Prise en charge de l'HTA résistante
Quelle place pour la dénervation rénale?

JM Krzesinski

Néphrologie-Hypertension

CHU Liège - ULg

Histoire clinique

- Femme de 70 ans, HTA depuis 15 ans.
- Imparfaitement contrôlée depuis 1 an, la situation s'aggravant depuis 6 semaines.
- PA mesurée assise en consultation:170/96 mmHg en dépit d'une trithérapie:

  - Lisinopril 40 mg,
  - HCTZ 12.5 mg
  - Atenolol 50 mg.

Est-ce une HTA résistante?

Definition of Resistant HTA

- 2007 ESH-ESC guidelines for the management of arterial hypertension. *J Hypertens 2007; 25: 1105-1187.* « When lifestyle measures and at least three drugs in adequate doses has failed to lower systolic and diastolic BP to goal. »

- The Seventh Report of the Joint National Committee. *JAMA 2003; 289: 2560-72.*

« the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. »

Prevalence of Resistant Hypertension in the United States, 2003–2008

Stephen D. Persell (*Hypertension*. 2011;57:1076-1080.)

Table 1. Classification of Adults With Hypertension in the United States

Classification	No. of Participants	Among All Hypertensive Adults, % (SE)	Among Drug-Treated Hypertensive Adults, % (SE)
Uncontrolled, no drug treatment	1520	30.7 (1.2)	
Controlled hypertension, ≤3 drugs	2035	40.8 (1.1)	58.9 (1.2)
Uncontrolled hypertension, ≤2 drugs	1136	19.6 (0.8)	28.3 (1.1)
Resistant hypertension, uncontrolled, ≥3 drugs or controlled ≥4 drugs	539	8.9 (0.6)	12.8 (0.9)

Uncontrolled indicates a mean systolic pressure of ≥140 or diastolic ≥90 mm Hg.

Characteristics:
Older > 75y
Blacks
Diabetes
Obesity
Lower GFR
Higher µA
Higher CVD (PAD)

Gestion d’une HTA apparemment résistante

- La patiente est bien traitée par une trithérapie dont un diurétique
- Pseudorésistance? HTA blouse blanche?

Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

Alejandro de la Sierra, Julián Segura, José R. Banegas, Manuel Gorostidi, Juan J. de la Cruz, Pedro Armario, Anna Oliveras, Luis M. Ruilope

practice. Resistant hypertension is present in 12% of the treated hypertensive population, but among them more than one third have normal ambulatory blood pressure. A worse risk profile is associated with true resistant hypertension, but this association is weak, thus making it necessary to assess ambulatory blood pressure monitoring for a correct diagnosis and management. (*Hypertension*. 2011;57:898-902.) • Online Data Supplement

Resistant HTA 12%
1/3 WCHT

Histoire clinique

Proposition d'automesure de PA à domicile

PA mesurée avec un appareil au bras validé (automesure.com) avec 2 mesures matin et 2 le soir:

Moy des PA des 6 derniers jours: 155/88 mmHg

Cible idéale <135/85 mmHg

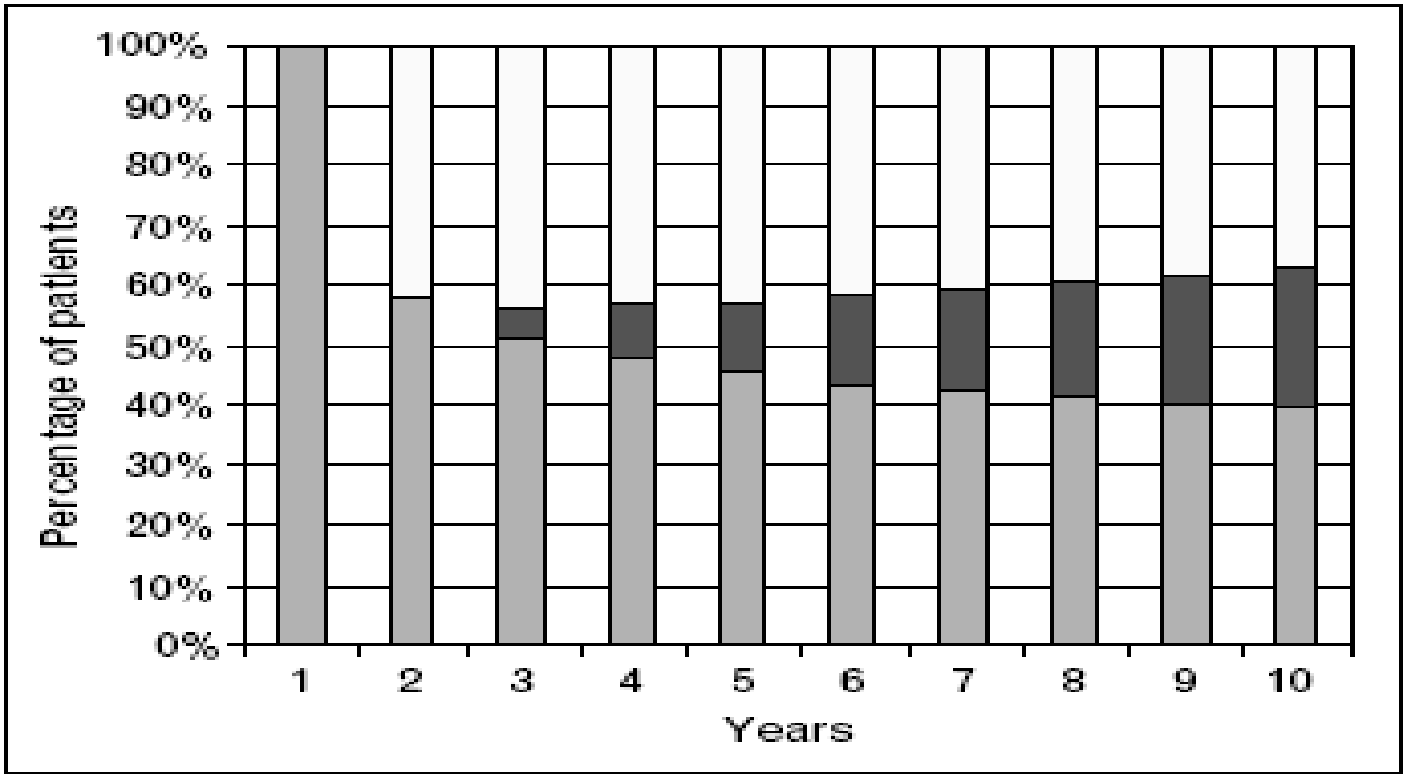
Gestion de l'HTA dite résistante

- Patiente traitée par 3 médicaments antiHTA dont un diurétique sans HTA de la blouse blanche

- Pseudorésistance?: non adhésion au traitement?

J Hypertens 23:2101–2107 © 2005

Fig. 1



Percentage of users in each of the 10 intervals. □ Non-users; ■ restarters; ▩ continuous users.

Rate and determinants of 10-year persistence with antihypertensive drugs

Boris L.G. Van Wijk, Olaf H. Klungel, Eibert R. Heerdink and Anthonius de Boer

Which is more important for the efficiency of hypertension treatment: hypertension stage, type of drug or therapeutic compliance?

Javier Mar[a] and Fernando Rodríguez-Artalejo[b]

Conclusions There are large variations in the cost-effectiveness of arterial hypertension treatment depending on age, sex, arterial hypertension stage, drug used and compliance. Improvement of treatment compliance yields the greatest gain both in effectiveness and efficiency.

J Hypertens 19:149–155 © 2001 Lippincott Williams &

Histoire clinique

- FC 64/min
- K 3.8 mmol/l, créatinine 1.0 mg/dl (eGFR 55ml/min), acide urique légèrement accru
- Bandelette urinaire négative
- La patiente affirme prendre régulièrement son traitement.

Gestion de l'HTA dite résistante

- Patiente traitée par 3 médicaments antiHTA dont un diurétique sans HTA de la blouse blanche, sans Pseudorésistance
- Interférence médicamenteuse?

Histoire clinique

- Pas de consommation d’alcool ni de tabagisme
- Polyarthrose invalidante traitée par paracétamol et ibuprofène depuis 2 mois.

Table 2. Medications That Can Increase Blood Pressure or Antagonize Antihypertensive Therapy

- Anabolic steroids
- Anti–vascular endothelial growth factor therapy (bevacizumab)
- Bronchodilators
- Calcineurin inhibitors
- Corticosteroids
- Decongestants
- Herbals (St John's wort, ma huang)
- Erythropoietic-stimulating agents
- Monoamine oxidase inhibitors
- Nonsteroidal anti-inflammatory drugs
- Oral contraceptives
- Tricyclic antidepressants

Liquorice
Cocaine
Alcohol

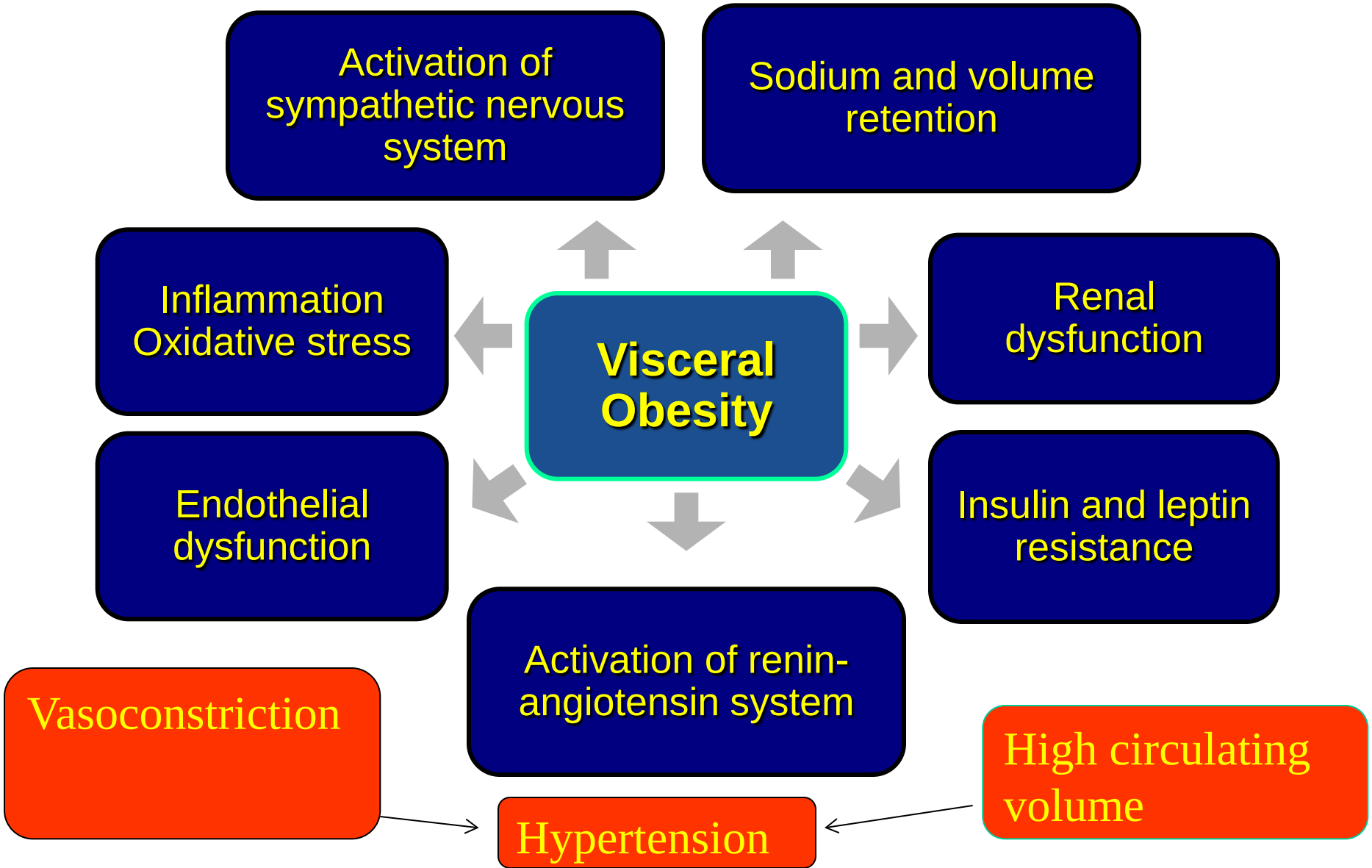
Gestion d’une HTA dite résistante

- Patiente traitée par 3 médicaments antiHTA dont un diurétique sans HTA de la blouse blanche, sans pseudorésistance mais avec potentielle interférence médicamenteuse
- Mauvaise hygiène de vie ou alimentaire?(SM, gain de poids, apport en NaCl accru,..)?

