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Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease

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ABSTRACT

Background and objectives: Sympathetic activation is a hallmark of ESRD and adversely affects cardiovascular prognosis. Efferent sympathetic outflow and afferent neural signalling from the failing native kidneys are key mediators and can be targeted by renal denervation (RDN). Whether this is feasible and effective in ESRD is not known.

Design, setting, participants and measurements: In an initial safety and proof-of-concept study we attempted to perform RDN in 12 patients with ESRD and uncontrolled blood pressure (BP). Standardized BP measurements were obtained in all patients on dialysis free days at baseline and follow up. Measures of renal noradrenaline spillover and muscle sympathetic nerve activity were available from 5 patients at baseline and from 2 patients at 12 month follow up and beyond.

Results: Average office BP was 170.8 ± 16.9/89.2 ± 12.1 mm Hg despite the use of 3.8 ± 1.4 antihypertensive drugs. All 5 patients in whom muscle sympathetic nerve activity and noradrenaline spillover was assessed at baseline displayed substantially elevated levels. Three out of 12 patients could not undergo RDN due to atrophic renal arteries. Compared to baseline, office systolic BP was significantly reduced at 3, 6, and 12 months after RDN (from 166 ± 16.0 to 148 ± 11, 150 ± 14, and138 ± 17 mm Hg, respectively), whereas no change was evident in the 3 non-treated patients. Sympathetic nerve activity was substantially reduced in 2 patients who underwent repeat assessment.

Conclusions: RDN is feasible in patients with ESRD and associated with a sustained reduction in systolic office BP. Atrophic renal arteries may pose a problem for application of this technology in some patients with ESRD.

1. Introduction

The renal sympathetic nerves are major contributors to the complex pathophysiology of hypertension, both experimentally and in humans [1]. Renal sympathetic nerve activity is elevated in patients with various forms of hypertension as demonstrated by application of radiotracer dilution methodology to measure overflow of noradrenaline (NA) from the kidneys [2–4]. Augmentation of renin release [5], tubular sodium (Na^+) reabsorption [6], and renal vascular resistance [7,8] are direct consequences of efferent renal sympathetic nerve stimulation and the major components of neural regulation of renal function. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in blood pressure control such as the heart and peripheral blood vessels, mainly by modulating posterior hypothalamic activity [9]. Abrogation of renal sensory afferent nerves has been demonstrated in various experimental models to have salutary

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effects, not only on blood pressure, but also on organ specific damage caused by chronic sympathetic over-activity, as reviewed previously [10,11].

Sympathetic activation is a hallmark of end-stage renal disease and adversely affects cardiovascular prognosis [12]. Hypertension is present in the vast majority of these patients [13] and plays a key role in the progressive deterioration of renal function and in the exceedingly high rate of cardiovascular events, which represent the primary cause of morbidity and mortality in this patient group [14–16]. While successful renal transplantation can restore kidney function, sympathetic over-activity typically remains unaltered, most likely due to continued afferent signalling arising from the failing native kidneys [17,18]. Indeed, compelling evidence from experimental models in conjunction with the demonstration of normalised central sympathetic outflow after bilateral nephrectomy in patients with end stage renal disease [18] clearly indicate that afferent signalling via renal sensory nerves is a powerful modulator of sympathetic drive [19,20].

The recent introduction of a catheter-based radiofrequency (RF) ablation approach to directly target both efferent and afferent renal nerves appears an obvious useful therapeutic approach in this context. Indeed, recent clinical trials in patients with resistant hypertension and normal renal function demonstrated the safety and efficacy of renal sympathetic denervation [21,22]. Furthermore, there is accumulating evidence for additional beneficial effects of renal denervation on central sympathetic nerve activity [23] and insulin sensitivity [24,25], both of which are of particular relevance in patients with end-stage renal disease.

Against this background we initiated a prospective pilot study to assess the feasibility and efficacy of catheter-based renal nerve ablation in patients with end-stage renal disease.

2. Methods

The renal denervation studies in patients with ESRD were approved by the local Ethics committees at participating centres in accordance with the Declaration of Helsinki.

Patients were enrolled and treated in centres that already had experience with renal denervation from the previous Symplicity HTN-1 trial [21] in Melbourne, Minneapolis, Erlangen and Homburg, and continuously followed at 3, 6, and 12 months and then on a yearly basis. Systolic, diastolic and mean arterial blood pressure, as well as routine serum biochemistry were measured before and after treatment. All patients gave written informed consent.

Eligible patients were ≥18 years and had uncontrolled office blood pressure of >140/90 mm Hg, despite being treated with ≥3 antihypertensive drugs with no changes in medication for a minimum of 4 weeks prior to enrolment. Patients were included if they had end-stage renal disease with concurrent haemodialysis treatment for at least 6 months prior to the study.

