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## Original research article

# The influence of catheter-based renal sympathetic denervation on renal function and renal arteries



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## ABSTRACT

**Objective:** Currently investigated non-pharmacological minimally invasive method for the treatment of resistant hypertension is percutaneous denervation of renal sympathetic nerve fibres by radiofrequency catheter-based ablation. We assessed its influence on renal function and renal arteries.

**Methods:** The first 38 patients treated with catheter-based renal denervation at our centre between September 2011 and December 2012 were included in the study. Changes in renal function and changes in renal artery morphology at 12 months after the procedure have been analyzed.

**Results:** Mean age was  $57.6 \pm 11$  years, the majority (63.9%) were men. Average estimated glomerular filtration rates (eGF) were  $1.25 \text{ ml/s/1.73 m}^2$  before denervation and  $1.30 \text{ ml/s}^{-1}/1.73 \text{ m}^{-2}$  12 months after intervention. Changes in eGF did not reach statistical significance. New haemodynamically non-significant renal artery stenosis (40%) has occurred in only one case after procedure.

**Conclusion:** In agreement with the results of several studies, our findings suggest that renal denervation (RDN) appears to be a safe therapeutic approach.

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## Introduction

Arterial hypertension is the most frequent cardiovascular disease [1]. Approximately 1 billion people worldwide suffer from hypertension, and it is projected that this number will increase to 1.5 billion by 2025 [2]. Its prevalence is expected to increase especially in developing countries [3]. Despite several available antihypertensive drugs and their unquestionable

beneficial effects, hypertension control is still unsatisfactory [4,24]. This fact is attributed to a number of factors such as inappropriate blood pressure measurement, physician inertia, excessive salt intake or secondary causes of hypertension. Apart from the white coat syndrome, patient non-compliance to a pharmacological therapy is a very frequent phenomenon [5]. If these factors are excluded and uncontrolled hypertension persists despite the use of at least 3 antihypertensive drugs of different classes at maximally tolerated doses

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including a diuretic, we speak of resistant hypertension. The true prevalence of resistant hypertension remains unknown because of the absence of a specifically designed large prospective study with forced titration. Analyses of clinical trials suggest a prevalence to range from 10% to almost 30% of general hypertensive patients in different studies [6,7].

Accumulated evidence indicates that human sympathetic nervous system deregulation contributes to the development of arterial hypertension [8,9]. Sympathetic overactivity has been demonstrated in both essential and secondary forms of hypertension patients, such as obesity-related hypertension, end-stage renal disease hypertension and in obstructive sleep apnea [10].

Over the last few decades, growing knowledge about the role of the chronic sympathetic overactivity in hypertension pathophysiology has resulted in the development of an innovative non-pharmacological therapy that modulates sympathetic activation – percutaneous renal sympathetic denervation. It is an endovascular procedure that uses radiofrequency energy to destroy the perirenal sympathetic nerve fibres. RDN decreases both efferent and afferent renal sympathetic nerve activity. Anatomical regrowth of afferent renal nerves has not been shown and efferent renal nerves might be able to regrow to some extent [11]. Primary end point in the renal artery ablation sympathectomy is to reduce production of catecholamines, especially noradrenaline. The renin-angiotensin-aldosterone system is influenced simultaneously. After bilateral renal sympathectomy, the noradrenaline content in the kidney is reduced by 47% [12]. Renal perfusion is improved simultaneously [13]. Catheter-based sympathectomy does not affect negatively other organ systems and does not cause postural hypotension. It has a beneficial effect on myocardial remodelling and other vascular changes associated with severe hypertension and sympathetic overactivity [14].

Brandt and colleagues [15] demonstrated that RDN in resistant hypertension patients was associated with a regression of left ventricle hypertrophy and an improvement of the diastolic function at 6-months follow-up visit, compared with the control group. RDN may also influence other diseases associated with sympathetic hyperactivity like chronic heart failure, diabetes mellitus or sleep apnea syndrome [16].