Histoire médicale

- IMC 32 kg/m²
- Prise de poids de 10 Kg en 5 ans
- Rajoute régulièrement du sel pour manger les PdT
- Récolte d’urines sur 24h: excrétion sodée de 220 mmol (soit 13g de NaCl)

Mechanisms linking central obesity to hypertension



Lifestyle Modification

Modification	Approximate SBP reduction (range)
Weight reduction	5–20 mmHg/10 kg weight loss
Adopt DASH eating plan	8–14 mmHg
Dietary sodium reduction	2–8 mmHg
Physical activity	4–9 mmHg
Moderation of alcohol consumption	2–4 mmHg

Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension

reduction. These results indicate that excessive dietary sodium ingestion contributes importantly to resistance to antihypertensive treatment. Strategies to substantially reduce dietary salt intake should be part of the overall treatment of resistant hypertension. (*Hypertension*. 2009;54:475-481.)

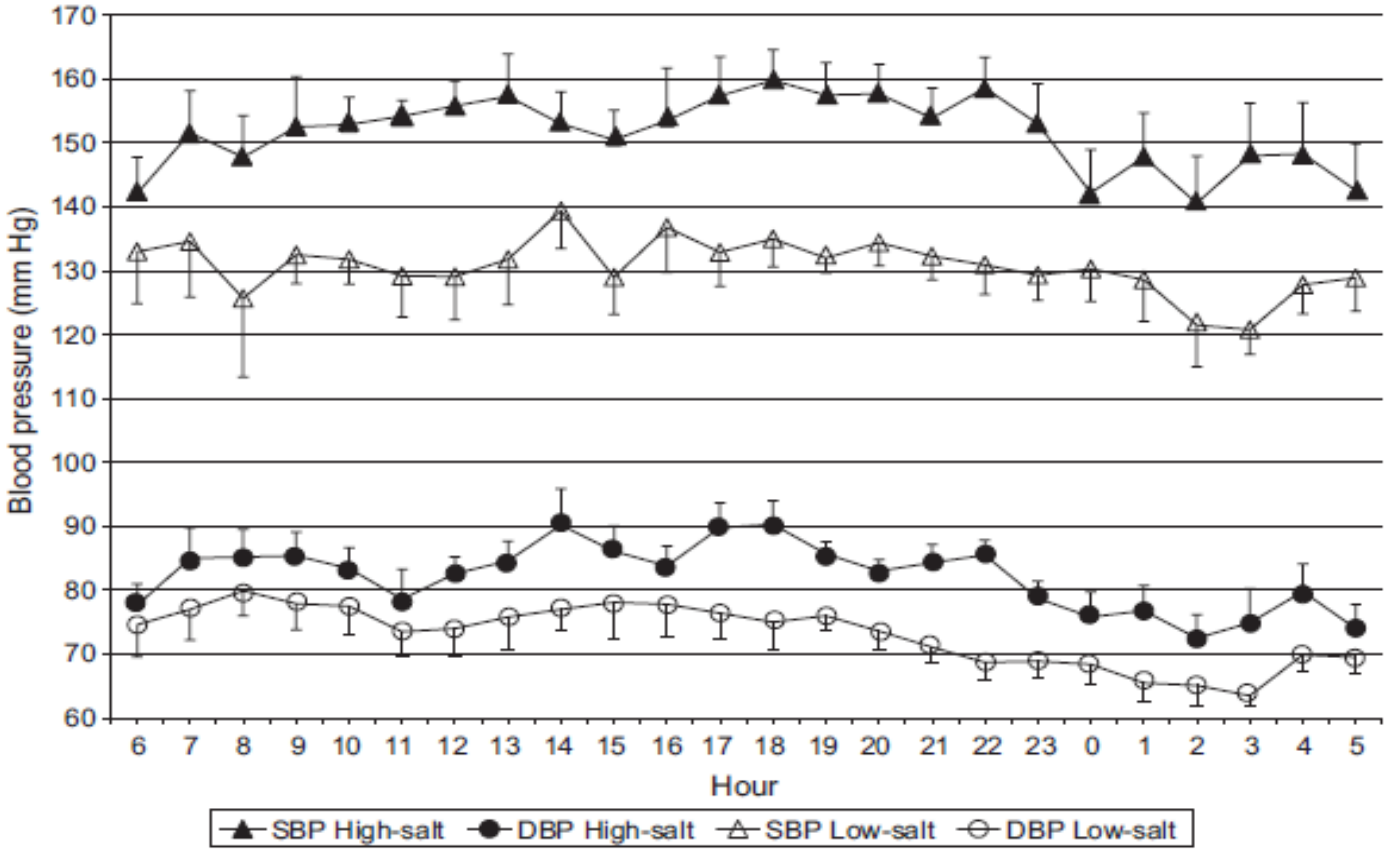


Figure. Comparison of 24-hour ambulatory blood pressure values during low- and high-salt diet. Data presented as mean±SE.

Gestion d’une HTA résistante

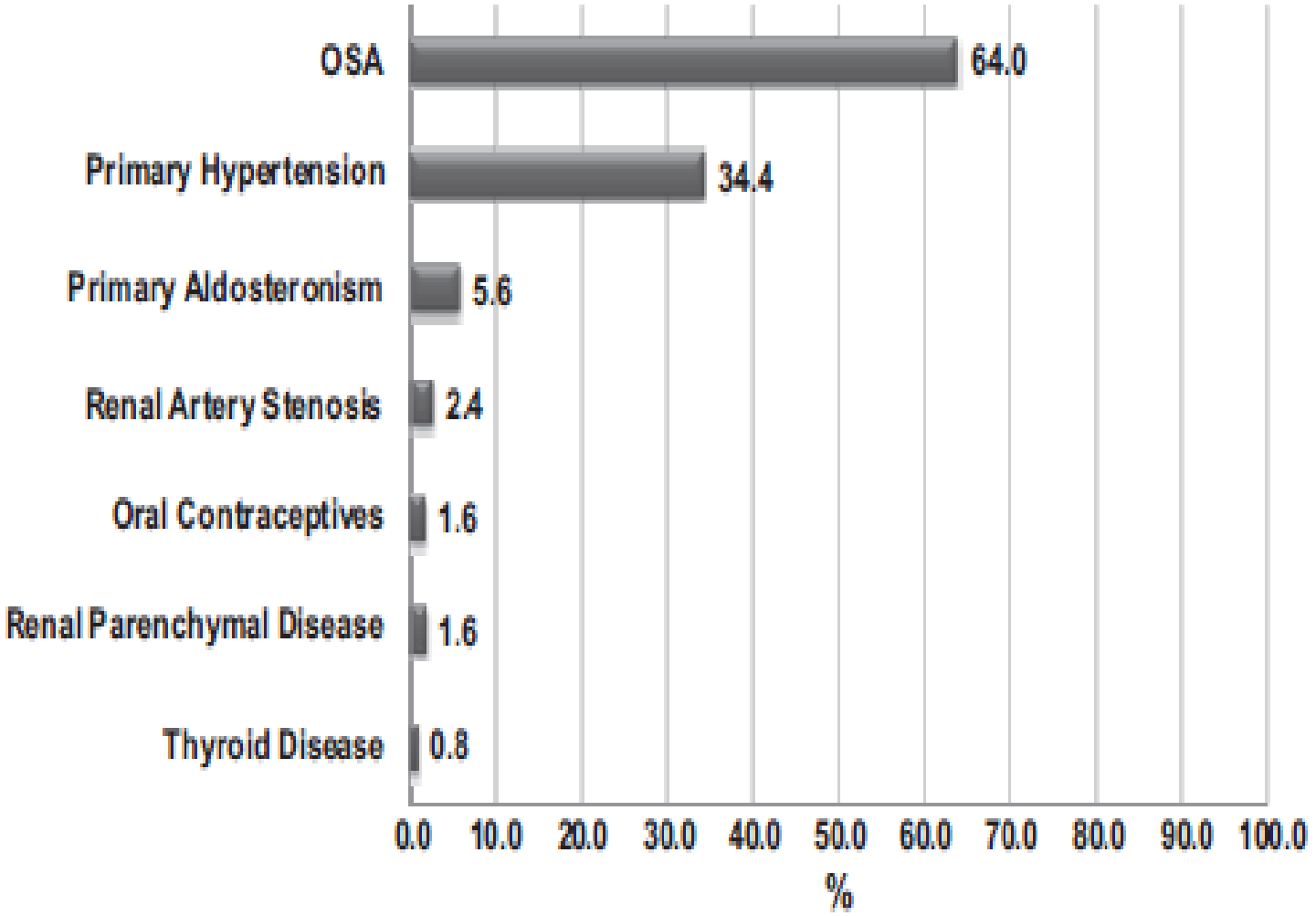
- Patiente traitée par 3 médicaments antiHTA dont un diurétique sans HTA de la blouse blanche, sans pseudo résistance mais prise d’AINS et mauvais comportement alimentaire
- Causes secondaires?
- Pas de souffle vasculaire, pas de ronflement nocturne ou de fatigue exagérée la journée, pas de céphalées.

Obstructive Sleep Apnea

The Most Common Secondary Cause of Hypertension Associated With Resistant Hypertension

Rodrigo P. Pedrosa, Luciano F. Drager, Carolina C. Gonzaga, Marcio G. Sousa, Lilian K.G. de Paula, Aline C.S. Amaro, Celso Amodeo, Luiz A. Bortolotto, Eduardo M. Krieger, T. Douglas Bradley, Geraldo Lorenzi-Filho

(*Hypertension*. 2011;58:811-8



Approche thérapeutique d'une HTA résistante

- Patiente traitée par 3 médicaments antiHTA dont un diurétique sans HTA de la blouse blanche, sans prseudo résistance mais prise d'AINS et mauvais comportement alimentaire
- Pas de cause identifiée à l'HTA
- Optimalisation du traitement

Description of Antihypertensive Use in Patients With Resistant Hypertension Prescribed Four or More Agents

Michele R. Hanselin, Joseph J. Saseen, Richard R. Allen, Joel C. Marrs and Kavita V. Nair

Hypertension published online October 31, 2011

There were 5 442 410 patients with hypertension identified based on ICD-9-CM, and 140 126 met study criteria for this definition of resistant hypertension. Baseline characteristics

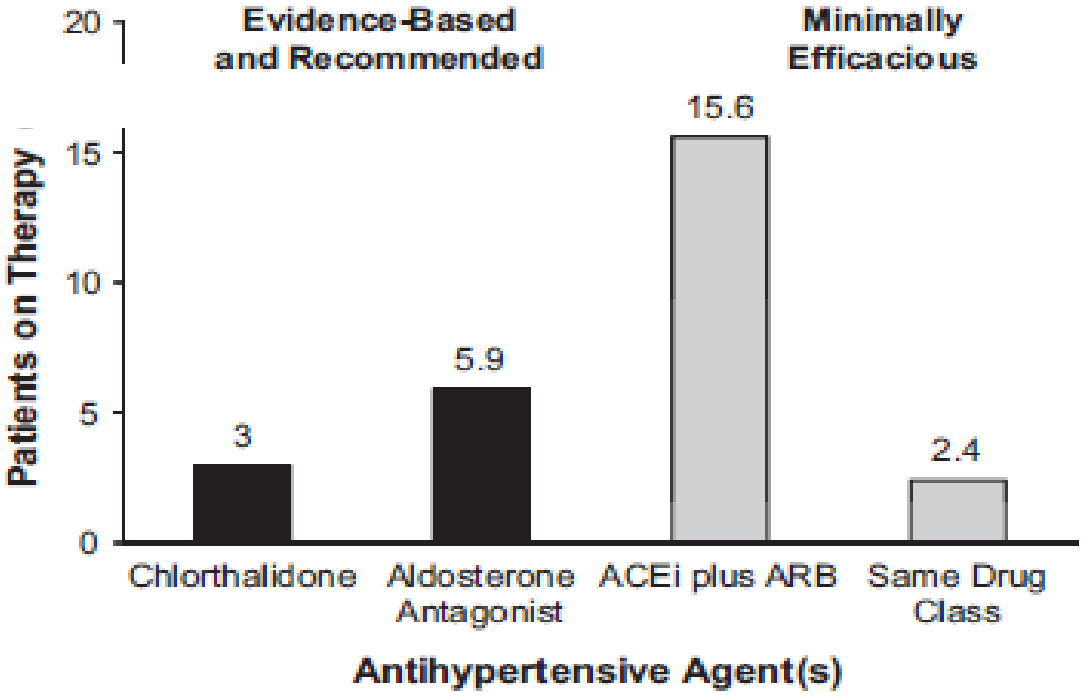


Figure 4. Percentage of patients on evidence-based and recommended versus minimally efficacious antihypertensive therapy. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.


