Παθοφυσιολογία και κλινική προσέγγιση της ανθεκτικής υπέρτασης

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Hypertension control

BP control
248 studies, 44 rather satisfying

	Mean prevalence (standard deviation), expressed in %			
Sex	Hypertension	Awareness	Treatment	Control[a]
All countries				
Men	37.8 (10.9)	46.2 (16.2)	29.2 (14.2)	31.9 (13.0)
Women	32.1 (10.6)	58.5 (16.2)	40.6 (16.2)	36.8 (14.0)
Developed				
Men	40.8 (9.8)	49.2 (15.9)	29.1 (14.6)	33.2 (13.6)
Women	33.0 (10.1)	61.7 (13.6)	40.6 (15.0)	38.4 (13.5)
Developing				
Men	32.2 (10.6)	40.6 (15.5)	29.2 (13.8)	29.6 (118)
Women	30.5 (11.5)	52.7 (19.1)	40.5 (18.7)	34.0 (14.8)

Pereira, J Hypertens 2009


$100 for speeding and
$250 for misleading
the public
IM SEXY

BP control
248 studies, 44 rather satisfying

	Mean prevalence (standard deviation), expressed in %				
Sex	Hypertension	Awareness	Treatment	Control[a]	Control[b]
All countries					
Men	37.8 (10.9)	46.2 (16.2)	29.2 (14.2)	31.9 (13.0)	10.5 (9.3)
Women	32.1 (10.6)	58.5 (16.2)	40.6 (16.2)	36.8 (14.0)	16.9 (12.0)
Developed					
Men	40.8 (9.8)	49.2 (15.9)	29.1 (14.6)	33.2 (13.6)	10.8 (9.7)
Women	33.0 (10.1)	61.7 (13.6)	40.6 (15.0)	38.4 (13.5)	17.3 (11.4)
Developing					
Men	32.2 (10.6)	40.6 (15.5)	29.2 (13.8)	29.6 (118)	9.8 (8.6)
Women	30.5 (11.5)	52.7 (19.1)	40.5 (18.7)	34.0 (14.8)	16.2 (13.2)

Pereira, J Hypertens 2009

BP control
Copenhagen City Heart Study

Treatment of hypertension

- 1976-1978: 6.5%
- 2001-2004: 18.1%

Control of hypertension

- 1976-1978: 21% **1,4%**
- 2001-2004: 26% **4,7%**

Andersen, J Hypertens 2010

Deaths attributed to high blood pressure worldwide

	Deaths			
	Stroke	Ischaemic heart disease	Hypertensive disease	Other cardiovascular disease
East Asia and Pacific	951	471	254	97
Europe and central Asia	709	1024	100	150
Latin America and the Caribbean	144	169	71	43
Middle East and north Africa	71	155	61	29
South Asia	449	711	62	75
Sub-Saharan Africa	179	148	50	52
Low-income and middle-income economies*	2502	2678	598	445
High-income economies	418	668	109	197
World†	2921	3346	706	642

7.6 million per year

Lawes, Lancet 2008

Are we doing the same ???

Resistant hypertension

Resistant Hypertension

Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic.

JNC-7 2003

Prevalence of resistant hypertension

Persell, NHANES: 12.8 %

De la Sierra, Spain: 12.2 %

Hypertension 2011


L'C

Pseudoresistance

Table 1 Causes of Pseudo-Resistant Hypertension

Improper blood pressure measurement
Heavily calcified or arteriosclerotic arteries that are difficult to compress (in elderly persons)
White-coat effect
Poor patient adherence
Side effects of medication
Complicated dosing schedules
Poor relations between doctor and patient
Inadequate patient education
Memory or psychiatric problems
Costs of medication
Related to antihypertensive medication
Inadequate doses
Inappropriate combinations
Physician inertia (failure to change or increase dose regimens when not at goal)

Bakris, JACC 2008

Truly resistant hypertension

ABPM or HBP

• Brown	2001	85/118	72%
• Muxfeldt	2005	313/497	63%
• Douma	2008	192/289	67%
• De Souza	2010	175/236	75%
• Douma	2008	1.286/1.913	66%
• De la Sierra	2011	8295	62,5%

Drug – induced hypertension

TABLE 2: Drugs inducing or exacerbating hypertension.

(i) Nonsteroidal anti-inflammatory drugs
(ii) Oral contraceptives
(iii) Sympathomimetics
(iv) Illicit drugs
(v) Glucocorticoids
(vi) Mineralocorticoids
(vii) Cyclosporine, tacrolimus
(iix) Erythropoietin
(ix) Herbal supplements
(x) VEGF inhibitors

Doumas, Int J Hypertens 2011

Prevalence of resistant hypertension

Persell, NHANES: 12.8 %

De la Sierra, Spain: 12.2 %

Evaluating the True Prevalence of Resistant Hypertension

To the Editor:

We are grateful to de la Sierra et al[1] and Persell[2] for their worthy effort to provide significant information about the prevalence of true resistant hypertension.[1,2] These important articles fill a long-lasting gap in the hypertension field, yet we believe that several concerns interfere in the evaluation of this phenomenon in addition to those discussed in the accompanying editorial comments[3,4] and should be cautiously acknowledged.

37.5% in a previous study.[1] Even with modest estimations, subtraction of white-coat resistant hypertension would shatter the reported prevalence of resistant hypertension. Second, exclusion of secondary hypertension was not warranted, although such forms are highly prevalent in resistant patients, especially primary aldosteronism in >10%,[7] obstructive sleep apnea, and drug-induced secondary hypertension. It would be very interesting to know whether patients with secondary hypertension or concomitant administration of NSAIDS and oral contraceptives were included in the study population. Third, salt intake is not

Douma, Hypertension 2011

Estimated total number of adults with hypertension

Measure	n
Total number worldwide in 2000	972 million
Total number in economically developed countries in 2000	333 million
Total number in economically developing countries in 2000	639 million
Total number worldwide in 2025	1.56 billion

Kearney PM et al. *Lancet* 2005; 365:217-223.

Resistant hypertension Management

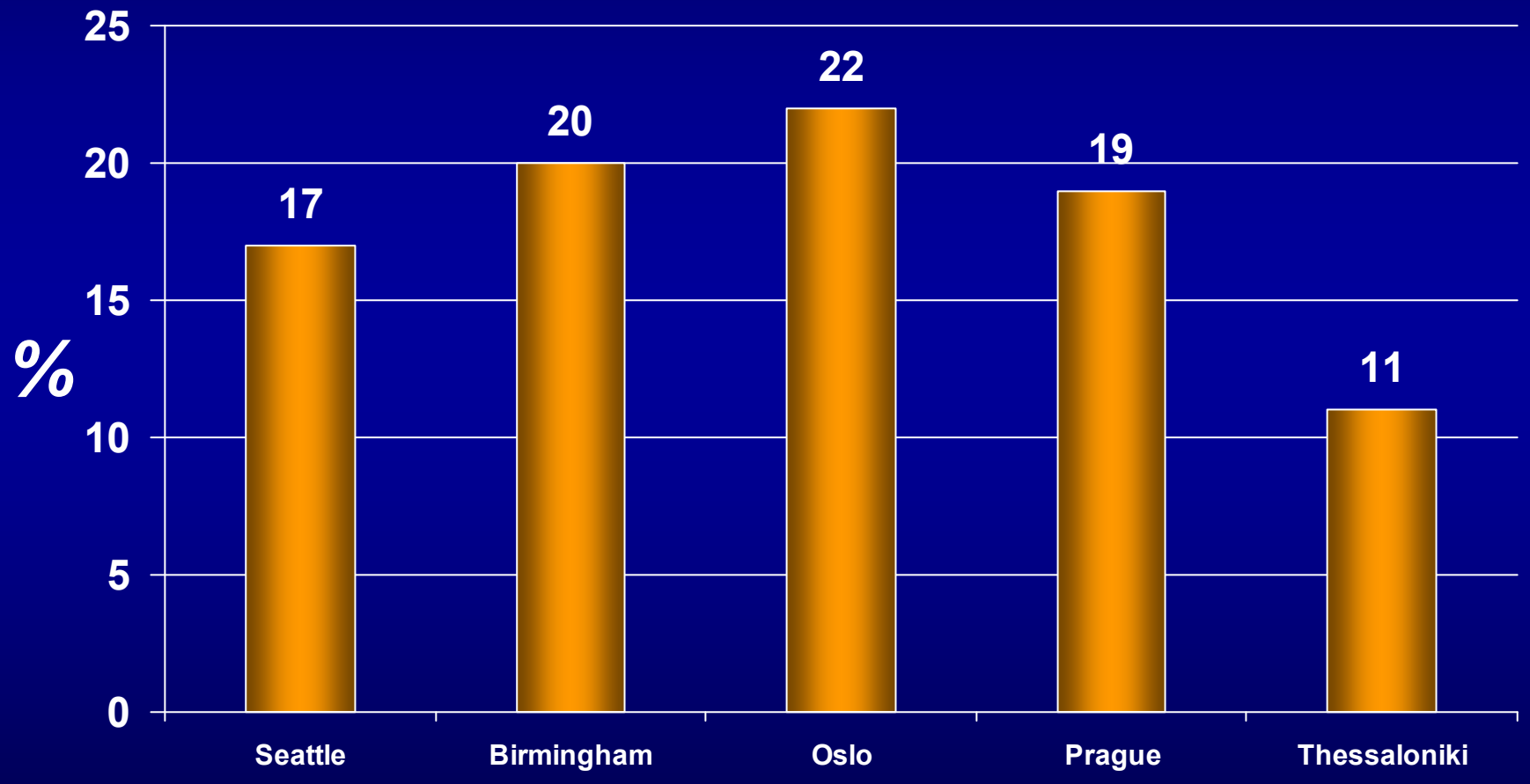
Common Secondary Causes of Resistant Hypertension and Rational for Treatment

Int J Hypertens 2011

Charles Faselis,[1] Michael Doumas,[1] and Vasilios Papademetriou[2]

- **Chronic kidney disease**
- **Renovascular hypertension**
- **OSAS**
- **Primary aldosteronism**

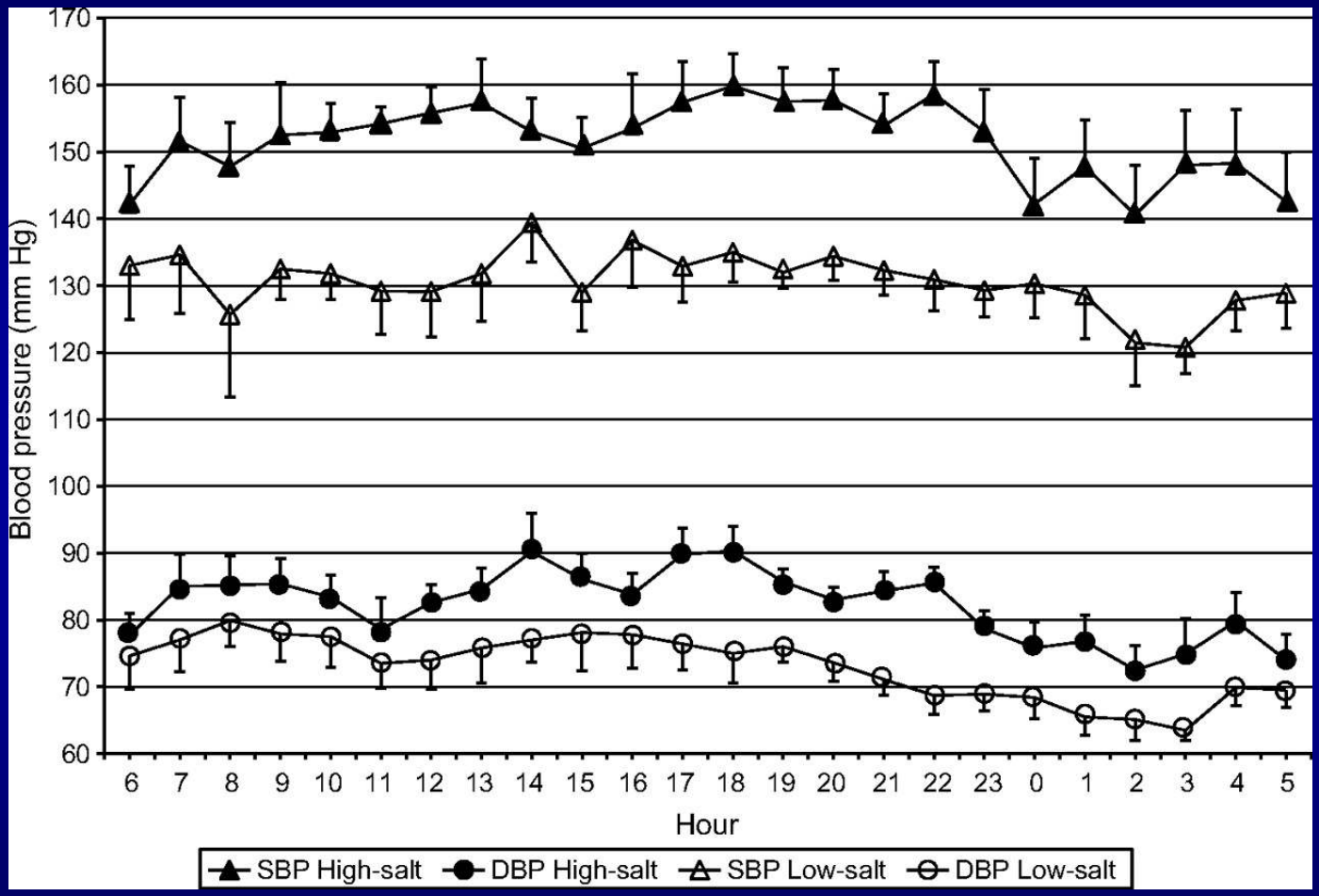
PREVALENCE OF PRIMARY ALDOSTERONISM IN PATIENTS WITH RESISTANT HYPERTENSION



Lifestyle Modifications

Modification	Approximate SBP Reduction (range)
Weight Reduction	5-10 mmHg/10kg
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

Comparison of 24-hour ambulatory blood pressure values during low- and high-salt diet



-22.7mmHg

-9.1mmHg

Pimenta, E. et al. Hypertension 2009;54:475-481

DIETARY SODIUM INTAKE

Table. Comparison of Two Trials of Sodium Reduction

Feature	Trial by Pimenta et al[4] (n=12)	DASH-Sodium Trial (Subset of Participants With Untreated Hypertension)[3] (n=168)
% on antihypertensive medication	100%	0%
% black	50%	61%
% female	67%	63%
Mean±SD age, y	55.5±9.4	50.3±10.6
Mean±SD baseline sodium excretion, mmol/day	194.7±68.6	153.4±74.6
Highest and lowest sodium levels provided during feeding, mmol/day	250 vs 50	150 vs 50
Mean±SD baseline systolic BP, mm Hg	145.8±10.8	143.0±7.8
Mean±SD baseline diastolic BP, mm Hg	83.9±11.2	88.5±4.5
Mean (95% CI) systolic BP reduction, mm Hg	22.7 (11.8, 33.5)	8.3 (6.6, 10.0)
Mean (95% CI) diastolic BP reduction, mm Hg	9.1 (3.1, 15.1)	4.1 (3.3, 5.4)

Data taken from Trial by Pimenta et al[4] of patients with resistant hypertension and the DASH-Sodium Trial[3] of patients with untreated hypertension.

Pimenta, E. et al. Hypertension 2009;54:475-481

Evaluation of Resistant Hypertension

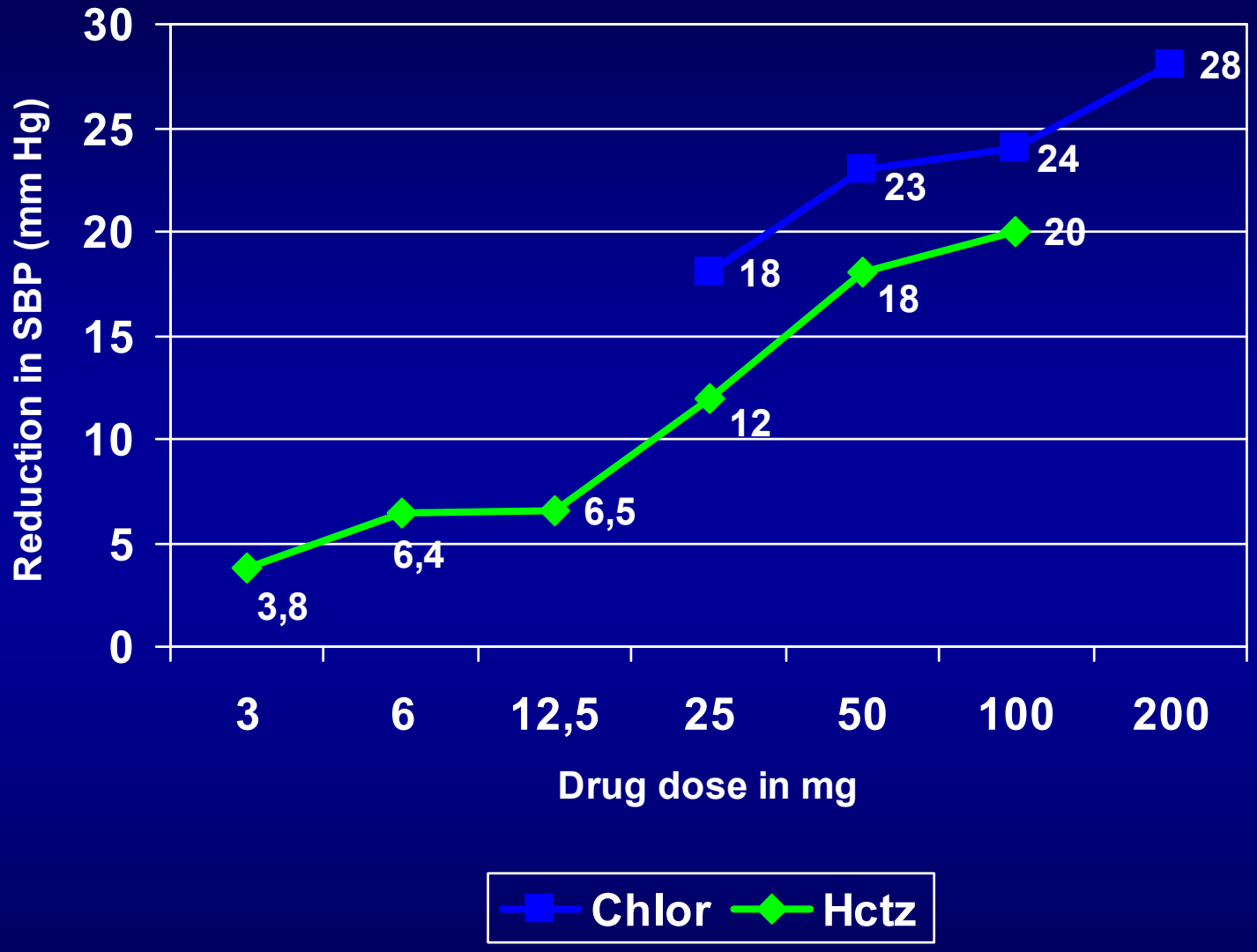
- Measurement
- Adherence to treatment
- Clinical inertia
- Lifestyle
- Drug-induced
- Secondary hypertension

Doumas, Int J Hypertens 2011

Resistant hypertension
Drug therapy

Approach to Therapy of Resistant Hypertension: Additional Pharmacologic Therapy

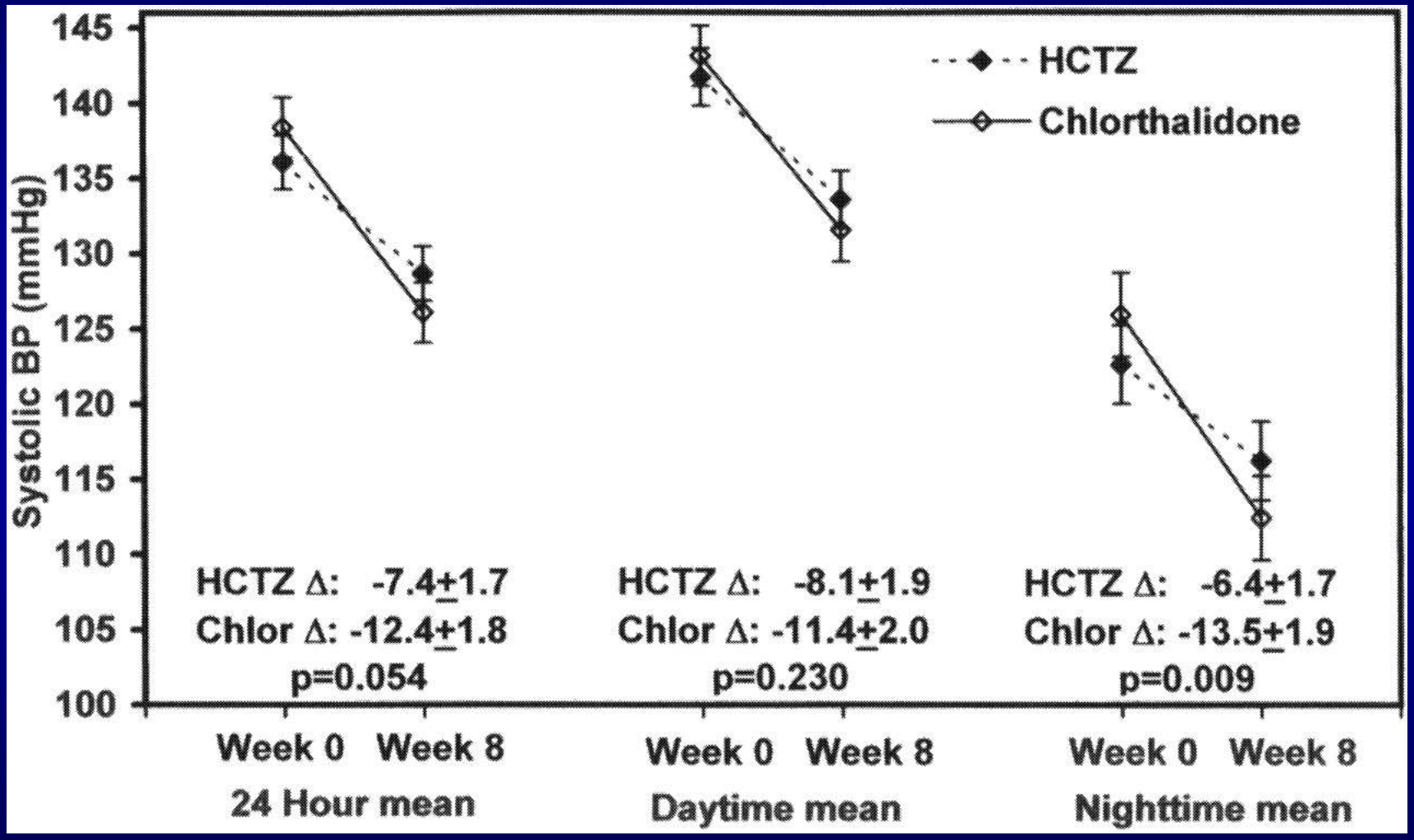
- Thiazides
- Spironolactone
- Endothelin receptor antagonist (Darusentan)
- Clonidine
- α1-adrenergic receptor antagonist
- Minoxidil
- Reserpine
- Hydralazine



Effects of HCTZ and chlorthalidone on SBP as a function of daily dose (mg)

