La dénervation rénale pour le traitement de l'HTA réfractaire

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Université de Montréal

Membre du Programme Éducatif Canadien en Hypertension

Divulgation de conflits d'intérêts potentiels

12e congrès annuel de la SSVQ

Les URGENCES vasculaires : une approche interdisciplinaire

23, 24 et 25 novembre 2012

Dr Michel Vallée, Conférencier

Conférencier: Merck, Novartis, Sanofi, Shire, Takeda – 2011-2012

Consultant : Takeda, Novartis, Merck – 2011-2012

Objectifs

- Comprendre la physiopathologie des relations entre le système nerveux sympathique et le rein;
- Décrire la technique de dénervation sympathique rénale par radiofréquence;
- Connaître les résultats et les indications de la dénervation rénale par radiofréquence.

HTA réfractaire

En dehors de l’HTA secondaire

(90% HTA réfractaire = HTA essentielle)

Prévalence HTA réfractaire

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.

Table 3. No. of Antihypertensive Medications Used in the Past Month Among Adults With Resistant Hypertension

No. of Hypertensive Medication Drug Classes*	N	% (SE)
3	240	43.0 (2.7)
4	220	43.2 (2.6)
≥5	79	13.8 (2.1)

Environ 5%

Hypertension. 2011;57:1076-1080

Prévalence HTA réfractaire

Table 4. Type of Antihypertensive Medications Used in the Past Month Among Adults With Resistant Hypertension

Antihypertensive Medication Class	Subclass	Number	Percentage (SE)
ACE inhibitor		317	57.0 (2.8)
ARB		209	40.9 (2.8)
β-blocker		402	75.5 (2.1)
Calcium channel blocker		354	66.5 (2.4)
	Dihydropyridine	272	50.7 (2.4)
	Nondihydropyridine	88	17.0 (2.5)
Diuretic		458	85.6 (2.4)
	Thiazide like	300	58.5 (3.3)
	HCTZ	279	55.1 (3.3)
	Loop	176	30.4 (3.1)
	Potassium sparing	57	12.5 (2.0)
	Aldosterone antagonist	20	3.0 (0.8)
α-Adrenergic receptor antagonist		108	17.7 (1.7)
Central-acting and other antiadrenergic drugs		58	10.0 (1.4)
Direct vasodilator		32	4.7 (0.9)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide.

Hypertension. 2011;57:1076-1080

Prévalence HTA réfractaire

- Vrai HTA réfractaire: RARE
- 8.9% (5%?) de tous les patients avec HTA (NHANES 2011) *Hypertension*. 2011;57:1076-1080
- Le traitement semble sous-optimal (sous utilisation d'aldactone surutilisation clonidine et alpha-bloqueurs)
- Pourquoi s'y intéresser?
  - Risque d'événement cardiovasculaire 4X plus élevé (HTA réfractaire comparé à HTA dans les cibles) Duprez et al, J Clin Hypert 2007:9;13-8

Blood Pressure. 2005; 14 (Suppl 2): 42–45
Journal of Hypertension 2005, **23**:1441–1444
N Engl J Med 2006;355:385-92.
J Cardiovasc Pharmacol Ther 2006; 11: 113
American Journal of Therapeutics 10. 122–126 (2003)

HTA réfractaire: trucs

1) Aldactone
2) HCTZ hautes doses vs indapamide et chlorthalidone
3) Utilisation d'agents plus efficaces dans une même classe (indapamide/perindopril/olmesartan/azilsartan)
4) Bloqueurs combinés alpha/beta (carvedilol / labetalol)
5) Chronothérapie (ASA HS et BCC HS et …)
6) Éviter de substituer un thiazide pour du lasix en IRC si pas d'indication
7) Utilisation de combos, simplification du traitement.

Twynsta (HS) + aldactazide (AM) (68c + 45c) 2 pilules pour 4 rx

Telmisartan / amlodipine / aldactone / hydrochlorothiazide

Aldactone: suppose un suivi serré (clinique HTA?)

En tout temps: Éviter clonidine!

Faire un effort honnête pour éviter les alpha-bloqueurs.

Dénervation rénale: dernier recours.

Efficacy of Low-Dose Spironolactone in Subjects With Resistant Hypertension

Mari Konishi Nishizaka, Mohammad Amin Zaman, and David A. Calhoun

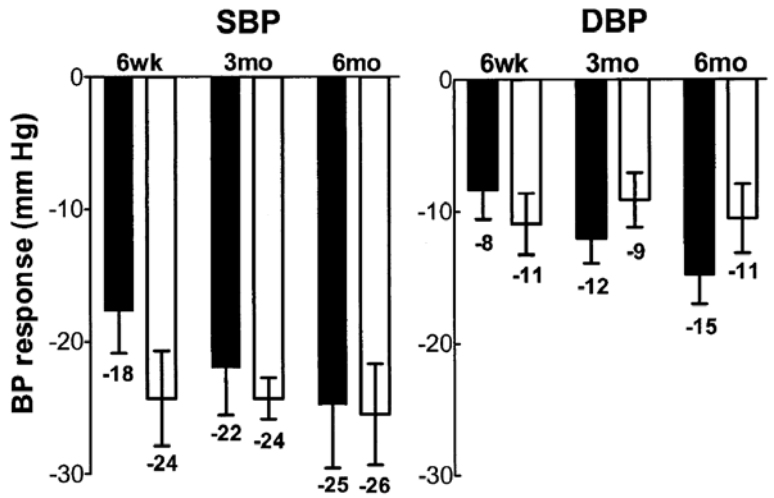


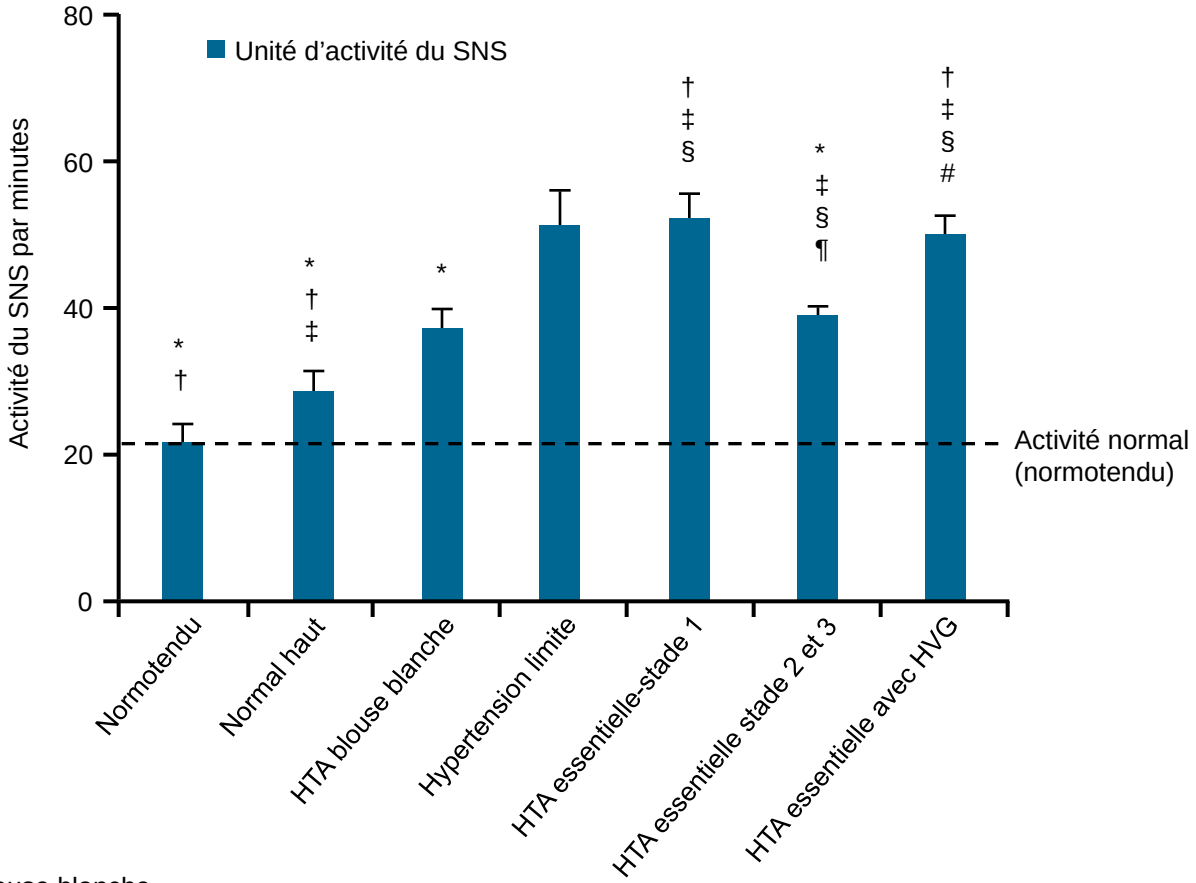
FIG. 2. Spironolactone-induced reduction in systolic blood pressure (SBP) and diastolic BP (DBP) at 6 weeks, 3 months, and 6 months follow-up in subjects with primary aldosteronism (**filled bars**, *n* = 34) and without primary aldosteronism (**open bars**, *n* = 42). BP reduction was not significantly different between primary aldosteronism and non-primary aldosteronism subjects at any time point.

HTA réfractaire = hypersensibilité à l'aldostérone?

AJH 2003; 16:925–930

Le SNS est activé en HTA

- Le SNS est activée de façon à peu près proportionnel au niveau d'HTA



*P<0.05 Comparé avec hypertension limite.
†P<0.05 Comparé avec hypertension de la blouse blanche.
‡P<0.05 Comparé avec normotendu.
§P<0.05 Comparé avec normal haut.
¶P<0.05 Comparé avec HTA essentielle stade 1.
#P<0.05 Comparé avec HTA essentielle stade 2 et 3.
Adapté de Smith P, et al. *Am J Hypertens*. 2004; 17:217-222.

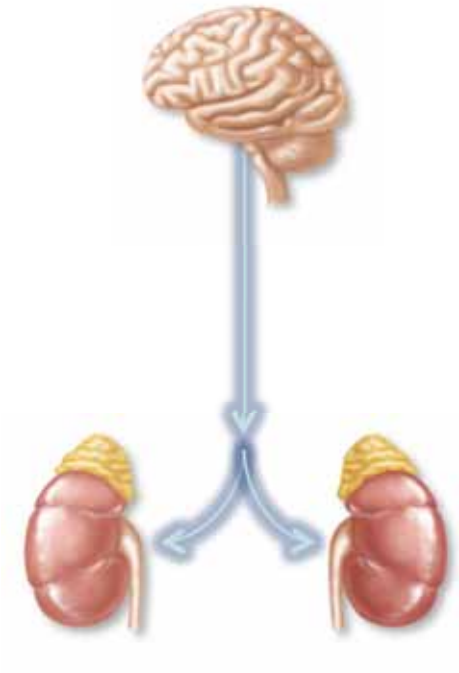
HTA réfractaire

- Prévalence 5-9%
- >90% réponse à l'aldactone
  - Patients hypersensibles aux effets de l'aldostérone
- Les 10% pourrait bien avoir une autre cause??
  - Patients avec un système nerveux sympathique (SNS) hyperactivé ou patients hypersensibles aux catécholamines

Lien entre le SNS et le rein

Système nerveux sympathique (SNS) et l'innervation rénale

Nerfs efférents



Le système nerveux sympathique active le SRAA et directement la rétention de Na+

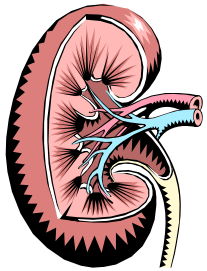
Nerfs afférents

Le rein active lui-même le SNS: vasocontriction, etc

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

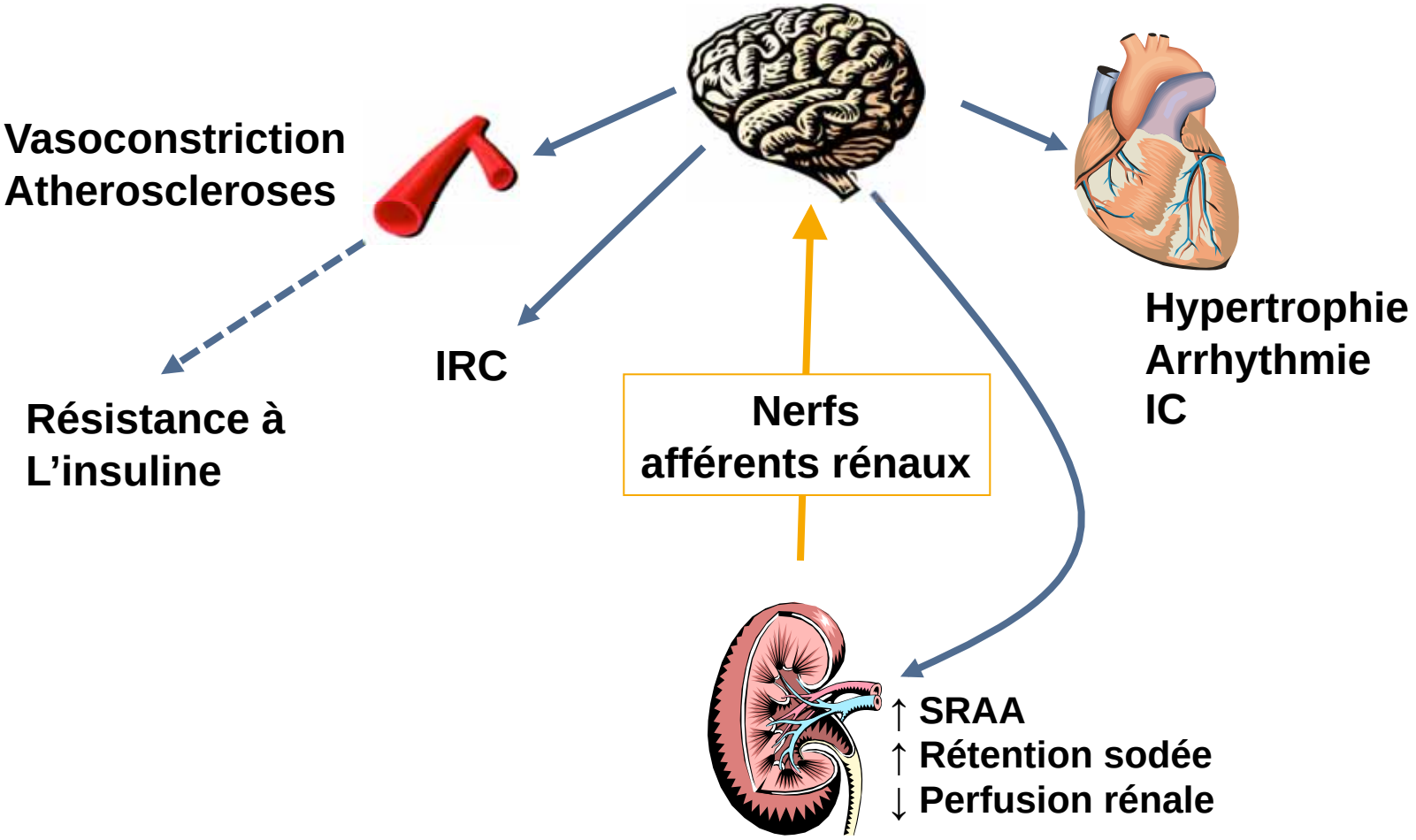
SNS: voies efférentes aux reins: les reins comme cibles du SNS

