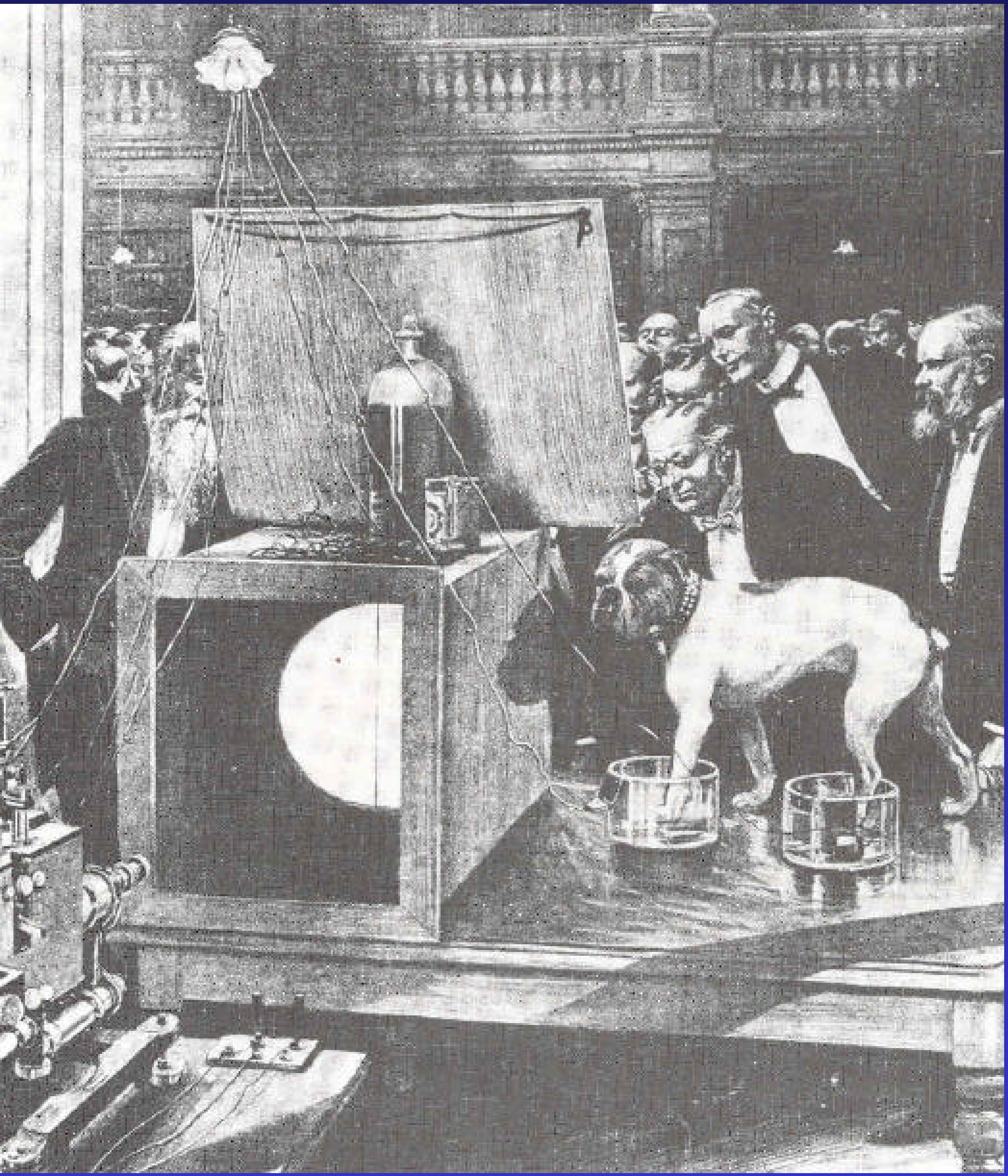


Physiologic Mechanisms of Heart Rate Variability

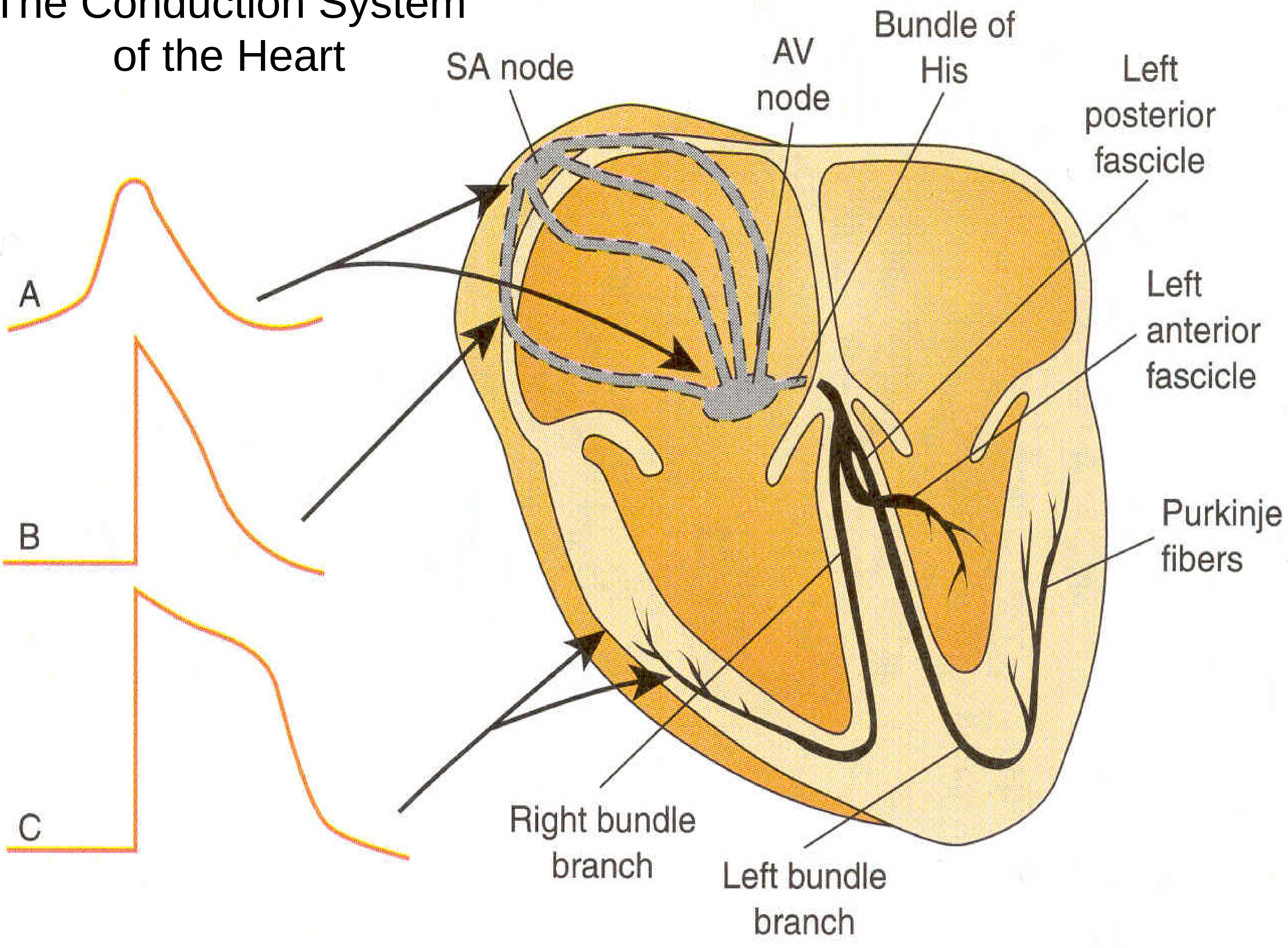
Harald M. Stauss, MD, PhD
The University of Iowa,
Iowa City, IA

Demonstration of the ECG to the Royal Society in London, UK by Augustus Waller's bulldog, Jimmie, in 1909.

Objectives

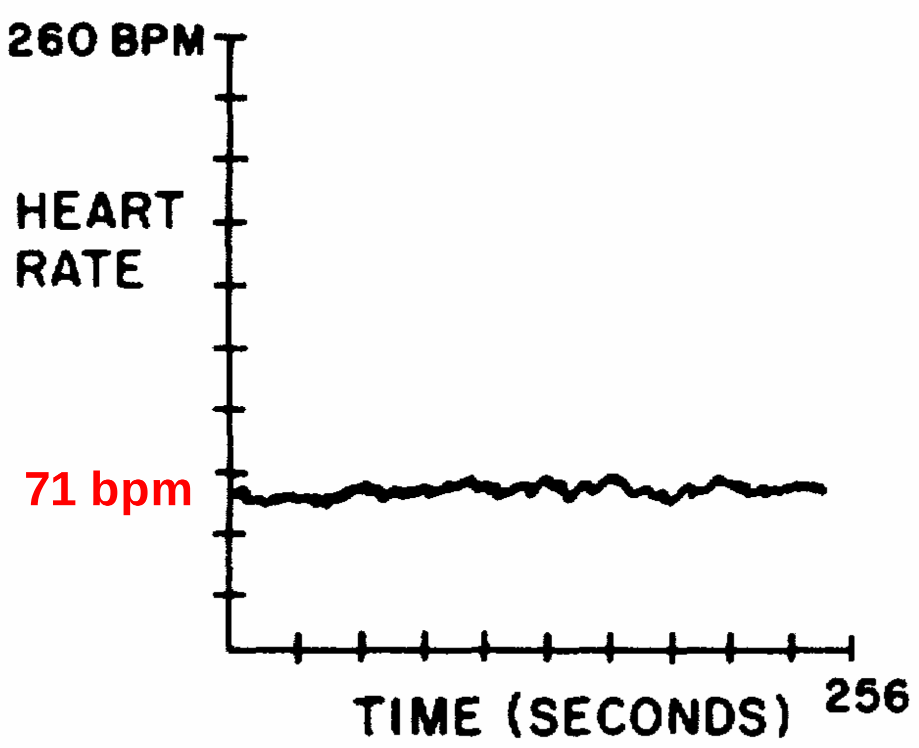
- Effects of sympathetic and parasympathetic innervation on ion currents driving the slow action potentials of the sinus node.
- Physiologic mechanisms for the major periodicities in heart rate variability.
- Importance of the time delays in sympathetic and parasympathetic signal transduction for heart rate variability.
- Heart rate spectral analysis as indicator of cardiac autonomic balance.

The Conduction System of the Heart

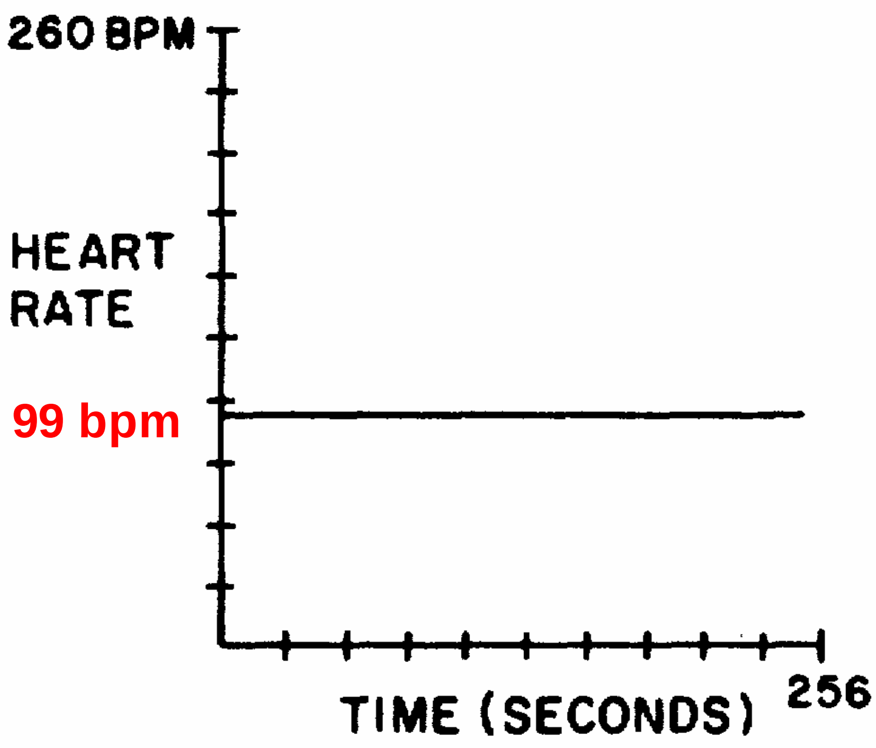


Heart rate is almost constant in denervated hearts and intrinsic heart rate is ~100 bpm

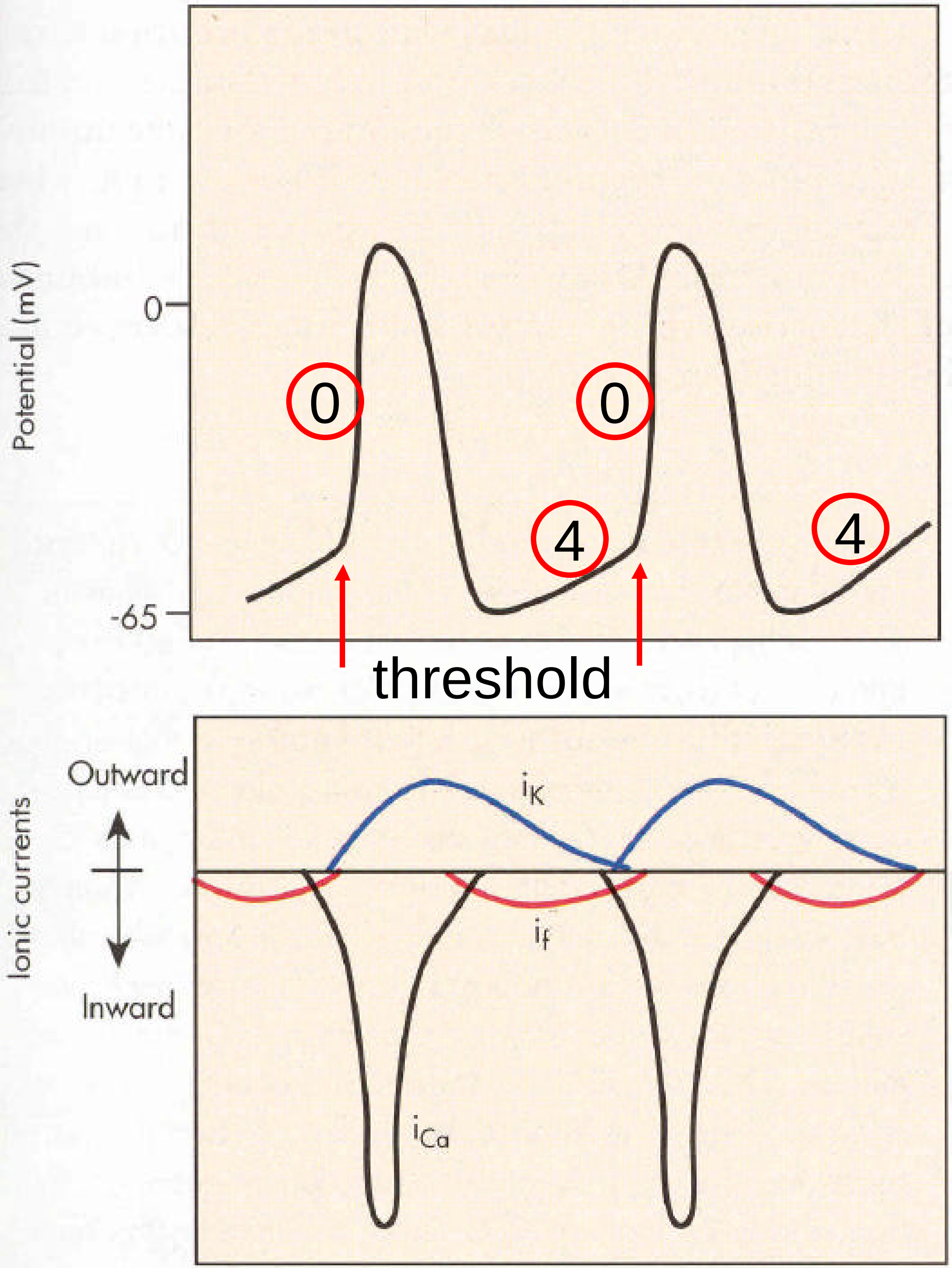
Control Subject



Cardiac Transplant Patient



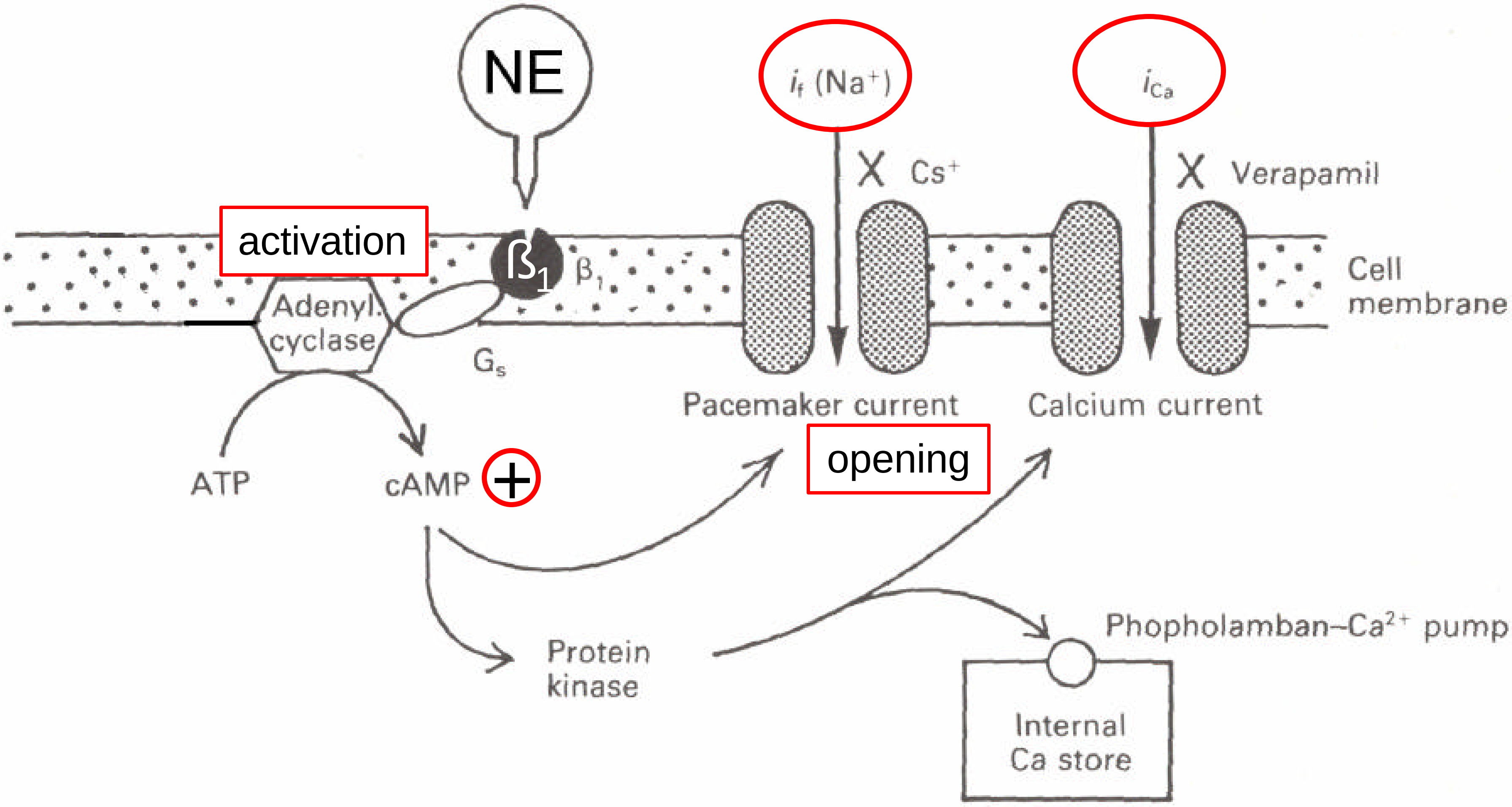
Sands, KEF et al., *Circulation* 79:76-82, 1989



The slow action potential in the sino-atrial node

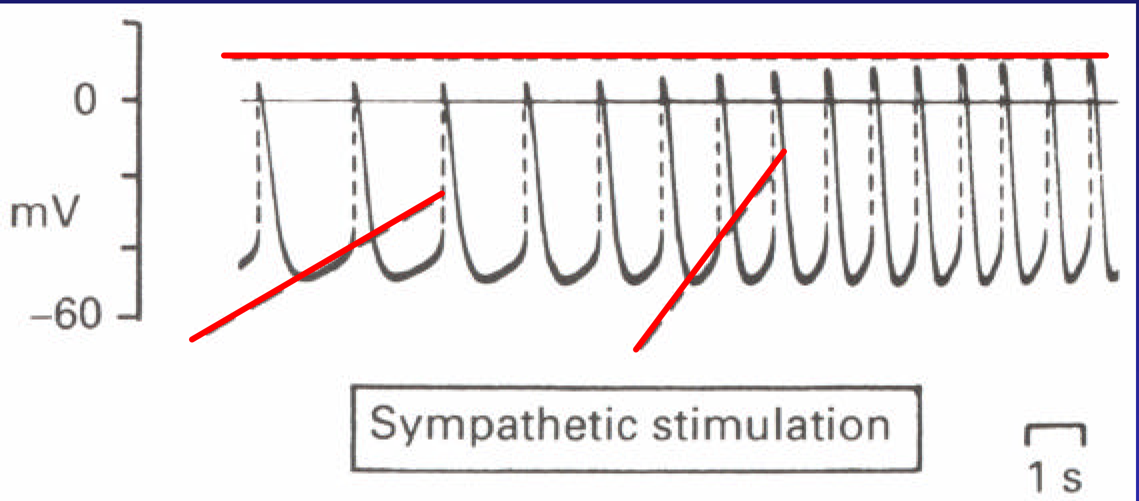
- The slow response action potentials in the SA node, are characterized by a slow, spontaneous rise (depolarization) in the membrane potential during phase 4 of the action potential.
- Once a threshold level is reached, phase 0 of the next action potential is initiated.
- The important currents are I_{Ca}, I_f, and I_K.
  I_{Ca} causes the depolarization,
  I_K causes the repolarization,
  I_f (mainly Na^+) causes the slow depolarization in phase 4.

