

## Technical aspects of renal denervation in end-stage renal disease patients with challenging anatomy

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### ABSTRACT

We describe our preliminary experience with percutaneous renal denervation in end-stage renal disease patients with resistant hypertension and challenging anatomy, in terms of the feasibility, safety, and efficacy of this procedure. Four patients with end-stage renal disease patients with resistant hypertension (mean hemodialysis time, 2.3 years) who had been taking at least four antihypertensive medications underwent percutaneous renal denervation. Renal artery eligibility included the absence of prior renal artery interventions, vessel stenosis <70%, or extended calcifications (more than 30% of the vessel circumference). No cut-off values of vessel diameter were used. All patients were successfully treated with no intra- or postprocedural complications, and all showed 24-hour ambulatory blood pressure reduction at the 12-month follow-up. Percutaneous renal denervation is a feasible approach for end-stage renal disease patients with resistant hypertension with encouraging short-term preliminary results in terms of procedural efficacy and safety.

Hypertension is present in the vast majority of end-stage renal disease (ESRD) patients, and sympathetic overactivity plays a crucial pathogenetic role in the maintenance and aggravation of this disease (1). Afferent sympathetic signaling, derived from the native failing kidneys, plays a causal role in renal efferent sympatho-excitation and potentiates the adverse effect of the chronically increased sympathetic drive (2). Renal sympathetic activation combined with renal vasoconstriction increases renin secretion and enhances sodium and water reabsorption, contributing to the development of systemic hypertension with implications in the development and progression of chronic kidney disease (CKD) (3); this mechanism independently predicts cardiovascular events and mortality in ESRD (4). Evidence from various experimental models of kidney injury indicates that percutaneous renal denervation (PRD) or pharmacological blockade of the sympathetic nervous system can exert beneficial effects by reducing the progression of CKD (5). However, PRD has been mainly performed in patients with relatively normal kidney function (4). Renal denervation to control hypertension in CKD is a new topic and may become a valuable new treatment option for a large number of patients with CKD. A few encouraging small series have been reported in the literature concerning renal denervation (6). We report here our preliminary experience with PRD in ESRD patients with renal hypertension and difficult anatomy (mean vessel diameter, 3.1 mm) in terms of the feasibility and safety of the procedure, as well as the efficacy in terms of blood pressure control, at the 12-month follow-up.

### Technique

This pilot study was approved by the Ethics Committee at our institution, and informed consent was obtained from all treated patients. To evaluate vessel wall calcification and the correct angulation of the c-arm before the procedure, angio-computed tomography (CT) was performed in all patients (Fig. 1). Because renal artery (RA) diameter reduction is a frequent finding in hemodialysis patients, no RA diameter cut-off value was used in the current study (mean diameter, 3.1 mm; range, 2.5–4.2 mm), and a 30% extension of circumferential parietal wall calcifications was considered sufficient to achieve efficient ablation.

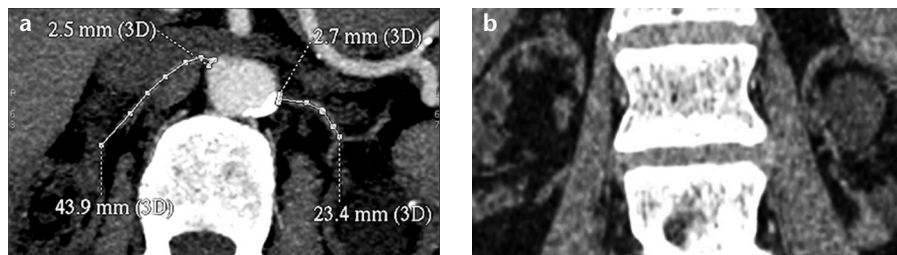
To ensure adequate vasodilation and prevent vasospasm, premedication based on fenoldopam (Corlopam, Zeneus Pharma Italia, Rome, Italy) was administered 24–48 hours before the procedure, whereas nitroglycerin was administered after selective catheterization of each RA.