Rx
HCT2
Rx
Chlorthal
C. Lynn

Hypertension 2006

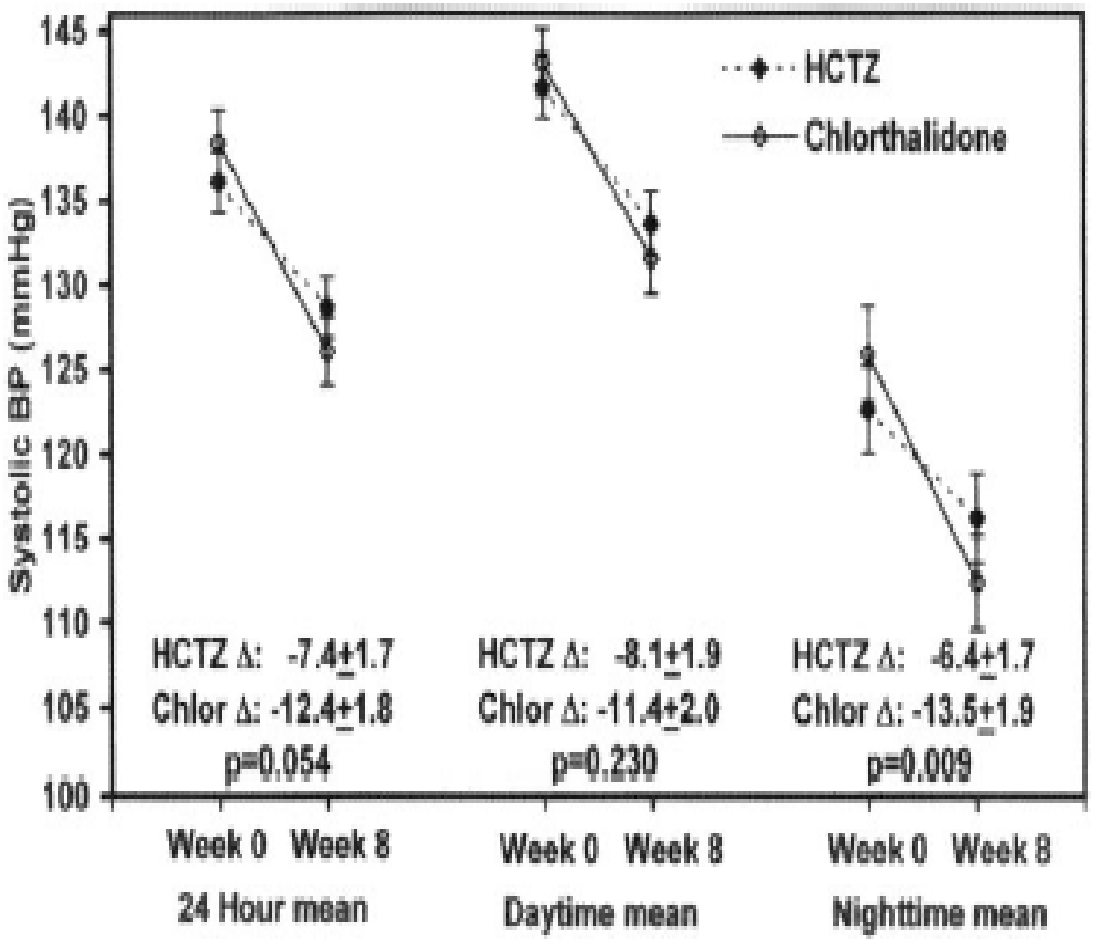


Figure 2. Mean 24-hour, daytime, and nighttime ambulatory SBP with change from baseline.

Efficacy of Spironolactone Therapy in Patients With True Resistant Hypertension

Fabio de Souza, Elizabeth Muxfeldt, Roberto Fiszman and Gil Salles

Hypertension 2010, 55:147-152: originally published online October 26, 2009

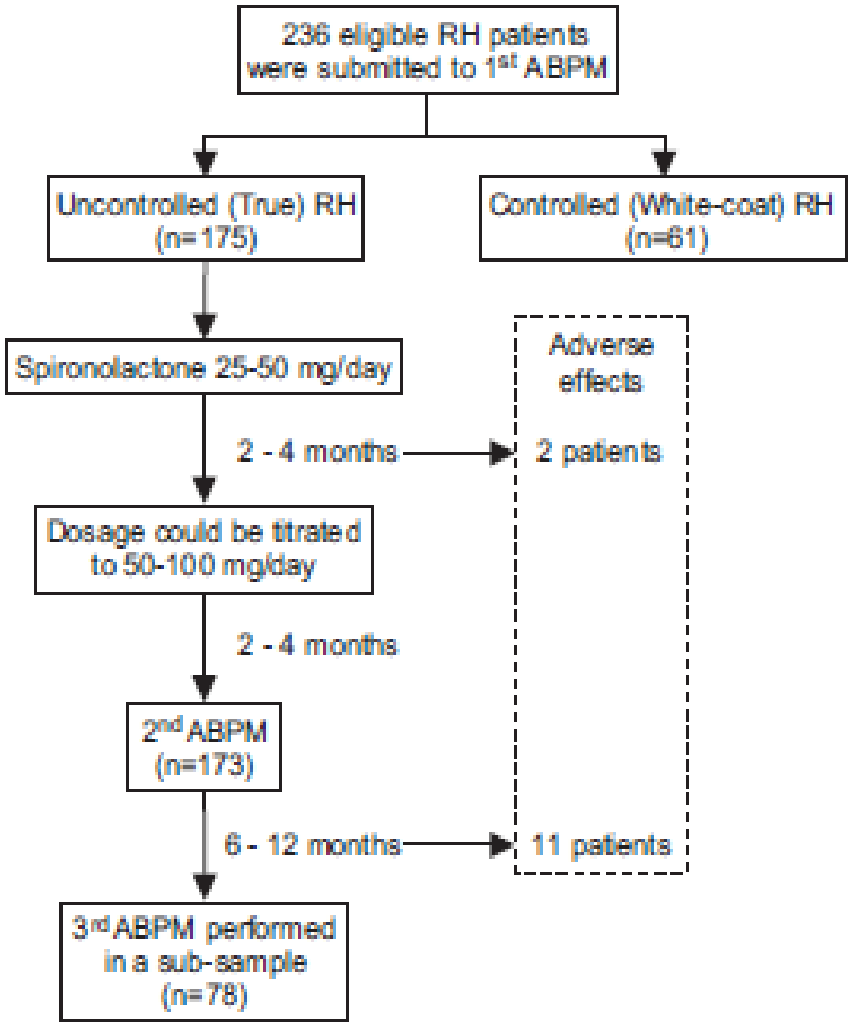


Figure 1. The flowchart of the study.

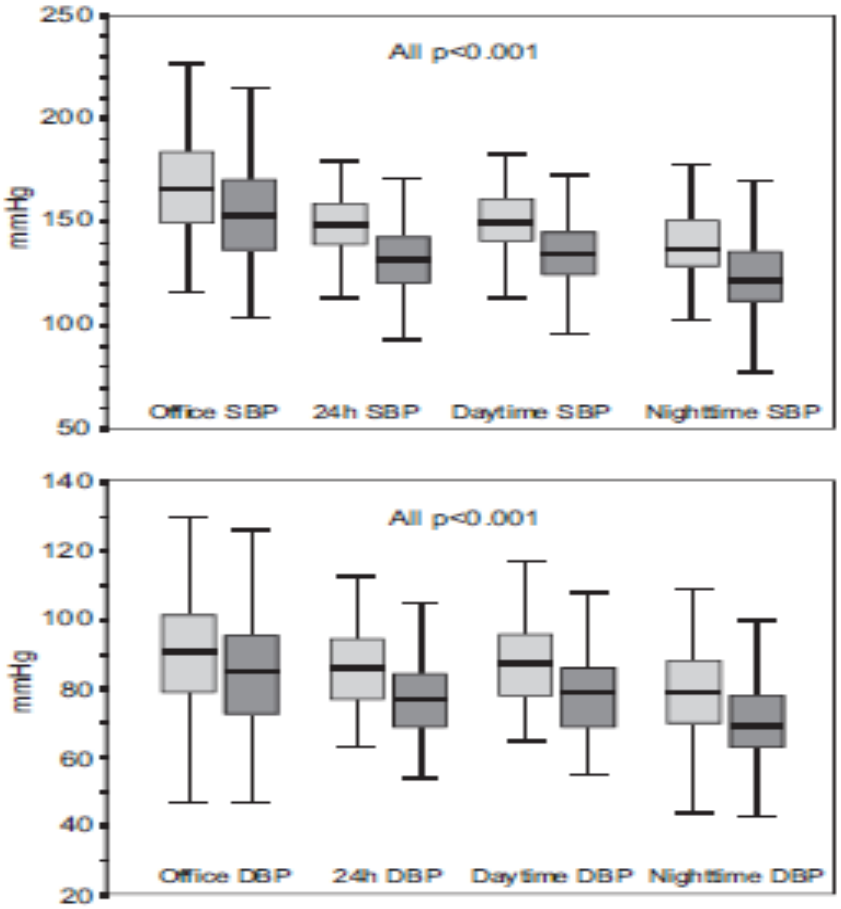


Figure 2. Box-plot graphic representation of office and ambulatory systolic (top) and diastolic (bottom) blood pressure before (clear box) and during (dark box) spironolactone administration. *P* values refer to paired *t* test comparisons of BPs before and during spironolactone use.

Chronotherapy Improves Blood Pressure Control and Reverts the Nondipper Pattern in Patients With Resistant Hypertension

Ramón C. Hermida, Diana E. Ayala, José R. Fernández, Carlos Calvo

after therapy ($P<0.001$). Results indicate that, in resistant hypertension, time of treatment may be more important for blood pressure control and for the proper modeling of the circadian blood pressure pattern than just changing the drug combination. (***Hypertension*. 2008;51:69-76.**)

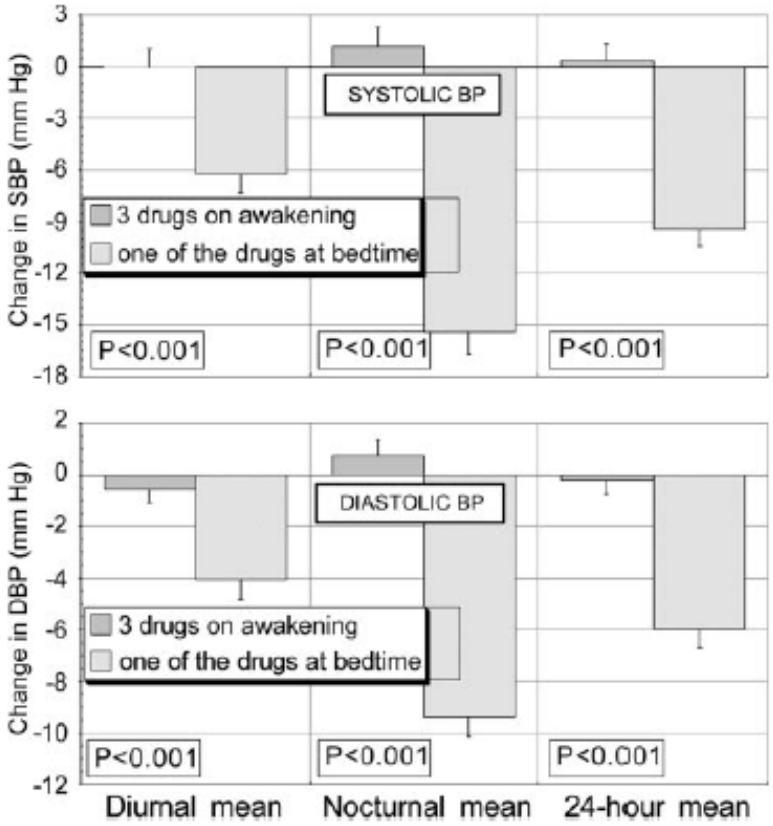


Figure 2. Changes (in millimeters of mercury) in the diurnal (active hours), nocturnal (sleep time), and 24-hour mean of SBP (top) and DBP (bottom) after 3 months of therapy in patients with resistant hypertension receiving 3 antihypertensive drugs on awakening or receiving 2 drugs on awakening and 1 drug at bedtime. *P* values are shown for comparison of effects between

Histoire clinique

Proposition

- Perte de poids et limitation du NaCl à 6g/j
- Stop AINS et stimulation pour le recours à du tramadol et à la physiothérapie
- Intensification du traitement antiHTA

  - aldactazine et nébivolol 5 mg au matin et IEC+AC en 1 c le soir

- Stimulation du suivi tensionnel à domicile.
- Et si cela ne marche pas?

