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CLINICAL RESEARCH

Endovascular Renal Denervation in End-Stage Kidney Disease Patients: Cardiovascular Protection—A Proof-of-Concept Study

Neil A. Hoye[1,2,5], Luke C. Wilson[1,5], Gerard T. Wilkins[1], David L. Jardine[3], Tracey L. Putt[1], Ari Samaranayaka[4], John B.W. Schollum[1] and Robert J. Walker[1]

[1]Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, Otago, New Zealand; [2]Department of Renal Medicine, St. James's University Hospital, Leeds, UK; [3]Department of Medicine, University of Otago, Christchurch, Otago, New Zealand; and [4]Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, Otago, New Zealand

Introduction: Sympathetic neural activation is markedly increased in end-stage kidney disease (ESKD). Catheter-based renal denervation (RDN) reduces sympathetic overactivity and blood pressure in resistant hypertension. We investigated the effect of RDN on sympathetic neural activation and left ventricular mass in patients with ESKD.

Methods: Nine ESKD (6 hemodialysis and 3 peritoneal dialysis) patients with dialysis vintage of ≥11 months were treated with RDN (EnligHTN system). Data were obtained on a nondialysis day; at baseline, 1, 3, and 12 months post-RDN.

Results: At baseline sympathetic neural activation measured by muscle sympathetic nervous activity (MSNA) and plasma norepinephrine concentrations were markedly elevated. Left ventricular hypertrophy (LVH) was evident in 8 of the 9 patients. At 12 months post-RDN, blind analysis revealed that $MSNA_{frequency}$ (–12.2 bursts/min^1, 95% CI [–13.6, –10.7]) and LV mass (–27 g/m^2, 95% CI [–47, –8]) were reduced. Mean ambulatory BP (systolic: –24 mm Hg, 95% CI [–42, –5] and diastolic: –13 mm Hg, 95% CI [–22, –4]) was also reduced at 12 months. Office BP was reduced as early as 1 month (systolic: –25 mm Hg, 95% CI [–45, –5] and diastolic: –13 mm Hg, 95% CI [–24, –1]). Both ambulatory and office BP had clinically significant reductions in at least 50% of patients out to 12 months.

Discussion: Catheter-based RDN significantly reduced MSNA and LV mass as well as systemic BP in this group of patients with ESKD.

Kidney Int Rep (2017) **2,** 856–865; http://dx.doi.org/10.1016/j.ekir.2017.04.012
KEYWORDS: dialysis; left ventricular hypertrophy; renal denervation; sympathetic neural over-activity

Chronic kidney disease (CKD) is characterized by sympathetic neural activation, which increases in severity as the condition progresses.[1] Such sympathetic hyperactivity results from afferent nerve impulses derived from the diseased native kidneys.[2,3] Surgical ablation ameliorates this sympathetic overactivity and prevents both hypertension[4] and the progression of renal disease[5] in experimental models. These findings have recently been replicated in humans with CKD following endovascular, catheter-based renal denervation (RDN).[6–8] Interest has thus been generated in the technique's sympatholytic effects,[9] particularly in CKD research.[10]

As well as contributing to hypertension and disease progression, pathological activation of the sympathetic nervous system is associated with higher incidence of sudden cardiac death in CKD and end-stage kidney disease (ESKD).[11] Specifically, increased muscle sympathetic nerve activity (MSNA) associates with the composite of all-cause mortality and nonfatal cardiovascular events;[12] plasma norepinephrine predicts survival and incident cardiovascular events;[13] and heart rate variability (a marker of autonomic dysfunction) predicts both hospitalization[14] and patient mortality.[15] Left ventricular hypertrophy (LVH)

Correspondence: Robert J. Walker, Department of Medicine, Dunedin School of Medicine, University of Otago, PO Box 56, Dunedin 9054, New Zealand. E-mail: rob.walker@otago.ac.nz

[5]Joint equal first authors.