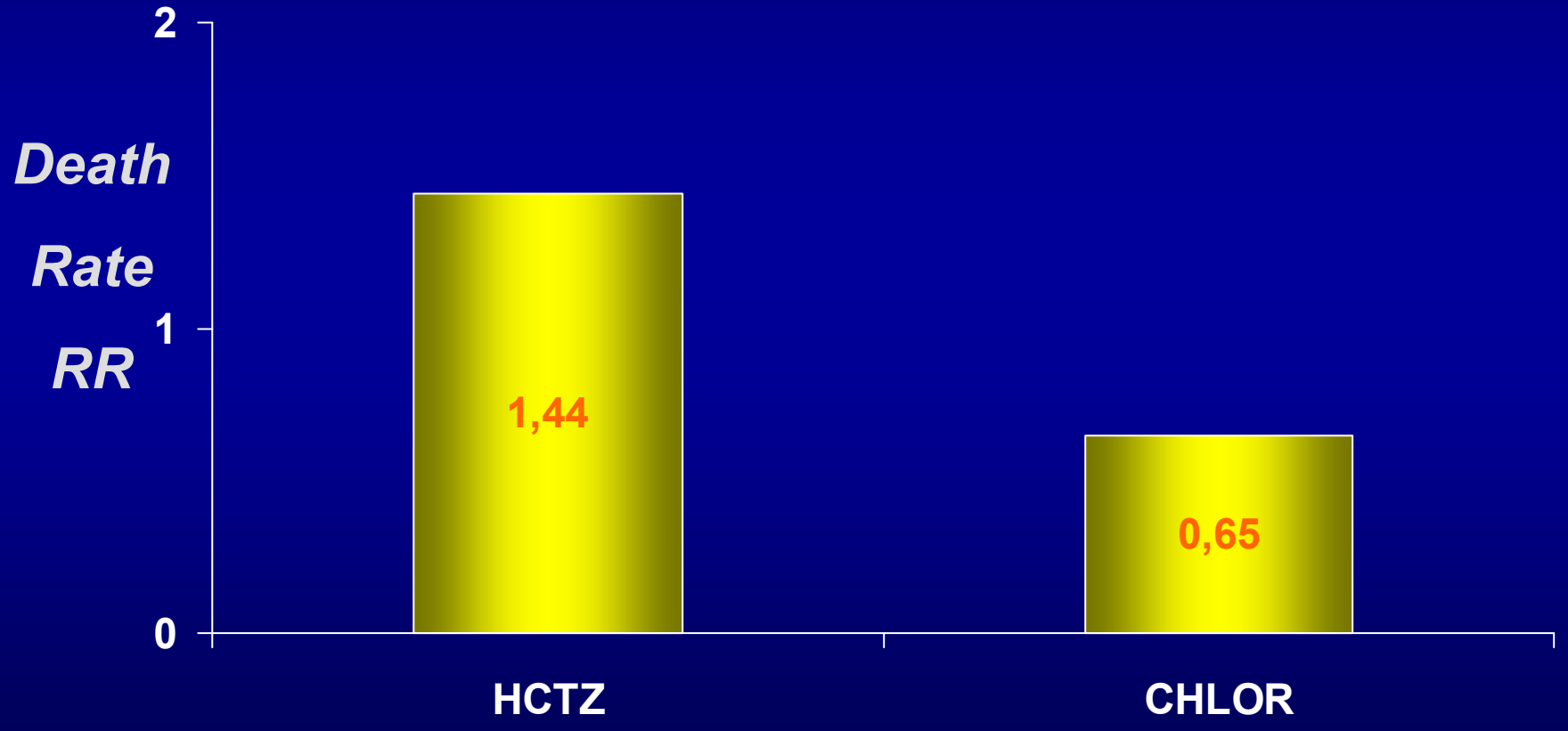
Carter BL. Hypertens 2004; 43:4-9

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



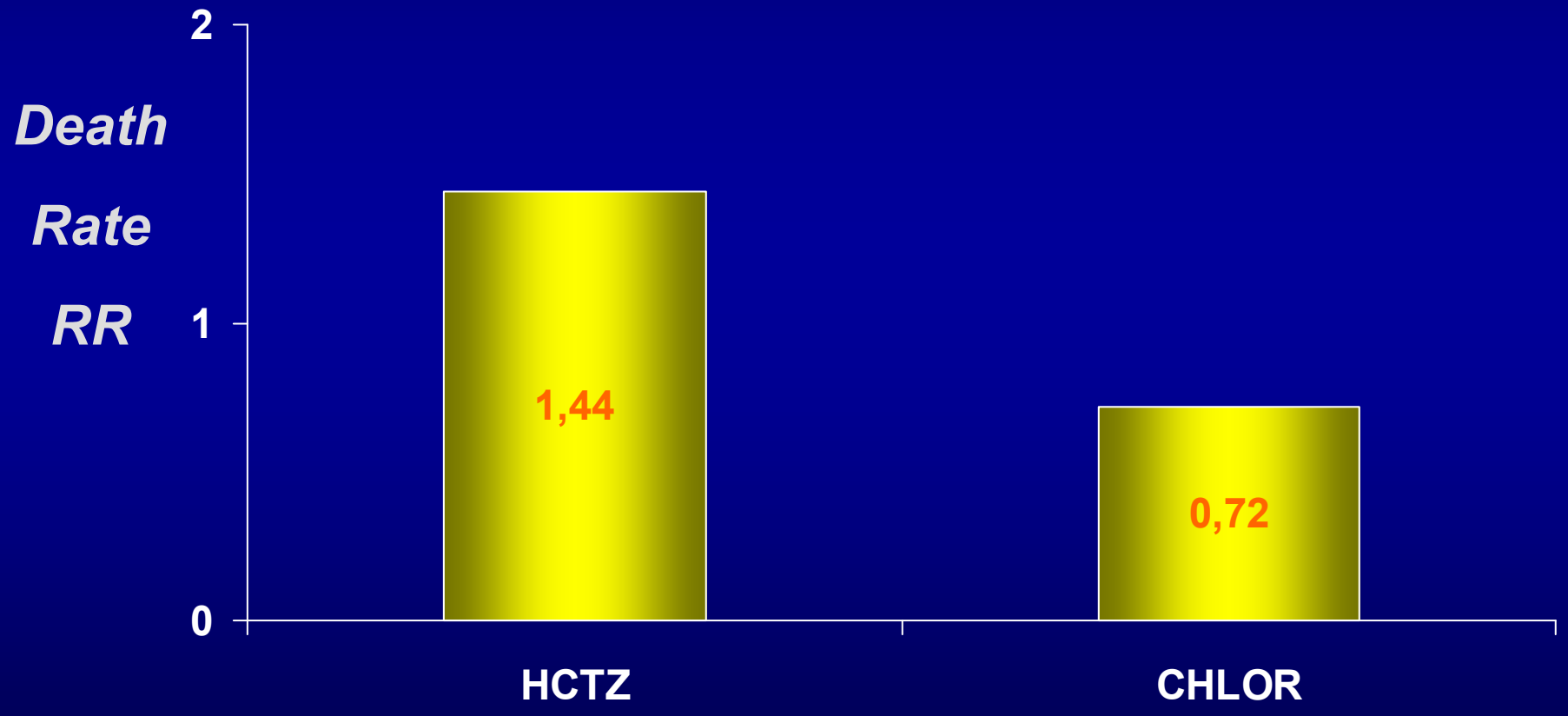
Ernst, M. E. et al. Hypertension 2006

Chlorthalidone vs hydrochlorothiazide



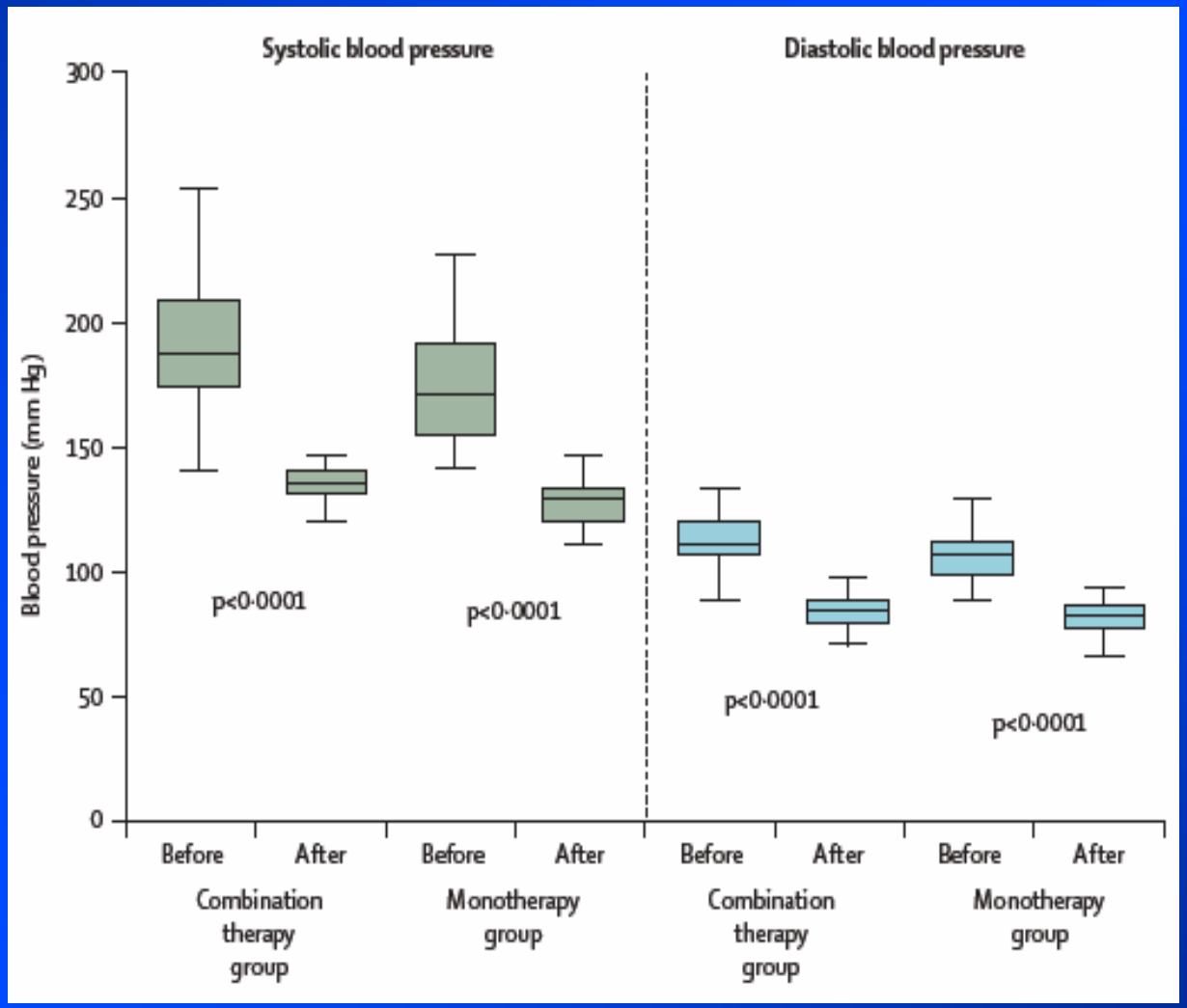
MRFIT, Circulation 1990

Switch of hydrochlorothiazide to chlorthalidone



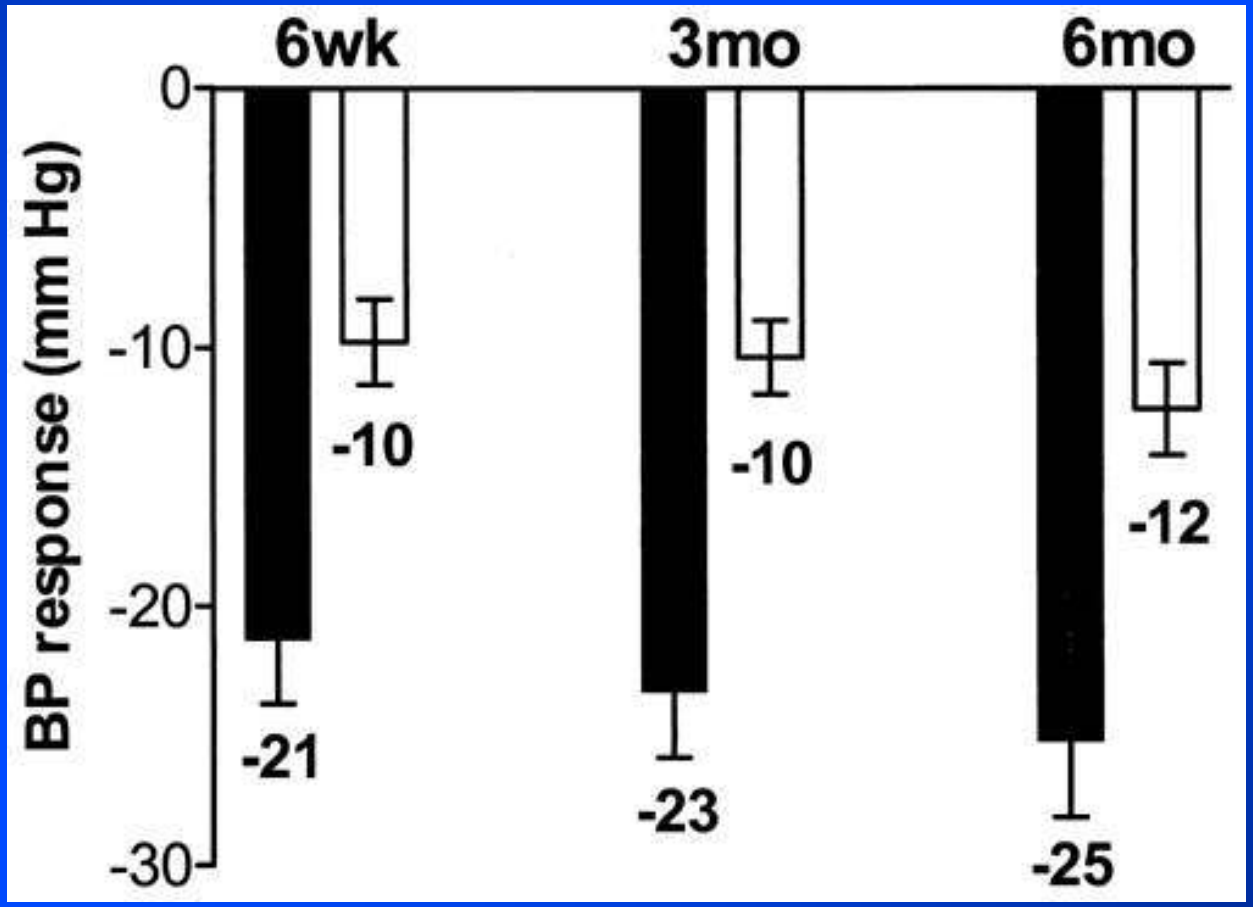
MRFIT, Circulation 1990

Primary aldosteronism



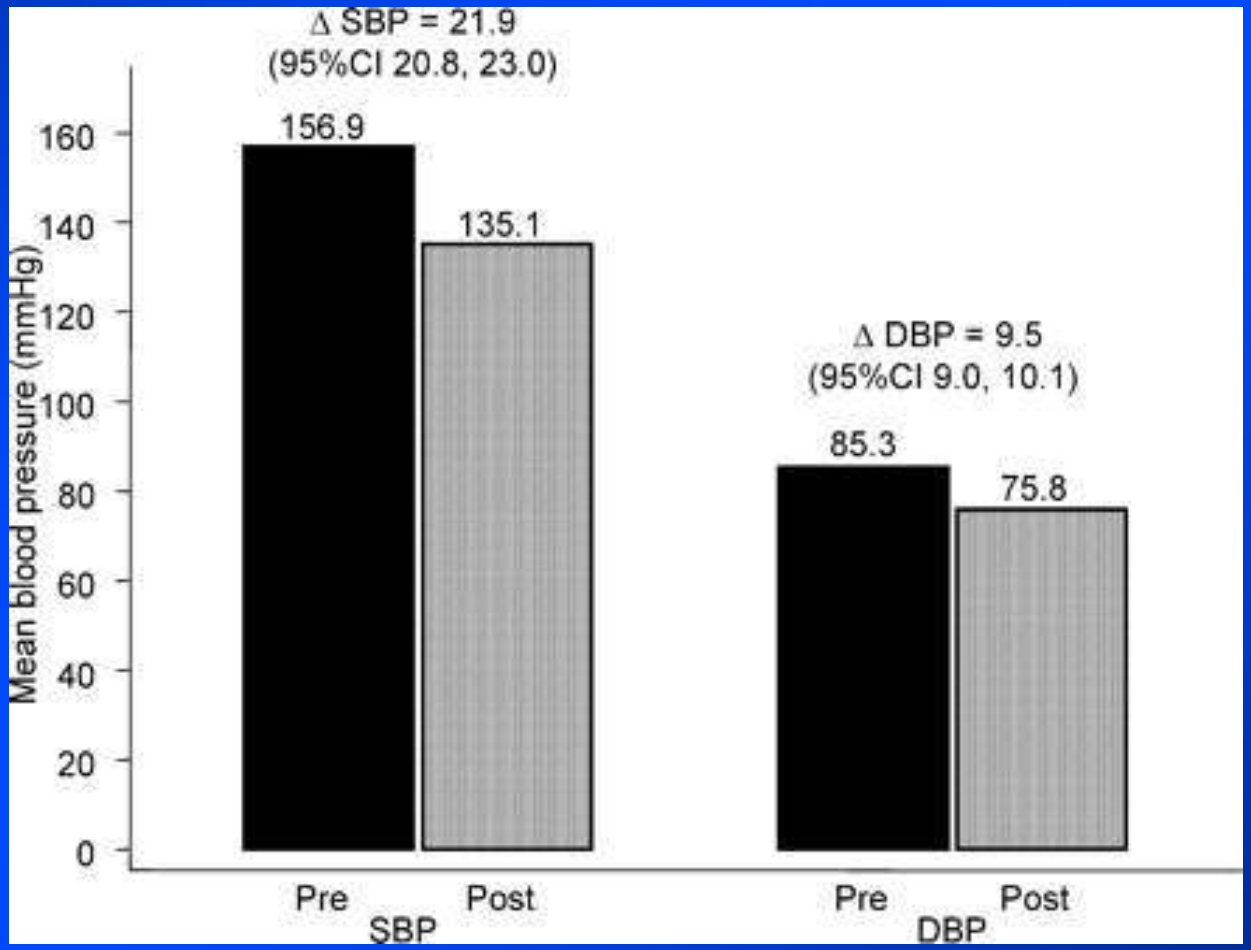
Douma, Lancet 2008

Resistant hypertension
Small clinical studies



Nishizaka, Am J Hypertens 2003

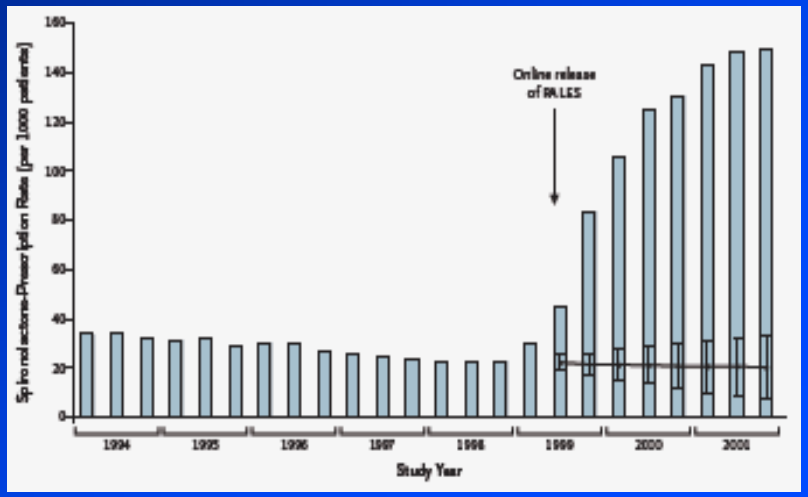
Resistant hypertension
ASCOT trial

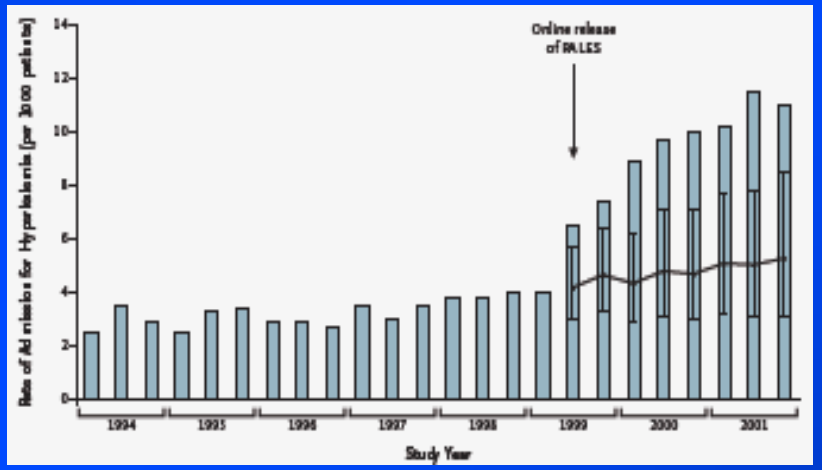


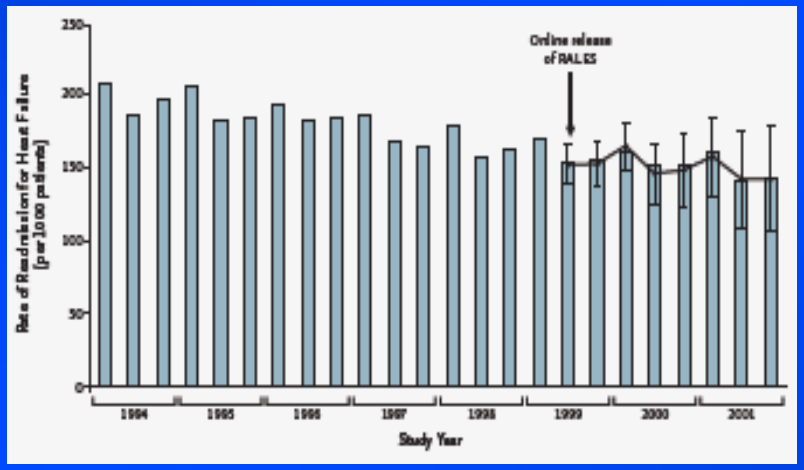
Chapman, Hypertension 2007

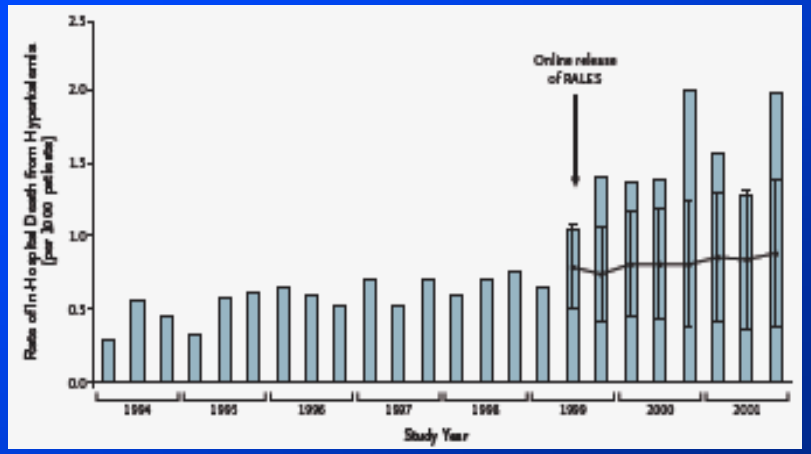

CBS
NEWS

Adverse effects - Hyperkalemia









Juurlink, NEJM 2004

Hyperkalemia – Renal function

- Check serum potassium at **3d, 1w, 3w, 3 to 6m** according to potassium levels
- Check serum creatinine at the same timepoints

- Extreme caution when GFR<30 or Creatinine **>2.5**mg/dl or potassium >4.8
- Stop if creatinine >4 or potassium >6mg/dl

Doumas,2011

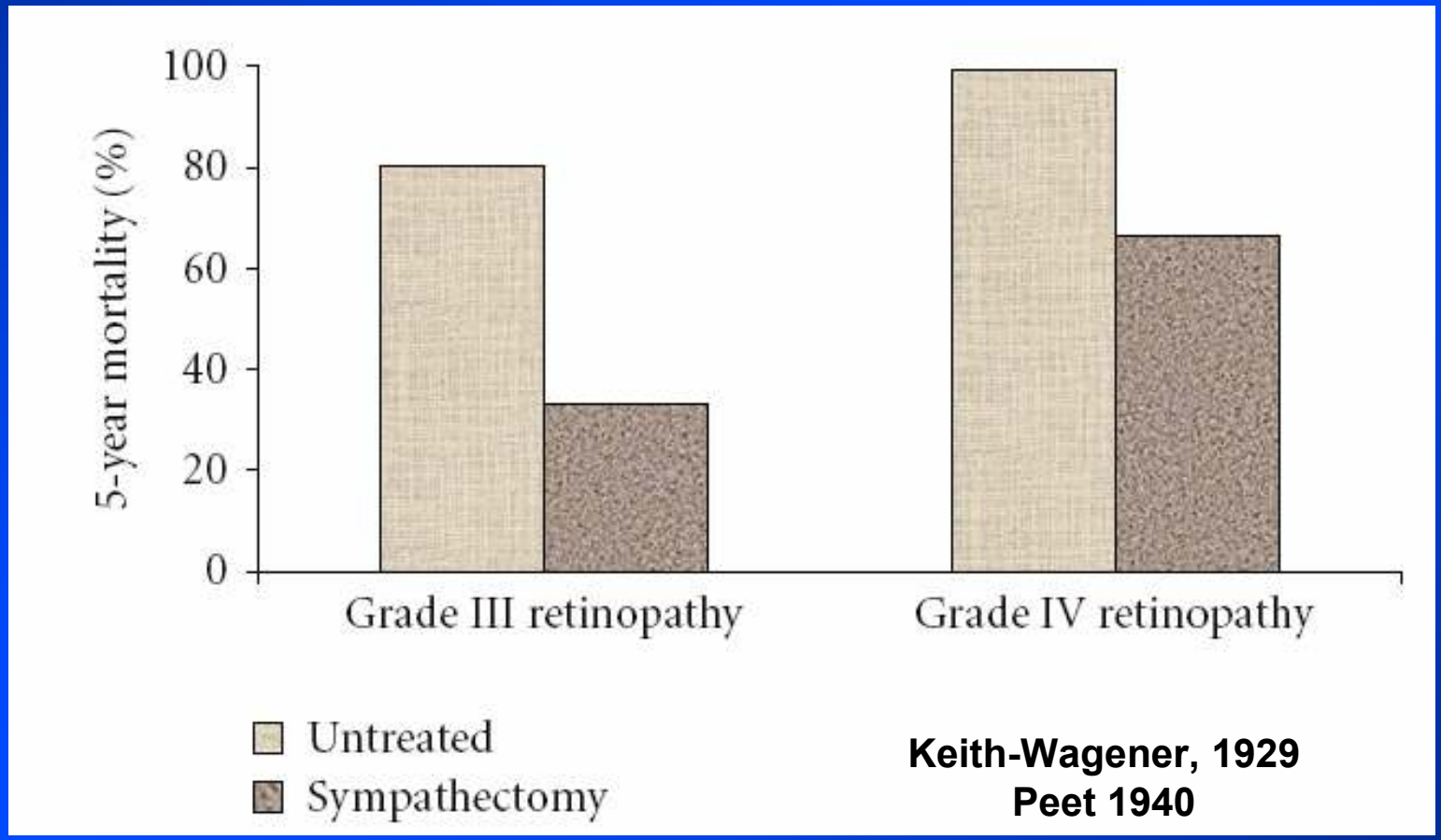

BP is still high
You need one more drug.
I think it's the eighth one.
I don't know what to do next !!!
What about interventional therapy??? It's all over the news. Have you heard ???


NEVER EVER
GIVE UP

Yes
We can !!!

Resistant hypertension
Interventional therapy

Malignant hypertension - Sympathectomy



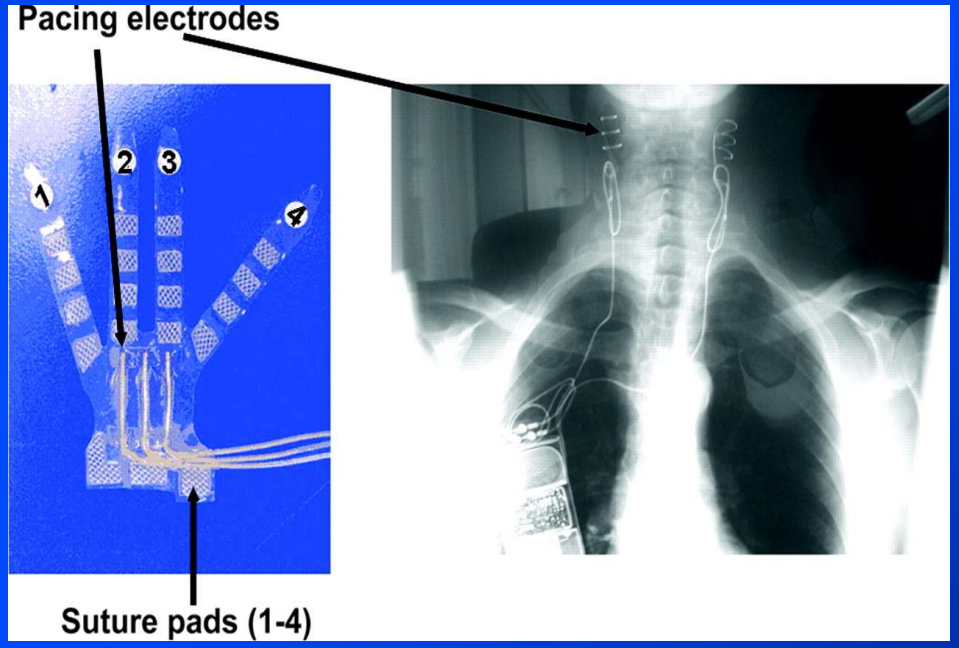
Keith-Wagener, 1929
Peet 1940

Doumas, Int J Hypertens 2011

Carotid baroreceptor activation

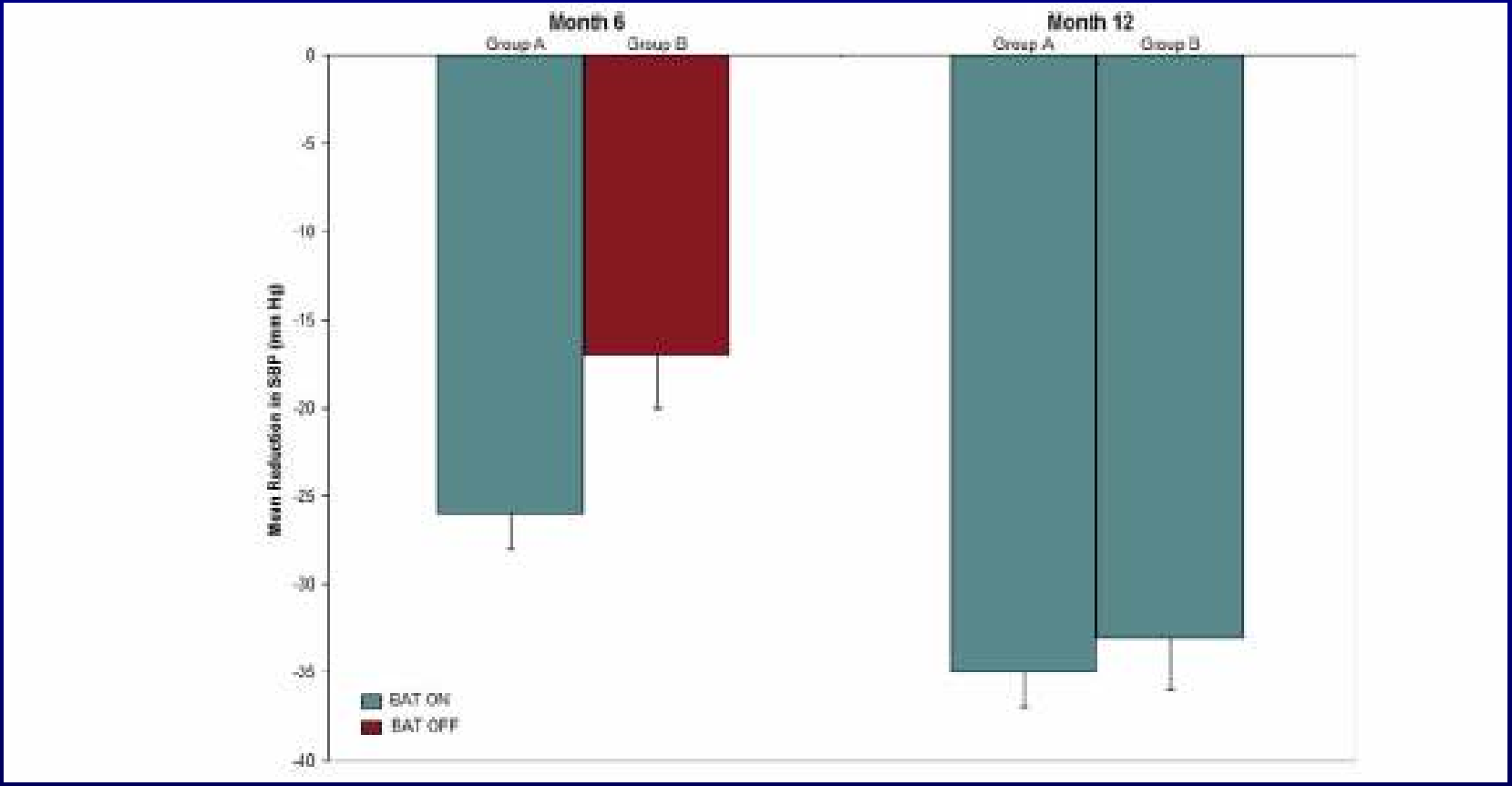
Carotid baroreceptor stimulation as a therapeutic target in hypertension and other cardiovascular conditions

Michael Doumas, Daqing Guo & Vasilios Papademetriou[†]
[†]*University Medical Center, Hypertension and Cardiovascular Research Clinic, Veterans Affairs and Georgetown Washington DC*



Expert Opinion on Therapeutic Targets, 200

Blood Pressure Reduction with Baroreceptor Stimulation Therapy



Bisognano, JACC 2011

Carotid baroreceptor stimulation for the treatment of resistant hypertension and heart failure

Michael Doumas, Charles Faselis, Vasilios Papademetriou

Curr Hypertens Reports 2012; 00:000-000

Efficacy

Safety

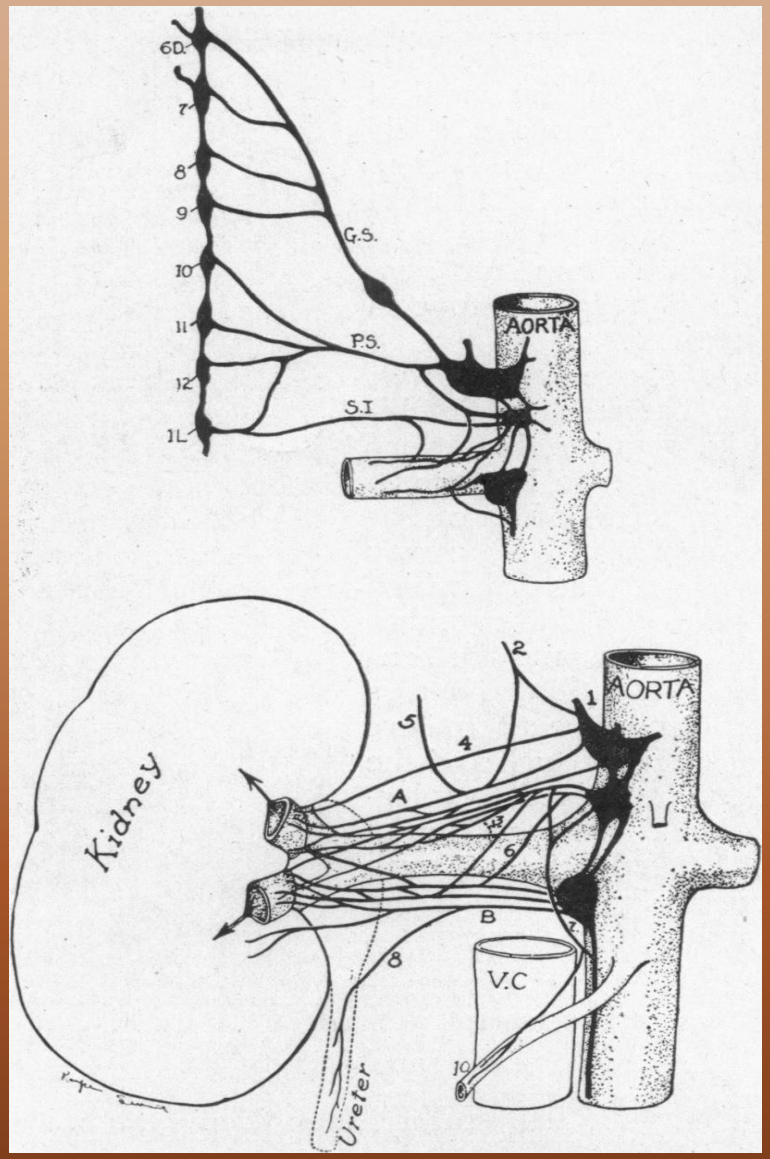
Battery improvements

Diastolic heart failure

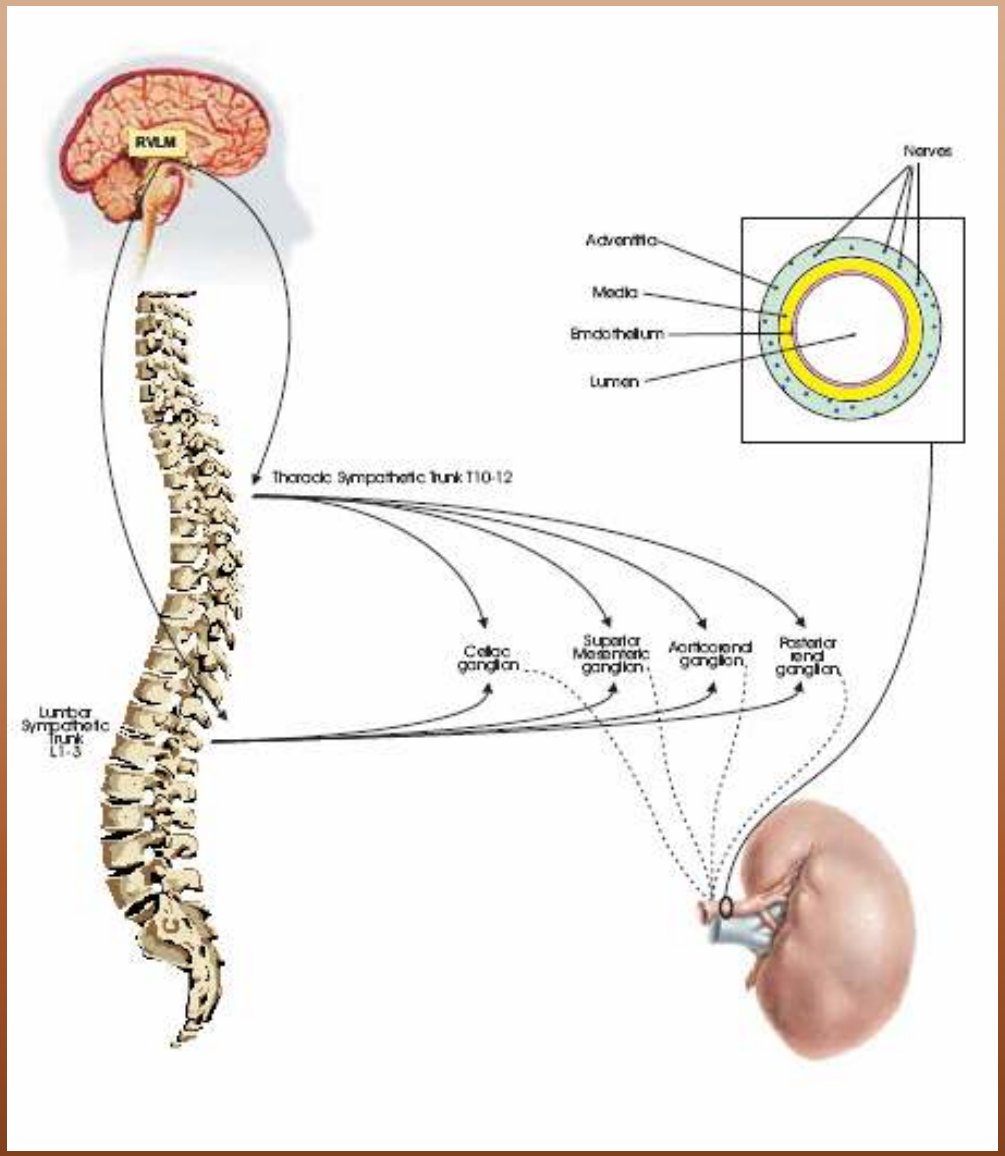
Doumas, Curr Hypertens Rep 2012

Renal sympathetic denervation

Renal Nerves and Resistant/Malignant Hypertension

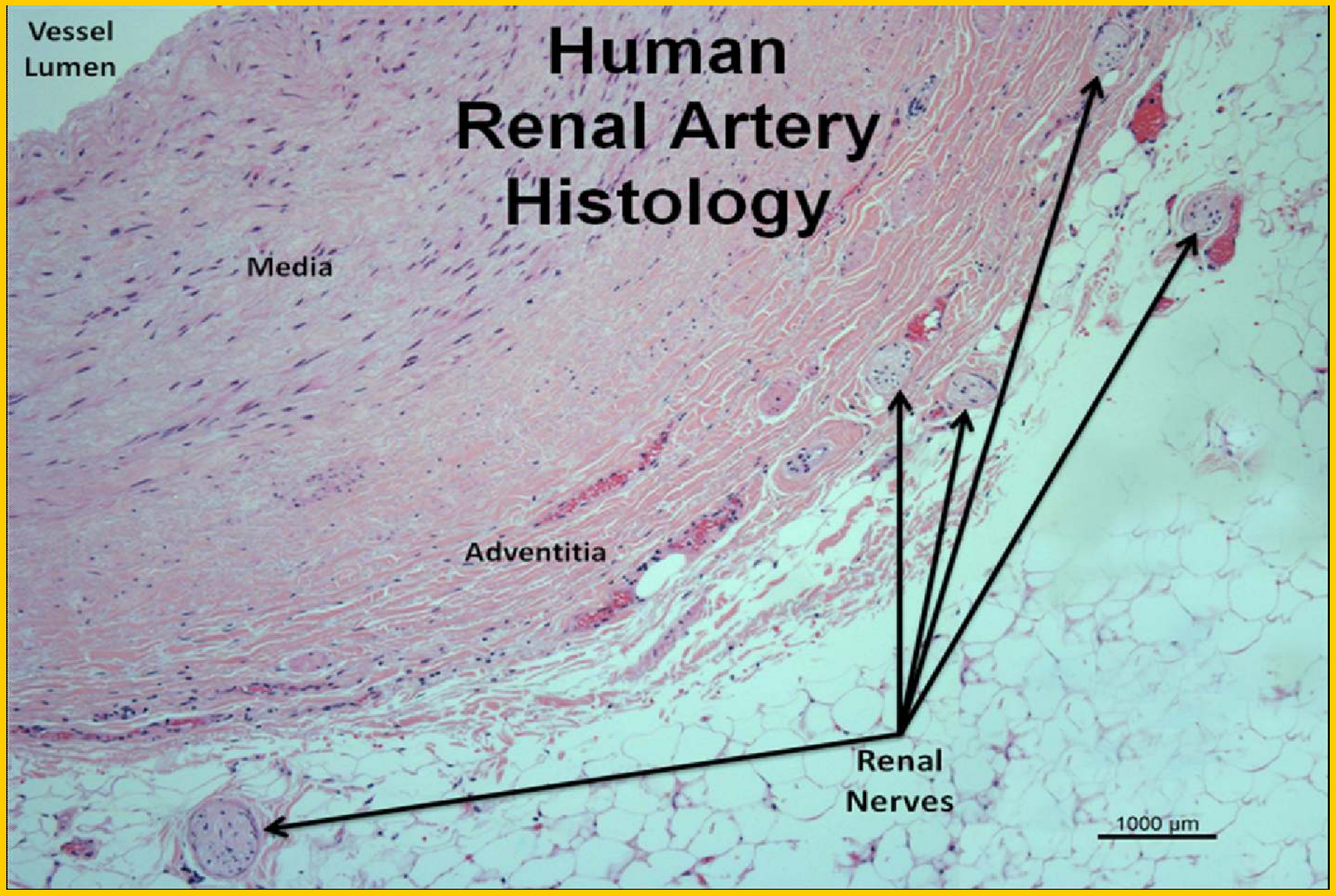


Gibson, Calif Med1936



Doumas, Am J Cardiol 2010

Renal sympathetic denervation

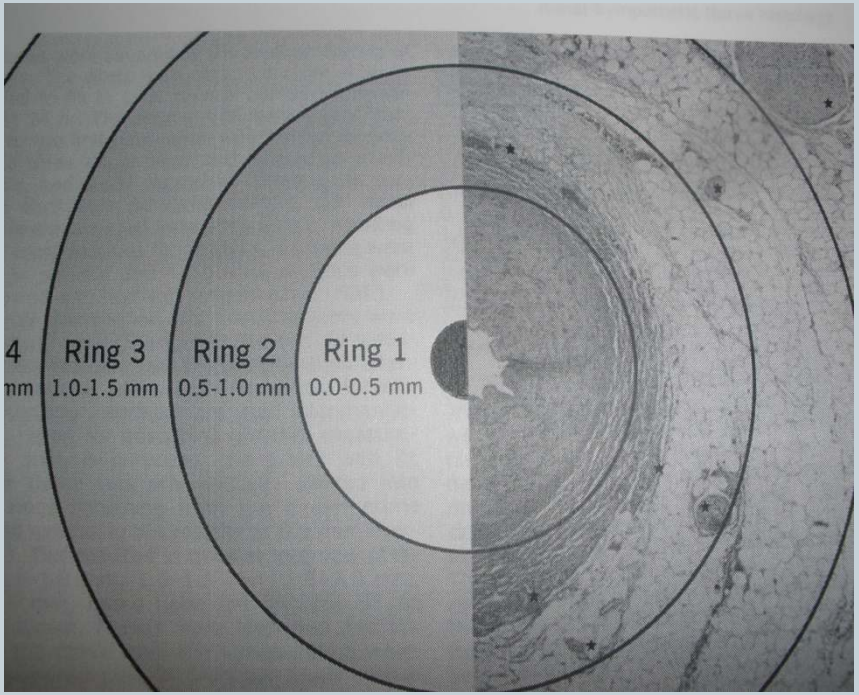


Micro-anatomy of Renal Nerves

Distance from Lumen Center	Schematic artery cross section

- % Fibers

1.	0-0.5 mm	1.0%
2.	0.5-1.0 mm	48.3%
3.	1.0-1.5mm	25.6%
4.	1.5-2.0mm	15.5%
5.	2.0-2.5mm	9.5%



Renal efferent *activation*

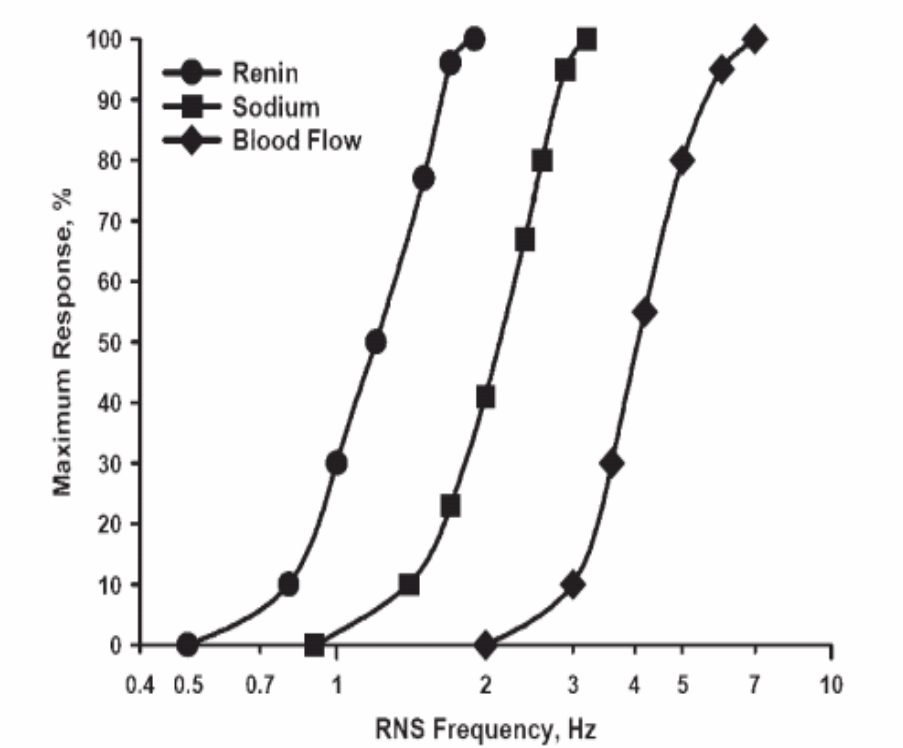


Fig. 1. The relationship between renal nerve stimulation (RNS) frequency and maximum response of renin secretion rate (RSR) (increase), urinary sodium excretion (decrease) and renal blood flow (RBF) (decrease). [From DiBona GF (10a).]

