Effects of Renal Sympathetic Denervation on Blood Pressure, Sleep Apnea Course, and Glycemic Control in Patients With Resistant Hypertension and Sleep Apnea

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Abstract—Percutaneous renal sympathetic denervation by radiofrequency energy has been reported to reduce blood pressure (BP) by the reduction of renal sympathetic efferent and afferent signaling. We evaluated the effects of this procedure on BP and sleep apnea severity in patients with resistant hypertension and sleep apnea. We studied 10 patients with refractory hypertension and sleep apnea (7 men and 3 women; median age: 49.5 years) who underwent renal denervation and completed 3-month and 6-month follow-up evaluations, including polysomnography and selected blood chemistries, and BP measurements. Antihypertensive regimens were not changed during the 6 months of follow-up. Three and 6 months after the denervation, decreases in office systolic and diastolic BPs were observed (median: 34/13 mm Hg for systolic and diastolic BPs at 6 months; both \( P < 0.01 \)). Significant decreases were also observed in plasma glucose concentration 2 hours after glucose administration (median: 7.0 versus 6.4 mmol/L; \( P = 0.05 \)) and in hemoglobin A1C level (median: 6.1% versus 5.6%; \( P < 0.05 \)) at 6 months, as well as a decrease in apnea-hypopnea index at 6 months after renal denervation (median: 16.3 versus 4.5 events per hour; \( P = 0.059 \)). In conclusion, catheter-based renal sympathetic denervation lowered BP in patients with refractory hypertension and obstructive sleep apnea, which was accompanied by improvement of sleep apnea severity. Interestingly, there are also accompanying improvements in glucose tolerance. Renal sympathetic denervation may conceivably be a potentially useful option for patients with comorbid refractory hypertension, glucose intolerance, and obstructive sleep apnea, although further studies are needed to confirm these proof-of-concept data. (Hypertension. 2011;58:559-565.)

Key Words: drug resistance ▪ hypertension ▪ obstructive sleep apnea ▪ renal sympathetic denervation ▪ blood pressure ▪ glycemic control

Obstructive sleep apnea (OSA) is considered an etiologic factor in the development of hypertension\(^1\) and in the evolution of resistant hypertension.\(^2\) OSA is also independently associated with an increased risk of cardiovascular events, including atrial fibrillation, ischemic heart disease, heart failure, stroke, and sudden cardiac death.\(^3\) Several mechanisms, including endothelial dysfunction and systemic inflammation, may be responsible for the association between OSA and cardiovascular disease. However, increased sympathetic activity, consistently evident in OSA patients, likely plays a key role, especially in the development of resistant hypertension. Expert panels have recommended consideration of OSA and its treatment as a part of the management of patients with resistant hypertension.\(^4\)–\(^9\) The possibility that OSA is a consequence as well as a cause of increased sympathetic tone has not been considered previously.

Therapeutic renal sympathetic denervation by the application of discrete, low-dose radiofrequency energy to the renal artery endothelial surface via a percutaneous catheter-based procedure has been reported to reduce blood pressure (BP) by the selective reduction of renal sympathetic efferent and afferent signaling.\(^10\)–\(^12\) The procedure is associated with

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The sponsor of the study participated in the design of the study, analysis of data, and review of the final article. All of the data were maintained at the investigation site. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication. Correspondence to Adam Witkowski, Department of Interventional Cardiology and Angiology, Alpejska 42, 04-628, Warsaw, Poland. E-mail witkowski@hbz.pl

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attenuated central sympathetic outflow, as evidenced by reductions of total body noradrenaline and of muscle sympathetic nerve activity. In a recently published randomized trial, it has been shown that this procedure is associated with significant BP reduction in patients with treatment-resistant hypertension.

