

# BEYOND BLOOD PRESSURE: PERCUTANEOUS RENAL DENERVATION FOR THE MANAGEMENT OF SYMPATHETIC HYPERACTIVITY AND ASSOCIATED DISEASE STATES

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# SNS and cardiovascular system

- The sympathetic nervous system has a fundamental role in maintaining the physiological homeostasis of the cardiovascular system.
- A number of cardiovascular diseases have been shown to be characterized by a **marked increase in sympathetic drive to the heart and the peripheral circulation.**
- This is the case for

HYPERTENSION

ARRHYTHMIAS

HEART FAILURE

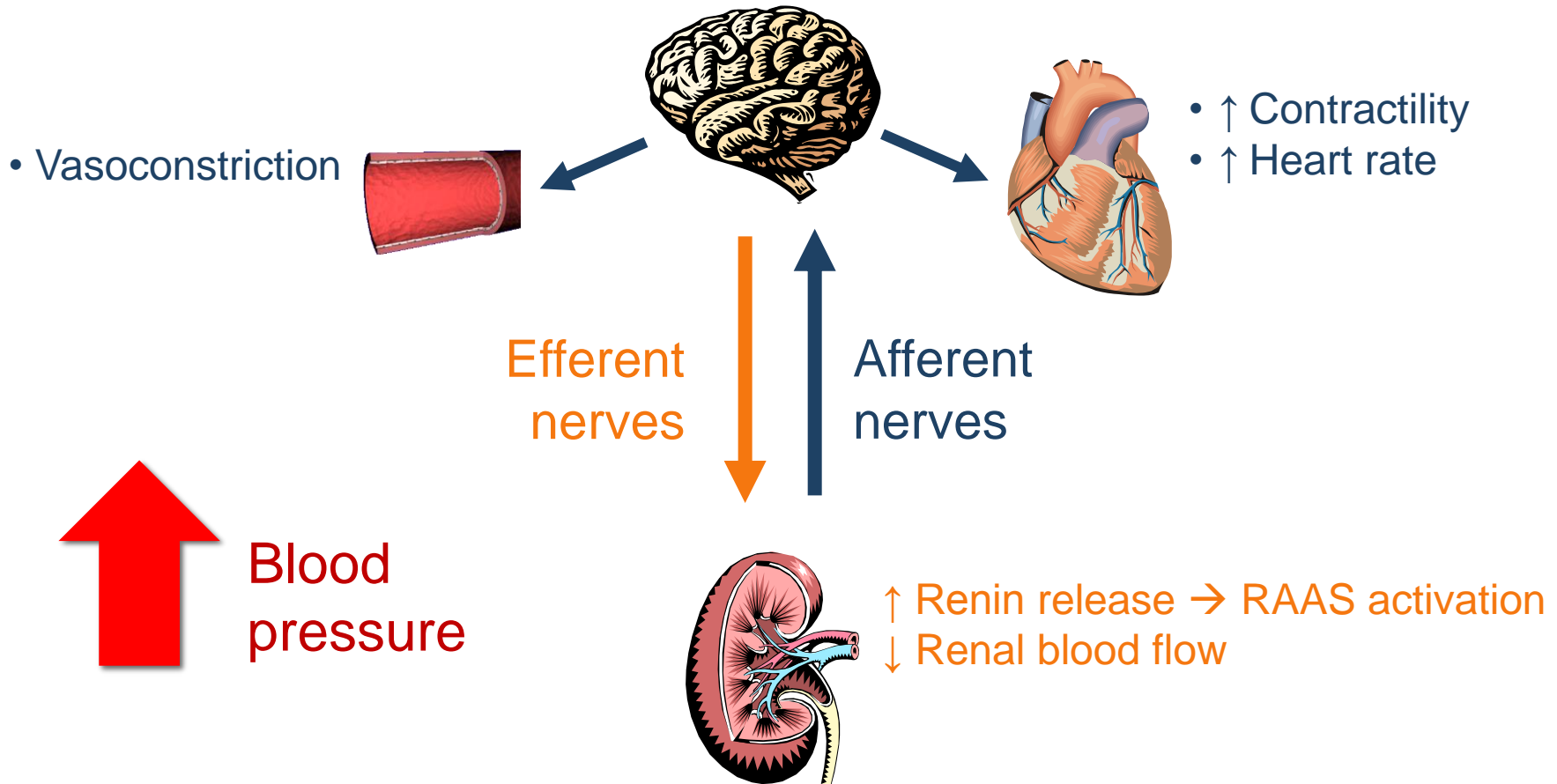
METABOLIC SYNDROME

CHRONIC RENAL DISEASE

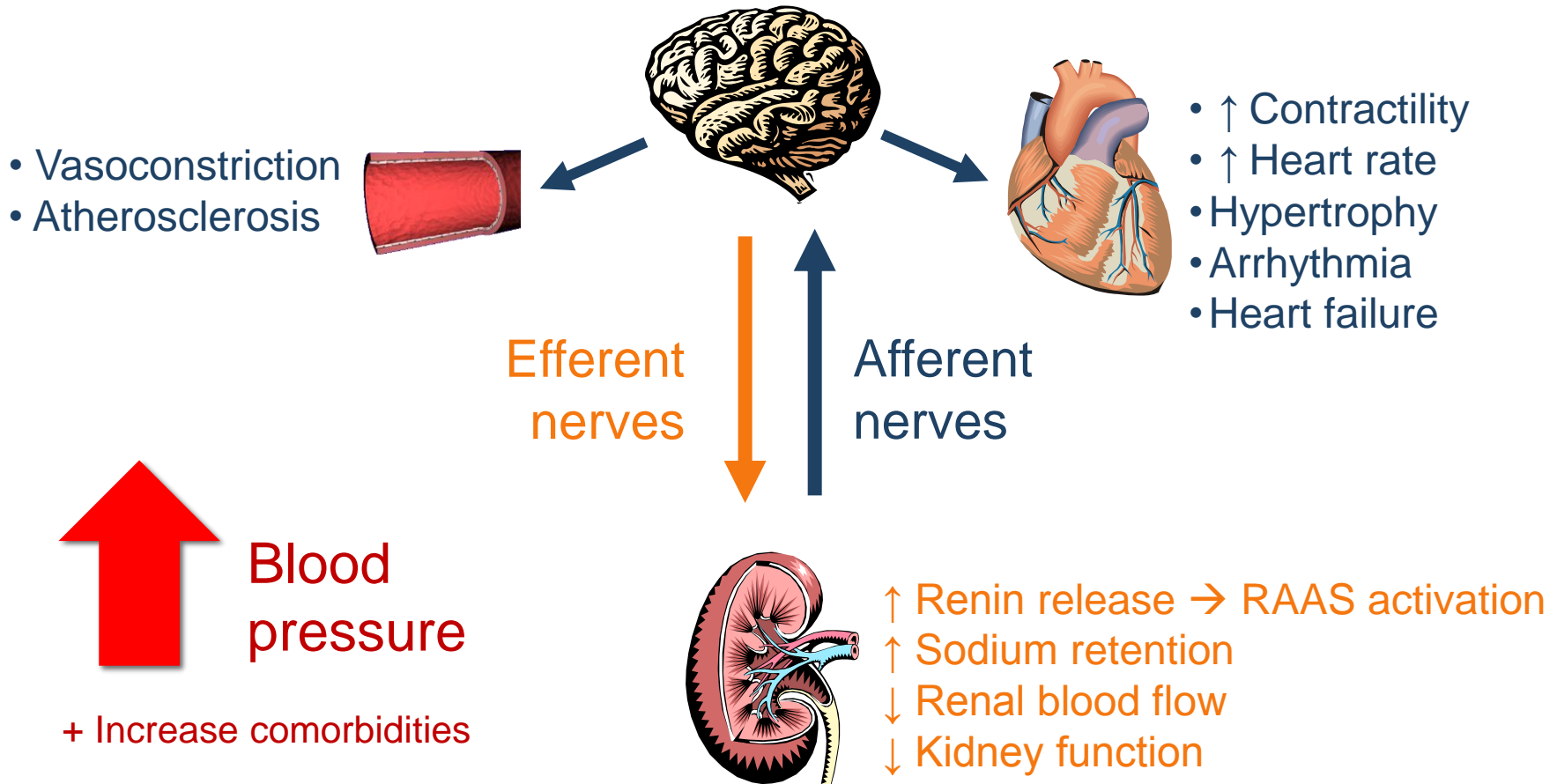
OBSTRUCTIVE SLEEP APNEA



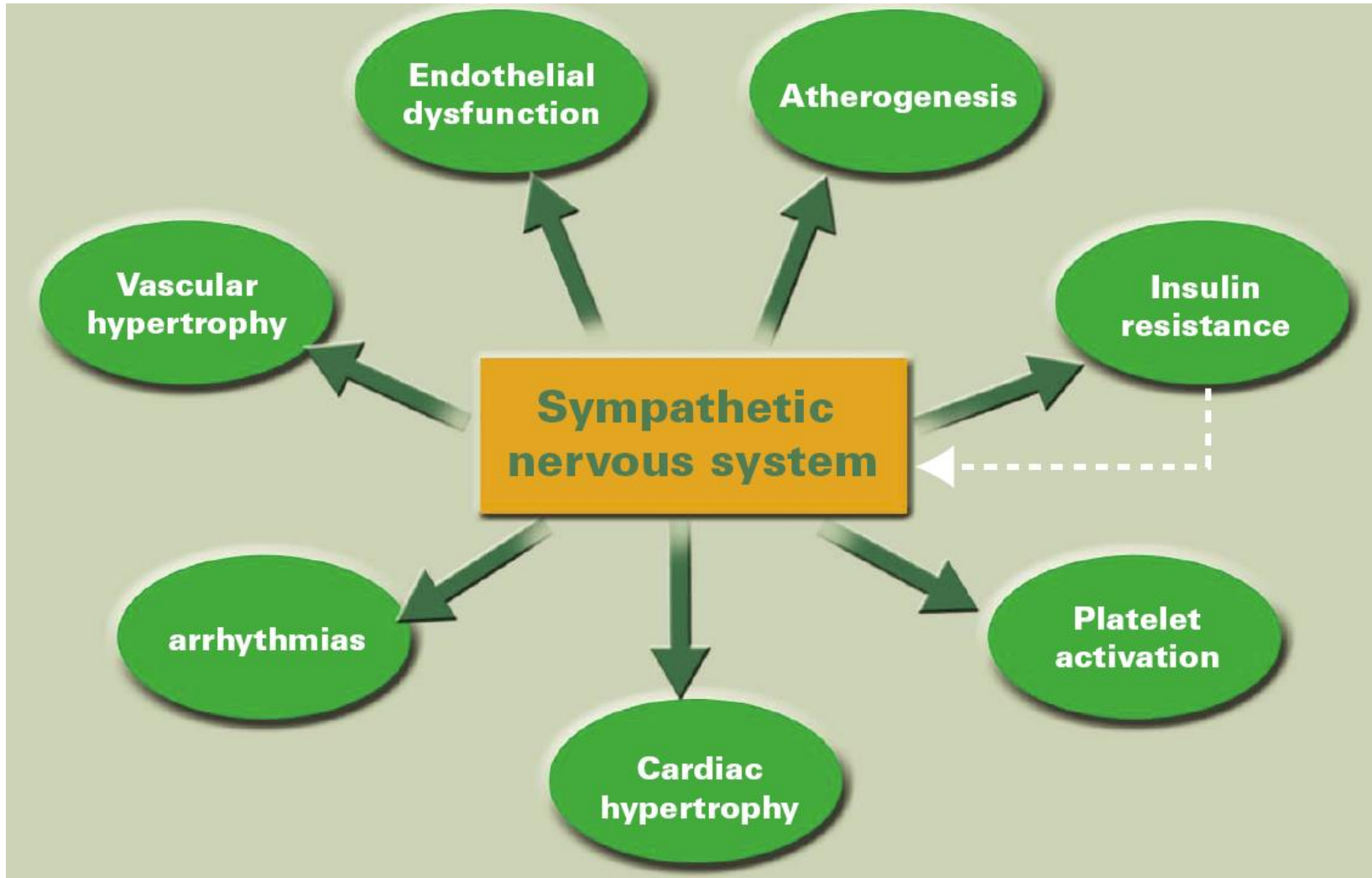
# Renal Nerve and Sympathetic Activity: Kidney as Origin and Recipient of Central Sympathetic Drive



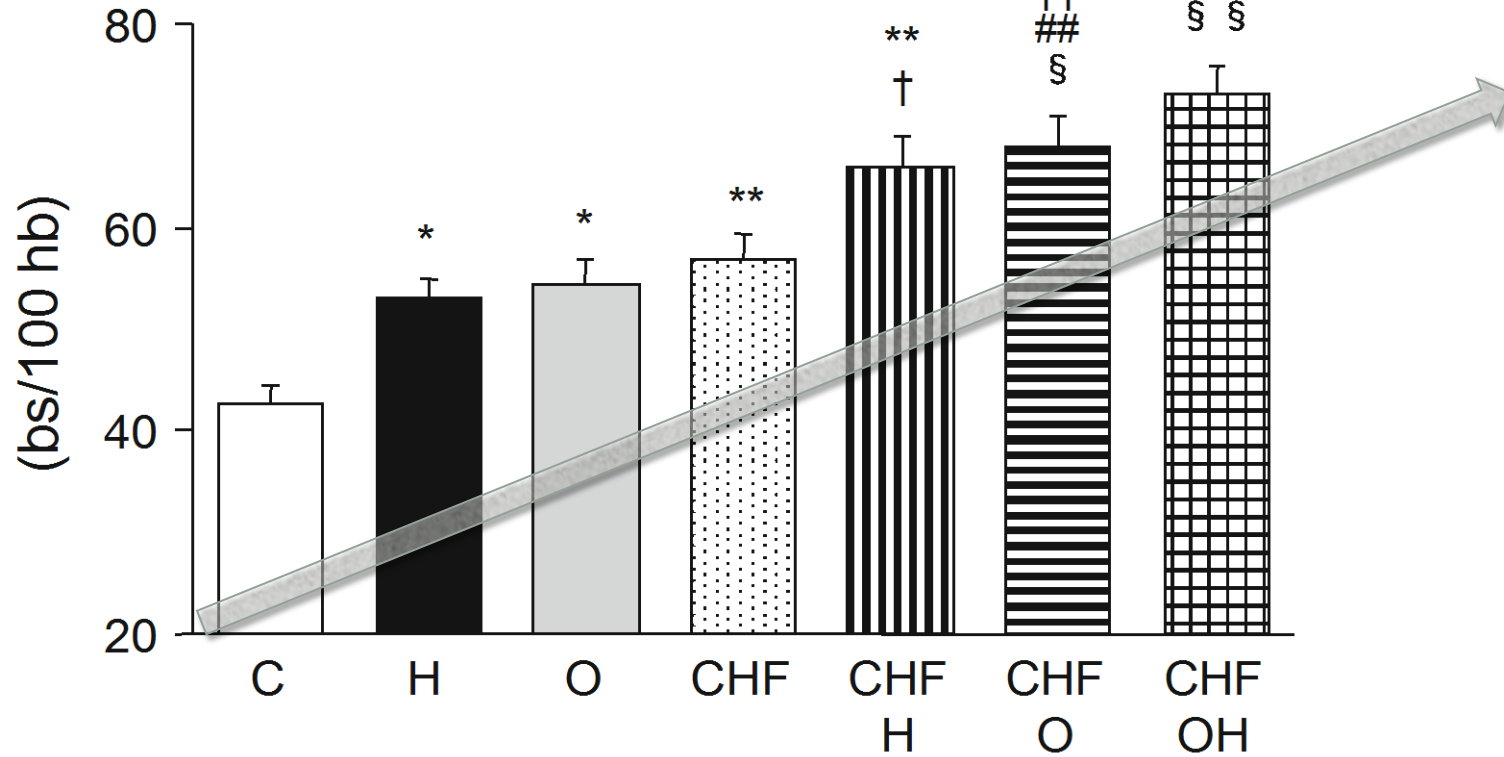
# Renal Nerve and Sympathetic Activity: Kidney as Origin and Recipient of Central Sympathetic Drive



# Consequences of SNS Activation



# MSNA



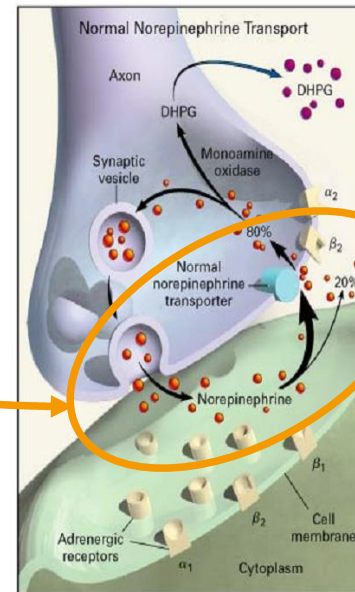
- C = control
- H = hypertension
- O = obesity
- CHF = congestive heart failure
- CHF H = CHF + H
- CHFOH = CHF + O + H



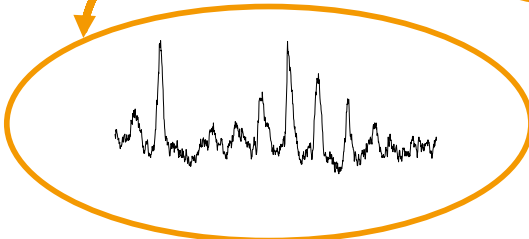
# How to quantify human sympathetic nervous system activity



Sympathetic  
Nerve Traffic



Noradrenaline



muscle sympathetic nerve activity MSNA



This is best done by recording postganglionic nerve traffic (clinical microneurography) and measuring transmitter release from sympathetic nerves to plasma (noradrenaline “spillover”)