Received 5 February 2017; revised 17 April 2017; accepted 26 April 2017; published online 4 May 2017

appears key to this relationship. LVH is common in ESKD, affecting ~75% of patients[16] and correlates with sympathetic activity.[17] LVH has a major effect on prognosis,[16] and importantly, regression with therapy has been reported to improve survival.[18]

Endovascular RDN reduces LVH and improves systolic and diastolic function both in resistant hypertension[19–21] and CKD stages 2 to 4.[22] These data are however lacking in ESKD, and RDN studies as a whole are sparse in this population. Five case studies have reported RDN as feasible and efficacious in ESKD, despite the presence of smaller renal artery luminal diameter and atrophic kidneys.[23–28] Schlaich *et al.*[27] have thus far reported the largest cohort of 9 successful denervations in ESKD. Post-RDN office systolic blood pressure (BP) and MSNA were reduced, but ambulatory parameters were unchanged. Notably, there was no assessment of cardiac function in that cohort and MSNA data were only collected in 2 patients post-RDN, 1 of whom had a subsequent renal transplant and received tacrolimus immunosuppression, known to reduce sympathetic activity.[29]

Accordingly, the relationship between RDN, sympathetic activity and LV mass in ESKD requires further investigation. We hypothesized that RDN would reduce sympathetic overactivity and potentially improve cardiovascular outcomes as measured by direct improvement in LV mass.

METHODS

This study was an investigator-initiated and -analyzed study, independent of St. Jude Medical, Inc. The study was approved by the Lower South Health and Disability Ethics Committee, New Zealand (reference LRS/12/05/012) and registered with the Australian New Zealand Clinical Trials Registry ([ANZCTR], trial number: ACTRN12613000562774). It complied with the Declaration of Helsinki. Those patients who were eligible gave written informed consent prior to their participation.

Patients

In November 2012, all dialysis-dependent ESKD patients under the care of the Southern District Health Board, New Zealand, were screened. Inclusion criteria for study participation were the following: (i) age over 18 years; (ii) office blood pressure >140/90 mm Hg during a short break nondialysis day for hemodialysis patients, despite antihypertensive treatment; (iii) intact native kidneys; (iv) dialysis therapy for at least 3 months; (v) clinical stability for the last 3 months, in other words, no evidence of fluid overload or myocardial ischemia, no change in antihypertensive therapy, and no change in dialysis prescription. Exclusion criteria were the following: (i) previous renal transplantation; (ii) significant renovascular abnormalities identified at the time of renal angiography, in other words, multiple or short-length main renal arteries or marked renal artery stenosis; (iii) severe vascular disease; and (iv) inability to provide consent. Nine ESKD (6 hemodialysis and 3 peritoneal dialysis) patients were recruited into this proof-of-concept study (Figure 1).

Measures

All variables (unless stated) were assessed prior to RDN (baseline), and at 1 month (1M), 3 months (3M), and 12 months (12M) post-RDN. At all time points, measurements were taken on a short break nondialysis day for hemodialysis patients. The peritoneal dialysis patients were assessed at the same time of day (morning) throughout the study, with dialysate present within the peritoneum and having completed their morning dialysate exchange.

Office BP was measured in triplicate using an automated BP system (Connex ProBP 3400 series; Welch Allyn, Skaneateles Falls, NY) according to guidelines.[30] Ambulatory BP monitoring (Oscar2 Blood Pressure Monitoring System; SunTech Medical, Inc., Morrisville, NC) was performed every 20 minutes throughout

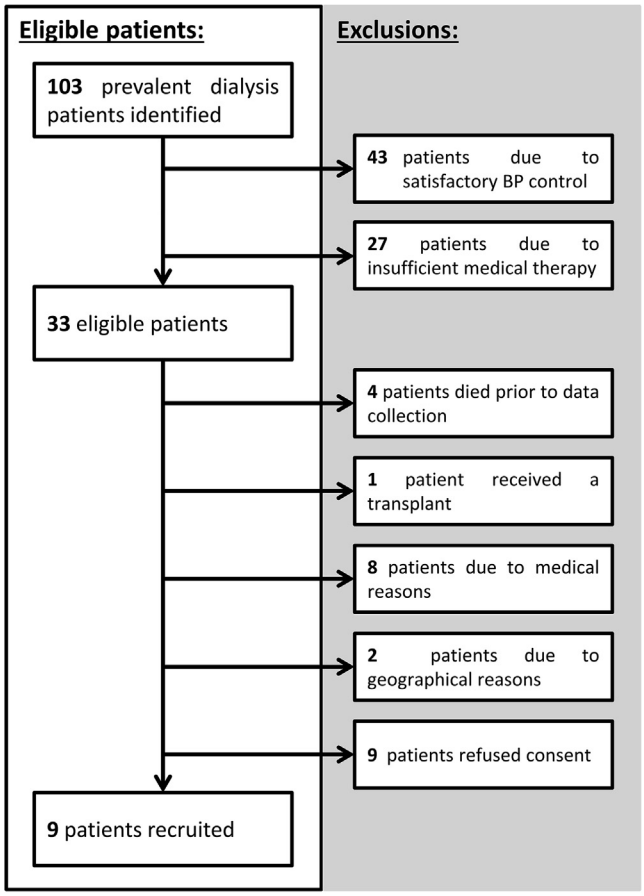

Figure 1. Patient recruitment and reasons for exclusions.