Nerf efférents rénaux

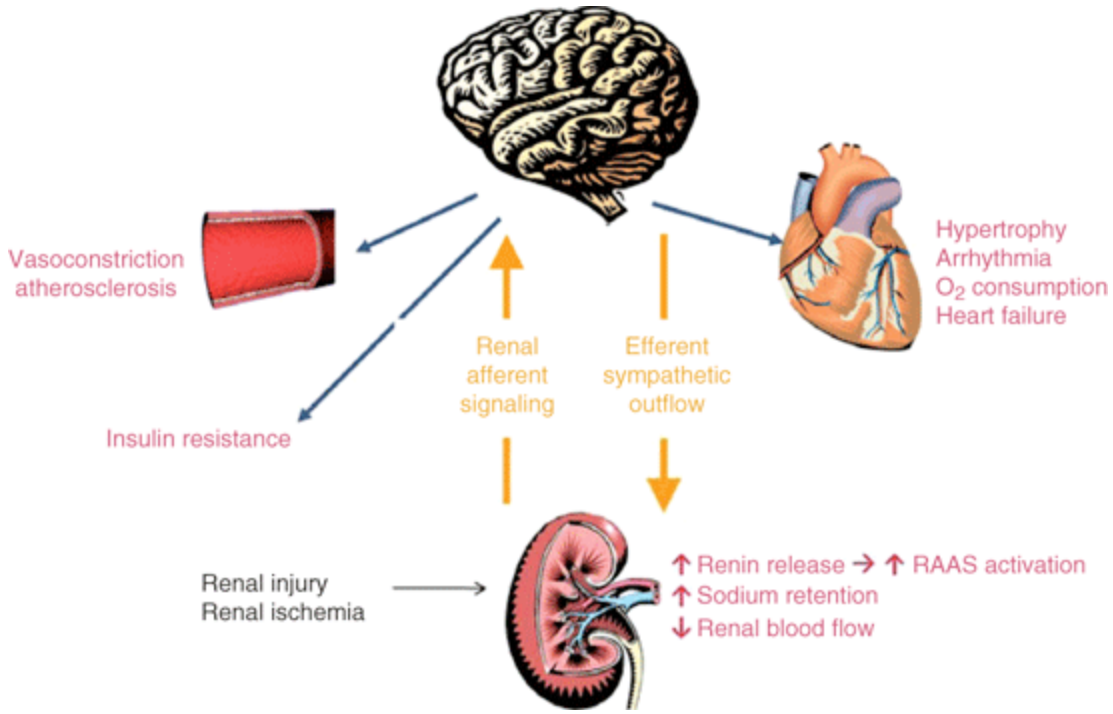


↑ SRAA
↑ Rétention sodée
↓ Perfusion rénale

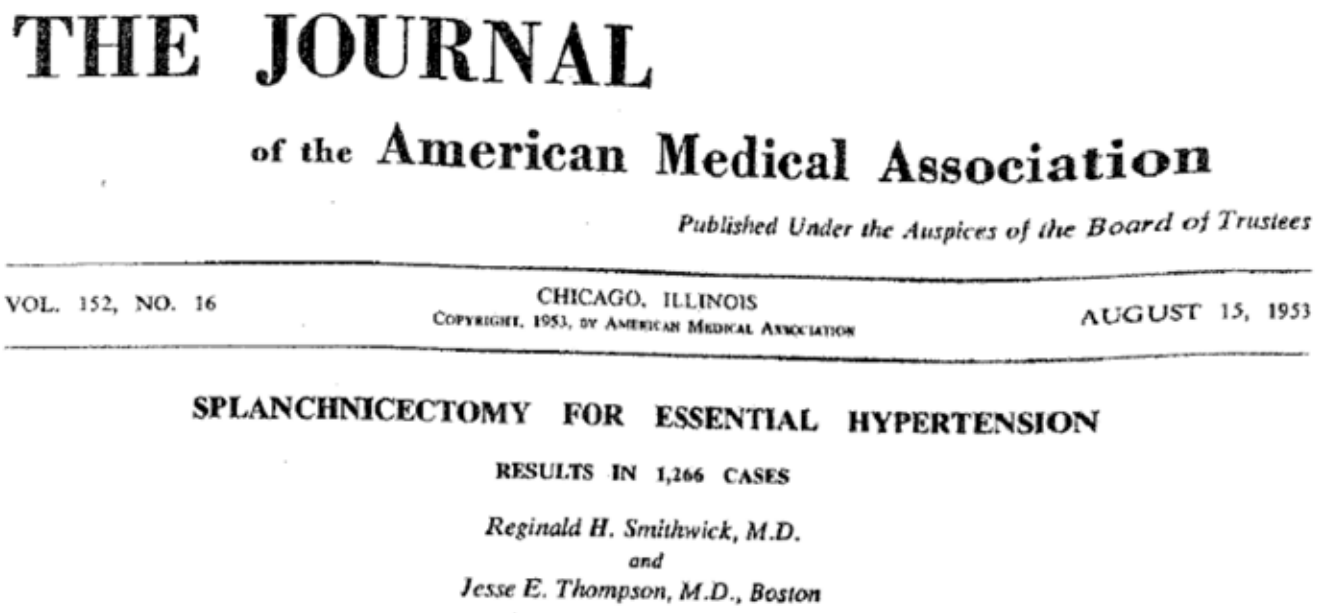
Activation du SNS par les reins: voies afférentes ou les reins comme source d'activation du SNS



Innervation sympathique rénale



La dénervation rénale



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SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

- Très efficace pour diminué la TA
- Mais complications opératoires +++
  - Morbidité et mortalité péri-opératoire
  - HTO
  - Incontinences double
  - Etc.

Anatomie de l’innervation rénale

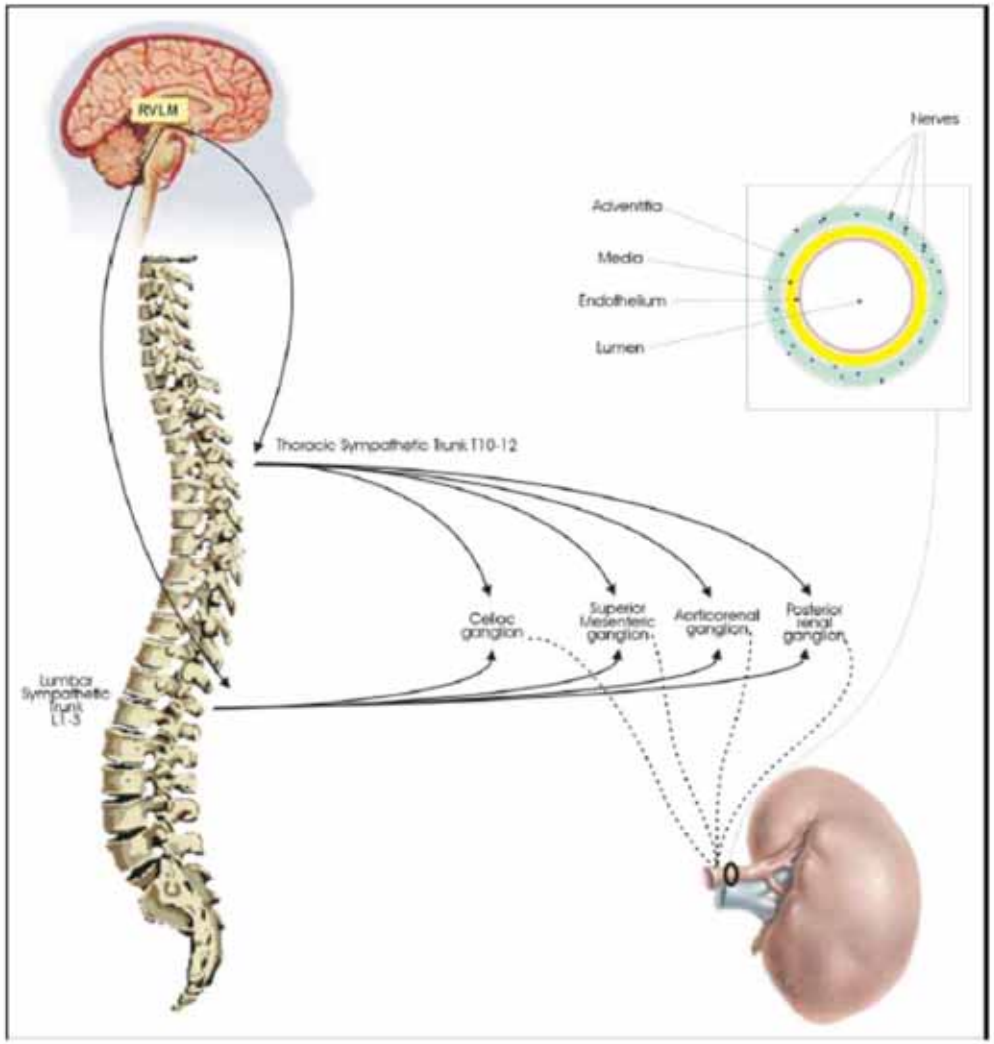
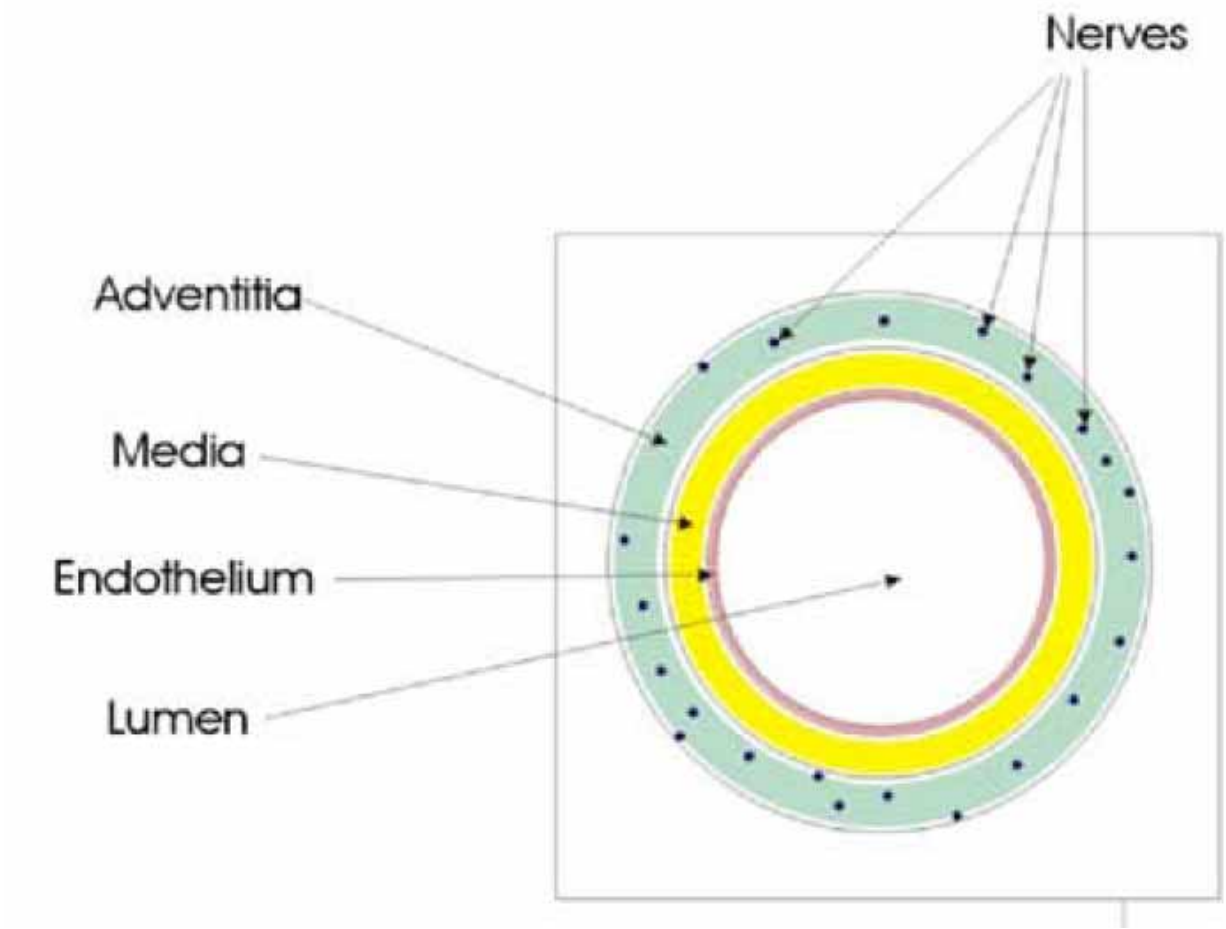


Figure 1. Schematic representation of renal sympathetic innervation. RVLM = rostral ventrolateral medulla.

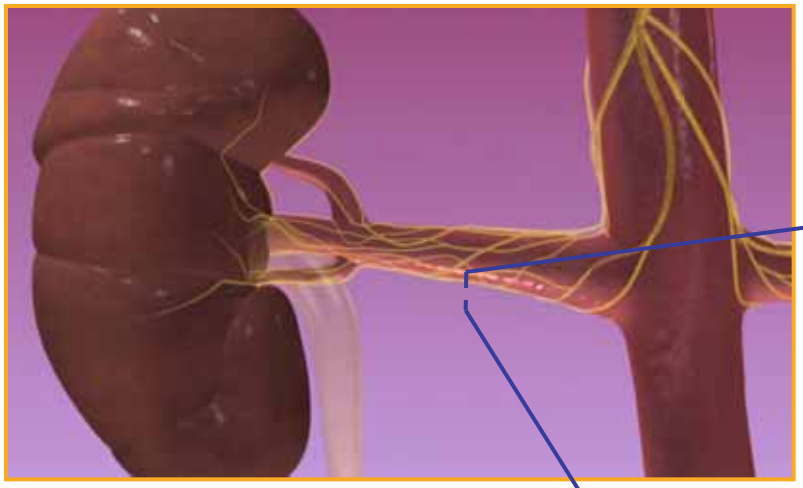
(Am J Cardiol 2010;105:570–576)

Anatomie de l’innervation rénale

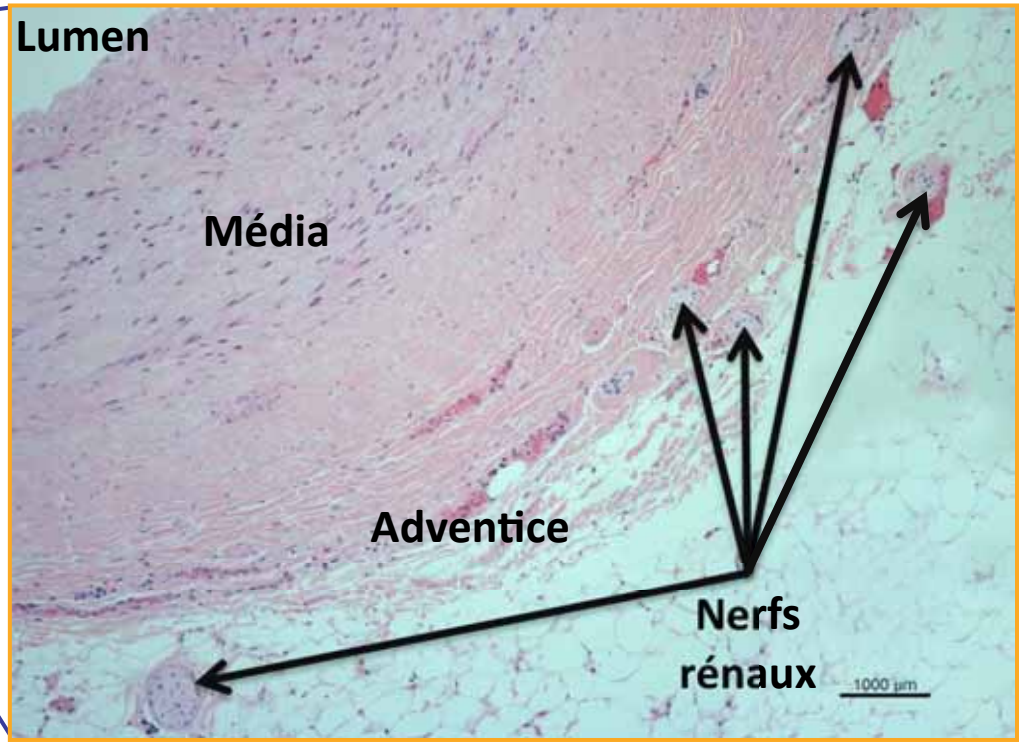


(Am J Cardiol 2010;105:570–576)

Anatomie des nerfs rénaux



- Les nerfs origines de T10-L2
- Les nerfs voyagent dans l'adventice des artères rénales.