Sympathetic ß$_1$-adrenergic receptor stimulation increases i_f and i_{Ca}

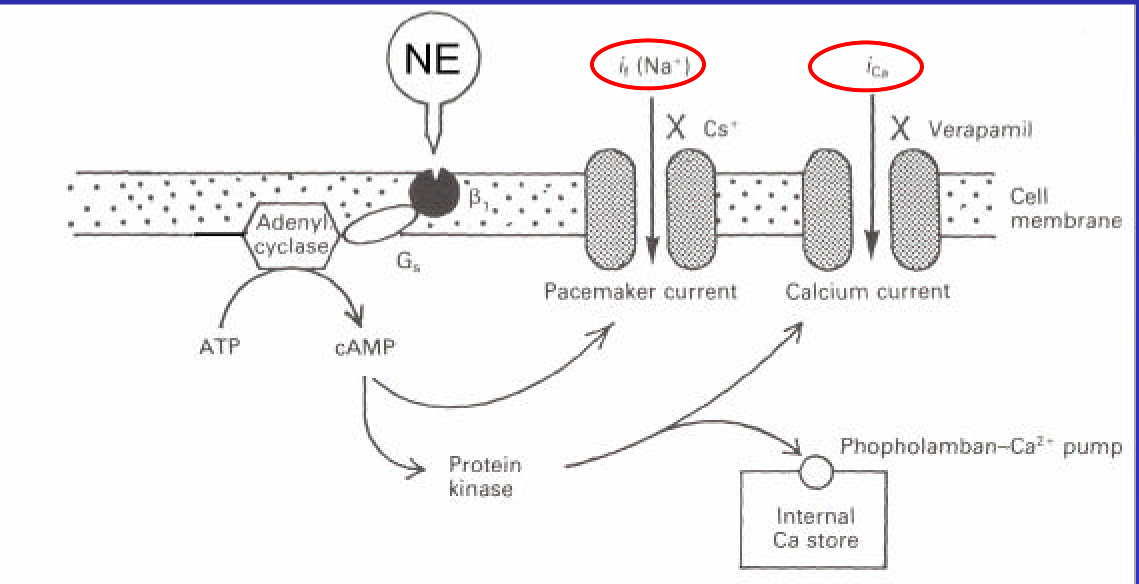


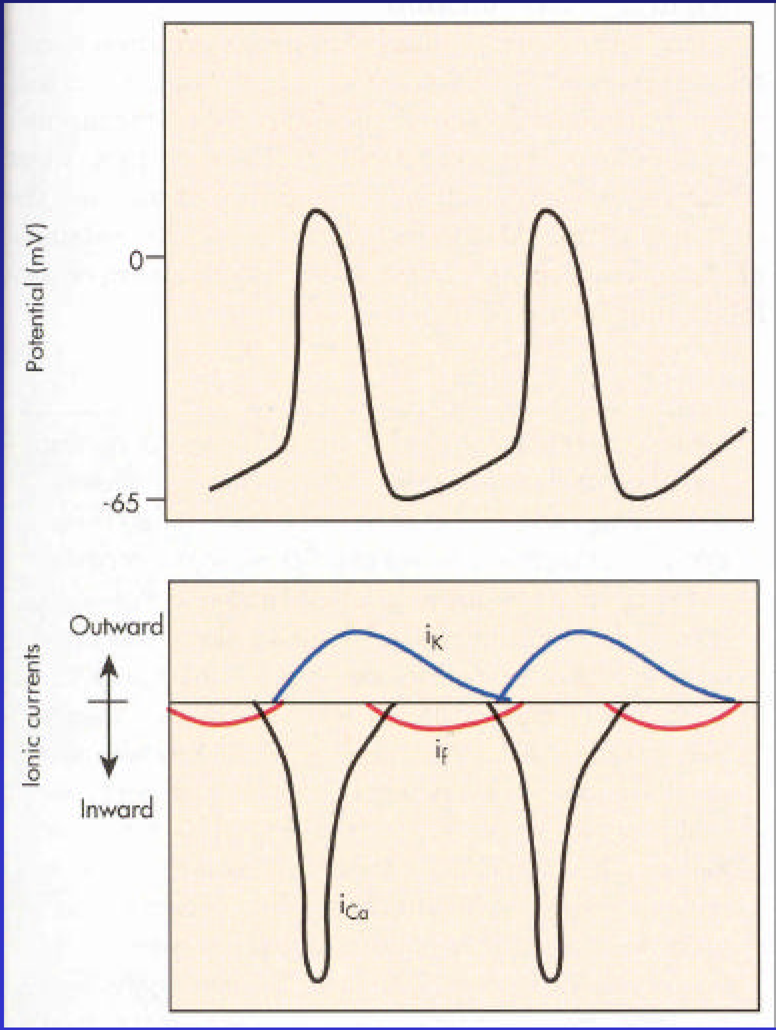
Levick JR, An Introduction to Cardiovascular Physiology, 2nd edition, 1994

Sympathetic activation increases heart rate by increasing i_f

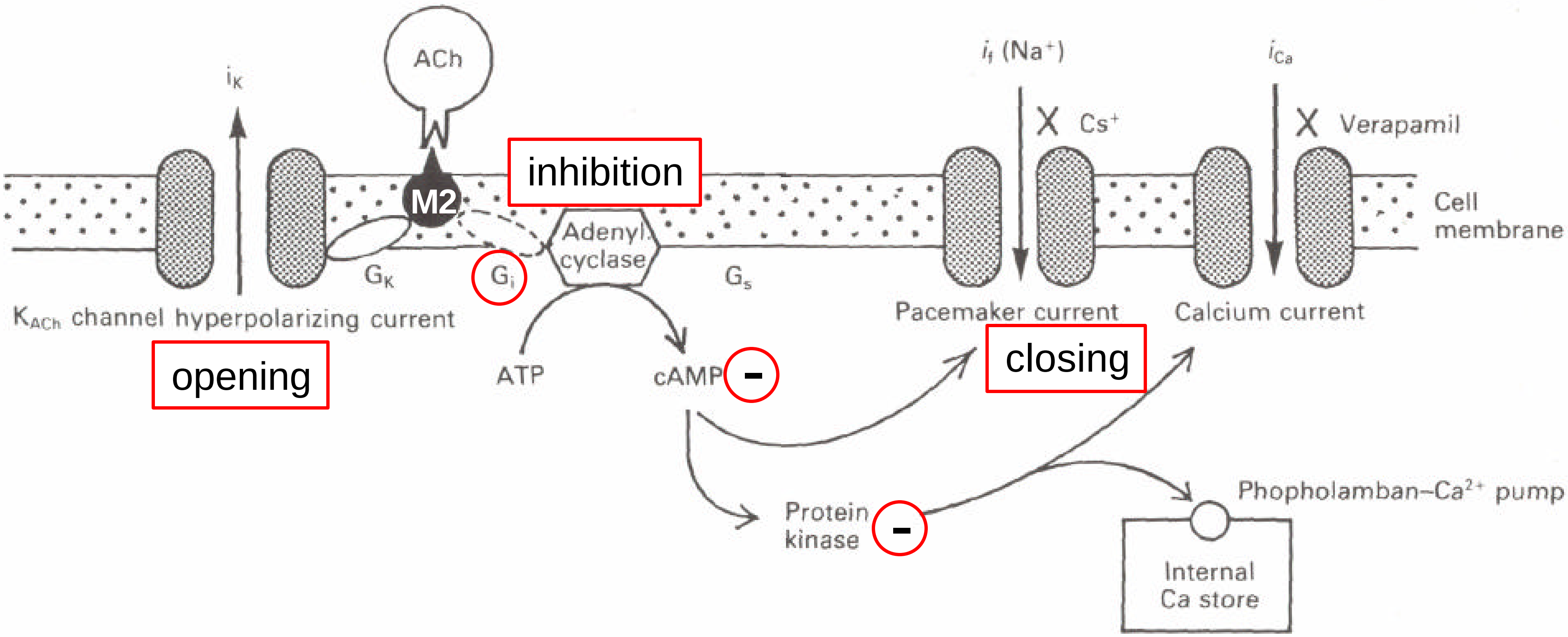


Hutter OF and Trautwein W, *J General Physiol.* 39:715-733, 1956



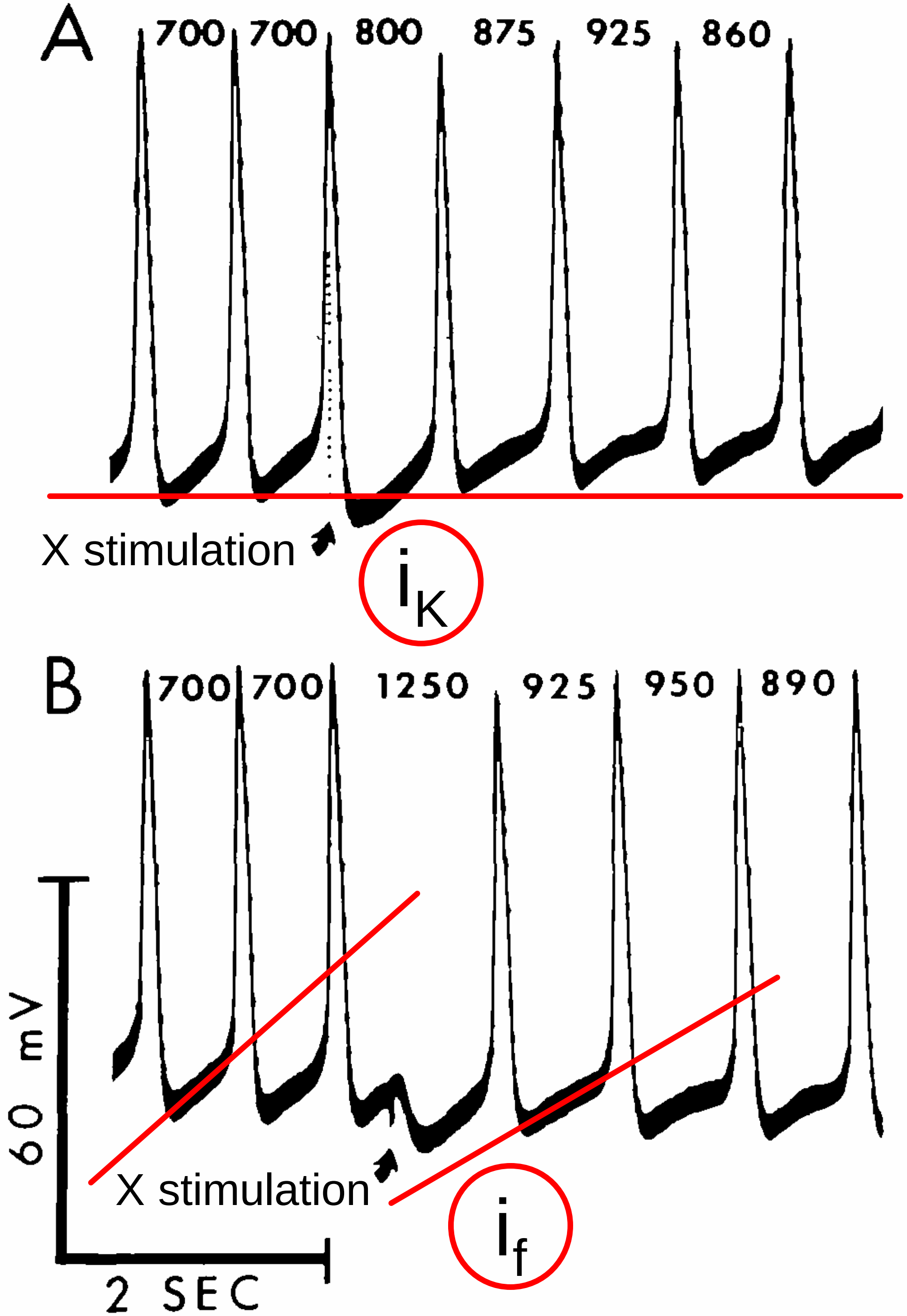


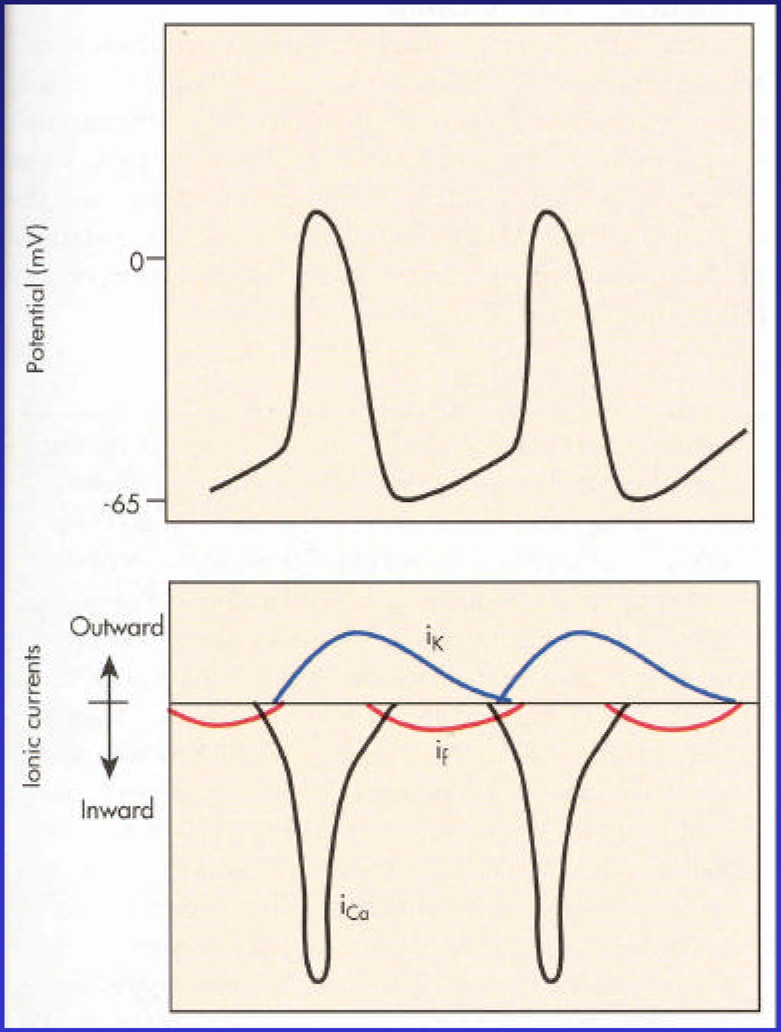
Parasympathetic M2-muscarinic receptor stimulation increases i_K and decreases i_f and i_{Ca}



Levick JR, An Introduction to Cardiovascular Physiology, 2nd edition, 1994

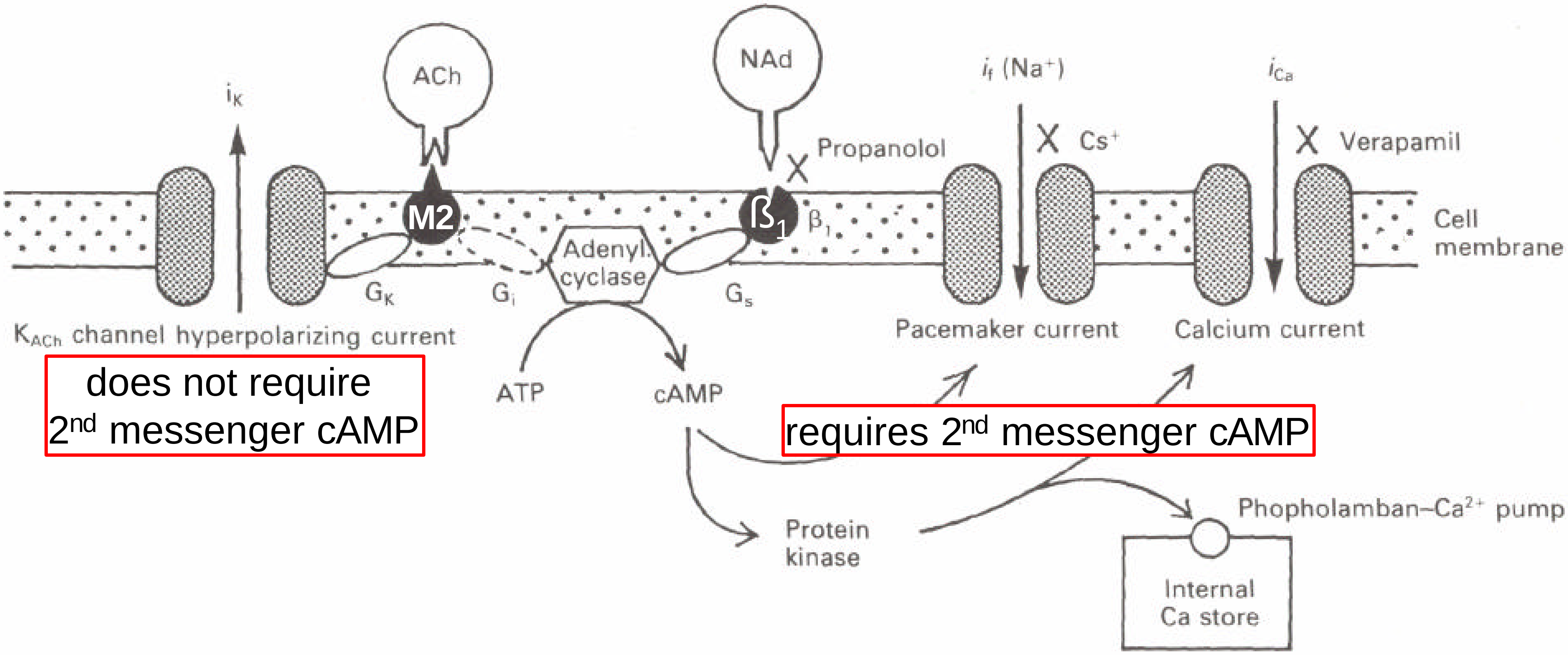
Parasympathetic activation reduces heart rate by increasing i_K and decreasing i_f





Jalife J and Moe GK, *Circ. Res.* 45:595-608, 1979

Summary: Autonomic Control of Heart Rate



Levick JR, An Introduction to Cardiovascular Physiology, 2nd edition, 1994

Physiological Origin of Heart Rate Variability

- Day-night periodicity
- Respiratory sinus arrhythmia
- 10s rhythm and slower fluctuations

Physiological Origin of Heart Rate Variability

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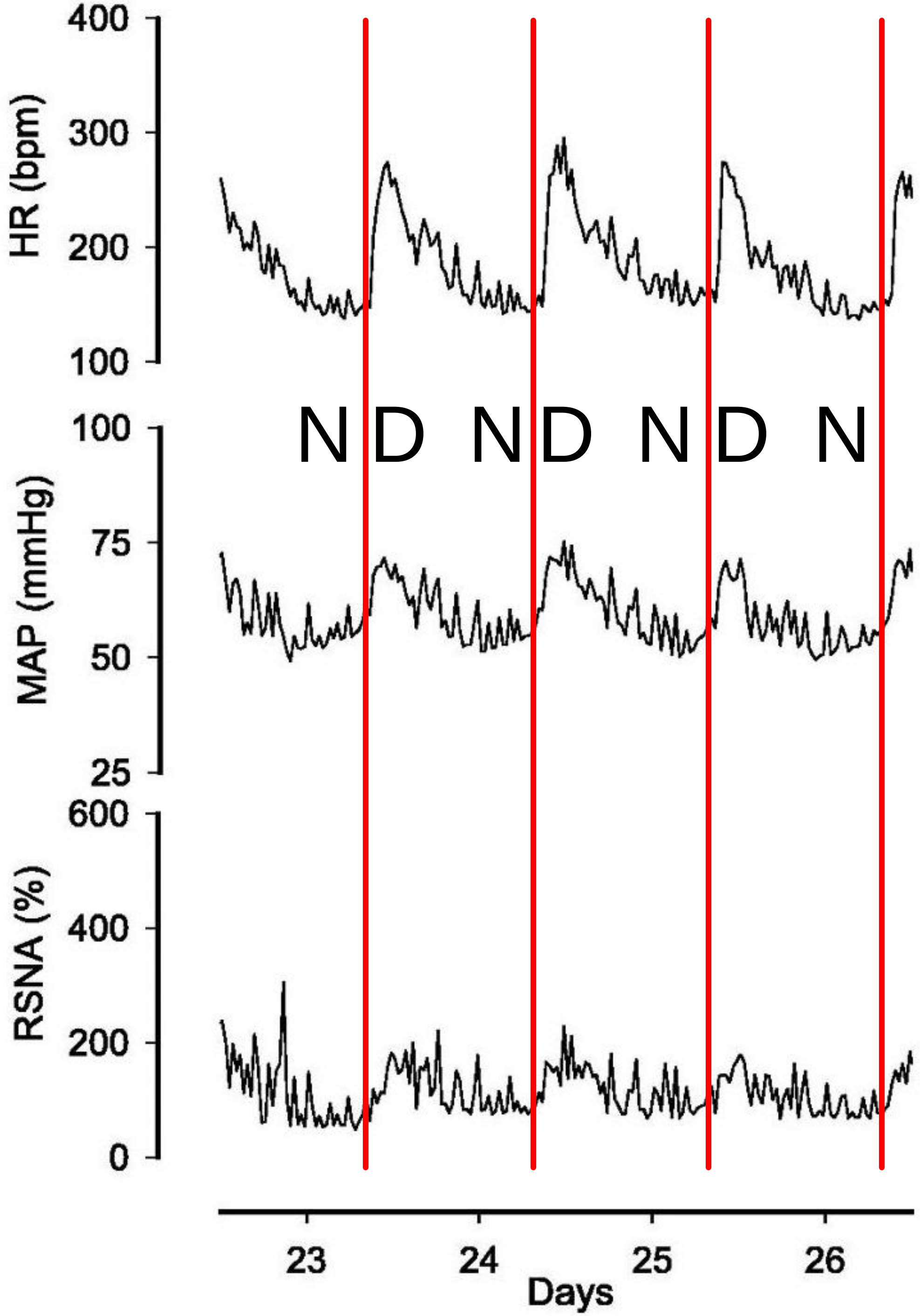


Day-night Periodicity

- Heart rate, mean blood pressure, and renal sympathetic nerve activity recorded 3 weeks after implantation of catheters and electrodes in a conscious rabbit.
- Note the strong day-night periodicity in heart rate and mean blood pressure that are accompanied by similar oscillations in sympathetic nerve activity.

Malpas SC, *Am J Physiol Regul Integr Comp Physiol* 286: R1-R12, 2004

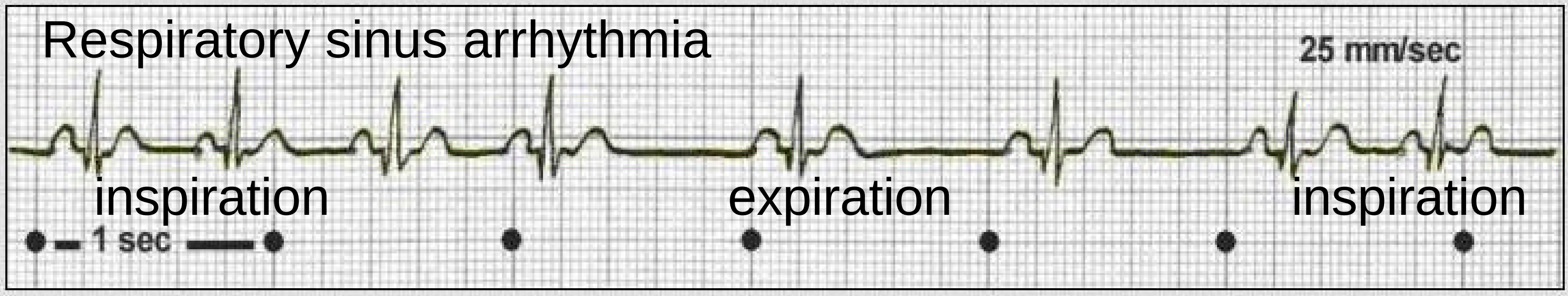
Day-night Periodicity

- Day-night periodicity of heart rate is related to circadian changes in autonomic nerve activity.

