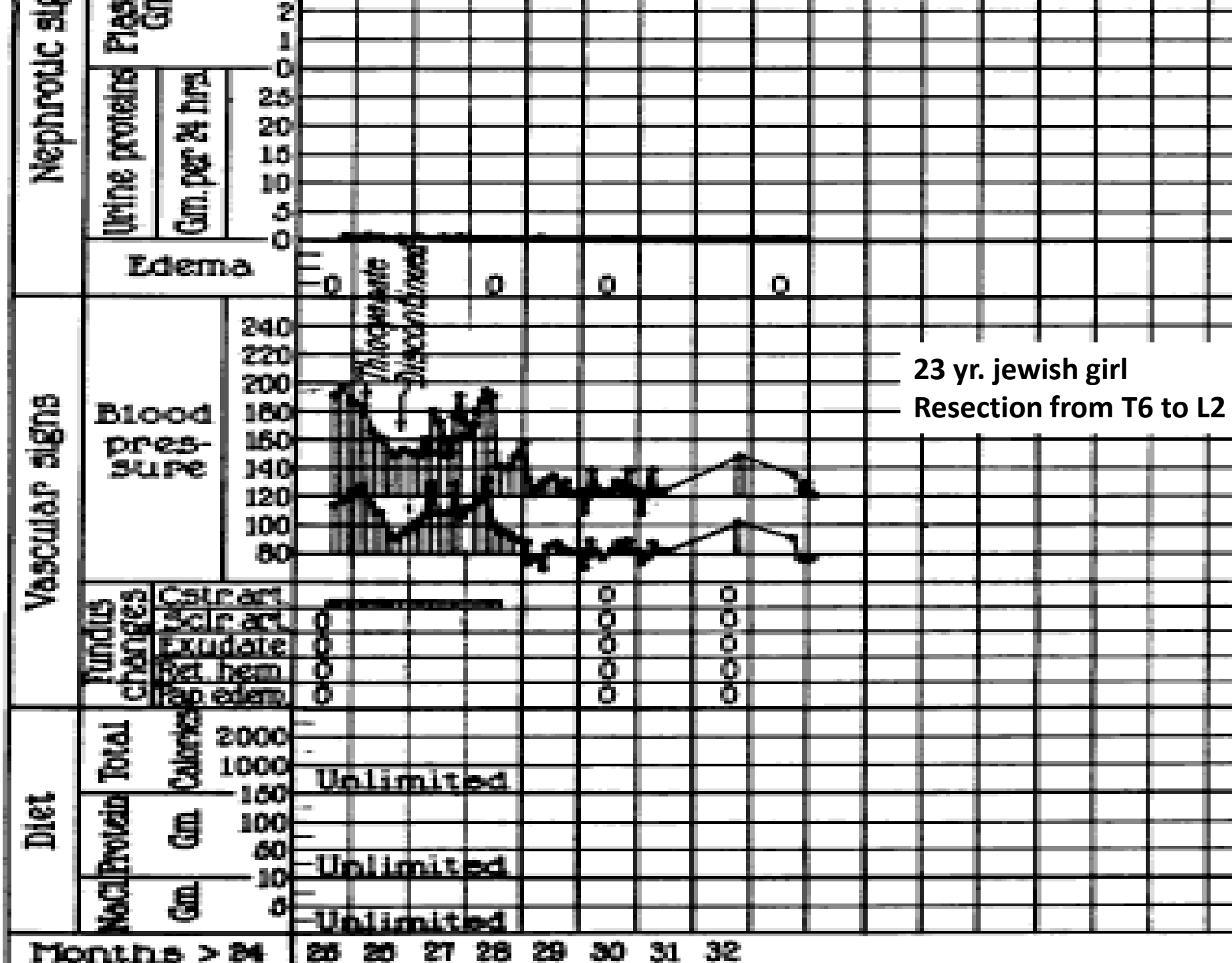
Recent Treatment of Uncontrolled & Resistant Hypertension

박 창 규
고려대 구로병원 심혈관센타

A SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION

Irvine H. Page and George J. Heuer

J Clin Invest. 1935 January; 14(1): 22–26.


Nephrotic signs
Plasma Gm.
Urine proteins Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Fundus changes
Sclr.art.
Exudate
Hmr. hem
Hap. edem.
Diet
Total Calories
Protein Gm.
Salt Gm.
Months > 24
23 yr. jewish girl
Resection from T6 to L2
Unlimited
Unlimited
Unlimited

Surgical Sympathectomy

Sympathectomy: An Early Surgical Precedent

Dr. Reginald H. Smithwick

THE JOURNAL

of the American Medical Association

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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

THE BRITISH JOURNAL OF SURGERY

1952

SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION*

A REVIEW OF 76 PATIENTS

BY C. J. LONGLAND AND W. E. GIBB

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

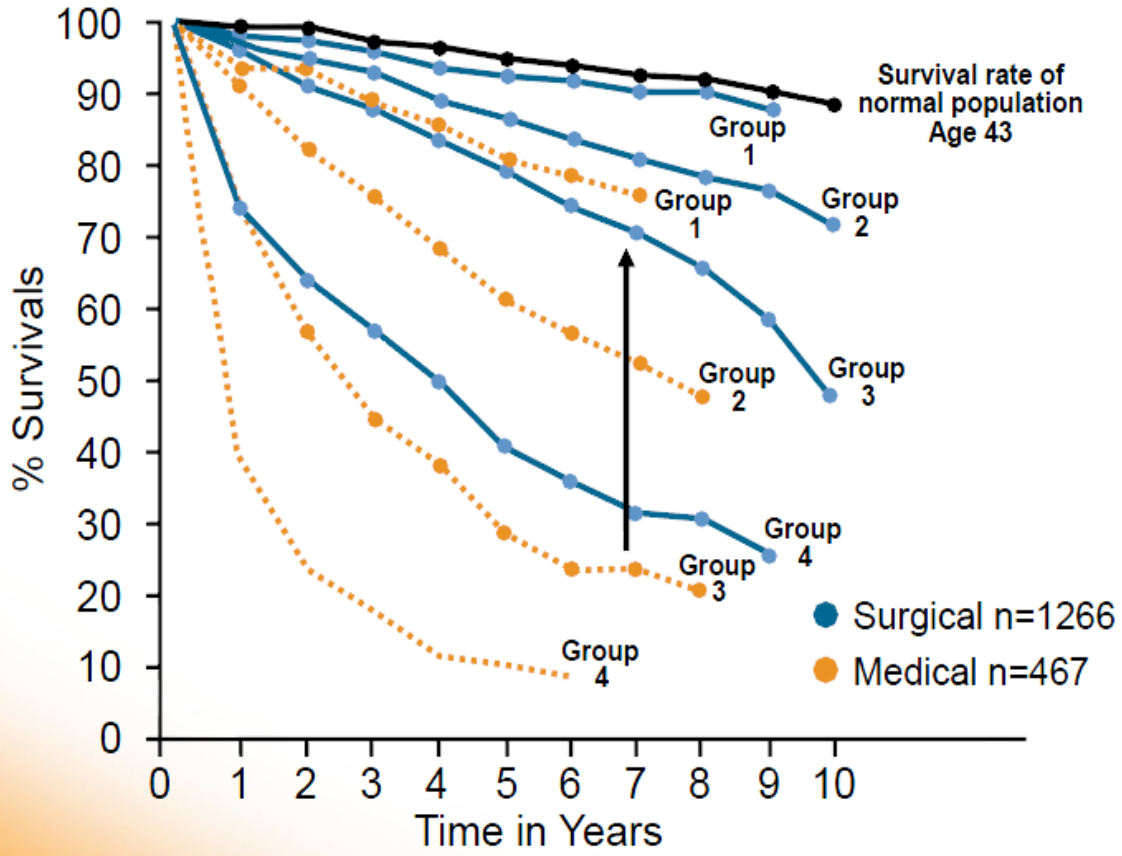
BRADFORD CANNON

...om the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

Photo of Dr. Smithwick reproduced with permission from *JAMA*.

Surgical Sympathectomy



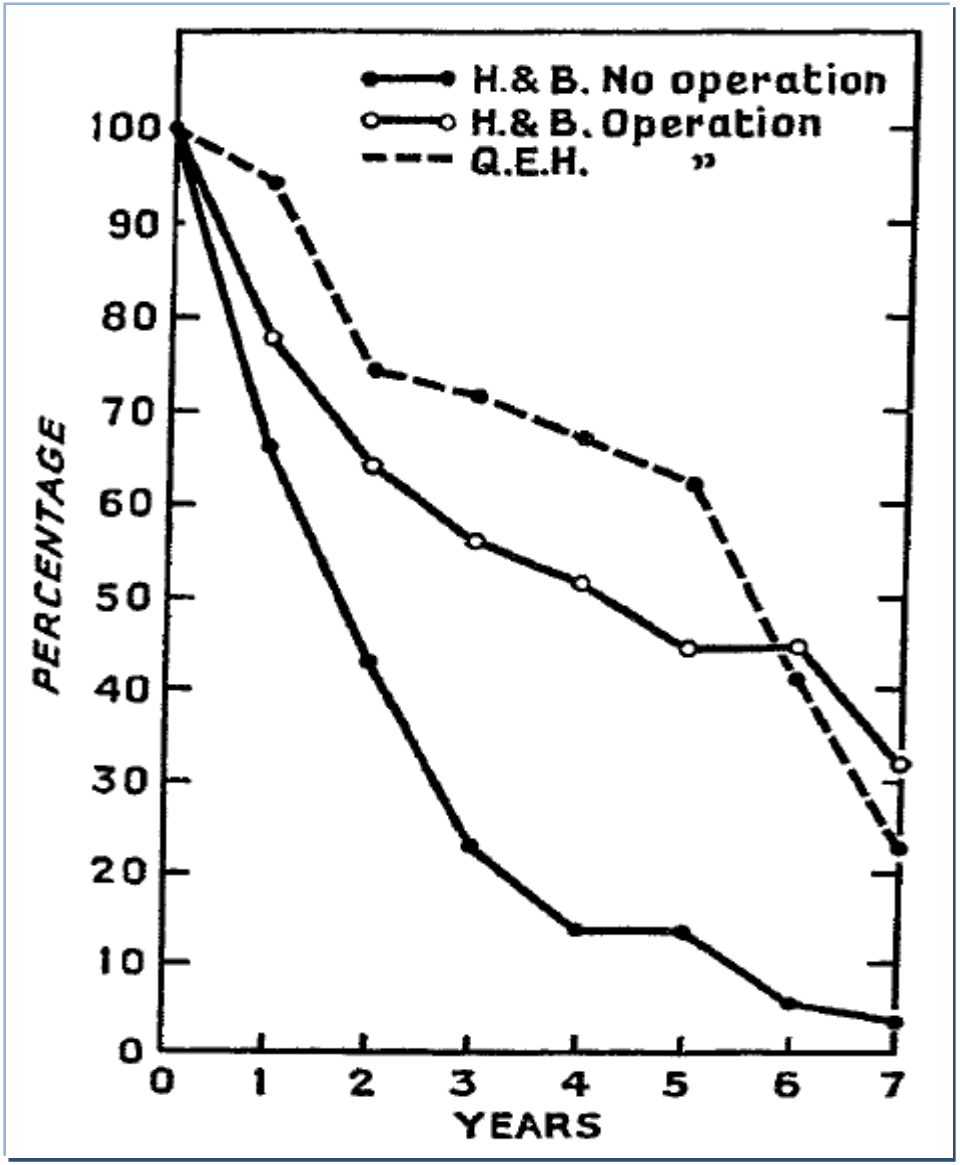
However, surgical sympathectomy was associated with significant morbidity[2]

