Effect of Renal Nerve Denervation for Resistant Hypertension in Thai Patients: A Report of the First Cases Series in Thailand

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Background: *Hypertension is a major contributor to death. A significant portion of the patients is still in resistant hypertension with current medical treatment. Renal nerve denervation can reduce sympathetic activity, and subsequently reduce BP in western population.*
Objective: *To evaluate the effect of renal nerve denervation in treatment of resistant hypertension in Thai patients.*
Material and Method: *The present study is a case series of the first four Thai patients who underwent renal nerve denervation at Faculty of Medicine Siriraj Hospital. All patients had resistant hypertension. Baseline medical records, including demographic data, baseline systolic and diastolic blood pressure (BP), ambulatory BP monitoring, number and dose of anti-hypertensive medications before and after renal nerve denervation, were recorded. Patients were followed-up at 1 month, 3 month and 6 months after the procedure.*
Results: *Patients were taking antihypertensive medications ranging from 5 to 8 types of drug classes, but in all cases, their blood pressure was still not under control at baseline range from 160-190 of systolic BP and 100-120 mean BP. One of the patients had a history of hemorrhagic stroke as a consequence of un-control hypertension. All of them had blood pressure reduction immediately at the end of the first 24 hrs, and this was sustained until follow-up at 3-6 months. The mean of systolic BP reduction is 35.2± 9.9 mmHg at 3-months follow-up. The mean reduction of the number of anti-hypertensive medications was 3.5±3.0 at 3-month follow-up.*
Conclusion: *The authors found that the percutaneous renal nerve denervation was very effective in blood pressure reduction in these first four cases of Thai patients with resistant hypertension.*

Keywords: *Resistant hypertension, Renal nerve denervation, Blood pressure reduction, Sleep apnea*

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Hypertension is a major contributor to death worldwide. Every 20/10 mmHg increase in blood pressure correlates with a doubling cardiovascular (CV) mortality[1]. Keeping blood pressure under control is the primary target both of primary and secondary prevention in reducing the CV events. A portion of patients is still not able to get BP under control with current medical therapy. Resistant hypertension defined as BP above the goal (>140/90 mmHg) despite compliance with full doses of 3 antihypertensive drugs of different classes, or drugs from > 4 antihypertensive drug classes regardless of blood pressure[2]. Resistant hypertension is present in about 9-12% of the treated hypertensive patients[2,3]. These patients will be subsequently confronted with complications of hypertension, such as hemorrhagic stroke, myocardial infarction, heart failure and renal failure. Increased sympathetic activity has been shown to correlate with hypertension[4]. Surgical sympathectomy has been proved to be effective treatment of hypertension[5,6], but it is a very invasive treatment. It is rarely performed in current practice. Percutaneous renal sympathectomy/ renal denervation has been showed to be technically feasible, and resulted in blood pressure reduction in

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western population[7,8].

The authors firstly evaluate the effect of percutaneous renal nerve denervation in treatment of resistant hypertension in Thai patients.

Material and Method

The present study was a case series of four patients on whom was first performed a percutaneous renal nerve denervation at Faculty of Medicine Siriraj Hospital, Mahidol University. The inclusion criteria in selecting the patients for percutaneous renal denervation included resistant hypertensive patients whom age older than 18 year old. The patients was excluded if they had chronic renal insufficiency (eGFR <45 ml/min), patients with significant valvular heart disease, patient with a history of myocardial infarction or stroke within 6 months, and patient in whom had been placed a pacemakers or automatic implantable cardioverter defibrillators (AICD) placement. All of these four patients underwent the procedure as the indication of resistant hypertension. Informed consent for the procedure and the case record form were obtained. Their baseline demographics, including age, sex, number and dose of antihypertensive drugs and previous complications resulting from un-controlled hypertension were recorded. Baseline systolic BP, diastolic BP, mean arterial BP, serum creatinine were recorded. Two of the patient had undergone 24-hour ambulatory blood pressure measurement at baseline and at 6 months after the procedure.

