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Renal Denervation in Moderate to Severe CKD

Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

ABSTRACT

Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) $<$ 45 ml/min per 1.73 m^2 is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3–4 CKD (mean eGFR, 31 ml/min per 1.73 m^2). We used CO_2 angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO_2 angiography. Mean baseline BP $\pm$ SD was 174$\pm$22/91$\pm$16 mmHg despite the use of 5.6$\pm$1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were $-$34/$-$14, $-$25/$-$11, $-$32/$-$15, and $-$33/$-$19 mmHg, respectively. Night-time ambulatory BP significantly decreased ($P<0.05$), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3–4 CKD and resistant hypertension.

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CKD contributes substantially to the global burden of cardiovascular morbidity and mortality.[1] Even a moderate reduction in GFR is predictive of an increased risk for coronary heart disease.[2,3] Accordingly, hypertensive patients with reduced GFR are at greater risk for cardiovascular disease than for ESRD.[3] The mortality from sudden cardiac death increases dramatically with the stage of CKD,[4] mainly because of ventricular arrhythmias.[5] Furthermore, the number of newly detected cases of CKD is expected to increase further,[6] particularly as a result of the increasing incidence of diabetes[7] and hypertension.[8]

Altered sympathetic cardiovascular regulation is an important mechanism contributing to the association between CKD and increased cardiovascular morbidity and mortality, as reviewed in detail elsewhere.[9] Sympathetic overactivity is implicated in the development and progression of CKD[10–13] and independently predicts cardiovascular events and mortality in ESRD.[14] Afferent signaling derived from the native failing kidneys plays a causal role in renal efferent sympathoexcitation and potentiates the adverse effect of chronically increased sympathetic drive.[9] Consequently, interruption of efferent and afferent renal fibers may possibly mitigate or reverse autonomic imbalance and reduce renal sympathetic outflow and arterial BP in CKD.

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Correspondence: Prof. Markus Schlaich, Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, P.O. Box 6492, St Kilda Road Central, Melbourne, Victoria 8008, Australia. Email: markus.schlaich@bakeridi.edu.au

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Selective catheter-based renal sympathetic nerve ablation is safe and effective in attaining improved and sustained BP control in patients with resistant hypertension and normal renal function.[15–17] Furthermore, additional benefits appear to be evident in patients with concomitant metabolic disorders or obstructive sleep apnea; glucose metabolism is improved and severity of sleep apnea is reduced.[18–20] These effects are likely to be mediated *via* alterations in renal afferent signaling, resulting in reductions in both renal and whole-body sympathetic outflow.[15,17]

Although results from these studies are promising and the rationale to expand the use of this novel technology to hypertensive patients with moderate to severe CKD is obvious, concerns have been raised with regard to the renal safety of such an approach.[21] Indeed, all patients treated in the initial clinical trials had an estimated GFR (eGFR) >45 ml/min per 1.73 m^2.

We therefore initiated a pilot study to assess short-term renal safety and efficacy in patients with resistant hypertension and concomitant moderate to severe CKD.

RESULTS

Baseline Characteristics

Table 1 presents baseline clinical characteristics of the 15 treated patients. The cohort had a mean age ± SD of 61±9 years. Body mass index was 33±8 kg/m^2, waist circumference was 114±17cm, and waist-to-hip ratio was 0.98±0.01. On average, patients were taking 5.6±1.3 antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II–receptor blockers, or dual blockade (4 of 15 patients); β-blockers; calcium-channel blockers; diuretics; α-blockers; vasodilators; centrally acting sympatholytic agents; and direct renin inhibitors. Average hypertension duration was 18±12 years. In two patients, obstructive sleep apnea had previously been diagnosed; both received continuous positive airway pressure treatment, which was not altered during this study. Eleven of 15 patients had type 2 diabetes (mean duration, 18±4 years) associated with diabetic nephropathy, which contributed to CKD, and were receiving combination therapy with insulin and oral hypoglycemic agents.

