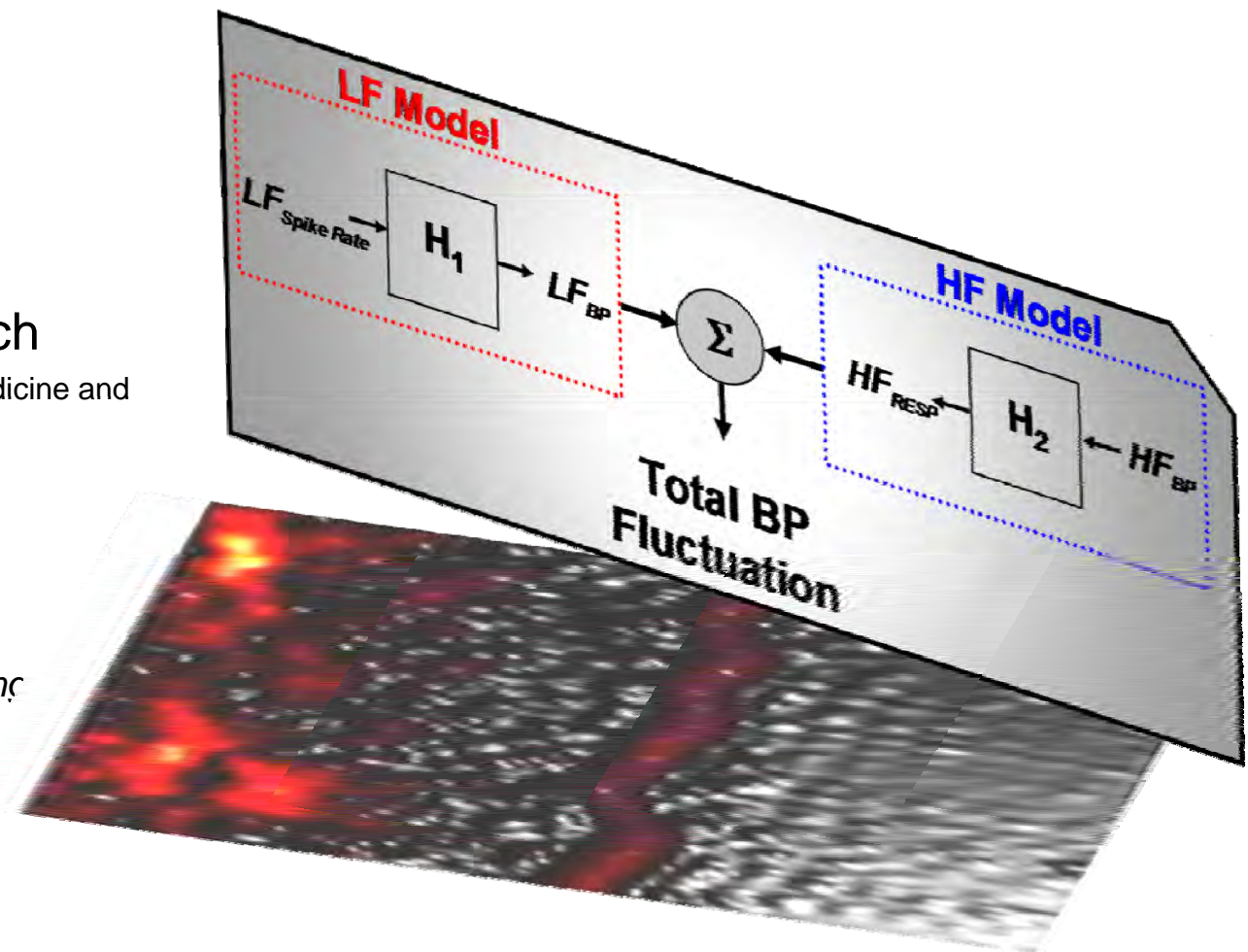


A Predictive Model of Spontaneous Blood Pressure Fluctuations Using Sympathetic Nerve Traffic

Dr. med. André Diedrich

Research Associate Professor of Medicine and
Biomedical Engineering

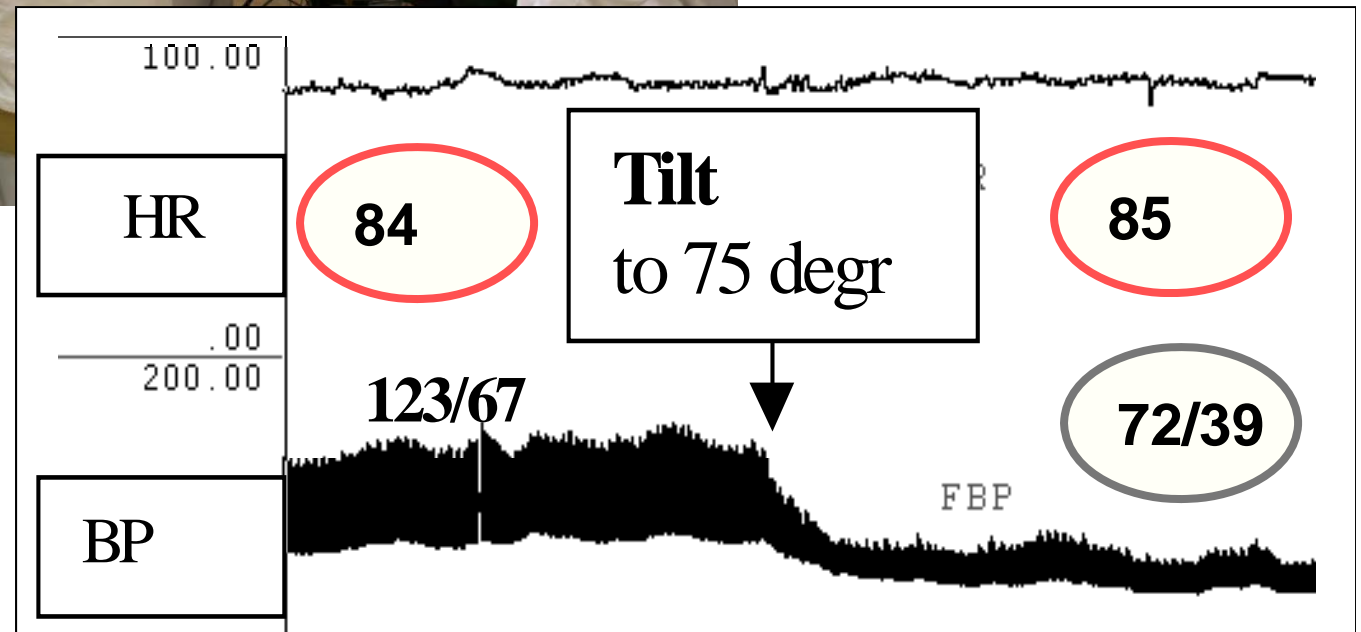
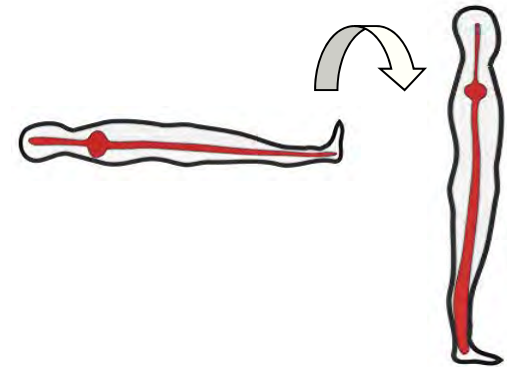
*Autonomic Dysfunction Center
Vanderbilt University
School of Medicine
School of Biomedical Engineering
Nashville, TN, USA*



Autonomic Dysfunction



Low Blood Pressure
during Standing
No Heart Rate Change



Outline

☐ Autonomic Dysfunction and Baroreflex

☐ Muscle Sympathetic Activity

☐ Heart Rate Variability and Sympathetic Activity

☐ Blood Pressure Variability and Sympathetic Activity

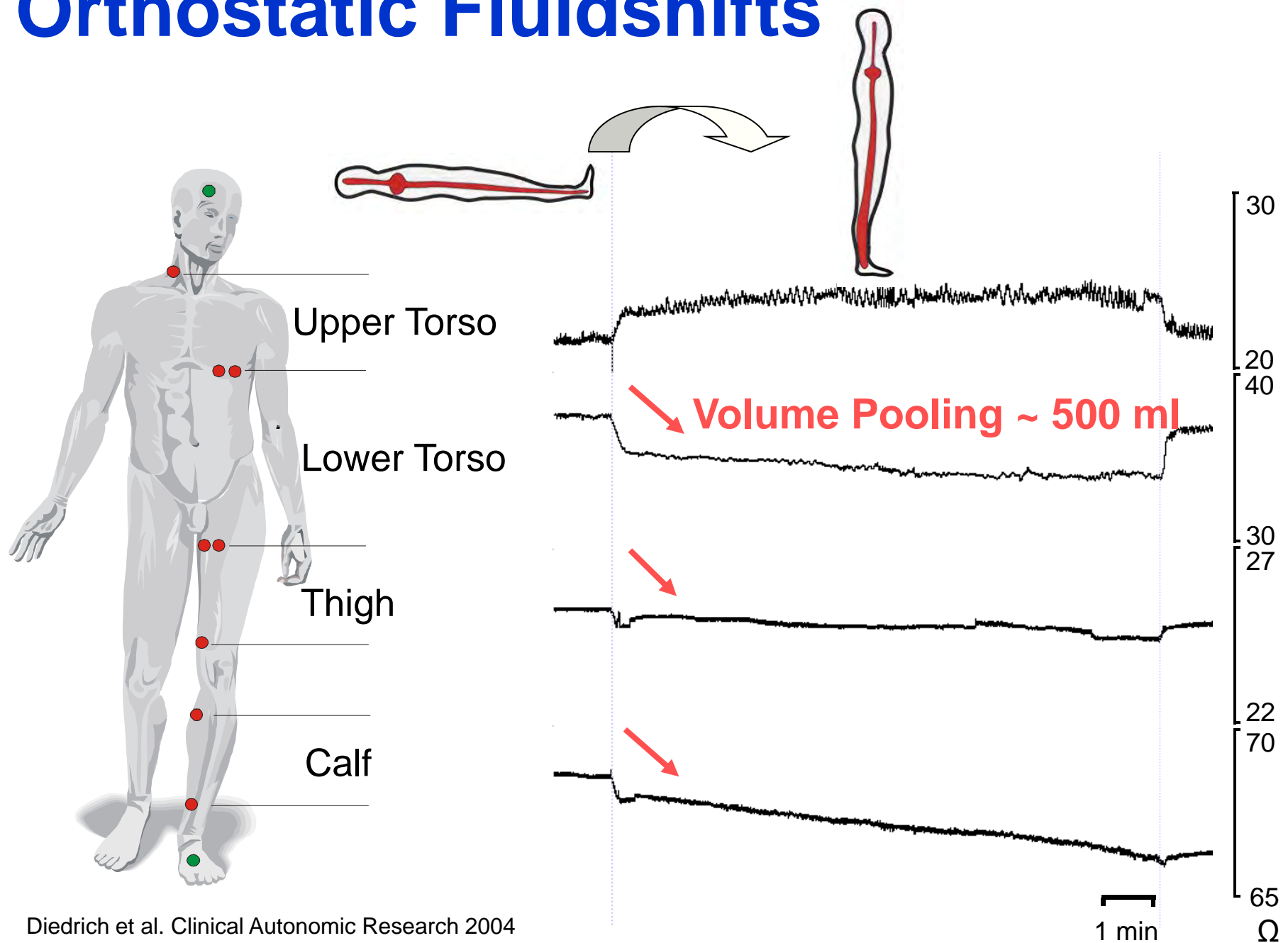
☐ Simplified Model of Blood Pressure Variability

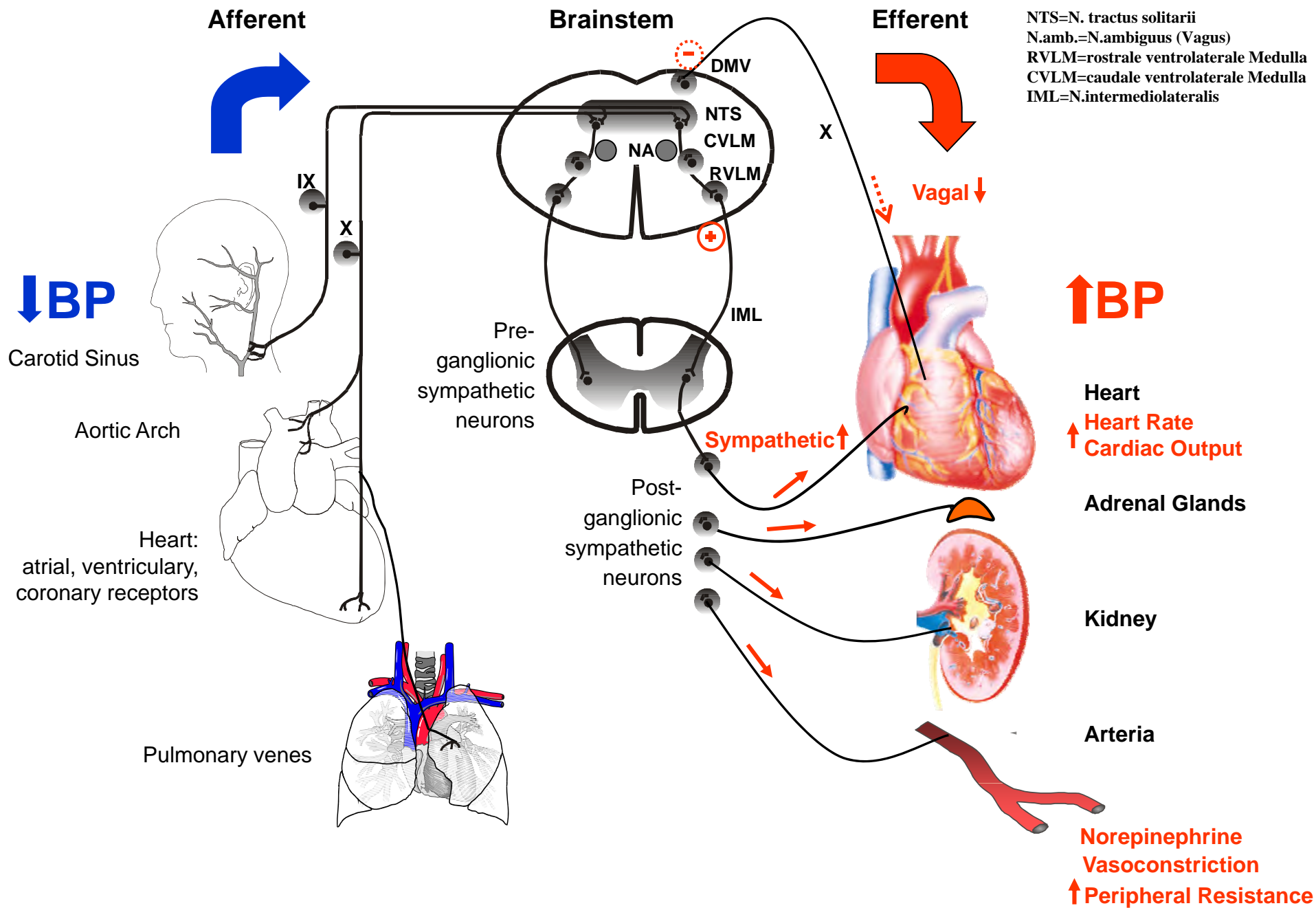
Orthostatic Intolerance



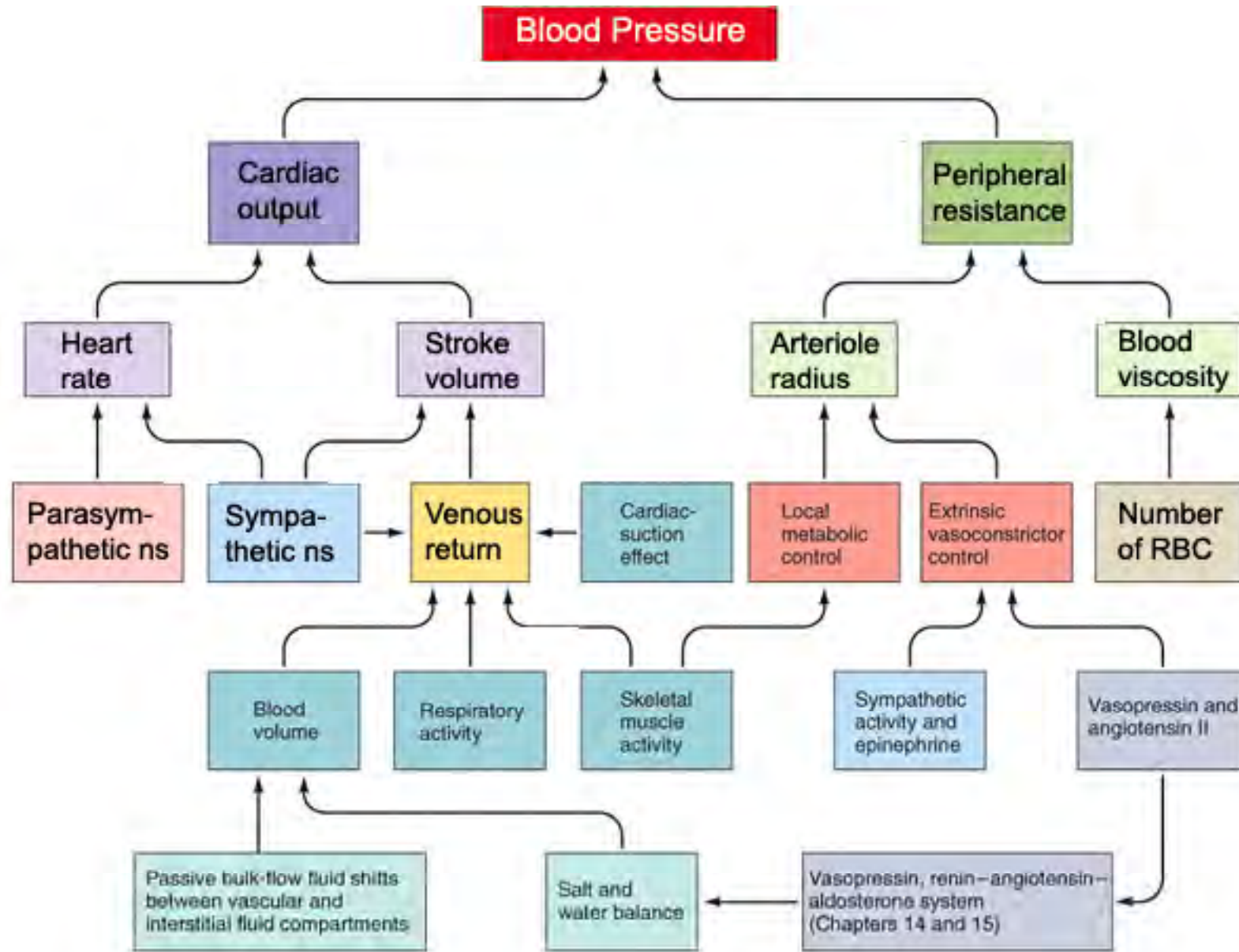
Orthostatic Intolerance is defined as the development of symptoms during upright position due to a failure to adjust adequate **blood flow, blood pressure, or heart rate** and which make it impossible to maintain upright body function and which can be relieved by returning to supine.

Orthostatic Fluidshifts





Factors of Blood Pressure



Pure Autonomic Failure

“...extensive and peculiar disturbance in the functional activity of the vegetative nervous system...”

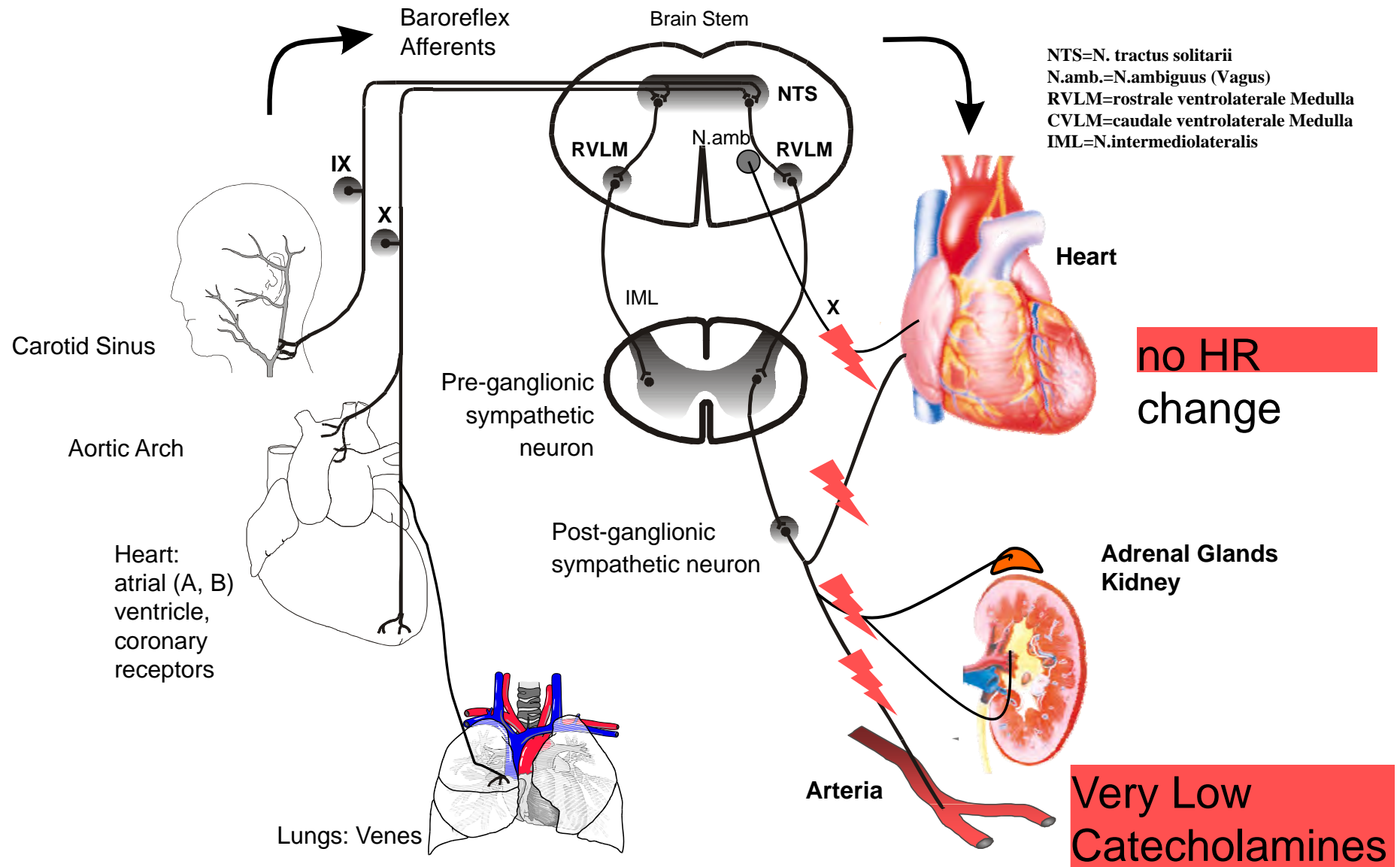
“...idiopathic hypotension...”



Bradbury and Eggleston 1925

- gradually progression of the disease (10-15 years, in older age)
- orthostatic hypotension
- impotence
- bowel & bladder dysfunction
- disorder of sweating and thermoregulation
- low resting NE level & insufficient increase during standing
- Lewy bodies

Dysfunction in Pure Autonomic Failure



Multiple System Atrophy

“... a sporadic, progressive, neurodegenerative disease of undetermined etiology, characterized by extrapyramidal, pyramidal, cerebellar, and autonomic dysfunction in any combinations....”



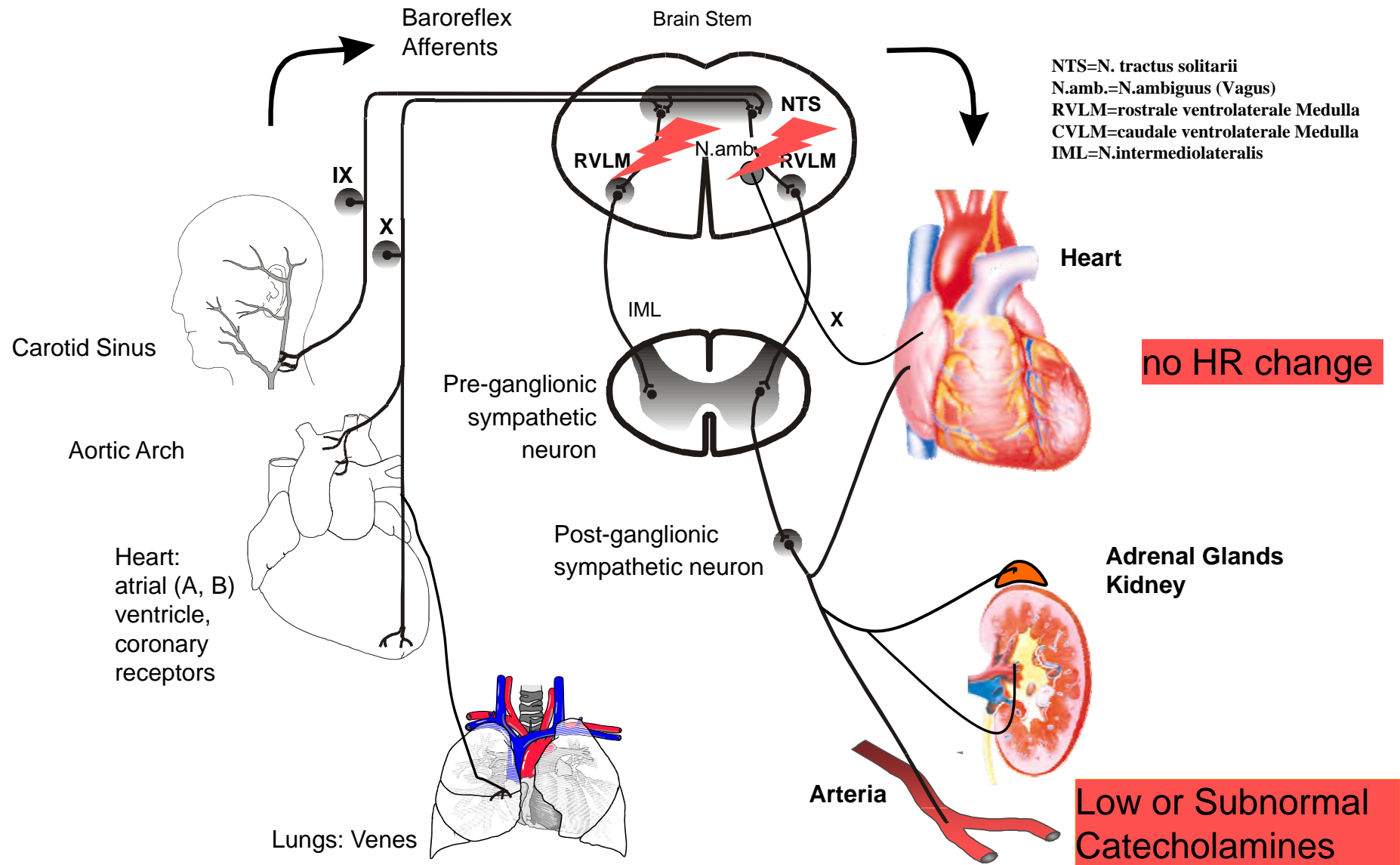
Shy and Drager 1960

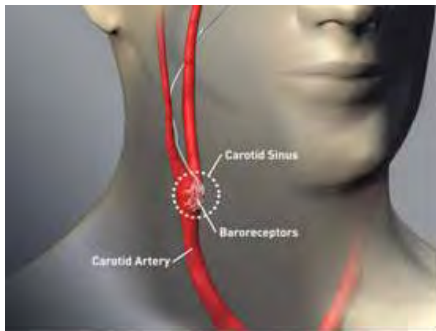
- **Fast progression** of the disease (6.2-9.5 years, age range **52-55 years**)
- Orthostatic hypotension
- Urinal and rectal incontinence, partial bladder emptying
- Erectile dysfunction
- Loss of sweating
- **Subnormal supine resting NE level** & insufficient increase during standing
- **Stridor**
- Rigidity, **Tremor**, Loss of associated movements
- **Poor response to levodopa**

