Intravascular Renal Denervation in Renal Dialysis Patients with Uncontrolled Hypertension: A Case Series of Four Patients

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Case series
Patient: Male, 24 • Female, 55 • Female, 56 • Male, 72
Final Diagnosis: Hypertension
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Intravascular renal denervation
Specialty: Cardiology

Objective: Unusual setting of medical care
Background: Hypertension is a common complication of renal dialysis and is inadequately controlled in approximately one-third of patients. Intravascular renal denervation is an option to control sympathetic overdrive and decrease blood pressure. Four renal dialysis patients are presented with uncontrolled hypertension who were treated with intravascular renal denervation.

Case Reports: In a renal dialysis unit, patients were screened for therapy-resistant hypertension, which was defined as an outpatient blood pressure >160/100 mmHg and a blood pressure by interdialytic ambulatory blood pressure monitoring (ABPM) >130/80 mmHg. Four patients were identified with a mean ABPM of 175/95 mmHg. The four patients included a 24-year-old man with neurogenic bladder undergoing hemodialysis; a 55-year-old woman with a history of type 1 diabetes mellitus undergoing hemodialysis; a 55-year-old woman with a history of type 1 diabetes mellitus undergoing peritoneal dialysis; and a 56-year-old woman with a history of autosomal dominant polycystic kidney disease (ADPKD) undergoing peritoneal dialysis; and a 72-year-old man with a history of ADPKD undergoing dialysis. Following intravascular renal denervation, one patient had antihypertensive medicines withdrawn at 12 months, and he remained normotensive up to renal transplantation at 24 months. In two patients, ABPM did not decrease until renal transplantation was performed. The fourth patient was not a candidate for renal transplantation, and he was also a non-responder for intravascular renal denervation. None of the patients experienced hypotension or other adverse events following intravascular renal denervation.

Conclusions: A case series of four patients showed that, for some patients who have unresponsive hypertension while on renal dialysis, intravascular renal denervation is a safe procedure.

MeSH Keywords: Autonomic Denervation • Blood Pressure Monitoring, Ambulatory • Dialysis • Hypertension • Kidney Transplantation • Patient Safety

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Background

Hypertension is one of the main challenges in treating patients with end-stage renal disease (ESRD). For patients who undergo hemodialysis prior to renal transplantation, between 78–96% of patients are hypertensive, and in only between 30–38% of them is hypertension adequately controlled with medication [1–3]. The prevalence of hypertension in patients with ESRD undergoing dialysis is increased in young patients of both sexes, and in all ethnic groups, when compared with the general population [1].

Hypertension is a modifiable risk factor for cardiovascular mortality and is responsible for 40% of cardiovascular deaths in patients on dialysis in United States, Australia, and New Zealand [4,5]. Renal transplantation does not necessarily normalize blood pressure. Post-transplant hypertension is present in between 70–90% of patients and is one of the main reasons for graft failure and premature cardiovascular death [6–8].

Sodium retention and volume overload are the main pathogenic mechanisms that result in patients with ESRD [3]. Other mechanisms include poor medical adherence, endothelial dysfunction, arterial stiffness caused by atherosclerosis, activation of the renin-aldosterone-angiotensin system, sleep apnea, and the treatment with recombinant erythropoietin also contribute to this complex pathogenic process [3].

In the past decade, increasing attention has been paid to the role of the activation of the sympathetic nervous system in the pathogenesis of hypertension [9–12]. Sympathetic overactivation is associated with hypertension and chronic kidney disease (CKD) and is partly responsible for the progression of organ damage in both diseases [13–15]. Sympathetic overactivation and hypertension in some patients can be reduced with thoracolumbar sympathectomy and splanchnectomy but has been believed to be at the cost of an unacceptably high risk of severe side effects [16]. In the past ten years, less invasive techniques have been developed.

Intravascular renal denervation in renal dialysis patients with uncontrolled hypertension is well described and has a favorably high prevalence of therapy-resistant hypertension in our dialysis unit and difficulties in recruiting new patients from other districts in Finland.