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# SNS and Vascular System

- The observation made in 1831 by Herich Weber that skin colour may change in response to emotional stress was the first notion of ***neuronal influences on the diameter of peripheral arteries.***
- 20 years later the effects of sympathetic nerves on peripheral blood vessels were described by Claude Bernard, who also found that ***transection of the spinal cord*** in the lower cervical region triggered a profound fall in blood pressure, indicating that the sympathetic drive came from above the site of transection





# Renal Denervation and SNS

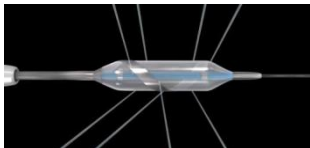
- Multiple animal models have demonstrated that renal denervation effectively
  - ✓ reduces SNS outflow to the kidney,
  - ✓ restoring physiological natriuresis and diuresis
  - ✓ reducing renin release.
- Surgical sympathectomy for uncontrolled hypertension had relative success controlling blood pressure, thereby reducing mortality; however, these nonselective surgical approaches were associated with significant morbidity, including bowel and bladder incompetence and severe postural hypotension.
- Advances in tolerability and safety afforded by minimally invasive, selective RDN have improved the risk–benefit profile for emerging catheter-based techniques



# Catheter-based RDN Therapy



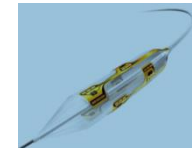
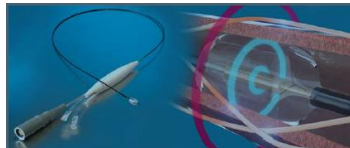
**COV: One Shot**