Gilman S et al. Clin Auton Res 1998 8(6): 359-62

Diedrich A et al. Encyclopedia of the Neurological Science 2003:264-270

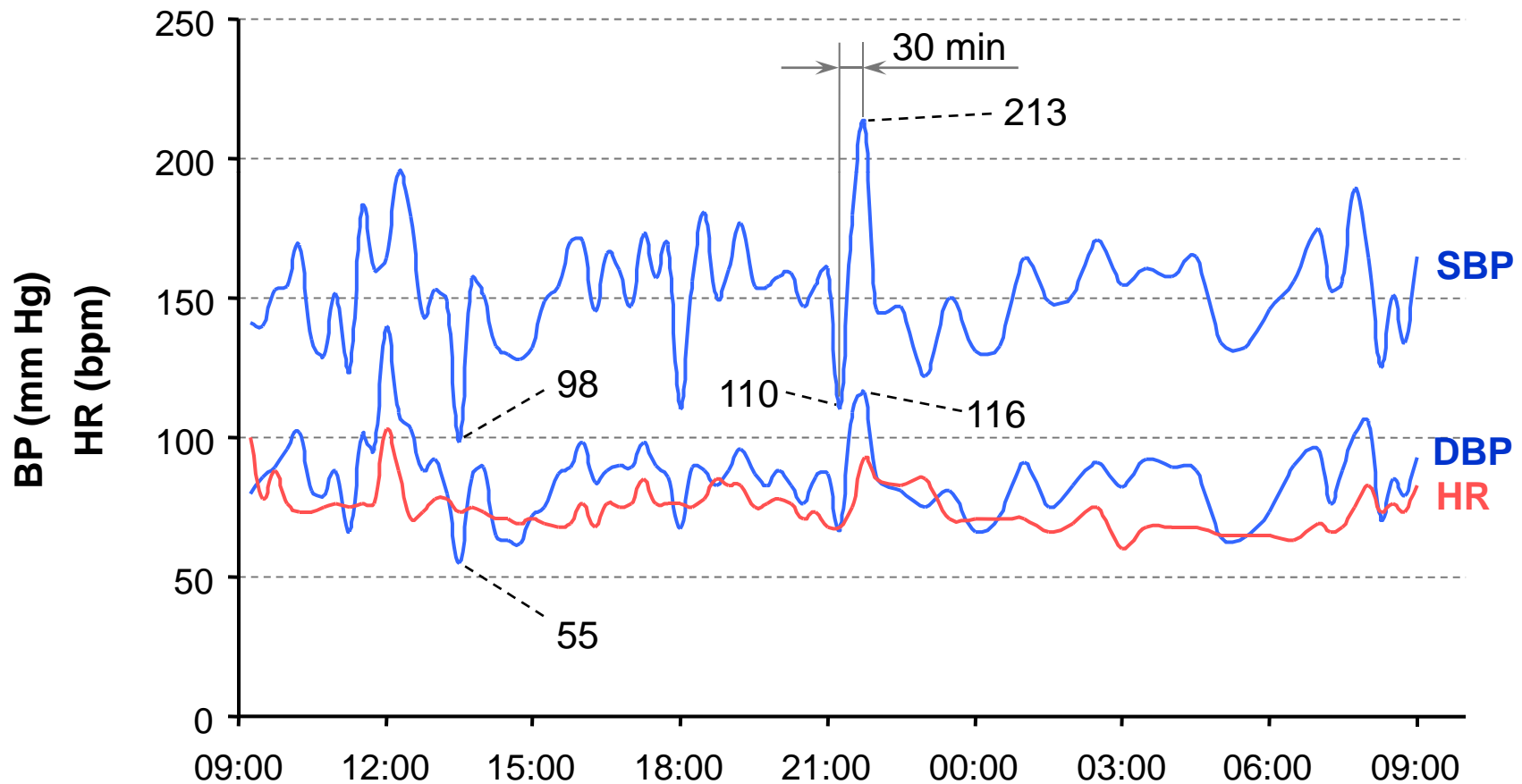
Dysfunction in Multiple System Atrophy



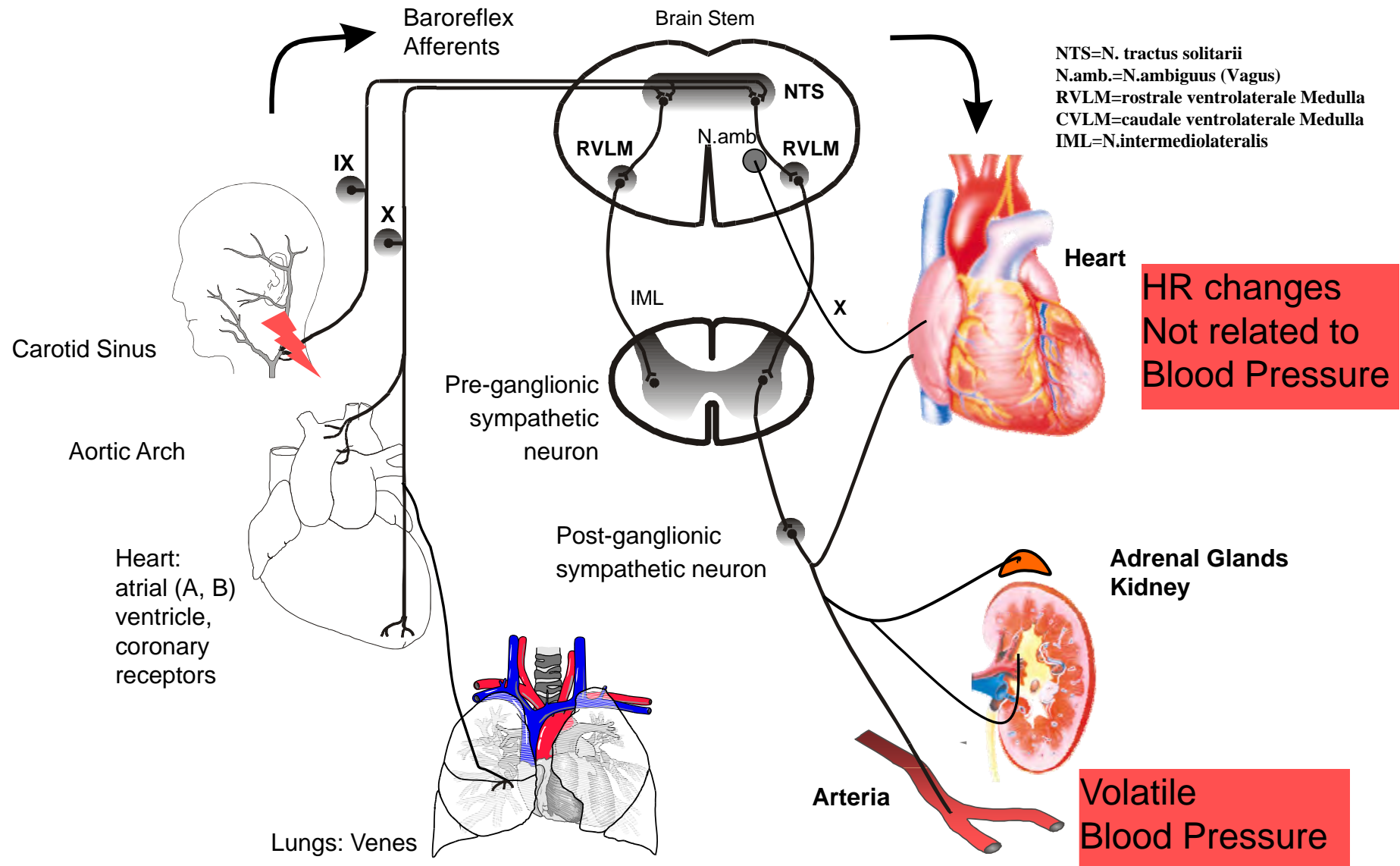


Baroreflex Failure

66 years, female,
Carotid body tumor resection (left side)
Implantation of carotid stent
Radiation



Dysfunction in Baroreflex Failure



Outline

❑ Autonomic Dysfunction and Baroreflex

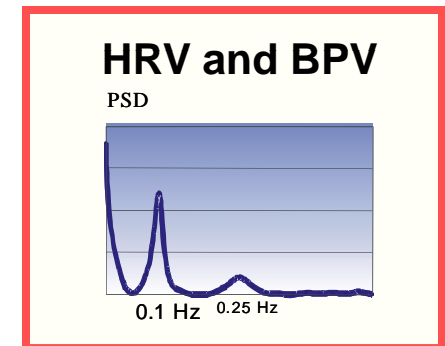
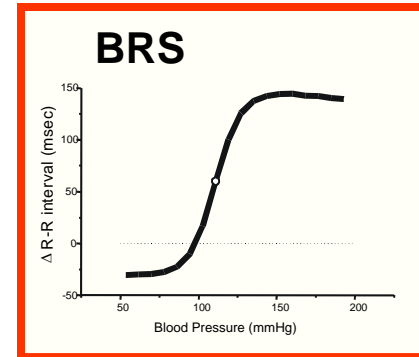
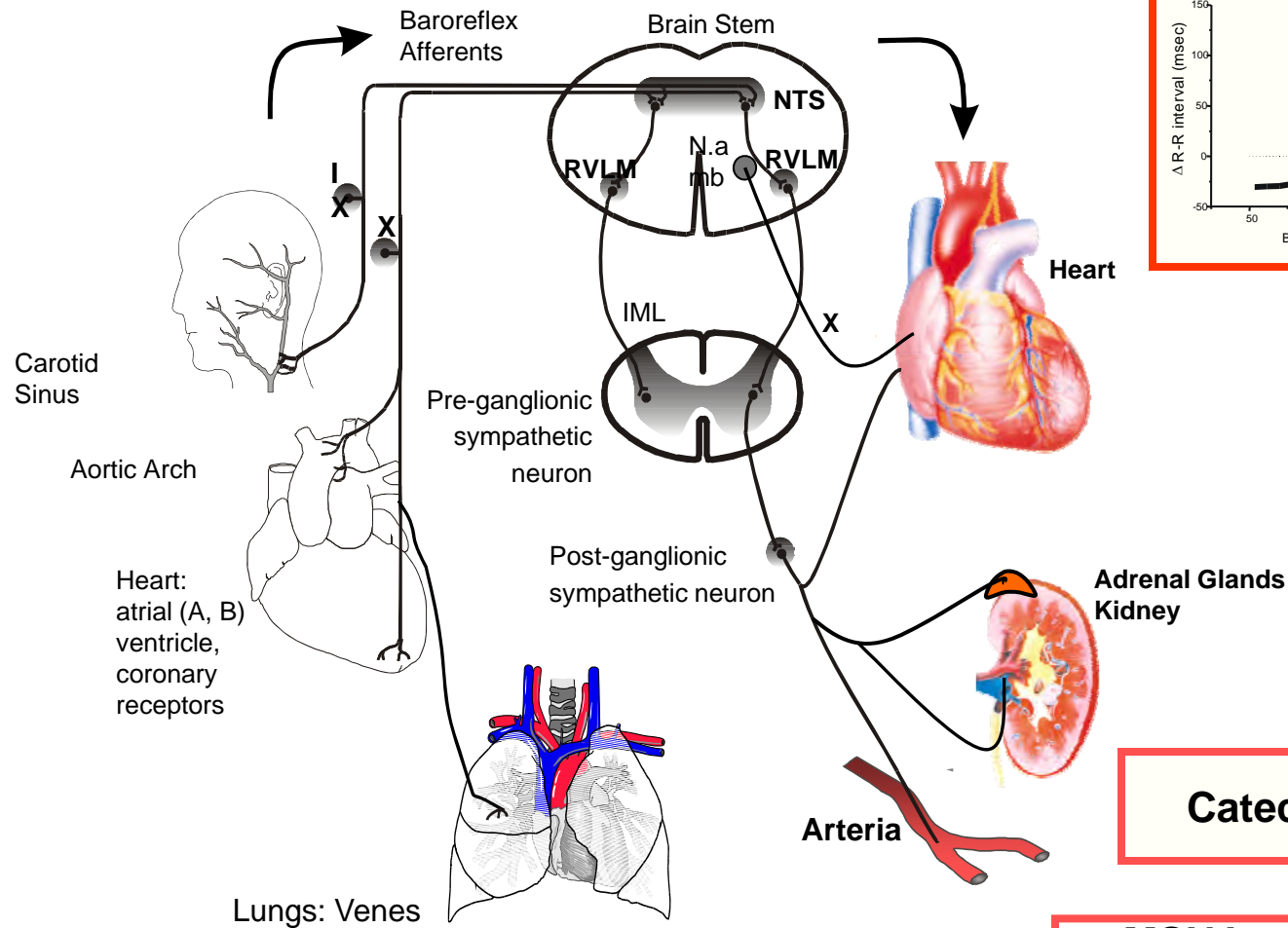
❑ **Muscle Sympathetic Activity**

❑ Heart Rate Variability and Sympathetic Activity

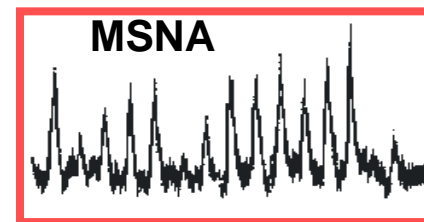
❑ Blood Pressure Variability and Sympathetic Activity

❑ Simplified Model of Blood Pressure Variability

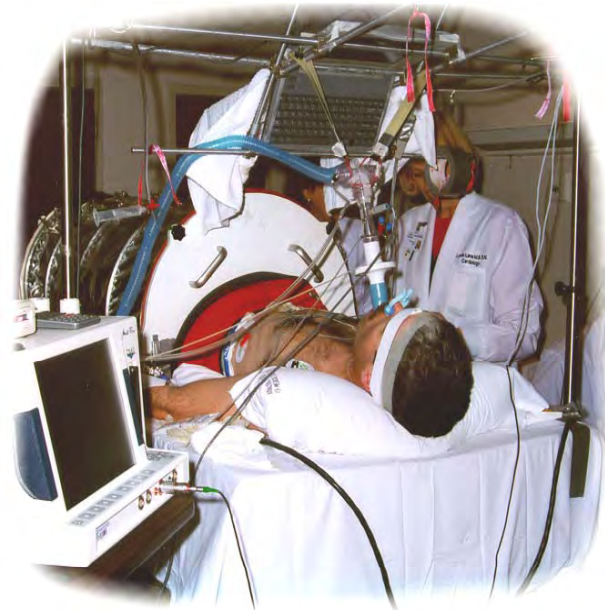
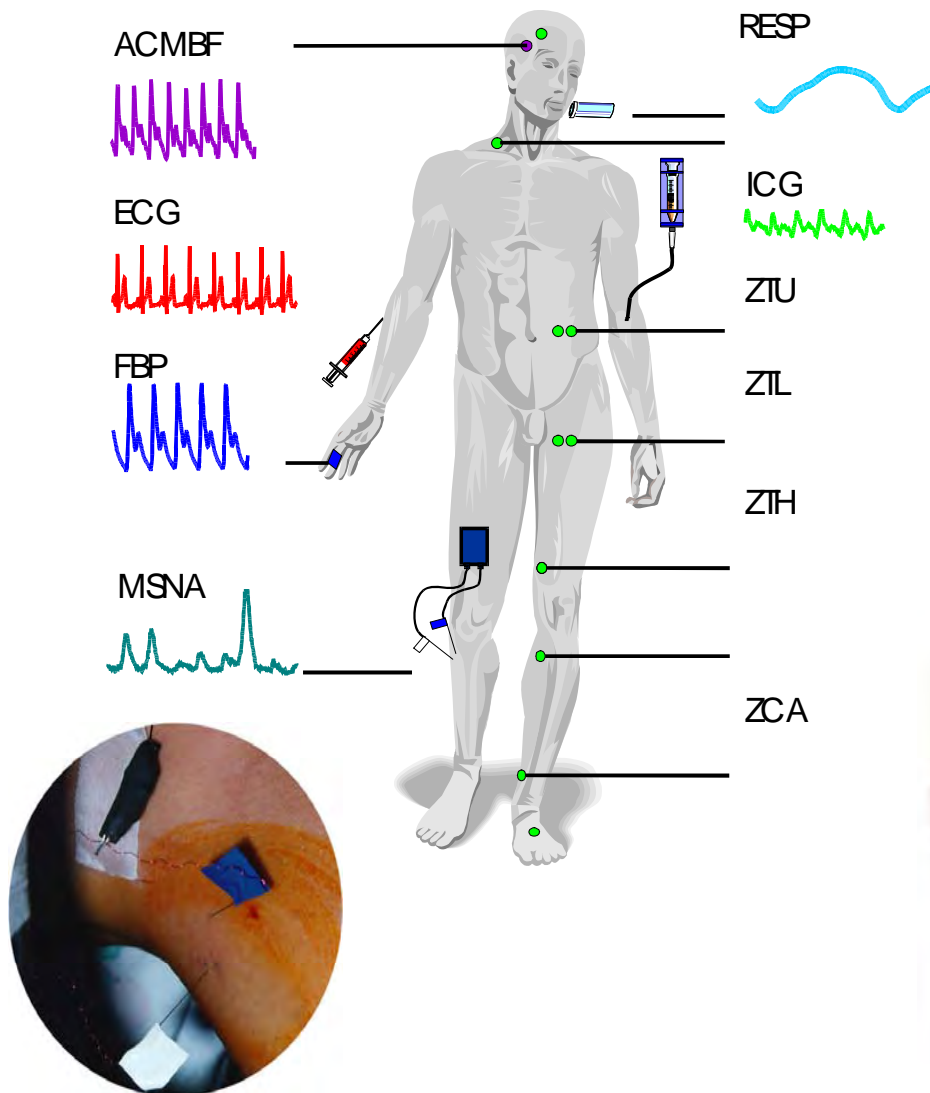
Measures of Baroreflex Function



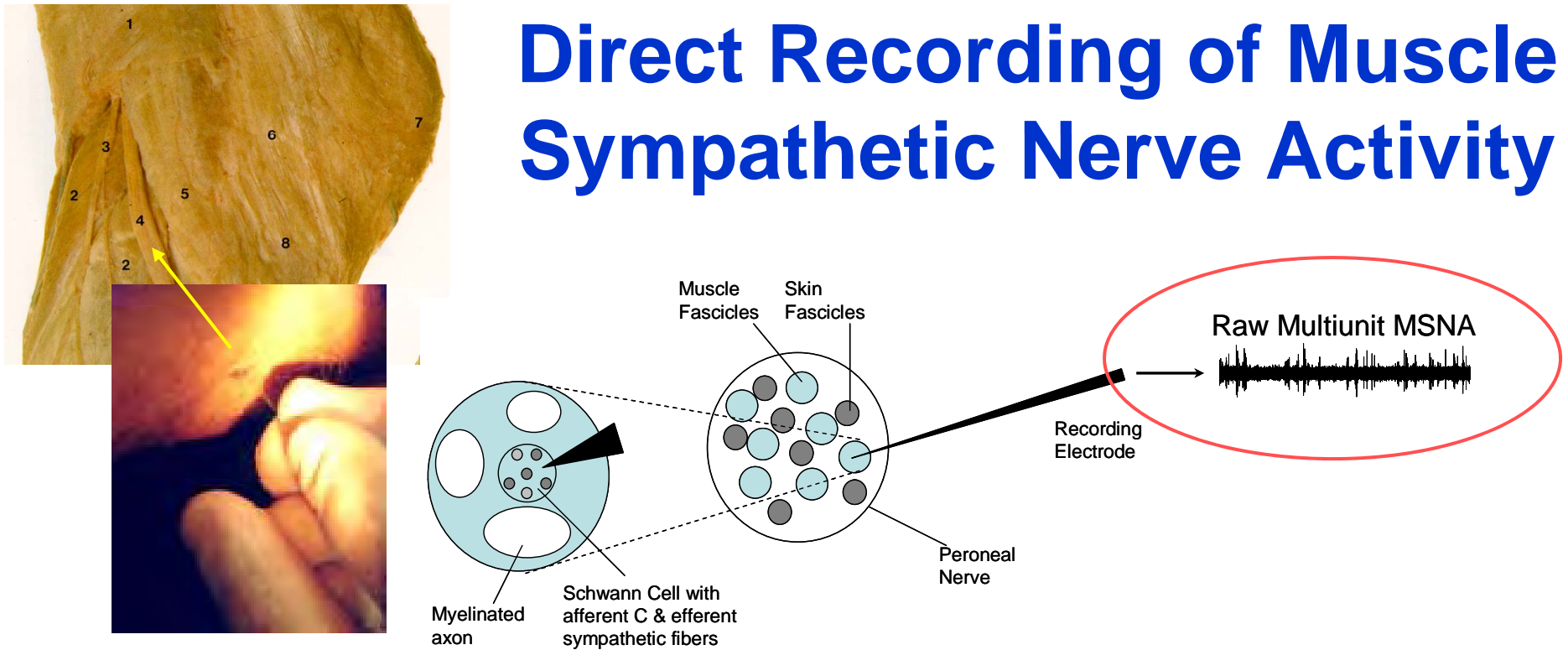
Catecholamine levels



Signals in Neuro-Cardiovascular Research

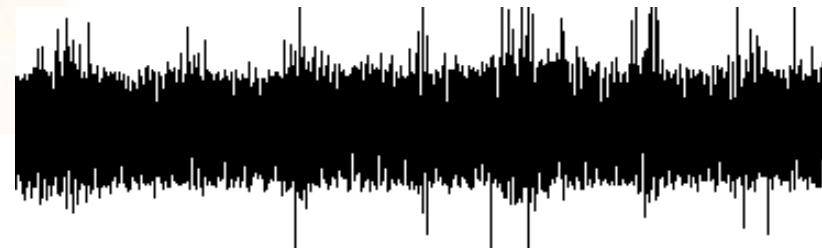
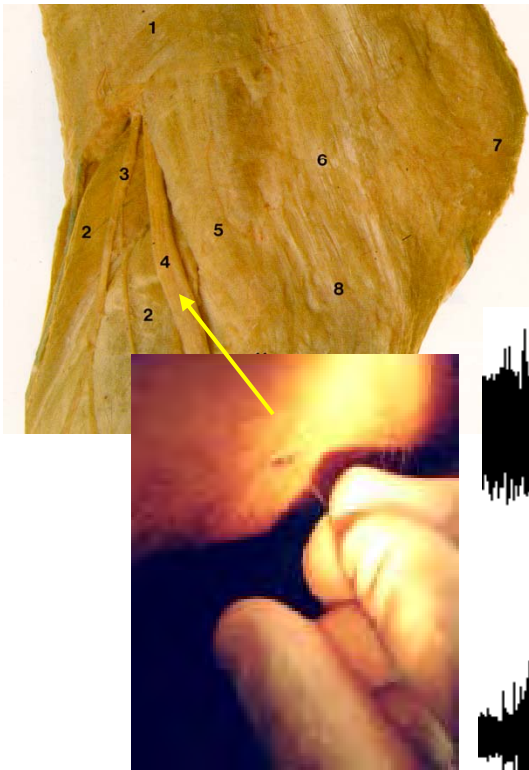


Direct Recording of Muscle Sympathetic Nerve Activity



- Sympathetic activity measured from neurons innervating a vascular bed supplying skeletal muscle is termed Muscle Sympathetic Nerve Activity (MSNA).
- Most MSNA is *multiunit* – activity from several sympathetic axons is recorded simultaneously.

Integrated Processing Method For Human Sympathetic Nerve Activity



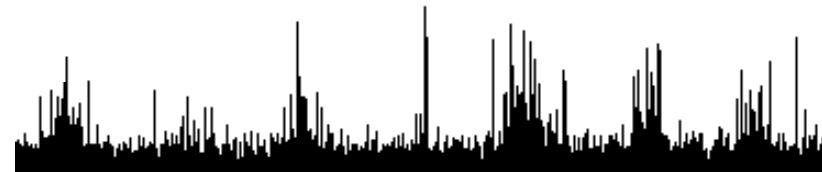
Raw MSNA

Bandpass Filter 0.7-2kHz



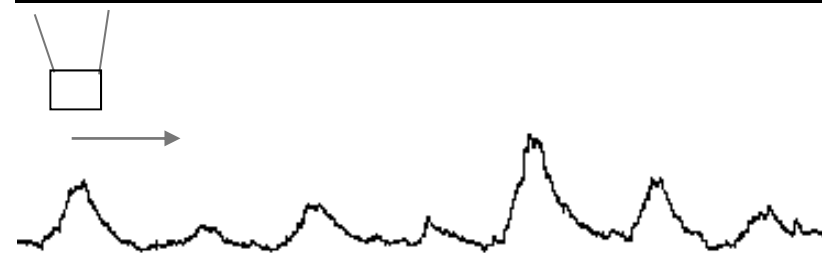
Filtered MSNA

Rectification and Thresholding

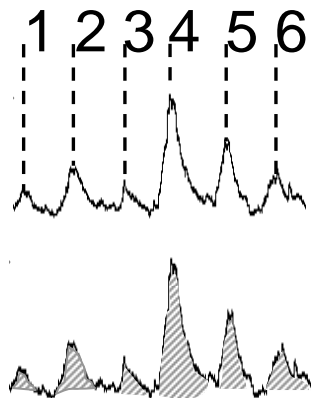


Discriminated MSNA

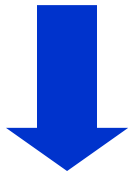
R-C Integrator 0.1 sec



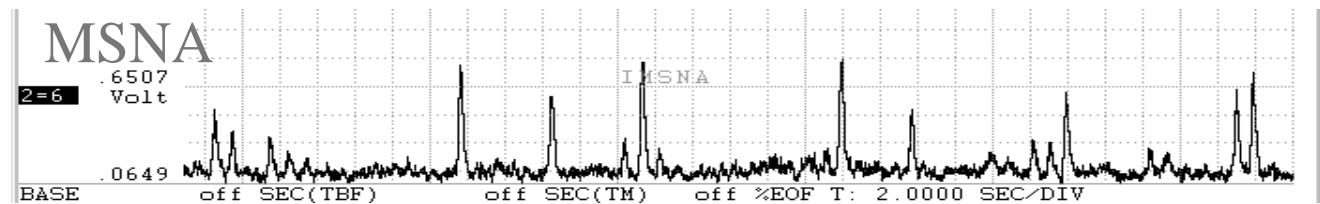
Integrated MSNA



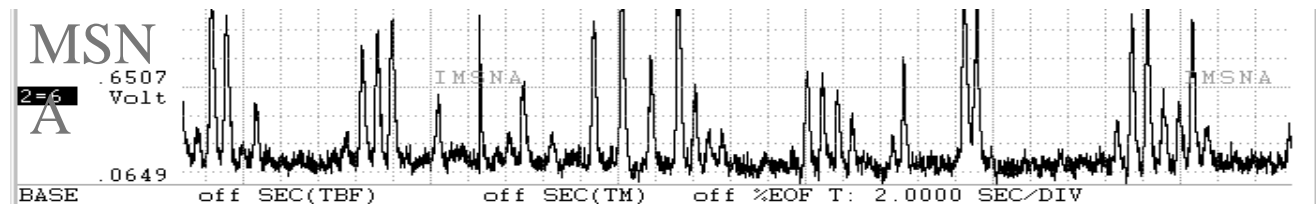
Sympathetic Activity during Upright Posture



