We have recently shown that resistant hypertensive patients are characterized by a sympathetic activation and a baroreflex impairment much greater for magnitude than the ones detectable in age-matched nonresistant hypertensives individuals.1 Whether these neuroadrenergic and reflex abnormalities can be reversed by renal denervation has been to date assessed in a case report and 3 studies,2–5 which have, however, provided conflicting results. Although one study failed to detect any effect of the procedure on muscle sympathetic nerve traffic (MSNA),5 the other 2 reported a reduction in sympathetic neural discharge which, although statistically significant, was of a modest degree compared with the concomitant marked reduction in blood pressure (BP) values.4,5

A common limitation of all the above-mentioned studies is that sympathetic activity was assessed only once or, at best, twice after renal denervation thus failing to provide serial information on the behavior of sympathetic nerve traffic over an extended follow-up period after the procedure. Furthermore, lack of sympathetic activity measurements in the earliest post–renal denervation phases did not allow to determine whether the hypothesized sympathetic effects preceded were concomitant to or followed the BP ones. This leaves 2 unanswered key questions: ie, whether the sympathetic neural responses to renal denervation are (1) responsible for its BP-lowering effects and (2) predictors of the antihypertensive response to the intervention.

The present study has been undertaken to examine in patients with true resistant hypertension whether and to what extent office and ambulatory BP responses to renal denervation are qualitatively, quantitatively, and temporally related to the MSNA responses, as well as to the modifications of the baroreflex–MSNA sensitivity. This was obtained by serial measurements of the above-mentioned variables according to...
a study design, which included 5 experimental sessions: ie, one before renal denervation and the others 2 weeks, 1 month, 3 months, and 6 months after bilateral renal nerves ablation. To our knowledge, this has never been performed before.

### Methods

#### Population

This investigator generated study population consisted of 27 patients (18 men and 9 women) with an age range between 46 and 78 years.

#### Table 1. Demographic, Anthropometric, Biochemical, Echocardiographic, and Hemodynamic Baseline Data in Essential Hypertensive Patients With HT and RHT Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (n=12)</th>
<th>RHT (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (males/females)</td>
<td>9/3</td>
<td>11/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.9±1.2</td>
<td>59.4±1.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.5±0.9</td>
<td>24.9±1.2</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.75±0.01</td>
<td>0.77±0.02</td>
</tr>
<tr>
<td>Clinic systo/diastolic BP</td>
<td>135.9±1.3</td>
<td>174.1±3.6</td>
</tr>
<tr>
<td>MSNA (burst/100 heart beats)</td>
<td>50.2±2.2</td>
<td>68.3±3.1</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>17.8±0.5</td>
<td>18.5±0.3</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>62.2±3.1</td>
<td>80.1±2.6</td>
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<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>6.9±0.4</td>
<td>8.2±0.5</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL per h</td>
<td>2.1±0.7</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>HOMA, a.u.</td>
<td>1.4±0.2</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>OSA, n</td>
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<td>2</td>
</tr>
<tr>
<td>LVEF, %</td>
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<td>58.1±1.4</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>107.1±4.4</td>
<td>116.0±4.1†</td>
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<tr>
<td>E/A ratio, a.u.</td>
<td>1.11±0.3</td>
<td>0.98±0.1†</td>
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<tr>
<td>Respiration rate, breaths/min</td>
<td>17.8±0.5</td>
<td>18.5±0.3</td>
</tr>
<tr>
<td>MSNA (burst/100 heart beats)</td>
<td>50.2±2.2</td>
<td>68.3±3.1*</td>
</tr>
<tr>
<td>Anti-HT drugs, n°/d</td>
<td>2.1±0.2</td>
<td>4.7±0.4*</td>
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<tr>
<td>ACEIs</td>
<td>41.4%</td>
<td>73.3%</td>
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<tr>
<td>ARBs</td>
<td>41.7%</td>
<td>60.0%</td>
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<tr>
<td>β-Blockers</td>
<td>33.3%</td>
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<td>α-Blockers</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>Diuretics</td>
<td>24.9%</td>
<td>100.0%</td>
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<tr>
<td>Centrally acting drugs</td>
<td>5.3%</td>
<td>39.9%</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>8.8%</td>
<td>40.1%</td>
</tr>
</tbody>
</table>

Data are shown as absolute mean±SEM or as percentage values (use of various anti-HT drugs). ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptors blockers; a.u., arbitrary units; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HOMA, homeostasis model assessment; HT, nonresistant hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MSNA, muscle sympathetic nerve activity; n°/d, number of antihypertensive drugs per day; OSA, obstructive sleep apnea; RHT, true resistant hypertension.