Patients were local anesthetized and prepared as for standard catheterization technique. A 6F sheath (Terumo® Inc Tokyo, Japan) inserted into right femoral artery. A 6F pigtailed inserted and positioned at the bony landmark of T12, L1 where the renal artery is located. Aortogram performed to reveal all renal arteries and its variation. LIMA 6F guide engaged into the renal artery. A simplicity catheter (Medtronic Inc, Minneapolis, MN, USA) was introduced into each renal artery via femoral access. Radiofrequency (RF) ablation was applied lasting up to 2 minutes each time and of 8 watts or less to obtain at least five ablations, separated both longitudinally and rotationally within each renal artery. During ablation, the catheter system monitored tip temperature and impedance, with altering of radiofrequency energy delivery in response to a predetermined algorithm. We did the RF ablation in all of the renal arteries sized more than 4 mm and all in the same setting.

Patients were followed-up at 1 month, 3 months and 6 months after the procedure. The Siriraj Institutional Review Board approved the study.

Statistical analysis

Continuous variables such as systolic blood pressure , diastolic blood pressure, mean arterial blood pressure, number of antihypertensive drugs are displayed as mean $\pm$ SD. Data were analyzed with SPSS Statistics v. 13.0.

Results

Four of the Thai resistant hypertension patients who had undergone percutaneous renal nerve denervation were recruited into this cases series. The first patient was a 46 year-old female with impaired fasting blood sugar, obstructive sleep apnea and resistant hypertension. She had taken Losartan 100 mg/day, Amlodipine 10 mg/day, Atenolol 50 mg/day, Doxazocin 12 mg/day, hydralazine 300 mg/day and hydrochlorothiazide 25 mg/day but her blood pressure remained at 160/80 mmHg. Her baseline 24-hour ambulatory blood pressure measurement was showed in Fig. 1. After renal nerve denervation, her systolic BP dropped to 150 mmHg, her mean arterial blood pressure dropped from 110 mmHg to 90 mmHg

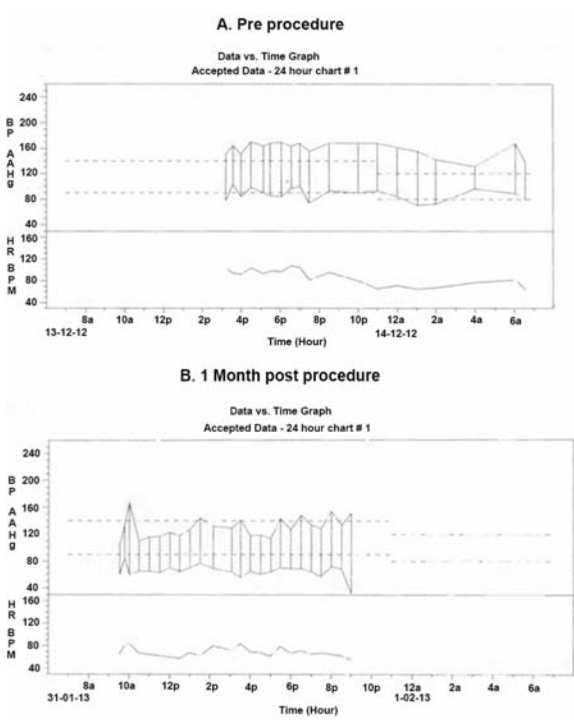

Fig. 1 24 hour ambulatory blood pressure measurement before (A) and at 1 Month after (B) the renal nerve denervation procedure in patient 1.