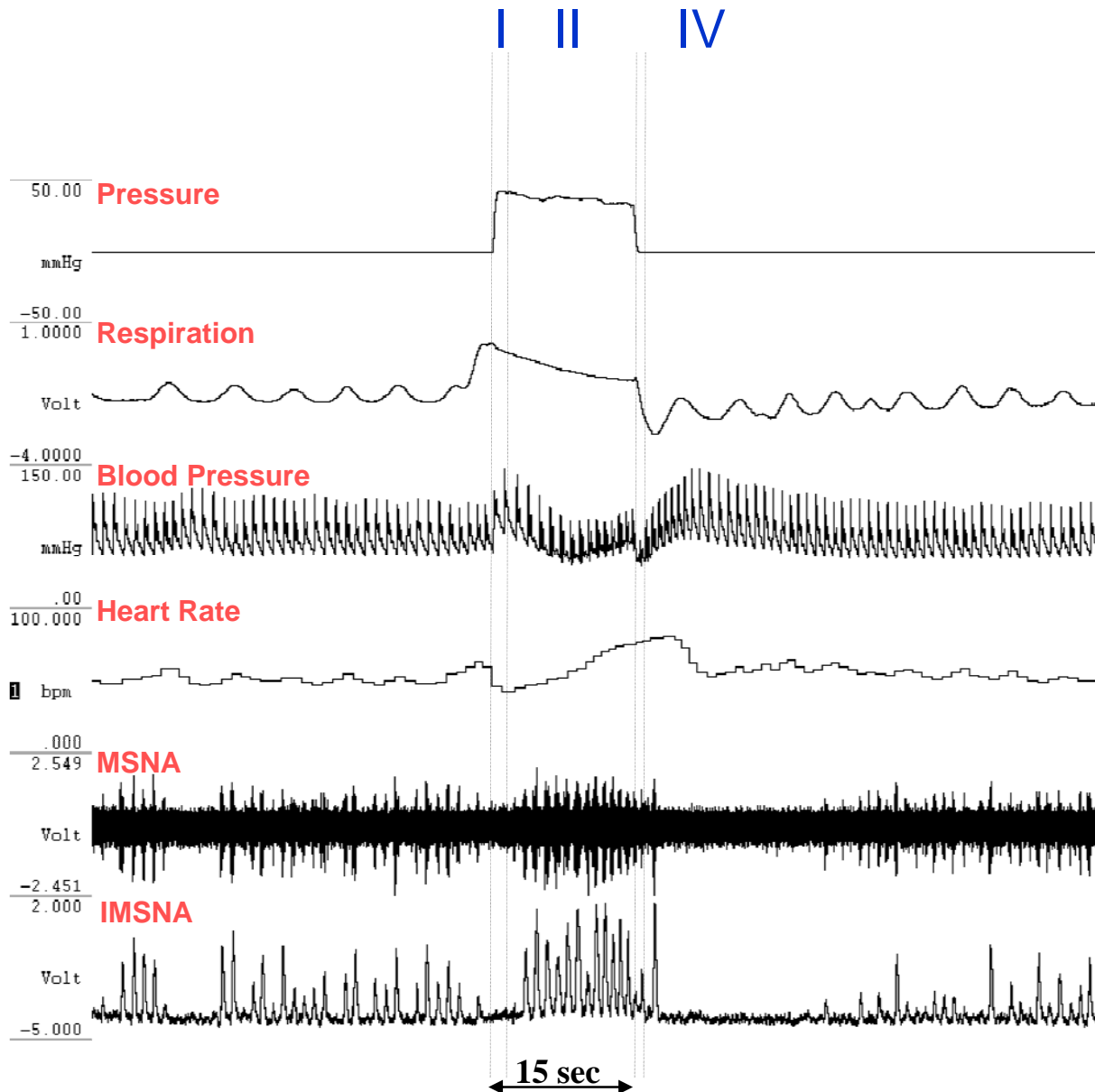
26 bursts/min



52 bursts/min



Sympathetic Activity during Valsalva Maneuver



PHASE I

- ↑ Intrathoracic Pressure
- ↑ Stroke Volume
- ↑ BP
- ↓ Sympathetic Nerve Activity

PHASE II

- High Intrathoracic Pressure
- ↓ Venous Return
- ↓ BP
- ↑ Sympathetic Nerve Activity

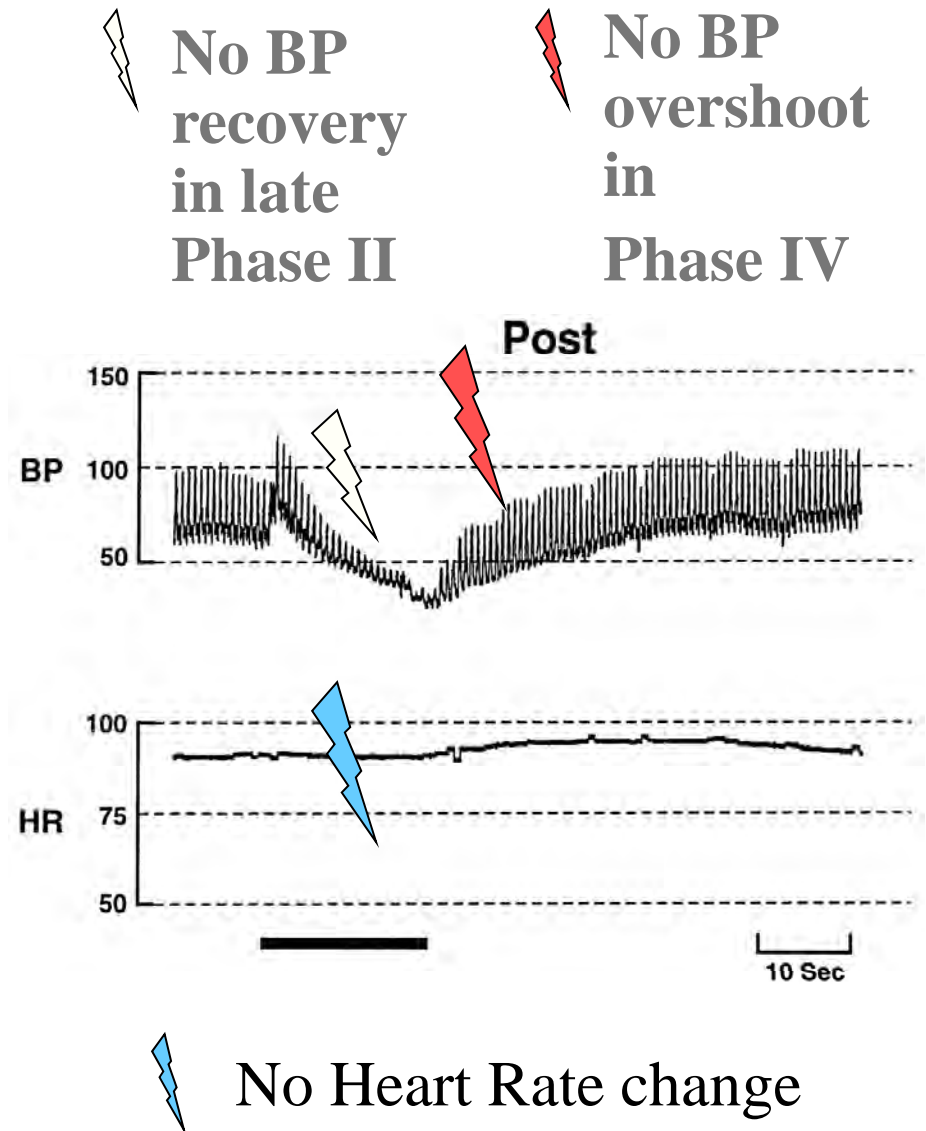
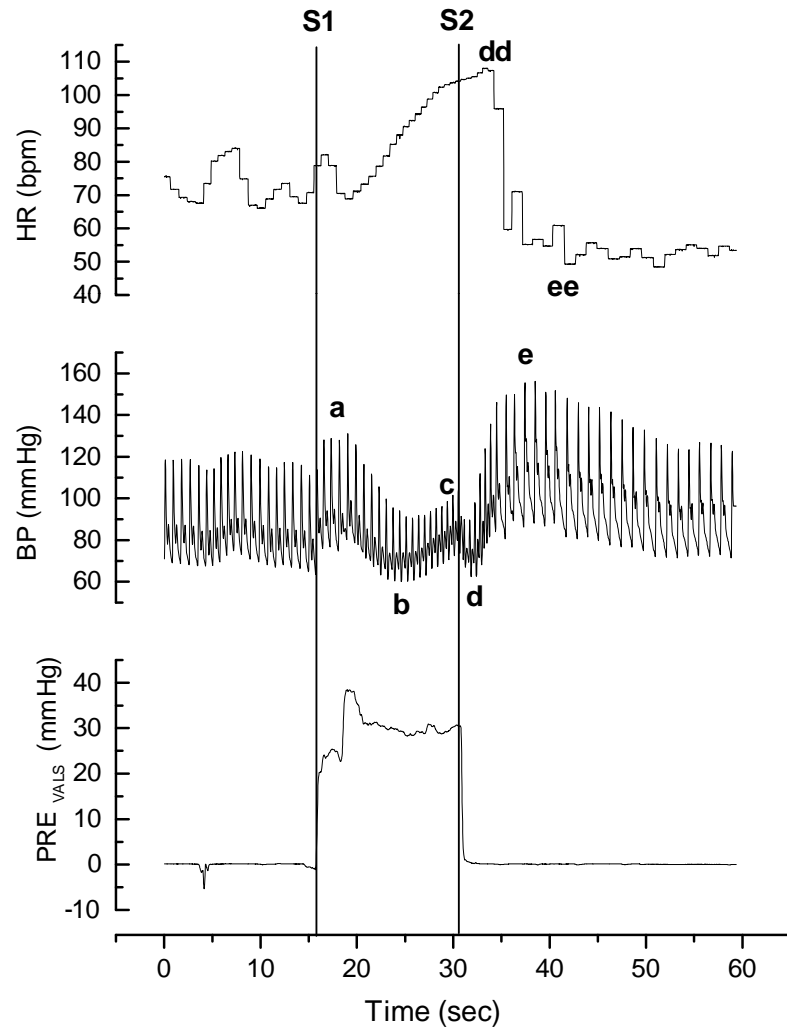
PHASE III

- Release
- Further Drop in BP
- High Sympathetic Nerve Activity

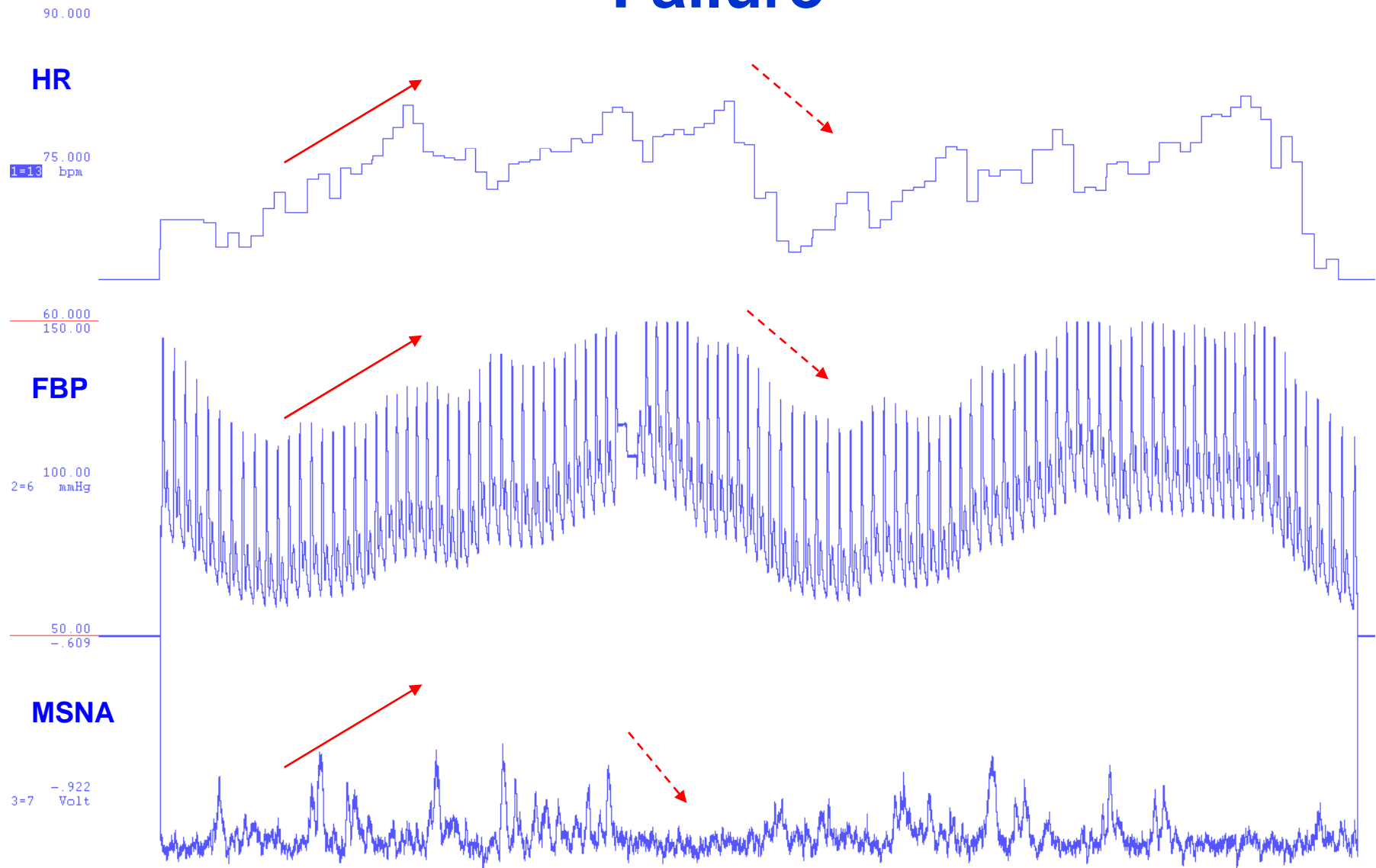
PHASE IV

- BP Overshoot
- Abolished Sympathetic Nerve Activity

Valsava Response in Autonomic Dysfunction



Volatile Blood Pressure in Baroreflex Failure



Outline

❑ Autonomic Dysfunction and Baroreflex

❑ Muscle Sympathetic Activity

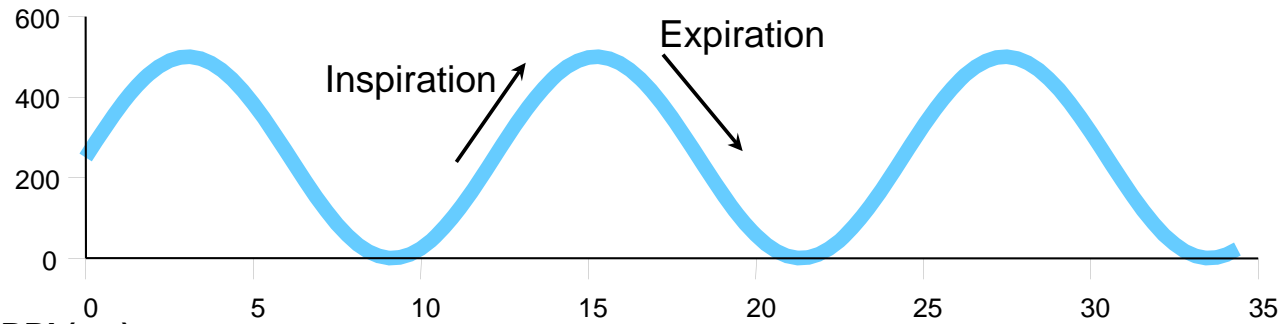
❑ Heart Rate Variability and Sympathetic Activity

❑ Blood Pressure Variability and Sympathetic Activity

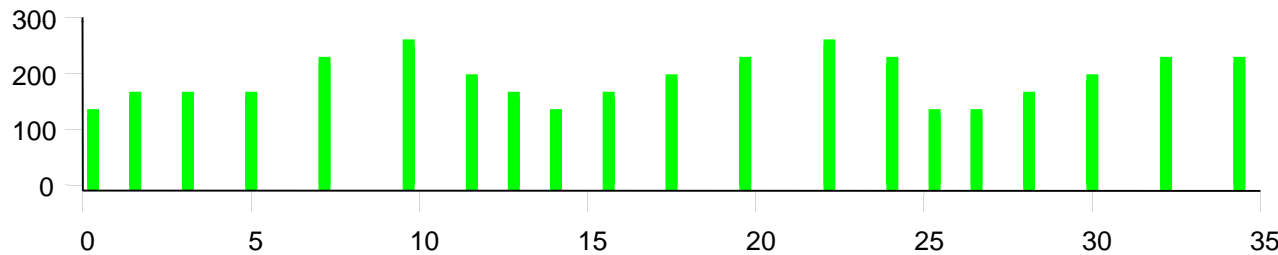
❑ Simplified Model of Blood Pressure Variability

Respiratory Sinus Arrhythmia

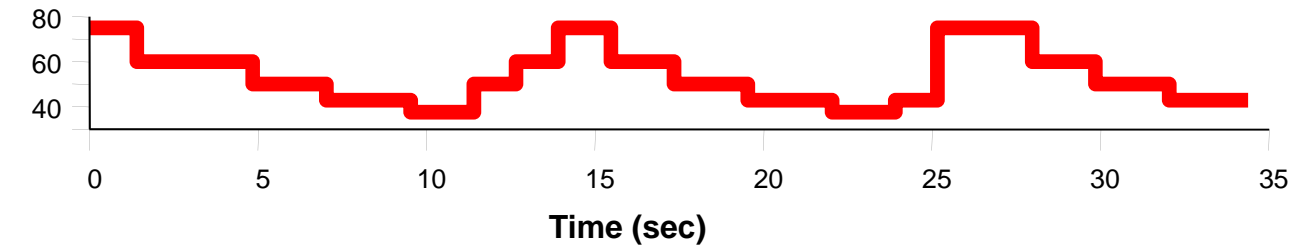
Tidal Volume



RRI (ms)



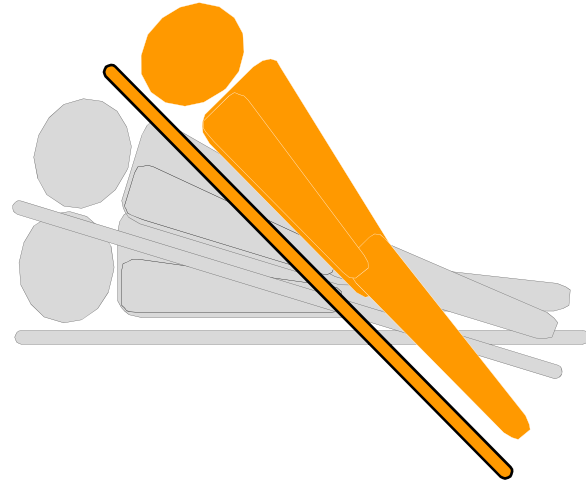
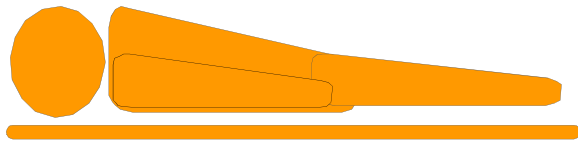
HR (bpm)



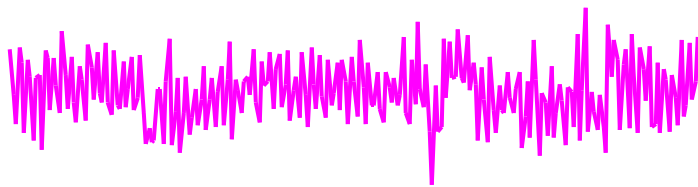
Respiratory sinus arrhythmia is characterized by:

- an **increase** of heart rate (shortening of RRI) during **inspiration**, and
- a **decrease** of heart rate (prolongation of RRI) during **expiration**

HRV and Cardiovascular Control

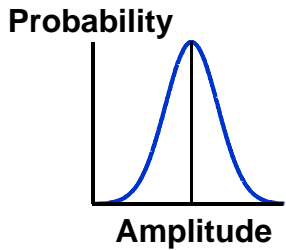


Heart Rate



How do we quantify the visible differences
in Heart Rate Variability?

Classification of Heart Rate Variability Measures

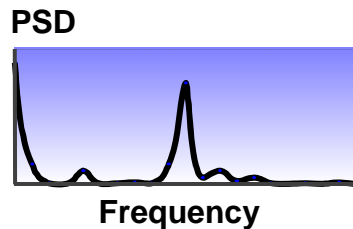
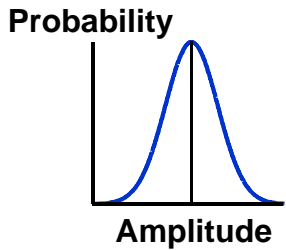


- **Time domain measures**

Treat the RR interval sequence as an **unordered set** of intervals (or pairs of intervals) and employ different techniques to express the variance or ranges of such data.

Statistical Methods (SD, RMSSD, PNN50)
Geometric Methods

Classification of Heart Rate Variability Measures



- **Time domain measures**

Treat the RR interval sequence as an unordered set of intervals (or pairs of intervals) and employ different techniques to express the variance or ranges of such data

Statistical Methods (SD, RMSSD, PNN50), Geometric Methods

- **Frequency domain measures**

Power spectral density analysis provides information on how the power (variance) of the **time dependent ordered** RR intervals distributes as a **function of frequency**.

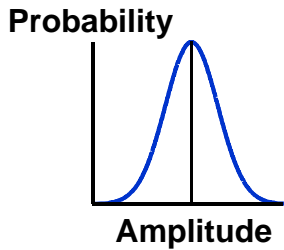
FFT based Power Spectral Density

Lomb Periodogram

ARMA Model based (parametric)

Wavelet based spectral analysis

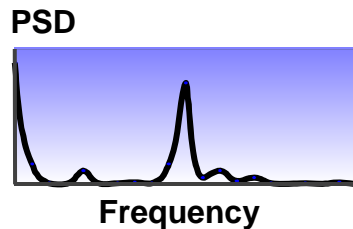
Classification of Heart Rate Variability Measures



- **Time domain measures**

Treat the RR interval sequence as an unordered set of intervals (or pairs of intervals) and employ different techniques to express the variance or ranges of such data

Statistical Methods (SD, RMSSD, PNN50), Geometric Methods



- **Frequency domain measures**

Power spectral density analysis provides information on how the power (variance) of the time dependent ordered RR intervals distributes as a function of frequency.

FFT based Power Spectral Density, Lomb Periodogram, ARMA Model based (parametric), Wavelet based spectral analysis



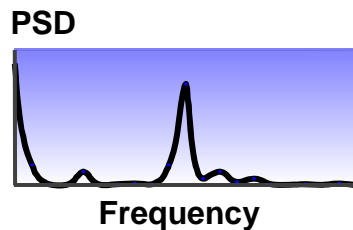
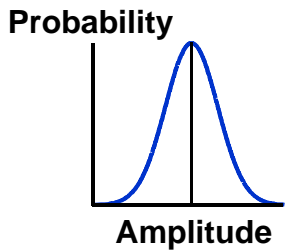
- **Nonlinear measures**

Complexity analysis also based on the time dependent ordering of the RR interval sequence

*Point Caré Plot
Power Law Slope (1/f noise)
Detrended Fluctuation Analysis (FDA),
Lyapunov Exponents for stability
Fractal Dimension
Aproximate Entropy (ApEn)
Symbolic Analysis*

Task Force. Circulation 1996;93:1043-1065
Joseph E. Mietus; Source HRV Course 2006
Goldberger et al. PNAS 2002 99 Suppl. 1: 2466-2472.

Heart Rate Variability Measures



- **Time Domain Measures**

Statistical Methods (SD, RMSSD, PNN50)
Geometric Methods

- **Frequency Domain Measures**

FFT based Power Spectral Density
Lomb Periodogram
ARMA Model based (parametric)
Wavelet based spectral analysis

- **Nonlinear/Complexity Measures**

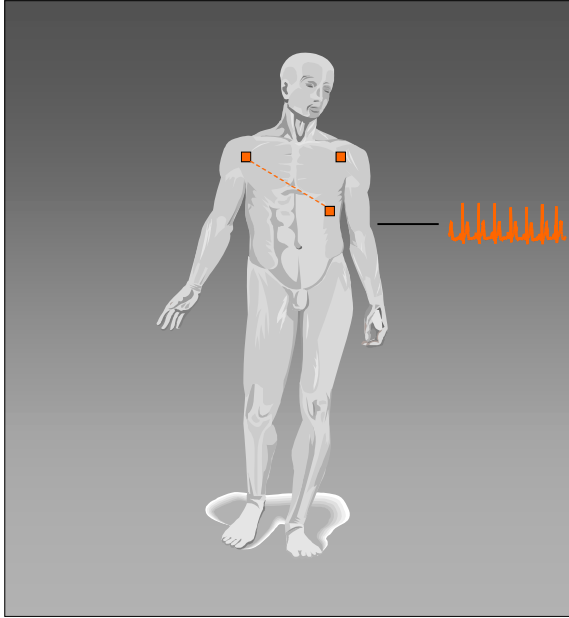
Point Caré Plot
Power Law Slope ($1/f$ noise)
Detrended Fluctuation Analysis (FDA),
Lyapunov Exponents for stability
Fractal Dimension
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Symbolic Analysis

Task Force. Circulation 1996;93:1043-1065

Joseph E. Mietus; Source HRV Course 2006

Goldberger et al. PNAS 2002 99 Suppl. 1: 24662472.

