

Renal denervation in the management of hypertension.

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Outline of presentation

Rationale for renal denervation

Introduction

Sympathetic hyperactivity: pathogenesis
why important
treatment options

Renal denervation

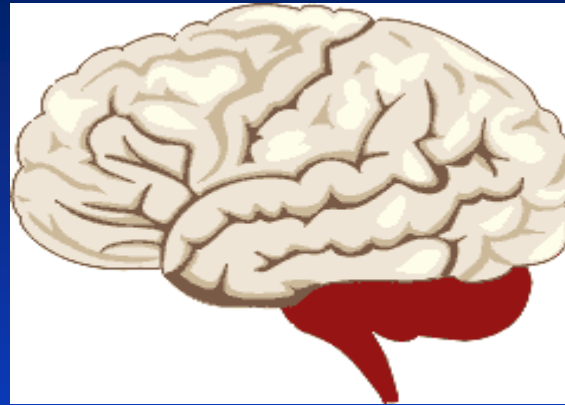
Procedure

First results

Remaining questions

Sympathetic nervous system

Afferent signals



Efferent sympathetic activity

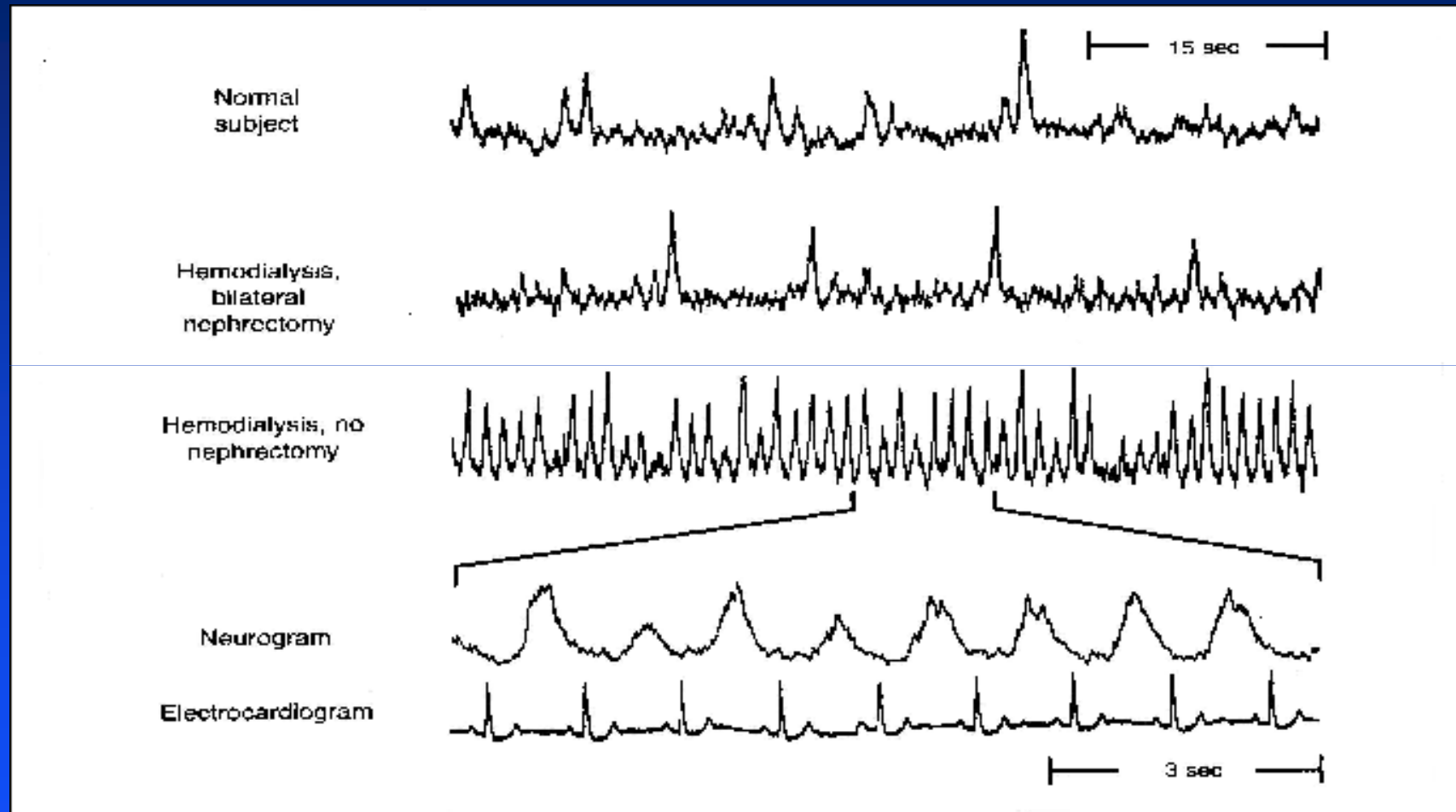


microneurography

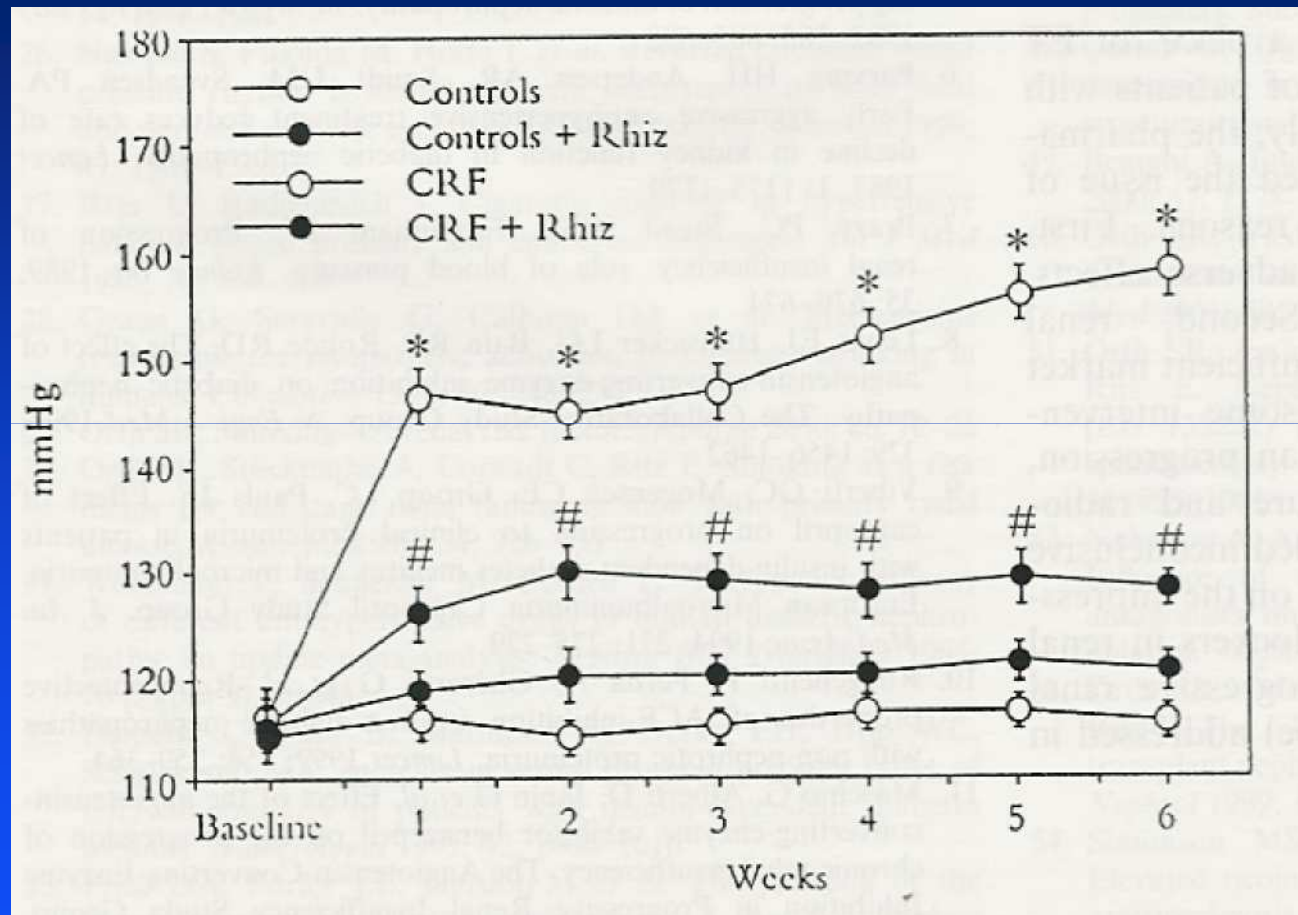


Effects on heart,
vascular system
and kidneys.

