Sympathetic activity and methods to assess sympathetic nerve activity

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Outline of Presentation

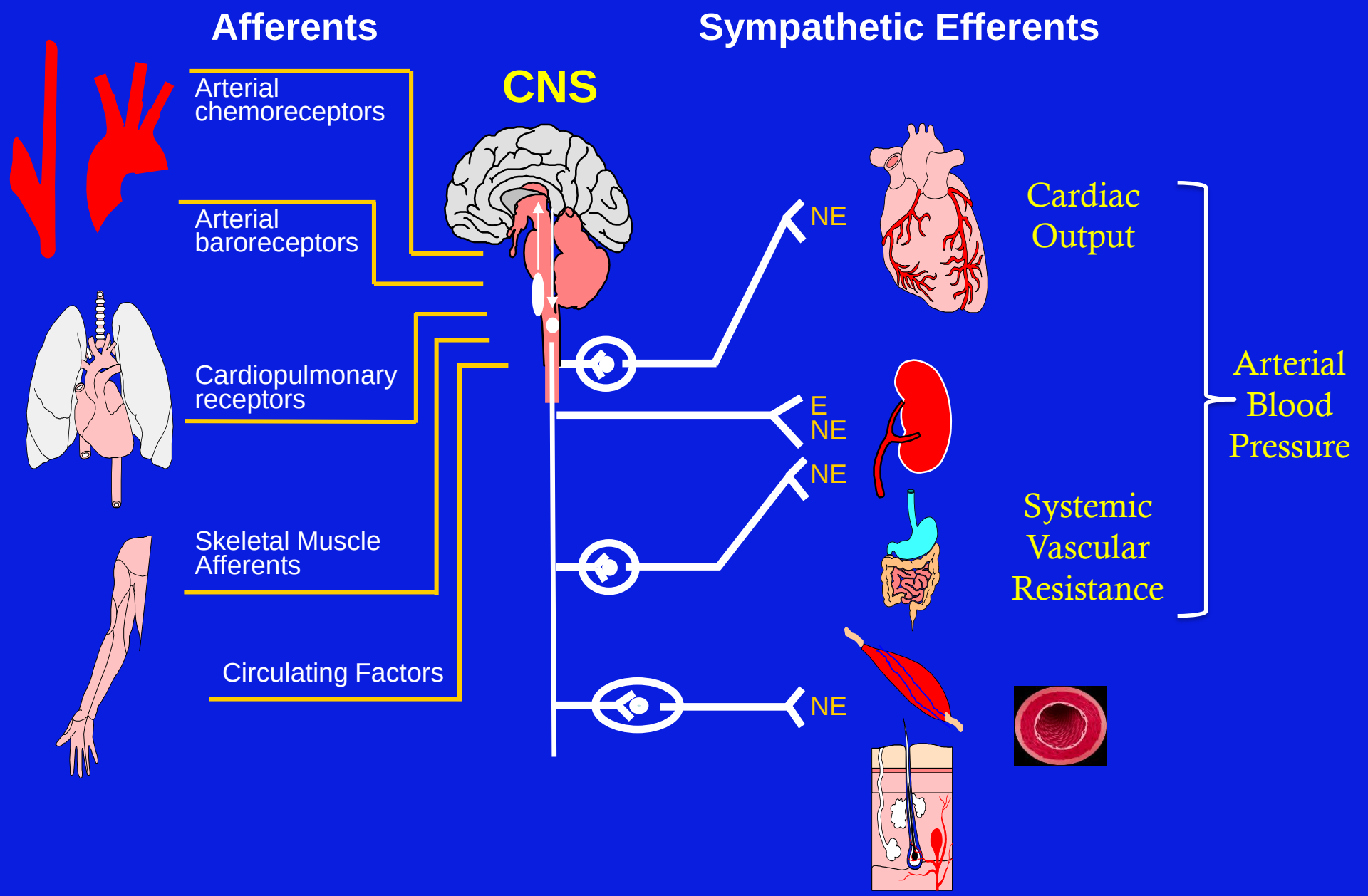
- Sympathetic nervous system-
  Importance of studying- Sympathetic Overactivity
  Deleterious consequences beyond increasing blood pressure (BP)

- Assessing sympathetic nerve activity (SNA) in humans (microneurography)

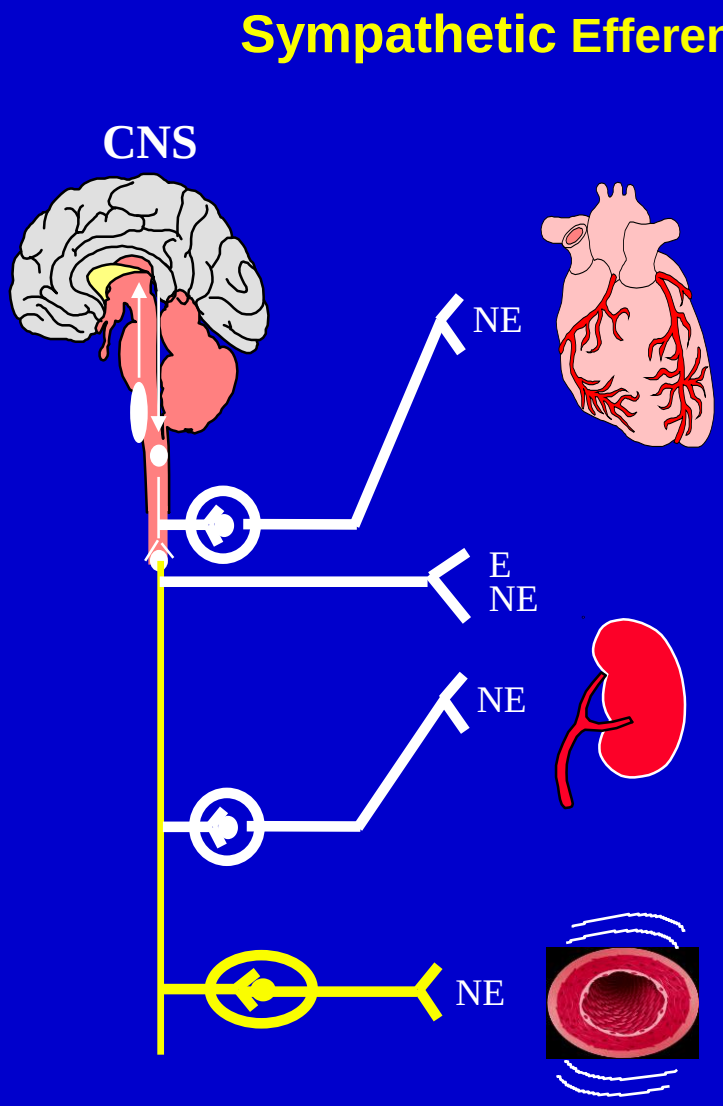
- Obtaining quality **muscle** SNA recordings
  Technical Aspects
  Key Fundamentals

- Sympathetic Vascular Transduction

Sympathetic nervous system



Chronic Sympathetic Overactivity



Hypertrophy

Apoptosis

Arrhythmias & Sudden Cardiac Death

Attenuated Reflexes

↑ Renin

↑ Renal Vascular Resistance

↑ Na^+ reabsorption

↓ Glomerular function

↑ Peripheral Vascular Resistance

↑ Vascular Hypertrophy

Hypertension

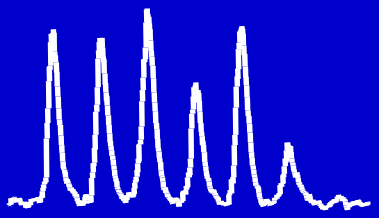
Potential pathological consequences of elevated central sympathetic nerve activity

Vascular effects	*Cardiac effects*
VSM cell hypertrophy and proliferation	Cardiac myocyte hypertrophy
Medial thickening	Left ventricular hypertrophy
Endothelial cell damage	↑ Incidence of arrhythmia
Endothelial dysfunction	Tachycardia
Arterial stiffness	
↑ Blood pressure variability	*Renal effects*
↑ Peripheral vascular resistance	Renal vasoconstriction
Hypertension	Sodium and fluid retention
Atherosclerosis	Glomerulosclerosis
	Microalbumineria
Metabolic effects	RAAS activation
Insulin resistance	
↑ Plasma insulin concentration	
Dyslipidemia	

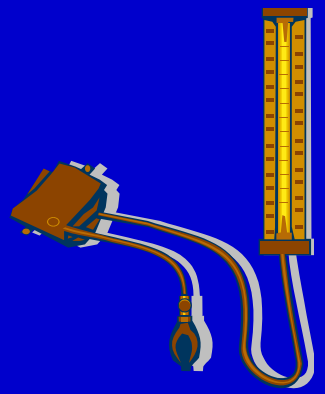
VSM, vascular smooth muscle; RAAS, Renin-angiotensin-aldosterone system.

Fisher JP. et al. Auton Neurosci., 2009

Sympathetic Overactivity Not Only About High Blood Pressure

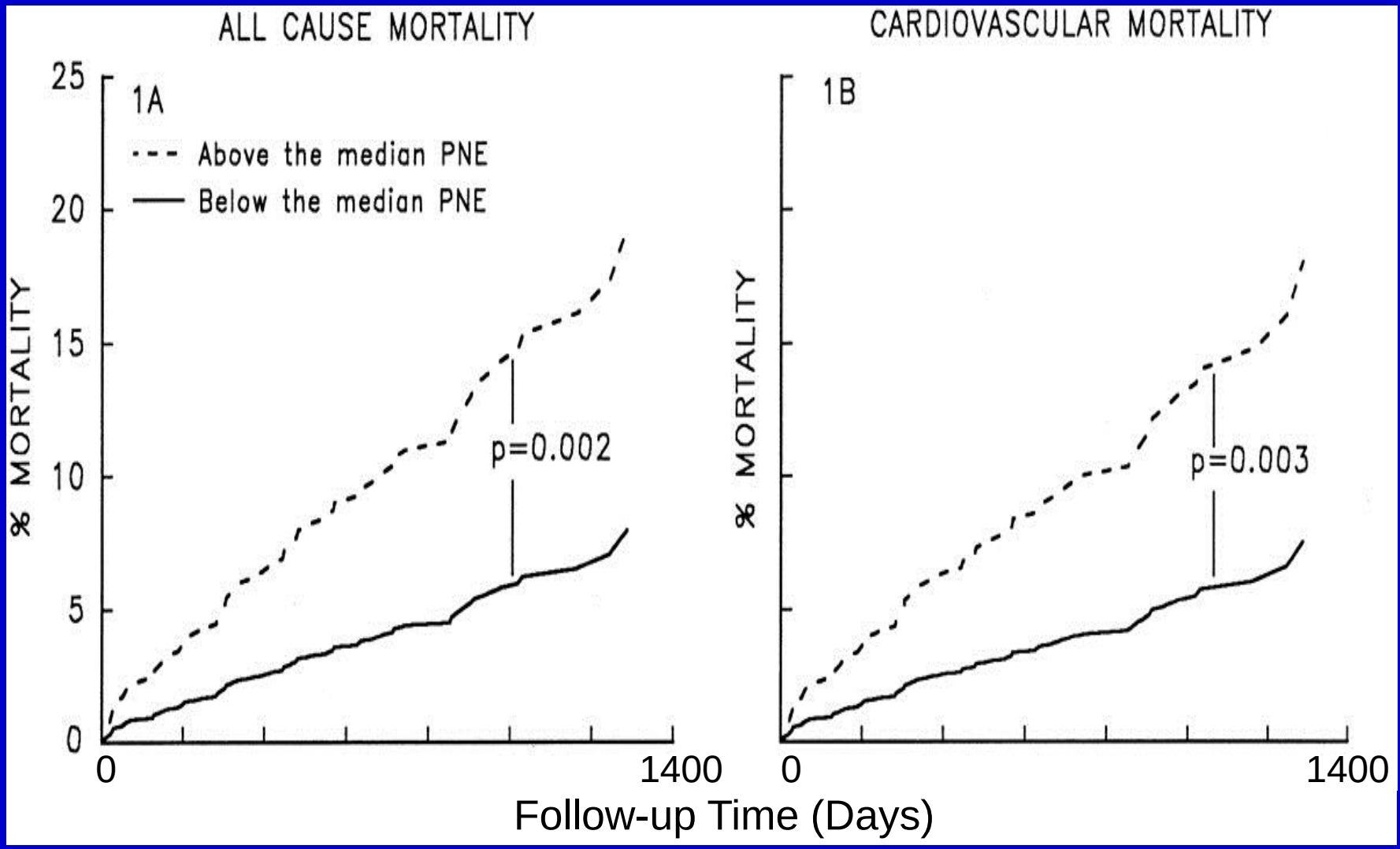


Sympathetic Overactivty



High Blood Pressure

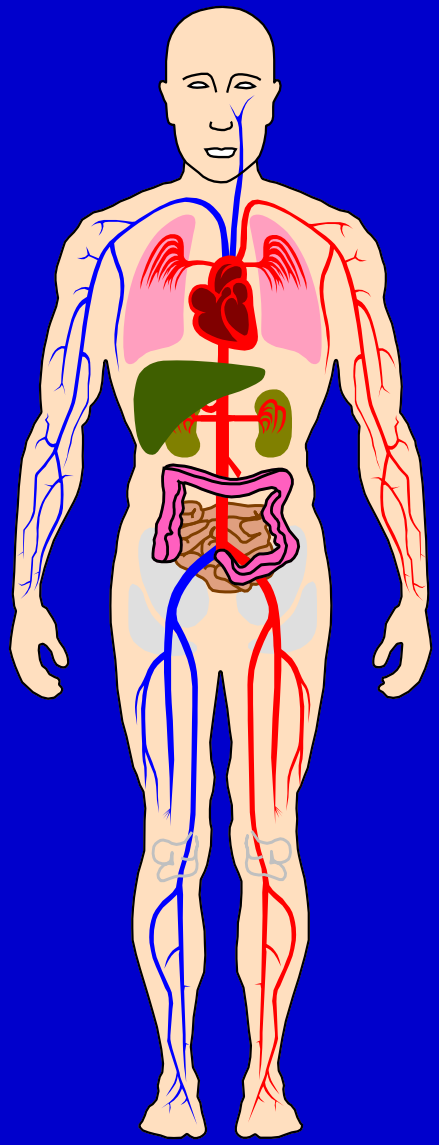
Sympathetic Overactivity and Increased Mortality