Processing ECG for HRV Analysis

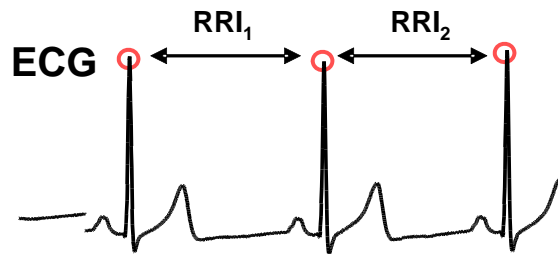


Recording

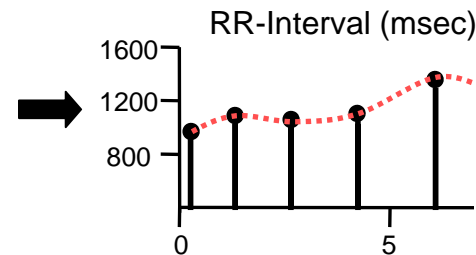
ECG Lead II

Processing

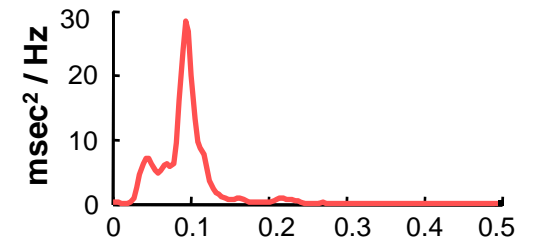
1. Detect R-Peaks
2. Quantify Fluctuations Using Time Domain Measures or Spectral Analysis



Time Series

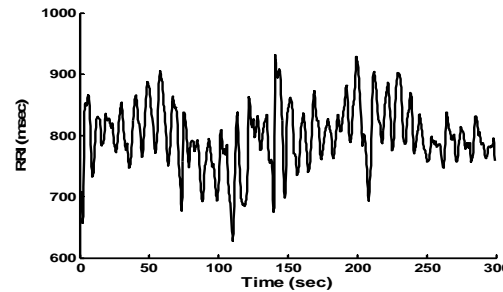


Spectra

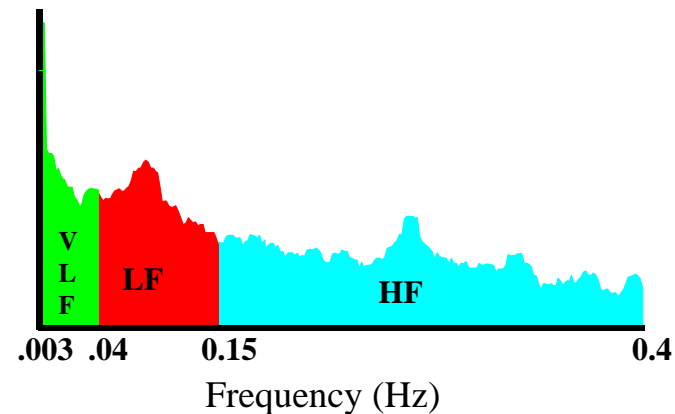


Power Spectrum Density and Power

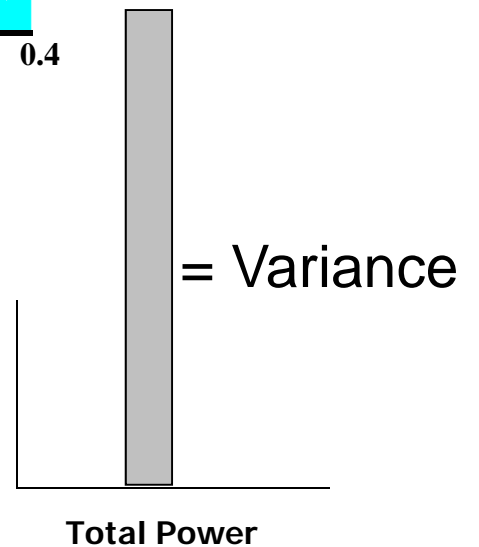
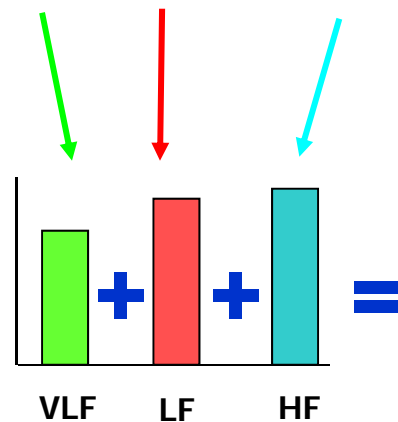
R-R intervals
(msec)



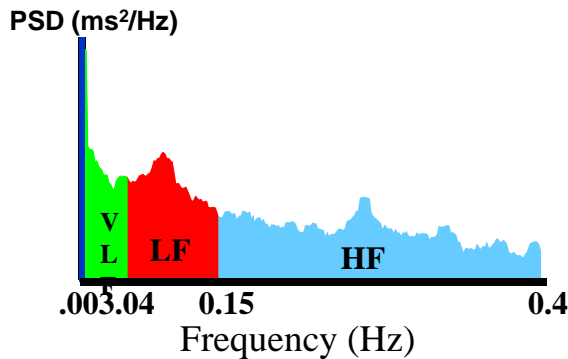
Power Spectrum
Density
(msec²/Hz)



Power
(msec²)



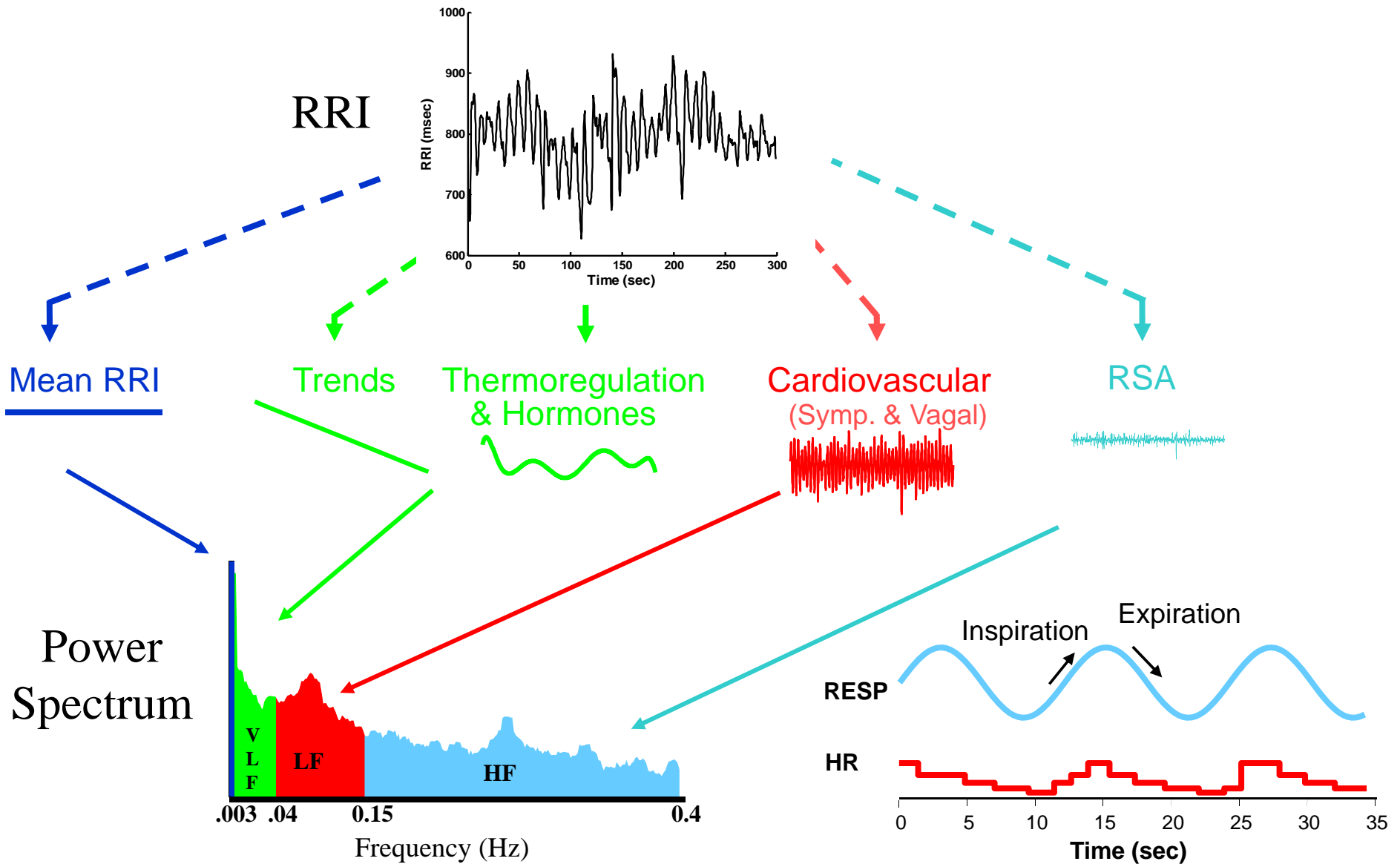
Summary Spectral Analysis



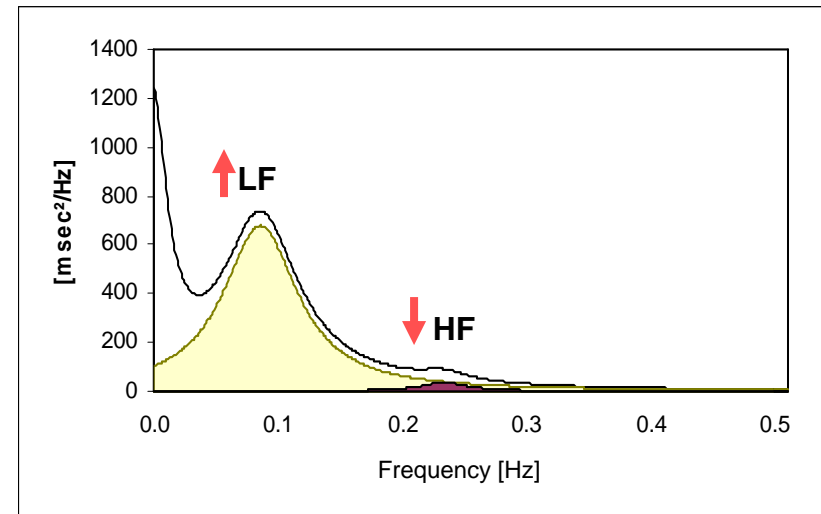
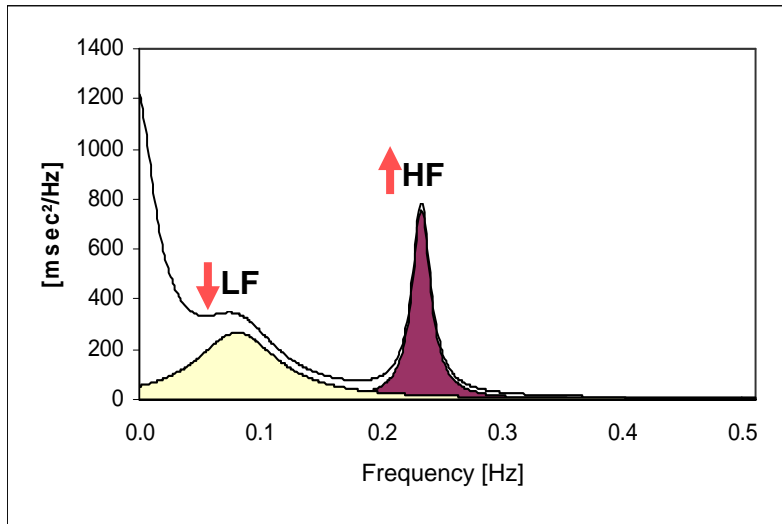
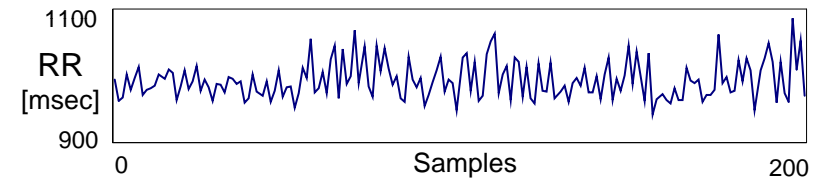
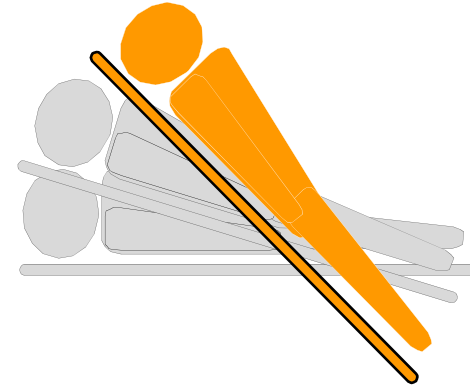
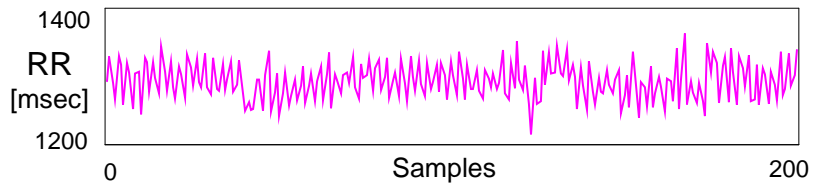
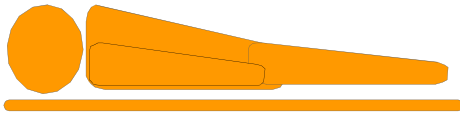
- Power Spectral Density Function (PSD) displays the distribution of power (squared amplitude) of oscillations in dependency of their frequency
(unit of spectra: ms^2/Hz)
- Power is the Area of PSD over a definite frequency range (unit of calculated power: ms^2)
- Total Power calculated from PSD is equal Variance calculated in time domain

Total Power = Variance

What Contributes to Heart Rate Variability?

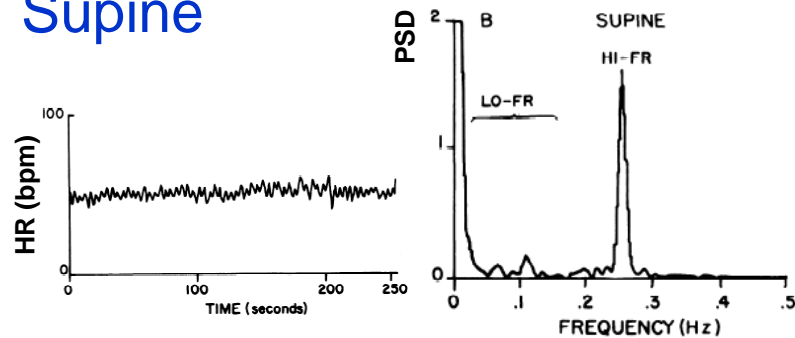


HRV and Orthostatic Stress

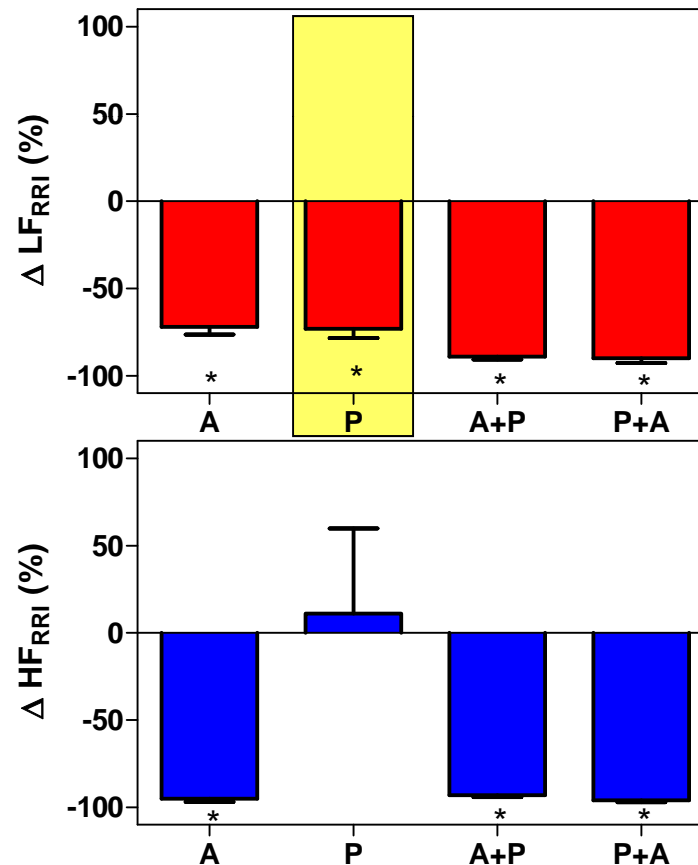
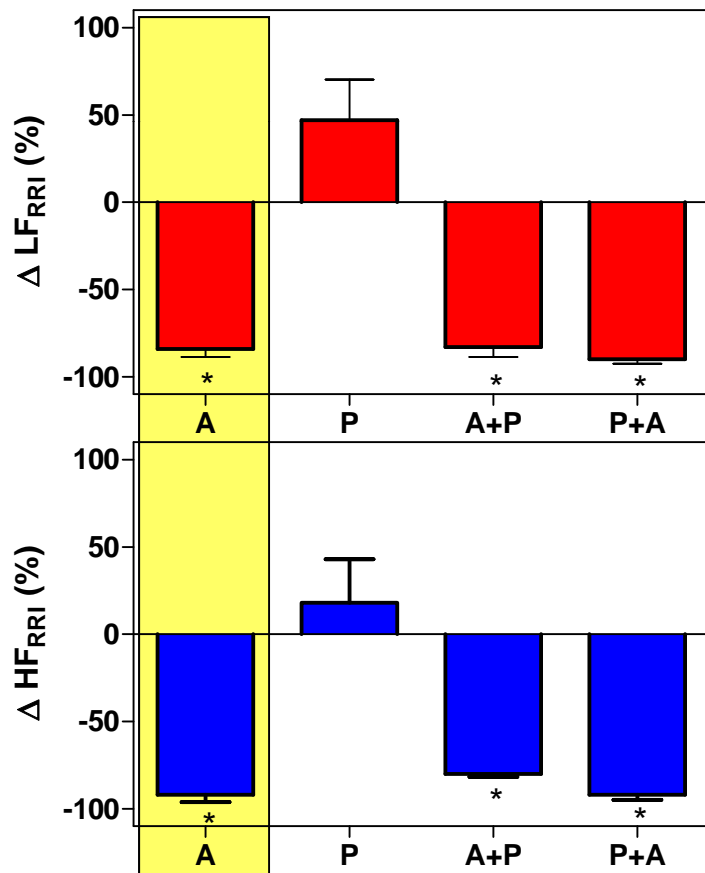
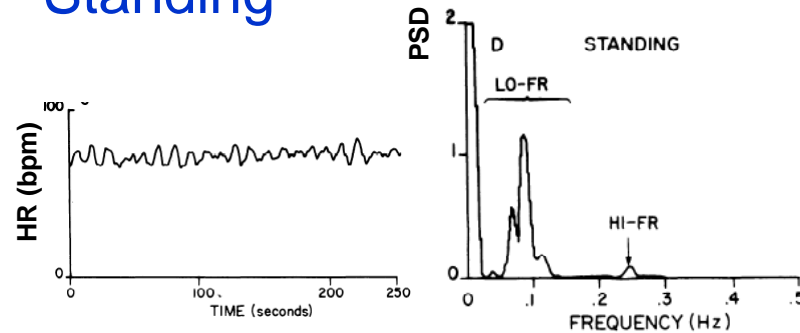


Cardiac Autonomic Blockade

Supine



Standing



A Atropine
P Propranolol

Summary Cardiac Autonomic Blockade

Atropine

↓LF ↓HF

- Parasympathetic (muscarinic) receptor blockade with atropine reduces LF and HF spectral power of heart rate.

Propanolol

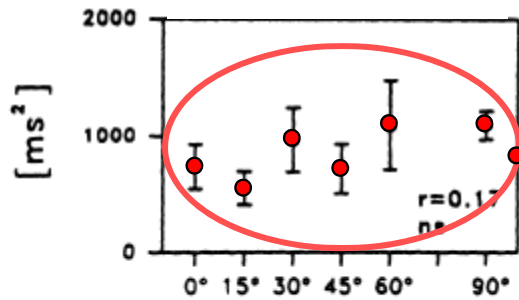
↓LF

- Sympathetic (β 1-adrenergic receptor) blockade with propanolol causes a decrease in LF spectral power of heart rate if sympathetic system is activated.
- Sympathetic β 1-adrenergic receptor blockade does not affect HF spectral power of heart rate.

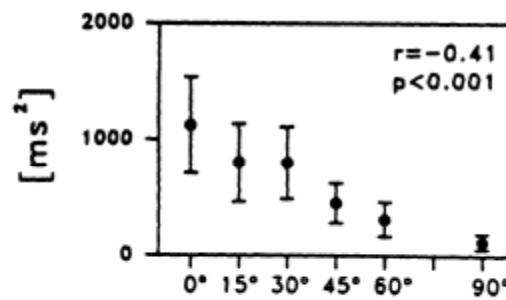
HRV and Normalized Units



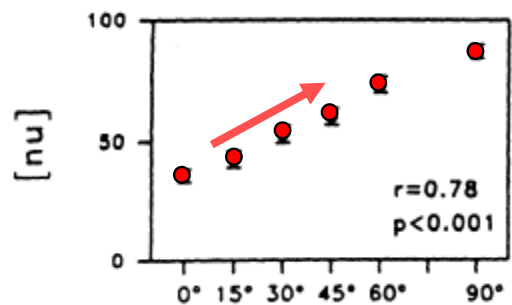
LF absolute



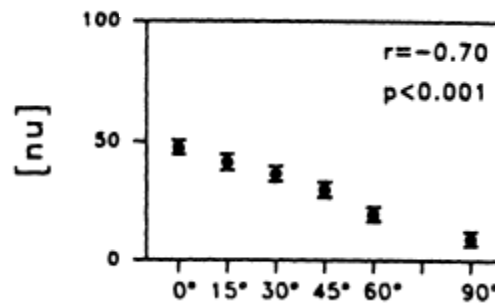
HF absolute



LF normalized

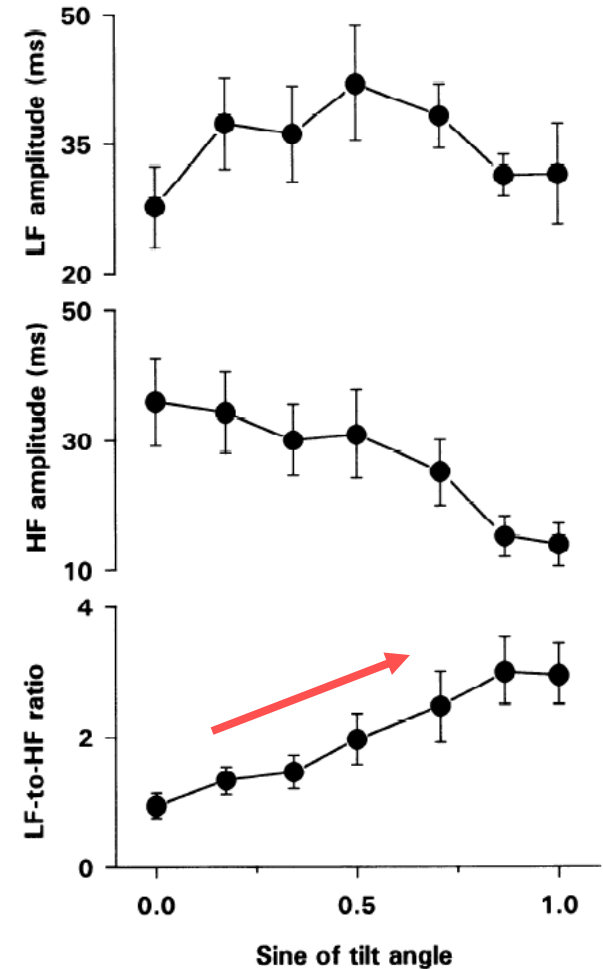


HF normalized



$$nLF = LF / (\text{Total Power} - VLF)$$

$$nHF = HF / (\text{Total Power} - VLF)$$

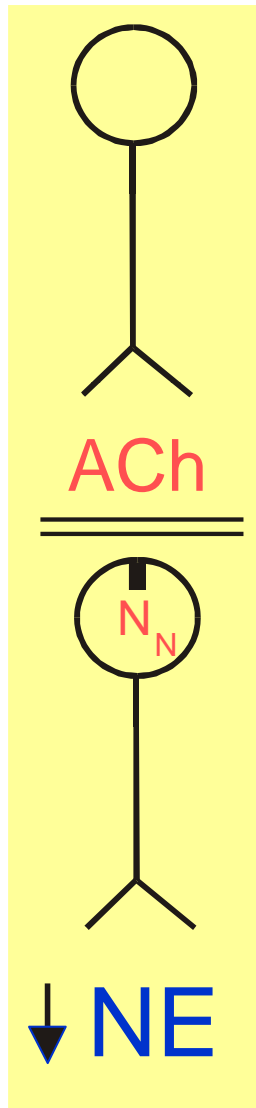


N. Montano, T. G. Ruscone, A. Porta; F. Lombardi; M. Pagani, A. Malliani
Circulation, 1994, 90:1826-1831

S. Mukai and J. Hayano
J Appl Physiol, Jan 1995; 78: 212 - 216.

Ganglionic Blockade

using Trimethaphan Camsylate (Afronad®)

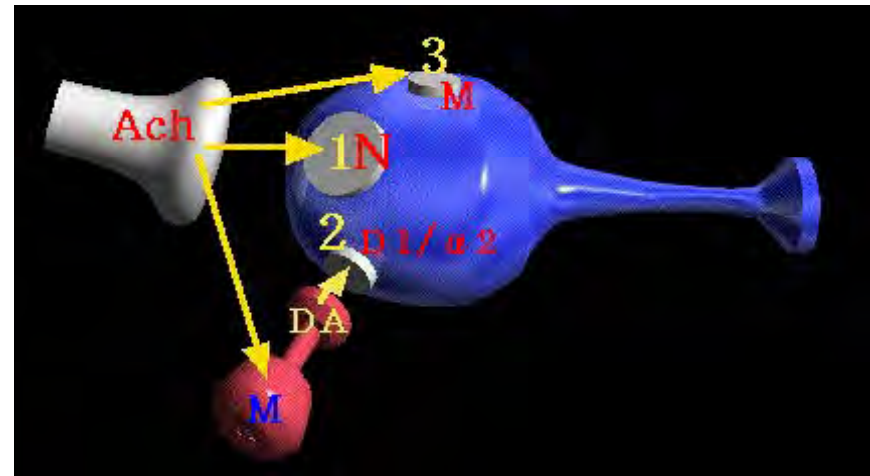
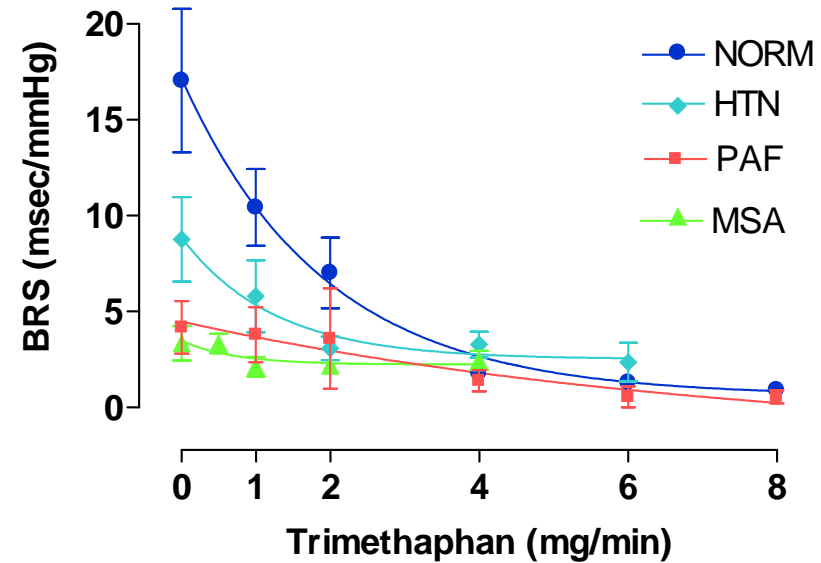


Trimethaphan

N_N-Nicotinic Antagonist

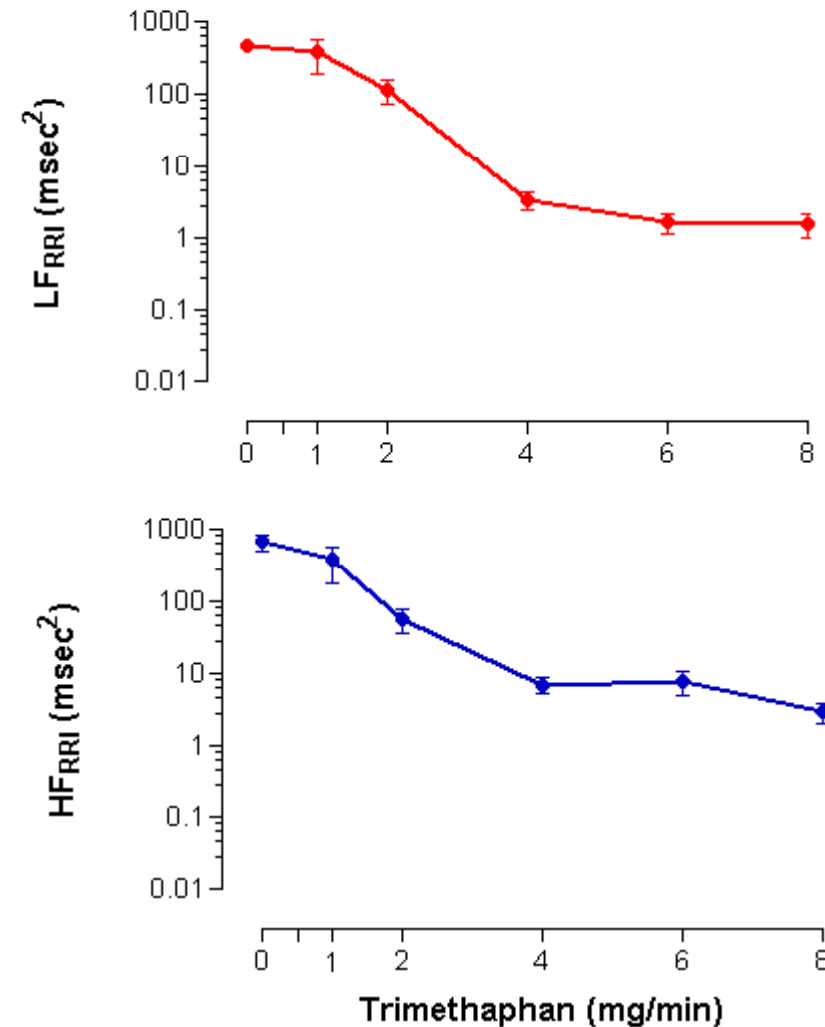
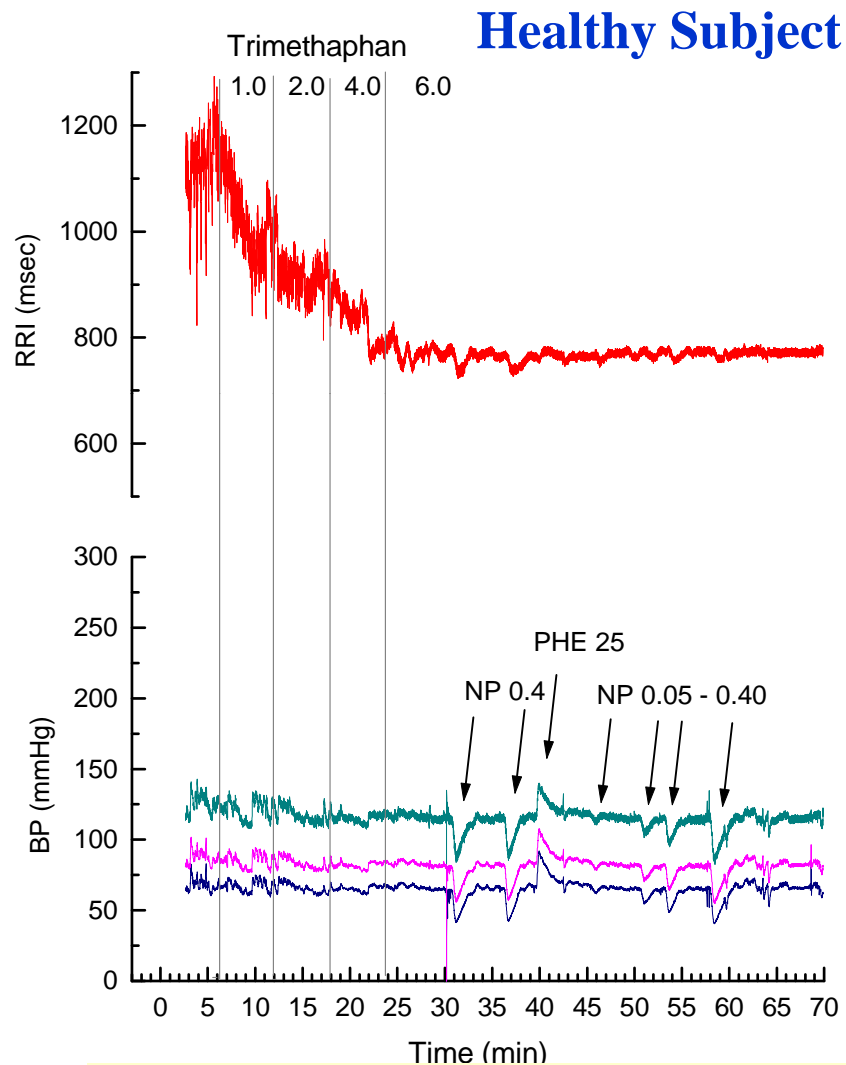
Blockade
of
nicotinic receptors
in autonomic ganglia

