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Reduction of Blood Pressure Following After Renal Artery Adventitia Stripping During Total Nephroureterectomy: Potential Effect of Renal Sympathetic Denervation

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Case series
Patients: Male, 85 • Male, 89
Final Diagnosis: Essential hypertension
Symptoms: High blood pressure
Medication: Anti-hypertensive agents
Clinical Procedure: Operation
Specialty: Cardiology and Hypertension

Objective: Unusual or unexpected effect of treatment

Background: Catheter-based renal sympathetic denervation has been reported to be effective for treatment resistance hypertension in Australia and Europe. However, in the blinded SYMPLICITY HTN-3 trial, renal denervation did not achieve a significant decrease in blood pressure (BP) in comparison to sham controls. There have been various discussions on the factors that influenced this result.

Case Reports: Two men on antihypertensive therapy underwent unilateral radical nephroureterectomy for cancer of the renal pelvis. When the renal artery adventitia was stripped and cauterized just before renal artery ligation, the measured BP of the 2 men increased after stripping adventitia and decreased gradually after cauterization of the renal artery. This was presumably due to removal of renal artery sympathetic nerves, similar to the mechanism of catheter-based renal sympathetic denervation, although anesthesia, fluid infusion, and/or mesenteric traction may have had an influence.

Conclusions: A similar strategy involving thoracolumbar sympathectomy was reported about 50 years ago. The clinically significant blood pressure reduction in these patients suggests renal denervation is effective.

MeSH Keywords: Hypertension • Nephrectomy • Sympathectomy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/908891

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Background

Hypertension is a very common lifestyle-related disease, and it is estimated that approximately 43 million persons have hypertension in Japan [1]. The prognosis of resistant hypertension is poor, and its management is difficult. In some patients, acceptable control of the office blood pressure (BP) and/or home BP cannot be achieved despite the use of multiple antihypertensive agents. In Australia and Europe, it has been reported that catheter-based renal sympathetic denervation [2] is effective for resistant hypertension [3–5]. As a mechanism, suppression of sodium absorption in the renal tubule and sympathetic hyperactivity to the whole body were considered. SYMPLICITY HTN-3 renal denervation trial (SH-3) randomized patients into renal denervation or sham procedure [6]. Catheter-based renal denervation was performed according to the Instructions for Use of the Symplicity™ RDN system following renal angiography to confirm suitable anatomy. However, this controlled trial did not demonstrate significant reduction of BP with renal denervation compared to sham treatment [6], although there has been considerable discussion of this outcome [7].

Cancer of the renal pelvis is treated by nephroureterectomy. For intraoperative management of the renal artery, the peri-arterial tissues containing renal sympathetic nerves [8] are stripped to expose the vessel and it is ligated after cauterization. However, there have been no reports about the detailed changes of BP during the process of stripping the renal artery adventitia. Based on the expected effect of renal denervation, we hypothesized that careful intraoperative monitoring might be able to detect a decrease of BP when the peri-arterial tissues are carefully stripped, and the renal artery is cauterized. Accordingly, we performed such monitoring in 2 patients undergoing nephroureterectomy.

Case Reports

Case 1

An 85-year-old male underwent curative surgery for left renal pelvic cancer. His past history included hypertension and he was taking an angiotensin II receptor blocker. But his BP was not under control. Laparoscopic left nephroureterectomy was performed under general anesthesia, with the adventitia around the renal artery (which probably contains renal sympathetic nerves) being stripped off and cauterized carefully just before renal artery ligation (Figure 1). The noninvasively measured BP increased after the renal artery adventitia was stripped, while the pulse rate was unchanged. Then BP decreased gradually after cauterization of the renal artery, although the pulse rate still showed no change (Figure 2). The noninvasive BP increased from 93/63 mmHg to 120/70 mmHg after stripping of the renal artery adventitia, while the pulse rate changed from 62 bpm to 64 bpm. After cauterization of the adventitia, the BP gradually decreased from 98/61 mmHg to 78/52 mmHg and the pulse rate changed minimally from 62 bpm to 63 bpm.

