Control of the CV System

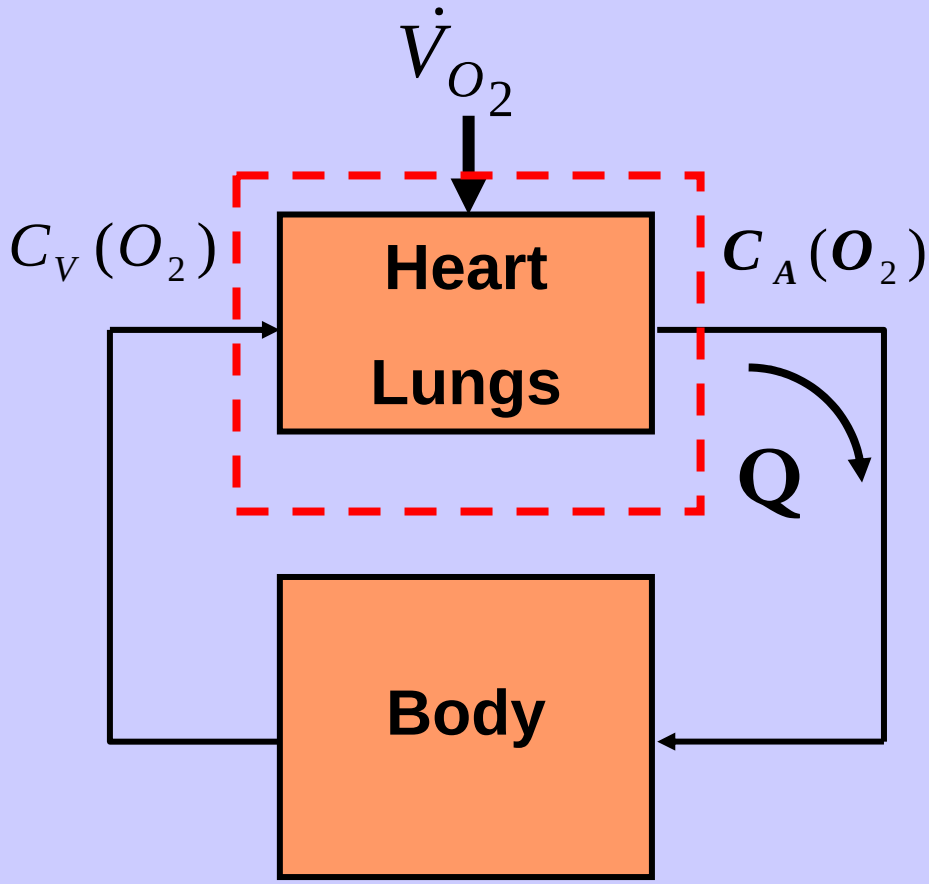
Cardiac Output and Oxygen Uptake

$$Q\left[C_A(O_2) - C_V(O_2)\right] = \dot{V}_{O_2}$$

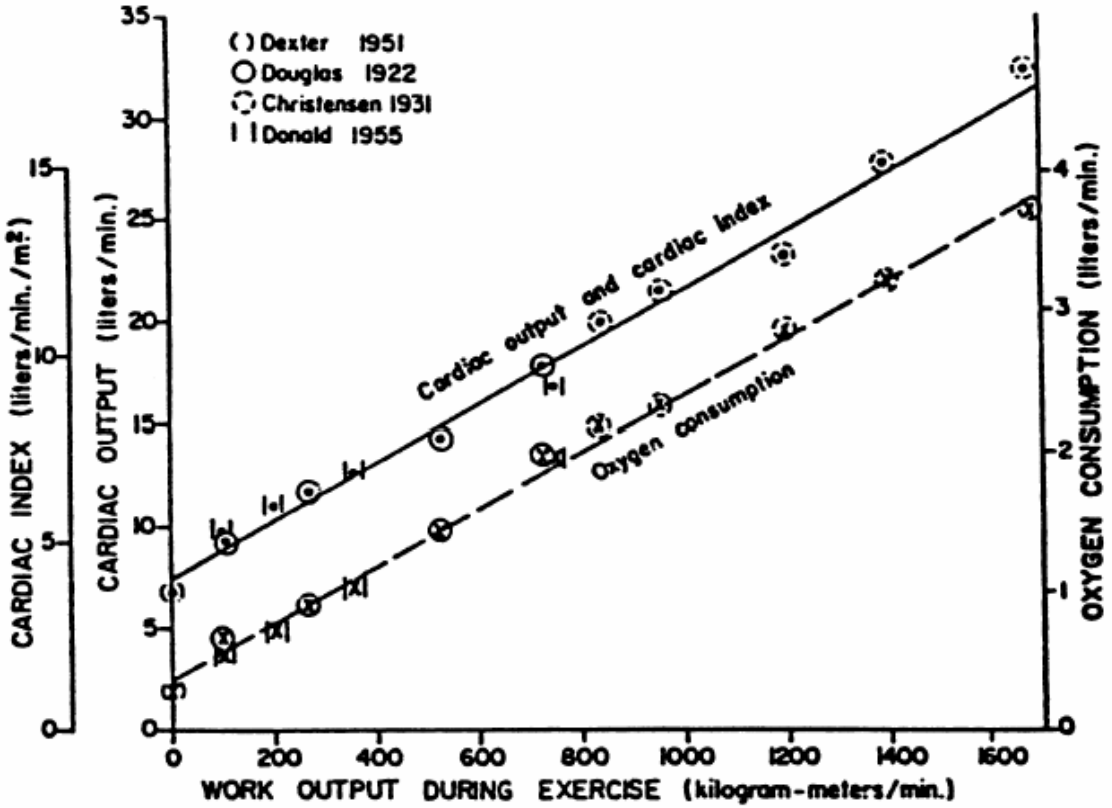
$C_V(O_2) \equiv ml\ \ O_2 / ml\ \ blood$

$C_A(O_2) \equiv ml\ \ O_2 / ml\ \ blood$

$V_{O_2} \equiv ml\ \ O_2 / \min$



Cardiac Output and Oxygen Consumption



Relationship between cardiac output and work output (solid curve) and between oxygen consumption and work output (dashed curve) during exercise. [Data derived from studies by Douglas and Haldance (1922); Christensen and Mitteilung (1931); Dexter, Whittenberger, Haynes, Goodale, Gorlin, and Sawyer (1951); and Donald, Bishop, Cumming, and Wade (1955).]

Challenges to the CV System

Seconds to Minutes

- Standing up
- Eating a big meal
- Running for the bus

Minutes to Hours

- Fever
- Blood loss
- Myocardial infarction

Hours to Days

- Extreme heat, cold
- Fluid deprivation
- Space flight

Weeks to Months

- Long-term space flight
- Marathon training
- High altitude living

CV System: Parallel Connection

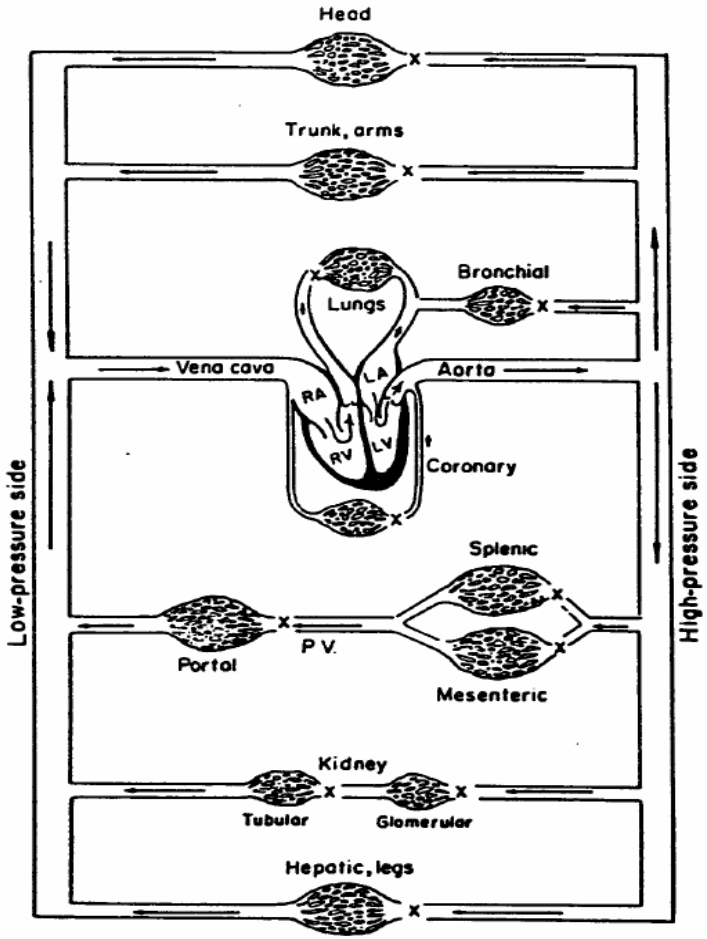
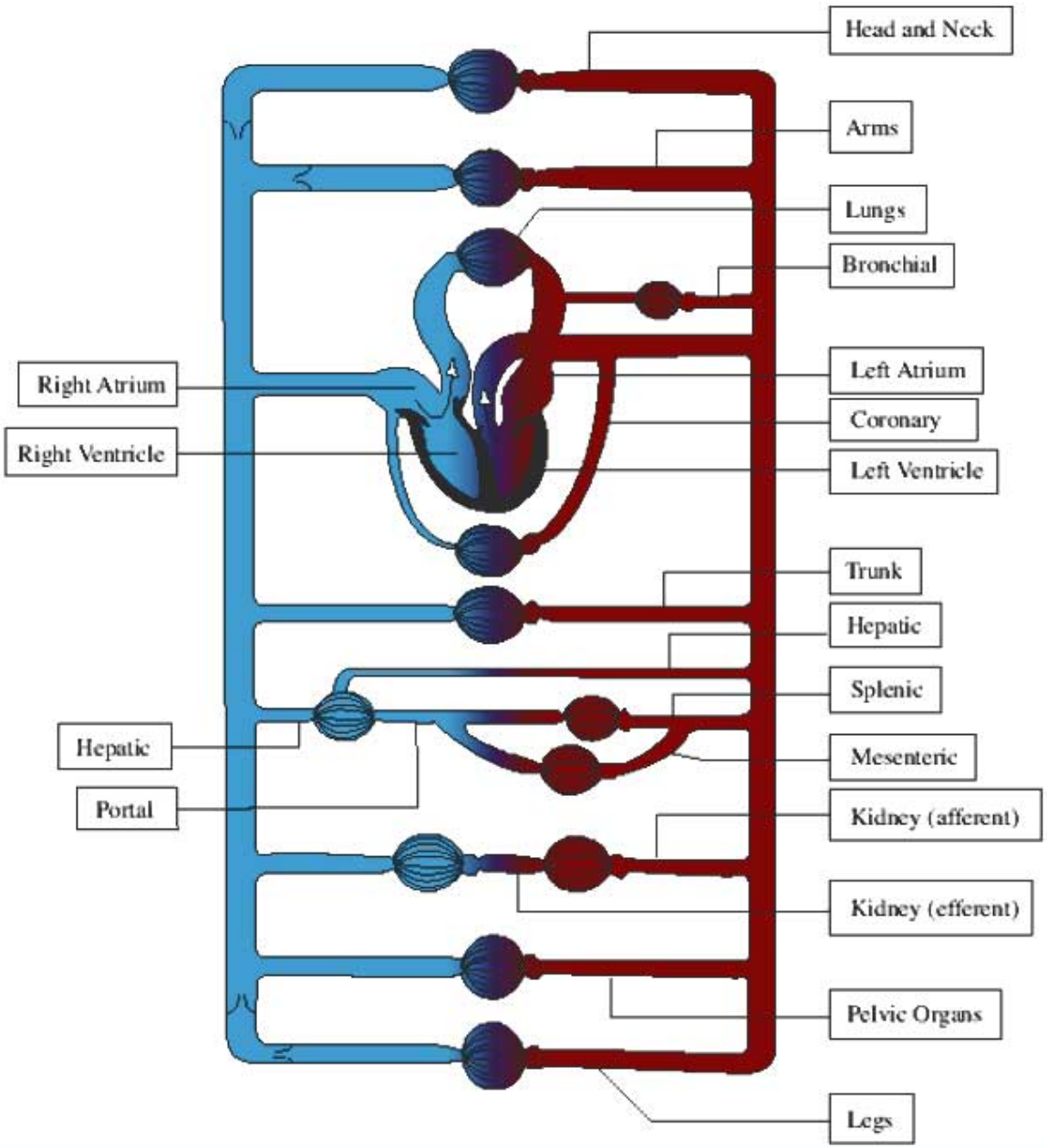
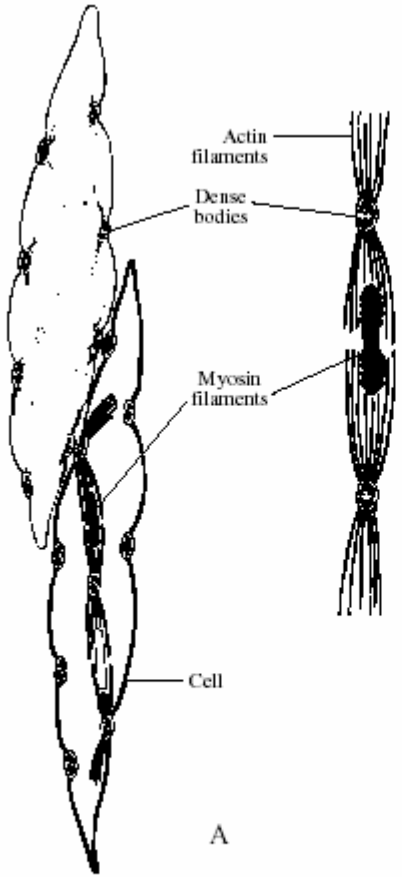