Reduction
of
sympathetic &
parasympathetic
tone



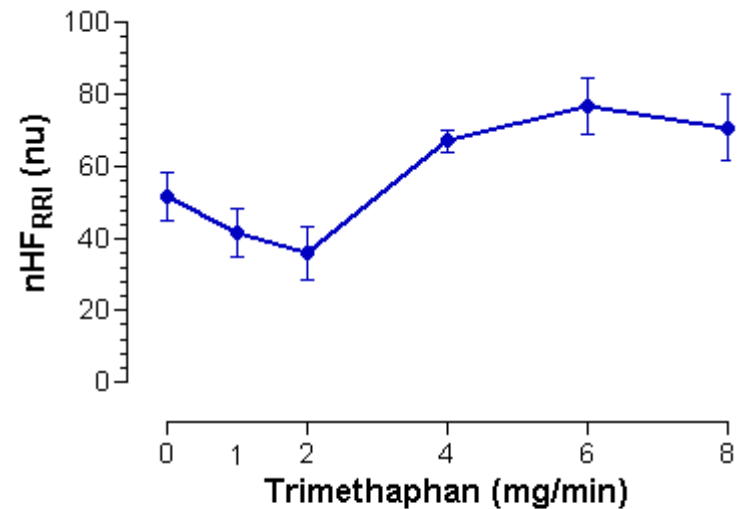
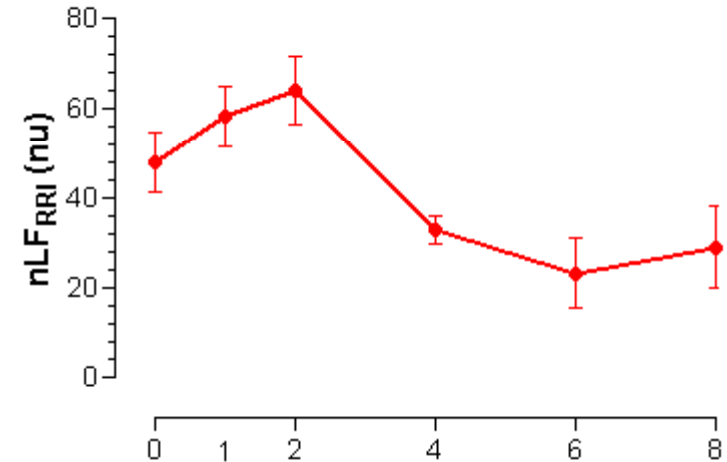
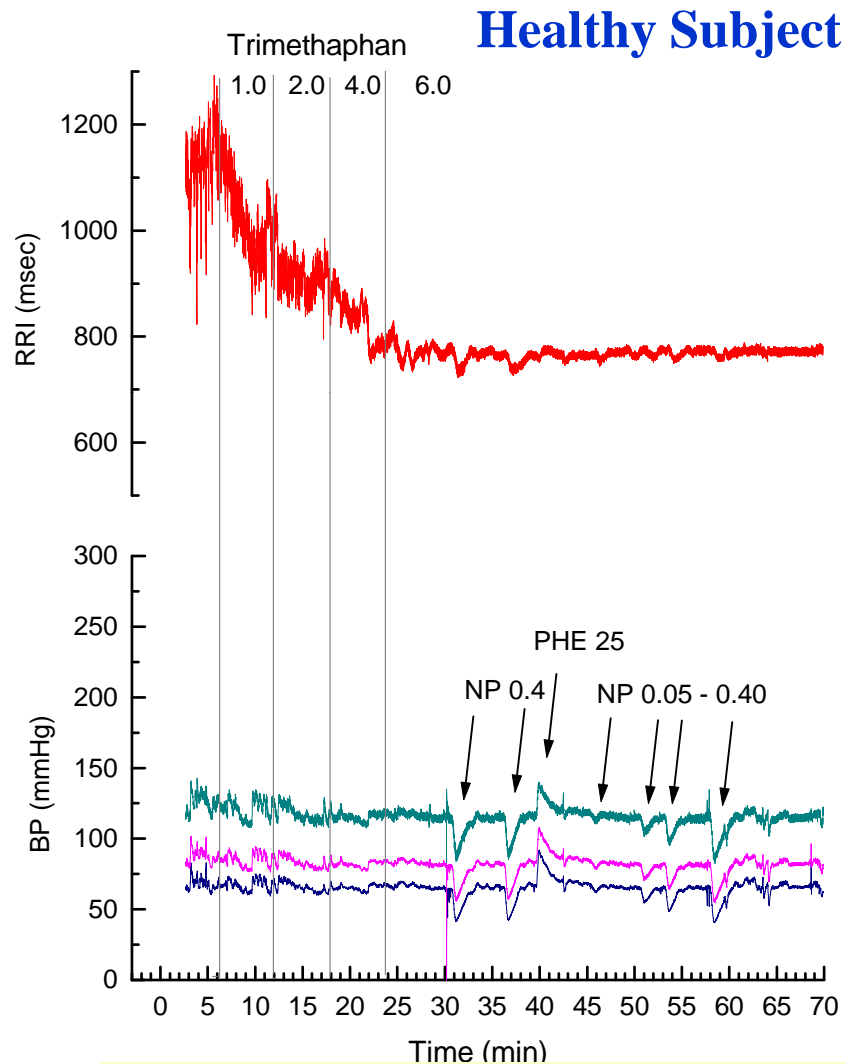
<http://pharma1.med.osaka-u.ac.jp/textbook/Ganglion/Ganglion.html>

Effects of Ganglionic Blockade on HRV



Ganglionic blockade abolish LF & HF_{RRI}

Blockade and Normalized Units of HRV

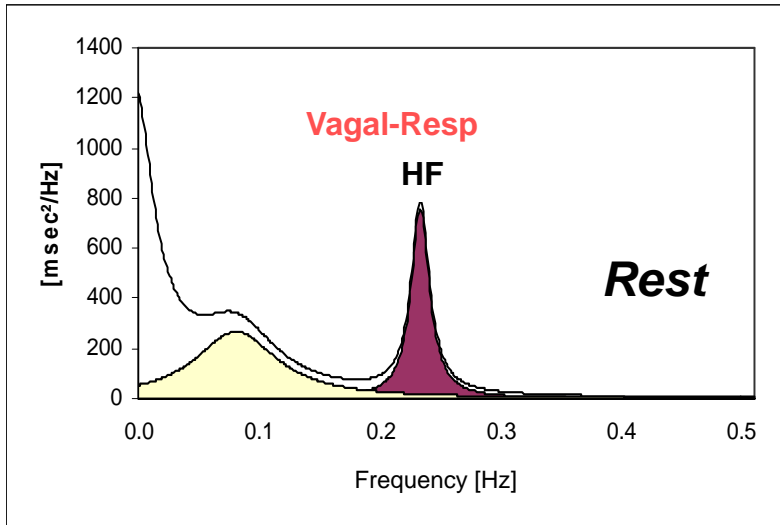


Normalized units do not reflect blockade

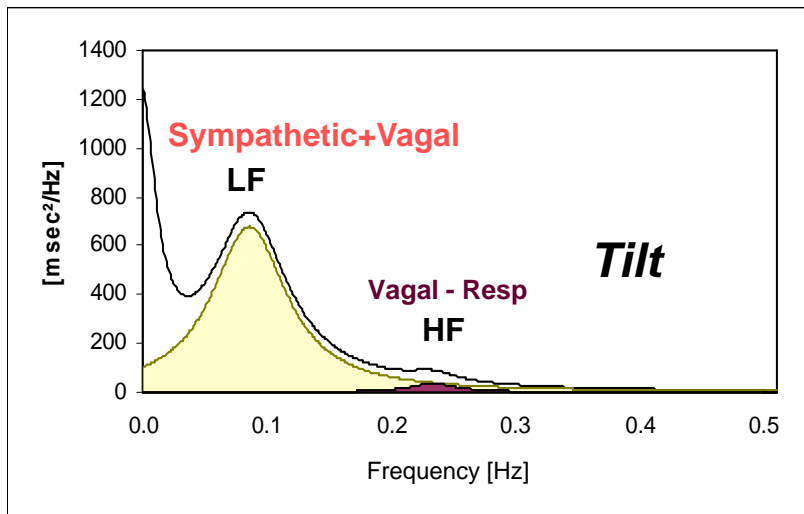
Summary Ganglionic Blockade

- Ganglionic Blockade reduces absolute values of LF and HF of Heart Rate Variability which indicated that these parameters reflect neural control.
- The use of normalized values of HRV do not reflect the reduced vagal control to the heart during blockade.

Summary Heart Rate Variability



- Heart Rate Variability is mostly neural mediated.
- Activation of the sympathetic nervous system are reflected in changes in LF
- Cardiac autonomic blockade demonstrated that:



HF spectral power of RRI is modulated by the **vagal** nervous system only.

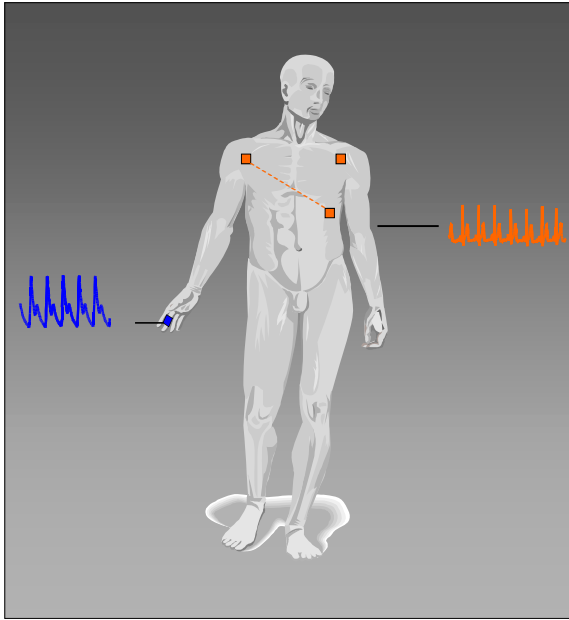
LF spectral power of RRI is modulated by the **sympathetic** and **vagal** nervous system.

- The use of normalized values does not reflect autonomic control to the heart always.

Outline

- ❑ Autonomic Dysfunction and Baroreflex
- ❑ Muscle Sympathetic Activity
- ❑ Heart Rate Variability and Sympathetic Activity
- ❑ **Blood Pressure Variability and Sympathetic Activity**
- ❑ Simplified Model of Blood Pressure Variability

Processing Continuous Blood Pressure

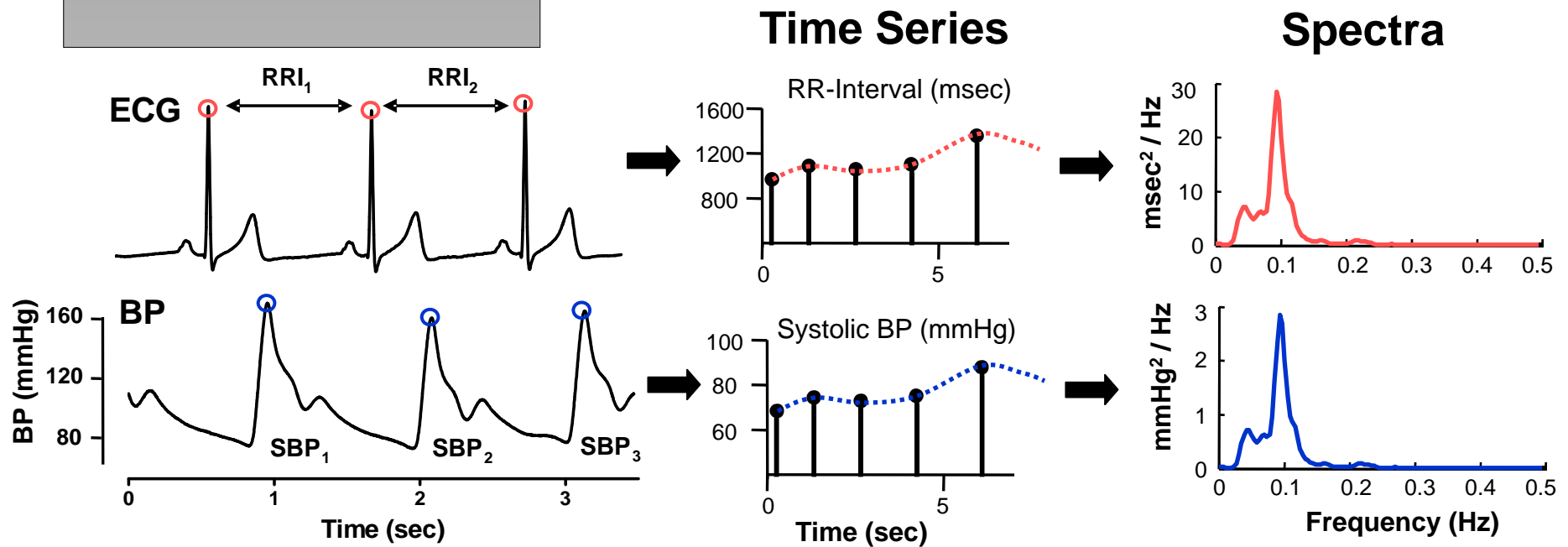


Recording

1. ECG Lead II
2. Continuous Blood Pressure
(arterial line, non-invasive volume clamp)

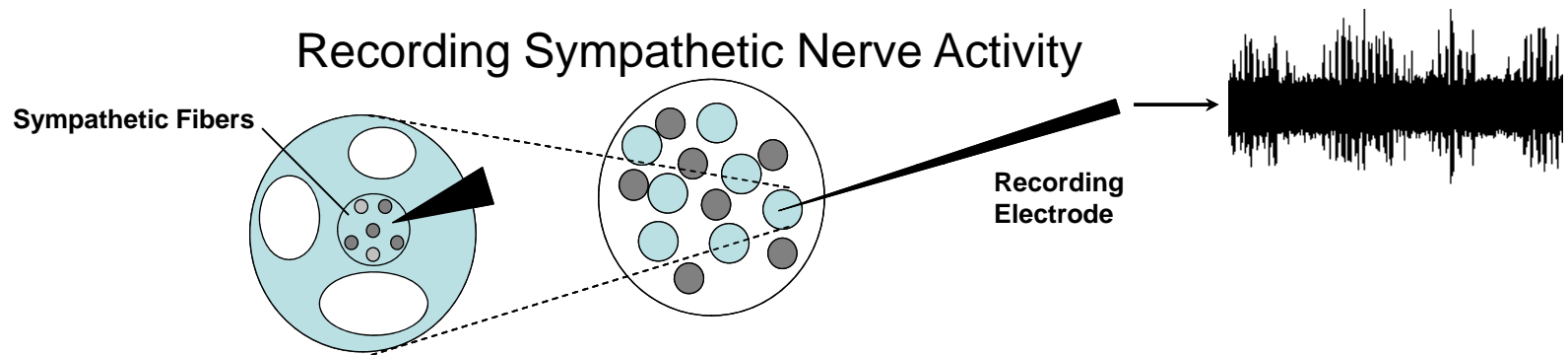
Processing

1. Detect R-Peaks
2. Detect Diastolic & Systolic BP
3. Quantify Fluctuations Using Spectral Analysis

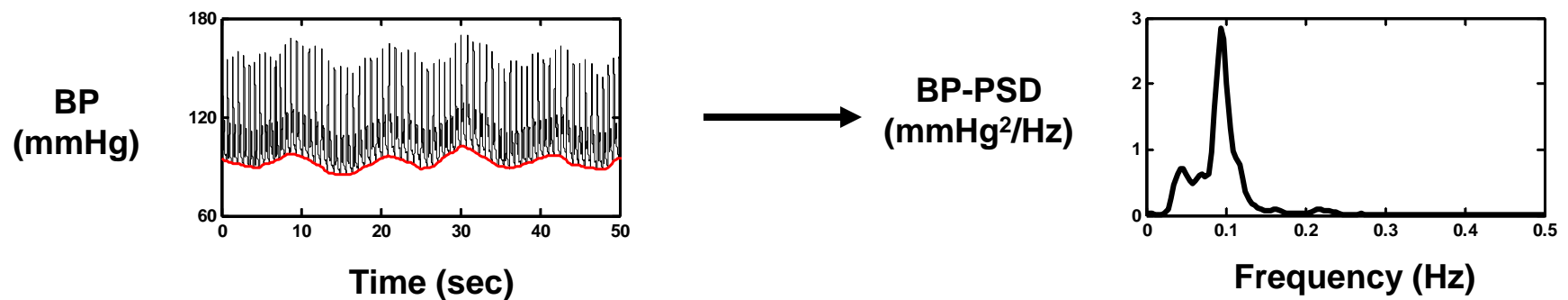


Blood Pressure Variability and Sympathetic Activity

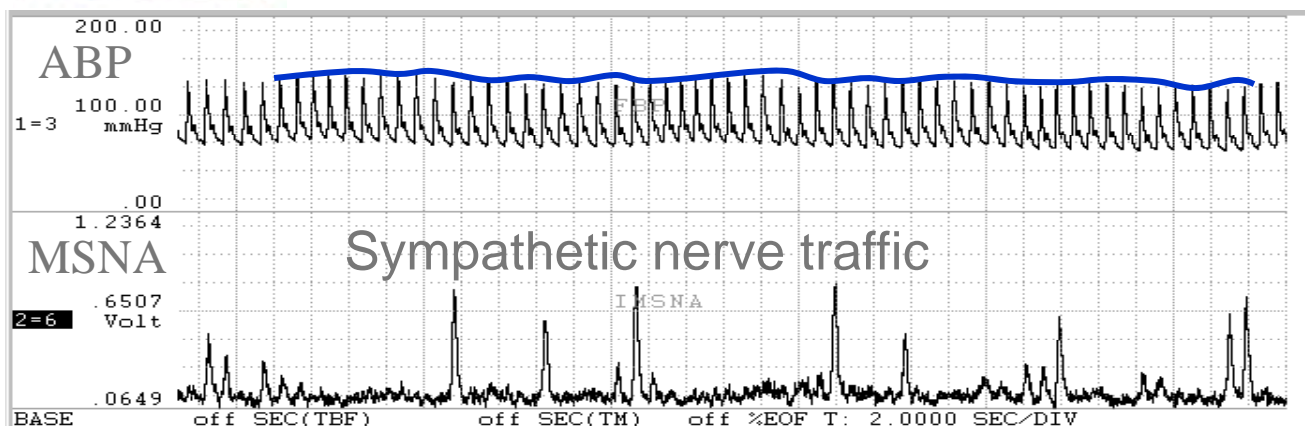
1. Direct Assessment: Raw Sympathetic Activity



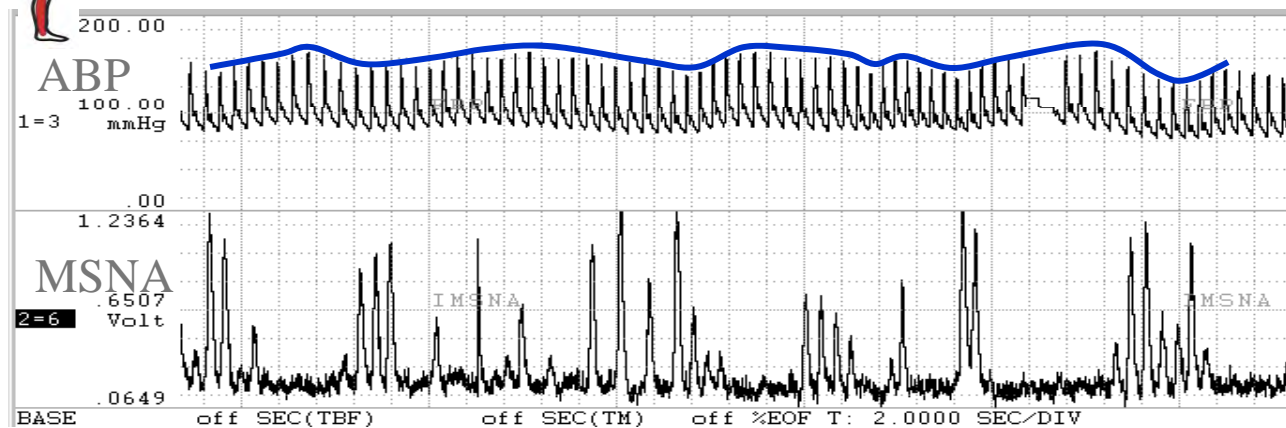
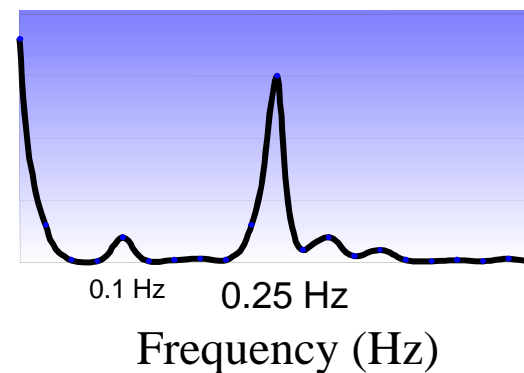
2. Indirect Assessment: Blood Pressure Variability



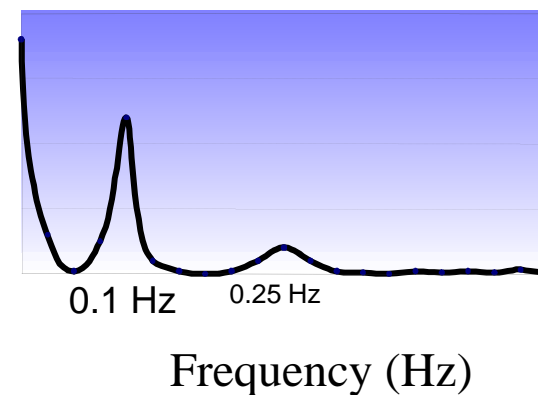
Blood Pressure Variability & Sympathetic Activity



PSD SBP



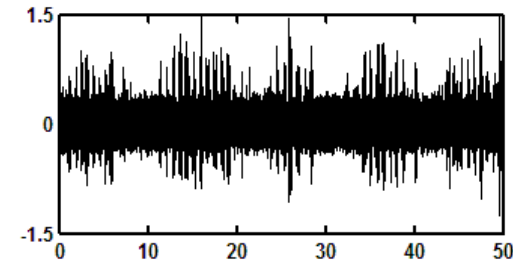
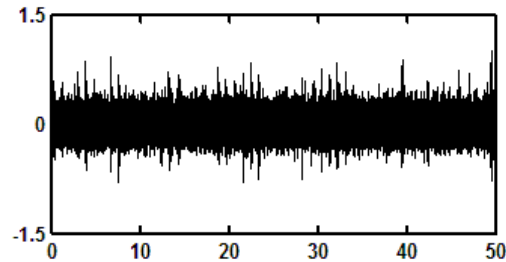
PSD SBP



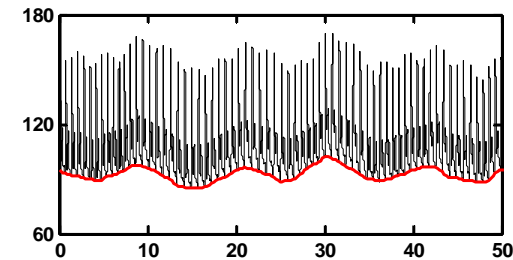
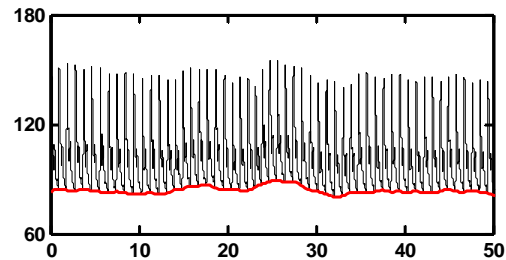
Indirect Assessment of Autonomic Function



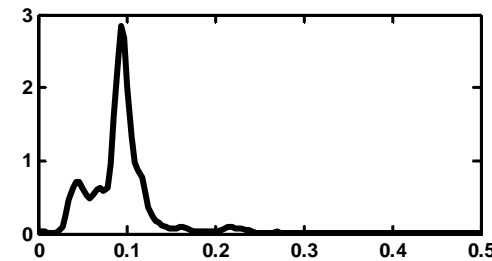
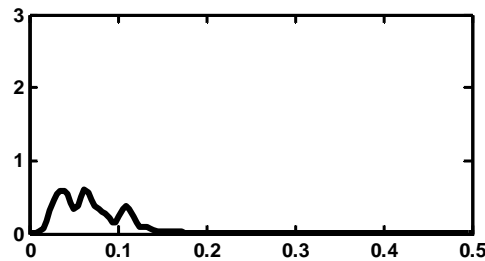
Nerve Activity (μV)



BP (mmHg)



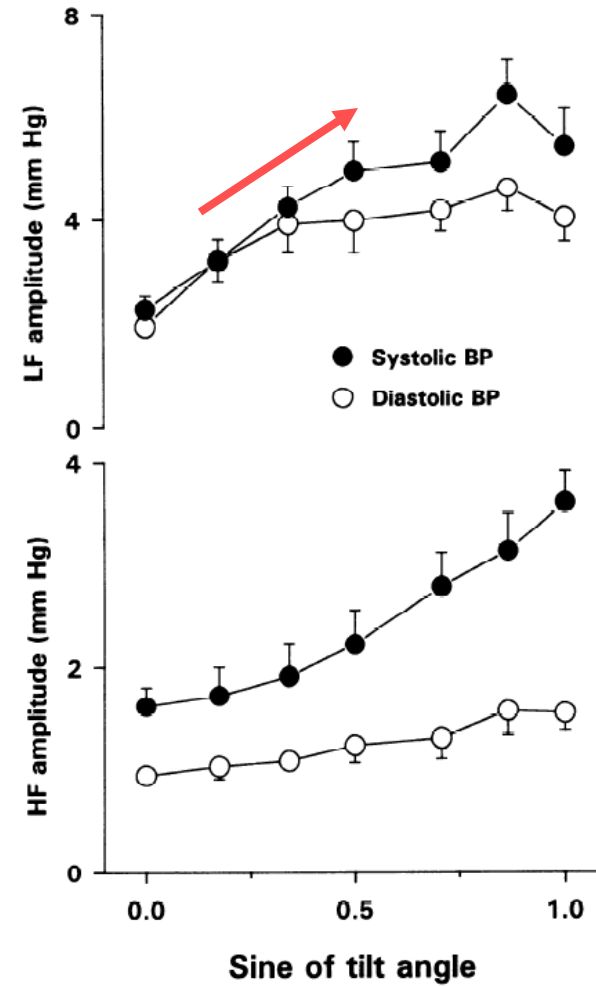
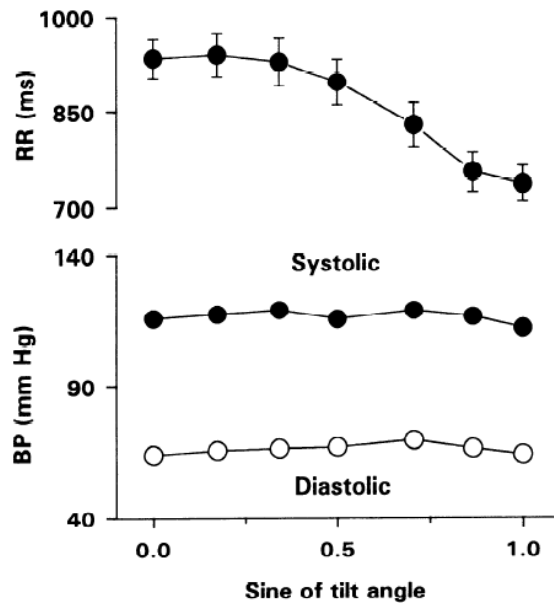
BP-PSD (mmHg²/Hz)



