Catheter-Based Renal Nerve Ablation and Centrally Generated Sympathetic Activity in Difficult-to-Control Hypertensive Patients
Prospective Case Series

Julia Brinkmann,* Karsten Heusser,* Bernhard M. Schmidt, Jan Menne, Gunnar Klein, Johann Bauersachs, Hermann Haller, Fred C. Sweep, Andre Diedrich, Jens Jordan, Jens Tank

Abstract—Endovascular renal nerve ablation has been developed to treat resistant hypertension. In addition to lowering efferent renal sympathetic activation, the intervention may attenuate central sympathetic outflow through decreased renal afferent nerve traffic, as evidenced by a recent case report. We tested the hypothesis in 12 nonpreselected patients with difficult-to-control hypertension (aged 45–74 years) admitted for renal nerve ablation. All patients received ≥3 antihypertensive medications at full doses, including a diuretic. Electrocardiogram, respiration, brachial and finger arterial blood pressure, and muscle sympathetic nerve activity were recorded before and 3 to 6 months after renal nerve ablation. Heart rate and blood pressure variability were analyzed in the time and frequency domain. Pharmacological baroreflex slopes were determined using the modified Oxford bolus technique. Resting heart rate was 61±3 bpm before and 58±2 bpm after ablation (P=0.4). Supine blood pressure was 157±7/85±4 mm Hg before and 157±6/85±4 mm Hg after ablation (P=1.0). Renal nerve ablation did not change resting muscle sympathetic nerve activity (before, 34±2 bursts per minute; after, 32±3 bursts per minute P=0.6), heart rate variability, or blood pressure variability. Pharmacological baroreflex control of heart rate and muscle sympathetic nerve activity did not change. We conclude that reduced central sympathetic inhibition may be the exception rather than the rule after renal nerve ablation in unselected patients with difficult-to-control arterial hypertension. (Hypertension. 2012;60:1485-1490.) ● Online Data Supplement

Key Words: renal nerve ablation ■ arterial hypertension ■ sympathetic nerve traffic ■ baroreflex

Some patients with hypertension have blood pressures that are extremely difficult to control even with ≥3 simultaneously administered medication classes, including a diuretic. A proof-of-concept study and a subsequent randomized-controlled trial suggested that catheter-based renal nerve ablation can lower blood pressure in such patients.1,2 The idea is based on solid physiological studies suggesting that efferent and afferent renal nerves contribute to arterial hypertension1 and that they comprise a sensible treatment target.4 In fact, surgical splanchnic sympathetic denervation has been applied before any dietary or medical antihypertensive treatment.4 Catheter-based renal nerve ablation decreased renal norepinephrine spillover, reflecting efferent activity by 47%.2 The mechanisms likely contribute to the blood pressure–lowering effect because efferent renal sympathetic nerves activate the renin-angiotensin system6,7 and directly stimulate tubular sodium retention.8,9 In addition, reduced afferent renal nerve traffic may have elicited a central nervous sympatholytic response. Indeed, massive reductions in muscle sympathetic nerve activity (MSNA) and systemic norepinephrine spillover have been reported in a single patient after renal nerve ablation.10 Similarly, removal of the diseased native kidney reduced MSNA in renal transplant recipients.11 These clinical observations translate the experimental finding that renal afferents convey signals to the brain, thus raising sympathetic activity and blood pressure12,13 from animals to humans.

Received July 3, 2012; first decision July 16, 2012; revision accepted August 30, 2012.
From the Institute of Clinical Pharmacology (J.B., K.H., J.J., J.T.), Department of Nephrology and Hypertension (B.M.S., J.M., H.H.), and Department of Cardiology and Angiology (G.K., J.B.), Hannover Medical School, Hannover, Germany; Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University, Nashville, TN (A.D.); Department of Chemical Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands (F.C.S.).
*These authors contributed equally to this article.
This trial is registered at ClinicalTrials.gov with trial identifier NCT01355055 (http://www.clinicaltrials.gov/ct/show/NCT01355055).
The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.201186/-/DC1.
Correspondence to Jens Jordan, Institute of Clinical Pharmacology, Hannover Medical School,Carl-Neuberg-Str 1, 30625 Hannover, Germany. E-mail jordan.jens@mh-hannover.de.
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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.112.201186

1485
Moreover, they suggest that afferent signals from the kidney sustain sympathetic tone even in patients without overt renal disease. Therefore, we tested the hypothesis that MSNA reduction is a typical response to catheter-based renal nerve ablation in patients with difficult-to-control hypertension. Furthermore, we hypothesized that the extent of sympathoinhibition is related to the decrease in arterial pressure.