Sympathetic hyperactivity in dialysis patients



Blood pressure in subtotally nephrectomized rats with CRF. Influence of dorsal rhizotomy i.e. renal afferent denervation.



* $P < 0.01$ vs other groups, # $P < 0.05$ vs control rats

Blood pressure after intrarenal phenol injection

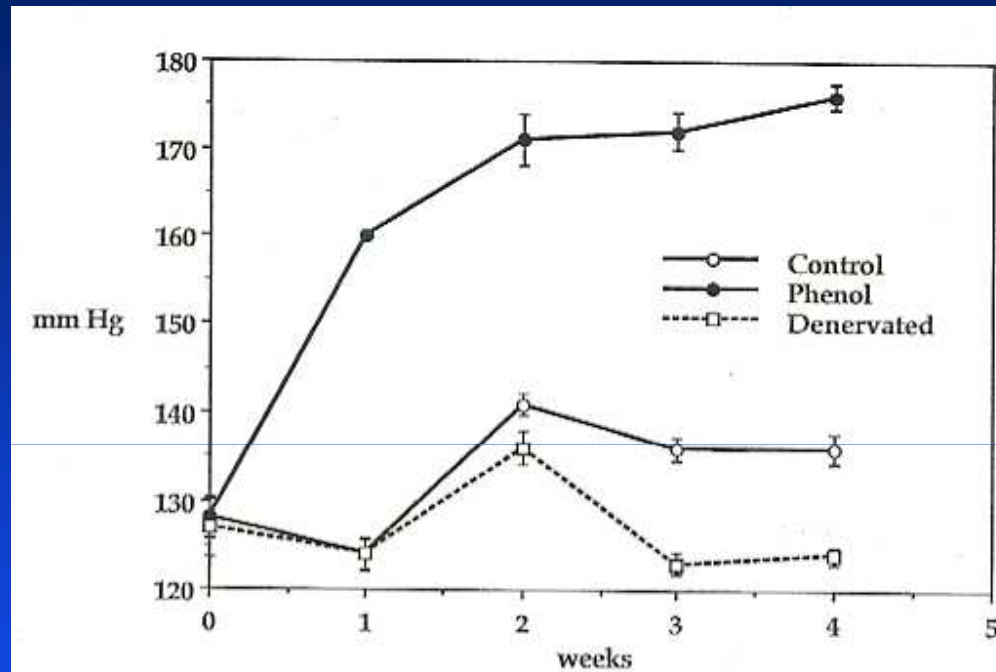
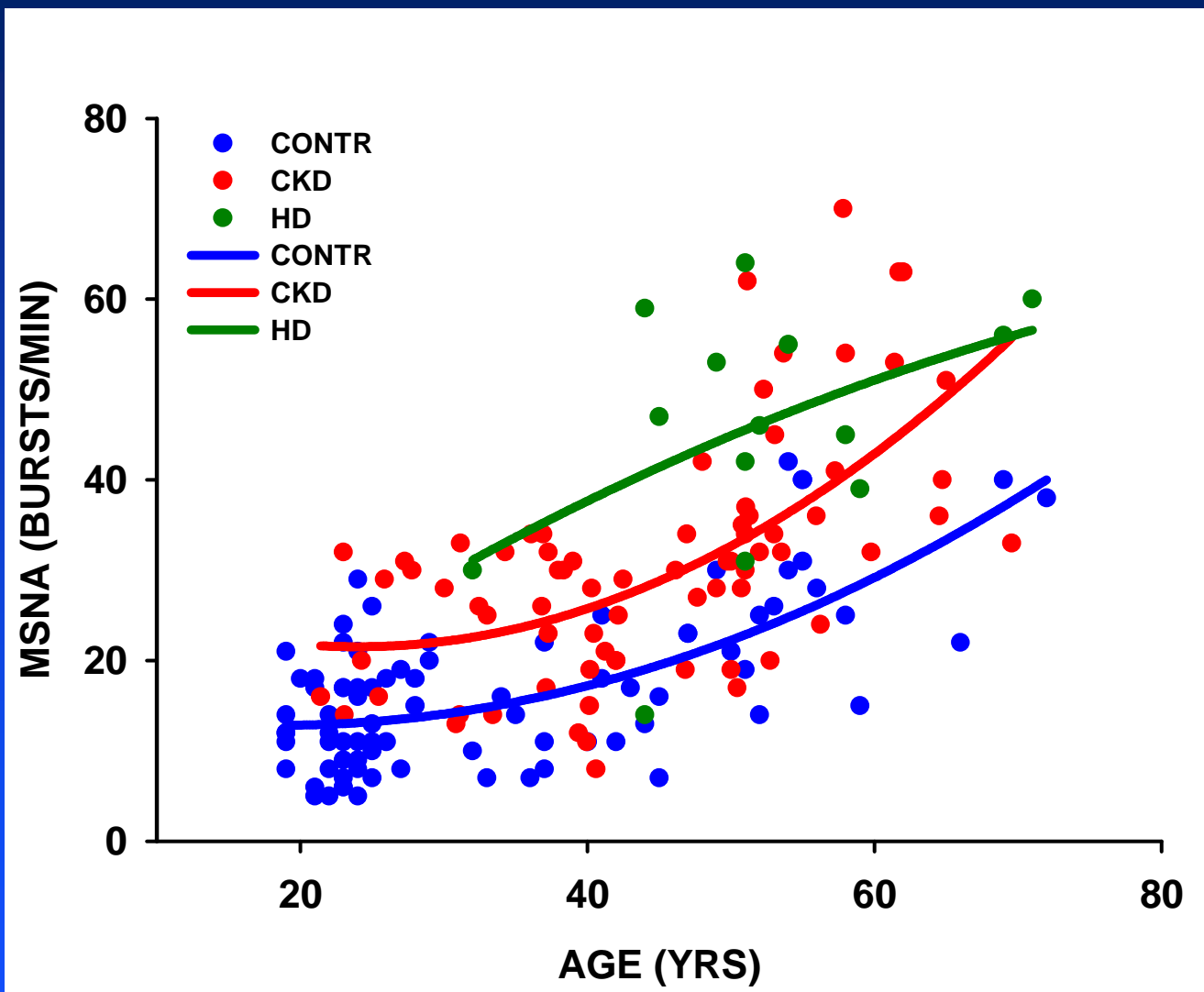


FIGURE 1. The line graphs show levels of systolic arterial pressure in Sprague-Dawley rats who received 50 μ L of 10% phenol in the lower pole of the right kidney (closed circles) and those who received only the vehicle (open circles) and rats that were subjected to renal denervation before administration of phenol (open squares). Each group comprised five to seven rats. Values are expressed as means \pm SEM.