Renal transplantation does not decrease sympathetic activity because of afferent signals arising from the native non-functional kidney or kidneys [14,23]. Renal transplantation, combined with bilateral open or laparoscopic nephrectomy, restores the sympathetic activation to physiological levels [14,24], and effectively decreases blood pressure [21,22]. The Impact of Sympathetic Renal Denervation (ISAR-DENERVE) study showed that post-transplant hypertension may also be treated by intravascular renal denervation [26].

This report presents four cases of patients on renal dialysis with uncontrolled hypertension who were treated with intravascular renal denervation at a single center. These four cases were initially enrolled in a clinical trial (TreatDialRDN; NCT01881035) that planned to recruit 30 patients with the aim of determining the safety and efficacy of intravascular renal denervation in severely hypertensive patients with end-stage renal disease initially on hemodialysis or peritoneal dialysis, but without excluding the possibility of renal transplant during follow-up. This recent clinical trial was interrupted because of the unexpectedly low prevalence of therapy-resistant hypertension in our dialysis unit and difficulties in recruiting new patients from other districts in Finland.

Case Reports

Ethical statement

The treatment of resistant hypertension by intravascular renal denervation in patients undergoing dialysis therapy was approved by the Ethics Committee of the University of Turku, Finland, and was conducted in accordance with the Declaration of Helsinki. All patients were informed about the study, and they provided written informed consent. The four patients described in this case series are included in a multicenter clinical trial (TreatDialIRDN), which is registered at ClinicalTrials.gov (NCT01881035) with the intention of recruiting at least 30 patients. The initial effect of intravascular renal denervation on Patient 1 has been published in a previous case report [12]. The four cases reported in this case series includes the findings at 24-month follow-up after the procedure of intravascular renal denervation.

Selection of four cases from a single dialysis unit

There were 47 patients in our dialysis unit that were reviewed, of which 83% (39/47) of these had hypertension, but only five patients (11%) had an outpatient or ‘office’ blood pressure >160/100 mmHg while taking the maximal tolerated antihypertensive medication. Four of these five patients were willing to participate in the case series.
From our center, four patients were included who were >18 years old, with end-stage renal disease (ESRD) and drug-resistant hypertension, defined as an outpatient blood pressure of >160/100 mmHg and blood pressure on ambulatory blood pressure monitoring (ABPM) of >130/80 mmHg. Blood pressure was calculated as the mean value before and after dialysis.

Table 1 summarizes the baseline clinical and demographic characteristics of the four cases in this series. The median age was 56 years (range, 24–72 years). Patient 1 was a 24-year-old man with neurogenic bladder undergoing hemodialysis. Patient 2 was a 55-year-old woman with a history of type 1 diabetes mellitus undergoing peritoneal dialysis. Patient 3 was a 56-year-old woman with a history of autosomal dominant polycystic kidney disease (ADPKD) undergoing peritoneal dialysis. Patient 4 was a 72-year-old man with a history of ADPKD undergoing hemodialysis.

Table 2 summarizes the antihypertensive medications before intravascular renal denervation, and at 24 months.

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**Characteristics of the four patients in the cases series**

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The mean duration of dialysis was 29 months (±15 months). The mean number of antihypertensive drugs was 4.0 (±0.8). The mean ABPM in BCM confirmed that the mean dry weight equivalent state blood pressure was 175/95 mmHg (±3.3/12.5 mmHg). The mean daytime blood pressure measurement was 178/97 mmHg (± 5.3/12.2 mmHg) and the mean night-time blood pressure was 174/92 mmHg (±4.0/12.8 mmHg). Three of the four patients were waiting for a renal transplant.

**Ambulatory blood pressure monitoring (ABPM), the use of the body composition monitor (BCM), and intravascular renal denervation**

During dialysis, in the four cases, ambulatory blood pressure monitoring (ABPM) was performed using a validated SpaceLabs Medical 90217 ambulatory blood pressure monitor (Spacelabs).
Healthcare, Snoqualmie, United States). ABPM commenced immediately after dialysis and was continued for 24 to 48 hours to cover the whole interdialytic period. Blood pressure was measured every 30 minutes during the daytime and every 60 minutes during the night-time.