Methods

Patients

After renal nerve ablation had been established at our center, we included 12 patients (11 men and 1 woman; Table 1) with difficult-to-control arterial hypertension referred for catheter-based renal nerve ablation. Patients had to have uncontrolled essential hypertension despite treatment with ≥3 antihypertensive medications at full doses, including a diuretic. The mean number of antihypertensive drugs was 7±2. Patient characteristics are summarized in Table 1. Mean body mass index was 31.2±8 kg/m². All patients were judged to be compliant by their treating physicians. In addition, we checked compliance with the antihypertensive drug regimen through phone interviews before each study visit. Medication and body mass index remained constant during the study. Participants were excluded if they had secondary hypertension. The study was approved by the local research ethics committees. Written informed consent was obtained.

Catheter-Based Renal Nerve Ablation

The right femoral artery was punctured after local anesthesia and a 6F sheath was placed. Four to 8 radiofrequency applications along both main renal arteries were applied (maximum 8 watts, maximum 75°C for 2 minutes) using the Symplicity Catheter System (Ardian). The distance between applications was 5 mm. The catheter was rotated 90° between applications. Visceral pain during the procedure was relieved by fentanyl and midazolam. After the procedure, puncture site was closed with a closure device (AngioSeal; St. Jude Medical, Minneapolis, MN), the groin was compressed for 4 hours, and patients received 100 mg of aspirin QD for 4 weeks.

Cardiovascular and Sympathetic Measurements

We conducted our measurements before and 5 months (range, 3–6 months) after renal nerve ablation after an overnight fast in the morning hours. During testing, patients remained in the supine position. An ECG was continuously recorded (Niccomo, Medis GmbH). Noninvasive finger blood pressure recording was used (Finometer, Finapres Medical Systems) and adjusted against brachial oscillometric blood pressure measurements (Dinamap, Critikon). We obtained blood samples for plasma catecholamine determination with high-pressure liquid chromatography and consecutive electrochemical detection after a resting period of 30 minutes.

MSNA was recorded from the right peroneal nerve (Nerve Traffic Analyzer 662C-3, Biomedical Engineering Department, University of Iowa). Data were analog-to-digital converted and analyzed using a program written by one of the authors (A.D.). We determined the following MSNA parameters from the integrated nerve signal: burst frequency (bursts per minute), burst incidence (bursts per 100 heart beats), and area under the bursts per minute (arbitrary units). Heart rate and blood pressure variability, as well as baroreflex heart rate regulation, were assessed using spectral analysis, cross-spectral analysis, the transfer function between R-R intervals and systolic blood pressure, and the sequence technique, respectively, in 10 patients. Two patients had to be excluded because of cardiac arrhythmias. We assessed sympathetic and parasympathetic pharmacological baroreflex gains using the modified Oxford bolus technique in 6 patients. Pharmacological central sympathetic inhibition was tested in 5 patients using clonidine infusion (maximum, 2 µg/kg) to show the possible effect size on MSNA. We reasoned that patients with a larger clonidine response would also respond more to catheter-based renal nerve ablation. Methodological details regarding microneurography and baroreflex testing are provided in the online-only Data Supplement.

Table 1. Patient Characteristics

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<th>Identification No.</th>
<th>Age, y/sex</th>
<th>BMI, kg/m²</th>
<th>DM</th>
<th>CAD/MI</th>
<th>Stroke/TIA</th>
<th>Antihypertensive Medication</th>
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<td>28.7</td>
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<tr>
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<td>Bisoprolol, amlodipine, ramipril, spironolactone, torasemid, hydrochlorothiazide, moxonidine, minoxidil, urapidil</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DM, diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction; TIA, transient ischemic attack; m, male; f, female.
To detect such a decrease with 80% statistical power, 10 subjects are required. The relationship between changes in sympathetic activity and arterial pressure was assessed by linear regression analysis. A reduction of 15 bursts per minute to be clinically relevant.