Frequency-dependent

- Increase in renin secretion
- Decrease in Urinary sodium excretion
- Decrease in Renal Blood Flow

DiBona, Am J Physiol 2010

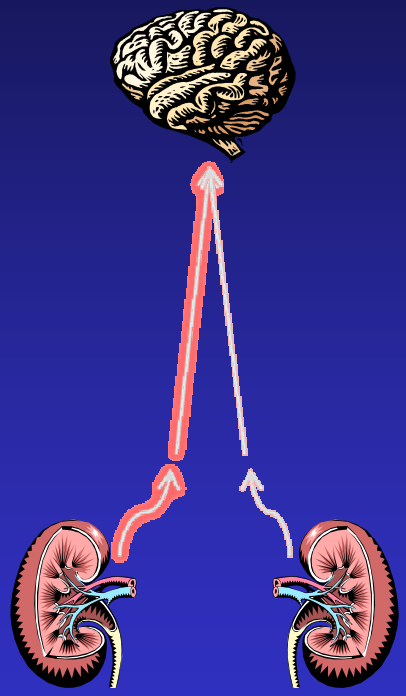
Renal efferent *denervation*

- Marked Natriuresis
- Increase in Urinary Volume
- Increase in Renal Blood Flow
- Decrease in PRA and renin release
- Decrease in noradrenaline spillover

DiBona, Am J Physiol 2010

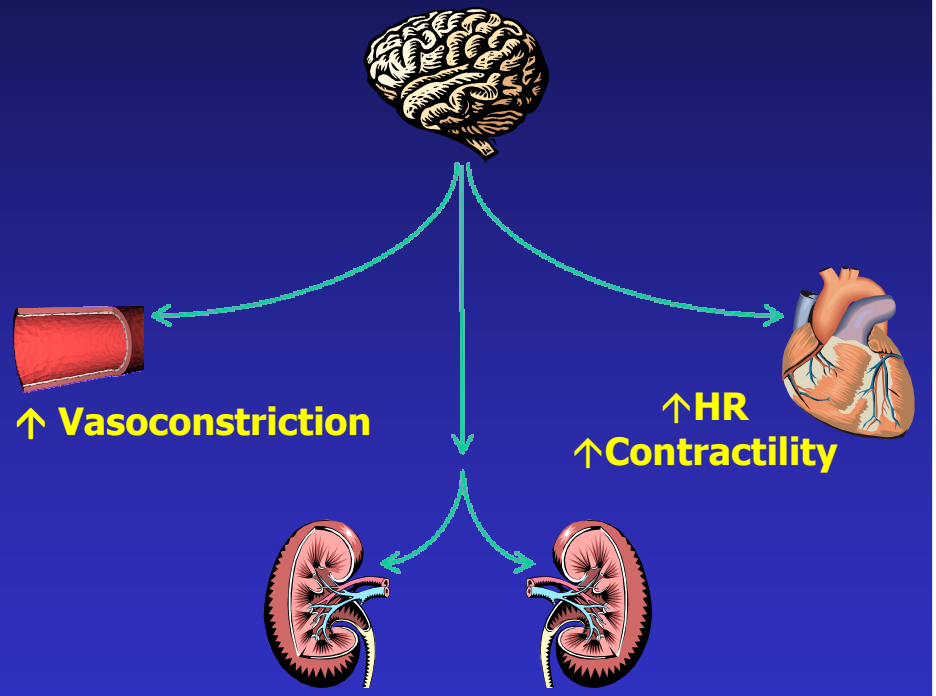
Renal Nerves and the SNS

Afferent Renal Sympathetics



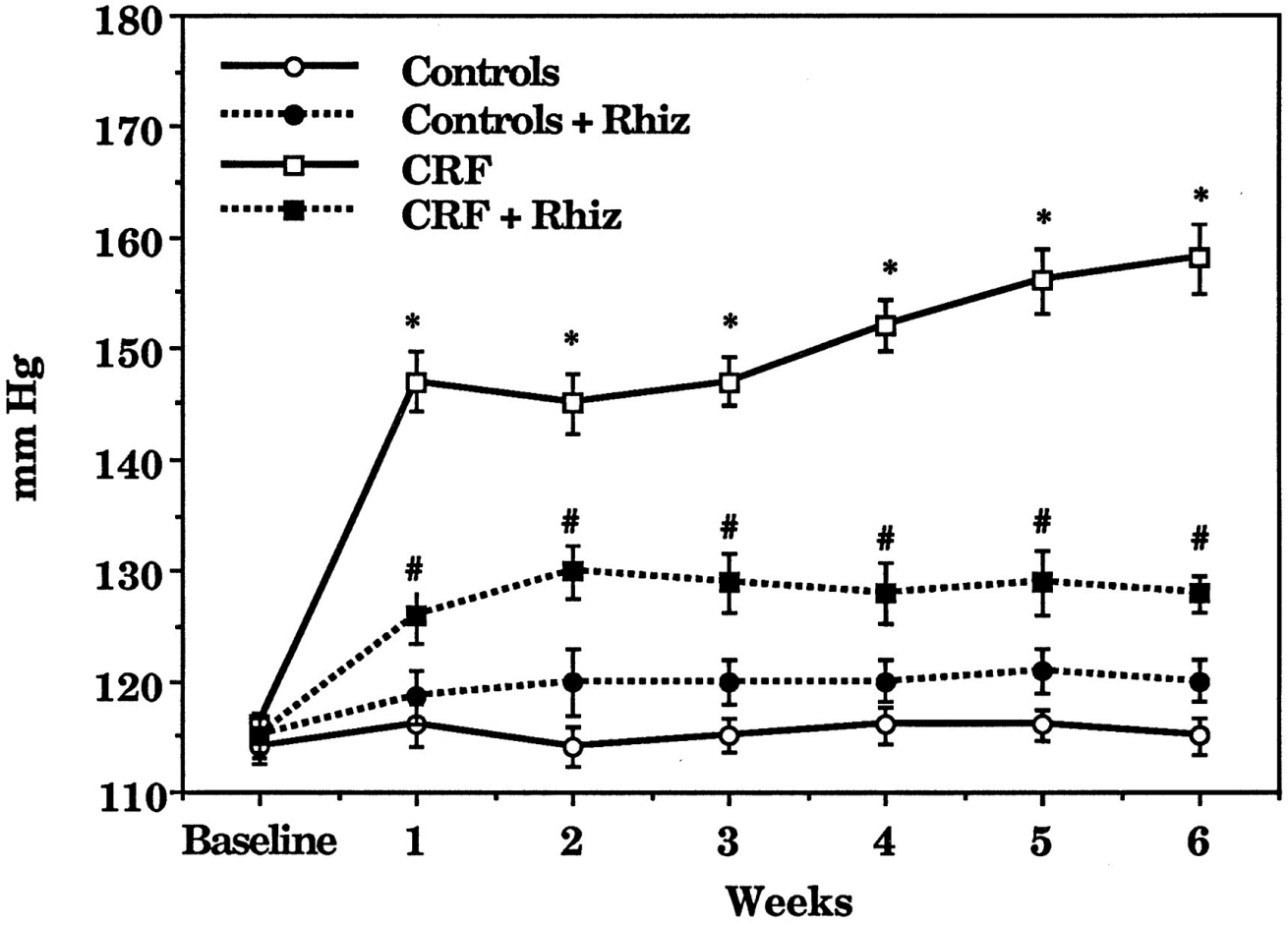
The kidney is a source of central sympathetic drive in hypertension, heart failure, chronic kidney disease, and ESRD

Efferent Sympathetic Activation



Patients cannot develop and/or maintain elevated BP without renal involvement

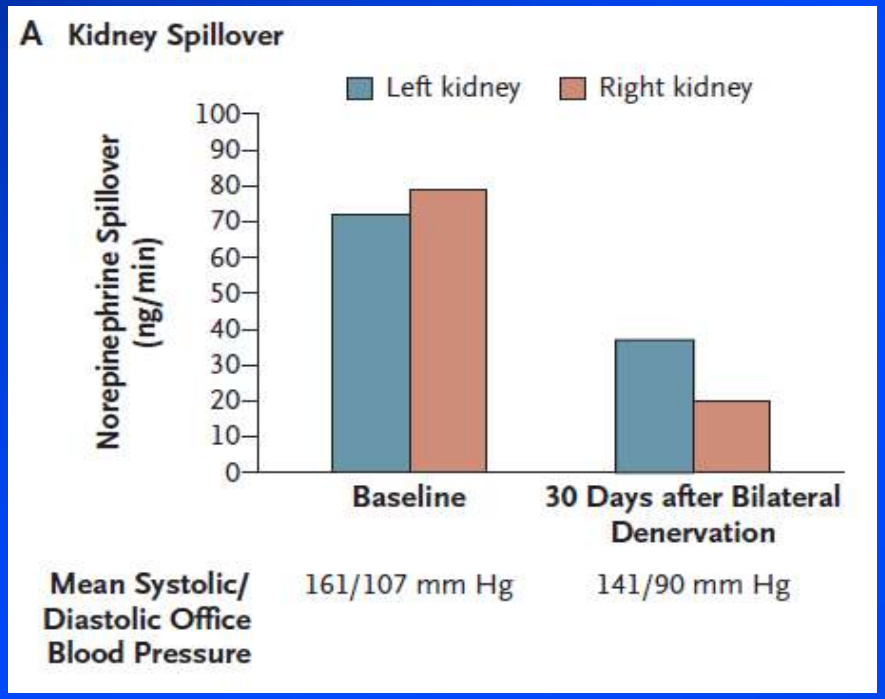
Renal Afferent Denervation Prevents Hypertension In Rats With Chronic Renal Failure

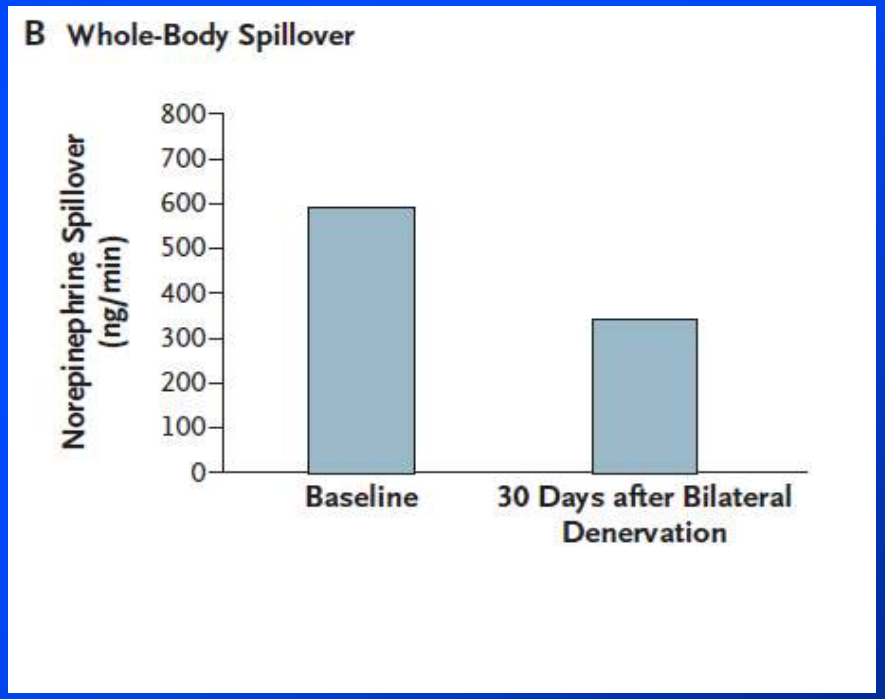


Campese V M , Kogosov E Hypertension 1995;25:878-882

American Heart Association
Learn and Live

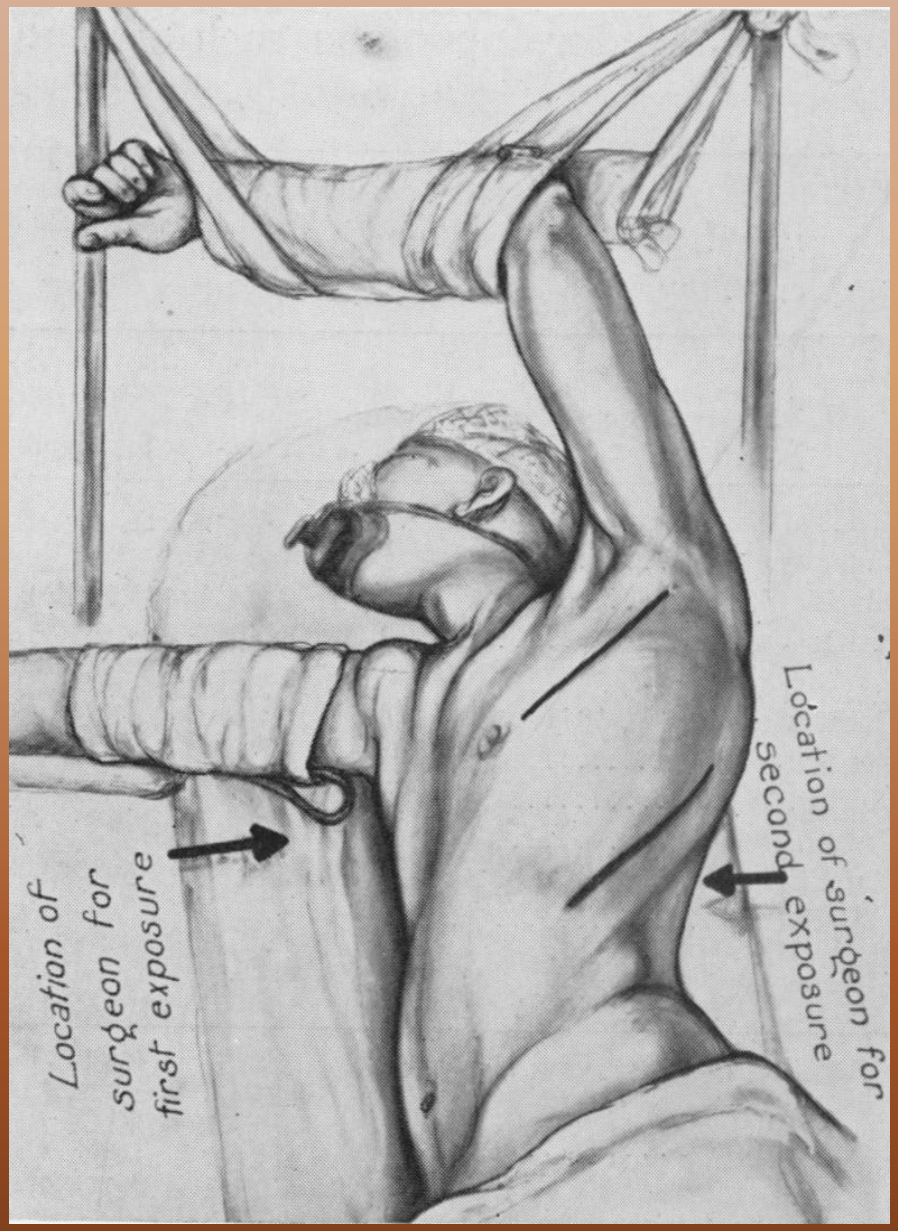
Renal sympathetic denervation

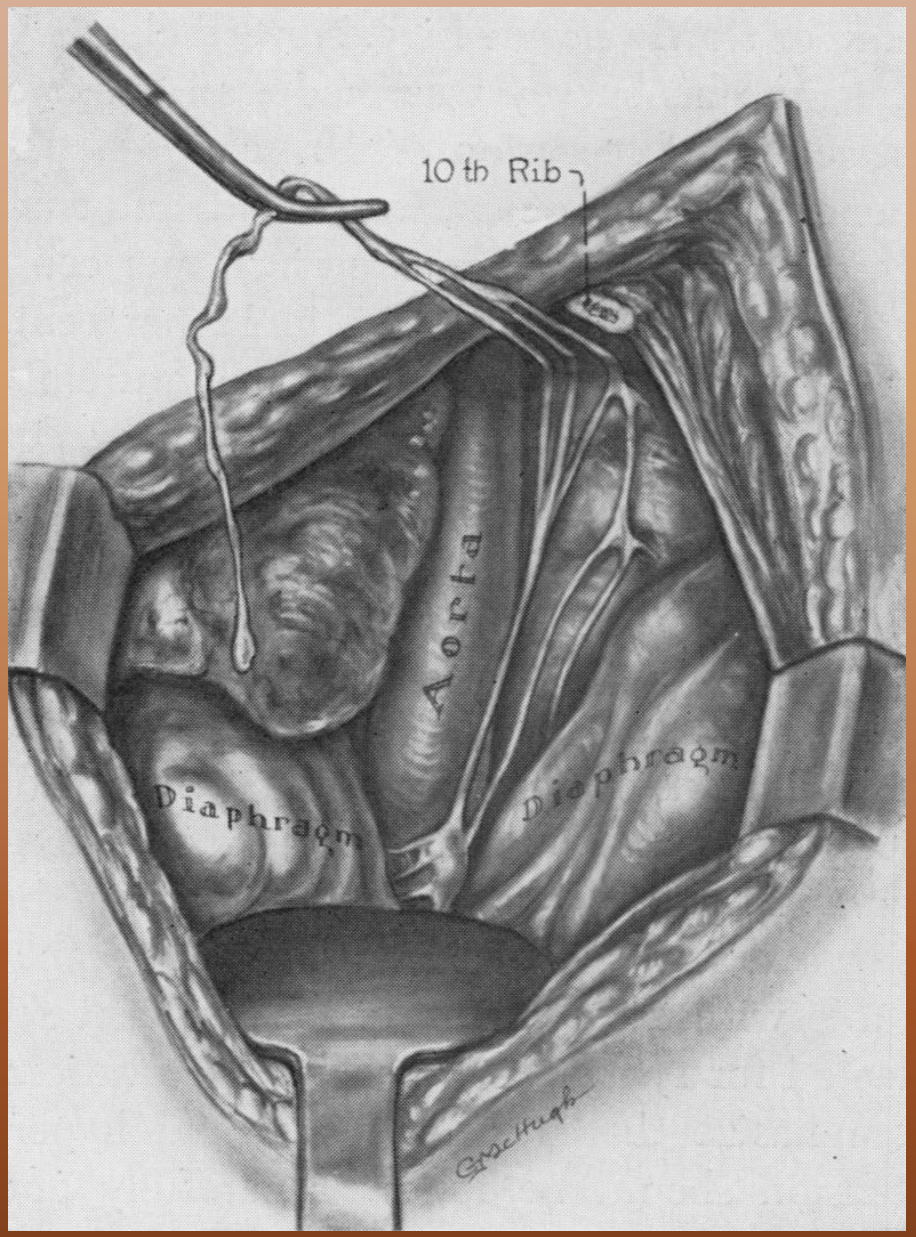




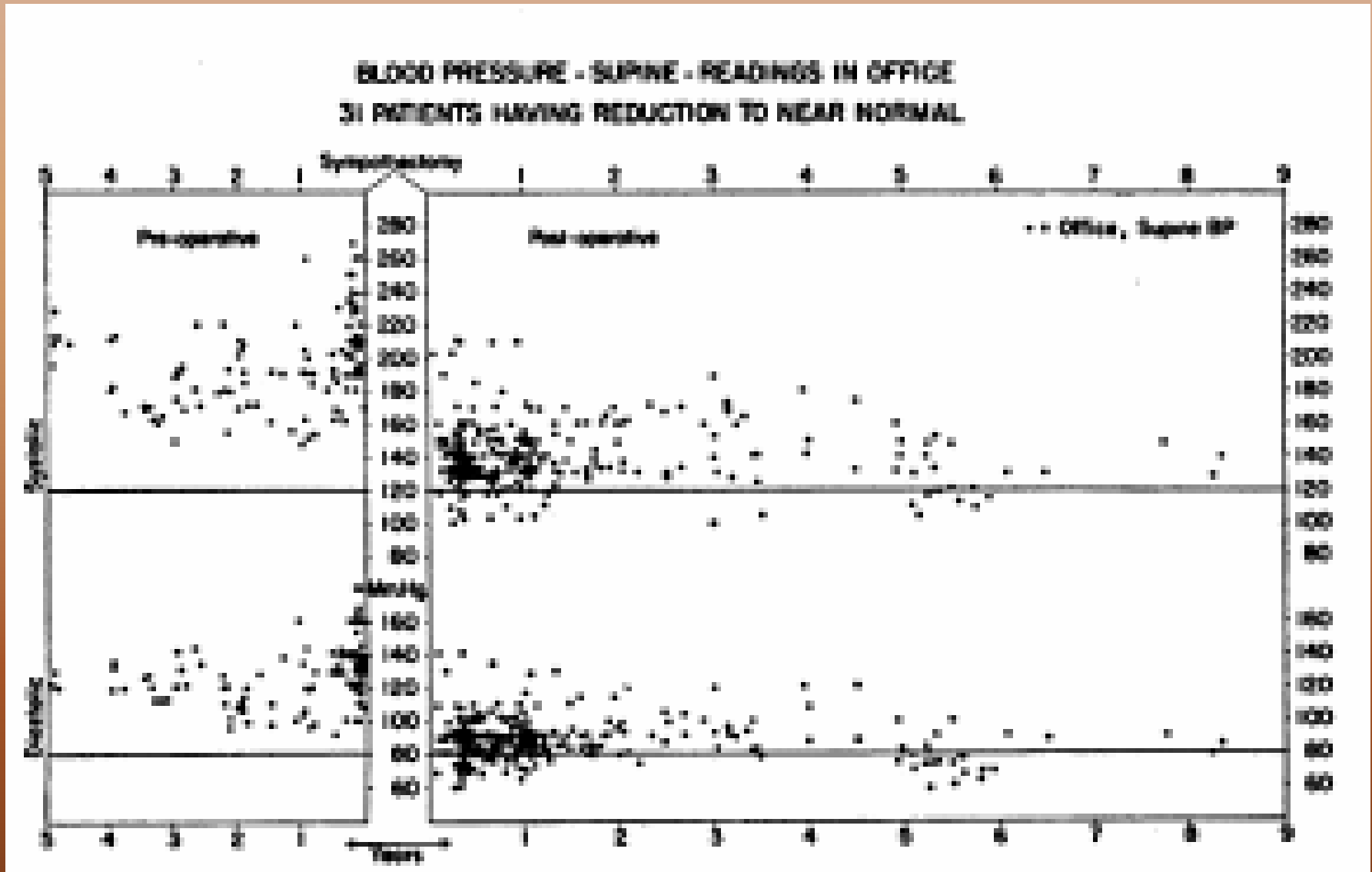
Schlaich, NEJM 2009

The past





Grimson, Ann Surg 1941



Grimson, Ann Surg 1949

TABLE II.
CHANGE IN HEART SIZE

	Cases
Enlarged before operation	31
Normal size 3 to 6 months after operation	20
Reduced but still enlarged	8
No change	2
Larger	1

Reduction of size in 90%; 64% to normal.

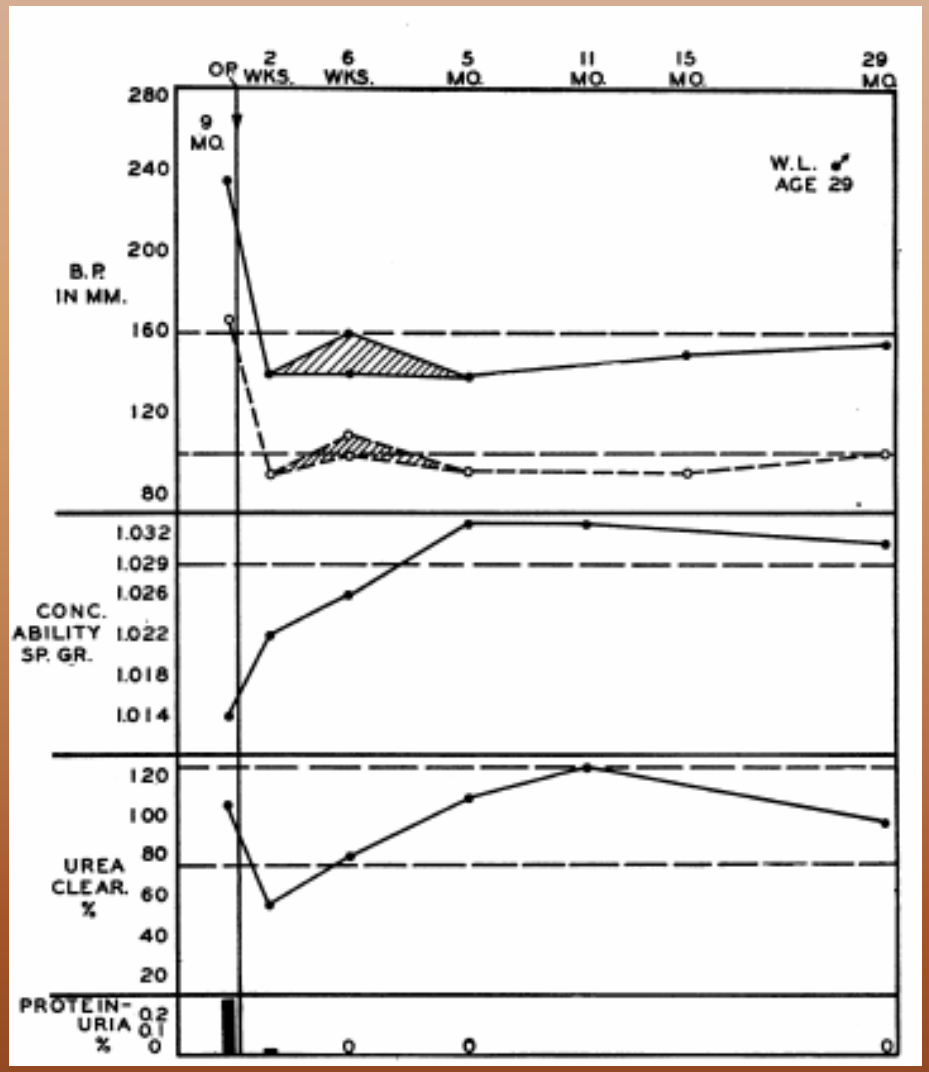
TABLE III.
EFFECT OF SYMPATHECTOMY AT VARIOUS LEVELS ON ANGINA

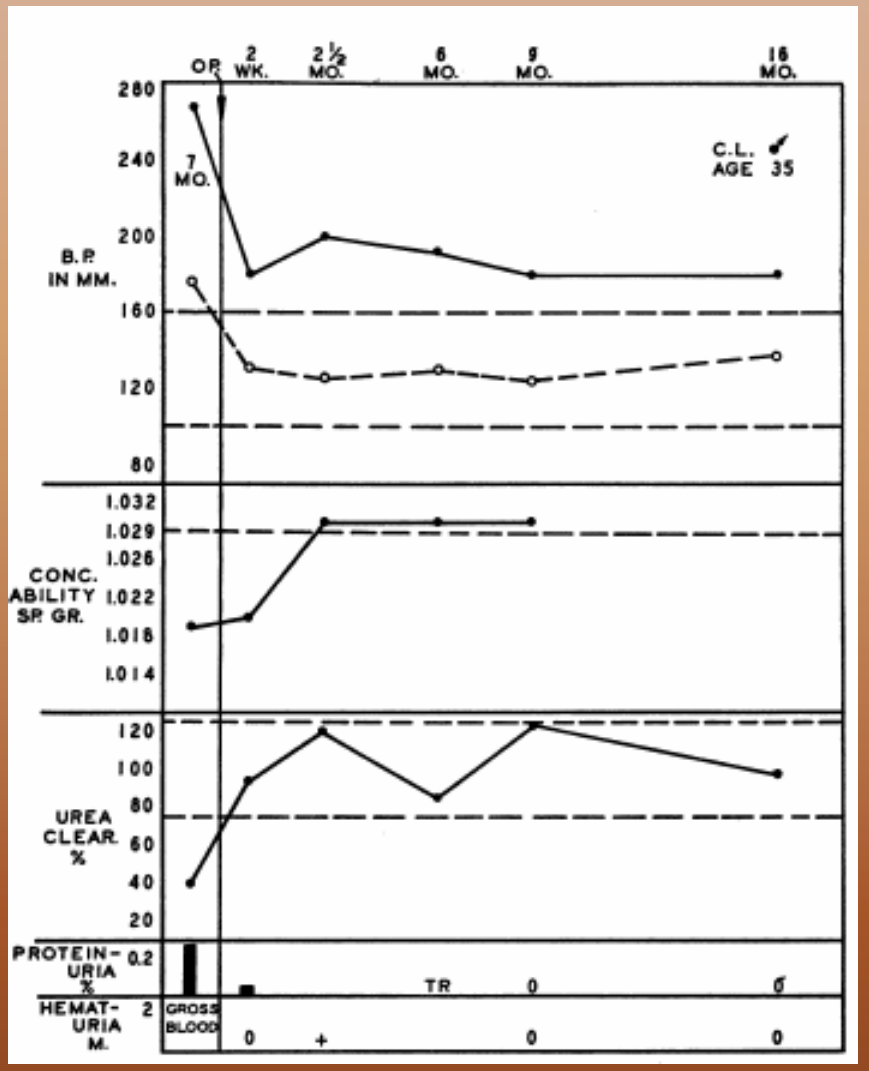
	T-1,2 T-3	T-4	T-5 and above*
Total cases	8	15	10
Abolition†	1	9	7
Partial relief	2	2	3
Same	0	1	0
Worse	0	1	0
Died	5	1	0

Summary:

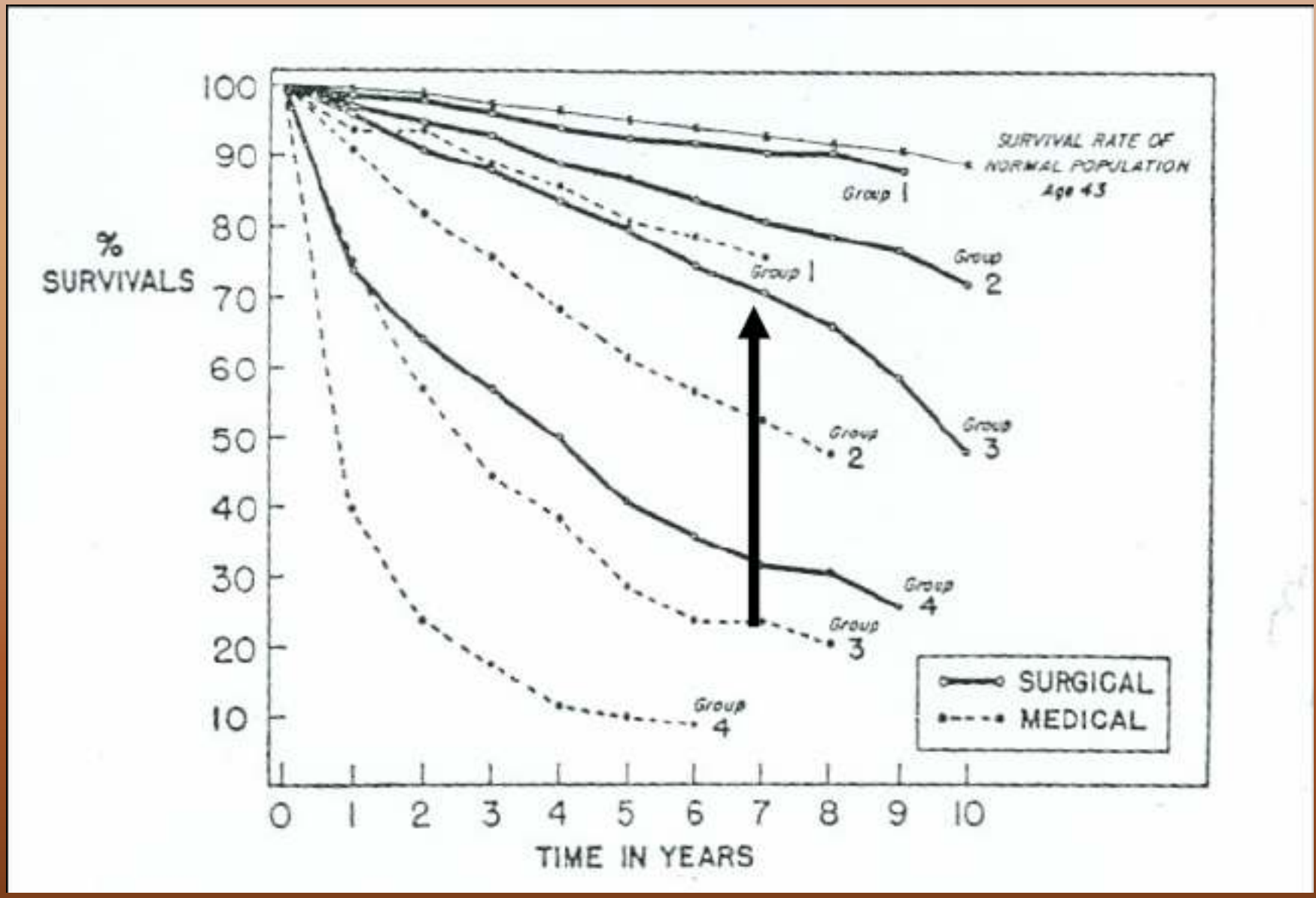
Below T-4 level	12.5%	satisfactory relief of pain
T-4 level	73.0%	" " " "
Above T-4 level	100.0%	" " " " ‡

Evans, Canad Med Ass J 1951





Peet, J Clin Invest 1936



Smithwick, JAMA 1953

Operative mortality of splanchnicectomy according to hypertension severity

TABLE I. SPLANCHNICECTOMY FOR HYPERTENSION: OPERATIVE MORTALITY

GROUP*	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
1	299	2	0.7
2	1,399	20	1.4
3	486	21	4.3
4	219	24	10.9
Total	2,403	67	2.8

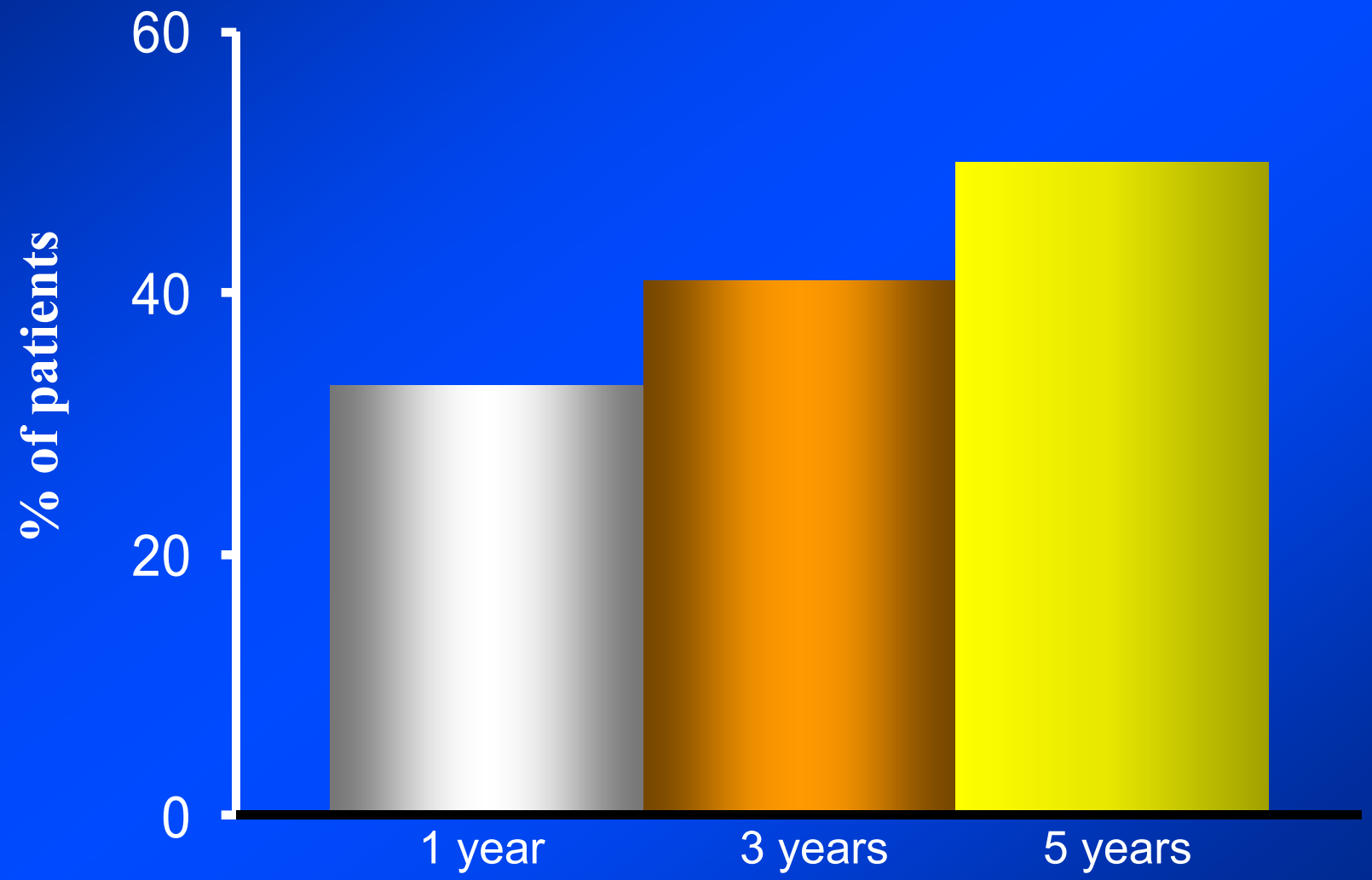
Smithwick, J Chronic Dis 1955

Adverse effects of splanchnicectomy

- Thoracic duct injuries
- Atelectasia
- **Orthostatic hypotension and tachycardia**
- Palpitations
- Breathlessness
- Anhidrosis
- Cold hands
- Intestinal disturbances
- **Loss of ejaculation**
- **Sexual dissatisfaction**

Doumas, Am J Cardiol 2010

Treatment discontinuation



Corrao, J Hypertens 2008

The present
The future???

