EFFECT OF RENAL DENERVATION ON KIDNEY FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Running title: Renal denervation in CKD

Dagmara Hering[1], Petra Marusic[1], Jacqueline Duval[2,], Yusuke Sata[2], Geoffrey A Head[3], Kate M Denton[4], Sally Burrows[1], Antony S Walton[5], Murray D Esler[2,5], Markus P Schlaich[1,2,5]

[1]School of Medicine and Pharmacology - Royal Perth Hospital Unit, University of Western Australia, Australia; [2]Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; [3]Neuropharmacology Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; [4]Cardiovascular Program, Monash Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, Australia; [5]Heart Centre Alfred Hospital, Melbourne, Australia

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Address for correspondence:

Professor Markus Schlaich

School of Medicine and Pharmacology - Royal Perth Hospital Unit, Faculty of Medicine, Dentistry & Health Sciences, University of Western Australia

Level 3, MRF Building, Rear 50 Murray St, Perth WA 6000

Ph: +61 8 9224 0382, Fax: +61 8 9224 0374

E-mail: markus.schlaich@uwa.edu.au

ABSTRACT

Aims: Renal denervation (RDN) can reduce blood pressure (BP) and slow the decline of renal function in chronic kidney disease (CKD) up to one year. Whether this effect is maintained beyond 12 months and whether the magnitude of BP reduction affects estimated glomerular filtration rate (eGFR) is unknown.

Methods and Results: We examined eGFR in 46 CKD patients (baseline eGFR ≤60ml/min/1.73m^2) on a yearly basis from 60 months before to 3, 6, 12 and 24 months after RDN. Ambulatory BP was measured before and after RDN. Linear mixed models analysis demonstrated a significant progressive decline in eGFR from months 60 to 12 months (-15.47±1.98 ml/min/1.73m^2, P<0.0001) and from 12 months to baseline prior to RDN (-3.41±1.64 ml/min/1.73m^2, P=0.038). Compared to baseline, RDN was associated with improved eGFR at 3 months (+3.73±1.64 ml/min/1.73m^2, P=0.02) and no significant changes at 6 (+2.54±1.66 ml/min/1.73m^2, P=0.13), 12 (+1.78±1.64 ml/min/1.73m^2, P=0.28), and 24 (-0.24±2.24 ml/min/1.73m^2, P=0.91) months post procedure were observed. RDN significantly reduced daytime SBP from baseline to 24 months post procedure (148±19 vs 136±17 mmHg, P=0.03) for the entire cohort. Changes in SBP were unrelated to the eGFR changes at 6 (r=0.033, P=0.84), 12 (r=0.01, P=0.93) and 24 months (r=-0.42, P=0.17) follow-up.

Conclusion: RDN can slow further deterioration of renal function irrespective of BP lowering effects in CKD. RDN-induced inhibition of sympathetic outflow to the renal vascular bed may account for improved eGFR via alterations of intrarenal and glomerular hemodynamics.

Key words: blood pressure, renal function, chronic kidney disease, renal denervation

INTRODUCTION

With growing prevalence of uncontrolled hypertension and diabetes contributing to the development and progression of chronic kidney disease (CKD), the worldwide prevalence of newly diagnosed CKD patients is expected to rise further. [1] Mechanisms underlying CKD are complex and multifactorial with sympathetic nervous system (SNS) activation playing a critical role in disease development, progression and adverse outcomes. [2, 3] Increased sympathetic activation is evident in the early phases of the disease and closely related to the deterioration of renal function [4], target organ damage [5] and has predicted cardiovascular (CV) and total mortality in patients with end-stage renal disease. [6] Moreover, increased noradrenaline release from the renal sympathetic nerves has been shown to predict poor CV outcome in heart failure patients independent of overall sympathetic activity, renal function (GFR) and organ damage (left ventricular ejection fraction). [7] Recognition of adverse effects of augmented sympathetic overdrive in the pathophysiology of CKD has led to the implementation of renal denervation (RDN) therapy targeting the neurogenic component of this condition. Evidence from several pilot studies has demonstrated the safety and effectiveness of RDN in patients with resistant hypertension (RH) and associated CKD [8-10], polycystic kidney disease [11] and in patients with end stage renal disease on haemodialysis. [12, 13] Importantly, RDN was not associated with deterioration of renal function. [8] More recently RDN has been shown to slow or even halt the decline in renal function one year post procedure in 27 patients with mean ambulatory blood pressure >130/80 mmHg with stage 3 and 4 CKD. [14] Based on our previous clinical experience with therapeutic RDN in this high risk patient cohort [8, 13], RDN was offered to hypertensive CKD patients with office BP >140/90mmHg on at least three antihypertensive drugs including a diuretic if tolerated. In this CKD patient cohort, we collected renal function data over the previous 60 months prior to RDN and up to 24 months following the RDN procedure

aiming to assess the association between RDN induced BP changes and changes in eGFR post procedure.