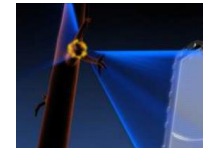
**STJ: EnligHTN**



**RECOR**



**BSX: Vessix**



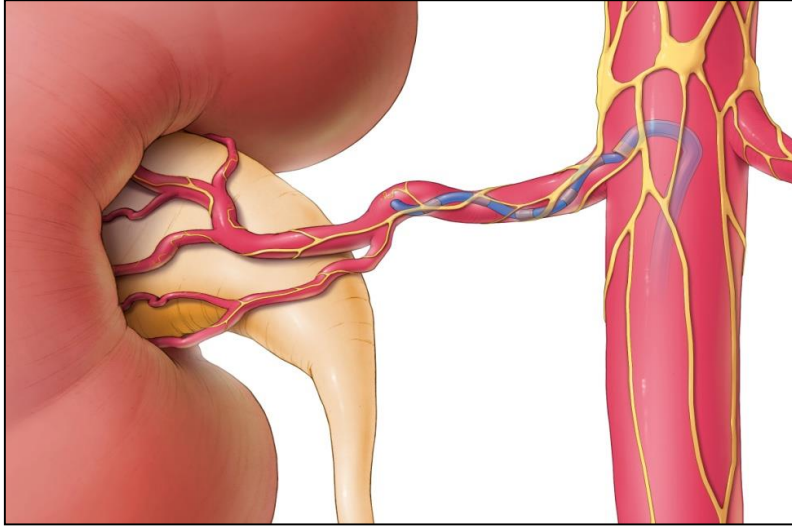
and more...



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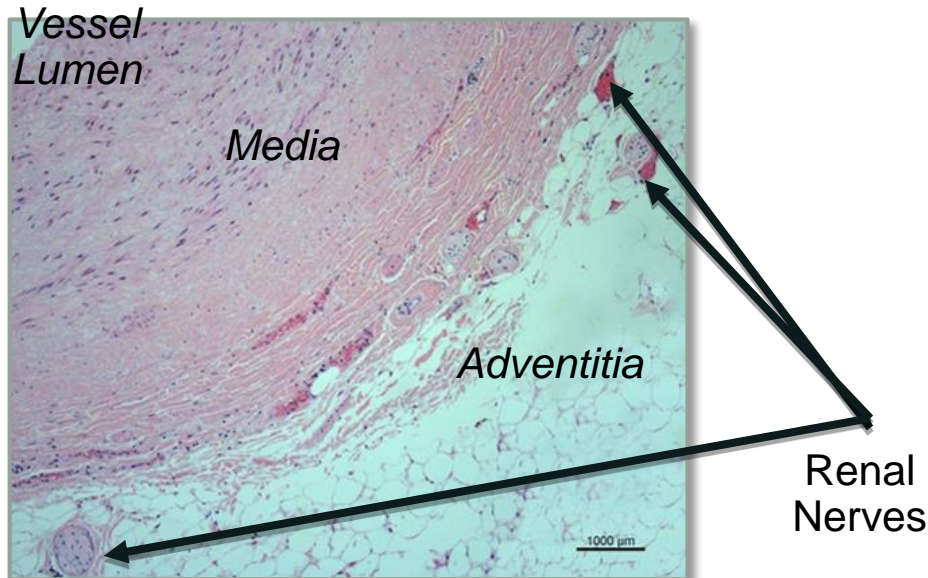
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# Renal Nerve Anatomy

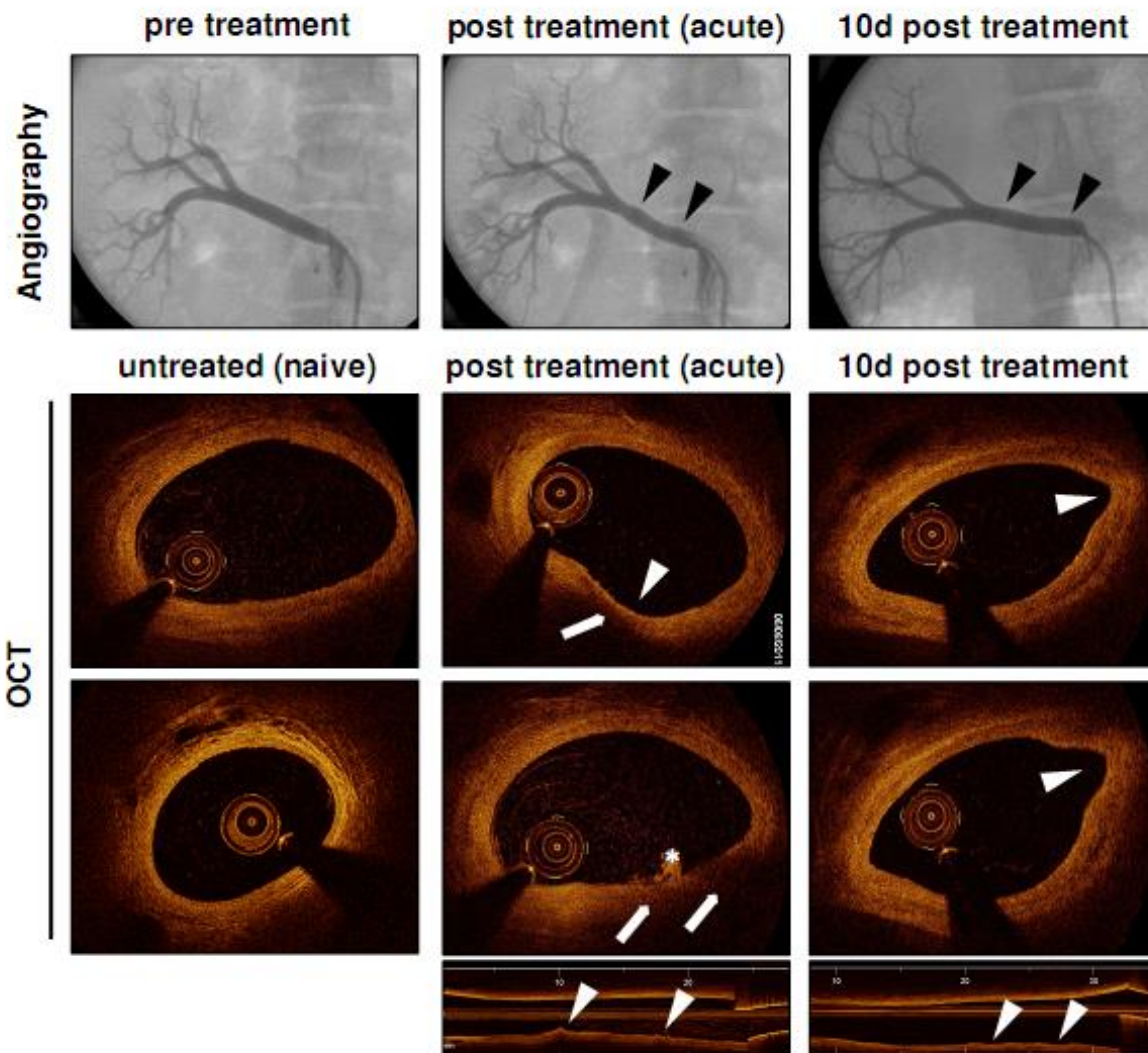
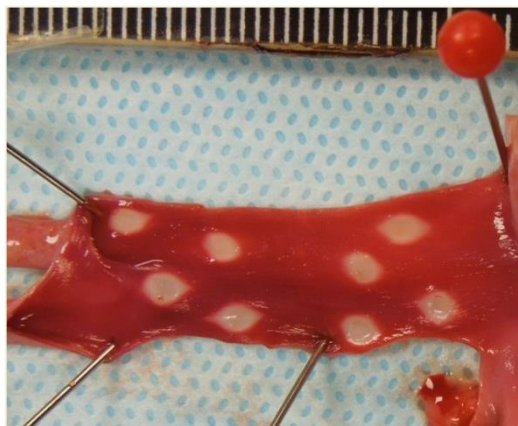


The *renal plexus* is located around the renal artery and contains postganglionic fibers from the sympathetic nervous system (T10 to L2).

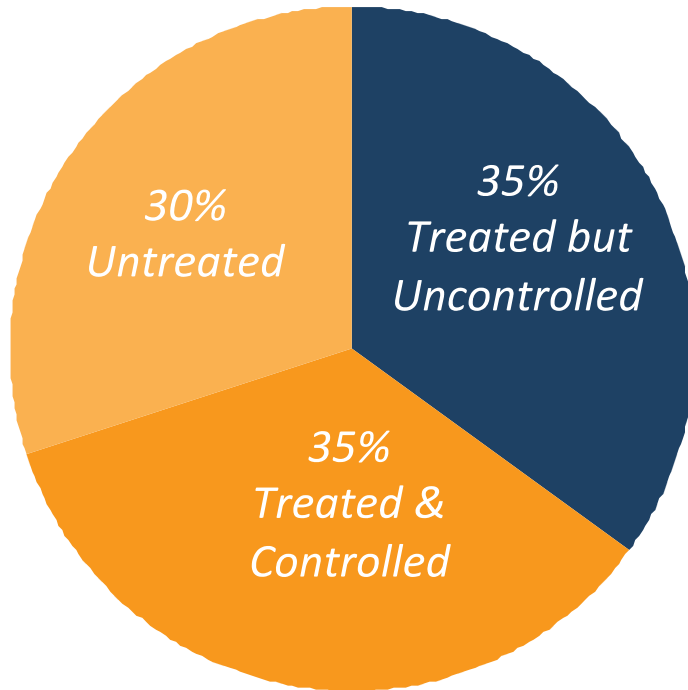
The nerve fibers from the plexus enter the kidney with the branches of the renal artery and regulate the vascular tone and the secretion of renin.