NE levels above (n=255) or below (n=254) median value of 393 pg/mL in CHF

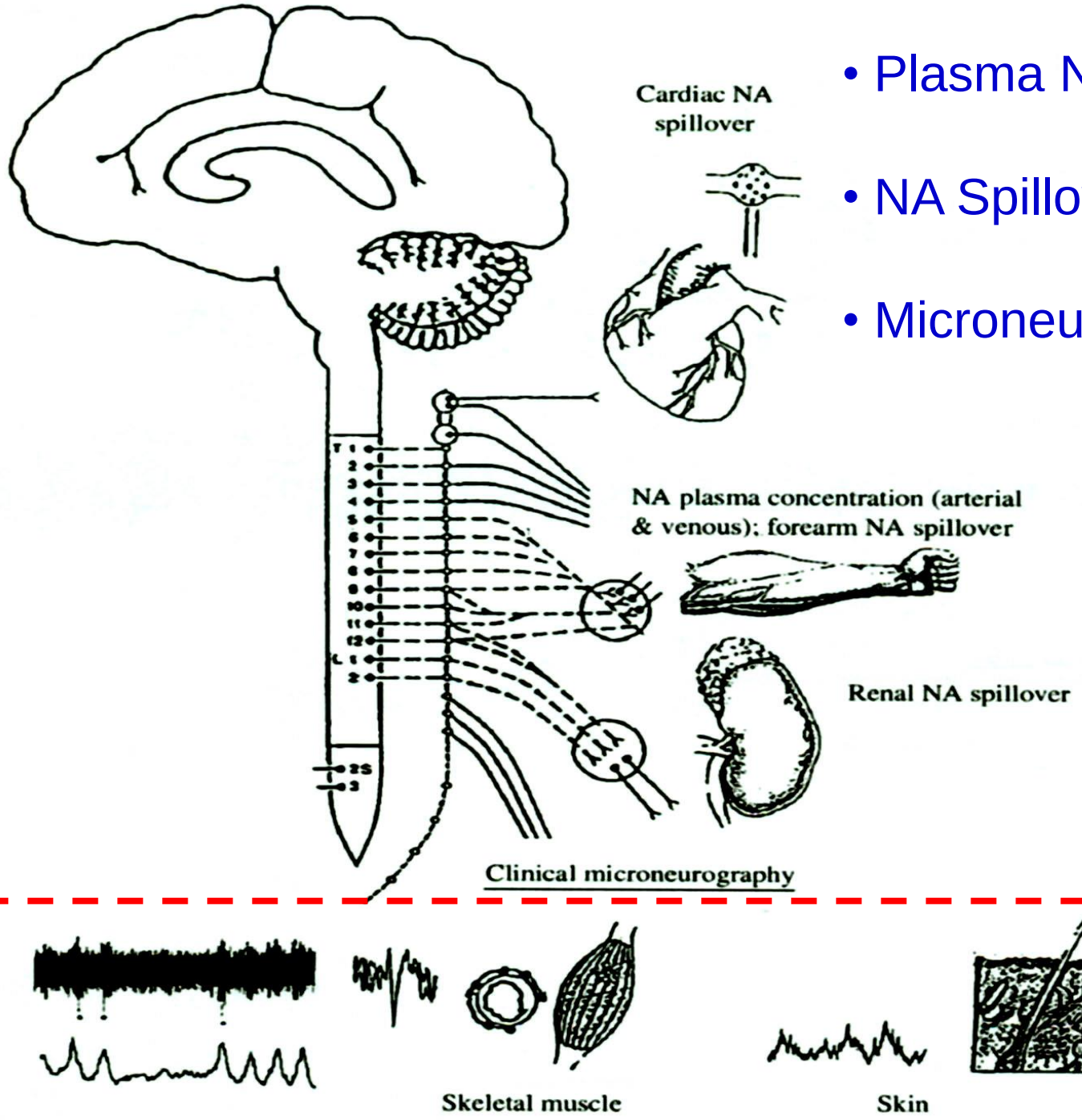
Benedict et al. Circulation 1996

Heightened SNA in Disease



Disease-

Renal Disease, Heart Failure, Hypertension, Obesity, Type 2 Diabetes, Metabolic Syndrome, Sleep Apnea, Chronic Obstructive Pulmonary Disease

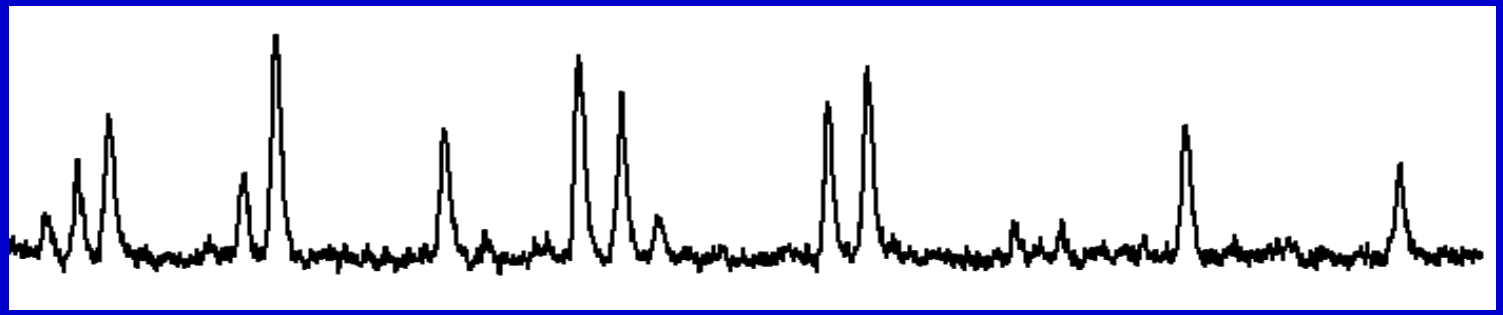


- Plasma NA
- NA Spillover
- Microneurography

Esler M, 2003

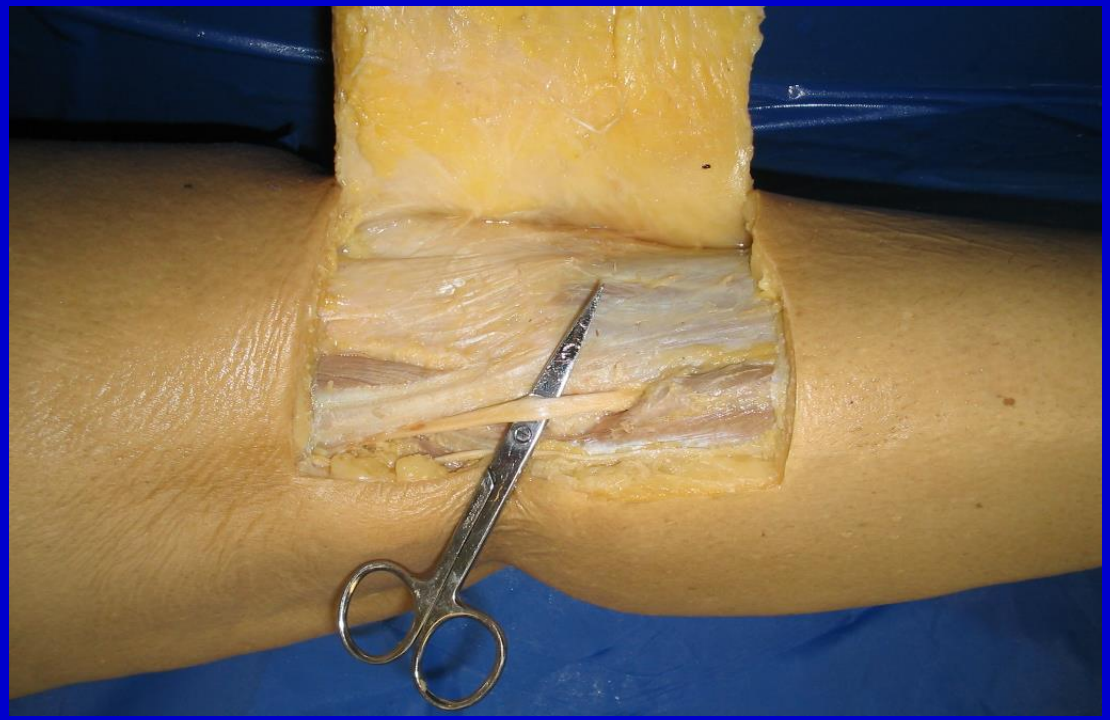
Microneurography

Muscle SNA



Sites Used To Obtain SNA Recordings

1) Radial Nerve
2) Median Nerve
3) Tibial Nerve
4) Peroneal Nerve at Popliteal Fossa and Fibular Head



Nerve thickness measurements

Mean: 2.4 ± 0.7 × 0.7 ± 0.2 mm
Range: 1.1–4.2 × 0.5–1.3 mm

Canella C et al., 2009

Identification of Nerve Location

Palpation: Palpate fibular head- anatomically posterior

External Stimulation: Map the peroneal nerve with external stimulation- Typically 0.5 to 4 volts stimulation:

Elicits involuntary twitches and paresthesia

Use stimulating pen electrode to localize and find site that provides largest twitch with lowest voltage.

Inserting Electrodes and Probing for Nerve

1) Probing and Listening for Insertion Discharge

Insert recording electrode and probe using sound only
When hit nerve makes distinct noise (Insertion Discharge)

2) Internal Stimulation
Position by stimulation through electrode

3) Doppler Guided

Curry T & Charkoudian N; Auton Neurosci, 2011

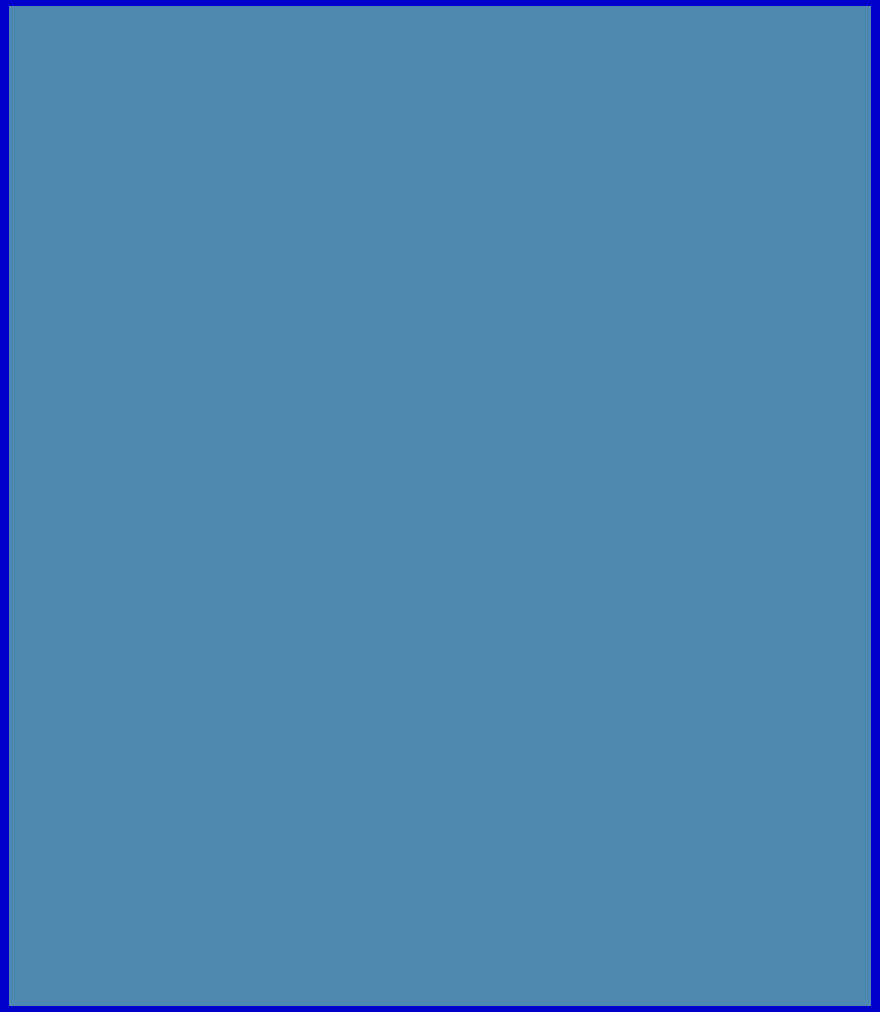
Inserting Electrodes and Probing for Nerve Con't

1) Place ground (reference) electrode 2-3 cm away from main site

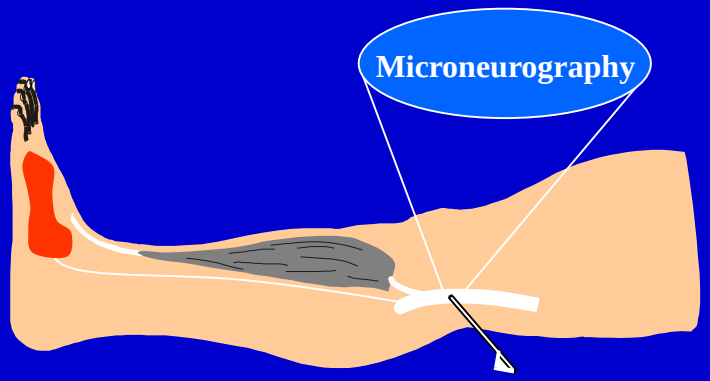
2) Enter skin at angle using markings and information from external stimulation