A body composition monitor (BCM) (Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany) was used to confirm that the patients were equivalent in dry weight after dialysis before the ABPM was used. The use of the BCM was based on different electrical resistances in different tissues to distinguish between extracellular water from total body water, and lean tissue from adipose tissue [11]. Blood pressure was calculated as the mean value of blood pressure before and after dialysis. Secondary causes of hypertension were excluded in the four cases selected for this case series.

Intravascular renal denervation was performed using a single electrode Symplicity Catheter (Medtronic, Dublin, Republic of Ireland). Nerve ablations were performed at distances of 5 mm, beginning from the distal part of the main renal arteries, pulling the ablation catheter back and rotating it 90° circumferentially before the next ablation. The delivered energy was between 4–6 W for each ablation, and the ablation time was two minutes. If the ablation was interrupted for any reason, the ablation was recommenced to reach the total ablation time of two minutes in each patient. The intention was to perform four ablations to each of the territories of the renal arteries supplying the superior, inferior, anterior, and posterior quadrant, and avoiding major side branches.

The outcome of intravascular renal denervation and 24-month follow-up

During the first three months, all four patients were still undergoing dialysis. Blood pressure was unchanged, and the mean ABPM was 175/100 mmHg (±8.3/9.0 mmHg), the mean daytime blood pressure was 182/103 mmHg (±6.4/7.6 mmHg), and the mean night-time blood pressure was 175/100 mmHg (SD 16.1/19.1 mmHg). At six months the Patient 1 received a renal transplant, and two other patients received a transplant within 24 months. The timepoints of renal transplantation and the detailed blood pressure values from each of the four patients are shown in Figure 1. Before renal transplantation, the mean blood pressure was 154/80 mmHg (±33.7/17.1 mmHg). After 24 months the mean ABPM was 144/75 mmHg (±6.2/4.2 mmHg), the mean daytime blood pressure was 146/86 mmHg (±6.0/4.54 mmHg), and the mean night-time blood pressure was 140/71 mmHg (±8.5/4.2 mmHg).

BCM confirmed the fluid state in the four cases to be equivalent in dry weight before each ABPM. The heart rate was not affected by intravascular renal denervation. The intake of antihypertensive medicines was recorded before every ABPM, and reduction in antihypertensive medication was undertaken, if required, during the follow-up. Antihypertensive medicines were unchanged in one patient, decreased in two patients, and stopped in one patient during the follow-up. The mean number of antihypertensive drugs was 2.0 (±1.8) by the end of the follow-up. Antihypertensive medications in the four cases, before intravascular renal denervation, and at the end of the follow-up, are presented in Table 2.

A mean of 3.7 ablations was successfully delivered per artery. The total number of ablations in each patient (Patient 1 to Patient 4) were 7, 8, 4 and 8 respectively. Patient 3 had only one kidney and one renal artery available for treatment, because of a previous nephrectomy for a nonfunctional polycystic kidney. There were no immediate or late clinical complications of intravascular renal denervation. None of the patients experienced hypotension during dialysis treatment or after intravascular renal denervation. No control angiography was performed because of the presence of non-functional native kidneys as a starting point.

Patient 1, a 24-year-old man with congenital vesicoureinary reflux and neurogenic urinary bladder, was a responder for intravascular renal denervation. He was normotensive and without antihypertensive medication one year after intravascular renal denervation. The effect of renal denervation lasted at least until renal transplantation, which was performed 24 months after intravascular renal denervation and was the reason for missing the follow-up visit and ABPM at 24 months. He had previously had severe hypertension and left ventricular hypertrophy in on transthoracic ultrasound prior to intravascular renal denervation. This patient’s case has been previously described in detail in a previously published case report [12].
The body weight increased in two patients and decreased in two patients during the 24-month follow-up period. The changes in body weight were +15 kg, –4 kg, –7 kg and +5 kg, respectively. The BMI did not correlate with the response to the renal denervation procedure. Patient 1, who had the best response to renal denervation, had the most weight gain (15 kg).

**Discussion**

The prevalence of hypertension in patients on dialysis while awaiting renal transplantation has been reported to be high [2]. Patients with end-stage renal disease (ESRD) with severe drug-resistant hypertension >160/100 mmHg has been reported to be present in about 40% of patients as determined by an office blood pressure >160/100 mmHg [1]. The exclusion of volume overload measured with bioimpedance spectroscopy has not been used in previous studies, and as these four cases have shown, the effect of intravascular renal denervation on inter-dialytic ambulatory blood pressure monitoring (ABPM) was slow to develop and varied between patients.