We encountered no procedure-related serious adverse events. Although antihypertensive medications were kept constant, 4 patients presented in the emergency department with severe hypertensive episodes after renal nerve ablation. Moreover, parasympathetic baroreflex heart rate control and baroreflex control of sympathetic nerve traffic did not change (Table 2). Individual MSNA recordings before and 3 to 6 months after renal nerve ablation are presented for 11 patients in the online-only Data supplement.

Discussion

Our study is the first to show that, after catheter-based renal nerve ablation, patients with difficult-to-control arterial hypertension do not exhibit a consistent and clinically relevant MSNA reduction. In fact, MSNA was almost identical before and after the procedure. Only a few patients responded to this treatment. Finally, changes in blood pressure and MSNA were not related to each other. In fact, changes in systolic blood pressure tended to be negatively correlated with the changes in MSNA and catecholamines in this group of patients, indicating baroreflex counterregulation instead of central inhibition.

We applied several complementary methods to gauge renal nerve ablation influences on central autonomic regulation, including measurements of heart rate variability, blood pressure variability, baroreflex function, plasma catecholamines, and MSNA. Microneurographic MSNA measurements are considered as a standard method in human studies on central sympathetic regulation.20 We and others showed excellent reproducibility of MSNA measurements over weeks and

Figure 2. Individual and mean values for blood pressure, heart rate (HR), and muscle sympathetic nerve activity (MSNA) measurements before (pre) and after (post) renal nerve ablation. SBP indicates systolic blood pressure.
Given a surprisingly low intraindividual variability over years,1,2 MSNA is a suitable readout for longitudinal studies in small samples. Central sympathetic inhibition is associated with heart rate, blood pressure, plasma norepinephrine, and MSNA reductions. Furthermore, the baroreflex set point for the regulation of heart rate and sympathetic activity is shifted to lower blood pressure values.15 Finally, sympathetic inhibition is commonly but not always associated with improved heart rate variability through the parasympathetic nervous system.24–26

We recapitulated these findings in our patients when we infused the sympatholytic drug clonidine.

However, it is not entirely clear that radiofrequency energy application always leads to sufficient disruption of renal afferent and efferent nerves. In fact, there is no clinically applicable readout to confirm procedural success. We are confident that our findings are valid because we strictly adhered to recommendations for conducting the procedure provided by the catheter manufacturer. Moreover, experienced operators were in charge of the procedure, and our study was begun after the methodology had been practiced in our center in a sufficiently large number of patients. Studies in large animals suggest that endoluminal radiofrequency energy delivery affects renal nerve supply.27 More detailed animal studies may be needed to assess long-term safety and efficacy. These studies could also address the question of whether and when regrowth of disrupted renal nerves fibers occurs after the procedure as it does within months to years after solid organ transplantation.28

An alternative explanation for our findings is that the treatment effect to catheter-based renal nerve ablation is more variable (ie, patient dependent) and of lesser magnitude than previously believed.

Compared with earlier clinical trials including carefully selected patients with severe drug-resistant arterial hypertension,1,2 our patients showed lower blood pressure readings before treatment, and some patients were on fewer medications. We suggest that a more benign clinical phenotype may reflect the clinical reality in Germany. As early as 1941, Grimson4 noted that the blood pressure response to surgical sympathetic denervation is variable and that some patients do not respond at all. The same could also apply to patients treated with catheter-based renal nerve ablation. It is tempting to speculate that interruption of sympathoinhibitory renal afferents29 could contribute to the variability in the response to renal nerve ablation.

It is also possible that the response to renal nerve ablation depends on baseline sympathetic activity. In the case report by Schlaich et al.,10 MSNA was 56 bursts per minute before renal nerve ablation. In our patients, MSNA ranged between 21 and 45 bursts per minute. The large variability in MSNA between patients with resistant hypertension further supports the observation that sympathetic support of blood pressure is not increased in all patients.30 Presence or absence of obesity could also contribute to the variability.

Yet, none of these measurements changed significantly after renal nerve ablation. Overall, these observations suggest that renal nerve ablation did not elicit a consistent central sympatholytic response at least at rest.

