Journal of
Hypertension and Management

Eysenck and Sulke. J Hypertens Manag 2016, 2:020
Volume 2 | Issue 2
ISSN: 2474-3690

Review Article: Open Access

Can Effective Treatment of Resistant and Uncontrolled Hypertension Improve Outcomes from Atrial Fibrillation Ablation?

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Abstract

Atrial fibrillation (AF) ablation can be considered as a first-line therapy for AF rhythm control in symptomatic patients [1-3]. However, the number of AF recurrences during long-term follow-up is significant [1]. Recurrences may be due to progression of structural and electrical atrial dysfunction, frequently secondary to hypertension [4].

In recent years, there has been great interest in non-pharmacological methods to manage uncontrolled and resistant hypertension. Renal denervation and formation of a central iliac anastomosis are examples. In addition, renal denervation has yielded promising results in the prevention and treatment of AF. We have analysed the potential explanations for this in detail. A central iliac arteriovenous anastomosis, meanwhile, reduces arterial stiffness which is not targeted by sympathomodulation [5,6]. Arterial stiffness has been shown to be a strong and independent predictor of future AF in hypertensive patients. We have extrapolated this train of thought and suggest that a central iliac anastomosis may have its' own niche in the clinical conundrum of AF management in the context of poorly controlled hypertension. Our aim is to provide evidence that AF ablation with a central iliac anastomosis is more effective than AF ablation alone in those with resistant hypertension.

Keywords

Resistant hypertension, Uncontrolled hypertension, Atrial fibrillation, Atrial fibrillation ablation

Introduction

AF is the most common sustained arrhythmia, with a prevalence of approximately 1.60% in the United Kingdom in 2014 [1-3]. AF is a progressive disease in which arrhythmia-induced remodeling facilitates evolution from paroxysmal AF to persistent and permanent forms [7-9]. Such self-perpetuation has been attributed to AF-related changes in atrial structure and function that facilitate progression of the disease [7-9]. Hypertension is the major cause through inducing atrial hypertrophy and structural remodeling of the atria, thereby increasing susceptibility to developing and maintaining AF [4,7-9]. Approximately 20-30% of hypertensives have resistant hypertension [10,11]. In recent years, there has been great interest in non-pharmacological methods to manage resistant hypertension. Renal denervation and formation of a central iliac anastomosis are examples [5,11-14].

Renal denervation has been shown to be effective in reducing systolic and diastolic blood pressure in patients with resistant hypertension [12-14]. In addition, renal denervation significantly improves AF outcomes when combined with AF ablation [15,16]. Meanwhile, the ROX Coupler iliac arterio-venous anastomosis device (ROX Ltd., California USA) alters mechanical arterial properties and reduces blood pressure in patients with resistant hypertension [5,6]. Controlling hypertension in such a way might prevent the progression of AF and augment outcomes from AF ablation. We have reviewed world literature to evaluate the data regarding hypertension control and progression and treatment of AF.

The Structural Effects of Hypertension and Development of Atrial Fibrillation

Hypertension occurs in 65-70% of AF patients, making this the most common co-morbidity found in AF registries in Europe [17,18]. Long-standing hypertension may cause left atrial enlargement early, before any evidence of left ventricular hypertrophy (LVH) or atrial arrhythmia [4]. The magnitude of atrial enlargement correlates with the degree of hypertension, and may be the result of raised left atrial filling pressures and impairment of left ventricular diastolic function [17-19]. Enlargement of the left atrium is important in the progression from hypertension to AF. Studies have demonstrated that hypertensive patients with a history of paroxysmal AF have larger left atria than patients without paroxysmal AF. In the Framingham study, the risk of developing AF increased by 39% for each 5 mm increase in left atrial size, after adjustment for other risk factors [20].

LVH is itself, also an important risk factor for AF [19,20]. In the Framingham cohort, patients with an electrocardiogram (ECG) determined diagnosis of LVH had a 3.8 fold increased risk of developing AF. The risk of developing AF increases by 28% for each 4 mm increase in echocardiographically measured left ventricular wall thickness [20].