OSA is highly prevalent in resistant hypertension, affecting ≥80% of these patients, and OSA-mediated sympathetic activation likely promotes increased BP and BP resistance to pharmacological treatment. Because catheter-based renal denervation causes substantial and sustained BP reduction in patients with resistant hypertension by reducing the effect of sympathetic activity on renal BP regulation, it may be postulated that patients with OSA in particular may benefit from this procedure. Therefore, we evaluated the effects of this procedure on BP level and on sleep apnea course in patients with proven resistant hypertension and comorbid OSA.

Materials and Methods

Patients
The Renal Denervation in Patients With Refractory Hypertension Study (NCT00483808) is a nonrandomized, open-label postmarket clinical follow-up study to collect additional data on the safety and physiological response of renal denervation in patients with refractory hypertension. In the Institute of Cardiology (Warsaw, Poland), 13 patients with resistant hypertension were included in this study. Of this group, 10 patients were diagnosed with sleep apnea, with an apnea/hypopnea index (AHI) of >5 events per hour before renal denervation. These patients subsequently underwent renal denervation and completed a 3-month and 6-month follow-up evaluation.

Inclusion criteria included age ≥18 years, systolic BP of ≥160 mm Hg (an average of 3 office BP readings), receiving and adhering to full doses of an antihypertensive drug regimen of ≥3 drugs (including a diuretic) for a minimum of 2 weeks before screening, and an estimated glomerular filtration rate of ≥45 mL/min, using the Modification of Diet in Renal Disease equation.

Before entering the study, all of the patients had secondary forms of hypertension excluded, such as primary aldosteronism, renovascular hypertension (based on computed tomography-angiography), pheochromocytoma, coarctation of the aorta, renal parenchymal disease, and Cushing disease. All of the patients had normal ejection fractions on echocardiography and no clinical signs and symptoms of heart failure.

All of the patients provided written, informed consent, and the study was approved by the institutional ethics committee.

Study Procedure
All of the patients underwent complete full-night polysomnography. Baseline evaluations consisted of vital signs, physical examination, review of medications, blood chemistries (including fasting plasma glucose concentration, plasma glucose concentration 2 hours after glucose administration, level of glycosylated hemoglobin A, serum creatinine, 24-hour aldosterone, and sodium excretion), office blood-pressure measurement, ambulatory BP measurements (ABPMs), and renal duplex Doppler.

All of the these measurements, including polysomnography, ABPM, and renal duplex Doppler, were repeated on follow-up assessment at 3 months and 6 months, excluding 24-hour aldosterone excretion, which was not performed at 6 months. In one patient (patient No. 9), ABPM and 24-hour aldosterone and sodium excretion were not performed at 3-month follow-up, and in one patient (patient No. 4), ABPM was not performed at 6 months.

Laboratory Methods
Blood samples for all of the biochemical evaluations were taken after overnight fasting. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation. An oral glucose tolerance test was performed with a 75-g glucose load. Glucose concentrations were measured in a fasting state and 2 hours after glucose administration. Creatinine and glucose were determined by routine methods. Twenty-four-hour urinary collections for aldosterone and sodium were obtained.

Office BP Measurements
BP was measured with the patient in the sitting position after a 5-minute rest, using an automated device (Omron 705 IT) with a printout for each measurement. Three consecutive readings were performed. If the difference between readings was >10 mm Hg, further measurements were taken so as to obtain 3 consistent readings. The average of these 3 readings was recorded.

Ambulatory BP Measurements
In all of the patients, ABPMs were recorded using a SpaceLabs 90207 or 90217 (Ambulatory Monitoring, Redmond, WA). Readings were obtained every 15 minutes during the day (6:00 AM to 10:00 PM) and every 30 minutes during the night (10:00 PM to 6:00 AM). Division on sleep and activity periods was made following the recording based on data from patient diary. Recordings had to be repeated when <70% of the reading were valid. Thresholds of increased BP were used according to European Society of Hypertension/European Society of Cardiology 2007 criteria.

