

EXCEPTIONAL CASE

Successful treatment of refractory hypertension with bilateral nephrectomy in a patient with chronic kidney disease stage 3

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ABSTRACT

We present a case of life-threatening refractory hypertension (rHTN) in a patient with stage 3b chronic kidney disease that was unresponsive to open surgical renal denervation (RDN) but responded to bilateral nephrectomy (BLN). Both RDN and BLN reduce the increased sympathetic activation in rHTN. However, RDN has yet to show reductions in blood pressure adequate for the average patient with rHTN, and BLN has thus far been reserved for patients with preexisting end-stage kidney disease (ESKD). Our case suggests that there are patients with rHTN that warrant consideration of BLN prior to developing ESKD.

Keywords: nephrectomy, refractory hypertension, renal denervation, sympathetic nervous system

INTRODUCTION

Uncontrolled refractory hypertension (rHTN) causes long-term vascular damage and increased mortality [1]. Advancements in antihypertensive medications have led to a significant decline in rates of rHTN over the past few decades. However, if these fail, there remain limited nonpharmacologic treatment options. Targeting the sympathetic input to the kidneys has gained attention with ongoing studies in renal denervation (RDN).

Studies prior to the emergence of antihypertensive medications demonstrated that surgical splanchnicectomy, disrupting sympathetic nerves in the thoracic and lumbar regions, was effective at substantially decreasing blood pressure (BP), but brought disabling side effects secondary to its untargeted approach [2–4]. With subsequent enhancements in the efficacy and tolerability of antihypertensive medications, including the

development of minoxidil in the 1970s, this nonspecific approach to rHTN fell out of favor [5].

More specific approaches of removing sympathetic output from the kidney focus on various means of RDN, attempting to achieve the same effect of splanchnic sympathectomy without the systemic side effects. Recent randomized sham-controlled RDN trials include SPYRAL HTN-ON MED, SYRAL HTN-OFF MED and RADIANCE-HTN SOLO [6]. While successful in lowering BP, they demonstrated on average only a 4–8 mmHg placebo subtracted reduction in systolic BP (SBP) [6]. These BP reductions would not be adequate for the average patient with rHTN. It has been proposed that the marginal success of these RDN trials is because of insufficient renal sympathetic ablation (on average as low as 40%) as well as sympathetic nerve regrowth [7, 8].

Ultimately, the best way to completely disrupt sympathetic output from the kidneys is to remove them. Several studies have

Received: 22.6.2021; Editorial decision: 20.9.2021

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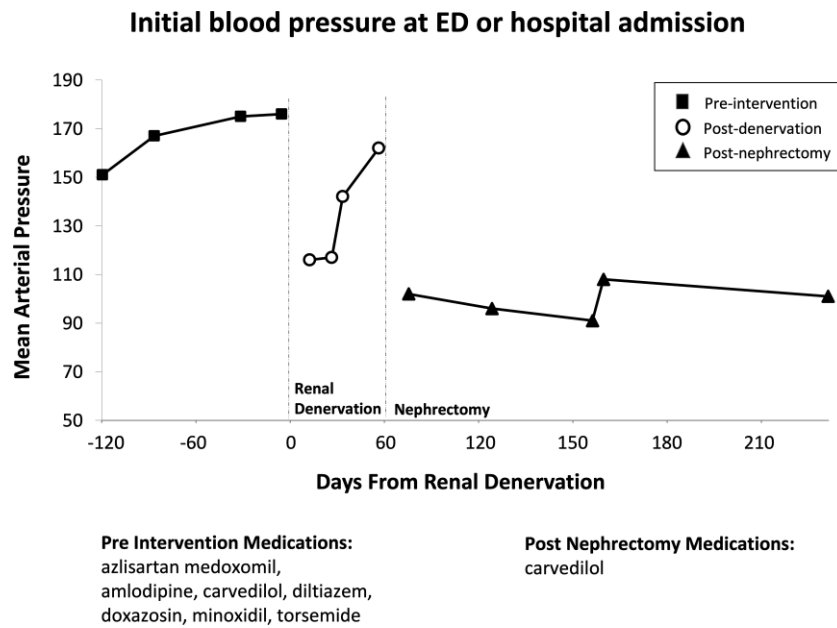


FIGURE 1: Mean arterial pressure during emergency department visits and hospitalizations before RDN, post-RDN and post-nephrectomy.