Dénervation rénale pour le traitement de l'HTA réfractaire

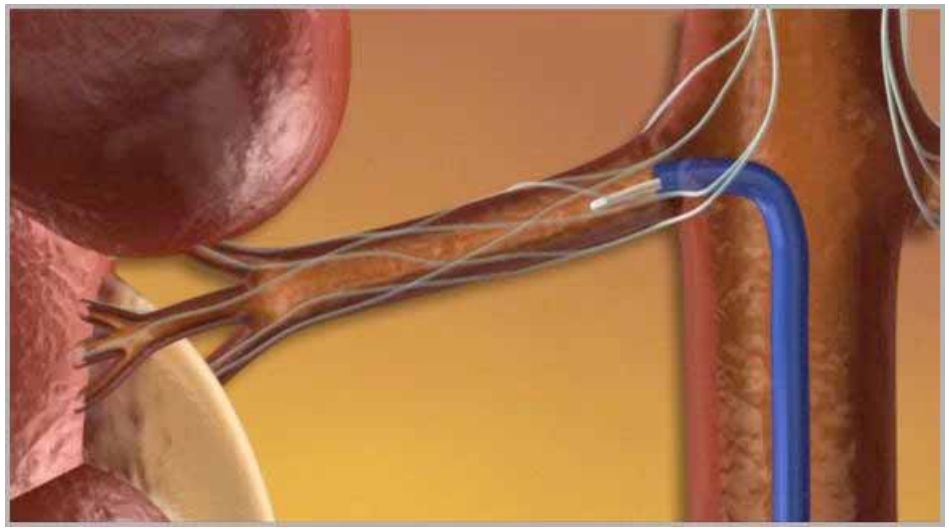
- Splanchinectomy for essential hypertension, results in 1266 cases, Smithwick R., JAMA 1953

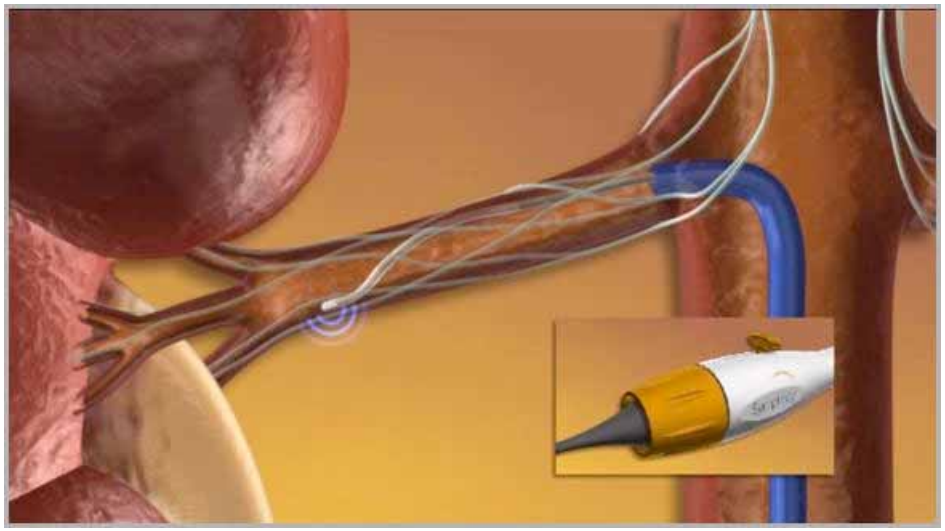
Efficace, mais complications opératoires +++

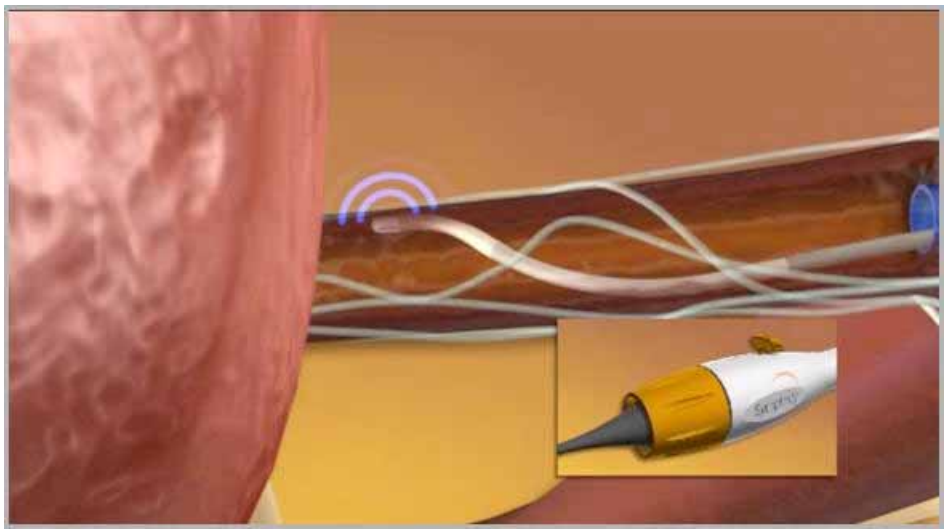
- <u>Retour de cette stratégie thérapeutique avec des méthodes moins invasives ciblant les artères rénales:</u>
  - Simplicity, Medtronic ™ (radiofréquence)
  - St. Jude Medical's EnligHTN™ (radioféquence)
  - Vessix's V2™ (électricité)
  - Covidien's OneShot™ (radiofréquence par ballon)
  - Recor's Paradise™ (ultrason)
  - Biosense Webster (Radiofréquence de 2^{e} génération)
  - Cryothérapie
  - Produits chimiques

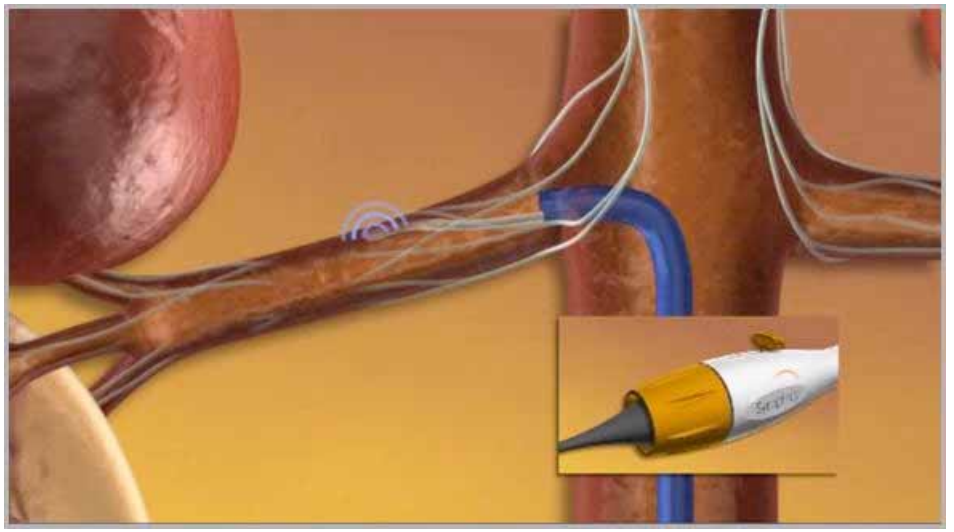
Symplicity™ Renal Denervation System, Medtronic

Procédure: Symplicity™ Renal Denervation System, Medtronic









Procédure: Symplicity™ Renal Denervation System, Medtronic

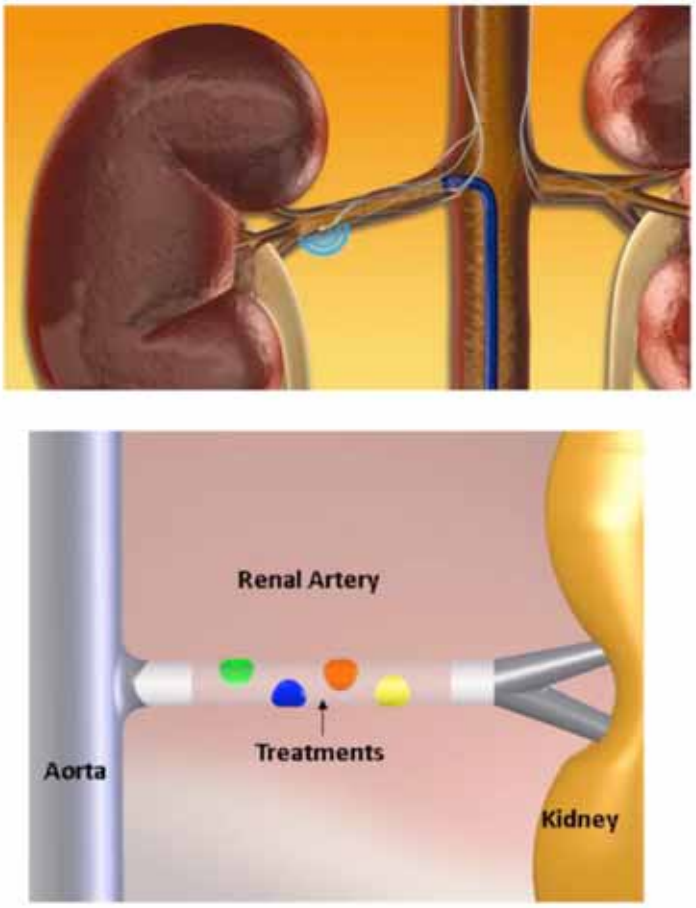
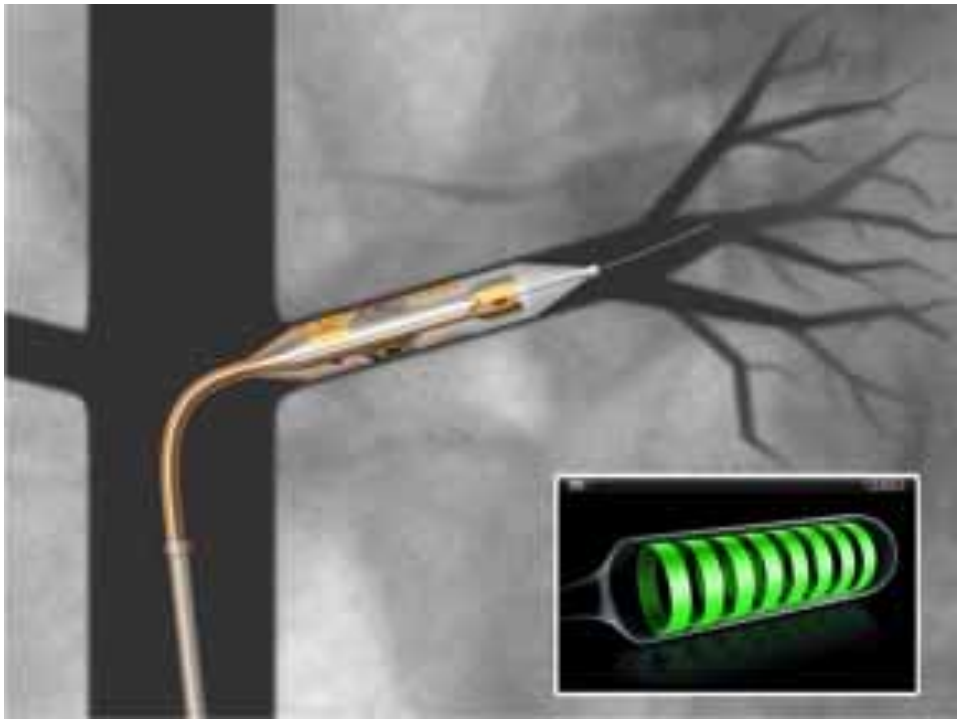


FIGURE 1 | Schematic illustration of the percutaneous catheter-based approach to functionally denervate the human kidney. Similar to a routine angiogram access to the renal artery is obtained via a sheath in the femoral artery. The treatment catheter is then introduced into the renal artery and discrete RF ablation treatments lasting 2 min each are applied along the renal artery as illustrated. Up to six ablations are performed in each artery which are separated both longitudinally and rotationally to achieve circumferential coverage of the renal artery. Catheter tip temperature and impedance are constantly monitored during ablation and RF energy delivery is regulated according to a predetermined algorithm.

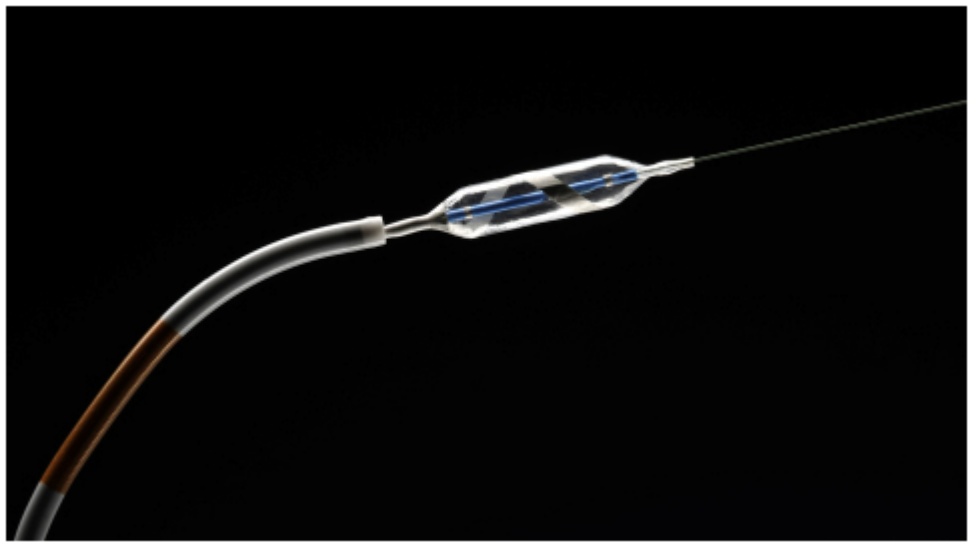
•Front Physiol. 2012;3:10. Epub 2012 Feb 2.