# OCT imaging of a radiofrequency ablation in Renal Arteries



# Hypertension Epidemiology



- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Reduction of systolic BP by 10 mmHg reduces risk of stroke by 30%
- Only half of all treated hypertensives are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025





# What's Resistant Hypertension?

Resistant hypertension is defined by American Heart Association as<sup>1</sup>: "

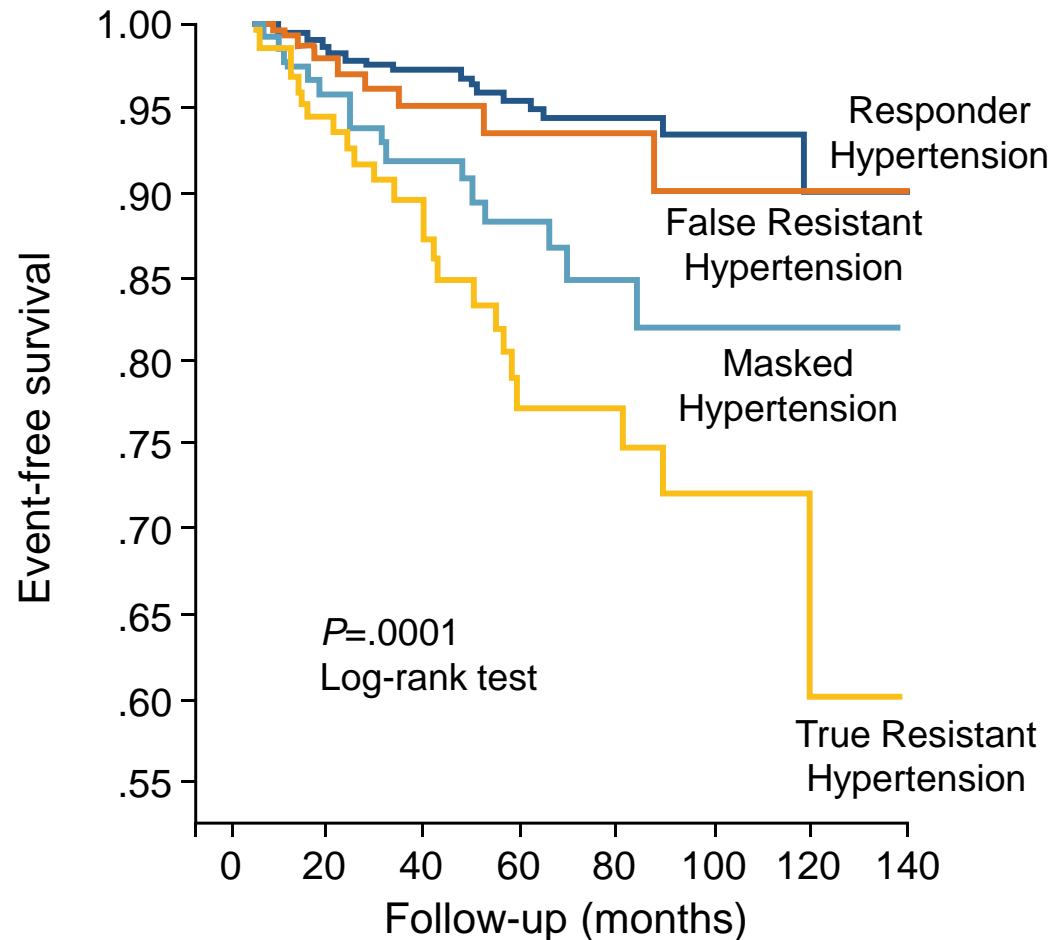
Patients who remain above goal blood pressure\* despite 3 antihypertensive medications of different classes administered at optimal doses, ideally including a diuretic"

\* $\leq 140/90$  mmHg or  $\leq 130/80$  if diabetes, kidney disease or coronary "artery disease"

Patients with controlled blood pressure that require 4 or more medications"



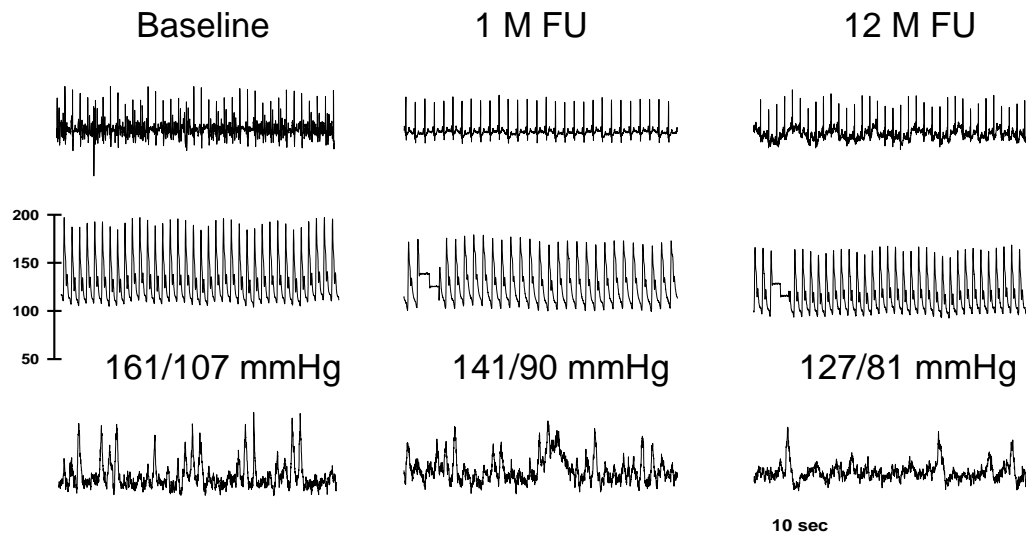
# Patients With True Resistant Hypertension are at Increased Risk for CV Events



CV=cardiovascular.  
Pierdomenico SD et al. *Am J Hypertens.* 2005;18:1422-1428.

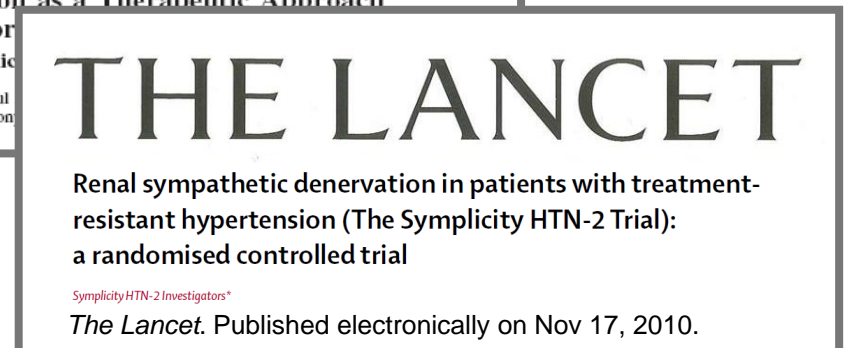
# Renal Denervation and Resistant Hypertension

- In early studies of refractory hypertension, RDN reduced sympathetic hyperactivity.
- Several initial studies have revealed statistically significant ***reductions in both noradrenaline spillover and muscle sympathetic nerve activity*** in patients who have undergone RDN, often independent of antihypertensive effects