Fundamental questions

a) is it meaningful with a rationale behind it?

b) is this effective and safe?

c) what are the long-term results?

d) can it be widely applied?

e) are there limitations? what else has to follow? Who for?

Doumas, Lancet 2009

Renal sympathetic denervation: the jury is still out

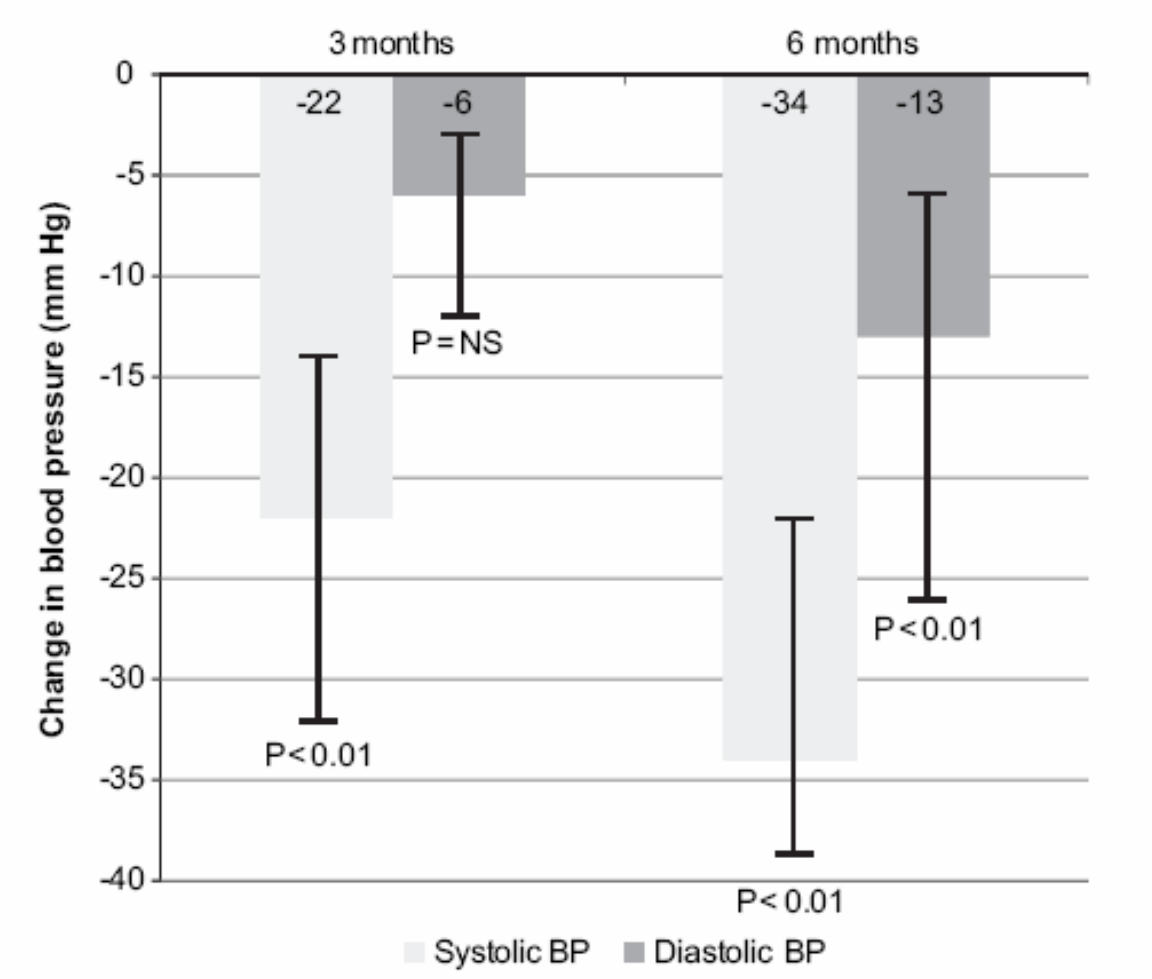
Panel: **Research targets for renal sympathetic denervation**

- Clarification of pathophysiological mechanisms that mediate reductions in blood pressure
- Effects on target organ damage
  - Left ventricular hypertrophy
  - Carotid intima-media thickness
  - Albuminuria
  - Pulse-wave velocity
  - Ankle brachial pressure index
  - Retinopathy
- Efficiency in subgroups of patients with hypertension
  - Elderly patients
  - Isolated systolic hypertension
  - Chronic kidney disease
  - Heart failure
  - Diabetes
  - Obesity
  - Sleep-apnoea syndrome
- Efficiency in milder forms of essential hypertension
- Efficiency at initial stages of hypertension
- Alternative methods for achieving renal denervation
  - Ultrasound
  - Microwaves
  - Laser
  - Cryotherapy
  - Robotic surgery

Doumas, Lancet 2010

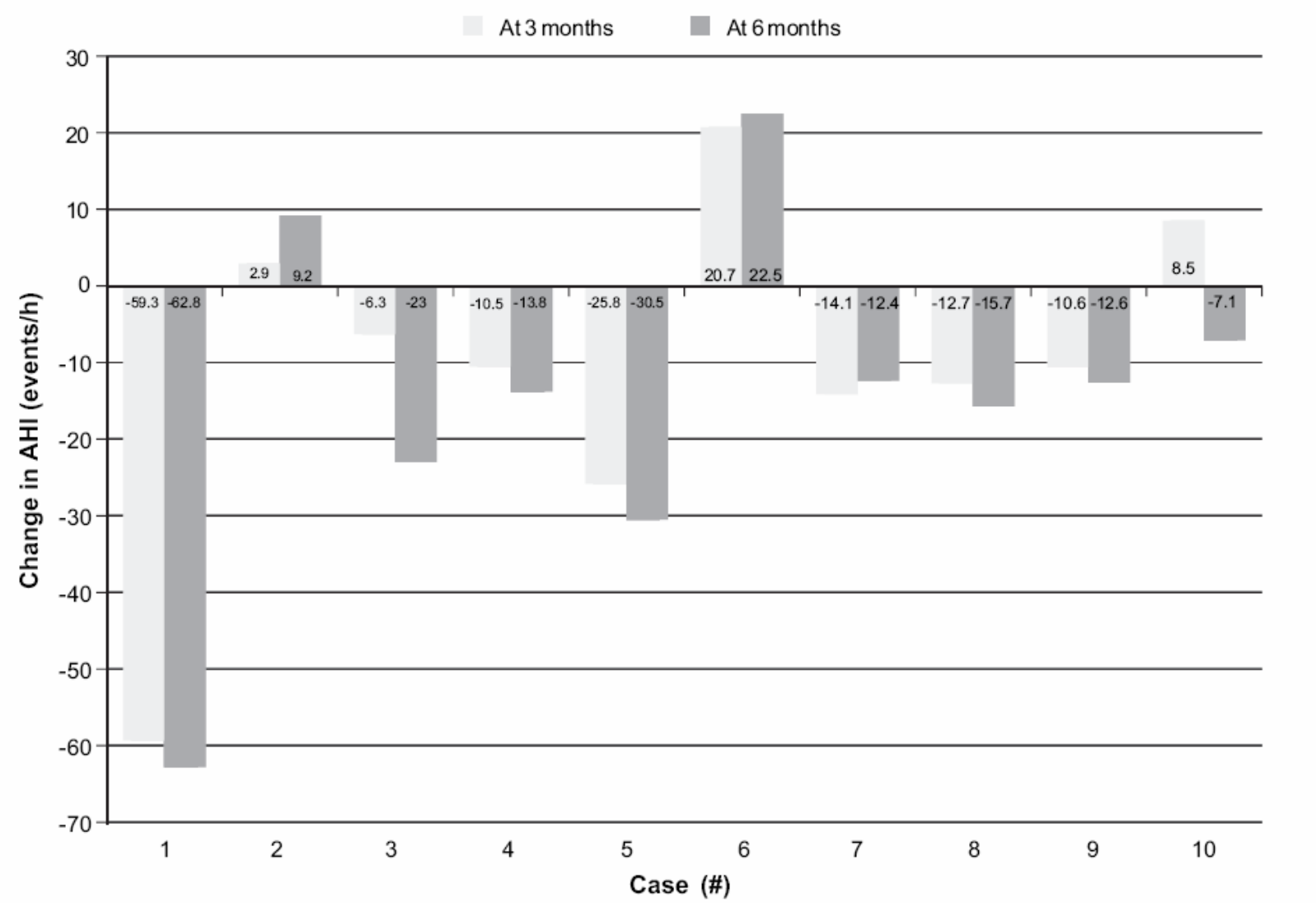
Other disease conditions

RSD in sleep apnea syndrome patients
Changes in blood pressure



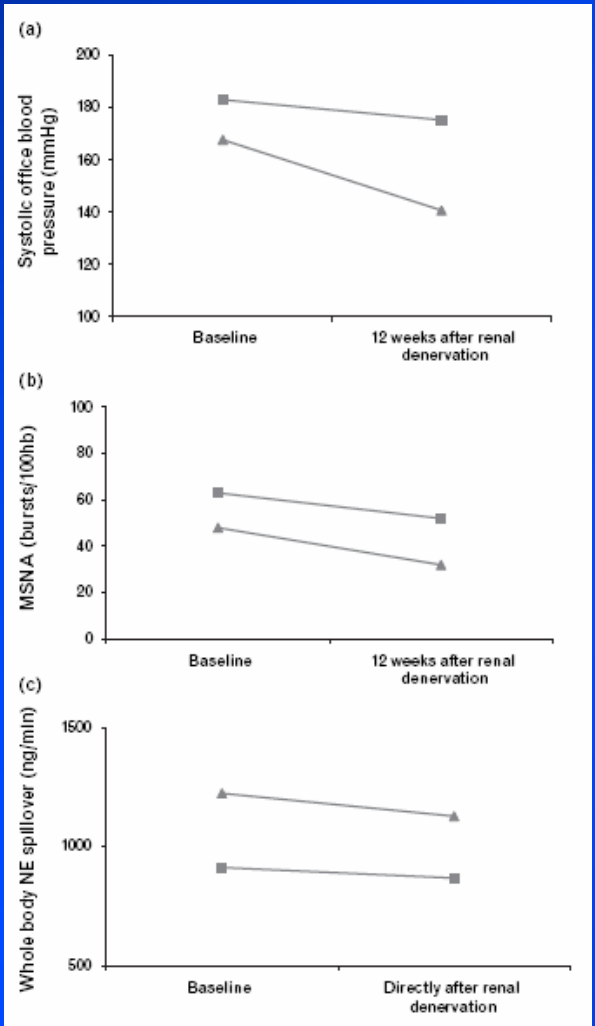
Witkowski, Hypertension 2011

RSD in sleep apnea syndrome patients
Changes in apnea/hypopnea index



Witkowski, Hypertension 2011

Polycystic ovary syndrome

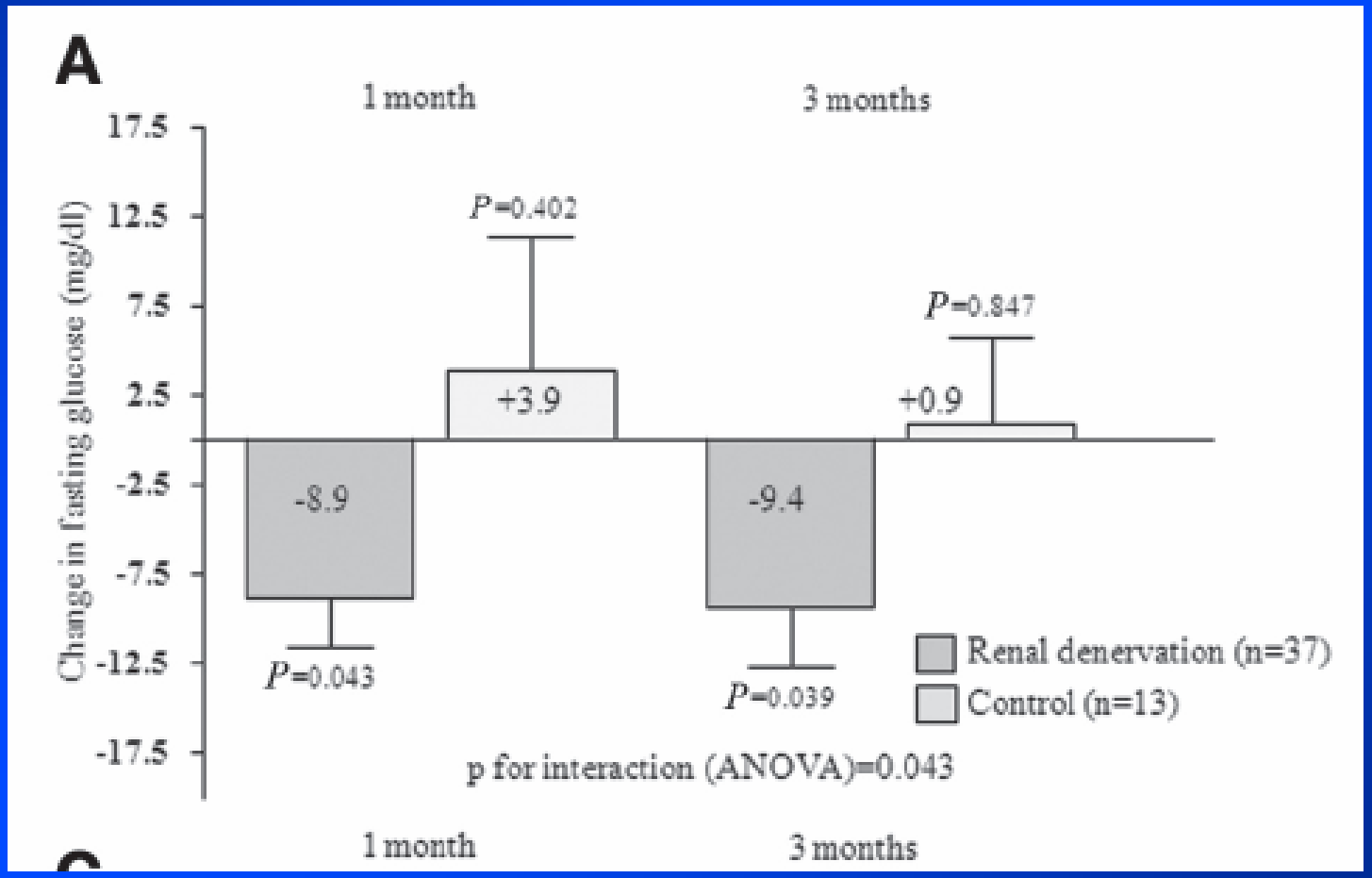


Even regular menses re-occurred in one patient after 3-year amenorrhea following RSD

Significant improvements in insulin sensitivity

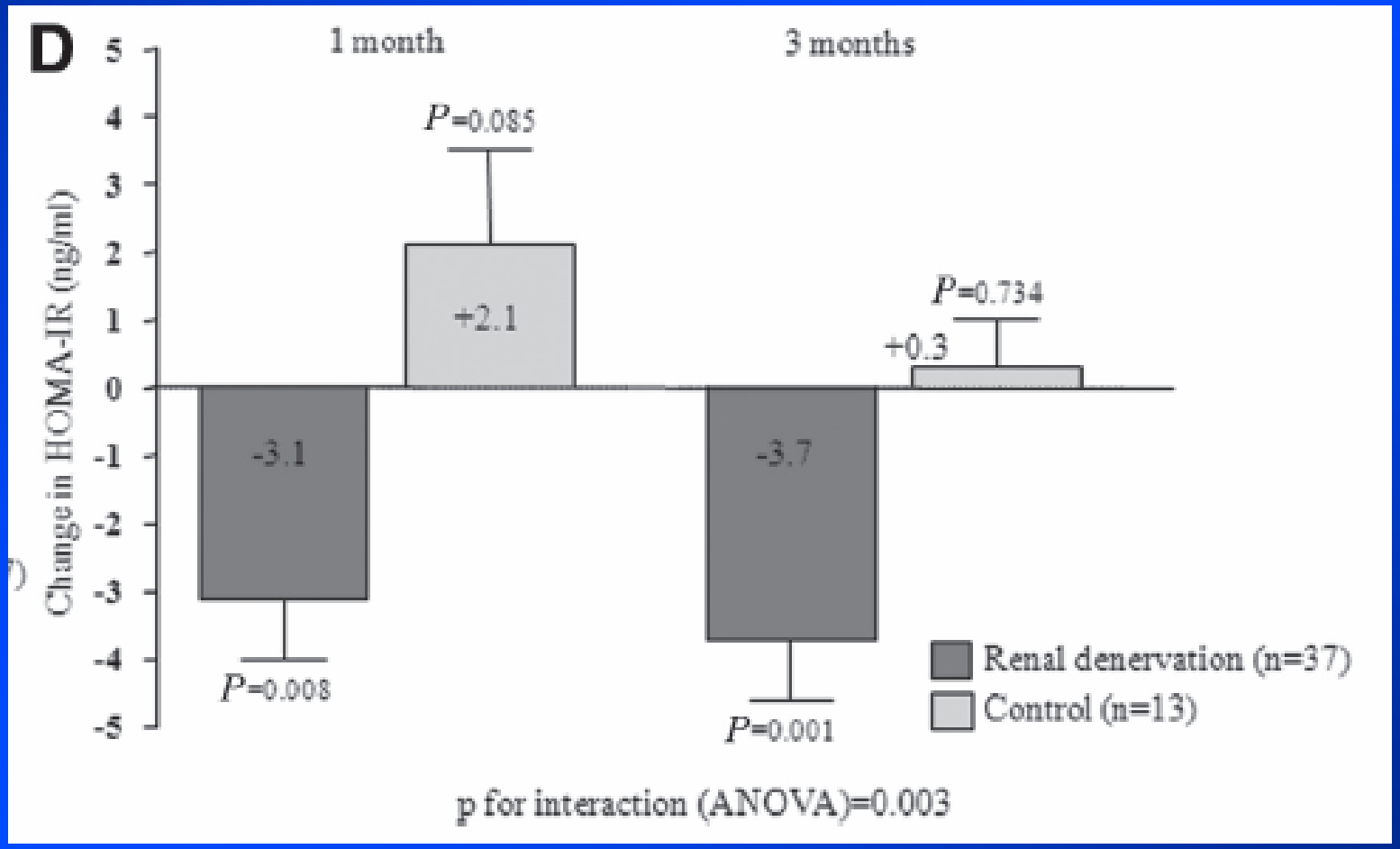
Schlaich, J Hypertens 2011

RSD and glucose metabolism
Fasting glucose



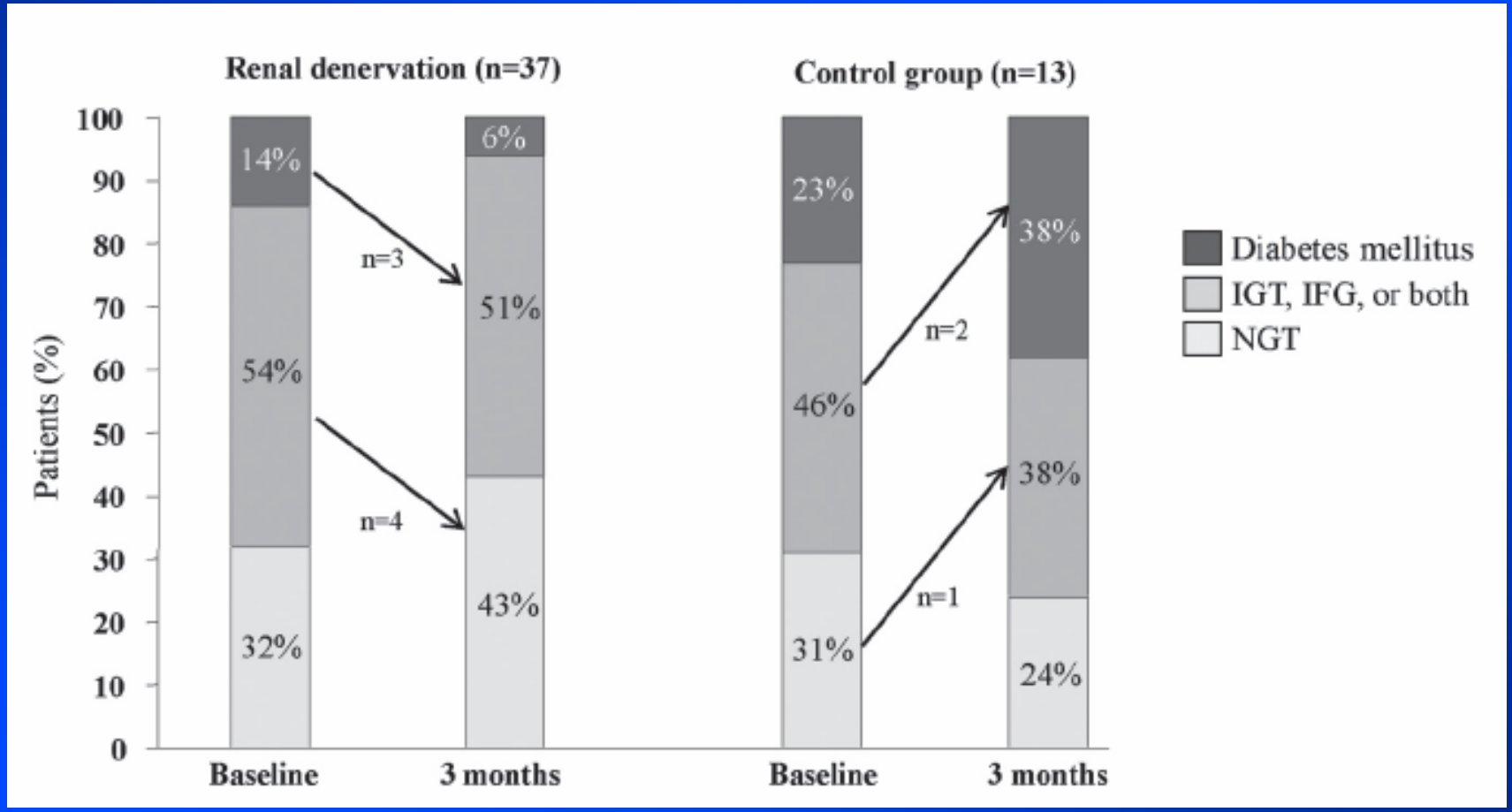
Mahmoud, Circulation 2011

RSD and glucose metabolism
Insulin resistance - HOMA



Mahmoud, Circulation 2011

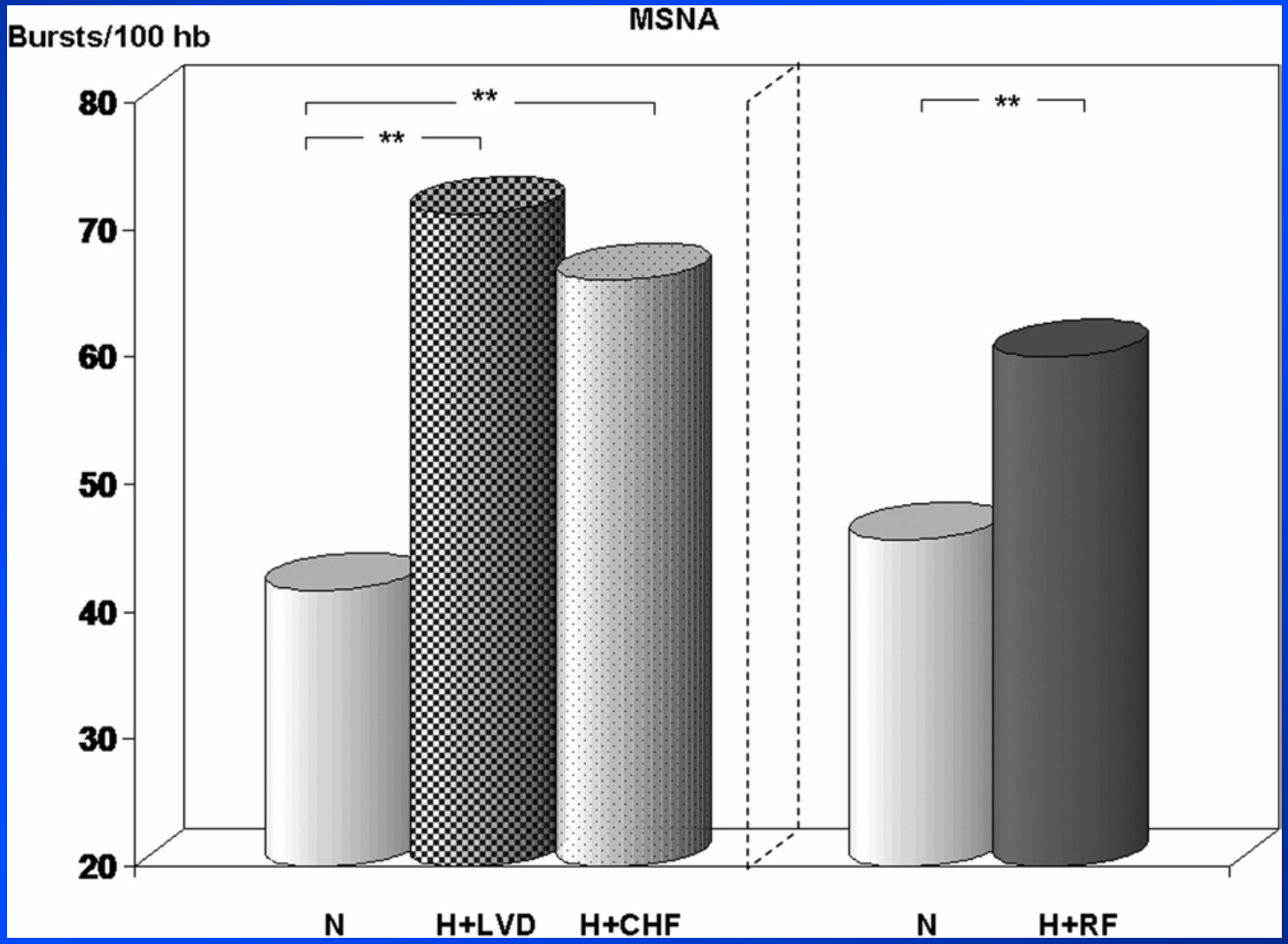
RSD and glucose metabolism
IGT – DM rates



Mahmoud, Circulation 2011

Chronic kidney disease

MSNA in CKD

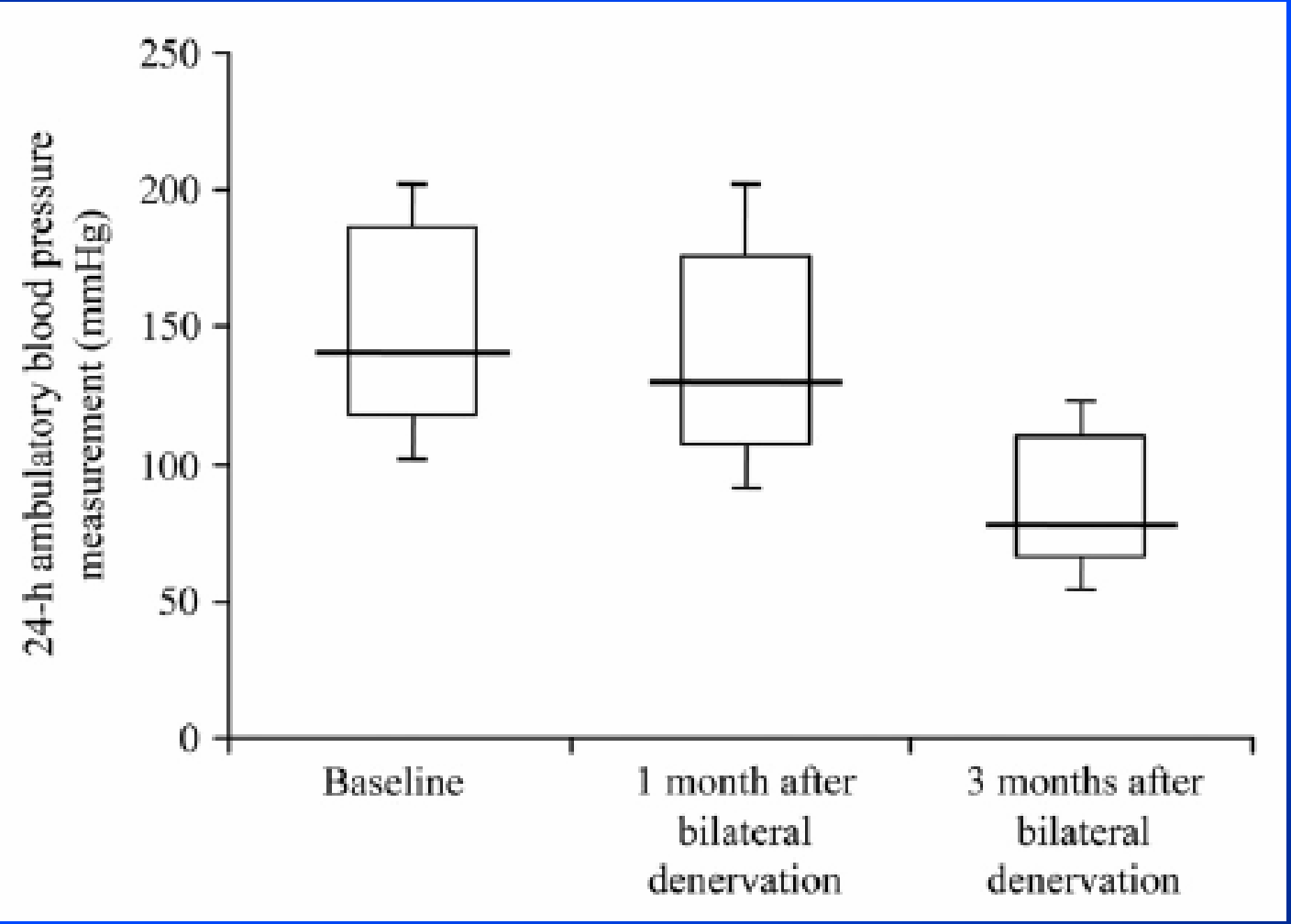


Grassi, Can J Cardiol 2012

Catheter-based radiofrequency ablation therapy of the renal sympathetic-nerve system for drug resistant hypertension in a patient with end-stage renal disease

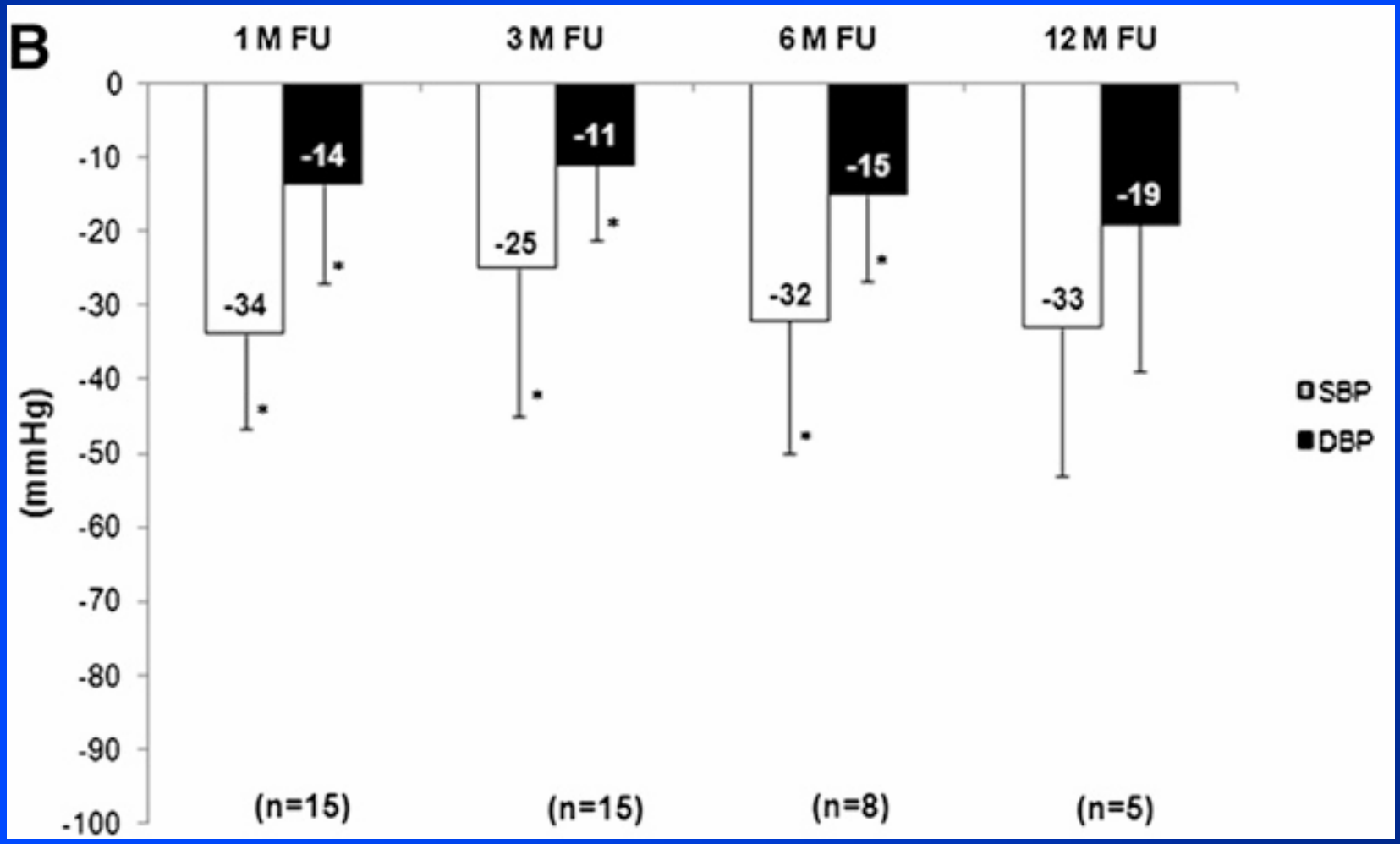
D. Prochnau [a,*], A. Lauten [a], M. Busch [b], H. Kuehnert [a], H.R. Figulla [a], R. Surber [a]

[a] Department of Internal Medicine I, Friedrich Schiller University, Jena, Germany
[b] Department of Internal Medicine III, Friedrich Schiller University, Jena, Germany