Polysomnography
The Epworth Sleepiness Scale was evaluated before the sleep study. The diagnosis of OSA was made by standard attended polysomnography with an Alice 5 (Respironics Inc, Murraysville, PA) device. The electroencephalogram, electrooculogram, and electromyogram of chin muscles, as well as ECG were simultaneously recorded. Oral-nasal airflow (with thermal and pressure sensing device), thoraco-abdominal respiratory movements, body position, snoring, and oximetry were also obtained. The polysomnographic recordings were scored manually using 30-second epochs following the criteria of Rechtschaffen and Kales for sleep and wake determination and sleep staging. Abnormal respiratory events were evaluated according to the standard criteria of the American Academy of Sleep Medicine Task Force. Apneas were defined as a cessation of airflow for ≥10 seconds and hypopneas as ≥50% decrease in airflow from baseline in amplitude of a valid measure of breathing during sleep for ≥10 seconds, associated with either an oxygen desaturation of >3% or an arousal. AHI indicating the number of apneic and hypopneic episodes per hour of sleep and oxygen desaturation index were calculated. Other measures obtained were minimal and average nocturnal oxygen saturation and the percentage of sleep time spent with oxygen saturation of hemoglobin <90%. Patients receiving continuous positive airway pressure (CPAP) treatment had polysomnography performed without CPAP. The initial and the follow-up polysomnograms were scored and interpreted by an experienced investigator blinded to the clinical status of the patients.

Renal Ultrasound and Doppler Studies
For renal ultrasound, an HD11 (Philips, Eindhoven, the Netherlands) with a multiphase 2- to 4-MHz convex array transducer was used. The intrarenal arteries were visualized in the color duplex mode. Doppler ultrasonography spectral analysis included mean resistive index (peak systolic velocity − end diastolic velocity/peak systolic velocity) obtained from 3 Doppler curves at different sites of the each kidney. Measurements were made by 2 experienced investigators who were blinded to the clinical status of patients. Interobserver and intraobserver coefficients of variance of resistive index were 5.6% and 4.7%, respectively (n=12).
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
</tr>
<tr>
<td>Men/women, n</td>
<td>7/3</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.5 (42.5 to 58.0)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.9 (26.0 to 35.0)</td>
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<tr>
<td>GFR, ml/min/1.73 m²</td>
<td>81.3 (75.0 to 90.0)</td>
</tr>
<tr>
<td>No. of antihypertensive medications</td>
<td>5.0 (4.0 to 5.25)</td>
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<tr>
<td>Patients with/without diabetes mellitus, n</td>
<td>4/6</td>
</tr>
<tr>
<td>Hemoglobin A1C, %</td>
<td>6.1 (5.9 to 6.7)</td>
</tr>
<tr>
<td>24-h urinary aldosterone, μg/24 h</td>
<td>17.2 (15.5 to 35.7)</td>
</tr>
<tr>
<td>24-h urinary sodium, mEq/24 h</td>
<td>198.2 (110.2 to 218.7)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale, points</td>
<td>9.00 (6.50 to 13.25)</td>
</tr>
<tr>
<td>AHI, events per h</td>
<td>16.3 (13.3 to 50.7)</td>
</tr>
<tr>
<td>ODI, events per h</td>
<td>13.0 (7.1 to 43.8)</td>
</tr>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>173 (167 to 180)</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>106 (91 to 114)</td>
</tr>
<tr>
<td>Ambulatory 24-h systolic BP, mm Hg</td>
<td>140 (131 to 144)</td>
</tr>
<tr>
<td>Ambulatory 24-h diastolic BP, mm Hg</td>
<td>82 (79 to 91)</td>
</tr>
<tr>
<td>Ambulatory daytime systolic BP, mm Hg</td>
<td>147 (131 to 151)</td>
</tr>
<tr>
<td>Ambulatory daytime diastolic BP, mm Hg</td>
<td>87 (82 to 96)</td>
</tr>
<tr>
<td>Ambulatory nighttime systolic BP, mm Hg</td>
<td>128 (114 to 132)</td>
</tr>
<tr>
<td>Ambulatory nighttime diastolic BP, mm Hg</td>
<td>76 (69 to 85)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) unless otherwise specified. BP indicates blood pressure; ODI, oxygen desaturation index; AHI, apnea/hypopnea index; GFR, glomerular filtration rate.