MSNA in various stages of CKD



Controls n=80

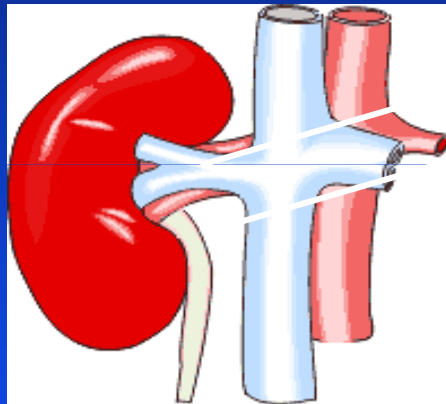
CKD n=74

HD n=17

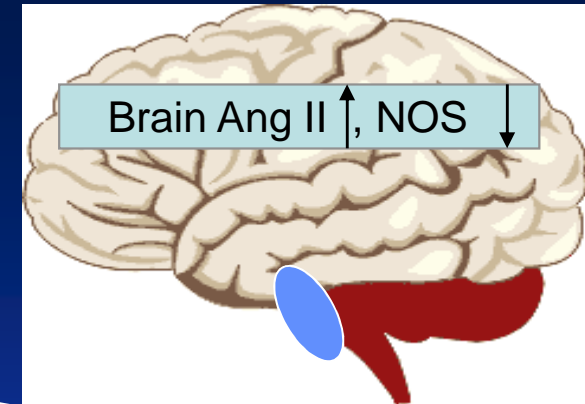
Hypertension 2009

Pathogenesis of sympathetic hyperactivity

Kidney injury/ischemia



Restoration of kidney perfusion



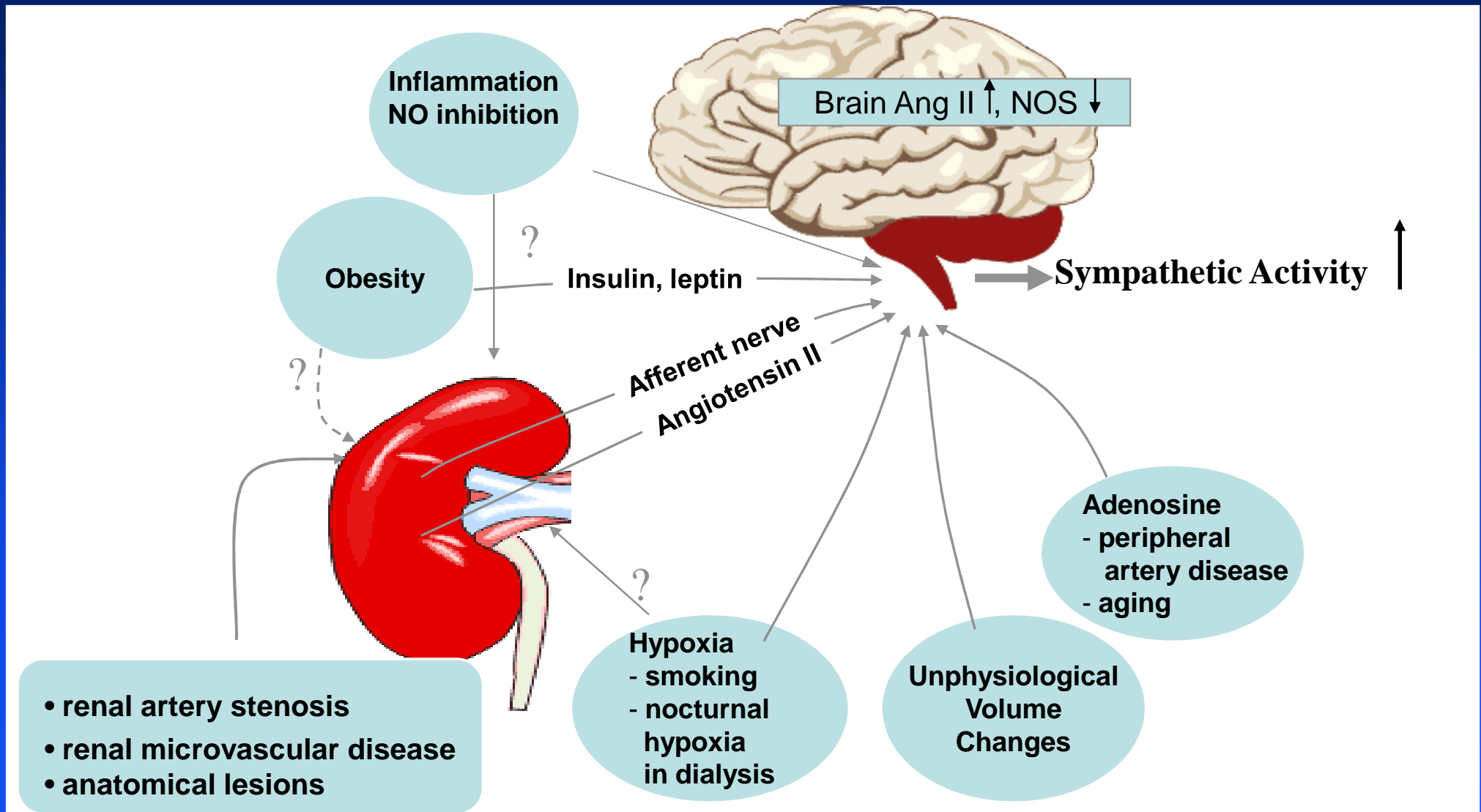
afferent nerve activity +

Ang II +

sympathetic activity

Effects on heart, vascular system and kidneys.

Pathogenesis of sympathetic hyperactivity in chronic kidney disease patients



Disease states associated with sympathetic hyperactivity

- Heart failure
- Various forms of hypertension:
 - Essential hypertension
 - Hypertension associated with kidney injury/failure
 - Renovascular hypertension
 - Malignant hypertension
 - Pre-eclampsia
 - Obesity / metabolic syndrome
 - Hypocapnia-associated hypertension
 - Alcohol associated hypertension

Sympathetic hyperactivity

- Contributes to hypertension
- Associated with both functional and structural CV end organ damage
- Associated with CV prognosis
- These effects are independent of blood pressure