St. Jude Medical’s EnligHTN™

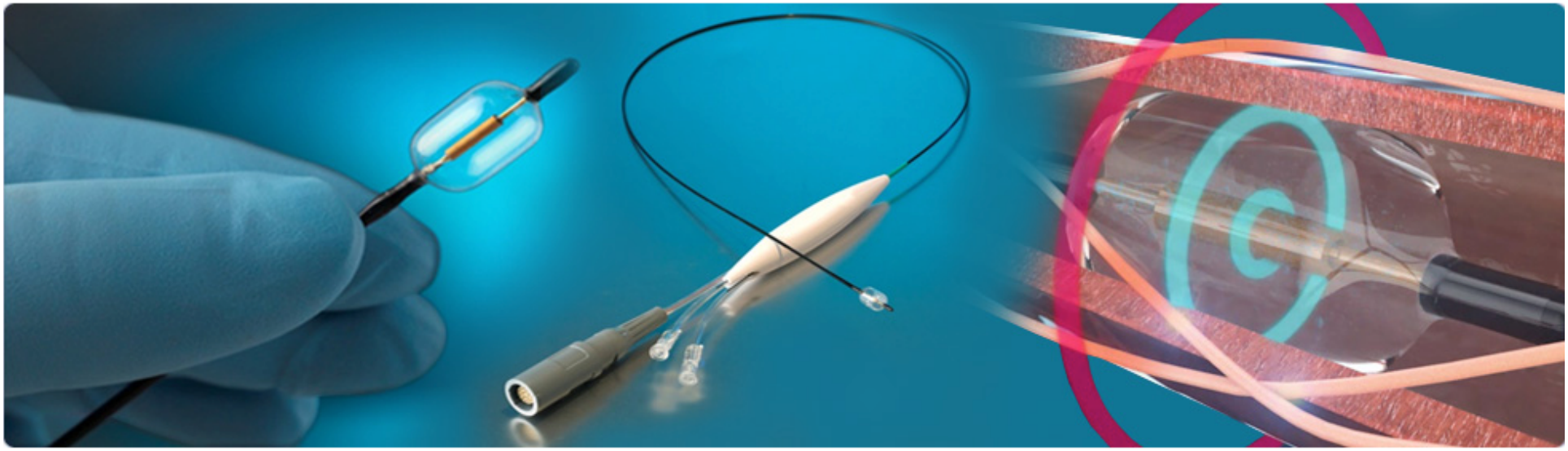
Vessix's V2™



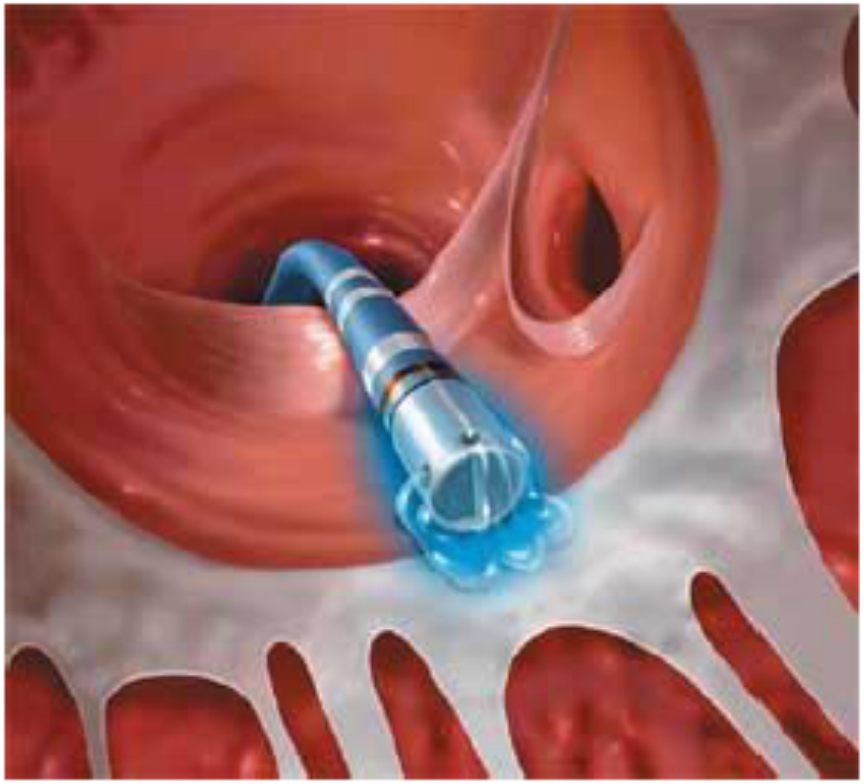
Covidien’s OneShot™

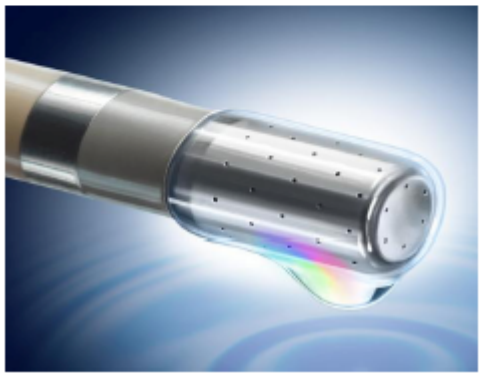


Recor’s Paradise™



Cryothérapie





Symplicity™ Renal Denervation System, Medtronic

Dénervation rénale

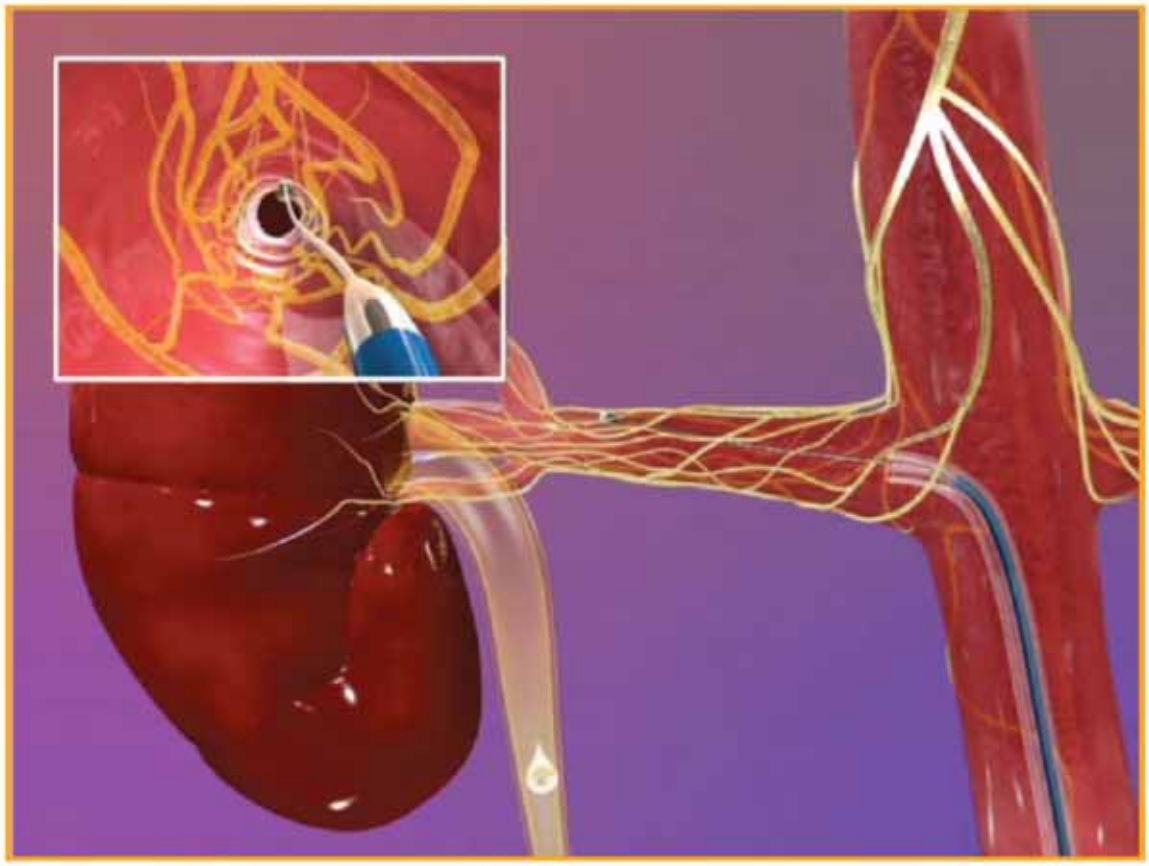
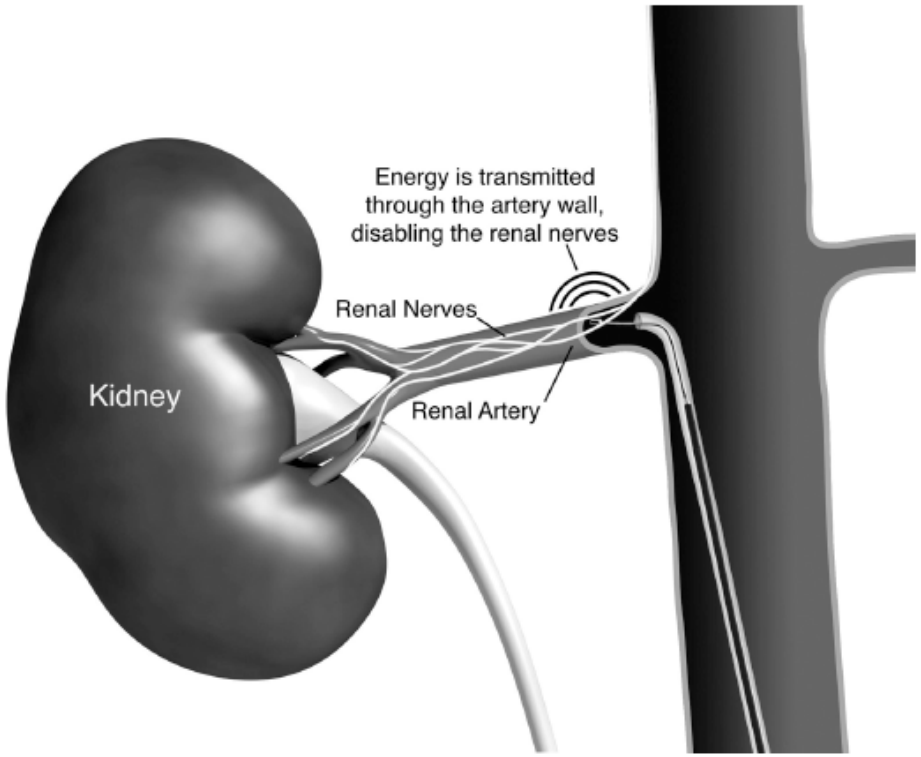
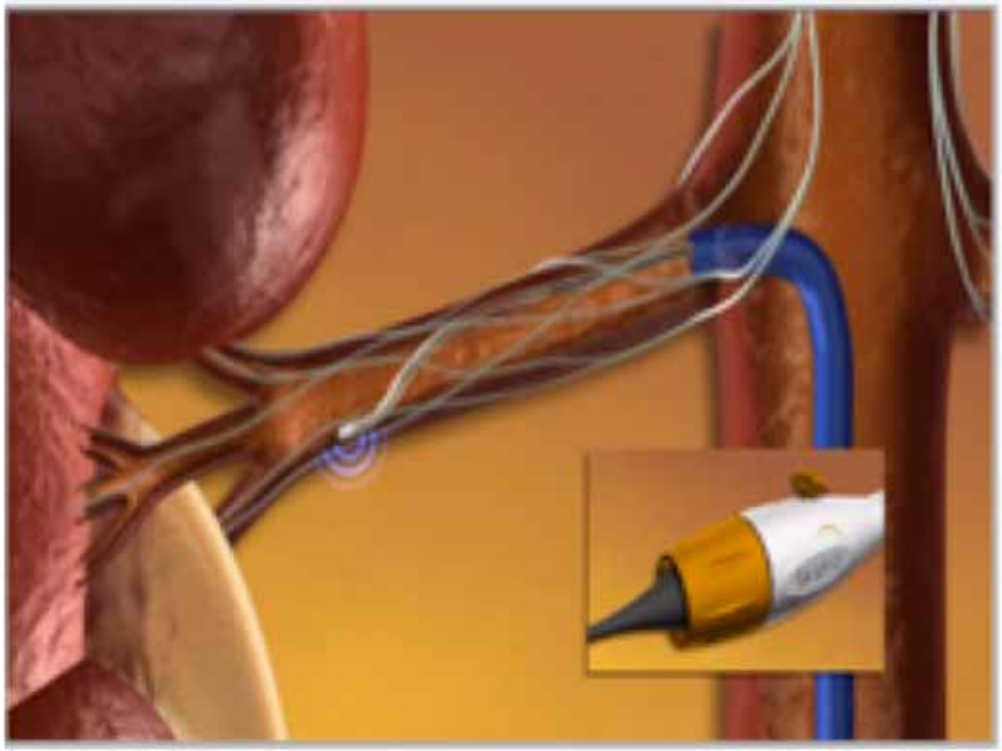


Figure 2. Percutaneous renal denervation procedure. Graphic of catheter tip in distal renal artery is shown.

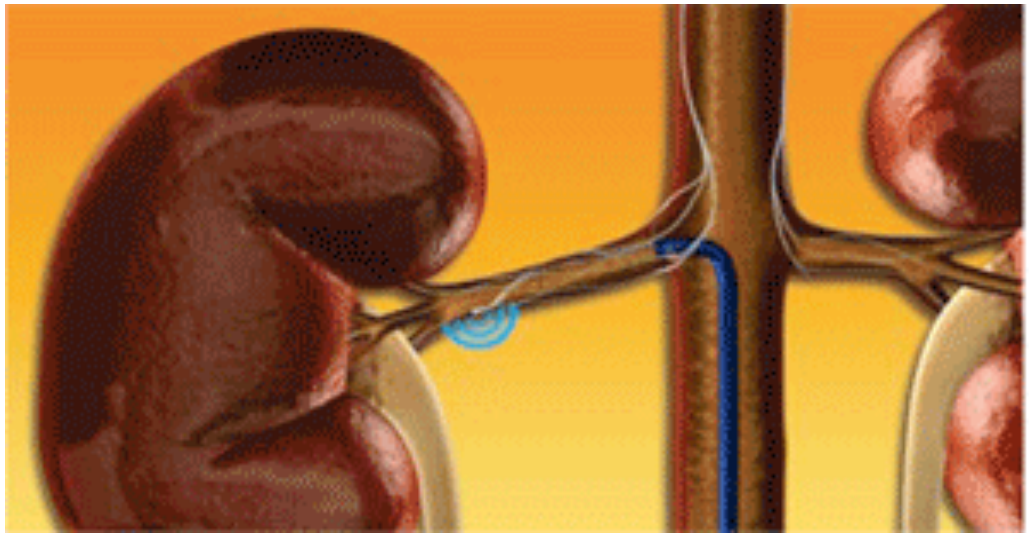
Dénervation rénale

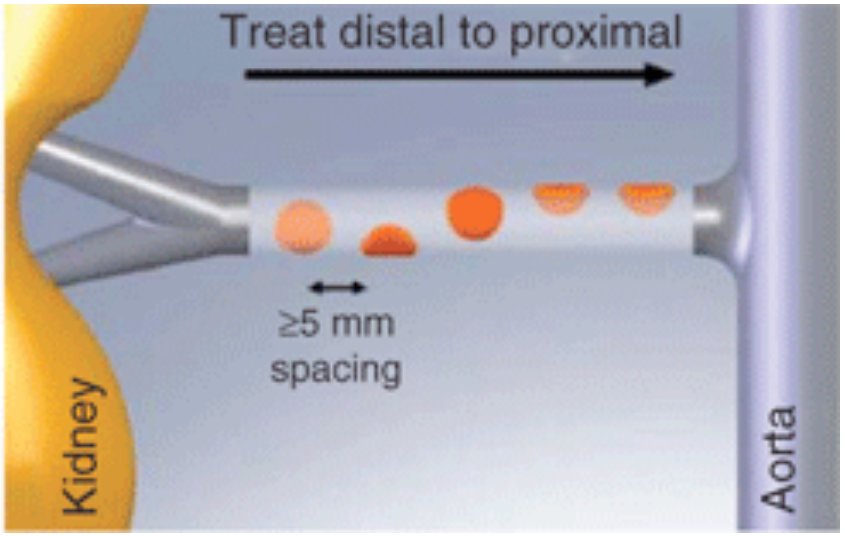


Dénervation rénale



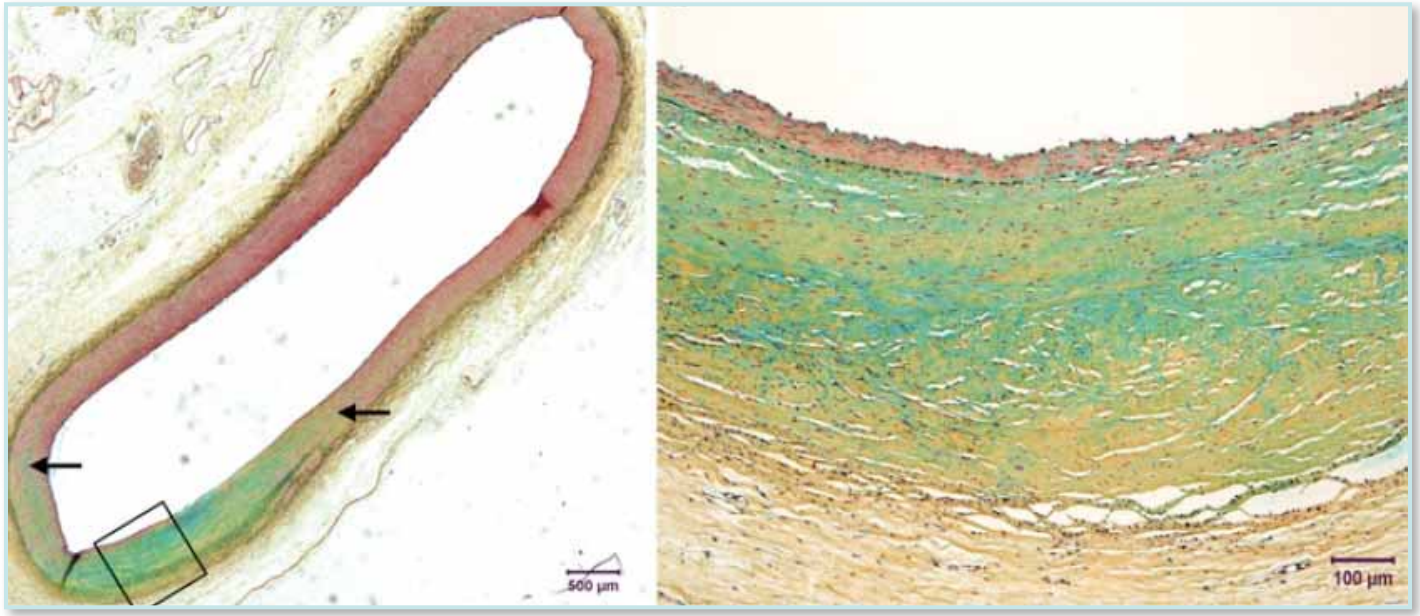
Dénervation rénale





Histologie 6 mois post-procédure (modèle porcin)

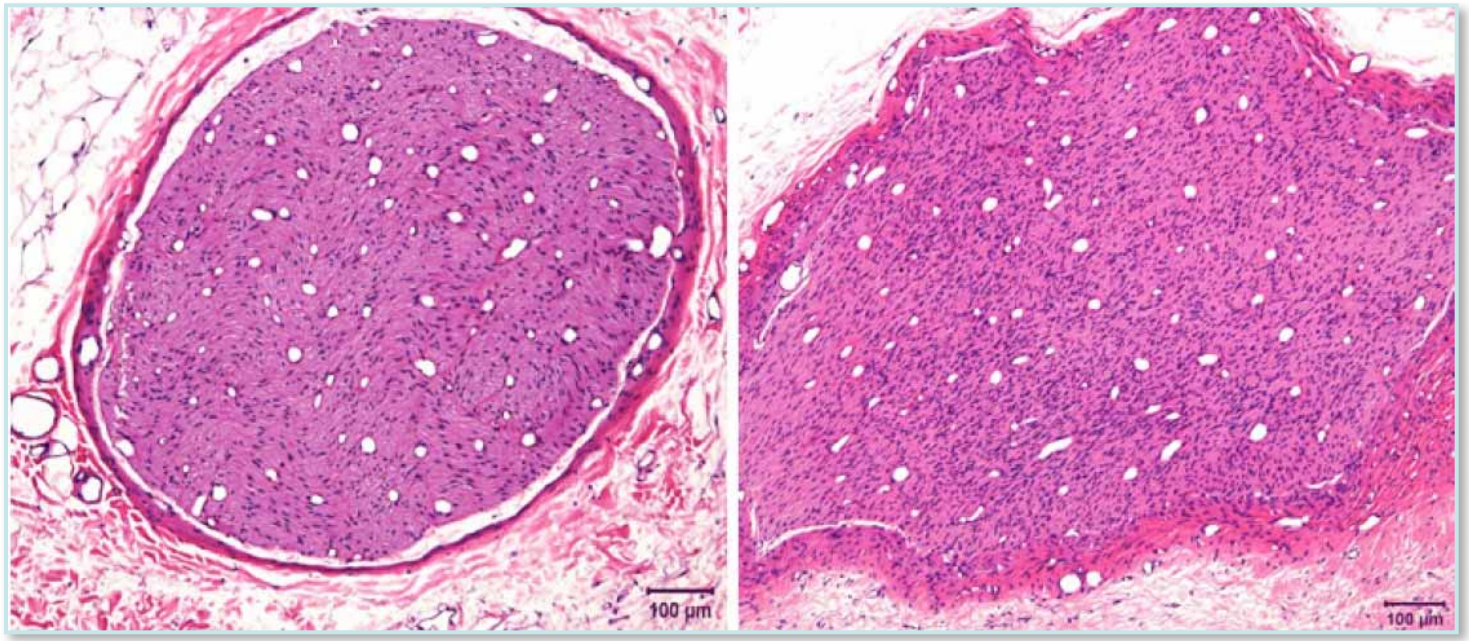
- Lésions à la média et l'adventice
  - Fibrose (vert et jaune)



Rippy MK, et. al. *Clin Res Cardiol*. 2011;doi:101007s00392-011-0346-8.