Figure 3: Arrangement of the parallel routes by which the circulation passes from the aorta to the vena cava. Representatives of the different categories of route discussed in the text are indicated. The Xs indicate the location of control points where arterioles may control the flow. *RA*, right atrium; *LA*, left atrium; *RV*, right ventricle; *LV*, left ventricle; *PV*, portal vein. (from Green, H.D.: Circulation: Physical Principles, in Glasser, O. [ed.]: *Medical Physics*, Vol. 1 [Chicago: The Year Book Publishers, Inc., 1949], p. 210. Original illustration kindly furnished by H.D. Green.)


Head and Neck
Arms
Lungs
Bronchial
Left Atrium
Coronary
Left Ventricle
Right Atrium
Right Ventricle
Trunk
Hepatic
Splenic
Hepatic
Mesenteric
Portal
Kidney (afferent)
Kidney (efferent)
Pelvic Organs
Legs

Smooth Muscle Cells



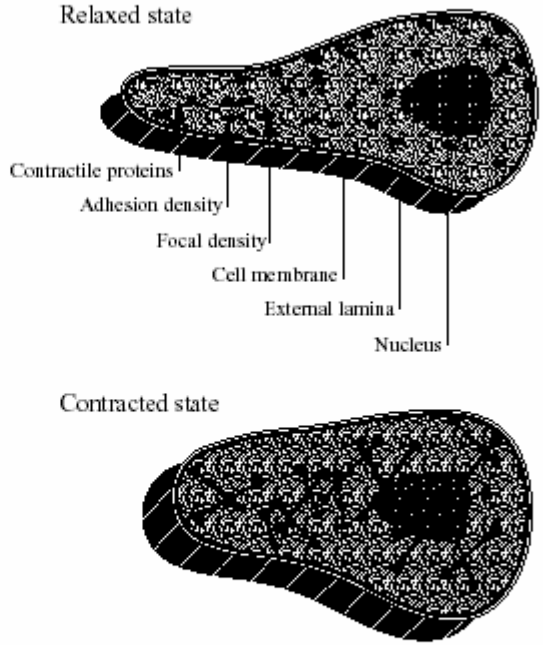


Figure 4: *Cartoons of smooth muscle cell. A. Physical structure of contractile elements. B. Contractile function.*

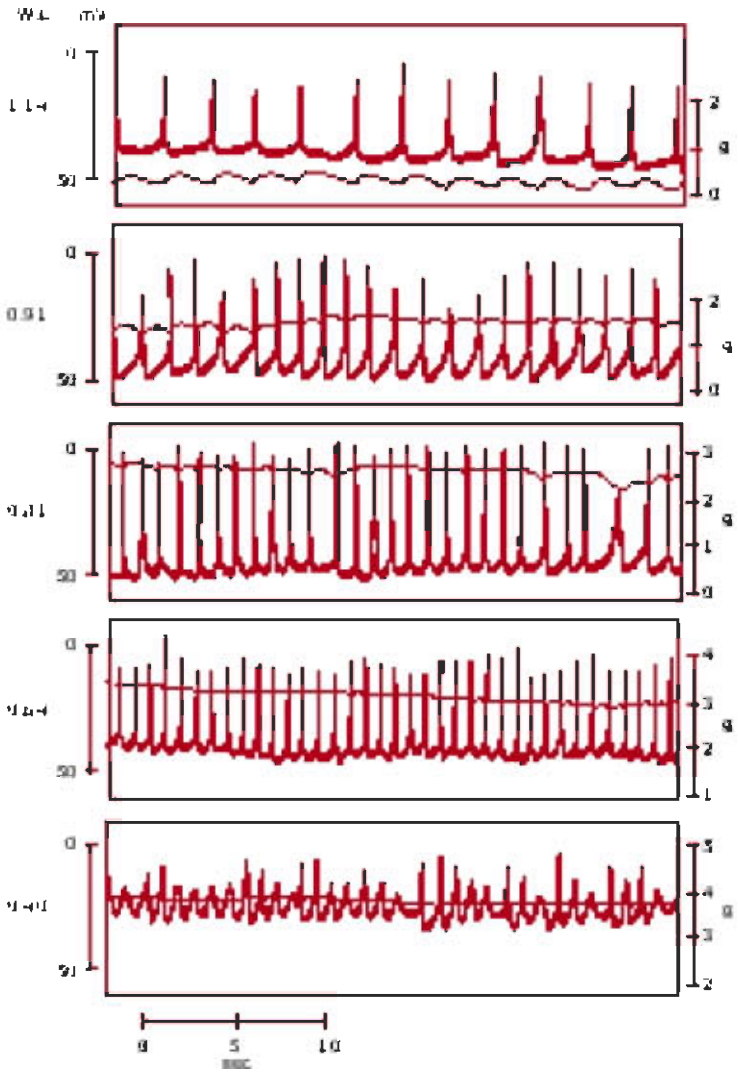


Figure 5: *Action potentials and tension in a strip of intestinal smooth muscle showing increased frequency of spontaneous action potentials in response to increased tension.*

Figure by MIT OCW.