In one patient with a short duration of severe hypertension, all antihypertensive drugs used were withdrawn due to the onset of hypotension, and he remained normotensive until the end of follow-up and renal transplantation. In two patients ABPM was unchanged before renal transplantation but decreased after renal transplantation. The fourth patient, who was not a candidate for renal transplantation, was a non-responder to the intravascular renal denervation procedure.

A reduction in systolic blood pressure values of >10% between daytime to night-time is a normal finding. The lack of diurnal variability in systolic blood pressure is known to be associated with renal failure and is present in 82% of patients on hemodialysis [13]. The lack of diurnal variation in blood pressure is a risk factor for increased mortality in the general population [14]. A change in status from non-diurnal variation to diurnal variation in blood pressure is associated with a reduced risk of death due to cardiovascular disease [15].

In a small study of six patients with moderate to severe renal impairment, intravascular renal denervation restored physiologic diurnal variation in blood pressure, even without an overall effect on ABPM [21]. In this case series, only one patient reversed diurnal blood pressure status completely, and he was a young man with a short duration of hypertension. This finding might be explained by the fact that irreversible hypertensive arteriolar changes did not have time to develop in this patient, and he did not have diabetes, which also affects the autonomic nervous system. However, this patient did have left ventricular dilatation and mild systolic dysfunction with left ventricular hypertrophy before renal denervation. Ischemic heart disease was excluded using angiography, and the cardiac changes, as imaged on transthoracic ultrasound, were not found at one year after renal denervation, which might support...
the possibility that renal denervation has a beneficial effect on hypertensive cardiomyopathy.

At six-month follow-up in the ISAR-DENERVE study of 18 patients following renal transplantation, nine patients who underwent intravascular renal denervation, when compared with the control group had a significantly reduced outpatient blood pressure by 23/9 mmHg (±14.5/8.7 mmHg), although there was no change in mean ABPM [26]. However, three of the nine patients who underwent intravascular renal denervation reversed their non-diurnal variation in hypertension status to normal, compared with no change in the control group [26]. In the four patients described in this case series, intravascular renal denervation was performed in patients with end-stage renal disease before renal transplantation. Therefore, it might be possible that isolating the non-functional kidney from the sympathetic nervous system by intravascular renal denervation could result in a sympathetic blockade that becomes evident after circulating renal toxins, including urea and creatinine, have been reduced following renal transplantation.

This case series of four patients included cases from a single unit and is anticipated to be part of a future larger multicenter clinical study (TreatDialRDN), which will allow for analysis of the findings from a larger study population, including statistical analysis [27,28]. The importance of presenting these four cases has been to demonstrate the use of interdialytic ABPM, as systolic ABPM has been shown to be a better predictor of mortality in patients on hemodialysis when compared with blood pressure data obtained during dialysis [24]. Also, fluid retention is a part of the pathophysiologic process in drug-resistant hypertension and end-stage renal disease. These four cases have shown that confirming that the patients were equivalent in dry weight after dialysis before the start of ABPM using the body composition monitor (BCM) was a valuable approach, as BCM is more precise and reproducible than clinical evaluation alone in determining body fluid (edema) status [12]. The body weight of the first patient increased by 15 kg in the 24 months after intravascular renal denervation, but using BCM, body fat could be distinguished from fluid retention.

Conclusions

A case series of four patients with end-stage renal disease undergoing dialysis while awaiting renal transplantation, who had hypertension that was unresponsive to medication, underwent intravascular renal denervation. These four patients were initially part of a clinical trial that failed to recruit more than four patients (TreatDialRDN; NCT01881035). The findings from these four cases showed good safety for the procedure and suggested an approach to evaluating body composition and the use of interdialytic ambulatory blood pressure monitoring (ABPM). Although the outcome on the effects on blood pressure varied, this case series supports the need for large-scale, multicenter controlled studies to determine the role of intravascular renal denervation in this patient population, before and after renal transplantation.

Conflict of interest

None.

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