Physiological Origin of Heart Rate Variability

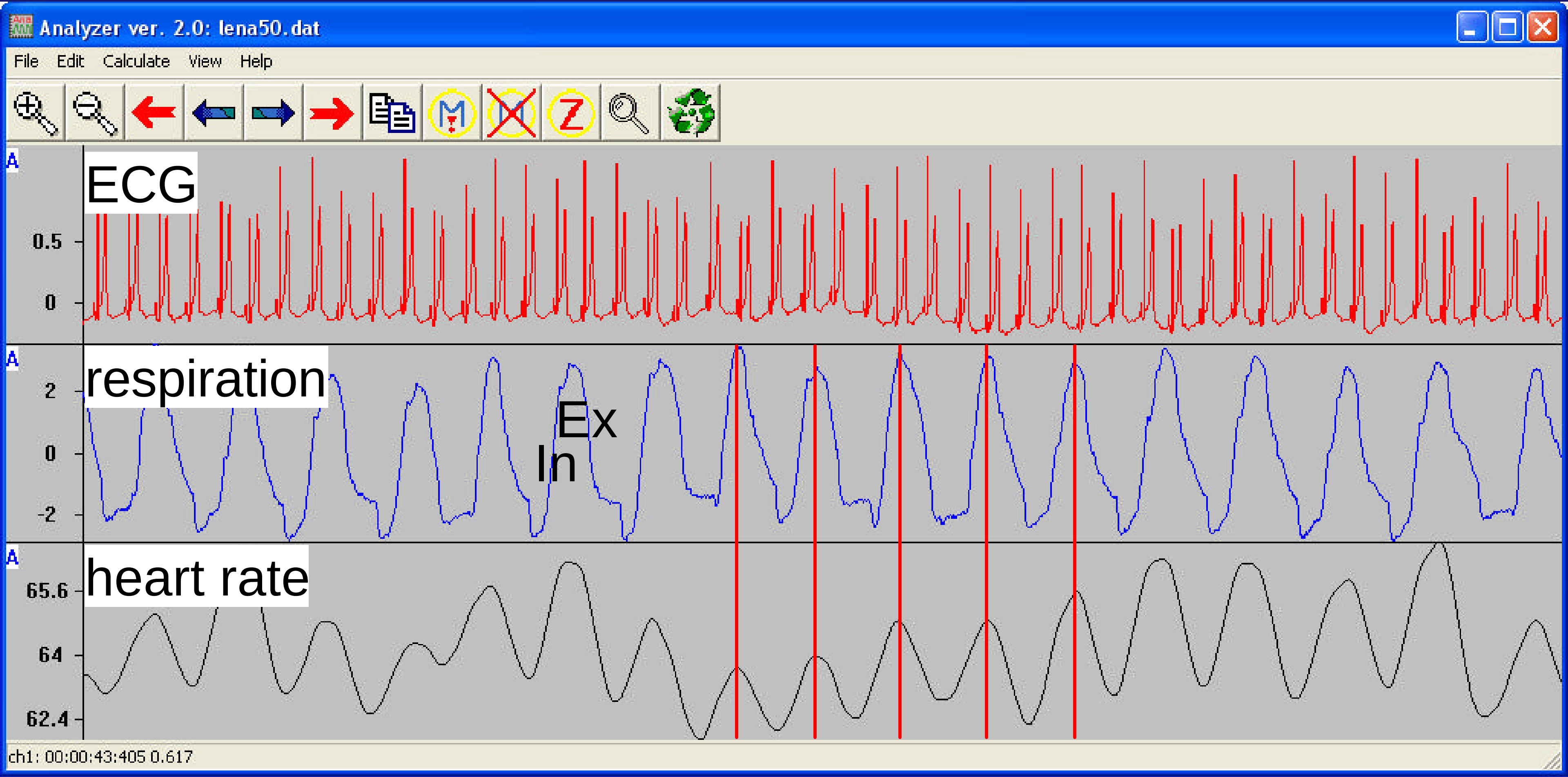
- Day-night periodicity
- Respiratory sinus arrhythmia
- 10s rhythm and slower fluctuations

Respiratory Sinus Arrhythmia



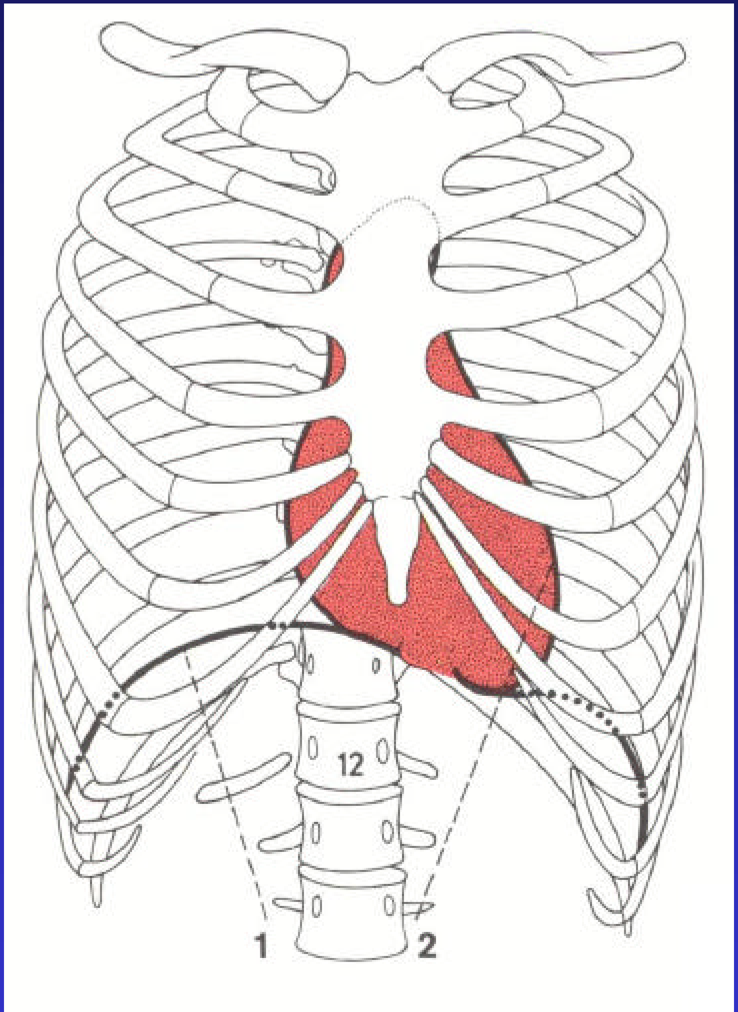
- Tachycardia during inspiration
- Bradycardia during expiration.

Respiratory Sinus Arrhythmia



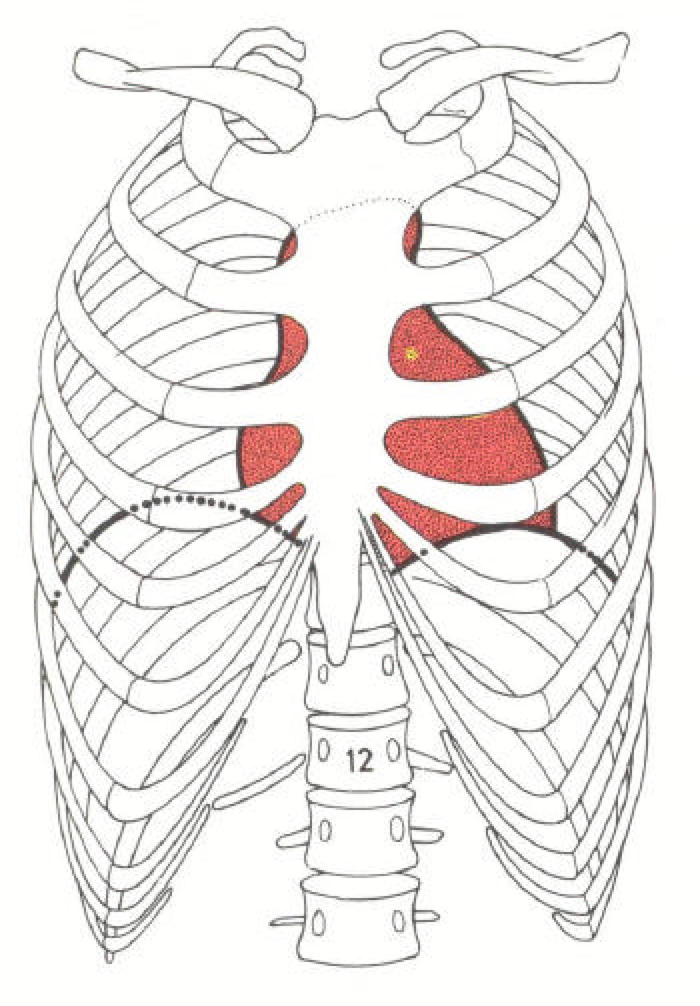
Young female subject with strong respiratory sinus arrhythmia

Inspiration



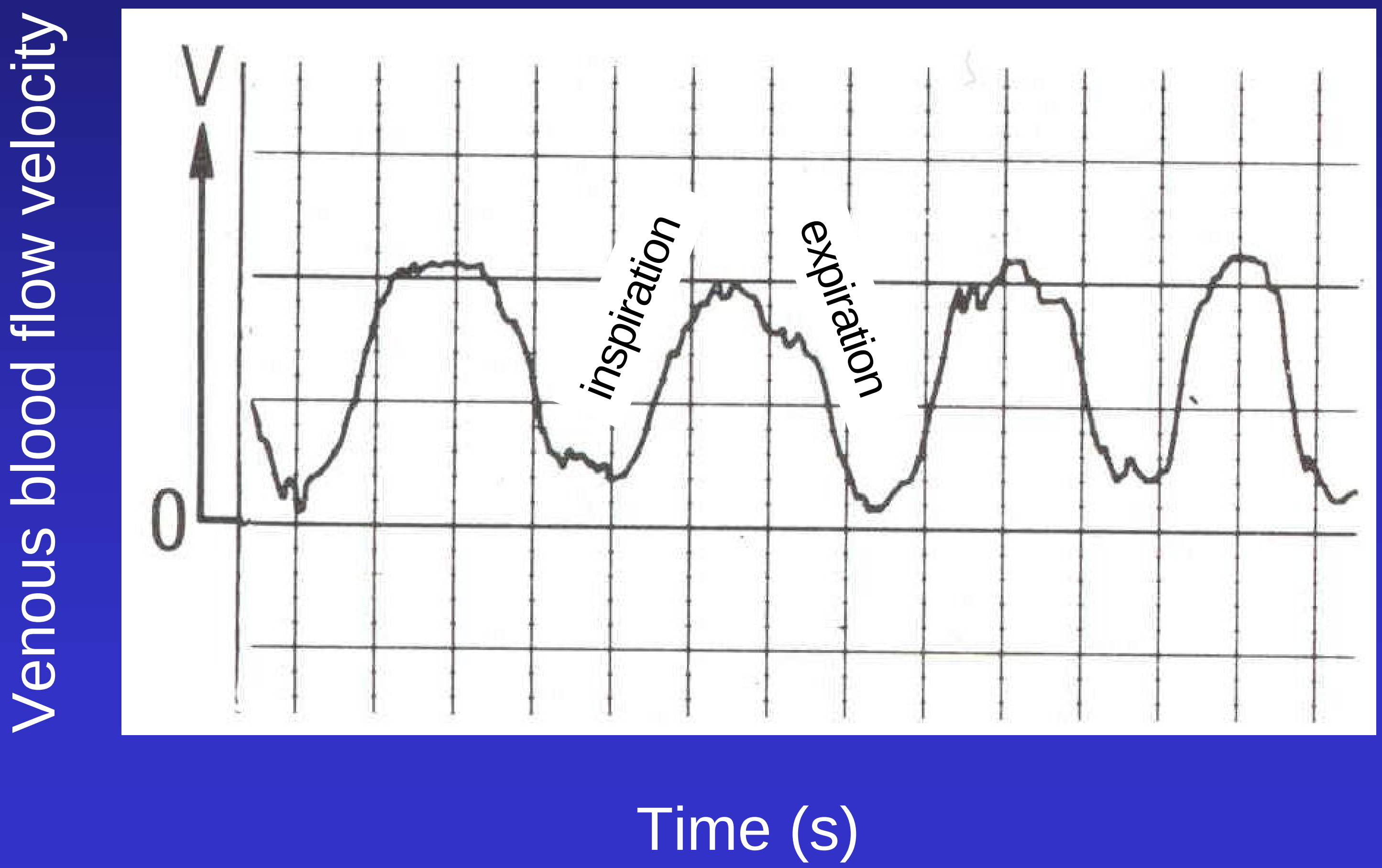
- P_{thorax} ⇩
- Venous return ⇧

Expiration

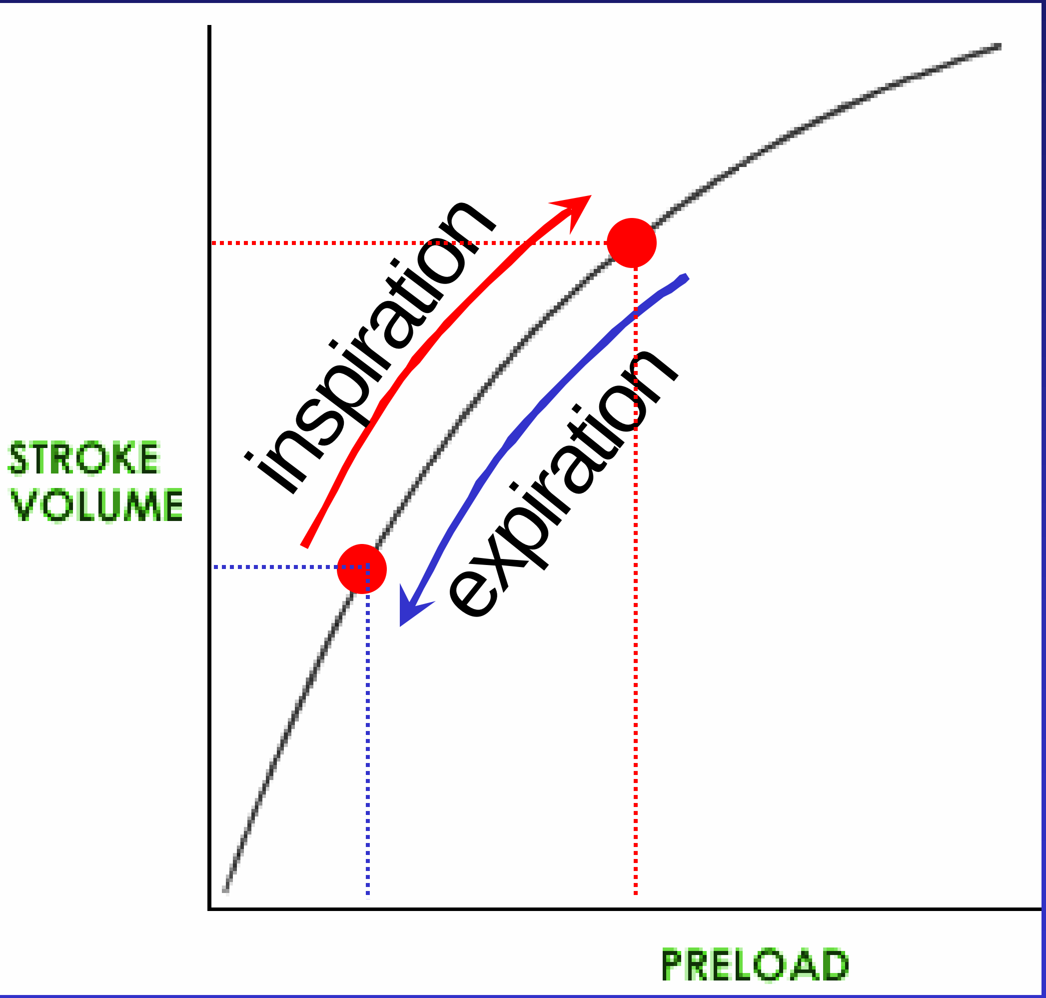


- P_{thorax} ⇧
- Venous return ⇩

Venous return to the heart: respiratory pump (alternating changes in intrathoracic and abdominal pressure)

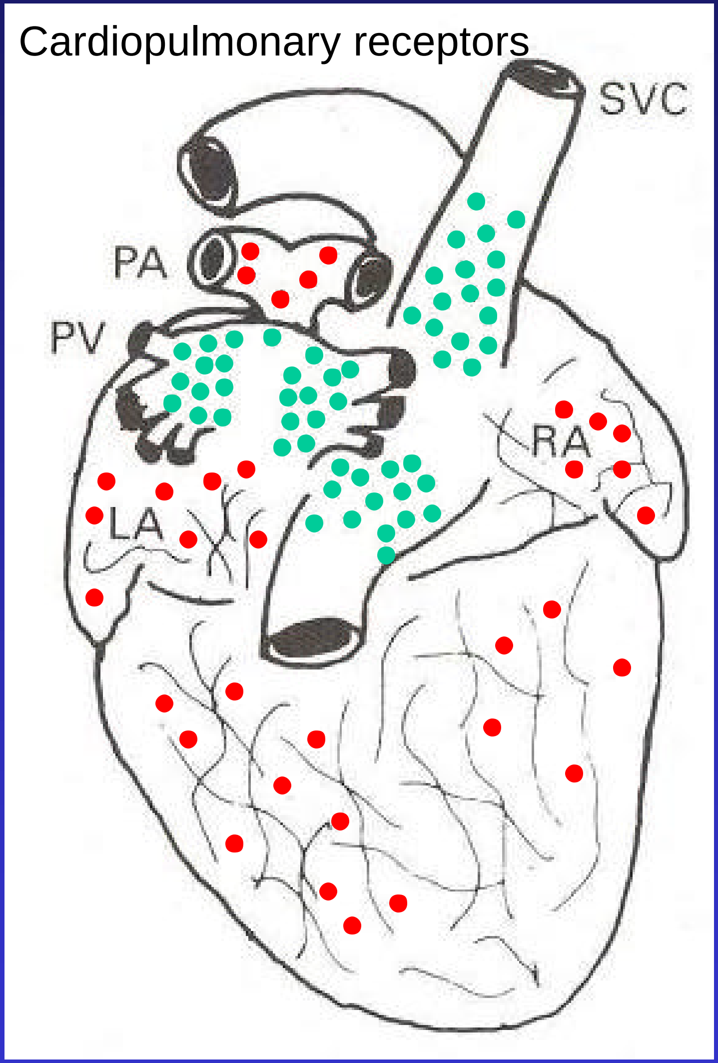


Frank-Starling Mechanism

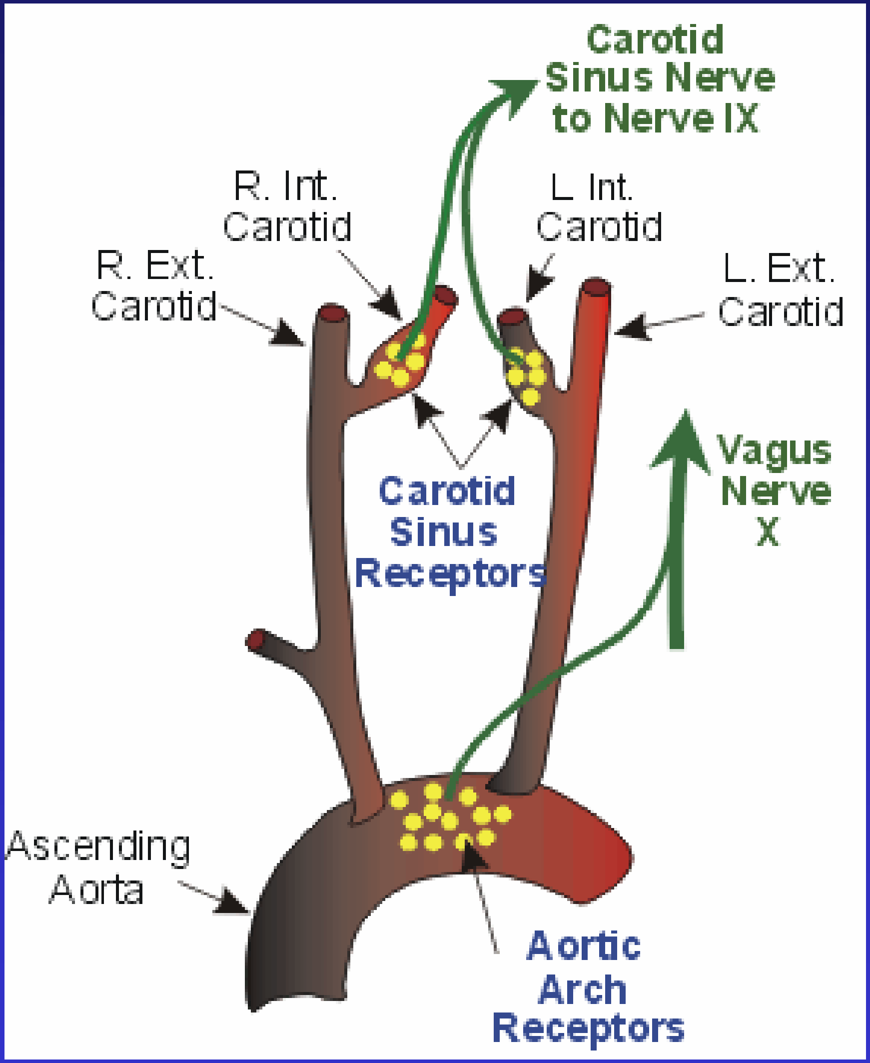


- During inspiration, greater venous return to the heart (preload) causes an increase in stroke volume (SV).
- During expiration, reduced venous return to the heart causes a decline in SV.
- According to:
  BP = SV * HR * TPR
  blood pressure will fluctuate with respiration.

Cardiopulmonary and baroreceptors detect respiratory changes in cardiac filling and arterial pressure

