Hypertension

Effect of Renal Sympathetic Denervation on Glucose Metabolism in Patients With Resistant Hypertension

A Pilot Study

Felix Mahfoud, MD; Markus Schlaich, MD; Ingrid Kindermann, MD; Christian Ukena, MD; Bodo Cremers, MD; Mathias C. Brandt, MD; Uta C. Hoppe, MD; Oliver Vonend, MD; Lars C. Rump, MD; Paul A. Sobotka, MD; Henry Krum, MBBS, PhD; Murray Esler, MBBS, PhD, FRACP; Michael Böhm, MD

Background—Hypertension is associated with impaired glucose metabolism and insulin resistance. Chronic activation of the sympathetic nervous system may contribute to either condition. We investigated the effect of catheter-based renal sympathetic denervation on glucose metabolism and blood pressure control in patients with resistant hypertension.

Methods and Results—We enrolled 50 patients with therapy-resistant hypertension. Thirty-seven patients underwent bilateral catheter-based renal denervation, and 13 patients were assigned to a control group. Systolic and diastolic blood pressures, fasting glucose, insulin, C peptide, hemoglobin A1c, calculated insulin sensitivity (homeostasis model assessment–insulin resistance), and glucose levels during oral glucose tolerance test were measured before and 1 and 3 months after treatment. Mean office blood pressure at baseline was 178/96±3/2 mm Hg. At 1 and 3 months, office blood pressure was reduced by −28/−10 mm Hg (P<0.001) and −32/−12 mm Hg (P<0.001), respectively, in the treatment group, without changes in concurrent antihypertensive treatment. Three months after renal denervation, fasting glucose was reduced from 118±3.4 to 108±3.8 mg/dL (P=0.039). Insulin levels were decreased from 20.8±3.0 to 9.3±2.5 μIU/mL (P=0.006) and C-peptide levels from 5.3±0.6 to 3.0±0.9 ng/mL (P=0.002). After 3 months, homeostasis model assessment–insulin resistance decreased from 6.0±0.9 to 2.4±0.8 (P=0.001). Additionally, mean 2-hour glucose levels during oral glucose tolerance test were reduced significantly by 27 mg/dL (P=0.012). There were no significant changes in blood pressure or metabolic markers in the control group.

Conclusions—Renal denervation improves glucose metabolism and insulin sensitivity in addition to a significantly reducing blood pressure. However, this improvement appeared to be unrelated to changes in drug treatment. This novel procedure may therefore provide protection in patients with resistant hypertension and metabolic disorders at high cardiovascular risk.


Key Words: sympathectomy ■ glucose metabolism disorders ■ hypertension ■ insulin resistance ■ sympathetic nervous system

Renal sympathetic afferent and efferent nerves play an important role in blood pressure regulation. Increased renal sympathetic drive is a common feature in patients with various forms of hypertension, and is associated with components of the metabolic syndrome.1–3 There is a bidirectional relationship between sympathetic overactivity inducing insulin resistance and hyperinsulinemia producing sympathetic activation, thus initiating a vicious cycle.4 A percutaneous, catheter-based approach to reduce renal sympathetic afferent and efferent activity with application of intra-arterial radio-frequency energy has been used successfully to treat drug-resistant hypertension and has been demonstrated to reduce muscle sympathetic nerve activity and renal and total body noradrenaline spillover.5–7 Given the involvement of the sympathetic nervous system in metabolic control, it is plausible to speculate that reduction of sympathetic activity by renal denervation may have a substantial effect on glucose metabolism in hypertensive patients. The present study was

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From the Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany (F.M., I.K., C.U., B.C., M.B.); Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia (M.S., M.E.); Herzcentrum der Universität zu Köln, Klinik III für Innere Medizin, Köln, Germany (M.C.B., U.C.H.); Klinik für Nephrologie, Universitätskliniken Düsseldorf, Germany (O.V., L.C.R.); Ohio State University, Columbus, and Ardian, Inc., Palo Alto, CA (P.A.S.); and Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (H.K.).
Correspondence to Felix Mahfoud, MD, or Michael Böhm, MD, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Strasse 1, 66421 Homburg/Saar, Germany. E-mail felix.mahfoud@uks.eu
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designed to evaluate the relation between sympathetic activity and glucose metabolism and the role of therapeutic renal denervation in patients with resistant hypertension.