Based on the available evidence from clinical studies, catheter-based renal denervation has a favourable short-term safety profile. During follow-up of patients from the multicenter, observational Symplicity HTN-1 trial [17] and from the randomized controlled Symplicity HTN-2 trial [18], no statistically significant changes in renal function and no vascular complications such as significant stenoses of treated renal arteries were seen.

The longest available follow-up was at 2 years in the Symplicity HTN-1 trial [19] with enlarged cohort of 153 patients at 19 centres in Australia, Europe and USA, in which renal function remained unchanged during the first year of follow-up. Estimated glomerular filtration rate data of 2 years after the intervention were only available for 10 patients, in which there was a mean reduction in eGF of  $16 \text{ ml/min}^{-1}/1.73 \text{ m}^{-2}$ . Five of these 10 patients had spironolactone or other diuretic added to the antihypertensive treatment after the first year of follow-up. In the remaining patients without newly added

spironolactone or other diuretic to the treatment, there was a reduction in estimated glomerular filtration rate ( $7.8 \text{ ml/min}^{-1}/1.73 \text{ m}^{-2}$ ). No patient showed doubling of serum creatinine, development of chronic kidney disease stage IV or the requirement for dialysis.

Adverse effects of renal denervation on glomerular filtration rate or renal artery structure was not shown during 6 months of follow-up in the study of Mahfoud and colleagues [20].

Worthley and colleagues [2] studied the safety of renal artery denervation in 46 patients at 4 centres in Australia and Greece using the EnlighHTN catheter (multi-electrode system). The follow-up interval was 6 months. No acute or late serious vascular complications occurred and small, non-clinically relevant changes in average estimated glomerular filtration rate were reported ( $87 \pm 19 \text{ ml/min}^{-1}/1.73 \text{ m}^{-2}$  before RDN compared with  $82 \pm 20 \text{ ml/min}^{-1}/1.73 \text{ m}^{-2}$  6 months after RDN).

Gosain and colleagues [21] analyzed 19 studies investigating the effect of renal denervation on renal function and renal haemodynamics. They did not find a significant worsening of renal function, changes in renal artery anatomy or development of clinically significant stenosis.

The safety of renal sympathetic denervation has also been confirmed in a recently published multicentre, prospective, blinded, randomized and controlled Symplicity HTN-3 trial [22]. Only one new renal artery stenosis of more than 70% was verified at 6-month follow-up period.

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## Methods

Our aim was to analyze the safety of renal sympathetic denervation based on the changes in renal function and changes in renal artery morphology from baseline to 12 months.

A total of 39 patients underwent catheter-based renal denervation treatment at our centre from 1.9.2011 to 17.12.2012 with subsequent follow-up to 1 year. One patient was excluded from the study due to absence of 1-year follow-up visit. A total 38 patients were included in the analysis. All the patients were confirmed the diagnosis of resistant hypertension and met all indication criteria of renal denervation. Patients underwent procedure with the use of radiofrequency energy delivered by the Medtronic Ardian Symplicity™ Renal Denervation System. The procedure was done in the catheterization laboratory in local anaesthesia by interventional cardiologist and arrhythmologist. Unfractionated heparin was administered with activated clotting time (ACT) monitoring. ECG and vital signs were monitored during the procedure. The intervention was performed via femoral access. A 6 French guiding catheter sheath was inserted to femoral artery, aortography with non-selective renal angiography using the pigtail catheter was performed subsequently. The lumen of the main renal artery was catheterized using RDND1 catheter (Medtronic, Denver, USA). After renal artery engagement and completion of a renal angiogram, the Symplicity ablation catheter was inserted to the renal artery minimally 5 mm from the main renal artery bifurcation and at the site where renal artery was minimally 4 mm in diameter.