In addition, the role of arterial stiffness appears key but poorly understood. Kjeldsen, *et al.* examined associations between noninvasive measures of vascular function and new-onset AF [20]. The study sample included patients aged ≥ 45 years from the Framingham Heart Study offspring and third-generation cohorts. Higher augmentation index, baseline brachial artery diameter, and lower flow-mediated dilation were associated with increased risk of incident AF. Central pulse pressure, when adjusted for age, gender, and hypertension

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Citation: Eysenck W, Sulke N (2016) Can Effective Treatment of Resistant and Uncontrolled Hypertension Improve Outcomes from Atrial Fibrillation Ablation?. J Hypertens Manag 2:020

Received: August 11, 2016: **Accepted:** October 24, 2016: **Published:** October 26, 2016

was associated with incident AF. Higher pulsatile load assessed by central pulse pressure and greater apparent wave reflection measured by augmentation index were associated with increased incident AF [20]. However, targeting arterial stiffness as a means of improving the management of AF has not been assessed.

Device-Based Therapy for Hypertension

Renal denervation

Activation of the renal sympathetic nervous system plays a major role in the development and progression of hypertension [21,22]. A catheter-based approach to denervate the kidneys has been introduced into clinical practice, and has been shown to reduce blood pressure and sympathetic activity in patients with resistant hypertension. Surgical denervation has been shown to be an effective means of reducing sympathetic outflow to the kidneys, augmenting natriuresis and diuresis, and reducing renin release, without adversely affecting other functions of the kidney [21,22].

Substantial and progressive reductions in office blood pressure measurements were observed in two initial randomised controlled trials [12,13]. Boehm, *et al.* was the first blinded, randomised, sham-procedure controlled trial of renal denervation for treatment resistant hypertension [14]. Disappointingly, renal denervation did not reach the primary efficacy endpoint of decrease in 24-hour ambulatory blood pressure levels [14]. In spite of a significant reduction in blood pressure at 6 months compared with baseline of 14.1 mmHg for renal denervation and 11.7 mmHg for the sham treatment group, the difference of - 2.29 mmHg in office systolic blood pressure between the two groups was not significant (p = 0.26). Similarly, in both groups significant decreases in 24-hour ambulatory blood pressure levels at 6 months as compared to baseline were noted, whereas the difference between the two arms of - 1.96 mmHg remained non-significant (p = 0.98). There is now considerable ongoing debate regarding the true efficacy of renal denervation in lowering blood pressure.

Renal denervation and atrial fibrillation ablation

There are data to indicate that activation of the renal sympathetic nervous system also plays a role in the development of AF [21,22]. An increased parasympathetic tone results in a shortening of the atrial refractory period, creating a substrate for re-entry, whereas sympathetic tone enhances spontaneous triggered activity [21,22]. Moreover, activation of the renin angiotensin-aldosterone system (RAAS) in patients with hypertension induces left atrial fibrosis and conduction block in the left atrium, resulting in development of AF. Effective blockage of the RAAS by angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARBs) are effective in both primary and secondary prevention of AF in patients with hypertension [18].

Multiple studies have explored the possibility that renal denervation could augment outcomes following AF ablation. Zou, *et al.* investigated the inducibility of AF during atrial rapid pacing after renal sympathetic denervation in an animal model [23]. Thirteen dogs were used for the study as follows: control group (seven dogs) and renal sympathetic denervation group (six dogs). In the control group, dogs were subjected to atrial pacing at 800 beats/min for 7 hours, and atrial effective refractory period was measured every hour in the status of non-pacing. Subsequently, pacing was stopped and the burst pacing (500 bpm) was repeated to induce AF three times. In the renal sympathetic denervation group, after each renal artery ablation, the procedure of pacing and electrophysiological measurement was exactly the same as the control group. Blood was collected before and after pacing to measure the levels of renin, angiotensin II and aldosterone. There was a persistent decrease in atrial effective refractory period in both groups. However, 7 hours after cessation of pacing, the induced number of times and duration of AF were higher in the control group than that in the renal sympathetic denervation group (1.0 ± 1.26 vs. 3.14 ± 2.54, P = 0.03; 16.5 ± 25.1 vs. 86.6 ± 116.4, P = 0.02). The plasma aldosterone concentration increased significantly 7 hours after rapid pacing in the control group (renin, 119.8 ± 31.1 vs. 185.3 ± 103.5 pg/ml, P < 0.01; aldosterone, 288.2 ± 43.1 vs. 369.6 ± 109.8 pg/ml, P = 0.01). The levels of renin and aldosterone showed a decreasing trend in the renal sympathetic denervation group, but this did not attain statistical significance. The authors concluded that episodes of AF could be decreased by renal sympathetic denervation during short-time rapid atrial pacing [23]. This effect might have a relationship with decreased activity of the RAAS.