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Methods

This study was approved by the ethics committees at all participating centers in accordance with the Declaration of Helsinki. Patients were treated between March 2009 and May 2010 with subsequent follow-up to 3 months. Systolic, diastolic, and mean arterial blood pressures, as well as fasting glucose, insulin, C peptide, glycosylated hemoglobin (HbA1c), and glucose levels during oral glucose tolerance test (OGTT), were measured. All patients gave written informed consent.

Eligible patients were >18 years of age and had an office blood pressure of ≥160 mm Hg (≥150 mm Hg for patients with type 2 diabetes mellitus) despite being treated with at least 3 antihypertensive drugs (including 1 diuretic), with no changes in medication for a minimum of 2 weeks before enrollment. Patients were included if they were not pregnant and had a glomerular filtration rate ≥45 mL·min⁻¹·1.75 m⁻² (using the Modified Diet in Renal Disease formula). Patients with renal artery anatomy ineligible for treatment (main renal arteries < 4 mm in diameter or < 20 mm in length; hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery; a history of prior renal artery intervention, including balloon angioplasty or stenting; multiple main renal arteries in either kidney), type 1 diabetes mellitus, myocardial infarction, unstable angina pectoris, cerebrovascular accident within the last 6 months, or hemodynamically significant valvular disease were excluded from the study. Fifty patients were enrolled; 37 were prospectively assigned to the treatment group following protocols of ongoing therapeutic renal denervation trials (NCT00666438 and NCT00888433), and 13 patients, constituting the control population, were assigned to continued medical therapy (NCT00664638 and NCT00888433), and 13 patients, constituting the control group, were assigned to continued medical therapy and were scheduled for renal denervation in 6 months. Of these, 26 patients (renal denervation, n=17; control group, n=9) were included in the randomized controlled Symplicity Hypertension-2 trial. In all other patients, the measurements were performed as an extension to the Symplicity protocol (NCT00888433) using the same inclusion and exclusion criteria.

Renal angiograms were performed via femoral access to confirm anatomic eligibility. The treatment catheter (Symplicity and Flex by Arsidian Inc, Palo Alto, CA) was introduced into each renal artery by use of a renal double curve or left internal mammary artery guiding catheter. Radiofrequency ablations lasting up to 2 minutes each were applied with low power of 8 W to obtain up to 6 ablations separated (>5 mm) both longitudinally and rotationally within each renal artery. Treatments were delivered from the first distal main renal artery bifurcation to the ostium. Catheter tip impedance and temperature were constantly monitored, and radiofrequency energy delivery was regulated according to a predetermined algorithm. Patients were given heparin to achieve an activated clotting time of 250 seconds.

Diffuse visceral pain occurred during the radio energy delivery that was managed with intravenous anxiolytics and narcotics. The median procedure time (from initiation to completion of radiofrequency delivery) was 42 minutes.