### Measurements

Measurements included body mass index, waist:hip ratio, sphygmomonometric, and beat-to-beat finger (Finapres; Ohmeda 2003, Englewood, FL)³ systolic and diastolic BP, heart rate (palpatory or ECG measurements) and respiration rate (pneumotachograph).

The study protocol was approved by the Ethics Committee of the Istituto Auxologico Italiano, Milan, and of the IRCCS Multimedica, Sesto San Giovanni (Milan), Italy. All subjects gave written consent to the study after being informed of its nature and purpose. All subjects were studied on an outpatient basis.

### Cohort and Data Analysis

In the 15 true resistant hypertensive patients, 5 experimental sessions were performed. The first session was performed 2 days who were recruited between 2011 and 2013. Fifteen patients had a true resistant essential hypertensive state based on lack of office and ambulatory BP control, despite the daily administration of at least 3 antihypertensive drugs (4–5 drugs; Table 1).⁶ The patients were included in the Italian Symplicity Registry belonging to the Global Symplicity Register. Details about the investigator generated studies are mentioned in the article describing the rationale and design of the registry. The remaining 12 patients had an essential hypertensive state of moderate to severe degree, which achieved BP control with the daily administration of 2 antihypertensive agents. Patients were excluded from the study if they had clinical conditions known to affect sympathetic cardiovascular function or a poor adherence to antihypertensive drug treatment. Smokers (5 resistant hypertensive patients and 4 nonresistant hypertensive controls) were asked to refrain from smoking during the 24 hours before each study session. The study design, which included 5 experimental sessions: ie, 1 experimental session, which included 5 experimental sessions: ie, 2 days before renal denervation and the others 2 weeks, 1 month, 3 months, and 6 months after bilateral renal nerves ablation. To our knowledge, this has never been performed before.
before the renal denervation, whereas the other 4 sessions were performed 15 days, 1, 3, and 6 months after the procedure. In the 12 nonresistant hypertensives, who served as controls, 2 experimental sessions spaced by a 6-month interval were performed.

In each experimental session the patients came to the laboratory in the morning, after a light breakfast and an overnight abstinence from alcohol and coffee consumption. They were put in the supine position and fitted with the intravenous cannula and the various measuring devices, except the microelectrode for MSNA recording. Blood samples for various assays were taken 30 minutes after positioning the venous cannula, after which BP was measured 3x with a mercury sphygmomanometer and a microelectrode was inserted into the right or left peroneal nerve to obtain MSNA. Sympathetic nerve traffic was recorded together with finger BP, heart rate, and respiration rate during a 30-minute period in a quiet semidark room kept at the constant temperature of 22°C to 24°C. Renal denervation was performed using a radiofrequency ablation catheter (Simplicity; Medtronic Ardian Inc, Palo Alto, CA), following the protocol and sequence of interventions (which included renal angiograms) described in previous articles.2–4 On average in each single patient, an average number of 11.1±2.4 radiofrequency ablations along both main renal arteries were applied.

Data were analyzed by a single investigator unaware of the experimental design and of the belonging of each patient to the 2 different groups or to the different experimental sessions. Office, 24-hour, and finapres mean systolic and diastolic BP, office, 24-hour, and finapres mean heart rate, respiration rate, plasma renin activity, plasma aldosterone, homeostasis model assessment index, resting MSNA and MSNA–baroreflex sensitivity obtained in individual subjects were averaged separately for each group and for each experimental session and expressed as means±SEM. In Table S1 in the online-only Data Supplement, data are also shown as mean changes±SD when compared with the pre–renal denervation control values. An analysis was also made of BP and MSNA data from 2 subgroups of resistant hypertensive patients, which were separately considered based on (1) an office systolic BP response 6 months after renal denervation above or below the median value and (2) a MSNA response 6 months after renal denervation above or below the median value. Comparisons between data obtained in the different experimental sessions were made by 1-way ANOVA. The paired t test with Bonferroni correction was used to locate the difference between the post–renal denervation and pre–renal denervation values. The Spearman analysis was used to correlate changes in different variables. A value of P<0.05 was taken as the level of statistical significance.