while antihypertensive drugs were reduced from 6 to 5 drugs. These benefits were sustained at 6 months as her systolic BP dropped to 130 mmHg with mean arterial BP 85 mmHg while anti-hypertensive drugs were reduced to 4 drugs. This patient has a history of sleep apnea. She felt her sleep had improved. Her sleep test after RDN showed apnea/hypoxia index (AHI index) at 41 per hour. The other three patients had similar response for blood pressure reduction as described in Table 1. The second patient has been followed-up for only 5 months. He was admitted to a private hospital after a fall and developed fatal subdural hematoma. His blood pressure on admission was at 100/60 mmHg. The fourth patient had significant reduction of her blood pressure in the first 24 hours. Her antihypertensive drugs were decreased from 8 to 3 drugs. She was discharged on three antihypertensive drugs but had to be re-admitted within 1 week after the procedure, due to hypotension. She did well after stopping all of anti-hypertensive drugs.

Two of these patients had fasting blood glucose and HbA1C before and after RDN. Both of these patients did not have any significant decline in either fasting blood glucose or HbA1C after RDN.

The pattern of the systolic BP reduction, mean arterial reduction and number of antihypertensive drugs is shown in Fig. 2-4, respectively. The mean reduction of systolic blood pressure was 35$\pm$10.8 mmHg at 1 month, and 35.2$\pm$9.9 mmHg at 3 months. The mean reduction of mean arterial blood pressure was 15.1$\pm$7.9 mmHg at 1 month and 16.2$\pm$5.5 at 3 months. The number of antihypertensive drugs was decreased to 1.7$\pm$1.2 at 1 month and 3.5$\pm$3.0 at 3 month. None of these patients had any complication related to the procedure.

Discussion

The present study has shown that the percutaneous renal denervation is feasible and very effective blood pressure reduction in Thai patients. The effect of blood pressure reduction was sustained at 6 months. Even though the antihypertensive drugs use cannot all be terminated, the most important point is that all of the patients' blood pressure is reduced below 140/90 mmHg. This is similar to the SIMPLICITY HTN-2 report that in the renal nerve denervation group (RDN group) 90% of the patients had systolic BP >160 mmHg. At 6-month after RDN, only 18% of the patients had systolic BP >160 mmHg[8]. The reduction of blood pressure and antihypertensive drugs was started slightly during the first 24 hours but the effect of RDN was clearly noted at 1 month.

The sympathetic innervation of the kidney is achieved through a dense network of postganglionic neurons that innervate the kidney[9]. Renal sympathetic nerve activation increases noradrenalin production for nerve ending. When it activated, beta1 adrenergic receptors increase rennin secretion. Through the alpha one receptor, it increases sodium and fluid reabsorption, renal vasoconstriction and decrease renal blood flow. The afferent renal sympathetic innervation also sending the signals travels to the renal cardiovascular center in the CNS. When it activated, it promoted vasopressin and oxytocin release, regulated systemic vascular resistance and blood pressure control. In the patients with chronic over-stimulation of renal sympathetic activity, RDN will decrease sympathetic innervation, which eventually decrease rennin secretion, decrease water and sodium retention and increase renal blood flow.

Muscle sympathetic nerve activity (MSNA) and renal norepinephrine (NE) spill over can represent central sympathetic activity. Schlaich et al, measured the MSNA and renal NE spill over before and after RDN[10]. He found that there was 27% reduction of MSNA together with 20 mmHg of systolic BP and 17 mmHg of diastolic BP at 1 month. The effect of RDN continued at 12 month as demonstrated by 66% reduction of MSNA together with 34 mmHg of systolic BP and 26 mmHg of diastolic BP. The renal NE spill over was three times higher than normal at baseline. After RDN, renal NE spill over was reduced 48% from the left kidney and 75% from the right kidney. Plasma rennin activity was reduced by 50% and improved in renal blood flow from 719 to 1,126 ml per minute after RDN.