- **Group 1:** Patients with persistently elevated BP, minimal/no eyeground changes nor abnormalities in cerebral, cardiac, or renal nerves
- **Groups 2-4:** Patients with increasing amounts of cardiovascular disease

nplicity™
Denervation System

1. Adapted and reproduced with permission from Smithwick RH, Thompson JE. *JAMA*. 1953;152:1501-1504.
2. Gewirtz JR, et al. *Cardiol J*. 2011;18:97-102.

Long term survival over 7 years
Subgroup with grade IV retinopathy



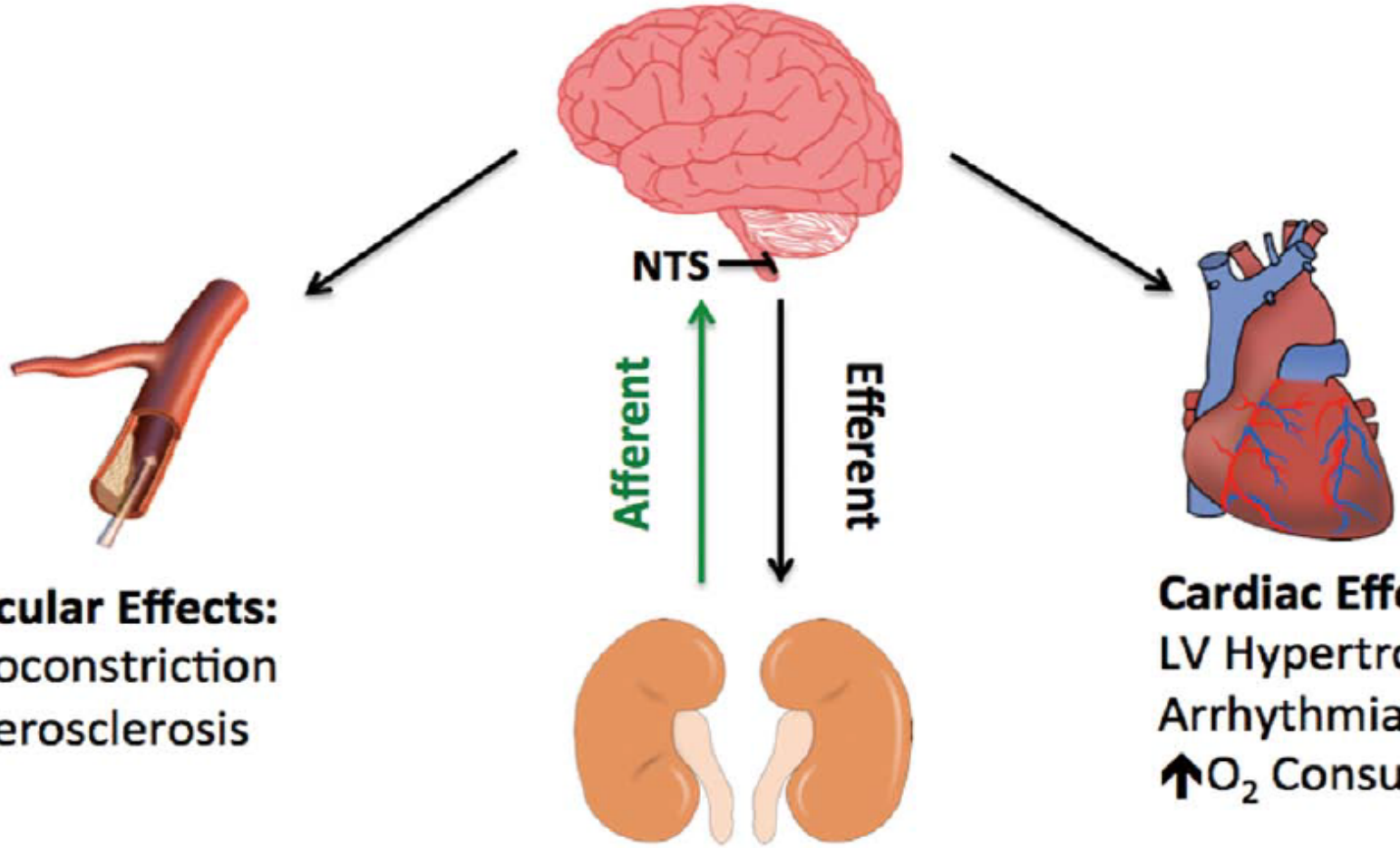
Common side effect

- Severe orthostatic hypotension:
- orthostatic tachycardia, palpitation
- Cold hand, anhidrosis, GI and bladder dysfunction
- Asthmatic symptoms and atelectasis
- Loss of ejaculation, sexual dysfunction

Surgical Sympathetic Denervation

- Immediate surgical mortality: 2-7.3%
- 25% died within 3-5 years .
- Blood pressure reduction was inconsistent and observed in only 50% of cases
- **The procedure was abandoned in the mid-late 1960** s when effective and much better-tolerated orally active anti-hypertensive drugs became available

Renal Sympathetic Activation in Hypertension

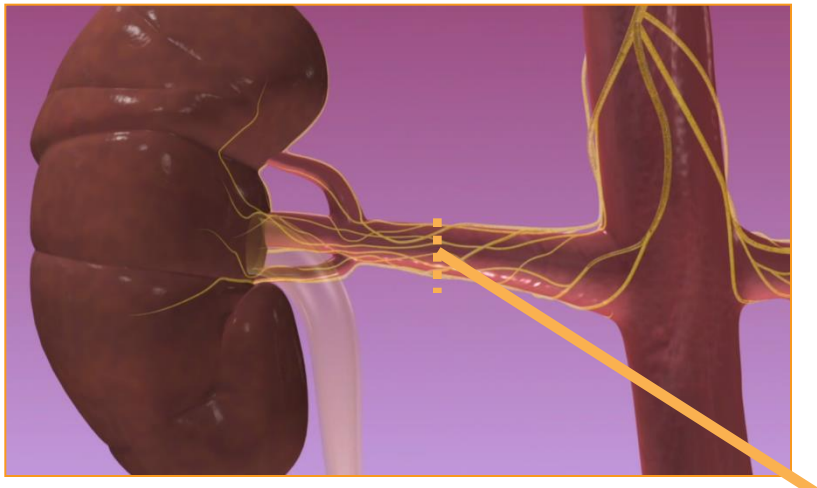


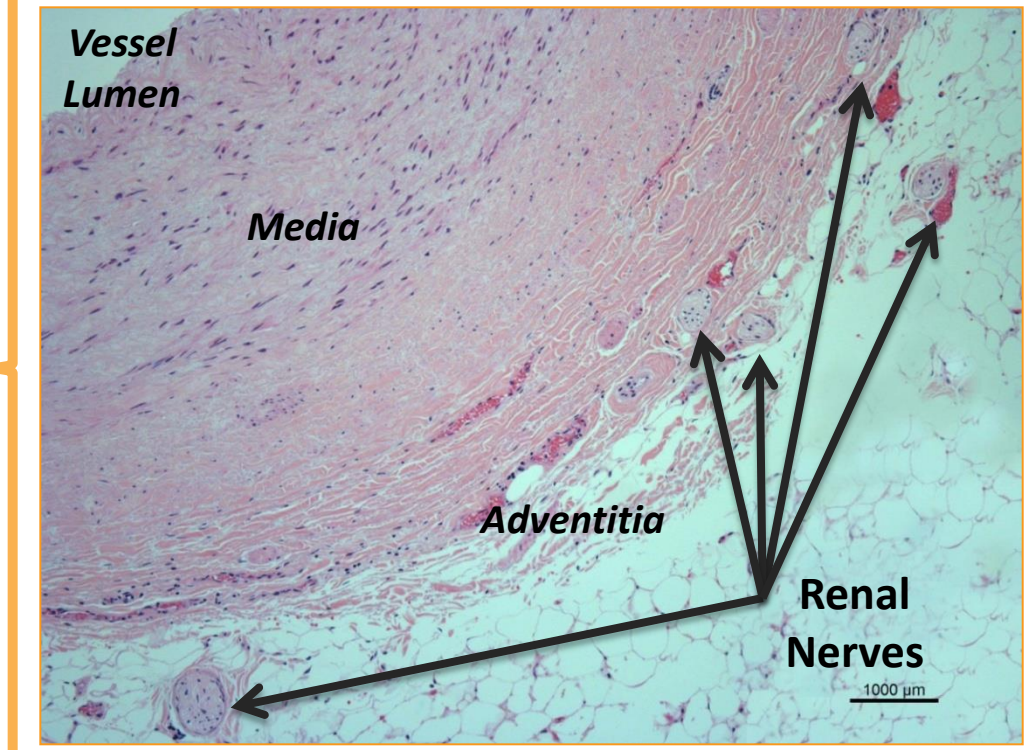
Vascular Effects:
Vasoconstriction
Atherosclerosis

Cardiac Effects:
LV Hypertrophy
Arrhythmias
↑O_2 Consumption

↑Renin Release β1 receptor
↑Sodium retention α2β receptor
↓Renal blood flow α1A receptor