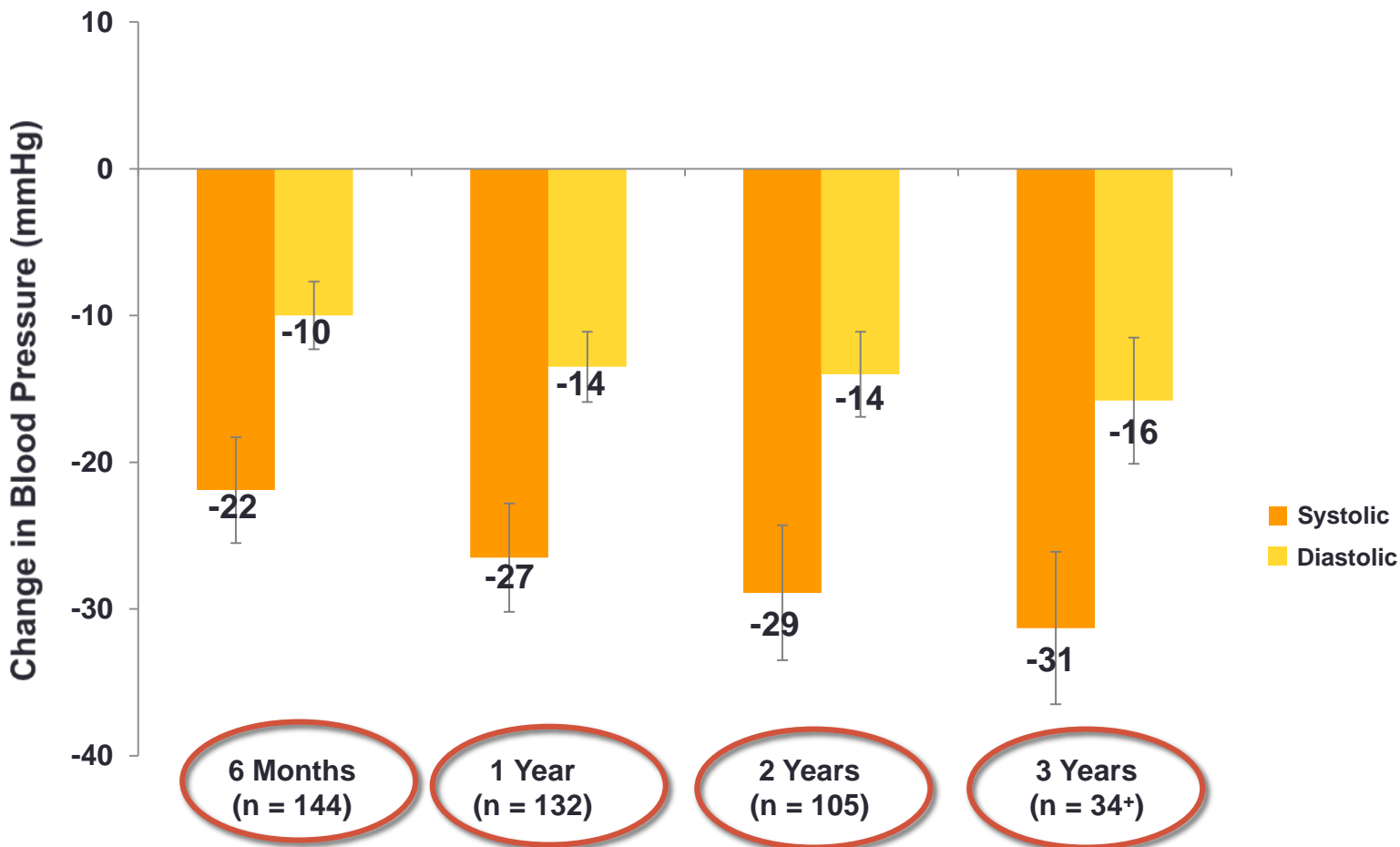




# Results Recognised for Their Importance



# Symlicity HTN-1: Significant, Sustained Blood Pressure Reduction for at Least Three Years

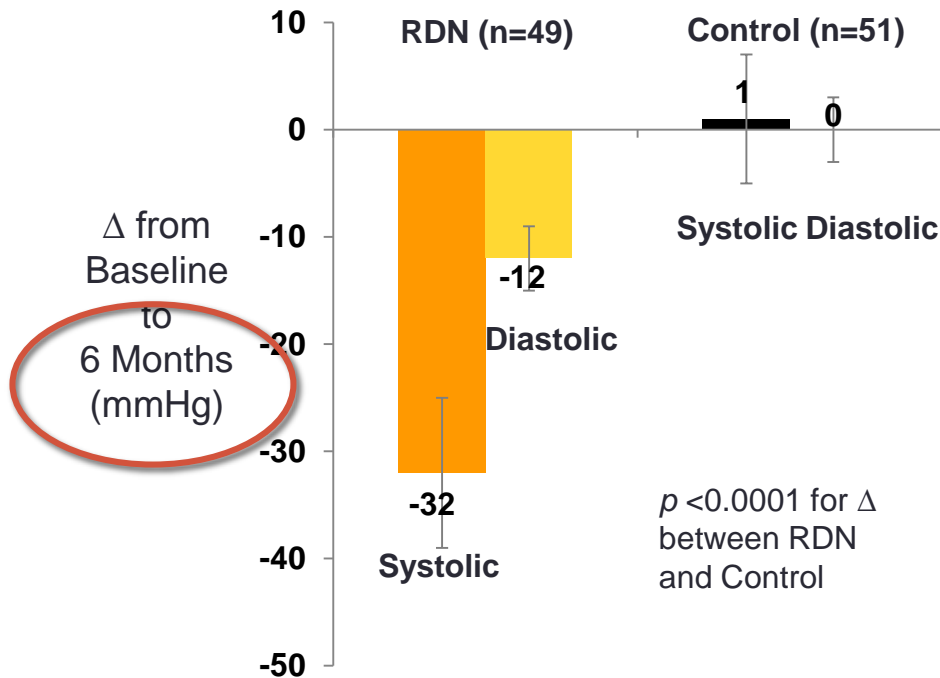


$p < 0.01$  for  $\Delta$  from baseline for all time points.

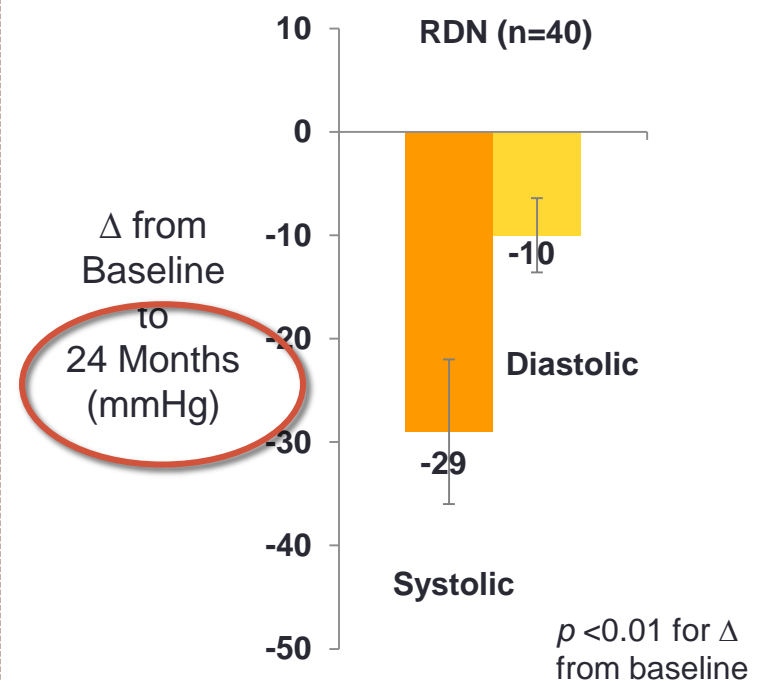
+ Number of patients represents data available at time of data-lock.

# Symplicity HTN-2: RDN Superior to Medical Management at 6M, BP Reduction Sustained to 24M\*

Primary Endpoint  
(6M post Randomisation)



Latest Follow-up  
(24M post Randomisation)

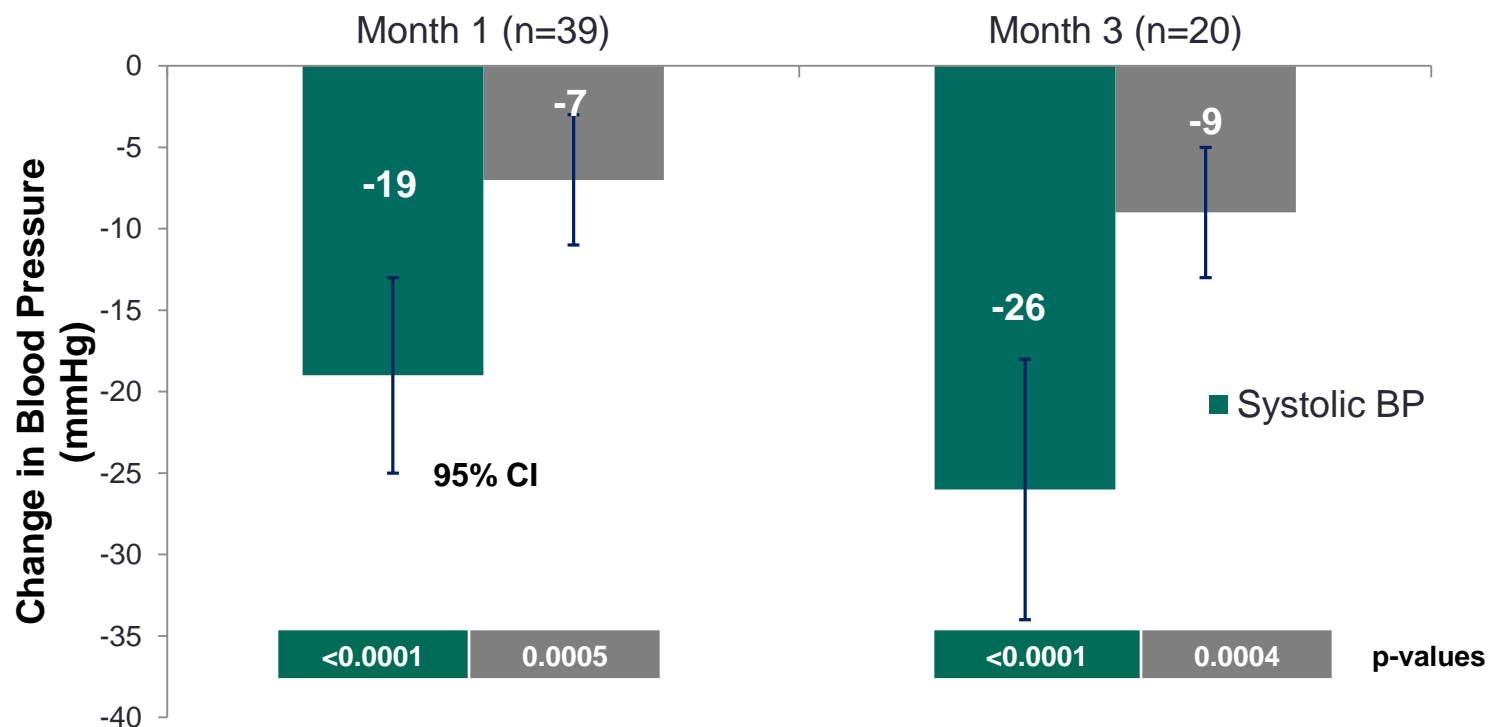


## Primary Endpoint:

- >80% of RDN patients had  $\geq 10$  mmHg reduction in SBP
- 5 patients had  $\leq 5$  mmHg reduction in SBP



# EnligHTN III – Office BP Reduction from Baseline



*EnligHTN therapy with the II generator system delivers a rapid and significant reduction in Office BP that is sustained through 3 months*



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## Symplivity HTN-3: No Significant Blood Pressure Reduction in RDN patients compared with a sham control.