Patients were kept under mild sedation. All treated patients underwent PRD of both renal arteries. At the beginning of the procedure,

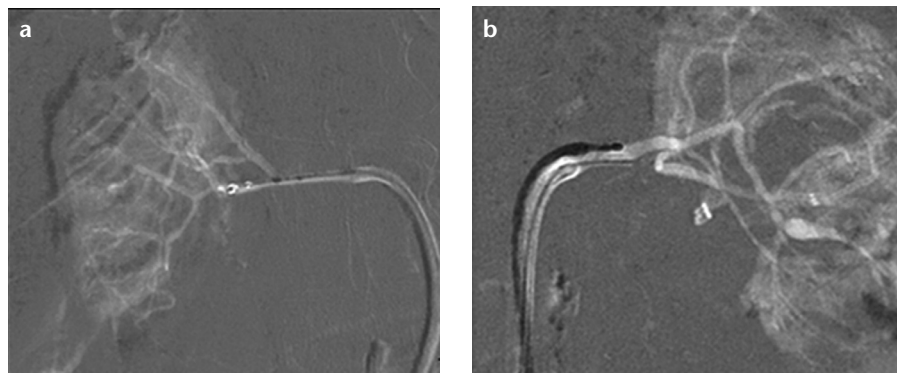
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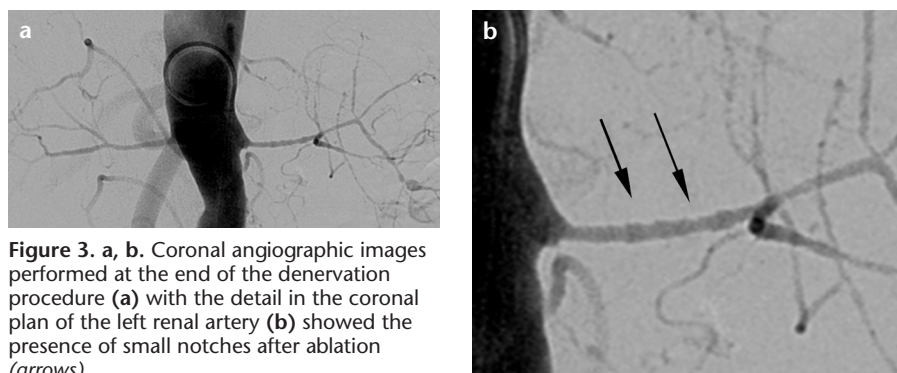
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**Figure 1.** a, b. Axial (a) and coronal (b) preprocedural angio-CT assessment of renal artery wall calcifications and vessel atrophy.



**Figure 2.** a, b. Coronal angiographic images with right (a) and left (b) renal artery catheterization under "road-mapping" showed a reduced renal artery caliber.



**Figure 3.** a, b. Coronal angiographic images performed at the end of the denervation procedure (a) with the detail in the coronal plan of the left renal artery (b) showed the presence of small notches after ablation (arrows).

3000 IU heparin were administered to ensure an activated clotted time of at least 200–250 s.

Through a right trans-femoral retrograde approach, both RAs were catheterized with a 6 F guide catheter with RDC1 morphology (Boston Scientific, Natick, Massachusetts, USA) connected through a "Y" tap to an heparinized-saline bag at constant pressure to provide permanent flushing of the endothelium during ablation. Once the catheter was in the RA, 200 µg of nitroglycerin were selectively administered in each RA. The guidewire was then replaced with a Symplicity catheter (Medtronic, Fridley, Minnesota, USA) and, using "road mapping", the tip of the catheter was placed at the distal section of

the RA, and low-power radiofrequency (5–8 watts) was delivered to the endothelial layer for 2 min (Fig. 2). A final angiogram was performed to control the procedure results and exclude any intra-procedural complication (Fig. 3a). Hemostasis of the access site was obtained at first using manual compression, and then held with a 24-hour bandage. Vital signs were monitored continuously for 24 hours, and blood counts were evaluated at the end of the procedure and after three hours.

## Cases

### Case 1

This case was a 39-year-old male ESRD and renal hypertension patient with a

history of malignant nephroangiosclerosis due to untreated long-standing hypertension. His medical therapy was based on eight different antihypertensive drugs. The hemodialysis therapy was begun two months prior to PRD.