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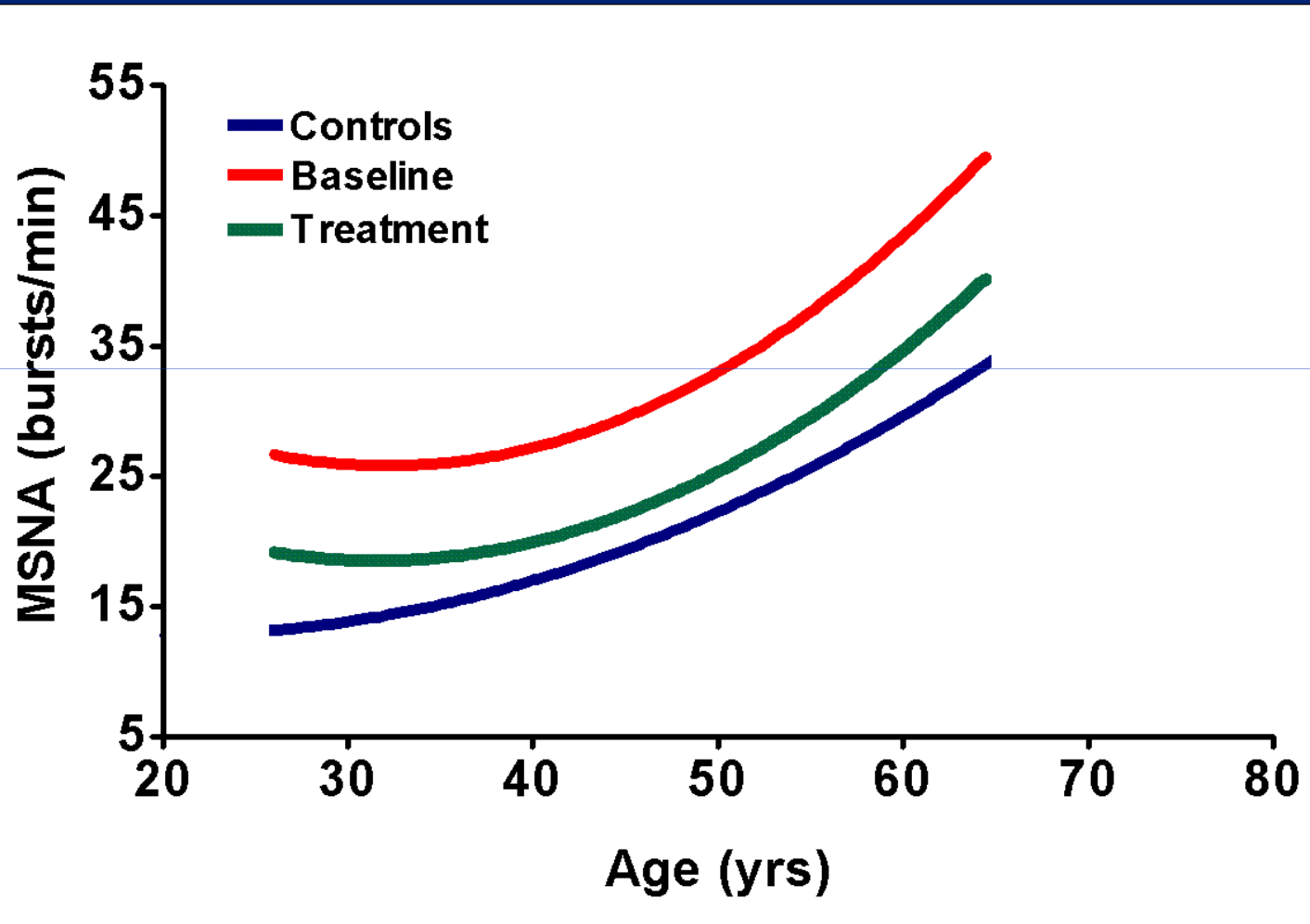
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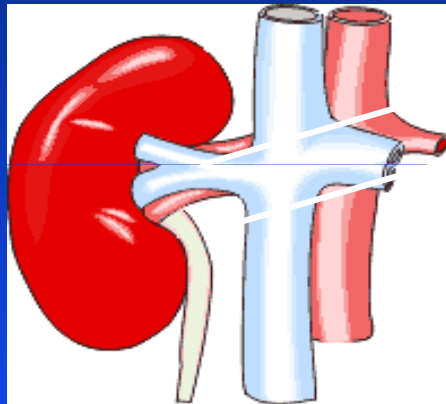
Effect of RAS inhibitors on MSNA



NEJM 1999; 340: 1321-8,
JASN 2003; 14: 425-30,
JASN 2004; 15: 2902-07,
Hypertension 2007; 49: 506-10
Nephrol Dial Transplant 2011

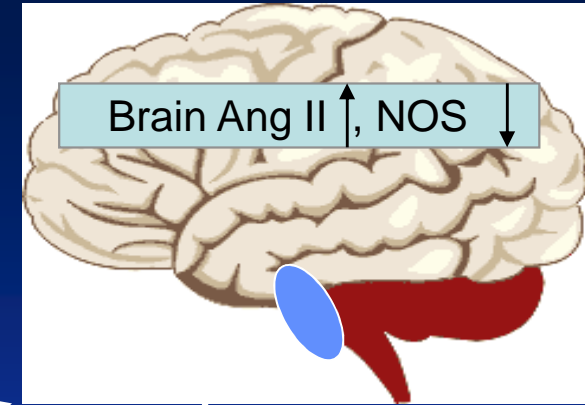
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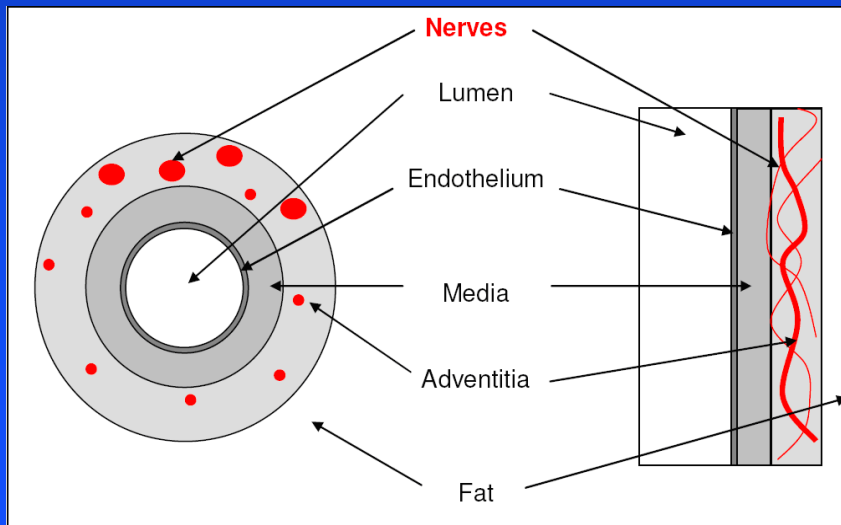
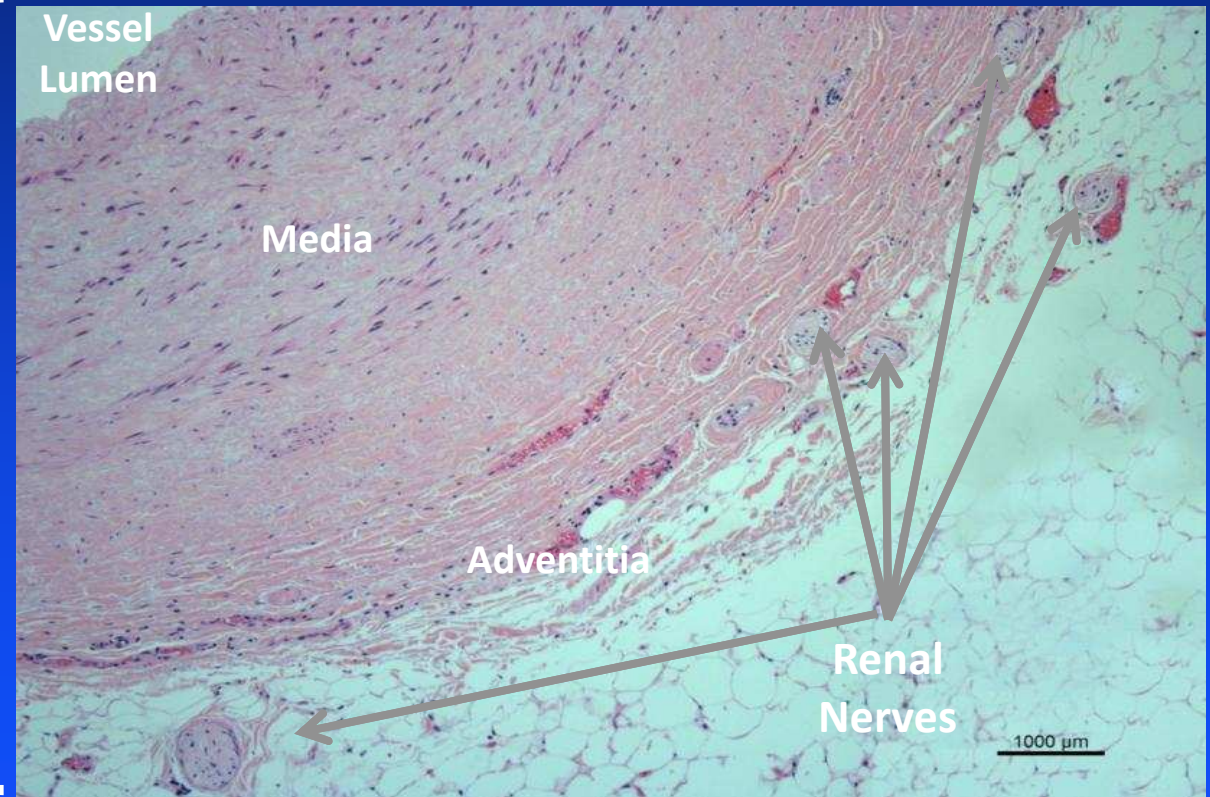
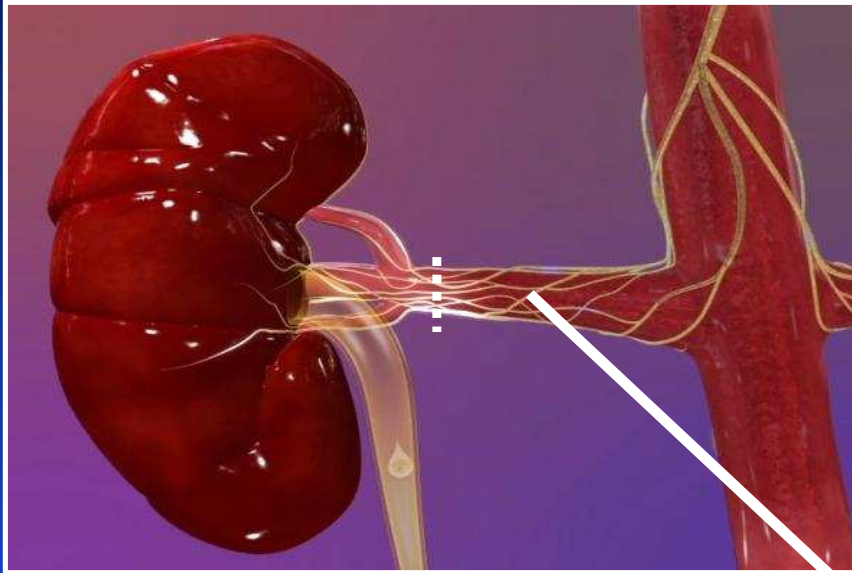