METHODS

Subjects

The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients. In this prospective observational study a total of 46 patients (28 males, 18 females) with eGFR ≤60 ml/min/1.73m^2 were included. Office and 24-hour ambulatory blood pressure monitoring (ABPM) and heart rate were assessed at baseline, 3, 6, 12 and 24 months after RDN. To assess renal function before RDN, we collected pathology results from previous 60 months before the procedure when possible. One patient from the study cohort was a current smoker. All patients underwent a comprehensive medical history, physical examination and review of medication. Patients were interviewed whether they had taken their complete medication at defined doses at each visit. Treating physicians and patients were instructed not to change medications except when medically required. Hypertension was diagnosed as per European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines [15] and the current statement of the American Heart Association. [16] Twelve patients previously diagnosed with OSA but remained hypertensive despite adequate treatment efforts including continuous positive airway pressure (CPAP) treatment in 5 patients were included in this study. One patient with a previous stroke ≥6 months and three patients with a history of transient ischaemic attack were also included.

Study protocol

Blood results, office and 24-hour ambulatory blood pressure (BP) and heart rate (HR) monitoring were obtained at baseline (before RDN) and at 3, 6, 12 and 24 months post procedure. eGFR from the previous 60 months (n=25), 48 months (n=34), 36 months (n=43), 24 months (n=45) and 12 months (n=46) were retrospectively collected from 46 CKD patients who were scheduled for RDN. On the first visit, BP was measured as described below

followed by fasting blood sampling for biochemistry assessment. 24-hour ABPM measurements were performed before and after RDN.

Serum biochemistry

Routine blood tests and eGFR were performed in all patients at each time visit as described previously. [3]

Office-seated and ambulatory blood pressure

Automated unobserved office seated BP was measured after 5 minutes of rest on both arms and was calculated as the average of three consecutive measurements within a 1-minute interval at baseline and during each visit at follow-up using a validated device (Omron HEM-907, Omron Healthcare Singapore PTE Ltd). The arm with higher BP readings was used for subsequent measures at follow-up.

24-hour ABPM was performed using a validated device (Spacelabs 90207 or 90217 recorder; Spacelabs Healthcare, Washington, USA) as described previously. [3]

Catheter-based renal denervation (RDN)

Bilateral RDN was performed using a radiofrequency ablation catheter (Symplicity^{TM}; Medtronic Ardian Inc., Palo Alto, California, USA) as described previously. [17]

Peri-and post-procedural medications

Baseline medication was kept unchanged for at least 6 weeks prior to RDN and was maintained in 23 (50%) patients at all follow-up visits. Antihypertensive medication was either reduced or stopped in 9 patients at follow-up due to achieved BP control. Five out of 46 patients required an increase in dose of antihypertensive drugs whereas the remaining 9 patients had both (a reduction and an increase) in BP lowering drugs from baseline to follow-up. Female subjects were post-menopausal and were not receiving hormone replacement therapy.

Statistical analysis

Data are presented as mean ± SD. Statistical analysis was performed using SIGMA PLOT 13.0 (Build 13.0.0.83, No 775201235, 2014 Systat Software, Inc.). Linear mixed models analysis was performed using STATA/IC 13.1 (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA) for BP and eGFR changes over time. This analysis utilises maximum likelihood estimation, which is known to produce unbiased estimates when missing data is MAR (missing at random), retaining all participants in the analysis even if data are incomplete. For ambulatory DBP and HR, the model was bootstrapped to obtain p values that are robust to departures from normality. To determine if relationships over time varied according to daytime SBP from baseline, the interaction of time and baseline daytime SBP was investigated. A p-value of <0.05 was considered significant.

RESULTS

Table 1 summarizes baseline clinical characteristics of the 46 treated patients. The cohort had a mean age of 66±9 years. Body mass index was 32±6 kg/m^2, waist circumference was 107±15 cm, and waist-to-hip ratio was 0.94±0.09. On average, patients were taking 4.9±1.9 antihypertensive drugs, including angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker or dual blockade, β-blockers, calcium-channel blockers, diuretics, α-blockers, vasodilators and centrally acting sympatholytic agents. All patients had a history of hypertension and 22 (48%) patients had type 2 diabetes.