Frequency (Hz)

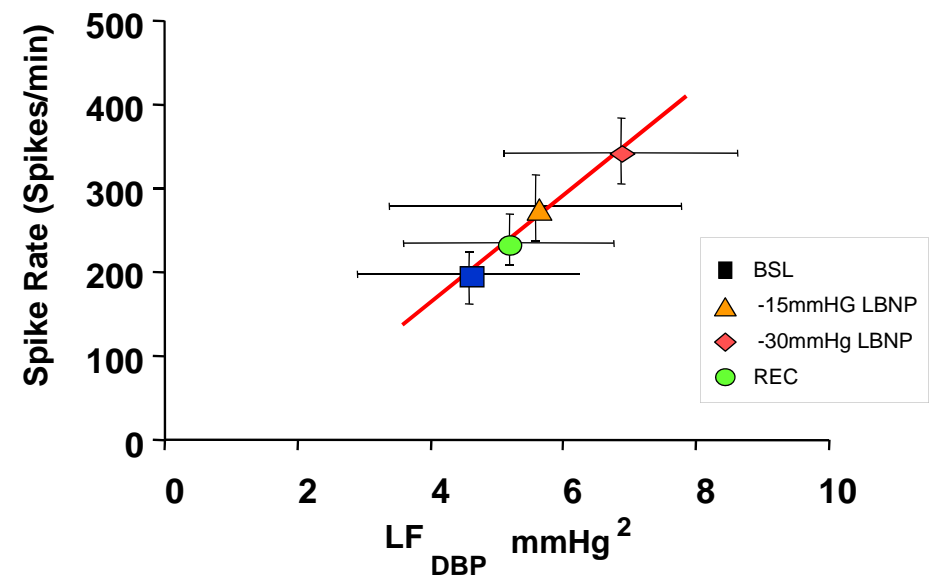
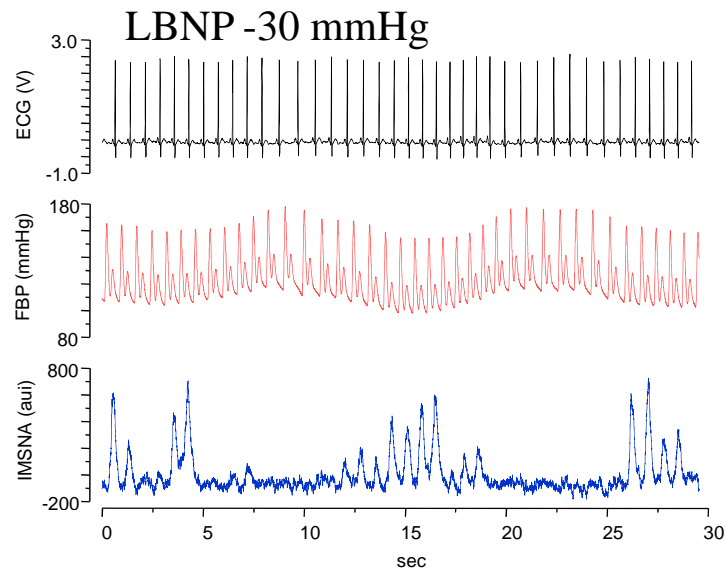
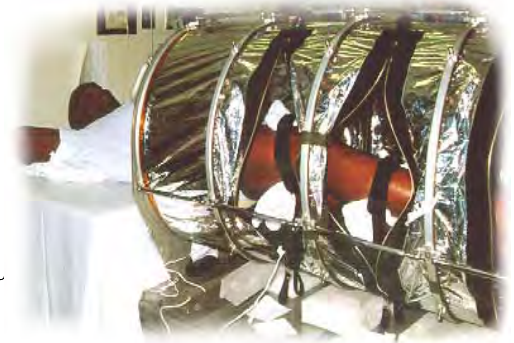
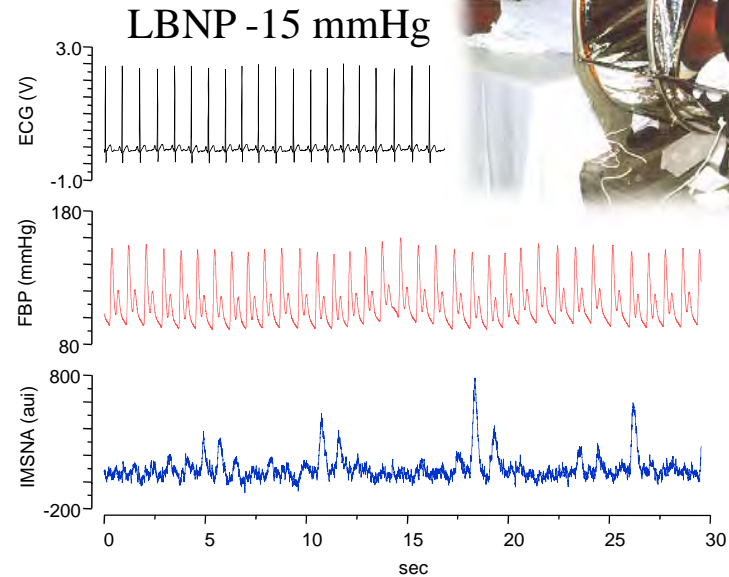
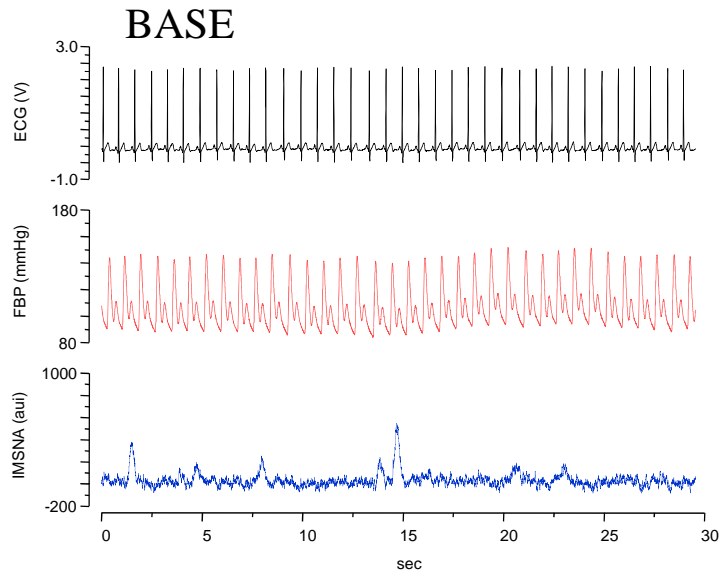
Frequency (Hz)

BPV during Graded Tilt



Orthostatic stress increases LF_{SBP}

BP Variability during LBNP



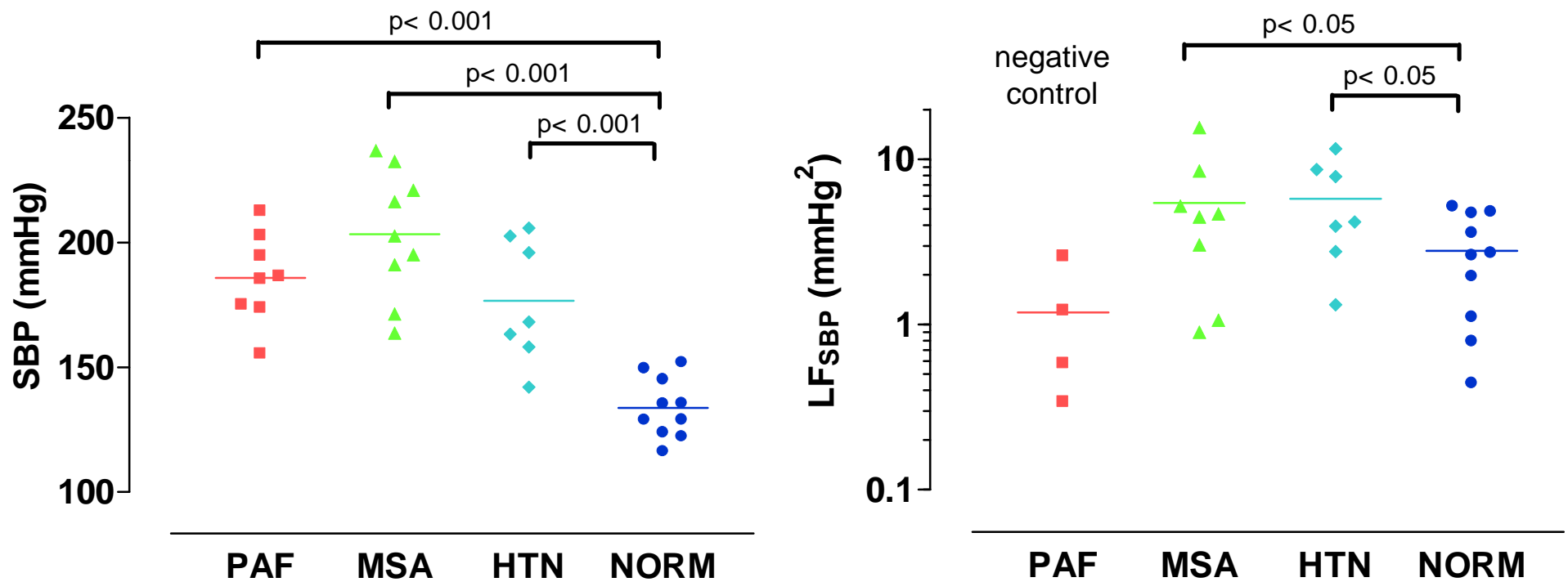
LF component of BP has suggestive relationship to Spike Rate

Diedrich et al. 2001

Summary BPV and Sympathetic Activation

LF of Blood Pressure Variability
reflects sympathetic activation
during orthostatic stress
and lower body negative suction

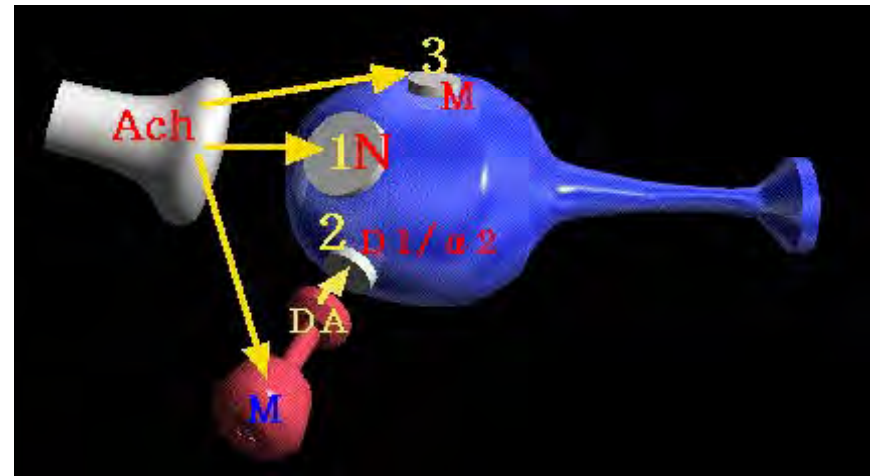
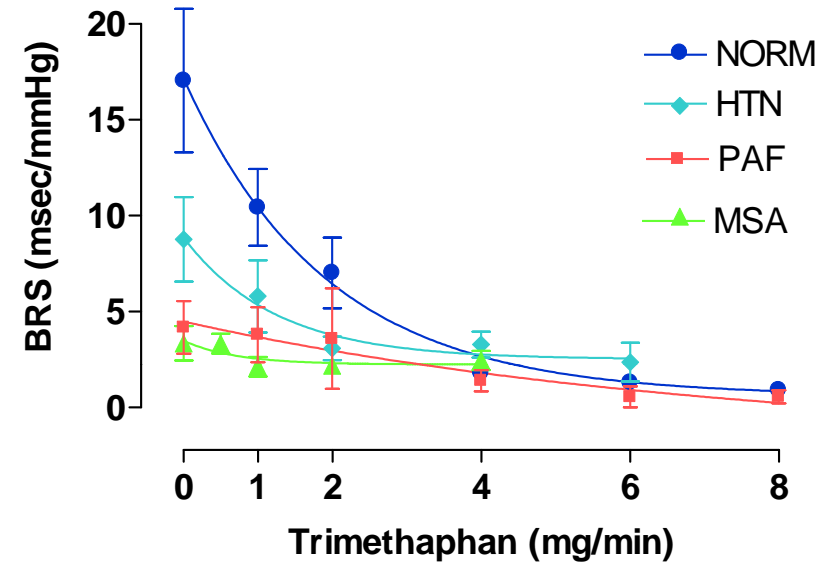
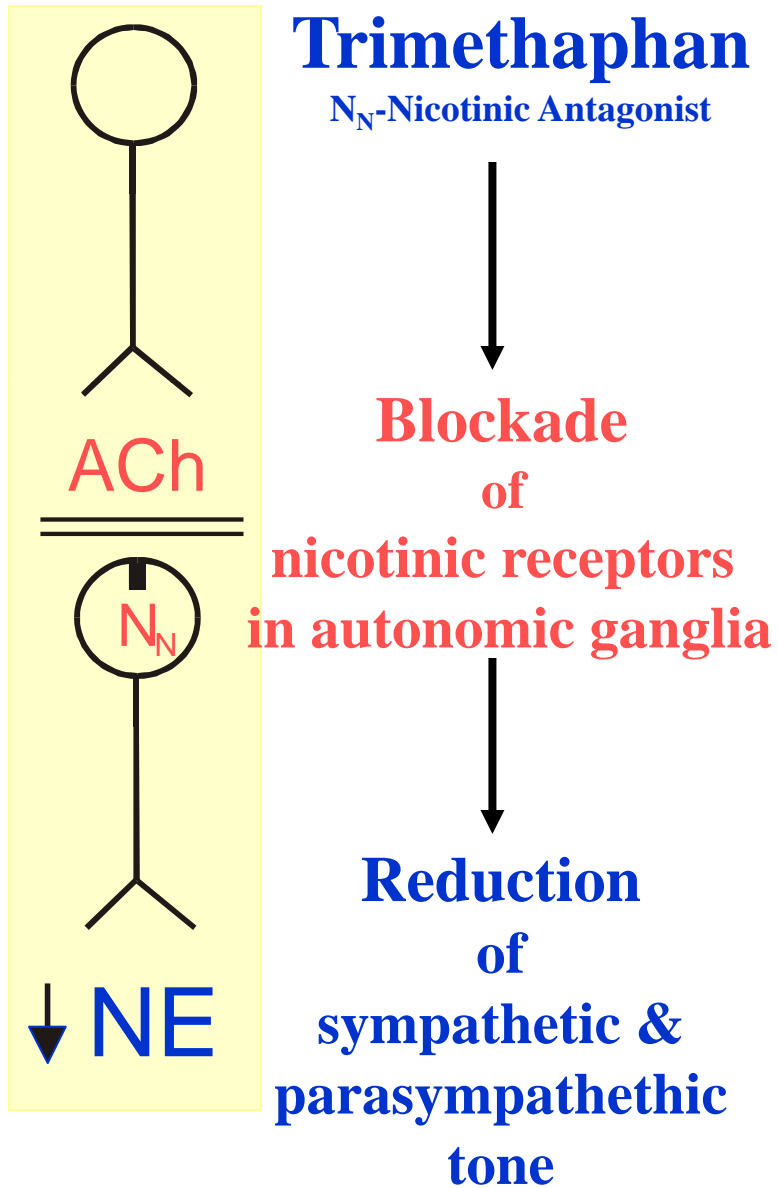
Hypertension and Blood Pressure Variability



MSA and HTN Patients with high supine BP have higher LF_{SBP}.

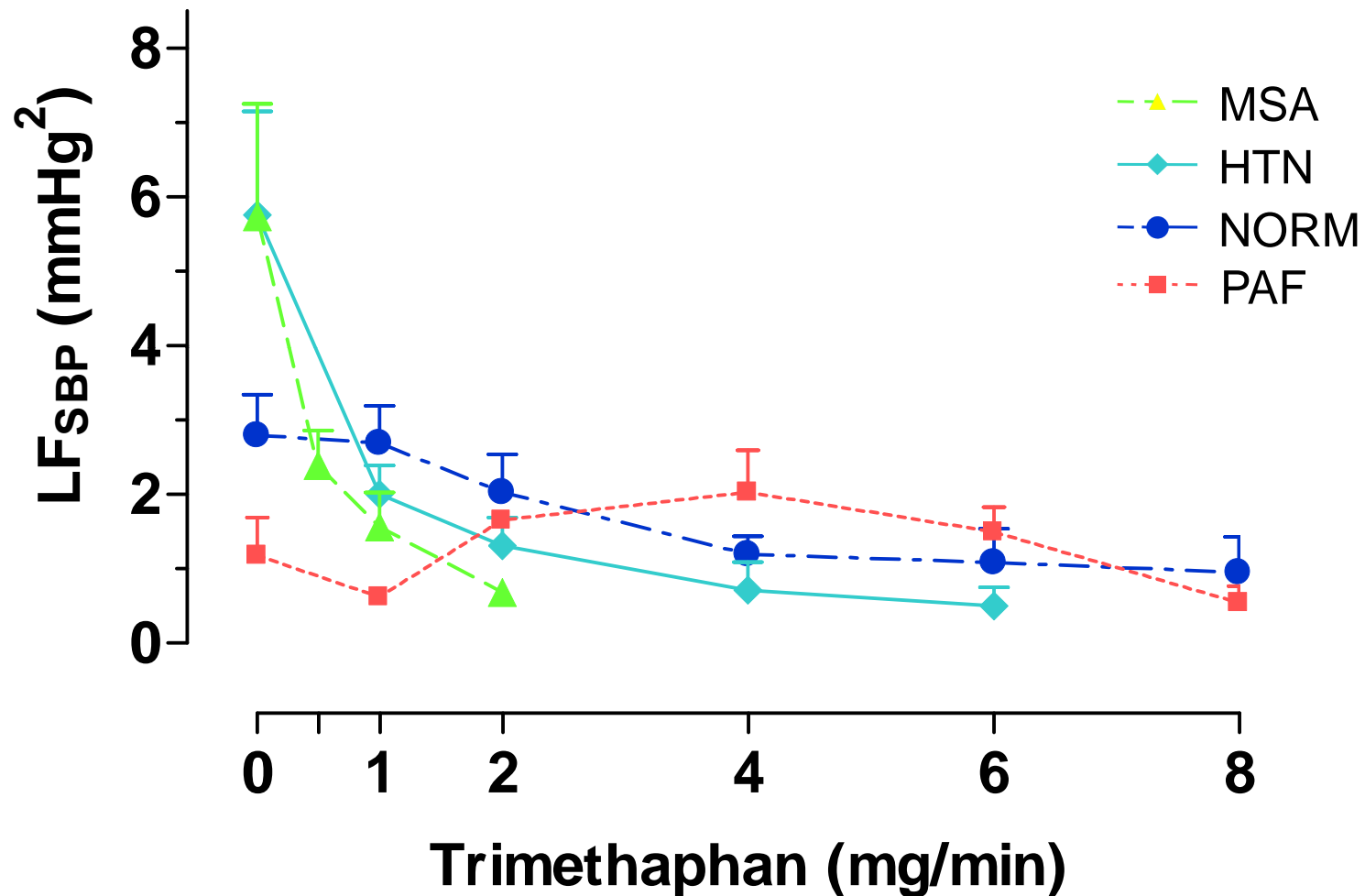
Ganglionic Blockade

using Trimethaphan Camsylate (Afronad®)



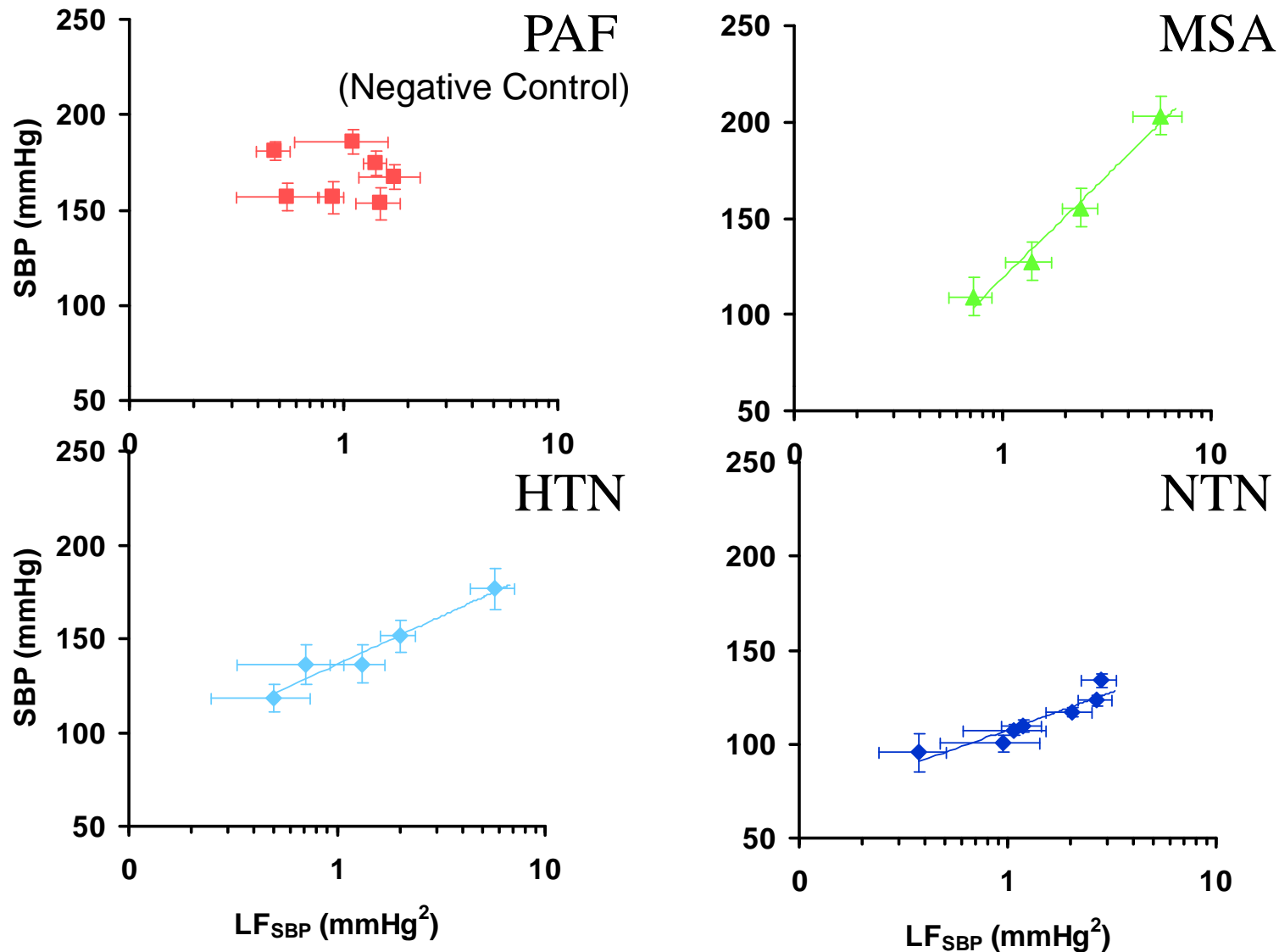
<http://pharma1.med.osaka-u.ac.jp/textbook/Ganglion/Ganglion.html>

Effects of Ganglionic Blockade on LF_{SBP}



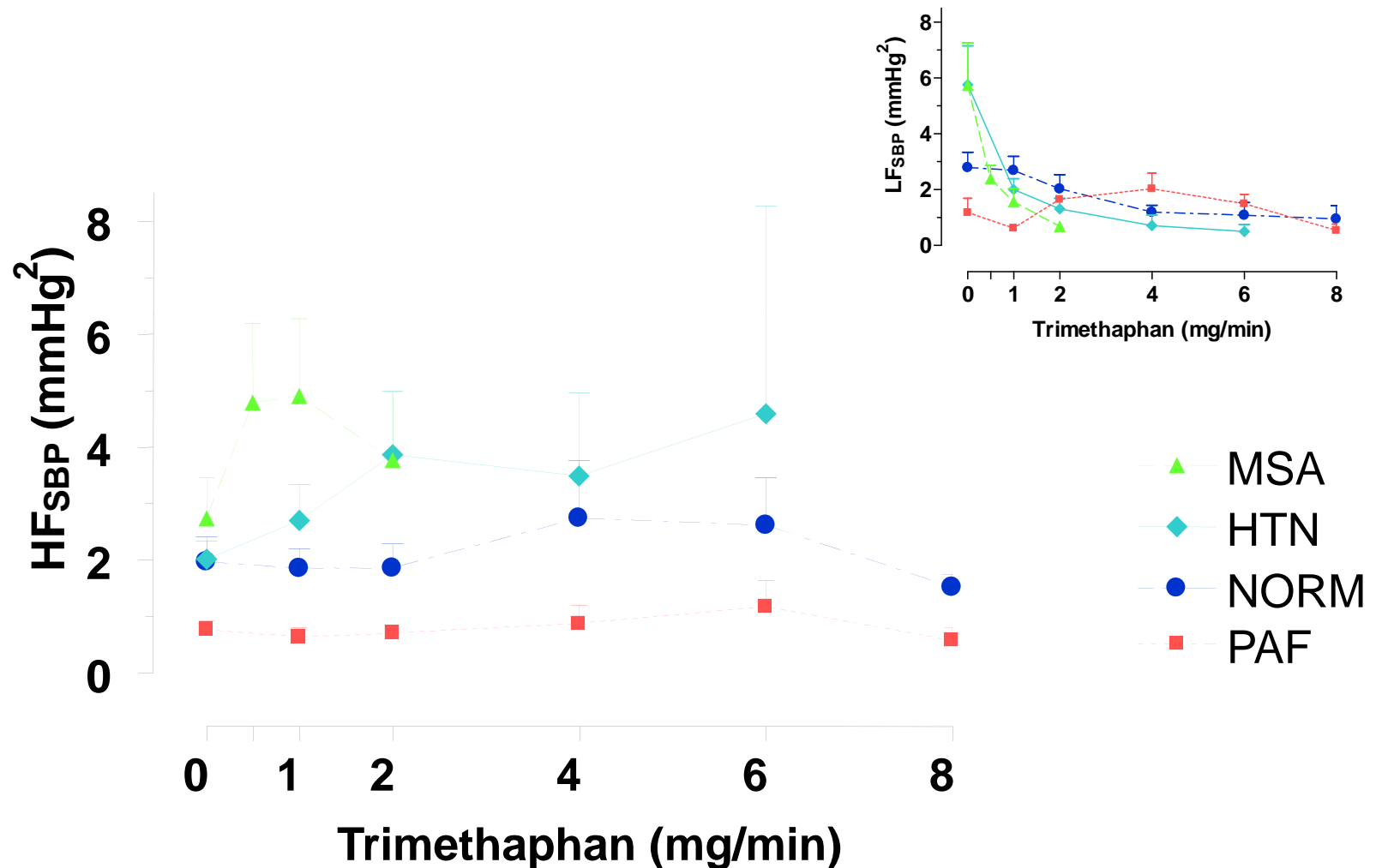
Ganglionic blockade abolish LF_{SBP} .