The mean systolic blood pressure reduction in the present study is 35 mmHg which is similar to in the SIMPLICITY HTN-2, in which the mean reduction of office systolic BP is 32 mmHg. Pathological increase activation of sympathetic nervous system not only resulted in resistant hypertension. There was reported recently the correlation of chronic over stimulation of sympathetic nervous system with left ventricular hypertrophy, impaired fasting blood sugar, sleep apnea. One of our patients had history of sleep apnea. After RDN, she felt her sleep was better. Unfortunately, she did not have a sleep test before the RDN. Her sleep test after RDN showed apnea/hypoxia index at 41. Witkowski et al reported[11] a tendency of improvement obstructive sleep apnea severity in 8 of 10 patients after RDN. It is postulated that chronic fluid accumulation may underlie the high prevalence of

Table 1. Clinical characteristics, co-morbidities, blood pressure measurements, number and doses of antihypertensive drugs before and at 3 months after the renal nerve denervation in 4 patients

Pt	Age (years)	Co-mobid	Antihypertensive before	BP before (mmHg)	Antihypertensive after	BP after (mmHg)
1	47	IFG OSA	Losartan 100 mg/d HCTZ 25 mg/d Amlodipine 10 mg/d Atenolol 25 mg/d Doxazosin 12 mg/d Hydralazine 100 mg/d	161/81	Losartan 100 mg/d Amlodipine 10 mg/d Atenolol 25 mg/d Doxazosin 8 mg/d	131/61
2	71	DM HTN CAD	Ramipril 10 mg/d Amlodipine 10 mg/d Atenolol 50 mg/d Doxazosin 2 mg/d Hydralazine 300 mg/d	173/66	Amlodipine 10 mg/d Atenolol 50 mg/d Hydralazine 150 mg/d	141/56
3	80	CAD s/p CABG HTN Cholesterol	Losartan 100 mg/d Atenolol 50 mg/d Enalapril 40 mg/d HCTZ 25 mg/d	159/75	Losartan 100 mg/d Atenolol 50 mg/d Enalapril 40 mg/d	136/71
4	41	Heamorrhagic stroke	Furosemide 80 mg/d Losartan 100 mg/d Carvedilol 50 mg/d Manidipine 40 mg/d Hydralazine 200 mg/d Spironolactone 50 mg/d Alphamethyldopa 2000 mg/d Minoxidil 10 mg/d	163/96	-	125/94

BP = blood pressure; IFG = impaired fasting glucose; OSA = obstructive sleep apnea; DM = diabetic mellitus; HTN = hypertension; CAD = coronary artery disease; CABG = coronary artery bypass graft; HCTZ = Hydrochlorothiazine

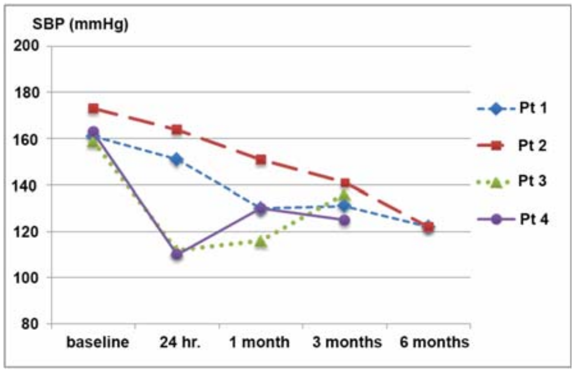

Fig. 2 Pattern of systolic blood pressure reduction at 24 hr, 1 month, 3 months and 6 months after renal nerve denervation.

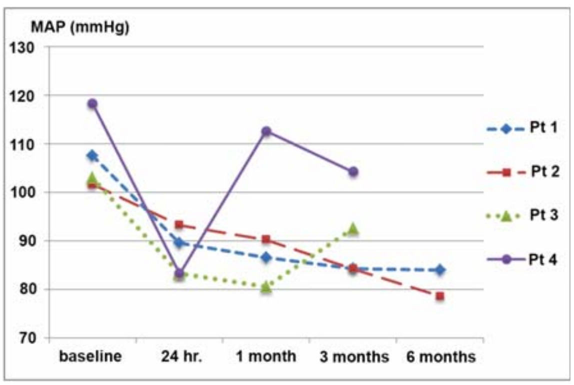

Fig. 3 Pattern of mean arterial blood pressure reduction at 24 hr, 1 month, 3 months and 6 months after renal nerve denervation.