In humans, 27 patients with symptomatic AF and drug-resistant hypertension were randomised by Pokushalov, *et al.* to AF ablation only (n = 14) or AF ablation+renal denervation (n = 13) [15]. The primary endpoint of the study was the recurrence of any atrial tachyarrhythmia > 30s after a single ablation procedure after the first 3 months had elapsed. The main findings of this prospective double-blind randomised study were that renal artery denervation had a positive impact on AF recurrences in hypertensive patients with refractory AF who also underwent AF ablation and renal artery ablation resulted in sustained improvement in systolic and diastolic blood pressure control over 1 year follow-up. This study had multiple significant limitations. Firstly, the patients did not have long-term beat-to-beat monitoring. Instead ECGs and 24-hour Holters were used to measure for AF recurrence [16]. Secondly, office blood pressure measurements were used to ascertain blood pressure response. It is widely accepted that 24 hour blood pressure monitors provide a much more accurate account of a patient's blood pressure. Thirdly, this study comprised only 27 patients. The implications for the wider AF community remain unclear.

Vorobyoff, *et al.* investigated whether renal sympathetic denervation was a safe and effective treatment option in patients with paroxysmal AF utilizing implantable loop recorders for their continuous atrial rhythm monitoring abilities [16]. Subjects (n = 30) with symptomatic paroxysmal AF and hypertension aged 18-75 years who had experienced at least one documented relapse of AF during a single trial of antiarrhythmic drug therapy were enrolled and randomised (1:1) to one of 2 arms [16]. In group 1 (active treatment) patients underwent a pulmonary vein isolation followed by renal sympathetic denervation. In group II (control), only PVI was performed. Follow-up included symptoms confirmed by an implantable loop recorder. The primary endpoint was freedom from arrhythmia (AF/atrial flutter/atrial tachycardia) > 30 seconds following a blanking period of 3 months. Primary endpoint was observed in 3/15 (20%) in the group I vs. 2/15 (13.3%) in the group II (P = 0.62). Median of time to AF recurrence was 82 days in group I vs. 15 days in group II (P = 0.02). Therefore, renal denervation did not prevent recurrence of AF at the 6-month follow-up, but increased time to AF recurrence during blanking period [16].

Liang, *et al.* investigated the close association between renal impairment and AF recurrence [24]. Unilateral renal insufficiency was induced in beagles by embolization of small branches of the renal artery in the right kidney using gelatin sponge granules. The Sham group (n = 6) underwent the same procedure, except for embolization. Then animals in the renal denervation group underwent radiofrequency ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters, blood pressure, left ventricular end-diastolic pressure, and AF inducibility were investigated. The activity of the sympathetic nervous system, RAAS, inflammation and atrial interstitial fibrosis were measured. The investigators found that heart rate, P wave duration and BP were increased by renal insufficiency, which were prevented or attenuated by renal denervation. Atrial effective refractory period was shortened and AF inducibility was increased by renal insufficiency, which was prevented by renal denervation. Antegrade Wenckebach point was shortened, atrial and ventricular rates during AF were increased by renal insufficiency, which were attenuated or prevented by renal denervation. Levels of norepinephrine, renin and aldosterone in plasma, norepinephrine, angiotensin II, aldosterone, interleukin-6 and high sensitivity C-reactive protein in atrial tissue were elevated, and atrial interstitial fibrosis was enhanced by renal insufficiency, which were attenuated by renal denervation. The authors concluded that renal denervation significantly reduced AF inducibility, prevented the atrial electrophysiological changes in a model of renal insufficiency by combined reduction of sympathetic

drive and RAAS activity, and inhibition of inflammation and fibrotic pathway in atrial tissue [25].

There is growing evidence for the role of renal denervation in augmenting outcomes following AF ablation. In altering sympathetic tone renal denervation is thought to lower blood pressure. It is either by this alteration in sympathetic tone or through the lowering of blood pressure that outcomes from AF ablation can improve.

Central iliac arteriovenous anastomosis

A central iliac arteriovenous anastomosis has been shown to alter mechanical arterial properties and reduce blood pressure in patients with resistant and/or uncontrolled hypertension [5]. The device was developed by ROX Medical (California, USA) and is named the 'Coupler' (Figure 1).

