

# **New Approaches In The Management Of Refractory Hypertension**

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- Potential of implantable carotid sinus stimulator for drug-resistant hypertension
- Catheter-based renal sympathetic denervation for resistant hypertension

- Resistant HTN is defined as a failure to achieve BP goal when 3 or more antihypertensive agents, including a diuretic are used
- Baroreceptors (pressure receptors) are located in various organs and modulate changes in pressure in response to a wide variety of stimuli
- Stimulation of baroreceptors attenuates increases in BP
- Baroreceptor activation could be used as a method to achieve BP goal in concert with BP medication

# An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial

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**Background:** A large number of patients have hypertension that is resistant to currently available pharmacologic therapy. Electrical stimulation of the carotid sinus baroreflex system has been shown to produce significant chronic blood pressure decreases in animals. The phase II Rheos Feasibility Trial was performed to assess the response of patients with multidrug-resistant hypertension to such stimulation.

**Methods:** The system consists of an implantable pulse generator with bilateral perivascular carotid sinus leads. Implantation is performed bilaterally with patients under narcotic anesthesia (to preserve the reflex for assessment of optimal lead placement). Dose-response testing at 0 to 6 V is assessed before discharge and at monthly intervals thereafter; the device is activated after 1 month's recovery time. This was a Food and Drug Administration-monitored phase II trial performed at five centers in the United States.

**Results:** Ten patients with resistant hypertension (taking a median of six antihypertensive medications) underwent implantation. All 10 were successful, with no significant morbidity. The mean procedure time was 198 minutes. There were no adverse events attributable to the device. Pre-discharge dose-response testing revealed consistent ( $r = .88$ ) reductions in systolic blood pressure of 41 mm Hg (mean fall is from 180-139 mm Hg), with a peak response at 4.8 V ( $P < .001$ ) and without significant bradycardia or bothersome symptoms.

**Conclusions:** A surgically implantable device for electrical stimulation of the carotid baroreflex system can be placed safely and produces a significant acute decrease in blood pressure without significant side effects. (J Vasc Surg 2006;44:1213-8.)

## Implantable Carotid Sinus Stimulator for the Treatment of Resistant Hypertension: Local Effects on Carotid Artery Morphology

*Luis A. Sanchez,<sup>1</sup> Karl Illig,<sup>2</sup> Mark Levy,<sup>3</sup> Michael Jaff,<sup>4</sup> Gregory Trachiotis,<sup>5</sup> Charles Shanley,<sup>6</sup> Eric Irwin,<sup>7</sup> Jeffrey Jim,<sup>1</sup> Martin Rossing,<sup>8</sup> and Robert Kieval,<sup>8</sup> St. Louis, Missouri; Rochester, New York; Richmond, Virginia; Boston, Massachusetts; Washington, DC; Detroit, Michigan; Minneapolis and Maple Grove, Minnesota*

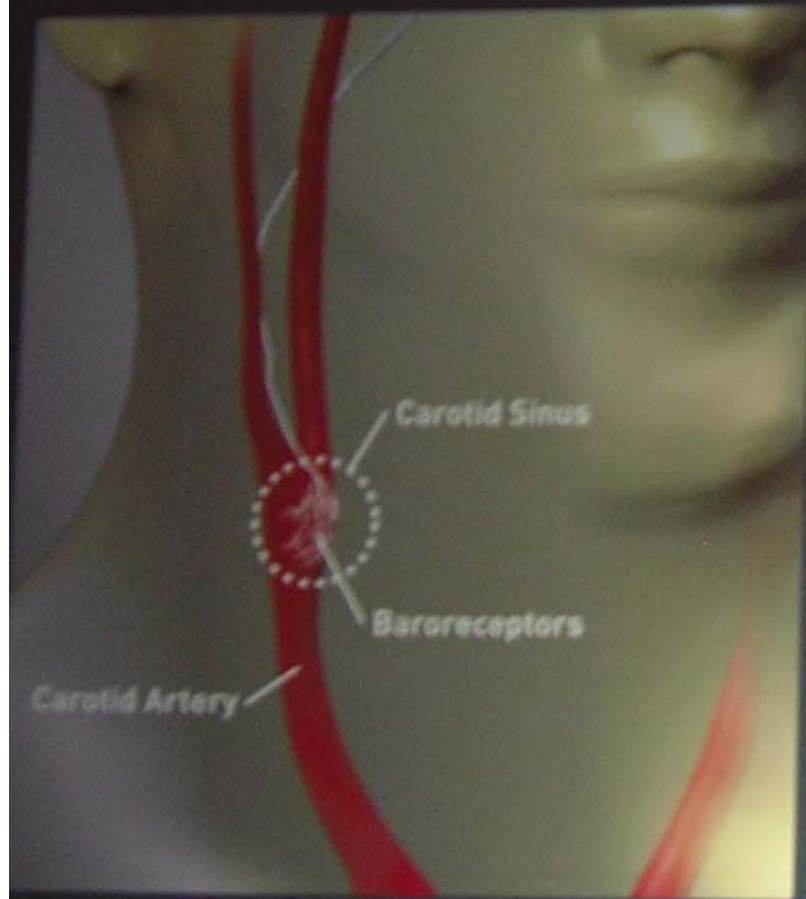
**Background:** The Rheos™ System is a chronically implanted carotid sinus baroreflex activating system with a pulse generator and bilateral pervascular carotid sinus leads (CSLs) that is being evaluated in prospective clinical trials for the treatment of drug-resistant hypertension. We evaluated carotid artery structural integrity after implantation of the CSLs.