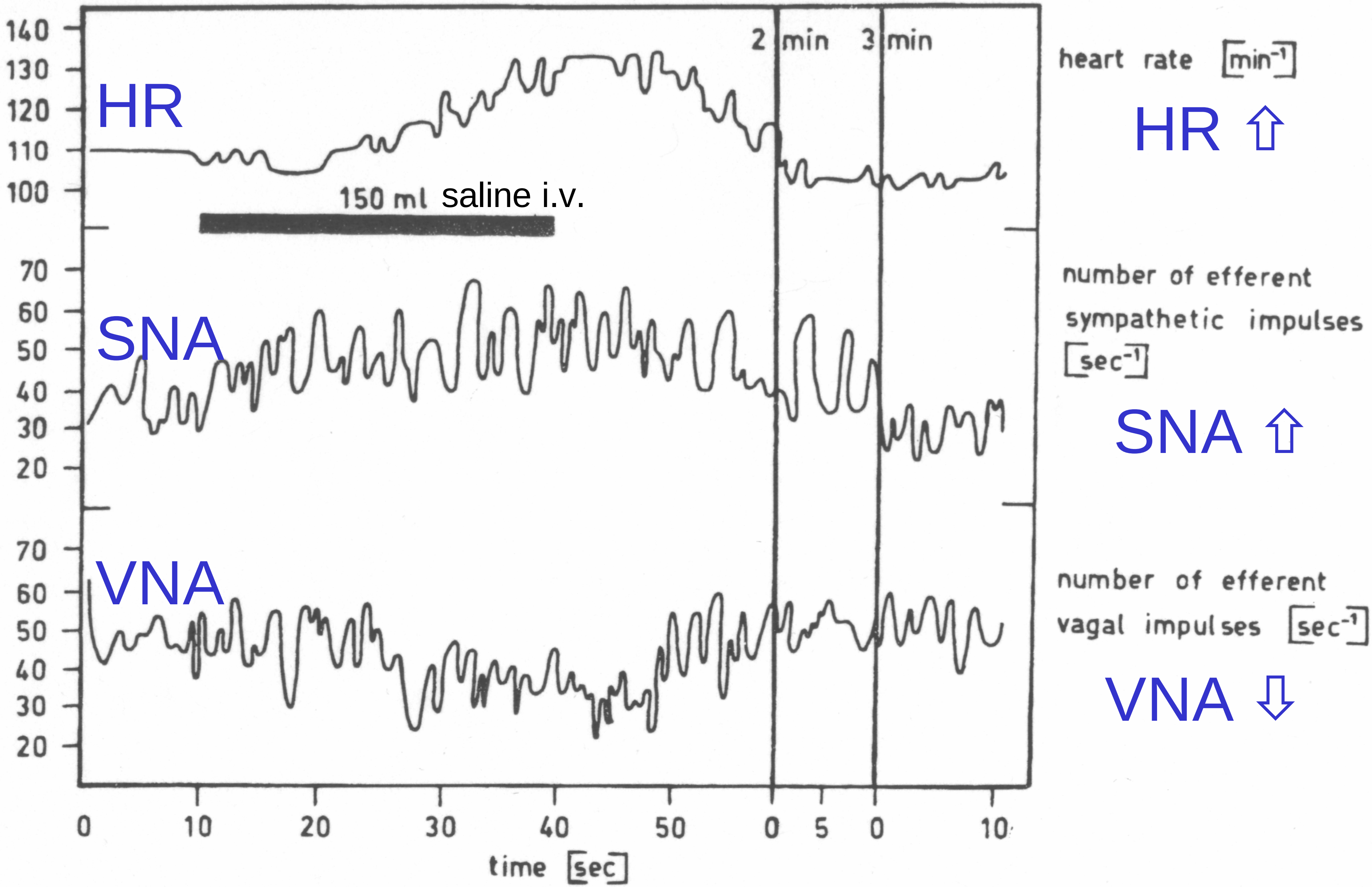


Cardiopulmonary receptors



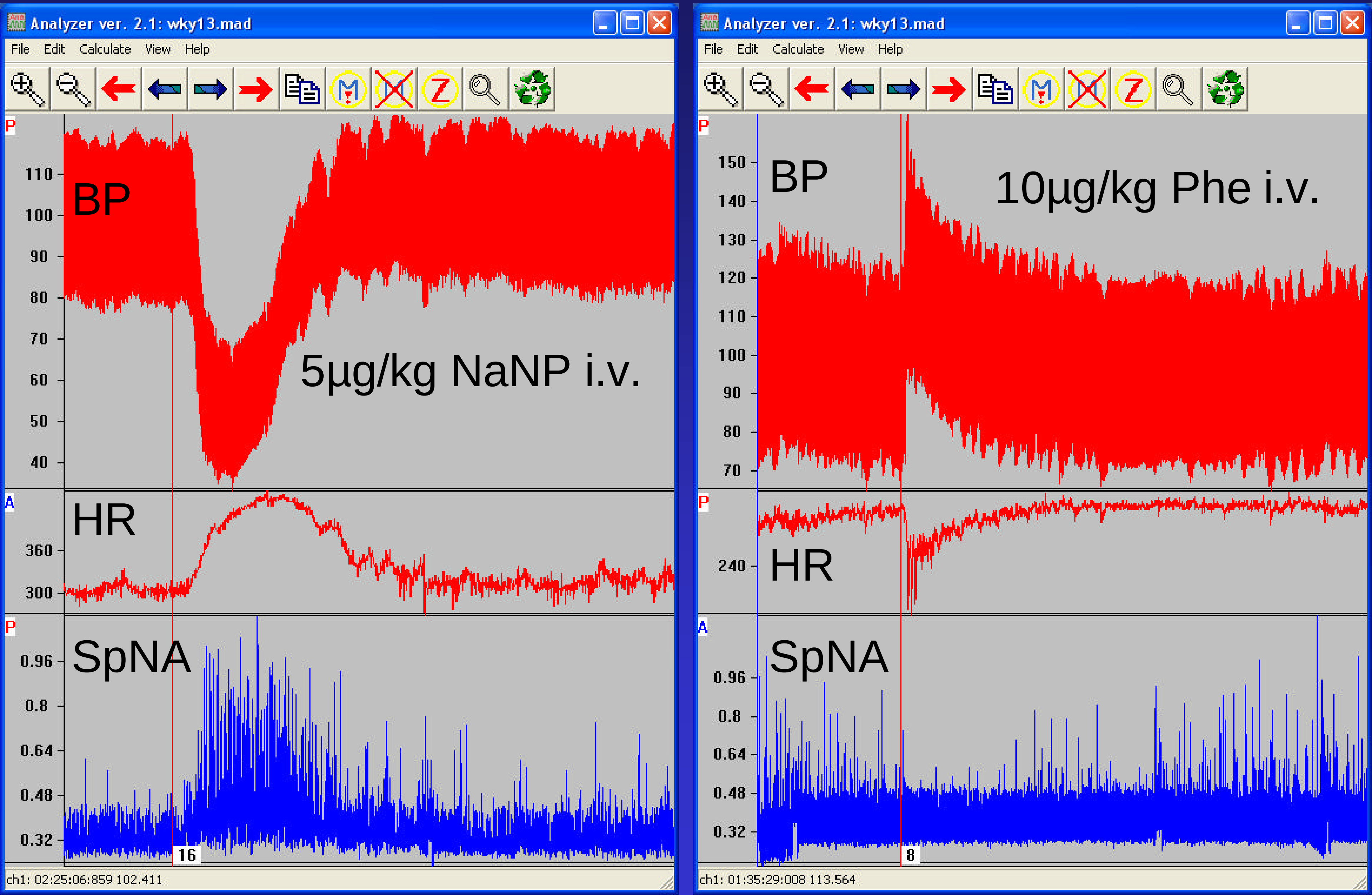
Baroreceptors

Bainbridge reflex in anesthetized dogs



Hakumäki MOK, Acta Physiol. Scand. 85:415-417, 1972

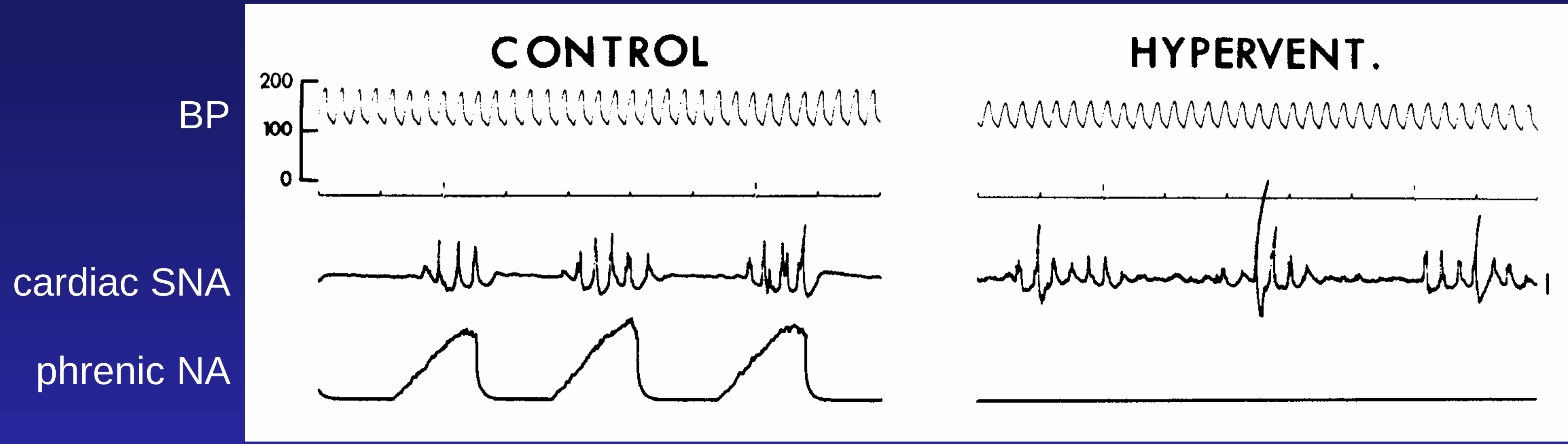
Baroreflex responses to Na-NP and Phe



Modulation of respiratory sinus arrhythmia by the Bainbridge and baroreceptor reflexes

- Respiratory sinus arrhythmia is characterized by a tachycardia during inspiration and a bradycardia during expiration.
- Increased cardiac filling during inspiration elicits a tachycardia via the Bainbridge reflex that promotes respiratory sinus arrhythmia.
- Increased cardiac filling during inspiration elicits an increase in stroke volume (Frank-Starling mechanism) and blood pressure. This activates the baroreflex that opposes the tachycardia caused by the Bainbridge reflex. Thus, the baroreceptor reflex limits respiratory sinus arrhythmia.
- The intensity (amplitude) of respiratory sinus arrhythmia can be seen as the balance of the Bainbridge reflex and the baroreceptor reflex.

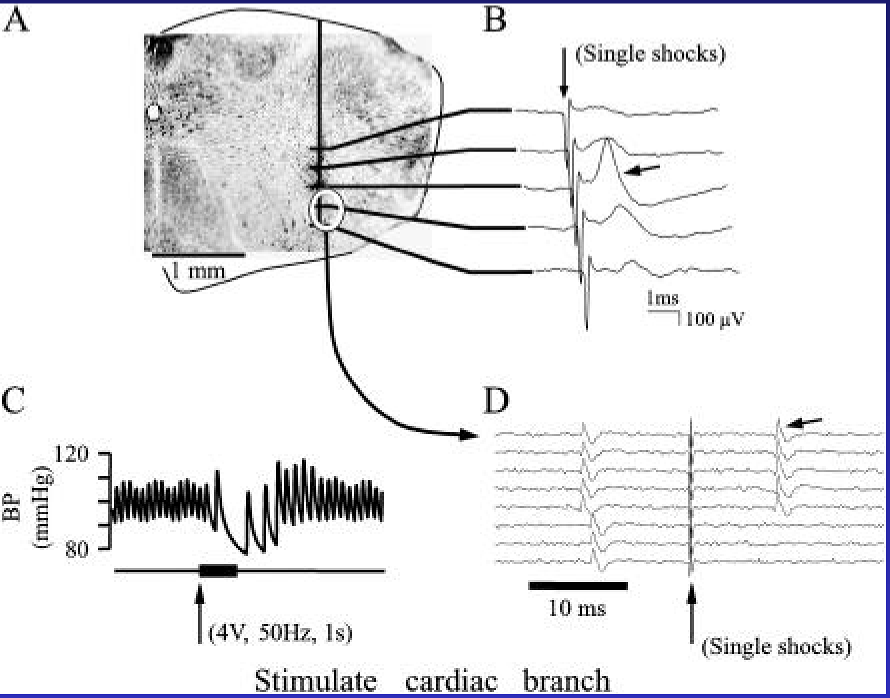
Central respiratory and sympathetic oscillators

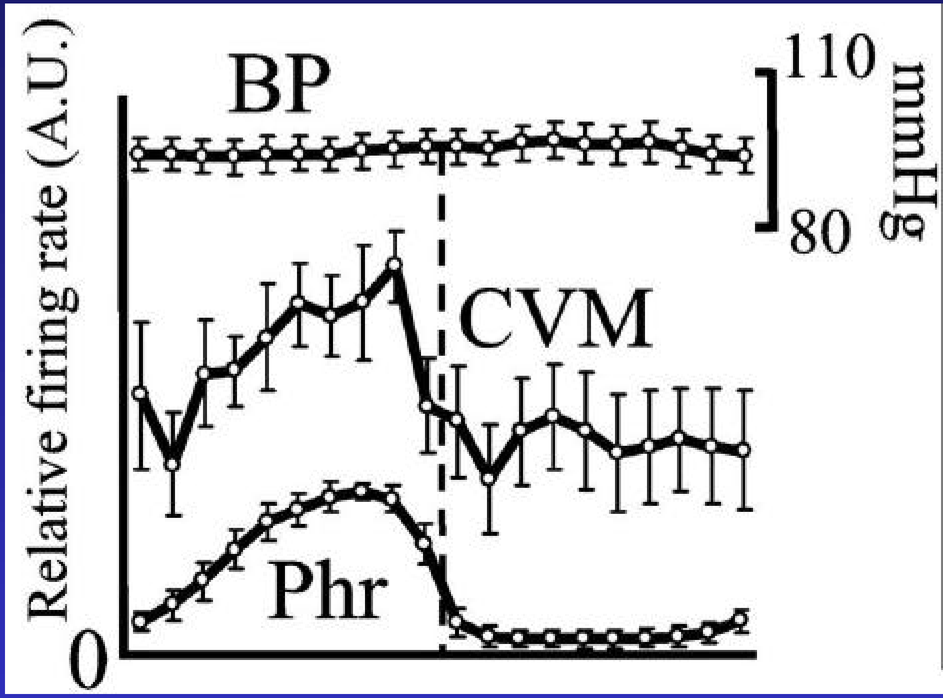


- Anesthetized, paralyzed, vagotomized, and ventilated cats.
- Pneumothoracotomy to prevent BP variability caused by changes in intrathoracic pressure.
- Hyperventilation (right) silenced the central respiratory oscillator (phrenic nerve activity lost) but not the central sympathetic oscillator (oscillations in cardiac SNA maintained).
- Independent respiratory and sympathetic oscillators are normally entrained by peripheral inputs (cardiopulmonary receptors, baroreceptors etc.) to operate at the same frequency.

Barman SM and Gebber GL, Am J Physiol 231:1601-1607, 1976

Cardiac vagal motoneurons (N. ambiguus) are coupled to the respiratory oscillator





- Placement of recording electrodes in CVM in the N. ambiguus.
- Location verified by stimulation of peripheral vagal nerve fibers.

- Firing rate of CVM follows firing rate of the phrenic nerve.
- This respiratory rhythm persists even if the ventilator is switched off.

Rentero N et al., Am J Physiol 283:R1327-R1334, 2002

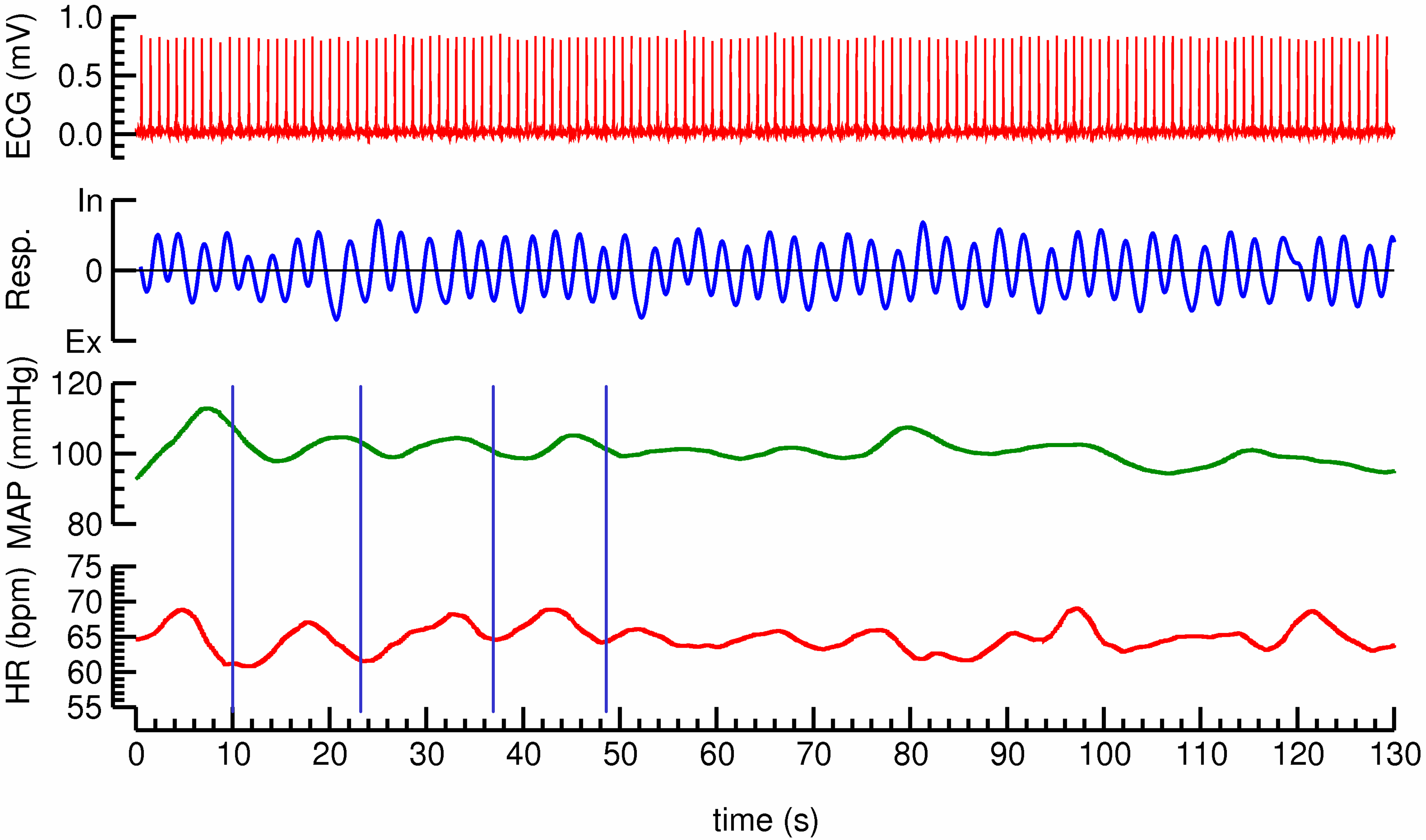
Respiratory Sinus Arrhythmia

- The exact mechanisms causing respiratory sinus arrhythmia are not fully understood.
- Some studies suggest the existence of independent respiratory and autonomic (sympathetic and parasympathetic) oscillators in the brainstem.
- The central respiratory oscillator is linked to sympathetic and parasympathetic centers in the brainstem.
- The Bainbridge reflex and the baroreceptor-heart rate reflex normally entrain cardiac autonomic nerve activity to the rhythm of the central respiratory oscillator.

Physiological Origin of Heart Rate Variability

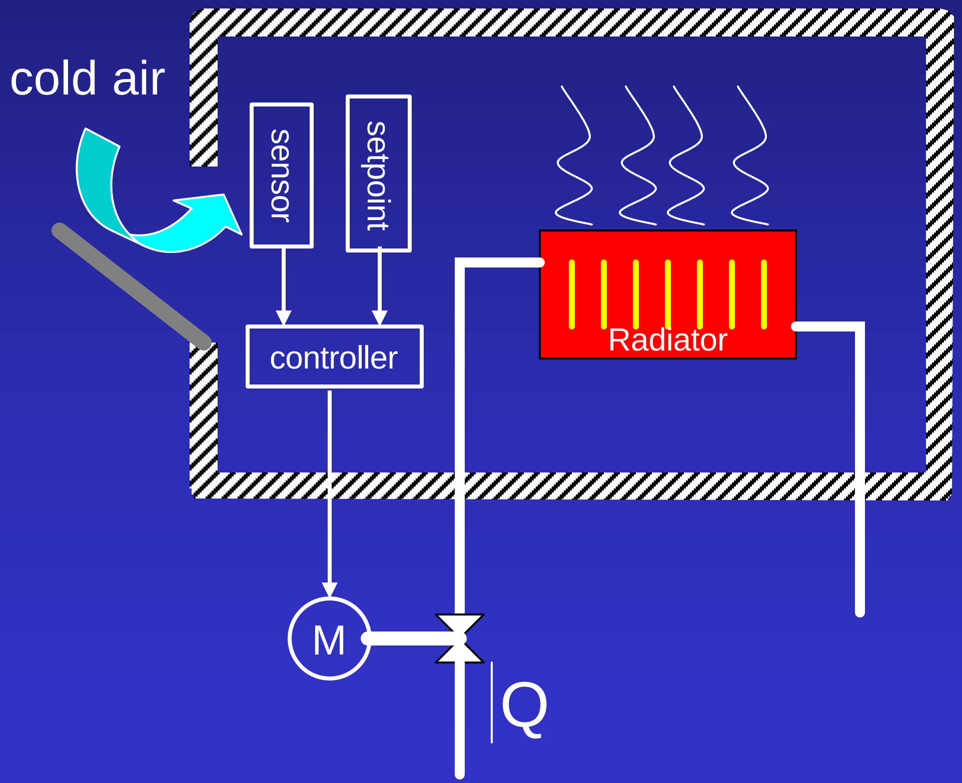
- Day-night periodicity
- Respiratory sinus arrhythmia
- 10s rhythm and slower fluctuations

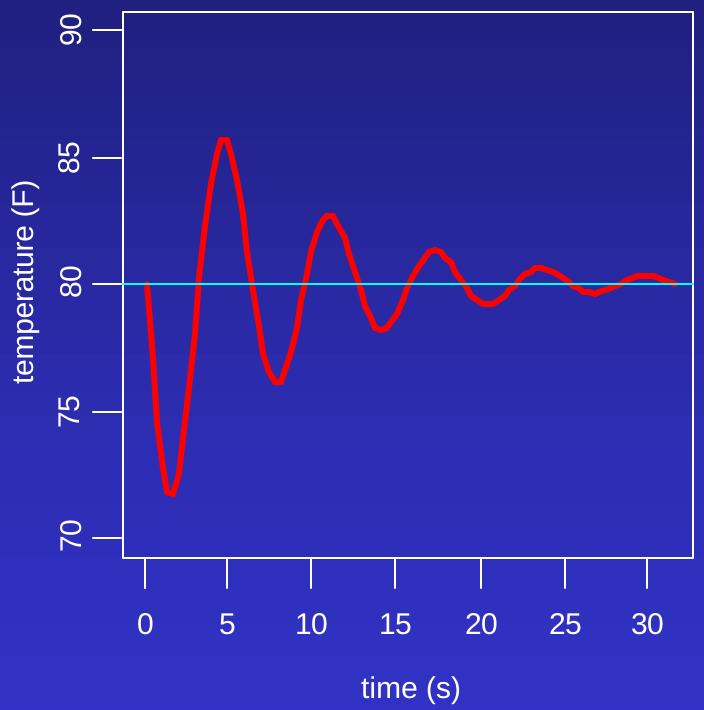
10s oscillation in heart rate



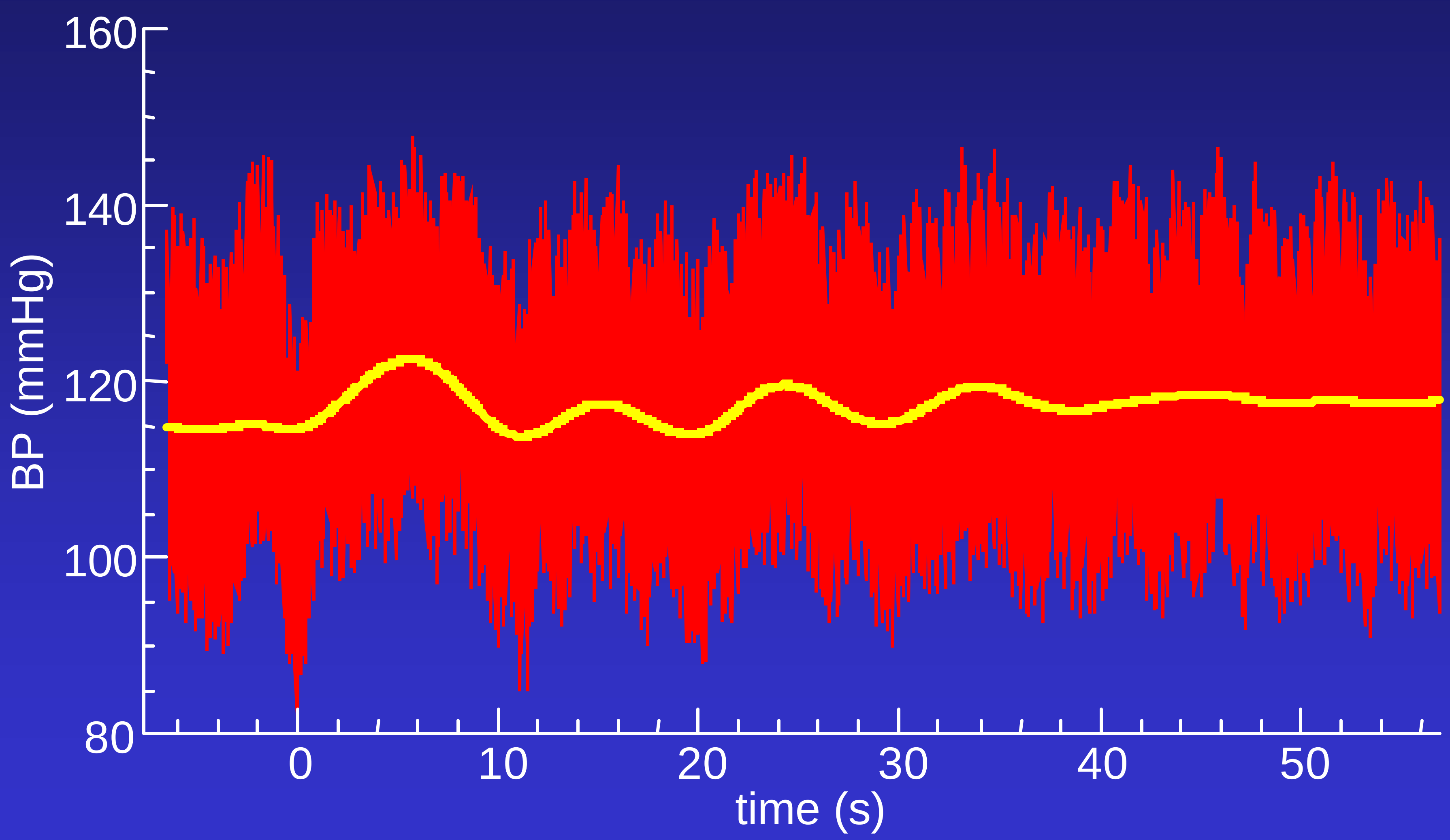
Spontaneous HR fluctuations with a period duration of ~10s.