A randomised controlled hypertension trial of this device commenced in 2012. The procedure involves placement of the coupler between the distal external iliac vein and artery, above the level of the femoral head and ischial spine. The technique adds a low-resistance, high-compliance venous segment to the central arterial tree. This technique is associated with an immediate and significant reduction in blood pressure and reduces the risk of hospitalised hypertensive crises [5]. The mechanism of action is purported to be

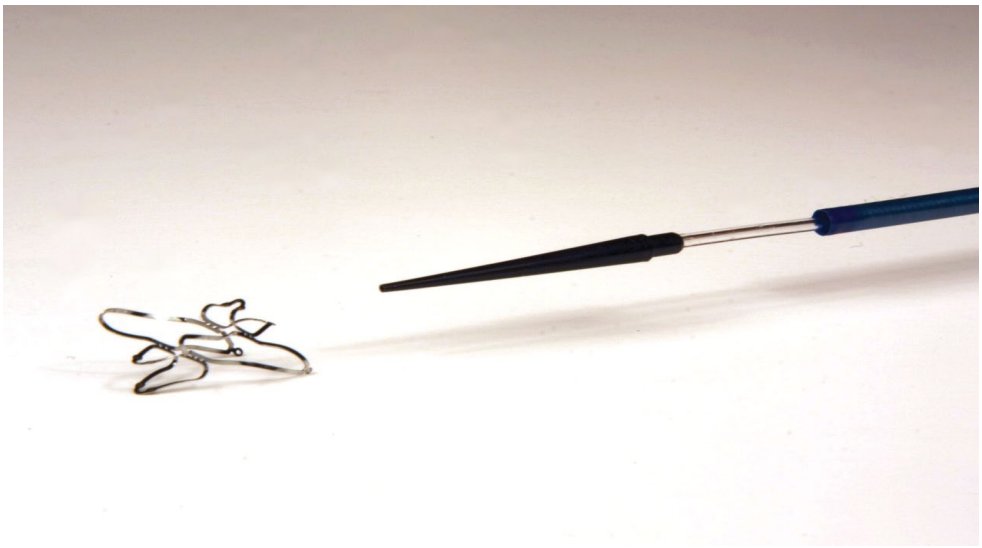

Figure 1: Arteriovenous ROX coupler and deployment catheter.

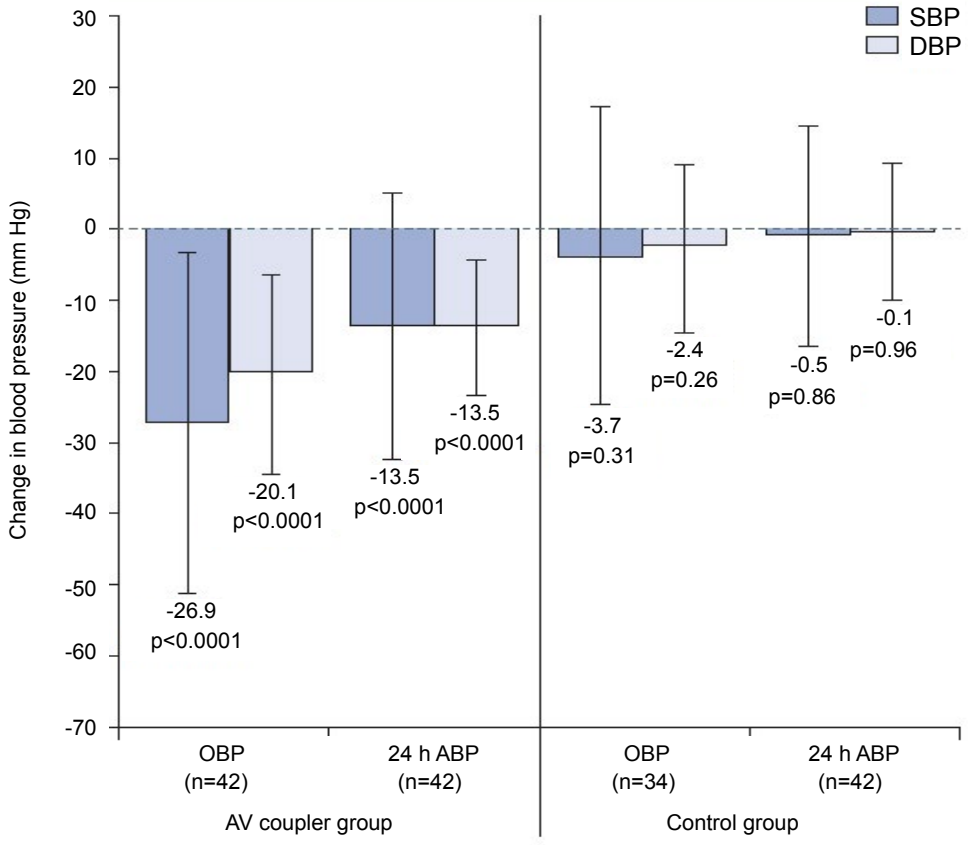

Figure 2: Change from baseline in blood pressure at 6 months.