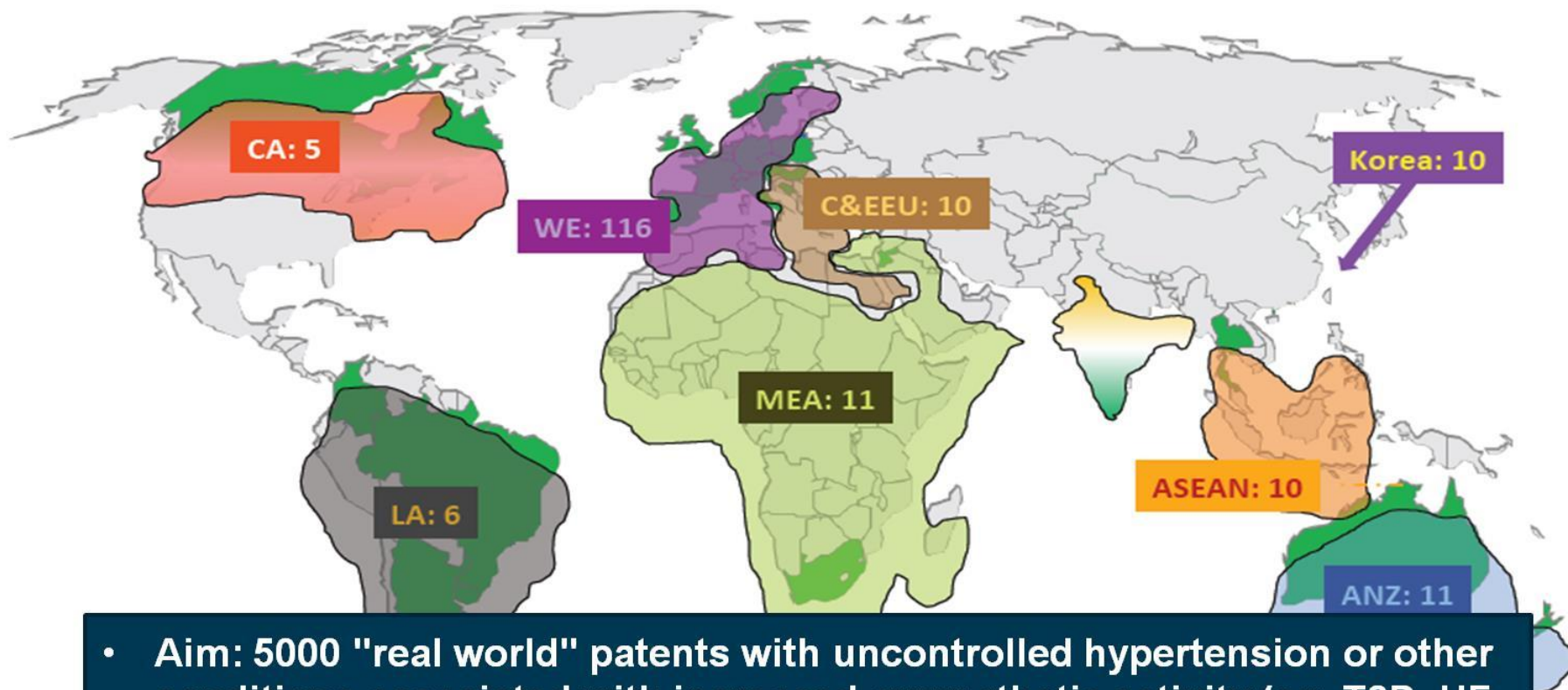
- the blinded SYMPLICITY HTN-3 trial did not show a significant difference in the reduction of systolic blood pressure in patients with resistant hypertension six months after renal denervation as compared with a sham control.
- The primary safety endpoint of the trial was met.

## Symplicity HTN-3: No Significant Blood Pressure Reduction in RDN patients compared with a sham control.

- It was suggested that the lack of demonstrated efficacy of RDN may have been due to:
  - lack of statistical power
  - the trial was well conceived but not rigorously executed.
- In addition, legitimate concerns were raised as to whether the denervation procedure was sub-optimal in many cases due to insufficient delivery of appropriate energy in the renal arteries as a consequence of the inexperience of the investigators.

# Global SYMPLICITY Registry

## *Locations and Inclusion Criteria<sup>a,b</sup>*



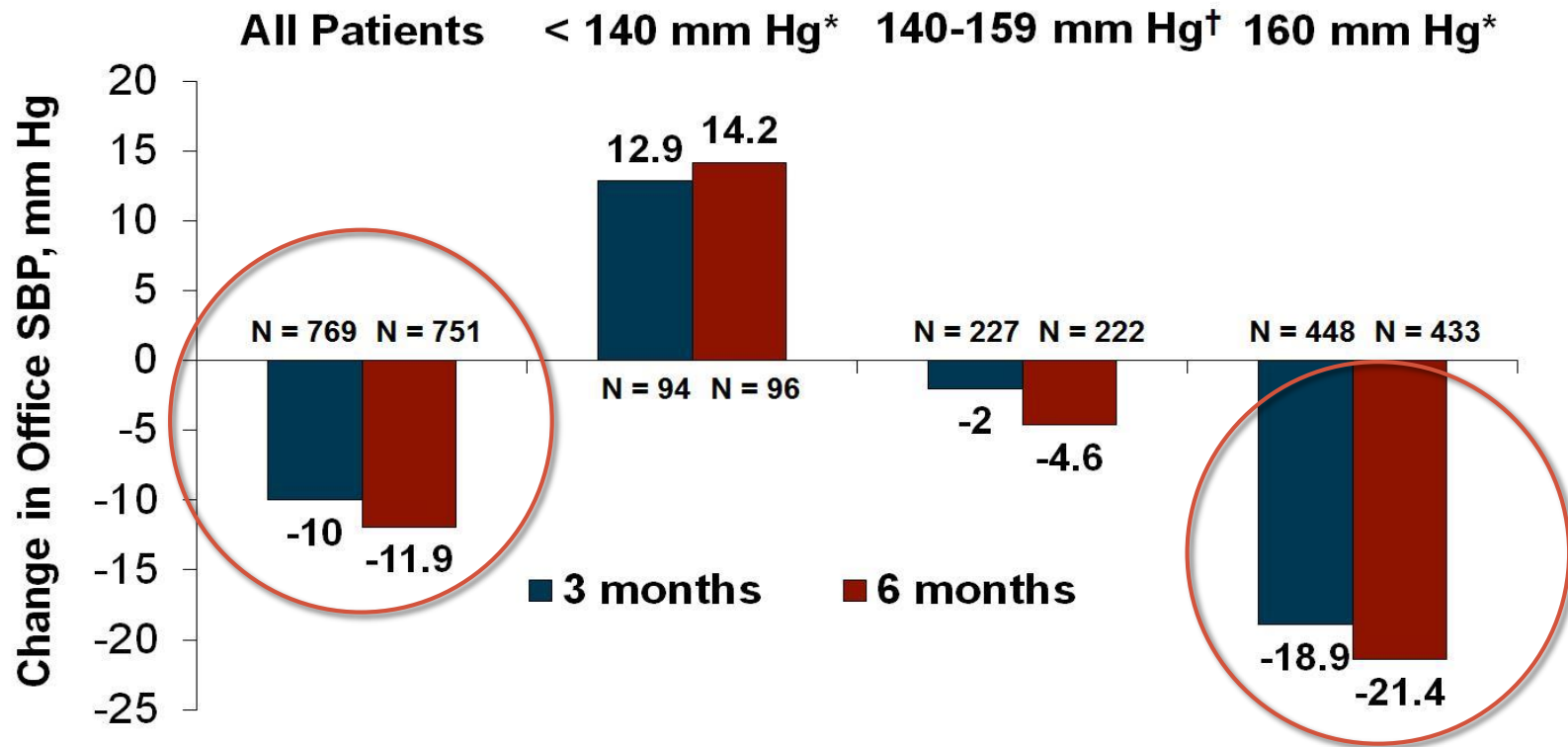
- Aim: 5000 "real world" patents with uncontrolled hypertension or other conditions associated with increased sympathetic activity (eg, T2D, HF, renal insufficiency)
- Age > 18 y
- Use of SYMPLICITY RDN catheter

a. ClinicalTrials.gov website. NCT01534299.<sup>[3]</sup>

b. Mahfoud F. EuroPCR 2014.<sup>[4]</sup>

# SYMPPLICITY Registry

## Change in Office SBP



\* $P < .001$  for both 3- and 6-month change from baseline.

† $P = .14$  at 3 months and  $P = .0006$  at 6 months.

Böhm M, et al. ACC 2014. Abstract 403-10.<sup>[5]</sup>



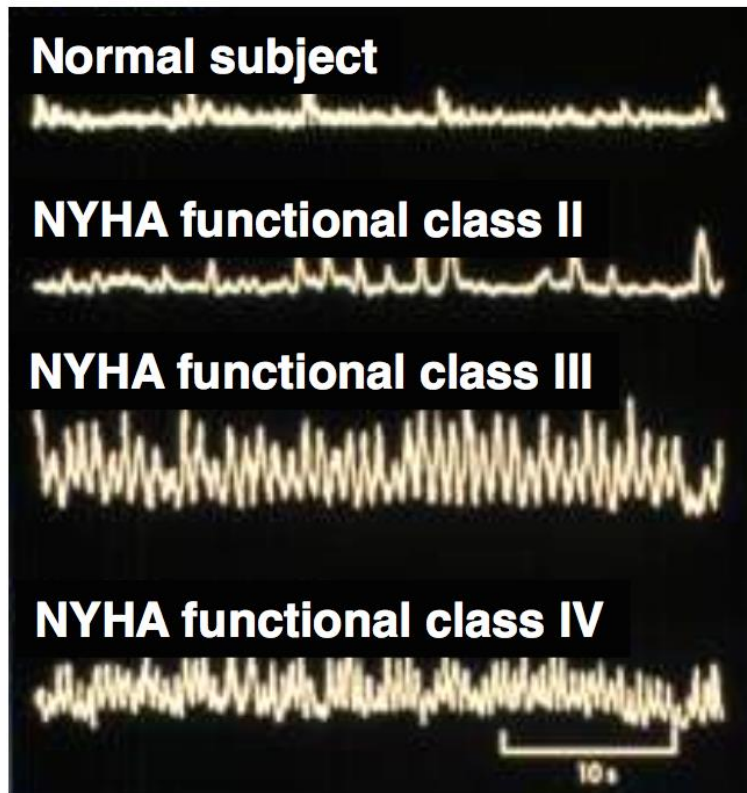
# Systolic Heart Failure

- The consistent benefits of pharmacological neurohormonal blockade observed in clinical trials of systolic heart failure support the **primacy of sympathetic activation in progression of ischemic and nonischemic dilated cardiomyopathies**; however,
- the role of SNS activity in reacting to versus precipitating and worsening systolic heart failure is unclear and raises legitimate questions about potential treatment benefit.