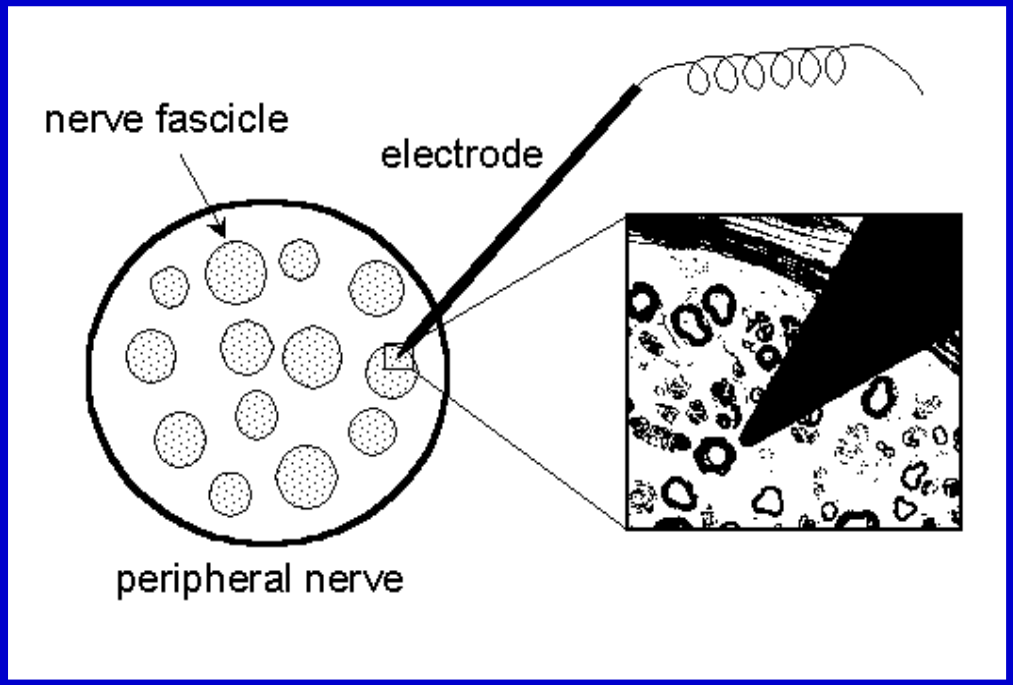
3) Start timer- Maximal time 60 minutes

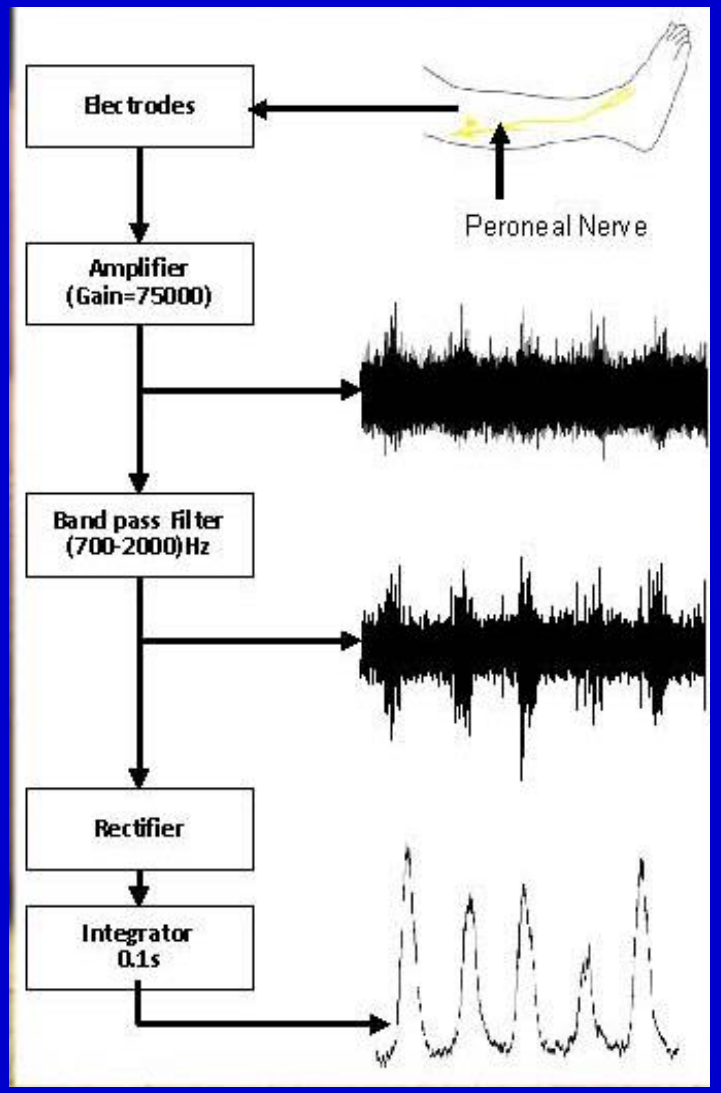
4) Move electrode forward and then anterior and posterior – Use fibular head as key landmark



Optimizing Signal- How it works



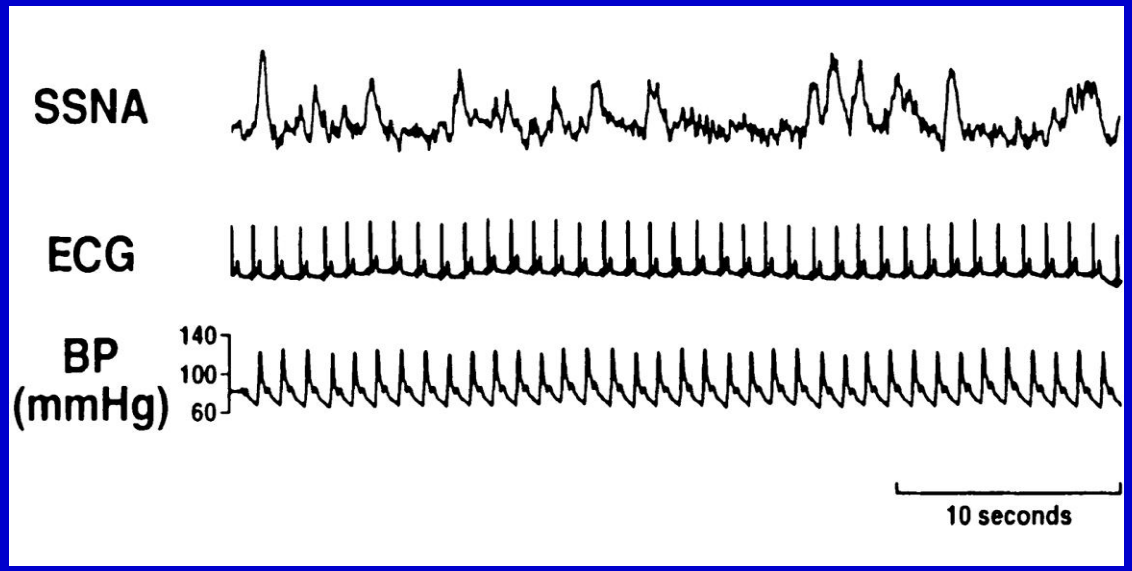




Characteristics of Muscle SNA vs. Skin SNA

Muscle SNA

- Narrow Based Bursts
- Pulse synchronous
- Regulated via the arterial baroreceptors
- Not increased by arousal
- Associated with muscle afferents

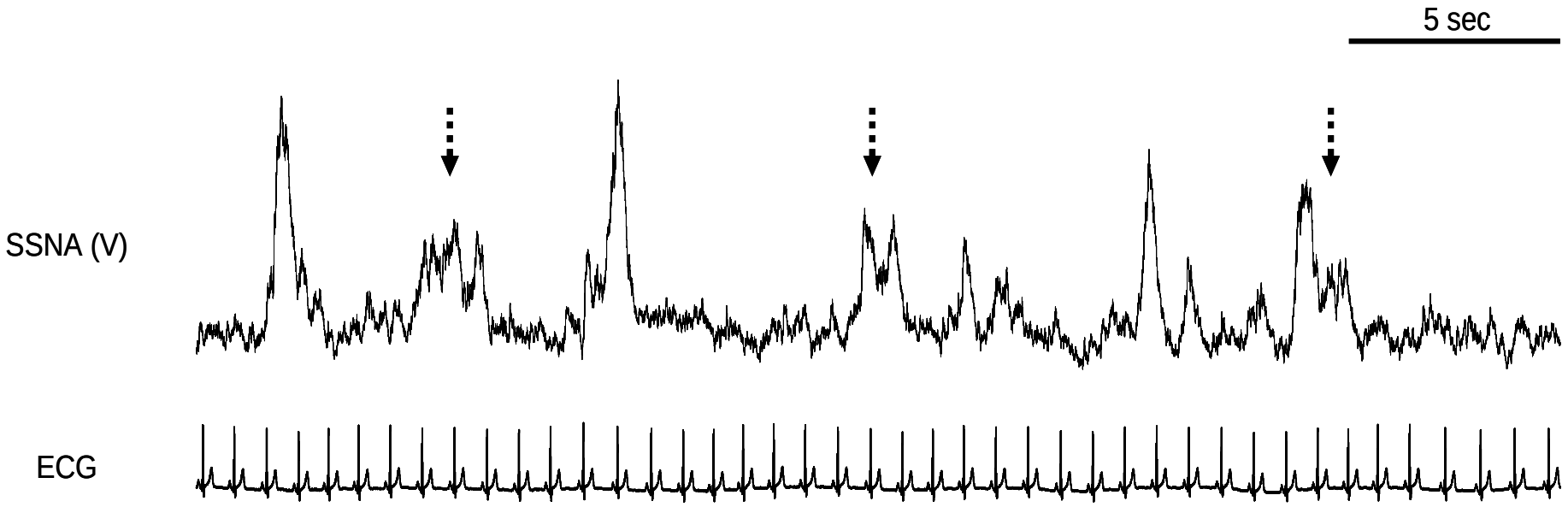


Skin SNA

- Broad Based Bursts
- Not Pulse synchronous
- Not regulated by the -arterial baroreceptors
- Highly variable discharge pattern
- Increased by arousal
- Skin afferents

Example of Skin SNA

Difficulties with assessing and analyzing skin SNA

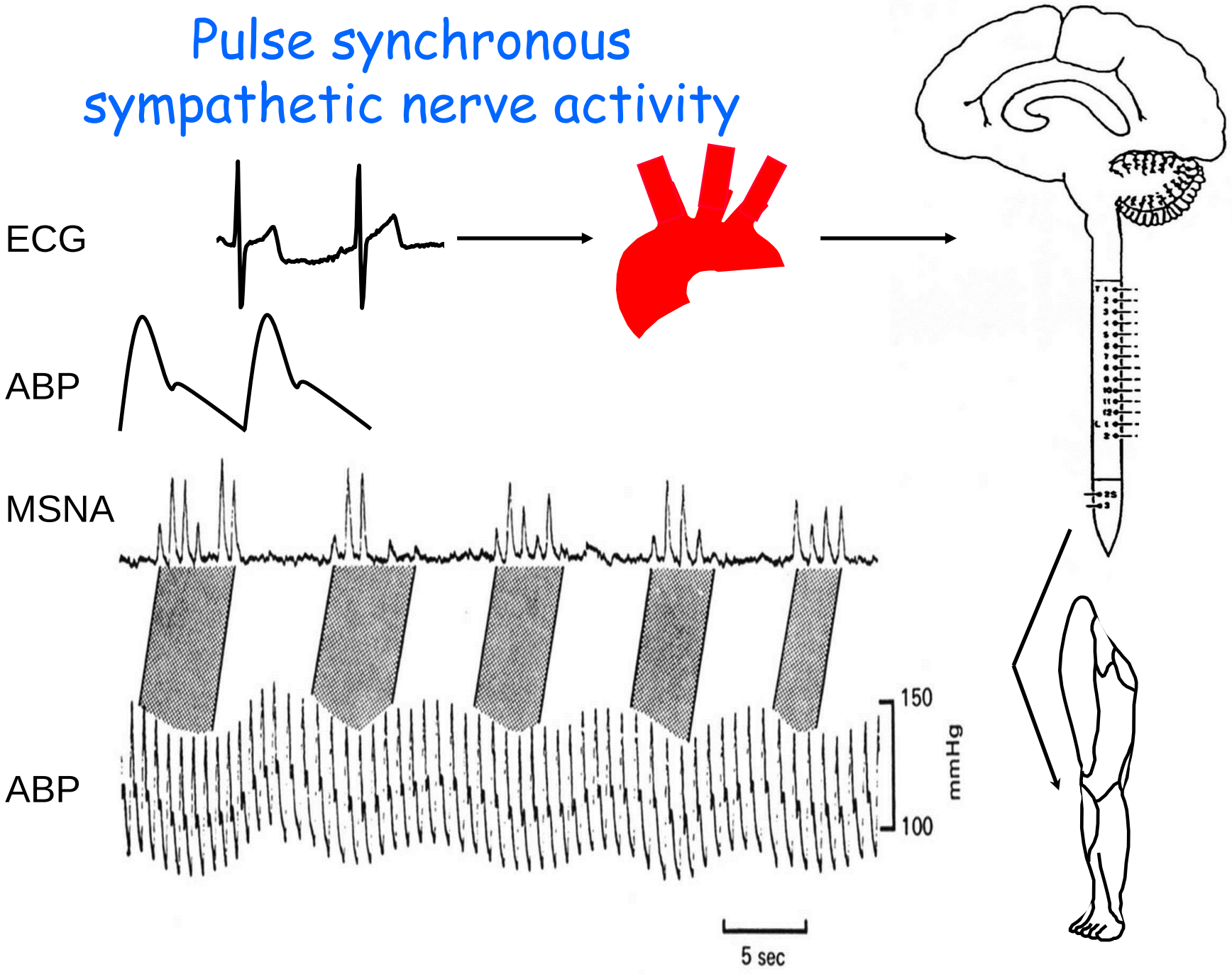


Multiunit SSNA recording is comprised of vasoconstrictor, sudomotor, pilomotor and possibly active vasodilator fibers