Table 1. Medications regimens for the 6 months prior to RDN

Drug class	Regimen 1	Regimen 2
Alpha-1 blocker		Doxazosin 4 mg BID
Angiotensin II receptor blockers		Azilsartan medoxomil 80 QD
Beta-1 selective vasodilator	Nebivolol 40 mg QD	
Calcium channel blockers	Amlodipine 10 mg BID, diltiazem 180 BID	Amlodipine 10 mg QD, diltiazem SR 300 QD
Combined alpha- and beta-blockers		Carvedilol 25 mg BID
Diuretic	Torsemide 20 mg BID	Torsemide 40 mg BID, chlorthalidone 25 mg QD
Renin antagonist	Aliskiren 300 mg QD	
Vasodilators	Minoxidil 20 mg TID	Minoxidil 15, 10, 15

shown that bilateral nephrectomy (BLN) is the most effective method at lowering BP in rHTN [9]. BLN thus became popular for rHTN in patients with end-stage kidney disease (ESKD) in the 1970s to lower BP, and it also improved survival and reduced neurological, ocular and cardiovascular complications [1]. Previous studies also show a consistent improvement in quality of life measures in these patients [1, 10]. Authors of several of these studies have thus argued for early nephrectomy in ESKD patients with rHTN [11].

We present a case of severe rHTN in a patient with stage 3b CKD, unresponsive to open surgical RDN (OS-RDN), who underwent BLN as a last resort to treat what we considered a life-threatening condition. This resulted in an abrupt and persistent decrease in BP.

CASE REPORT

A 43-year-old white woman with stage 3b CKD [estimated glomerular filtration rate (eGFR) 38 mL/min/1.73 m²] with a 16-year history of HTN presented with a resting SBP between 180 and 240 mmHg on maximal doses of eight different antihypertensive medications including minoxidil (Figure 1, Table 1). Her past medical history is notable for polycystic ovarian syndrome

and type 2 diabetes. Her kidney function was initially normal, but started to decline 6 years after her initial HTN diagnosis (Figure 2). HTN workup occurred with regular follow-up at a comprehensive HTN center, which excluded all secondary causes including drug screenings, urine metanephrines, renal magnetic resonance imaging (MRI) and renin/aldosterone ratios. (Table 2). There were no issues with medication adherence and she was observed taking medications in clinic but consistently remained hypertensive, with the lowest measurement 172/90. Despite being trialed on several different home regimens, she continued to have frequent hospitalizations and ED visits for symptomatic HTN, averaging one every 3–4 weeks. The only regimen that controlled her BP to 130s systolic was the combination of intravenous calcium channel blockade and beta-blockers.

She initially underwent bilateral OS-RDN by severing all neural tissue entering the kidney. Briefly, this was done by retroperitoneal exploration of both kidneys with complete dissection of tissue around the renal artery, vein and ureter, similar to what would be done for living donor nephrectomy. Bilateral renal vein renin levels were measured before and after OS-RDN and were 9.1, 7.8 ng/mL/h and 0.7, 1.4 ng/mL/h, respectively. Despite an initial drop in BP to 140/70 mmHg on only two medications, within 4 weeks of OS-RDN, her BP rose to 240/120 despite reinitiating her pre-OS-RDN medications, and she was again symptomatic.

Table 2. Workup of secondary causes of hypertension

Potential causes of HTN	Patient workup
Congenital adrenal hyperplasia	11-beta-hydroxylase levels normal (8)
Cushing syndrome	Morning cortisol was not elevated (9, 8, 3) Dexamethasone suppression test normal (8)
Elicit substance use	All urine drug screening negative
Fibromuscular dysplasia	MRI angiogram without evidence of stenosis, aneurysmal dilation or beading (1)
Inaccurate office readings	The patient kept detailed logs of her home BP readings
Medication nonadherence	Patient with consistent follow-up with multiple providers, direct observed medication therapy in clinic, filled all medications regularly
Obstructive sleep apnea	Wears CPAP with good adherence per machine logs
Pheochromocytoma	24 h urine metanephrines normal (8, 3)
Primary hyperaldosteronism	Serum renin aldosterone ratio normal (9, 0) Systemic renin still low post-procedure
Renal artery stenosis	Renal ultrasound with Dopplers negative for RAS (4, 0)
Renal disease	Serum creatinine level and GFR normal for several years after HTN dx Negative/normal: ANA, C3, C4, hepatitis B and C and phospholipase A2 receptor antibody (8)
Thyroid disorders	TSH and T4 within normal limits (7, 6, 3, 1, 0)

(Numbers) indicate number of years prior to RDN that this workup was completed. CPAP, continuous positive airway pressure; RAS, reninangiotensin system; ANA, anti-nuclear antibody; TSH, thyroid-stimulating hormone.