# Sympathetic overactivity in HF

## Correlates with functional class



Microneurography



**MSNA** [ 10.4 bursts/min  
15.3 bursts/100 beats

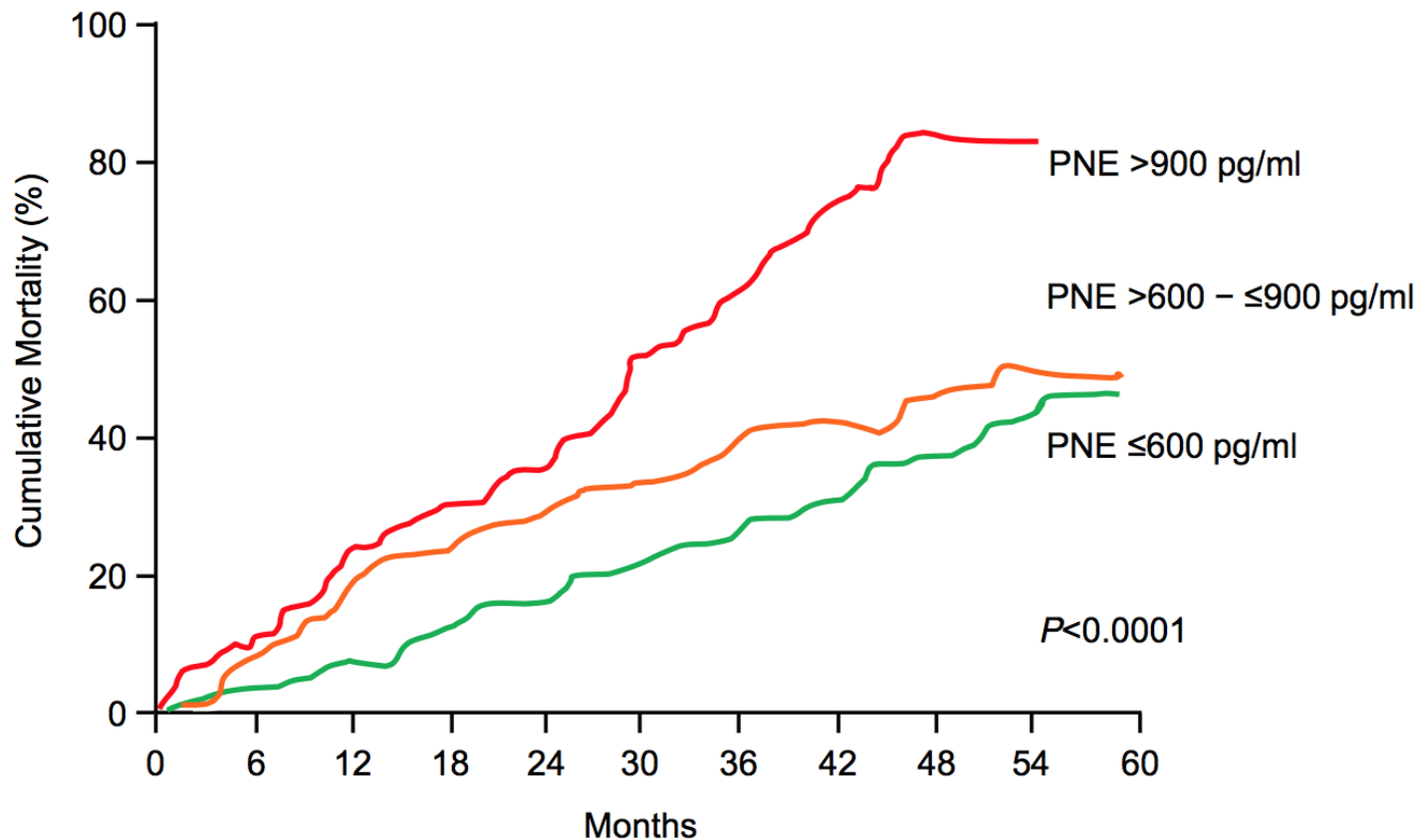
**MSNA** [ 18.8 bursts/min  
27.4 bursts/100 beats

**MSNA** [ 67.4 bursts/min  
95.7 bursts/100 beats

**MSNA** [ 99.4 bursts/min  
93.4 bursts/100 beats

# Sympathetic overactivity in HF

## Plasma norepinephrine strongly predicts survival



# Renal Denervation & Atrial Fibrillation

Electrical and structural remodelling are important synergistic contributors to the Afib substrate.  
Atrial fibrillation and other cardiac dysrhythmias result from complex electrophysiological interactions influenced by the autonomic nervous system and varied hemodynamic conditions.

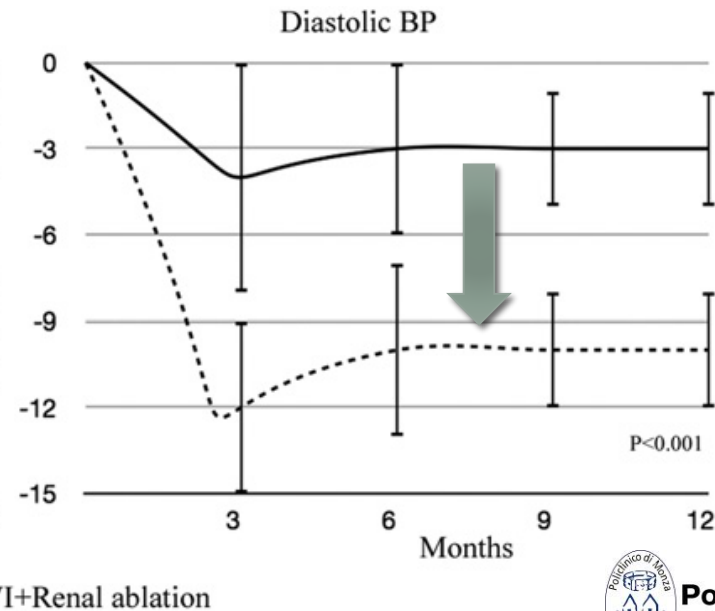
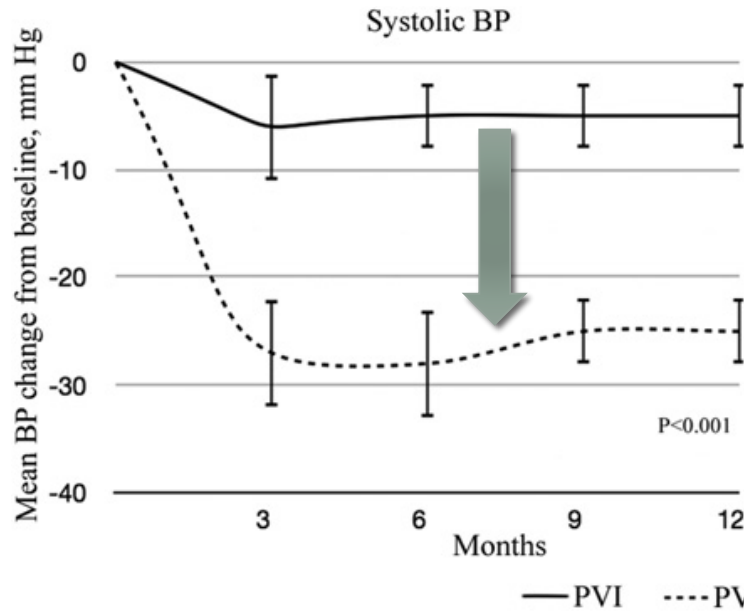
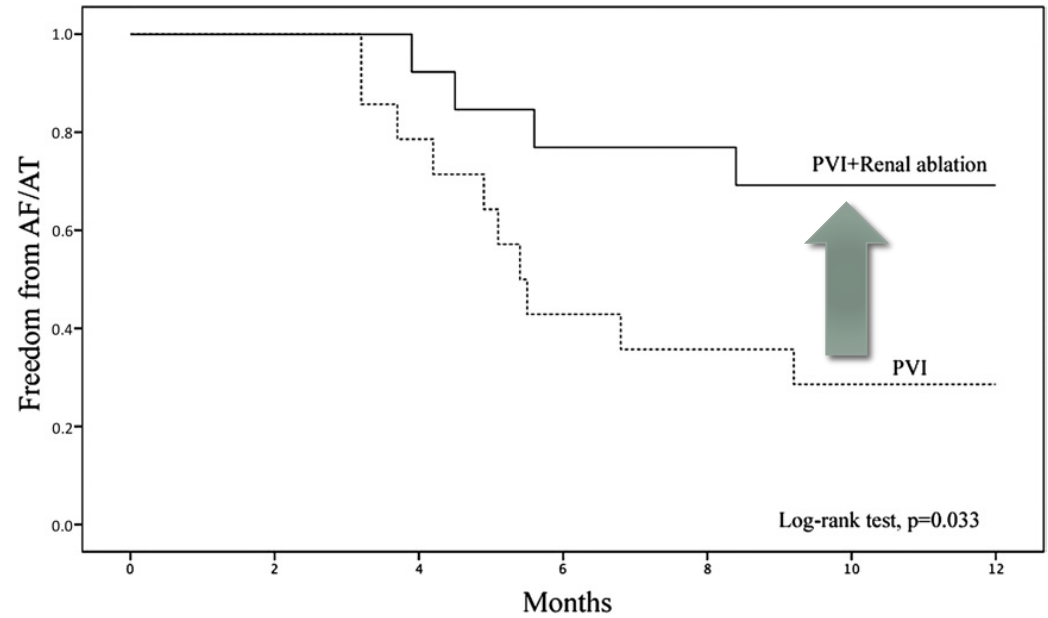
Studies have indicated that angiotensin II and aldosterone might be involved in atrial structural and electrical remodelling in patients with Afib.