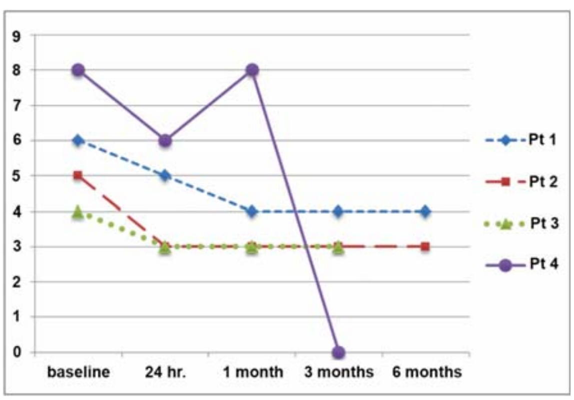

Fig. 4 Pattern of number of antihypertensive drugs reduction at 24 hr, 1 month, 3 months and 6 months after renal nerve denervation.

obstructive sleep apnea in patients with resistant hypertension. RDN decreased activation of renal sympathetic innervation and will decrease rennin secretion, decrease sodium and fluid reabsorption, and increase renal blood flow. By reducing total body fluid retention especially peri-pharyngeal, fluid accumulation may alleviate the severity of obstructive sleep apnea.

There is a correlation between sympathetic over-activity and insulin resistant and hyperinsulinemia[12,13] showed a reduction of fasting plasma glucose, insulin level and C-peptide at 3 months after RDN in 37 patients, but the level of HbA1C did not change compared to baseline. The combination of sympathetic nerve inhibition, reduction of noreadrenalin release and direct cellular effect may explain the improvement of glycemic control after RDN[14]. It has been reported that the increase in forearm noreadrenaline release together with reduced blood flow can induce acute insulin resistance. Sympathetic activation may impair ability of the cell to transport glucose across its membrane. In this small, first case series in Thai patients, the authors did not observe any significant difference in fasting blood glucose and HbA1C after RDN. This could be due to a very small sample size. In addition, the glycemic control has multiple causes that can affect the glucose metabolism. Further, well designed studies will need to confirm these specific findings in Thai patients.

In conclusion, from our early experience of RDN in Thai patients, the authors found that RDN is very effective in reduction of blood pressure toward the treatment goal with a minimal risk in the Thai patients with resistant hypertension.

Study limitation

This is a small case series of four patients. All of the percutaneous renal denervation treatment was done as result of resistant hypertension. Even the effect of RDN for blood pressure reduction was similar to the Western populations. The authors will require a larger scale of patients with longer term of follow-up.

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Potential conflicts of interest

None.

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การตอบสนองต่อการรักษาโดยการจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำเพื่อรักษาความดันโลหิตสูงผ่านสายสวนในคนไทยที่มีภาวะความดันโลหิตสูงแบบดื้อยา: การรักษาโดยการจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำครั้งแรกในคนไทย

ณัฐวุฒิ วงษ์ประภารัตน์, ดำรัส ตรีสุโกศล, วีรนุช รอบสันติสุข, พีระ บูรณะกิจเจริญ, ชุณหเกษม โชตินัยวัตรกุล, รุ่งทิวา พงษ์อัคคศิรา