Anatomy of Renal Artery



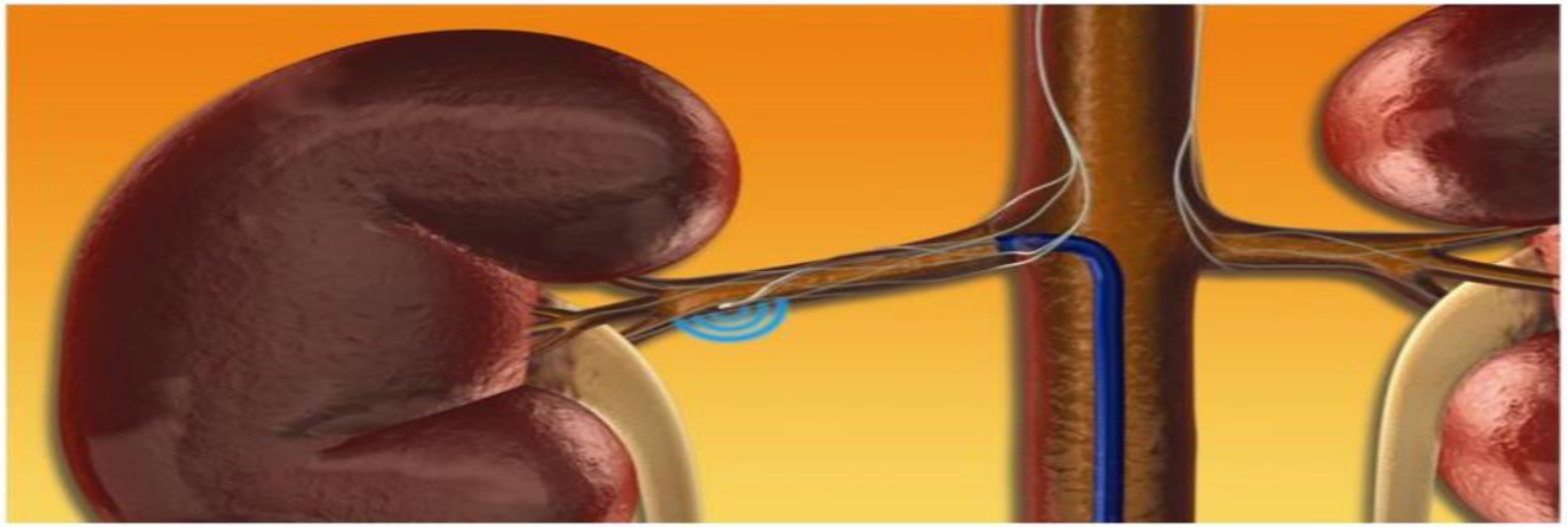


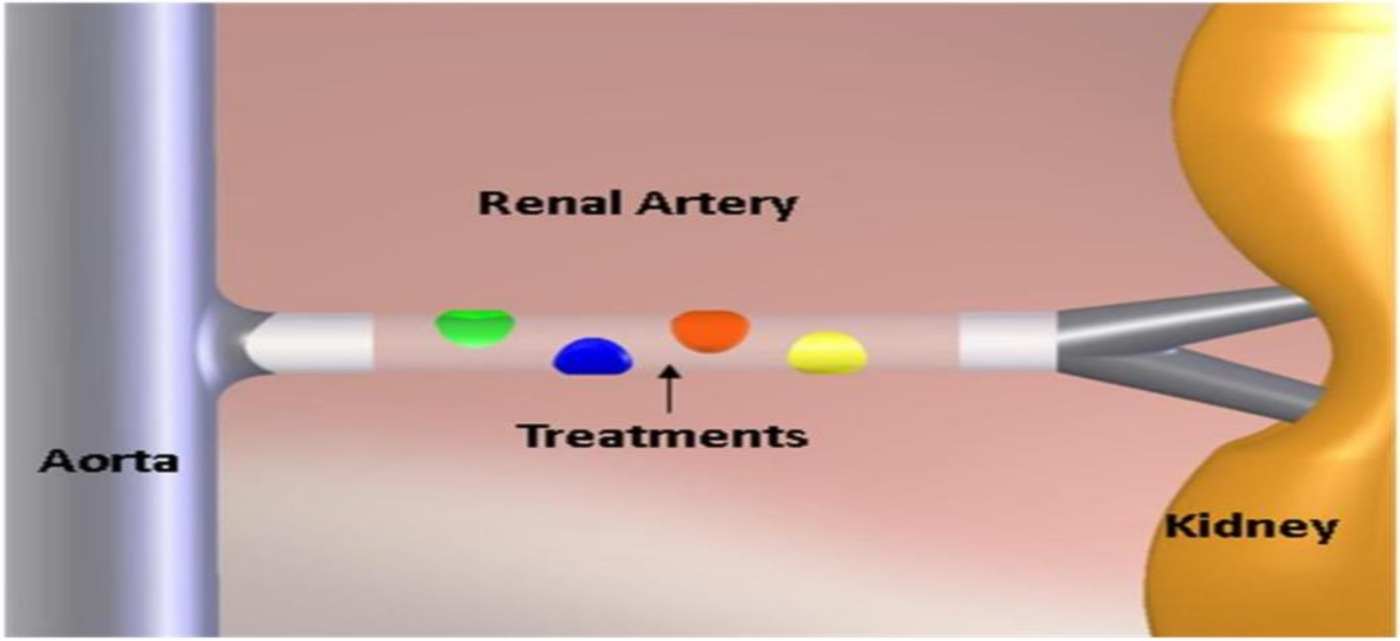
- Arise from **T10-L2**
- Follow the renal artery to the kidney
- Primarily lie within the **adventitia**
- Renal **efferent & afferent** nerves **travel together**

Symplicity® Catheter System™

- Low profile, electrode tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Standard interventional technique
- 40-minutes from first to last RF delivery

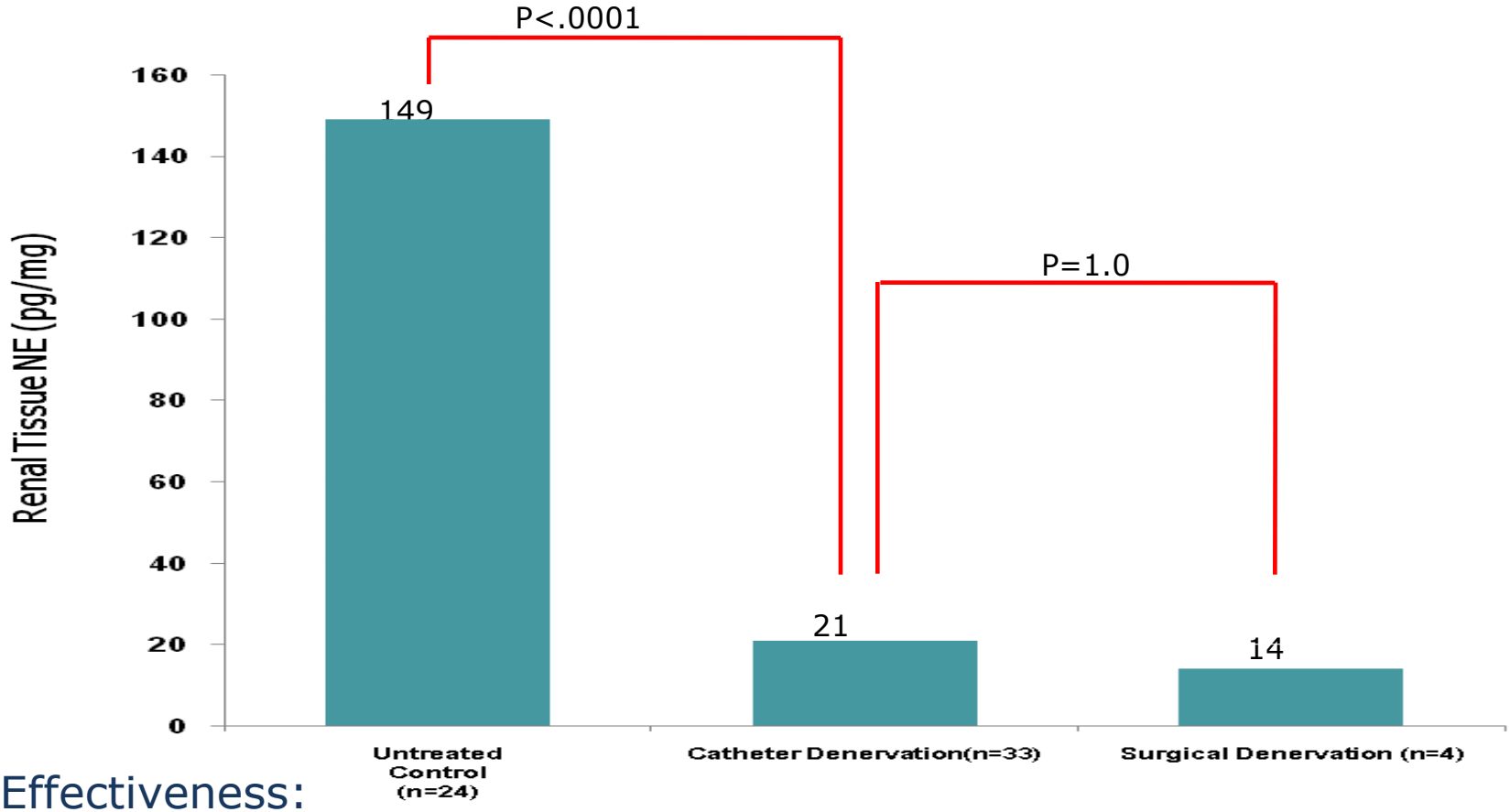
Percutaneous catheter-based approach to functionally denervate the human kidney