At baseline, average office systolic BP (SBP) while seated was 174±22 mmHg and diastolic BP (DBP) was 91±16 mmHg, with a heart rate of 64±9 beats/min. Baseline corresponding 24-hour ambulatory BP monitoring showed an average BP of 160±14/83±13 mmHg for daytime and 154±16/78±11 mmHg for night-time. At baseline, mean creatinine-based eGFR was 31.2±8.9 ml/min per 1.73 m^2 (interquartile range, 43–15 ml/min per 1.73 m^2), and mean plasma creatinine level was 186.7±64.4 μmol/L (interquartile range, 118–372 μmol/L).

Table 1. Baseline clinical characteristics and biochemical measures of the entire cohort of treated patients

Variable	Data
Age (yr)	61±9
Women	6 (40)
Type 2 diabetes	11/15 (73)
Obstructive sleep apnea	2/15 (13)
Pulmonary hypertension	1/15 (7)
Incidentaloma	1/15 (7)
Antihypertensive drugs (*n*)	5.6±1.3
ACEI	7/15 (47)
ARB	11/15 (73)
ACEI and ARB	4/15 (27)
β-blocker	11/15 (73)
calcium-channel blocker	12/15 (80)
α-blockers	4/15 (27)
diuretic	15/15 (100)
direct renin inhibitor	4/15 (29)
vasodilator	10/14 (27)
central acting sympatholytic	7/15 (47)
Office SBP (mmHg)	174±22 (154–223)
Office DBP (mmHg)	91±16 (61–118)
Heart rate (beats/min)	64±9 (50–75)
Creatinine estimated GFR (mL/min per 1.73 m^2)	31.2±8.9 (15–43)
Plasma creatinine level (μmol/L)	186.7±64.4 (118–372)

Unless otherwise noted, data are number/number of patients (%). Values expressed with a plus/minus sign are mean ± SD; ranges in parentheses are interquartile ranges. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II–receptor blocker.

Procedural Aspects

Renal angiography was performed before the introduction of the radiofrequency treatment catheter *via* femoral access, and anatomic eligibility and absence of significant vascular abnormality was confirmed in all patients. An average of 9.9±1.5 ablation treatments using a predetermined treatment protocol and algorithm were delivered in each patient, with no peri- or postprocedural complications. Average volume of the contrast agent, Visipaque (iodixanol), used during the procedure when CO_2 angiography was performed was 46.7±5.7 ml. Mean volume of the nonionic contrast agent, Iomeron 350 (iomeprol), used in renal catheterization in other patients was 82.5±21.9 ml. Angiographic evaluation after renal denervation revealed no compromise of treated arteries.

Effects of Renal Denervation

No statistically significant differences in postprocedural serum and urine biochemistry were observed (P>0.05) (Table 2). There were no significant alterations in kidney function, as assessed by estimation of GFR according to serum creatinine or cystatin C levels and according to plasma creatinine, cystatin C, or urea levels (Table 2). No disturbances in serum and urine electrolytes were observed (Table 2). Changes in creatinine-based eGFR in individual patients at 1 week and at 1, 3, 6, and 12 months after the procedure are depicted in Figure 1. No significant postprocedural changes occurred in effective renal plasma flow in the left (42.7%±6.7% versus 46.7%±5%) or the right (57.3%±8.2% versus 53.3%±6.2%) kidneys, respectively, or in the calculated kidney retention index in the left