Endovascular Treatment of Resistant and Uncontrolled Hypertension

Therapies on the Horizon

(J Am Coll Cardiol Intv 2013

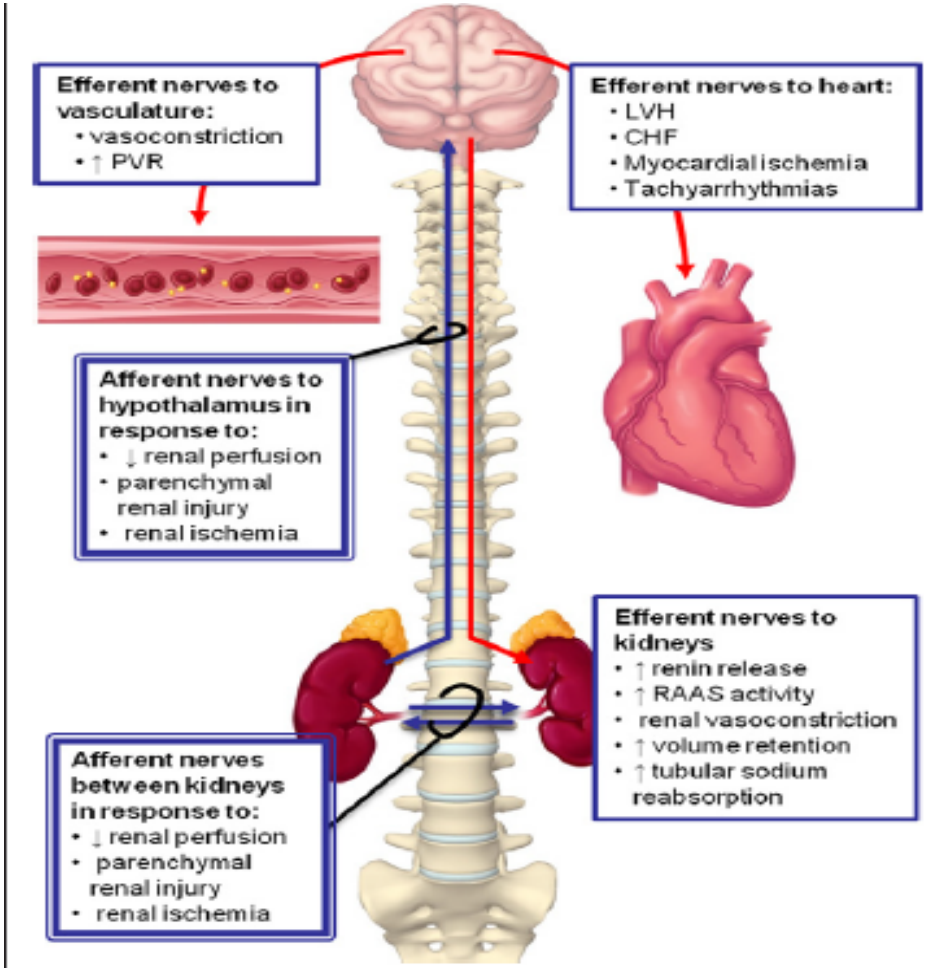


Figure 1. Pathways of Sympathetic Activity Leading to Hypertension

↑ = increased; ↓ = decreased; CHF = chronic heart failure; LVH = left ventricular hypertrophy; PVR = peripheral vascular resistance; RAAS = renin-angiotensin-aldosterone system.

Complications of sympathetic activation in HTA

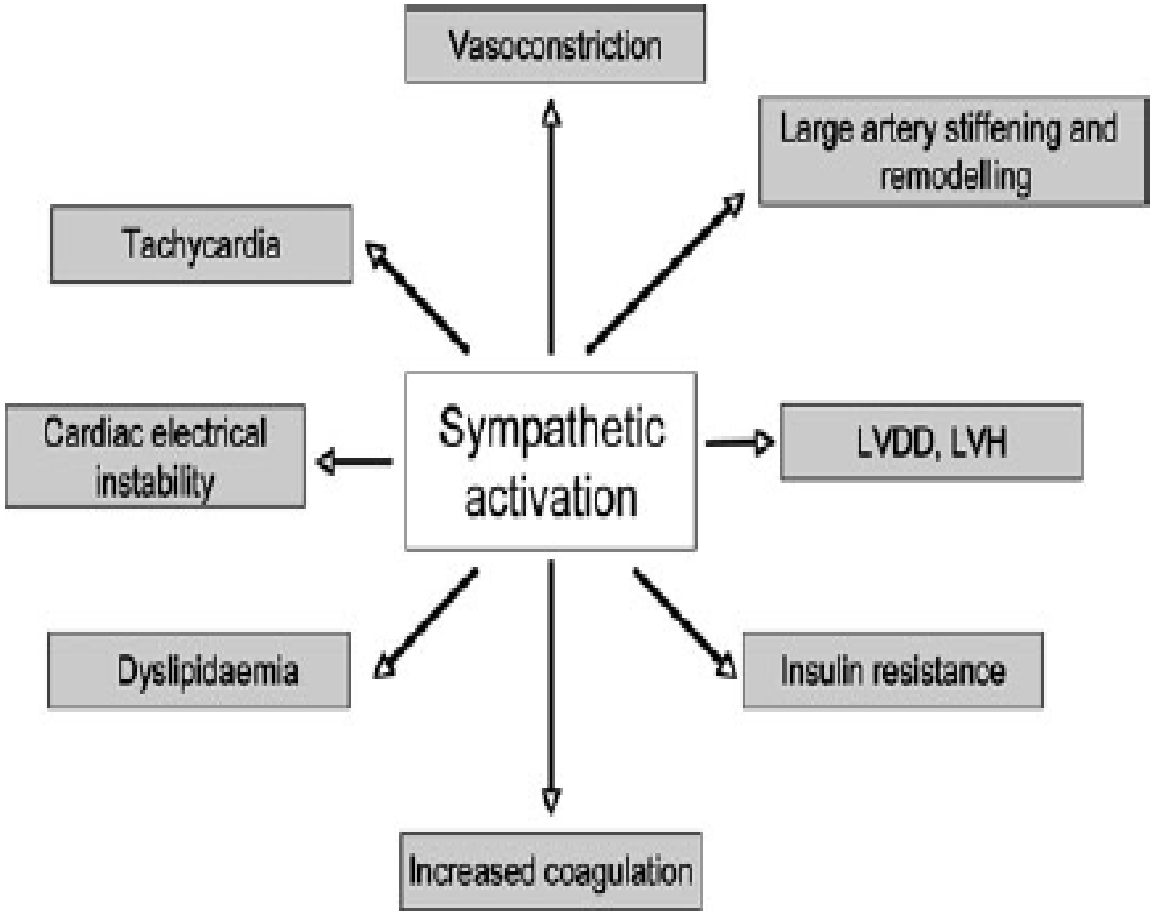


Figure 4. Schematic drawing of the adverse cardiovascular and metabolic effects of sympathetic activation in hypertension
Abbreviations: LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy.

Benefits from Treatment and Control of Patients with Resistant Hypertension

Michael Doumas,[1] Vasilios Papademetriou,[2] Stella Douma,[3] Charles Faselis,[1] Konstantinos Tsioufis,[2] Eugene Gkaliagkousi,[3] Konstantinos Petidis,[3] and Chrysanthos Zamboulis[3]

International Journal of Hypertension
Volume 2011, Article ID 318549, 8 pages
doi:10.4061/2011/318549

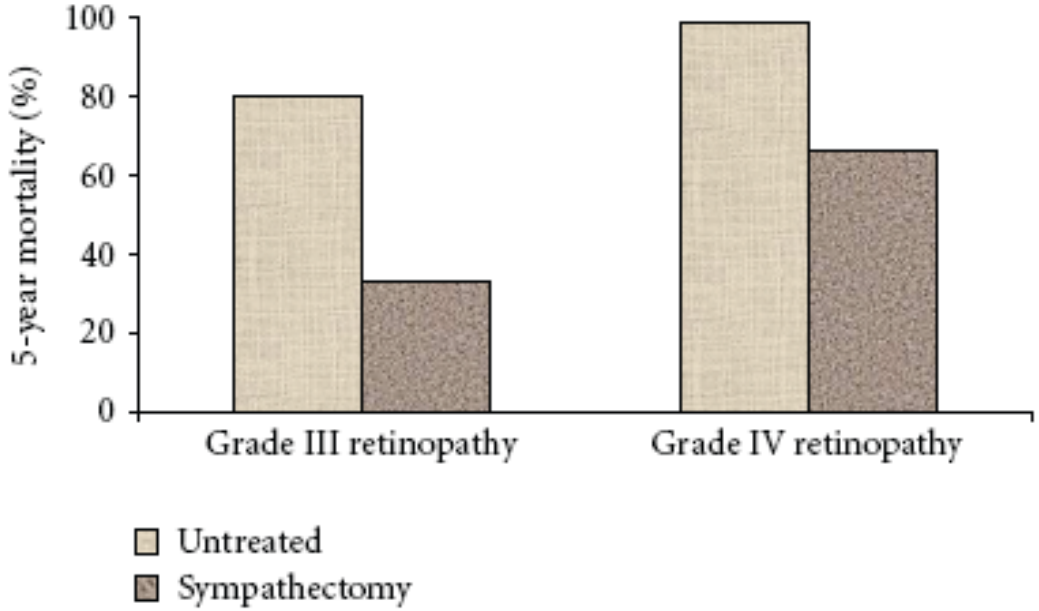


FIGURE 1: Five-year mortality rates (%) in untreated patients with malignant hypertension and Grade III or IV retinopathy compared to similar patients that underwent sympathectomy (modified from Keith et al. [25] and Peet et al. [26]).

1940

Different Approaches That Target the Sympathetic Nervous System in RH

Catheter-based radiofrequency renal nerve ablation (approved for use in Europe, Australia, and other countries; phase 3 trial ongoing in the USA)

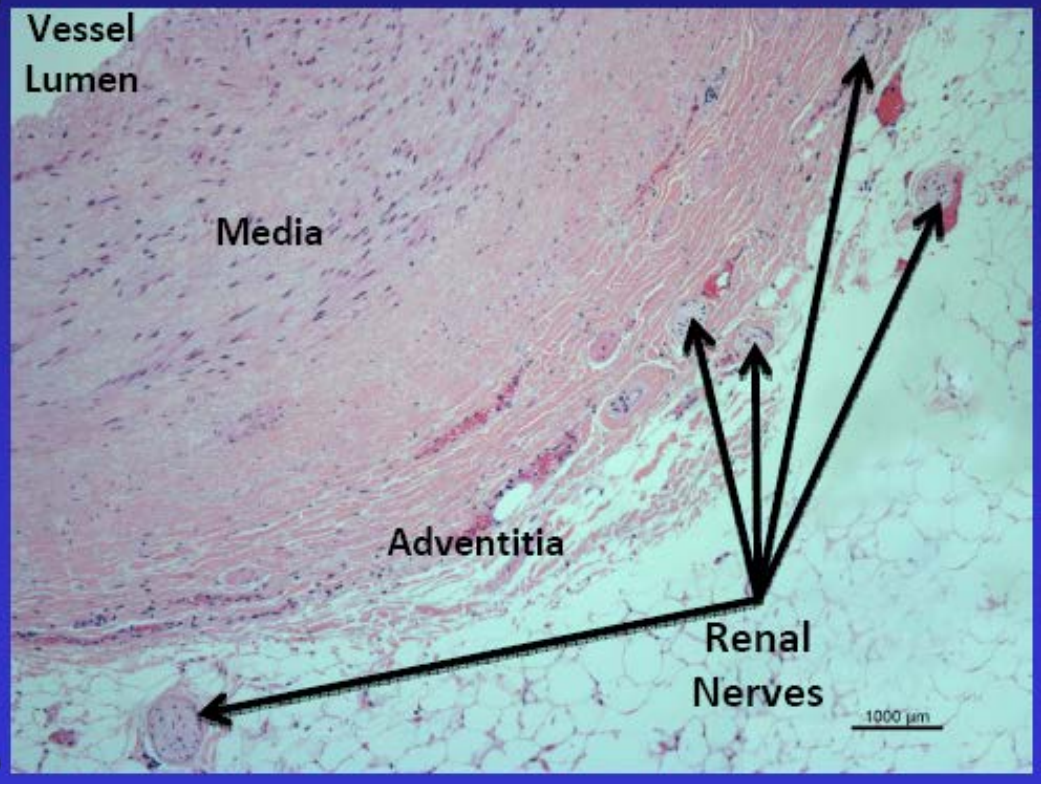
Other methodology for renal denervation (under investigation):

- Focused ultrasound
- Heat therapy

Carotid baroreceptor stimulation (under investigation)