the day and every 45 minutes at night. This allowed for calculation of systolic and diastolic BP for the daytime, nighttime and 24-hour periods, as well as nocturnal dipping status and the collection of ambulatory heart rate (AccuWin Pro, v3.4; SunTech Medical, Inc., Morrisville, NC). Echocardiography was performed at baseline, 3M, and 12M in the left decubitus position. A Vivid E9 ultrasound machine with a M5S 1.5 to 4.6 MHz matrix array probe was used according to guidelines.[31,32] Analysis was performed using EchoPAC (Version 112, GE Healthcare, Horten, Norway) by a blind observer, with each value obtained from the mean of 3 measurements. Hydration status was assessed by whole-body bio-impedance spectroscopy (BCM; Fresenius Medical Care, Bad Homburg, Germany),[33,34] those receiving peritoneal dialysis had their weight adjusted for an empty abdomen.[35] Multiunit MSNA was measured (by a single investigator, DLJ) in the supine position using microneurography (Nerve Traffic Analyser 662C-4; Engineering Electronics Shop, University of Iowa, IA).[36–38] A tungsten microelectrode was inserted into the right peroneal nerve and manipulated until a satisfactory MSNA signal was obtained. Beat-to-beat blood pressure (Finger-photoplethysmography; Finometer MIDI, Finapres Medical Systems, Enschede, the Netherlands) was simultaneously and continuously measured on the left side or contralateral side to patients' hemodialysis access. Respiratory rate (thoracic respiratory belt transducer, MTL1132; ADInstruments, Dunedin, New Zealand) and the heart's electrical activity (electrocardiography, lead II position; FE132; ADInstruments) were also continuously measured. Once a satisfactory signal had been obtained, the patient was allowed to rest for 15 minutes to reach steady-state, before 10 minutes of MSNA data was recorded during normal restful breathing. The data was sampled at 10 kHz with an analog-to-digital converter (PL3508/P; ADInstruments) and recorded via software (Labchart Pro v7.3; ADInstruments) for offline analysis by blinded observers (by NAH and LCW) to obtain MSNA burst frequency ($MSNA_{frequency}$; bursts/min) and incidence ($MSNA_{incidence}$; bursts per 100 heart beats).[36–38] Venous blood samples were procured, processed, and stored for future batched norepinephrine and epinephrine analysis (Christchurch Heart Institute, New Zealand).[39–41]

Renal Denervation

Endovascular RDN was performed using a multipolar EnligHTN catheter and GEN2 radiofrequency generator, which is capable of delivering 4 ablations simultaneously over 60 seconds (St. Jude Medical, Inc., Minneapolis, MN); procedures were performed via the right femoral artery and an 8-F sheath in all patients.[42] Eight ablation sites were attempted per main renal artery, the first set of 4 ablations was delivered prior to any arterial bifurcation as far distal in the vessel as possible, and then the device was withdrawn proximally, rotated 45°, and a further set of 4 ablations were done to achieve circumferential ablation. All procedures were performed by a single experienced interventional cardiologist (GTW) who was concurrently an interventional investigator in the EnligHTN II (NCT01705080) and EnligHTN III (NCT01836146) clinical trials.

Statistical Analysis

All statistical analyses were done by a biostatistician (AS) using Stata Statistical Software, version 13.1 (StataCorp LP, College Station, TX). The effect of RDN was explored by calculating each main dependent variable change from baseline to 1M, 3M, and 12M (i.e., change of interest = 1M − baseline). The mean changes at each of these time points were derived with associated 95% confidence intervals (CIs) by bootstrapping[43] with 200 replicates. Bootstrapping is a resampling (i.e., a single replicate) procedure with replacement, where the mean is calculated from each resample. Those 200 means were used to estimate the overall mean and CI. It provides a nonparametric way of estimating statistical quantities when other available formulas make inappropriate assumptions. Statistical significance was identified if the entire 95% CI were positive or negative (i.e., did not contain 0), at a level of $P < 0.05$. This approach was used due to the small sample size and to maximize the statistical power of the study with variations in the sample size during follow-up. In addition, the proportion of patients with a clinically significant reduction in office BP (defined as a ≥10 mm Hg systolic and ≥5 mm Hg diastolic reduction, respectively) and ambulatory BP (defined as a ≥5 mm Hg systolic and ≥2.5 mm Hg diastolic reduction, respectively) following RDN were calculated.