Then radiofrequency energy of 8 W lasting up to 2 min was applied, and then the ablation catheter was pulled back and rotated. Further point of ablation was distant from previous by minimally 5 mm and rotated  $\sim 90^\circ$ . This continued until radiofrequency energy was sequentially applied in several points to the renal artery ostium. The aim was a minimum of four ablation sites in each main renal artery. The ablation procedure was then repeated at the contralateral renal artery. In our analysis, 13.8% of patients did not receive four ablations on bilateral renal arteries. Procedural data were recorded for each patient, including blood pressure and heart rate before and at the end of the intervention, procedure time, volume of contrast used and number of ablations delivered in each renal artery.

Renal function was assessed by repeated measurements of serum creatinine concentration and estimated glomerular filtration rate using the MDRD (Modification of Diet in Renal Disease) formula. Normality of data was verified with use of box plots and Shapiro-Wilk test. The difference between eGF before RDN and eGF 12 months after the procedure was analyzed using paired *t*-test. A 2-tailed *p* value of  $<0.05$  was regarded as statistically significant.

Renal artery evaluation was conducted in all patients by computed tomographic angiography at 6 months with the exception of one patient, in whom magnetic resonance angiography was done because of radiation protection.

## Patient characteristics

Baseline demographic, clinical condition, and medication data for the 38 patients are shown in Tables 1 and 2. Three patients did not take a diuretic. They were all documented as "diuretic intolerant" in the past. However, diagnosis of resistant hypertension was confirmed by testing the patient's blood to check for levels of medications they were taking and secondary causes of hypertension were excluded in a specialized office for resistant hypertension. From all the patients who were screened for eligibility for RDN, only 7% were indicated to denervation procedure. In total, 10 patients (26,32%) received both an angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker. In previous guidelines, at a time when the patients underwent the renal denervation procedure, the use of combination of two

**Table 1 – Baseline characteristics.**

Mean age at baseline (years $\pm$ SD)	57.6 $\pm$ 11
Gender (female) (%)	36.1
MI $\pm$ SD (kg/m <sup>2</sup> )	31.7 $\pm$ 4.5
Average eGF before RDN (ml/s <sup>-1</sup> /1.73 m <sup>-2</sup> )	1.25
Average number of antihypertensive drugs $\pm$ SD	5.5 $\pm$ 1.9
Dyslipidaemia (% patients)	68.4
Type 2 diabetes mellitus (% patients)	47.4
CAD (% patients)	31.6
Chronic kidney disease (% patients)	7.9
OSAS (% patients)	5.3

OSAS – obstructive sleep apnoea syndrome; BMI – body mass index; SD – standard deviation; CAD – coronary artery disease; eGF – estimated glomerular filtration rate; RDN – renal denervation.

**Table 2 – Medication data.**

Antihypertensive agent	Number of patients (%)
Angiotensin-converting enzyme inhibitor	26 (68.42%)
Angiotensin II receptor blocker	19 (50.00%)
Calcium channel blocker	29 (76.32%)
Diuretic	36 (94.74%)
Aldosterone antagonist	13 (34.21%)
Centrally acting sympatholytic agent	21 (55.26%)
Direct-acting renin inhibitor	5 (13.16%)
$\beta$ -blocker	29 (76.32%)
$\alpha$ -blocker	17 (44.74%)

different blockers of the RAS (renin-angiotensin system) was allowed. In two patients with type 2 diabetes mellitus, the above-mentioned combination of antihypertensive agents was indicated because of proteinuria.

## Results

Unilateral renal artery denervation was performed in 2 patients for anatomical reasons. The remaining 36 patients underwent bilateral denervation procedure. The mean procedure time was 84 min and the mean number of circumferential ablations delivered was 5.6 for the right and 5.1 for the left renal arteries. The mean contrast volume used was 227.3 ml. In the Symplicity HTN-3 trial the mean volume of contrast used was 177 ml, while it was 227.3 ml in our patient cohort. The explanation offered for slightly higher use of contrast is the maximized effort to adequately performing the procedure which is crucial for interruption of the renal sympathetic nerves and sustained blood pressure reduction. Good apposition between the ablation catheter and target ablation sites in the renal artery in anterior and posterior position have been achieved by using the biplane X-ray system (Philips, Integris Allura FD 20/10).