Negative feedback systems have an intrinsic tendency to oscillate

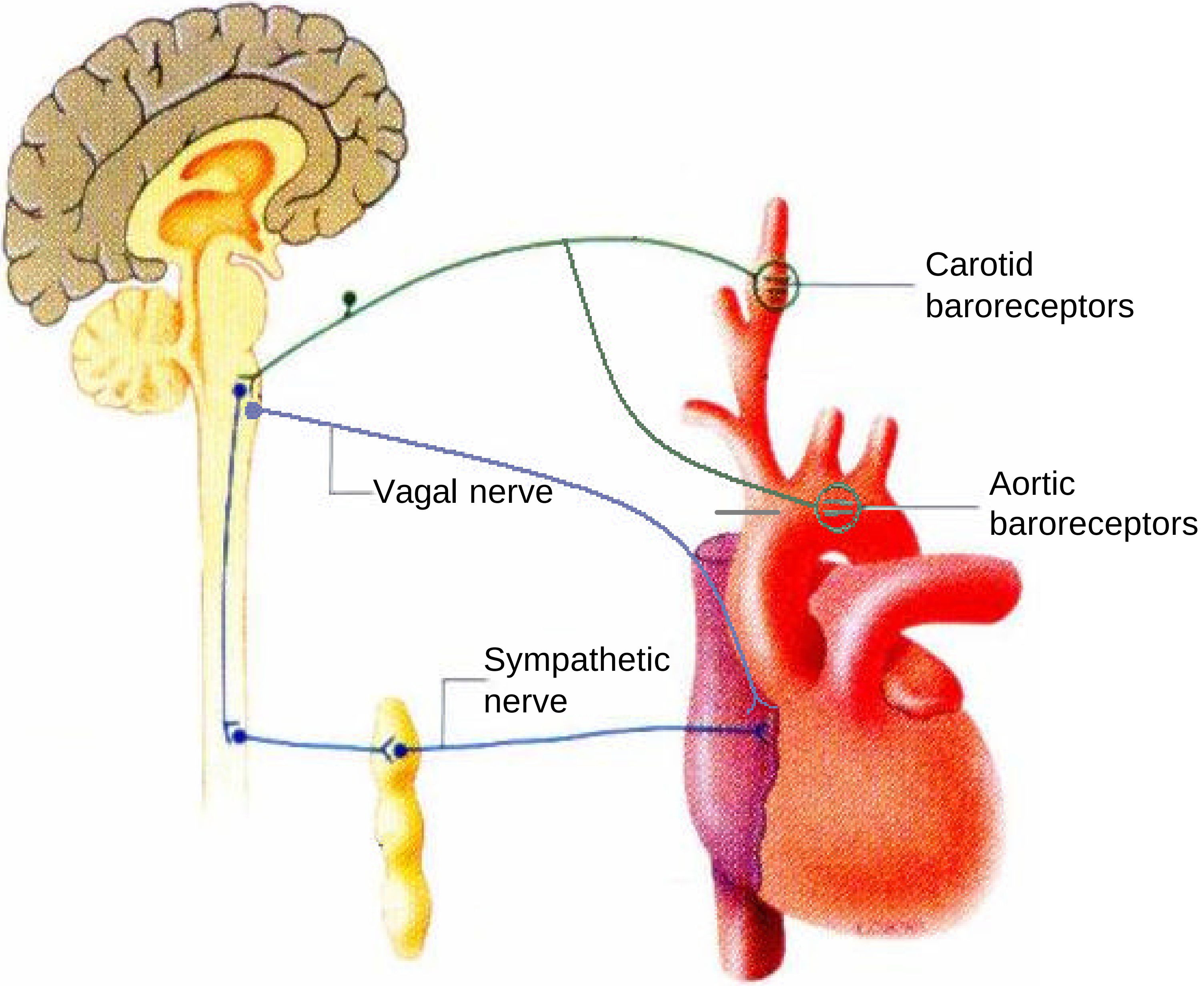




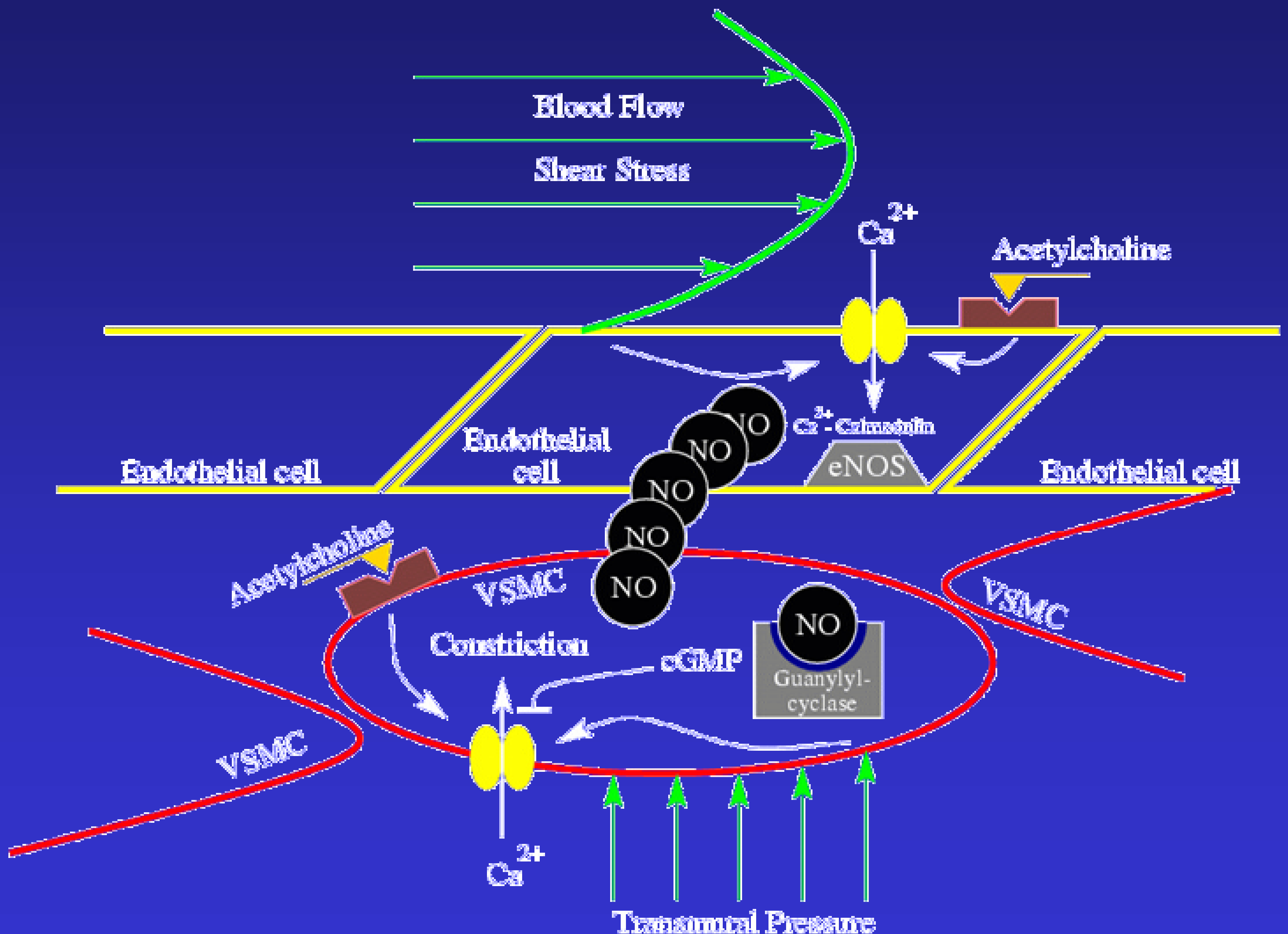
Feedback Oscillations in Arterial Blood Pressure



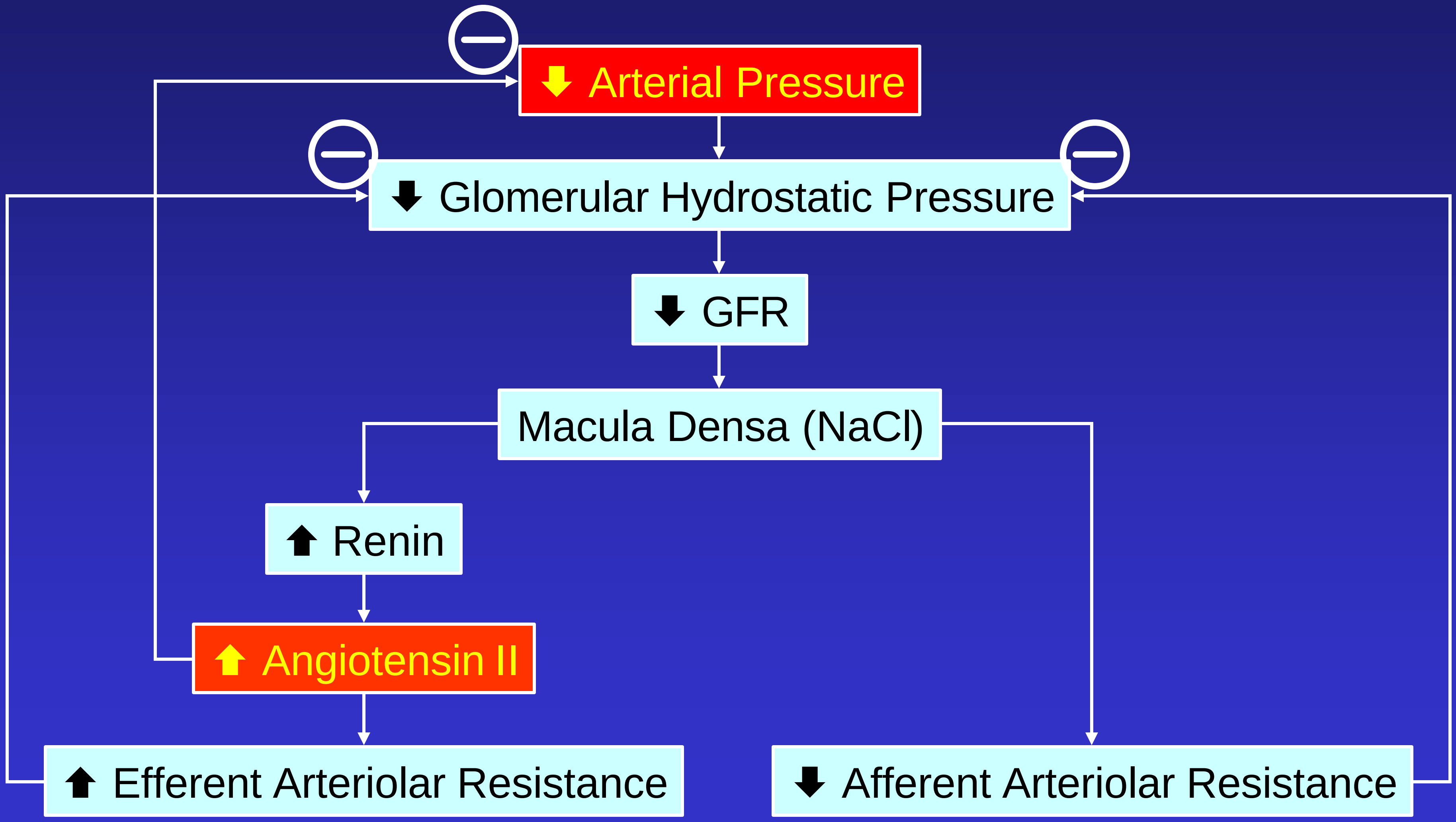
BP control by the baroreceptor reflex



Blood pressure control by the local endothelial NO system



Blood pressure control by the renin-angiotensin system

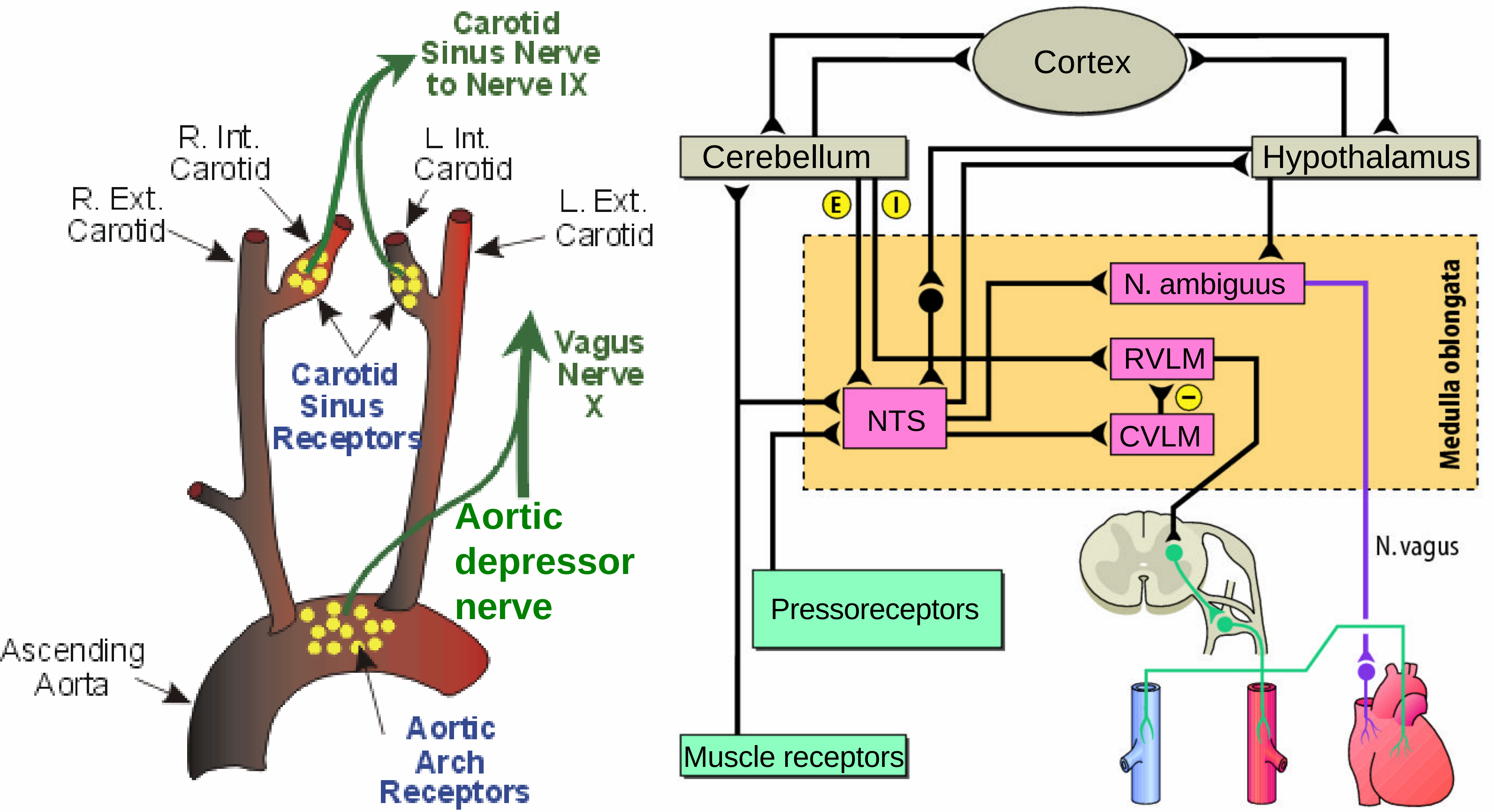


Time Delays in BP control

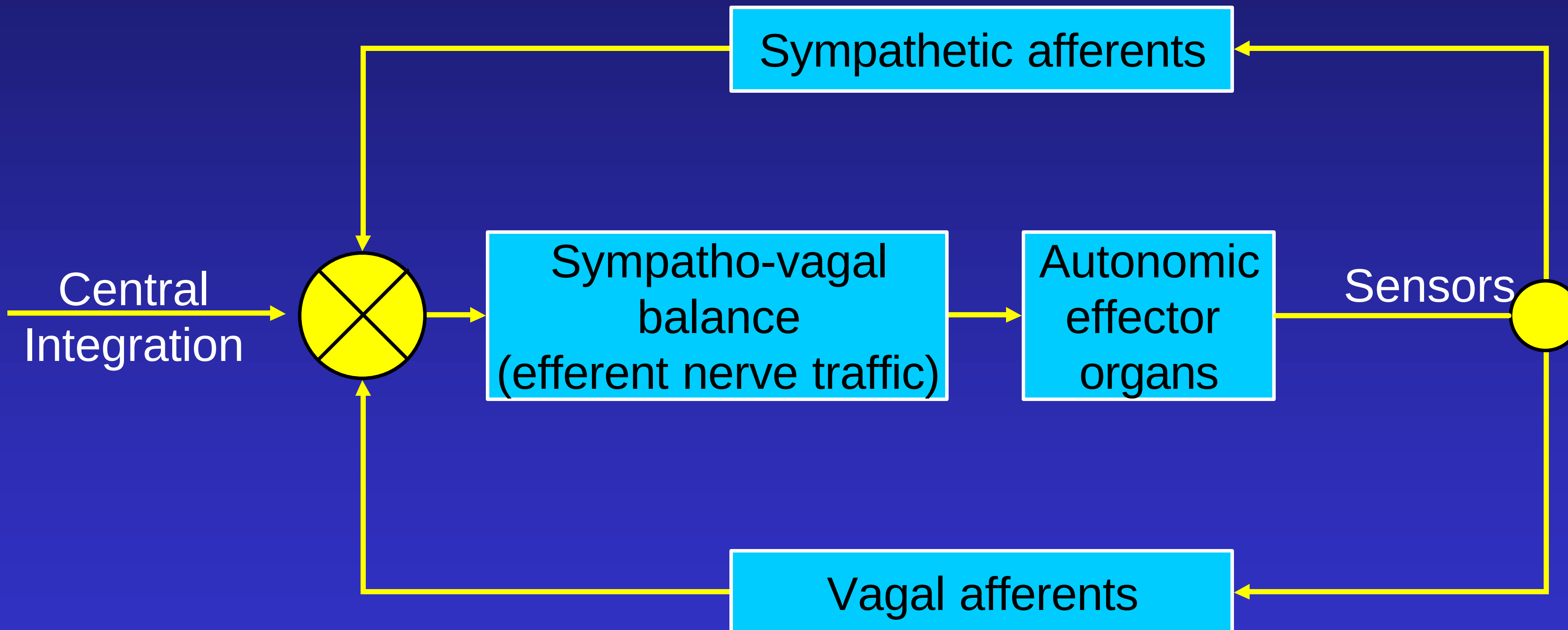
Baroreflex	**Endothelial NO system**	**Renin-Angiotensin System**
Response time of baroreceptors	Sensing of shear stress	Reduction of sodium concentration in the distal tubulus
Afferent nerve conduction	Release of NO from endothelial cells	Renin release
Central processing	Diffusion of NO to VSMC	Formation of ANG I
Efferent nerve conduction	Formation of cGMP	Formation of ANG II
End-organ responses (e.g., vasoconstriction)	End-organ response (vasodilatation)	End-organ response to ANG II (e.g., vasoconstriction)

Different time delays cause regulatory oscillations at different frequencies !

Link between blood pressure variability and heart rate variability



Neural Control of the Cardiovascular System



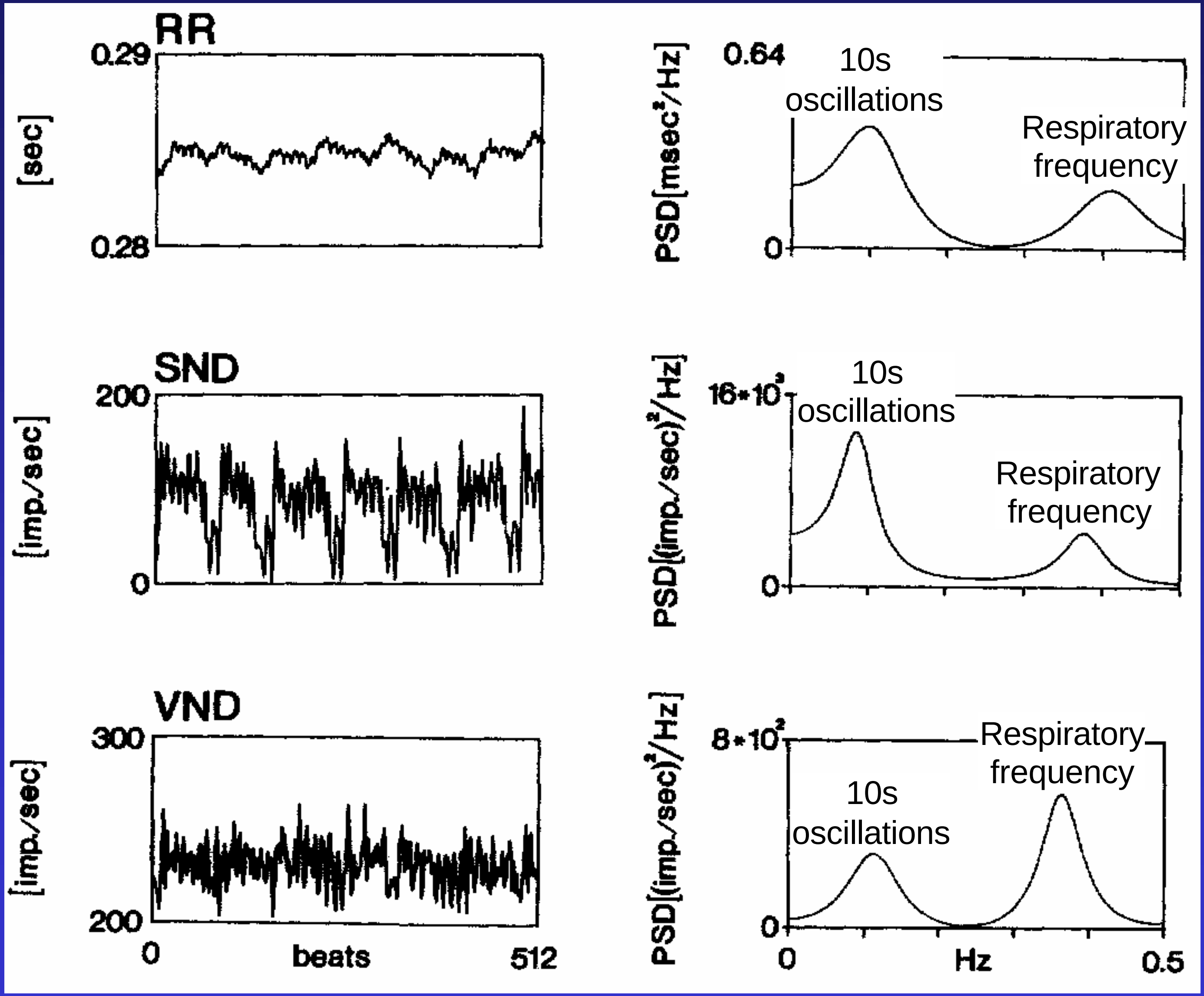
Malliani A et al., Circulation, 84:482-492, 1991

Spectral analysis of RR intervals and sympathetic and vagal nerve discharges in a cat

RR-interval

Sympathetic nerve activity

Vagal nerve activity



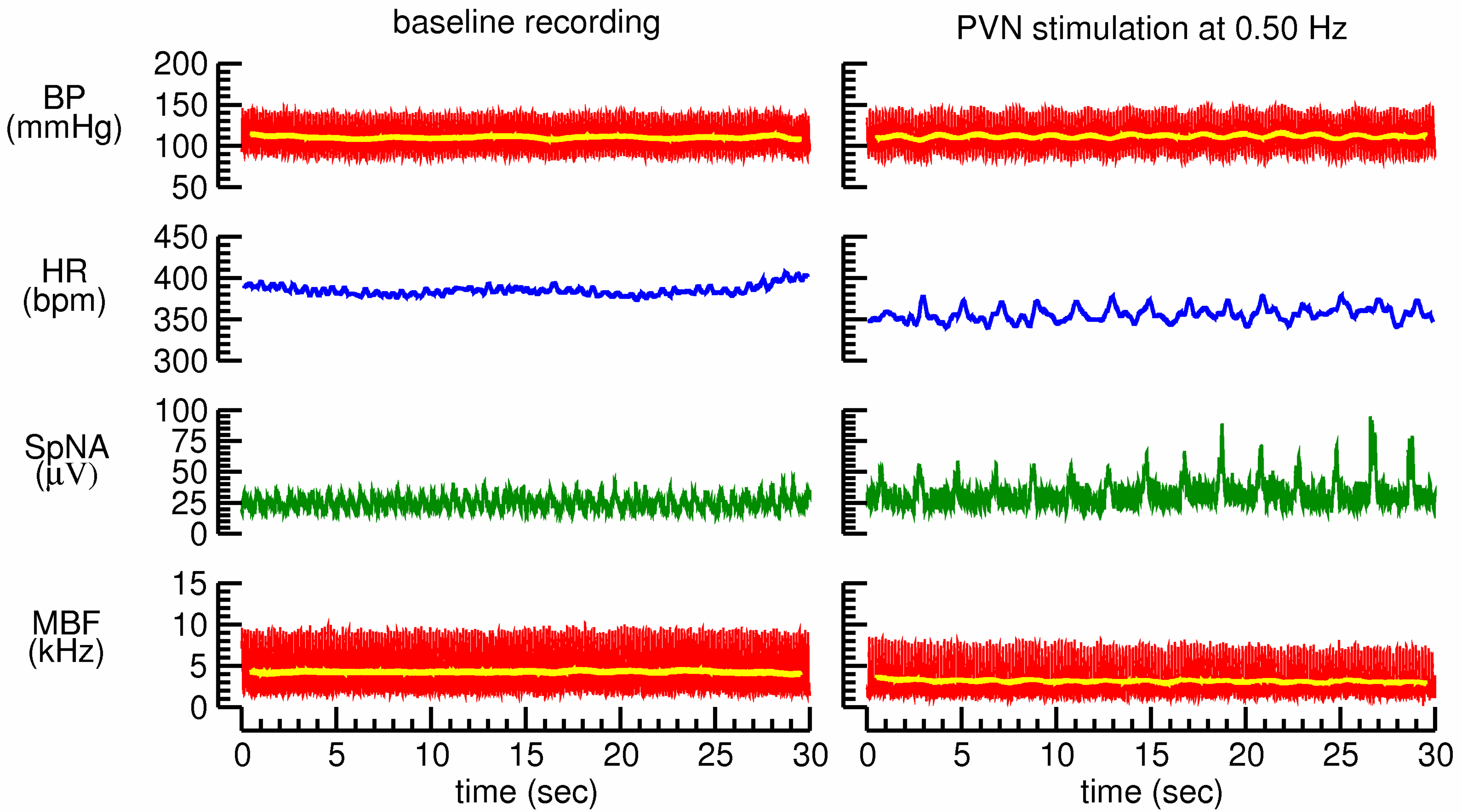
Lombardi F et al., J. Auton. Nerv. Syst. 30 (Suppl.):S97-S99, 1990

Nerve transduction to the sinus node

- Cardiac sympathetic and parasympathetic neuronal activity contains frequency components at:
  - The heart rate
  - The respiratory rate
  - The resonance frequency of the baroreceptor-heart rate reflex
  - The resonance frequencies of slower blood pressure regulating systems
- Does the sinus node respond to all these frequencies with corresponding fluctuations in heart rate?