sympathetic activity

Effects on heart,
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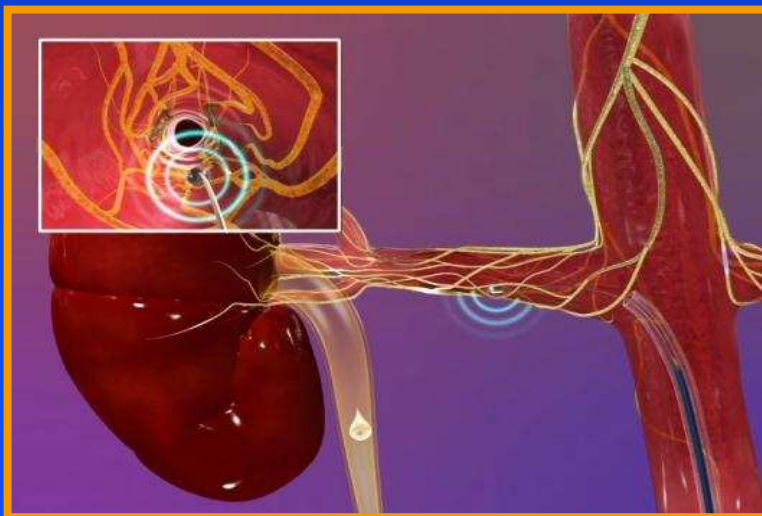
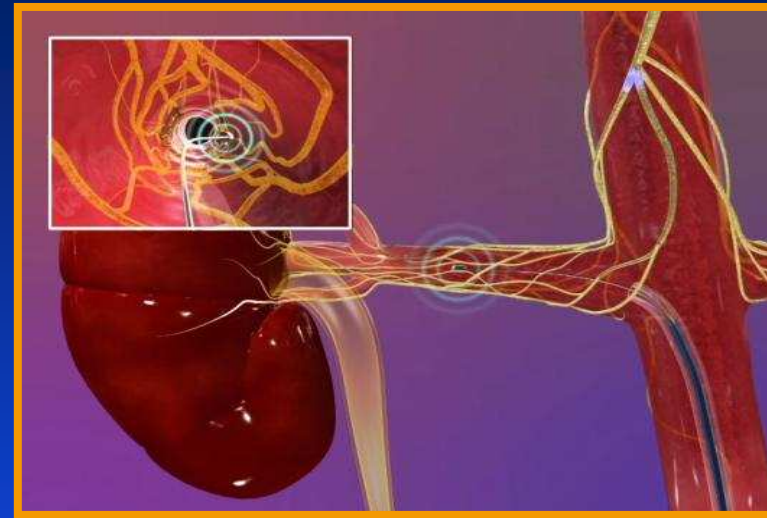
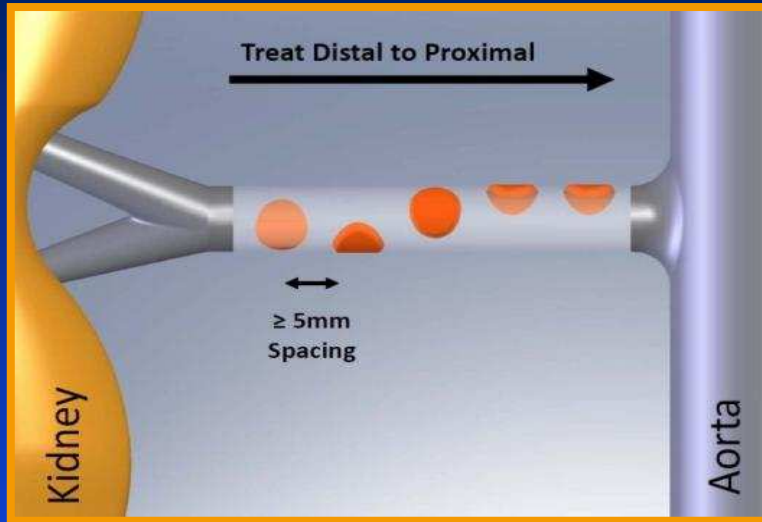
Renal Nerves as a Therapeutic Target