At baseline (Table 1), mean creatinine-based eGFR was 46.2±13.0 ml/min./1.73m^2 (interquartile range: 60 to 11ml/min./1.73m^2), and mean plasma creatinine 138.8±74.5 μmol/L (interquartile range: 82 to 496 μmol/L).

Figure 1 demonstrates linear mixed model (LMM) analysis of eGFR based on estimates of means and standard error from 60 months prior to RDN out to 24 months post procedure in the entire study cohort of 46 patients. A significant decline in eGFR (model based estimates of means and standard error) was observed from months 60 to 12 months (-15.47±1.98 ml/min/1.73m^2, P<0.0001) and from 12 months to baseline prior to RDN (-3.41±1.64 ml/min/1.73m^2, P=0.038). Compared to baseline, eGFR increased significantly at 3 months (+3.73±1.64 ml/min/1.73m^2, P=0.02), and remained unchanged at 6 months (+2.54±1.66 ml/min/1.73m^2, P=0.13), 12 months (+1.78±1.64 ml/min/1.73m^2, P=0.28) and 24 months (-0.24±2.24 ml/min/1.73m^2, P=0.91) post procedure.

At baseline, the average office-seated systolic blood pressure (SBP) was 152±27 mmHg and diastolic blood pressure (DBP) was 77±19 mmHg, with a heart rate (HR) of 75±21 beats per min (bpm).

Baseline daytime BP averaged 148±19 mmHg for SBP, 80±13 mmHg for DBP with corresponding night-time BP of 139±19 mmHg for SBP and 70±12 mmHg for DBP (Table 2). For the entire cohort, daytime SBP and DBP significantly decreased at 24 months follow-up (Table 2). There were no significant changes in night-time BP at follow-up (Table 2). Mean 24-hour DBP was reduced and there was a trend towards a significant reduction in mean 24-h SBP at follow-up (P=0.056) (Table 2).

There was no association between changes in daytime SBP and changes in eGFR at 6 months (r=0.033, P=0.84), 12 months (r=0.01, P=0.93) and 24 months follow-up.

Given that baseline daytime SBP has previously been shown to be an important determinant of the BP response to RDN, further analysis based on longitudinal mixed model (LMM) estimates of the entire study cohort was performed to investigate a possible interaction between baseline daytime SBP and time for both night-time and daytime SBP and DBP using the 25^{th}, 50^{th} and 75^{th} percentiles, respectively (Figure 2). As illustrated in Figure 2, the pattern of temporal changes in BP was similar for each percentile, indicating that in this cohort of CKD patients baseline daytime SBP does not appear to be a major determinant of the BP response to RDN. Similarly, changes in LMM estimates of eGFR over time were not influenced by baseline daytime SBP percentiles (Figure 3), thereby supporting the notion that RDN *per se,* rather than RDN-induced BP changes, may contribute to improvement and stabilisation of eGFR in this cohort.

There were no significant changes in plasma potassium from baseline (4.3± 0.5 mmol/L) to 3 (4.2±0.5 mmol/L), 6 (4.2±0.7 mmol/L), 12 (4.3±0.6 mmol/L) and 24 months (4.2±0.6 mmol/L) post procedure (P=0.81), and sodium electrolytes from baseline (140±3.3 mmol/L) to 3 (140±2.6 mmol/L), 6 (140±3.3 mmol/L), 12 (139±2.8 mmol/L) and 24 months (140±3.4 mmol/L) follow-up (P=0.86); haemoglobin from baseline (130.7±24.4 g/L) to 3 (132.7±13.9

g/L), 6 (131.0±16.1 g/L), 12 (132.4±18.5 g/L) and 24 (130.3±15.2 g/L) months follow-up (P=0.66) and glucose from baseline (7.4±3.4 mmol/L) to 3 (7.1±4.7 mmol/L), 6 (6.2±1.6 mmol/L), 12 (6.2±1.6 mmol/L and 24 months (6.5±1.8 mmol/L) follow-up (P=0.14). Creatinine levels did not significantly change from baseline (139.5±74.05 μmol/L) to 3 (133.7±74.7 μmol/L), 6 (138.5±83.2 μmol/L), 12 (140.6±74.6 μmol/L) and 24 (157.3±77.3 μmol/L) months after the procedure (P=0.06). The increase in the mean creatinine level for the group was primarily driven by a single patient in whom creatinine rose from 114 at baseline to 210 μmol/L at 24 months, explained predominantly by deterioration of comorbidities already diagnosed prior to renal denervation including worsening heart failure in the context of atrial fibrillation, aortic stenosis, and obstructive sleep apnoea.