Cannot make group comparisons with skin SNA measures

Example of Muscle SNA

Pulse synchronous sympathetic nerve activity

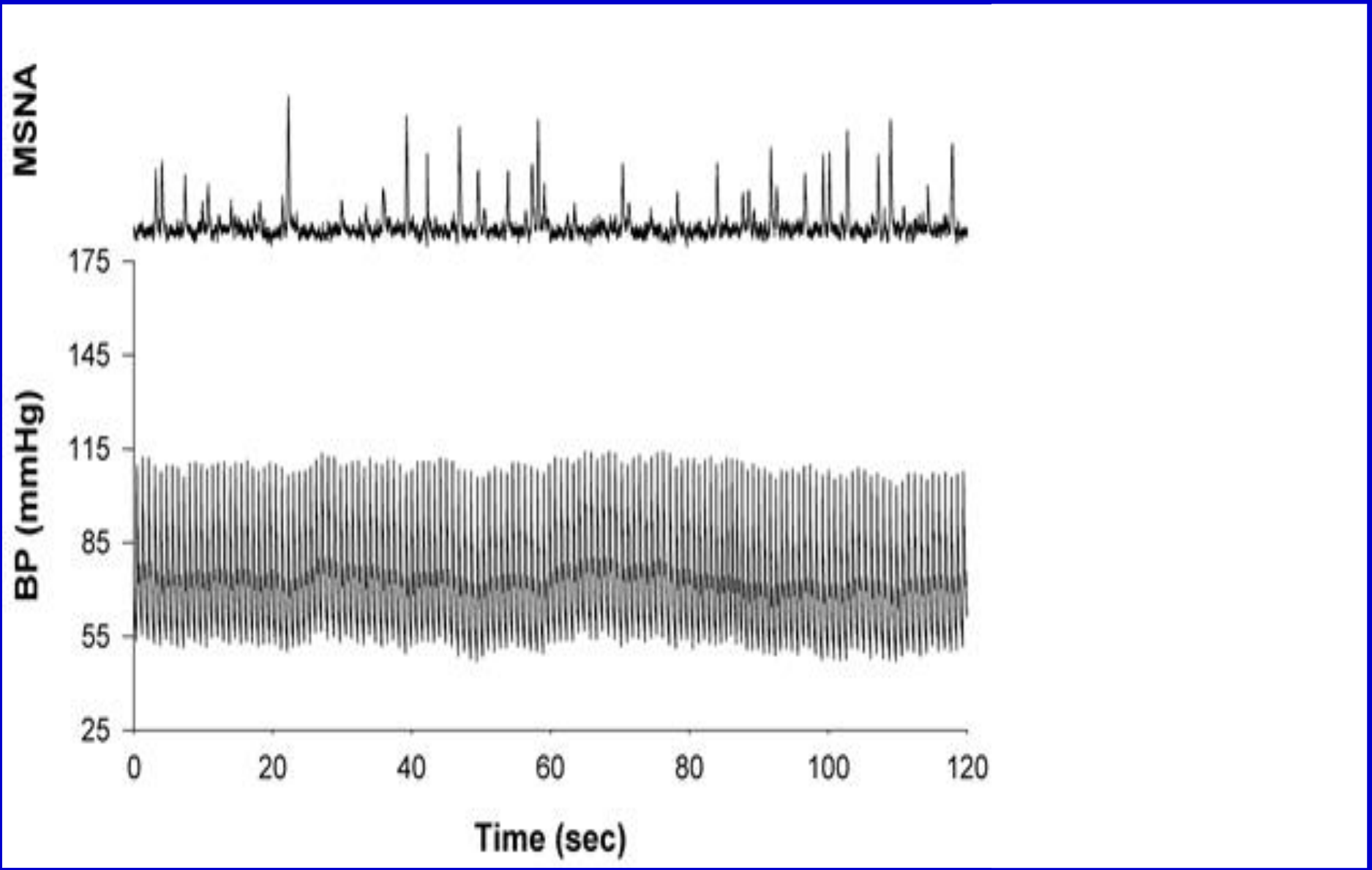


Key Fact in Adjusting Electrodes to Maximize Recording Quality

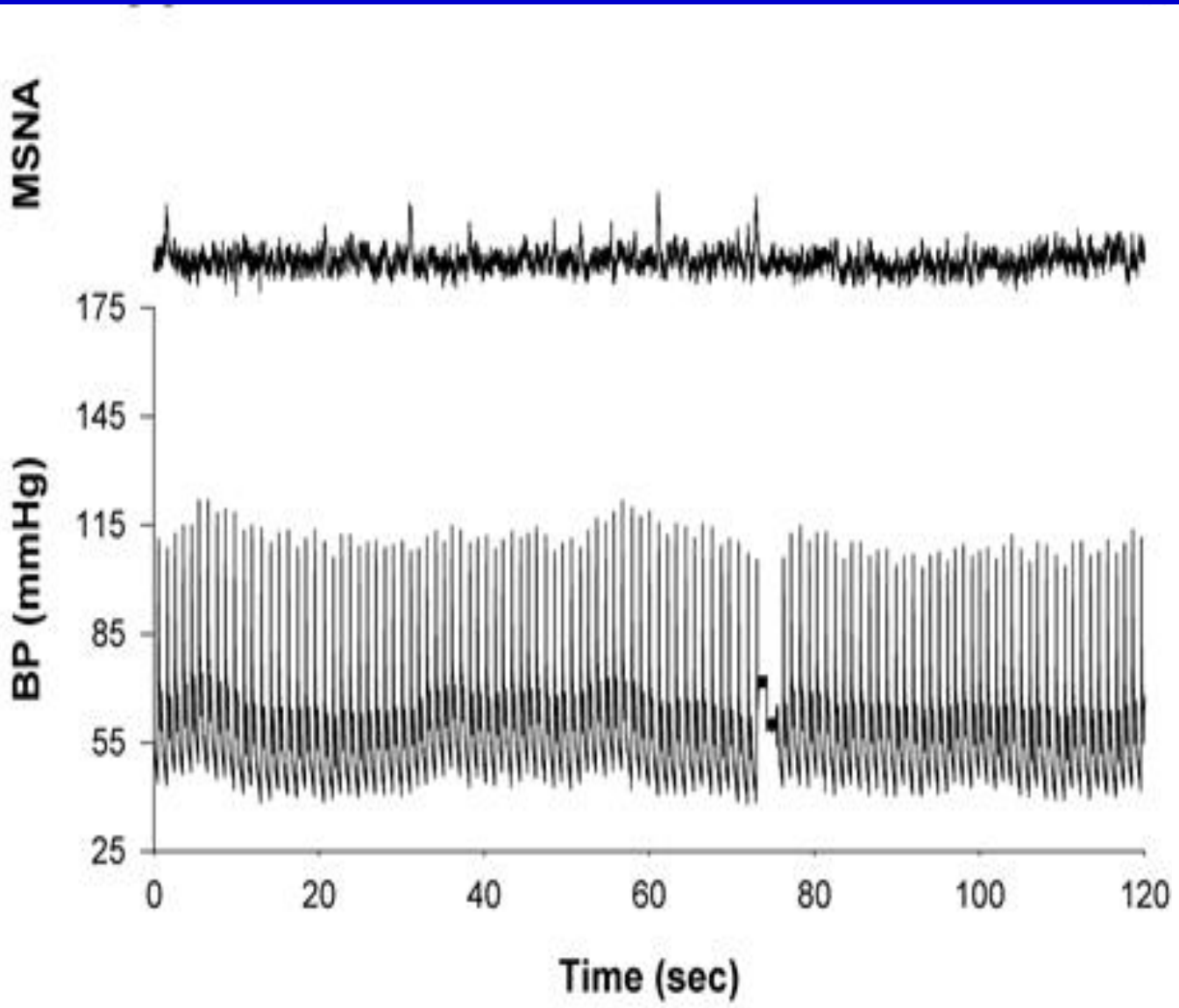
Nerve sites frequently improve spontaneously over time.
Need to be patient!
Especially in cases with low nerve traffic

Use breath hold to assess and determine quality of location

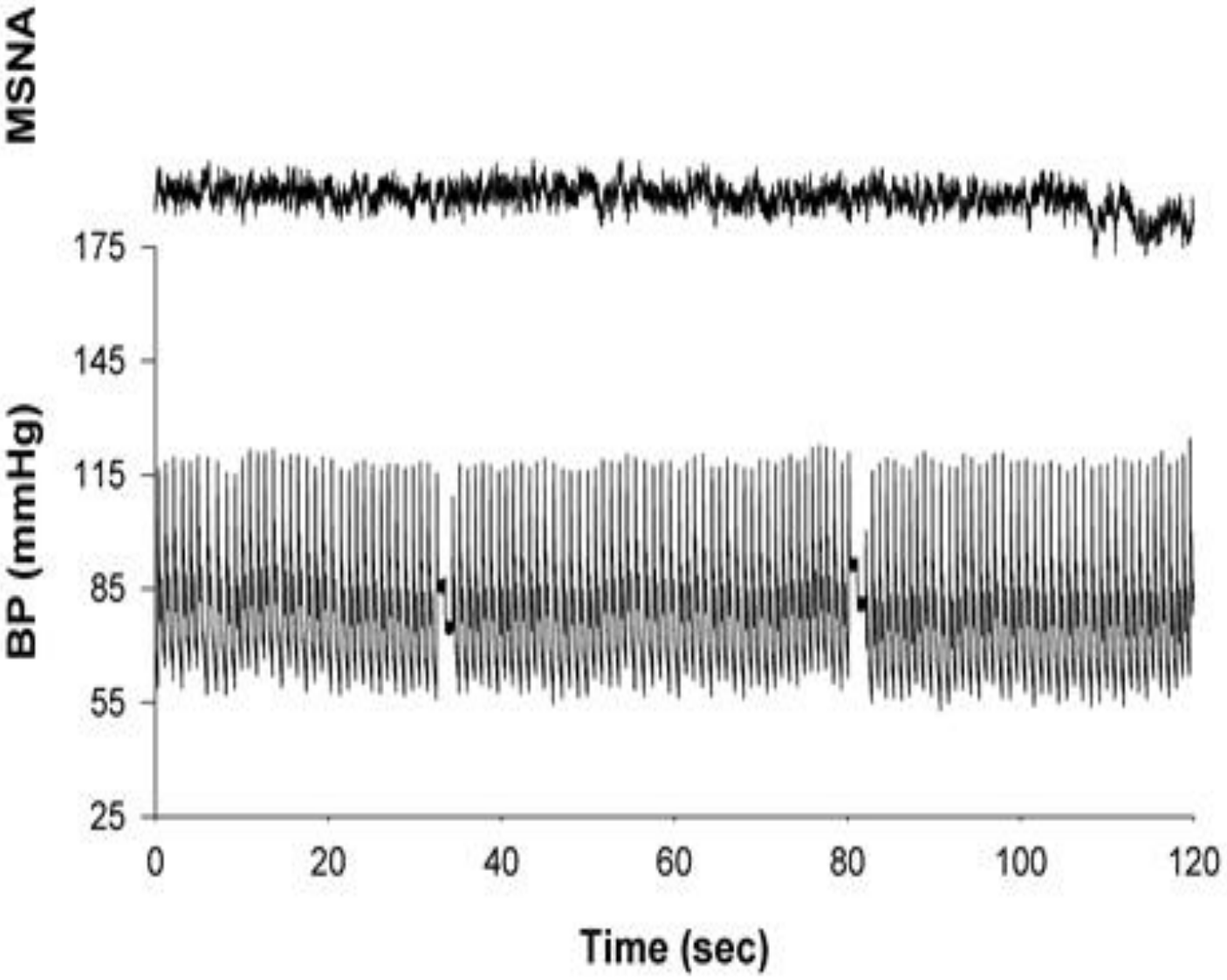
High Quality MSNA Signal



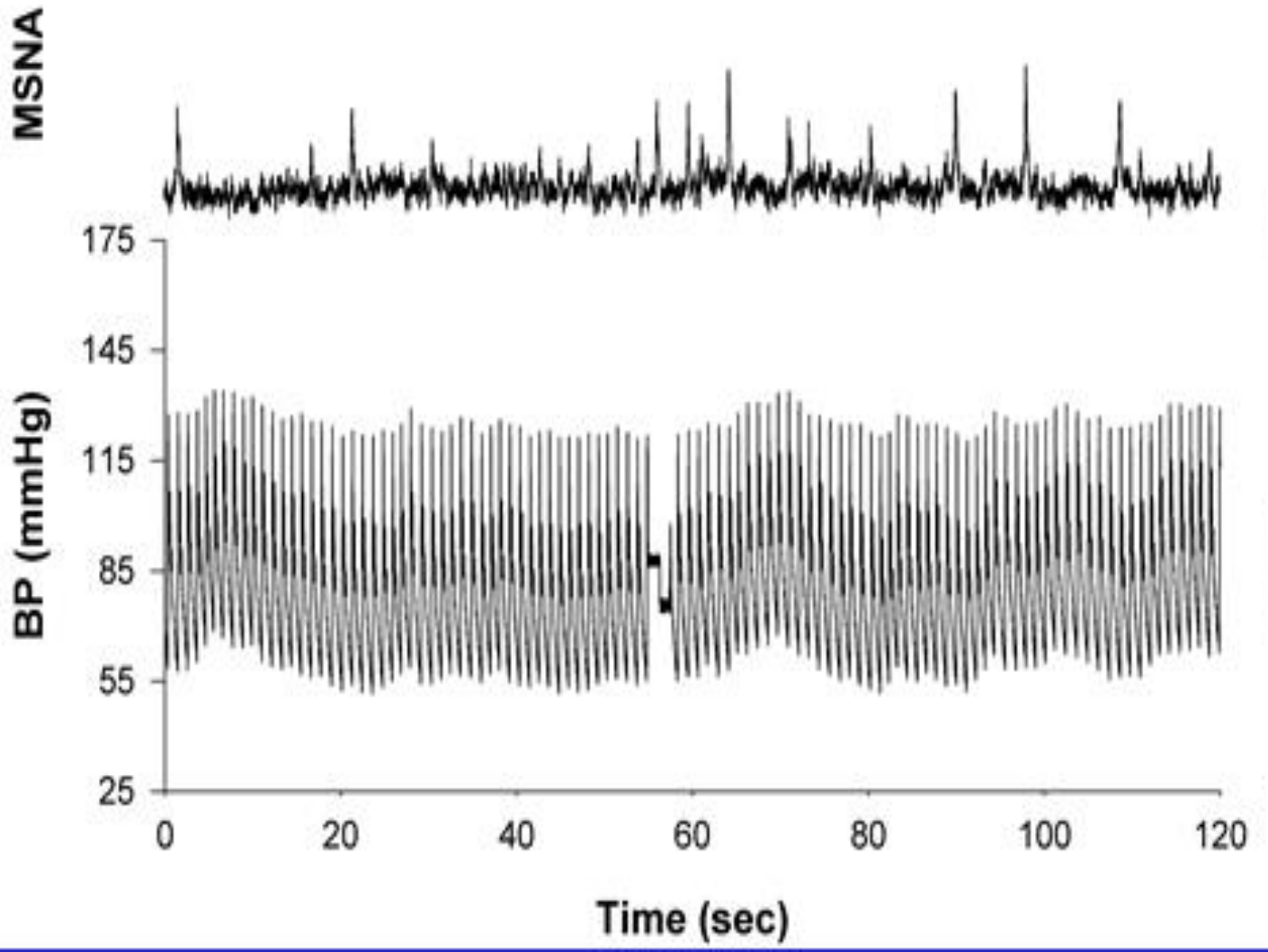
Low Quality MSNA Signal



Low Baseline Traffic with Reasonable MSNA Site



Medium Quality MSNA Signal but…….