Table 2. Changes in biochemical measures

Variable	Baseline (*n*=15)	3-Month Follow-up (*n*=15)	6-Month Follow-up (*n*=8)	*P* Value
Plasma creatinine (μmol/L)	186.7±64.4	184.7±57.3	217.4±60	0.28
Urea (mmol/L)	23.9±10.9	23.4±10.8	21.9±12.6	0.73
Creatinine eGFR (mL/min per 1.73 m^2)	31.2±8.9	32.6±8.9	29.04±7.3	0.22
Cystatin C eGFR (mL/min per 1.73 m^2)	24.5±10 (*n*=7)	26.2±13.5 (*n*=7)	31.5±15.3 (*n*=4)	0.68
Cystatin C (mg/L)	2.14±0.45	2.11±0.54	1.99±0.67	0.74
Sodium (mmol/L)	140.4±4.4	140.2±2.9	141.0±3.2	0.97
Potassium (mmol/L)	4.4±0.5	4.6±0.7	4.2±0.6	0.12
Hemoglobin (g/L)	119.7±15.7	126.2±16	124.9±12.4	0.08
Hemoglobin A_{1c} (%)	8.31±2.4	8.12±2.03	7.64±1.62	0.82
BNP (ng/L)	564±391	469±428	372±386	0.17
UACR (mg/g)	592±955	533±956	355±276	0.21
Total cholesterol (mmol/L)	4.96±1.79	4.84±1.73	4.23±0.79	0.97
LDL cholesterol (mmol/L)	2.7±0.7	2.7±0.9	2.38±0.6	0.82
HDL cholesterol (mmol/L)	1.06±0.4	1.04±0.3	1.01±0.2	0.94
Triglycerides (mmol/L)	2.41±2.3	2.42±2.2	1.97±0.8	0.76
24-hr creatinine clearance in urine (mL/min per 1.73 m^2)	43.9±12.4	46.5±15.3	45.0±8.2	0.64
Proteinuria (g/24 hr)	1.41±0.52	0.82±0.36	0.81±0.76	0.24
Sodium excretion in urine (mmol/24 hr)	169.3±56.7	187.3±59.4	152.0±86.9	0.77
Potassium excretion urine (mmol/24 hr)	90.3±23.8	88.3±22.8	67.0±34.1	0.22

Data are mean ± SD. eGFR, estimated GFR; UACR, urinary albumin-to-creatinine ratio.

(47%±9.7% versus 47.7%±11.6%) or the right (47.7%±20.9% versus 51.7%±20.3%) kidneys, as assessed by ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG-3) scanning.

Plasma hemoglobin concentrations tended to increase in all individuals after the procedure, whereas average brain natriuretic peptide (BNP) levels, urinary albumin-to-creatinine ratio, proteinuria, and glycated hemoglobin tended to gradually decrease after the procedure (Table 2). However, none of these changes were statistically significant. There was no change in average body weight (102.3±30 kg at baseline) at 3-month (101.2±29 kg) and at 6-month (99.3±27 kg) follow-up.

Mean changes in average office SBP and DBP at 1, 3, 6, and 12 months after the procedure are depicted in Figure 2. Mean decrease in seated office BP was −34/−14, −25/−11, −32/−15, and −33/−19 mmHg for SBP and DBP at 1, 3, 6, and 12 months after the procedure, respectively (Figure 2B).

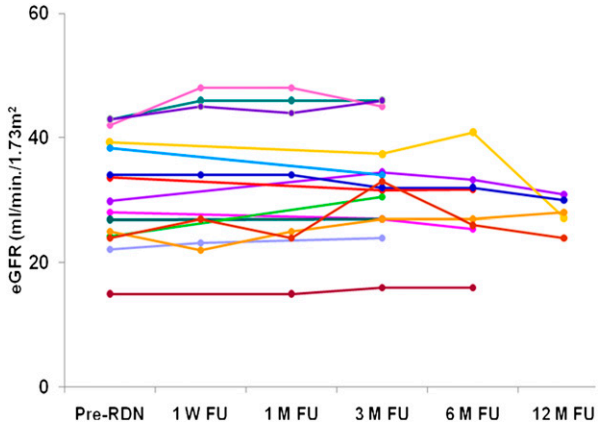

Figure 1. Individual changes in creatinine-based estimated GFR before renal denervation (pre-RDN); at 1 week (W); and at 1-, 3-, 6-, and 12-month (M) follow-up (FU).