- Arise from ~ T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

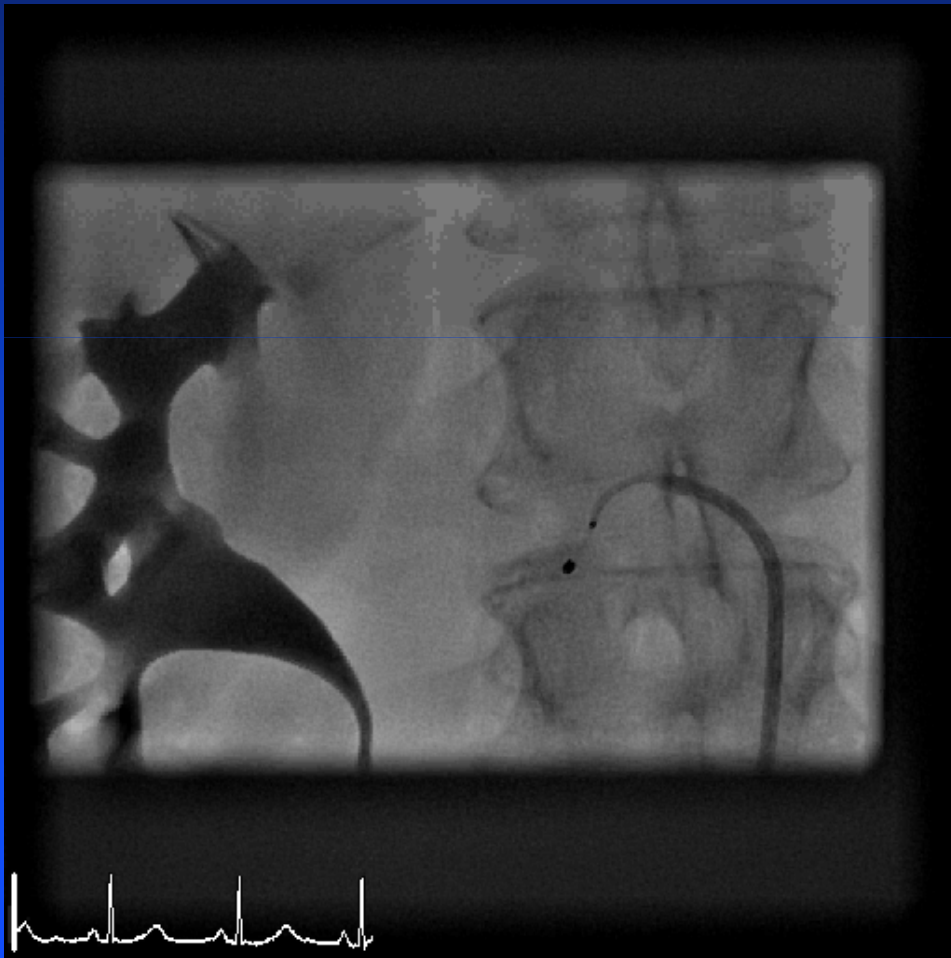


Multiple Discrete Treatments

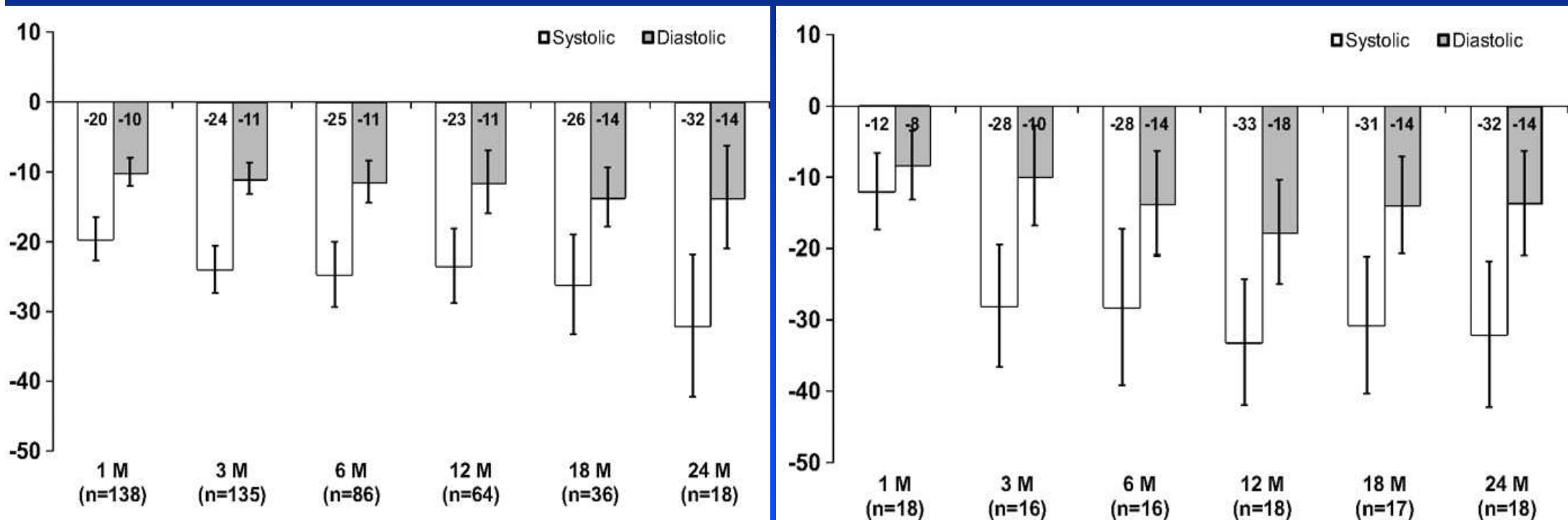
maximize nerve coverage without applying circumferential energy in a single segment