Periodic stimulation of the PVN in conscious rats

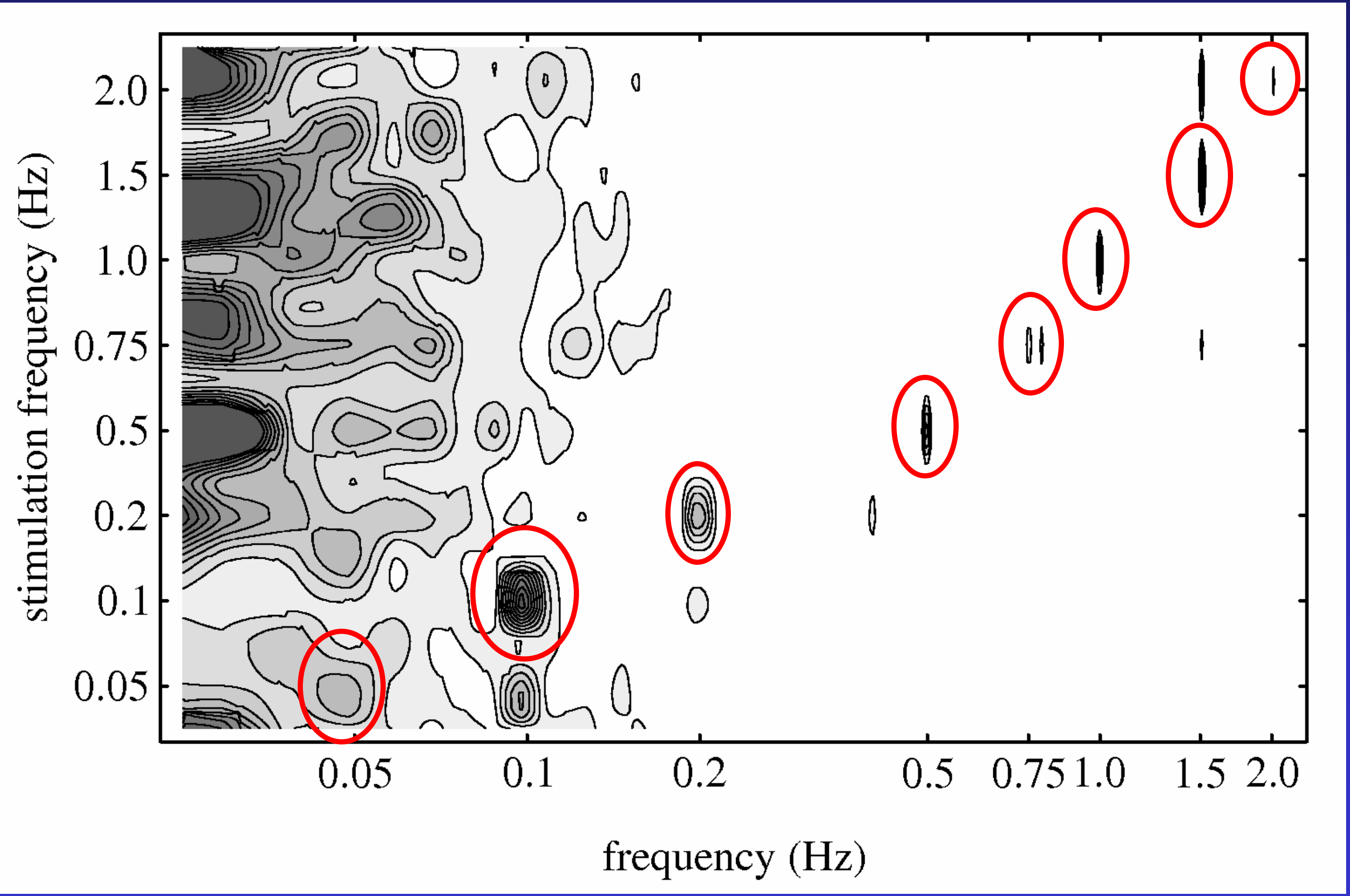
The PVN projects to sympathetic and parasympathetic preganglionic neurons



Stauss HM et al., Am J Physiol 273:H786-H795, 1997

HR responses to PVN stimulation in rats

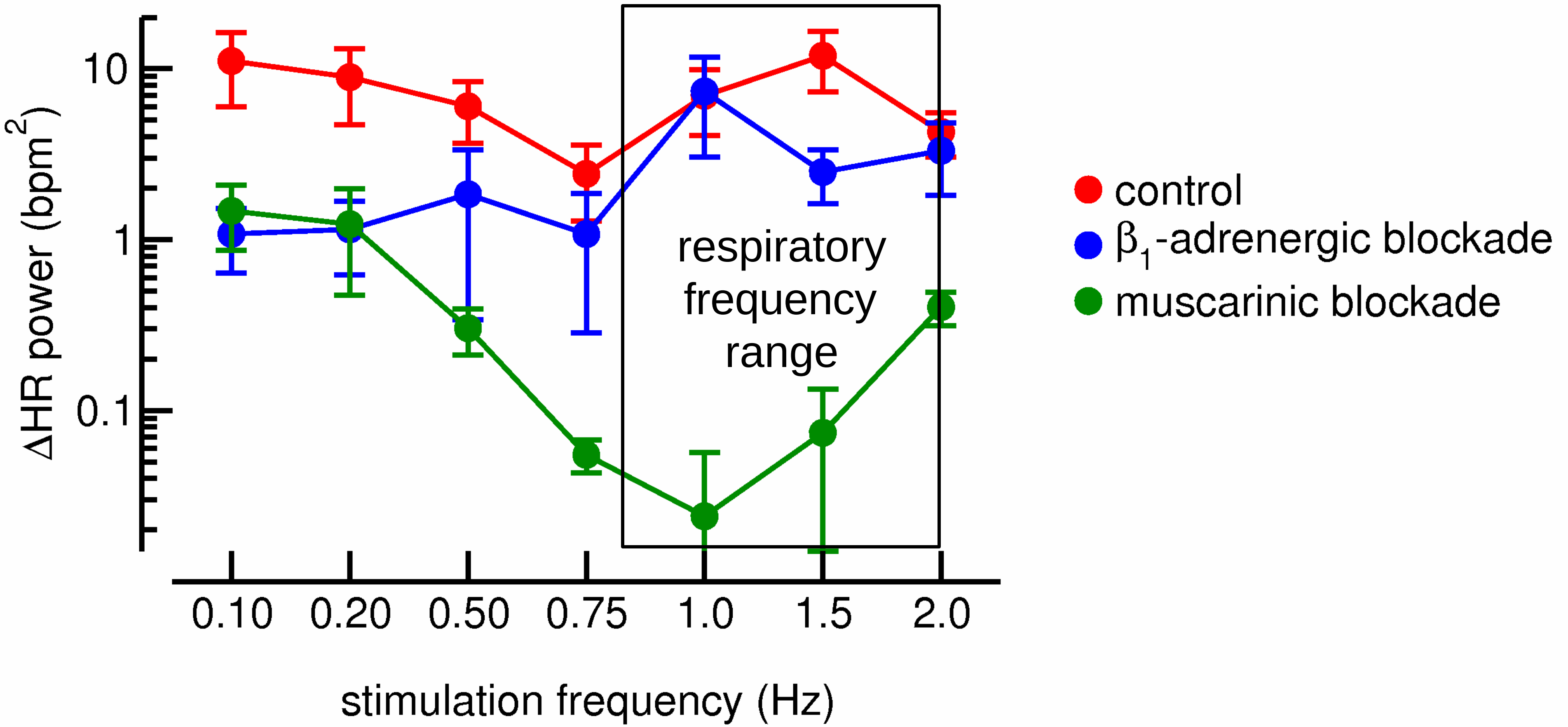
Stimulation frequencies from 0.05 Hz to 2.0 Hz
elicited corresponding HR oscillations



Stauss HM et al., Am J Physiol 273:H786-H795, 1997

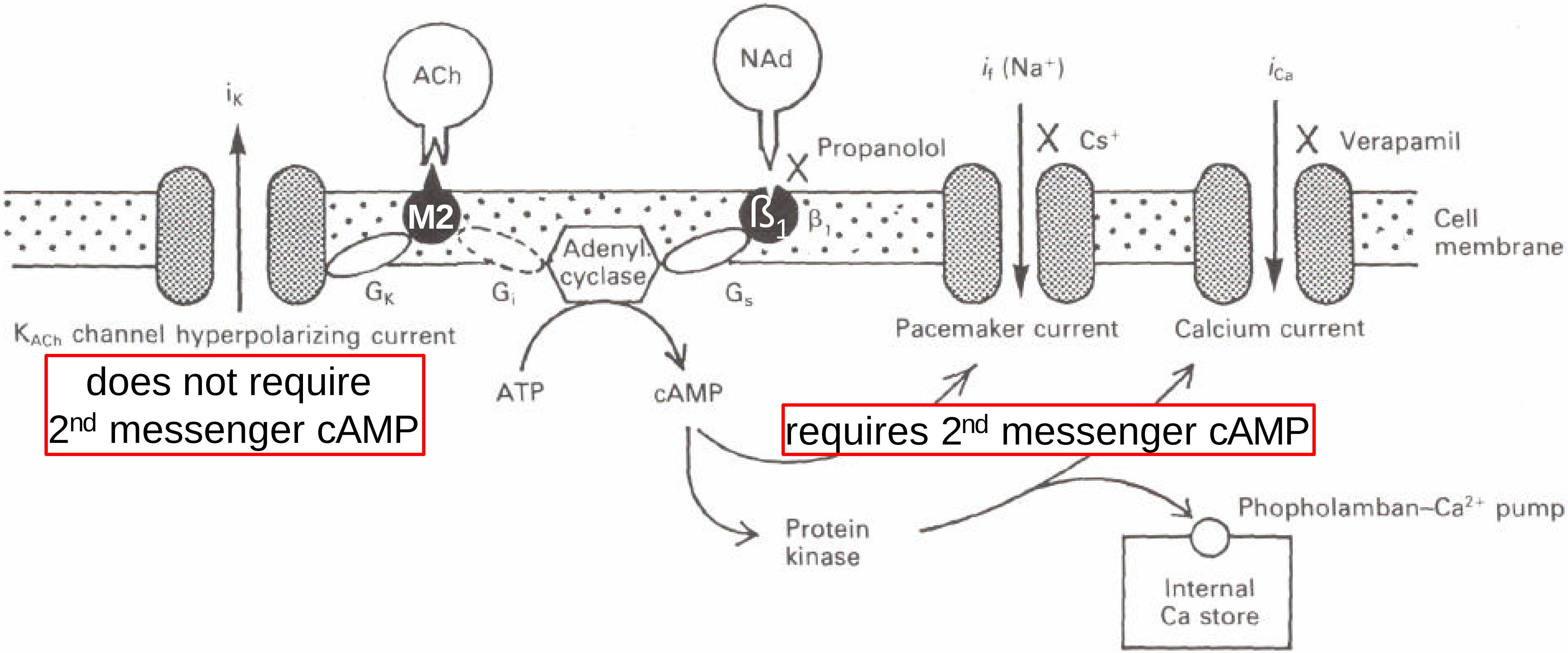
HR responses to PVN stimulation in rats

- Sympathetic modulation of HR is limited to frequencies below the respiratory frequency.
- Parasympathetic modulation of HR can operate at frequencies up to the respiratory frequency.



Stauss HM et al., Am J Physiol 273:H786-H795, 1997

Summary: Autonomic Control of Heart Rate



Parasympathetic control of heart rate is faster than sympathetic control of heart rate!

Levick JR, An Introduction to Cardiovascular Physiology, 2nd edition, 1994

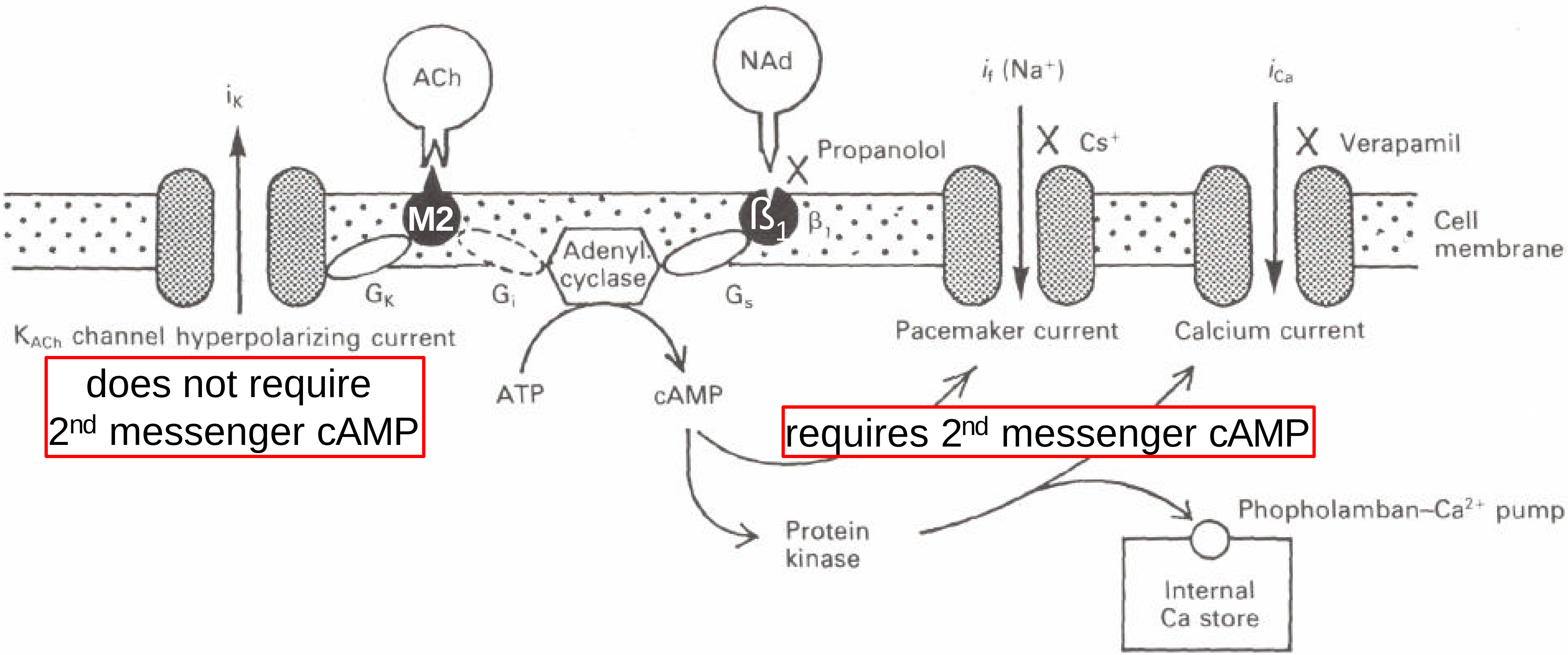
Summary

- Intrinsic heart rate is almost constant and ~100 bpm.
- Sympathetic modulation of heart rate depends on synthesis of the second messenger cAMP.
- Parasympathetic modulation of heart rate depends on opening of K_{ACh}-channels and inhibition of cAMP.
- The major periodicities in heart rate variability include:
  - Day-night periodicity
  - Respiratory sinus arrhythmia
  - 10s rhythm and slower fluctuations
- Sympathetic and parasympathetic nerve traffic contains frequency components at the respiratory frequency.
  However, only parasympathetic signal transduction is fast enough to generate respiration-related heart rate variability.

Part II

- Perturbations of the sympathetic nervous system
- Autonomic blockades
- Autonomic balance (LF/HF ratio)

Summary: Autonomic Control of Heart Rate



Parasympathetic control of heart rate is faster than sympathetic control of heart rate!

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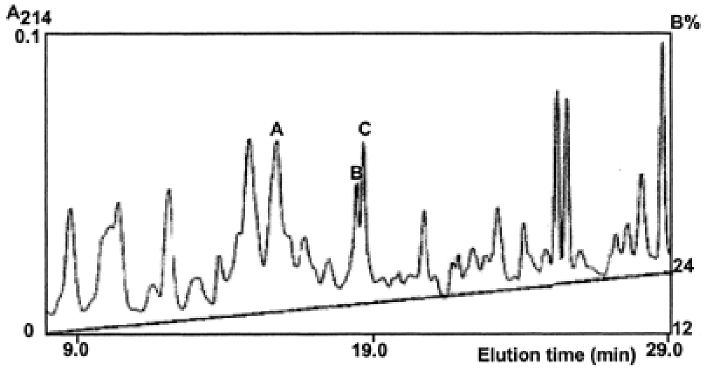
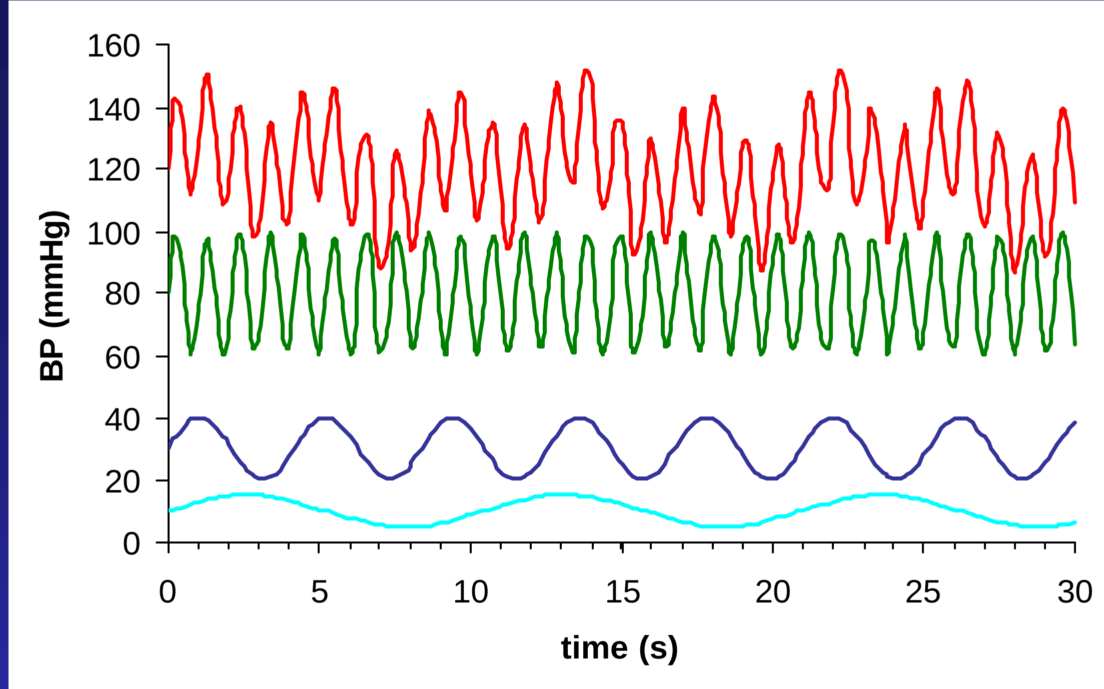
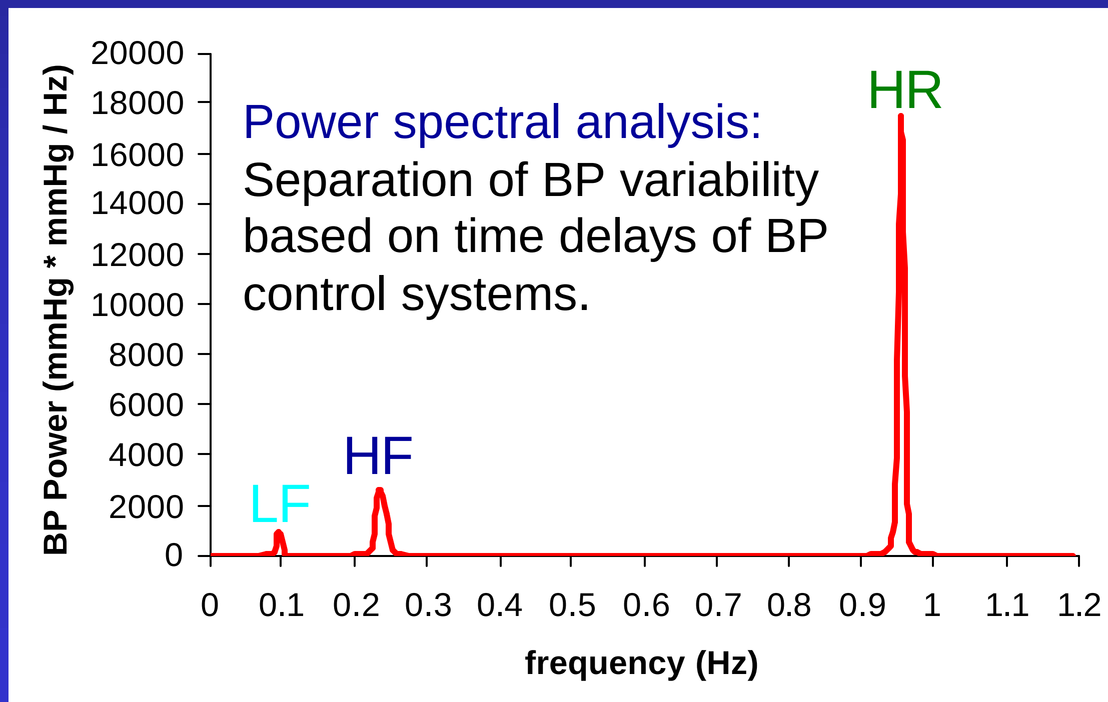
Power Spectral Analysis: The HPLC approach



Peak	Amino acid sequence	Theoretical mass (Da)	Observed mass (Da)	Mass difference (ΔDa)
A	KGEPGEAAYVYR (104-115)	1339.664	1679.9462	340
B	DGTPGEKGEKGDAG LLGPKGETGDVGMT GAEGPR(62-95)	3240.544	4276.8440	1036
C	DGTPGEKGEKGDAG LLGPKGETGDVGMT GAEGPR(62-95)	3240.544	4260.9057	1020

HPLC: Separation of chemical compounds based on physical or chemical characteristics.