BPV and SBP during Ganglionic Blockade



There exist a correlation between BP drop and decrease in LF_{SBP}

Effects of Ganglionic Blockade on HF_{SBP}

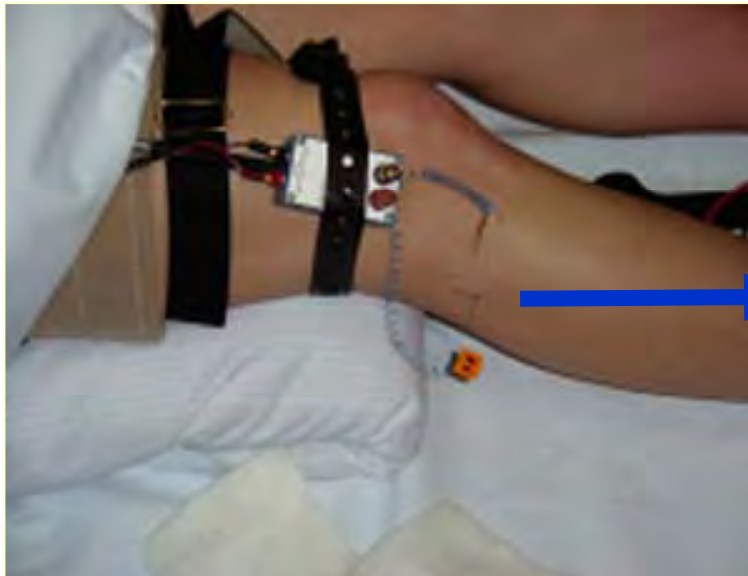
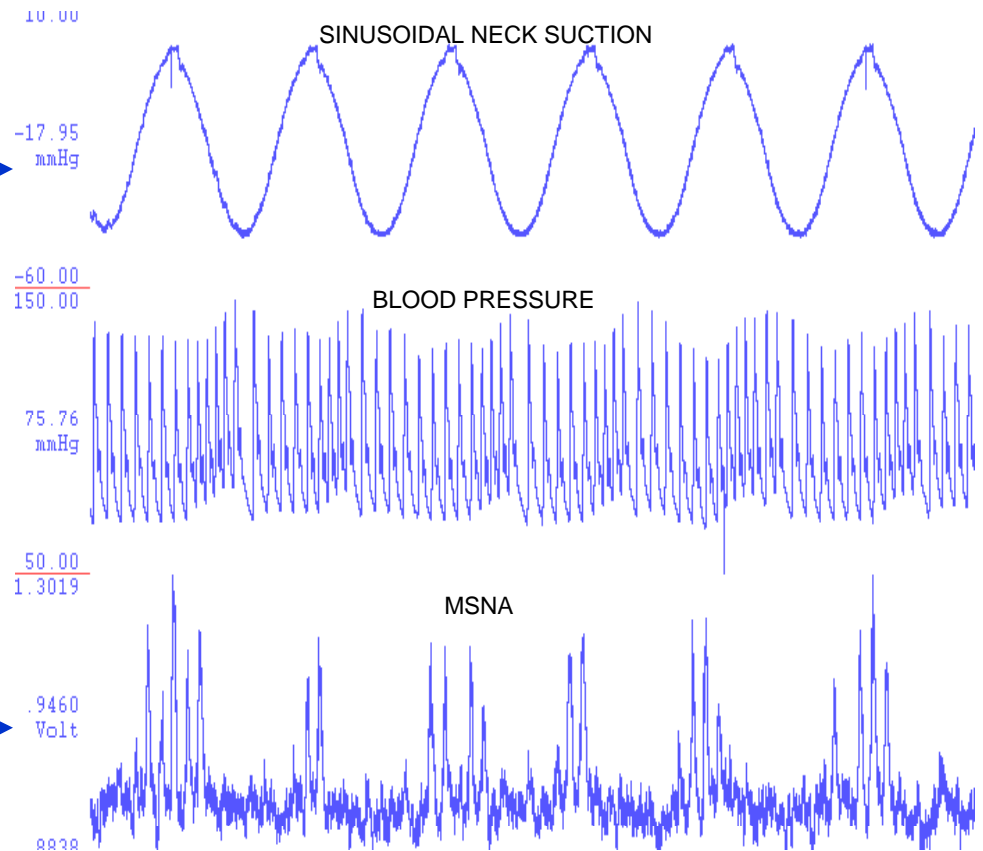


Ganglionic blockade abolish LF_{SBP} but not HF_{SBP} .

Response to Sinusoidal Neck Suction



Right and left cups for Neck Suction from 0 to -50 mmHg.

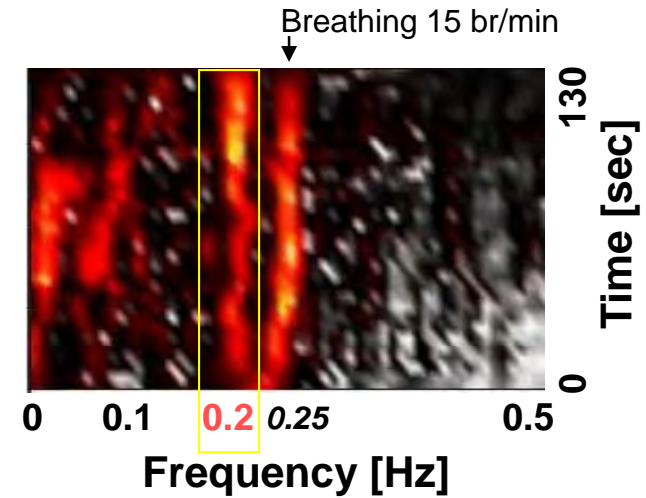
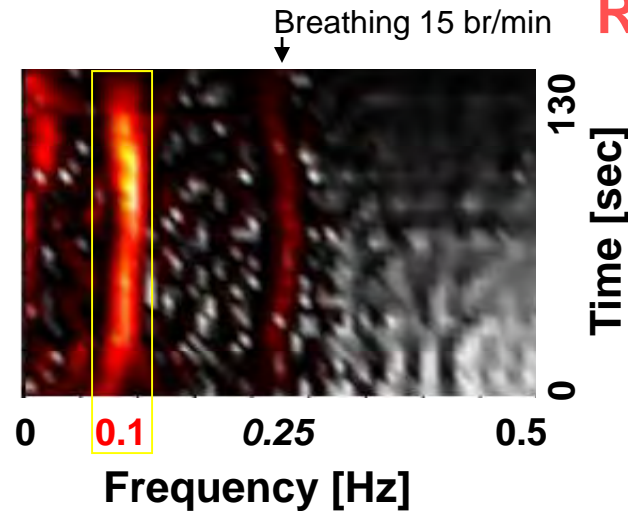


HRV & BPV Response to Neck Suction

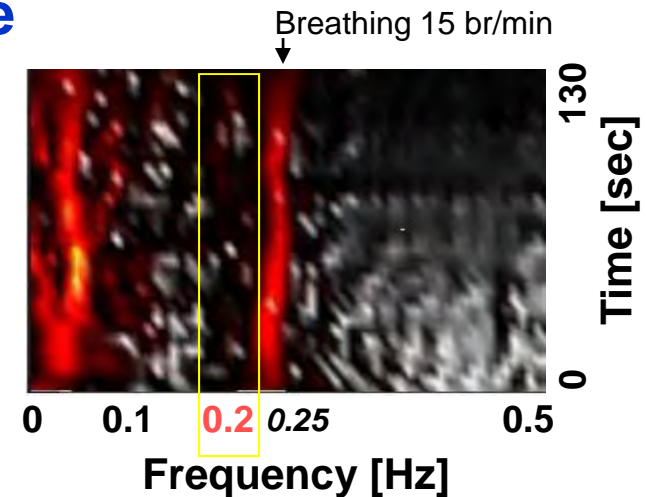
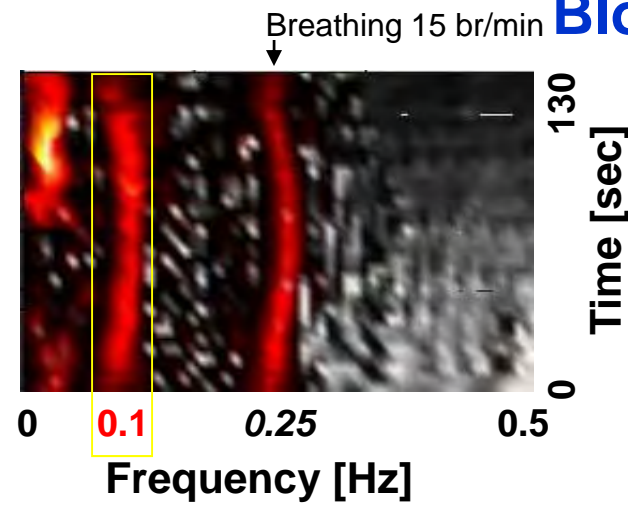
Neck Suction 0.1 Hz

Neck Suction 0.2 Hz

R-R Intervals

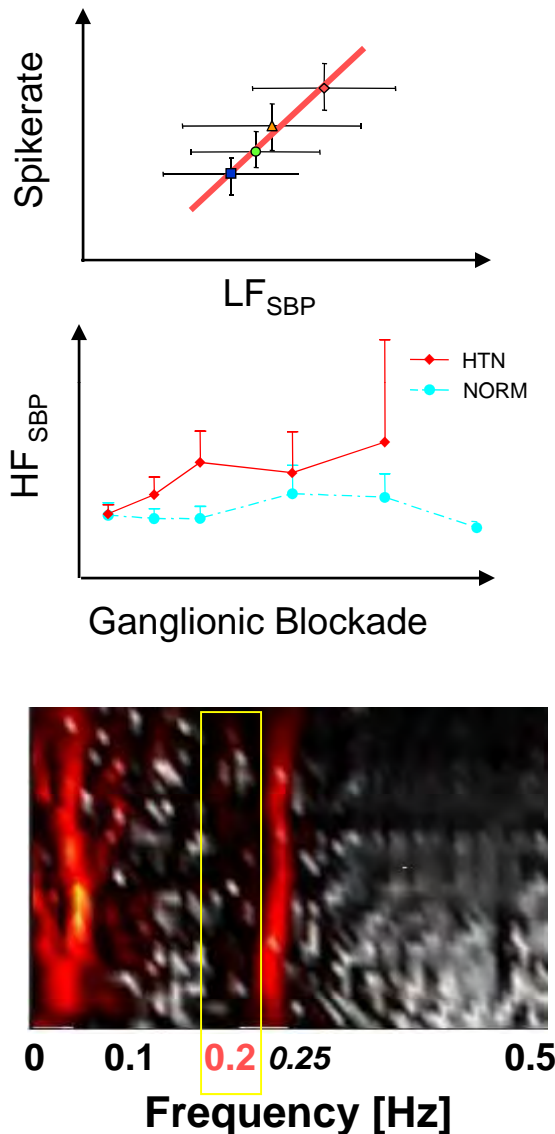


Blood Pressure



No BP Response during 0.2 Hz

Summary Blood Pressure Variability

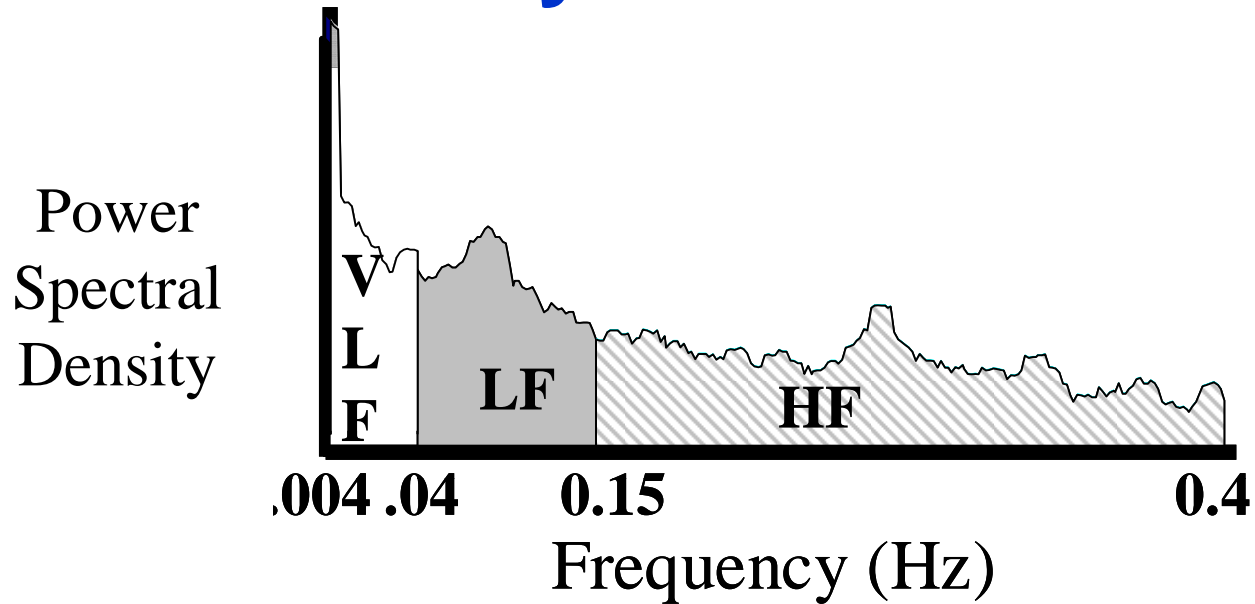


- Activation of the sympathetic nervous system are reflected in increase of LF_{BP}
- Ganglionic blockade reduces LF_{BP} but it does not reduce HF_{BP}
- Neck suction at high frequency range does not modulate HF_{BP}

HF spectral power of BP is not neural but **mechanical** modulated

LF spectral power of BP is modulated by the **sympathetic** nervous system.

Summary HRV and BPV



VLF	LF _{RRI}	LF _{SBP}	HF _{RRI}	HF _{SBP}
Trends	Sympathetic <u>and</u> Vagal Influence on HR	Sympathetic Influence on Vascular Tone	Neural Vagal Influence on HR at Breathing Frequency	Mechanical Respiratory Modulation of Blood Pressure
Thermoregulation & Hormones				

Outline

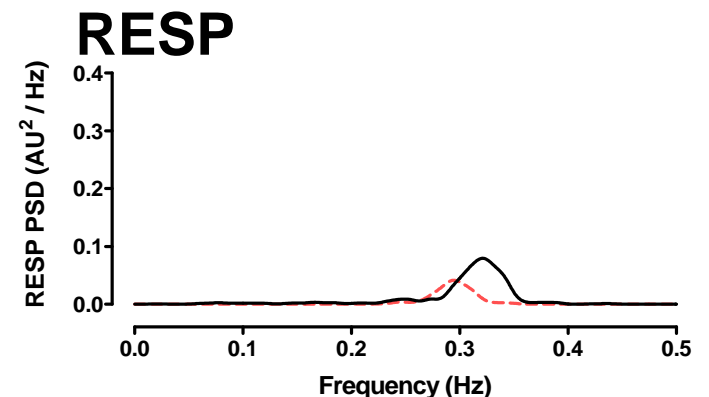
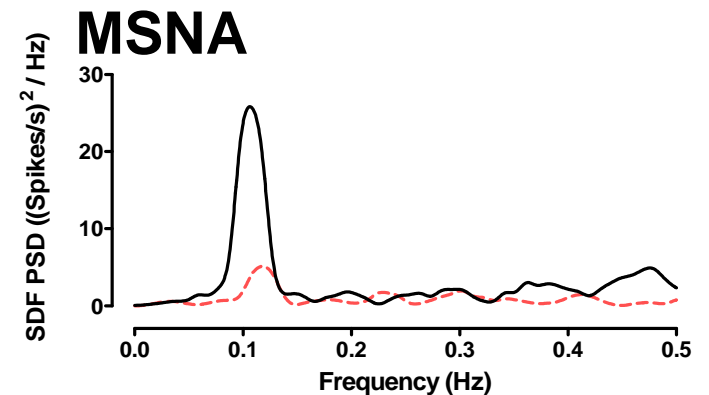
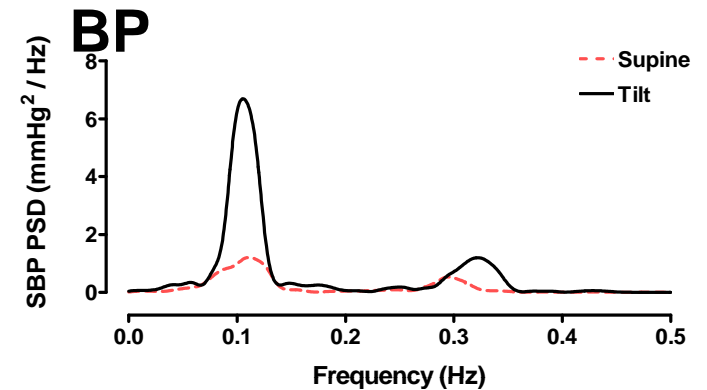
- ❑ Autonomic Dysfunction and Baroreflex
- ❑ Muscle Sympathetic Activity
- ❑ Heart Rate Variability and Sympathetic Activity
- ❑ Blood Pressure Variability and Sympathetic Activity
- ❑ **Simplified Model of Blood Pressure Variability**

Model of Blood Pressure Fluctuations

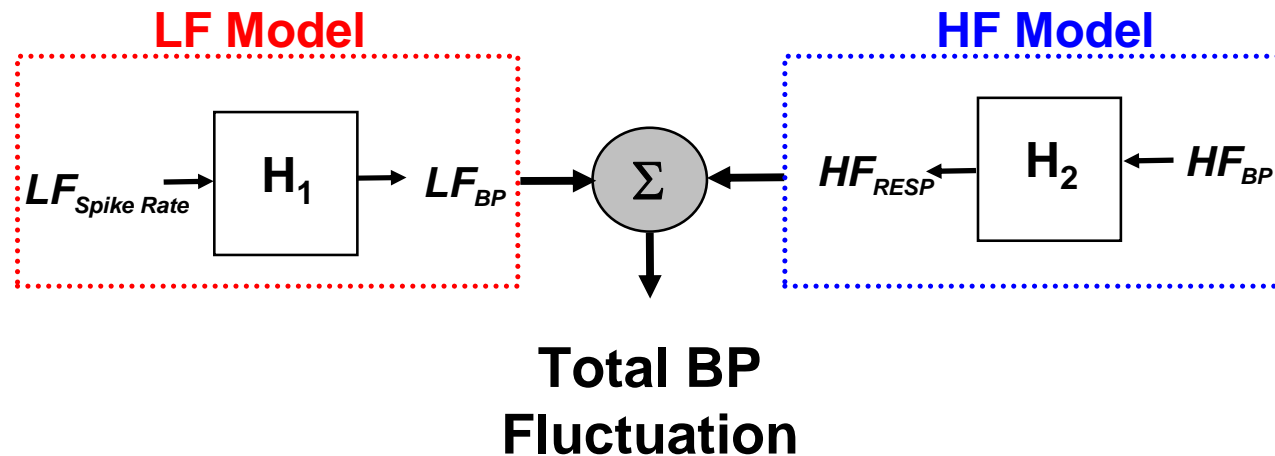
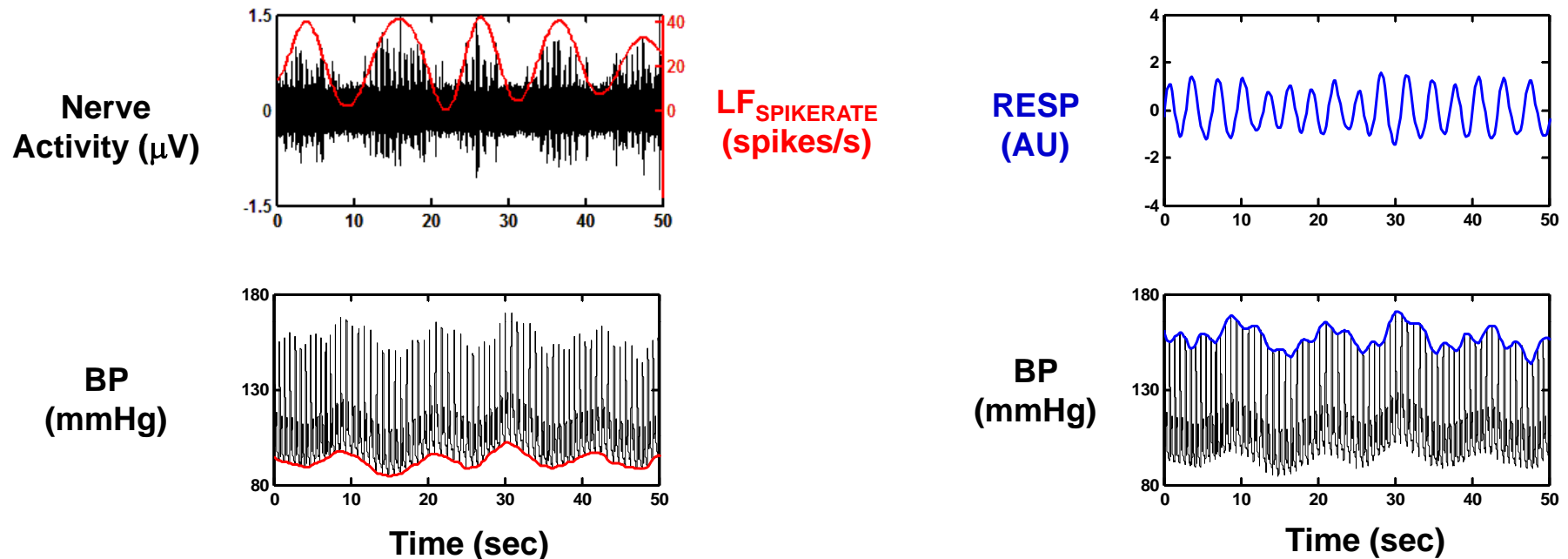
Assumptions:

The major contributors to the oscillations found in systolic blood pressure are:

1. Low Frequency Modulation from the Sympathetic Activity
2. High Frequency Mechanical Oscillations from the Respiration

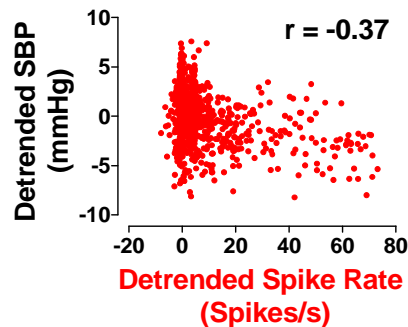
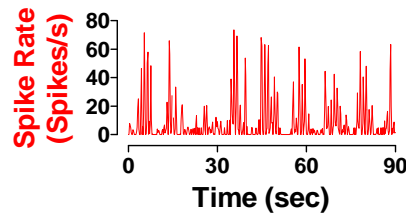
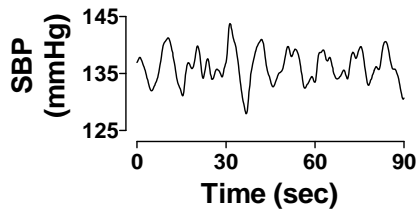


Model of Blood Pressure Fluctuations



Evidence for Neural-Sympathetic Influence on BP Fluctuations

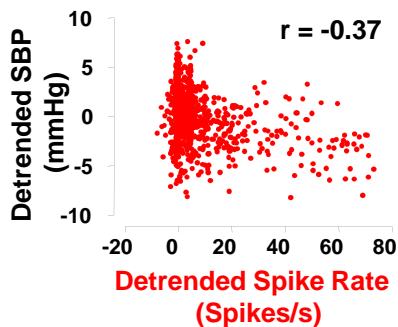
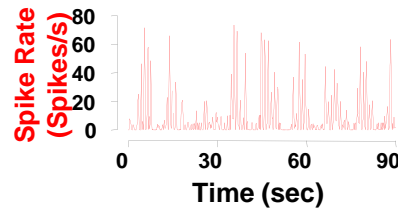
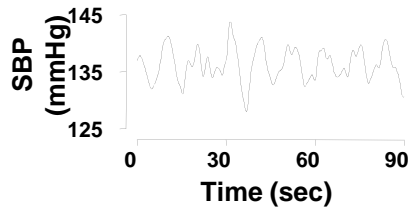
Original Time Series



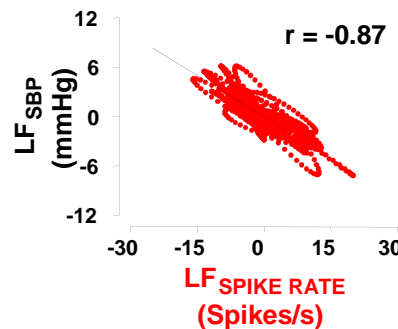
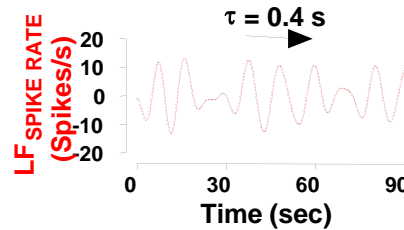
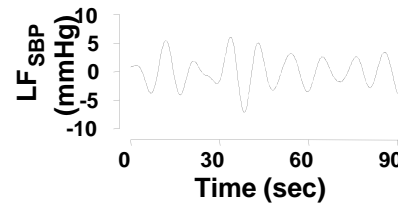
No correlation between Beat-to-Beat Spike Rate and Blood Pressure Change

Evidence for Neural-Sympathetic Influence on BP Fluctuations

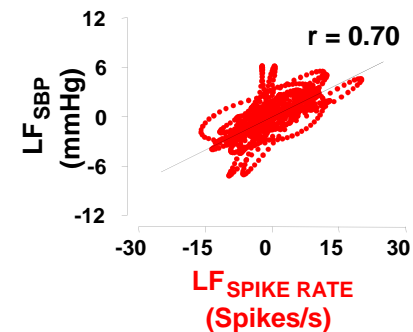
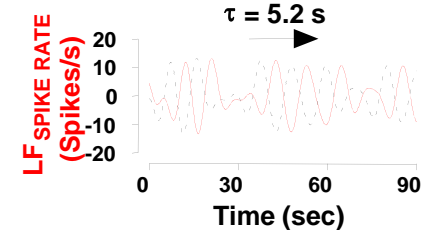
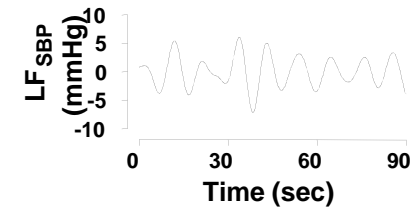
Original Time Series



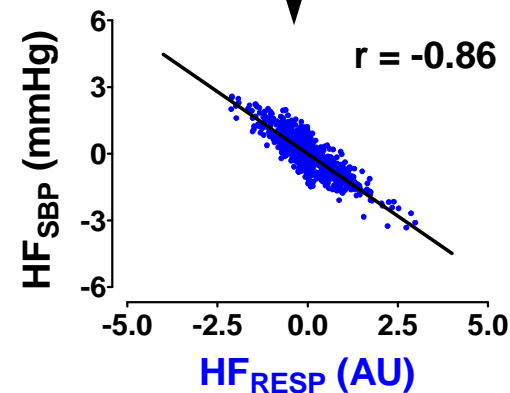
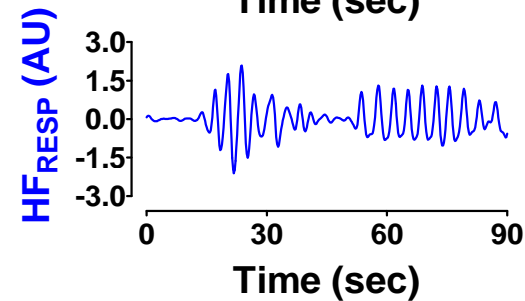
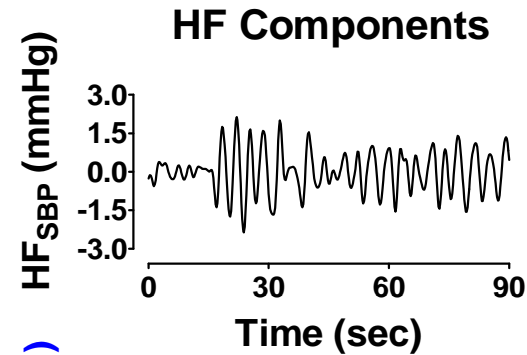
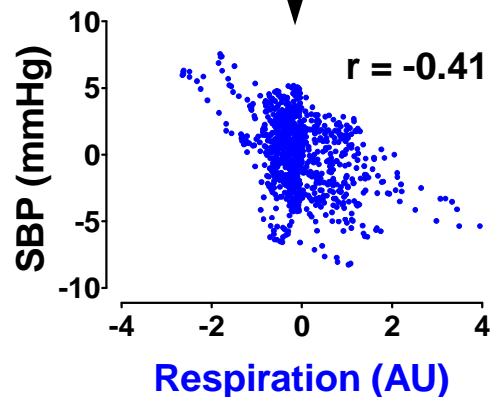
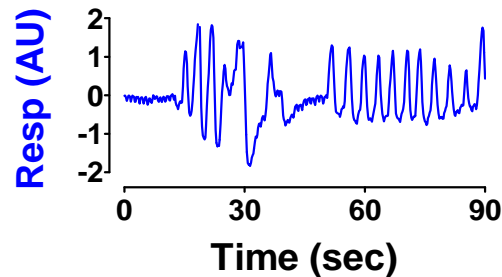
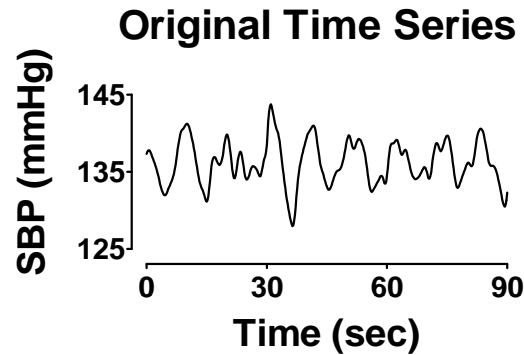
Feedback LF
BP \rightarrow Spike Rate