Source: Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial, the Lancet 2015 [5].

to increase aortic compliance [6]. Incorporating a segment of vein in the central arterial circuit is expected to cause a reduction of blood pressure through improved arterial compliance and lowering of vascular resistance.

In a large open-label, multicenter, prospective, randomized controlled trial between October, 2012 and April, 2014 significant reductions in blood pressure could be achieved in patients with uncontrolled essential hypertension, despite inadequate response to multiple antihypertensive drugs (Figure 2).

The ROX Coupler and AF Ablation: Can Exploiting the Physical Properties of the Arterial Vasculature Augment Outcomes following AF ablation?

There are grounds for optimism that the ROX Coupler may improve outcomes from AF ablation. Firstly, the significant reduction in blood pressure should offset the aforementioned structural and electrical cardiac effects induced by longstanding hypertension. The creation of a small, fixed, centrally located arteriovenous anastomosis using the ROX coupler results in an immediate and sustained reduction in systemic arterial pressure, as predicted by the addition of low-resistance and high-compliance venous attachment. Theoretically this reduction in arterial resistance addresses a key, independent risk for the development of AF. Secondly, the reduction of left ventricular work following reduction of high systemic arterial pressure causes the heart to operate at a more efficient match of preload and afterload, predicting reduced cardiac oxygen consumption and reduced myocyte stress [6]. These predict improved exercise tolerance and improvement in LVH. As already described, LVH is an independent risk factor for the development of AF.

The ROX Coupler vs. Renal Denervation

In the ROX Control HTN study, 17 patients (n = 10 in the arteriovenous coupler group and n = 7 in the control group) had previously undergone renal denervation. Those in the arteriovenous coupler group had significant mean reductions in systolic and diastolic office blood pressure and systolic and diastolic mean 24 h ambulatory blood pressure at 6 months. In contrast, mean changes in the control patients who had undergone renal denervation were not significant for office or 24 h ambulatory blood pressure. A possible explanation for this inadequate response to renal denervation is that resistant hypertension is due, in part, to arterial stiffness which is not targeted by sympathomodulation. This is the principle upon which renal denervation relies. In addition, unlike renal denervation, the ROX Coupler is fully reversible and implantation is comparatively pain-free.

Renal artery denervation is reserved only for those with drug-resistant hypertension. The vast majority of those with hypertension are not currently eligible for renal artery denervation. In contrast, the ROX Coupler has a track record of safety when used in a variety of clinical settings. It offers an attractive option as an additional procedure in patients with hypertension and AF ablation.

Discussion

The association between hypertension and AF has been well established. Whilst conventional treatment for AF in the form of antiarrhythmic medications and pulmonary vein isolation are effective, therapies directed upstream of the electrical aspects of AF, towards the underlying anatomical substrate of left atrial enlargement and LVH, may provide additional benefit. In particular, it has been shown that aggressive treatment of hypertension may reverse the associated structural cardiac changes, and reduce the burden of AF. Two novel device-based therapies for the treatment of resistant and uncontrolled hypertension may augment AF ablation. Renal denervation has previously been shown to significantly improve outcomes from AF ablation in both animal and human models. A central iliac arteriovenous anastomosis, meanwhile, reduces arterial stiffness which is not targeted by sympathomodulation. Arterial stiffness has been shown to be a strong predictor of future AF in hypertensive patients, independently of age, 24-h pulse pressure and left atrial diameter. There are grounds for optimism that the significant blood pressure lowering effects of a ROX Coupler, and its' mechanism of action, could significantly augment outcomes from AF ablation in those patients with resistant hypertension.

The ROX procedure is a minimally invasive, catheter-based procedure which is safe in a variety of clinical settings. It offers an attractive option as an additional procedure in those with hypertension and AF undergoing ablation as it is fully reversible, unlike renal denervation. Given the increased efficacy of a ROX Coupler over renal denervation it is the opinion of the authors' that this device will augment outcomes from AF ablation to a much greater degree. Numerous beneficial autonomic mechanisms may be implicated, and we hypothesise that the key factors include a reduction in systemic vascular resistance and reduction in afterload, resulting in an overall reduction in cardiac work, thereby offsetting the progression of atrial damage, a key factor in the progression from hypertension to AF.