ภูมิหลัง: *ภาวะความดันโลหิตสูงเป็นสาเหตุสำคัญที่นำไปสู่การเสียชีวิตในผู้ป่วยคนไทยพบว่าจำนวนหนึ่ง มีภาวะความดันโลหิตสูงแบบดื้อยาโดยได้รับยาควบคุมความดันโลหิต 3-4 ชนิด แล้วยังไม่สามารถควบคุมระดับความดันโลหิตที่สูงได้ การรักษาโดยใช้การจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำ (renal nerve denervation) สามารถลดการทำงานของระบบประสาทอัตโนมัติ (sympathetic activity) นำไปสู่การลดลงของความดันโลหิตจากการศึกษาในผู้ป่วยชาวตะวันตก อย่างไรก็ดีขณะนี้ยังไม่มีข้อมูลของการรักษาแบบนี้ในคนไทย*

วัตถุประสงค์: *เพื่อทำการศึกษาผลการจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำ (renal nerve denervation) ในการรักษาคนไทยที่มีภาวะความดันโลหิตสูงแบบดื้อยา (resistant hypertension)*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบ case series ในการรักษาคนไทยที่มีภาวะความดันโลหิตสูง แบบดื้อยาที่ได้รับการทำการจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำ (renal nerve denervation) ที่คณะแพทยศาสตร์ศิริราชพยาบาล ซึ่งมีการรักษาวิธีนี้เป็นแห่งแรกในประเทศไทย ผู้ป่วยทั้งหมดมีภาวะความดันโลหิตสูงแบบดื้อยา ก่อนการทำการรักษาโดยใช้การจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำ ผู้ป่วยจะได้รับการบันทึกข้อมูลพื้นฐานบันทึกความดันโลหิตทั้งตัวบนและตัวล่าง (systolic, diastolic blood pressure) การวัด ambulatory blood pressure แบบ 24 ชม. และได้รับการบันทึกข้อมูลของยาลดความดันโลหิตทั้งขนาดและจำนวนยาลดความดันโลหิต ทั้งก่อนและหลังการทำ renal nerve denervation การศึกษานี้จะติดตามผู้ป่วยที่ 1 เดือน 3 เดือน และ 6 เดือน หลังจากทำหัตถการ*

ผลการศึกษา: *ผู้ป่วยทั้ง 4 รายเป็นผู้ป่วยที่มีภาวะความดันโลหิตสูงแบบดื้อยาโดยรับยาความดัน เฉลี่ย 5-8 ชนิดแล้วยังไม่สามารถควบคุม ระดับความดันโลหิตให้อยู่ในระดับที่เหมาะสมได้ ผู้ป่วยจะมีความดันโลหิต ก่อนการทำหัตถการโดยเฉลี่ยประมาณ 160-190 ของความดันโลหิตตัวบน (systolic blood pressure) และ 100-120 ของความดันเลือดแดงเฉลี่ย (mean arterial pressure) หนึ่งในผู้ป่วยที่ได้รับการรักษาเคยมีประวัติเลือดออกในสมองจากผลของการที่ควบคุมความดันโลหิตสูงไม่ได้ ผลการรักษาหลังจากที่ทำ renal nerve denervation จากผู้ป่วยทั้ง 4 รายพบว่าความดันโลหิตสูงลดลง ตั้งแต่ 24 ชม. แรกและความดันโลหิตยังลดอย่างต่อเนื่อง เมื่อมีการติดตามที่ 3 เดือน และ 6 เดือน โดยเฉลี่ยค่าความดันโลหิตที่ลดลงอยู่ที่ 35.2±9.9 มิลลิเมตรปรอท จำนวนของยาควบคุมความดันโลหิตที่ใช้สามารถลดลงโดยเฉลี่ยอยู่ที่ 3.5±3.0*

สรุป: *จากการศึกษานี้การทำการจี้หลอดเลือดไตด้วยคลื่นวิทยุความถี่ต่ำเพื่อรักษาความดันโลหิตสูงผ่านสายสวน (percutaneous renal nerve denervation) เป็นการรักษาที่ได้ผลดีในคนไทยจากผลการศึกษาที่ได้รับเบื้องต้นทั้ง 4 ราย*