Renal Denervation

Eligible patients had to have renal artery anatomy appropriate for treatment including (proven before study on computed tomography) main renal arteries ≥4 mm in diameter and ≥20 mm in length and no anatomically significant renal artery stenosis in either renal artery. A history of previous renal artery intervention, including balloon angioplasty or stenting, and multiple main renal arteries in either kidney were exclusion criteria. After confirmation of eligibility by screening aortography, the treatment catheter (Simplicity, Aridian Inc, Palo Alto, CA) was introduced into each renal artery via femoral access. Discrete, radiofrequency ablations of ≤8 watts were applied, lasting ≥2 minutes each, to obtain ≤6 ablations separated both longitudinally and rotationally within each renal artery. During ablation, the catheter system monitored tip temperature and impedance, altering radiofrequency energy delivery in response to a predetermined algorithm.

Statistical Analysis

The results throughout are presented as median and interquartile range. For comparison between measures before and after denervation, Wilcoxon signed-rank test was used. Comparison of the prevalence rates among groups was performed using the χ² test. The degree of association between variables was assessed using Pearson correlation coefficients (r). P<0.05 was considered statistically significant. Data analysis was carried out using statistical software PASW Statistics 18 (SPSS Inc, Chicago, IL).

Results

The study included 10 patients (7 men and 3 women; median age: 49.5 years; interquartile range: 42.5 to 58.0 years). Baseline characteristics of these patients are presented in Table 1. In all of the patients, baseline sitting systolic office BP was >160 mm Hg despite treatment with ≥3 antihypertensive drugs (median number of antihypertensive drugs: 5.00; interquartile range: 4.00 to 5.25). In all of the patients, BP levels in ABPM were higher than the threshold used in European Society of Hypertension/European Society of Cardiology 2007 guidelines. All of the patients had been receiving an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, as well as a diuretic and a β-blocker. Other antihypertensive drugs were used as follows: calcium channel blockers in 8 patients, α-blocker in 2 patients, and centrally acting antihypertensive drugs in 2 patients. One patient (No. 9) was treated with spironolactone. In all of the patients antihypertensive regimens were not changed during the 6 months of follow-up.

Before the denervation 8 patients were diagnosed with OSA syndrome and 2 with mixed sleep apnea syndrome (obstructive and central; Tables 1 and 2). There were 5 patients with mild sleep apnea (AHI <15 per hour) and 5 patients with moderate-to-severe apnea (AHI >15 per hour). Two patients were treated with nasal CPAP (CPAP therapy began 3 and 4 months before entering the study; the patients remained on CPAP during study). In 7 patients abdominal obesity was present at baseline, 6 patients met the European Society of Hypertension/European Society of Cardiology 2007 criteria for metabolic syndrome, and 4 patients were diagnosed with diabetes mellitus and received oral antidiabetic drugs.

Three months after the denervation, office systolic BP decreased in all except 1 patient, and 6 months after denervation decreases in office systolic BP in all of the patients were observed (Table 2). The median reduction was 22 mm Hg (interquartile range: 18 to 34 mm Hg; P<0.01) and 34 mm Hg (interquartile range: 22 to 39 mm Hg; P<0.01) at 3 and 6 months, respectively (Figure 1). A nonsignificant decrease in diastolic BP was observed at 3 months, followed by significant reduction in clinic diastolic BP at 6 months (median: 13 mm Hg; interquartile range: 6 to 26 mm Hg; P<0.01; Figure 1). There were no differences in reductions of systolic and diastolic BPs between the patients with mild and moderate-to-severe sleep apnea. A significant decrease in sitting clinic heart rate was also observed at 6 months (median: 86 bpm, interquartile range: 74 to 93 bpm versus median: 68 bpm, interquartile range: 58 to 84 bpm; P<0.05).