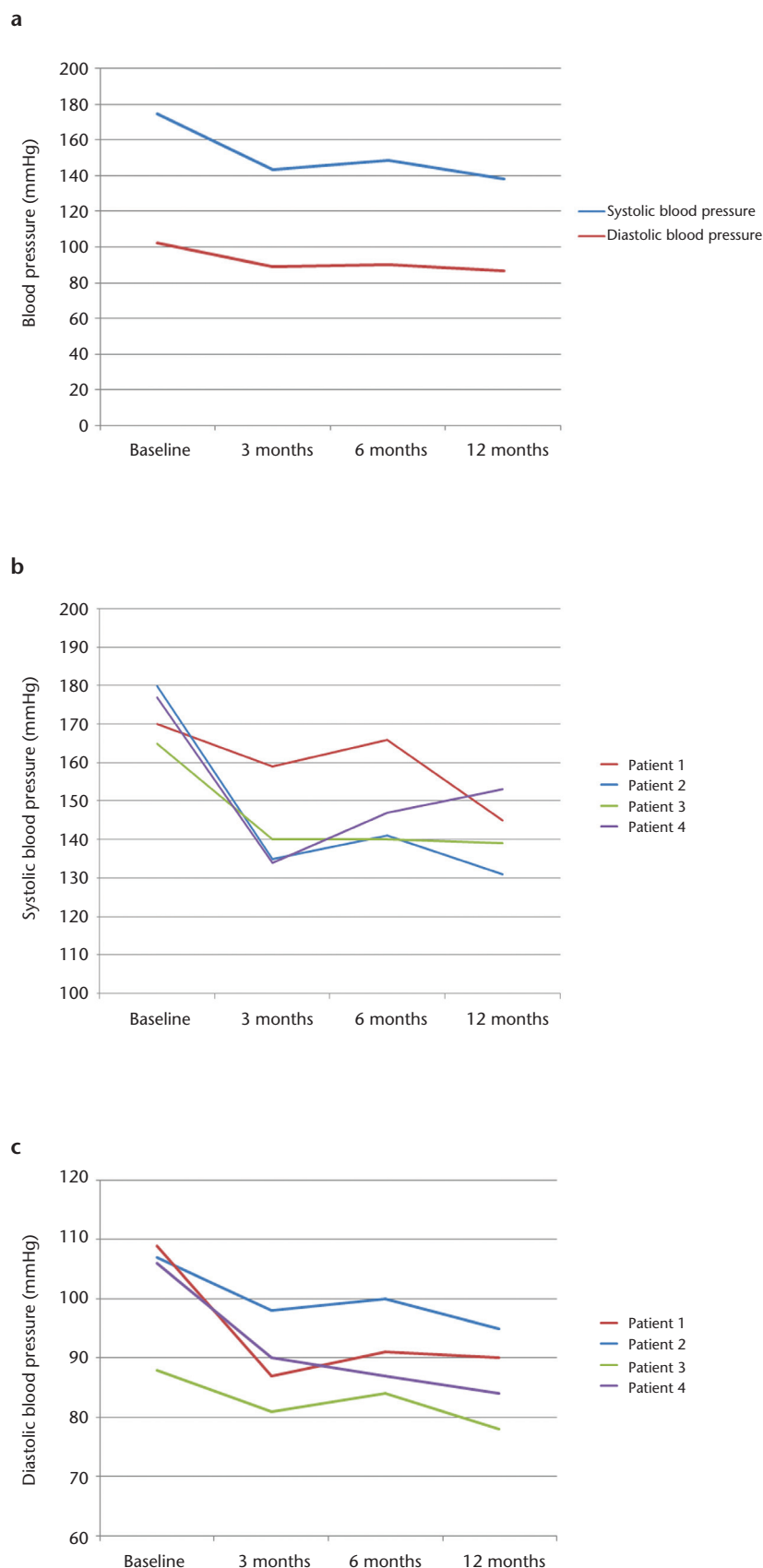
His mean 24-hour ambulatory blood pressure before PRD was 180/103 mmHg, which was reduced to 135/98, 141/100, and 131/87 mmHg (-45/-5, -39/-3, and -49/-16, respectively) at the 3-, 6-, and 12-month follow-up, respectively. Reduction of three medications (an angiotensin II antagonist, alpha-blockers, and a diuretic) was necessary at three months, and one additional medication was discontinued at six months (a vasodilator); the final medical therapy at 12 months was based on two medications (angiotensin converting enzyme inhibitors and beta-blockers). This was the only patient with residual diuresis who showed a reduction in urinary protein excretion from 1330 to 560 mg/24 hours at three months.

### Case 2

This case was a 22-year-old female ESRD and renal hypertension patient with a history of recurrent renal infections due to a congenital malformation of the urinary tract. Her medical therapy was based on seven different antihypertensive drugs. The hemodialysis therapy was begun four years prior to PRD. The mean 24-hour ambulatory blood pressure before PRD was 170/109 mmHg, and was reduced to 159/87, 166/91, and 145/77 mmHg (-11/-22, -4/-18, and -25/-32, respectively) at the 3-, 6-, and 12-month follow-ups, respectively, after PRD with reduction of only an antihypertensive medication (angiotensin converting enzyme inhibitor) at the 12-month follow-up.