Preclinical Efficacy of RDN

- Extensive research in >300 swine

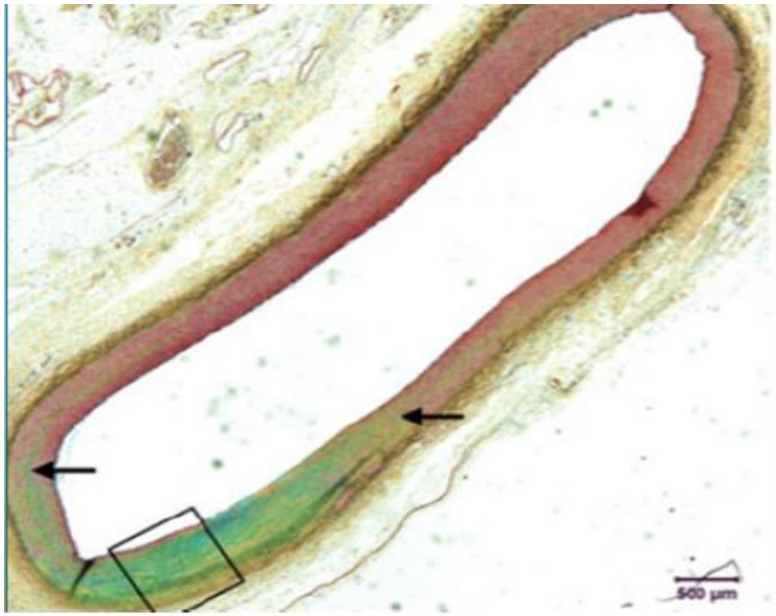


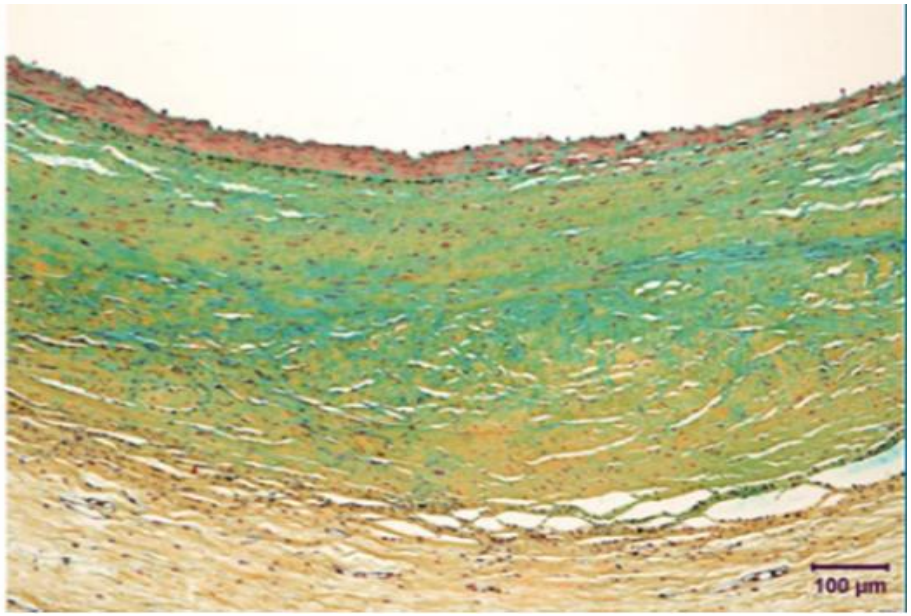
- Effectiveness:
  - Statistically significant reduction in renal tissue NE
- Safety :
  - By 180 days, arteries were well healed (no inflammatory cells)
  - No stenosis or luminal reduction seen in any treated artery

Six Month Post-Procedure Histology

Movat's Pentachrome Stain

- **Minimal intimal thickening** and minimal internal elastic lamina injury overlying areas of **mild** full thickness **medial** fibrosis (Yellow [fibrosis] with green [proteoglycan deposition]) and **adventitial fibrosis** (yellow)



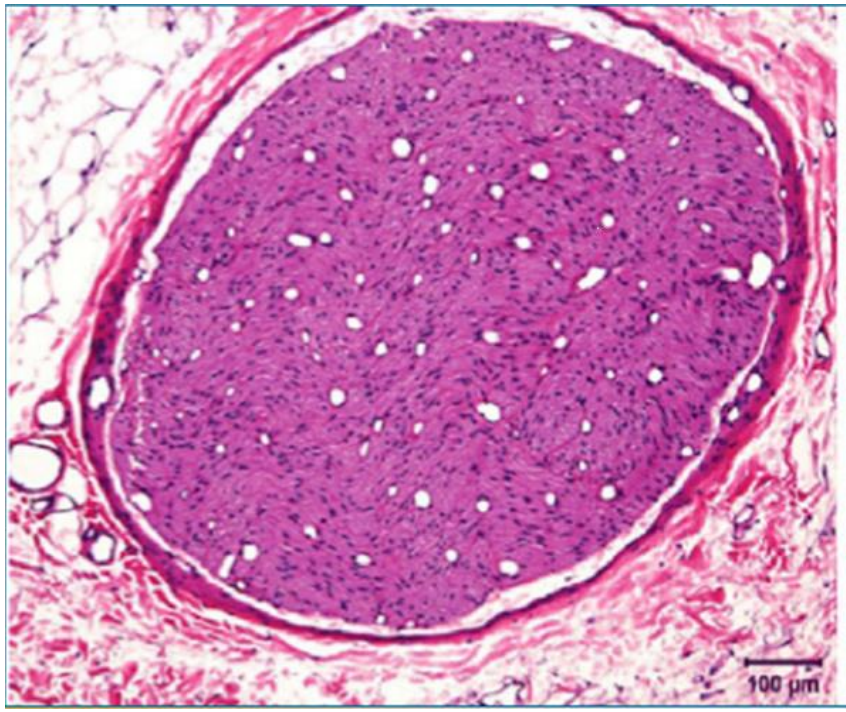


1. Calhoun DA, et al. *Circulation.* 2008;117:e510-e526
2. Kaplan NM. *J Hypertens.* 2005; 23:1441-1444.
3. Persell SD. *Hypertension.* 2011;57:1076-1080

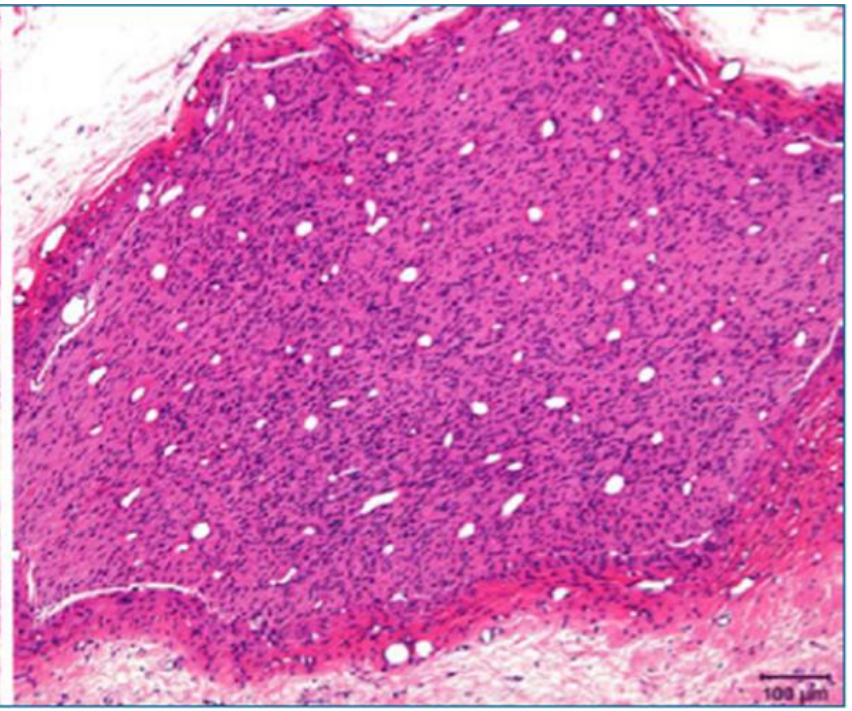
Six Month Post-Procedure Histology

- **Nerve from untreated vessel:** Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- **Nerve from treated vessel:** Periarterial **nerve bundle** has a **hypercellular** appearance and the **perineurium** has a **thickened** and **fibrotic** appearance.

Nerve from Untreated Vessel

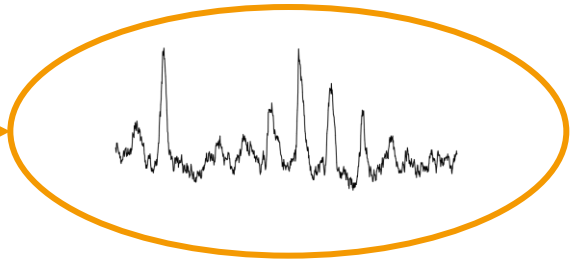


Nerve from Treated Vessel



Quantifying Human SNS Activity

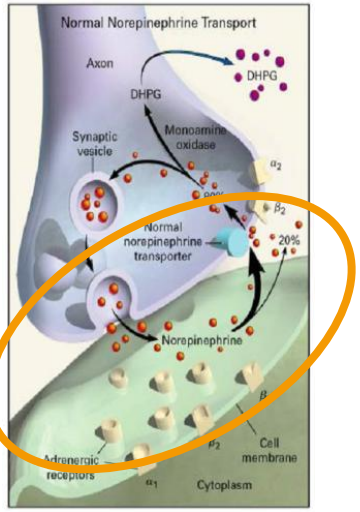
Central Sympathetic Nerve Activity



Muscle Sympathetic Nerve Activity (MSNA)

recording postganglionic nerve traffic

Renal Sympathetic Nerve Activity

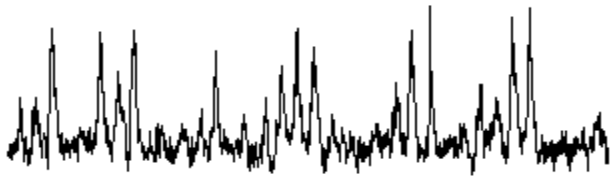


Norepinephrine Spillover

measuring transmitter release from sympathetic nerves to plasma

Direct Measurement of Reduced Central Sympathetic Nerve Activity

Denervation of Patient w/Essential HTN:

	** 59 year old male on 7 HTN meds*	MSNA (burst/min)		BP (mmHg)
Baseline		**56**	→	**161/107**
1 mo		**41** (-27%)	→	**141/90** (-20/-17)
12 mo		**19** (-66%)	→	**127/81** (-34/-26)

Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 →11.7 msec/mmHg)

Schlaich et al. NEJM. 2009; 36(9): 932-934.