Smooth Muscle Contraction

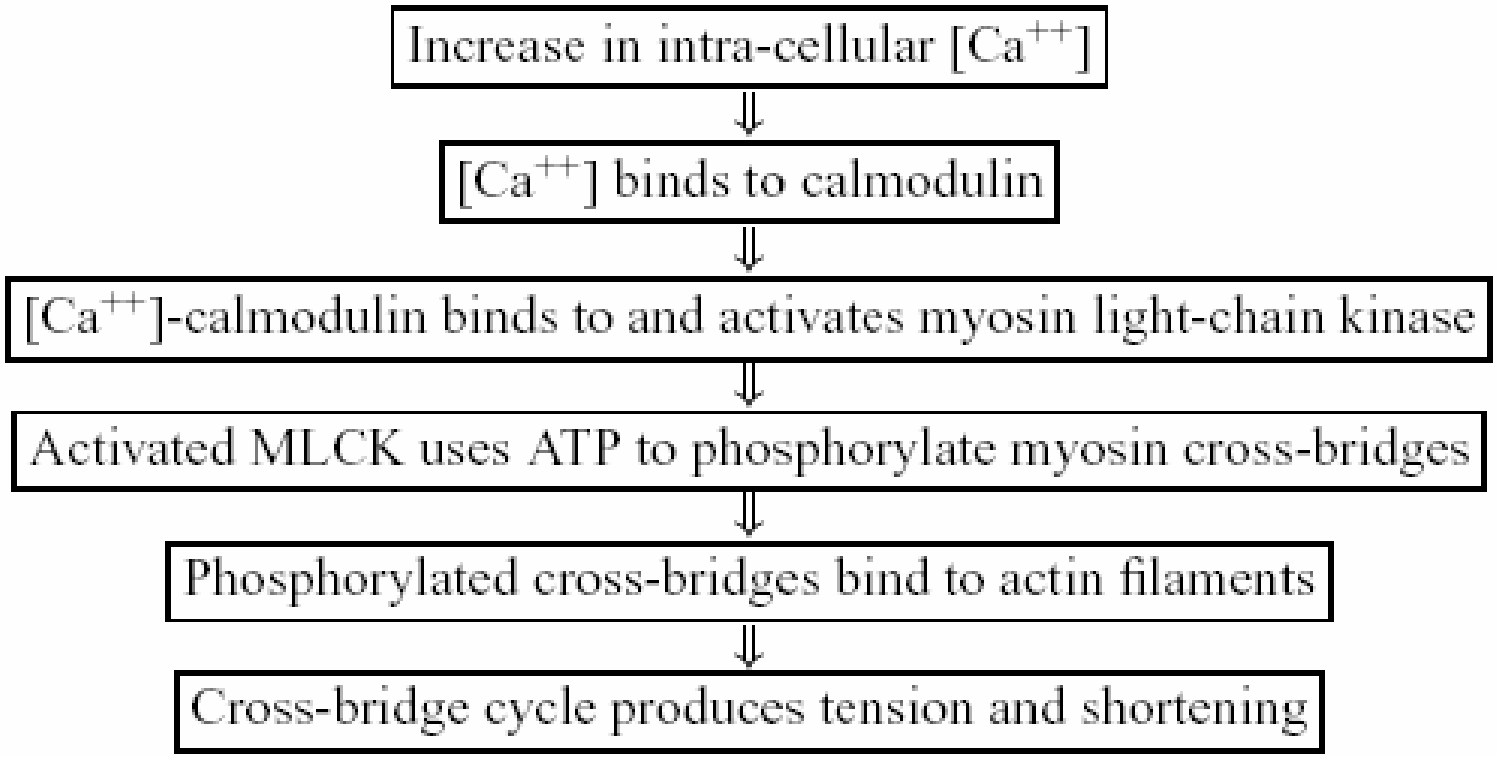


Figure 6: *Biochemical events leading to smooth muscle contraction*

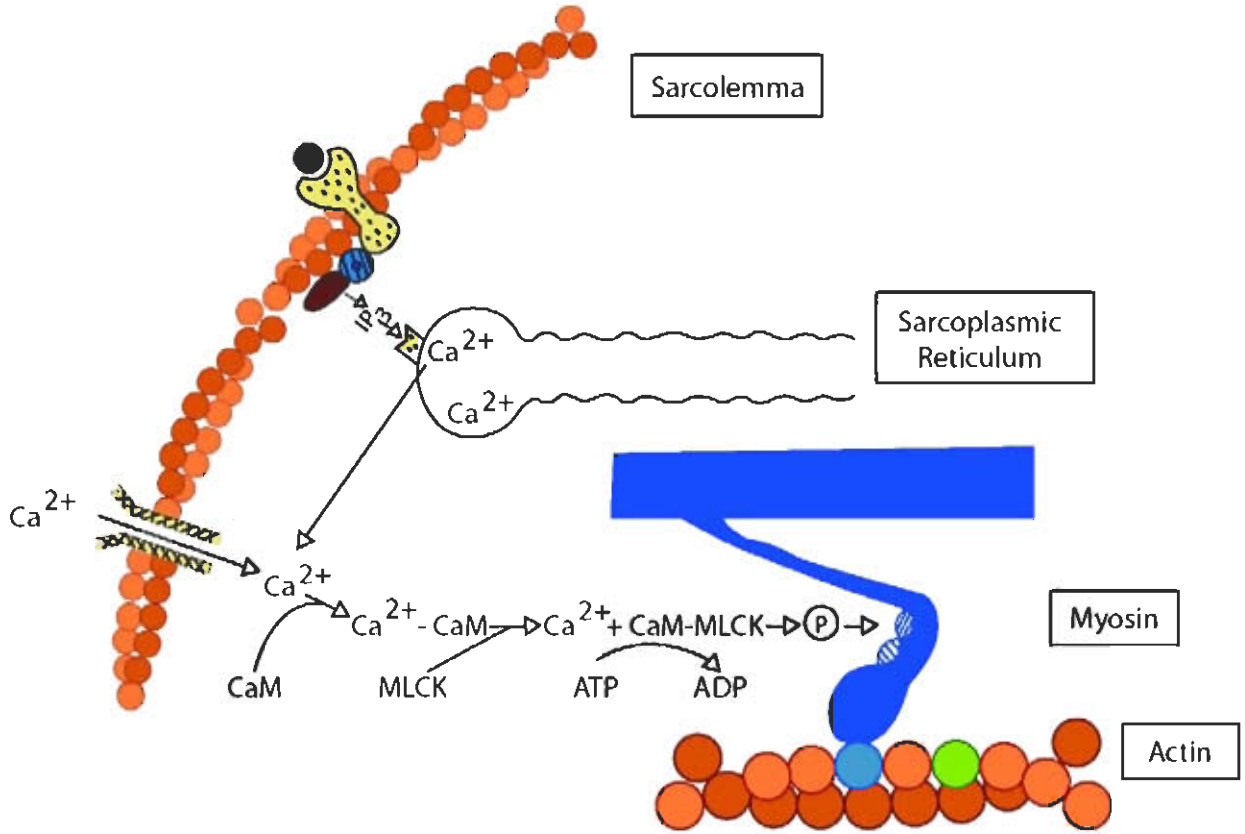


Figure 7: *Mechanism of Smooth Muscle Contraction. Calcium enters the cytoplasm through voltage or ligand gated membrane channels, or it can be released from intracellular stores in the the sarcoplasmic reticulum (SR). Intracellular store calcium release involves stimulating ligand activation of a series of second messengers to produce inositol triphosphate (IP_3). IP_3 binds to the Ca^{++} receptor on the SR membrane and increases cytoplasmic $[Ca^{++}]$. When cytoplasmic calcium reaches a threshold, contraction is initiated. Intracellular Ca^{++} forms complexes with calmodulin (CaM), a regulatory protein that activates the myosin light chain kinase (MLCK), which in turn phosphorylates one of the light chains of the myosin molecule and allows the myosin head to bind the actin filament, causing muscle contraction. (From Barany, M.,* Biochemistry of Smooth Muscle Contraction. *Academic Press, 1996).*

Figure by MIT OCW. After Barany, M., Biochemistry of Smooth Muscle Contraction. *Academic Press, 1996).*

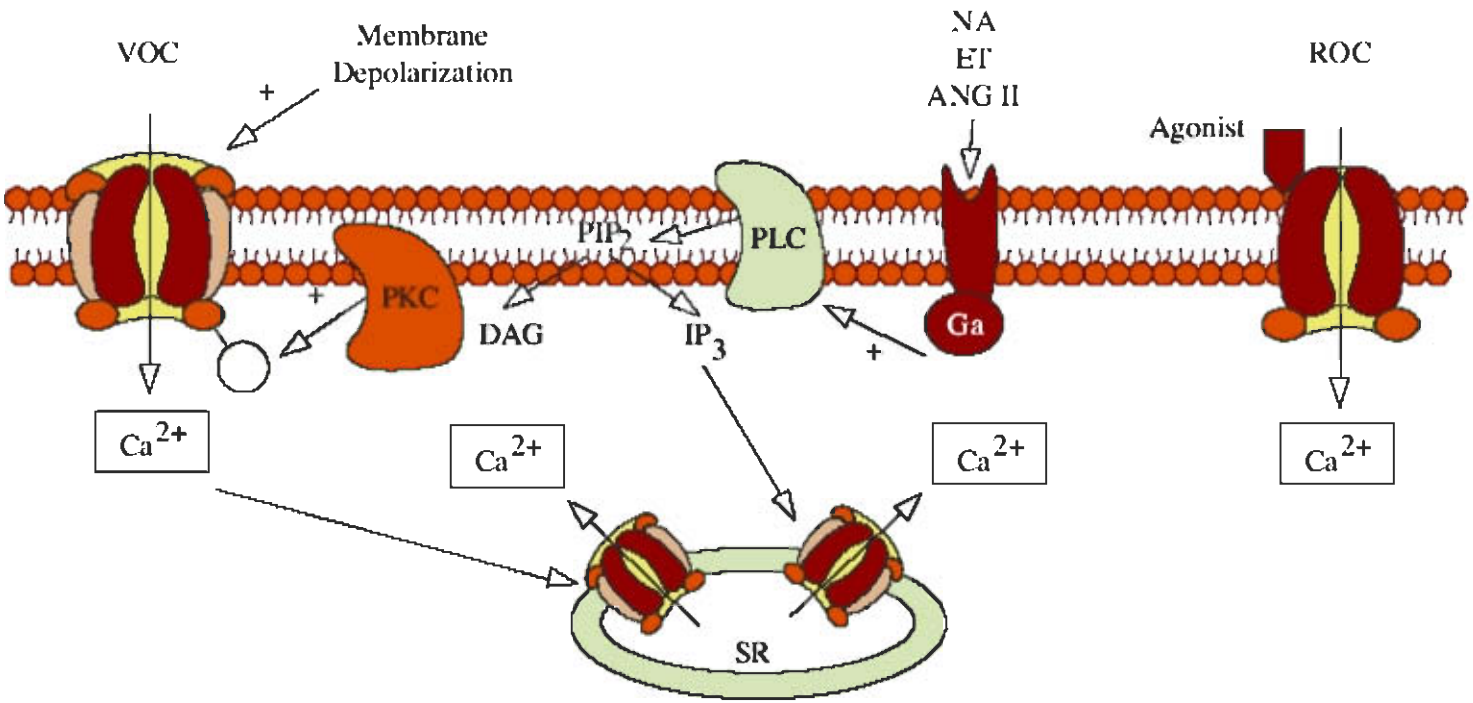
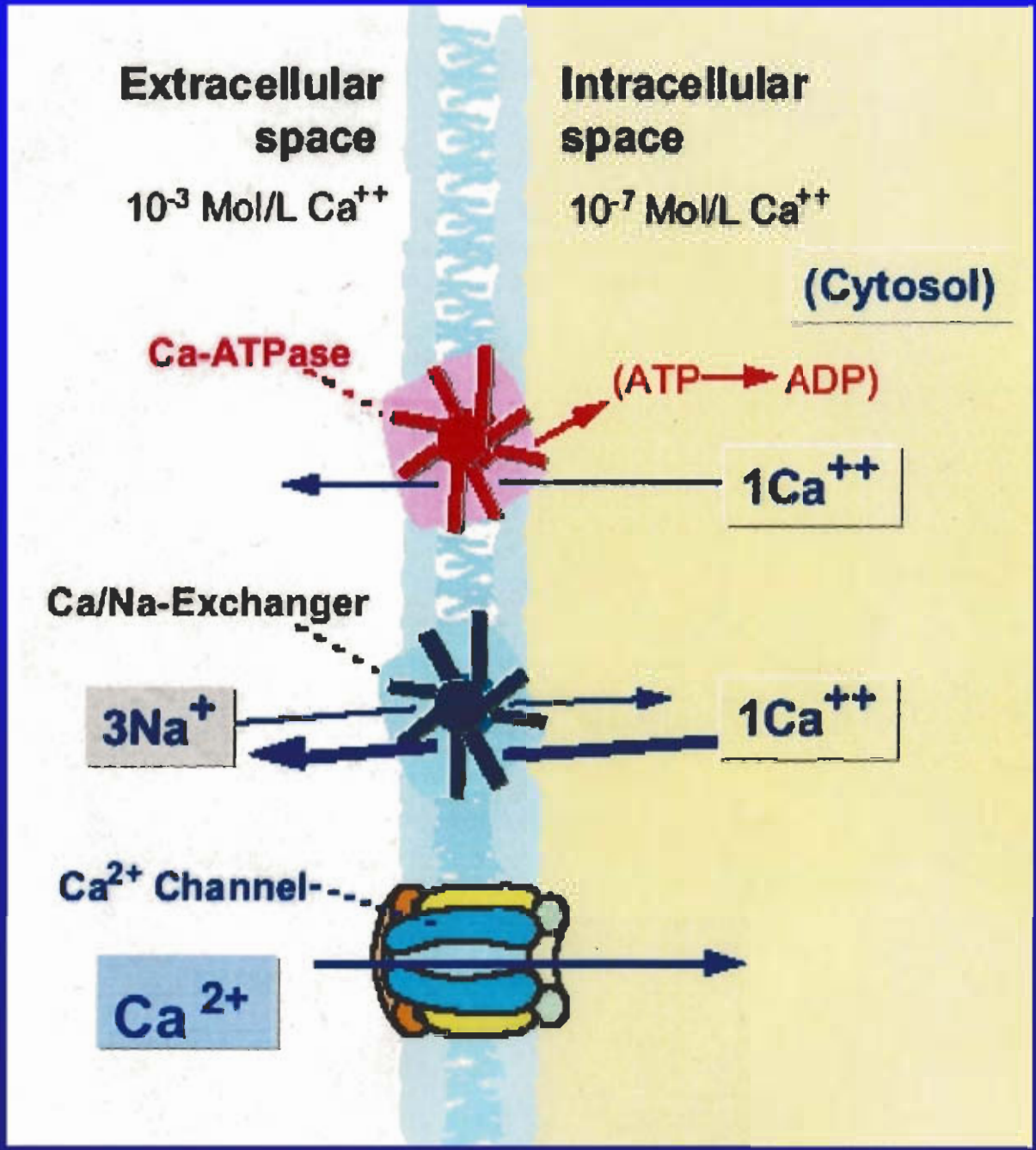


Figure 8: *Agonists such as norepinephrine (NA), endothelin (ET), and angiotensin II (ANG II) stimulate Ca^{++} release from the sarcoplasmic reticulum by binding G protein coupled receptors, activating phospholipase C (PLC) and causing inositol triphosphate (IP3) formation. Calcium can also enter cytoplasm through receptor operated calcium channels (ROC) or voltage operated channels (VOC).*

Figure by MIT OCW.