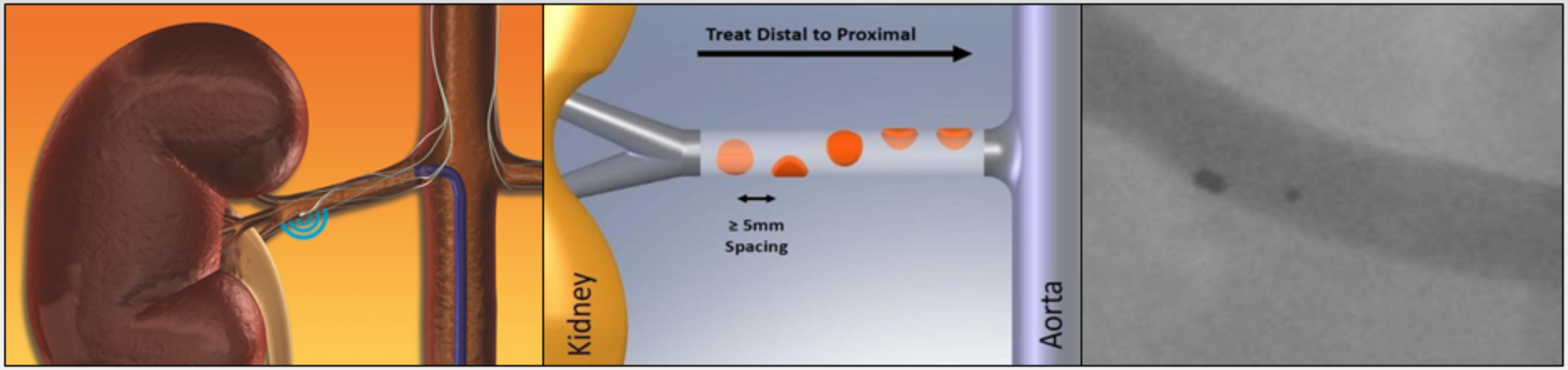
Renal Sympathetic Nerves as Therapeutic Target

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia



Catheter-Based Radiofrequency in Renal Nerve Ablation

- Standard interventional technique
- 4-6 two-minute treatments per artery
- No serious procedure- or device-related complications in Symplicity HTN-2



- Most common periprocedural problem was pain, which was solved with analgesia
- Longer-term complications (eg, vessel thrombosis) were mitigated with the prophylactic use of aspirin and clopidogrel

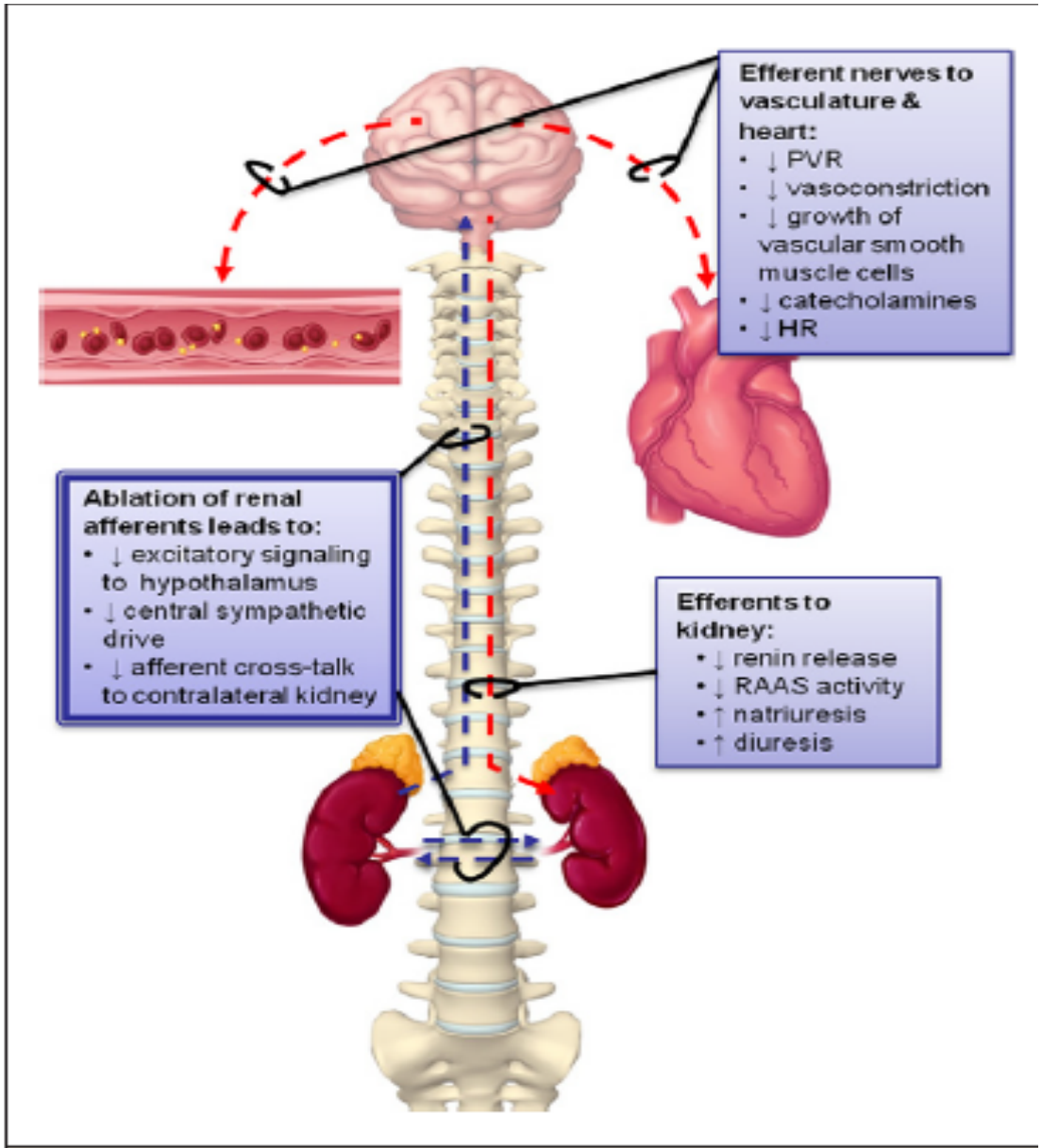


Figure 2. Proposed Pathways of Therapeutic Benefit of RSD

Table 1. Overview of Clinical Trials Enrolling Hypertensive Patients for Endovascular Renal Nerve Ablation

Product Name	Product Design	Clinical Trial Name	Hypertension Type Studied	Trial Status	Clinical Trial ID	Sponsor
Radiofrequency ablation						
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-1	Resistant	Active, not recruiting	NCT00664638	Medtronic Inc.
		SYMPLICITY HTN-2	Resistant	Active, not recruiting	NCT00888433	
		SYMPLICITY HTN-3	Resistant	Recruiting	NCT01418261	
		Effect of renal denervation on biological variables	Resistant	Recruiting	NCT01427049	
		Renal nerve ablation in CKD patients	Resistant, with Stage 3–5 CKD	Recruiting	NCT01442883	
		PRAGUE-15	Uncontrolled	Recruiting	NCT01560312	
		Renal denervation in patients with RH and OSA	Uncontrolled, with OSA	Recruiting	NCT01366625	
EnligHTN RFA catheter	Multielectrode RFA catheter	ARSENAL	Resistant	Active, not recruiting	NCT01438229	St. Jude, Inc.
Vessix V2 RFA catheter	Balloon-mounted RFA catheter	REDUCE-HTN	Resistant	Recruiting	NCT01541865	Vessix Vascular Inc.
OneShot RFA catheter	Irrigated, balloon-mounted RFA catheter	RAPID	Resistant	Recruiting	NCT01520506	Maya Medical Inc.
ThermoCool cryoablative catheter	Irrigated RFA catheter	SWAN HT	Uncontrolled	Recruiting	NCT01417221	Biosense Webster Inc.
		SAVE	Uncontrolled	Recruiting	NCT01628198	
		RELIEF	Uncontrolled	Recruiting	NCT01628172	
Chilli II cryoablative catheter	Irrigated RFA catheter	SAVE	Uncontrolled	Recruiting	NCT01628198	Boston Scientific Inc.
Ultrasonic ablation						
PARADISE ultrasonic catheter	Ultrasonic balloon catheter	REALISE	Resistant	Recruiting	NCT01529372	ReCor Medical Inc.
TIVUS ultrasonic catheter	Ultrasonic autoregulating balloon catheter	In development				Cardiosonic Ltd.
Kona medical ultrasonic system	Low-intensity external ultrasonic ablation system	In development				Kona Medical Inc.
Tissue-directed pharmacological ablation						
Bullfrog microinfusion catheter	Microneedle-equipped balloon catheter	In development				Mercator MedSystems Inc.

ARSENAL — Safety and Efficacy Study of Renal Artery Ablation In Resistant Hypertension Patients trial; CKD — chronic kidney disease; HTN — hypertension; OSA — obstructive sleep apnea; PARADISE — ReCor Percutaneous Renal Denervation System catheter; PRAGUE-15 — Renal Denervation In Refractory Hypertension trial; RAPID — Rapid Renal Sympathetic Denervation for Resistant Hypertension trial; REDUCE-HTN — Treatment of Resistant Hypertension Using a Radiofrequency Percutaneous Transluminal Angioplasty Catheter; RELIEF — Renal Sympathetic Denervation for the Management of Chronic Hypertension trial; REALISE — Renal Denervation by Ultrasound Transcatheter Emission trial; RFA — radiofrequency ablation; RH — resistant hypertension; SAVE — Impact of Renal Sympathetic Denervation on Chronic Hypertension study; SWAN HT — Renal Sympathetic Modification In Patients With Essential Hypertension study; SYMPLICITY HTN-1 — SYMPLICITY I: One-Year Results Following Sympathetic Renal Denervation In Refractory Hypertension trial; SYMPLICITY HTN-2 — Renal Sympathetic Denervation In Patients With Treatment-Resistant Hypertension trial; SYMPLICITY HTN-3 — Renal Denervation In Patients

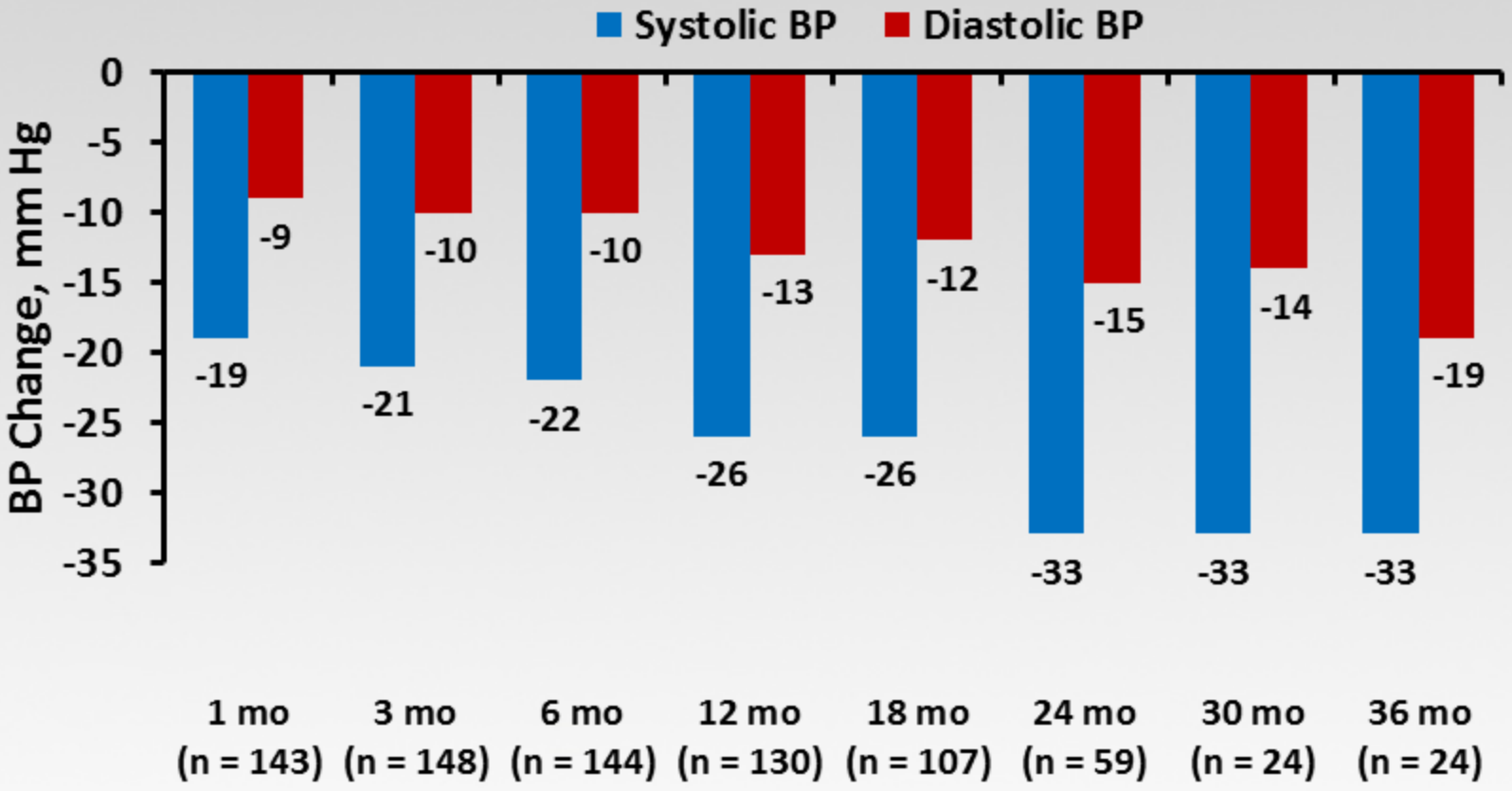
Table 2. Summary of the SYMPLICITY HTN-1 and SYMPLICITY HTN-2 Trials