Considering ABPMs, nonsignificant decreases in 24-hour, daytime, and nighttime systolic and diastolic BPs were observed at 3 and 6 months. The median reductions at 6 months in systolic BP were 6.0 mm Hg (interquartile range: 4.5 to 16.5 mm Hg), 7.0 mm Hg (interquartile range: 4.5 to 13.5 mm Hg), and 8.0 mm Hg (interquartile range: 4.0 to 23.5 mm Hg) for 24-hour, daytime, and nighttime BP values, respectively. Nonsignificant decreases in heart rate during 24-hour, daytime, and nighttime periods were observed, except for a significant decrease in 24-hour mean heart rate at 6 months (median: 73.50, interquartile range: 64.25 to 79.00 bpm versus median: 65.50, interquartile range: 58.50 to 72.50 bpm; P<0.05).

Significant decreases in plasma glucose concentration 2 hours after glucose administration at 3 and at 6 months (median: 7.0, interquartile range: 5.8 to 12.0 mmol/dL versus
median: 6.4, interquartile range: 4.1 to 10.1 mmol/dL at 6 months; \( P < 0.05 \) and in hemoglobin A1C level at 3 and 6 months (median: 6.1%, interquartile range: 5.9% to 6.7% versus median: 5.6%, interquartile range: 5.4% to 6.5% at 6 months; \( P < 0.05 \)) were observed. There were no changes in fasting plasma glucose and creatinine concentrations and estimated glomerular filtration rate at 3 and 6 months. No changes in 24-hour urine aldosterone and sodium excretion at 3 months were observed. No significant changes in weight and body mass index were observed at 6 months (for body mass index: median: 30.9 kg/m², interquartile range: 26.0 to 35.0 kg/m² versus median: 30.8 kg/m², interquartile range: 25.2 to 37.4 kg/m²; \( P \) value not significant). In all of the patients duplex Doppler ultrasonography revealed normal renal arteries, and a significant decrease in renal resistive index was observed at 6 months after denervation (median: 0.62, interquartile range: 0.59 to 0.67 versus median: 0.61, interquartile range: 0.54 to 0.63; \( P < 0.05 \)).

Decreases in AHI, nonsignificant at 3 months and a tendency toward significant at 6 months after renal denervation, were noted (median: 16.3 events per hour, interquartile range: 13.3 to 50.7 events per hour versus median: 4.5 events per hour, interquartile range: 1.6 to 27.3 events per hour; \( P = 0.059 \) at 6 months). Also, decreases in oxygen desaturation index were observed (median: 13.0 events per hour, interquartile range: 7.1 to 43.8 events per hour versus median: 8.7 events per hour, interquartile range: 1.9 to 26.2 events per hour; \( P = 0.11 \) at 6 months), and decreases in median Epworth Sleepiness Scale score at 3 months (\( P \) value not significant) and 6 months (median: 9.00 points, interquartile range: 6.50 to 13.25 points versus median: 7.00 points, interquartile range: 4.75 to 12.5 points; \( P < 0.05 \)) were also observed.

In 8 of 10 patients, an improvement in AHI was observed at 6 months (Figure 2). It should be noted that in all 3 of the patients with severe OSA before denervation (2 of whom were receiving CPAP treatment), an improvement in sleep apnea indices was observed. There were 2 patients (patients No. 2 and No. 5) with mixed (obstructive and central) sleep apnea. In one of them (No. 5), a reduction in sleep apnea indices was also observed with a change in AHI — 30.5 events per hour at 6 months (Table 2). In patients with improvements
in AHI, a significant decrease in 24-hour, daytime, and nighttime ABPM levels was observed, the latter being most pronounced (median: $-8/-4$ mm Hg, $-12/-5$ mm Hg and $-10/-8$ mm Hg for 24-hour, daytime, and nighttime, respectively; $P<0.05$ for all).

