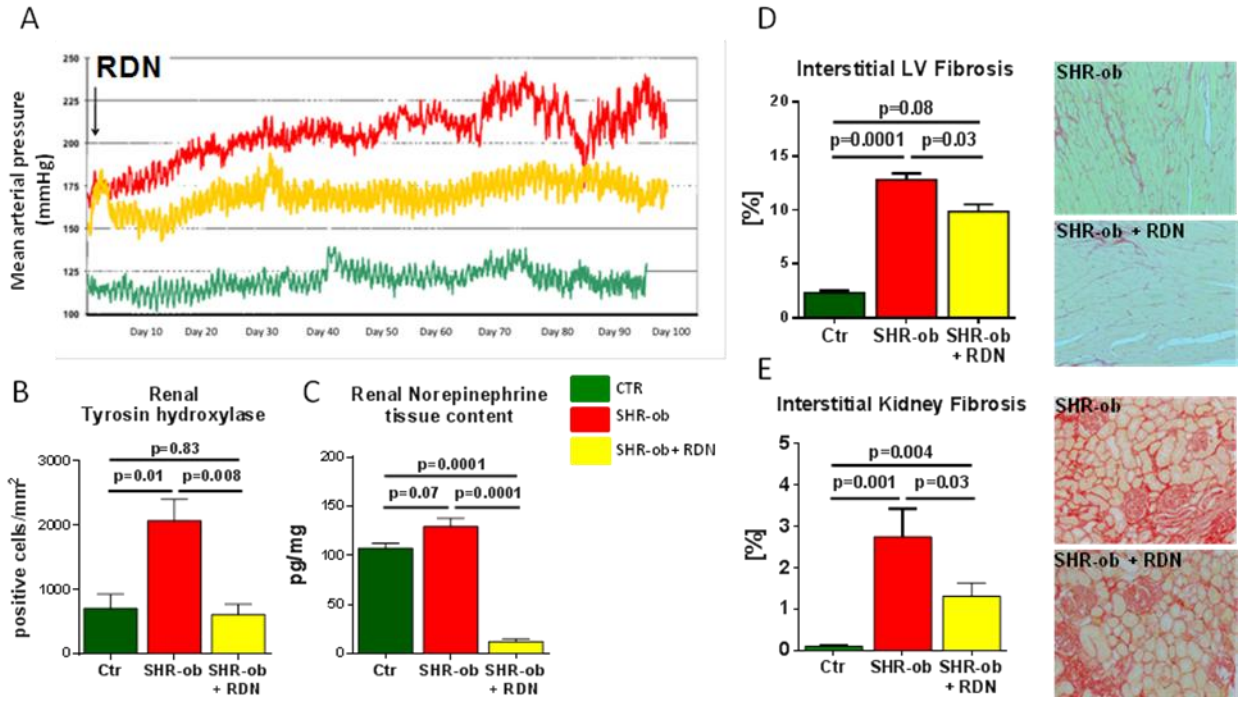
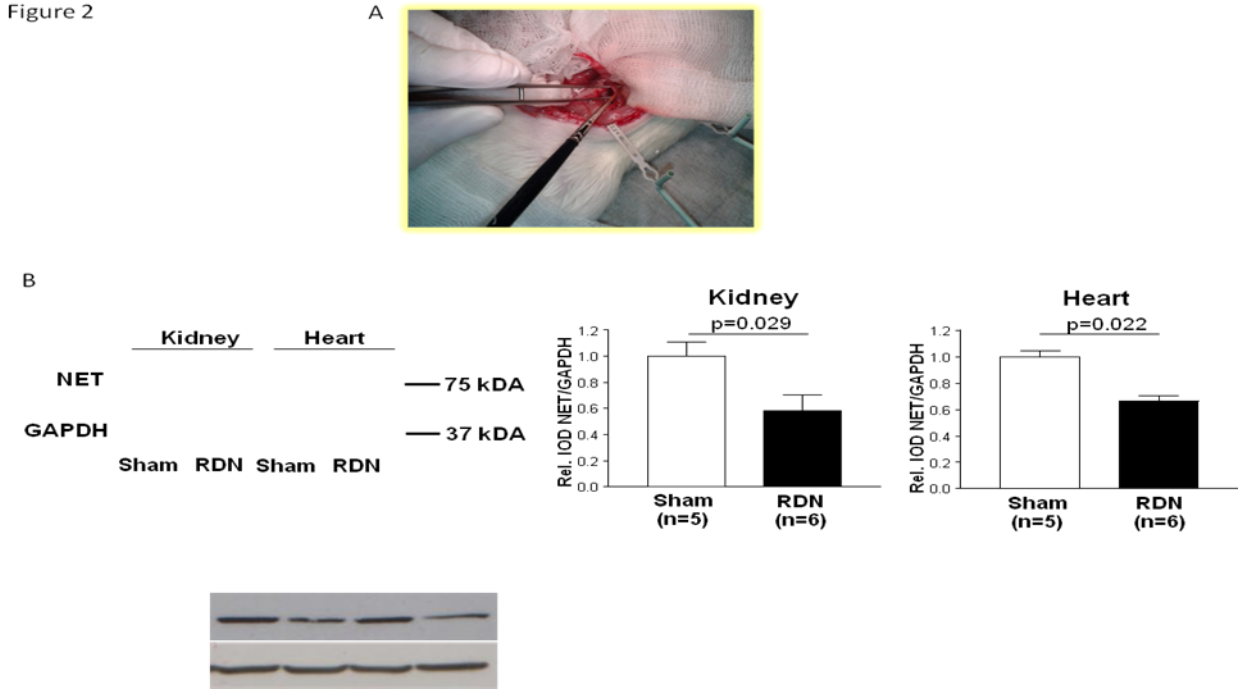