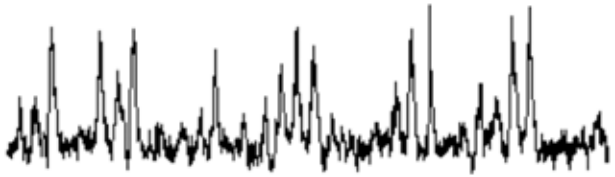
Histologie 6 mois post-procédure (modèle porcin)

- **Nerf non traité**
- **Nerf traité:**
  - Fibrose totale



Reproduced with permission from Rippy MK, et. al. *Clin Res Cardiol*. 2011;doi:101007s00392-011-0346-8.

Dénervation rénale: effet sur le SNS

		SNA (décharge/min)		***TA (mm Hg)***
Baseline		56	→	161/107
1 Month		41	→	141/90 (-20/-17)
12 Months		19	→	127/81 (-34/-26)

Schlaich MP, et al. *New Engl J Med*. 2009;361:932-934.

Dénervation rénale: effets physiologiques

	Départ	***1 Mois***	Δ
TA bureau (mm Hg)	161/107	141/90	
SNS (ng/min)			
• Rein G	72	37	-48%
• Rein D	79	20	-75%
SNS total (ng/min)	600	348	-42%
Activité de la rénine plasmatique (µg/l/hr)	0.3	0.15	-50%
Flow rénal (mL/min)	719	1126	57%
Masse VG (g/m^2)	78.8	73.1	-7%

Schlaich MP, et al. *New Engl J Med*. 2009;361:932-934.

Dénervation rénale: sur la TA en HTA réfractaire

Tension Artérielle

	Baseline	***1 Month***	Δ
Schlaich MP, et al. *New Engl J Med*. 2009;361:932-934 (1 patient)	161/107	141/90	-20/17
Poster 415 (ASN2012) (11 patients)	180/105	160/90	-20/15
Poster 418 (ASN2012) (6 patients)	171/106	151/95	-20/11
HTN1 (Lancet 2009, 373,1275)	177/100	150/90	-22/10
HTN2 (Lancet 2010, 376, 1903)	178/97	146/85	-32/12
Série patients en IRC JASN2012 (15 patients)	174/91	142/76	-32/15
Série Dr Vallée-ICM (8 patients)	185/105	161/90	-24/15

SNS et le traitement de l'HTA:

- Le SNS est activé en HTA essentielle
- Le SNS est hyperactivé (ou hypersensibilité?) dans certains cas d'HTA réfractaire (qui ne répondent pas à l'aldactone ?)
- La dénervation rénale diminue le SNS et le SRAA et la réponse exagérée de ces deux systèmes
- La dénervation rénale chirurgicale diminue le TA (mais complications +++)
- La dénervation rénale moins invasive (des artères rénales) diminue le TA
- Ceci devait être particulièrement intéressant dans un cas d'HTA réfractaire ne répondant pas à l'aldactone

Dénervation rénale pour le traitement de l'HTA réfractaire

- Ablation par radiofréquence (Simplicity, Medtronic)
  - Plusieurs études à date
    - HTN1: Cohorte sans contrôle
    - HTN2: seul RCT: TA / sécurité: 6 mois)
  - 2^{e} RCT en cours (HTN3)
  - Registre international en cours, avec ICM-HMR

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Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

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Stephan H. Schirmer, MD, PHD,§ Erland Erdmann, MD,† Michael Böhm, MD,§
Uta C. Hoppe, MD*†‡

Salzburg, Austria; and Cologne and Homburg/Saar, Germany

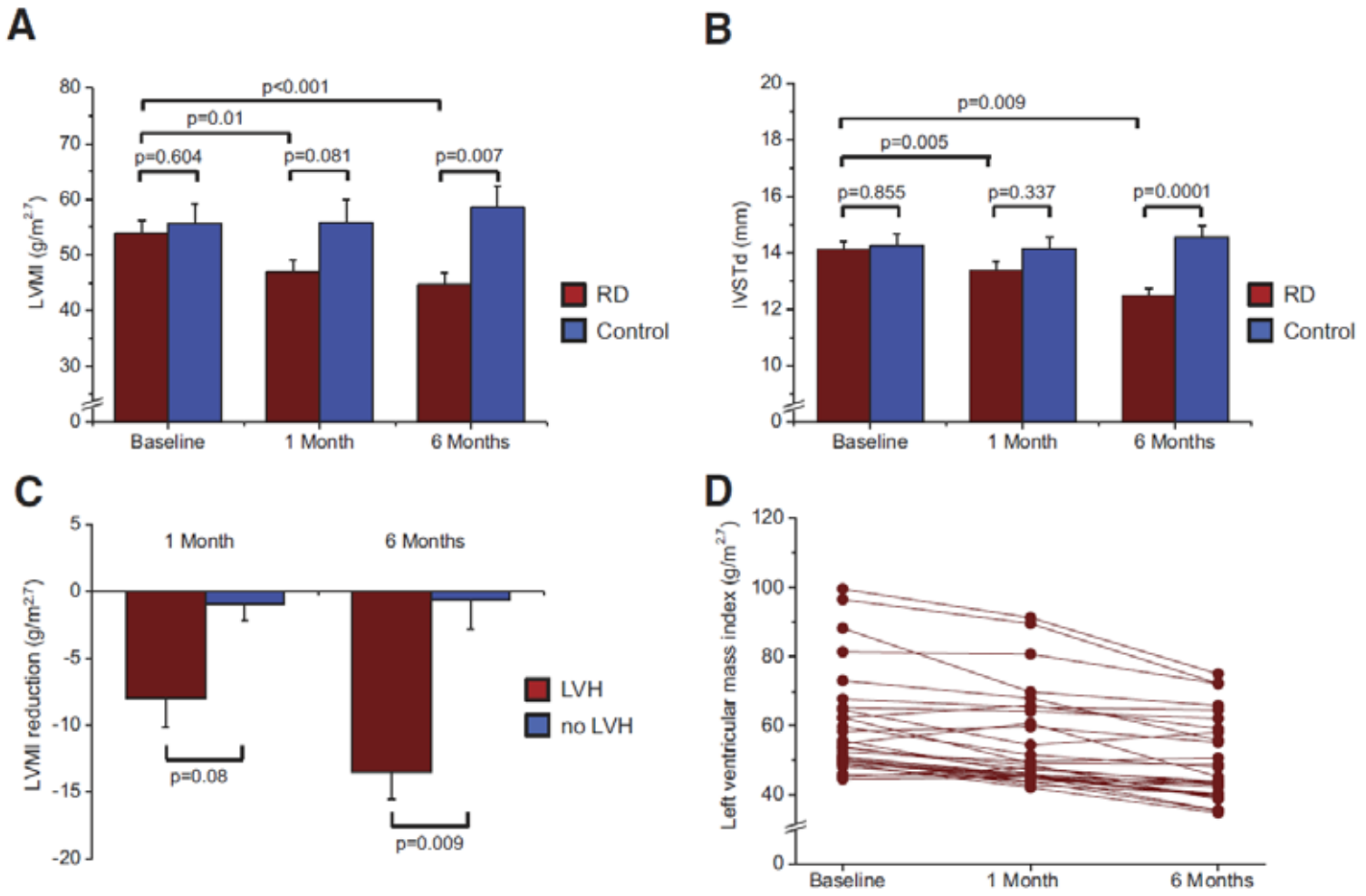
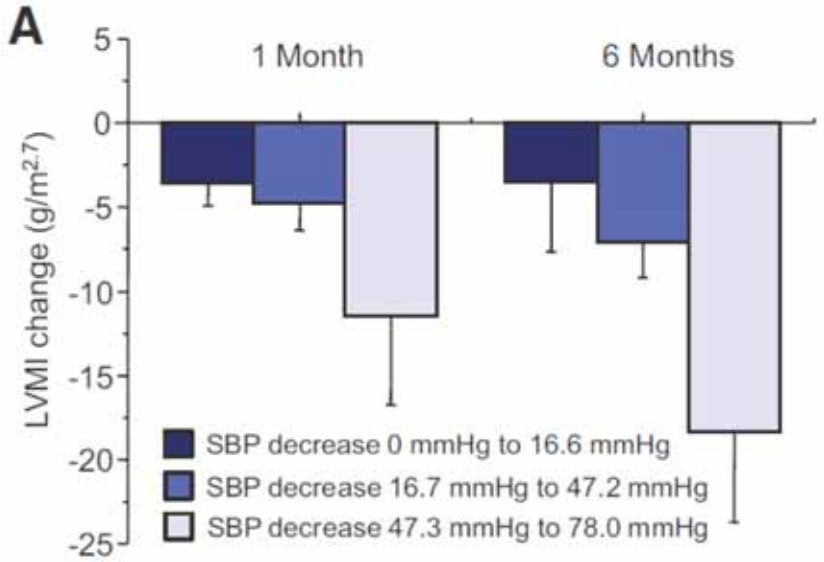


Figure 2 **Impact of RD on LV Mass**

(A) Left ventricular (LV) mass/height$^{2.7}$ and **(B)** end-diastolic interventricular septum thickness (IVSTd) measured in renal sympathetic denervation (RD) and control patients at baseline, 1 month, and 6 months. While there was a steady decrease in the average left ventricular (LV) mass and IVSTd after RD, these parameters slightly increased in control patients. In the treatment group, p for statistical trend was p = 0.004 for LV mass/height$^{2.7}$ **(A)**, p = 0.007 for IVSTd **(B)**. **(C)** Differential effect of RD on LV mass regression depends on the degree of left ventricular hypertrophy (LVH) at baseline. LV mass/height$^{2.7}$ regression by RD was significantly greater in those patients with LVH at baseline. Values are presented as mean ± standard error. **(D)** Regression of LV mass after RD in individual patients with a LVH at baseline (n = 29). LVMI = left ventricular mass index.

(J Am Coll Cardiol 2012;59:901–9)



(J Am Coll Cardiol 2012;59:901–9)

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

- HTN1
- 45 patients avec HTA dite réfractaire
- Pas de groupe contrôle
- Suivi de 1 an

Lancet 2009; 373: 1275–81

	All patients (N=50)	Patients undergoing procedure (N=45)	Patients not eligible for procedure (N=5)
Age (years)	57 (9)	58 (9)	51 (8)
Sex (female)	21 (42%)	20 (44%)	1 (20%)
Ethnic origin (non-white)	2 (4%)	2 (4%)	0
Type 2 diabetes mellitus	16 (32%)	14 (31%)	2 (40%)
CAD	11 (22%)	10 (22%)	1 (20%)
Hyperlipidaemia	34 (68%)	29 (64%)	5 (100%)
eGFR (mL/min/1·73 m²)	83 (22)	81 (23)	95 (15)
Heart rate (bpm)	73 (11)	72 (11)	79 (9)
Blood pressure (mm Hg)	177/100 (19/14)	177/101 (20/15)	173/98 (8/9)
Number of antihypertension drugs	4·7 (1·4)	4·7 (1·5)	4·6 (0·5)
ACE or ARB	47 (94%)	43 (96%)	4 (80%)
β blocker	39 (78%)	34 (76%)	5 (100%)
Calcium-channel blocker	36 (72%)	31 (69%)	5 (100%)
Vasodilator	8 (16%)	8 (18%)	0%
Diuretic	46 (92%)	43 (96%)	3 (60%)

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin II receptor blocker. bpm=beats per minute. CAD=coronary artery disease. eGFR=estimated glomerular filtration rate.

Table: **Baseline patient characteristics**

- Seulement 22% d'aldactone??????????

Lancet 2009; 373: 1275–81

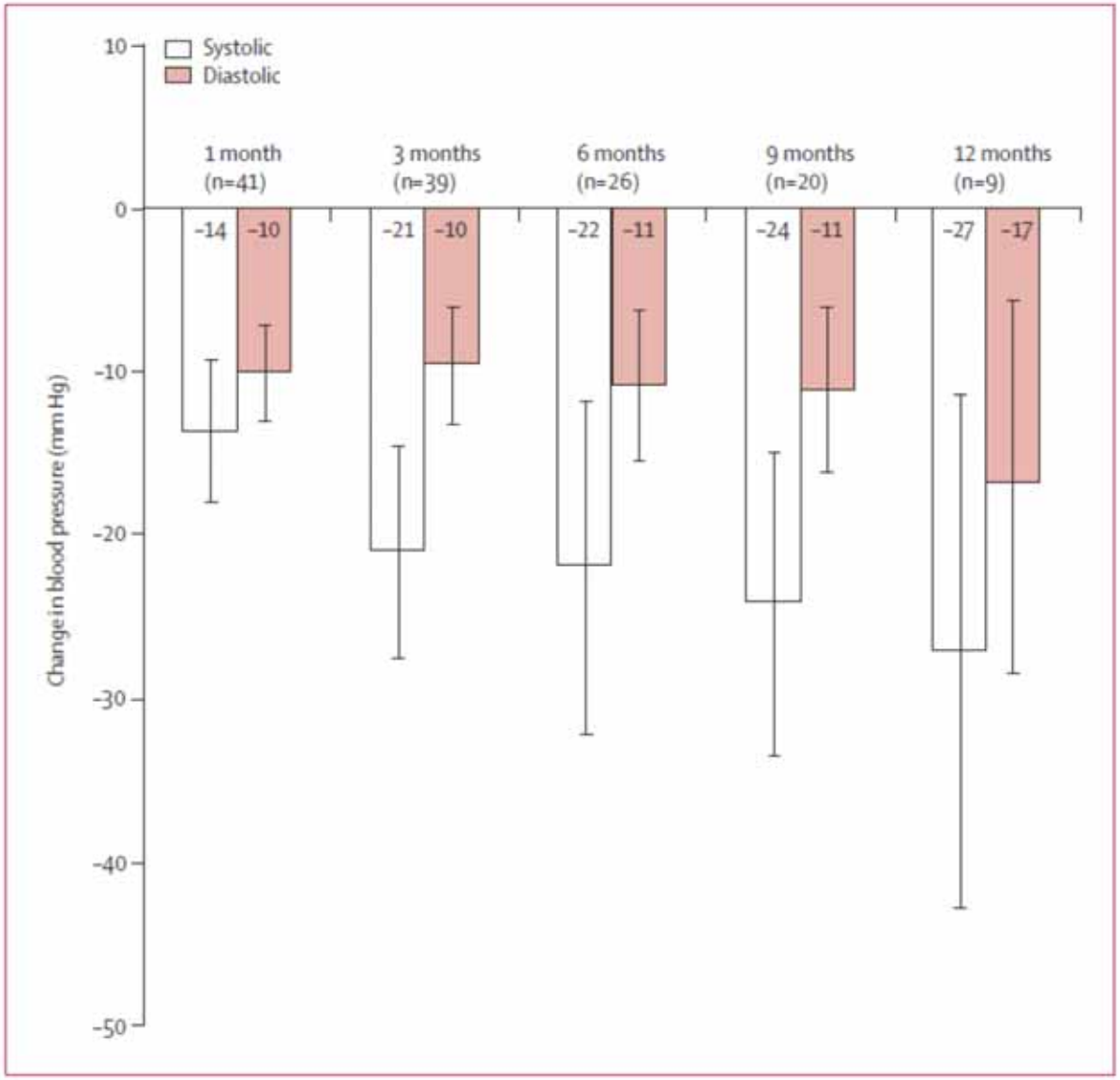
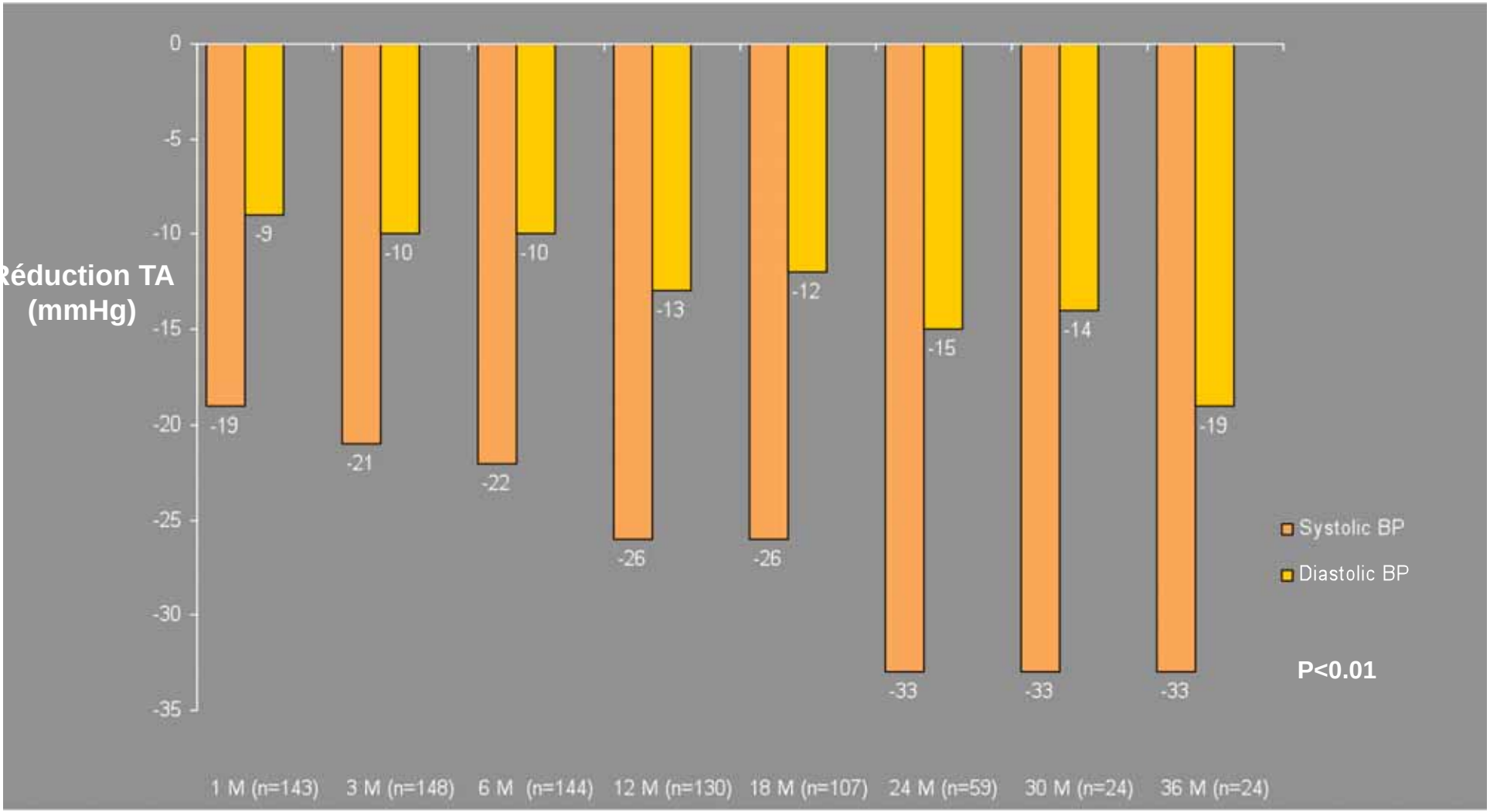


Figure 2: **Change in office blood pressure (95% CI) at 1, 3, 6, 9, and 12 months**
Numbers in parentheses indicate patients who had attended each predefined visit at the time of submission of this publication.