	SYMPLICITY HTN-1 (13)	SYMPLICITY HTN-2 (14)
Study characteristics		
Study design	• Nonrandomized, cohort, unblinded to treatment	• Randomized control, unblinded to treatment
Enrollment period	• June 2007 to November 2008	• June 2009 to January 2010
Patient population	• 45 subjects* • Mean age: 58 ± 9 yrs; 96% white, 44% women, 31% diabetic • Mean BP (mm Hg) at enrollment: 177/101 (SD 20/15)	• 106 subjects (52 treated, 54 control)* • Mean age: 58 ± 12 yrs; 97% white, 42% women, 67% diabetic • Mean BP (mm Hg) at enrollment: treatment group: 178/97 (SD 18/16); control group: 178/98 (SD 16/17)
Inclusion criteria	• Office-based SBP ≥160 mm Hg, on ≥3 antihypertensive medications, including a diuretic or drug intolerance	• Office-based SBP ≥ 160 mm Hg (or diabetics with SBP ≥150 mm Hg), on ≥3 antihypertensive medications, including a diuretic or drug intolerance
Exclusion criteria	• Known secondary cause of hypertension (except OSA or CKD) • Type I diabetes mellitus • Pregnancy • Significant valvular heart disease • Existing PPM or ICD • Use of clonidine, moxonidine, rilmenidine, or warfarin • Renovascular abnormalities† • CKD with eGFR <45 ml/min/1.73 m^2	• Type I diabetes mellitus • Pregnancy • Significant valvular heart disease • Existing PPM or ICD • Use of clonidine, moxonidine, rilmenidine, or warfarin • Renovascular abnormalities† • CKD with eGFR <45 ml/min/1.73 m^2 • Contraindications to MRI • History of recent MI, USA, or CVA within 6 months of enrollment
Outcomes		
Primary	• Acute procedural and long-term safety • Mean reduction in office-based SBP at 12 months	• Between-group difference in office-based mean SBP at 6 months

Table 2. Summary of the SYMPLICITY HTN-1 and SYMPLICITY HTN-2 Trials

	SYMPLICITY HTN-1 (13)				SYMPLICITY HTN-2 (14)			
Results								
Primary efficacy outcomes	Follow-up period, month(s)	Subjects available for follow-up analysis, n (%), N = 45	Mean change in office-based BP SBP/DBP (mm Hg)	95% CI	Follow-up period, month(s)	Mean change in BP SBP/DBP (mm Hg)	Follow-up period, month(s)	Mean change in BP SBP/DBP (mm Hg)
	1	41 (91)	−14/−10	4/3	1	−20/−7	1	0/0
	3	39 (87)	−21/−10	7/4	3	−24/−8	3	−4/−2
	6	26 (58)	−22/−11	10/5	6	−32/−12 (SD 23/11)	6	1/0 (SD 21/10)
	9	20 (44)	−24/−11	9/5	Denervation group (N = 49)‡		Control group (N = 51)‡	
	12	9 (20)	−27/−17	16/11				
Periprocedural safety outcomes	• Renal artery dissection (n = 1) • Pseudoaneurysm at femoral artery access site (n = 1) • No long-term vascular complications observed with post-procedure imaging studies (n = 18 had repeat renal angiograms <30 days after treatment; n = 14 had MRA, n = 17 had CTA within 6 months after treatment)				• 7 of 52 (13%) required atropine for intraprocedural bradycardia • Among treated subjects: TIA (n = 1), angina requiring coronary stent (n = 1), hypotension (n = 1), hypertensive crisis (n = 1), hospital admission for nausea and vomiting "possibly related to hypertension" (n = 1) • Among control subjects, TIA (n = 2), angina requiring coronary stent (n = 1)			
Nonresponders	• 6 of 45 (13%) had SBP reductions <10 mm Hg				• 5 of 49 (10%) treated subjects and 24 of 51 (47%) control subjects had no decline in SBP • 4 of 49 (8%) treated subjects and 6 of 51 (12%) control subjects had drug increases before 6-month follow-up			

Symplicity HTN-1: 36-Month Follow-up Sustained Reductions in Blood Pressure



P < .001 for systolic and diastolic BP changes from baseline

HYPERTENSION

Krum H, et al.[10]

Slide courtesy of Dr Murray Esler

theheart.org from WebMD

Medscape EDUCATION

Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension : One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

Murray D. Esler, Henry Krum, Markus Schlaich, Roland E. Schmieder, Michael Böhm and Paul A. Sobotka
for the Symplicity HTN-2 Investigators

Circulation. 2012;126:2976-2982

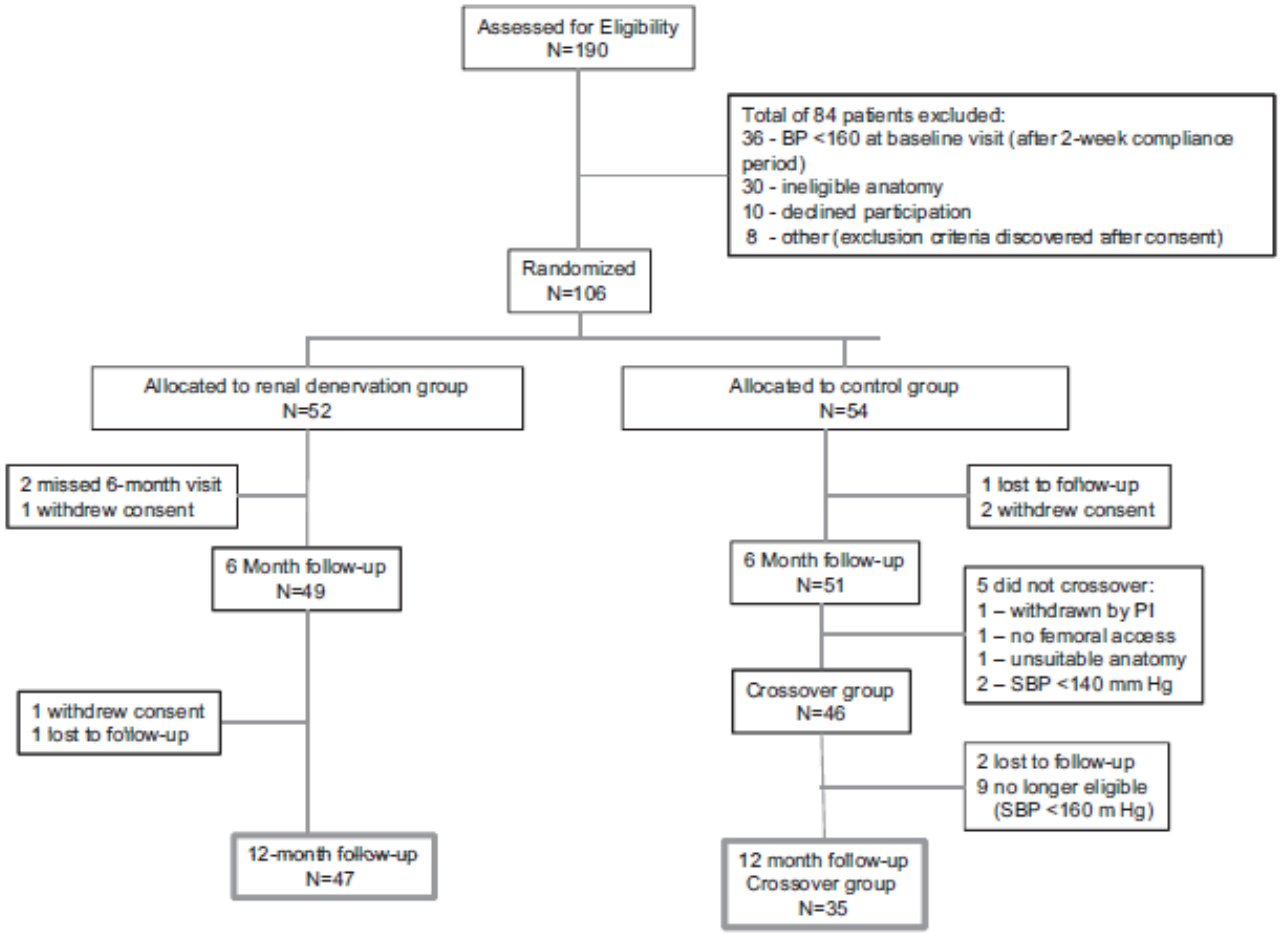


Figure 1. Patient disposition. At 12 months, follow-up data from 47 patients allocated to immediate renal denervation and 35 crossover patients meeting the same preprocedure eligibility criteria are available for analysis. BP indicates blood pressure; PI, principal investigator; and SBP, systolic blood pressure.

Conclusions—Control patients who crossed over to renal denervation with the Symplicity system had a significant drop in blood pressure similar to that observed in patients receiving immediate denervation. Renal denervation provides safe and sustained reduction of blood pressure to 1 year.

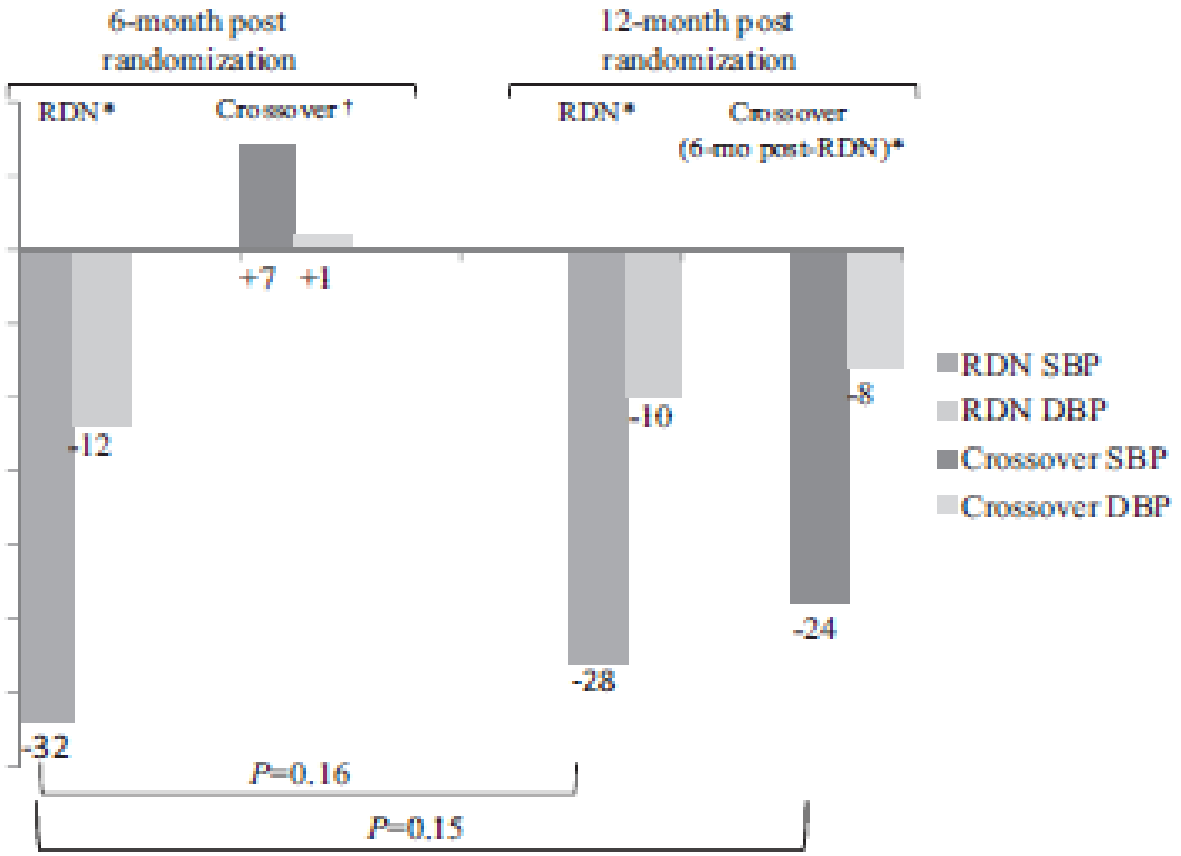


Figure 2. Change in office-based blood pressure. Both the initial renal denervation (RDN) group and the crossover group denervated at 6 months after randomization experienced significant drops in systolic (SBP) and diastolic blood pressure (DBP). *$P<0.001$ for SBP and DBP change after renal denervation; †$P=0.026$ for SBP change from baseline and $P=0.066$ for DBP change from baseline for the crossover group before denervation at 6 months.