Case 2

An 89-year-old male with resistant hypertension was taking 3 antihypertensive agents (a calcium channel blocker, an angiotensin II receptor antagonist, and a diuretic). He underwent open right nephroureterectomy under general anesthesia for renal pelvic cancer, with the adventitia around the renal artery being stripped off and cauterized as in Case 1. The invasively measured BP increased after stripping of the renal artery adventitia and then decreased gradually again after cauterization, as was noted in Case 1 (Figure 3). The invasive BP increased from 121/50 mmHg to 133/53 mmHg after stripping of the renal artery adventitia, while the pulse rate changed minimally from 75 bpm to 76 bpm. After cauterization of the adventitia, the BP gradually decreased from 133/53 mmHg to 98/47 mmHg and the pulse rate changed from 74 bpm to 71 bpm.

Discussion

Both patient cases reported here underwent unilateral radical nephroureterectomy for renal pelvic cancer, during which the renal artery adventitia was stripped off and cauterized. Monitoring revealed that the BP initially increased during these procedures and subsequently showed a gradual decrease. It is possible that these changes of BP were related to alteration of renal sympathetic activity when the peri-arterial tissues were stripped off and cauterized. Although there were fewer nerves surrounding the renal artery in the distal segments compared with the proximal and middle segments, the mean distance from renal artery lumen to nerve location is least in the distal segments compared with the proximal and middle segments [9]. It was possible that all these nerves had been removed by stripping and cauterizing.

The autonomic nervous system (sympathetic and parasympathetic systems) regulates BP in coordination with the renin-angiotensin system. Sympathetic activity is controlled by the rostral ventrolateral medulla. Direct evaluation of the sympathetic nerve system in humans can be performed by recording muscle sympathetic nerve activity and isotopic assessment of norepinephrine spillover [10], but these are invasive methods. Analysis of heart rate variability on the ECG has been used for noninvasive evaluation of sympathetic activity following renal denervation, but this method cannot be employed during surgery. Thus, the BP changes noted in our 2 patients were considered to be caused by interruption of the afferent and

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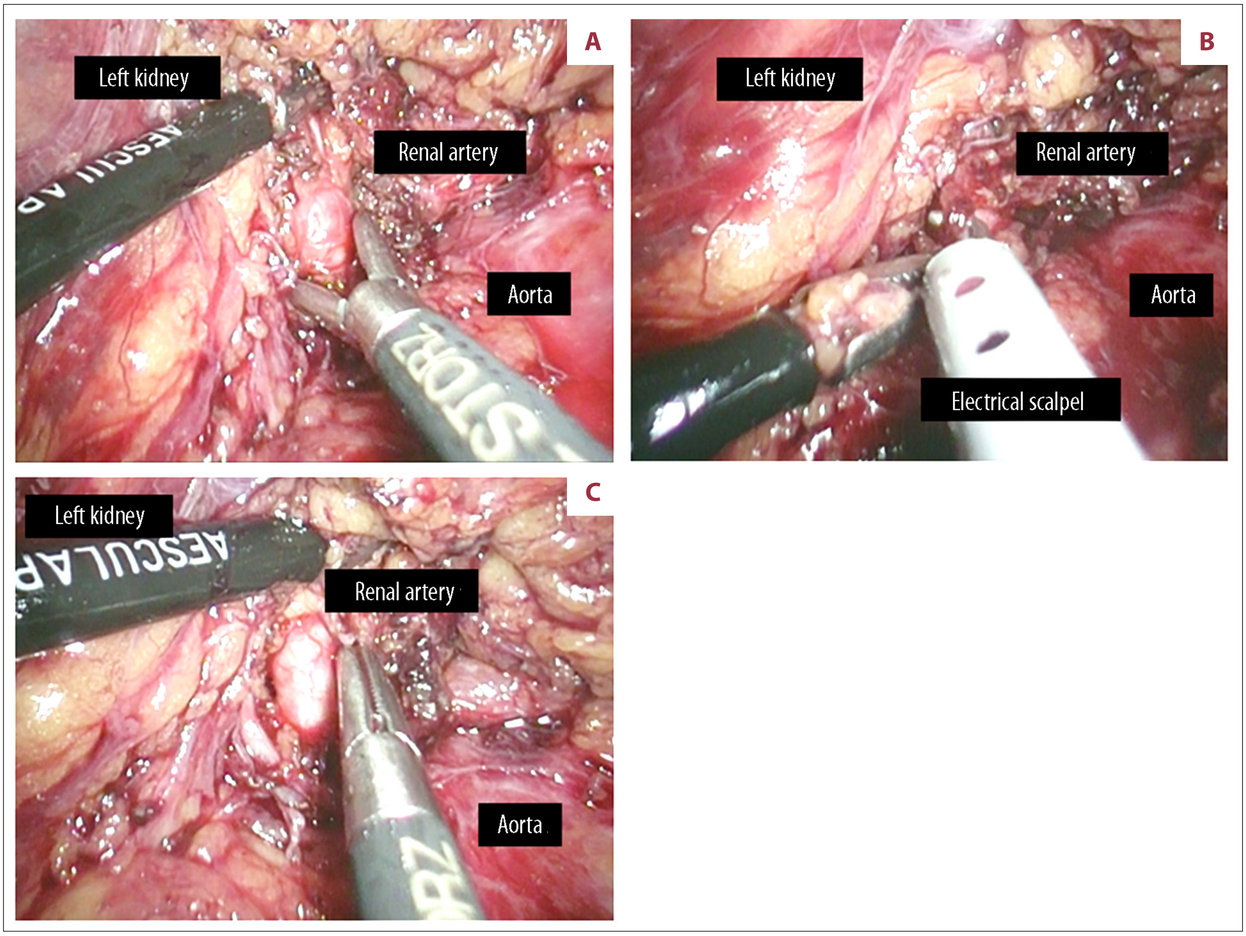