All patients underwent a complete history and physical examination, assessment of vital signs, review of medication, and blood chemistry (including serum creatinine), as well as assessment of fasting glucose, insulin, C peptide, and HbA1c at baseline and at each follow-up visit at 1 and 3 months. An OGTT was performed at baseline and after 3 months. The patients were instructed to fast for at least 8 to 12 hours before the OGTT and blood sampling. The OGTT consisted of fasting, 60-, and 120-minute glucose measures. According to the World Health Organization, the results of the OGTT were graded into 4 categories: normal (fasting glucose <110 mg/dL, 120-minute glucose ≤140 mg/dL), impaired fasting glycemia (fasting glucose ≥110 mg/dL, 120-minute glucose <140 mg/ dL), impaired glucose tolerance (fasting glucose <126 mg/dL, 120-minute glucose ≥140 mg/dL), and diabetes mellitus (fasting glucose ≥126 mg/dL, 120-minute glucose ≥200 mg/dL). Plasma glucose concentration was assessed with the glucose-oxidase method. Plasma insulin and C-peptide concentrations were measured by a chemiluminescent assay. We determined HbA1c using a high-performance liquid chromatography method. The glucose values are expressed in milligrams per deciliter, insulin as international microunits per milliliter, C peptide as nanograms per milliliter, and HbA1c, as percent. The insulin sensitivity index was calculated from fasting glucose and insulin values as described: homeostasis model assessment–insulin resistance (HOMA-IR)=(FPG×FPI)/405.9 where FPG and FPI are fasting plasma glucose and fasting plasma insulin, respectively. The Quantitative Insulin Sensitivity Check Index (ISQUICKI) was calculated as follows: ISQUICKI = 1/ [log(FPI)+log(FPG)].10 Patients were interviewed to determine whether they had taken their complete medication at defined doses. Office blood pressure readings were taken in a seated position after 5 minutes of rest according to the standard Joint National Committee VII guidelines.11 Averages of the triplicate measures were used. Physicians were instructed not to change medications except when medically required. Patients were instructed to remain adherent to their prescribed drugs and defined doses at each visit.

Statistical Analysis

Baseline data were compared between the renal denervation and control groups with the use of either an independent-samples t test for means or a χ² test for proportions. Changes in fasting glucose and in insulin, C peptide, HbA1c, HOMA-IR, ISQUICKI, and office blood pressures were analyzed from baseline to 1 and 3 months by 2-factor ANOVA with repeated measures. The Dunnett test was used to compute posthoc comparisons of significant values. A 2-tailed value of P<0.05 was regarded as statistically significant. Glucose levels during OGTT were analyzed with a paired t test to compare baseline with 3-month results. Simple associations were assessed with the Pearson tests for 2 independent proportions. Data are presented as mean±SEM. All statistical analyses were performed with SPSS statistical software (version 17.0, SPSS Inc, Chicago, IL).

Results

The treatment (n=37) and control (n=13) groups were well matched in terms of baseline characteristics, without significant differences between groups (Table 1). All patients were maintained on baseline antihypertensive medication and followed up for 3 months. Table 1 shows the demographic indicators and clinical characteristics. Most patients were male (n=37, 74%). The mean age was 59.7±1.4 years. On average, patients were taking 5.6±0.2 antihypertensive drugs, with 47 (94%) receiving an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or both; 44 (88%) taking β-blockers; 36 (72%) taking calcium channel blockers; and 34 (68%) receiving centrally acting sympatholytic agents. All patients received diuretics, with 14 (28%) taking aldosterone antagonists. Patients with type 2 diabetes mellitus (n=20, 40%) were diagnosed at least 12 months previously. Diagnosis was confirmed as recommended by the American Diabetes Association.12 Sixteen patients received antidiabetic drugs: metformin (n=15), gliclazide (n=5), or combined therapy. None of the patients changed the antidiabetic treatment during follow-up. None of the patients was on insulin treatment. Weight and body mass index were similar at baseline and at 3 months, and were unchanged in both groups.

At baseline, overall mean sitting office systolic blood pressure was 178±2.7 mm Hg, and mean sitting office diastolic blood pressure was 96±2.2 mm Hg, with a heart rate...
Three of the treated patients (9%) were nonresponders with a follow-up (Systolic 120/100 mm Hg; Diastolic 80/60 mm Hg; C peptide, ng/mL 4.9/0.5; Hemoglobin A1c, % 6.0/0.3; Insulin, μIU/mL 19.3±2.5; C peptide, ng/mL 4.9/0.5; HOMA-IR 5.7±0.7; ISQUICKI 0.32±0.01. eGFR indicates estimated glomerular filtration rate; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment–insulin resistance; and ISQUICKI Quantitative Insulin Sensitivity Check Index. Data are mean±SEM when appropriate. P for renal denervation versus control group.