Patients were scheduled for the follow-up visits at 1-, 3-, 6- and 12-month after intervention. Average estimated glomerular filtration rate before denervation was 1.25 ml/s<sup>-1</sup>/1.73 m<sup>-2</sup> and 12 months after intervention 1.30 ml/s<sup>-1</sup>/1.73 m<sup>-2</sup>. Using the level of statistical significance 5%, we found that changes in average eGF were not statistically significant ( $t = -1.5052$ ;  $df = 37$ ;  $p$  value = 0.1413) (Fig. 1).

During the follow-up period, we did not show a substantial deterioration of eGF 1 year after renal artery denervation as compared with eGF before renal denervation treatment in a given patient. Only 2 patients reported decrease in eGF of  $>20\%$  (decrease by 24% in one patient and decrease by 27% in the second of them) (Fig. 2). They were females. Both patients had a history of cancer (breast cancer and carcinoma of the common bile duct), one patient had a type 2 diabetes mellitus. Renal functions were normal before denervation treatment. In these two patients we observed no significant differences in mean volume of contrast used, number of ablations and procedure time as compared with the other patients. Regarding antihypertensive medications, in one patient the dose of spironolactone was increased at 6 months after the procedure, in the second patient no postprocedural changes in antihypertensive medication were reported.

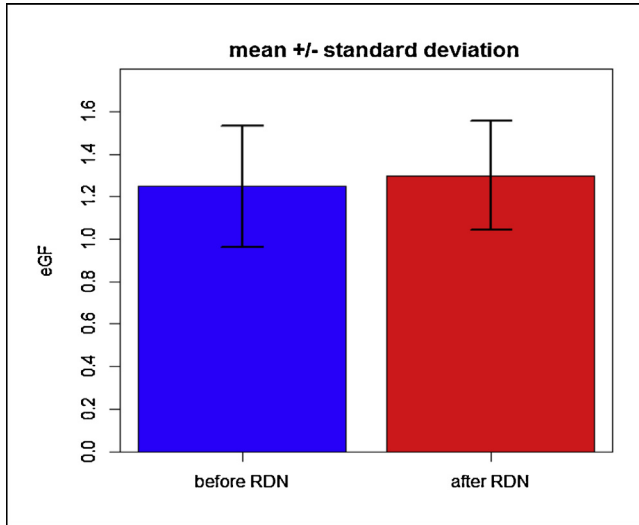


Fig. 1 – Graphic display of mean eGF before RDN and 1 year after RDN.

No patient experienced a twofold increase in serum creatinine, development of chronic kidney disease class IV or required dialysis.

No serious peri-procedural vascular complications occurred with the exception of one patient, in whom protracted renal artery spasm at the site of radiofrequency energy application making about 70% reduction in vessel lumen diameter has been reported (Fig. 3).

In all patients renal artery imaging was completed to evaluate signs of renal artery irregularities at the 6-month follow-up visit. This was assessed by computed tomographic



Fig. 3 – Protracted renal artery spasm at the site of radiofrequency energy application making about 70% reduction in vessel lumen diameter.

angiography with the exception of one patient. No evidence of haemodynamically significant renal artery stenoses or other new structural abnormalities of treated renal arteries was noted. One patient with peri-procedural renal artery spasm as mentioned above had a 6-month postprocedure magnetic resonance angiography because of radiation protection (the patient had a carcinoma of the common bile duct and regular abdominal computed tomographic scans to detect the cancer's stage were being performed). Haemodynamically non-significant renal artery stenosis at the site of initial spasm (about of 40% reduction in vessel lumen diameter) was identified. Six months later we did renal angiogram for this patient. There was no progression of renal artery stenosis (about 38% reduction in vessel lumen diameter) (Figs. 4 and 5).