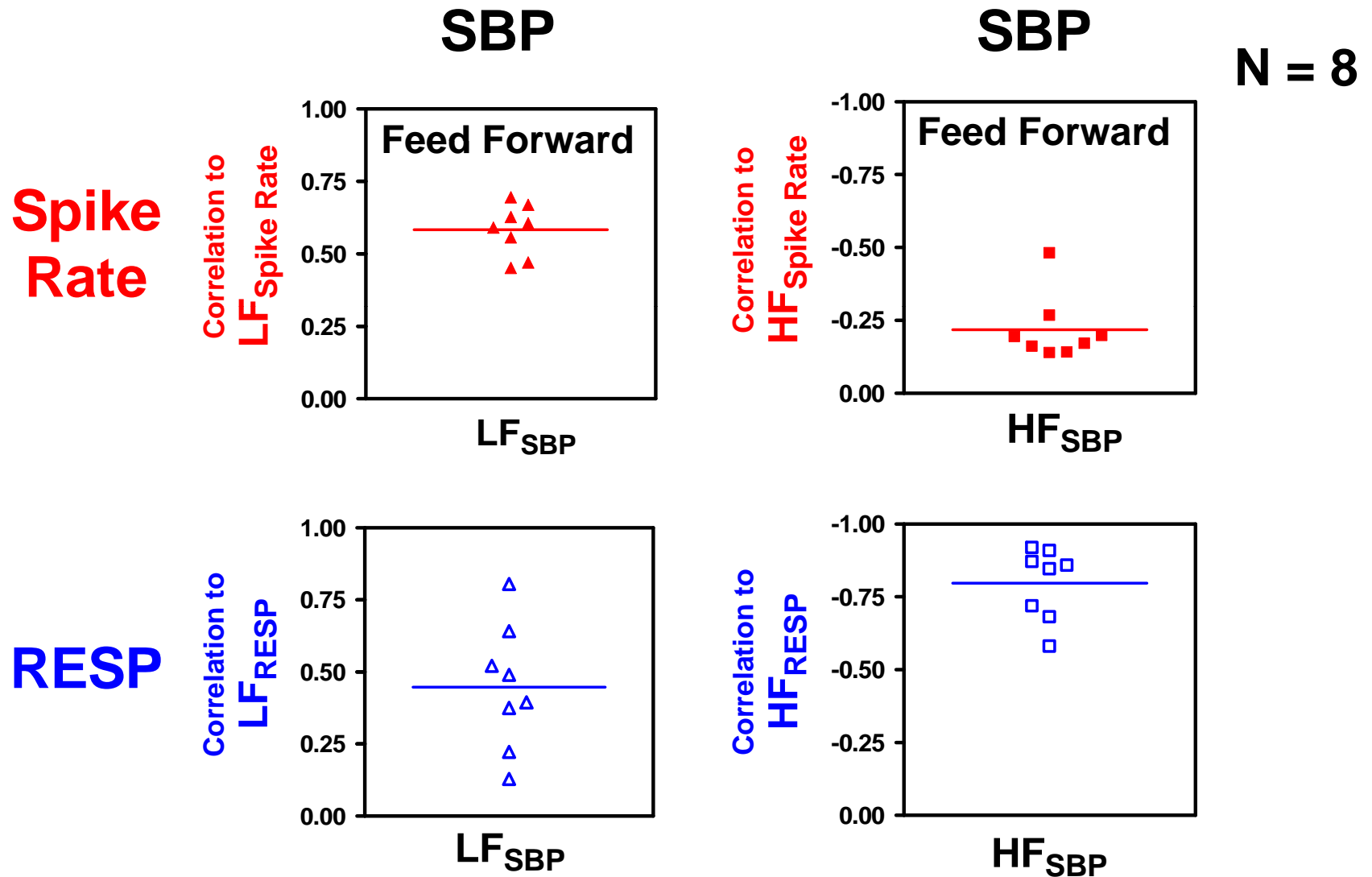
Feed Forward LF
Spike Rate \rightarrow BP



Evidence for Mechanical-Respiratory Influence on BP Fluctuations

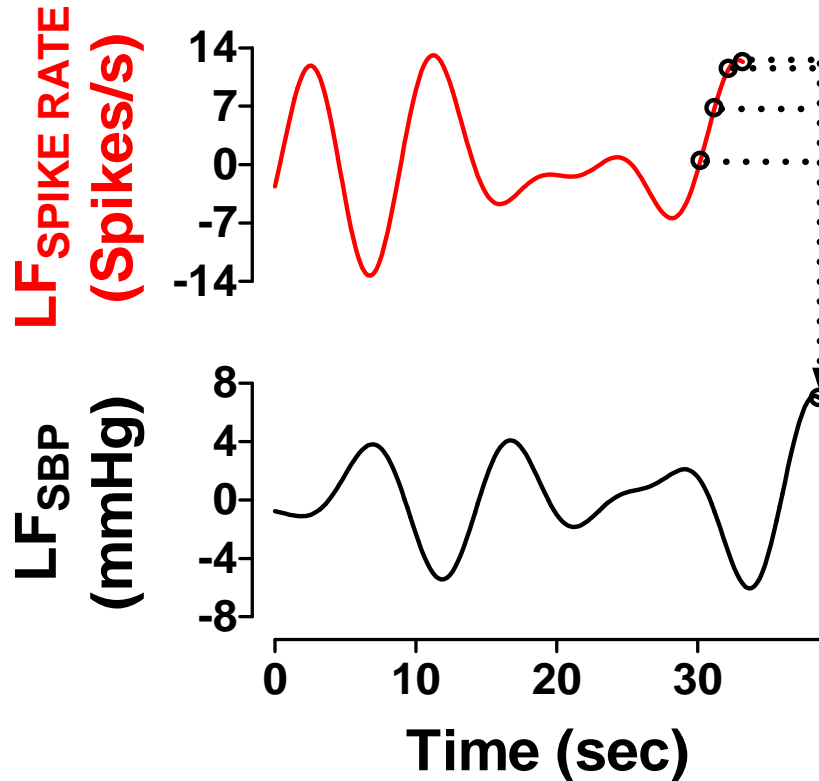


Group Correlations Values

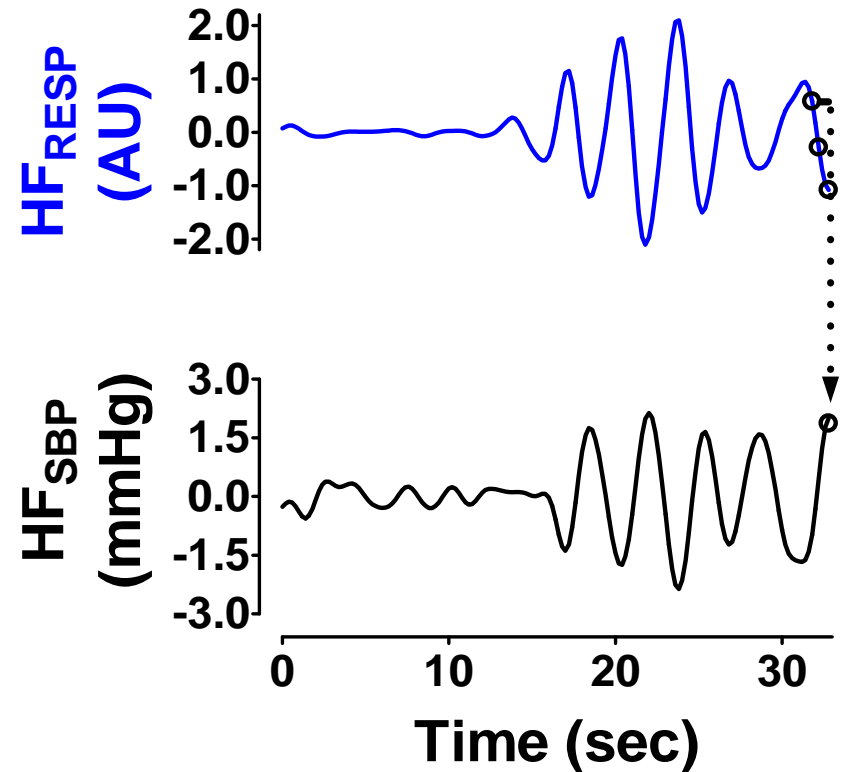


Improving Model With Past Values

LF Model



HF Model

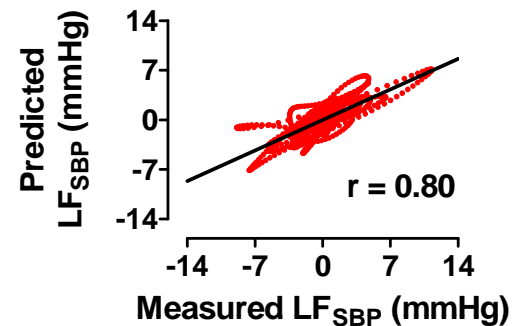
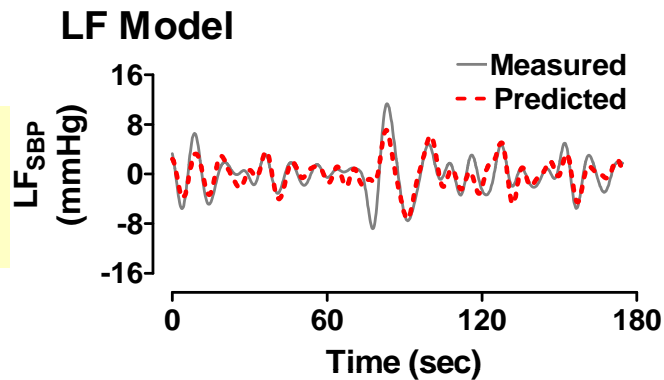


$$LF_{BP}(n) = \sum_{p=0}^{P-1} a(p) LF_{Spike\ Rate}(n-p)$$

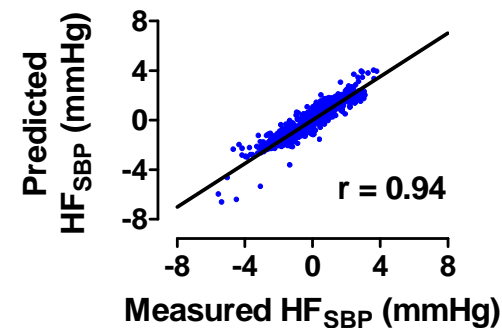
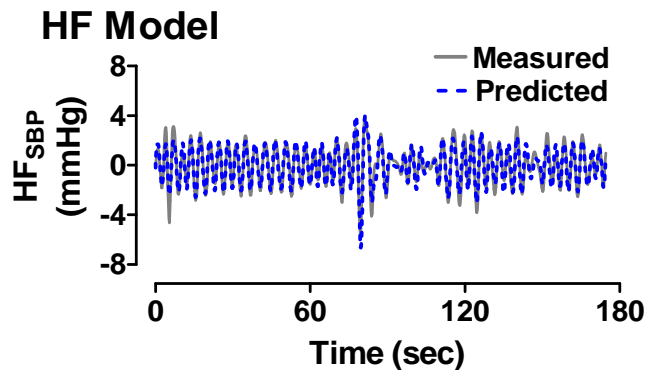
$$HF_{BP}(n) = \sum_{k=0}^{K-1} b(k) HF_{RESP}(n-k)$$

Baseline Results Using Past Values

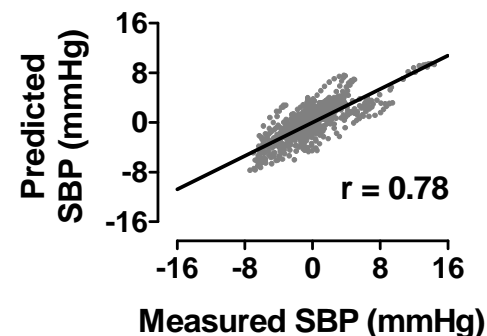
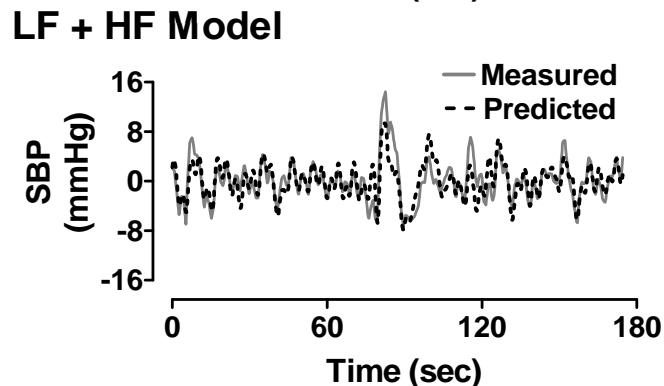
Using
MSNA



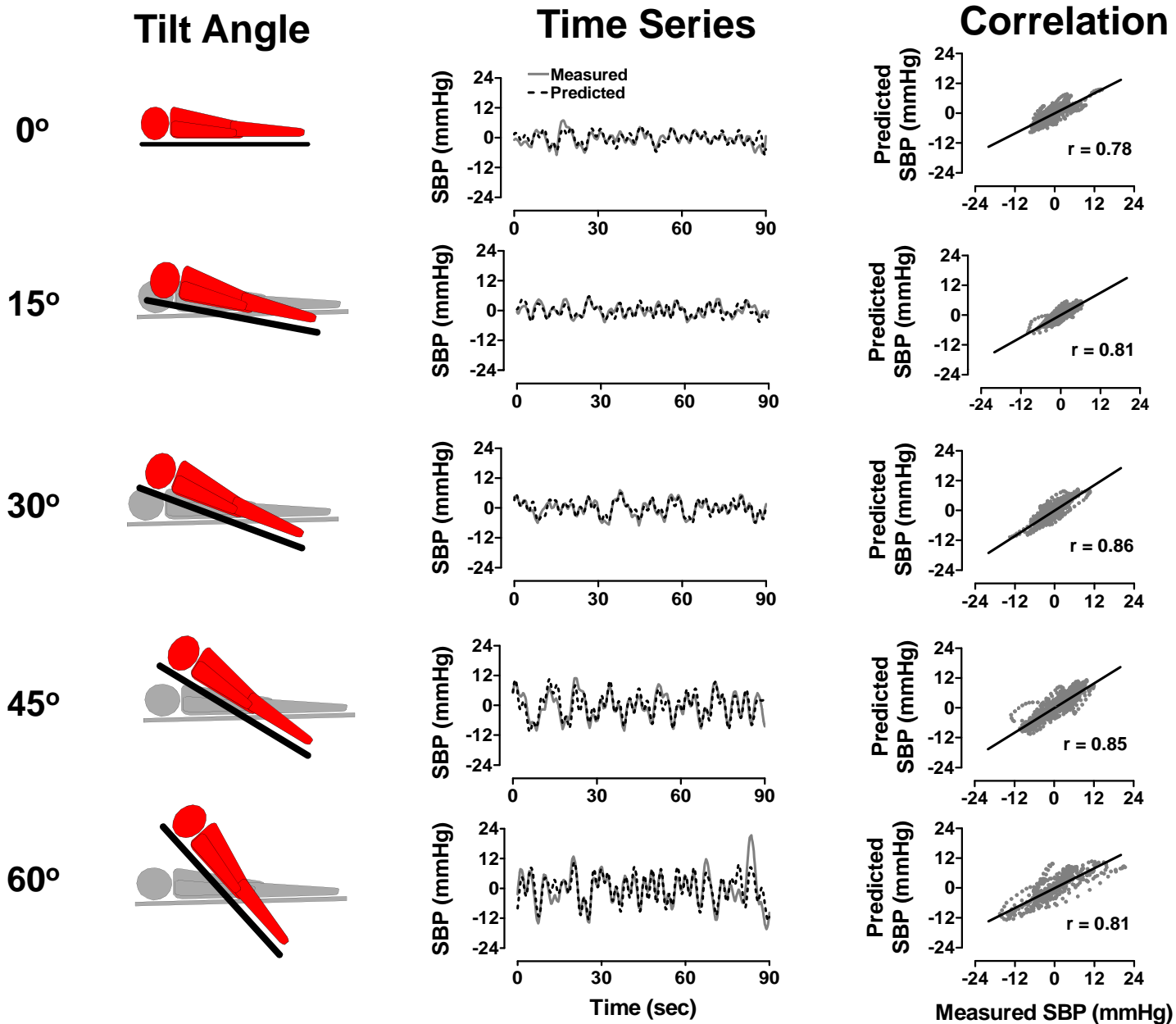
Using
RESP



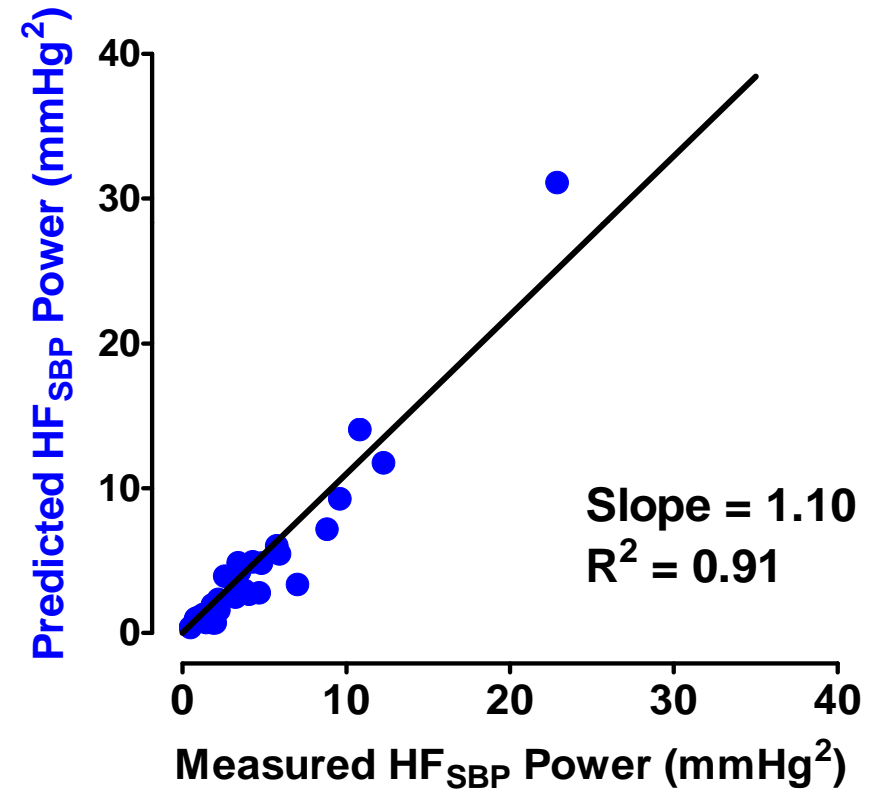
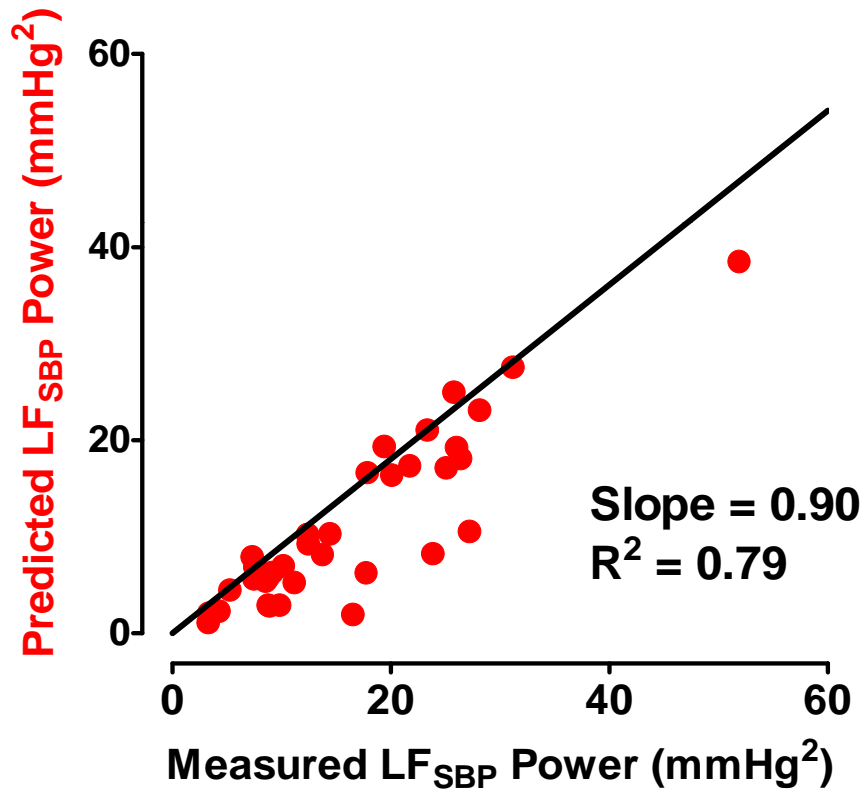
Using
Both



Model Performance During Tilt

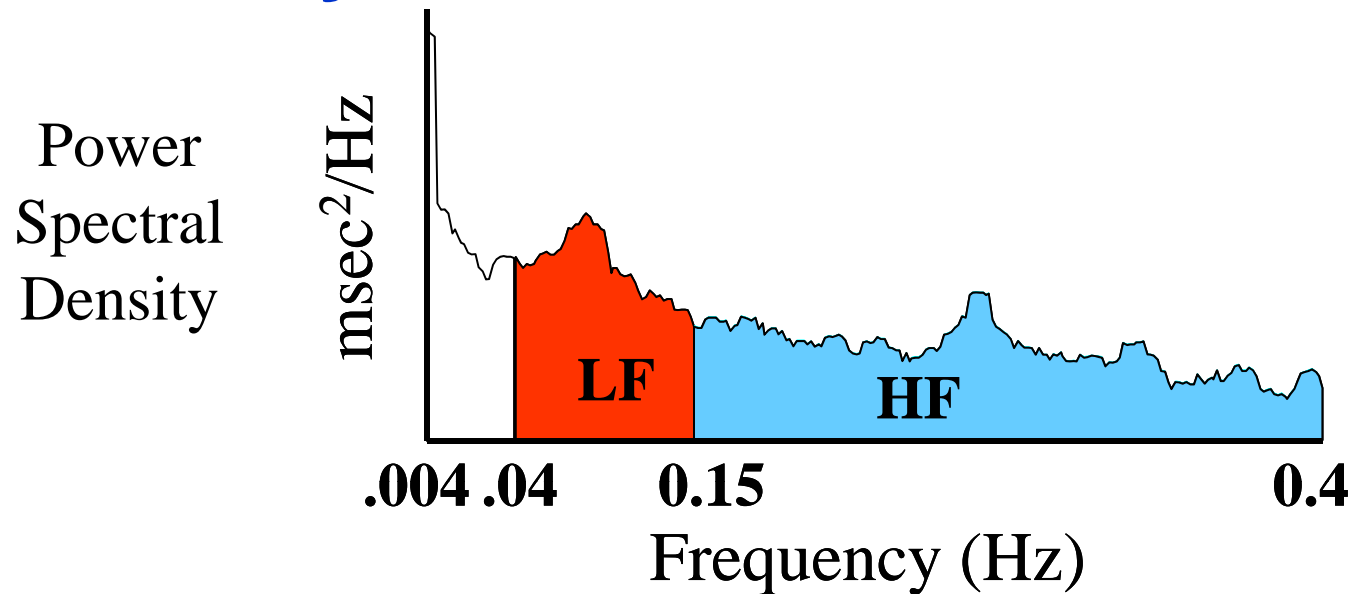


Measured versus Predicted Power during Rest & Tilt



Good Prediction of LF_{SBP} and HF_{SBP}

Summary of BP Fluctuation Model



LF_{SBP}

Sympathetic
Influence
Vascular

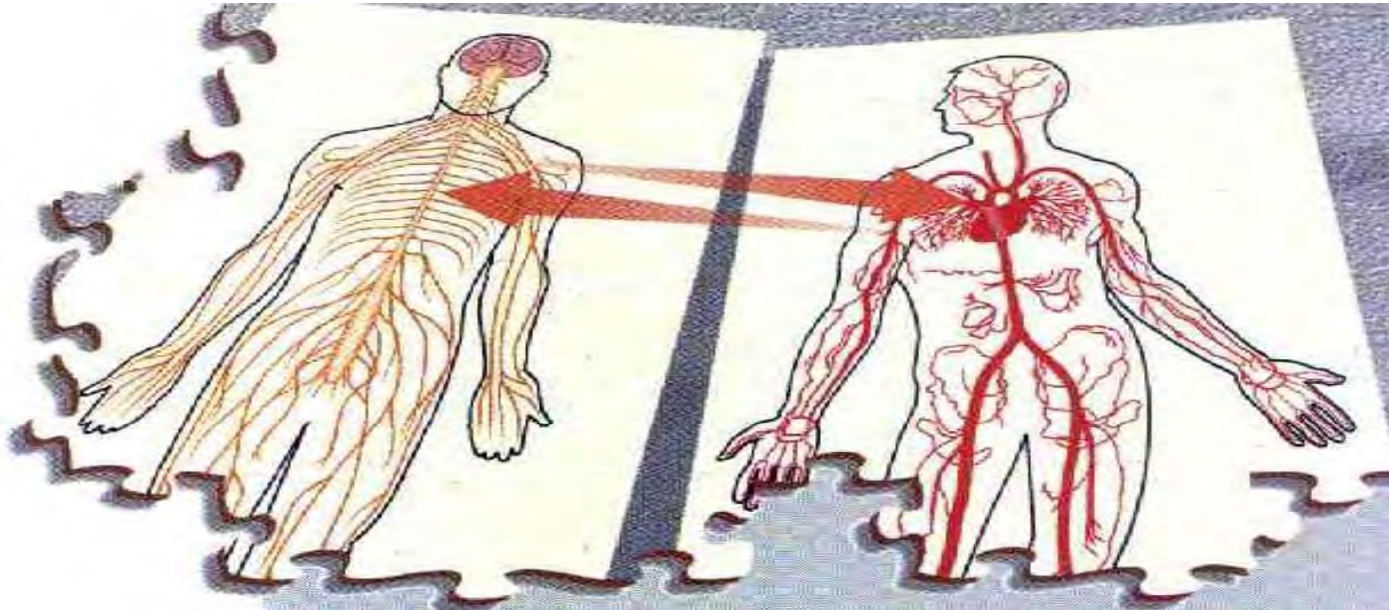
HF_{SBP}

Mechanical
Respiratory
Modulation of
Blood

- MSNA precedes and contributes to most of the variability in LF_{SBP}
- HF_{SBP} is mechanical, not autonomic

Summary of BP Fluctuation Model

- A simple two component model using neural sympathetic and mechanical respiratory inputs can explain the majority of BP fluctuation at rest and during orthostatic stress in healthy subjects.
- It is a useful tool to describe neural-cardiovascular interaction.



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