Table 4. Change From Before the Procedure in Office BP at 6 and 12 Months

	Renal Denervation Group (n=49)	*P*	Crossover Group (n=35)	*P*
6-mo change in BP				
SBP	−31.7±23.1	<0.001	−23.7±27.5	<0.001
DBP	−11.7±11.2	<0.001	−8.4±12.1	<0.001
12-mo change in BP				
SBP	−28.1±24.9	<0.001	N/A	
DBP	−9.7±10.6	<0.001	N/A	

Values are mean±SD. BP indicates blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; and N/A, not applicable. There was no 2-wk compliance period before the 6-mo follow-up after renal denervation for the crossover group. *P* values are for change in BP from preprocedure BP within each group.

Table 5. Proportion of Patients With a Medication Use Change After Renal Denervation

Medication Change, %*	Renal Denervation Group	Crossover Group
6 mo after procedure		
Decrease	20.9 (9/43)	18.2 (6/33)
Increase	11.6 (5/43)	15.2 (5/33)
12 mo after procedure		
Decrease	27.9 (12/43)	N/A
Increase	18.6 (8/43)	N/A

N/A indicates not applicable.

*Change in the number of medications or dose; P=NS for medication changes between the 2 groups at 6 mo after the procedure.

Table 6. Renal Function at Baseline and 6 and 12 Months

	Renal Denervation Group	Crossover Group
eGFR, mL/min per 1.73 m^2		
Baseline	76.9±19.3 (n=49)	88.8±20.7 (n=35)
6 mo	77.1±18.8 (n=49)	89.3±19.5 (n=35)
12 mo	78.2±17.4 (n=45)	85.2±18.3 (n=35)
Serum creatinine, mg/dL		
Baseline	1.03±0.29 (n=49)	0.84±0.21 (n=35)
6 mo	1.04±0.32 (n=49)	0.83±0.18 (n=35)
12 mo	1.01±0.28 (n=45)	0.86±0.20 (n=35)
Cystatin C, mg/L		
Baseline	0.91±0.25 (n=38)	0.78±0.17 (n=27)
6 mo	0.98±0.36 (n=40)	0.82±0.16 (n=26)
12 mo	0.98±0.30 (n=38)	0.89±0.20 (n=26)

Values are mean±SD. eGFR indicates estimated glomerular filtration rate.

Renal Hemodynamics and Renal Function After Catheter-Based Renal Sympathetic Denervation in Patients With Resistant Hypertension

Felix Mahfoud, Bodo Cremers, Julia Janker, Britta Link, Oliver Vonend, Christian Ukena,

(*Hypertension*. 2012;60:419-424.)

Table 2. Change in Blood Pressure, Renal Function, and Resistive Indices

	Treatment Group (n=88)				Control Group (n=12)			
Parameter	3 mo	*P* Value*	6 mo	*P* Value†	3 mo	*P* Value*	6 mo	*P* Value†
SBP, mm Hg	−22.7±2.3 (−13%)	<0.001	−26.6±2.5 (−15%)	<0.001	−7.2±7.6 (−4%)	0.301	−4.4±6.2 (−2%)	0.479
DBP, mm Hg	−7.7±1.3 (−8%)	<0.001	−9.7±1.5 (−10%)	<0.001	−4.1±4.7 (−4%)	0.403	−3.0±4.3 (−3%)	0.506
PP, mm Hg	−15.1±2.1 (−19%)	<0.001	−17.5±2.0 (−22%)	<0.001	−3.9±4.7 (4%)	0.430	−1.6±5.2 (−2%)	0.766
Cystatin C GFR, mL/min	−4.2±2.8 (−5%)	0.107	−4.0±2.8 (−5%)	0.161				
RRI	−0.017±0.003 (−2%)	0.037	−0.021±0.004 (−3%)	0.017				
UACR, mg/mmol	−0.49±0.51 (−31%)	0.335	−0.25±0.35 (−16%)	0.471				

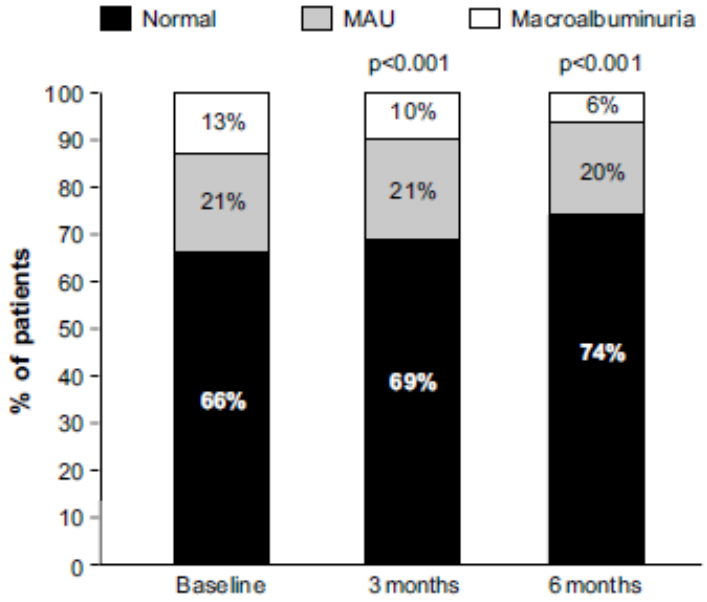


Figure 2. Proportion of patients with normal urinary albumin excretion (UAE), microalbuminuria (MAU), and macroalbuminuria at baseline and 3 and 6 months after renal denervation. *P* value (χ^2 test), *P*=0.001 refer to changes compared with baseline. ■, normal; ▩, MAU; □, macroalbuminuria.

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 Kądziela, Paweł Śliwiński,

(*Hypertension*. 2011;58:559-565.)

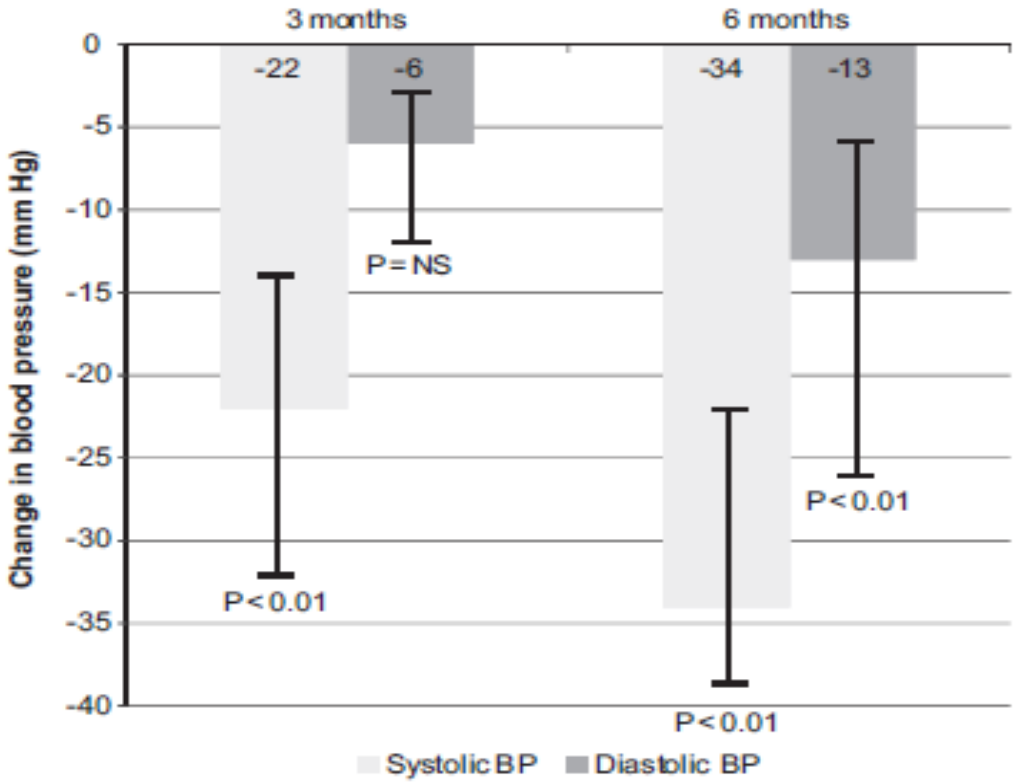


Figure 1. Median systolic and diastolic blood pressure (BP) changes after renal sympathetic denervation procedure at 3 and at 6 months of follow-up. Error bars represent interquartile range.

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 Kądziela, Paweł Śliwiński,

(*Hypertension*. 2011;58:559-565.)