Related Changes in Underlying Physiology

		Baseline	1 mo	Δ
Office BP	*(mmHg)*	161/107	141/90	
Renal NE spillover	*(ng/min)*			
- left kidney		72	37	-48%
- right kidney		79	20	-75%
Total body NE spillover	*(ng/min)*	600	348	-42%
Plasma Renin	*(µg/l/hr)*	0.3	0.15	-50%
Renal Plasma flow	*(ml/min)*	719	1126	57%

LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m^2) from baseline to 12 months

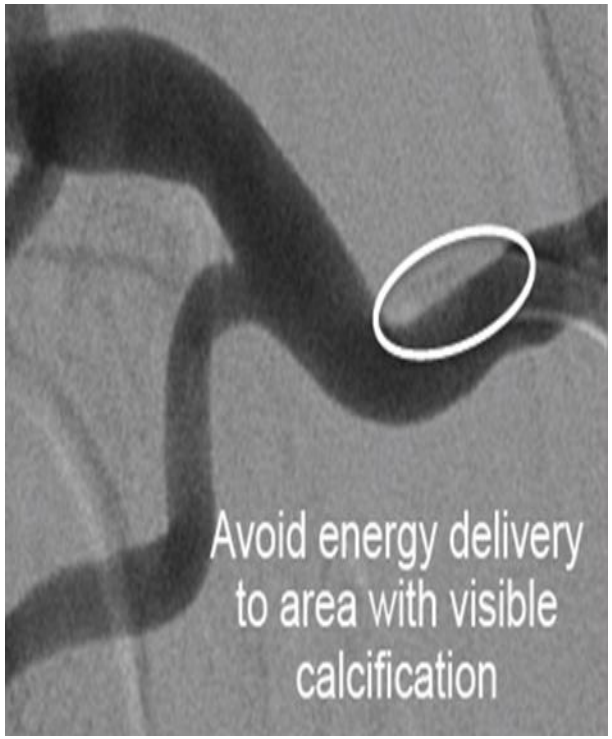
Consistent with Expected Effects of Denervation

Schlaich et al. NEJM. 2009; 36(9): 932-934.

Areas to Avoid

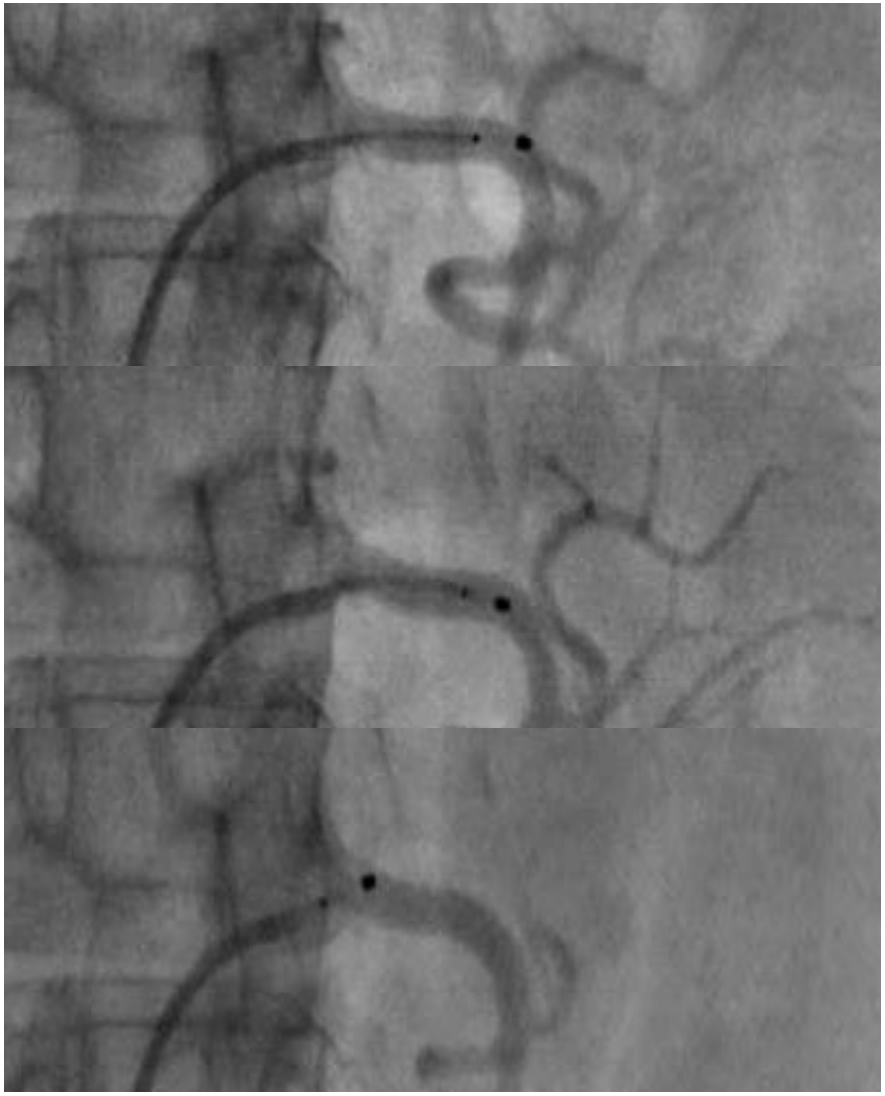
Atherosclerosis (Ostial Stenosis)

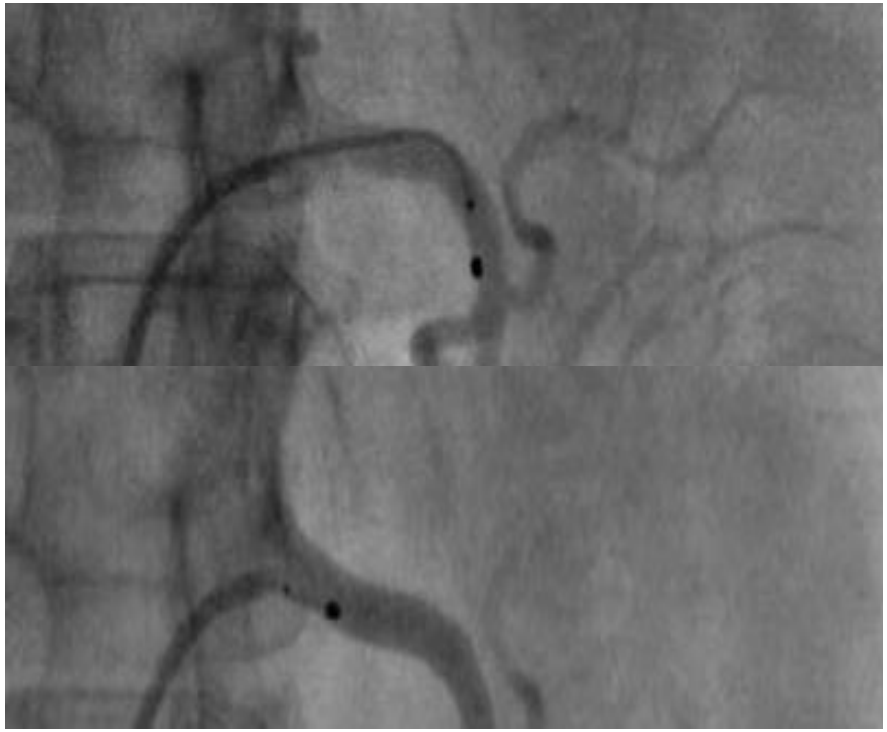
Calcification



Fibromuscular Dysplasia (FMD)

카테터 교감신경 절제술의 실제 사진





Angiographic Appearance

Pre-Procedure

Acute Post-Procedure

1 Month Follow-Up

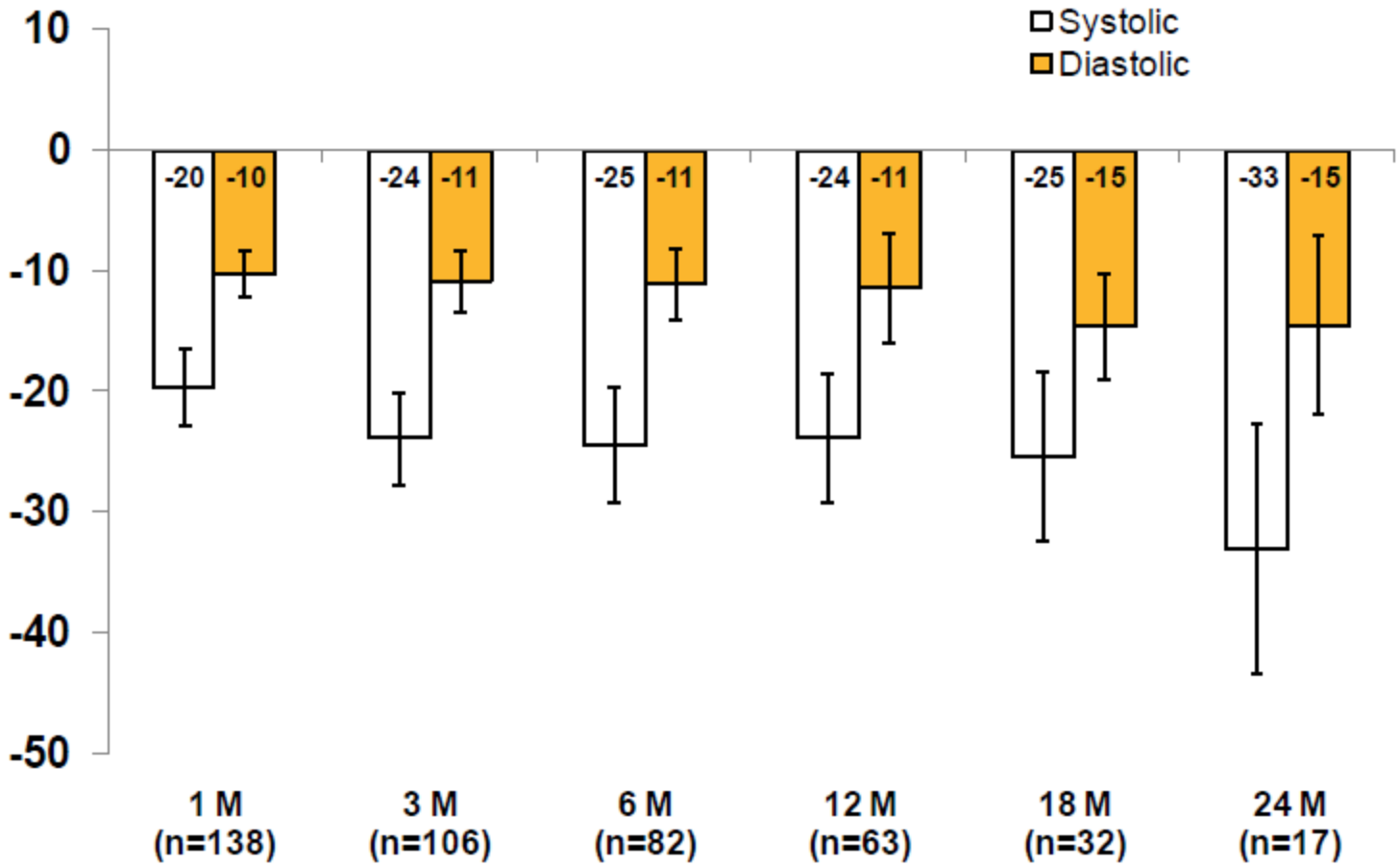
Symplicity HTN Trials:

- **Symplicity HTN-1 Study**
  - Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof of principle cohort study
- **Symplicity HTN-2 Study**
  - An international, multicenter, prospective, randomized, controlled study of the safety and effectiveness of renal denervation in patients with uncontrolled hypertension
- **Symplicity HTN-3 Study**
  - Multicenter, prospective, single-blind, randomized, controlled study of the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension

Krum H, et al. *Lancet.* 2009;373:1275-1281.
http://clinicaltrials.gov/ct2/show/NCT00888433
http://clinicaltrials.gov/ct2/show/NCT01418261

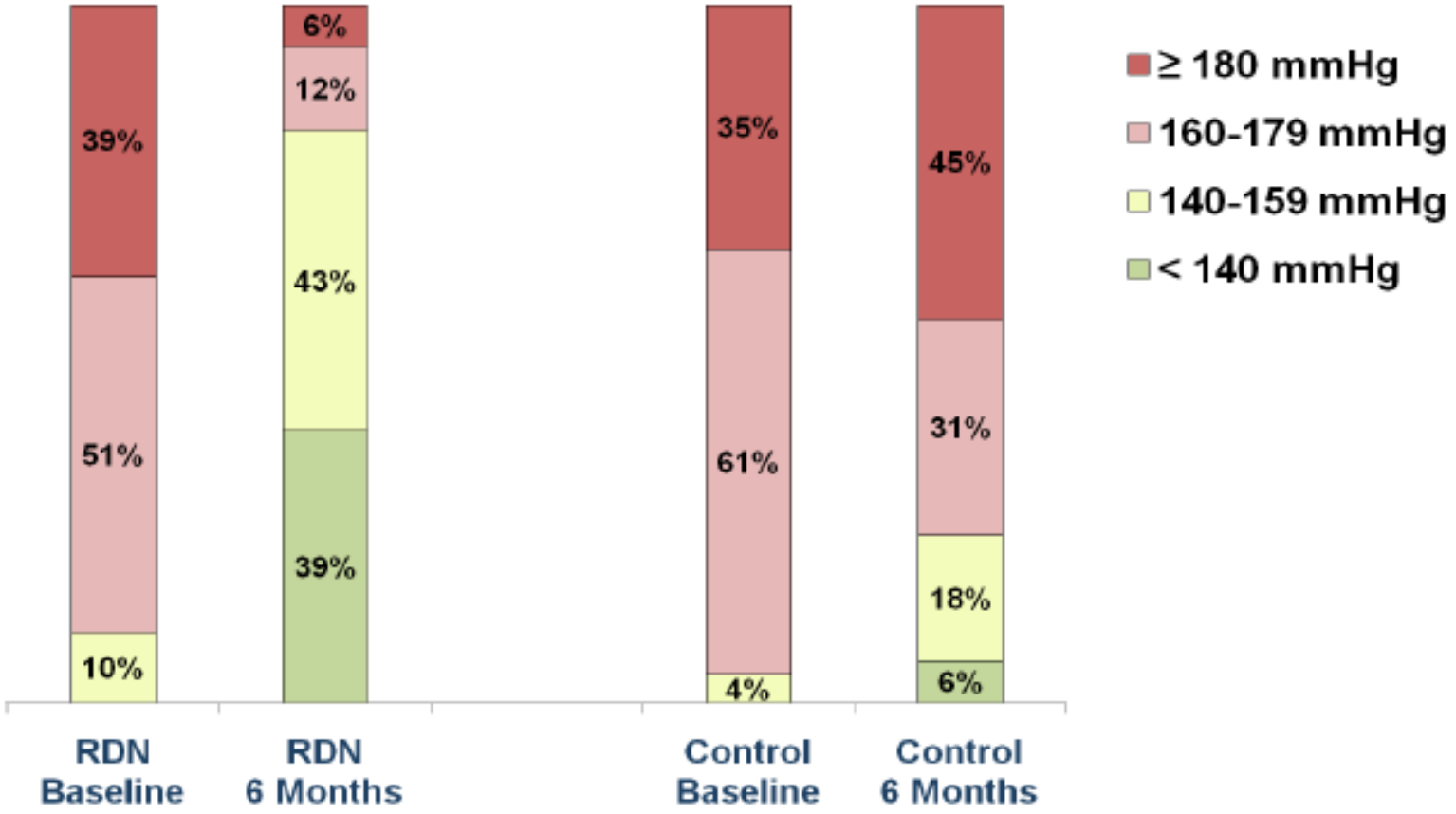
Symplicity HTN-2 Study

베이스라인 대비 진료실 측정 혈압 변화



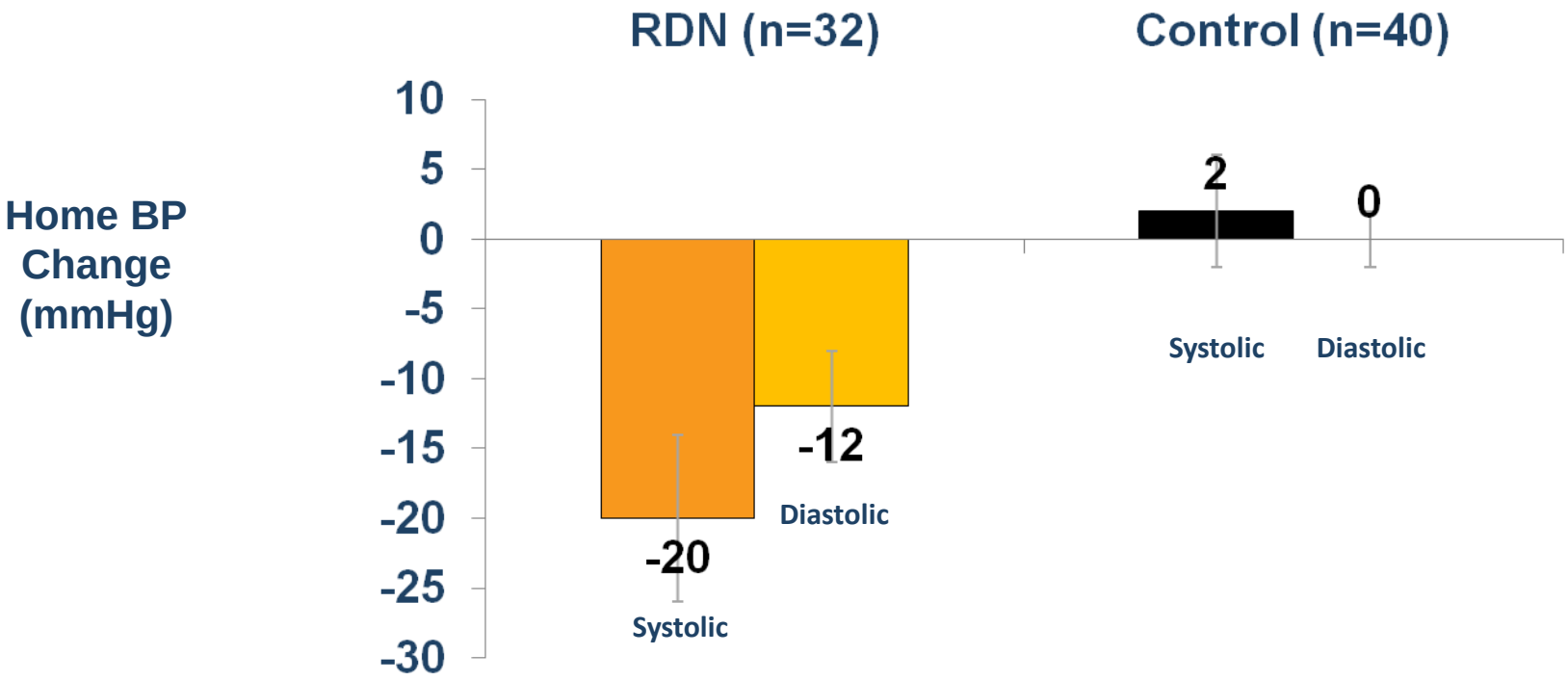
The Symplicity HTN-2 Trial

Office Systolic BP Distribution



Lancet 2010;376:1903-09

Home & 24 Hour Ambulatory BP



24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and **6-month**
- **RDN (n=20): -11/-7** mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- **Control (n=25): -3/ -1** mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Effects of Renal Denervation on BP Reduction in Symplicity HTN Trials

	Trials		
	Symplicity HTN-1[24]	Symplicity HTN-2[25]	Symplicity HTN-3[43]
Size (no.)	153	106	530
Mean baseline (mmHg)			
SBP	176	178	ND
DBP	98	96	
Decrease in BP			
1 month (mmHg)			
SBP	–20	–20	ND
DBP	–10	–7	
3 months (mmHg)			
SBP	–24	–24	ND
DBP	–11	–8	
6 months (mmHg)			
SBP	–25	–32	ND
DBP	–11	–12	
12 months (mmHg)			
SBP	–23	–28	ND
DBP	–11	–10	
24 months (mmHg)			
SBP	–31	ND	ND
DBP	–14		

Procedural Safety

No serious device or procedure related adverse events (n=52)

Minor adverse events

- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 post-procedural drop in BP
- 1 urinary tract infection
- 1 prolonged hospitalization for evaluation of paraesthesias
- 1 back pain treated with pain medications & resolved after one month

Other Safety

	RDN (n=49)	Control (n=51)
Composite CV Events		
Hypertensive event unrelated to non-adherence to medication	3	2
Other CV events	0	0
Other Serious AEs		
Transient ischemic attack	1	2
Hypertensive event after abruptly stopping clonidine	1	0
Hypotensive episode resulting in reduction of medications	1	0
Coronary stent for angina	1	1
Temporary nausea/edema	1	0