Procedural aspects

Renal angiograms were performed prior to the introduction of the RF treatment catheter via femoral access and anatomic eligibility and absence of significant vascular pathology was confirmed in all patients. An average of 12.9±3.3 total ablations treatments using a predetermined treatment protocol and algorithm were delivered in each patient without any peri-or post-procedural complications. Angiographic evaluation after renal denervation revealed no compromise of treated arteries.

DISCUSSION

The present findings are in line with our previous clinical experience indicating the safety, efficacy and feasibility of catheter-based renal nerve ablation in high risk patients with CKD. Our study revealed three major novel findings to indicate that bilateral sympathetic RDN (i) halts the progression of renal impairment in CKD patients with eGFR ≤60 ml/min/1.73m^2 irrespective of baseline BP levels; (ii) is not associated with acute, short-term and long-term deterioration of renal function, and (iii) induced BP changes are not associated with changes in renal function over time. These findings suggest that high risk patients with CKD and associated co-morbidities including uncontrolled hypertension, diabetes, obesity, and obstructive sleep apnoea may gain specific clinical benefit from RDN [18] through slowing of progression of renal impairment and thereby potentially delaying the requirement of renal replacement therapy.

The contribution of augmented sympathetic activation to the development and progression of CKD is well recognized. [2, 3] Control of hypertension and diabetes are mandatory in slowing the progression of kidney disease. However, currently available therapeutic efforts are insufficient to halt further renal progression and alternative treatment options are warranted. Inhibition of sympathetic nerve activity may be such a potential therapeutic approach in this cohort. Given that activation of efferent sympathetic and afferent sensory nerves arising from the failing kidneys have been described as crucial components in the scenario of CKD [19, 20], the rationale for therapeutic renal sympathetic nerve ablation aimed at targeting efferent and afferent renal nerves is apparent. Consistent with previous studies in patients with resistant hypertension, related co-morbidities and CKD, our present findings indicate that RDN halts the progression of renal function in patients with eGFR<60 ml/min/1.73m^2. RDN produced a significant reduction in ambulatory BP levels over time (Table 2) and nephron-protective effects which appear to be independent of BP lowering effects (Figure 3). Previous

studies have found that higher baseline clinic systolic and diastolic BP but not ambulatory BP predicts a greater BP reduction after RDN in patients with uncontrolled hypertension. [21] The effect on ambulatory BP lowering appears to be less pronounced in patients with isolated systolic hypertension [22] or absent in RH patients with moderately elevated and/or controlled BP. [21] In the present study we observed a greater BP reduction in patients with higher baseline daytime SBP levels (Figure 2). Moreover, while limited to a relatively small number of patients who reached 24 months follow-up (n=12), RDN appears to have a considerable impact on BP reduction 2 years post procedure in all treated patients including patients with either controlled or uncontrolled BP (Figure 2). This may indicate that in CKD patients, RDN-mediated inhibition of sympathetic outflow may primarily modulate the renal vascular bed with a systemic effect on BP occurring at a later stage (between 12-24 months post procedure). This observation may to some extant explain previous finding demonstrating inverse relationship between eGFR and BP response at short-term (6 months) follow-up. [23] Our study suggests that CKD patients benefit from RDN with a reduction in BP evident at longer-term follow-up.

Autoregulation of the kidney does not appear to be adversely affected after RDN as demonstrated by an improved (3 months) and preserved renal function (out to 24 months) despite significant BP reduction 24 months post procedure (Figure 3). Consistent with our previous findings, no incidence of electrolytes disturbances were reported in this cohort study after the procedure corroborating the concept that the denervated human kidney can maintain electrolyte and water homeostasis. [24]

While we included a relatively small number of patients in this study with a wide range of BP levels confirmed by 24-hour BP measurements, these findings are indicative of the short- and long-term safety and nephron-protective effects of renal nerve ablation in CKD and points to sympathetic activation as an important therapeutic target, particularly in view of the absence

of an association between BP and eGFR changes in our cohort. Although ABPM was not available in a few patients at follow-up, a robust linear mixed model analysis was used to account for missing values. While this is an observational prospective study with the lack of a control group as a limitation, these findings provide hypothesis generating data that will have to be substantiated in further large scale multicentre randomized clinical trials in CKD patients with various levels of BP in whom RDN appears to halt the disease progression. In view of current available device-based and invasive treatment options, RDN remains a valuable tool to slow the rate of progression of chronic kidney disease and its complications. Whether his may translate to improved patient outcomes warrants further investigation.