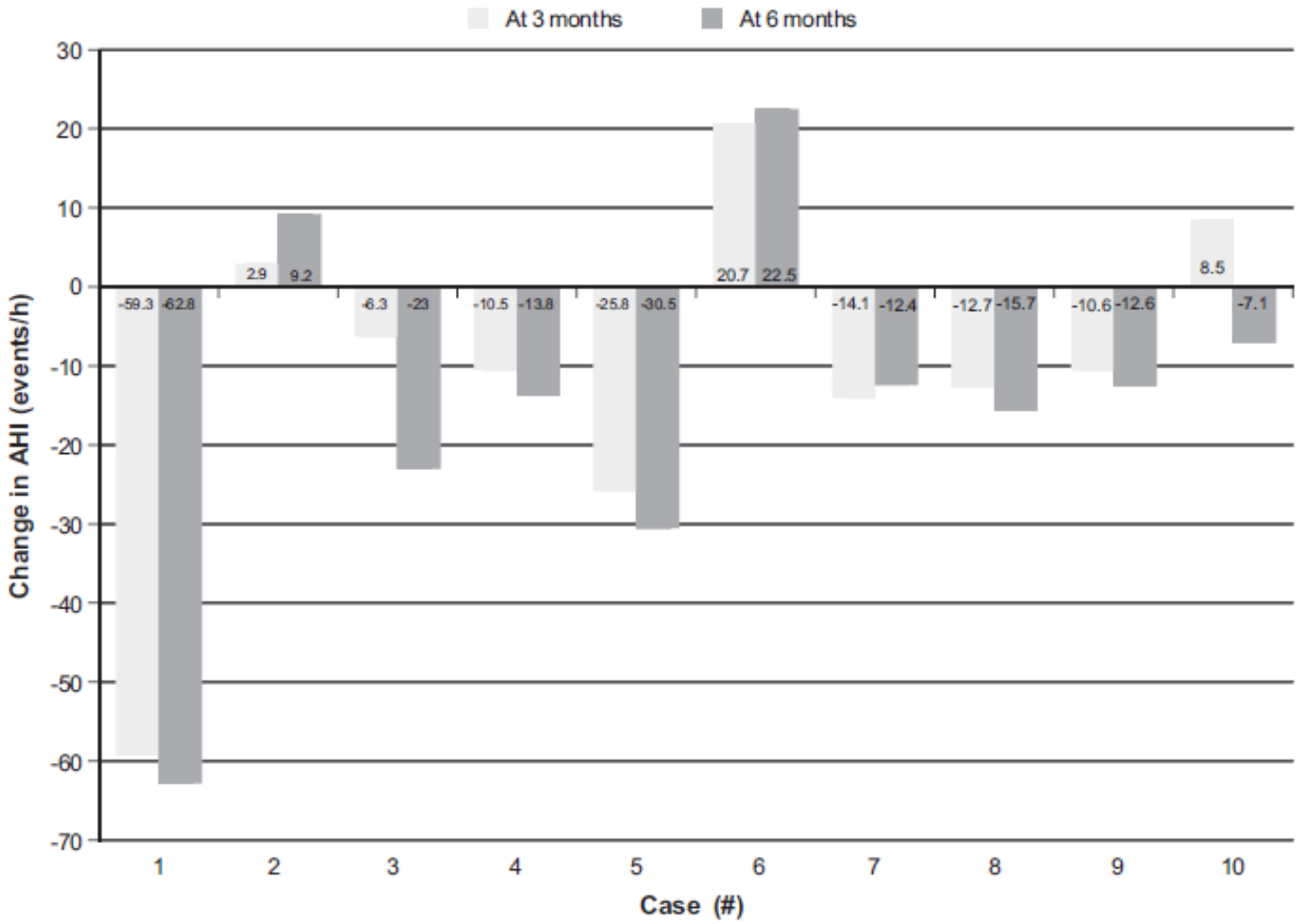


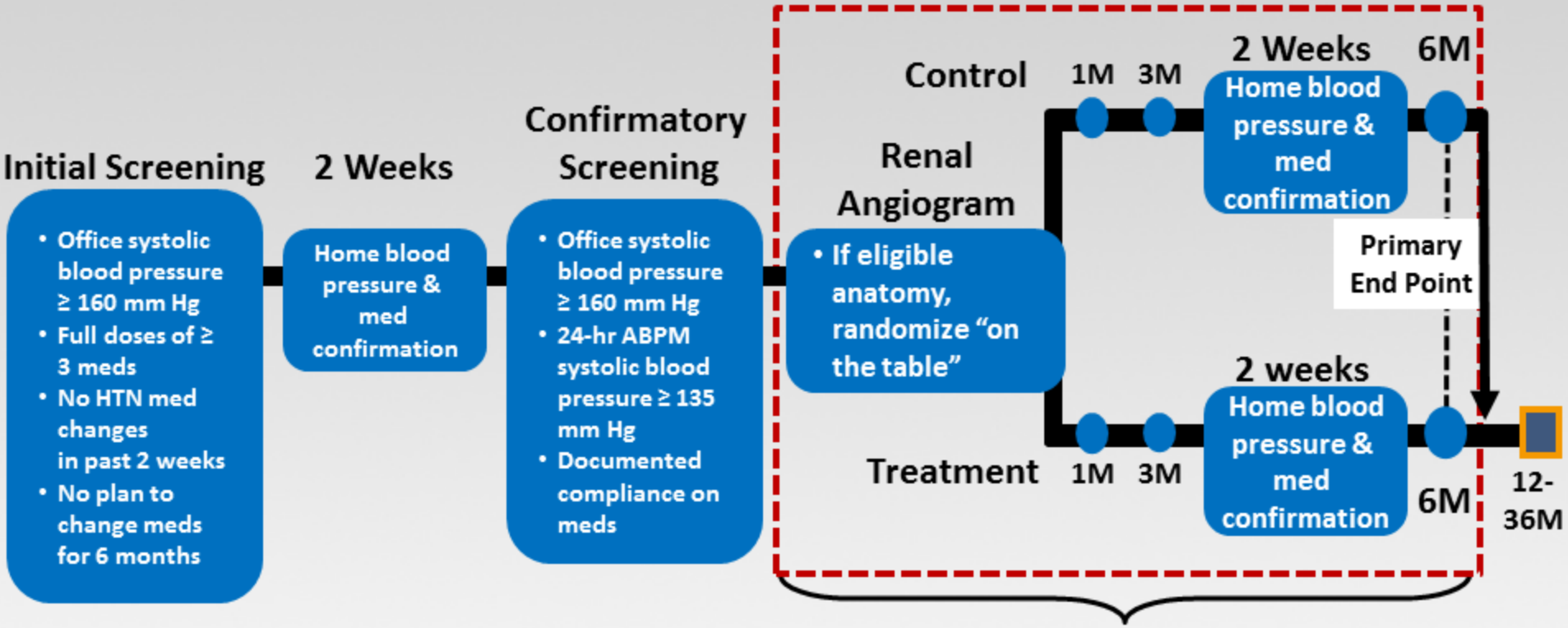
Figure 2. Changes of apnea/hypopnea index (AHI) at 3 and 6 months after denervation. Data of individual cases.

SYMPLICITY HTN-3 Trial: Inclusion Criteria

- Large interventional trial (500 patients)
- Multi-center, prospective, single-blind, randomized, controlled study
- Average systolic blood pressure ≥ 160 mm Hg (measured per guidelines)
- On stable medication regimen of full tolerated doses of ≥3 antihypertensive medications, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18 to 80 years

http://clinicaltrials.gov/ct2/show/NCT01418261[14]

SYMPLICITY-3: Study Design



- Patient and research staff assessing blood pressure and performing follow-ups are blinded to treatment status
- No changes in medications for 6 months

SYMPLICITY HTN-3 Trial: Endpoints

Primary Outcome Measure

- Change in office SBP (baseline to 6 months post-randomization)

Primary Effectiveness Outcome Measure

- Incidence of major adverse events through 1 month post-randomization (renal artery stenosis measured at 6 months)
- Baseline to 6 months, designated as safety issue

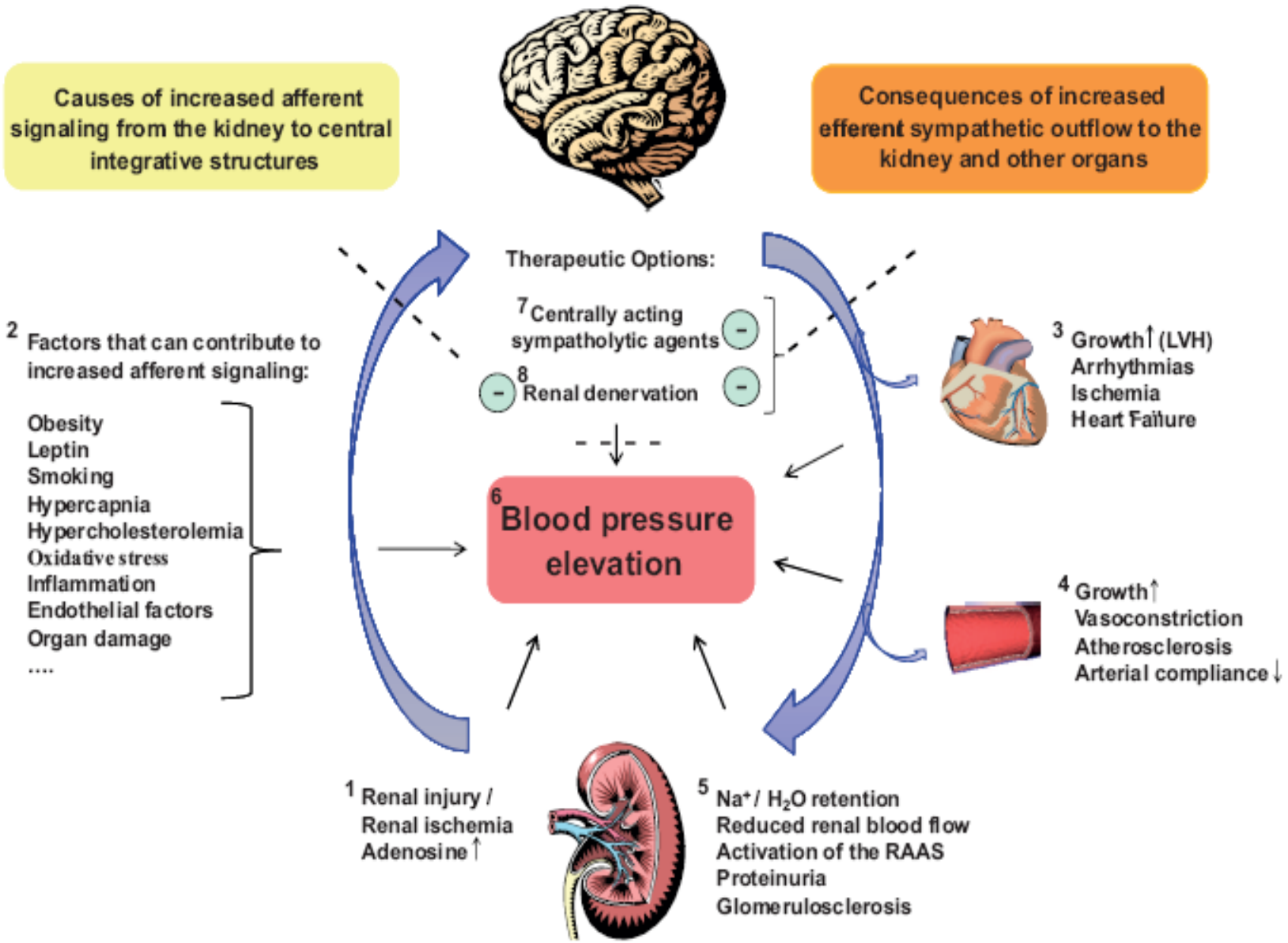
Secondary Outcome Measures

- Change in average 24-hour systolic blood pressure by ambulatory blood pressure monitoring (baseline to 6 months)

http://clinicaltrials.gov/ct2/show/NCT01418261[14]

EnligHTN (ARSENAL) Study

- Multi-electrode renal denervation system (different renal denervation system than the one used in the Symplicity trials)
- 46 patients
- Non-randomized, open-label safety/efficacy study
- Results followed up to 6 months
- Blood pressure reduction observed of around 30 mm Hg systolic/10 mm Hg diastolic


Causes of increased afferent signaling from the kidney to central integrative structures
Consequences of increased efferent sympathetic outflow to the kidney and other organs
Therapeutic Options:
7 Centrally acting sympatholytic agents
8 Renal denervation
6 Blood pressure elevation
2 Factors that can contribute to increased afferent signaling:
Obesity
Leptin
Smoking
Hypercapnia
Hypercholesterolemia
Oxidative stress
Inflammation
Endothelial factors
Organ damage
....
3 Growth↑ (LVH)
Arrhythmias
Ischemia
Heart Failure
4 Growth↑
Vasoconstriction
Atherosclerosis
Arterial compliance↓
1 Renal injury /
Renal ischemia
Adenosine↑
5 Na+ / H2O retention
Reduced renal blood flow
Activation of the RAAS
Proteinuria
Glomerulosclerosis

Renal Denervation : Ultima Ratio or Standard in Treatment-Resistant Hypertension

Alexandre Persu, Jean Renkin, Lutgarde Thijs and Jan A. Staessen

Hypertension. 2012;60:596-606;

Table 3. Center Requirements for the Application of Renal Denervation in Treatment-Resistant Hypertension

Characteristic	Specifications
Experience	Management of resistant hypertension
	High-volume interventional cardiology/radiology
Protocol	Written protocol for diagnostic work-up, procedure, and follow-up
	Written informed consent
	Ethical approval
	Contingency plans for the management of complication
	Insurance/business plan
Infrastructure	Availability of high-quality computerized tomographic/MRI
	Catheter laboratory
Multidisciplinary team	Hypertension specialists with experience in managing resistant hypertension and interventional cardiologists/radiologists with experience of the renal denervation procedure
	Access to nephrologists and vascular surgery
Transparency	Participation in registration program

Modified according to the Joint United Kingdom Societies Consensus on Renal Denervation for Treatment-Resistant Hypertension (http://www.bhsoc.org/docs/The-Joint-UK-Societies'-Consensus-on-Renal-Denervation-for-resistant-hypertension.pdf).

4 - Indications de la dénervation rénale par voie endovasculaire dans le traitement de l'HTA en 2012

En 2012, le consensus d'expert limite l'indication de la technique de dénervation rénale aux patients qui ont une HTA essentielle non contrôlée sous quadrithérapie ou plus :

- Avec un traitement comportant au moins un diurétique.
- La spironolactone à la dose de 25 mg ayant été inefficace.
- Avec au moins une PAS > 160 mm Hg et/ou une PAD > 100 mm Hg en consultation.
- Et confirmation d'une PAS > 135 mm Hg et d'une PAD > 85 mm Hg en AMT ou par MAPA (période diurne).
- Avec débit de filtration glomérulaire > 45 mL/min/1·73m².
- Avec anatomie des artères rénales compatible avec l'intervention.
- Avec la présence de 2 reins fonctionnels de taille ≥ 90 mm.
- Ayant bénéficié, avant la procédure, d'une exploration des artères rénales par une technique d'imagerie radiologique (angio TDM, angio IRM ou artériographie).
- Avec une absence d'antécédents d'angioplastie / stent sur les artères rénales cibles.
- Avec une voie d'abord compatible avec l'intervention.
- Avec une indication posée après discussion multidisciplinaire incluant un médecin ayant une pratique et une compétence dans la prise en charge des patients avec HTA.

La technique de dénervation rénale ne peut s'appliquer chez les patients hypertendus ayant :

- Une sténose d'une artère rénale > 30 %.
- Une dysplasie fibromusculaire artérielle rénale.
- Un âge de moins de 18 ans.
- Une grossesse en cours.

Conclusions

- HTA résistante touche 8% de la population hypertendue
- Nécessité d'une approche méthodique pour débusquer l'erreur dans la prise en charge
- Importance des médicaments interférant, du gain de poids et de l'alimentation trop salée.
- Recherche d'un SAHOS
- Haute dose de diurétique et souvent association avec la spironolactone.
- Et si cela résiste? …
- Dénervation rénale? 1% des hypertendus traités!