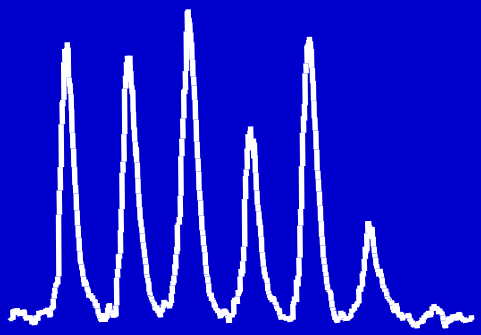
Sympathetic recordings: Quantifying multiunit MSNA

1. At rest:

   Can ONLY count bursts

   bursts/100 h.b. or bursts/min

   - Interobserver variability 8-10 %



2. To Provocation:

   In constant electrode site ONLY:

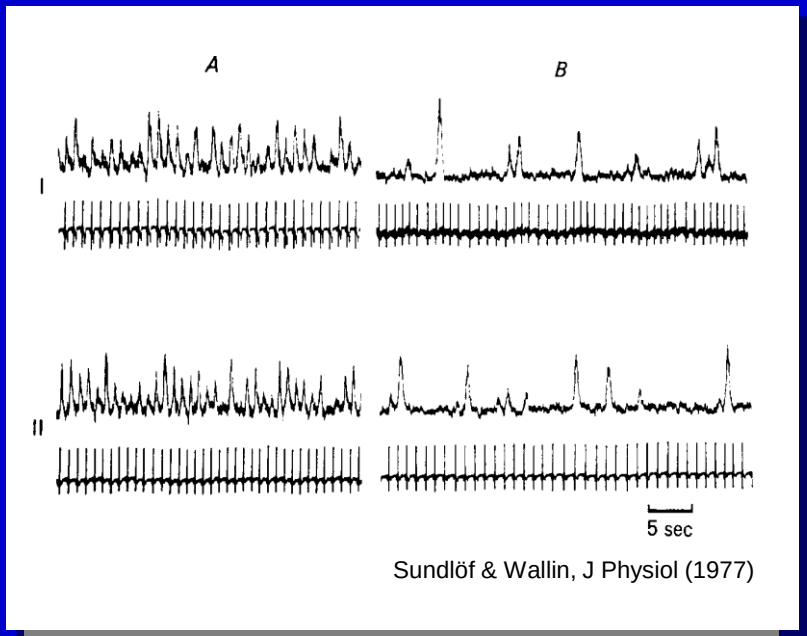
   Total activity = number of bursts x mean burst height or area

   Total MSNA = activity per beat

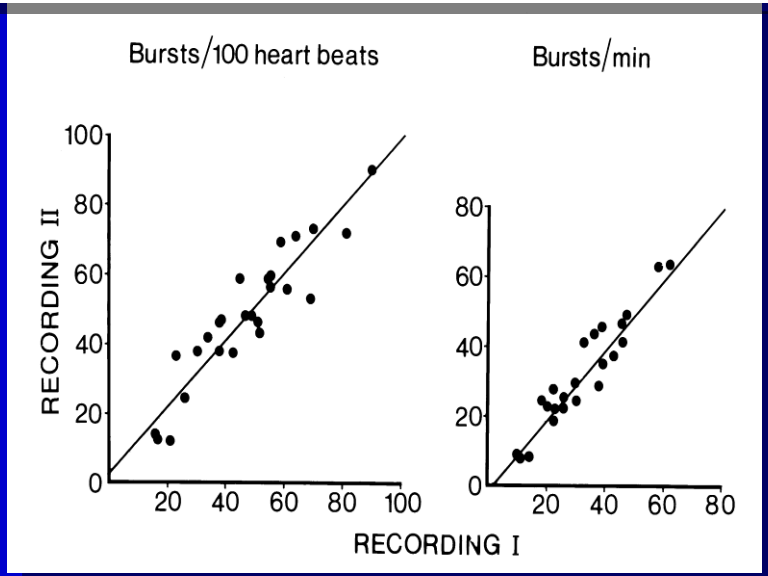
Burst height depends on distance between electrode tip and active fibers, a factor which varies between sites and cannot be determined. Thus, total activity measures CANNOT be used to compare groups.

Key Points for MSNA at rest: Reproducible Bursting

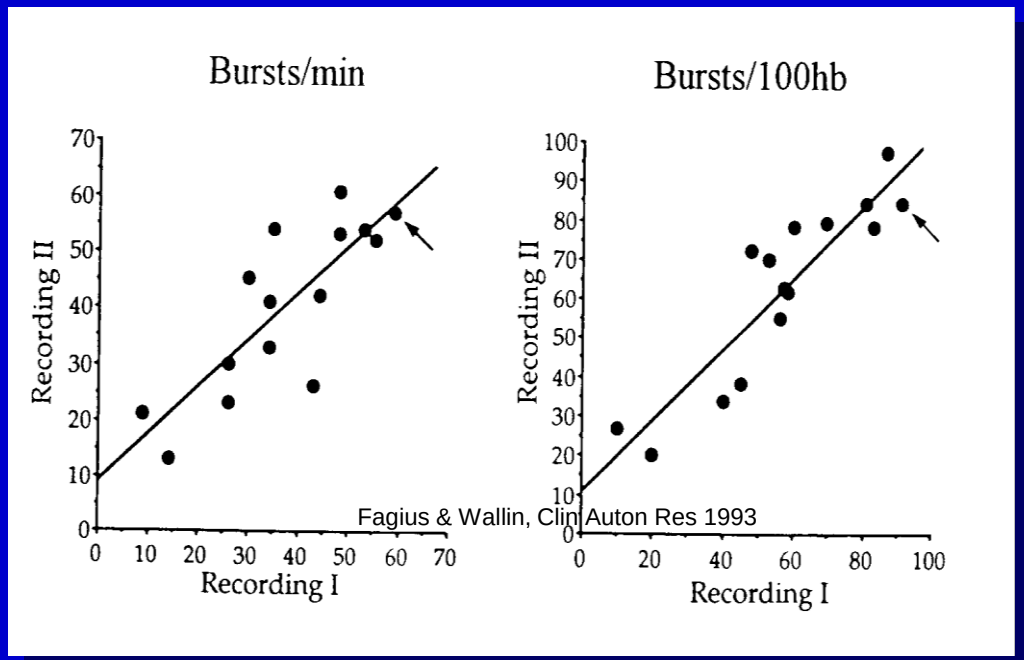
Intervals of weeks/months



Sundlöf & Wallin, J Physiol (1977)



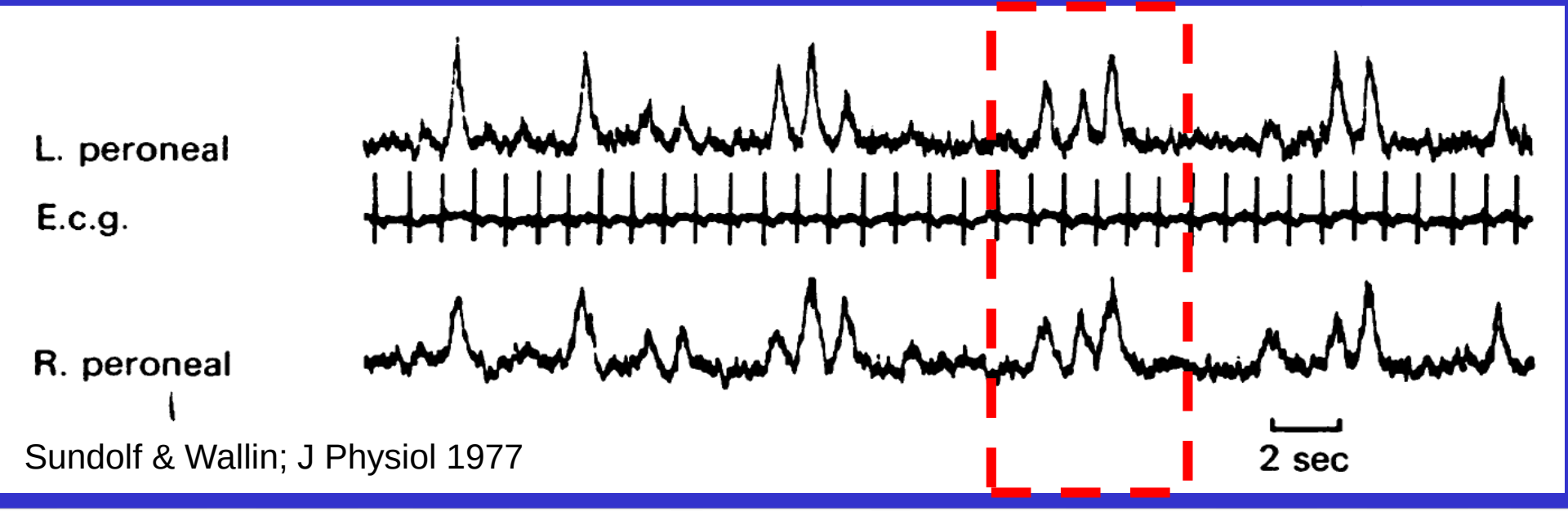
12 years follow up



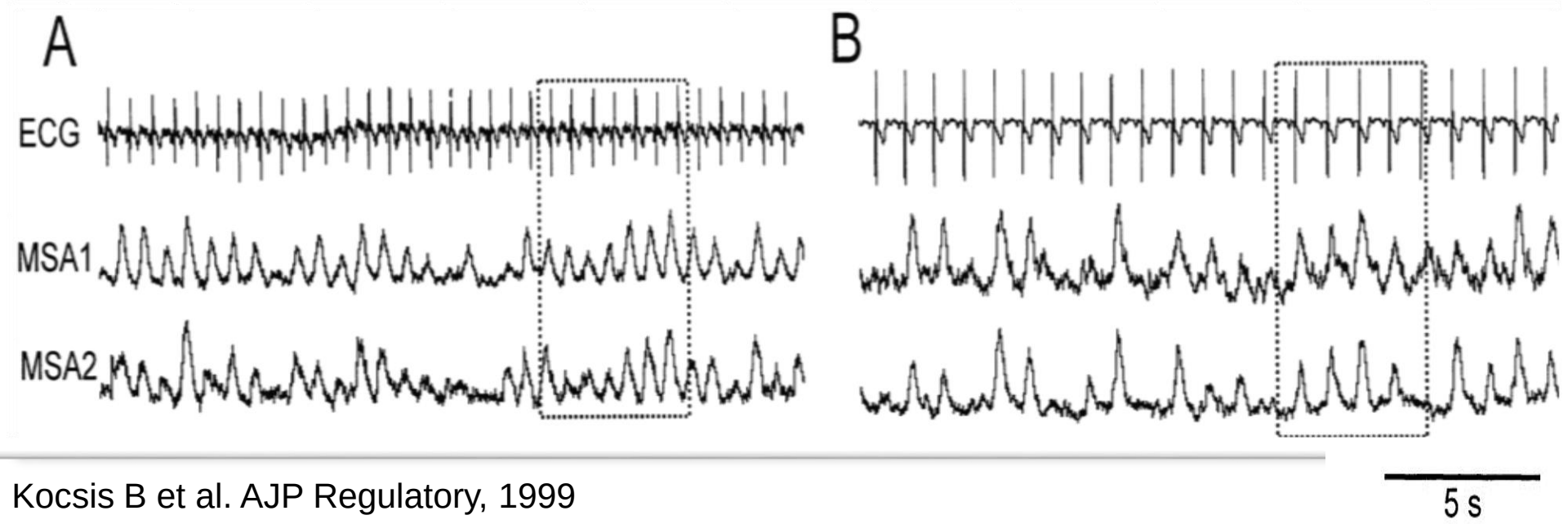
Fagius & Wallin, Clin Auton Res 1993

Implication: The reproducibility allows longitudinal studies to be made (of life style, of disease, of treatment)