PERSPECTIVES

Sympathetic activation is a common feature of CKD associated with disease progression and poor CV outcomes. RDN is a therapeutic approach aimed specifically at targeting this important mechanisms thereby potentially improving patient outcomes. This study demonstrates that RDN can halt the progression of CKD and improve BP control in CKD patients irrespective of baseline daytime BP levels. In the absence of a correlation between BP and eGFR changes, RDN induced sympathetic inhibition appears to be an important contributor to these beneficial effects and identifies the renal nerves as an attractive therapeutic target in this patient cohort.

STATEMENT OF COMPETING FINANCIAL INTERESTS

This study was funded in part by grants from the National Health and Research Council of Australia (NHMRC) and the Victorian Government's Operational Infrastructure Support Program.

DISCLOSURE

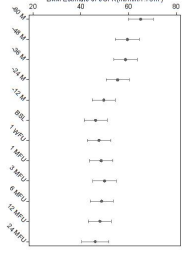
Drs Head, Denton, Esler and Schlaich are supported by career fellowships from the NHMRC. Drs Esler, Walton and Schlaich are investigators in studies sponsored by Medtronic. Dr Esler serves on scientific advisory boards of Abbott (formerly Solvay) Pharmaceuticals and Medtronic. Dr Schlaich has received honoraria and travel support from Abbott, BI, Servier, Novartis and Medtronic. The laboratories of Dr Schlaich receive research funding from BI and Cibiem.