Figure 2



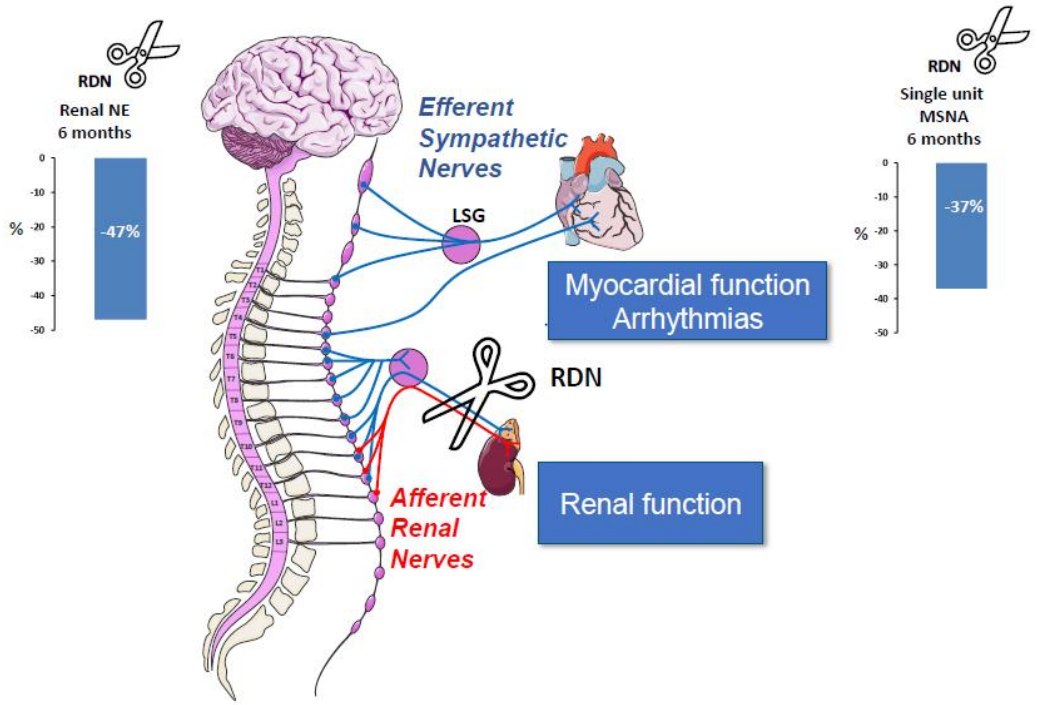

RDN
Renal NE
6 months
%
-47%
Efferent
Sympathetic
Nerves
LSG
Myocardial function
Arrhythmias
RDN
Afferent
Renal
Nerves
Renal function
RDN
Single unit
MSNA
6 months
%
-37%