Mean and maximum 24-hour night-time BP decreased significantly after the procedure (Table 3). Average night-time SBP had declined at 3-month follow-up (from 154±16 to 140±22 mmHg; *P*=0.03) and was 144±22 mmHg at 6-month follow-up (Table 3). Similarly, night-time DBP was markedly reduced at both 3 months (78±11 versus 70±8 mmHg; *P*=0.018) and 6 months (78±11 versus 75±14 mmHg; *P*=0.02) after the procedure (Table 3). Mean nocturnal decrease in SBP, assessed in a limited number of patients (*n*=10), was more pronounced at 3-month follow-up (141.5±25 versus 128.2±24 mmHg; *P*=0.02). Accordingly, the nondipping pattern observed at baseline was reverted to a physiologic dipping pattern in a significant number of patients after the procedure (*P*=0.01) (Table 3). The rate of SBP increase and BP power surge were considerably reduced after the procedure (Table 3). Marked postprocedure decreases in night-to-day BP ratios were observed (Table 3). Office and ambulatory heart rate values did not significantly change (Table 3).

Peripheral arterial stiffness assessed by augmentation index was significantly reduced 3 months after the procedure (51.3%±30.9% at baseline versus 38.7%±32.9% at follow-up; *P*=0.008) (Figure 3).

DISCUSSION

These findings summarize what we believe to be the first clinical experience with catheter-based renal nerve ablation in high-risk patients with moderate to severe renal impairment. The main results of this pilot study are as follows: (*1*) selective,

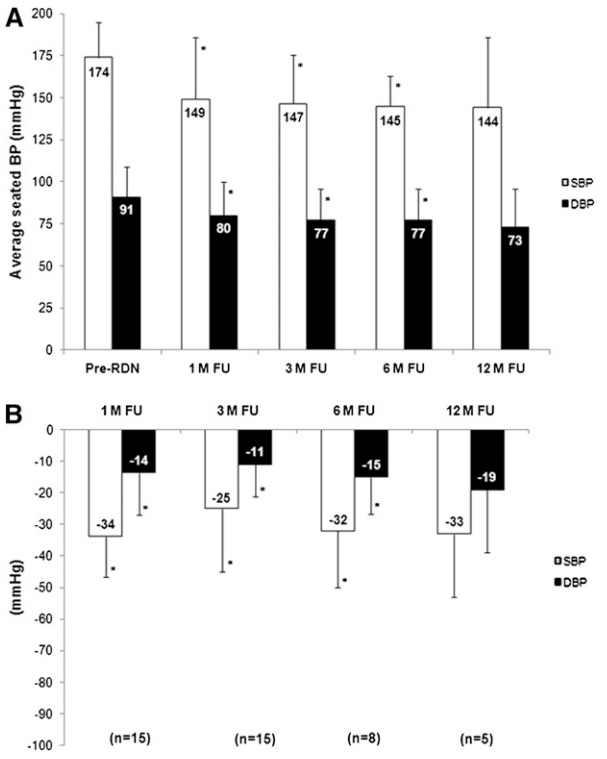

Figure 2. Office BP values at follow-up. Changes in average office BP (A) and mean decrease in office BP (B) at follow-up. Error bars represent SDs. *$P<0.001$ versus baseline (before the procedure). FU, follow-up; M, month; pre-RDN, prerenal denervation.

bilateral sympathetic renal denervation is safe and effective in patients with stage 3–4 CKD; (*2*) bilateral renal denervation is not associated with acute or short-term deterioration of renal function; and (*3*) bilateral renal nerve ablation may have beneficial effects beyond improved BP control, including a potential increase in hemoglobin concentration and reductions in proteinuria, BNP levels, and peripheral arterial stiffness index. These preliminary findings indicate that high-risk patients with chronic renal failure associated with several comorbid conditions, including resistant hypertension, diabetes, obesity, and obstructive sleep apnea, may obtain specific clinical benefit from bilateral renal denervation.