RESULTS

Patient Characteristics

Patient demography and baseline characteristics for the 9 individuals are described in Table 1. Causes of ESKD were glomerulonephritis ($n = 4$), polycystic kidney disease ($n = 2$), diabetes mellitus ($n = 2$), and of unknown origin ($n = 1$). The median dialysis vintage was 38 months (range 11–110). All patients were on antihypertensive therapy with a median of 3 (range 1–4) agents.

Individual patient measures at each time point are presented in Supplementary Table S1. At baseline, 6 patients had all measures assessed. The 2 patients with diabetes had unsuccessful MSNA measurement; therefore, they were not reassessed in follow-up. Another

Table 1. Baseline characteristics of the patients

Variable	
Demographics	
Age (yr)	59 ± 9
Weight (kg)	74 ± 12
Height (cm)	172 ± 8
BMI (kg/m^2)	25 ± 2
Dialysis vintage (mo [median (range)])	38 (11–110)
Male sex	8 (89%)
White ethnicity	8 (89%)
Antihypertensive drugs (n [median (range)])	3 (1–4)
Sympathetic nervous system activity	
$MSNA_{frequency}$ (bursts/min; $n = 7$)	59 ± 12 (≤42[b])
$MSNA_{incidence}$ (bursts per 100 heart beats; $n = 7$)	85 ± 9 (40 ± 22[a])
Plasma epinephrine (pmol/l; $n = 8$)	211 ± 65 (360[c])
Plasma norepinephrine (pmol/l)	5671 ± 3851 (3380[c])
Echocardiography	
LV mass (g/m^2)	169 ± 40
LV EDV (ml)	169 ± 59
LV ESV (ml)	103 ± 54
LV EF (%)	42 ± 15
GLS (%; $n = 8$)	−13 ± 4
TAPSE (mm)	20 ± 5
Diastolic dysfunction grade	2.0 ± 0.7
Left atrial diameter (mm)	45 ± 6
Indexed IVC size (mm/m^2)	11 ± 3
IVC collapsibility index	0.44 ± 0.20
Blood pressure	
Ambulatory SBP (mm Hg)	173 ± 19
Ambulatory DBP (mm Hg)	92 ± 11
Daytime SBP (mm Hg)	173 ± 19
Daytime DBP (mm Hg)	91 ± 13
Nighttime SBP (mm Hg)	175 ± 18
Nighttime DBP (mm Hg)	91 ± 8
Office SBP (mm Hg)	179 ± 28
Office DBP (mm Hg)	90 ± 17
Heart rate (beats/min)	71 ± 9
Body composition	
Total body water (l; $n = 8$)	43 ± 5
Overhydration (l; $n = 8$)	3.2 ± 1.7

BMI, body mass index; DBP, diastolic blood pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; IVC, inferior vena cava; LV, left ventricle; MSNA, muscle sympathetic nervous activity; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.
Unless otherwise indicated, values are presented as mean ± SD from 9 patients (unless n is stated). Normative value for MSNA in healthy male and female subjects as previously described by [a]Narkiewicz *et al.*[44] and [b]Hering *et al.*[9] Note that because $MSNA_{frequency}$ data is separated for sex and by age, therefore the highest normative value is presented. For $MSNA_{incidence}$ this approach was not presented, so the highest group mean ± SD is presented. [c]Upper limit of the normal range in 67 normotensive patients described by Lenders *et al.*[41]

patient was not assessed with BCM; therefore, this was not reassessed in follow-up. At 1M, 8 patients were fully assessed with their repeated baseline measures. One patient temporarily withdrew from the study to recover from a myocardial infarction but returned to study at 3M. At 3M, 7 patients were fully assessed with their repeated baseline measures. One patient did not consent to MSNA and another to echocardiographic measurements. At 12M, 3 patients were fully assessed with their repeated baseline measures. One patient had an unsuccessful MSNA assessment. Another patient had died. The other 4 patients did not consent to all measures. As a result, each patient is represented by a unique figure symbol that is consistent across all figures and panels.

RDN Procedure

All 9 patients were deemed to have had a technically successful RDN. A total of 143 ablation sites out of 144 were completed to 60 seconds in this cohort, with 142 (8 in all but 2 vessels) performed with acceptable temperature rises and impedances. During all procedures, the catheter and the electrodes functioned appropriately. A single renal artery was present in all of the study patients and the mean renal artery vessel diameter was 4.7 mm (SD: 1.5 mm) as measured on renal angiography. Angio-Seal (St. Jude Medical) was deployed in all patients post-procedure.