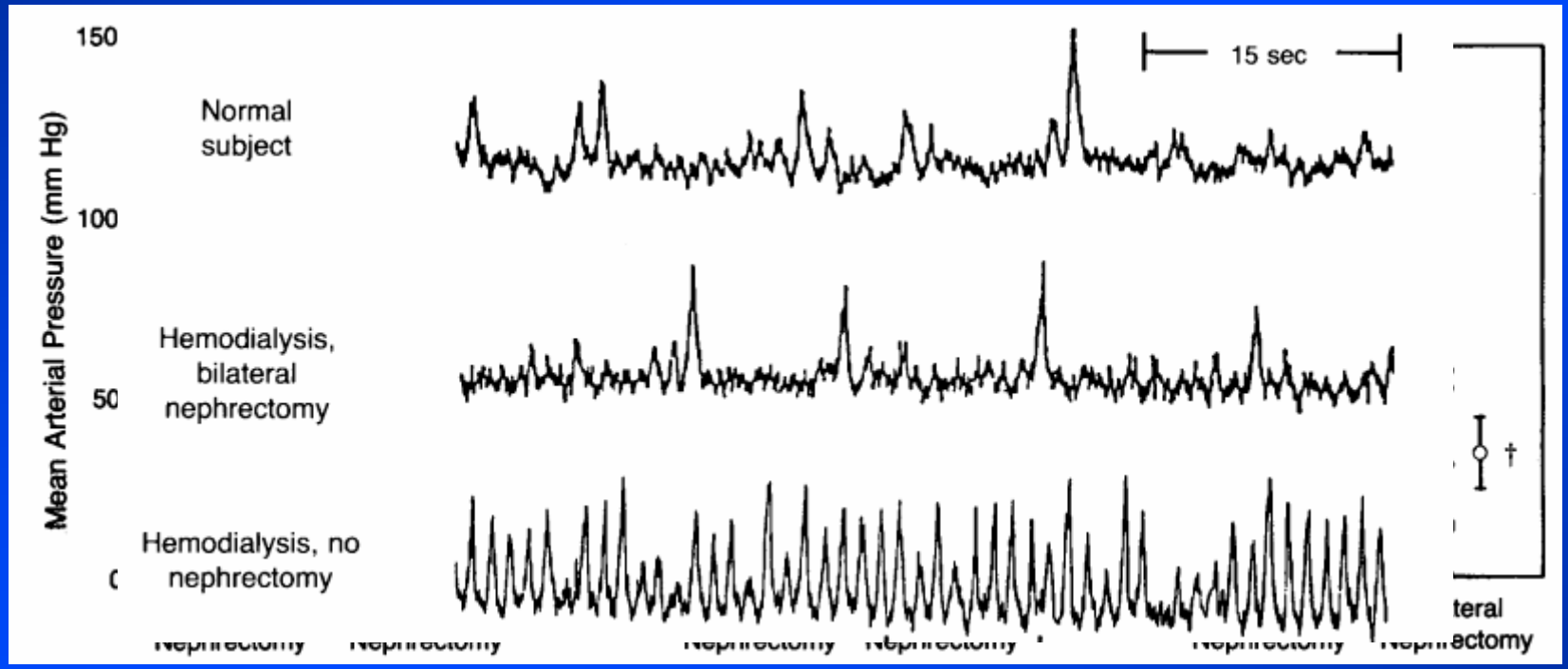
Prochnau, Int J Cardiol 2012

RSD in moderate-severe CKD



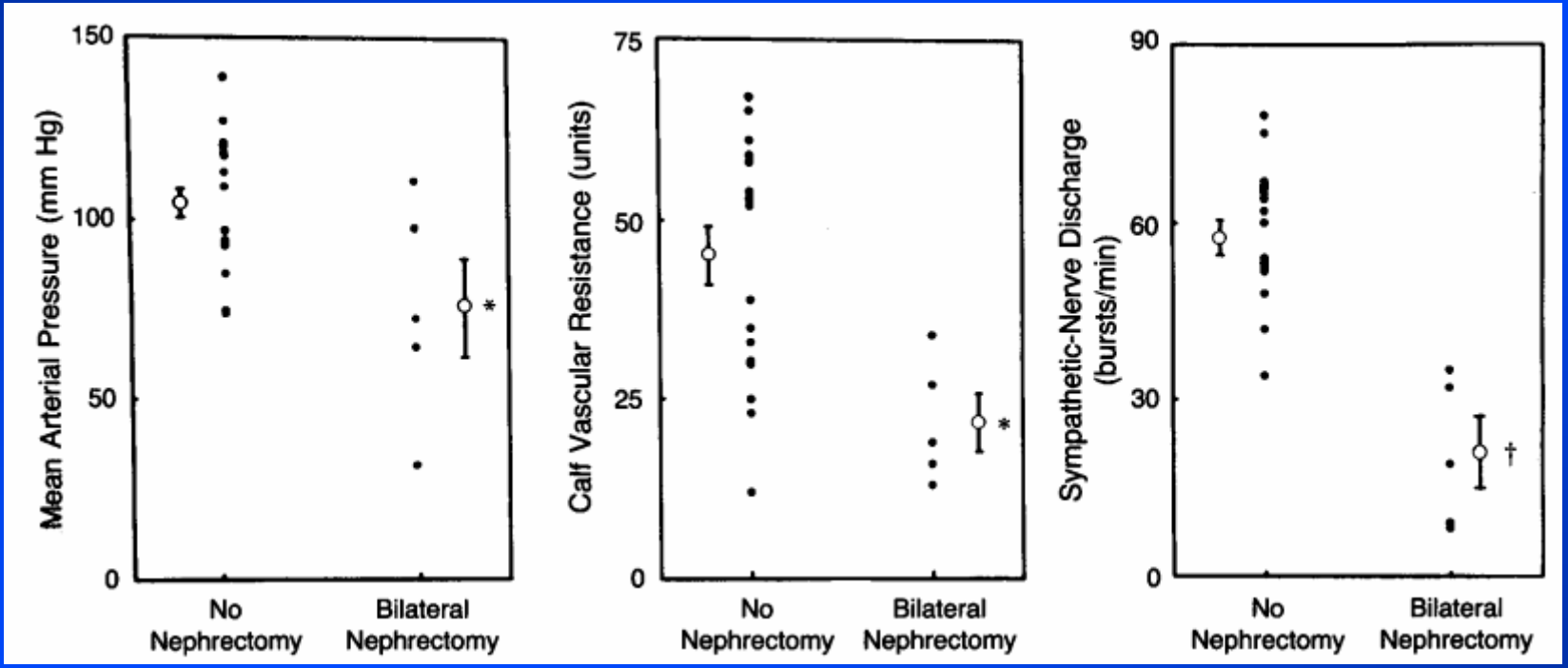
Hering, JASN 2012

Hemodialysis
Bilateral nephrectomy



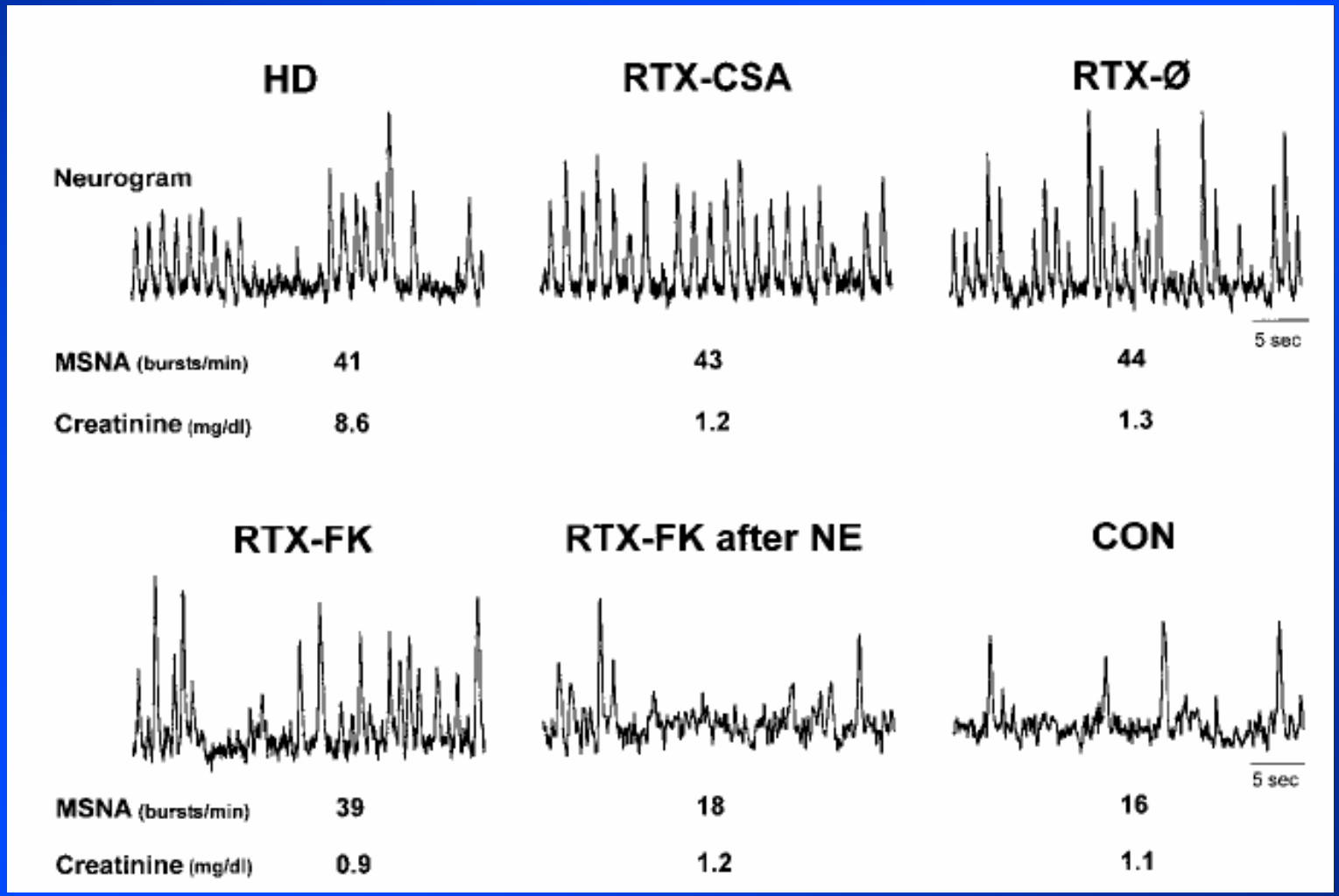
Converse, NEJM 1992

Hemodialysis
Bilateral nephrectomy



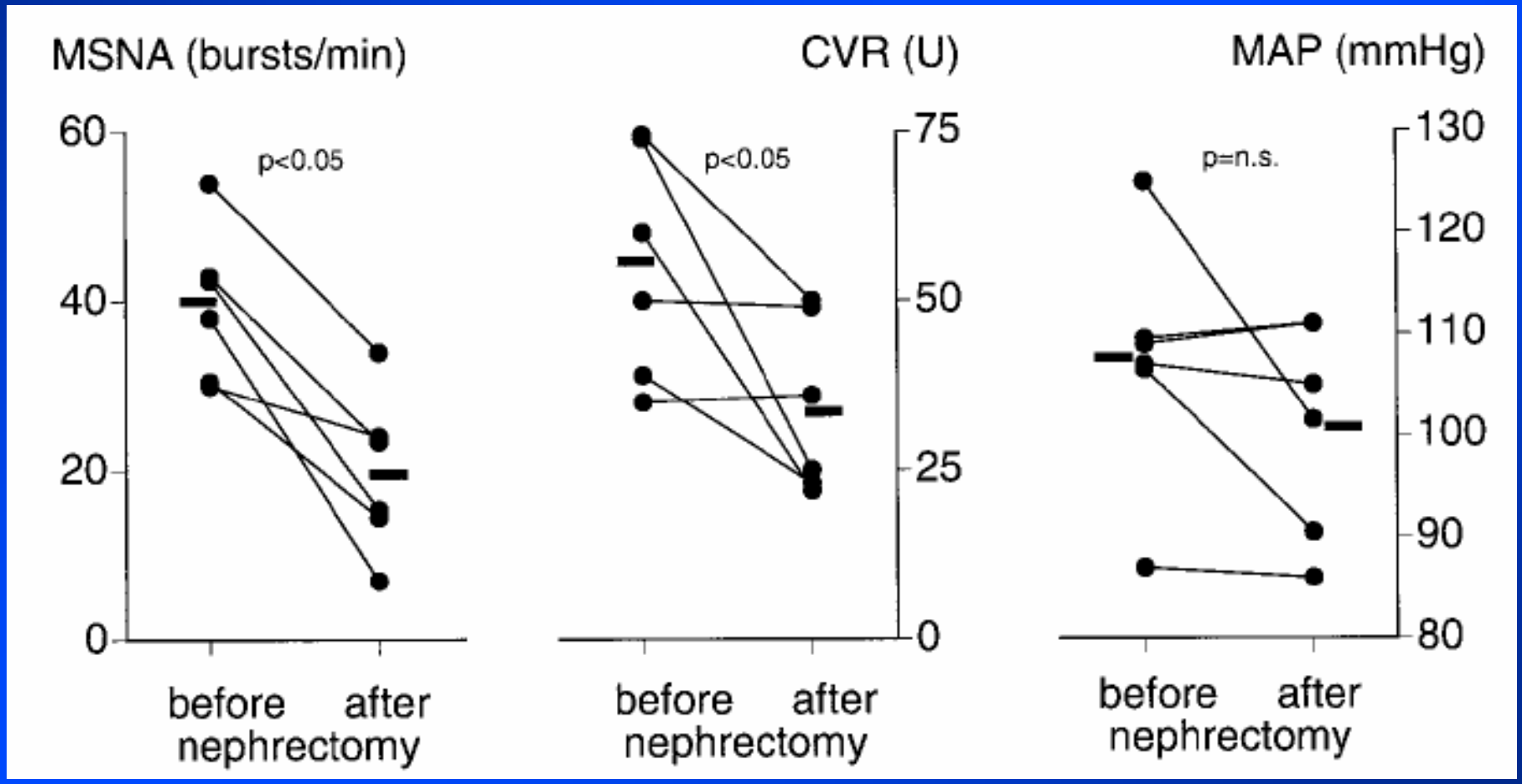
Converse, NEJM 1992

Transplantation
Bilateral nephrectomy



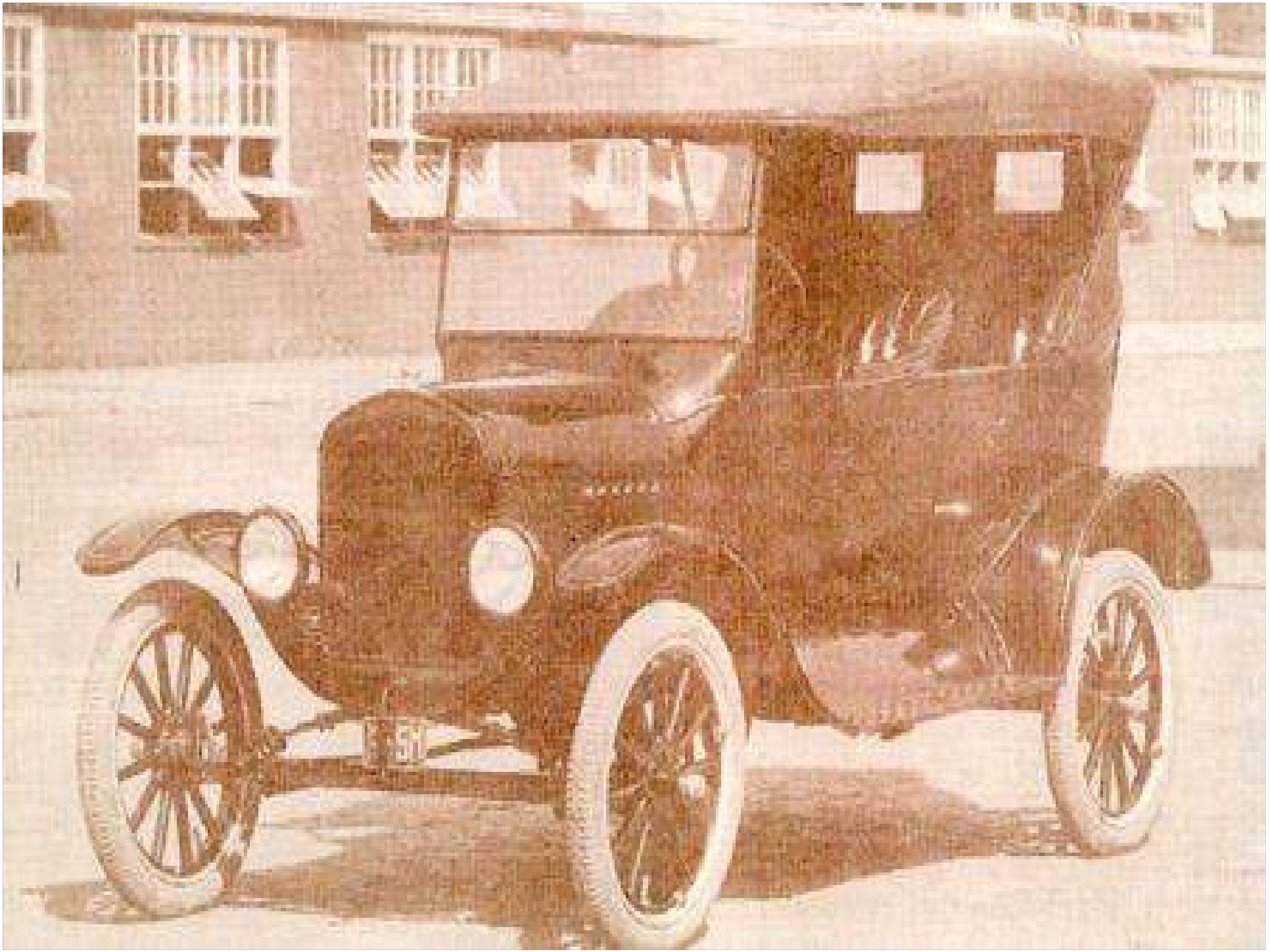
Hausberg, Circulation 2002

Transplantation
Bilateral nephrectomy



Hausberg, Circulation 2002

Great enthusiasm…



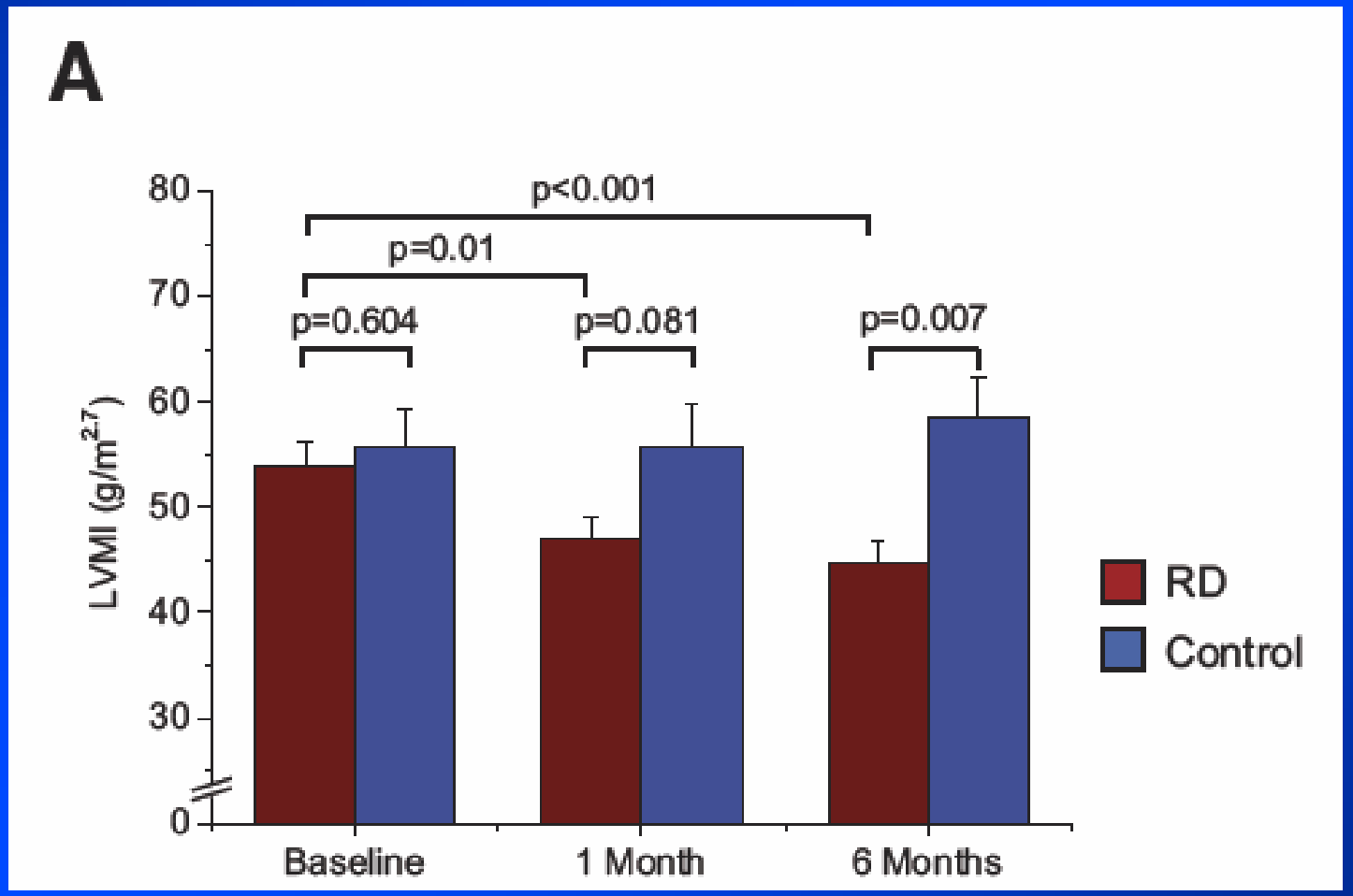
Personal point of view

- It is unlikely that the magic pill for hypertension will be found any time soon
- We may have or not the **"antibiotic of Hypertension"**
- We may even achieve or not **"Cure" of hypertension**
- ***We need further data***