Figure 1. Renal artery findings during laparoscopic nephroureterectomy. (**A**) The adventitia of the renal artery was exposed and stripped off with peeling forceps. Renal nerves are seen in tissues around the renal artery. (**B**) The adventitia of the renal artery was carefully cauterized using an electrical scalpel. (**C**) The adventitia was dissected to expose the renal artery.

efferent renal sympathetic nerve pathways, but it is difficult to prove that an effect on sympathetic nerves was involved.

When the renal artery was stimulated by stripping of the peri-arterial tissues, the BP increased transiently in both patients. An increase of renal sympathetic activity leads to increased renin secretion, enhanced sodium reabsorption, and elevation of BP as a result of decreased renal blood flow [11–13]. In addition, intraoperative maneuvers involving the renal artery might have promoted renin secretion by reducing blood flow to the kidney, thus increasing BP. Furthermore, electrical stimulation of the renal artery causes an increase of local renal arterial pressure [14], suggesting that direct renal artery stimulation might have increased autonomic activity and led to elevation of BP.

The BP decreased after the tissues around the renal artery had been stripped and cauterized, possibly because stimulation by the procedure had ceased. However, the base BP was lower after the procedure than before surgery and this suggests that the decline was not only due to the end of direct renal artery stimulation. In animal studies, unilateral activation of the renal sympathetic nervous system can increase systemic sympathetic activity and unilateral renal sympathetic denervation may not decrease the systemic BP, so it is considered that bilateral renal denervation is required to reduce BP [14]. However, catheter-based denervation is conducted inside the renal artery lumen, and it is possible that removal of sympathetic nerves from the peri-arterial tissues may have a different effect. In the present 2 cases, the renal artery adventitia was macroscopically stripped and cauterized, which may have achieved complete denervation. Accordingly, if complete renal denervation could be achieved by a catheter-based procedure, unilateral treatment might reduce BP.