Safety

One patient sustained a femoral pseudoaneurysm post-procedure that needed vascular surgical management. Further review of patients at 1 week revealed 6 of 9 had palpable femoral hematomata despite the application of Angio-Seal. One patient suffered a myocardial infarction 4 days post-RDN and another died in the period between 3M and 12M from dialysis-related complications.

Follow-up

The changes in the main dependent variables from baseline are presented in Figure 2.

Sympatholytic Effect

In all patients marked sympathetic activation was evident at baseline, as indicated by elevated $MSNA_{frequency}$ and $MSNA_{incidence}$ as well as elevated plasma norepinephrine levels (Table 1). A clear mean reduction in $MSNA_{frequency}$ of 20% (SD: 5%) and $MSNA_{incidence}$ of 17% (SD: 8%) was seen in the 3 patients successfully measured at 12M (unsuccessfully in 1 patient); these changes were not evident at 1M or 3M (including 2 of 3 patients accessed at 12M). Despite the reduction in MSNA, circulating plasma norepinephrine and epinephrine concentrations did not fall.

Left Ventricular Mass

At baseline, LV mass in 8 of 9 patients met the American Society of Echocardiography 2015 guidelines criteria for LVH.[31] Following RDN, mean LV mass was reduced by 8% (SD: 14%) at 3M and by 13% (SD: 19%) at 12M, indicating regression of LVH.

Blood Pressure

All patients were hypertensive at baseline with no evidence of nocturnal dipping (Table 1 and Supplementary Table S1). Antihypertensive therapy was kept constant after RDN, unless the change was