The contribution of heightened renal sympathetic activation to the development and progression of CKD is well established. Sympathetic activity is already elevated in early phases of chronic renal failure, and the magnitude of sympathetic overdrive increases with disease progression.[22] Evidence also suggests that the afferent sensory renal nerves in response to intra-renal injury have an excitatory influence on central sympathetic outflow.[10] Consequently, renal sympathetic efferent and afferent nerves exert a powerful influence on initiation, development, and maintenance of elevated systemic BP commonly present in patients with renal failure.[23]

Consistent with recent studies in patients with resistant hypertension and normal renal function,[16,24] renal denervation in our patients with stage 3–4 CKD was associated with a marked and sustained decline in seated office BP measurements.

In contrast to office BP readings, mean 24-hour BP and mean daytime BP were not significantly reduced after the procedure, possibly because of the limited number of patients with valid ambulatory BP monitoring data and substantial intraindividual variability. However, radiofrequency ablation treatment had a considerable effect on nocturnal BP control in our patient cohort. In addition, significant reductions in rate of BP increase, BP power surge, and night-to-day BP ratios were observed. Moreover, renal denervation diminished mean and maximum night-time BP and restored a physiologic dipping pattern in 9 of 10 patients. Of note, nocturnal BP is superior in predicting cardiovascular events compared with 24-hour mean or diurnal BP.[25] Accordingly, the night-to-day BP ratio has been found to predict all-cause mortality and cardiovascular events in hypertension, irrespective of confounding factors and 24-hour BP.[26] The potential clinical relevance of these observations needs to be delineated in future studies.

Another important observation from this pilot study is the absence of further deterioration of renal function in our patient cohort. Short-term (7 and 28 days) and mid-term (up to 12 months in two patients) follow-up of renal function assessed by plasma and urine testing, as well as ^{99m}Tc-MAG-3 scanning, demonstrated no evidence of aggravation of renal impairment. Autoregulation of the kidney did not appear to be adversely affected, as indicated by preserved renal function despite substantial BP reduction. Of note, antihypertensive medication was not changed after renal denervation until at least 6-month follow-up.

In a subset of patients, we applied CO_2 angiography in an attempt to further minimize the potential risk for contrast-induced nephropathy in CKD. Although the amount of iodine contrast required was reduced with CO_2 angiography (46.7 ± 5.7 ml versus 82.5 ± 21.9 ml), we did not encounter any intraprocedural or periprocedural problems with iodine or CO_2 angiography, respectively. Particularly, there was no evidence of embolic complications, reduction in GFR, or increases in serum creatinine, cystatin C, or urea levels. No abnormalities in effective renal blood flow or calculated kidney retention index were encountered after the procedure. In addition, although patients with renal failure are more vulnerable to the development of life-threatening electrolyte disturbances, hyperkalemia and hypokalemia were not reported in this cohort study after the procedure. Similarly, volume homeostasis, as assessed clinically by body weight, jugular venous distension, or pitting edema, was unchanged or improved after the procedure, supporting the concept that the denervated human kidney can maintain electrolyte and water homeostasis.[27] Whether CO_2 angiography is superior to iodine contrast imaging with regard to prevention of contrast-induced complications needs to be investigated in larger clinical studies.

Several other interesting observations may deserve further investigation in appropriately sized future clinical trials. We observed a tendency toward gradual increased serum hemoglobin levels in all treated patients. This could be of clinical relevance given that the prevalence of anemia increases with

Table 3. Office and ambulatory BP and heart rate before and after renal denervation