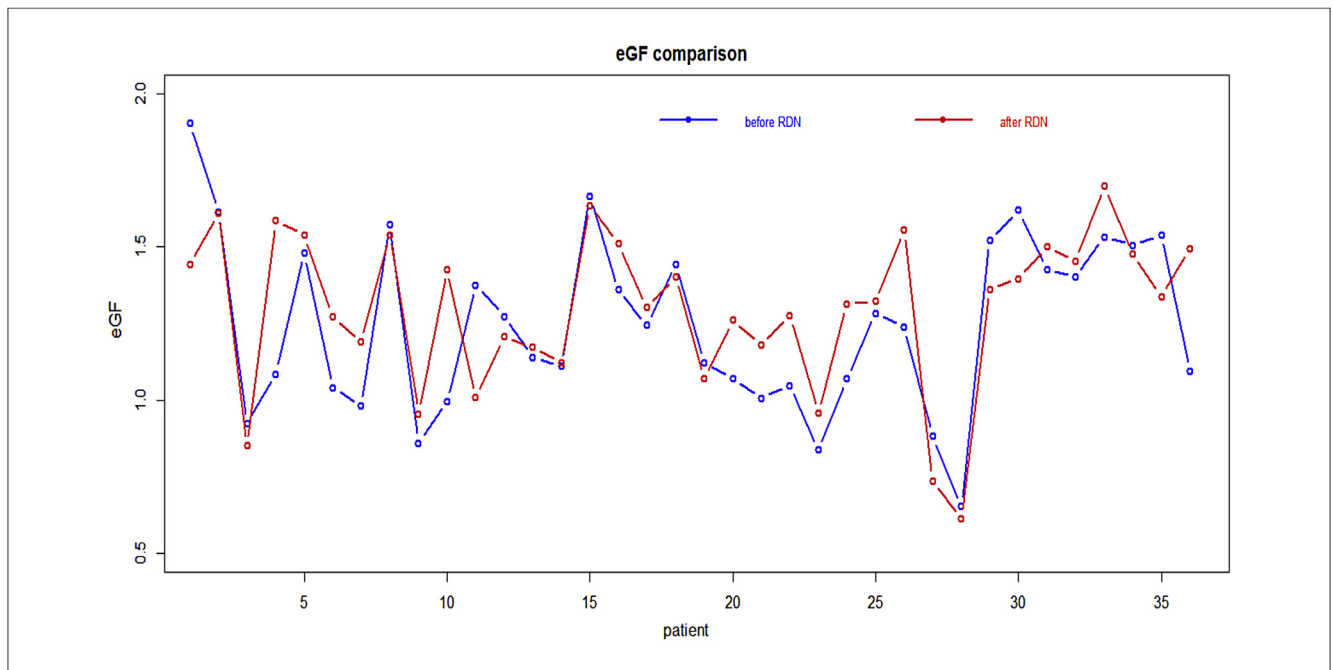
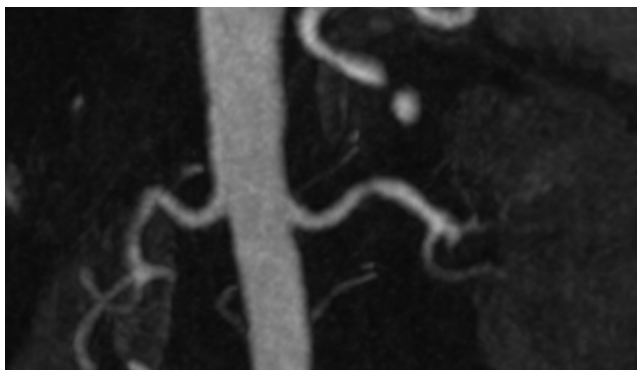
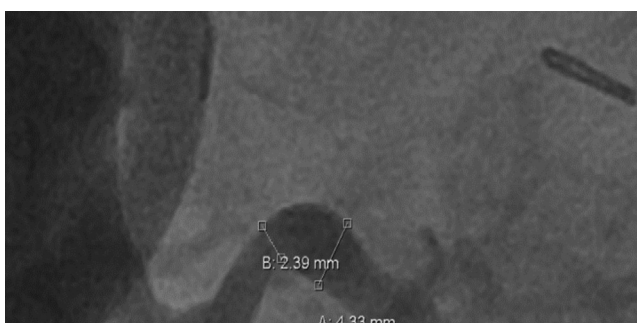


Fig. 2 – Graphic display of changes in eGF for each of the patients enrolled at baseline and 12 months.



