Catheter-Based Renal Denervation Reduces Hypoxia-Triggered Nocturnal Blood Pressure Peak in Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is associated with an increased risk of cardiovascular events during sleep.[1,2] Patients with OSAS are likely to be nondippers with diminished nocturnal blood pressure (BP) falls during sleep or risers with higher nocturnal BP than daytime BP.[3] Increased BP surge and variability may be triggers of a cardiovascular event,[4,5] and the exaggerated nocturnal BP surge triggered by periodic hypoxia-induced sympathetic overdrive may contribute to sleep-onset cardiovascular events in OSAS patients.[4,5] However, conventional ambulatory BP monitoring, which measures nocturnal BP at 30-minute intervals, cannot always detect nocturnal BP surges at the time of apneic episodes in OSAS patients.[5]

Initially, the BP-lowering effect of catheter-based renal denervation (RDN) was demonstrated in the SYMPLICITY HTN-1[6] and SYMPLICITY HTN-2 trials;[7] however, SYMPLICITY HTN-3, a randomized controlled trial with a sham group, did not demonstrate the effectiveness of RDN on office systolic BP, a primary endpoint, in the entire group with drug-resistant hypertension.[8] The pathophysiology of resistant hypertension is quite heterogeneous. In patients with hypertension caused by increased sympathetic overdrive, such as patients with OSAS, RDN may provide greater BP reduction. This idea is supported by a substudy of the SYMPLICITY HTN-2 trial that demonstrated a significant office BP–lowering effect in 10 hypertensive patients with OSAS.[9]

A previous experimental study demonstrated that the BP surge caused by apneic episodes was suppressed by RDN.[10] However, in humans it remains unclear whether catheter-based RDN could successfully suppress the hypoxia-induced nocturnal BP surge in patients with OSAS. Recently, we developed IT-based trigger nocturnal BP monitoring (ITNP), which can selectively measure hypoxia-induced BP peaks.[3,5,11–14] Using this BP monitoring device, we tested the hypothesis that the sympatholytic effect of catheter-based RDN significantly suppresses hypoxia-induced peaks of nocturnal BP in patients with OSAS.

This study involved two patients with drug-resistant hypertension and mild OSAS who were not being treated with continuous positive airway pressure (CPAP), were already enrolled in the Sleep Pressure and Disordered Breathing in Resistant Hypertension and Cardiovascular Disease (SPREAD) study, and had had their nocturnal BP monitored before RDN.[12] The SPREAD study is an ongoing nationwide prospective registry trial of high-risk patients with a history of cardiovascular events or OSAS and resistant hypertension. The purpose of this study is to clarify whether hypoxia-induced nocturnal BP peaks are independently associated with cardiovascular risk, especially with sleep-onset events in high-risk hypertensive patients with OSAS. In the SPREAD study, we ask study patients to place the cuff on the upper arm and the pulse oximeter on a finger of the opposite hand just before going to bed. The ITNP device automatically measures hypoxia-triggered nocturnal BP peaks along with nocturnal BPs at 30-minute fixed time intervals and sends the data to a cloud-based computer.

Renal denervation was performed on the two patients using the Symplicity system (Medtronic, Minneapolis, MN) according to the protocol of SYMPLICITY HTN-Japan by one of the authors (T.I.), an expert in this procedure. SYMPLICITY HTN-Japan was the first prospective, randomized controlled trial comparing RDN with standard pharmacotherapy for treatment of resistant hypertension (systolic BP ≥160 mm Hg on ≥3 antihypertensive drugs including a diuretic for ≥6 weeks) in Asia.[15] Patient 1 (a 65-year-old hypertensive man with diabetes and OSAS) was taking valsartan (80 mg twice daily, morning/evening), cilnidipine (10 mg twice daily, morning/evening), carvedilol (20 mg once daily, morning), eplerenone (50 mg once daily, morning), trichlormethiazide (2 mg once daily, morning), and insulin (NovoRapid 50, Diagramma AG, Dietikon, Switzerland; breakfast 8 U, lunch 4 U, dinner 6 U). Patient 2 (a 53-year-old man with diabetes and OSAS) was taking amlodipine (5 mg once daily, morning), eplerenone (25 mg once daily, bedtime), carvedilol (20 mg once daily, bedtime), and candesartan (8 mg/hydrochlorothiazide 6.25 mg combination once daily, morning). Both study patients met the enrollment criteria of HTN-Japan. In our university hospital, nine cases were enrolled in HTN-Japan.

Nocturnal BP monitoring was performed using ITNP for 3 months (1 month before and 2 months after catheter-based RDN) (Table I and Table II). Nocturnal BP data were successfully obtained by ITNP from 19 nights before, 22 nights during the first month after, and 20 nights during the second month after RDN for patient 1 and from 13 nights, 15 nights, and 16 nights, respectively, for patient 2.