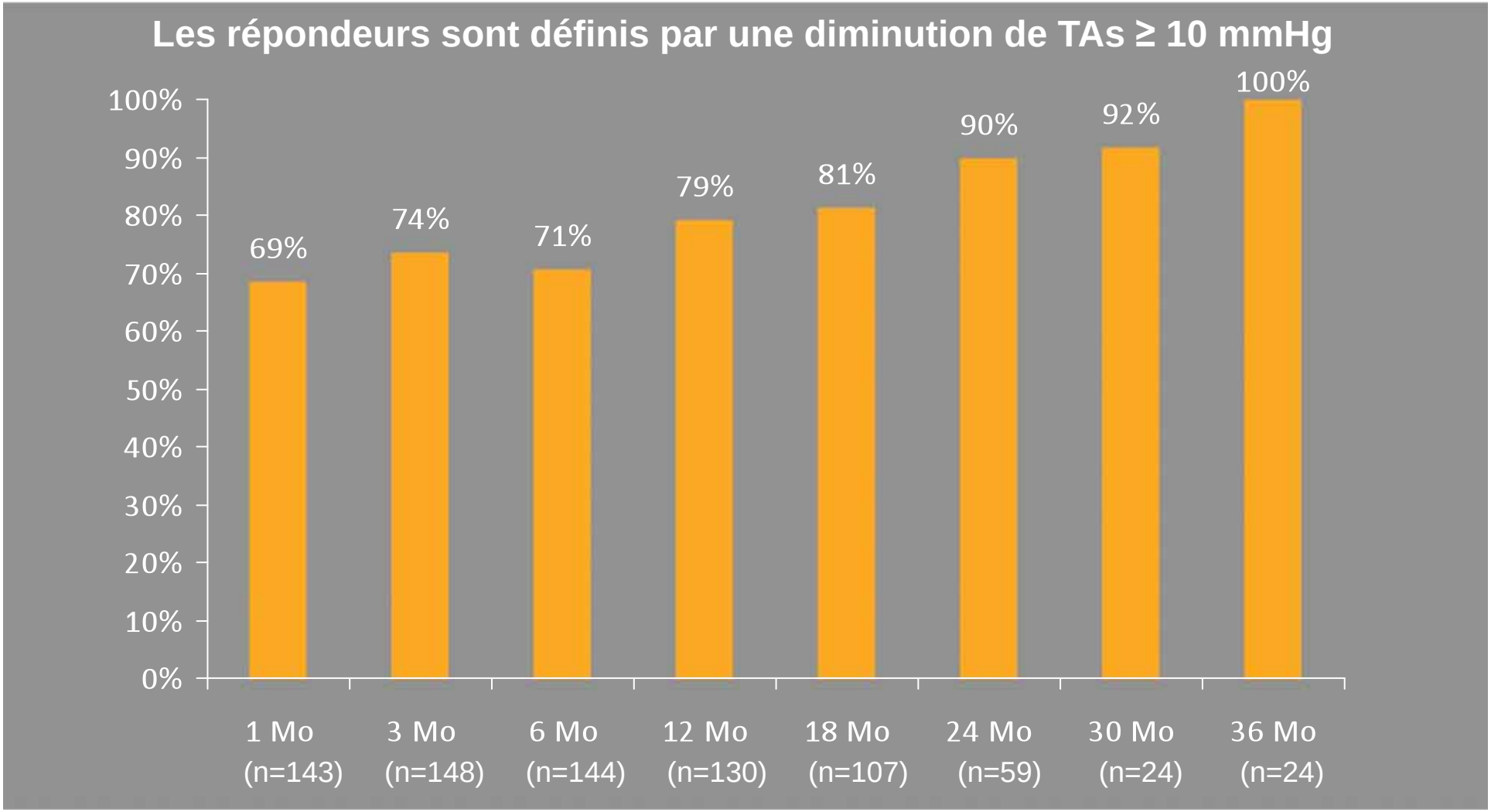
Symplicity HTN-1: étude de suivi: Réduction de la TA jusqu'à 3 ans



HTA réfractaire: hyper-réactivité du SNA sympatique?

*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Symplicity HTN-1 étude de suivi: Pourcentage de répondant jusqu'à 3 ans



*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

Lancet 2010; 376: 1903–09

	Renal denervation group (n=52)	Control group (n=54)
Baseline systolic blood pressure (mm Hg)	178 (18)	178 (16)
Baseline diastolic blood pressure (mm Hg)	97 (16)	98 (17)
Age (years)	58 (12)	58 (12)
Sex (female)	18 (35%)	27 (50%)
Race (white)	51 (98%)	52 (96%)
Body-mass index (kg/m²)	31 (5)	31 (5)
Type 2 diabetes	21 (40%)	15 (28%)
Coronary artery disease	10 (19%)	4 (7%)
Hypercholesterolaemia	27 (52%)	28 (52%)
eGFR* (mL/min per 1·73 m²)	77 (19)	86 (20)
eGFR* 45–60 mL/min per 1·73 m²	11 (21%)	6 (11%)
Serum creatinine (μmol/L)	91 (25)	78 (18)
Urine albumin-to-creatinine ratio (mg/g)†	128 (363)	109 (254)
Cystatin C (mg/L)‡	0·9 (0·2)	0·8 (0·2)
Heart rate (bpm)	75 (15)	71 (15)
Number of antihypertension medications	5·2 (1·5)	5·3 (1·8)
Patients on hypertension medication for more than 5 years	37 (71%)	42 (78%)
Patients on five or more medications	35 (67%)	31 (57%)
Patients receiving (drug class)		
ACE inhibitors/ARBs	50 (96%)	51 (94%)
Direct renin inhibitors	8 (15%)	10 (19%)
β blockers	43 (83%)	37 (69%)
Calcium-channel blockers	41 (79%)	45 (83%)
Diuretics	46 (89%)	49 (91%)
Aldosterone antagonist	9 (17%)	9 (17%)
Vasodilators	8 (15%)	9 (17%)
α-1 blockers	17 (33%)	10 (19%)
Centrally acting sympatholytics	27 (52%)	28 (52%)

Data are mean (SD) or number (%). eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[17] †42 participants in the renal denervation group and 43 participants in the control group used for between-group comparisons with the Wilcoxon rank-sum test for two independent samples. ‡39 participants in the renal denervation group and 42 participants in the control group had data for cystatin C available at baseline.

Table 1: **Baseline clinical characteristics, demographics, and background medications for participants assigned to renal denervation or control groups**

Lancet 2010; 376: 1903–09

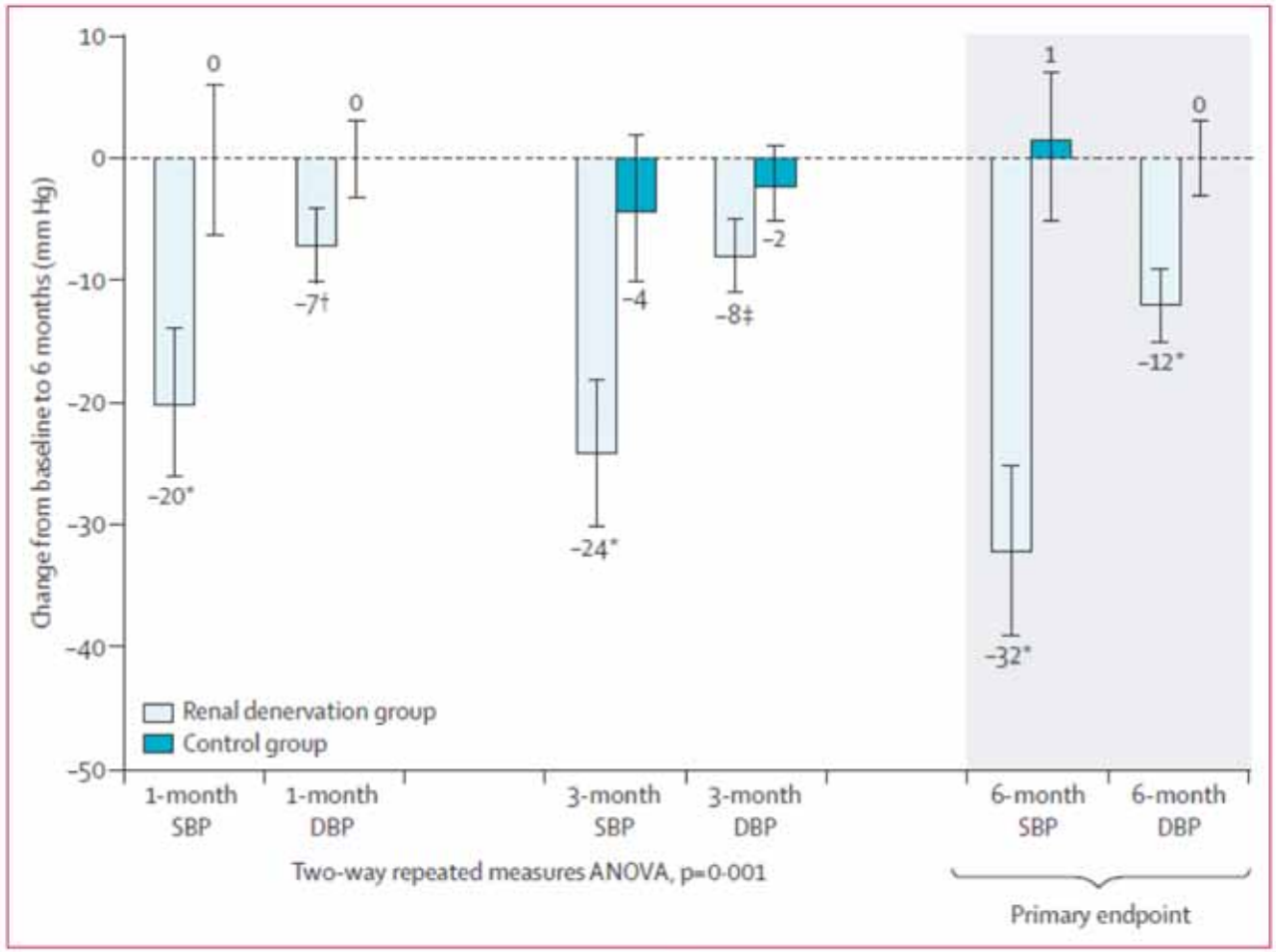


Figure 2: **Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups**

Error bars are 95% CI. Multivariable stepwise regression analysis of baseline characteristics, drugs, and treatment assignment was examined for predictors of increased 6-month systolic-blood-pressure response; only variables with p<0·15 on univariate screening were entered into the model with variables with p<0·05 remaining in the final model. Multivariable analysis of baseline characteristics showed that assignment to the renal denervation group (p<0·0001), higher baseline systolic blood pressure (p<0·0001), and slower heart rate (p<0·004) predicted increased 6-month blood-pressure reduction. SBP=systolic blood pressure. DBP=diastolic blood pressure. *p<0·0001. †p=0·002. ‡p=0·005.

Sécurité

- 1 pseudo anévrisme
- Fonction rénale stable
- Imagerie des AR stable à 6 mois

Lancet 2010; 376: 1903–09

Conclusions HTN1 et HTN2

- La dénervation rénale diminue substantiellement la TA de patients avec HTA réfractaire
- La sécurité de la procédure à court-moyen terme est démontrée
- Sécurité à long terme??
- Effet sur mortalité cardio-vasculaire??

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

- 50 patients avec HTA résistante distribués par randomisation dans HTN2
  - 37 dénervations rénales
  - 13 contrôles
- Tests pré-procédures puis à 3 mois

(*Circulation*. 2011;123:1940-1946.)

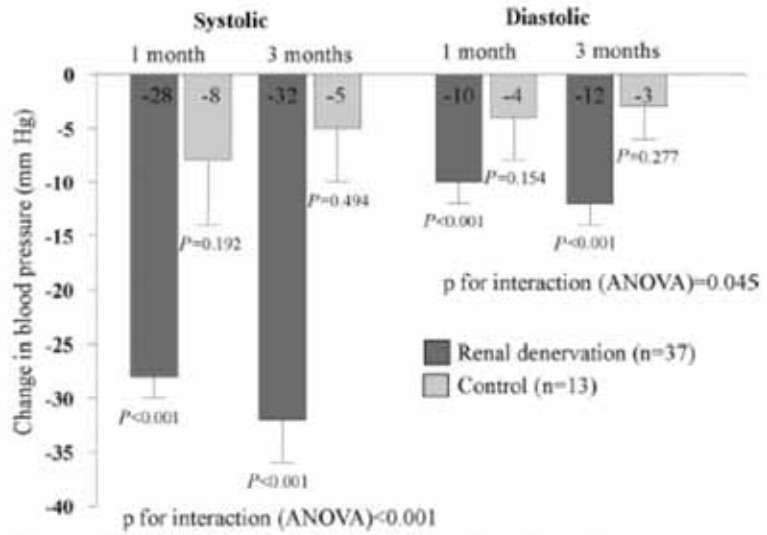


Figure 1. Change in systolic and diastolic office blood pressures (SEM) at 1 and 3 months compared with baseline. *P* values refer to change in blood pressure compared with baseline. Between-group effects, measured by 2-way repeated measures ANOVA, are given as *P* for interaction.

(*Circulation*. 2011;123:1940-1946.)