Extracellular space
10^{-3} Mol/L Ca^{++}
Intracellular space
10^{-7} Mol/L Ca^{++}
(Cytosol)
Ca-ATPase
(ATP → ADP)
$1Ca^{++}$
Ca/Na-Exchanger
$3Na^{+}$
$1Ca^{++}$
Ca^{2+} Channel
Ca^{2+}

Membrane Potential and Artery Tone

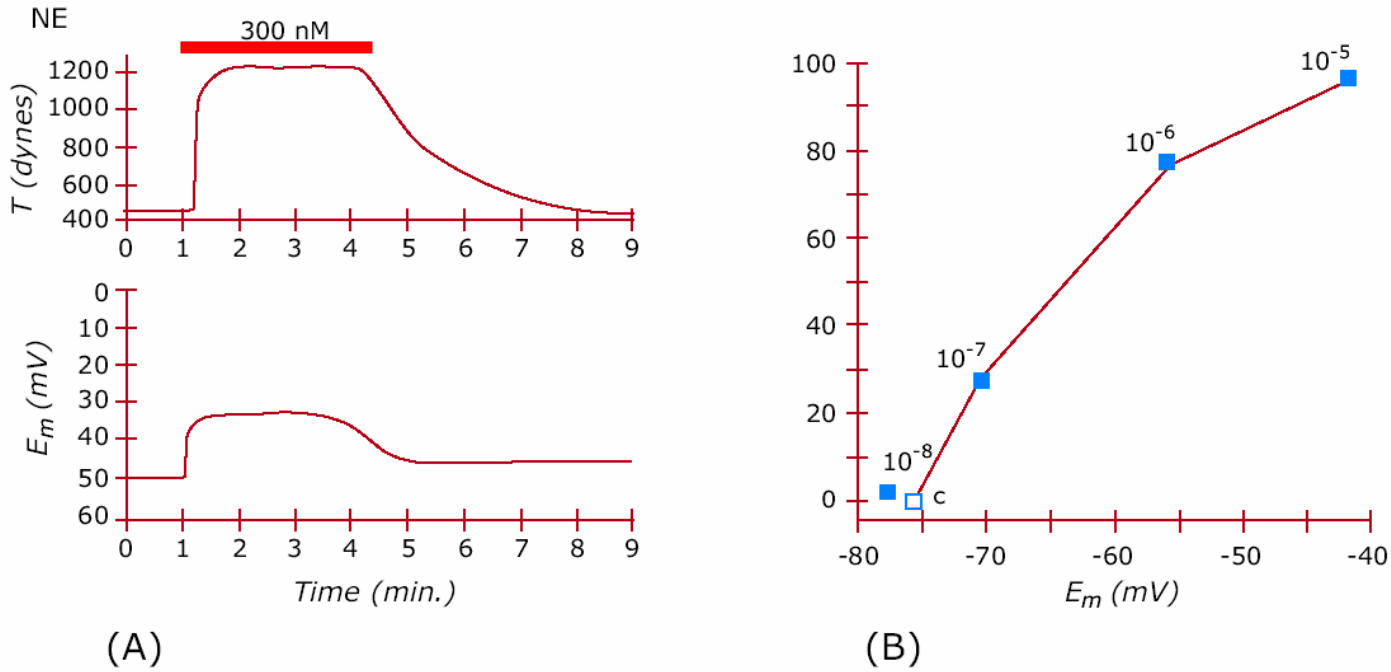
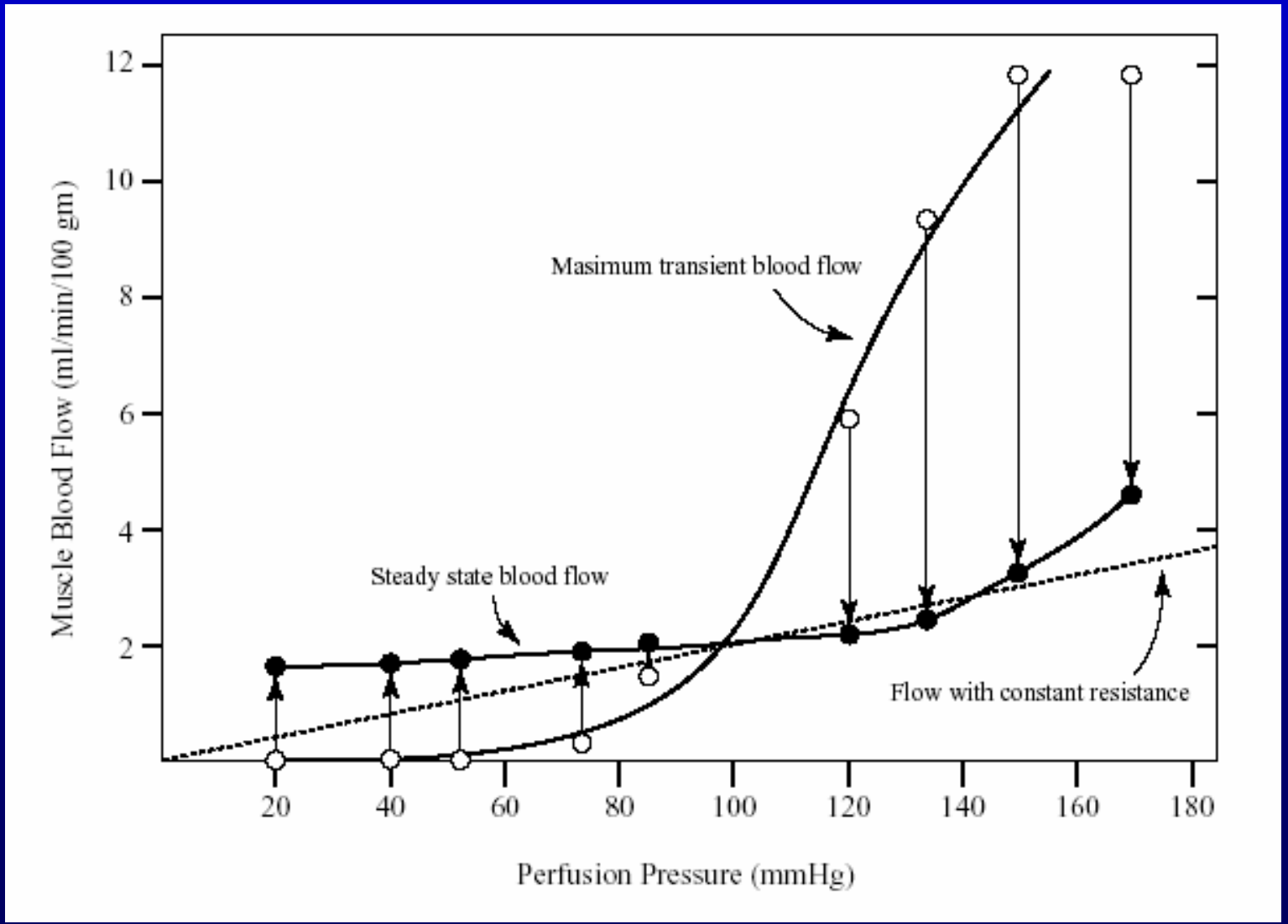


Figure 10: *Relationship between membrane potential and artery tone.* A. *Graded depolarization and corresponding tension allow a steady state tone to be developed in response to norepinephrine stimulation. The tracings (left) illustrate a typical relationship between artery tension and membrane potential (E_m). Both E_m and tension levels can be maintained relatively constant for many minutes during stimulation by vasoconstrictors.* B. *Different doses of norepinephrine causes various degrees of depolarization, allowingexperimental measurement of the relationship between tension (% of max) and membrane potential (mV). (From Sperelakis, N.,* Cell Physiology Source Book. *Academic Press, 1995: 568 and 570.)*

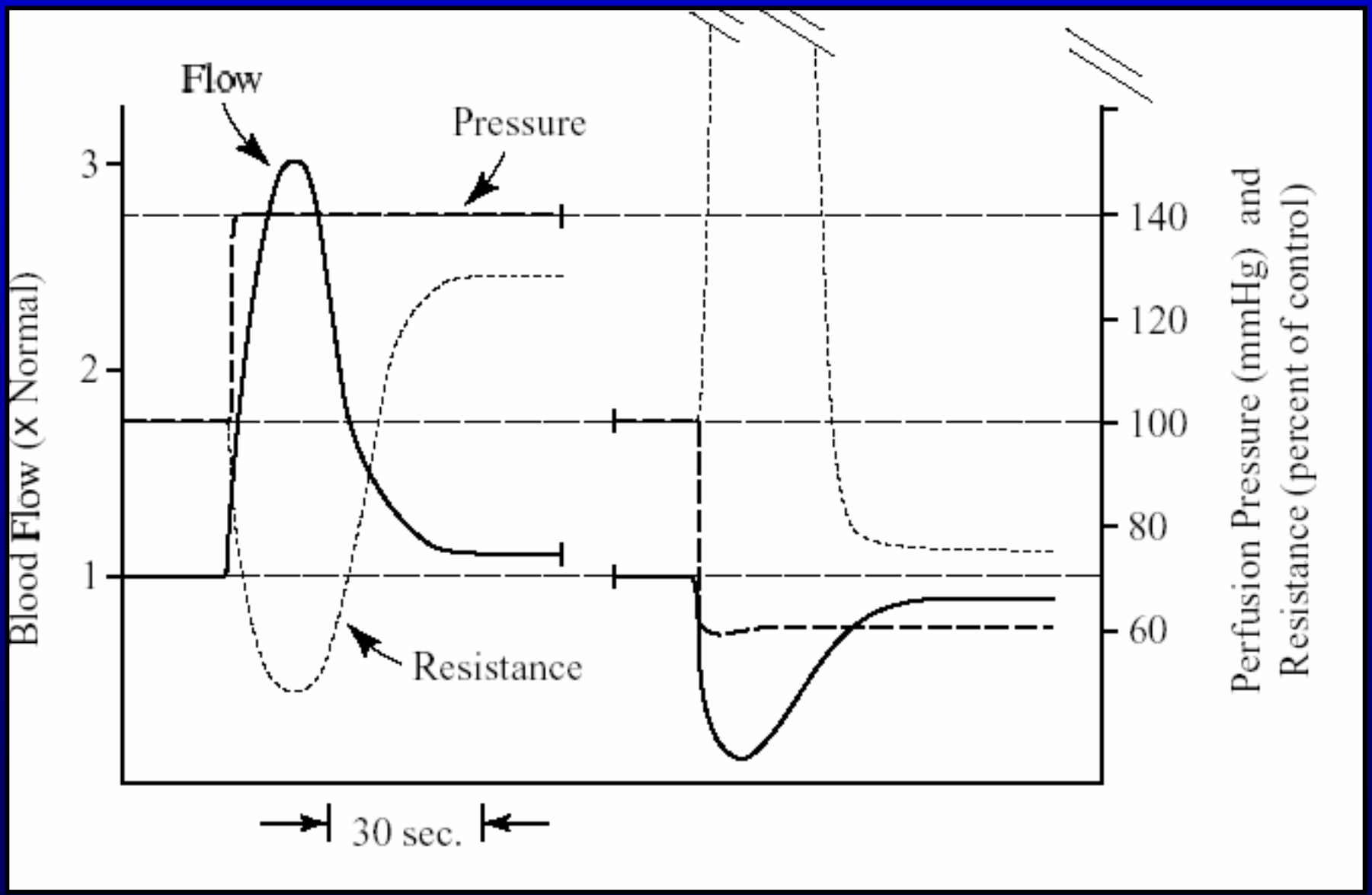
Table 2: Factors and Mechanisms that Control Smooth Muscle Contraction