Simultaneous recordings shows similar patterns of MSNA

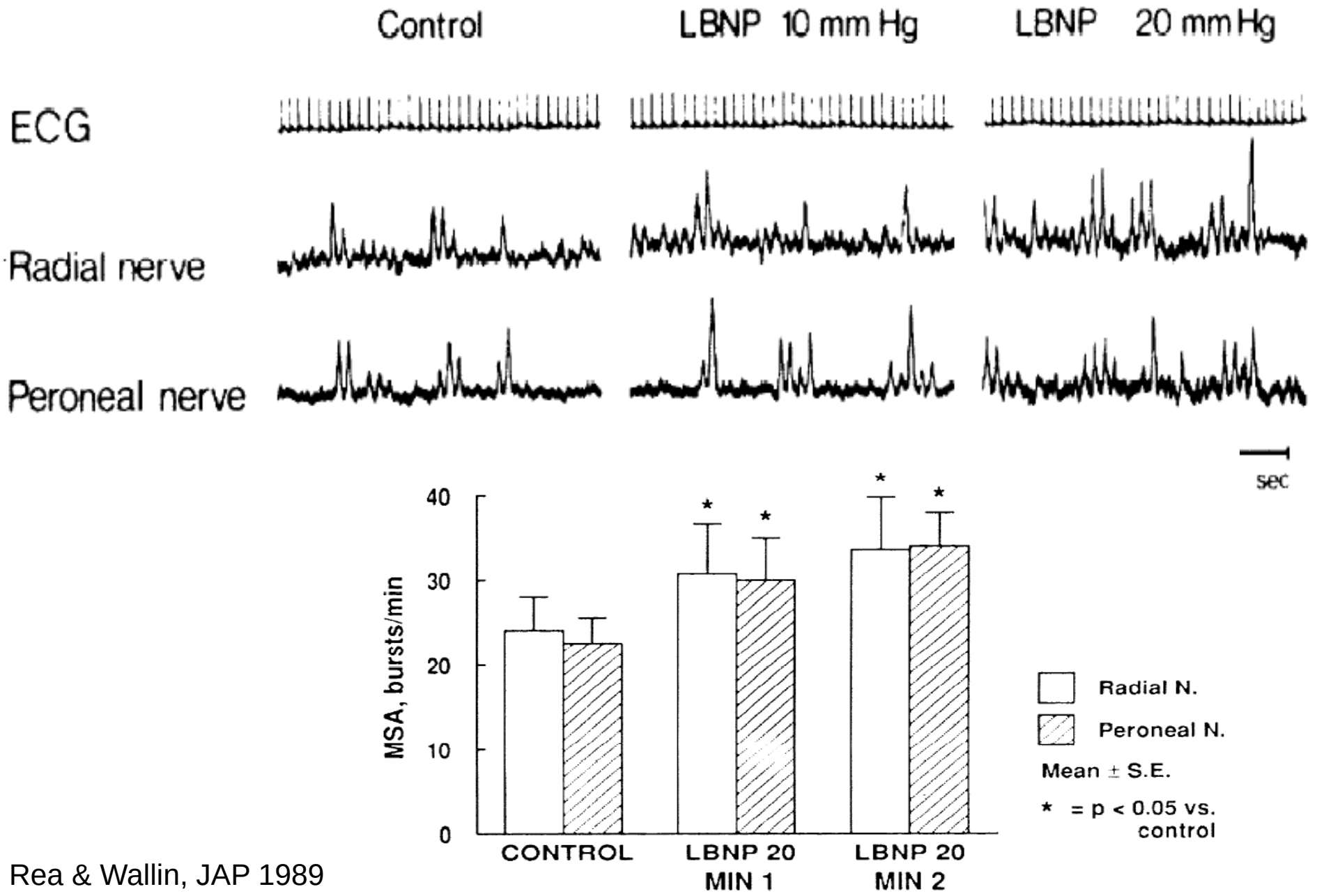


Sundolf & Wallin; J Physiol 1977



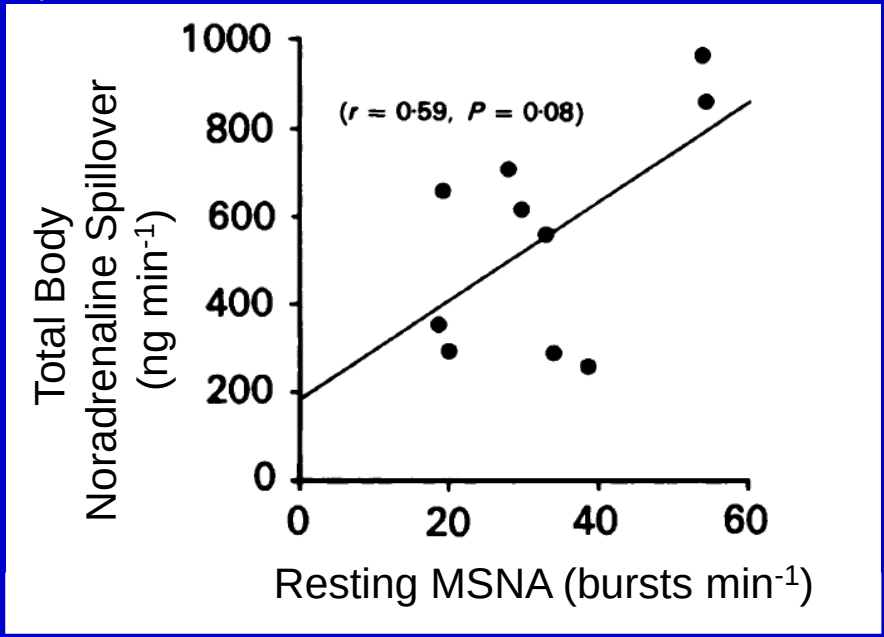
Kocsis B et al. AJP Regulatory, 1999

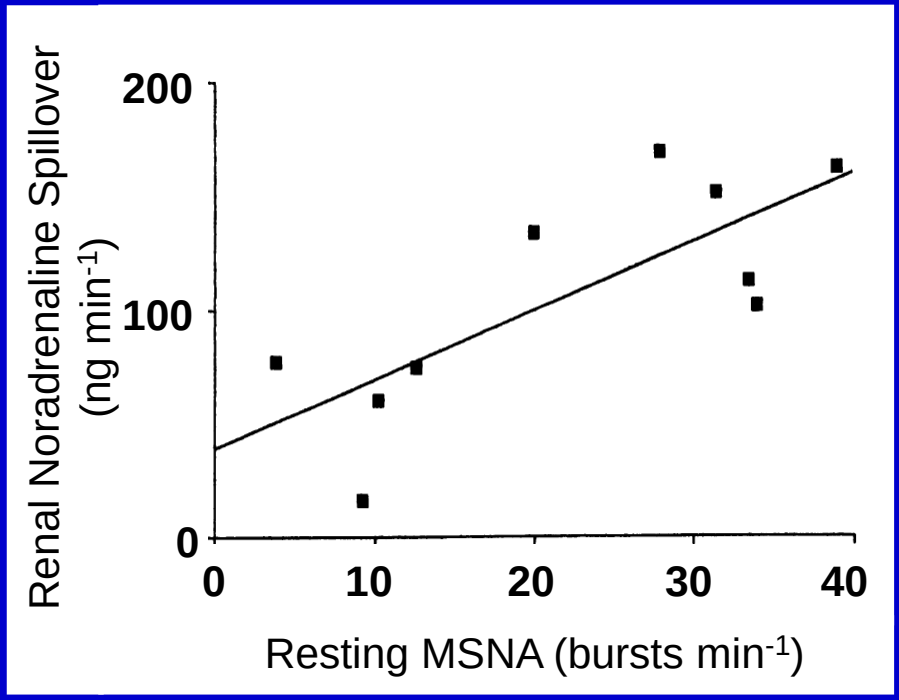
Similar patterns of MSNA obtained in arm and leg

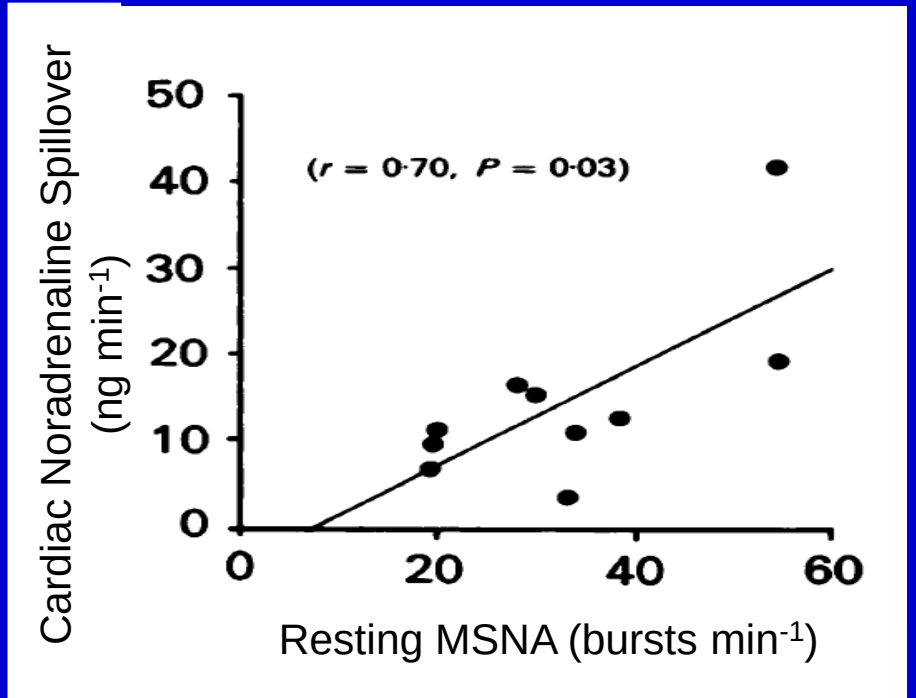


Rea & Wallin, JAP 1989

Important MSNA relationships





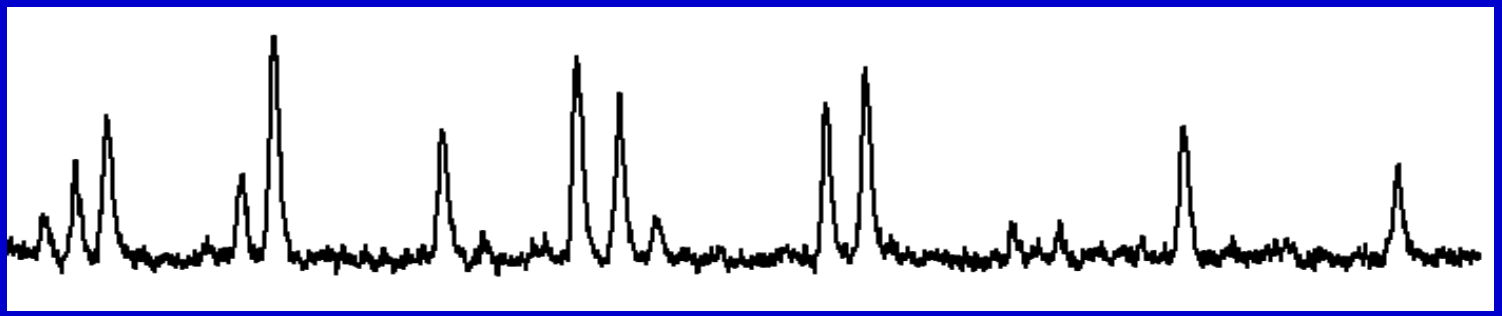


Summary of Important Points

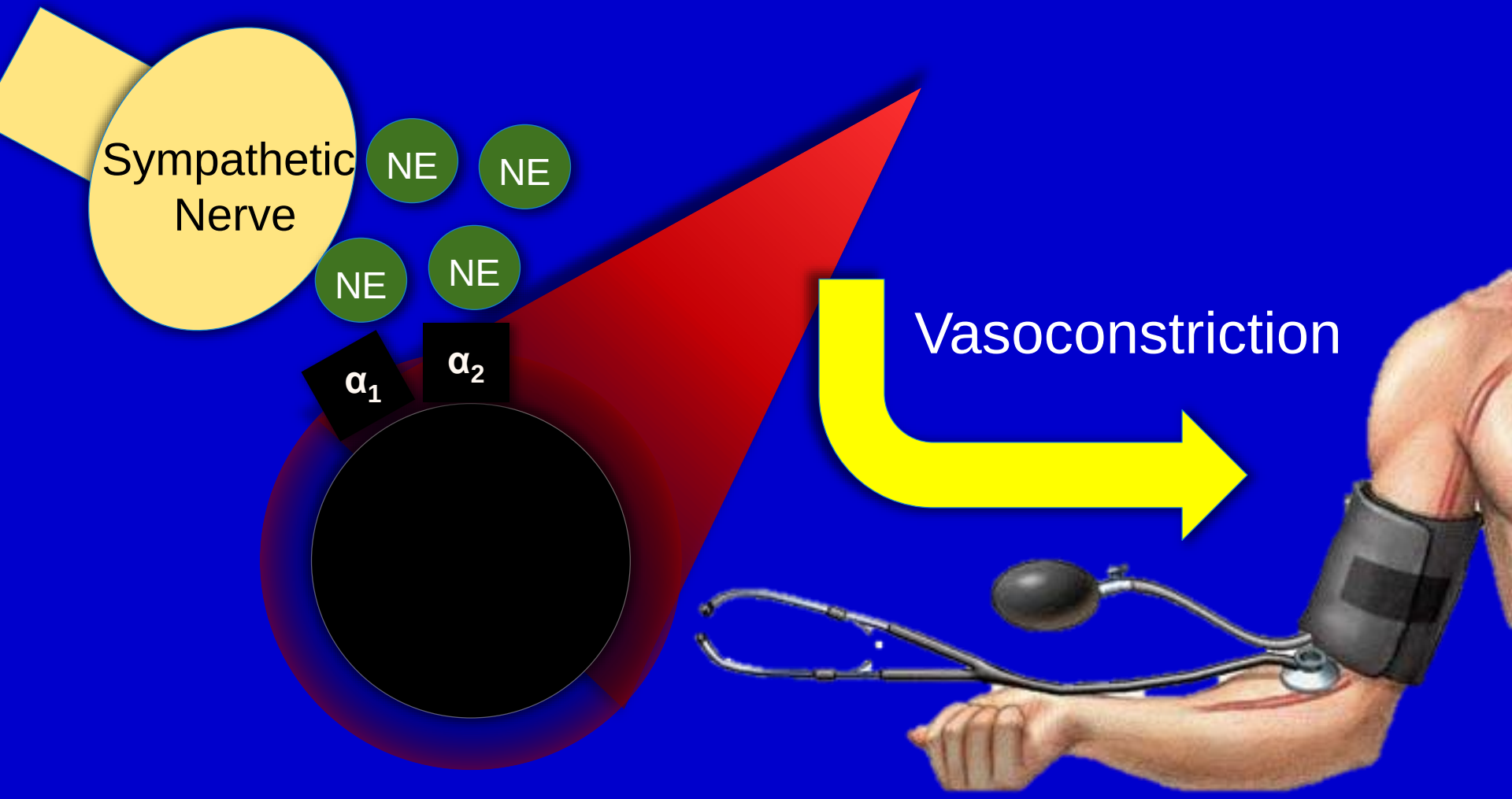
- Muscle Sympathetic Nerve Activity burst frequency is highly reproducible over time

- Similar MSNA bursting patterns when measured in leg and arm

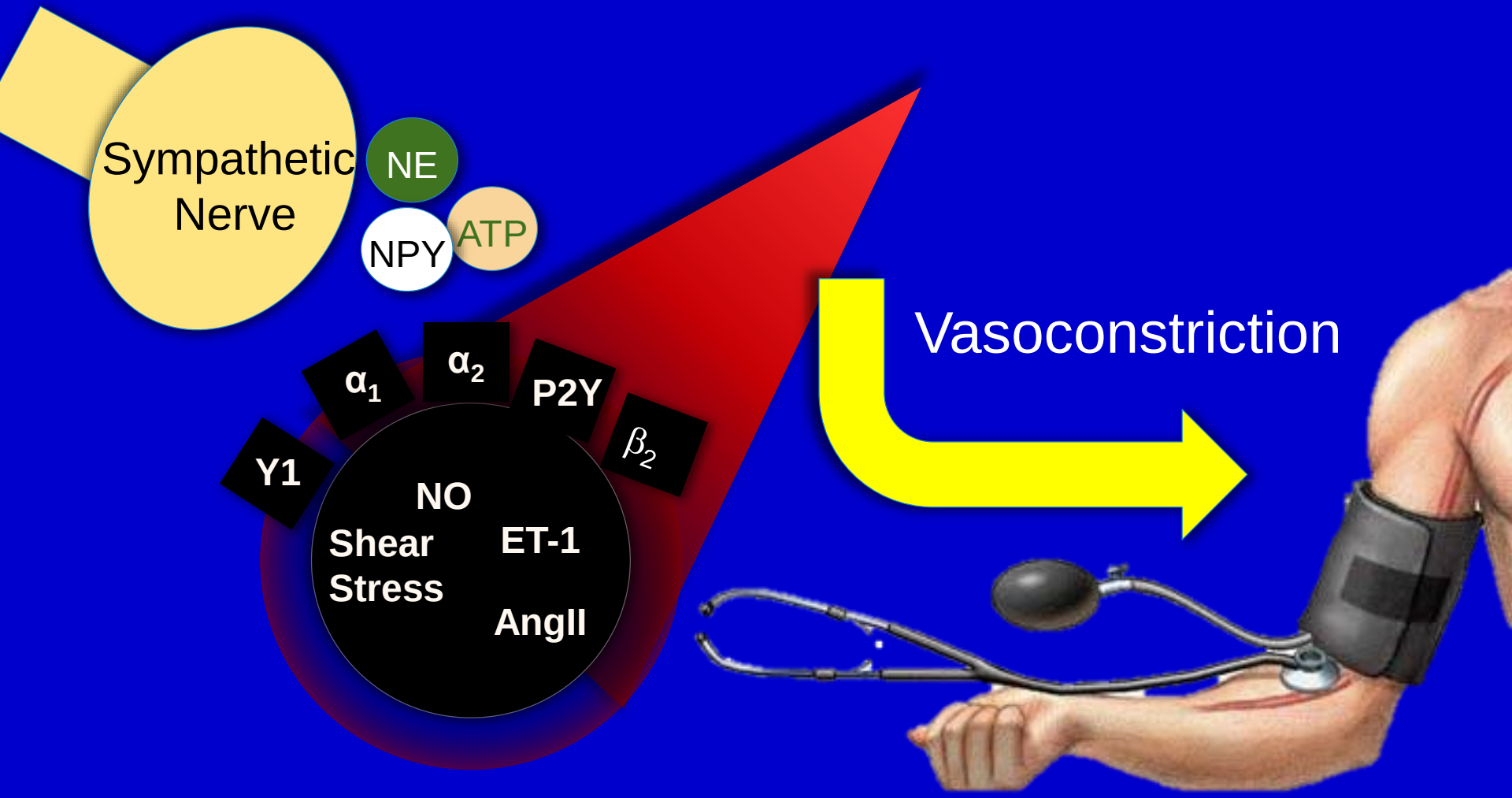
- Resting MSNA related to total body noradrenaline spillover as well as spillover to the kidney and the heart