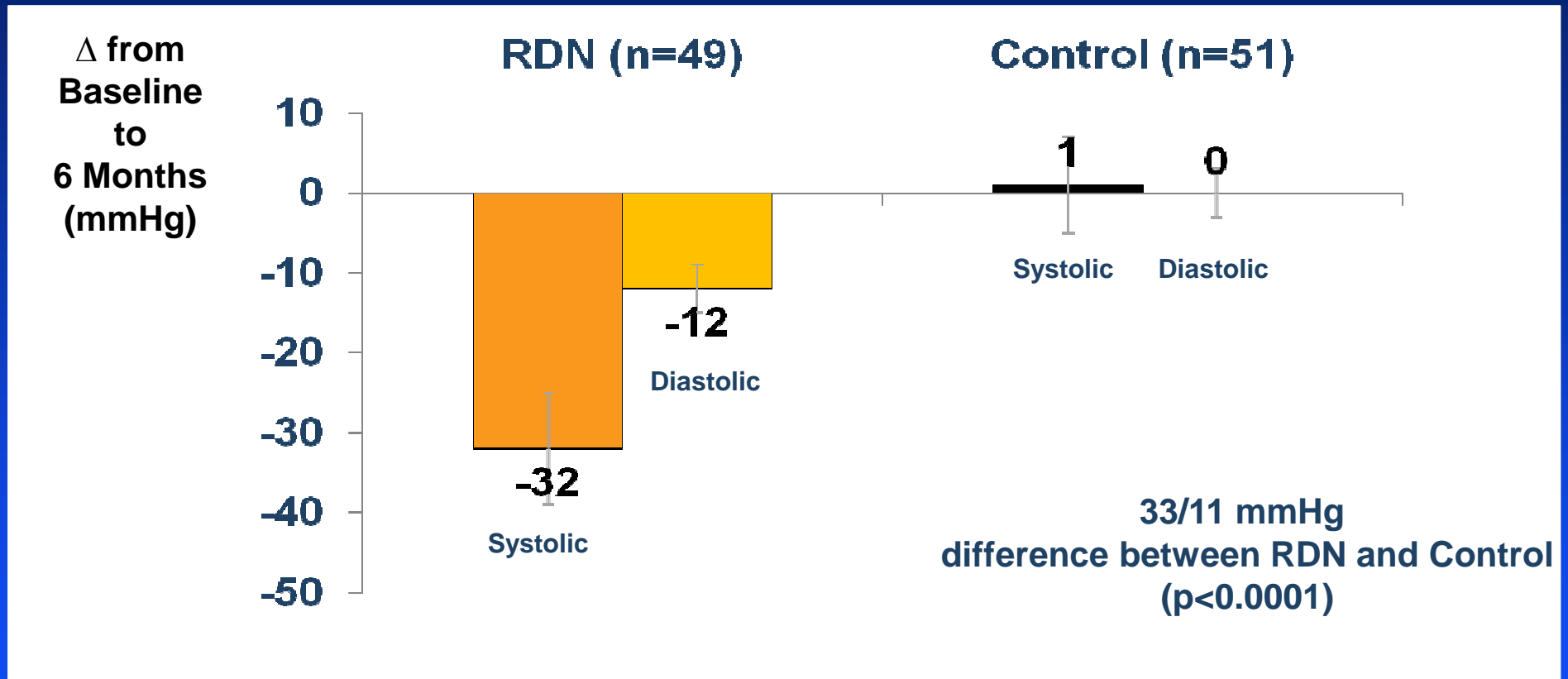
Renale denervation



Change in blood pressure

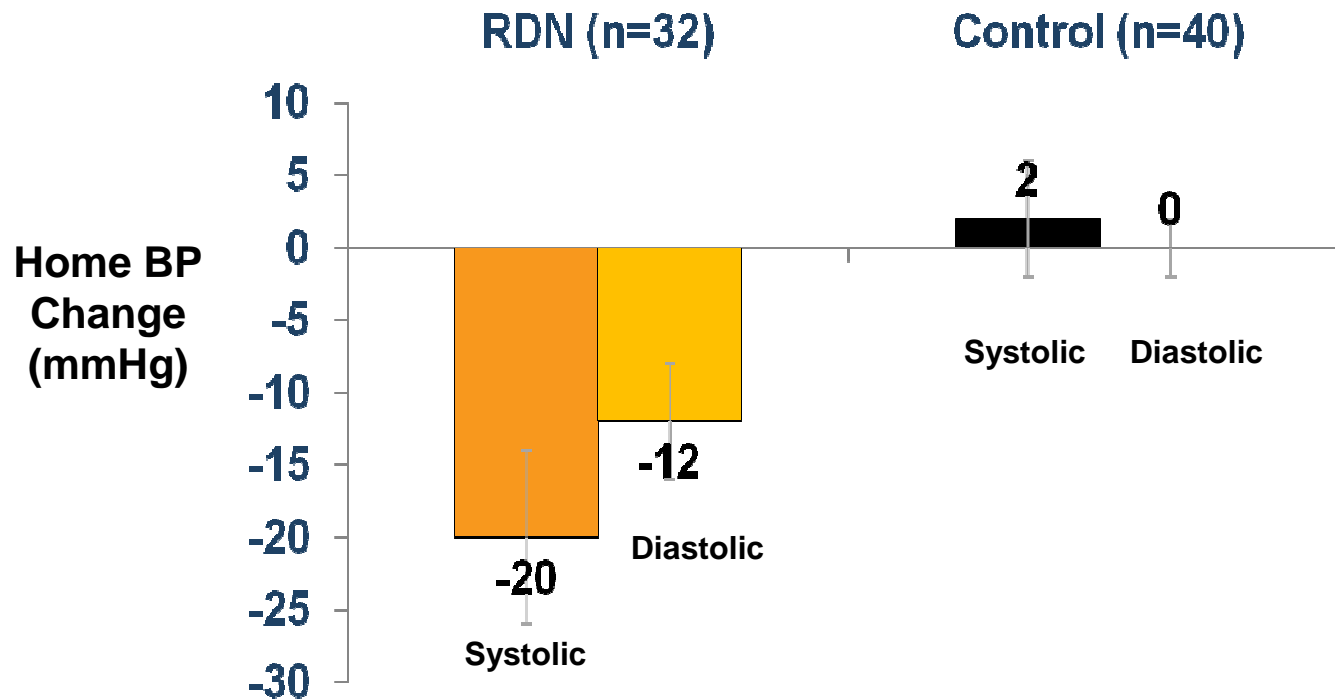


Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Home & 24 Hour Ambulatory BP

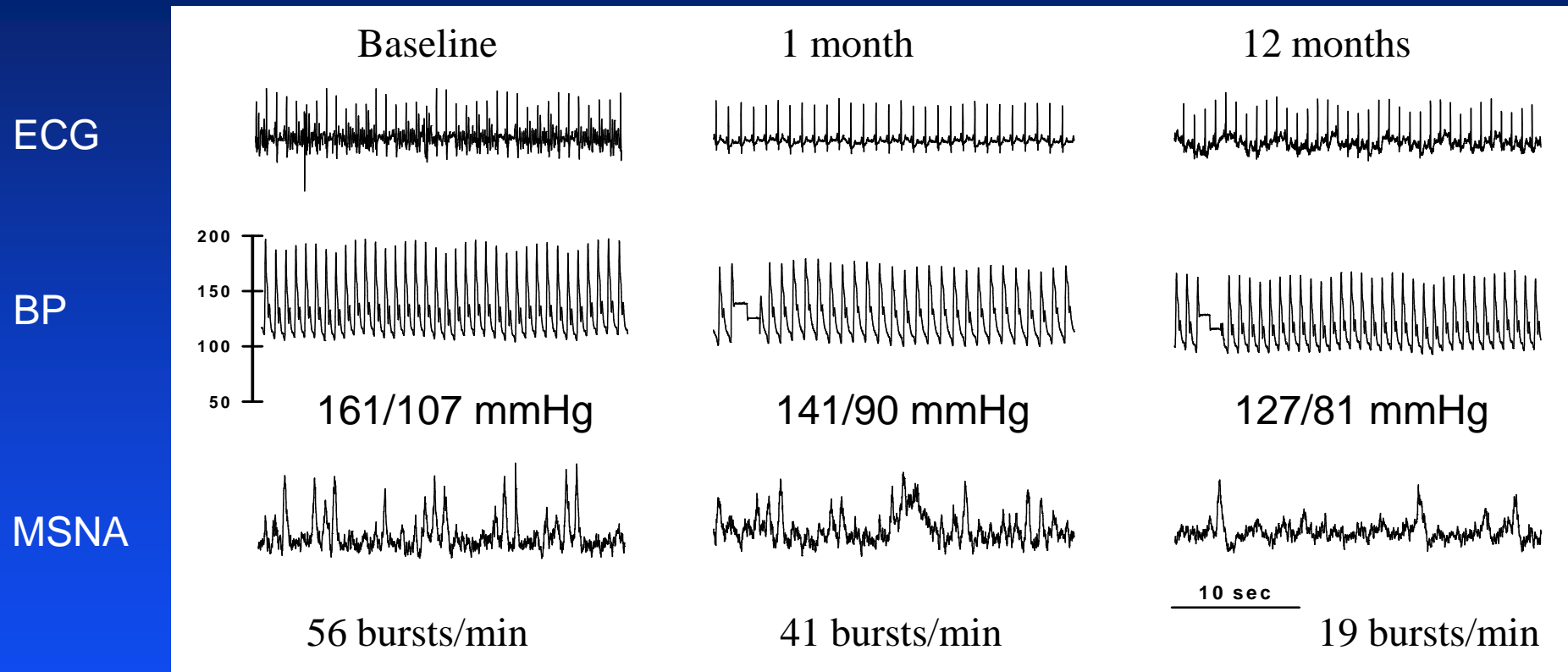


24-h ABPM:

- 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)