HTN is associated with LVH, left atrial enlargement, and slowing of the atrial conduction velocity.

Renal artery denervation was shown to decrease Afib episodes in animal models.



# A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension



— PVI    - - - PVI+Renal ablation



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# Renal Denervation & Atrial Fibrillation

Renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI.

- **Adjunctive Renal Sympathetic Denervation to Modify Hypertension as Upstream Therapy in the Treatment of Atrial Fibrillation (H-FIB)**

Estimated Study Completion Date: July 2017

- **Renal Sympathetic Denervation in Patients With Hypertension and Symptomatic Atrial Fibrillation (RSDforAF)**

Estimated Study Completion Date: July 2015



# Ventricular Tachyarrhythmias

- Ventricular tachyarrhythmias are prominent after ischemic insult, potentially driven by central sympathetic hyperactivity.
- The use of beta-blockers to prevent ventricular tachyarrhythmias is standard postmyocardial infarction practice, and RDN may play a similar role in autonomic modulation.
- Radical interventions, including surgical cardiac sympathetic denervation, have even been considered for patients with refractory ventricular tachycardia.



# RDN and ventricular arrhythmias

- The potential of RDN to suppress ventricular tachycardia in humans has been explored so far only in case reports and small series but suggests (in a variety of clinical situations including dilated and hypertrophic cardiomyopathy and refractory ventricular tachycardia and after myocardial infarction)

- ➔ • decreased in premature ventricular contractions,
- ➔ • decreased ventricular tachycardia burden
- ➔ • increased ventricular tachycardia–free intervals

- Two currently enrolling RCTs will address the use of RDN in patients vulnerable to ventricular tachyarrhythmias.





# Renal Denervation & Glucose Metabolism

Activation of the sympathetic nervous system contributes to insulin resistance, the metabolic syndrome, is associated with central obesity and risk of developing DM.



Inhibition of the sympathetic nervous system by moxonidine has been shown to improve glucose metabolism.



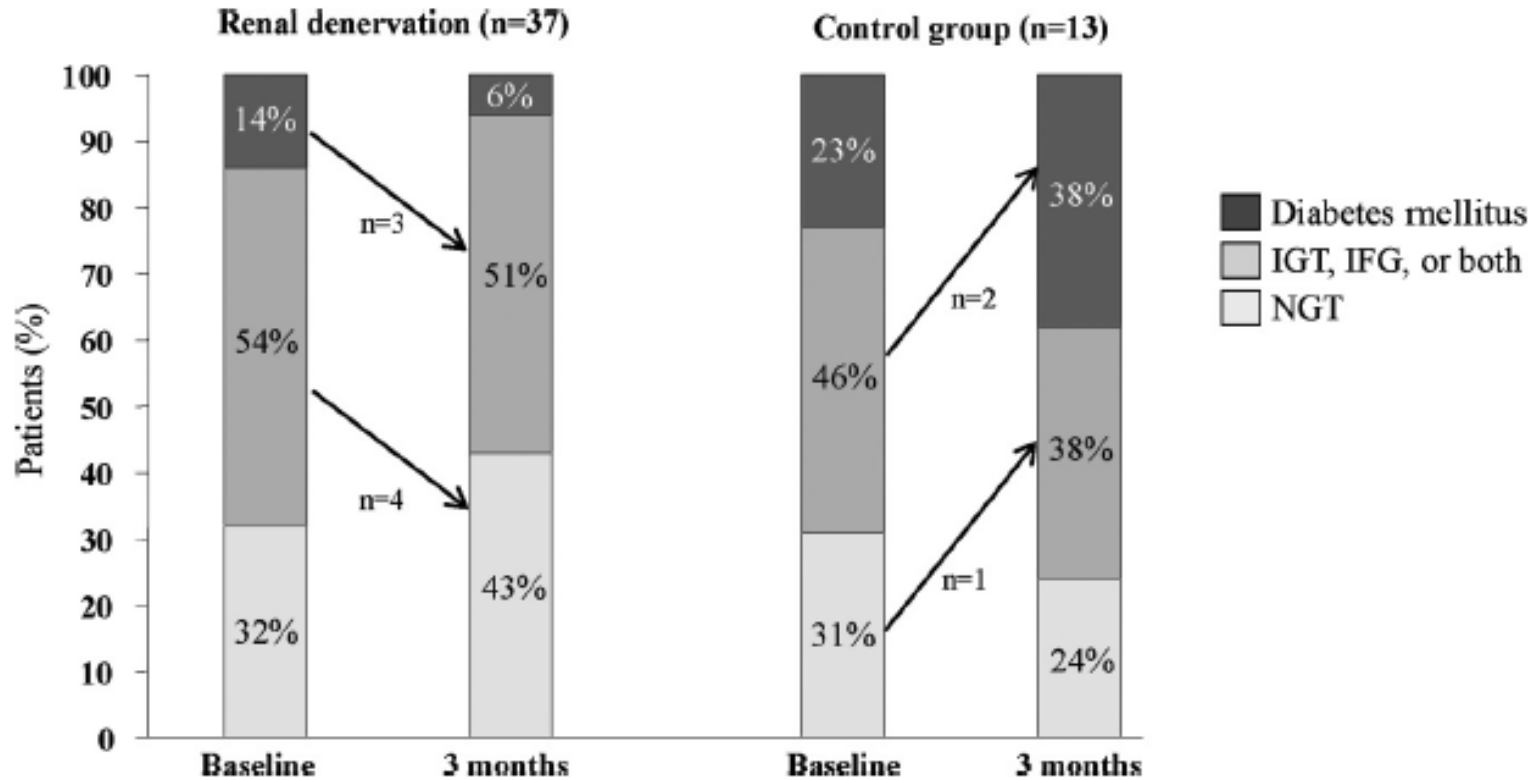
Renal sympathetic denervation decreases whole body norepinephrine spillover.



It is plausible to speculate that renal sympathetic denervation may have a substantial effect on glucose metabolism.



# Renal Denervation & Glucose Metabolism



Renal denervation improves glucose metabolism and insulin sensitivity.

# Renal Denervation & Glucose Metabolism

- These results have sparked great interest in the role of RDN as a metabolic regulator, with RCTs under way to assess this effect
- **Denervation of the REnal Artery in Metabolic Syndrome (DREAMS)**
  - Estimated Study Completion Date: June 2015
- **Renal Sympathetic Modification in Patients With Metabolic Syndrome**
  - Estimated Study Completion Date: August 2016



# RDN and Obstructive Sleep Apnea

- Sleep apnea is an independent cardiovascular risk factor characterized by **recurrent upper airway obstruction** and **intermittent hypoxia** stimulating SNS activity.
- Hypothesis-generating studies suggest a benefit of RDN in sleep apnea, but current data are limited in both power and scope; larger studies, such as those that are ongoing are needed to truly characterize the effect of RDN in sleep apnea.



# Sleep apnea and Hypertension

- Several experimental studies suggested that obstructive sleep apnea can induce an increase in blood pressure levels.
- In patients with obstructive sleep apnea, physiological dipping in nighttime blood pressure values is often lacking in association with nocturnal sympathetic activation and consequent increase in blood pressure
- There is also evidence that indicates the association between drug-resistant hypertension and obstructive sleep apnea



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

Adam Witkowski, Aleksander Prejbisz, Elżbieta Florczak, Jacek Kądziera, Paweł Śliwiński, Przemysław Bieleń, Ilona Michałowska, Marek Kabat, Ewa Warchoń, Magdalena Januszewicz, Krzysztof Narkiewicz, Virend K. Somers, Paul A. Sobotka, Andrzej Januszewicz

See Editorial Commentary, pp 542–543

**Abstract**—Percutaneous catheter-based renal sympathetic denervation (RSD) is a procedure for the treatment of resistant hypertension. We studied the effects of this procedure on blood pressure (BP), sleep apnea, and glycemic control in 10 patients with refractory hypertension and obstructive sleep apnea who underwent RSD. Selected blood chemistry values were measured at baseline and at 6 months of follow-up. Median (interquartile range) BP was 163/103 mm Hg before RSD and 129/80 mm Hg 6 months later (median change: −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.)

**Renal Sympathetic denervation may be a potentially useful option for patients with comorbid refractory hypertension, glucose intolerance and obstructive sleep apnea**

to reduce blood pressure (BP) and the effects of this procedure on blood pressure (BP), sleep apnea, and glycemic control in 10 patients with refractory hypertension and obstructive sleep apnea who underwent renal sympathetic denervation (RSD). Selected blood chemistry values were measured at baseline and at 6 months of follow-up. Median (interquartile range) BP was 163/103 mm Hg before RSD and 129/80 mm Hg 6 months later (median change: −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.)

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# Conclusions

- RDN moderates the SNS to improve physiological parameters in many chronic diseases.
- Despite the recent failure of SYMPPLICITY HTN-3 to reach its primary end point, emergent evidence in many alternative areas suggests the potential to overcome current therapeutic hurdles.
- Preliminary data continue to support the use of RDN to regulate SNS-derived pathology, with suggestions for benefit outside of strictly antihypertensive effects.



# Conclusions

- Like to initial results in resistant hypertension, lack of adequate sample size and controls limits interpretation and application of these results.
- Currently, > 100 registered RCTs are designed to address these questions and formulate new avenues of inquiry.