Activator/ligand	Channel/Receptor	Effect on VSM	Mechanism
Stretch	Stretch-activated Ca channels	Contraction	Stretch opens channels, allowing Ca^{++} to enter cytoplasm
Membrane depolarization	Voltage-gated Ca channels	Contraction	↑Ca influx as membrane is depolarized
Norepinephrine—(humoral or neurotransmitter)	α_1 adrenoceptors	Constriction	Activates phospholipase C (PLC) causing formation of inositol triphosphate (IP_3) that stimulates SR to release calcium into cytoplasm
Angiotensin II	A-II receptors	Constriction	Same as above
Endothelin (ET-1)	ET_A receptors	Constriction	Same as above
Acetylcholine	Muscarinic receptor	Constriction	Same as above
Membrane hyperpolarization	K^+ channels	Relaxation	Membrane hyperpolarization closes Ca channels
Epinephrine	β_2 receptors	Relaxation	Stimulates adenyl cyclase via G-protein to produce increased levels of cAMP that inhibits activity of MLCK and leads to relaxation.
Atrial naturetic protein (ANP)		Relaxation	Same as above
ATP, Adenosine	ATP receptor	Relaxation	Same as above
↓O_2, ↑CO_2, ↑[H^+] ↑[K^+], lactic acid		Relaxation	
Nitric Oxide (NO)	Diffuses into cell	Relaxation	Activates guanylyl cyclase to form ↑cGMP that causes relaxation by: 1. decreasing permeability of Ca^{++} channels, 2. hyperpolarizing membrane by increasing permeability of K^+ channels, 3. IP3 that reduces Ca release from SR, 4. Ca^{++} pump activity to lower calcium concentration.