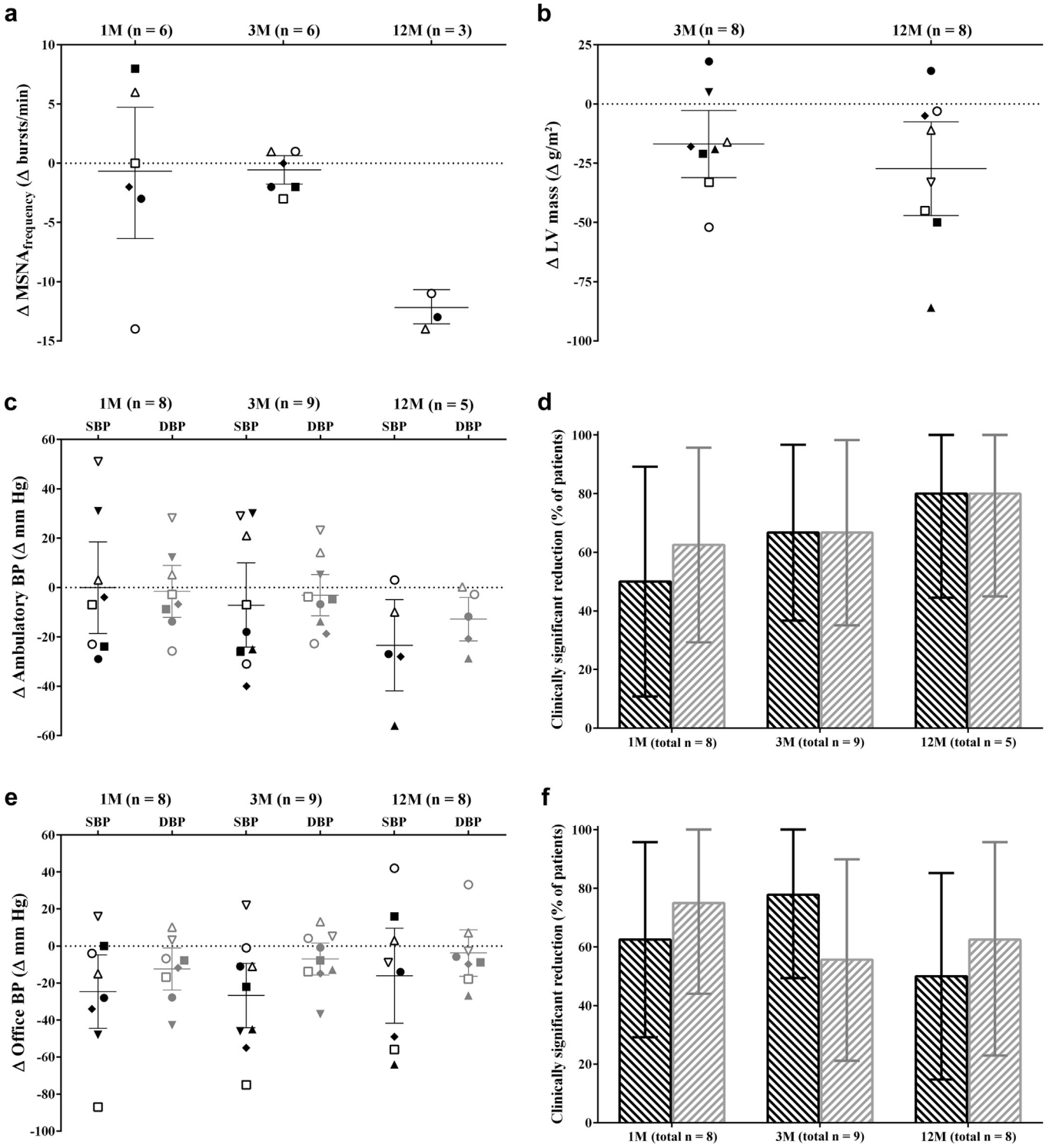

Figure 2. Change in main dependent variables following renal denervation. (a) Change in muscle sympathetic nervous activity (MSNA) burst frequency. (b) Change in left ventricular (LV) mass. (c) Change in ambulatory blood pressure (BP); systolic BP ([SBP], black symbols and lines) and diastolic BP ([DBP], gray symbols and lines). (d) Proportion of patients with a clinically significant reduction in ambulatory BP (defined as a $\geq$5 mm Hg systolic [black bars] and $\geq$2.5 mm Hg diastolic BP [gray bars] reduction, respectively). (e) Change in office BP; SBP (black symbols and lines), and DBP (gray symbols and lines). (f) Proportion of patients with a clinically significant reduction in office BP (defined as a $\geq$10 mm Hg systolic [black bars] and $\geq$5 mm Hg diastolic BP [gray bars] reduction, respectively). Except in d and f, values are shown for individual patients, each represented by a unique symbol, which is consistent across all panels, with mean and bootstrapped 95% confidence intervals overlaid, and statistical significance was identified if the entire 95% confidence interval was positive or negative (i.e., did not contain 0), at a level of $P < 0.05$. 1M, 1 month; 3M, 3 months; 12M, 12 months.

medically indicated. Two patients had medical therapy reduced by at least 1 agent and 1 patient required an additional agent (Supplementary Table S2). Following RDN, mean ambulatory (24-hour period) BP demonstrated a gradual and evolving reduction that became significant at 12M, with systolic and diastolic BP both being reduced by 14% (SD: 13%). A parallel pattern in mean nighttime BP was observed, with systolic and diastolic BP being reduced by 16% (SD: 11%) and by 15% (SD: 12%), respectively, at 12M. Nocturnal dipping pattern improved from 0% of patients at baseline to 40% of patients at 12M. Mean office systolic and diastolic BP fell by 12% (SD: 16%) and by 13% (SD: 16%), respectively, as early as 1M, but this effect waned at 12M. In both ambulatory and office BP, clinically significant reductions were observed in at least 50% of patients out to 12M. Ambulatory heart rate remained unchanged (Supplementary Figure S1).

Volume Status

At baseline clinical measures of hypervolemia were not overtly present, but BCM assessed mean fluid status of 3.2 l (SD: 1.7 l) as overhydrated, suggesting a degree of masked overhydration. Following RDN, individual body weights varied, but as a group, body weight did not change (Figure 3). Mean total body water as assessed by BCM was moderately reduced by 5% (SD: 6%) at 12M, but not at 1M or 3M. This occurred despite equipoise in dialysis ultrafiltration prescription and dry weight.

DISCUSSION

This clinical proof-of-concept study has demonstrated that endovascular RDN is technically feasible and potentially efficacious in dialysis-dependent ESKD. Denervation led to reductions in MSNA and LV mass, which were evident as early as 3M post-procedure and sustained out to 12M. Ambulatory BP and office BP were also improved over the duration of the study. These promising findings were observed despite the selection of an extremely high cardiovascular risk ESKD cohort.