Procedural Safety

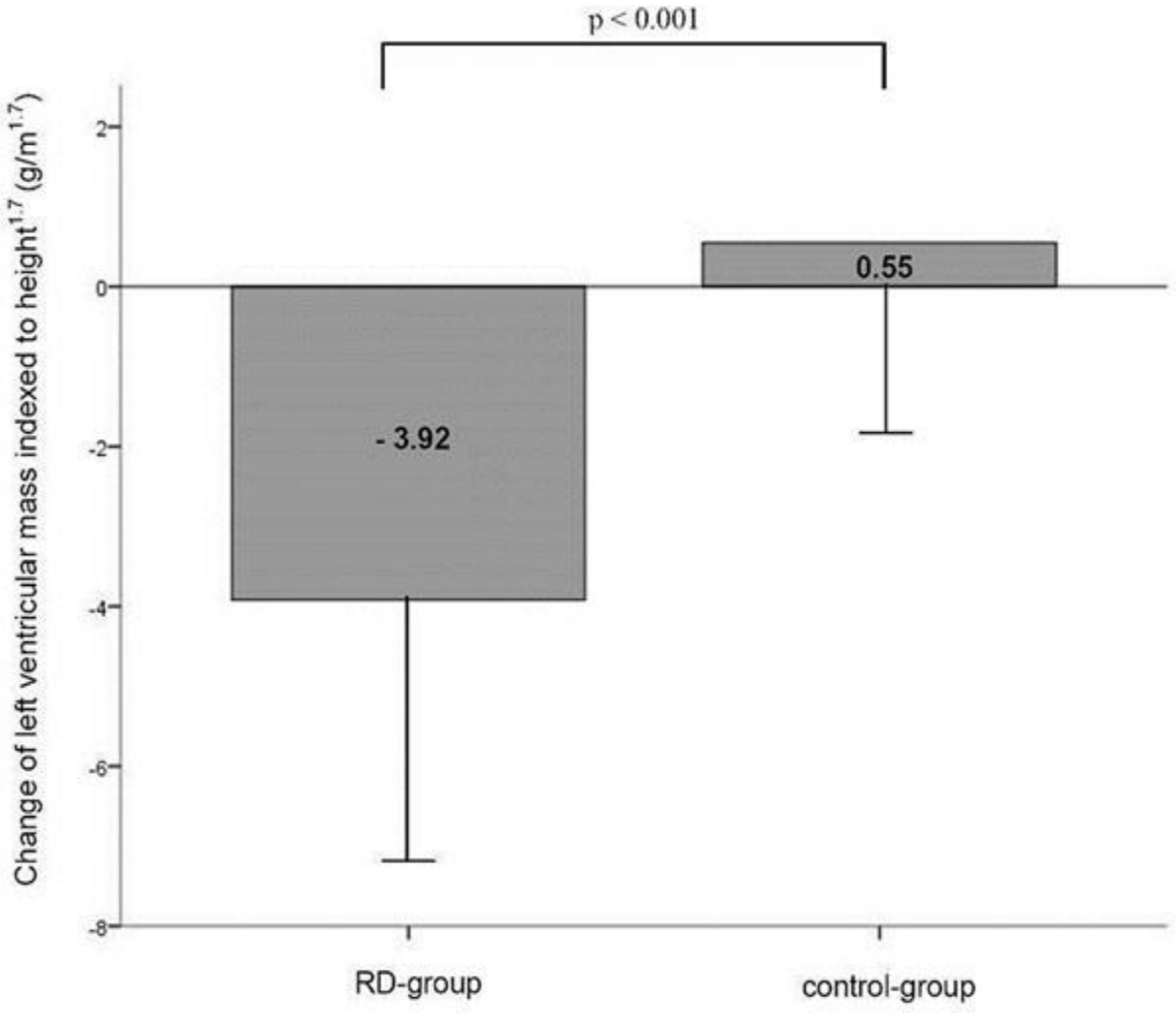
6-month renal imaging (n=43)

- No vascular abnormality at any RF treatment site
- 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

Renal Function

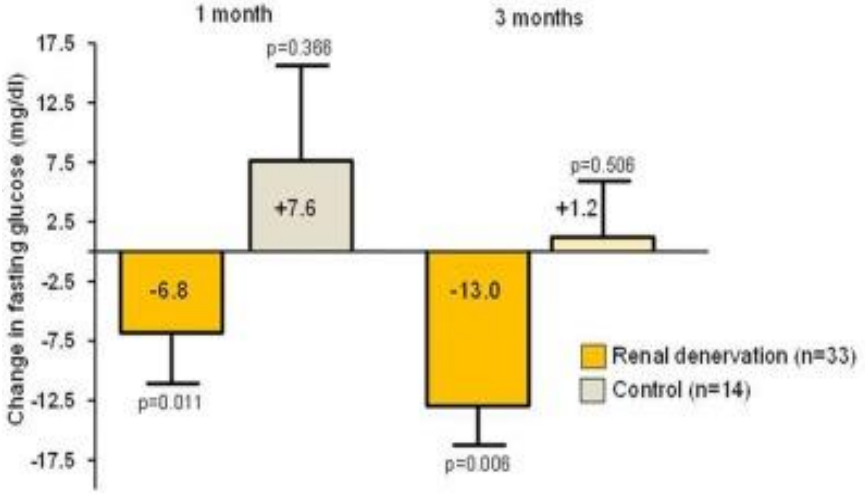
Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0, 0.1)	0.31

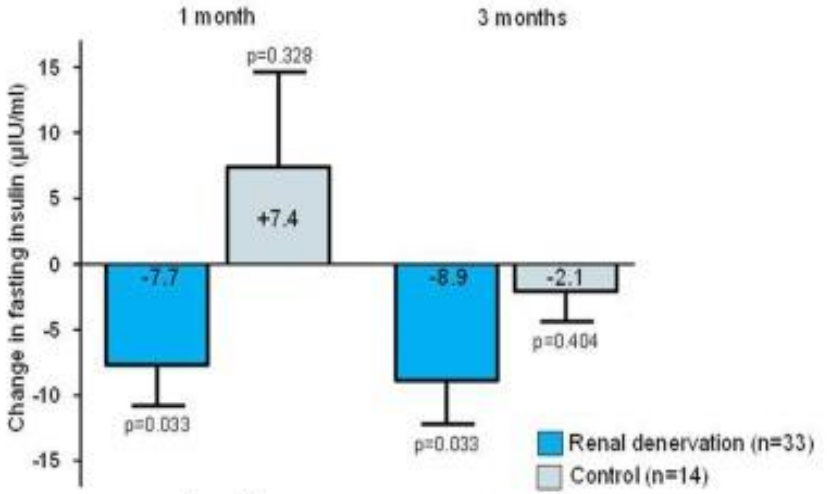
RSD; Impact of renal denervation on left ventricular mass

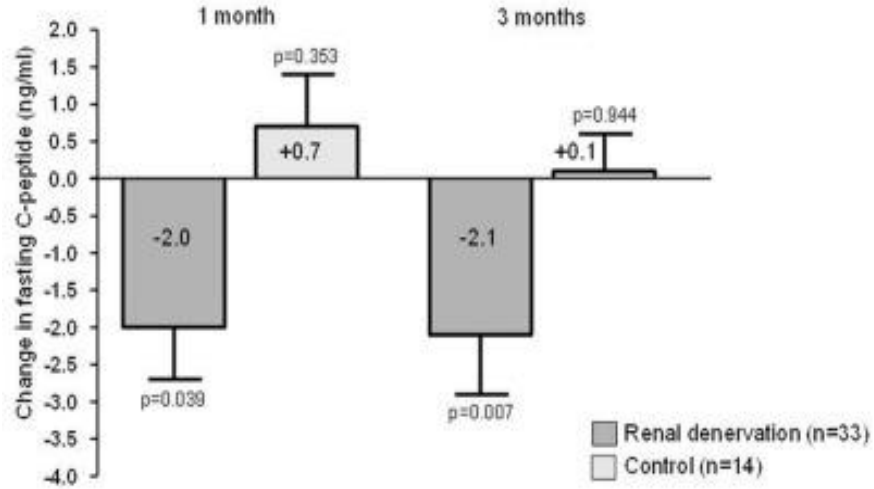


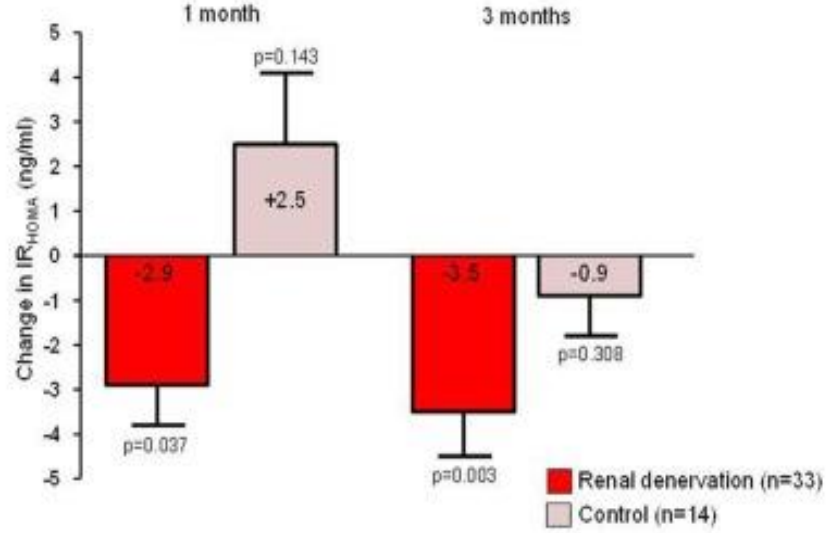
J Cardiovasc Magn Reson. 2013; 15(Suppl 1): E108.