**Discussion**

Our data show that, in patients with resistant hypertension and OSA, catheter-based renal denervation therapy causes substantial and significant reductions both in systolic and diastolic BPs, extending the previous reports of reduced BP in patients with resistant hypertension after renal denervation. Unexpectedly, in our patients, improvements in glycemic control were observed, and reduced OSA severity was noted in 8 of 10 subjects, even in 2 patients already receiving CPAP treatment.

It has been reported previously that therapeutic renal denervation led to a large and persistent decrease in BP in patients with resistant hypertension, which was evident as early as 1 month, further reduced at 3 months, and sustained through a subsequent 12-month assessment. In the recently published Symplicity HTN-2 Trial, 106 patients with treatment-resistant hypertension were randomly assigned to renal denervation or control groups. The between-group differences in BP at 6 months were $33/11$ mm Hg ($P=0.0001$), resulting from significant decrease in BP in the renal denervation group ($-32/12$ mm Hg; $P<0.0001$) and no change in BP in the control group.

It has also been demonstrated that, during the follow-up periods, there was no attenuation of BP reduction, suggesting no nerve fiber recovery, nerve fiber regrowth, or development of counterregulatory BP elevating mechanisms. In most of the patients studied, noradrenaline spillover from the kidneys confirmed a substantial degree of efferent renal denervation, consistent with the BP response.

A recent report describing longer-term data in these and similar patients subsequently treated with catheter-based renal denervation showed durability of the therapeutic effect. The catheter-based procedure resulted in substantial reductions in BP sustained for $\geq 2$ years, without significant adverse events, in 117 patients with resistant hypertension in a nonrandomized multicenter study. It is of note that 33% of subjects were diabetic and 22% had coronary artery disease. This study therefore suggests that the initial BP reduction observed at 12 months persists to $\geq 24$ months. Moreover, the magnitude of BP lowering postprocedure at 24 months was no less than and appeared to be numerically greater than that observed at 12 months. It has been postulated that the increase in antihypertensive effect with time, as seen in our study, may represent a predominant alteration in afferent signaling induced by the renal denervation procedure with a resetting of central sympathetic outflow. This may be associated with a resetting of the baroreflex around a lower homeostatic set point.

The effect of catheter-based therapy on BP in patients with resistant hypertension and proven comorbid OSA has not
been evaluated,\(^{10,12,18}\) nor has any previous study investigated the effects of renal denervation on OSA severity. OSA may occur in >80% of patients with resistant hypertension.\(^ {2,4,19}\) For the first time, we report on patients with both resistant hypertension and OSA (8 with OSA syndrome and in 2 with mixed obstructive and central sleep apnea). In all of the patients the catheter-based therapy caused substantial and significant reductions in systolic and diastolic BPs. It should be noted that the decreases in BP, both clinic and ambulatory, are comparable with those observed in the Symplicity HTN-2 Trial.\(^ {12}\) Although white-coat effect cannot be excluded, the discrepancy between clinic and ambulatory BP levels can be partially attributable to the fact that the higher clinic BP levels are the larger the discrepancy is between clinic and ambulatory BP levels.\(^ {20}\) However, in patients with improvements in sleep apnea course, the changes in ABPM levels were more pronounced and statistically significant.

Comorbid hypertension and OSA are also frequently associated with metabolic anomalies. A close relationship among visceral obesity, insulin resistance, and hyperleptinemia in patients experiencing OSA has been reported. Common pathophysiologic mechanisms linking OSA, obesity, and resistant hypertension have been proposed, including excessive sodium retention mediated by sympathetic nerve traffic to the kidneys, fat-induced alterations in renal function, increased production of aldosterone, and the renal effects of increased insulin.\(^ {4,21–23}\)

In our patients with resistant hypertension and OSA, catheter-based therapy was also accompanied by improvements in indices of glucose metabolism. This is in agreement with a recent report showing that significant BP reduction caused by renal sympathetic denervation is accompanied by an improvement of glucose metabolism attributed to increased insulin.\(^ {24}\)