Results

Baseline Values

As shown in Table 1, age, sex distribution, body mass index, waist:hip ratio, plasma renin, plasma aldosterone, homeostasis model assessment index, and the other laboratory variables (including echocardiographic parameters) were similar in resistant and nonresistant hypertensive patients. An obstructive sleep apnea state of mild-to-moderate degree was found in 2 of the 15 resistant hypertensive patients, whereas no patient displayed obstructive sleep apnea in the control group. As expected, office, ambulatory, and beat-to-beat finger BP values were significantly greater in resistant than in nonresistant hypertensives. This was the case also for MSNA, but not for heart rate, values that were markedly and significantly greater in the former than in the latter group.

Effects of Renal Denervation on BP and MSNA Relationships

Renal denervation was successfully performed in all 15 patients. No complication was reported during, immediately after and over the long-term period after the procedure. As shown in the individual and average absolute values of Figure 1, as well as in the mean changes reported in Table S1, renal denervation had no BP-lowering effect at the evaluation performed 15 days after the procedure. The intervention, however, was associated with a decrease in office, 24-hour, and finapres systolic and diastolic BP during the remaining follow-up period. The decreases were always less pronounced for 24-hour and finger than for office BP, and for all pressures they were highly heterogeneous in magnitude between patients. Renal denervation did not significantly affect heart rate, both when assessed via the palpatory method at the level of the radial artery (office), and when averaged during the 24-hour period or beat-to-beat by the finapres device.

Figure 2 shows the effects of renal denervation on MSNA and baroreflex–MSNA values in individual patients, as well as in the group as a whole. MSNA values were almost unchanged 15 and 30 days after the denervation procedure, whereas a significant reduction was observed after 3 and 6 months. Baroreflex–MSNA values showed a specular behavior, ie, virtually no change at the 15th- and 30th-day follow-up assessment and a significant increase thereafter. Both the MSNA and the baroreflex–MSNA responses to renal denervation substantially differed for magnitude between patients although the interindividual variability was less pronounced than the one characterizing BP. This is further documented by the data shown in Table S1, which shows the changes in office, beat-to-beat, ambulatory BP, and in MSNA detected 15 days, 1, 3, and 6 months after renal denervation. MSNA and baroreflex–MSNA changes observed after the procedure were significantly related to each other at the evaluations performed 3 months (r=0.51; P<0.05) and 6 months (r=0.54; P<0.05) after renal denervation.

As shown in Table 2, no correlation was found between baseline pre–renal denervation office or 24-hour BP and the corresponding BP changes after the denervation. Neither baseline MSNA values nor MSNA changes after renal denervation correlated with the BP changes seen at 3 and 6 months after the procedure, which also showed no correlation with the baroreflex–MSNA baseline values or changes. At the 6-month assessment after renal denervation, the MSNA reduction was similar for magnitude in the 2 subgroups of patients, which displayed an office systolic BP reduction greater or lower than the median value (−21.5±2.4 and −3.8±2.1 mmHg, respectively; Figure 3, left). Similarly, the systolic BP reduction detected at the 6-month assessment after renal denervation was similar for magnitude in the subgroups of patients, which displayed a MSNA reduction greater or lower than the median value (−19.1±2.3 and −10.2±1.0 bursts/min, respectively; Figure 3, right). Similar observations were made for clinic diastolic BP and for beat-to-beat finger BP.

Other Effects of Renal Denervation

Plasma aldosterone and plasma renin activity did not change at 15 days and 1 month after renal denervation, while showing a tendency to decrease at the 3rd month (data not shown).
and a statistical significant reduction at the 6 months after the denervation procedure (−1.9±0.4 and −1.0±0.3 ng/mL per hour; \(P<0.05\) for both). No significant change in body mass index, waist:hip ratio, plasma glucose, homeostasis model assessment index, plasma electrolytes, and estimated glomerular filtration rate was observed during the follow-up (data not shown). The number and daily dosage of antihypertensive medications remained unmodified throughout the follow-up period in 12 and changed in 3 patients. In 1 patient, spironolactone was stopped after the 3rd month, in another the dosage of the \(\beta\)-blocker used (metoprolol) was reduced after 1 month, whereas in the third patient, the reduction involved, after 3 months, the dosage of the calcium channel blocker used (nifedipine gastrointestinal therapeutic system).