Interventional management of hypertension

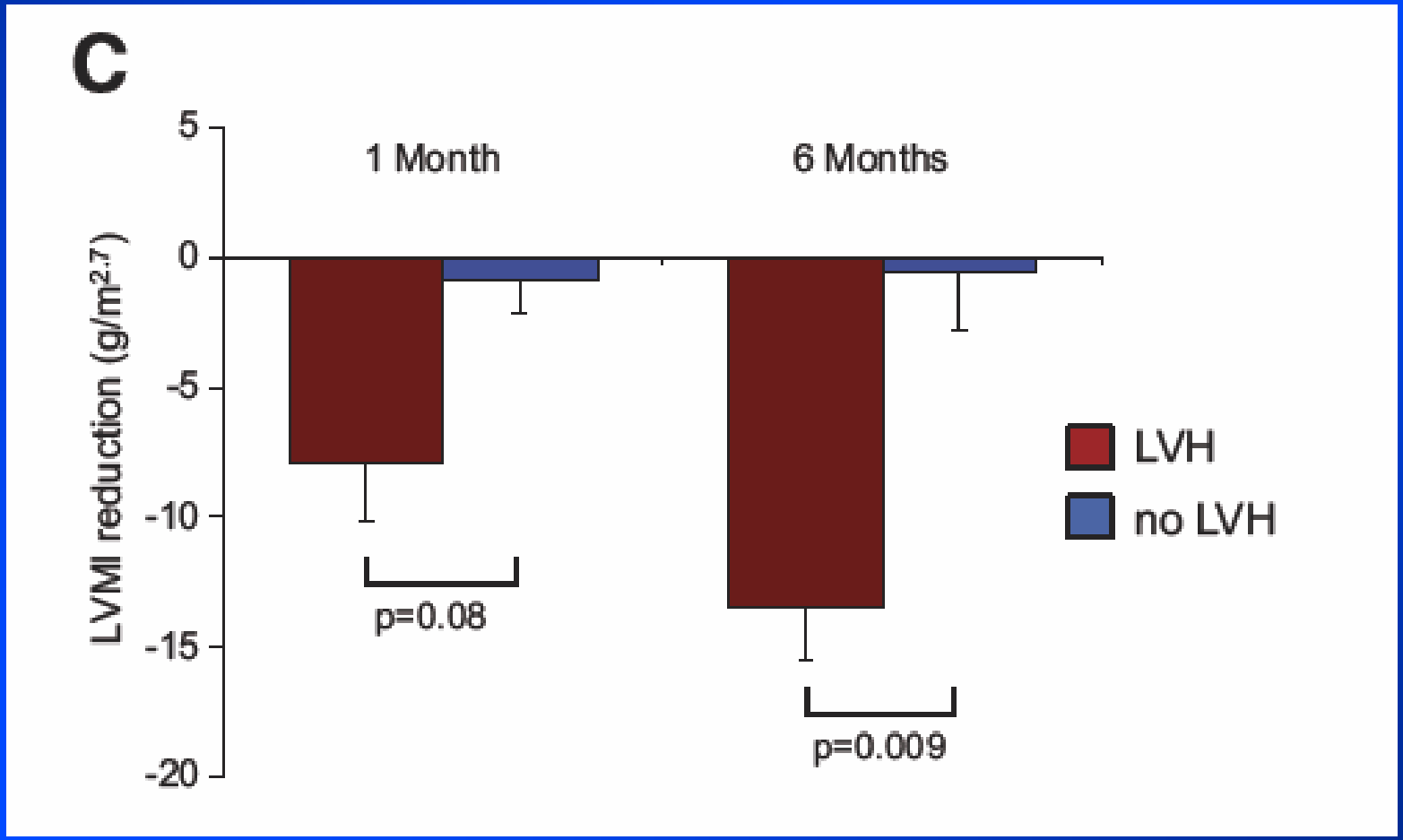
Effects on the heart

Left ventricular mass reduction



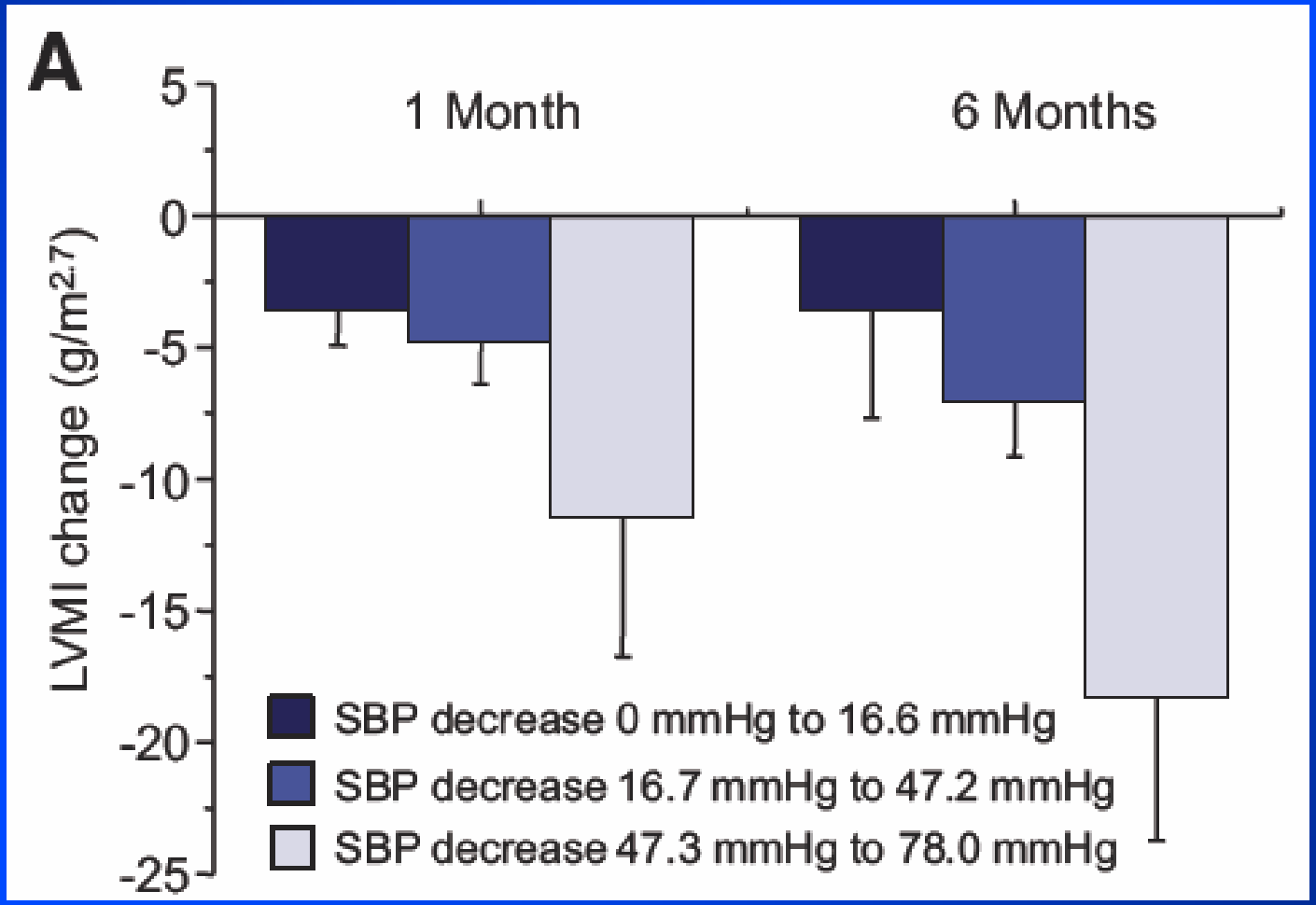
Brandt, JACC 2012

Left ventricular mass reduction according to LVH



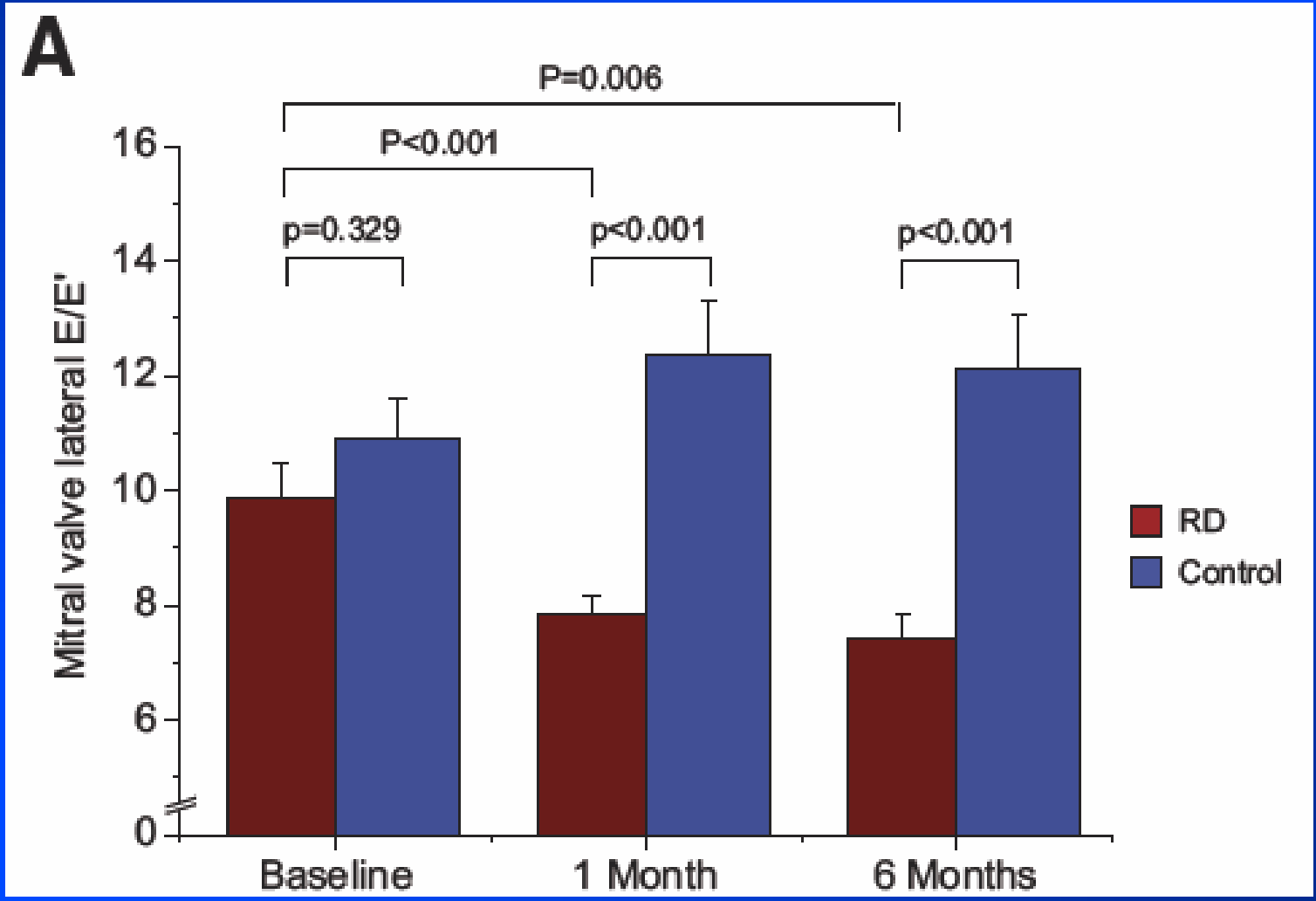
Brandt, JACC 2012

Left ventricular mass reduction according to blood pressure reduction



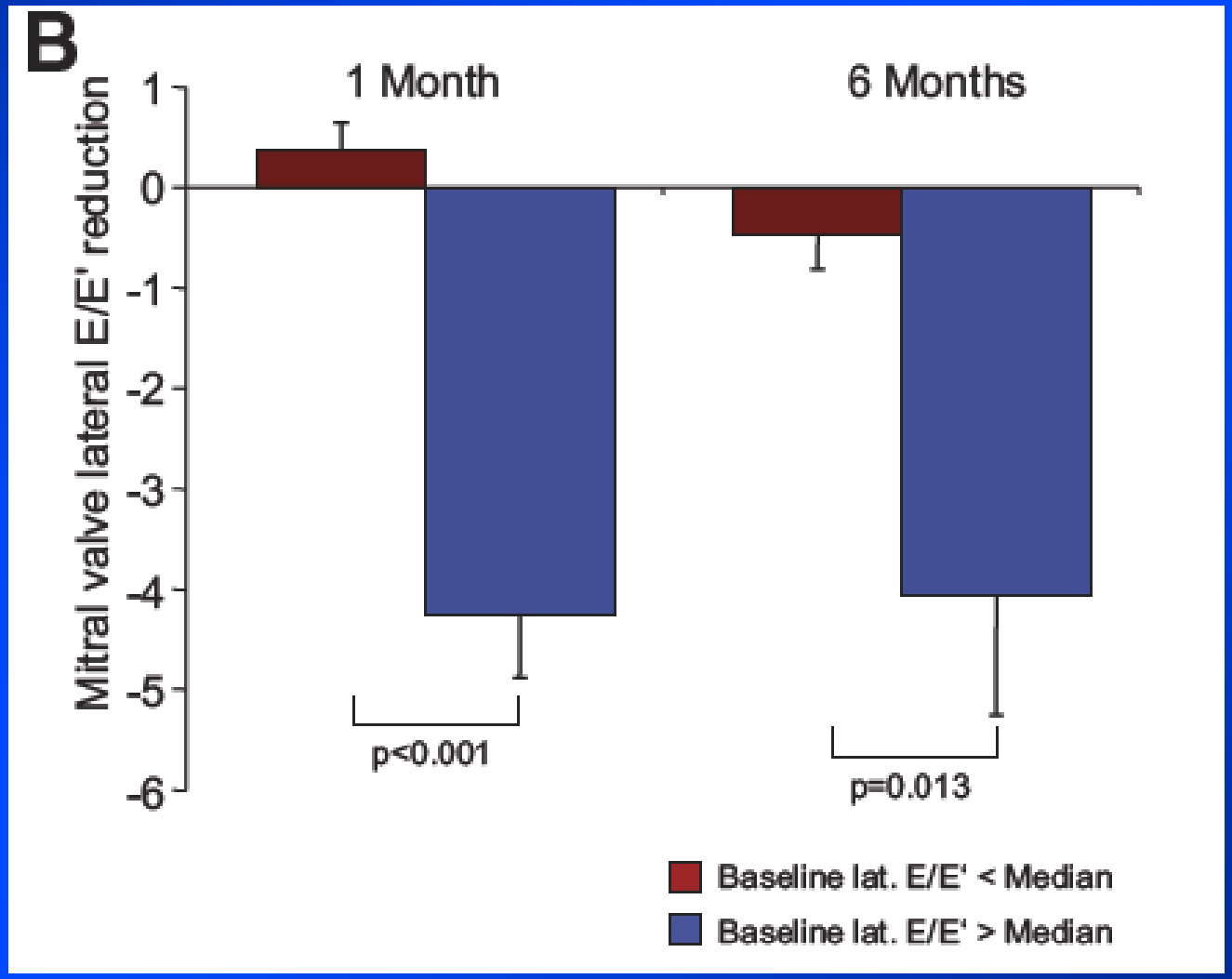
Brandt, JACC 2012

Left ventricular diastolic function



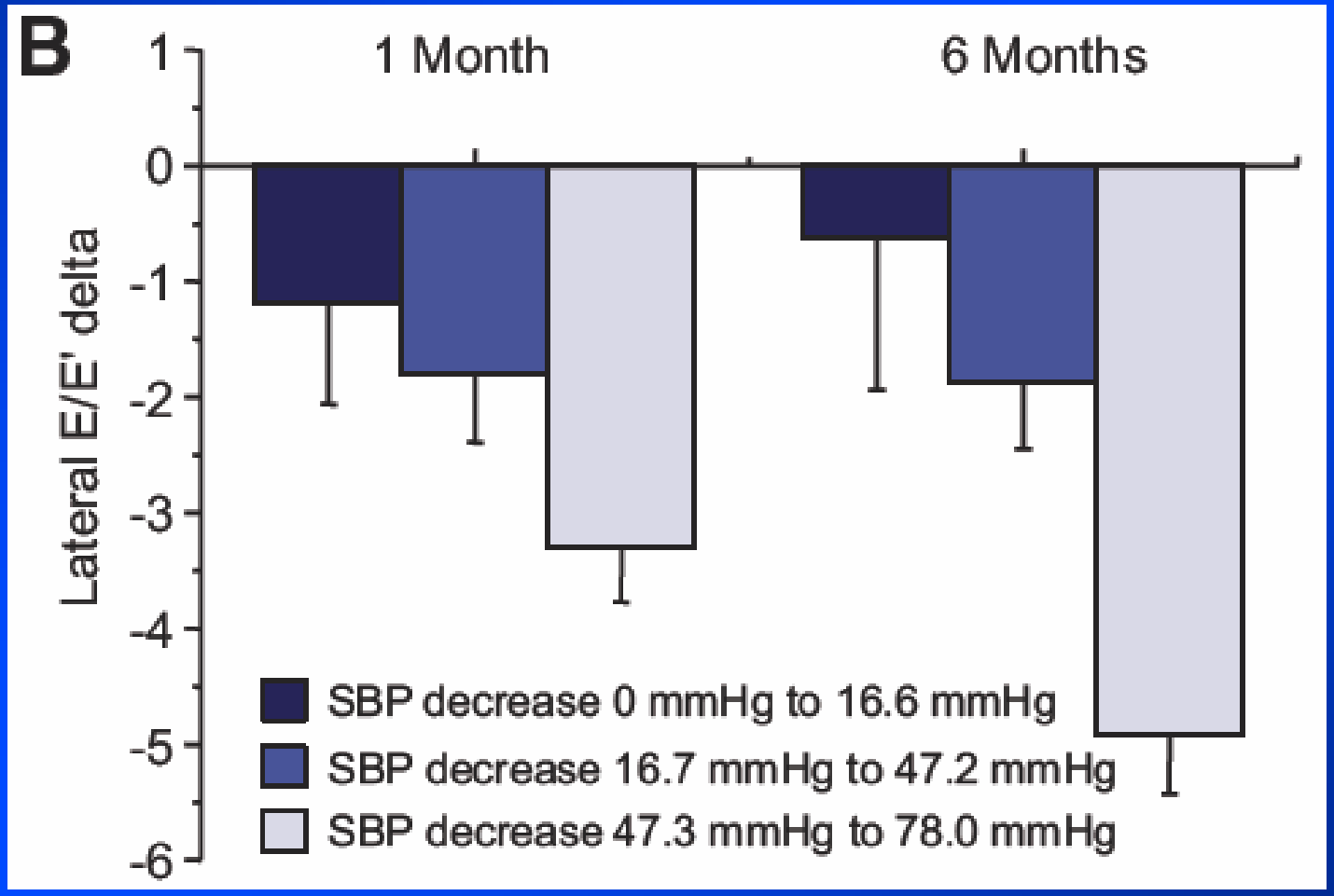
Brandt, JACC 2012

Left ventricular diastolic function according to baseline diastolic function



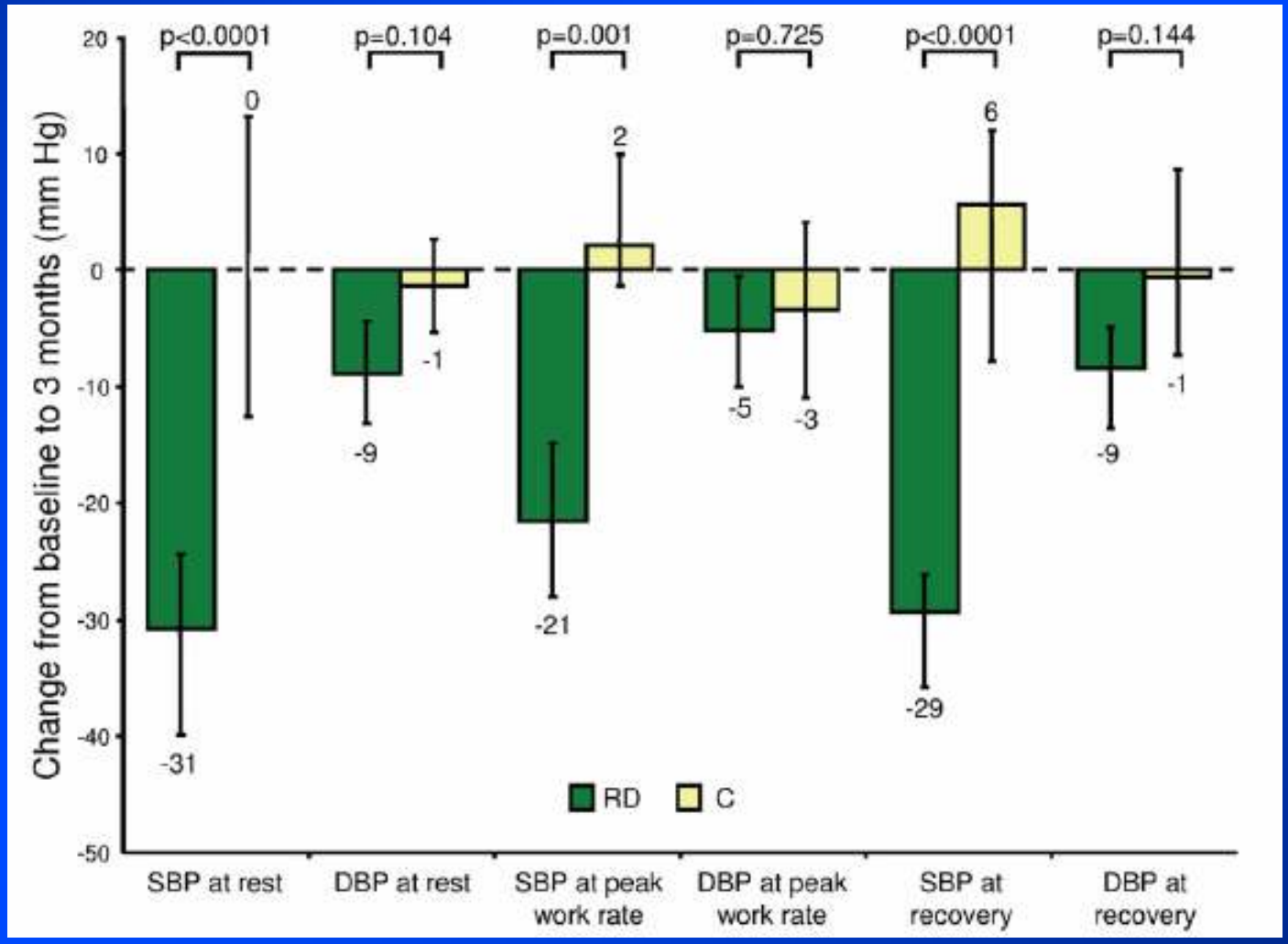
Brandt, JACC 2012

Left ventricular diastolic function according to blood pressure reduction



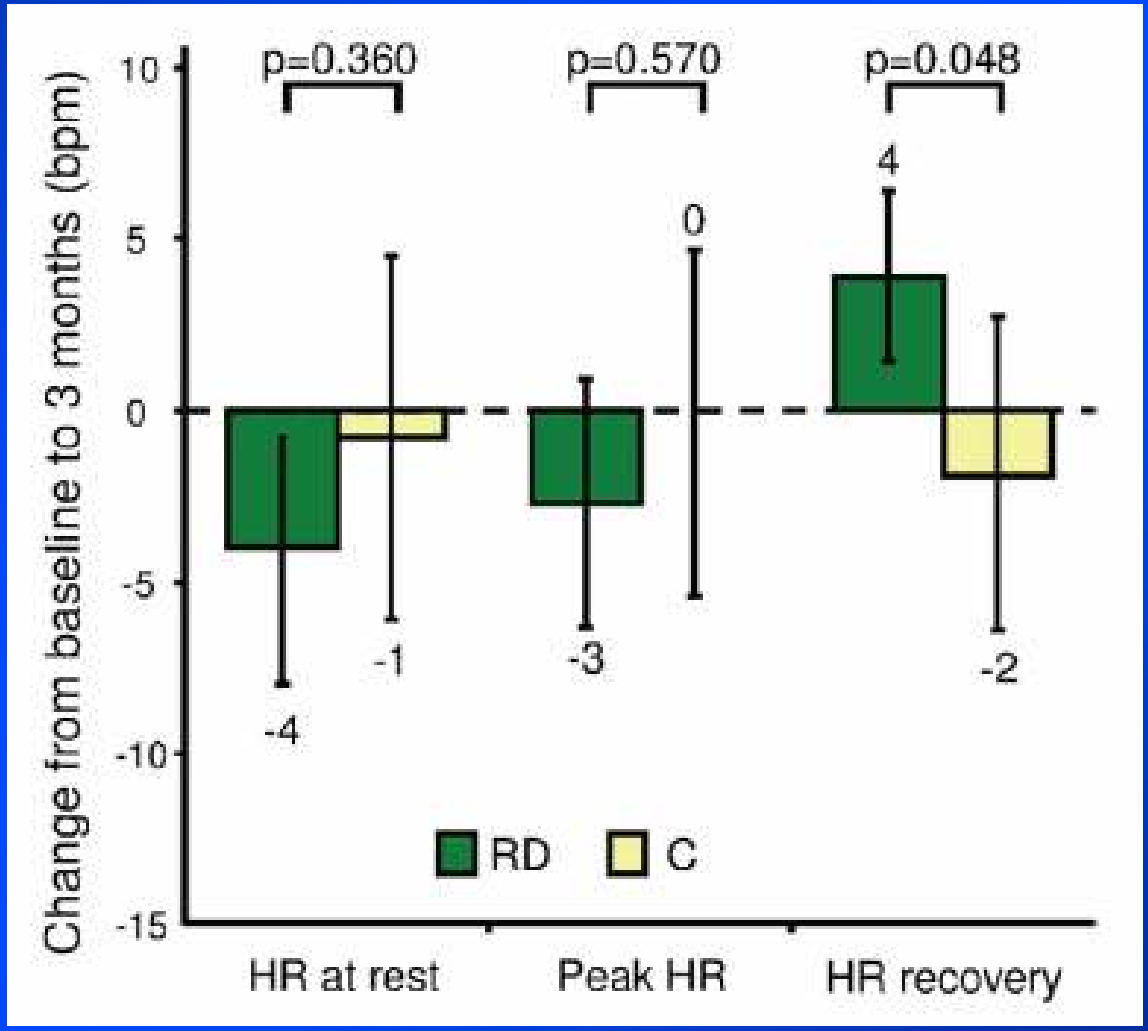
Brandt, JACC 2012

Exercise blood pressure



Ukena, JACC 2011

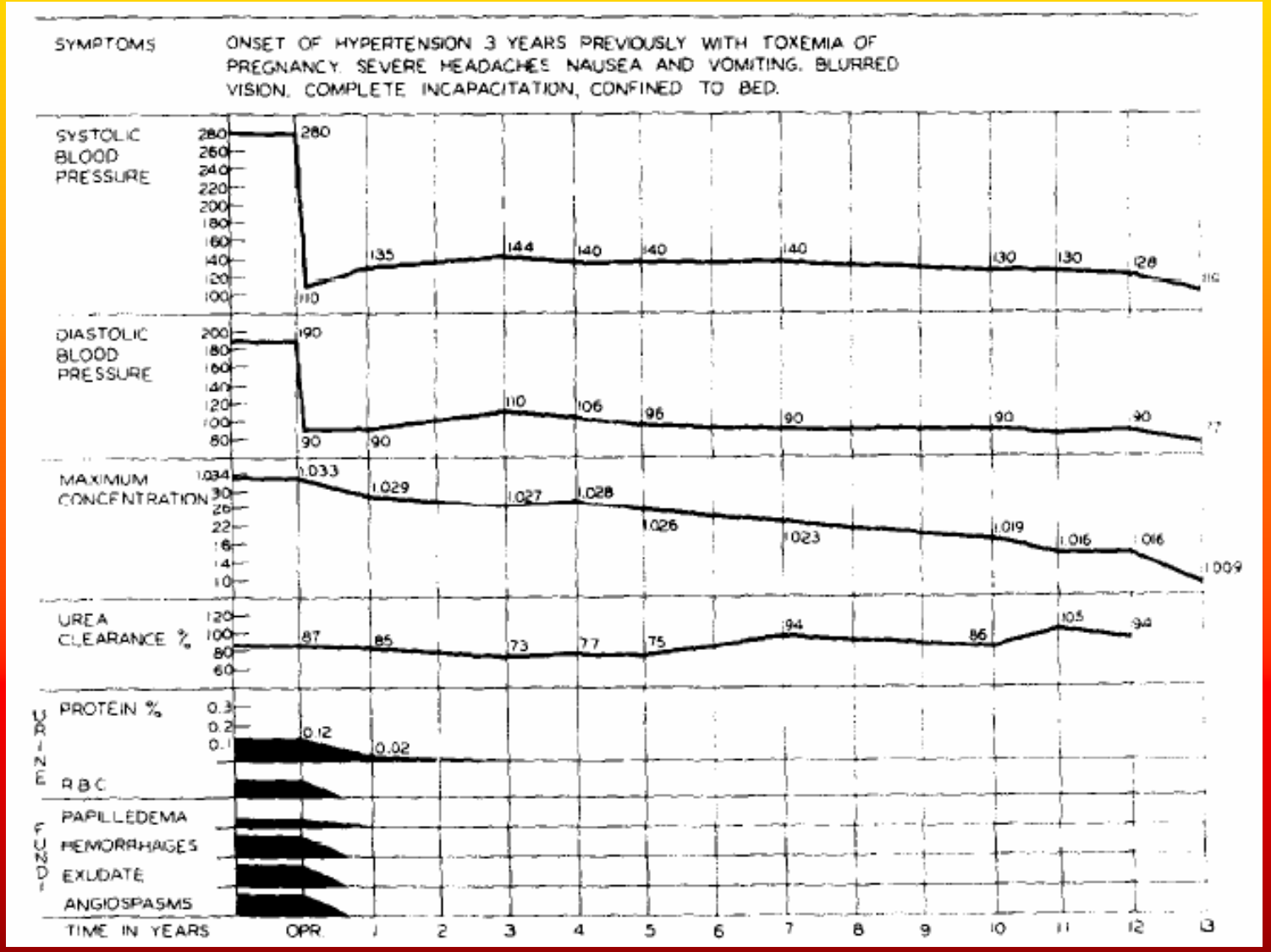
Exercise heart rate



Ukena, JACC 2011

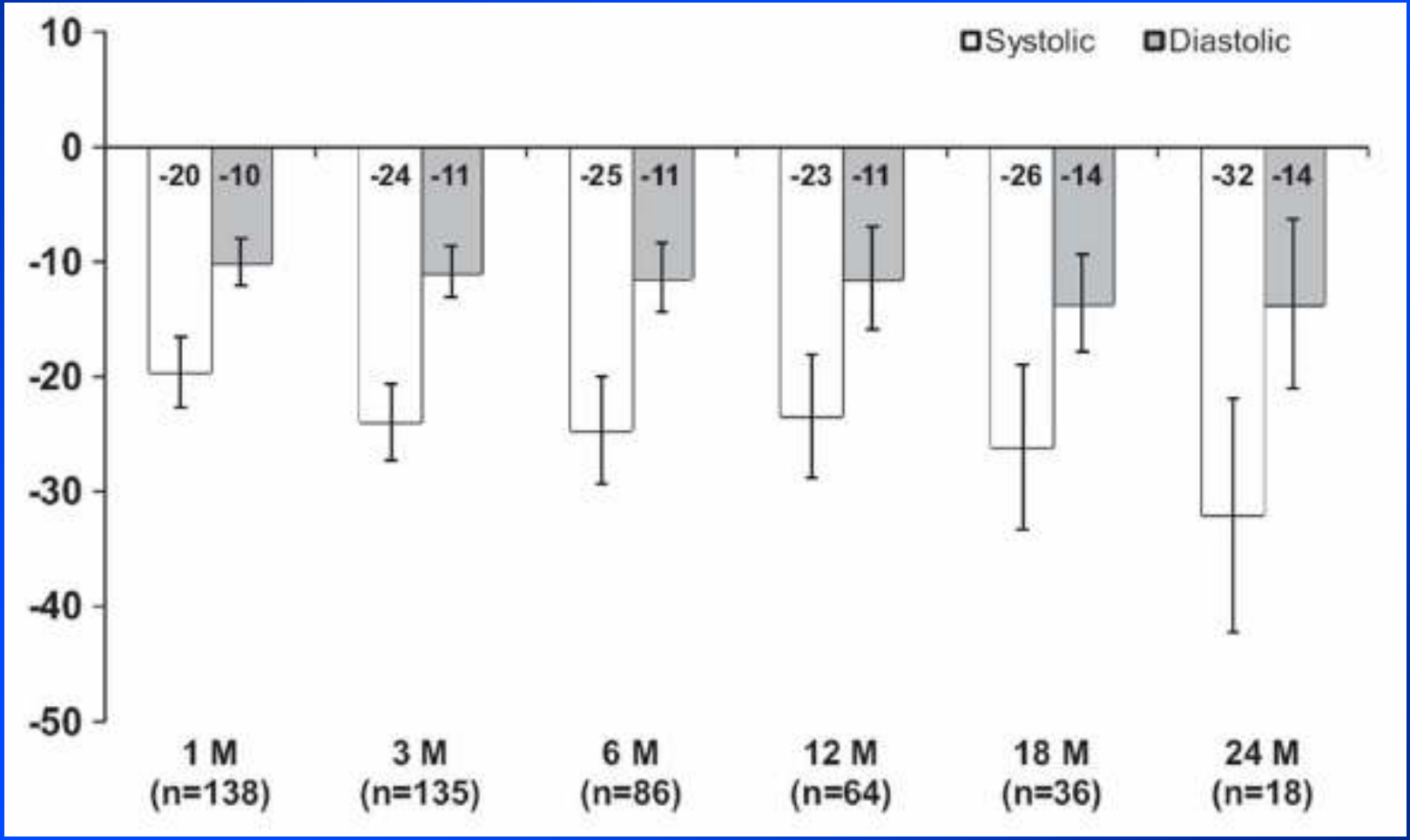
Long term efficacy

BP control was maintained long-term



Peet, Am J Surg 1948

2 year durability of bp reduction

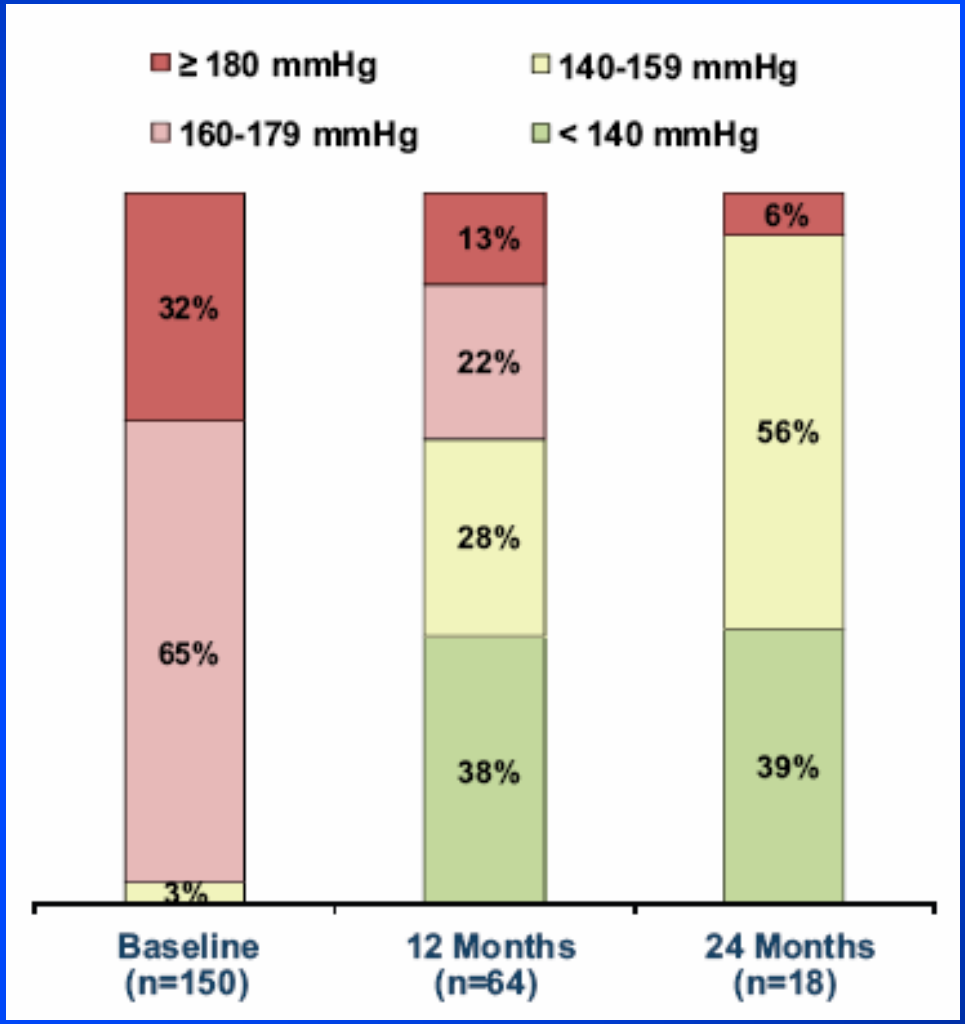


Krum, Hypertension 2011

Gradual bp decrease

- Gradual increase in blood pressure response rates, achieving 100% in 3 years
- Response defined as 10 mmHg bp reduction
- **But**
- Open label, small numbers
- Concomitant medications, salt
- Clinical significance in severe HTN?
- Mechanisms?