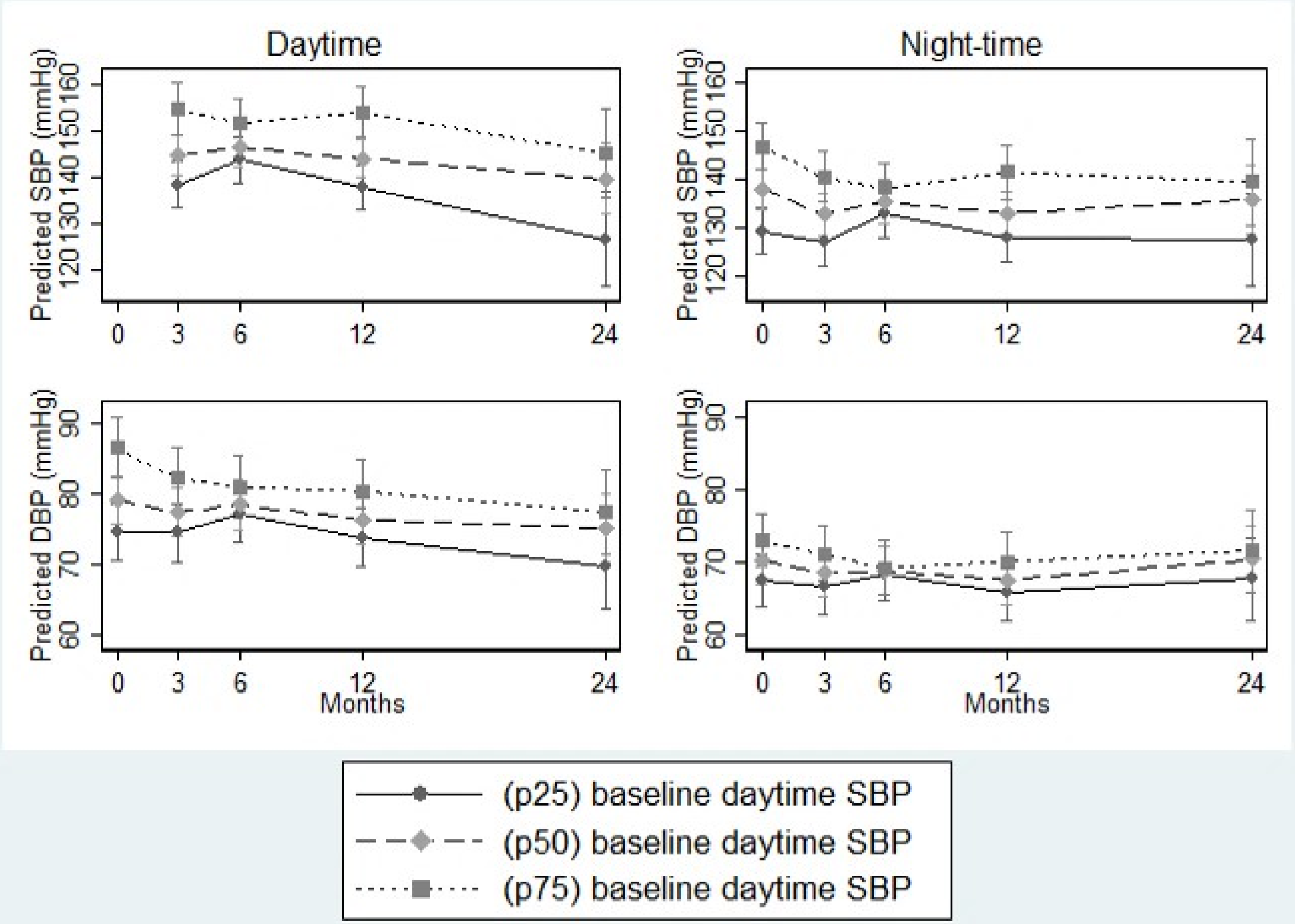
Figure Legends

Figure 1. Changes in creatinine-based estimated glomerular filtration rate (eGFR) in 46 patients before renal denervation from months 60 to baseline (pre-RDN), at 1week and 1, 3, 6, 12 and 24 month (M) follow-up (FU) using linear mixed model analysis. The number of patients at each time point: 60 M (n=25), 48 M (n=34), 36 M (n=43), 24 M (n=45) and 12 M (n=46).

Figure 2. The interaction between baseline daytime SBP as per 25^{th}, 50^{th} and 75^{th} percentile and time for night-time and daytime DBP and SBP at 3, 6, 12 and 24 months follow-up using linear mixed model (LMM) analysis.

Figure 3. The interaction between daytime SBP as per 25^{th}, 50^{th} and 75^{th} percentile and time for changes in eGFR at 3, 6, 12 and 24 months follow-up using linear mixed model (LMM) analysis.


LMM Estimate of eGFR(ml/min/1.73m²)
20
40
60
80
-60 M
-48 M
-36 M
-24 M
-12 M
BSL
1 MFU
1 MFU
3 MFU
6 MFU
12 MFU
24 MFU


Daytime
Night-time
Predicted SBP (mmHg)
120 130 140 150 160
Predicted DBP (mmHg)
60 70 80 90
0 3 6 12 24
Months
(p25) baseline daytime SBP
(p50) baseline daytime SBP
(p75) baseline daytime SBP