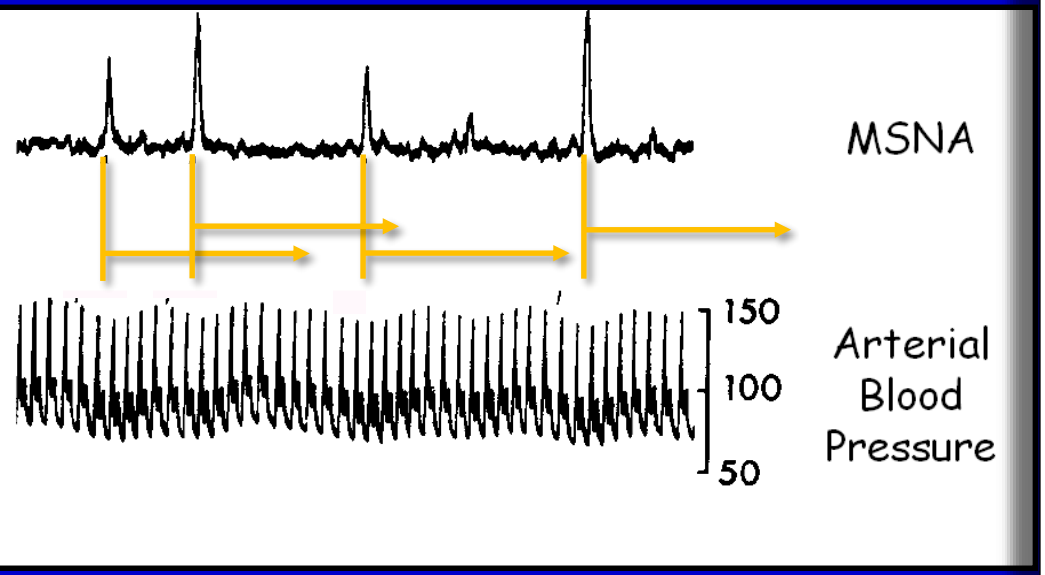
Sympathetic Vascular Transduction



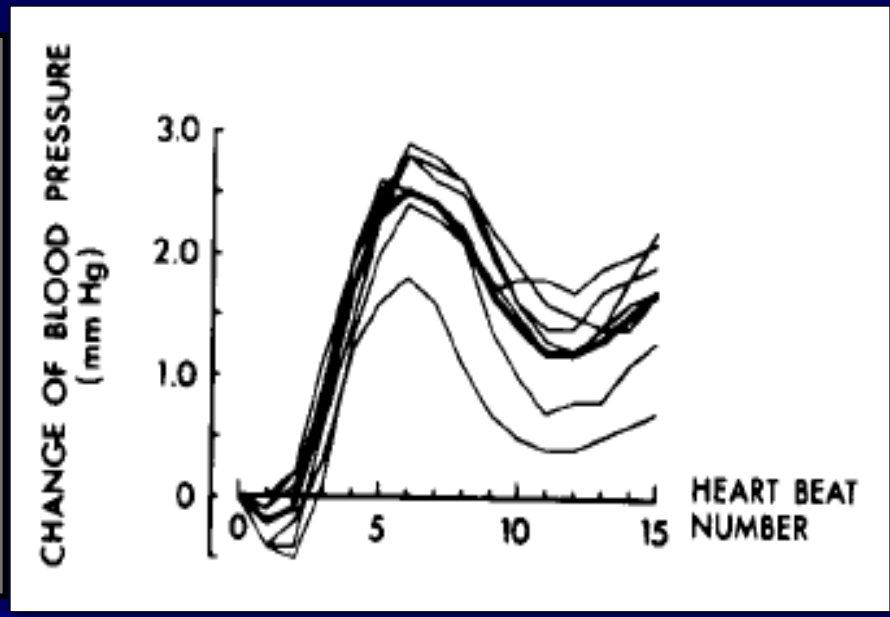
Sympathetic Vascular Transduction



Spontaneous Sympathetic Transduction to Blood Pressure



Spike Triggered Averaging of Beat-to-Beat Data



BP Response following MSNA bursts:

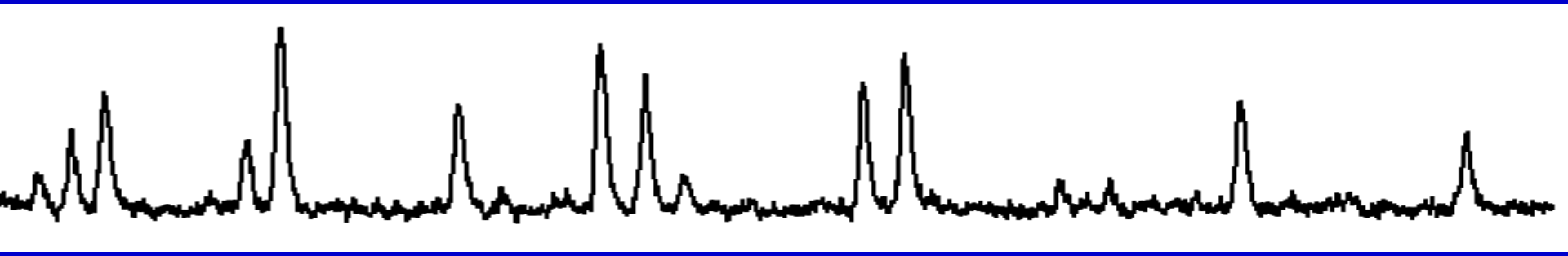
Magnitude = ~3 mmHg

Latency = ~5.5 sec

Wallin & Nerhed,
J Auton Nerv Sys, 1982

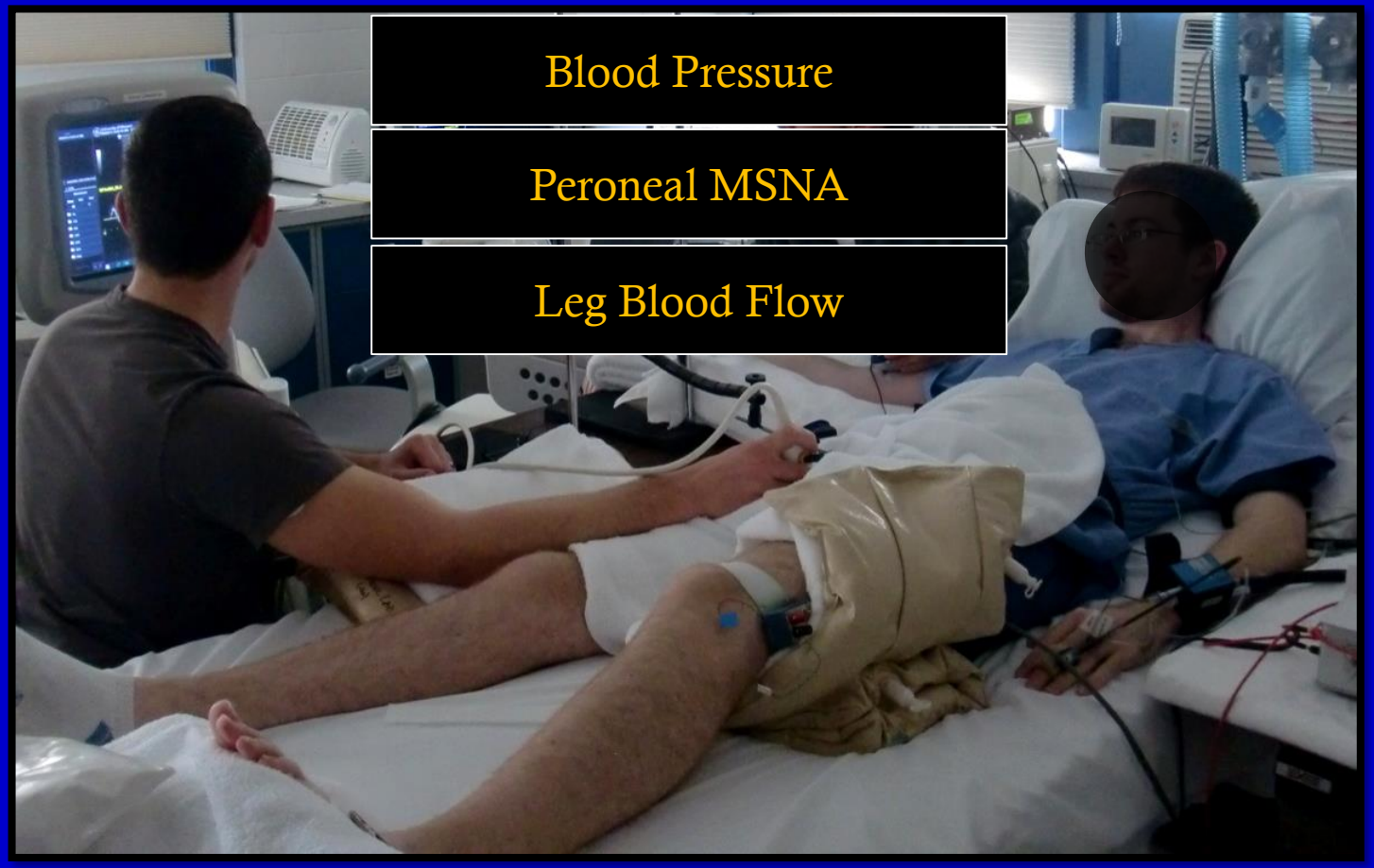
Hypotheses

Leg vascular conductance (LVC) would transiently decrease following MSNA bursts, whereas cardiac cycles without MSNA would exhibit a minimal or no decrease



Fairfax ST et al, *AJP Heart Circ* 304: H759-66, 2013

Beat to Beat Sympathetic Vascular Transduction

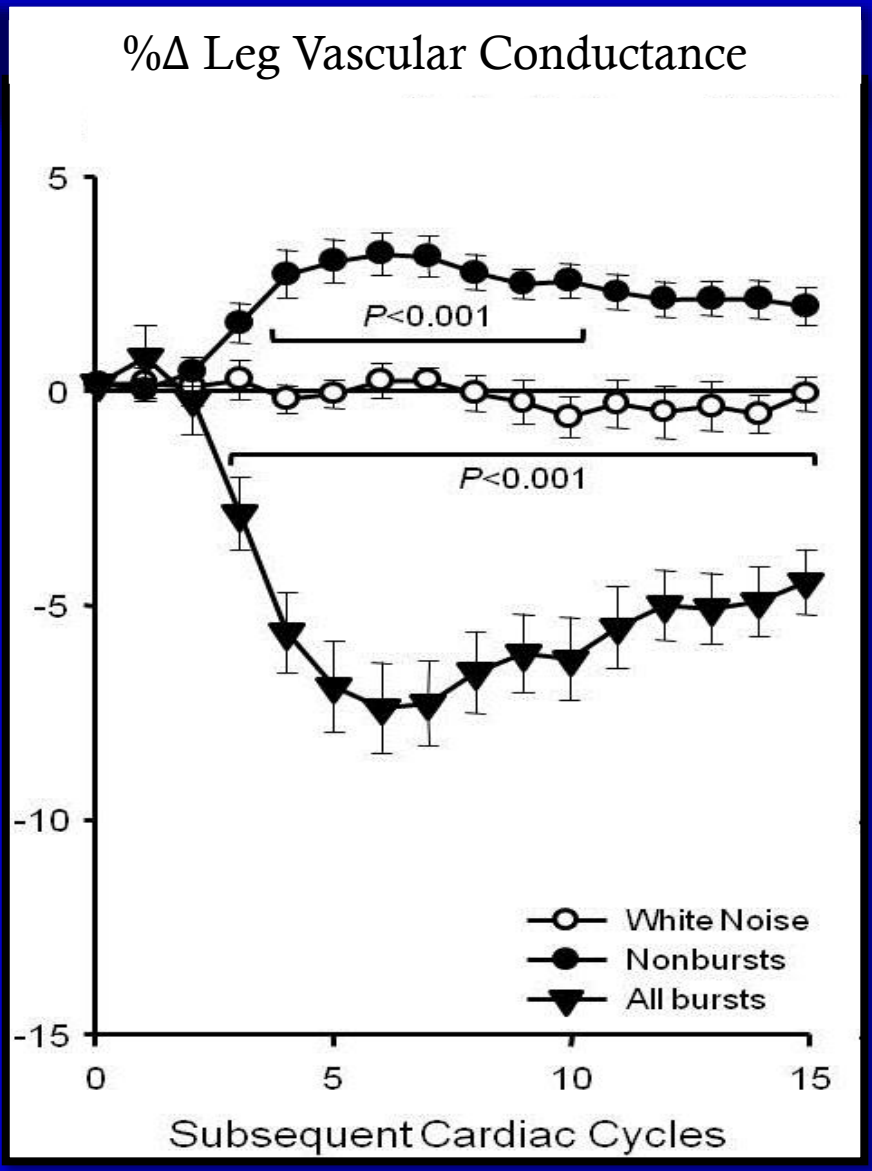


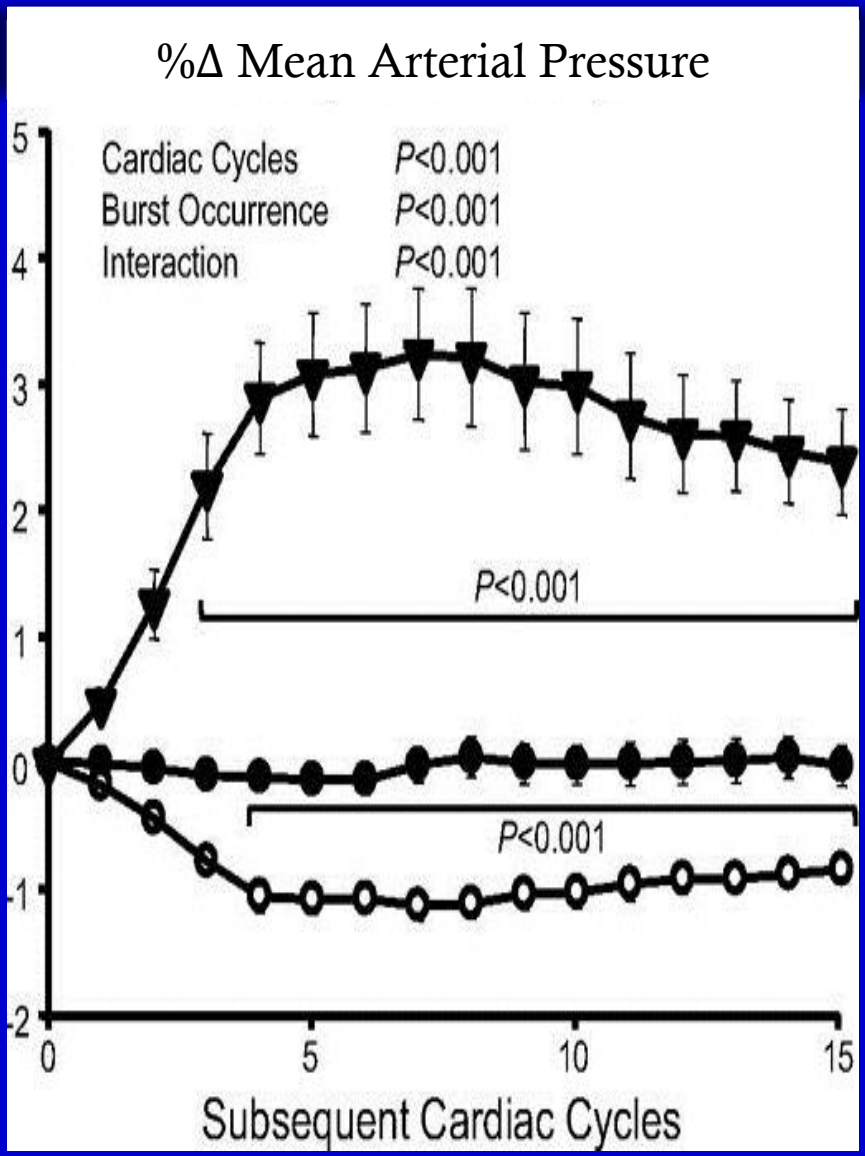
11 normotensive healthy young men (25±1 years, 176±2 cm, 79±2 kg)