The reduction in OSA severity in 8 of our 10 subjects and the trend to attenuated AHI for the sample overall suggest the possibility that renal denervation might ameliorate the sleep disorder as well as the hypertension. The mechanism of interaction between renal denervation and sleep apnea is of great interest. Resistant hypertension is characterized by significant fluid retention.\(^ {25}\) Renal denervation reduces salt avidity by efferent sympathetic renal nerve disruption. It might reduce total body fluid, which is thought to contribute to obstructive episodes, because peripherally released fluid accumulation may predispose to upper airway obstruction. It should also be noted that venous capacitance remains under the control of the sympathetic nervous system. Thus, it might be possible that renal denervation also affects venous capacitance and blood pooling.\(^ {26}\) It has been hypothesized that chronic fluid overload may underlie the high prevalence of OSA in patients with resistant hypertension. Indeed, treatment with a mineralocorticoid receptor antagonist substantially reduced the severity of OSA. The reduction in AHI observed in this study was of similar magnitude to that seen in our study sample.\(^ {27}\)

There is a very strong comorbidity among hypertension, sleep apnea, and insulin resistance, often manifesting as the metabolic syndrome. In fact, the sleep apnea-metabolic syndrome comorbidity has come to be known as “syndrome Z.”\(^ {28}\) Generally the perception has been that this comorbidity is explained, at least in part, on the basis of obesity. However, our present data suggest that there may be another fundamental common etiologic mechanism for these disease conditions, because BP, sleep apnea, and insulin resistance all trended toward an improvement after renal denervation, suggesting that perhaps sympathetic activation may be a common underlying mechanism predisposing to these 3 conditions. It is important that, in the studied sample characterized by pronounced metabolic abnormalities, we observed the improvements in measures of BP, sleep apnea, and glycemic control, even in the absence of significant changes in body mass index before and after renal denervation.

Because our data are observational, we cannot identify the exact mechanism responsible for any amelioration of sleep apnea. Nonetheless, it should be emphasized that renal denervation influences key mechanisms regulating sympathetic activation. The efferent sympathetic renal nerves can affect control of renal vascular resistance, increase rennin release, and regulate sodium and water excretion.\(^ {29}\) The afferent renal nerves enhance the activity of the sympathetic nervous system. It has been also suggested that, in conditions of high-sodium dietary intake, activation of the afferent renal nerves contributes to the arterial baroreceptor-mediated suppression of efferent sympathetic renal nerves in the overall goal of preventing sodium retention and maintaining water and sodium homeostasis.\(^ {29,30}\)

Therefore, renal denervation in patients with resistant hypertension and OSA might attenuate the effects of sympathetic activation additionally and independently of CPAP treatment. Whether the significant improvements in glycemic control are attributed to improved sleep apnea, because of reduced sympathetic activation, or other mechanisms remains to be determined.

Last, we need to consider the possibility that the fall in BP may itself contribute to the attenuation of sleep apnea. This may be mediated by baroreflex deactivation inducing changes in chemoreflex modulation of breathing control or by direct effects of lower BP on central ventilatory or airway control mechanisms.

Our study has a number of limitations. This is a nonrandomized, open-label study, and we present results from a selected patient population over a limited observational period. The modest sample size does not allow us to draw definitive conclusions. Further studies are warranted to assess the impact of renal denervation on sleep apnea and glycemic control and their relation to BP decline and cardiovascular risk. Last, there is no control group without OSA with which to make comparisons regarding BP responses over time.

**Perspectives**

Our results show, for the first time, that catheter-based renal sympathetic denervation may lower BP and improve glycemic control in resistant hypertensive patients with sleep-disordered breathing. This was accompanied by a trend to improvement in sleep apnea severity. Renal sympathetic denervation may conceivably be a potentially useful therapeutic option for patients with refractory hypertension and severe OSA, particularly in those with comorbid metabolic
dysregulation. More definitive randomized, controlled clinical trials are needed to confirm these initial proof-of-concept data. Also, further longitudinal follow-up of this group is required to ascertain the status of BP lowering, OSA severity, and glycemic control and the need for repeat procedure(s) or additional other therapy.

References
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