Figure 3. A. Muscle sympathetic nerve activity (MSNA) changes plotted against systolic blood pressure (SBP) changes after renal nerve ablation; (B) venous plasma norepinephrine changes plotted against SBP changes after renal nerve ablation.
However, average body mass indices in the Symplicity-HTN2 trial and in our study were almost identical (31 kg/m²).

Office blood pressure measurements in clinical trials leading to approval of the renal nerve ablation device in Europe may have overestimated the true treatment effect. In the randomized-controlled Symplicity HTN-2 trial, the control group exhibited no office blood pressure reduction after 6 months. The intervention group decreased blood pressure 32/12 mm Hg. Ambulatory blood pressure measurements obtained in 20 of 106 participants only showed an 11/7-mm Hg depressor response. We averaged repeated oscillometric supine blood pressure measurements obtained after a sufficient resting period.

The main weakness of our study is the small sample size and the lack of a control group. Yet, our study was sufficiently powered to show a clinically relevant MSNA change. In fact, the statistical power to show a 5 bursts per minute change in MSNA exceeded 80%. In the case report by Schlaich et al., MSNA decreased 15 bursts per minute after 30 days and 37 bursts per minute after 12 month. Thus, we conclude that reductions in centrally generated sympathetic activity may be the exception rather than the rule after renal nerve ablation in unselected patients with difficult-to-control arterial hypertension. Provided that the procedure actually led to renal nerve ablation, our findings challenge the idea that renal afferent traffic tonically augments centrally generated sympathetic activity in the absence of overt renal disease. The importance of kidney pathology for the sympathetic response to antihypertensive treatments is illustrated by studies on renin-angiotensin system inhibitors. In patients with kidney disease, renin-angiotensin system inhibition substantially reduced sympathetic activity. In patients with normal kidney function, however, sympathetic nerve traffic increased likely through baroreflex mechanisms.31

Perspectives

Given the high prevalence of drug therapy–resistant hypertension according to the currently used clinical criteria32,33 and the increased cardiovascular risk in these patients,34 new concepts to treat the condition more effectively are urgently needed. Intensive lifestyle interventions including aerobic exercise ameliorate hypertension in these patients.35 Moreover, in a recent study, 58% of patients with uncontrolled hypertension on triple antihypertensive therapy achieved their blood pressure goal when sequential pharmacological nephron blockade was added.33 Device-based antihypertensive treatments, such as catheter-based renal nerve ablation or electrical carotid sinus stimulation, are promising new approaches for patients not responding to intensive pharmacological therapy. Moreover, these therapies provide unique insight in human cardiovascular physiology. However, in the absence of long-term data on safety and efficacy from sufficiently large controlled clinical trials, sound clinical reasoning should prevail. In particular, device-based antihypertensive treatments should be restricted to patients with true resistant hypertension and high cardiovascular risk preferably in the setting of clinical trials or registries. Given the costs and short- and long-term potential risks of these procedures, a large proportion of nonresponders may not be acceptable. Methods to identify patients more likely to benefit from these procedures should be sought. We are concerned that, in Germany, >100 sites conduct catheter-based renal nerve ablation, and this number is steadily growing. Along with the widespread adoption of the procedure, the criteria for patient eligibility are softening.

Acknowledgments

The Deutsche Forschungsgemeinschaft supports J. Jordan and J. Brinkmann (Jo 284/6-1). The German Space Agency supports J. Tank and K. Heusser.

Disclosures

None.

References


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- A single case report suggested that renal nerve ablation profoundly attenuated central sympathetic nerve traffic.

- In our study, centrally generated sympathetic activity and blood pressure were not reduced after renal nerve ablation.

**What Is Relevant?**

- Reduction of centrally generated sympathetic activity may be the exception rather than the rule in difficult-to-control hypertensive patients without overt renal disease.

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**Novelty and Significance**

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**What Is Relevant?**

- Reduction of centrally generated sympathetic activity may be the exception rather than the rule in difficult-to-control hypertensive patients without overt renal disease.

**Summary**

Central sympathetic nerve traffic is not reduced after renal nerve ablation, thus challenging the proposed mechanism through which renal nerve ablation affects the cardiovascular system. Moreover, the proportion of nonresponders may be larger than previously believed.
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Hypertension. 2012;60:1485-1490; originally published online October 8, 2012; doi: 10.1161/HYPERTENSIONAHA.112.201186

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Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult to control hypertensive patients: Prospective case series

Short title: Renal nerve ablation and sympathetic activity


* Institute of Clinical Pharmacology, Hannover Medical School, Hannover, Germany
** Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany
*** Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany
**** Department of Medicine, Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN, USA
***** Department of Chemical Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Corresponding author:

Jens Jordan, M.D.