Measurement	Baseline (*n*=15)	3-Month Follow-up (*n*=15)	6-Month Follow-up (*n*=8)	*P* Values	
				Baseline versus 3-Month Follow-up	Between Treatments
SBP					
office (mmHg)	174±22	147±29	145±18	<0.001	<0.001
ABPM mean (mmHg)	159±14	153±16	154±21	0.24	0.49
ABPM daytime (mmHg)	160±14	156±19	160±14	0.53	0.84
ABPM night-time (mmHg)	154±16	140±22	144±22	0.03	0.10
maximum night-time (mmHg)	185±19	171±22	166±33	0.04	0.14
dipping status (%)	4±6	11±9	10±9	0.01	0.04
rate of rise (mmHg/hr)	12.07±7.7	2.09±1.6	4.8±6.1	0.05	0.03
BP power surge (log) (mmHg)	1.6±1.8	0.6±1.0	1.4±1.0	0.01	0.03
Night-to-day ratio	0.96±0.06	0.89±0.08	0.89±0.08	0.01	0.04
DBP					
office (mmHg)	91±16	77±19	77±19	0.002	0.001
ABPM mean (mmHg)	85±12	78±6	79±11	0.08	0.11
ABPM daytime (mmHg)	83±13	80±10	83±13	0.21	0.38
ABPM night-time (mmHg)	78±11	70±8	75±14	0.02	0.02
Maximum night-time (mmHg)	93±15	84±14	94±19	0.17	0.44
Dipping status (%)	6±7	12±10	10±7	0.01	0.02
Night-to-day ratio	0.94±0.07	0.88±0.09	0.90±0.07	0.01	0.02
Heart rate					
office (beats/min)	64±9	66±12	64±13	0.54	0.72
ABPM mean (beats/min)	64±11	67±10	64±12	0.12	0.28
ABPM daytime (beats/min)	65±9	64±9	65±13	0.55	0.8
ABPM night-time (beats/min)	65±9	63±8	63±12	0.33	0.57
Night-to-day ratio	0.98±0.06	0.96±0.06	0.98±0.06	0.36	0.38

Values are expressed as mean ± SD. Data are shown as a one-way repeated-measures ANOVA between treatments. 24-hr daytime, night-time, and maximum night-time BP; rate of SBP increase; BP power surge; and night-to-day ratios were obtained in limited number of patients at baseline (*n*=10), at 3 months (*n*=10), and at 6 months (*n*=6). ABPM, ambulatory BP monitoring.

deteriorating renal function[28] and is related to cardiac complications[29] and cerebrovascular events.[30] In this context, it is noteworthy that data from both experimental and human studies have suggested a role of renal sympathetic nerves in the modulation of erythropoiesis.[31,32] There was a trend toward reduction of urinary albumin excretion after renal denervation, which may represent additional beneficial effects of direct sympathetic modulation beyond BP reduction alone.[9,19,33] We also observed a trend toward reduction in plasma circulating BNP concentrations after renal denervation. Clinically, our patients were euvolemic and had no clinical history of heart failure or cardiac dysfunction. This may be relevant given that BNP is considered an independent predictor of cardiovascular death not only in cardiorenal syndrome but also in early-stage kidney disease in the absence of heart failure.[34] Finally, the improvement in augmentation index observed in our patients with CKD may also be of clinical significance. Higher augmentation index is associated with target-organ damage in hemodialysis patients[35] and with microalbuminuria in those with essential hypertension.[36] Amelioration in the arterial wave reflection is particularly significant because it has been found to predict all-cause mortality and cardiovascular disease in ESRD.[37,38] Our findings indicate that therapeutic renal denervation may rapidly affect the peripheral vasculature *via* a significant reduction of arterial stiffness in this patient cohort.

Although the small number of patients included in our pilot study is a limitation and precludes generalization of our findings to the large cohort of patients with various forms of chronic renal failure, this preliminary report provides guidance for further studies and clinical trials to properly assess the short- and long-term safety and efficacy of renal nerve ablation in CKD. It also emphasizes the concept that renal denervation may address crucial pathophysiologic mechanisms underlying the high cardiovascular morbidity and mortality rates in patients with CKD and may provide a valuable tool in slowing the rate of progression of CKD and its complications.