**Methods:** To assess the effect of chronic CSL attachment, 29 CSLs were implanted on the common carotid arteries of eight sheep. The studies were terminated at 3 and 6 months postimplantation to assess anatomic and histologic changes. Additionally, 10 patients with resistant hypertension were enrolled in the Rheos Multicenter Feasibility Trial. Duplex ultrasound (DUS) was performed before device implantation and at 1 and 4 months postimplantation in this patient cohort. An independent core laboratory assessed all DUSs.

**Results:** Ovine carotid angiography revealed no significant stenoses, while anatomic and histologic evaluations demonstrated electrode encapsulation in a thin layer of connective tissue with no evidence of stenosis, erosion, or inflammation. DUS evaluation revealed no significant increase in peak systolic velocities of the common and internal carotid arteries 1 and 4 months after initial implantation, indicating a lack of injury, remodeling, or stenosis.

**Conclusion:** The current data suggest that the CSLs used with the Rheos System are not associated with the development of carotid stenosis or injury. These short-term data support the concept of CSL placement and merit long-term investigation in a larger multicenter prospective trial.

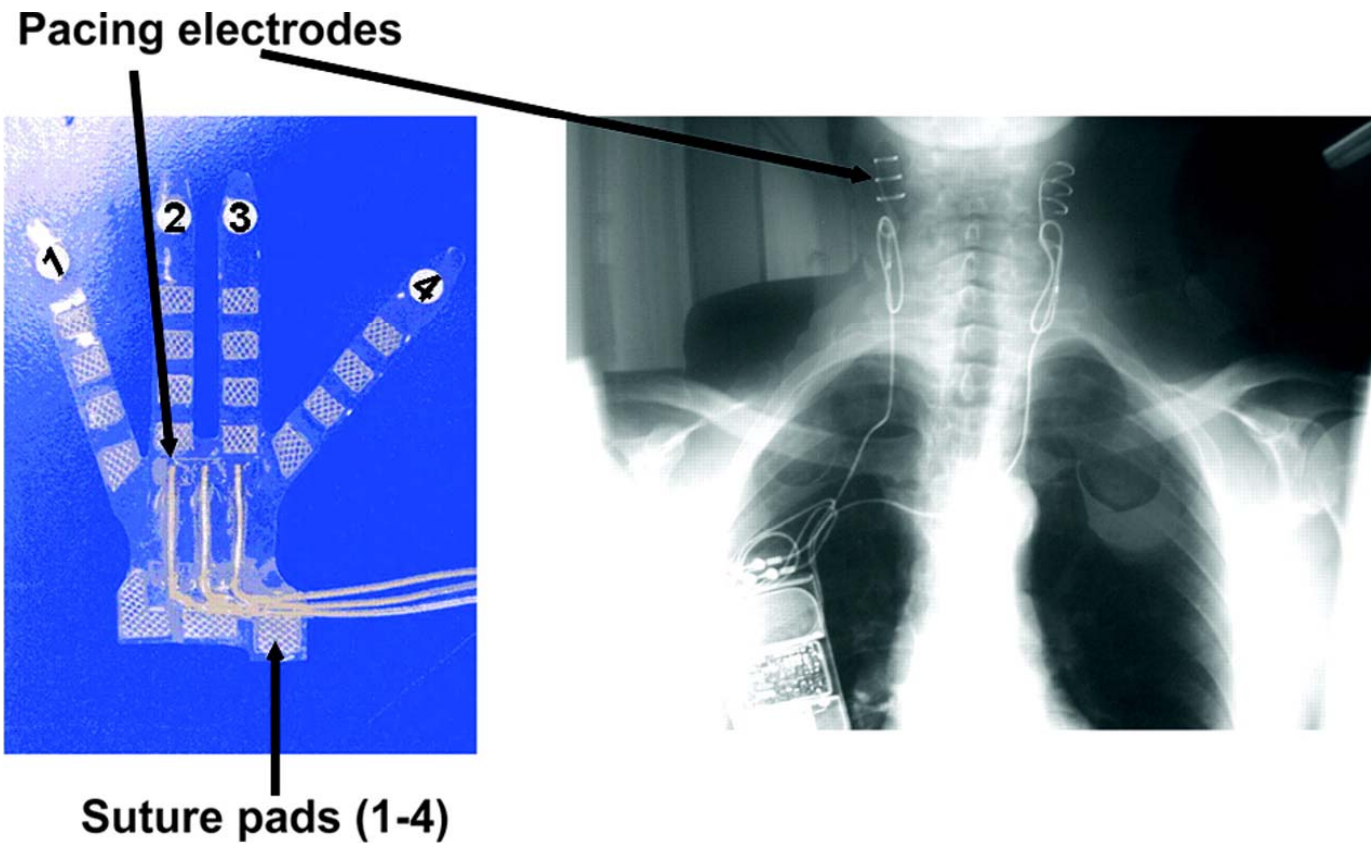
# Resistant Hypertension Treated with Baroreflex Activation