Figure 4

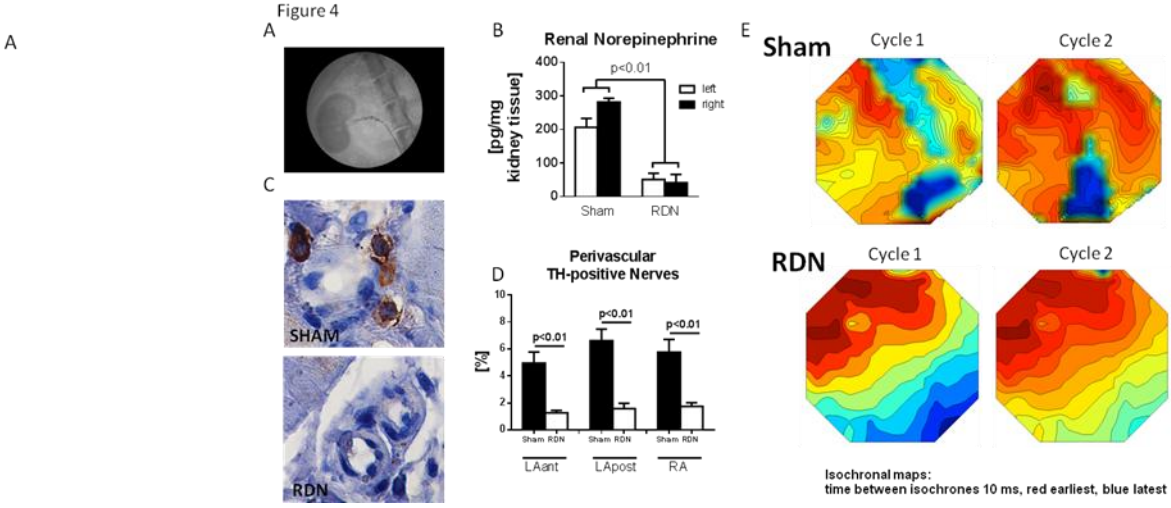
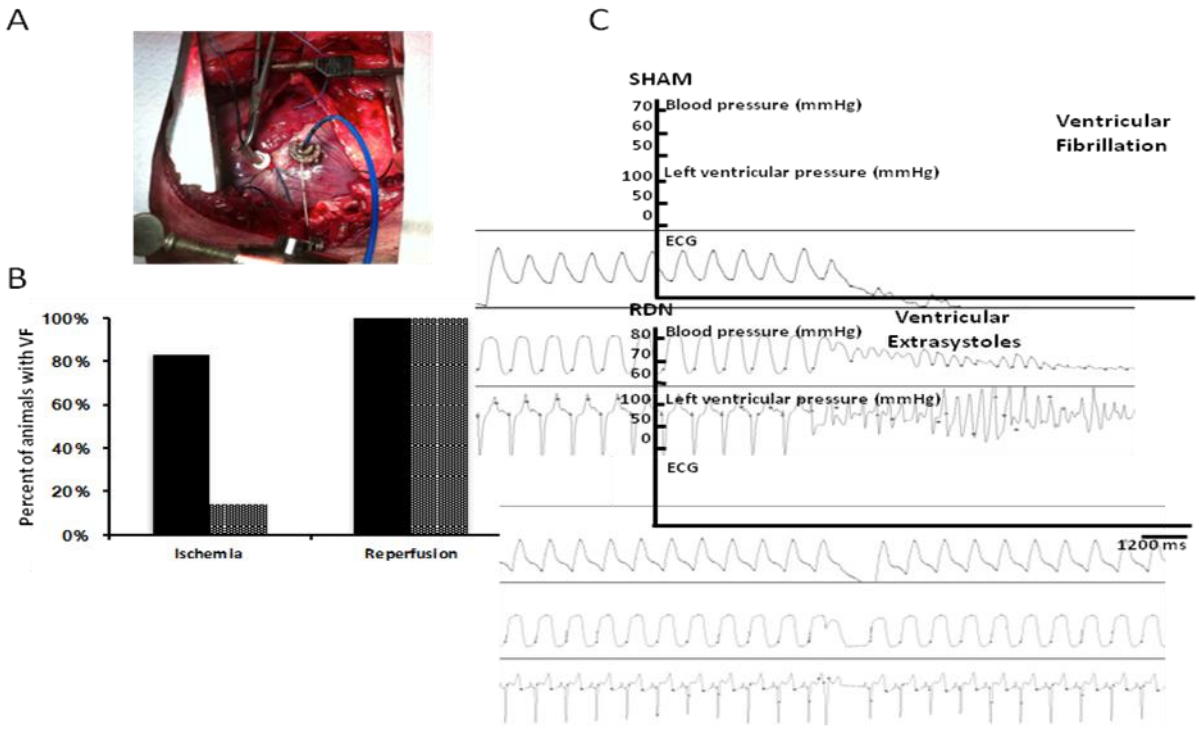

A
A
C
SHAM
RDN
B
Renal Norepinephrine
p<0.01
[pg/mg kidney tissue]
left
right
Sham
RDN
D
Perivascular
TH-positive Nerves
[%]
p<0.01
p<0.01
p<0.01
Sham RDN
Sham RDN
Sham RDN
LAant
LApost
RA
E
Sham
Cycle 1
Cycle 2
RDN
Cycle 1
Cycle 2
Isochronal maps:
time between isochrones 10 ms, red earliest, blue latest

Figure 5


A
B
C
Percent of animals with VF
100%
80%
60%
40%
20%
0%
Ischemia
Reperfusion
SHAM
Blood pressure (mmHg)
70
60
50
Left ventricular pressure (mmHg)
100
50
0
ECG
Ventricular
Fibrillation
RDN
Blood pressure (mmHg)
80
70
60
Left ventricular pressure (mmHg)
100
50
0
ECG
Ventricular
Extrasystoles
1200 ms