Conclusion

Arterial stiffness is a key, independent risk factor for the development of AF in hypertensive patients but has not been considered as a target in the management of AF. The ROX Coupler exploits the physical properties of the arterial vasculature and reduces arterial stiffness. It remains to be seen whether a central iliac arteriovenous anastomosis can improve outcomes from AF ablation in patients with resistant hypertension.

Disclosures

NS was an unpaid primary investigator in the ROX Control Hypertension (RH 02) trial.

References

1. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, et al. (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 22: 2719-2747.
2. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, et al. (2007) Outcome parameters for trials in atrial fibrillation: executive summary. Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J 28: 2803-2817.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J.
4. Miller JT, O'Rourke RA, Crawford MH (1988) Left atrial enlargement: an early sign of hypertensive heart disease. Am Heart J 116: 1048-1051.
5. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, et al. (2015) Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. The Lancet 385: 1634-1641.
6. Burchell AE, Lobo MD, Sulke N, Sobotka PA, Paton JF (2014) Arteriovenous anastomosis: is this the way to control hypertension? Hypertension 64: 6-12.
7. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA (1995) Atrial Fibrillation Begets Atrial Fibrillation A Study in Awake Chronically Instrumented Goats. Circulation 92: 1954-1968
8. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, et al. (2010) Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol 55: 725-731.
9. Kirchhof P, Schotten U (2006) Hypertension begets hypertrophy begets atrial fibrillation? Insights from yet another sheep model. Eur Heart J 27: 2919-2920.
10. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, et al. (2012) Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients Circulation 125: 1635-1642.
11. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, et al. (2008) Resistant Hypertension: Diagnosis, Evaluation, and Treatment. Circulation 117: 510-526.
12. Symplicity HTN-1 Investigators (2011) Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 57: 911-917.
13. Simplicity HTN-2 Investigators (2010) Renal sympathetic denervation in patients with treatment resistant hypertension (The Simplicity HTN-2 Trial): a randomised controlled trial. Lancet 376: 1903-1909.

14. Boehm M, Schlaich M, Narkiewicz K, Ruilope L, Williams B, et al. (2013) The blood pressure lowering effects of renal denervation in a real world population of patients with uncontrolled hypertension: Early outcomes from the Global SYMPLICITY registry. Eur Heart J 34: 673-674.

15. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, et al. (2012) A randomised 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 60: 1163-1170.

16. Vorobyoff AS, Bibikov VN, Korolev SV, Geraschenko AV, Sveshnikov AV (2015) Simultaneous renal sympathetic denervation and pulmonary veins isolation in patients with paroxysmal atrial fibrillation and hypertension. Europace 1099-5129.

17. Healey JS, Connolly SJ (2003) Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target. Am J Cardiol 91: 9G-14G.

18. Gerdts E, Oikarinen L, Palmieri V, Otterstad JE, Wachtell K, et al. (2002) Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy, the Losartan Intervention for endpoint reduction in hypertension (LIFE) study. Hypertension 39: 739-743.

19. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA (1993) Estimation of left atrial filling pressures using two dimensional and Doppler echocardiography in adult patients with cardiac disease: additional value of analysing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous mitral inflow velocity at atrial contraction. J Am Coll Cardiol 22: 1972-1982.

20. Kjeldsen SE, Aksnes TA, Wachtell K, Okin PM (2016) Arterial stiffness predicts incident atrial fibrillation in the Framingham Heart Study. A Mechanistic Contribution in People with High Blood Pressure or History of Hypertension. Hypertension 68.

21. Koepke JP, DiBona GF (1985) Functions of the renal nerves. Physiologist 28: 47-52.

22. Stella A, Zanchetti A (1991) Functional role of renal afferents. Physiol Rev 71: 659-682.

23. Zou MH, Zhao QY, Yu SB, Dai ZX, Wang XL, et al. (2012) Effects of renal sympathetic denervation on inducibility of atrial fibrillation during rapid atrial pacing. Zhonghua Yi Xue Za Zhi 92: 2868-2871.

24. Liang Z, Liu LF, Chen XP, Shi XM, Guo HY, et al. (2014) Establishment of a model or renal impairment with mild renal insufficiency associated with atrial fibrillation in canines. PLoS One 9.