systolic blood pressure reduction of <10 mm Hg. On average, patients received 5.6 antihypertensive drugs at baseline and were instructed not to change their medications unless adverse effects occurred. There were no changes in medication during the study period in any of the patients up to the 3-month follow-up, when repeated testing was performed. However, after the 3-month follow-up visit, in 13 treated patients, antihypertensive medication had to be reduced owing to hypotension associated with symptoms. Therefore, de-escalation in antihypertensive drug treatment became necessary. In 2 control patients and 1 treatment patient, antihypertensive medication had to be further increased after the development of symptoms or signs considered to be consequences of hypertension. To exclude postprocedural renovascular abnormalities, we performed renal duplex ultrasound at the 3-month follow-up and found no detectable abnormalities of the renal arteries. One patient developed a pseudoaneurysm at the femoral access site that was treated without further sequelae. No other complications were observed.

Three months after denervation, fasting glucose was reduced significantly from 118±3.4 to 108±3.8 mg/dL (P=0.039; Figure 2A); there were no significant changes in the control group. Insulin levels decreased from 20.8±3.0 to 9.3±2.5 μIU/mL (P=0.006; Figure 2B), which was associated with a reduction in C-peptide levels from 5.3±0.6 to 3.0±0.9 ng/mL (P=0.002; Figure 2C). At baseline, 13 patients in the treatment group had insulin levels ≥20 μIU/mL. Treatment decreased this number by 77% (n=10), with no changes in the control group. Changes in fasting glucose and insulin levels did not correlate to office systolic (r=0.141, P=0.433 and r=-0.242, P=0.175) or diastolic (r=0.05, P=0.806 and r=-0.184, P=0.313) blood pressure reduction. Insulin sensitivity, measured with HOMA-IR and ISQUICKI, increased significantly after renal denervation (Figure 2D). The HOMA-IR decreased from 6.0±0.9 to 2.4±0.8 (P=0.001), and the ISQUICKI increased from 0.32±0.01 to 0.36±0.01 (P=0.001). Even in the subgroup of patients (n=13) with diagnosed diabetes mellitus at study entry, renal denervation significantly reduced fasting glucose, insulin,
and C-peptide levels and improved insulin sensitivity after 3 months. The HbA_1c levels remained nearly at baseline values (5.7\%/11006.0\%) and did not change significantly during 3 months of follow-up. Mean reductions in glucose levels during OGTT after 3 months were \(-9.9\%12.0\) mg/dL (P=0.510) at 60 minutes and \(-27.10.1\) mg/dL (P=0.012) at 120 minutes in the treatment group but not in the control group. In 34 patients (treatment group, n=25; control group, n=9), the OGTT at baseline revealed 8 patients with impaired fasting glycemia, 18 patients with impaired glucose tolerance, and 8 patients with diabetes mellitus. After the procedure, 7 of 25 patients showed improvement in OGTT. Impaired fasting glycemia, impaired glucose tolerance, or both improved in 16% (n=4); the number of patients diagnosed with diabetes mellitus on the basis of OGTT was reduced by 12% (n=3); and the number of patients with normal glucose tolerance increased by 16% (n=4). Patients in the control group had no significant changes in glucose or insulin metabolism during follow-up, despite an increase in impaired fasting glycemia, impaired glucose tolerance, or both by 1 and an increase in diabetes mellitus by 2 (Table 2 and Figure 3).