Spike-triggered averaging of 20 minutes during quiet, awake, supine rest

Fairfax ST et al, *AJP Heart Circ* 304: H759-66, 2013

Beat to Beat Sympathetic Vascular Transduction

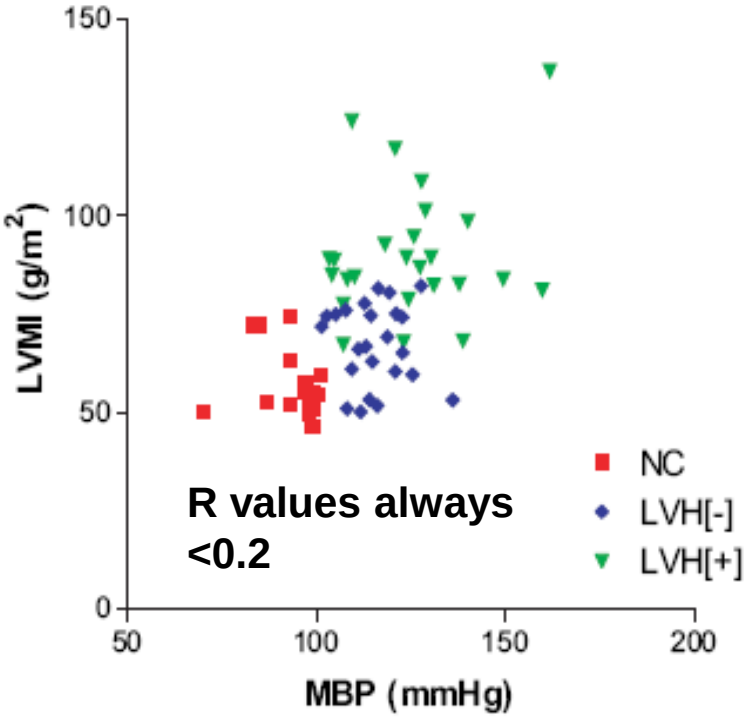


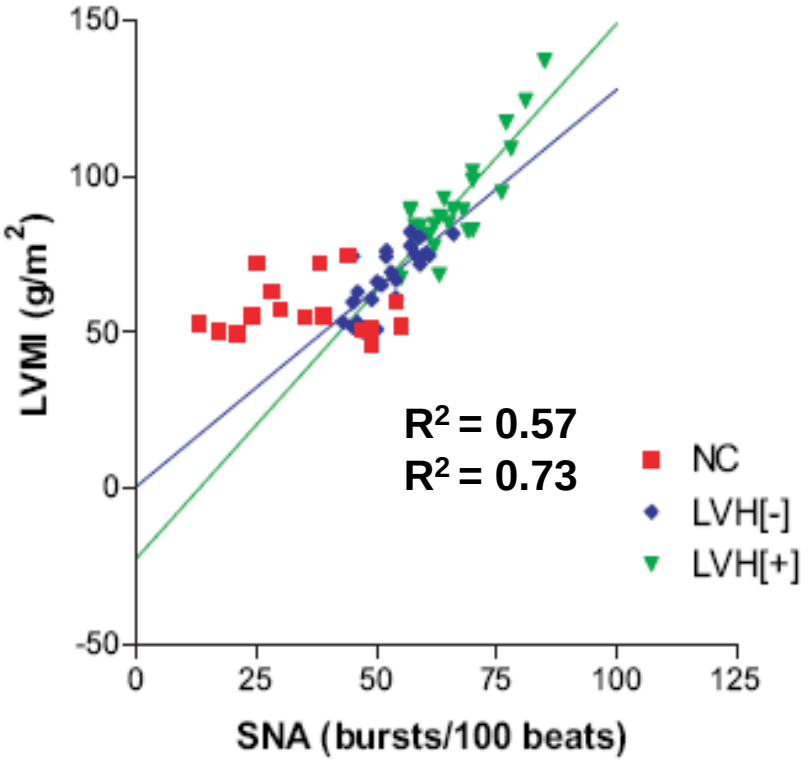


Fairfax ST et al, *AJP Heart Circ* 304: H759-66, 2013

Thank You!

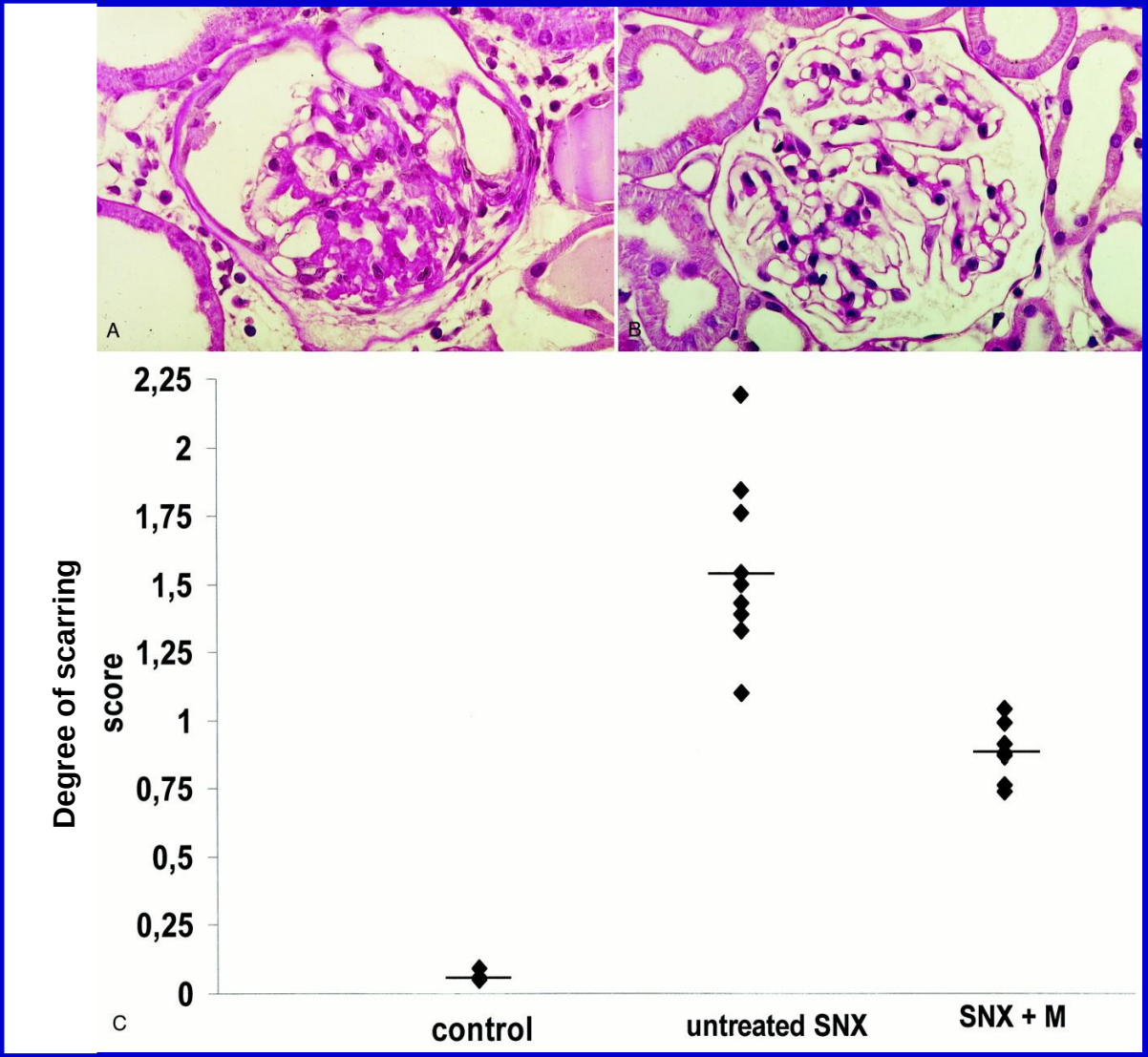
Left Ventricular Mass and SNA in Patients with Untreated Essential Hypertension





Burns J et al. Circulation 2007;115;1999-2005

Subpressor moxonidine treatment reduces glomerulosclerosis



SNX – Subtotal Nephrectomy (75% of right kidney removed to induce hypertension)

Amann K. et al. J Am Soc Nephrol 2000

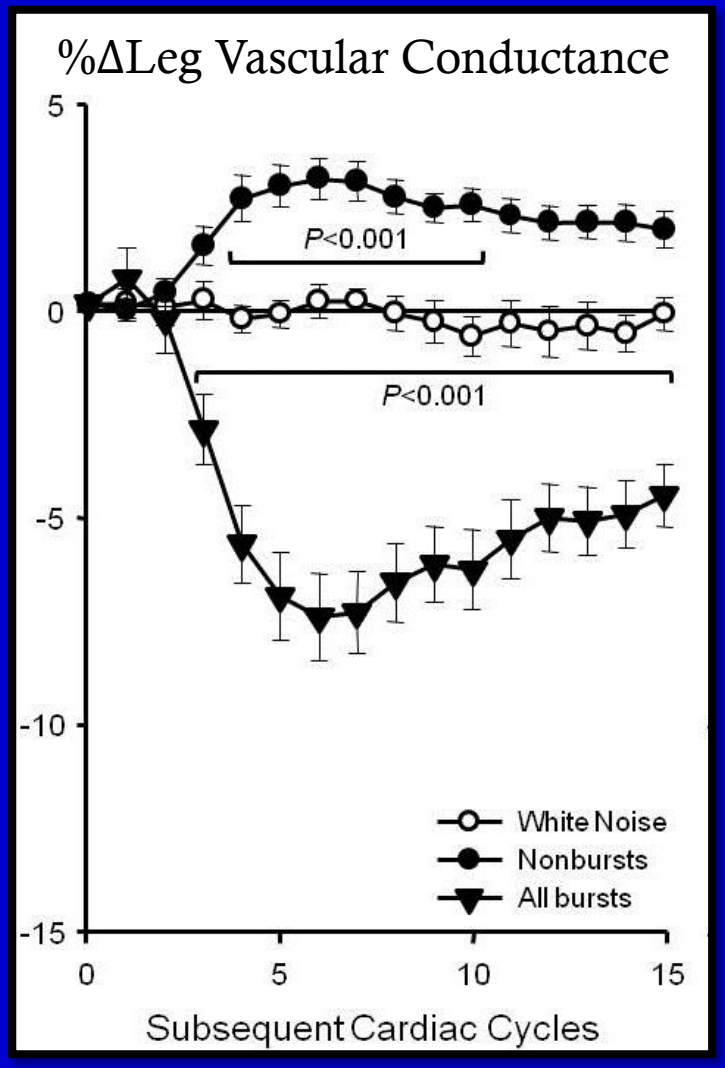
Potential pathological consequences of elevated central sympathetic nerve activity

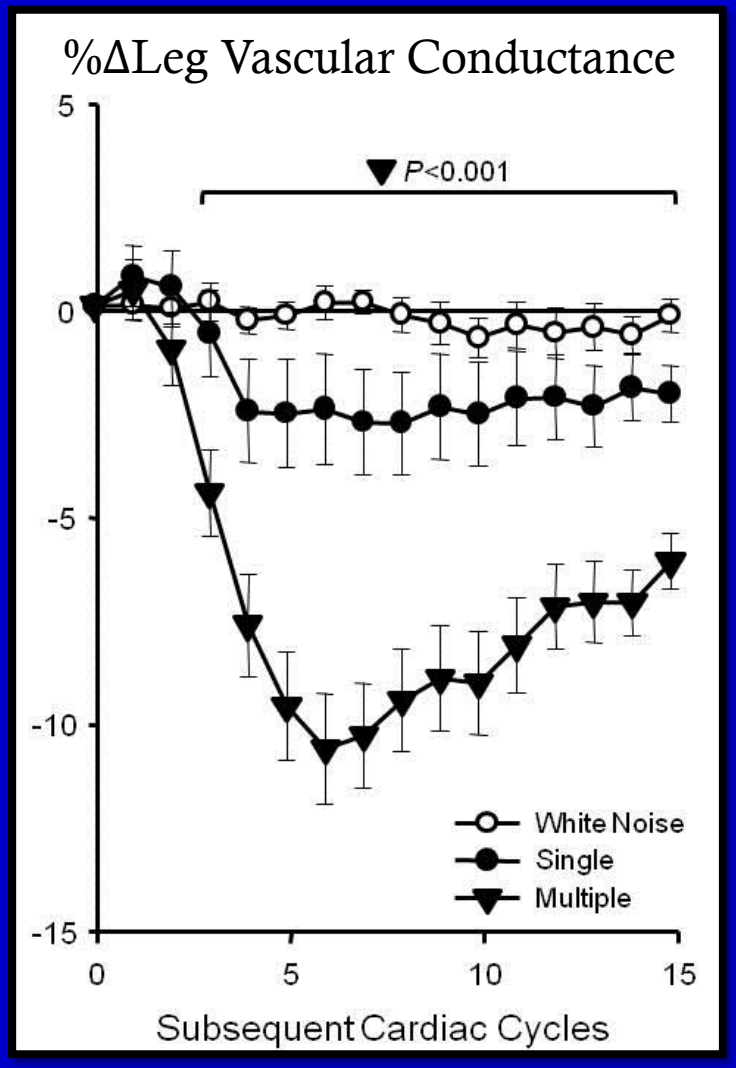
Vascular effects	*Cardiac effects*
VSM cell hypertrophy and proliferation	Cardiac myocyte hypertrophy
Medial thickening	Left ventricular hypertrophy
Endothelial cell damage	↑ Incidence of arrhythmia
Endothelial dysfunction	Tachycardia
Arterial stiffness	
↑ Blood pressure variability	*Renal effects*
↑ Peripheral vascular resistance	Renal vasoconstriction
Hypertension	Sodium and fluid retention
Atherosclerosis	Glomerulosclerosis
	Microalbumineria
Metabolic effects	RAAS activation
Insulin resistance	
↑ Plasma insulin concentration	
Dyslipidemia	

VSM, vascular smooth muscle; RAAS, Renin-angiotensin-aldosterone system.

Fisher JP. et al. Auton Neurosci., 2009

Beat to Beat Sympathetic Vascular Transduction





Fairfax ST et al, *AJP Heart Circ* 304: H759-66, 2013

Identification of Nerve Location (con't)