**Fig. 4 – Magnetic resonance angiogram 6 months after RDN: about 40% reduction in vessel lumen diameter at the site of initial renal artery spasm.**



**Fig. 5 – Renal angiogram 12 months after RDN: without progression of stenosis (about 38% reduction in vessel lumen diameter).**

## Discussion

Over the next few decades, incidence of resistant hypertension will likely increase given that it is strongly associated with older age and obesity [23]. Resistant hypertension patients have an increased cardiovascular risk [24,25]. Thus, in an effort to minimize hypertension target organ damage, early complex therapeutic intervention is important.

This study presents data from almost all patients remaining enrolled and followed through 12 months (no deaths, exits for any reason or lost to follow-up). Only one visit was missed due to the hospitalization for ischaemic stroke recurrence. The stroke occurred 11 months after renal denervation. Therefore we are assuming it had no relationship to the ablation procedure. We contacted the ward, where the patient was hospitalized regarding blood pressure values and antihypertensive treatment.

The safety of RDN seen in our study is comparable with results published in several other renal-denervation studies [2,17,19,21,26]. The safety of RDN has been proven in studies using the single electrode radiofrequency catheter system [17,19,22,26], as well as in study using the multi-electrode radiofrequency system [2].

With regard to published data on worsening renal function 2 years after denervation procedure, consistent follow-up of

renal function, especially for a longer-term period is required. It is interesting to speculate as to why renal functions worsened in two patients in our study. Procedure time and contrast volume were not significantly different from the other patients. A reduction in glomerular filtration rate in one patient may have been due to increased dose of spironolactone. Deterioration of renal function in the second patient is unclear.

Concerning vascular complications, the available evidence from clinical studies reveals that catheter-based renal denervation has an excellent short-term safety profile. In spite of small probability, a risk of renal artery stenosis during long-term follow-up cannot be excluded.

Our analysis has some limitations. First limitation is relative small sample size and we only focused on safety. Another limitation which needs to be considered in the interpretation of these results is the fact that follow-up of renal function and renal arteries anatomy for a longer period of time is necessary.

## Conclusions

Denervation of renal sympathetic nerves using a single electrode ablation catheter Symplicity was performed without compromising patient safety. Twelve months after the intervention there was no statistically significant decrease in eGFR. Only 2 patients reported decrease in eGFR of >20%. No patient experienced a twofold increase in serum creatinine, development of chronic kidney disease class IV or required dialysis.

No serious vascular events associated with renal denervation procedure occurred. In one patient, protracted renal artery spasm at the site of radiofrequency energy application resulting in about 70% reduction in vessel lumen diameter has been reported. Six months after the procedure, haemodynamically non-significant renal artery stenosis at the site of initial spasm (about of 40% reduction in vessel lumen diameter) was revealed. Six months later we did renal angiogram without detecting progression of stenosis.

Renal denervation is a method which is still in the advanced phase of clinical research. Further analyses and subgroup analyses are mandatory to investigate definitive appraisal of this therapeutic strategy in the management of resistant hypertension. Especially randomized trials investigating the efficacy and safety of catheter-based renal denervation during longer observation periods are necessary to detect changes in renal function and development of late renal artery stenoses.

The challenge is a selection of eligible patients and their subsequent follow-up, as well as how to assess the treatment effect of the renal denervation procedure (blood pressure decrease is not immediate, but occurs during the next days after procedure).

## Conflict of interest

All authors declare that they have no conflict of interest.

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## Ethical statement

All authors declare that the study was conducted by the ethical principles.

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## Informed consent

Written informed consent was obtained from all the patients.

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