RDN had a promising sympatholytic effect in this study. At baseline, MSNA was classified as moderately to extremely elevated.[9,44] It was significantly reduced by 12M in the 3 patients in whom repeat measurement was possible. Despite the decrease in MSNA, plasma norepinephrine did not significantly fall post-RDN. Plasma norepinephrine levels are an indicator of total body sympathetic activity but are subject to other variables that make it difficult to demonstrate a significant fall in a sample of this size.[45] By contrast, although MSNA levels vary between individuals, they are remarkably consistent when measured in the same individual over time.[46] MSNA increases as glomerular filtration rate decreases[1] and is elevated in ESKD irrespective of absolute, or changes in, volume status.[2] To our knowledge, the direct prognostic benefit of lowering MSNA in clinical cohorts including ESKD is unknown. Reducing the sympathetic burden (as indicated by other measures) in ESKD is known to lower all-cause and cardiovascular mortality.[47] Furthermore, an elevation in $MSNA_{frequency}$ of 10 bursts/min in CKD patients was independently associated with higher composite all-cause mortality and nonfatal cardiovascular events.[12] Therefore, the mean reduction in $MSNA_{frequency}$ of 12 bursts/min observed in this study may offer prognostic benefit. Such a sympatholytic effect has been previously reported in ESKD; however, it was essentially observed in only 1 patient at 12M post-RDN.[27]

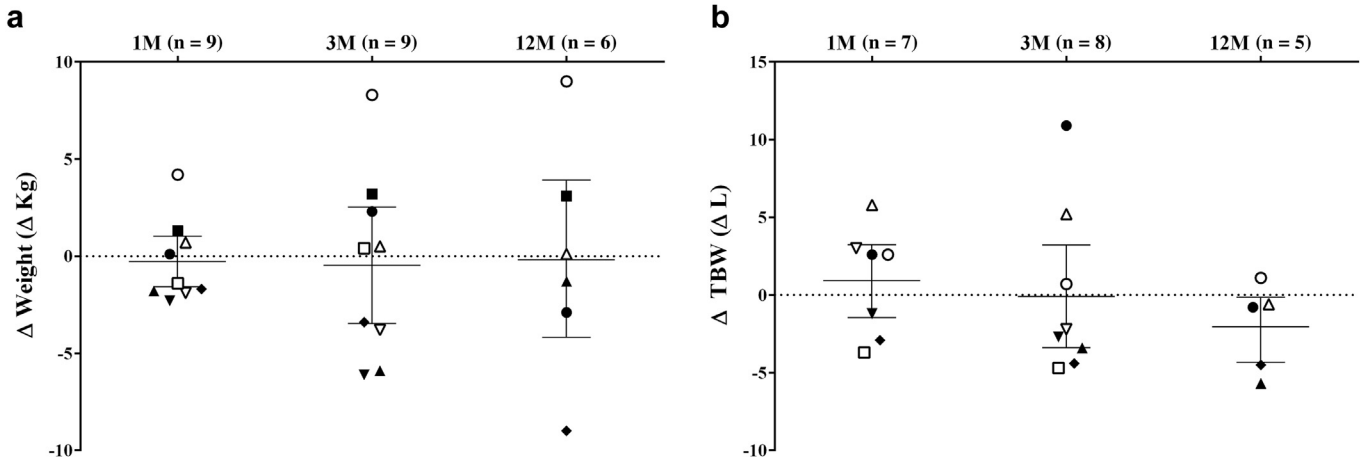

Figure 3. (a) Change in weight and (b) total body water (TBW) following renal denervation. In both panels, values are shown for individual patients, each represented by a unique symbol consistent across panels and with Figure 1, with means and bootstrapped 95% confidence intervals overlaid, and statistical significance was identified if the entire 95% confidence interval was positive or negative (i.e., did not contain 0), at a level of $P < 0.05$. 1M, 1 month; 3M, 3 months; 12M, 12 months.

The LV mass at baseline met criteria for defined LVH[31] in 8 patients in our cohort. Following RDN, mean LV mass was reduced by 8% at 3M and by 13% at 12M, therefore demonstrating clear regression of LVH. LVH is associated with elevated sympathetic signaling[17] and is an independent determinant of survival in ESKD.[48–50] Regression of LVH, that is, reducing LV mass to the level seen in our study, has been associated with reduced all-cause and cardiovascular mortality in ESKD with hazard ratios of 0.78 and 0.72, respectively.[18] Regression of LVH post-RDN has not previously been demonstrated in ESKD, but it has been observed after RDN in hypertensive patients[19,21] and in those suffering from CKD (stages 2–4).[22]

In addition to the sympatholytic effects on LV mass, RDN reduced mean ambulatory and mean nighttime systolic and diastolic BP at 12M, and this was associated with a reestablished nocturnal "dipping" pattern for 2 patients. Office systolic and diastolic BP were reduced as early as 1M but waned at 12M. Clinically significant reductions in ambulatory and office BP were observed in at least 50% of patients out to 12M. The reestablishment of nocturnal "dipping" may also confer prognostic benefit, as nondipping versus dipping has been associated with all-cause and cardiovascular mortality[51] in ESKD. Thus improved BP control post-RDN may also contribute to a reduction in the substantial cardiovascular disease risk in these patients.[51,52]