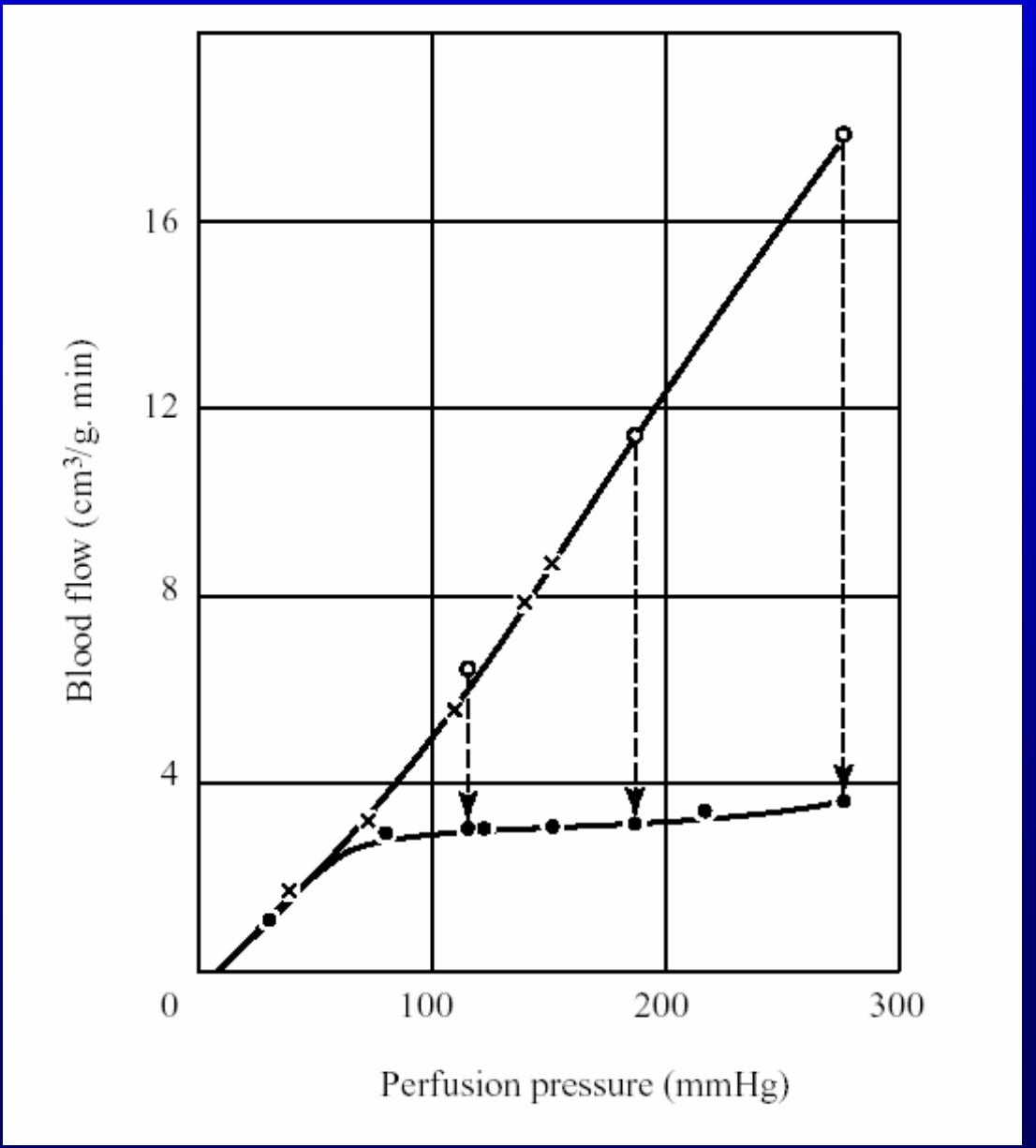
Autoregulation in canine hindlimb



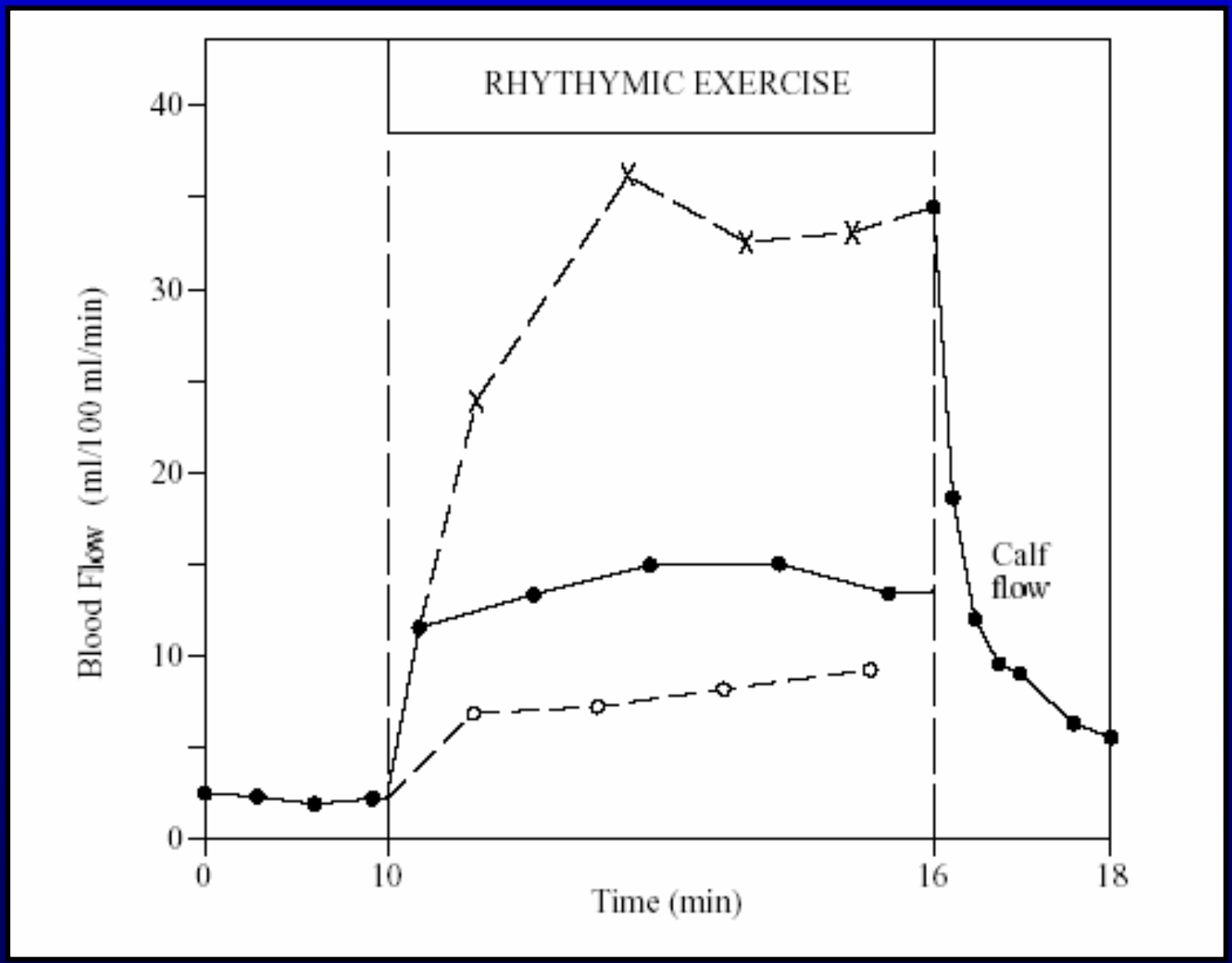
Dynamics of Autoregulation



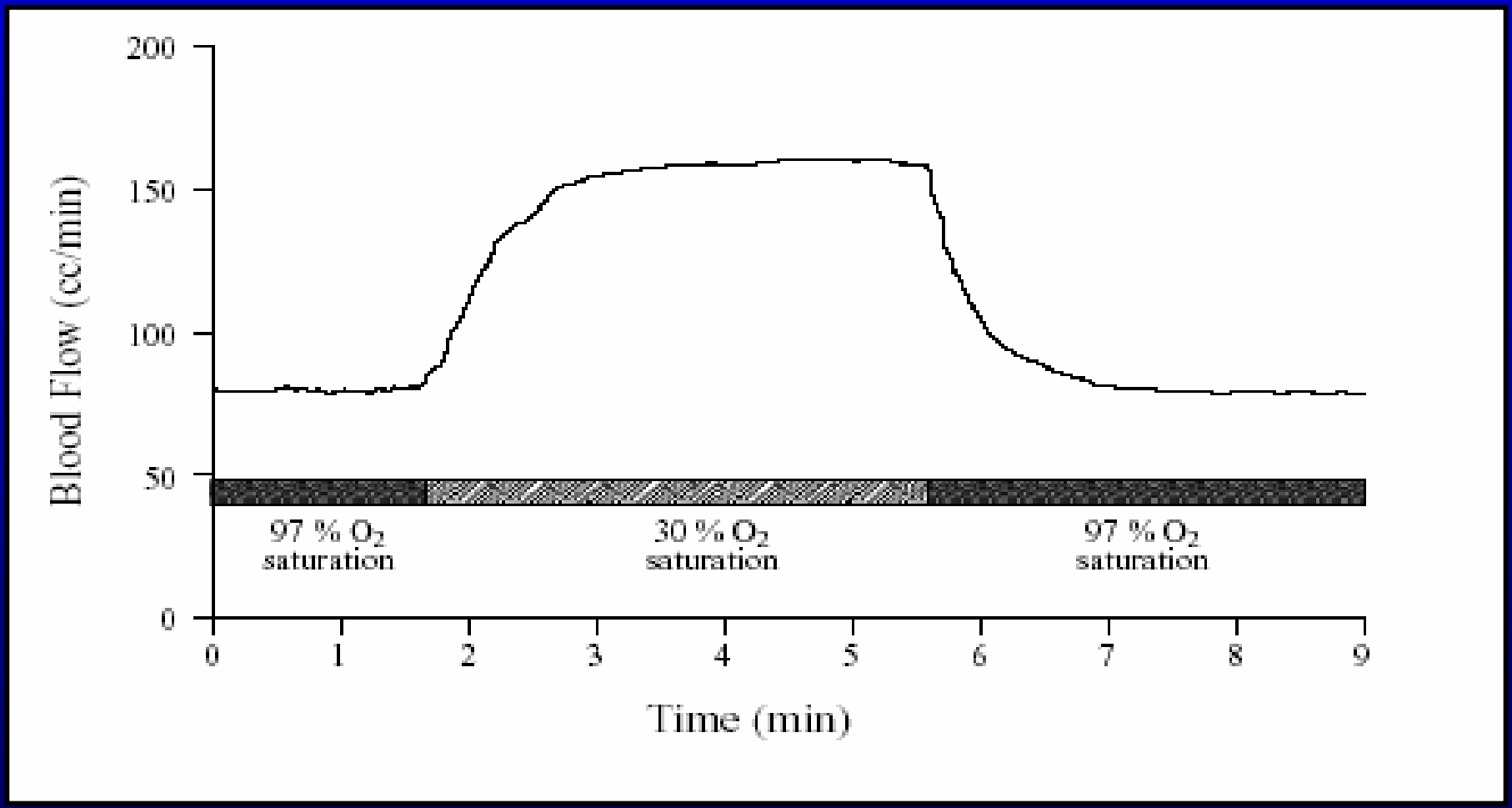
Autoregulation in Kidney



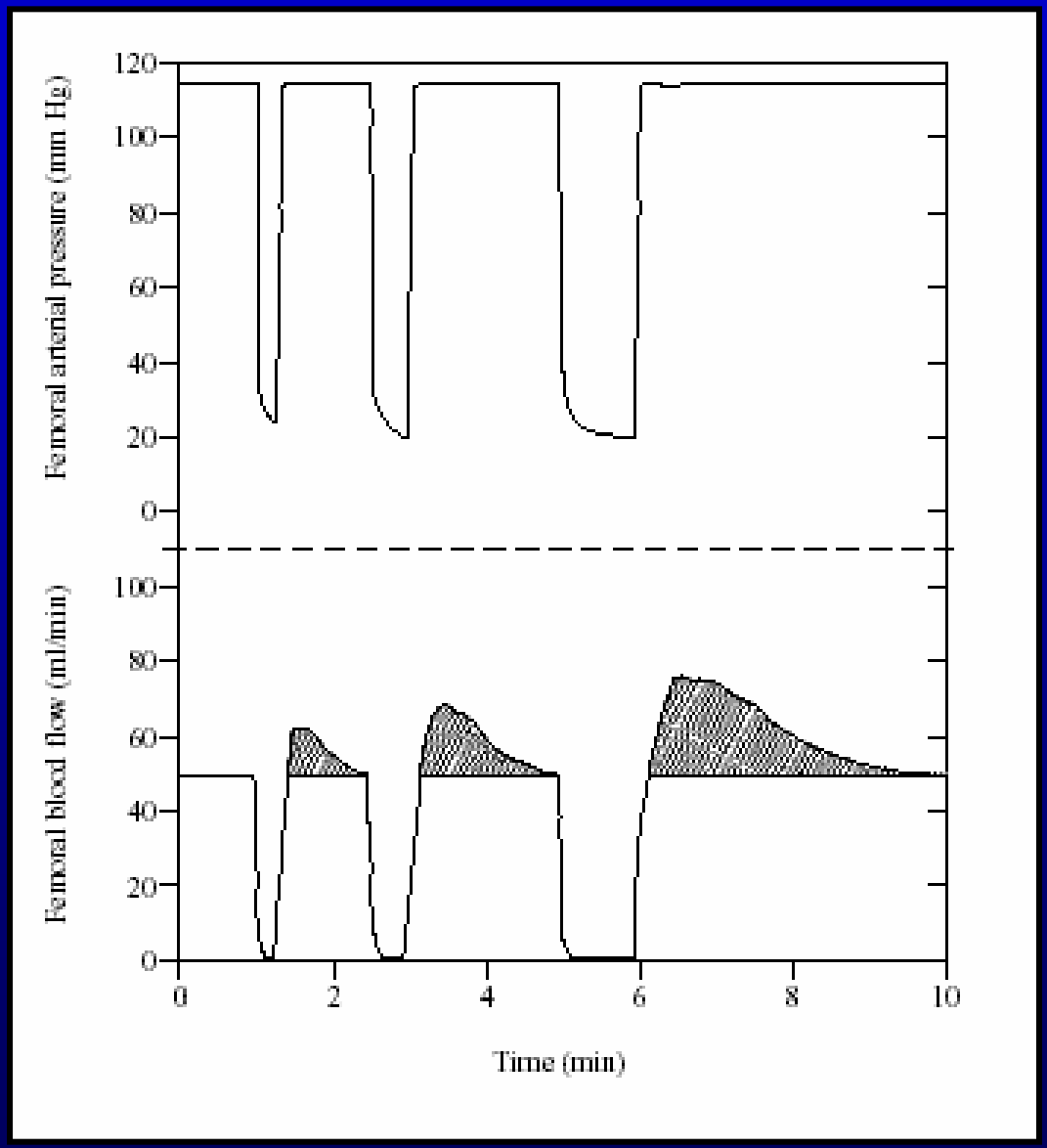
Exercise and Blood Flow



Autoregulation in Hypoxemia

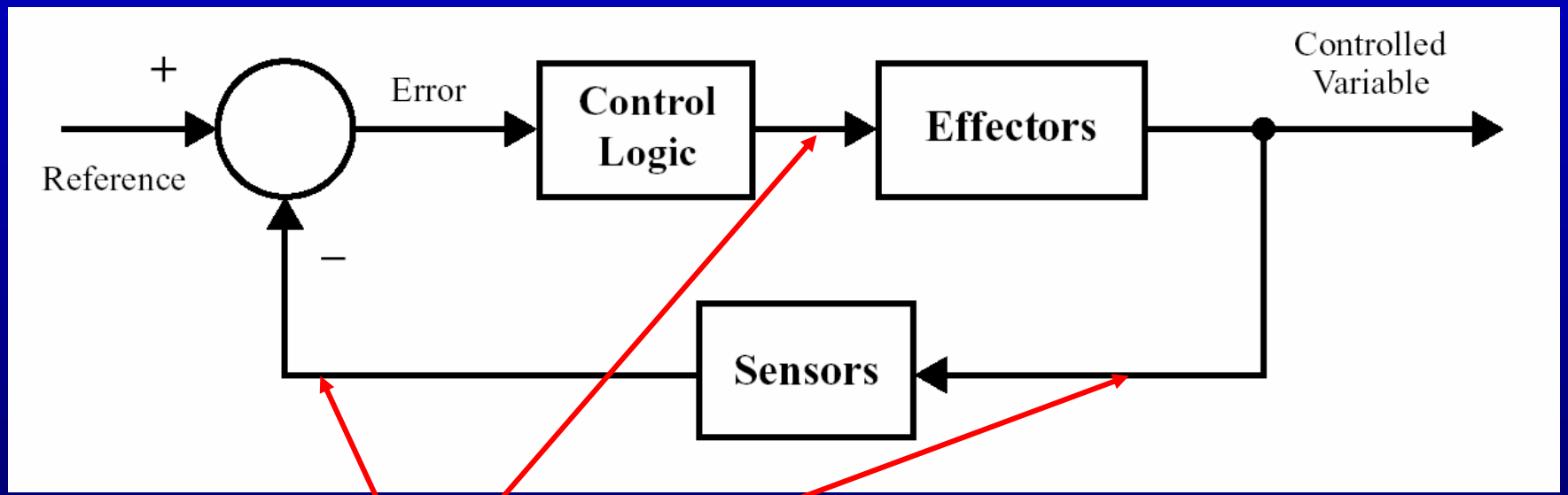


Reactive Hyperemia



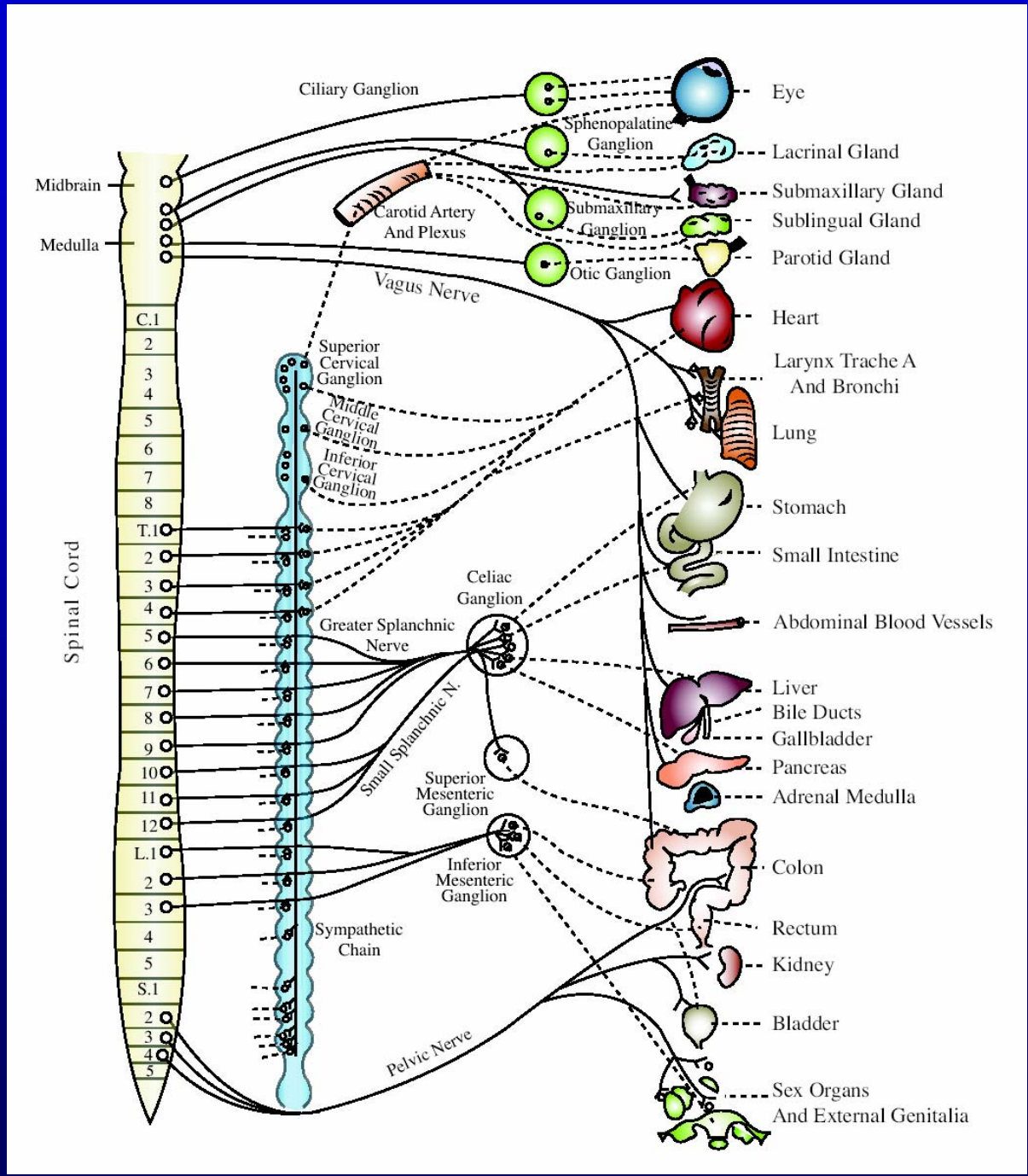
Extrinsic Control of the Cardiovascular System