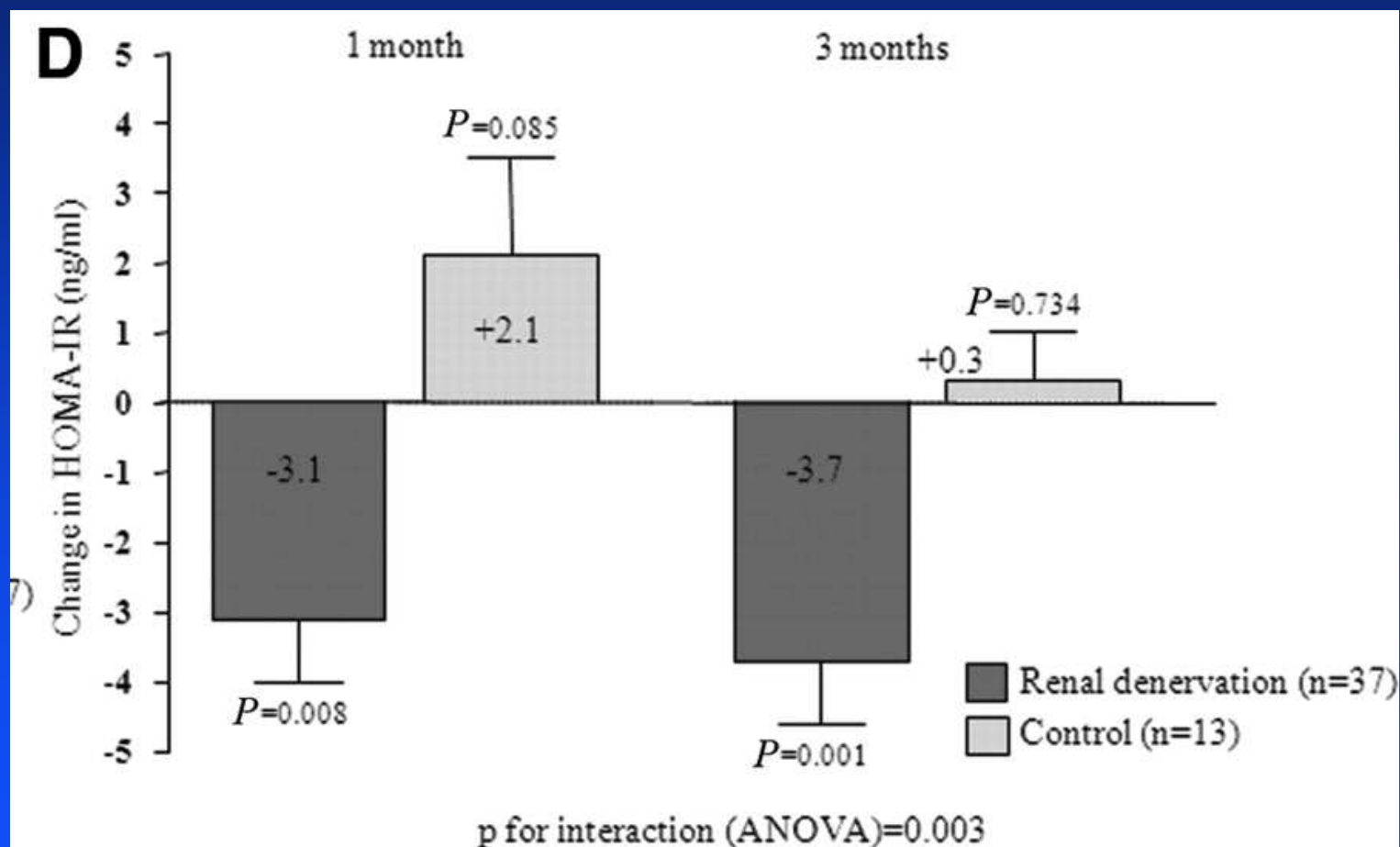
Lancet 2010; 376: 1903-09

Reduction of Systemic Sympathetic Drive: MSNA in Resistant Htn Patient

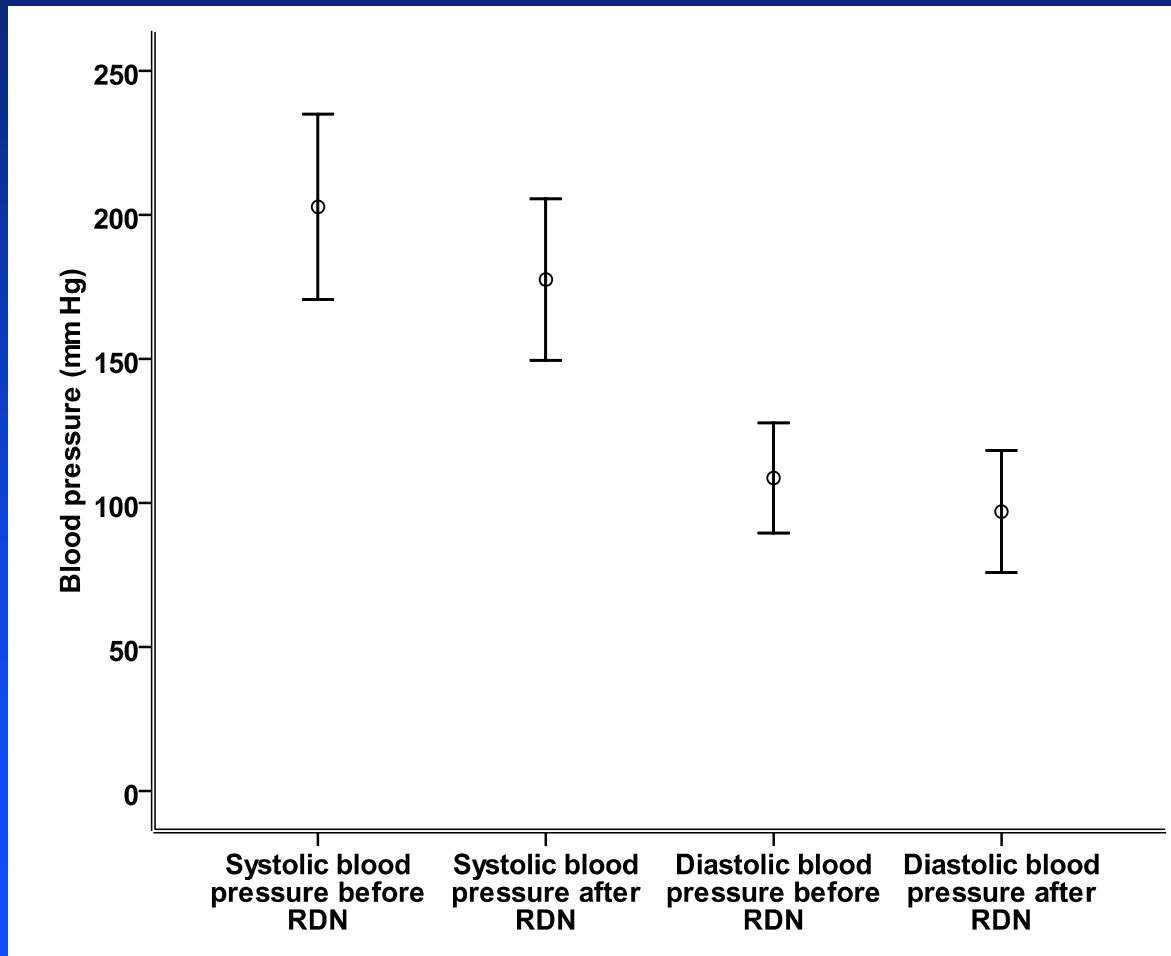


Improvement in cardiac baroreflex sensitivity after renal denervation
(from 7.8 to 11.7msec/mmHg).

Change in glucose / insuline



First results in UMCU



N=10

RR 203/109 (32/19) =>
178/97 (28/21) mmHg

Neth Heart J 2011

Remaining questions

- How to monitor the efficacy of intervention itself?
- Which patients especially benefit?
- Long term efficacy and safety?
- Effect on CV outcome?
- Effects other than blood pressure reduction?
- Cost effectiveness?
- etc

Present situation

- Procedure operational in UMCU, collaboration of nephrology, radiology, cardiology and epidemiology
- NSN grant: to learn more about effects
- Eligible patients: poorly controlled hypertension
- Patients referred to us will be analyzed in detail before and after treatment
- In progress: ZonMw: randomized trial
- Several other initiatives
- Collaboration: very welcome

Huidige situatie

- Indicatie: “resistant hypertension” of intolerantie voor medicatie
- Bij voorkeur: secundaire hypertensie is uitgesloten
- Bij voorkeur: info over nierart. beschikbaar
- Verwezen patienten: standaard pakket voor- en naonderzoek gericht op vaststellen determinanten van effectiviteit

Conclusions

- Present knowledge on sympathetic activity:
 - A certain level of baseline activity exists, which is *independent* of the kidneys
 - *Hyperactivity* originates in the diseased kidneys, already present after minimal kidney injury, kidney ischemia central in pathogenesis.
 - Hyperactivity contributes to hypertension. Contributes to pathogenesis of functional and structural CV organ damage independent of blood pressure and is associated with poor CV prognosis.
 - RAS inhibitors reduce sympathetic hyperactivity.
 - Renal denervation is an intervention, which fits into the pathophysiology, first results are promising, more research needs to be done.

Informatie

- www.renaledenervatie.nl
- renaledenervatie@umcutrecht.nl