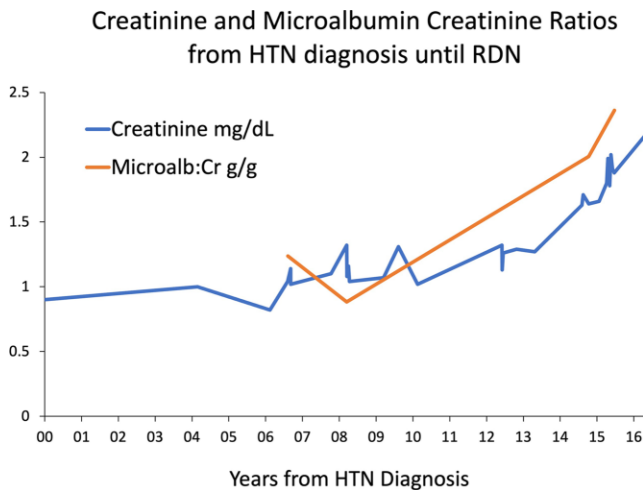


FIGURE 2: Trend in serum creatinine and urine microalbumin creatinine ratio from time of diagnosis of HTN to RDN 16 years later.

At this point, BLN was proposed as the only remaining option. Understanding the need for renal replacement therapy (RRT) following BLN, the patient consented to proceed. BLN was done in retroperitoneal approach through the same incisions as the OS-RDN. Follow-up BPs have persistently been in the 130/80 mmHg range on only carvedilol 12.5 mg twice daily (Figure 1).

DISCUSSION

Pre-ESKD BLN for rHTN has not been previously reported, and there are only limited case reports of surgical RDN from one institution in 1935 [12]. Decreasing sympathetic nerve input to the kidneys for BP control is supported by the effectiveness of alpha b-adrenergic blockers in many patients, splanchnic denervation observations as early as the 17th century, several BLN studies in ESKD or post-renal transplant, as well as catheter RDN in several animal studies [13].

Advancements in endovascular RDN are becoming more effective, but still only lower SBP by 4–8 mmHg placebo subtracted [7]. Our case failed to respond to OS-RDN despite complete dissection of all extramural autonomous nerves and surrounding connective tissue. This suggests that the effects of RDN of any form may be limited. Our patient’s BP initially appeared controlled following OS-RDN, but after 4 weeks, she re-presented to the hospital with uncontrolled HTN. One explanation for this, and one of the growing concerns about RDN, is renal nerve regeneration, which we were able to demonstrate by pathologic examination of the kidneys after nephrectomy (data not shown). Animal studies in sheep show both anatomical and functional regeneration of the renal nerves in less than a year following RDN [14]. While we do not have data for nerve regeneration in human RDN, previous human studies with transplanted kidneys showed evidence of renal nerve regeneration starting at 4 weeks posttransplant [15].

BLN for rHTN for patients on RRT was initiated in the 1970s. Almost 50 years later, despite enormous improvements in medications, there is still a role for this procedure. Requiring this in a patient pre-ESKD resulting in dialysis dependence was an extreme, but we felt life-saving, requirement to prevent stroke and other organ failure. She has been referred for transplantation. Advances in catheter ablation are encouraging, but long-term efficacy will need to be assessed. Currently, most RDN studies have not followed patients beyond a couple of months. This case raises concerns that long-term efficacy of RDN might face more challenges than solely improvement of technique.

CONFLICT OF INTEREST STATEMENT

G.L.B. has been a consultant with Merck, Bayer, Vascular Dynamics, KBP Biosciences, Ionis, Alnylam, Astra Zeneca, Quantum Genomics, Horizon and Novo Nordisk. He is on Research support–Steering committees of trials—Bayer, Vascular Dynamics, Quantum Genomics, Alnylam, Novo Nordisk—and is an editor at the *American Journal of Nephrology*.

All other authors have no conflict of interest or disclosures to report.

PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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