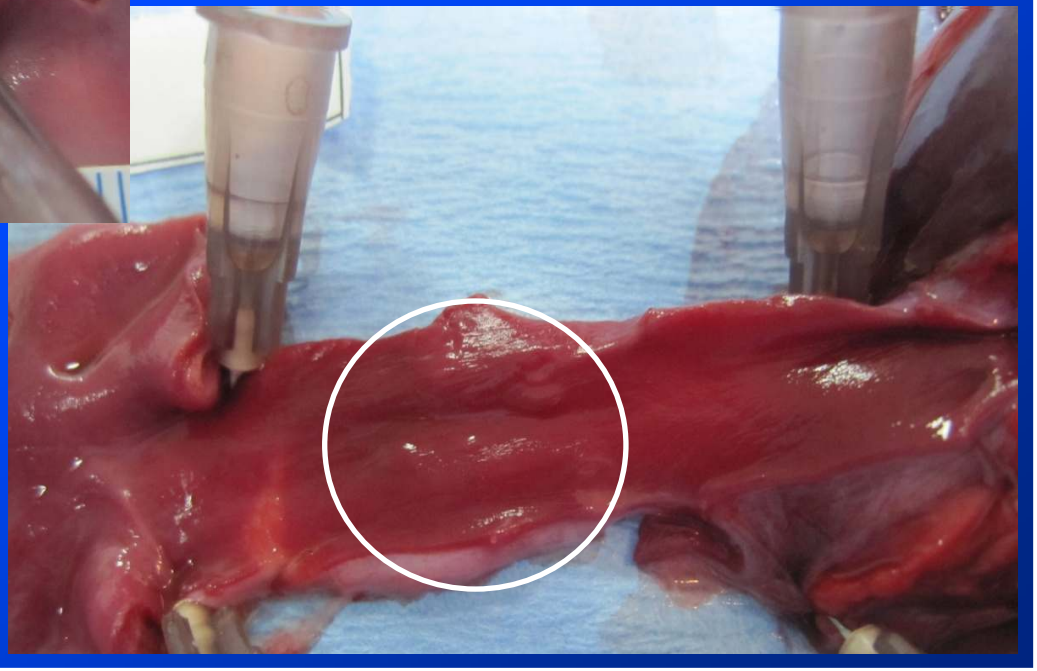
2 year control rates



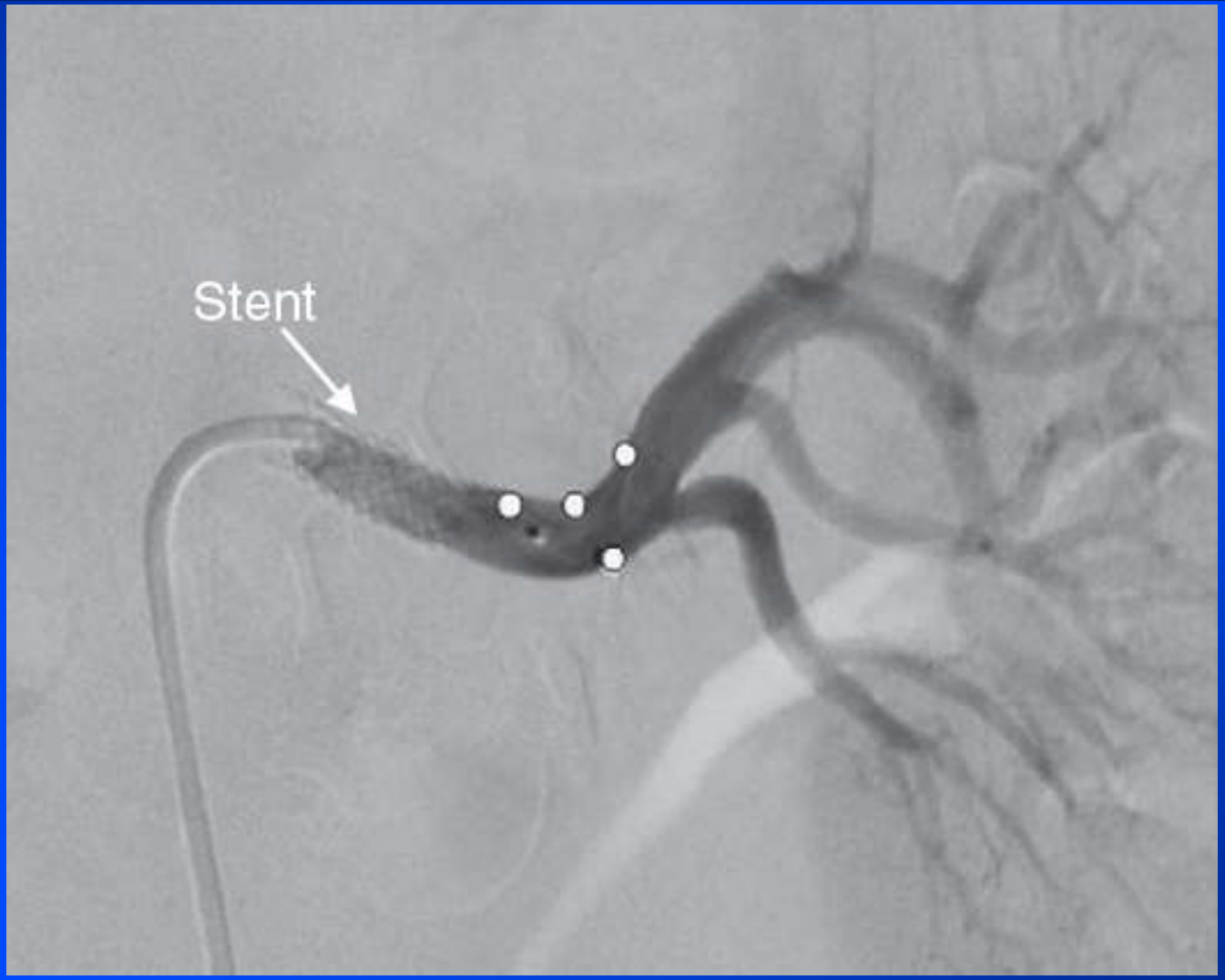
Krum, Hypertension 2011

Renal artery stenosis

Preclinical data
Imediately and one month after RSD

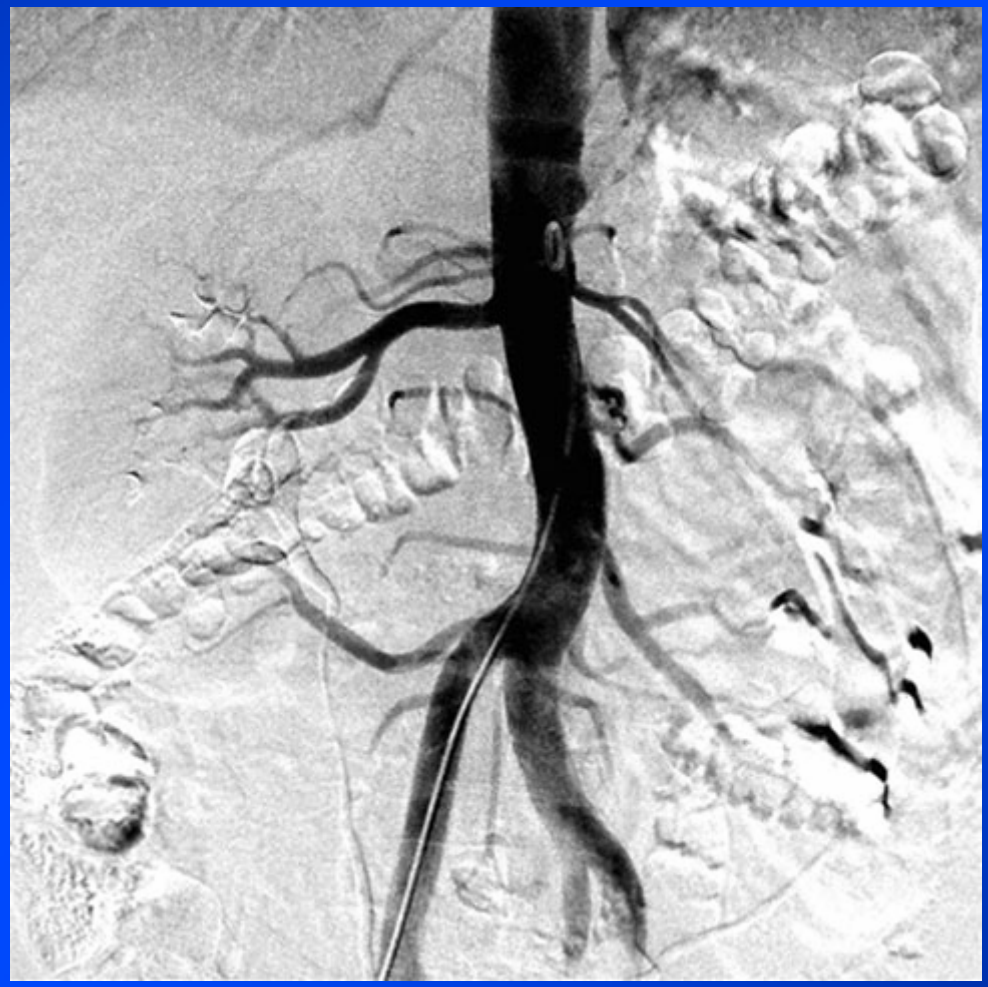


RSD in renovascular hypertension



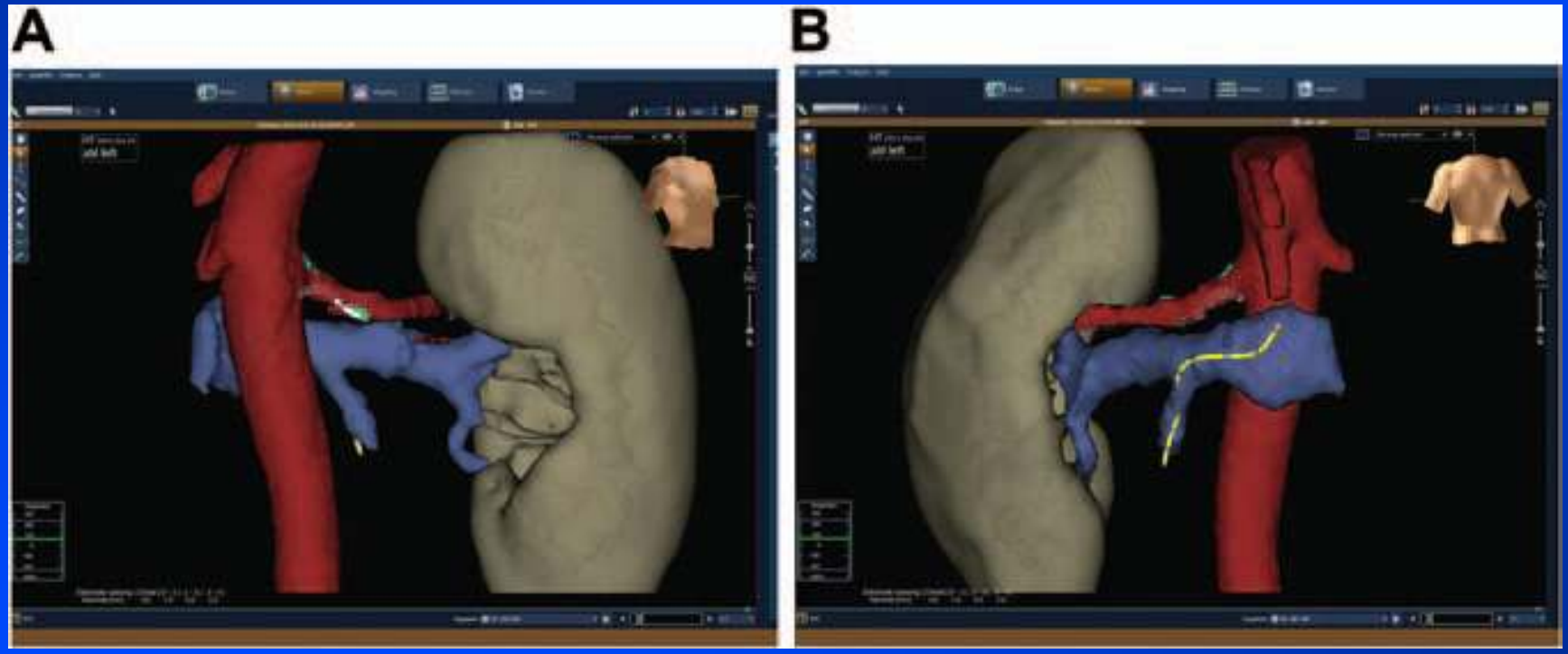
Hering, Int J Cardiol, 2011

Dual - auxiliary arteries



Contrast-induced nephropathy

3D – Renal sympathetic denervation
Minimal, if any, contrast



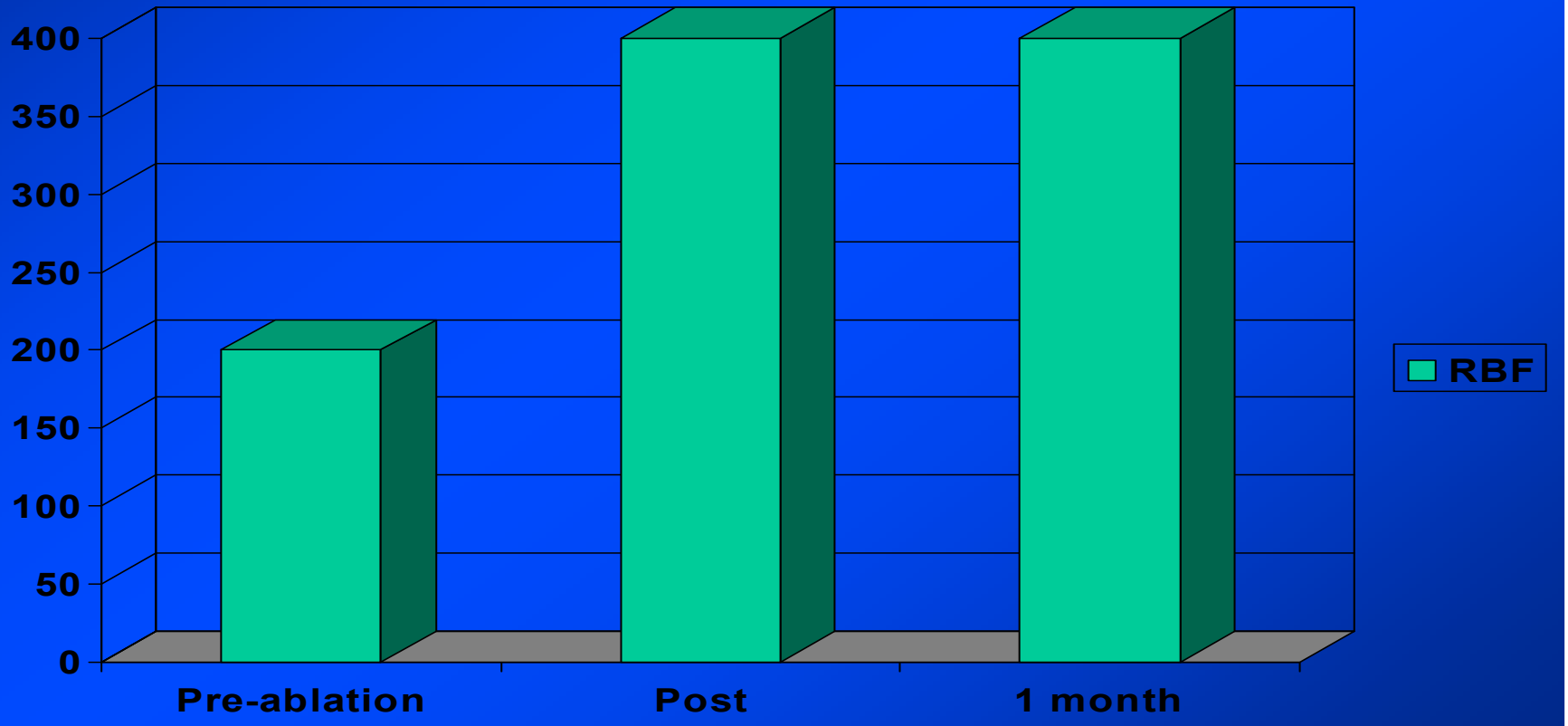
Anterolateral view

Posterior view

Lewalter, Hypertension 2012

Renal function

RSD – Renal blood flow



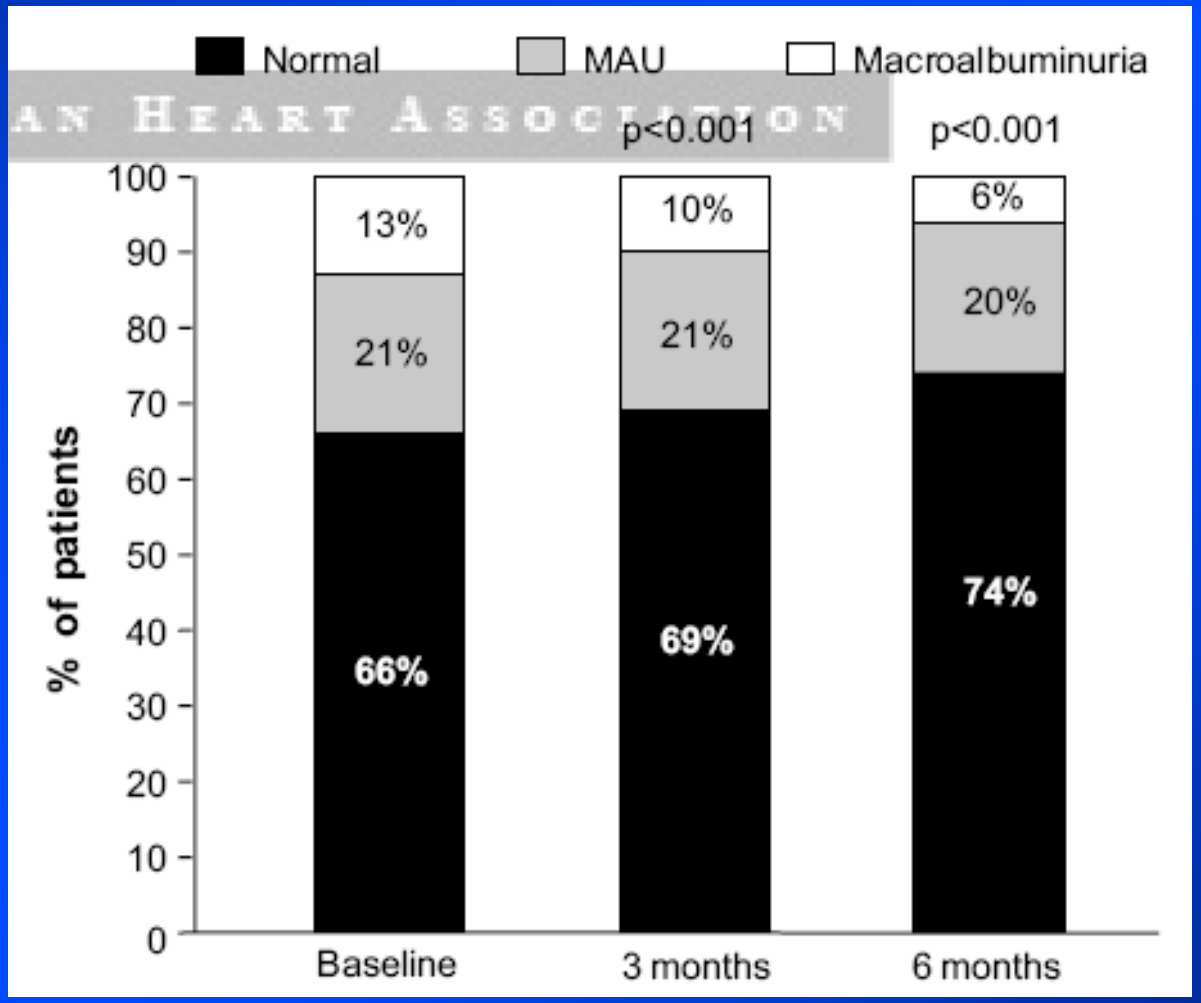
Unpublished data, Tsioufis

RSD and renal function

	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	−9.4±12.5 (−10%)	0.458	−15.1±11.1 (−15%)	0.208
RRI	−0.017±0.003 (−2%)	0.037	−0.021±0.004 (−3%)	0.017	+0.029±0.016 (+4%)	0.114	−0.002±0.022 (±0%)	0.943
UACR, mg/mmol	−0.49±0.51 (−31%)	0.335	−0.25±0.35 (−16%)	0.471	−0.48±0.56 (−32%)	0.407	+0.17±0.29 (+11%)	0.573

Mahmoud, Hypertension 2012

RSD and renal albumin excretion



Mahmoud, Hypertension 2012

Renal Sympathetic Denervation: Renal Function Concerns

To the Editor:

We have read the report of the Simplicity HTN-1 investigators on the 2-year durability of blood pressure reduction induced by catheter-based renal sympathetic denervation with great excitement[1] because it represents a promising approach for treatment of resistant hypertension.[2] However, several concerns arise that require clarification.

First, the effect of renal sympathetic denervation on renal function should be dealt with the greatest circumspection. In the 10 patients with available 2-year estimated glomerular filtration rate data, a decrease by −16.0 mL/min per 1.73 m^2 was noticed, which was as well observed to a lesser but significant degree (−7.8 mL/min per 1.73 m^2) in 5 of those patients who did not have spironolactone or another diuretic added after the first year of follow-up. This can be considered a dramatic fall when compared with the change observed in recent studies, for example, under antihypertensive treatment with ramipril (−1.96 mL/min per 1.73 m^2) or telmisartan (−3.05 mL/min per 1.73m^2) for the same follow-up period, in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial in high-risk patients.[3] Of note, patients undergoing renal denervation had significantly higher estimated glomerular filtration rate levels at baseline than the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial participants (83 versus 73.6 mL/min per 1.73 m^2, respectively). The impact of the 138 patients with available data on the first month after the procedure (−12/−8 versus −20/−10 mm Hg, respectively), ever since the third month of follow-up, their blood pressure reduction overcomes the mean blood pressure reduction of the whole group, which is particularly evident at 12 months (−33/−18 versus −23/−11 mm Hg, respectively). It would be interesting to know whether any antihypertensive drugs were added to these patients after the first month of follow-up, which might explain this divergence. The addition of low doses of spironolactone in patients with treatment-resistant hypertension may switch them over to the blood pressure control group,[4] and it seems that ≥5 of the 18 patients who completed the 2-year follow-up had spironolactone or another diuretic added after the first year.

Third, estimation of blood pressure reduction is based on office measurements and not on ambulatory blood pressure monitoring recordings, which is potentially limiting the validity of the findings.

Disclosures

None.

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2y - eGFR: - 16,0 ml/min/1.73m² - spiro

2y - eGFR: - 7,8 ml/min/1.73m²

Doumas, Hypertension 2011

The bright side of the moon

The future

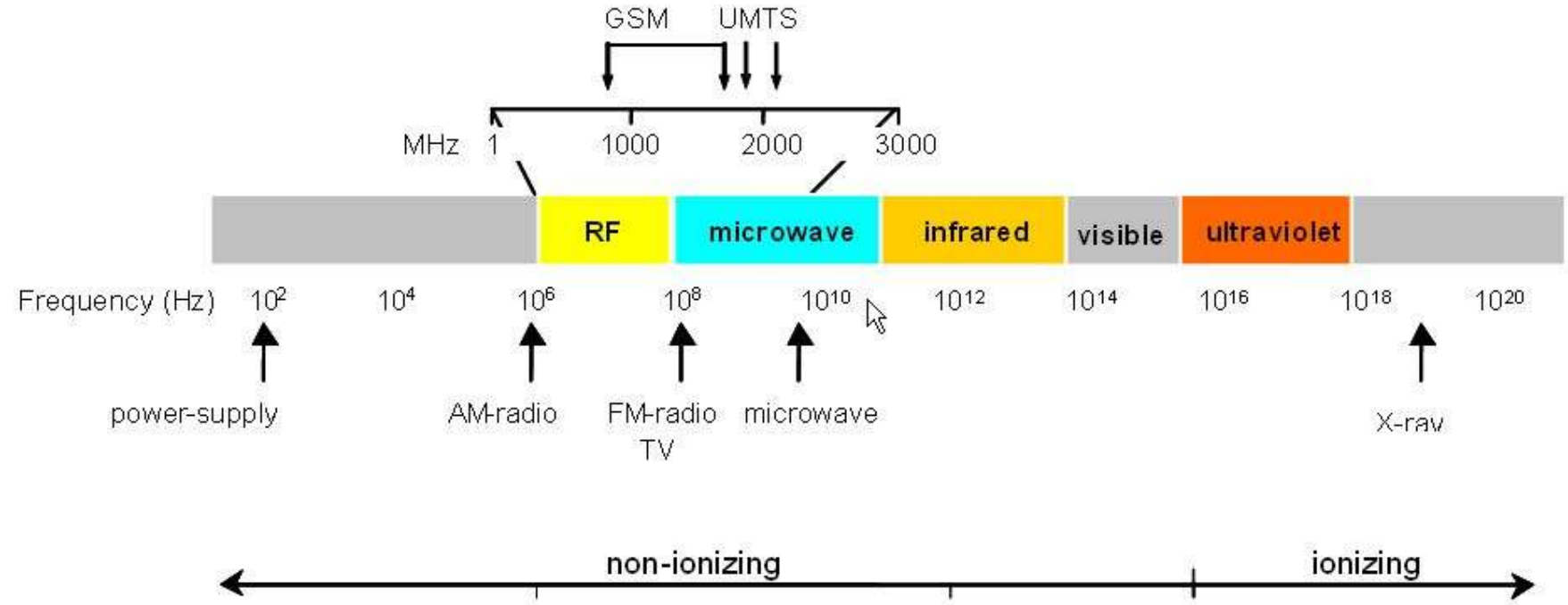
- To Improve CV outcomes?? Stroke, MI's? HF?
- Treatment of milder forms of HTN? Initial therapy?
- Hypertension in ESRD?
- Hypertension and HF, HFPEF??
- To slow atherosclerosis?
- Prevent diabetes?
- Prevent arrhythmia?
- Prevention of Renal Disease progression??
- ????

Other devices
St Jude

EnLigHTN
study

ASH 2011
New York

The future
Forms of energy

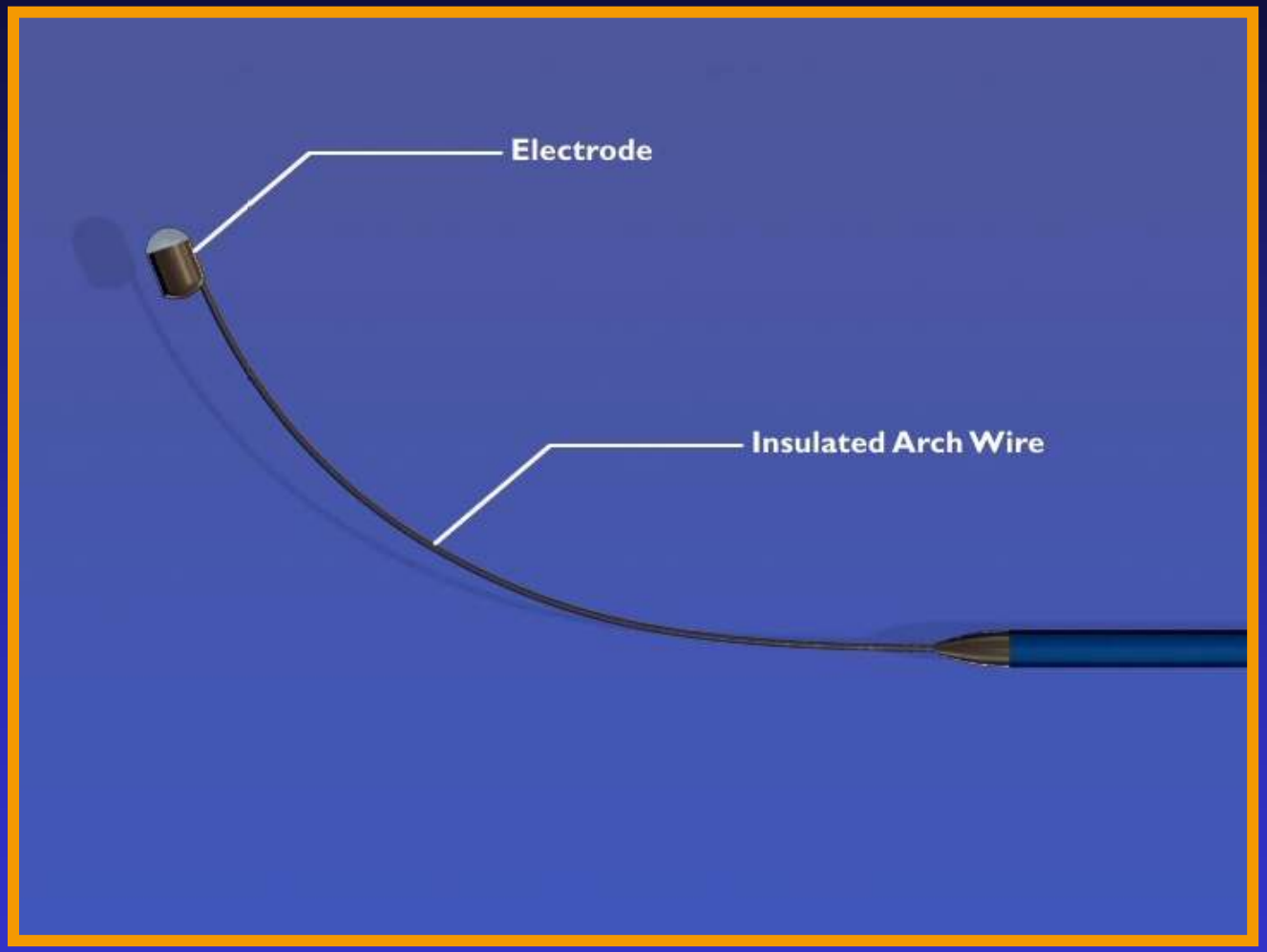


Other devices

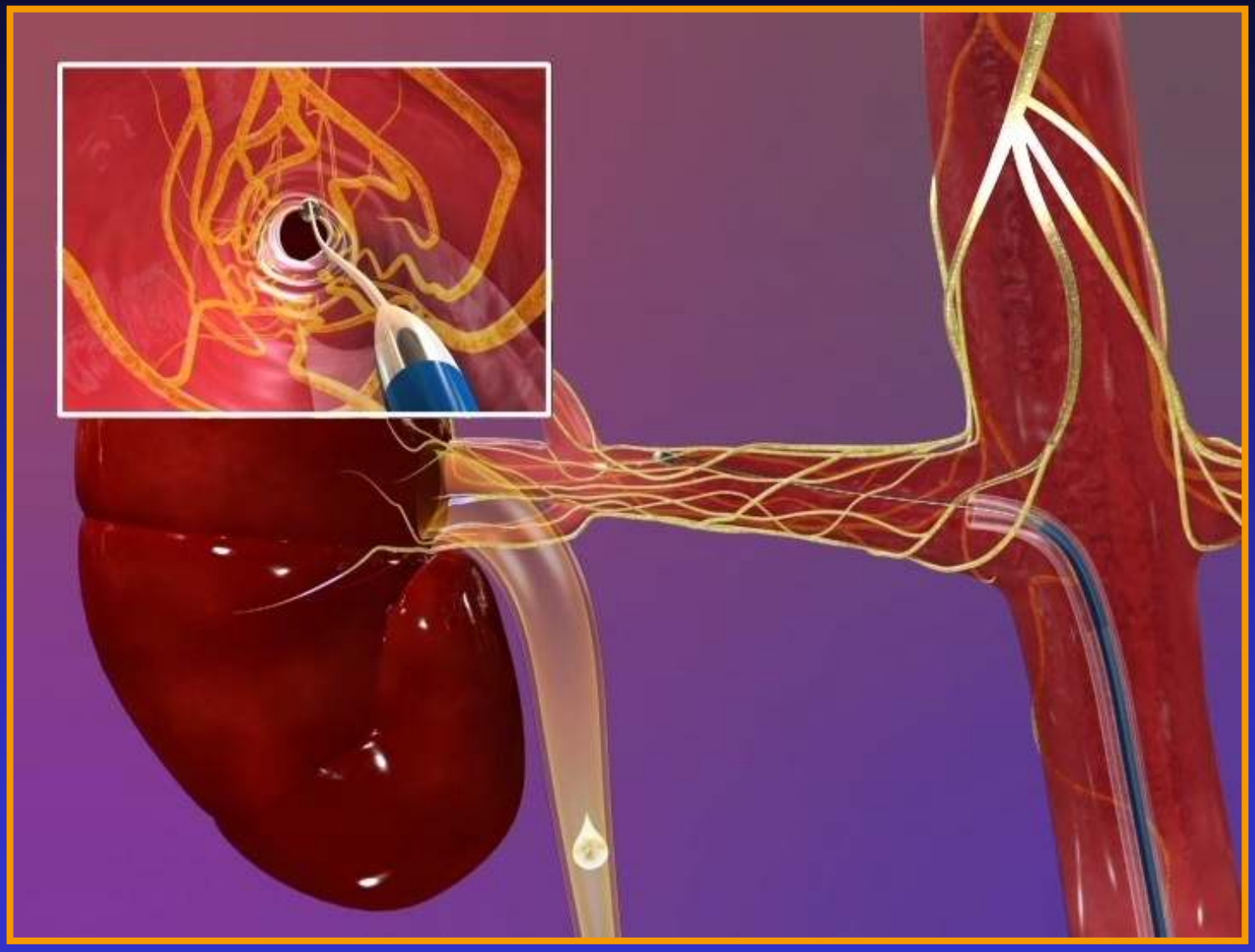
System	Overview	Data	BP drop mm Hg
Paradise (ReCor Medical)	Ultrasound energy	First-in-human (15 patients)	-32/-16 at 3 mo
Vascular renal denervation (Vessix)	Bipolar RF balloon catheter	REDUCE-HTN pilot (10 patients)	-30/-11 at 1 mo
Tivus (Cardiosonic)	Ultrasound energy	Animal data only	N/A

Symplicity® Catheter System

RF Ablation for Renal Denervation

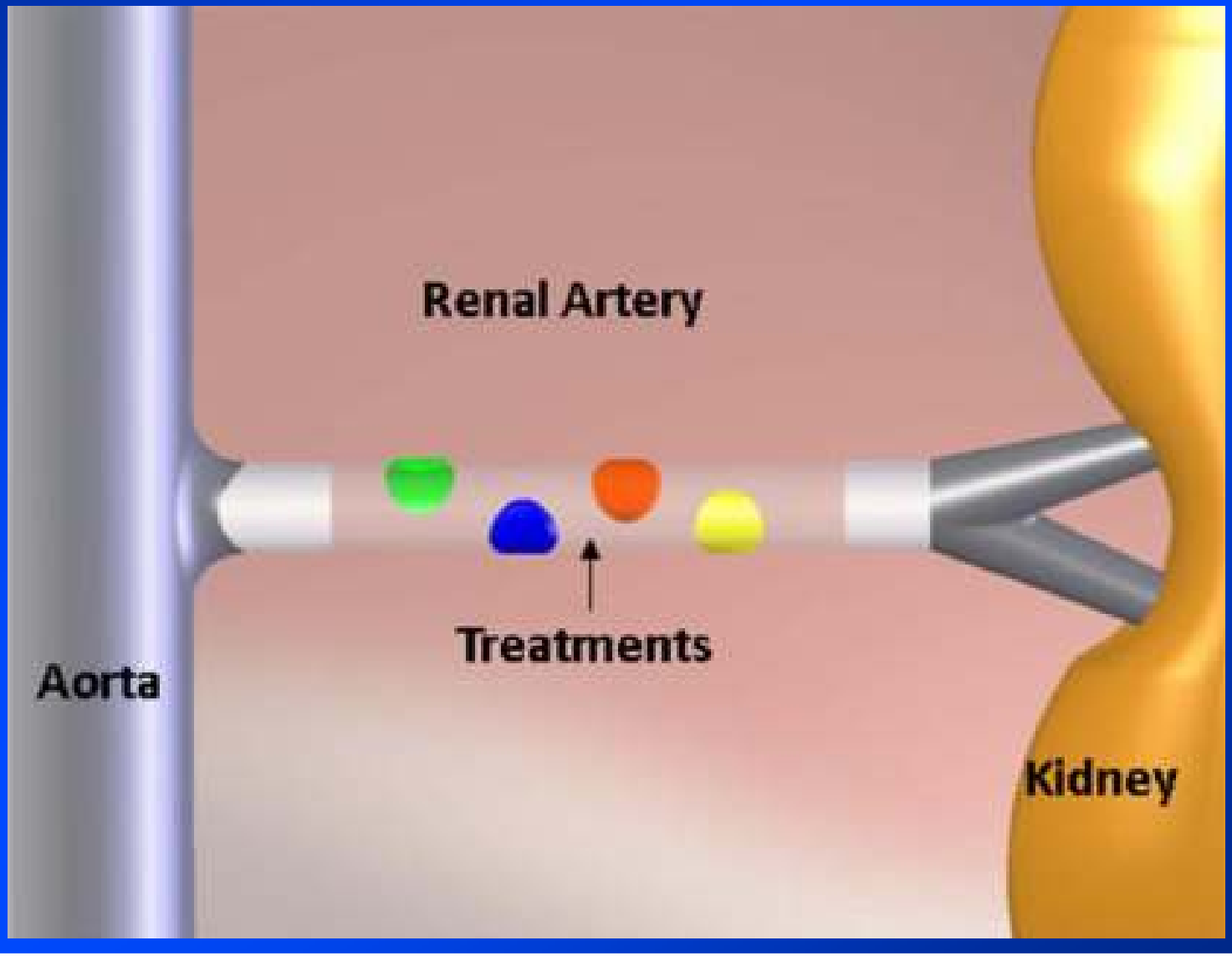


Placement



Renal sympathetic denervation
Schematic representation

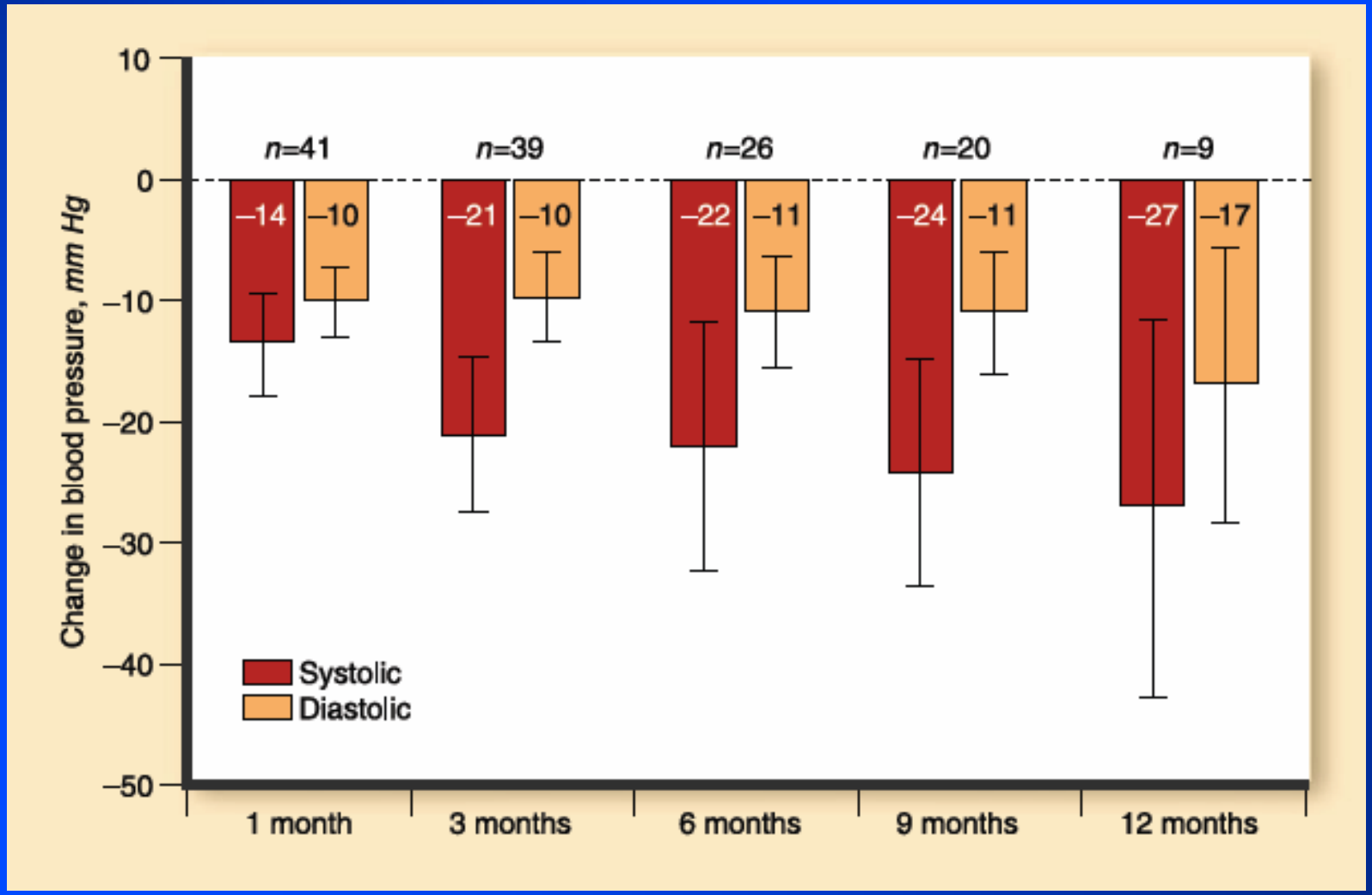
Renal sympathetic denervation
Schematic representation



Renal sympathetic denervation

Renal sympathetic denervation

Symplicity - 1



Krum, Lancet 2009

Interventional management of resistant hypertension

In the late 1940s, subdiaphragmatic splanchnicectomy was used for the treatment of severe hypertension.[1] Surgical sympathectomy was effective but carried a high price: prolonged hospitalisation, postural hypotension, syncope, impotence, and even difficulty in walking. and demanding techniques they used (noradrenaline spillover) to support their findings. Sympathetic renal activity has a role in the pathogenesis of hypertension, and renal denervation reduces blood pressure in animal models.[6] Not all experimental data, however, point in

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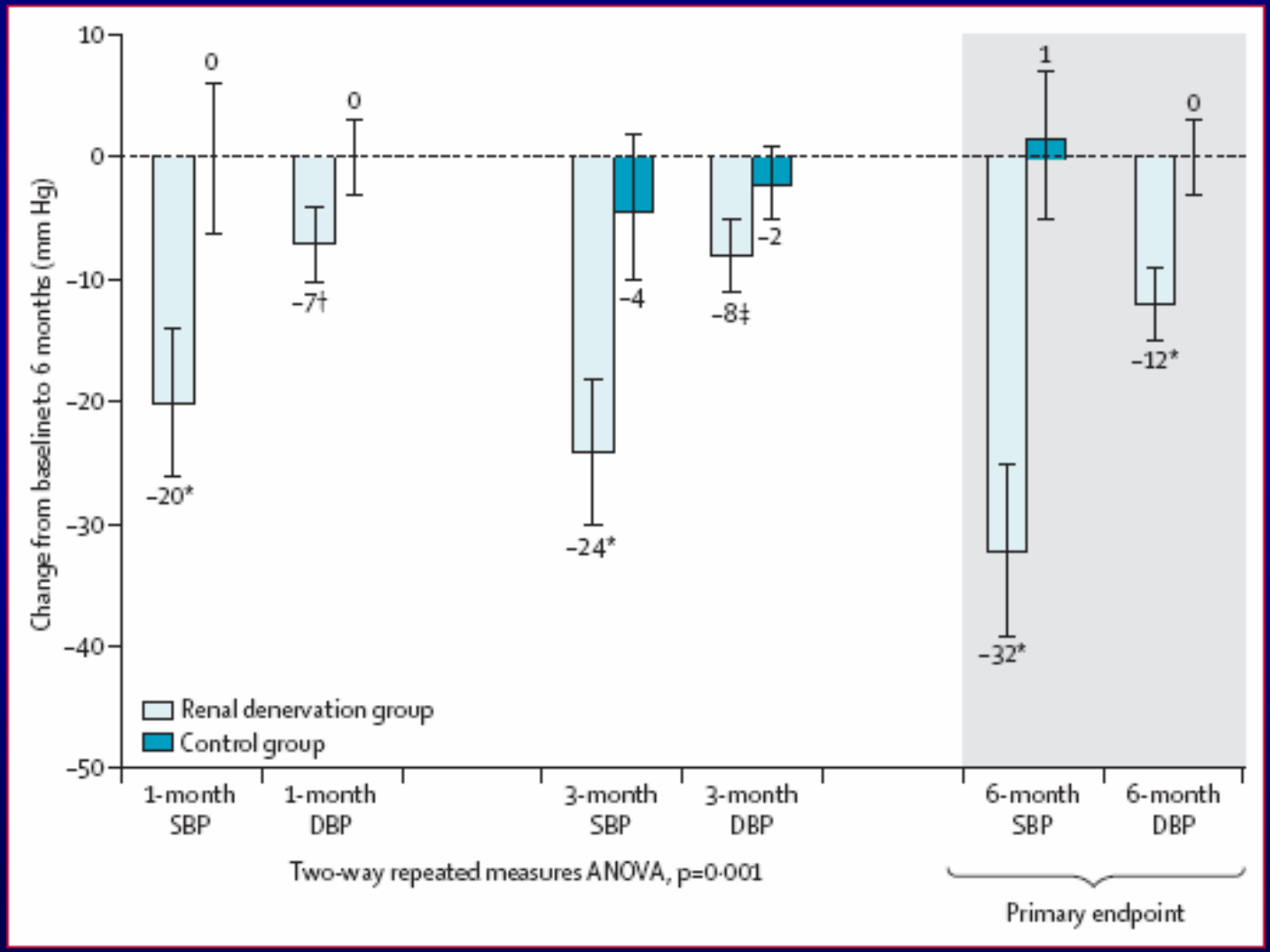
March 30, 2009
DOI:10.1016/S0140-6736(09)60624-3
See Online/Articles
DOI:10.1016/S0140-6736(09)60566-3

Need for a

Randomized, controlled study

Doumas, Lancet 2009

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



ABPM reduction

Should ambulatory blood pressure be mandatory in future studies in resistant hypertension?

Study (Author, Year)	Type of treatment	Treatment modality	Type of hypertension	Number of patients with office/ABPM measurements	Follow-up period	Baseline office SBP/DBP (mmHg)	Baseline 24-hour SBP/DBP (mmHg)	Reduction in office SBP/DBP (mmHg)	Reduction in 24-hour SBP/DBP (mmHg)	24-hour SBP reduction over office SBP reduction (%)	24-hour DBP reduction over office DBP reduction (%)
Mancia et al., 2004	Pharmacological	Antihypertensive medication	Moderate, Severe	About 5,800 (5,842 with SBP, 5,764 with DBP)	1 – 144 weeks	161.9/100.2	151.5/94.5	19.1/10.3	12.5/8.3	65%	81%
Ishikawa et al., 2008	Pharmacological	Antihypertensive medication	Moderate, Severe	1,246	1 week – 1 year	NA	NA	15.2/10.2	11.9/8.5	65%	83%
Bakris et al., 2010	Pharmacological	Darusentan	Resistant	364/ 279	14 weeks	151/88	134/78	15/10	10/8	67%	80%
Scheffers et al., 2010	Invasive	Rheos device	Resistant	37/26	3 months	179/105	NA	21/12	6/4	29%	33%
Krum et al, 2009	Invasive	RSD	Resistant	45/9 (responders)	1 month	177/101	NA	27/NA	11/NA	41%	NA
Simplicity HTN-2 investigators, 2010	Invasive	RSD	Resistant	49/20	6 months	178/96	NA	32/12	11/7	34%	58%
Witkowski et al., 2011	Invasive	RSD	Resistant, comorbid OSA	10	6 months	173/106	140/82	34/13	6/NA	18%	NA

Doumas, J Hypertens 2012

RSD in CKD patients

Table 3. Office and ambulatory BP and heart rate before and after renal denervation

Measurement	Baseline (*n*=15)	3-Month Follow-up (*n*=15)	6-Month Follow-up (*n*=8)	*P* Values	
				Baseline versus 3-Month Follow-up	Between Treatments
SBP					
office (mmHg)	174±22	147±29	145±18	<0.001	<0.001
ABPM mean (mmHg)	159±14	153±16	154±21	0.24	0.49
ABPM daytime (mmHg)	160±14	156±19	160±14	0.53	0.84
ABPM night-time (mmHg)	154±16	140±22	144±22	0.03	0.10
maximum night-time (mmHg)	185±19	171±22	166±33	0.04	0.14
dipping status (%)	4±6	11±9	10±9	0.01	0.04
rate of rise (mmHg/hr)	12.07±7.7	2.09±1.6	4.8±6.1	0.05	0.03
BP power surge (log) (mmHg)	1.6±1.8	0.6±1.0	1.4±1.0	0.01	0.03
Night-to-day ratio	0.96±0.06	0.89±0.08	0.89±0.08	0.01	0.04

Hering, JASN 2012

The dark side of the moon

Interventional management of resistant hypertension

In the late 1940s, subdiaphragmatic splanchnicectomy was used for the treatment of severe hypertension.[1] Surgical sympathectomy was effective but carried a high price: prolonged hospitalisation, postural hypotension, syncope, impotence, and even difficulty in walking. and demanding techniques they used (noradrenaline spillover) to support their findings. Sympathetic renal activity has a role in the pathogenesis of hypertension, and renal denervation reduces blood pressure in animal models.[6] Not all experimental data, however, point in

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See Online/Articles
DOI:10.1016/S0140-6736(09)60566-3

tension. Every innovative technique raises several questions that need to be answered: is this effective and safe; is it meaningful with a rationale; what are the long-term results; are there limitations; what else has to follow; and can it be widely applied?