Wireless Programming System



A, Electrode system that is implanted on both carotid sinuses is shown



Mohaupt, M. G. et al. Hypertension 2007;50:825-828

**Hypertension**

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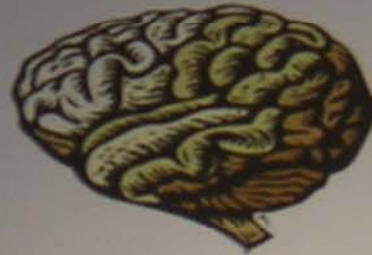
The activated sympathetic outflow to the human kidney is pivotal:

- The regulatory effects of the sympathetic nervous system on renin release, glomerular filtration and renal filtration and renal tubular reabsorption of sodium, are now seen to provide the:

**“Hypertensionogenic mechanism”**

Clin and Exper Hypertension 1989; 11 (Suppl 1): 75-89

# Renal Sympathetic Efferent Nerves



Renal Efferent Nerves



- ↑ Renin release
- ↑ Sodium retention
- ↓ Renal Blood Flow

# THE LANCET

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study  
*Lancet.* 2009;373:1275-1281

Henry Kahn, Markus Schillaci, Paul A. Sobotka, Jeffrey Sobotnik, Krzysztof Bartus, Bogdan Lupșcă, Anthony Wilton, Mark Savel, Julia Thumby, William T. Abraham, Murray Esler

## Initial Cohort – Reported in the *Lancet*, 2009:

- First-in-man, non-randomized
- Cohort of 45 patients with resistant hypertension (SBP  $\geq 160$  mmHg on  $\geq 3$  antihypertensive drugs, including a diuretic; eGFR  $\geq 45$  mL/min)
- 12-month data

## Expanded Cohort – Now available:

- Expanded cohort of patients (n=153)
- 24-month follow-up

# Symplicity<sup>®</sup> Catheter System<sup>™</sup> for selective radiofrequency renal denervation

Ardian Inc., Palo Alto, CA, USA

- 6F access
- Articulating tip with radiofrequency electrode



- Renal nerves lie in adventitia, encircling the renal arteries
- Median procedure time 38 minutes
- 4-6 focal 2-minute RF treatments along each renal artery

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April 1, 2009

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study.

## Abstract:

**BACKGROUND:** Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure  $\geq 160$  mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness. **METHODS:** We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous radiofrequency catheter-based treatment between June, 2007, and November, 2008, with subsequent follow-up to 1 year. We assessed the effectiveness of renal sympathetic denervation with renal noradrenaline spillover in a subgroup of patients. Primary endpoints were office blood pressure and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Renal angiography was done before, immediately after, and 14-30 days after procedure, and magnetic resonance angiogram 6 months after procedure. We assessed blood-pressure lowering effectiveness by repeated measures ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, numbers NCT 00483808 and NCT 00664638. **FINDINGS:** In treated patients, baseline mean office blood pressure was 177/101 mm Hg (SD 20/15), (mean 4.7 antihypertensive medications); estimated glomerular filtration rate was 81 mL/min/1.73m<sup>2</sup> (SD 23); and mean reduction in renal noradrenaline spillover was 47% (95% CI 28-65%). Office blood pressures after procedure were reduced by -14/-10, -21/-10, -22/-11, -24/-11, and -27/-17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/-2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months, respectively. One intraprocedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae. There were no other renovascular complications. **INTERPRETATION:** Catheter-based renal denervation causes substantial and sustained blood-pressure reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the management of this condition.

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# Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study



Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

## Summary

**Background** Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure  $\geq 160$  mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

**Methods** We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous radiofrequency catheter-based treatment between June, 2007, and November, 2008, with subsequent follow-up to 1 year. We assessed the effectiveness of renal sympathetic denervation with renal noradrenaline spillover in a subgroup of patients. Primary endpoints were office blood pressure and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after procedure. We assessed blood-pressure lowering effectiveness by repeated measures ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, numbers NCT 00483808 and NCT 00664638.

**Findings** In treated patients, baseline mean office blood pressure was 177/101 mm Hg (SD 20/15), (mean 4.7 anti-hypertensive medications); estimated glomerular filtration rate was 81 mL/min/1.73m<sup>2</sup> (SD 23); and mean reduction in renal noradrenaline spillover was 47% (95% CI 28–65%). Office blood pressures after procedure were reduced by –14/–10, –21/–10, –22/–11, –24/–11, and –27/–17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/–2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months, respectively. One intraprocedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae. There were no other renovascular complications.

**Interpretation** Catheter-based renal denervation causes substantial and sustained blood-pressure reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the management of this condition.

Published Online  
March 30, 2009  
DOI:10.1016/S0140-6736(09)60566-3

See Online/Comment  
DOI:10.1016/S0140-6736(09)60624-3

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