Endovascular RDN, by interrupting the afferent preganglionic and efferent post-ganglionic renal nervous supply, has demonstrated promising results in this study. We postulate that reduced sympathetic activity leads to the observed reduction in LV mass and ambulatory BP seen in this group of high-risk dialysis patients. Heightened sympathetic activity is an independent risk factor for LVH in ESKD[17,53] and is reduced during standard hypertensive treatment.[54] Furthermore, a small but significant reduction in LV mass was observed in those classified as nonresponders to RDN (systolic BP reduction $<$10 mm Hg). As such, sympathoinhibition might be a mechanism of LVH regression independent of BP reduction.[21,55] Though outside the scope of this paper and speculative in those with ESKD, the delayed progressive and evolving pattern observed, may be seen as a result of the time taken to reset central SNA and baroreceptor sensitivity, and for cardiovascular remodeling to manifest.[56–58]

While technically adequate RDN appeared to have occurred, the level of afferent and efferent nerve damage induced by the procedure is unknown. This shortcoming is not unique to this study.[59] Major but varied anatomical changes to patients' arteries as well as medial calcification may have limited the thermal energy delivered and the extent of RDN. These factors may explain some of the variation in response to RDN in our ESKD patients. Perhaps other methods of RDN such as modification of the radiofrequency treatment protocol, extracorporeal ultrasound, or chemical denervation may facilitate greater treatment success rates with less vascular complications.

The open-labeled design of this proof-of-concept study may have influenced the outcomes.[60] However this study focused on the sympatholytic and regression of LVH following RDN in ESKD, and these parameters were initially analyzed blindly. Furthermore, our patient cohort comprised established dialysis patients used to routine clinical surveillance every 3 months, including a thorough medical therapy review. Two patients had reductions and 1 patient had an increase in their medications (Supplementary Table S2). If these alterations in therapy were of any consequence, we would have seen an attenuation or reversal of the observed reductions in MSNA[61] and LV mass.[62] We observed a progressive and evolving pattern indicative of a treatment effect following denervation, which would argue against a possible Hawthorne or placebo effect, which generally wanes over time.[63]

Volume status was maintained as close as possible to baseline to avoid this as a confounding factor. As such, patient weights did not change over the study. Total body water (as assessed by BCM) had not changed by 3M, but it appeared to be reduced by 5% at 12M. LV mass may be affected by hydration status;[64] however, LV mass had fallen prior to changes in total body water.

The small and variable sample size, although larger than in previous case studies,[23–27] limited the statistical analysis approach used and led to wide CIs. Care is therefore needed when generalizing the results.

In summary, in this proof-of-concept study, endovascular RDN in ESKD patients has demonstrated a statistically significant sympatholytic effect combined with marked regression of LVH. Additionally a clear reduction in ambulatory BP was also observed. Such changes have substantial clinical implications in this high cardiovascular risk population. These preliminary findings need to be validated in a larger, randomized, sham-controlled trial, but they are promising in their own right.

DISCLOSURE

This work was supported by an unconditional equipment grant from St. Jude Medical, Inc., who provided the RDN catheters. Additional costs for the analyses were funded internally from the Department of Medicine, University of Otago. NAH was funded via the Tony Hocken Scholarship from the Department of Medicine. GTW has been an investigator in the EnligHTN II (NCT01705080)

and EnligHTN III (NCT01836146) clinical trials, which have been conducted independent to this study. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We firstly thank the participants who volunteered to take part in this study. We would also like to thank Fiona Roberts (cardiac physiologist/cardiac sonographer, Southern District Health Board) who acquired and analyzed the echocardiographic measures. The invaluable help of Christchurch Heart Institute for plasma catecholamine analysis is also appreciated. Some aspects of this work have been presented in abstract form at the European Renal Association–European Dialysis and Transplant Association 51st (2014) and 53rd (2016) Congress meetings and at Kidney Week 2015: American Society of Nephrology Annual Meeting (NAH).

SUPPLEMENTARY MATERIAL

Figure S1. Ambulatory heart rate following renal denervation over the study period.

Table S1. Measurements completed for the individual patients across the study along with baseline blood pressure.

Table S2. The prescribed antihypertensive therapy for each participant over the duration of the study.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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