Elements of a Control System

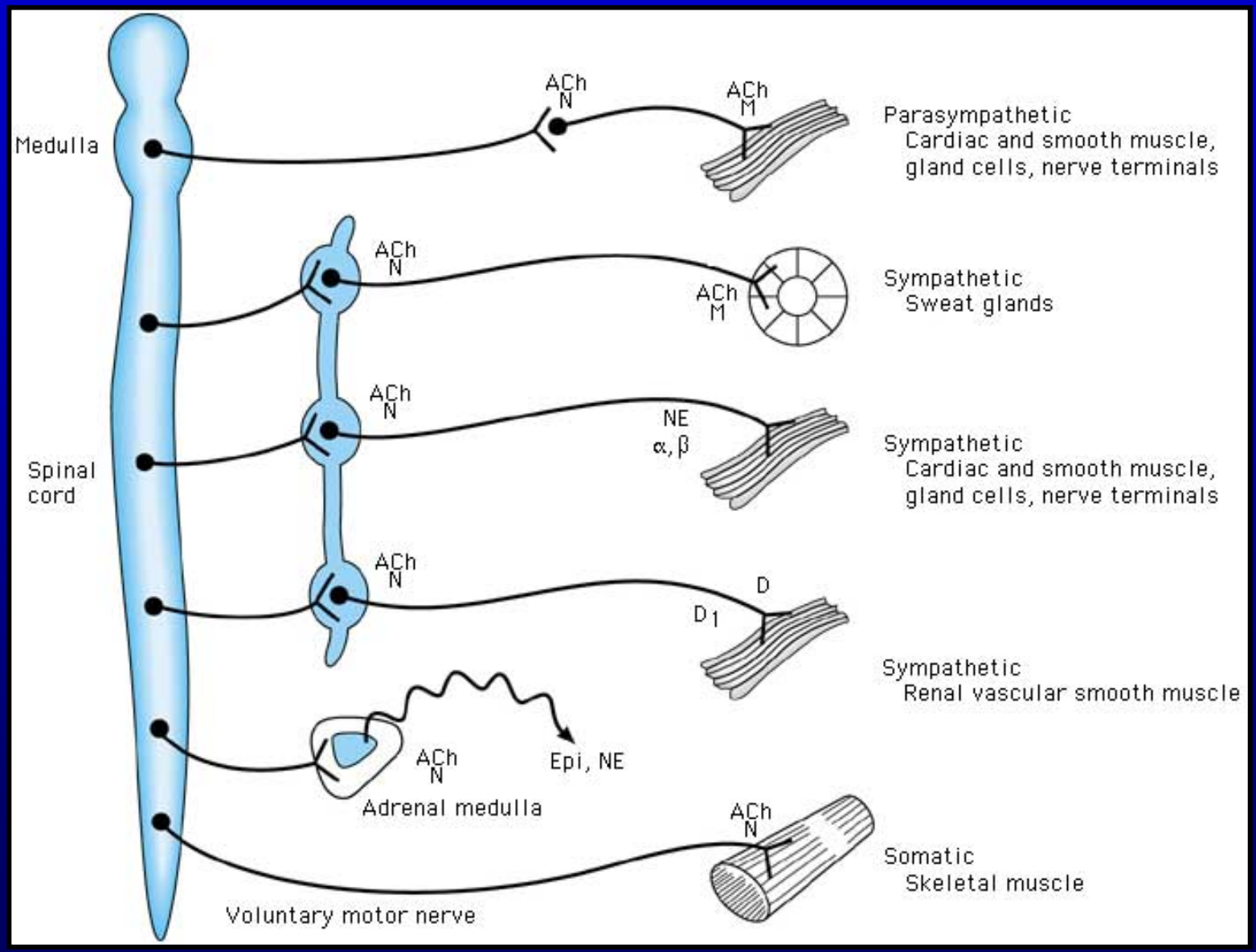


Communication system

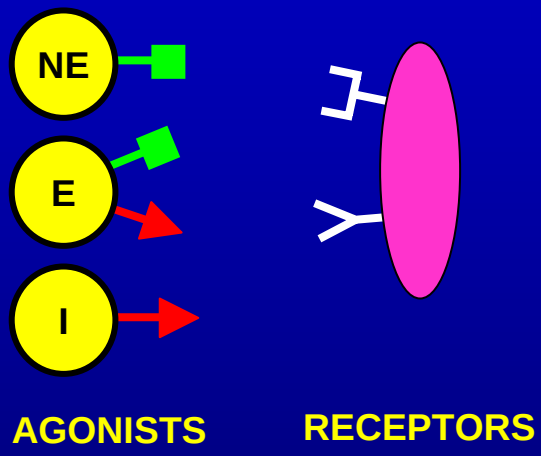
Autonomic Nervous System



Schema of the Autonomic NS



Adrenergic Receptors



α–receptors: vasoconstriction, intestinal relaxation, pupillary dilation

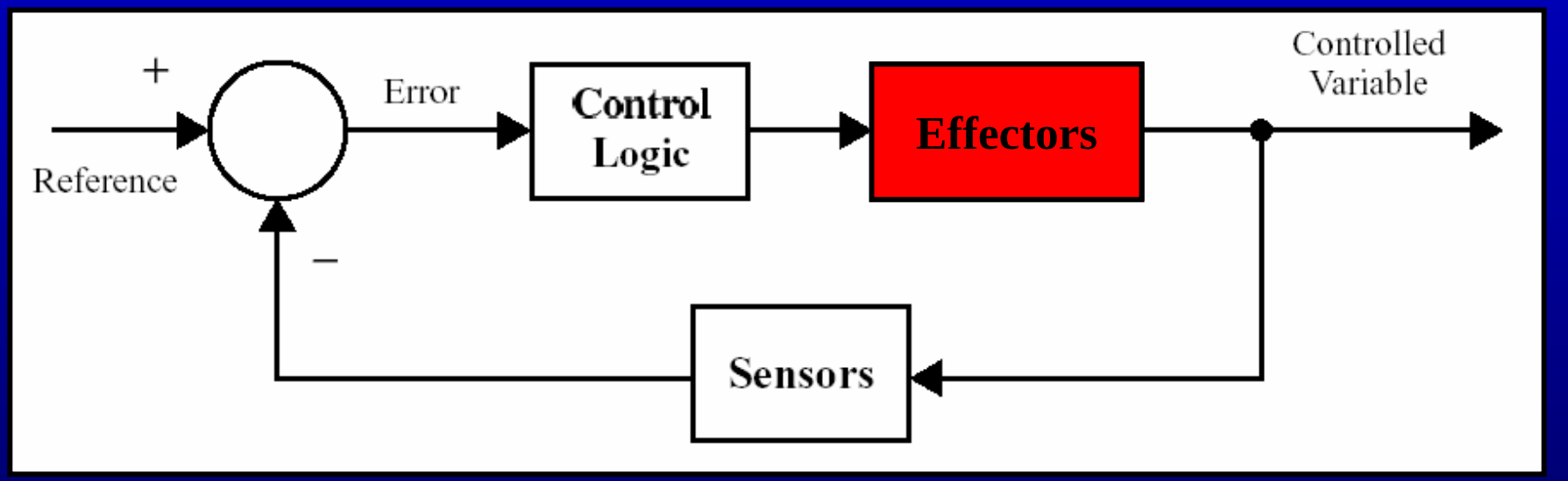
$\beta 1$– receptors: cardiac increased HR, contractility

$\beta 2$– vascular relaxation (dilation), bronchial dilation

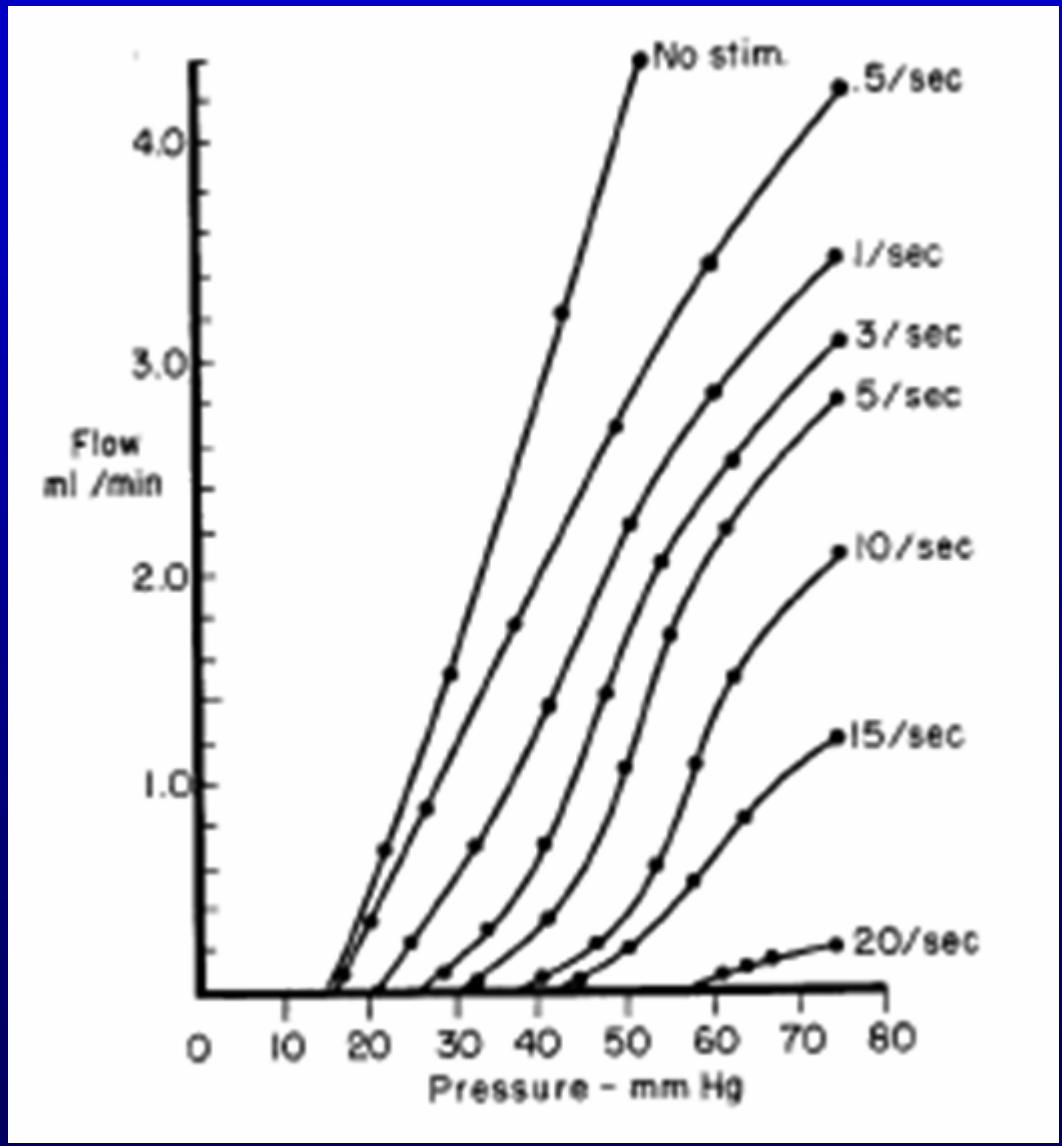
Table 3: Responses of Effector Organs to Autonomic Nerve Impulses