Institute of Clinical Pharmacology, Hannover Medical School

Carl-Neuberg-Str. 1, 30625 Hannover, Germany

phone: +49 511 532 2821, fax: +49 511 532 2750,

Email: jordan.jens@mh-hannover.de
Methods

MSNA:
MSNA was recorded from the right peroneal nerve. A unipolar tungsten electrode (tip diameter of 1-5 µm, shaft diameter of 200 µm) was inserted into a muscle nerve fascicle of the peroneal nerve in the popliteal space for multiunit recordings. Nerve activity was amplified with a total gain of 100,000, bandpass-filtered (0.7-2 kHz), and integrated by feeding the rectified signal through a ‘leaky integrator’ (resistance-capacitance integrating network, time constant 0.1 sec) using a nerve traffic analyzer system (University of Iowa, Bioengineering Dept.). Proper needle positioning was verified by the following criteria:

1. no skin paresthesias caused by needle insertion into nerve
2. tapping on the innervated muscle elicited spindle afferent discharges
3. stroking the skin of the lower leg or foot did not provoke afferent activity
4. pulse synchronicity of the bursts
5. arousal stimuli (loud noise) did not entail skin sympathetic nerve activity
6. end-inspiratory breath-hold or bolus injections of sodium nitroprusside induced or increased burst frequency
7. biphasic response in neural activity to Valsalva’s maneuver (activation during phase II, inhibition during phase IV)
8. the largest bursts in the integrated nerve signal had a signal-to-noise ratio greater than 3
9. internal electrical stimulation via the recording needle electrode caused muscle twitches without paresthesias
Analysis:
MSNA bursts in the integrated signal were accepted if they complied with the following criteria:
1. signal-to-noise ratio greater than 2
2. latency limit (burst maximum – preceding R wave: 1.0 – 1.6 sec)
3. burst-width limit (0.2 – 1.0 sec)
4. similar rising and falling gradient
5. no preceding premature beat.

Sympathetic baroreflex:
Sympathetic bursts result from disinhibition of sympathetic premotor neurons in the brainstem during diastolic pressure troughs. Low diastolic pressures are associated with high MSNA whereas high diastolic pressures are linked to low or absent MSNA. Plots of MSNA against a wider range of diastolic pressures show a sigmoidal relationship (sigmoidal baroreflex curve). The ratio between the changes in MSNA and in diastolic pressure, i.e. the slope of the sigmoidal baroreflex curve, varies with pressure. The slope at the steepest part of the curve’s center is referred to as baroreflex gain or baroreflex sensitivity.
To calculate sympathetic baroreflex gain we first assigned diastolic blood pressure values for each cardiac cycle to their related pressure bin (bin width: 1 mmHg). Then, we plotted the relative occurrence of MSNA bursts in each bin (i.e. burst incidence [%]) over diastolic blood pressure. Finally, baroreflex curves were fitted to the data by nonlinear regression (least-squares method) using the Boltzmann equation (GraphPad Prism software, version 5; GraphPad Software, San Diego, CA). The fitting procedure was constrained to maximum and minimum burst incidences of 100% and 0%, respectively, and weighted with bin occupation, i.e. the number of cardiac cycles in the pressure bin.

Modified Oxford-Bolus-Technique:
Intravenous bolus injections of sodium nitroprusside were followed by phenylephrine hydrochloride one minute later. Doses were adjusted individually for safety reasons with the goal to reach arterial pressure changes of at least 25 mmHg. The usual dose was 0.75 µg/kg for both substances.
Figure S1: Individual MSNA recordings before and 3-6 months after renal nerve ablation in eleven patients.
Figure S2: ECG, finger blood pressure, and MSNA recordings in the patient with the largest blood pressure reduction following renal nerve ablation, MSNA was 40 bursts/min before and 41 bursts/min after the procedure. Blood pressure was 222/101 mm Hg before and 156/72 mm Hg after renal nerve ablation.