Change in fasting glucose, insulin levels, C-peptide levels, and the HOMA-IR





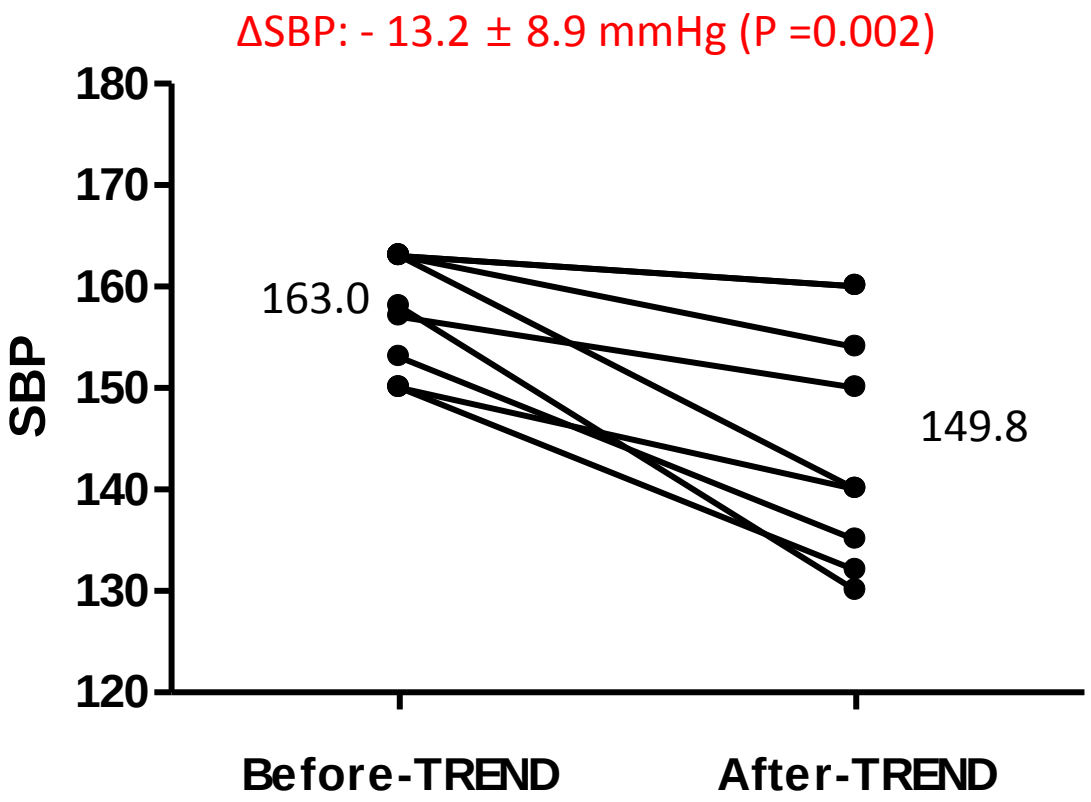




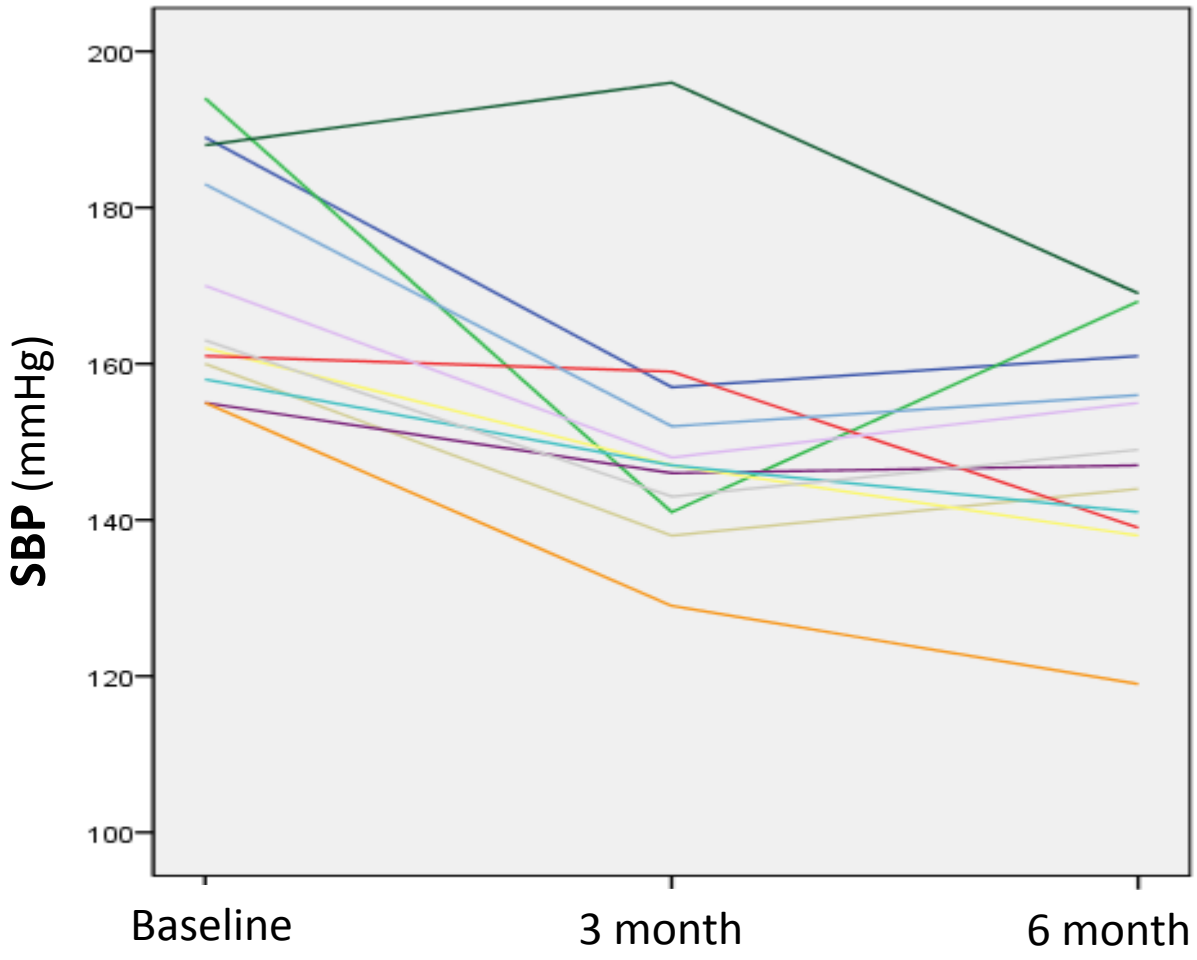
Front Physiol. 2012; 3: 10

O O 대 병원

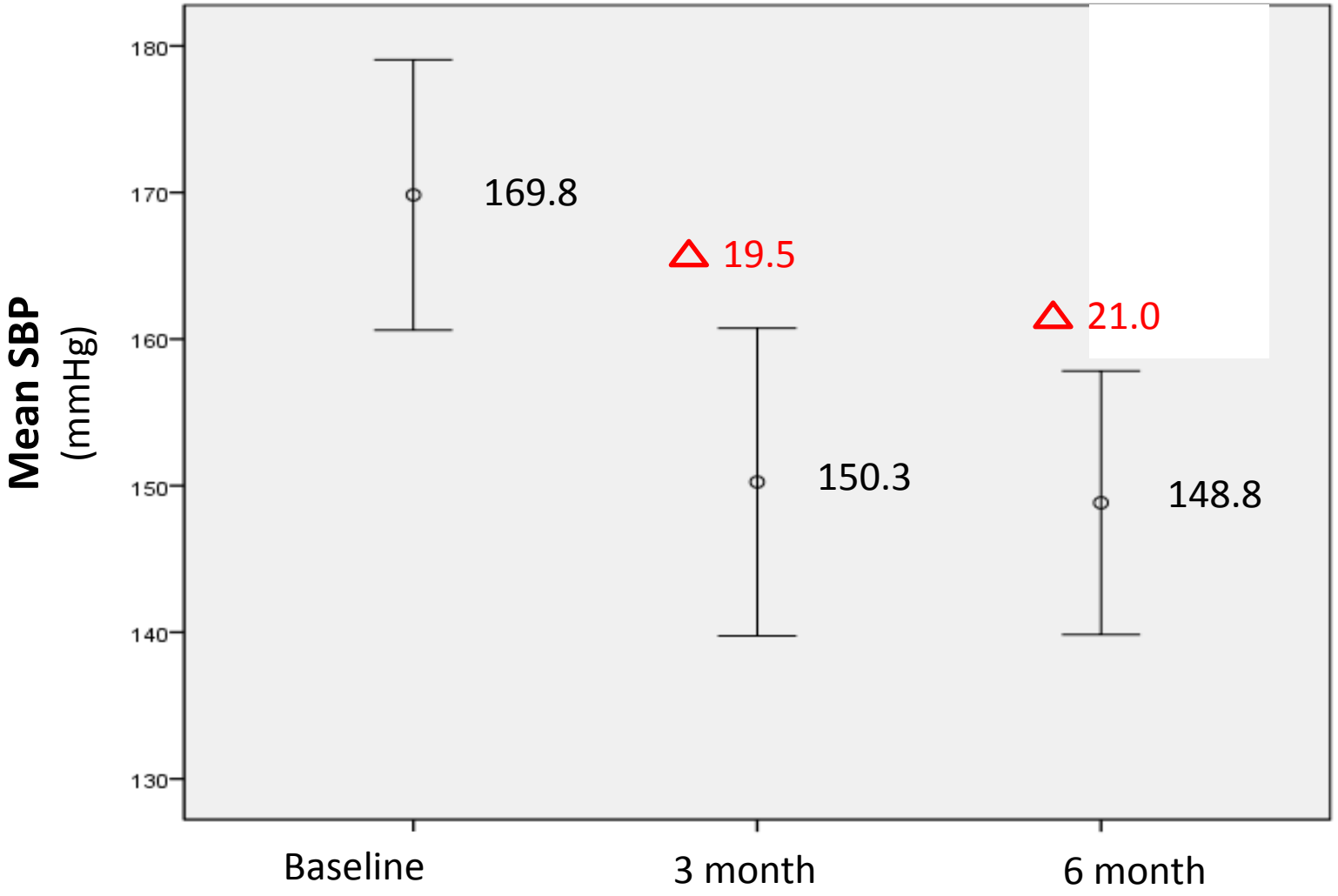
1달 뒤 강압 효과: 진료실 혈압



고려대 구로병원 RDS환자들의 6개월 결과



고려대 구로병원 RDS환자들의 6개월 mSBP변화



Clinical practice

Renal sympathetic denervation for the treatment of resistant hypertension with chronic renal failure: first-in-man experience

LUO Di, ZHANG Xin and LU Cheng-zhi

Hemodynamic characteristic at baseline, 1 month and 3 months after RSD

Variables	Baseline	1 month	3 months
Weight (kg)	72	70	70
BMI (kg/m2)	24.3	23.7	23.7
Office BP (mmHg)	205/85	160/80	145/75
ABPM (mmHg)	206.3/83.6	–	147.9/77
ADBP (mmHg)	214.0/84.3		149.7/78.7
ANBP (mmHg)	206.3/83.7		144.9/74.1
Heart rate (bpm)	57	62	65

Clinical characteristic at baseline, 1 month and 3 months after RSD

Variables	Baseline	1 month	3 months
BNP (pg/ml)	27906		8207
eGFR	7.86	12.41	12.56
EF (%)	55	–	58
LVEDD (mm)	58	–	53
Antihypertensive medication (mg/d)			
Amiodipine	10	5	5
Irbesartan-HCz	162.5	162.5	162.5
Arotinolol	10	10	0
Ebrantil (ml/h)	10	0	0

Future Targets of Renal Sympathetic Denervation Therapy

- Heart failure
- Sleep apnea
- Glycemic control
- Diuretic resistance
- Cardio-renal disorders

Conclusion

- Percutaneous catheter-based renal artery ablation for treatment of resistant hypertension have demonstrated a clinical benefit


Thanks for your attention !