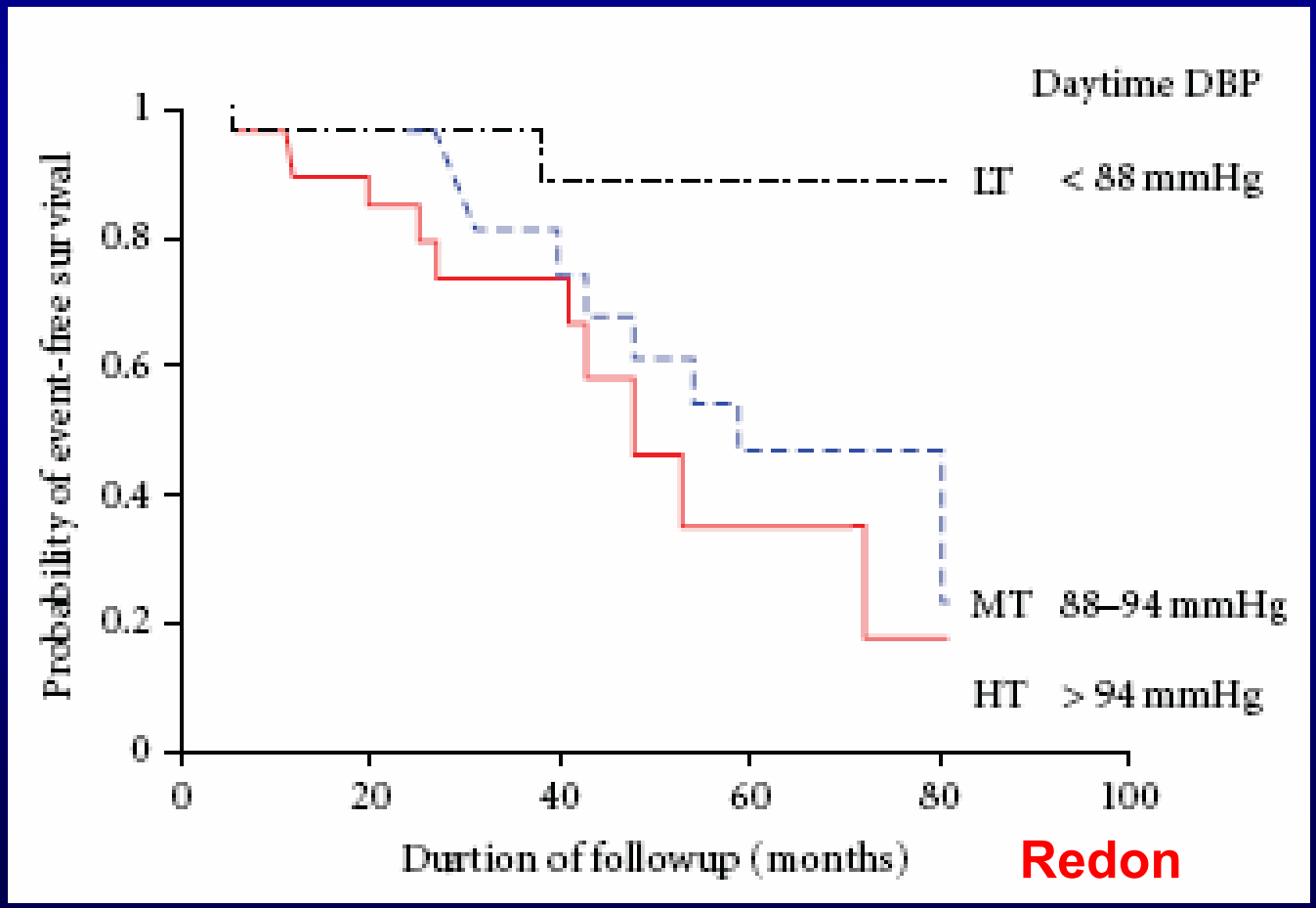
Concerns !!!

Doumas, Lancet 2009

Benefits from Treatment and Control of Patients with Resistant Hypertension

Int J Hypertens 2011

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]



Redon

In patients,

whose hearts have been beating with undue quickness and force,

I have often,

in a few seconds,

retarded their motion many pulsations in a minute,

by strong pressure on one of the carotid arteries

Parry 1799

THERAPEUTICS OF THE CIRCULATION

EIGHT LECTURES DELIVERED IN THE SPRING OF 1905
IN THE PHYSIOLOGICAL LABORATORY OF THE
UNIVERSITY OF LONDON

BY SIR LAUDER BRUNTON, Bt.,
M.D., D.Sc., LL.D. (Edin.), LL.D. (Aberd.), F.R.C.P., F.R.S.
CONSULTING PHYSICIAN TO ST BARTHOLOMEW'S HOSPITAL

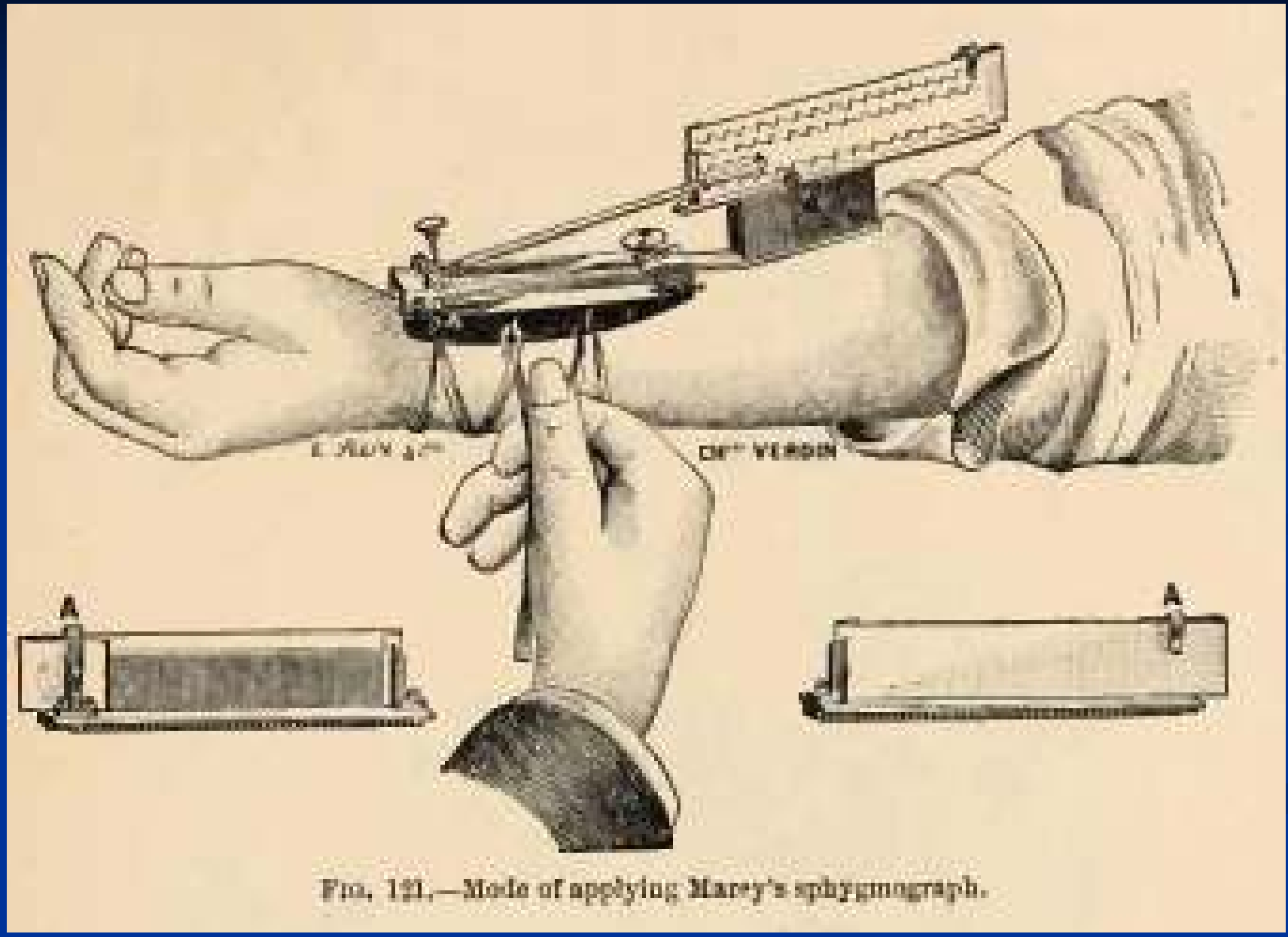


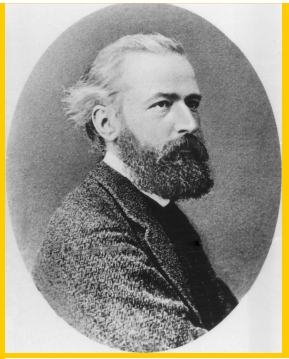
FIG. 121.—Mode of applying Marey's sphygmograph.

It may be doubted whether these instruments,

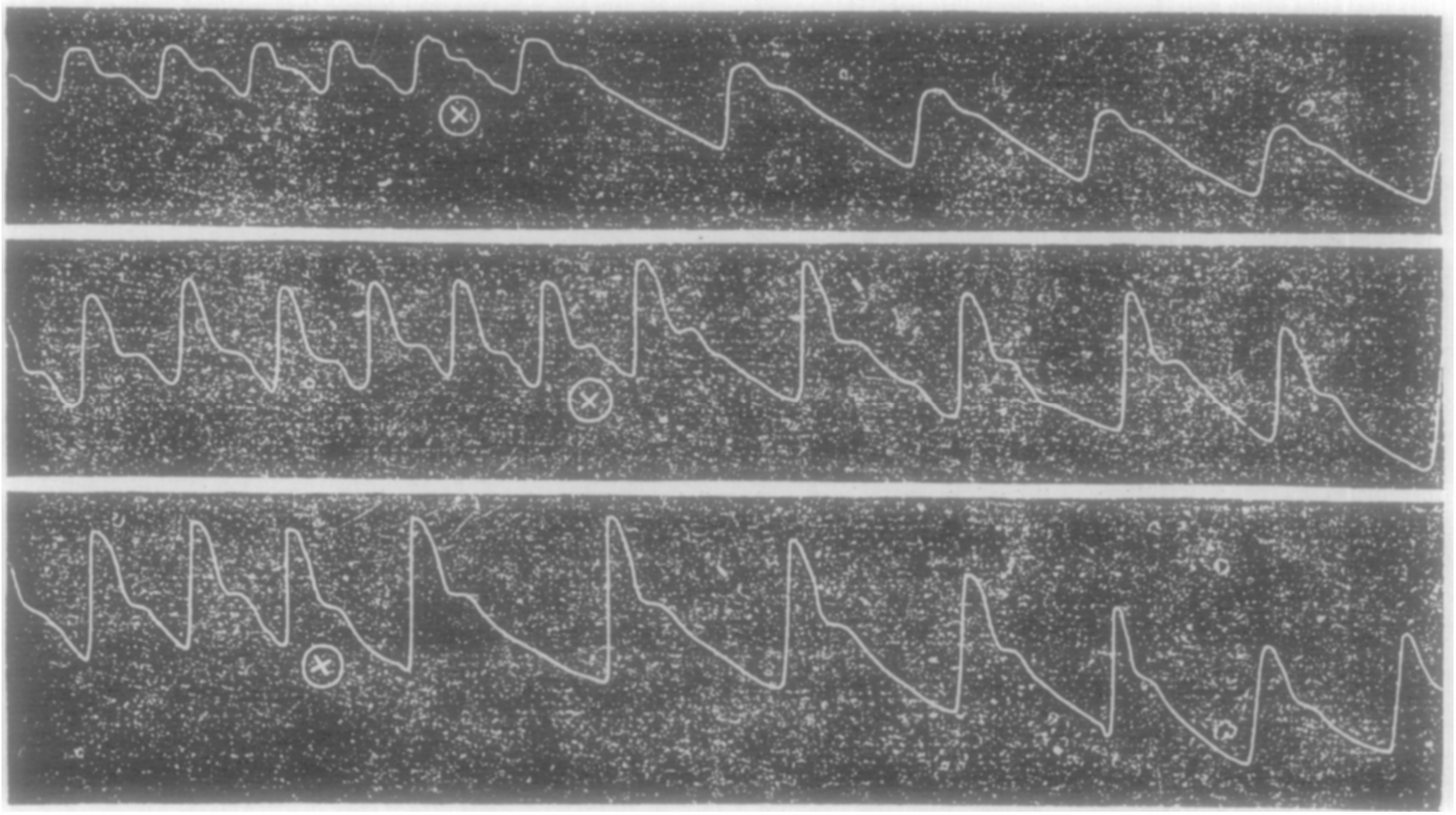
though very ingenious,

will ever prove actually useful in practice

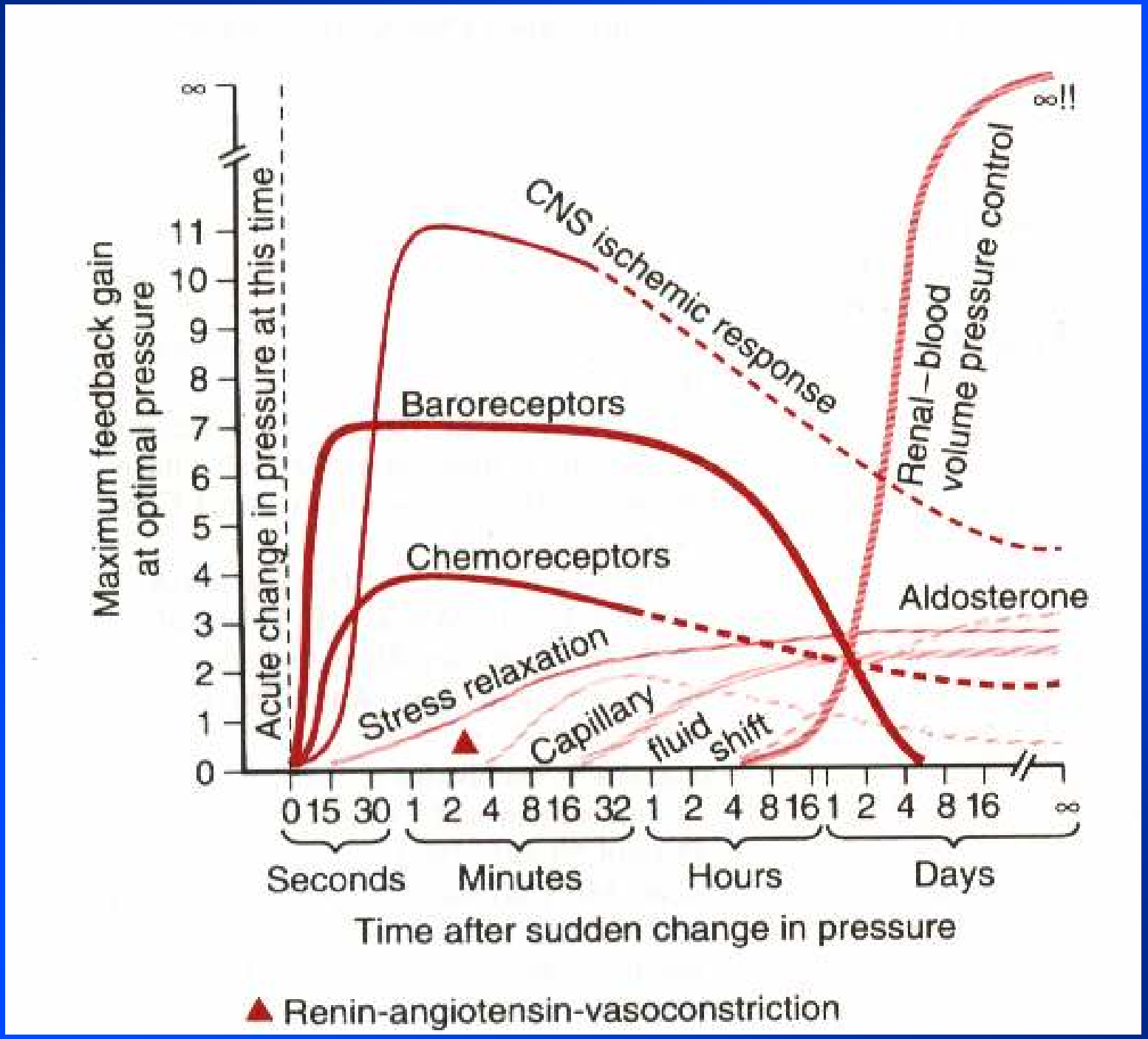
Lancet 1860, i:435



Carotid baroreceptor stimulation



Czermak 1865


Maximum feedback gain at optimal pressure
Acute change in pressure at this time
∞
11
10
9
8
7
6
5
4
3
2
1
0
CNS ischemic response
Baroreceptors
Chemoreceptors
Stress relaxation
Capillary fluid shift
Renal–blood volume pressure control
∞!!
Aldosterone
0 15 30 1 2 4 8 16 32 1 2 4 8 16 1 2 4 8 16 ∞
Seconds
Minutes
Hours
Days
Time after sudden change in pressure
▲ Renin-angiotensin-vasoconstriction

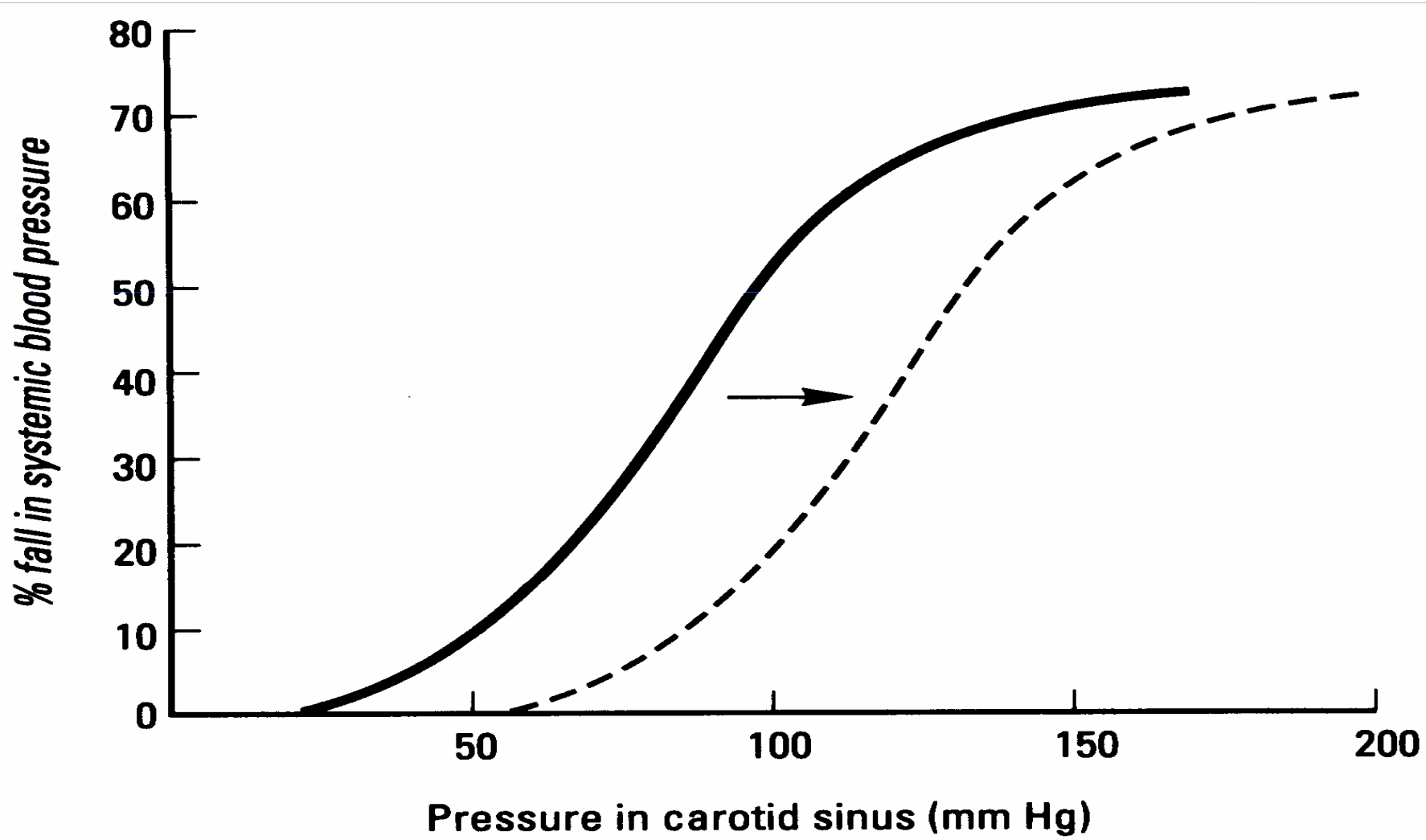


Figure 31–9. ***Solid line:*** Fall in system blood pressure produced by raising the pressure in the isolated carotid sinus of a normal monkey to various values. ***Dashed line:*** Response in a hypertensive monkey, demonstrating baroreceptor resetting.

Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia

EUGENE BRAUNWALD, M.D., STEPHEN F. VATNER, M.D., NINA S. BRAUNWALD, M.D., AND BURTON E. SOBEL, M.D., *San Diego*

From the Departments of Medicine and Surgery, University of California, San Diego, School of Medicine, La Jolla.

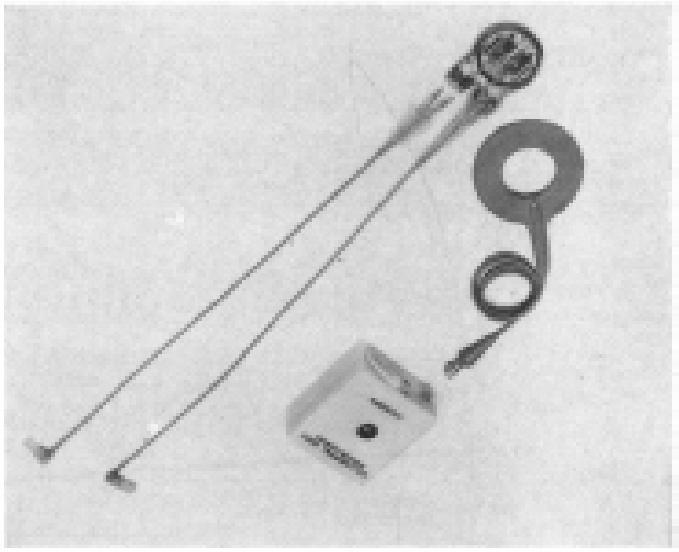
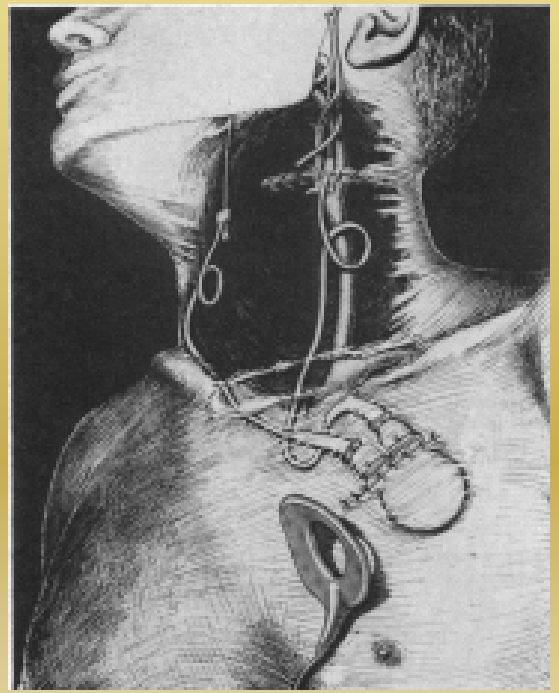
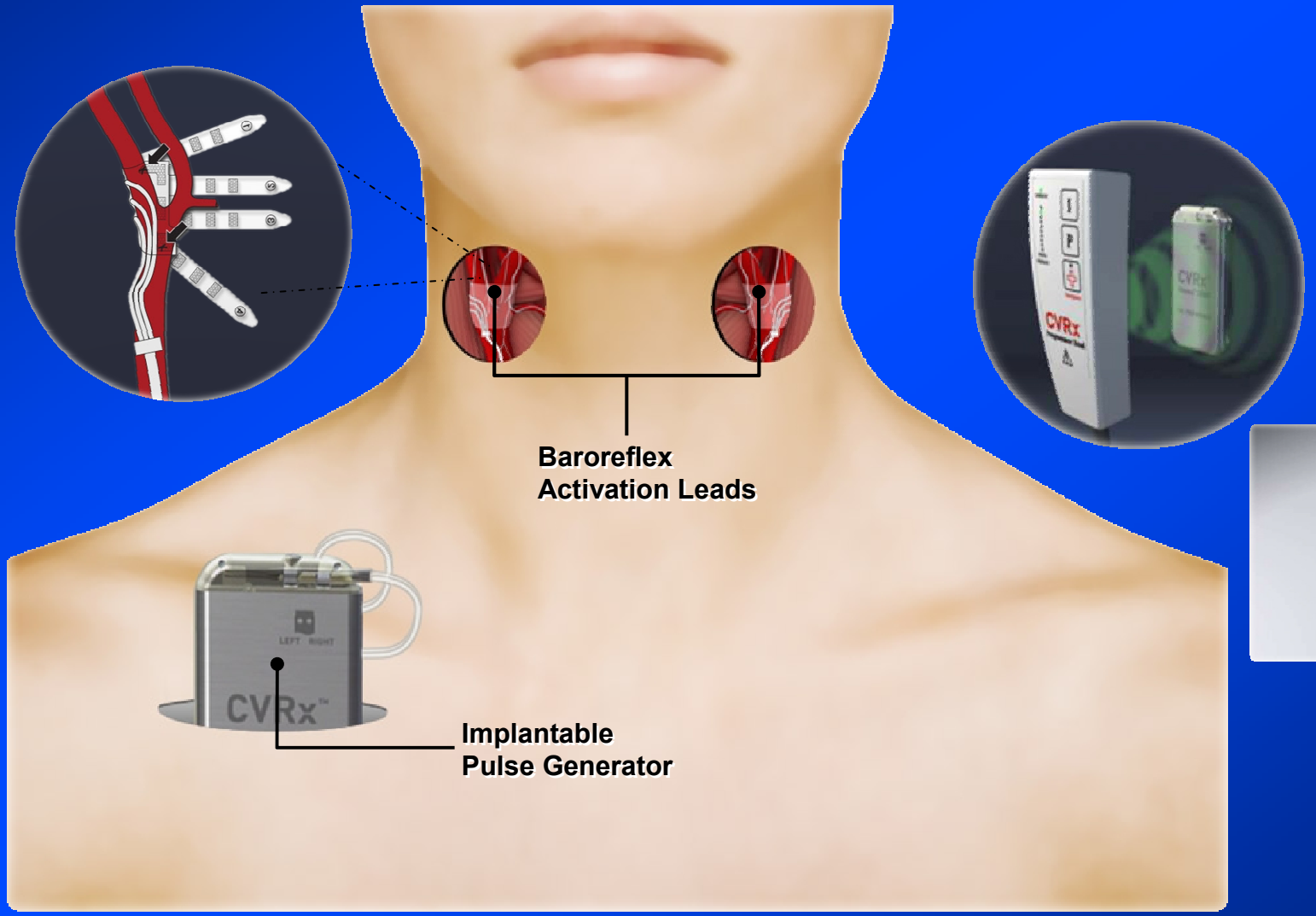


Figure 5.—The radiofrequency stimulator used in the treatment of angina pectoris. The transmitter and antenna are worn externally and are shown at the right. The implanted receiver unit is seen at the top.

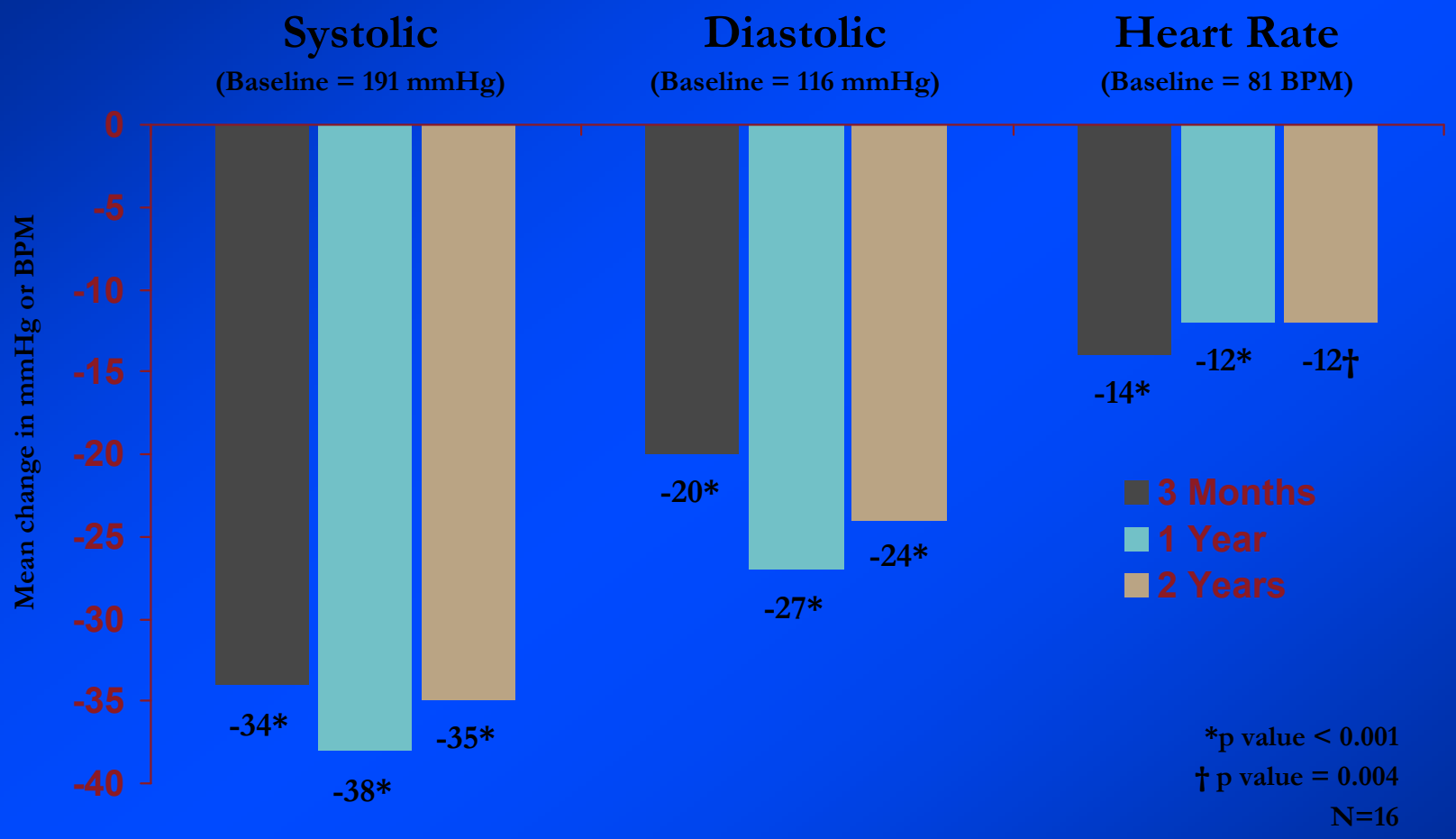


Carotid baroreceptor activation



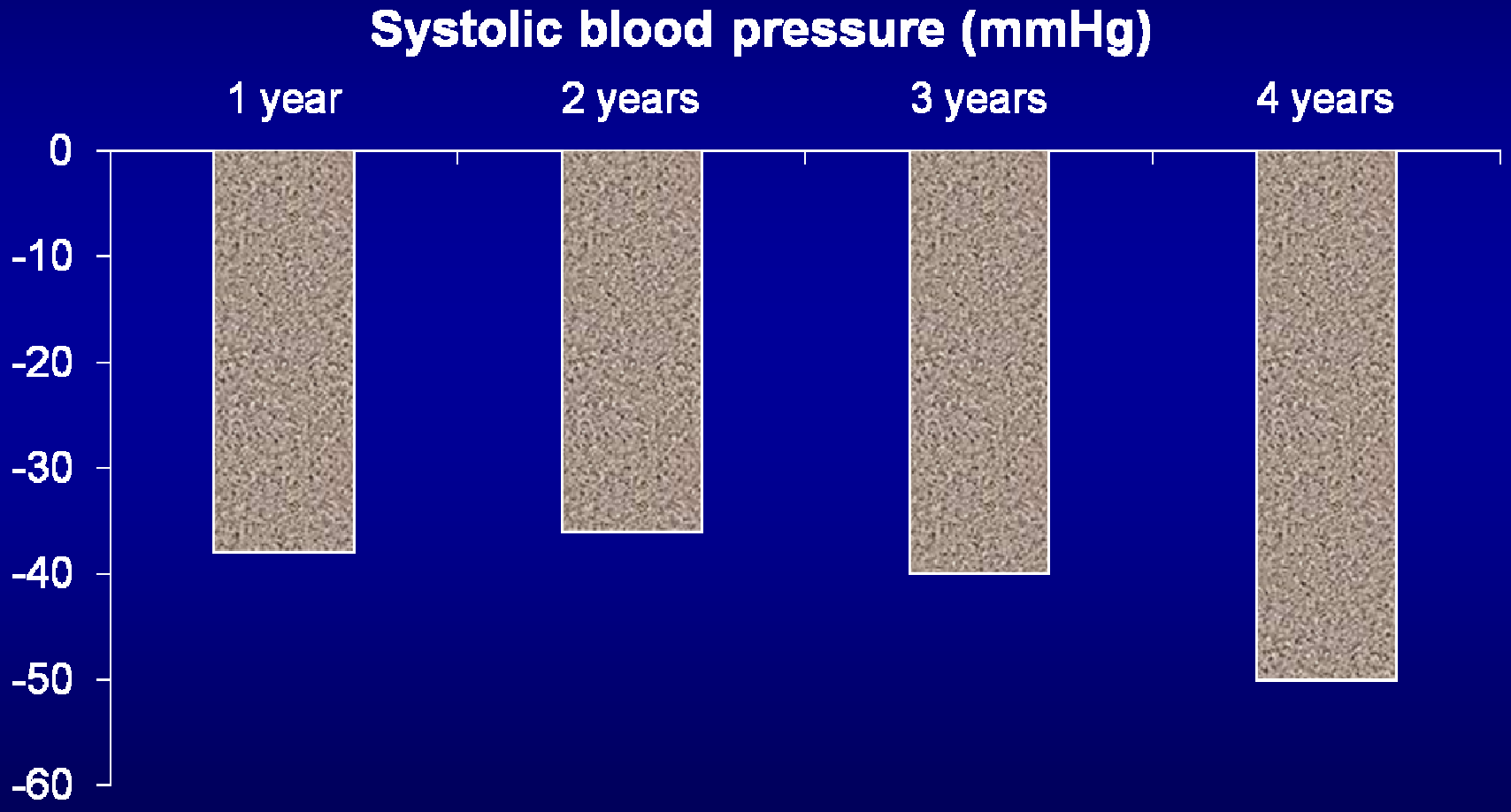
Programming System

Office BP Response to Rheos Therapy



Schelfers IJ. *Journal of Hypertension* 2008;26[Suppl 1]:S19.

Sustained Blood Pressure Reduction with Baroreceptor Stimulation Therapy



Doumas, Curr Hypertens Reports 2012