Figure 1. Office (left), ambulatory (middle), and beat-to-beat (right, finapres device) systolic (SBP) and diastolic (DBP) blood pressure values before (baseline), 15 days, 1 month, 3 months, and 6 months after bilateral renal denervation. Data are expressed as individual (thin gray lines) and mean±SEM (black solid line) values. Asterisks (*\(P<0.05\), **\(P<0.01\)) refer to the statistical significance between values recorded after the renal denervation procedure and those recorded before the intervention (baseline).

Figure 2. Muscle sympathetic nerve activity (MSNA), expressed as bursts incidence corrected for heart rate values (left), and spontaneous baroreflex control of MSNA (MSNA-BRS, right) values before (baseline), 15 days, 1 month, 3 months, and 6 months after bilateral renal denervation. Data are expressed as individual (thin gray lines) and mean±SEM (black solid line) values. Asterisks (*\(P<0.05\)) refer to the statistical significance between values recorded after the renal denervation procedure and those recorded before the intervention (baseline).
Control Group
In the nonresistant hypertensive patients who did not undergo renal denervation and served as controls baseline office, ambulatory and finger BP values recorded at baseline did not show any significant change when reassessed after 6 months. This was the case also for MSNA and other recorded variables (Figure 4).

Discussion
The present study provides 2 major sets of novel information on the BP and sympathetic effects of renal denervation in patients with true resistant hypertension. One, our data show that no quantitative relationship was detectable between the BP and the sympathetic responses to the denervation procedure at any time during a 6-month follow-up, despite the multiple recordings of either variable obtained over this period. Second, they further show that patients having a marked BP reduction in response to renal denervation can display a sympathoinhibition of magnitude almost indistinguishable from the one seen in patients with a BP response 6 to 7× less pronounced. Thus, renal denervation can lower sympathetic activity even when BP is not or not yet reduced. Furthermore, when the denervation procedure markedly lowers BP, this can occur also in absence of any similarly marked alterations of sympathetic drive and vice versa. These temporal, quantitative, and even qualitative discrepancies strongly suggest that the BP-lowering effects of renal denervation are not necessarily dependent to, and thus not necessarily triggered by, a decrease in central sympathetic outflow.

Our study does not clarify which mechanisms may concur to determine in the patients enrolled the BP-lowering effects of the renal denervation intervention. On the basis of present data, however, we can reasonably rule out that in our patients factors such reinforcement of the preceding drug treatment regimen, loss of body weight, or improvement in insulin resistance8,16–18 were responsible because, compared with the baseline condition, their modifications in the postdenervation period were trivial or absent. We can also exclude that a deactivation of the renin–angiotensin–aldosterone system19,20 played a major role, because, like resting MSNA values, this improvement showed a temporal discrepancy and no quantitative relationship with the BP effects, at variance from what has been reported for baroreflex heart rate control in a recent study.21 We are thus left with the possibility that (1) MSNA does not reflect overall sympathetic deactivation, which is not in line with its close correlation with general markers of sympathetic activity, such as plasma norepinephrine or norepinephrine spillover8,22–24 or (2) the BP reduction was not in line with its close correlation with general markers such as baroreflex–MSNA sensitivity; DBP, diastolic blood pressure; MSNA, muscle sympathetic nerve activity; and SBP, systolic blood pressure.
reduction of blood volume and cardiac output by denervation diuresis are involved. 26–29

Several other results deserve to be briefly discussed. One, our study is the first which systematically assessed the behavior of baroreflex–MSNA control before and after renal denervation on baroreflex–MSNA control, showing a clearcut improvement which achieved statistical significance at the 3rd and 6th months after renal denervation. Interestingly, these changes were significantly and directly correlated with the concomitant changes in MSNA values observed at the same time periods. This suggests that the reduction in MSNA associated with renal denervation has a baroreflex origin, ie, it is generated by an improved ability of this reflexogenic area to restraint sympathetic cardiovascular drive. Second, in our study, heart rate did not show any significant change in the short-term period after renal denervation, in contrast with the marked concomitant MSNA modifications. We can speculate that the dissociation between the behavior of heart rate and peripheral sympathetic nerve activity reflects the fact that renal denervation, despite having peripheral sympathoinhibitory effects, does not affect cardiac sympathetic outflow. A more likely hypothesis, however, is that the small sample size of the study, together with the short follow-up period, might have reduced the possibility to detect a decrease in heart rate. Indeed, recent large-scale studies with a prolonged follow-up have shown significant increase of heart rate after renal denervation. 30–32 Finally, our study confirms the now large body of evidence that the BP-lowering effects of renal denervation are greater in magnitude for office than for ambulatory measurements, 29,32 as also documented by the results of the Symplicity HTN-3, which failed, however, to detect any significant reduction in the office and ambulatory BP in resistant hypertensive patients 6 months after renal denervation when compared with a sham procedure. They add to this information the finding, however, that the finger BP effects reflect the ambulatory rather than the office values. Thus, the daily life effects of renal denervation can be inferred also by BP measurements performed in the office environment, provided that multiple values are collected.