CONCISE METHODS

Separate study protocols were approved by the institutional ethics committees from the two participating centers (Baker IDI Heart & Diabetes Institute and Alfred Hospital, Melbourne, Australia, and University of Homburg/Saar, Homburg, Germany). Informed written consent was obtained from all patients. Patients enrolled in Melbourne participated in a study examining the link between sympathetic nervous system activity and chronic renal failure. Subsequently, patients with resistant

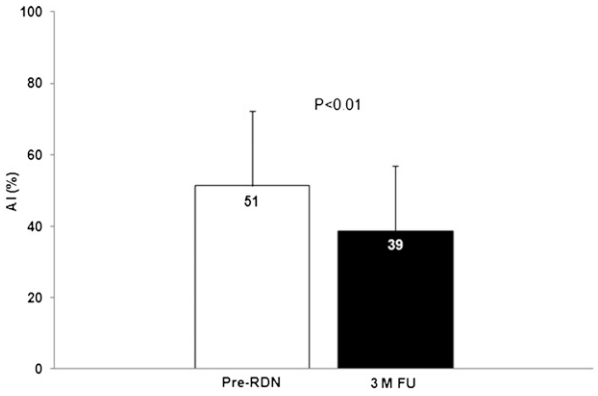

Figure 3. Peripheral augmentation index before and after 3-month follow-up. Error bars represent SDs. AI, augmentation index; FU, follow-up; M, month; pre-RDN, prerenal denervation.

hypertension and with moderate to severe CKD (stage 3–4) were offered the opportunity to undergo renal nerve ablation for BP control and were followed up clinically. The procedure is approved in Australia (by the Therapeutic Goods and Drug Administration), and separate written consent was obtained.

Patients

In this pilot study, we treated 15 patients (9 men and 6 women) with CKD (stage 3–4) and grade 3 systemic arterial hypertension. Patients underwent a complete medical history and physical examination. All participants had been evaluated previously and treated at specialized hypertension clinics in Australia and in Germany and were referred to our hypertension clinics for further management. Hypertension was diagnosed on the basis of the current European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension.[39] Patients had previously been screened for secondary forms of hypertension according to current guidelines.[39]

Peri- and Postprocedural Medications

To assess the true effects of renal denervation on BP and additional measures, baseline medication was unchanged for at least 3 months before renal nerve ablation and treatment was maintained at follow-up. In both centers (Germany and Australia), patients and physicians were instructed not to change the medications after the procedure unless clinically indicated. Medication records and adherence of each patient were comprehensively reviewed and documented at each visit.

Serum and Urine Biochemistry

Routine blood tests (hemoglobin, glucose level, hemoglobin A_{1c}, lipid profile, kidney and liver function, electrolytes); urinary albumin-to-creatinine ratio (morning spot urine); eGFR calculated using the Modified Diet in Renal Disease[40] formula; and 24-hour urine collection for sodium and potassium excretion, creatinine clearance, and proteinuria assessment were performed at baseline (before renal denervation) and at 3-, 6-, and 12-month follow-up, where available. In addition, BNP was sampled from the femoral artery directly before (prerenal denervation) and after the procedure in patients who underwent renal nerve ablation in Australia (n=7). Long-term effects of renal nerve ablation on BNP were assessed in venous samples as a part of routine test before the procedure and at follow-up.

BNP Assays

BNP was measured in arterial plasma using the Abbott AxSYM MEIA Automated immunoassay (Abbott, Abbott Park, IL) and was performed at the Alfred Hospital Pathology Department in Melbourne.

Seated Office and Ambulatory BP

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

Twenty-four-hour BP and heart rate monitoring was performed with a validated device (Spacelabs 90207 or 90217 recorder; Spacelabs Healthcare, Issaquah, WA) before the procedure and at 3-, 6-, and 12-month follow-up. The devices were programmed to obtain measurements every 15 minutes from 6 a.m. to 10 p.m., and every 30 minutes from 10 p.m. to 6 a.m. Patients were asked to continue their regular activities during the recordings and to go to bed no later than 11 p.m. The daytime period was defined as the interval from 8 a.m. to 10 p.m., and night-time was defined as the interval from midnight to 6 a.m. All patients were asked to record a sleep-awake time during this period.