Interventions that increase sympathetic nerve activity increase LF spectral power of HR

- Upright tilt
- Application of the vasodilator nitroglycerin
- Coronary artery occlusion
- Exercise
- Mental arithmetic stress

Effect of 90° tilt in a young human subject

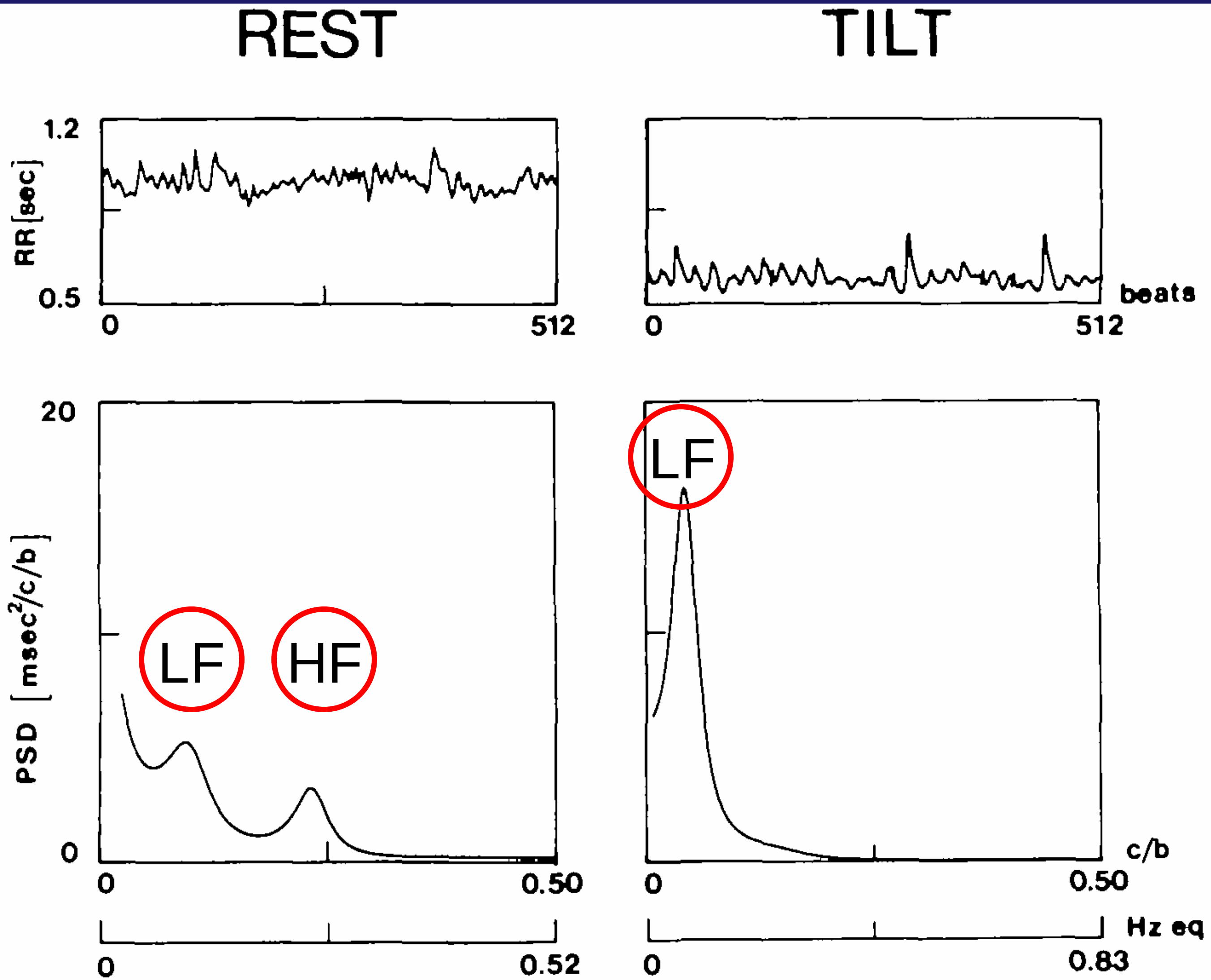


FIGURE 3. *R–R interval series, i.e., tachogram at rest and during passive upright 90° tilt. On the autospectra (bottom panels), two clearly separated low- and high-frequency components are present at rest. During tilt, the low-frequency component becomes preponderant.*

Pagani M et al., Circ. Res. 59:178-193, 1986

Application of nitroglycerin before and after cardiac sympathectomy in a dog

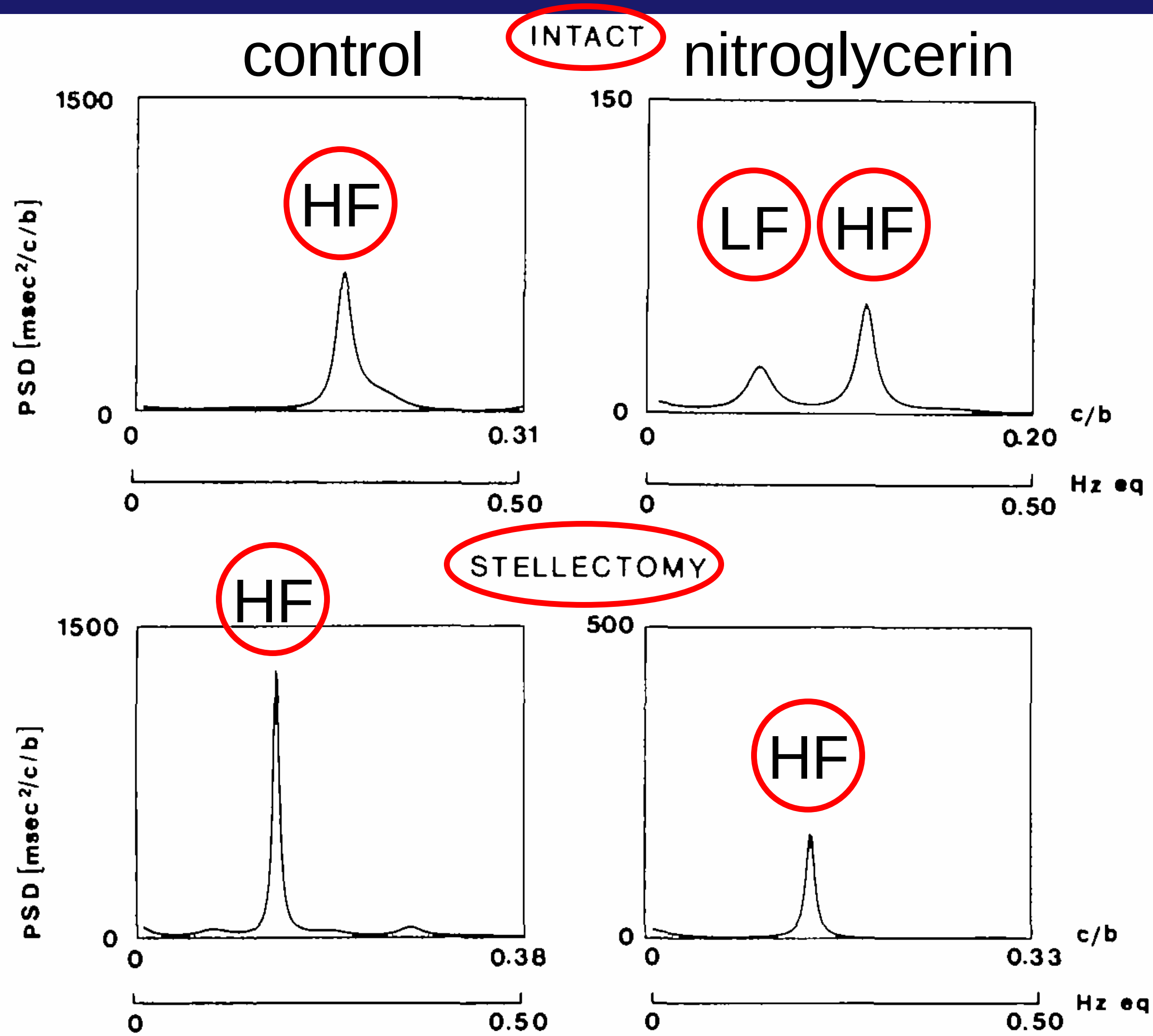
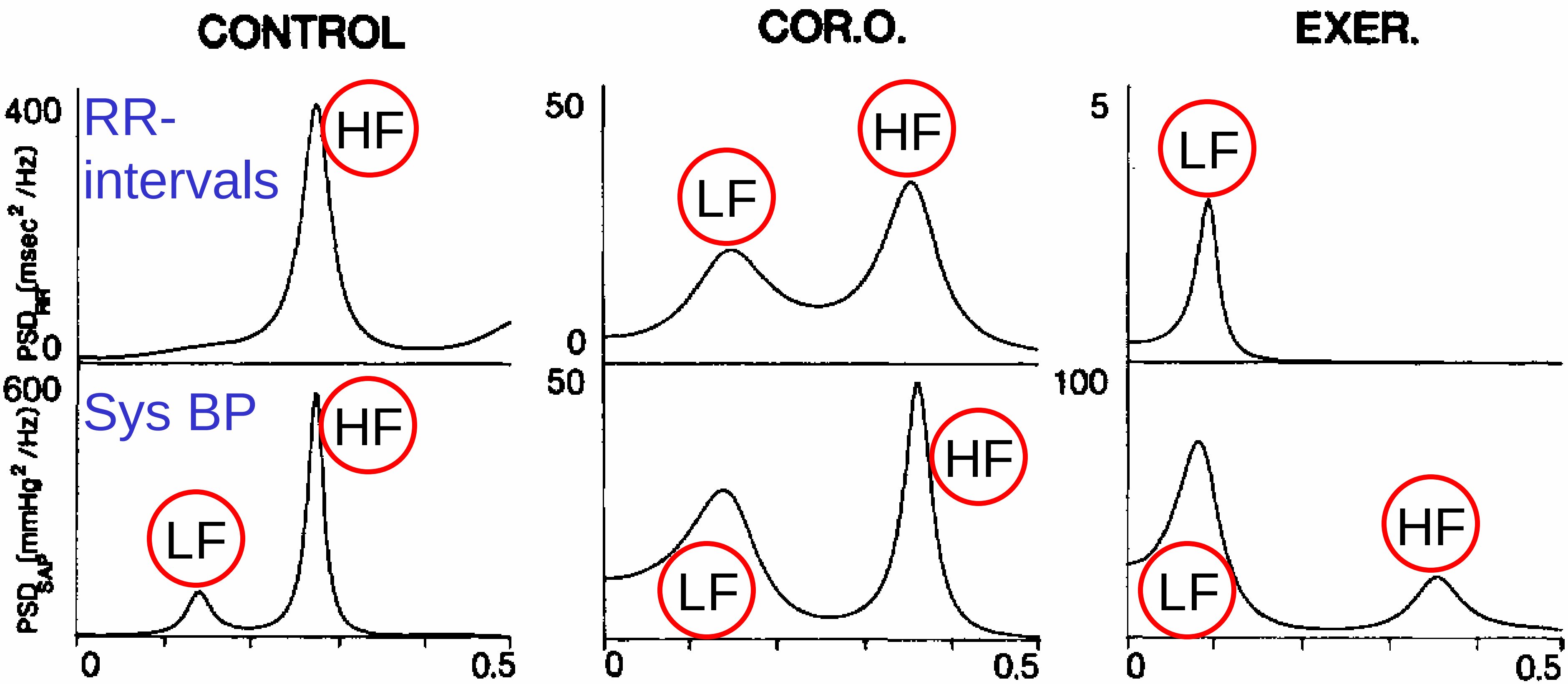


FIGURE 8. *Autospectra of R–R interval variability of a conscious healthy dog in control conditions (left panels) and during an IV infusion of nitroglycerin to excite the sympathetic outflow. The top panels were obtained with cardiac nerves intact, the bottom panels after full recovery from bilateral stellectomy. Note the presence of a large low-frequency component during nitroglycerin infusion only in the neurally intact situation.*

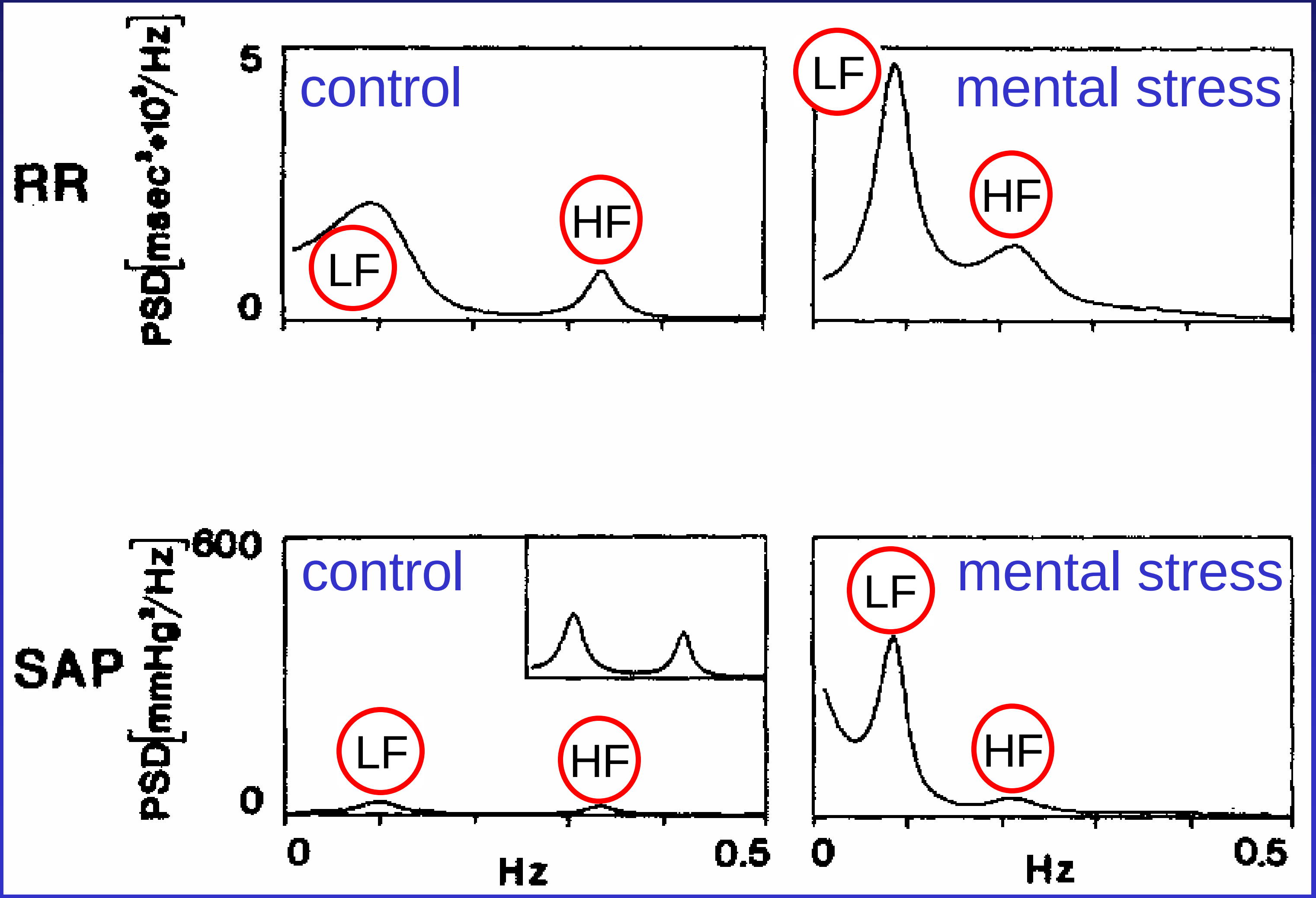
Pagani M et al., Circ. Res. 59:178-193, 1986

HR and BP variability responses to coronary artery occlusion and exercise in dogs



Malliani A et al., Circulation, 84:482-492, 1991

HR and BP variability responses to mental arithmetic stress



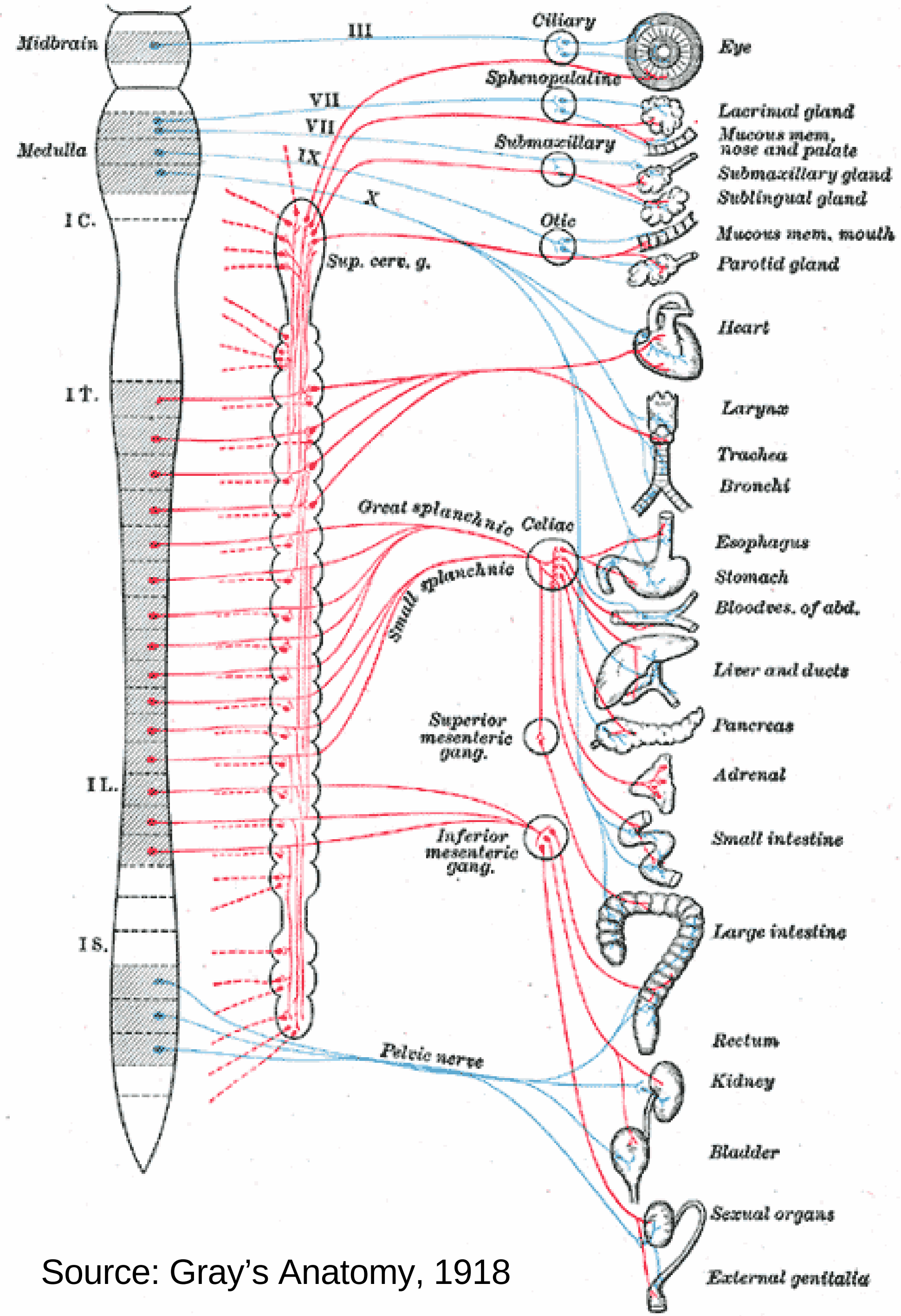
Malliani A et al., Circulation, 84:482-492, 1991

Perturbations of the SNS

- All interventions that enhance sympathetic nervous system activity also increase LF spectral power of heart rate (or RR interval).

Cardiac autonomic receptor blockades

- Ganglionic blockade.
- Parasympathetic (muscarinic) blockade.
- Sympathetic $ß_1$-adrenergic receptor blockade.

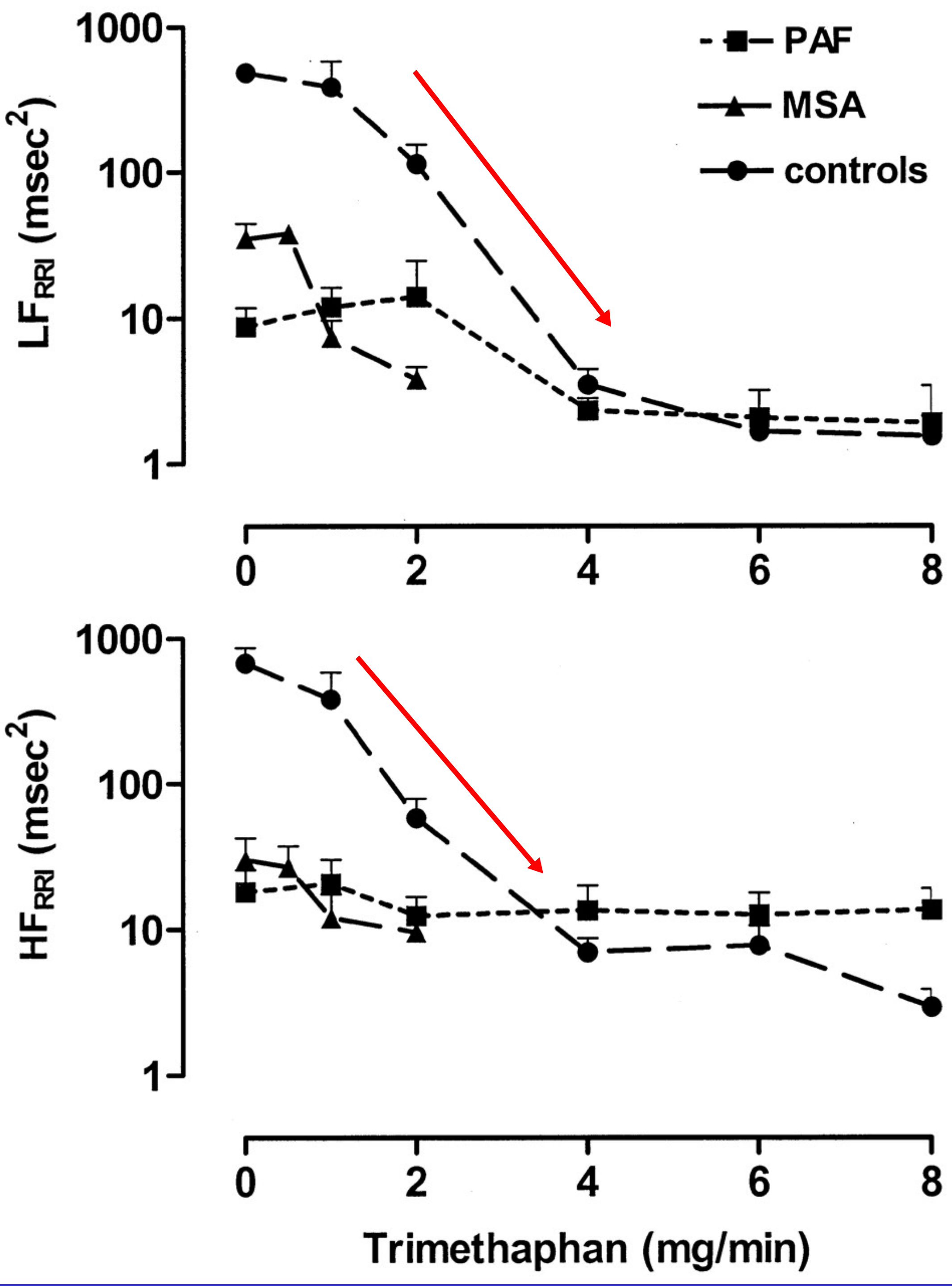


Source: Gray's Anatomy, 1918

Ganglionic blockade

- Blockade of signal transduction from the first to the second autonomic neuron.
- Affects sympathetic and parasympathetic nervous system.
- Drugs: trimethaphan, hexamethonium, etc.

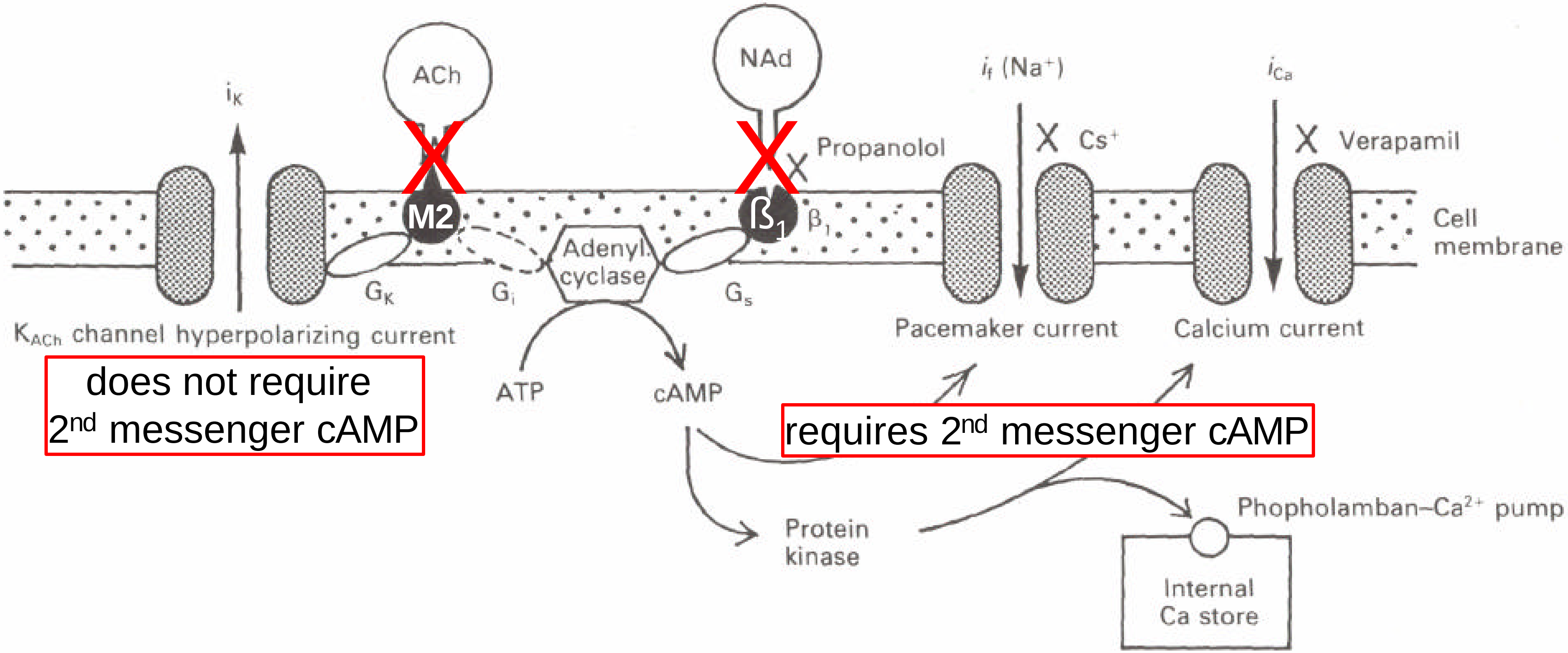
Effect of ganglionic blockade on LF and HF heart rate variability



- Ganglionic blockade (trimethaphan) dose-dependently reduced LF and HF spectral power of RR intervals.