Our study has some limitations. One, although superimposable to the sample size of previous studies assessing the effects of renal denervation on sympathetic nerve traffic, 3–5 our study population was small. This can have affected, at least in part, the study results, by increasing the variability of the MSNA responses to renal denervation or by preventing to detect a statistical significance in the various correlations performed. It should be underlined, however, that, with the exception of the 15-day assessment, MSNA variability, as expressed by the SD value (Table S1), was much smaller than the BP one and almost superimposable at 1, 3, and 6 months after the procedure. Finally, the total number of experimental sessions performed in the actively treated group (n=5) was so large as to make the effects seen in any individual patient robust. Two, patients were under antihypertensive drugs, which could per se affect sympathetic activity (β-blockers, angiotensin-converting enzyme -inhibitors,
share any relationship with the effects of the procedure on sympathetic neural outflow traffic and baroreflex function of adrenergic drive. They also show that neither neural nor reflex variables may be of help in predicting the BP responses to the procedure, which seem to be only in part dependent on these factors. As already mentioned, the small sample size of the present study calls for further investigations to confirm the present findings.

Disclosures

G. Grassi and G. Mancia received consulting and lecture fees from Medtronic. The other authors report no conflicts.

References

14. Park SH, Shih C, Nohrega TP, Bailey KR, Seward JB. Two-dimensional echocardiographic calculation of left ventricular mass as recommended by


Novelty and Significance

What Is New?

• The study examined whether and to what extent office and ambulatory blood pressure responses to renal denervation are qualitatively, quantitatively, and temporally related to the sympathetic nerve traffic responses, as well as to the modifications of the baroreflex–sympathetic sensitivity during a follow-up postdenervation period amounting to 6 months.

What Is Relevant?

• The results document for the first time that the blood pressure–lowering effect of the denervation temporally precedes the appearance of the sympathoinhibitory response, and that no relationship is detectable between the blood pressure and the sympathetic responses to the denervation procedure at any time during the 6-month follow-up.

Summary

The study shows that the blood pressure reduction associated with renal denervation does not share a relationship with the effects of the procedure on sympathetic neural outflow traffic and baroreflex control of adrenergic tone. Neither neural nor reflex variables may be of help in predicting the blood pressure responses to the procedure, which seem to be only in part dependent on these factors.
Blood Pressure Responses to Renal Denervation Precede and Are Independent of the Sympathetic and Baroreflex Effects

Guido Grassi, Gino Seravalle, Gianmaria Brambilla, Daniela Trabattoni, Cesare Cuspidi, Rocco Corso, Federico Pieruzzi, Simonetta Genovesi, Andrea Stella, Rita Facchetti, Domenico Spaziani, Antonio Bartorelli and Giuseppe Mancia

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BLOOD PRESSURE RESPONSES TO RENAL DENERVATION PRECEDE AND ARE INDEPENDENT ON THE SYMPATHETIC AND BAROREFLEX EFFECTS.

Guido Grassi¹,², Gino Seravalle³, Gianmaria Brambilla¹, Daniela Trabattoni⁴, Cesare Cuspidi¹,³, Rocco Corso⁵, Federico Pieruzzi⁵, Simonetta Genovesi⁵, Andrea Stella⁵, Rita Facchetti¹, Domenico Spaziani⁶, Antonio Bartorelli⁴, Giuseppe Mancia¹,³.

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Running title: BP and MSNA responses to renal denervation.

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S1. Changes in office, beat-to-beat and 24 hour systolic and diastolic blood pressure (SBP and DBP respectively) values observed 15 days, 1 month, 3 months and 6 months following renal denervation. The corresponding changes in muscle sympathetic nerve traffic (MSNA) are also provided. Data are shown as means ± standard deviations.

<table>
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<th>Variable</th>
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<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
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<td></td>
<td></td>
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<tr>
<td>Δ SBP</td>
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<tr>
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<td>Δ MSNA</td>
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S1