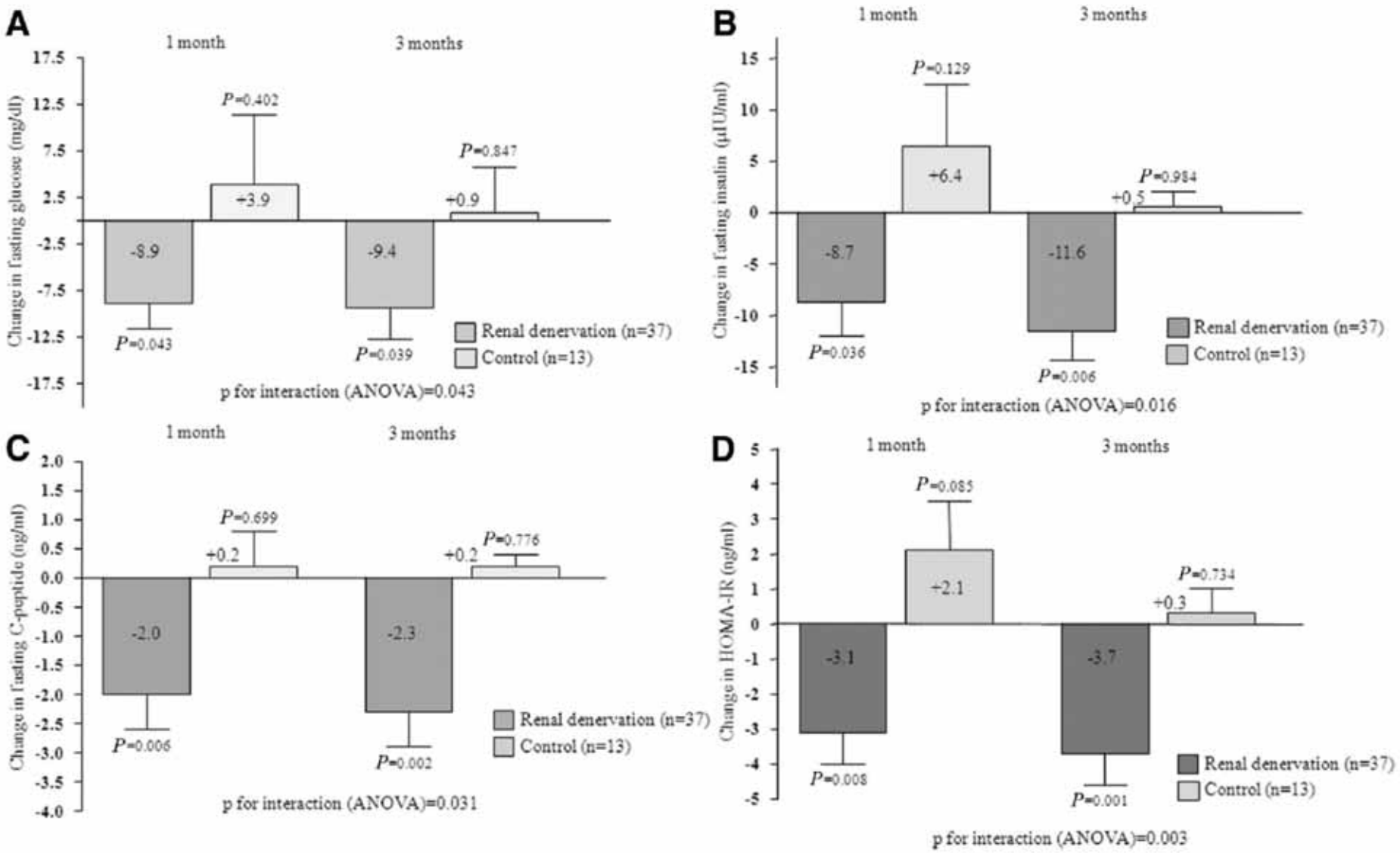


Figure 2. Change (SEM) in fasting glucose (**A**), fasting insulin (**B**), C-peptide (**C**), and homeostasis model assessment–insulin resistance (HOMA-IR; **D**) at 1 and 3 months compared with baseline. *P* values refer to change compared with baseline. Between-group effects, measured by 2-way repeated measures ANOVA, are given as *P* for interaction.

(*Circulation*. 2011;123:1940-1946.)

Conclusions

- La dénervation rénale améliore la sensibilité à l'insuline et le métabolisme global
- Ceci est probablement causé par la baisse de l'activité globale du SNS, car les catécholamines diminuent la sensibilité à l'insuline, et/ou l'amélioration de la microcirculation tissulaire

(*Circulation*. 2011;123:1940-1946.)

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, Przemysław Bieleń, Ilona Michałowska, Marek Kabat, Ewa Warchoł, Magdalena Januszewicz, Krzysztof Narkiewicz, Virend K. Somers, Paul A. Sobotka, Andrzej Januszewicz

- 10 patients avec HTA réfractaire et SAHS
- Dénervation rénale
- Suivi de 6 mois

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

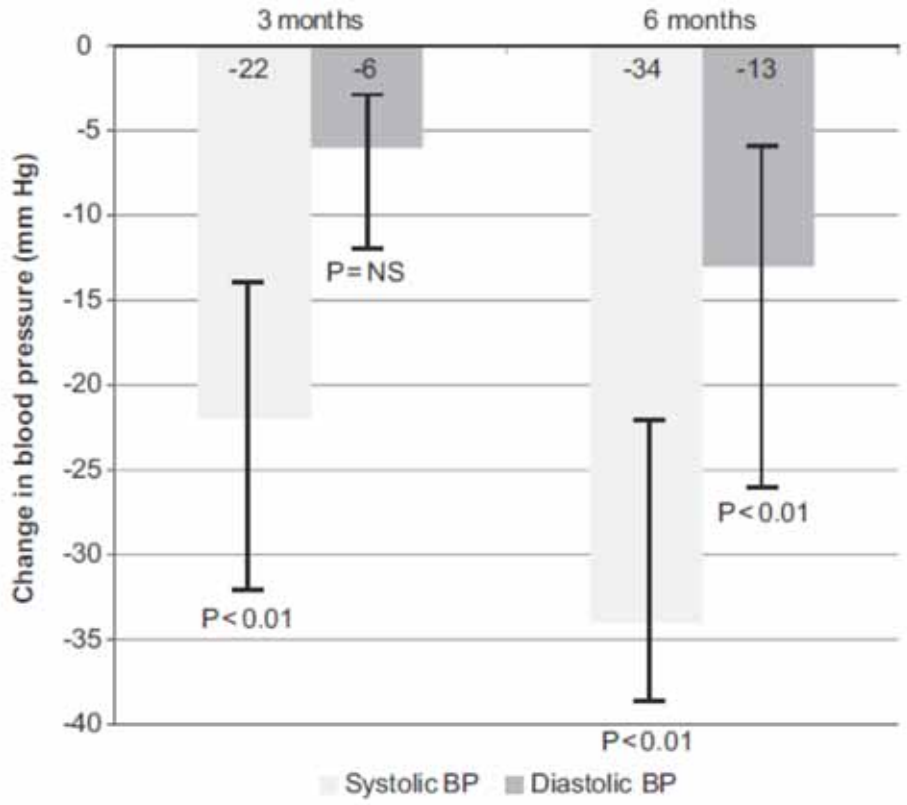


Figure 1. Median systolic and diastolic blood pressure (BP) changes after renal sympathetic denervation procedure at 3 and at 6 months of follow-up. Error bars represent interquartile range.

- Diminution de la glycémie 2h PC 75g glucose à 6 mois

7.0 à 6.4 mmol/L

P<0.05

- Diminution HbA1C à 6 mois

6.1 à 5.6%

P<0.05

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

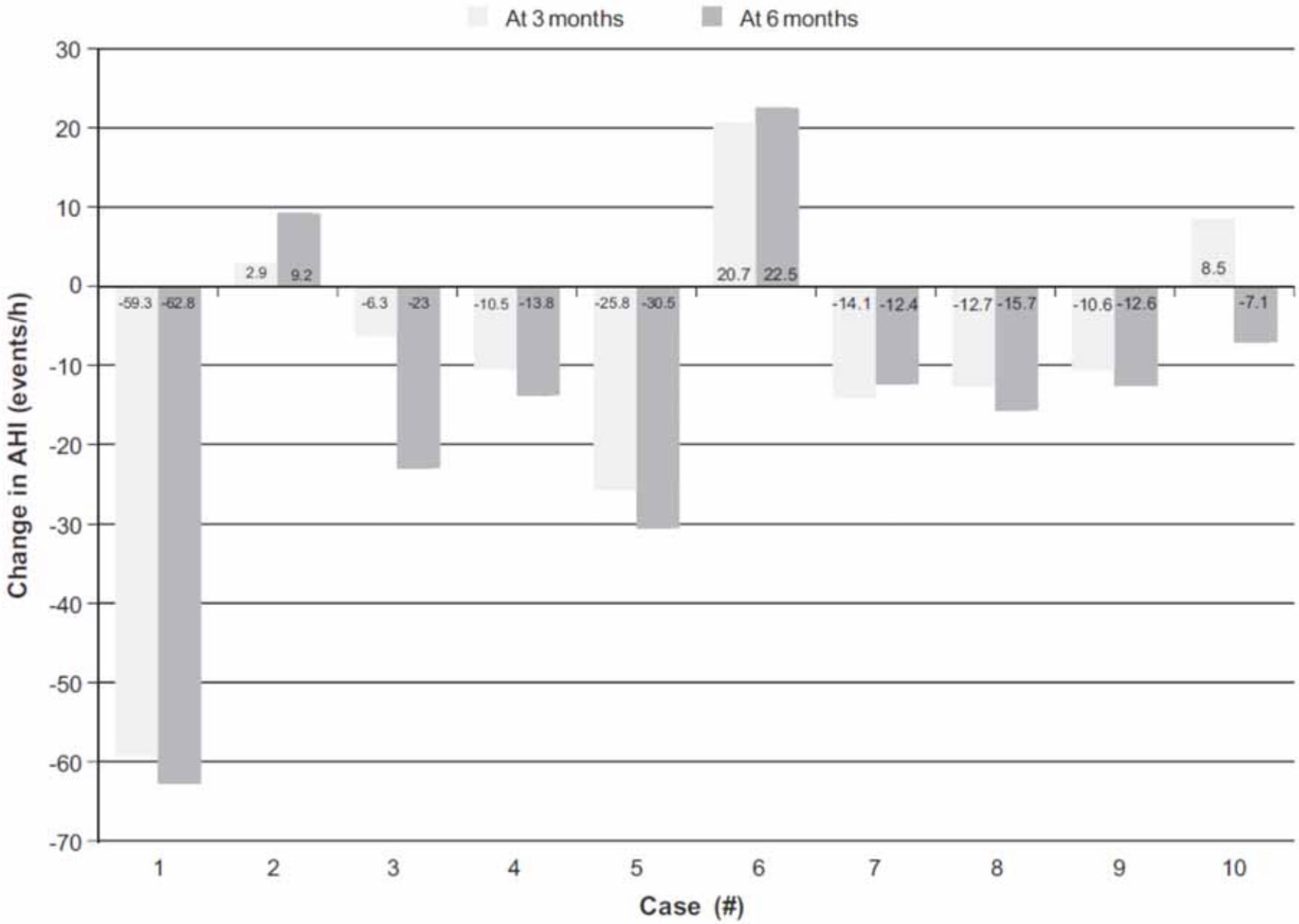


Figure 2. Changes of apnea/hypopnea index (AHI) at 3 and 6 months after denervation. Data of individual cases.

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

Conclusions

- On confirme la baisse de TA et l'amélioration de la sensibilité à l'insuline suite à la DR dans une population de patients avec SAHS.
- L'amélioration de la sévérité de l'AS suite à la DR est spectaculaire et peut s'expliquer par la réduction de la rétention hydro-sodée suite à la diminution de l'activité du SNS intra rénal, et/ou réduction de la TA elle-même.

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

Cardiorespiratory Response to Exercise After Renal Sympathetic Denervation in Patients With Resistant Hypertension

Christian Ukena, MD,* Felix Mahfoud, MD,* Ingrid Kindermann, MD,* Christine Barth, MD,* Matthias Lenski, MD,* Michael Kindermann, MD,* Mathias C. Brandt, MD,† Uta C. Hoppe, MD,†‡ Henry Krum, MBBS, PHD,§ Murray Esler, MBBS, PHD,‖ Paul A. Sobotka, MD,¶# Michael Böhm, MD*

Homburg/Saar and Köln, Germany; Melbourne, Victoria, Australia; Columbus, Ohio; and Palo Alto, California

- 46 patients avec HTA résistante distribués par randomisation dans HTN2
  - 37 dénervations rénales
  - 9 contrôles
- Tests pré-procédures puis à 3 mois

JACC Vol. 58, No. 11, 2011
September 6, 2011:1176–82

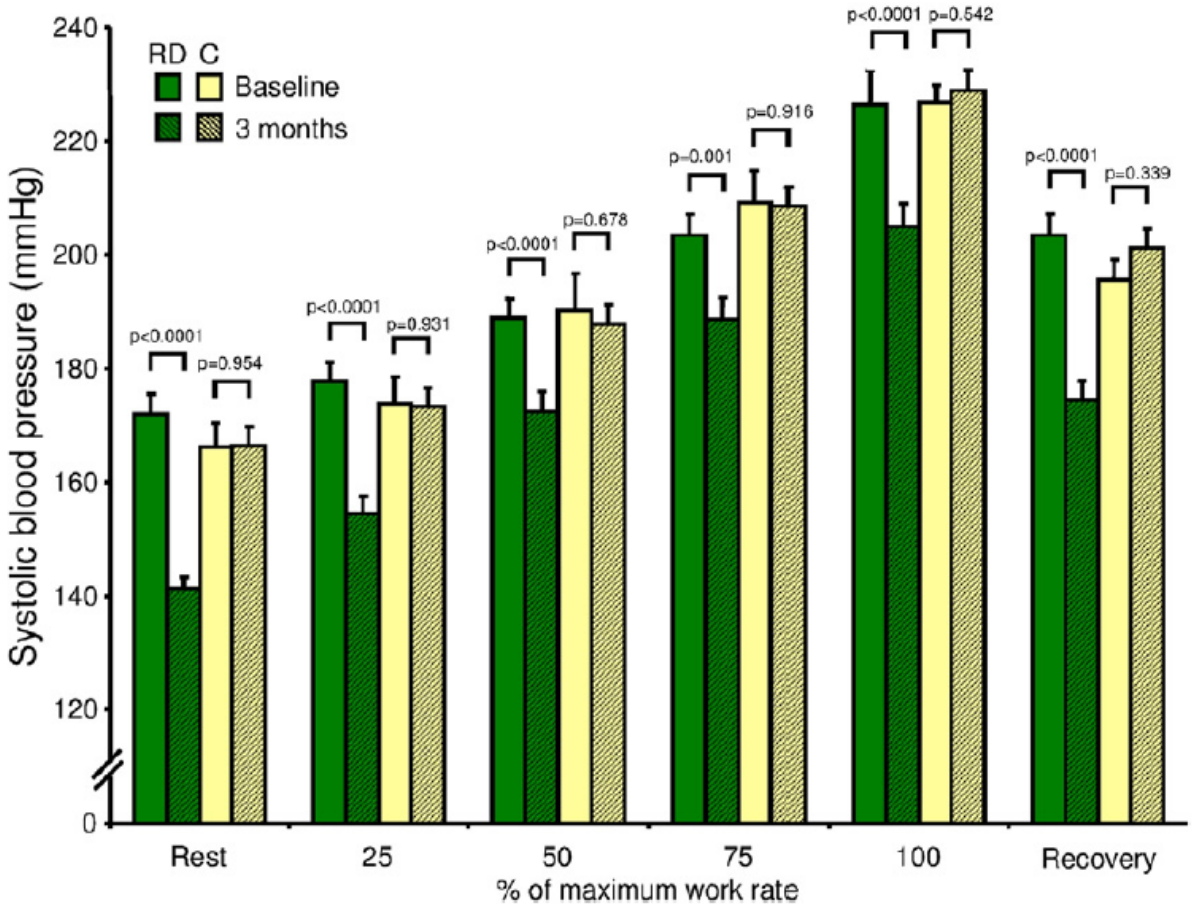


Figure 2 **SBP at Different Stages of Exercise**

Systolic blood pressure in the RD **(green)** and C **(yellow)** groups at different stages of exercise (quartiles of maximum achieved work rate) at baseline **(solid)** and 3 months **(shaded). Error bars** are standard error of the mean. Abbreviations as in Figure 1.

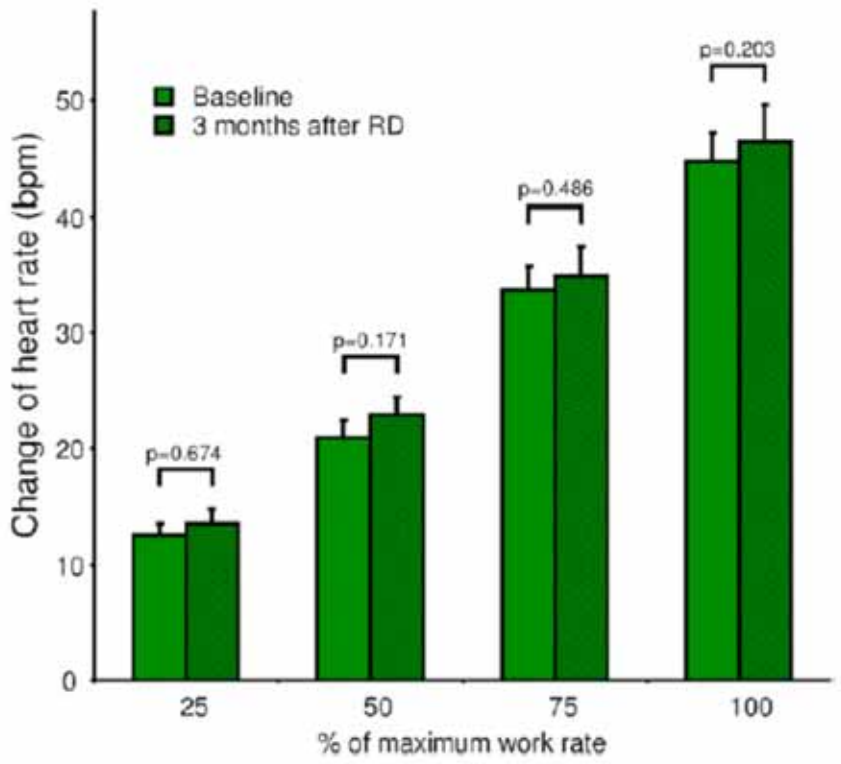


Figure 5 **Change of HR at Different Stages of Exercise**

Change in HR (difference between exercise HR and HR at rest) in the RD group at different stages of exercise (quartiles of maximum achieved work rate) and recovery at baseline and 3 months. **Error bars** are standard error of the mean. Abbreviations as in Figures 1 and 3.