Using ambulatory BP recordings, we analyzed additional measures, such as morning BP power surge (the rate of SBP increase multiplied by the amplitude), the rate of morning increase in SBP (the rate of transition from day to night BP), the night-to-day BP and heart rate ratios, and nocturnal decrease in SBP (the average of the lowest SBP and the two readings immediately preceding and following the lowest value). For final 24-hour BP measurements, we used only recordings with the proportions of valid values for the day and night periods as recommended in the guidelines.[39] However, a few patients (n=4) were unable to tolerate ambulatory monitoring because of sleep disturbances and local arm discomfort during night-time measurements (n=2 at baseline; n=2 at 3-month follow-up). Thus, for this detailed assessment of nocturnal BP values, dipping pattern, rate of BP increase, and BP power surge, we used data from the limited number of patients at baseline (n=10) and at 3-month (n=10) and 6-month (n=6) follow-up.

Renal Scintigraphy

To assess renal blood flow and renal perfusion, patients treated in Melbourne underwent renal dynamic scintigraphy before and 3 months after the renal ablation procedure. Standard 20-minute renal imaging was carried out immediately after intravenous injection of 350 MBq of ^{99m}Tc-MAG-3. We measured effective renal plasma flow and calculated the kidney retention index in each kidney (left to right index); a calculated kidney retention index $<$30% was considered normal.

Catheter-Based Renal Denervation

Radiofrequency catheter (Simplicity; Medtronic Ardian Inc., Palo Alto, CA) was introduced into each renal artery *via* femoral access. All patients underwent bilateral renal nerve ablation in one session, with

the catheter positioned in the lumen of the renal artery, as described elsewhere.[16,17] To minimize local visceral pain during the energy delivery, anxiolytics and analgesics were administered intravenously.

CO_2 Renal Angiography

To reduce contrast exposure and potential effect of contrast-induced nephrotoxicity, renal CO_2 angiography was performed to visualize renal arteries in all investigated patients treated in Melbourne. CO_2 gas can be used as an alternative to iodinated contrast. When injected into a blood vessel, CO_2 bubbles displace blood, allowing vascular imaging. CO_2 was delivered by the OptiMed CO_2-Angioset system; 20 ml of CO_2 was injected on each occasion. This allowed adequate imaging of the vessel to determine catheter position.

Peripheral Arterial Tonometry

Augmentation index was assessed noninvasively by peripheral arterial tone signal using an EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel). EndoPAT bio-sensors were placed on the index finger of each hand. Peripheral augmentation index and augmentation index corrected to a heart rate of 75 beats/min were calculated automatically through a computer algorithm provided by Itamar Medical. Augmentation index is considered an indirect measure of peripheral arterial stiffness. This measurement was obtained in all patients (n=7) who underwent renal denervation in Melbourne.

Statistical Analyses

Data are presented as mean ± SD with interquartile range where indicated. Statistical analysis was performed using SigmaStat, version 3.5 (Systat Software, Point Richmond, CA). Comparisons between baseline and post-intervention data were made by one-way repeated-measures ANOVA. We have not included data from 12-month follow-up for statistical analysis of BP because only five patients completed this time point. Augmentation index before and after the procedure was compared by paired t test. A P value < 0.05 was considered to represent a statistically significant difference.

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DISCLOSURES

D.H. has no financial conflict of interest. F.M., A.S.W., H.K., M.B., B.C., M.D.E., and M.P.S. have been investigators in studies supported by Medtronic and have received speakers fees from Medtronic and pharmaceutical companies. G.W.L. has received honoraria from Medtronic, Pfizer, and Wyeth Pharmaceuticals for presentations. The Neurovascular Hypertension & Kidney Disease laboratory currently receives research funding from Medtronic Inc. (formerly Ardian Inc.), Abbott (formerly Solvay) Pharmaceuticals, Allergan Inc., and Servier. M.D.E. serves on scientific advisory boards of Abbott Pharmaceuticals and Medtronic. M.P.S. serves on scientific advisory boards for Abbott Pharmaceuticals, Novartis Pharmaceuticals, and Medtronic. He has received honoraria from Abbott, Servier, Novartis, Boehringer Ingelheim, and Medtronic for presentations. P.A.S. is an employee of Ardian Medtronic. These organizations played no role in the study design or analysis and interpretation of data described here or in the preparation, review, and approval of the manuscript.

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