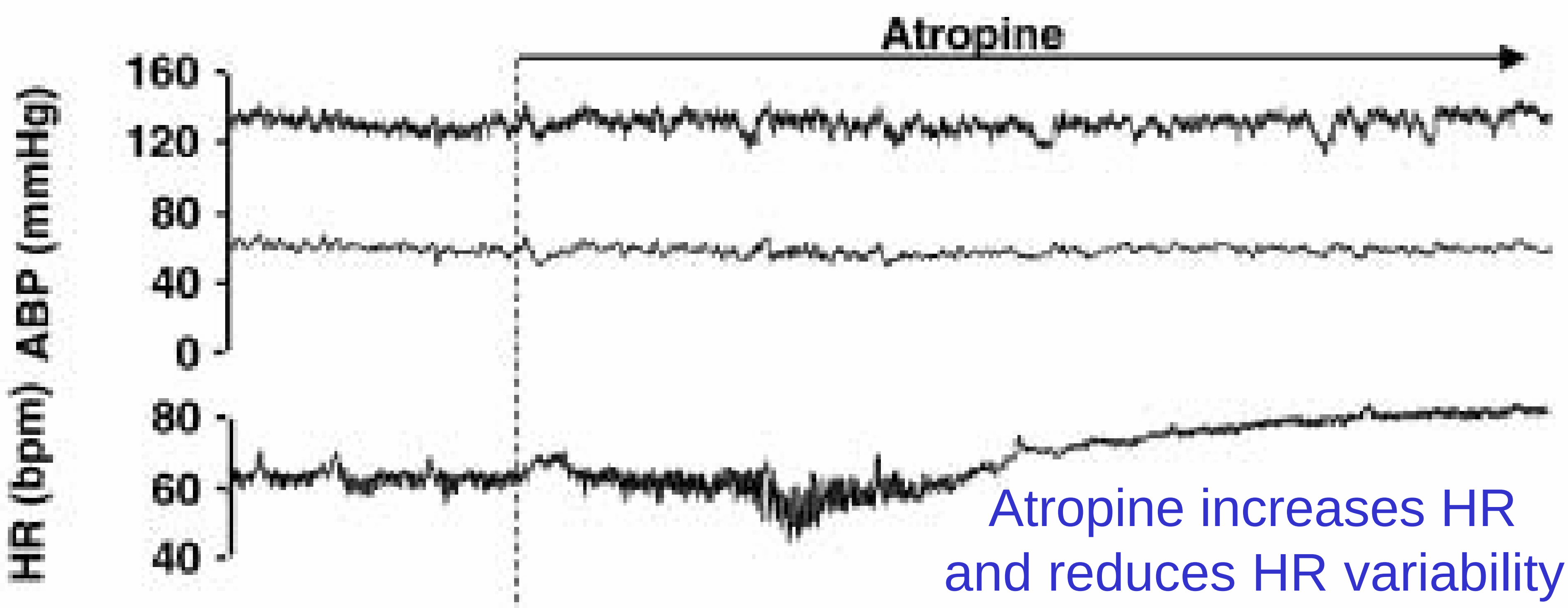
Diedrich A et al.,
Circulation 106:2238-2243, 2002

Cardiac Autonomic Receptor Blockades



Levick JR, An Introduction to Cardiovascular Physiology, 2nd edition, 1994

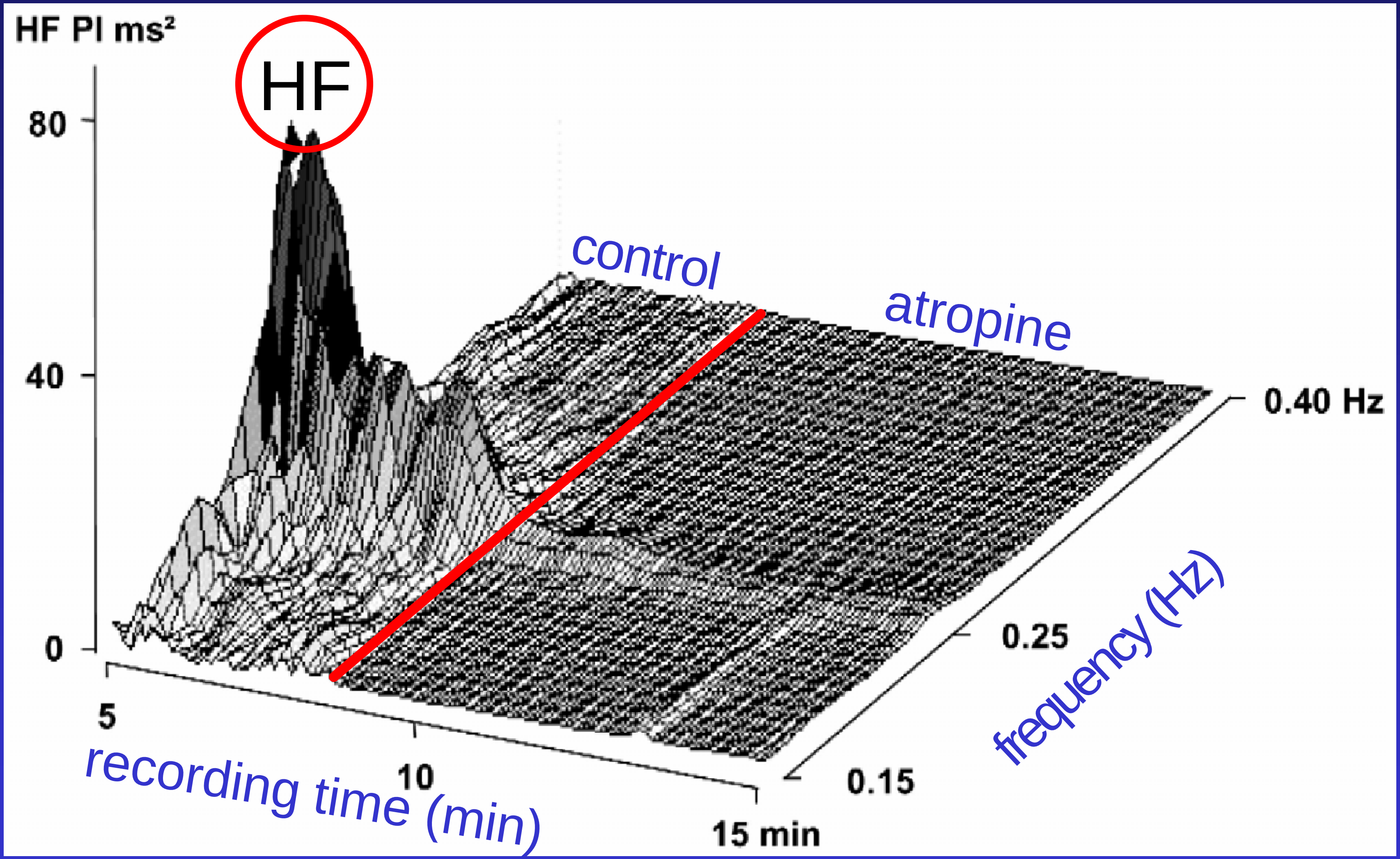
BP and HR response to atropine in a human subject



Atropine increases HR and reduces HR variability

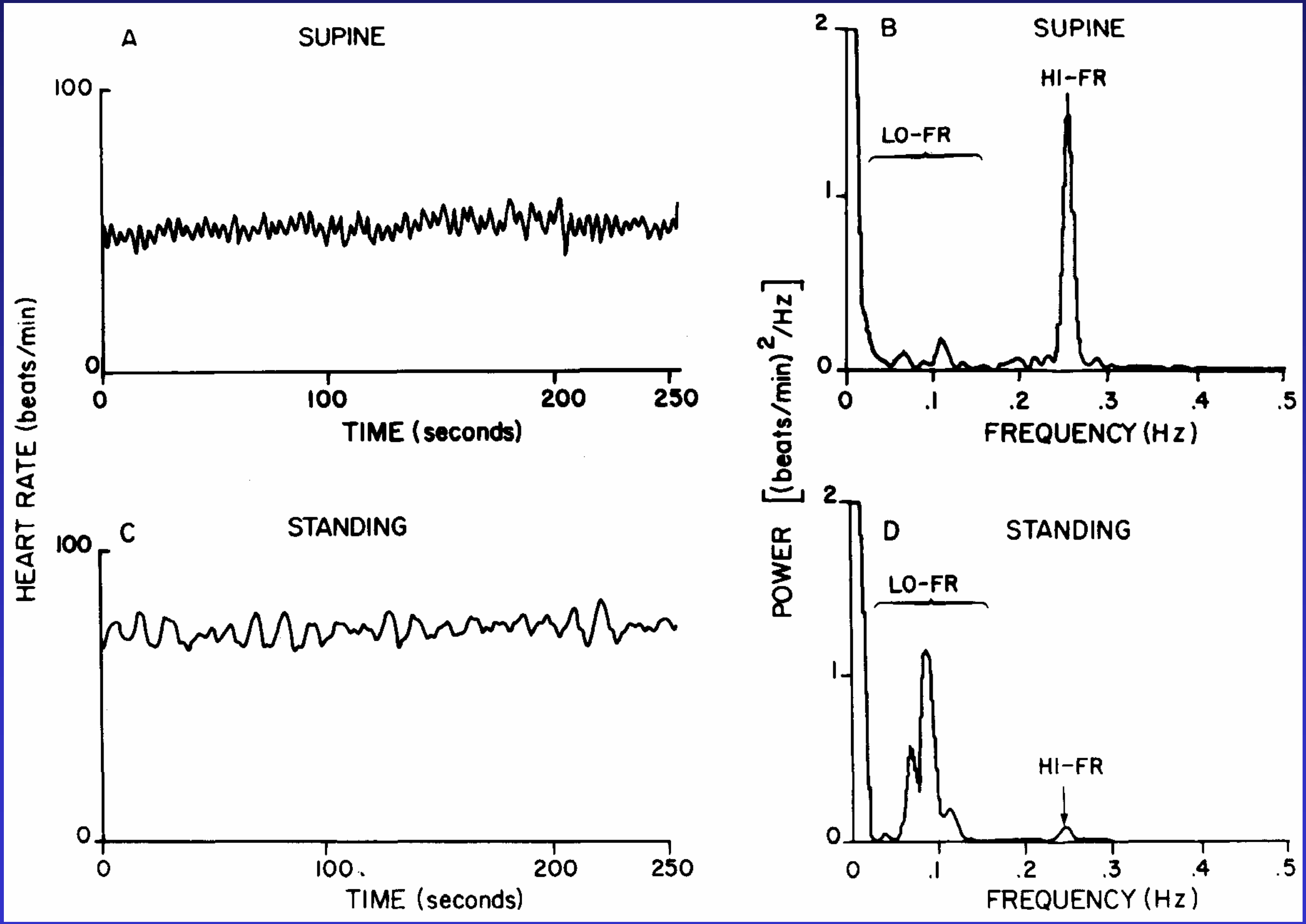
Médigue C et al., Pflügers Arch. Europ. J. Physiol. 441:650-655, 2001

Spectral analysis of pulse intervals during atropine infusion in a human subject

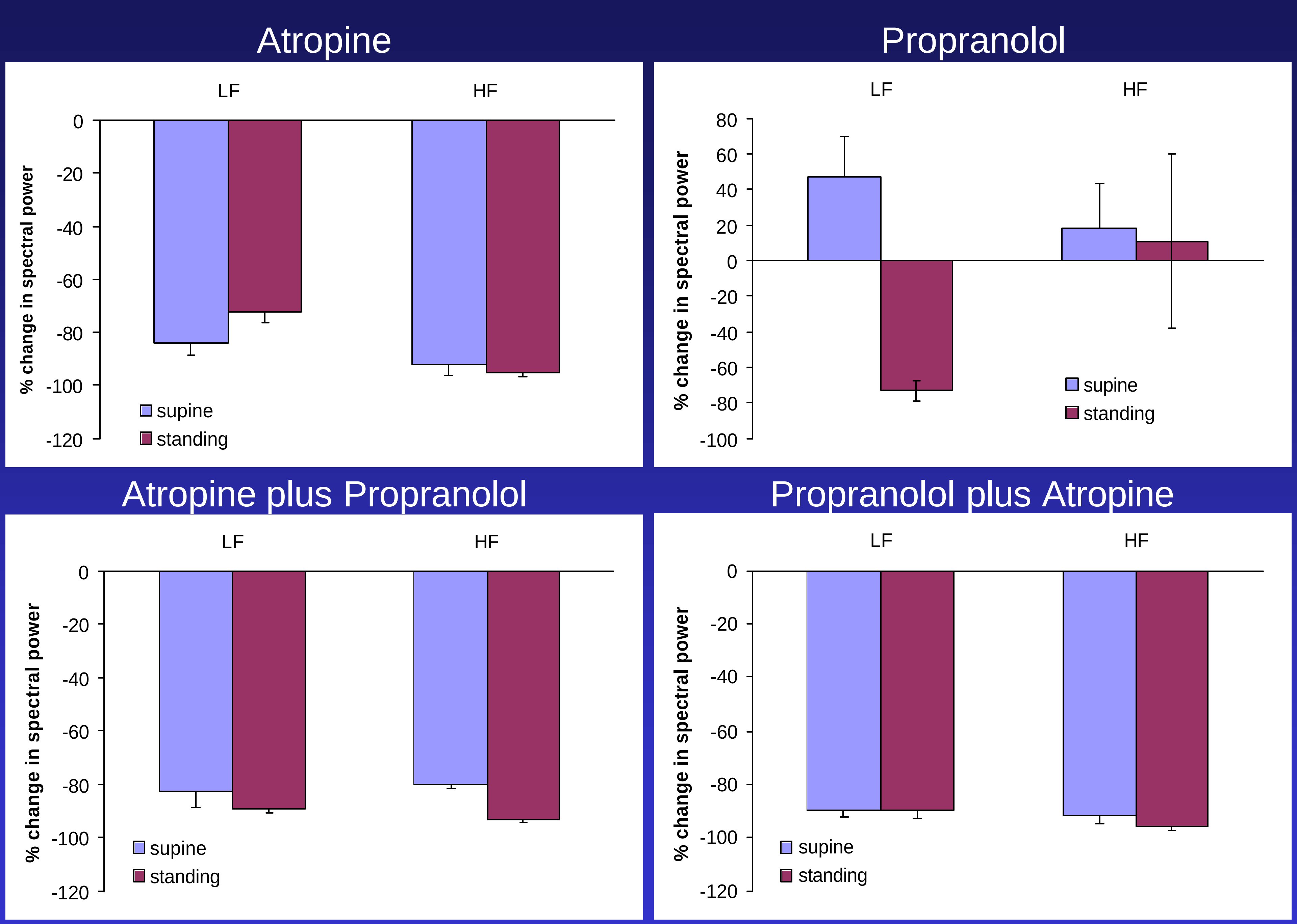


Elghozi JL et al., Autonomic Neuroscience: Basic and Clinical 90:116-121, 2001

The effect of autonomic receptor blockers depends on baseline conditions



Pomeranz B. et al., Am. J. Physiology: Heart Circ. Physiol. 248:H151-H153, 1985

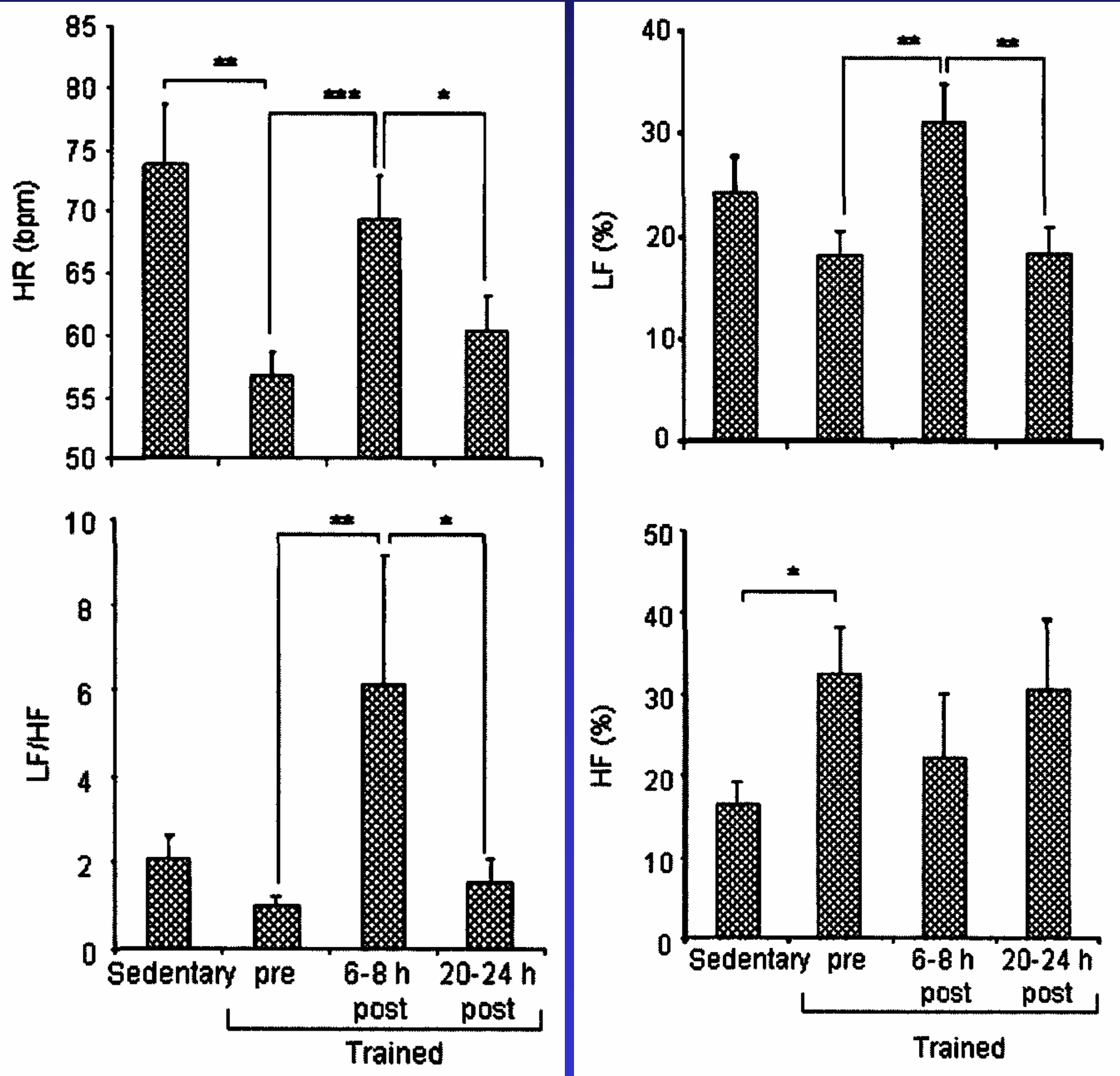


Pomeranz B. et al., Am. J. Physiology: Heart Circ. Physiol. 248:H151-H153, 1985

Cardiac Autonomic Receptor Blockades

- Parasympathetic (muscarinic) receptor blockade reduces LF and HF spectral power of heart rate.
- Sympathetic $ß_1$-adrenergic receptor blockade causes an increase or decrease in LF spectral power of heart rate, depending on baseline levels of cardiac sympathetic tone.
- Sympathetic $ß_1$-adrenergic receptor blockade does not affect HF spectral power of heart rate.

HR Spectral Analysis in High-Altitude Trained Marathon Runners

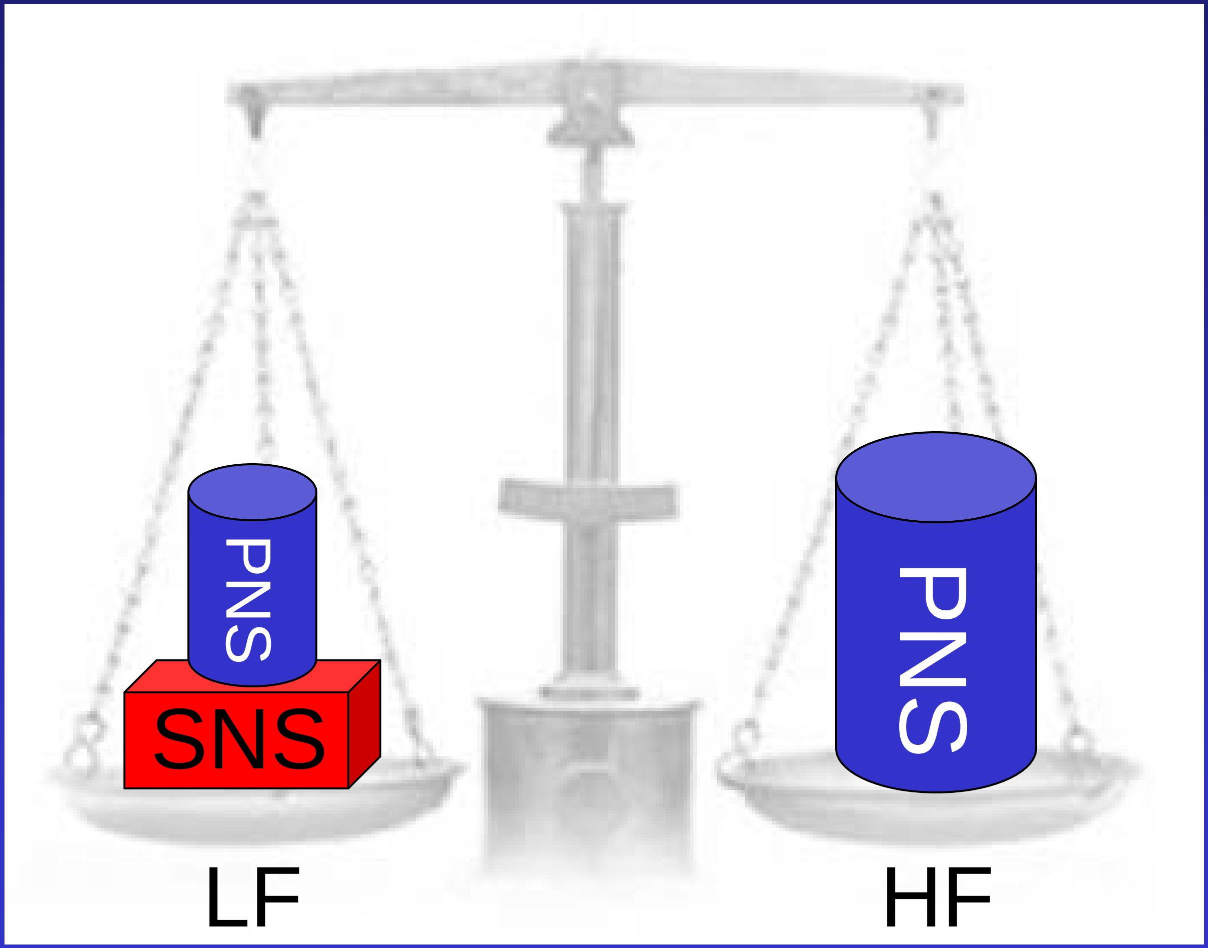


Cerro de Pasco, Peru, elevation 13,000 feet

Cornolo J, et al.
Med. Sci. Sports Exerc. 37:2148, 2005

Autonomic Balance – LF/HF ratio

Low Frequency High Frequency



Low Frequency:
Sympathetic and Parasympathetic

High Frequency:
Only parasympathetic

LF/HF ratio:
Greater values reflect sympathetic dominance.
Smaller values reflect parasympathetic dominance.

Summary Part II

- Perturbations of the sympathetic nervous system are reflected in changes in LF (~0.1 Hz) spectral power of heart rate.
- Cardiac autonomic blockade experiments demonstrated that:
  - LF spectral power of heart rate is modulated by the sympathetic and parasympathetic nervous system.
  - HF spectral power of heart rate is modulated by the parasympathetic nervous system only.
- The ratio of LF/HF spectral power of heart rate reflects cardiac autonomic balance.