Conclusions

- La dénervation rénale ne change pas la réponse physiologique normale à l'exercice
- La dénervation rénale semble sécuritaire pour les patients faisant de l'exercice

JACC Vol. 58, No. 11, 2011
September 6, 2011:1176–82

Procédure

- Douleur abdo. diffuse nécessitant injection de narcotiques/propofol, limitée au moment même de la procédure (anesthésiste)
- Durée moyenne 34 minutes
- Complications:
  - Risque de pseudo anévrisme fémoral (1%)
  - Fonction rénale stable et perte prévue par baisse de TA (10 cc/min)
  - Artériographie à 1 mois et angio RMR à 6 mois: aucune complication

Conclusions: effets de la dénervation rénale

- Manœuvre non –pharmacologique
- Diminution de TA importante
- Répondeurs / non-répondeurs
  - 70% de répondeurs à 6 mois
- Réduction de l'HVG
- Réduction du RACU
- Réduction de la rigidité vasculaire
- Fonction diastolique: favorable
- Profil métabolique: favorable
- Réduction de l'apnée du sommeil
- Réponse physiologique à l'exercice normale
- Sécurité: semble acceptable (court-moyen terme)

Dénervation rénale: indications

- HTA réfractaire
  - Non réponse à l'aldactone
- Intolérances aux médicaments
- Inobservance?
- Ceux qui veulent réduire leur nombre de médicaments anti-HTA
- Selon la physiologie: situations cliniques ou le SN sympathique est activé:
  - IRC, dialysé, greffé rénaux, IC

SYMPATHETIC OVERACTIVITY IN PATIENTS WITH CHRONIC RENAL FAILURE

RICHARD L. CONVERSE, JR., M.D., TAGE N. JACOBSEN, M.D., ROBERT D. TOTO, M.D., CHARLES M.T. JOST, M.D., FRANK COSENTINO, D.O., FETNAT FOUAD-TARAZI, M.D., AND RONALD G. VICTOR, M.D.

Abstract *Background.* Hypertension is a frequent complication of chronic renal failure, but its causes are not fully understood. There is indirect evidence that increased activity of the sympathetic nervous system might contribute to hypertension in patients with end-stage renal disease, but sympathetic-nerve discharge has not been measured directly in patients or animals with chronic renal failure.

Methods. We recorded the rate of postganglionic sympathetic-nerve discharge to the blood vessels in skeletal muscle by means of microelectrodes inserted into the peroneal nerve in 18 patients with native kidneys who were undergoing long-term treatment with hemodialysis (of whom 14 had hypertension), 5 patients receiving hemodialysis who had undergone bilateral nephrectomy (of whom 1 had hypertension), and 11 normal subjects.

Results. The mean (±SE) rate of sympathetic-nerve discharge was 2.5 times higher in the patients receiving hemodialysis who had not undergone nephrectomy than in the normal subjects (58±3 vs. 23±3 bursts per minute, $P<0.01$). In contrast, the rate of sympathetic-nerve discharge was similar in the patients receiving hemodialysis who had undergone bilateral nephrectomy (21±6 bursts per minute) and the normal subjects. The rate of sympathetic-nerve discharge in the patients receiving hemodialysis who had not undergone nephrectomy was also significantly higher ($P<0.01$) than that in the patients with bilateral nephrectomy, and it was accompanied in the former group by higher values for vascular resistance in the calf (45±4 vs. 22±4 units, $P<0.05$) and mean arterial pressure (106±4 vs. 76±14 mm Hg, $P<0.05$). The rate of sympathetic-nerve discharge was not correlated with either plasma norepinephrine concentrations or plasma renin activity.

Conclusions. Chronic renal failure may be accompanied by reversible sympathetic activation, which appears to be mediated by an afferent signal arising in the failing kidneys. (N Engl J Med 1992;327:1912-8.)

Renal Denervation in Moderate to Severe CKD

Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

- 15 patients IRC
- Suivi 12 mois

J Am Soc Nephrol 23: ●●●–●●●, 2012. doi: 10.1681/ASN.2011111062

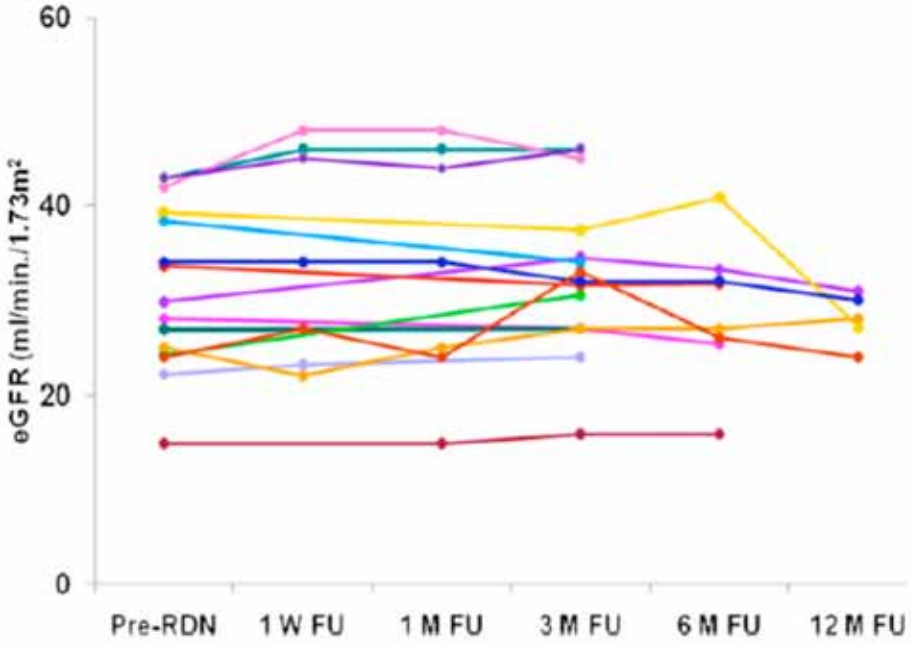
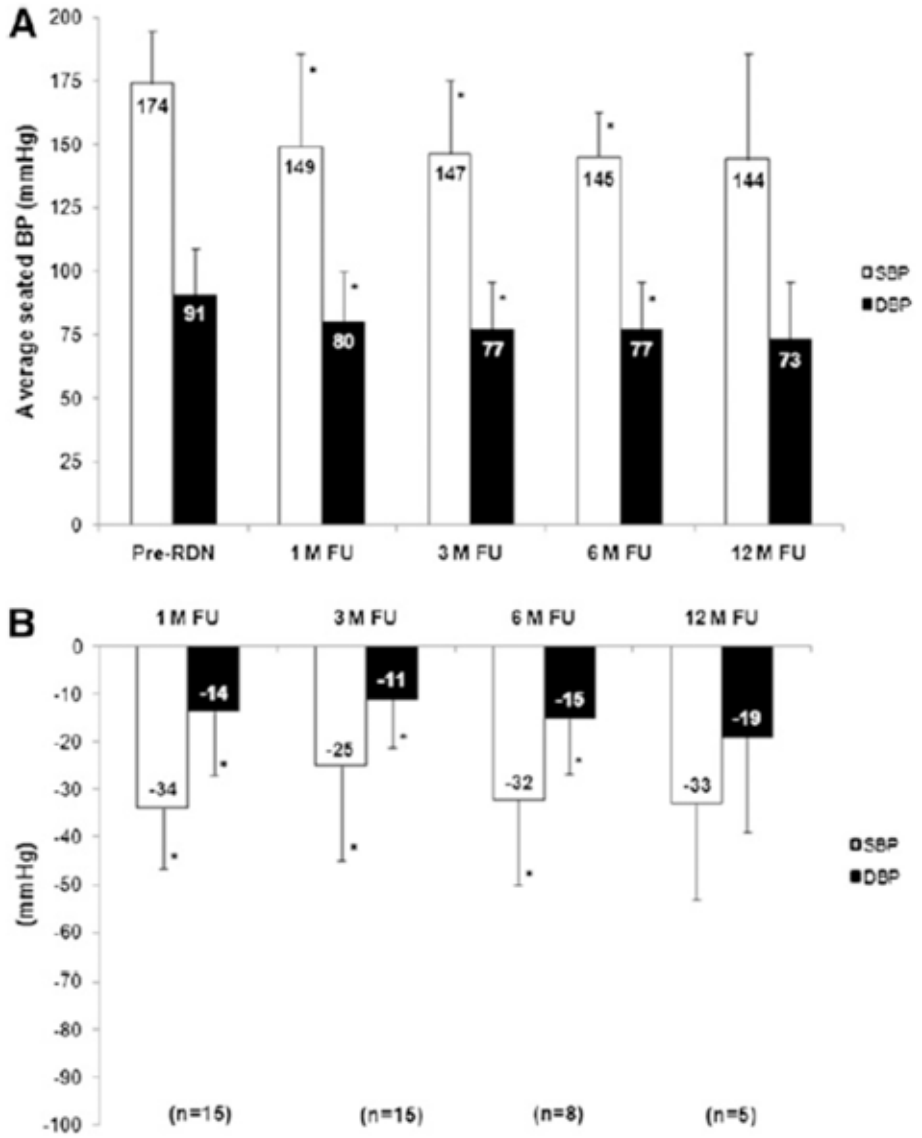


Figure 1. Individual changes in creatinine-based estimated GFR before renal denervation (pre-RDN); at 1 week (W); and at 1-, 3-, 6-, and 12-month (M) follow-up (FU).



J Am Soc Nephrol 23: ●●●–●●●, 2012. doi: 10.1681/ASN.2011111062

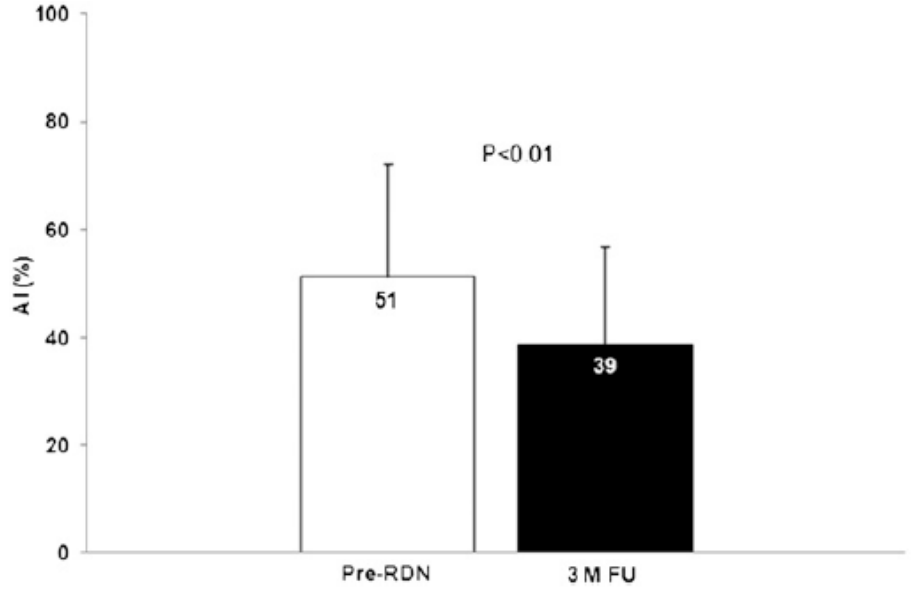


Figure 3. Peripheral augmentation index before and after 3-month follow-up. Error bars represent SDs. AI, augmentation index; FU, follow-up; M, month; pre-RDN, prerenal denervation.

Patients en hémodialyse: 2 case-report

Renal Denervation in a Hypertensive Patient With End-Stage Renal Disease and Small Arteries: A Direction for Future Research

Christian Ott, MD;[1] Axel Schmid, MD;[2] Tilmann Ditting, MD;[1] Paul A. Sobotka, MD;[3,4] Roland Veelken, MD;[1] Michael Uder, MD;[2] and Roland E. Schmieder, MD[1]

- Diminution de TA de 172/100 à 134/70 mmHg (-38/30)

J Clin Hypertens (Greenwich). 2012;14:799–801. ©2012

Renal sympathetic nerve ablation for the treatment of difficult-to-control or refractory hypertension in a haemodialysis patient

Nicola Di Daniele[1], Marianna De Francesco[1], Leano Violo[1], Alessio Spinelli[2] and Giovanni Simonetti[2]

- Diminution de TA de 185/105 à 155/90 mmHg (-30/15)

Nephrol Dial Transplant (2012) 27: 1689–1690

Dénervation rénale: indications

- Approuvé par santé Canada en 03/2012
  - Indication: HTA réfractaire
- Un seul programme clinique en Amérique du Nord:
  - ICM - Clinique HTA HMR
  - Réservé pour non réponse ou impossibilité de donner de l’aldactone

HTA réfractaire: trucs

1) Aldactone
2) HCTZ hautes doses vs indapamide et chlorthalidone
3) Utilisation d'agents plus efficaces dans une même classe (indapamide/perindopril/olmesartan/azilsartan)
4) Bloqueurs combinés alpha/beta (carvedilol / labetalol)
5) Chronothérapie (ASA HS et BCC HS et …)
6) Éviter de substituer un thiazide pour du lasix en IRC si pas d'indication
7) Utilisation de combos, simplification du traitement.

Twynsta (HS) + aldactazide (AM) (68c + 45c) 2 pilules pour 4 rx

Telmisartan / amlodipine / aldactone / hydrochlorothiazide

Aldactone: suppose un suivi serré (clinique HTA?)

En tout temps: Éviter clonidine!

Faire un effort honnête pour éviter les alpha-bloqueurs.

Dénervation rénale: dernier recours.

Conclusions

- Prévalence 5-9%
- >90% réponse à l'aldactone
  - Patients hypersensibles aux effets de l'aldostérone
- Les 10% qui restent semblent bien répondre à la dénervation rénale
  - Patients avec un SNS hyperactivé ou patients hypersensibles aux catécholamines

Table 1 Autonomic Modulation Studies (Ongoing or Completed)

Trial Name	Disease	Sponsor	ID #
Spinal cord stimulation			
Defeat HF	HFrEF	Medtronic	NCT01112579
SCS Heart	HFrEF	ST. Jude	NCT01362725
Baroreceptor activation therapy			
DEBuT-HT	HTN	CVRx	NCT00710190
DEBuT-HET	HTN	CVRx	NCT00710294
Rheos Feasibility Trial	HTN	CVRx	NCT01077180
Rheos Pivotal Trial	HTN	CVRx	NCT00442286
HOPE 4 HF	HFpEF	CVRx	NCT00957073
XR-1 BAT	HTN	CVRx	NCT01471834
XR-1 HF	HFrEF	CVRx	NCT01471860
Vagal nerve stimulation			
CardioFit	HFrEF	Biocontrol	NCT00461019
INOVATE-HF	HFrEF	Biocontrol	NCT01303718
NECTAR-HF	HFrEF	Boston Scientific	NCT01385176
ACES II	HFpEF	Medtronic	NCT01458483
Renal artery denervation			
SWAN HT	HTN	Biosense Webster	NCT01417221
SWAN HF	HFr&pEF	Biosense Webster	NCT01402726
ARSENAL	HTN	St. Jude	NCT01438229
SYMPLICITY HTN I, II, III	HTN	Medtronic	NCT01418261
SYMPLICITY HF	HFrEF	Medtronic	NCT01392196

ACES II = Acute Carotid Sinus Endovascular Stimulation II Study; Arsenal = Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients; CardioFit = CardioFit™ for Treatment of Heart Failure; DEBuT-HT = Device Based Therapy in Hypertension Trial; Defeat-HF = Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure; HFpEF = heart failure with a preserved ejection fraction; HFrEF = heart failure with a reduced ejection fraction; HOPE 4 HF = Health Outcomes Prospective Evaluation for Heart Failure With EF ≥ 40%; HTN = hypertension; Inovate-HF = Increase of Vagal Tone in CHF; Nectar-HF = Neural Cardiac Therapy for Heart Failure Study; Rheos Pivotal Trial = Rheos™ Baroreflex Hypertension Therapy System; SCS Heart = Spinal Cord Stimulation For Heart Failure; SWAN-HF = Renal Sympathetic Modification in Patients With Heart Failure; SWAN-HT = Renal Sympathetic Modification in Patients With Essential Hypertension; Symplicity HTN-3 = Renal Denervation in Pat… Uncontrolled Hypertension; SymplicityHF = Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment Clinical Trial; XI… Barostim Neo System in the Treatment of Resistant Hypertension; XR-1 HF = Barostim Neo System in the Treatment of Heart Failure.

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Merci de votre attention!!

Questions?
Commentaires?