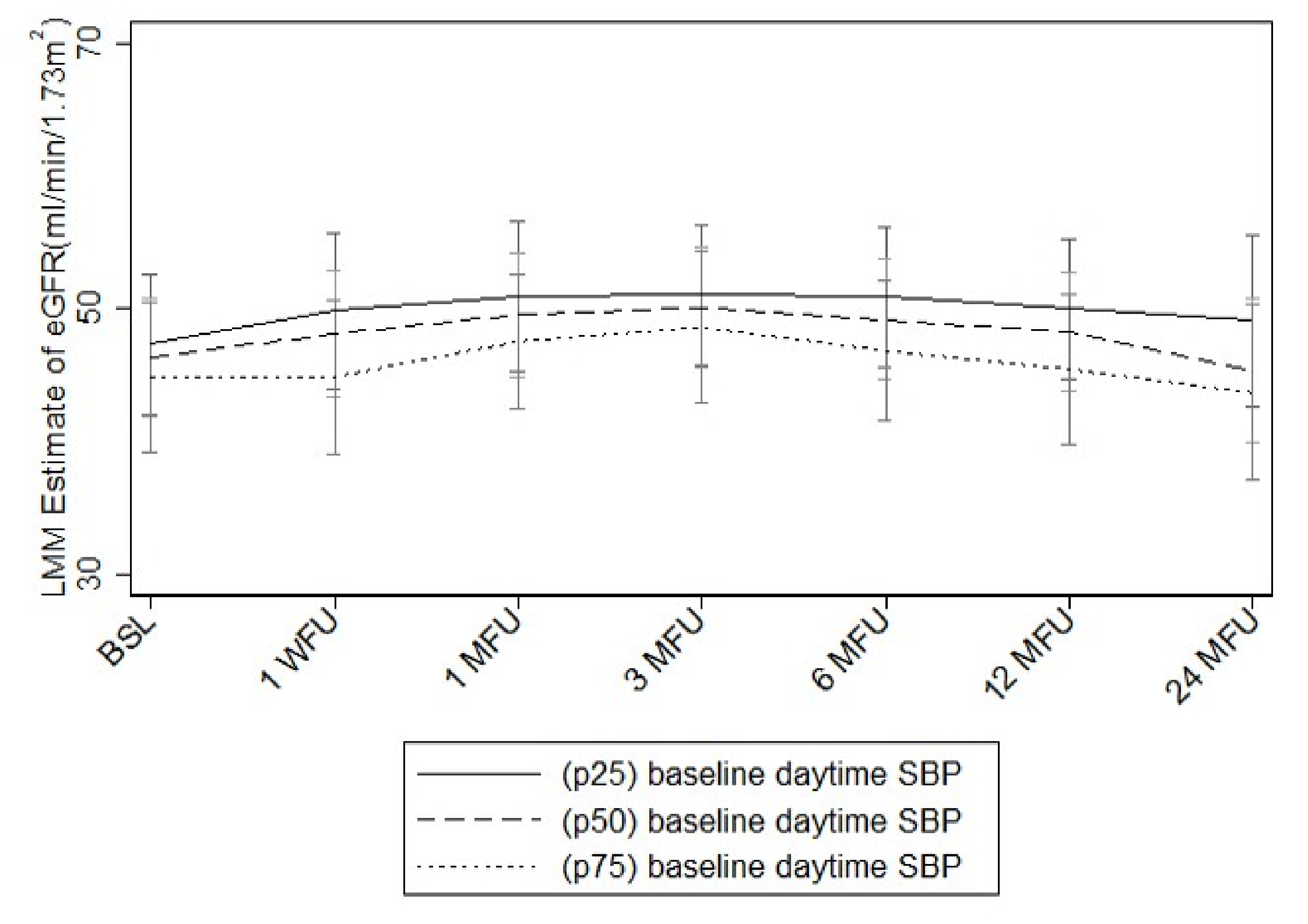

LMM Estimate of eGFR(ml/min/1.73m^2)
70
50
30
BSL
1 WFU
1 MFU
3 MFU
6 MFU
12 MFU
24 MFU
(p25) baseline daytime SBP
(p50) baseline daytime SBP
(p75) baseline daytime SBP

Table 1. Baseline clinical characteristics and biochemical parameters of the study cohort.

Parameter	**Number (n=46)**
Age (years)	66±9
Gender (males)	28 (61%)
T2DM	22 (48%)
OSA	12 (26%)
CAD	13 (28%)
Number of antihypertensive drugs	4.9±1.9
ACEI	21 (46%)
ARB	33 (72%)
β-blocker	26 (57%)
Calcium-channel blocker	34 (74%)
α-blockers + vasodilators	29 (63%)
Diuretic	41 (89%)
Aldosterone antagonists	17 (37%)
Centrally acting sympatholytics	28 (61%)
Office SBP (mmHg)	152±27
Office DBP (mmHg)	77±19
HR (bpm)	75±21
eGFR (mL/min/1.73m^2)	46.2±13.0
Plasma creatinine (μmol/L)	138.8±74.5

Data are mean±SD and /or percentage (%). T2DM indicates type 2 diabetes mellitus; OSA: obstructive sleep apnea; CAD, coronary artery disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; bpm: beat per minute; eGFR: estimated glomerular filtration rate.

Table 2. Ambulatory blood pressure and heart rate before and after renal denervation in all treated patients.

Parameter	**Baseline (n=46)**	**3 M FU (n=39)**	**6 M FU (n=39)**	**12 M FU (n=41)**	**24 M FU (n=12)**	***P-value***
Mean SBP (mmHg)	145±18	141±16	142±14	141±19	134±18*	*0.056*
Maximum mean SBP (mmHg)	185±21	186±24	184±20	183±24	177±21	*0.40*
Daytime SBP (mmHg)	148±19	145±17	147±15	145±20	136±17**	*0.03*
Maximum daytime SBP	184±20	186±24	184±21	183±24	176±21	*0.49*
Night-time SBP (mmHg)	139±19	133±17	135±16	134±20	132±24	*0.29*
Maximum night-time SBP	165±23	161±20	161±20	159±24	157±28	*0.36*
Mean DBP (mmHg)	76±11	74±11	74±11	73±12†	71±8†	*0.001*
Maximum mean DBP (mmHg)	104±13	103±13	101±14	100±16	104±17	*0.31*
Daytime DBP (mmHg)	80±13	78±12	78±14	76±14‡	72±7***	*0.0002*
Maximum daytime DBP	103±12	104±13	100±14	99±15	104±17	*0.45*
Night-time DBP (mmHg)	70±12	69±11	68±12	68±11	68±13	*0.31*
Maximum night-time DBP	85±13	88±17	83±14	83±13	84±13	*0.11*
Mean HR (bpm)	66±11	65±10	65±11	64±10	66±8	*0.59*
Daytime HR (bpm)	68±12	68±11	66±11	66±11	67±8	*0.42*
Night-time HR (bpm)	62±12	61±10	61±11	61±10	62±10	*0.80*