All patients had a complete history and physical examination, assessment of vital signs, and review of medication. Patients were interviewed whether they had taken their complete medication at defined doses. Medications were not changed after the procedure unless blood pressure control was achieved or if medically required. Standardized office blood pressure readings were measured in a seated position after at least 5 min of rest by trained research personnel. Readings were performed on the arm contralateral to the arteriovenous fistula for dialysis access and were obtained on a mid week dialysis free day. Averages of the triplicate measures were calculated and used for analysis. Ambulatory blood pressure monitoring was performed with Spacelab® monitors on a mid week dialysis free day. Data were collected locally and statistical analysis of the entire data set was performed in Melbourne. Several measures such as noradrenaline spillover and microneurography to assess sympathetic nerve activity were only available in the initiating centre in Melbourne, explaining the lower number of patients in whom these studies could be carried out.

2.1. Renal denervation procedure

The renal nerves, carrying both sympathetic efferent and sensory afferent nerve fibers, are circumferentially distributed in the adventitia around the renal artery. A radiofrequency ablation catheter (Symplicity®, Medtronic Ardian Inc, Mountain View, California, USA) was positioned in the lumen of the renal artery to allow ablation of renal nerves susceptible to this type of energy, as previously described in detail [21]. In 5 patients bilateral renal artery and vein sampling and selective renal angiography were performed prior to and 3 months after bilateral renal nerve ablation for assessment of regional NA kinetics.

2.2. Microneurography

Multiunit postganglionic sympathetic nerve activity (MSNA) was recorded using microneurography in the peroneal nerve, as described previously [3,4].

2.3. Noradrenaline kinetics

Assessment of noradrenaline kinetics were only performed at the Baker IDI Heart & Diabetes Institute, as described previously [3].

2.4. BNP assays

Brain natriuretic peptide was measured in plasma using the Abbott AxSYM MEIA Automated immunoassay (Abbott, Abbott Park, Ill) at the Alfred Hospital Pathology Department.

2.5. Statistical analysis

Changes in blood pressure were analyzed from baseline to 3, 6, and 12 months by repeated measures analysis of variance with pair-wise comparison of significant values. A 2-tailed value of $P<0.05$ was regarded as statistically significant.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Patient characteristics

A total of 12 patients with ESRD and uncontrolled hypertension were enrolled in this study. Confirmed (renal biopsy) or presumed (medical history and concomitant/underlying disease) causes of ESRD were hypertensive nephrosclerosis (n = 4), glomerulopathies (n = 5; specifically focal segmental glomerulosclerosis (n = 1), fibrillary glomerulnephritis (n = 1), membranous glomerulopathy (n = 3)), IgA nephropathy (n = 1), nephrolithiasis (n = 1) and bilateral atrophic kidneys of unknown origin (n = 1). Average duration of hemodialysis was 3.6 ± 2.6 years. Pre-procedural renal artery Doppler ultrasound or alternative imaging did not reveal evidence for renal artery stenosis in any of the patients. Average office baseline BP was 170.8 ± 16.9/89.2 ± 12.1 mm Hg with a corresponding 24 hour ABPM of 164.8 ± 10.1/99.12 ± 9.2 mm Hg (obtained only in n = 10) (Table 1), despite the use of 3.8 ± 1.4 antihypertensive drugs. None of the patients had signs or symptoms of hypervolemia, as assessed by physical examination including pulmonary auscultation, assessment of jugular vein distension and absence of peripheral pitting oedema. Their hemodialysis regimens (3 weekly sessions of 4–5 h each) and dry weight were stable for at least the previous 3 months and unchanged during follow up to ascertain unaltered volume status. Application of radiotracer dilution methodology to measure renal and whole body NA spillover and microneurography to assess muscle sympathetic nerve activity could be obtained in 5 patients at baseline and revealed marked sympathetic activation in all 5 patients (Table 2).

Table 1
Baseline characteristics of the entire study cohort (n = 12) (mean ± SD).

Age (years)	47.4 ± 13.0
Weight (kg)	68.3 ± 12.2
Height (cm)	168.0 ± 11.0
BMI (kg/m^2)	24.1 ± 2.7
Office systolic BP (mm Hg)	170.8 ± 16.9
Office diastolic BP (mm Hg)	89.2 ± 12.1
24 h ambulatory SBP (mm Hg) (n = 10)	164.8 ± 10.1
24 h ambulatory DBP (mm Hg) (n = 10)	99.2 ± 9.2
Heart rate (beats/min)	81.5 ± 13.2
Number of antihypertensive drugs	3.8 ± 1.4
Drug classes used	
ACE-inhibitors	6/12
Angiotensin receptor blockers	8/12
Beta-blockers	8/12
Calcium-channel blockers	8/12
α-blockers	5/12
Vasodilators	6/12
Centrally acting sympatholytic agents	5/12