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CLINICAL RESEARCH

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

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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.

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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)

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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 Heath 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 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

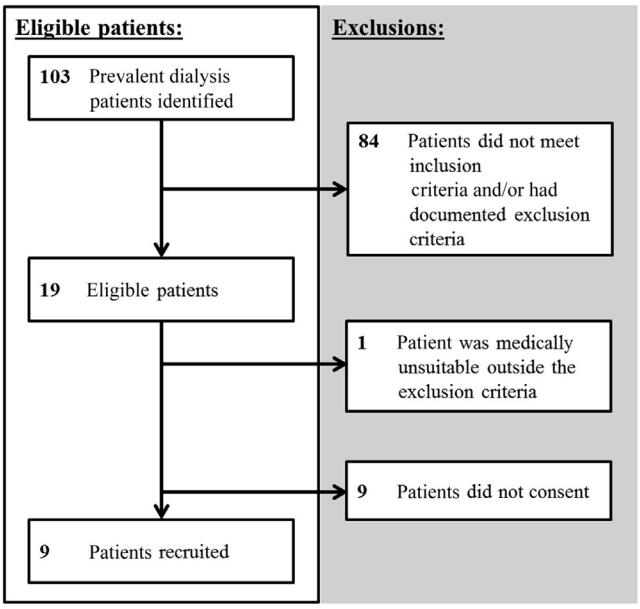

Figure 1. Patient recruitment and reasons for exclusions.

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