Values expressed as mean ± SD. The linear mixed model analysis for a comparison to baseline was used for statistical analysis. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beat per minute.

*P=0.003 vs baseline; **P=0.001 vs baseline; ***P<0.001 vs baseline; †P=0.005 vs baseline; ‡P=0.01 vs baseline

References

[1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131:e29-322.

[2] Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, et al. Sympathetic activation in chronic renal failure. J Am Soc Nephrol. 2009;20:933-9.

[3] Hering D, Esler MD, Schlaich MP. Chronic kidney disease: role of sympathetic nervous system activation and potential benefits of renal denervation. Eurointervention. 2013;9:R127-R35.

[4] Grassi G, Quarti-Trevano F, Seravalle G, Arenare F, Volpe M, Furiani S, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. Hypertension. 2011;57:846-51.

[5] Zoccali C, Mallamaci F, Tripepi G, Parlongo S, Cutrupi S, Benedetto FA, et al. Norepinephrine and concentric hypertrophy in patients with end-stage renal disease. Hypertension. 2002;40:41-6.

[6] Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation. 2002;105:1354-9.

[7] 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;26:906-13.

[8] Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, et al. Renal Denervation in Moderate to Severe CKD. J Am Soc Nephrol. 2012.

[9] Kiuchi MG, Maia GL, de Queiroz Carreira MA, Kiuchi T, Chen S, Andrea BR, et al. Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood

pressure and renal function in patients with chronic kidney disease and resistant hypertension. Eur Heart J. 2013;34:2114-21.

[10] Kiuchi MG, Chen S, Graciano ML, de Queiroz Carreira MA, Kiuchi T, Andrea BR, et al. Acute effect of renal sympathetic denervation on blood pressure in refractory hypertensive patients with chronic kidney disease. Int J Cardiol. 2015;190:29-31.

[11] Shetty SV, Roberts TJ, Schlaich MP. Percutaneous transluminal renal denervation: a potential treatment option for polycystic kidney disease-related pain? Int J Cardiol. 2013;162:e58-9.

[12] Di Daniele N, De Francesco M, Violo L, Spinelli A, Simonetti G. Renal sympathetic nerve ablation for the treatment of difficult-to-control or refractory hypertension in a haemodialysis patient. Nephrol Dial Transpl. 2012;27:1689-90.

[13] Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. Int J Cardiol. 2013;168:2214-20.

[14] Ott C, Mahfoud F, Schmid A, Toennes SW, Ewen S, Ditting T, et al. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. J Hypertens. 2015;33:1261-6.

[15] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25:1105-87.

[16] Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51:1403-19.

[17] Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension. 2013;61:457-64.

[18] Schlaich MP, Hering D, Sobotka P, Krum H, Lambert GW, Lambert E, et al. Effects of renal denervation on sympathetic activation, blood pressure, and glucose metabolism in patients with resistant hypertension. Front Physiol. 2012;3:10.

[19] DiBona GF, Kopp UC. Neural control of renal function. Physiological reviews. 1997;77:75-197.

[20] DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol. 2010;298:R245-53.

[21] Mahfoud F, Ukena C, Schmieder RE, Cremers B, Rump LC, Vonend O, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. Circulation. 2013;128:132-40.

[22] Mahfoud F, Bakris G, Bhatt DL, Esler M, Kandzari D, Kario K, et al. Reduced Blood Pressure Lowering Effect of Catheter-Based Renal Denervation in Patients with Isolated Systolic Hypertension: Data from Pooled Symplicity Htn Trials. Journal of the American College of Cardiology. 2015;65:A1527-A.

[23] Vink EE, Verloop WL, Bost RBC, Voskuil M, Spiering W, Vonken EJ, et al. The blood pressure-lowering effect of renal denervation is inversely related to kidney function. Journal of Hypertension. 2014;32:2045-53.

[24] DiBona GF. The sympathetic nervous system and hypertension: recent developments. Hypertension. 2004;43:147-50.