### Case 3

This case was a 65-year-old female ESRD and renal hypertension patient with a history of recurrent renal infections treated with antibiotic therapy. Her medical therapy was based on four different antihypertensive drugs. The hemodialysis therapy was begun four years prior to PRD. Her mean 24-hour ambulatory blood pressure before PRD was 165/88 mmHg, which was reduced to 140/81, 140/84, and 139/73



**Figure 4. a–c.** Average systolic and diastolic blood pressure values of all ( $n=4$ ) (a) and individual patients (b, c) at baseline and during the scheduled follow-up.

mmHg (-25/-7, -25/-4, and -26/-15, respectively) at the 3-, 6- and 12-month follow-ups, respectively, after PRD with no change in the medical therapy (beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, and vasodilators) during the follow-up.

#### Case 4

This case was a 42-year-old female ESRD and renal hypertension patient with a history of rapidly progressive glomerulonephritis. Her medical therapy was based on seven different anti-hypertensive drugs. The hemodialysis therapy was begun 2.5 years prior to PRD. Her mean 24-hour ambulatory blood pressure before PRD was 177/106 mmHg, which was reduced to 134/91, 147/87, and 153/111 mmHg (-33/-15, -30/-19, and -24/+5, respectively) after PRD with reduction of one medication at three months (vasodilator) that was administered again at 12 months due to a blood pressure increase.

A mean of 4.4 ablations were performed within each RA consecutively (three of four patients received six ablations per artery). In all patients, the final renal angiogram showed only discrete irregularities of the vessel wall but no flow that limited RA stenosis (Fig. 3).

On average,  $130 \pm 20$  cc of contrast medium was necessary to perform both the preplanning evaluation and complete PRD. Blood pressure reduction was resumed (Fig. 4).

The patients' weight before the procedure did not differ at the 12-month follow-up.

No peri- and postprocedural complications were observed during the 12-month follow-up.

All patients were discharged two days after the procedure.

#### Discussion

PRD has been performed mainly in patients with relatively normal kidney function. However, the evidence for over-activation of the sympathetic nervous system in renal failure dates back to 1973, when higher levels of the adrenergic neurotransmitters nor-epinephrine and epinephrine were found in circulating plasma of patients with elevated blood pressure values

or advanced renal dysfunction in the pre-dialysis stage (1, 7).

Hering et al. (6) recently reported the safety and effectiveness of PRD in 15 patients with renal hypertension and stages 3–4 CKD. We speculated that PRD could also be used in high-cardiovascular-risk ESRD patients with renal hypertension to reduce the morbidity and mortality of this hypertensive population (8).

The first concern regarding the safety of PRD in these patients is the need for reduced contrast exposure, but the PRDs were scheduled as elective procedures, thereby allowing adequate prehydration to minimize the risk of contrast nephropathy and planning angio-CT on the same day as the scheduled dialysis session. To avoid treating atrophic renal arteries, we preferentially selected patients with a short history of dialysis (five years or less).

Regarding small renal vessels (<4 mm in three of four patients), the most challenging technical issue in PRD was to achieve ablation of the predichotomous portion of the RA without causing trauma or vasospasm of the vessel wall that would preclude completion of the ablations in the same session. Before Symplicity catheter advancement in the artery, to obtain slight vasodilatation of the RA and reduce the vasospasm risk, premedication based on fenoldopam was administered 24–48 hours before the procedure, whereas nitroglycerin was administered after the selective catheterization of each RA. Subsequently, once the distal portion of the catheter is advanced to the level of RA bifurcation, we suggest avoiding turning the deflection knob

of the catheter tip to prevent injuries such as spasms and parietal dissections of the small vessel; this precaution seemed sufficient to ensure effective contact between the catheter tip and vessel wall, as indicated by the impedance value. We noticed a more rapid increase in temperature in these small vessels during the ablation than in greater diameter vessels (>4 mm). This issue was also discussed by Henring et al. (6) and may be related to the denervation catheter causing subocclusion of the thin vessels. Additionally, continuous flushing of the catheter with heparinized saline does not result in constant cooling of the wall at the level of the ablation site. Thus, frequent automatic locking of the generator before 120 s may occur, with the need to repeat the ablation at the same point several times until the total time established is reached, increasing the procedural time (mean of 60–90 s more per ablation site) (6–8).

In our cases, procedure-related complications were not observed, except for the detection of small notches at the level of the treated vessel wall on the final angiogram (Fig. 3). This finding did not differ from that in non-ESRD patients.

In all four treated patients, a mean 4-hour ambulatory blood pressure reduction of -36/-16 mmHg was obtained at the 12-month follow-up.

## Conclusion

Although renal denervation has been evaluated in selected patients with renal disease, large, multicenter trials of the effects of this procedure in large cohorts of patients with CKD have not

been performed to date. Thus, this pioneering case series that shows encouraging results will facilitate the design of further studies.

## Conflict of interest disclosure

The authors declared no conflicts of interest.

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