Other possible causes of BP changes during surgery include the use of vasopressors, anesthesia, fluid infusion, mesenteric traction, and dehydration. In the present case study of 2 patients, additional administration of vasopressors and anesthetics or fluid infusion were not conducted at the time of stripping and cauterization of the tissues around the renal

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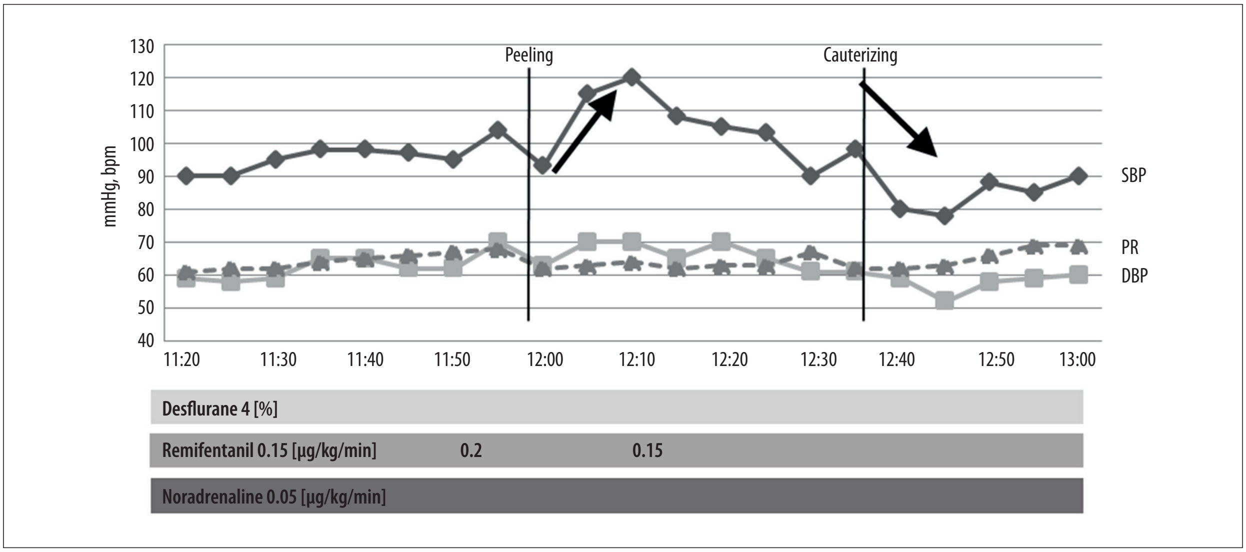

Figure 2. Changes of BP and pulse rate during surgery in Case 1.

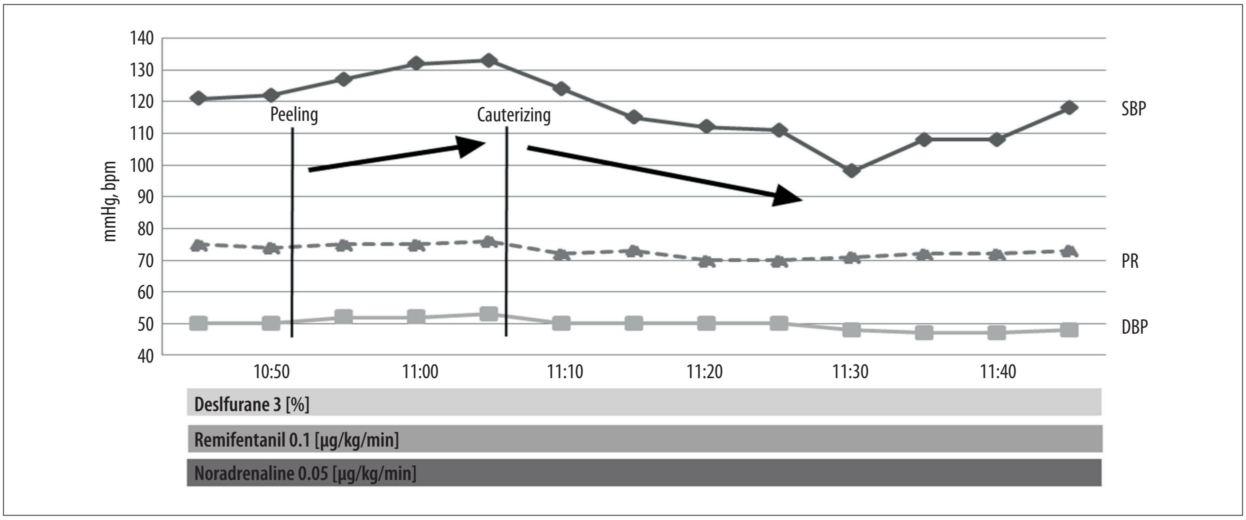

Figure 3. Changes of BP and pulse rate during surgery in Case 2.

artery. There was also no evidence of mesenteric traction syndrome, which is characterized by facial flushing, tachycardia, and low BP. Accordingly, the potential influence of these factors on the changes of BP was ruled out.