### Discussion

The data identify the renal sympathetic nervous system as an important regulator of insulin resistance and show that renal nerve ablation substantially improves insulin sensitivity and glucose metabolism, in addition to significantly reducing blood pressure. Percutaneous renal denervation may represent the first nonpharmaceutical approach for treating insulin resistance and drug-resistant hypertension. Activation of the sympathetic nervous systems contributes to insulin resistance\(^{13}\) and the metabolic syndrome\(^{14}\) and is associated with central obesity\(^{15}\) and risk of developing diabetes mellitus.\(^3\) Although insulin itself exhibits sympathoexcitatory effects,\(^{16,17}\) renal denervation allows examination of the direct role of the sympathetic nervous system, without causing further systemic pharmacological interactions, in mediating insulin resistance and its consequences. Inhibition of the sympathetic nervous system by moxonidine has been shown to improve glucose metabolism by decreasing glucagon secretion and increasing skeletal blood flow with less glycogenolysis and gluconeogenesis,\(^{18}\) which is in favor of the pathophysiological relation between the central nervous system and insulin resistance.\(^{19}\) However, the use of centrally acting sympatholytics is nonspecific and limited by adverse effects, leading to high nonadherence rates.\(^{20}\) Elevated fasting glucose levels, impaired glucose tolerance, and diabetes mellitus have been associated with an increased risk of cardiovascular disease\(^{21–24}\) resulting from stimulation of inflammation, oxidative stress, and thrombotic activity,\(^{25}\) as well as inhibition of vascular smooth muscle cell apoptosis.\(^{26}\) Approximately 50% of patients with essential hypertension are considered to be insulin resistant.\(^{27}\) Insulin resistance is involved in type 2 diabetes mellitus, with a progression from impaired fasting glycemia to impaired glucose tolerance and to overt diabetes mellitus. Renal denervation may reduce the progression from insulin resistance to frank diabetes mellitus, or, in some cases, may reverse underlying diabetes mellitus. Compared with the Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes...
mellitus (CANOE) trial, which examined the impact of 2 hypoglycemic agents and failed to show significant changes in insulin resistance, as measured by HOMA-IR, therapeutic renal denervation substantially reduces insulin and glucose levels and calculated insulin resistance. A clinical strategy of significantly reducing central sympathetic outflow, measured by muscle sympathetic nerve activity, is associated with blood pressure reductions of \( \frac{-32}{-12} \) mm Hg \( (P<0.0001) \) after 6 months compared with the control group without affecting other pelvic, abdominal, or lower-extremity innervation and with no evidence of late renovascular complications within 24 months. Effective denervation of the efferent renal sympathetic fibers was shown in 10 patients by measurement of renal noradrenaline spillover, which was reduced by 47% after treatment. Renal denervation also reduced central sympathetic outflow, measured by muscle sympathetic nerve activity, indicating an alteration in afferent sympathetic drive. The substantial improvement in insulin sensitivity and glucose metabolism in response to renal denervation was associated with a reduction in cardiovascular risk factors.

The blood pressure reductions shown here are in line with the findings of a proof-of-concept study and the recently published results of the randomized controlled trial. Catheter-based renal denervation resulted in impressive office-based blood pressure reductions of \( \frac{-32}{-12} \) mm Hg \( (P<0.0001) \) after 6 months compared with the control group without affecting other pelvic, abdominal, or lower-extremity innervation and with no evidence of late renovascular complications within 24 months. Effective denervation of the efferent renal sympathetic fibers was shown in 10 patients by measurement of renal noradrenaline spillover, which was reduced by 47% after treatment. Renal denervation also reduced central sympathetic outflow, measured by muscle sympathetic nerve activity, indicating an alteration in afferent sympathetic drive. The substantial improvement in insulin sensitivity and glucose metabolism in response to renal denervation was associated with a reduction in cardiovascular risk factors.

### Table 2. Change in Blood Pressure and Glucose Metabolism at 1 and 3 Months

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<td>1 mo (n=37)</td>
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<td>SBP, mm Hg</td>
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<td>Body mass index, kg/m²</td>
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<td>Insulin, μIU/mL</td>
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<td>HOMA-IR</td>
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SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; OGTT, oral glucose tolerance test (performed at baseline and 3 months); HOMA-IR, homeostasis model assessment–insulin resistance; and ISQUICKI, Quantitative Insulin Sensitivity Check Index. Data are mean±SEM (relative changes) compared with baseline values when appropriate.