This study demonstrated that catheter-based RDN significantly reduced hypoxia-induced nocturnal systolic BP peaks by 10 mm Hg (Table I and Table II). The hypoxia-induced peak nocturnal BP could be only selectively detected by this new ITNP device with the trigger function of BP measurement. Oxygen saturation is continuously monitored by pulse oximetry, and the device sends a signal for cuff inflation when the oxygen is below the variable thresholds of hypoxia. The hypoxia-induced peak nocturnal BP would be triggered by the sympathetic overdrive associated with each apneic episode. In fact, studies performed in hypertensive patients with OSAS have shown that bedtime dosing of sympatholytic drugs, such as doxazosin and carvedilol, significantly reduce hypoxia-induced peak

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TABLE I. Changes in BP Parameters by Renal Denervation (Patient 1)

BP Parameter	−1–0 Months 19 Nights	0–1 Month 22 Nights	1–2 Months 20 Nights
Nighttime BP measured by 30-min fixed interval function			
Systolic BP, mm Hg	134.2±12.2	127.7±7.2[a]	123.1±6.3[c,d]
Diastolic BP, mm Hg	76.5±4.6	75.1±3.5	72.5±2.6[b,d]
Pulse rate, beats per min	52.9±3.3	55.4±2.9[b]	56.5±3.1[c]
Minimum nighttime systolic BP, mm Hg	113.3±8.8	108.5±6.6[a]	106.5±5.7[b]
Nighttime BP measured by oxygen-triggered function			
Hypoxia-peak systolic BP, mm Hg	164.2±19.4	152.9±17.6[a]	153.5±16.1[a]
Systolic BP, mm Hg	144.1±16.8	132.3±10.4[b]	132.2±8.6[b]
Diastolic BP, mm Hg	78.5±6.1	76.5±4.8	76.5±5.1
Pulse rate, beats per min	52.4±3.5	54.7±2.8[a]	56.0±2.6[c]
Morning BP			
Systolic BP, mm Hg	169.2±15.4	160.1±8.4[a]	145.6±10.1[c,e]
Diastolic BP, mm Hg	90.1±5.9	89.7±3.6	83.0±3.5[c,e]
Pulse rate, beats per min	55.1±4.5	59.6±4.6[b]	59.4±3.4[b]
Oxygen desaturation index, per hour	9.2±3.3	11.1±4.5	13.0±5.6[b]

Home nocturnal blood pressures (BPs) were self-measured using IT-based nocturnal BP monitoring for 3 months (1 month before and 2 months after catheter-based renal denervation). Data are shown as the mean+standard deviation of BP parameters of 19 nights before, 22 nights during the first month, and 20 nights during the second month after renal denervation. [a]*P*<.05, [b]*P*<.01, [c]*P*<.001 vs before 1 month, by *t* test. [d]*P*<.05, [e]*P*<.001 vs after 1 month, by *t* test.

TABLE II. Changes in BP Parameters by Renal Denervation (Patient 2)

BP Parameter	−1–0 Months 13 Nights	0–1 Month 15 Nights	1–2 Months 16 Nights
Nighttime BP measured by 30-min fixed interval function			
Systolic BP, mm Hg	127.4±8.3	124.5±8.9	118.4±6.9[b,d]
Diastolic BP, mm Hg	72.5±3.5	72.8±4.6	71.5±3.8
Pulse rate, beats per min	52.8±4.5	53.5±5.3	49.0±4.1[a,e]
Minimum nighttime systolic BP, mm Hg	107.2±7.1	100.1±9.9[a]	96.5±4.8[c]
Nighttime BP measured by oxygen-triggered function			
Hypoxia-peak systolic BP, mm Hg	162±17	152±17[a]	152±19
Systolic BP, mm Hg	143±11	136±11[a]	127±11[c,d]
Diastolic BP, mm Hg	83±6	81±5	77±5[b,e]
Pulse rate, beats per min	53±3	54±7	51±5
Morning BP			
Systolic BP, mm Hg	153.5±9.5	151.1±16.0	132.7±16.9[c,e]
Diastolic BP, mm Hg	87.5±3.9	88.0±6.3	81.8±7.8[b,d]
Pulse rate, beats per min	49.5±1.9	50.3±2.6	47.4±3.4[a,e]
Oxygen desaturation index, per hour	13±4	13±6	22±7[c,f]

Data are shown as the mean+standard deviation of blood pressure (BP) parameters of 13 nights before, 15 nights during the first month, and 16 nights during the second month after renal denervation. [a]*P*<.05, [b]*P*<.01, [c]*P*<.001 vs before 1 month, by *t* test. [d]*P*<.05, [e]*P*<.01, [f]*P*<.001 vs after 1 month, by *t* test.

nocturnal BP.[3,13] Thus, these cases suggest that the risk of sleep-onset cardiovascular events in OSAS patients might be reduced by catheter-based RDN.

In our previous study,[3] CPAP also effectively suppressed the hypoxia-induced peak nocturnal BP in hypertensive patients with OSAS. The average of nocturnal BPs measured at 30-minute intervals was also reduced in the study patients. CPAP is the standard therapy for patients with OSAS, and it significantly reduces nocturnal BP, especially in patients with nondipping nocturnal BP falls.[3,5] However, the indication for use of CPAP is moderate to severe OSAS with an apnea-hypopnea index >20 per hour. In the two patients described here, the severity of OSAS was mild, with an apnea-hypopnea index of 5 to 15 per hour; therefore, they were not treated with CPAP. In addition, even in OSAS patients treated with CPAP, significant hypoxia-induced peak nocturnal BP sometimes occurs, and the risk of cardiovascular events is not suppressed in those with poor adherence to CPAP.[5]

Thus, considering the results of this study, RDN might be an effective approach to reduce sleep-onset cardiovascular events in high-risk patients with OSAS, regardless of CPAP treatment, by suppressing hypoxia-induced nocturnal BP peaks. This study also indicates that hypertensive patients with OSAS might be promising candidates for a high-risk target for RDN. For these reasons, the effectiveness of RDN in hypertensive patients with OSAS should be tested in future clinical trials.

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