Evaporation may induce dehydration when organs are exposed to air intraoperatively, but the duration of surgery was too short for this to be likely to influence BP in our patients.

It appeared in both cases that the decrease in BP after cauterization was transient followed by some BP recovery to close to baseline. Other sympathetic nervous system and renin angiotensin system might be supplemented.

The concept of renal denervation for treatment of hypertension is not new. In the 1950s, surgical renal denervation was advocated for management of hypertension [15], and sympathectomy [16] was conducted. Of course, this was too invasive for routine antihypertensive treatment. Moreover, those studies [15,16] (as with recent clinical trials) did not involve careful evaluation of the BP response such as by ambulatory monitoring or assessment of the effect of sham surgery, so it is unclear whether sympathetic denervation resulted in a significant decrease of BP.

Recently, a clinical study of ultrasound-based renal denervation in patients with resistant hypertension was initiated in Japan and Korea (REQUIRE; ClinicalTrials.gov Identifier: NCT02918305). The ultrasound system used in the study (Paradise system) can cauterize the entire vessel lumen, after which the vessel is cooled by a balloon to avoid excessive arterial wall heating and tissue damage [17]. Prospective open label clinical studies

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have demonstrated the safety and efficacy of renal denervation in patients with resistant hypertension [18,19]. Moreover, the REDUCE HTN REINFORCE study using the Vessix system (ClinicalTrials.gov Identifier: NCT02392351) and the SPYRAL HTN OFF-MED trial using the Symplicity Spyral catheter [20] have been initiated to assess renal denervation for hypertension.

However, the number of eligible patients enrolled in the REQUIRE trial so far is quite small and patient recruitment is challenging [21]. Based on the results of SH-3 [6], renal denervation is generally seen as being of doubtful value for hypertension and patient enrollment also appears slow in the other studies. In order to complete enrollment in these studies, positive results regarding renal denervation are needed. In this context, the present observations may suggest the clinical significance of renal denervation for decreasing the BP.

In the present two cases, operative findings indicated that the renal artery has thick walls and dense surrounding tissues. Therefore, if intraluminal renal denervation is performed, the nerves outside the renal artery will not be cauterized unless very strong voltage is applied, but this could lead to vascular injury that may result in dissection or stenosis. It is possible that the catheter used in SH-3 might not have cauterized the peri-arterial nerves, which may help to explain the less than significant BP reduction in that study [6]. The Paradise system protects the vessel wall with its cooling balloon and the ultrasound penetrates deeper into the tissue [17,22], so it may achieve more potent BP reduction.

In our patients, we removed the kidney immediately after resection of the renal artery; nephrectomy involves significant invasion, making it difficult to evaluate the long-term BP lowering effect of renal denervation. In normal rats, it has been reported that afferent renal sympathetic denervation by bilateral rhizotomy inhibited salt sensitive hypertension [23].

After bilateral surgical renal denervation, it would be interesting to investigate whether BP was increased or not after electrical stimulation of the renal artery in accordance with the method of Chinushi et al. [14]. In humans, it is not possible to conduct bilateral surgical RDN to investigate its BP-lowering effect, but the results of further clinical trials of catheter-based renal denervation are awaited.

Conclusions

In the 2 patient cases reported here, reduction of BP might have occurred due to disruption of the sympathetic nerves around the renal artery, a similar mechanism to the antihypertensive effect observed in previous trials of catheter-based renal denervation. Although the findings might have been incidental, the change of BP was clinically significant, and we considered it to represent the effect of renal denervation.

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