*One month versus baseline.
†Three months versus baseline.

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denervation may be explained by a combination of beneficial effects of sympathoinhibition, reduced release of noradrenaline on regional hemodynamics, and direct cellular effects.\textsuperscript{15,30--32} There is evidence that the increase in forearm noradrenaline release accompanied by reduced blood flow is associated with a markedly reduced glucose uptake, indicating an impaired ability of the cell to transport glucose across its membrane.\textsuperscript{33} This is related to the neurally mediated reduction in the number of open capillaries, resulting in an increased distance that insulin must travel to reach the cell membrane from the intravascular compartment.\textsuperscript{32} This situation is further aggravated by the fact that the insulin-mediated increase in muscle perfusion is reduced by \textasciitilde30\% in insulin-resistant states.\textsuperscript{30} The relevance of these hemodynamic consequences of sympathetic activation is highlighted by studies demonstrating a direct relationship between muscle sympathetic nerve activity and insulin resistance, and by an inverse relationship between insulin resistance and the number of open capillaries.\textsuperscript{15} The findings of our study using a novel interventional approach to substantially reduce sympathetic nerve activity in humans provide further persuasive evidence for a significant role of the sympathetic nervous system as a regulator of insulin sensitivity and glucose metabolism.

Our study has some potential limitations, including potential interference with drug effects. However, there were no changes in medication in the first 3 months, when testing occurred. A decrease in antihypertensive drugs that have been shown to influence insulin sensitivity (eg, \(\beta\)-blockers, diuretics, angiotensin-converting enzyme inhibitors)\textsuperscript{\textsuperscript{\textregistered}12} could have had an impact on our results. Despite the fact that patients and physicians were instructed not to change medication during the study period, it is possible that patients changed it themselves. Adherence to the prescribed drug regimen was an inclusion criterion of the study. Authors had full access to all data, and had final responsibility for the design, data interpretation, and report writing. The corresponding author was involved in the study design, data interpretation, and report writing. The corresponding author had full access to all data, and had final responsibility for the decision to submit the paper for publication. All authors have worked at centers receiving per-patient payment for study involvement as part of the Symplicity HTN-1 or HTN-2 study.

**Disclosures**

Dr Sobotka is an employee of Ardian Inc. All authors received scientific support from Ardian Inc.

**References**


**CLINICAL PERSPECTIVE**

Increased renal sympathetic drive is common in patients with various forms of hypertension, and is associated with components of the metabolic syndrome, such as essential hypertension, hyperinsulinemia, type 2 diabetes mellitus, and obesity. Recently, a minimally invasive, catheter-based approach to reduce renal sympathetic afferent and efferent activity has been used successfully to treat drug-resistant hypertension and demonstrated to reduce sympathetic activation. The present pilot study was aimed at investigating the effect of renal denervation on glucose metabolism in 50 patients with resistant hypertension. Thirty-seven patients underwent renal denervation, and 13 were assigned to the control group. Systolic and diastolic blood pressures, fasting glucose, insulin, C-peptide, hemoglobin A1c, calculated insulin sensitivity, and glucose levels during an oral glucose tolerance test were measured before and 1 and 3 months after treatment. Besides a significant reduction in office blood pressure by $-28/10$ and $-32/12$ mm Hg at 1 and 3 months, renal denervation also significantly reduced fasting glucose, insulin, and C peptide. Calculated insulin sensitivity was significantly enhanced after renal denervation. There were no significant changes in blood pressure or metabolic markers in the control group. These findings suggest that renal denervation improves glucose metabolism and insulin sensitivity in addition to a significant blood pressure reduction, which might be explained by a combination of beneficial effects of sympathoinhibition, reduced release of noradrenaline on regional hemodynamics, and direct cellular effects, and may therefore raise hopes that both important features of cardiovascular risk can be addressed simultaneously.
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