EFFECTOR ORGANS	ADRENERGIC IMPULSES		CHOLINERGIC IMPULSES
	Response Type	*Responses*	*Responses*
Eye			
Radial muscle, iris	α	Contraction (mydriasis) ++	
Sphincter muscle, iris			Contraction (miosis) +++
Ciliary muscle	β	Relaxation for far vision (slight effect)	Contraction for near vision +++
Heart			
S-A node	β	Increase in heart rate ++	Decrease in heart rate; vagal arrest +++
Atria	β	Increase in contractility and conduction velocity ++	Decrease in contractility, and (usually) increase in conduction velocity ++
A-V node	β	Increase in automaticity and conduction velocity ++	Decrease in conduction velocity; A-V block +++
His-Purkinje system	β	Increase in automaticity and conduction velocity +++	Little effect
Ventricles	β	Increase in contractility, conduction velocity, automaticity, and rate of idioventricular pacemakers +++	Slight decrease in contractility claimed by some
Arterioles			
Coronary	α, β	Constriction +; dilatation ++	Dilatation ±
Skin and mucosa	α	Constriction +++	Dilatation
Skeletal muscle	α, β	Constriction ++; dilatation ++	Dilatation +
Cerebral	α	Constriction (slight)	Dilatation
Pulmonary	α, β	Constriction +; dilatation	Dilatation
Abdominal viscera; renal	α, β	Constriction +++; dilatation +	
Salivary glands	α	Constriction +++	Dilatation ++
Veins (Systemic)	α	Constriction ++	
Lung			
Bronchial muscle	β	Relaxation +	Contraction ++
Bronchial glands		Inhibition (?)	Stimulation +++
Stomach			
Motility and tone	α, β	Decrease (usually) +	Increase +++
Sphincters	α	Contraction (usually) +	Relaxation (usually) +
Secretion		Inhibition (?)	Stimulation +++
Intestine			
Motility and tone	β	Decrease (usually) +	Increase +++
Sphincters	α	Contraction (usually) +	Relaxation (usually) +
Secretion		Inhibition (?)	Stimulation +++
Gallbladder and Ducts		Relaxation +	Contraction +
Urinary Bladder			
Detrusor	β	Relaxation (usually) +	Contraction +++
Trigone and sphincter	α	Contraction ++	Relaxation ++
Adrenal Medulla			Secretion of epinephrine and norepinephrine

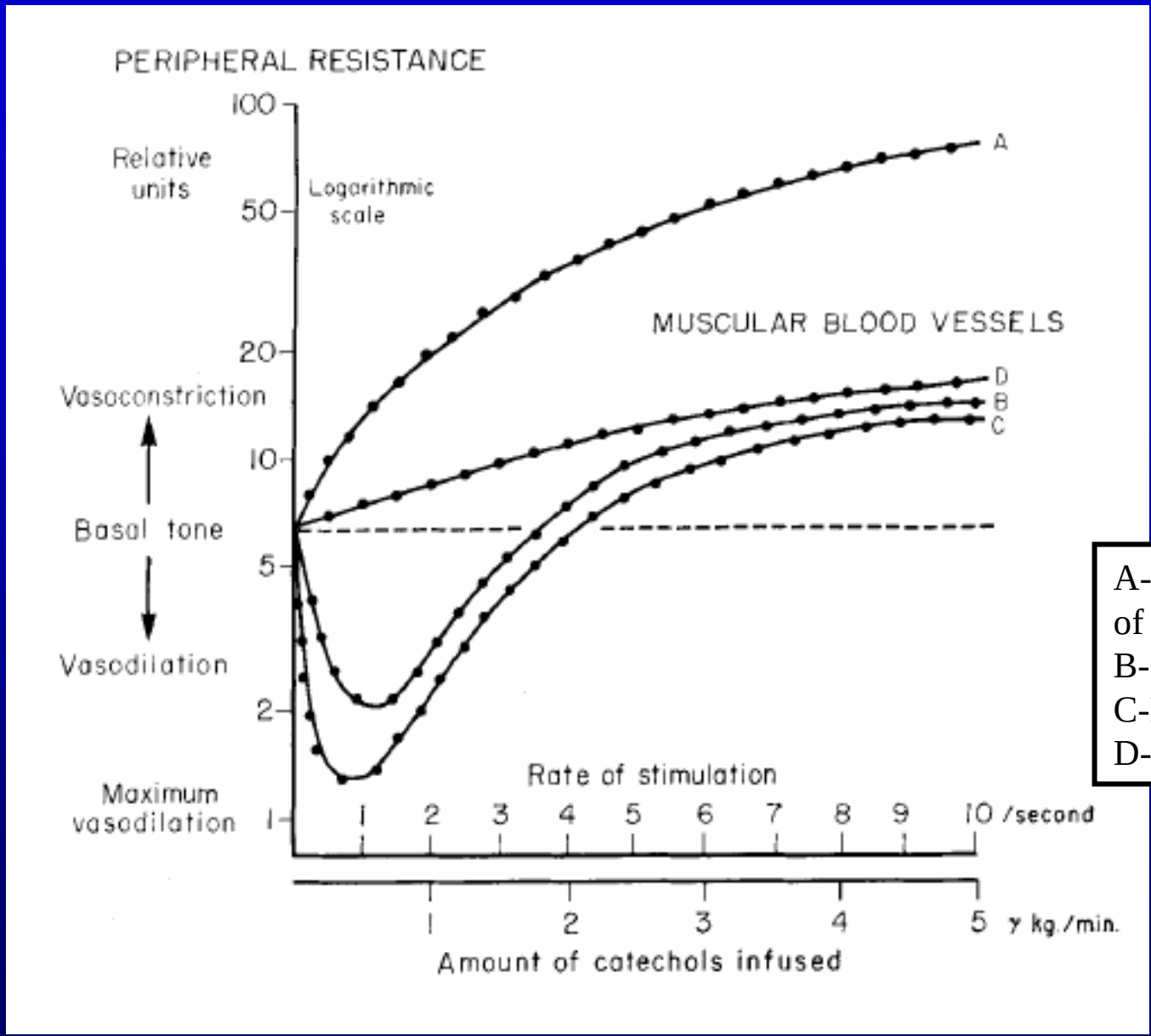
Effectors


+
Reference
Error
Control Logic
Effectors
Controlled Variable
–
Sensors

Effector: Resistance

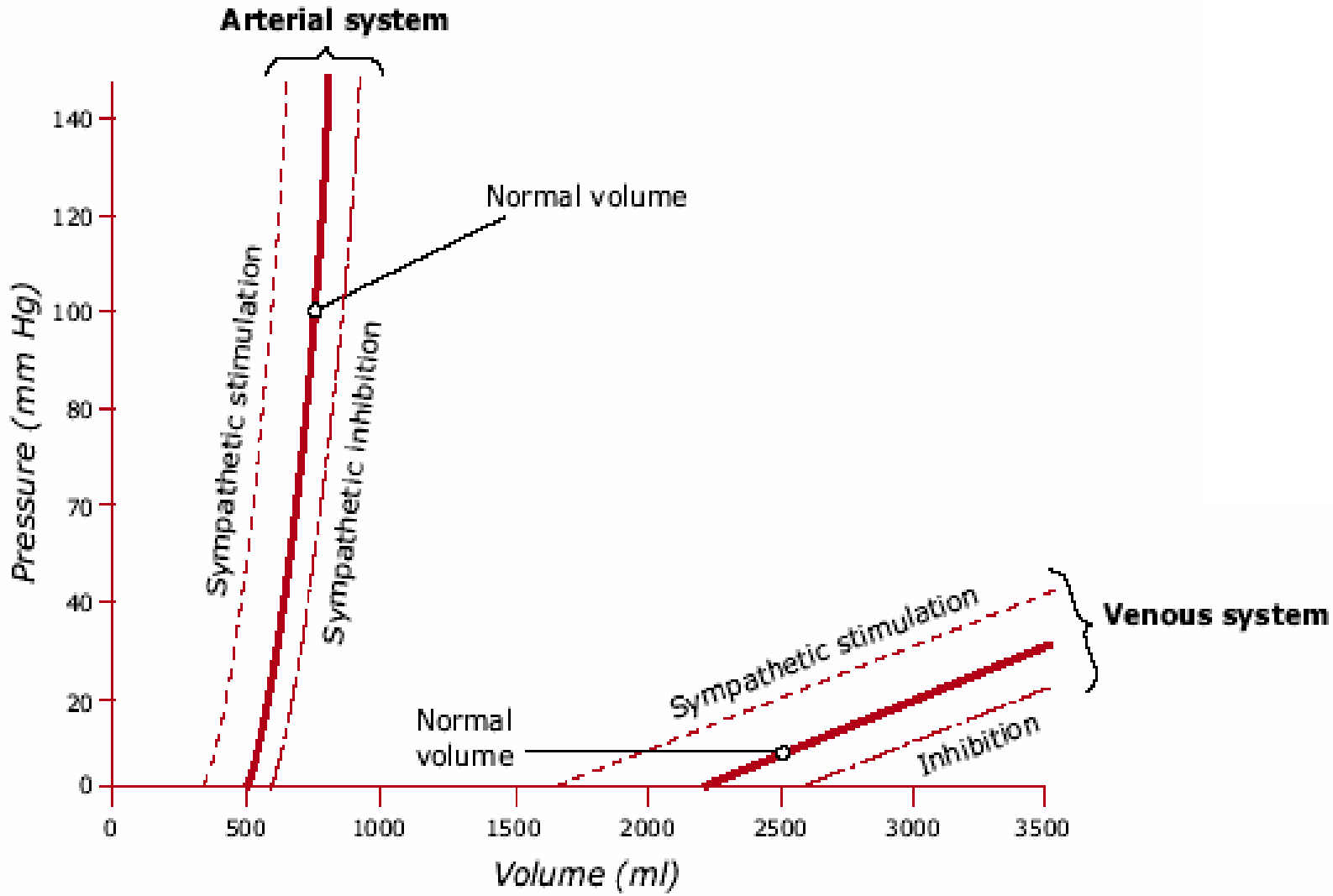


Rabbit ear vascular bed with increasing Sympathetic stimulation

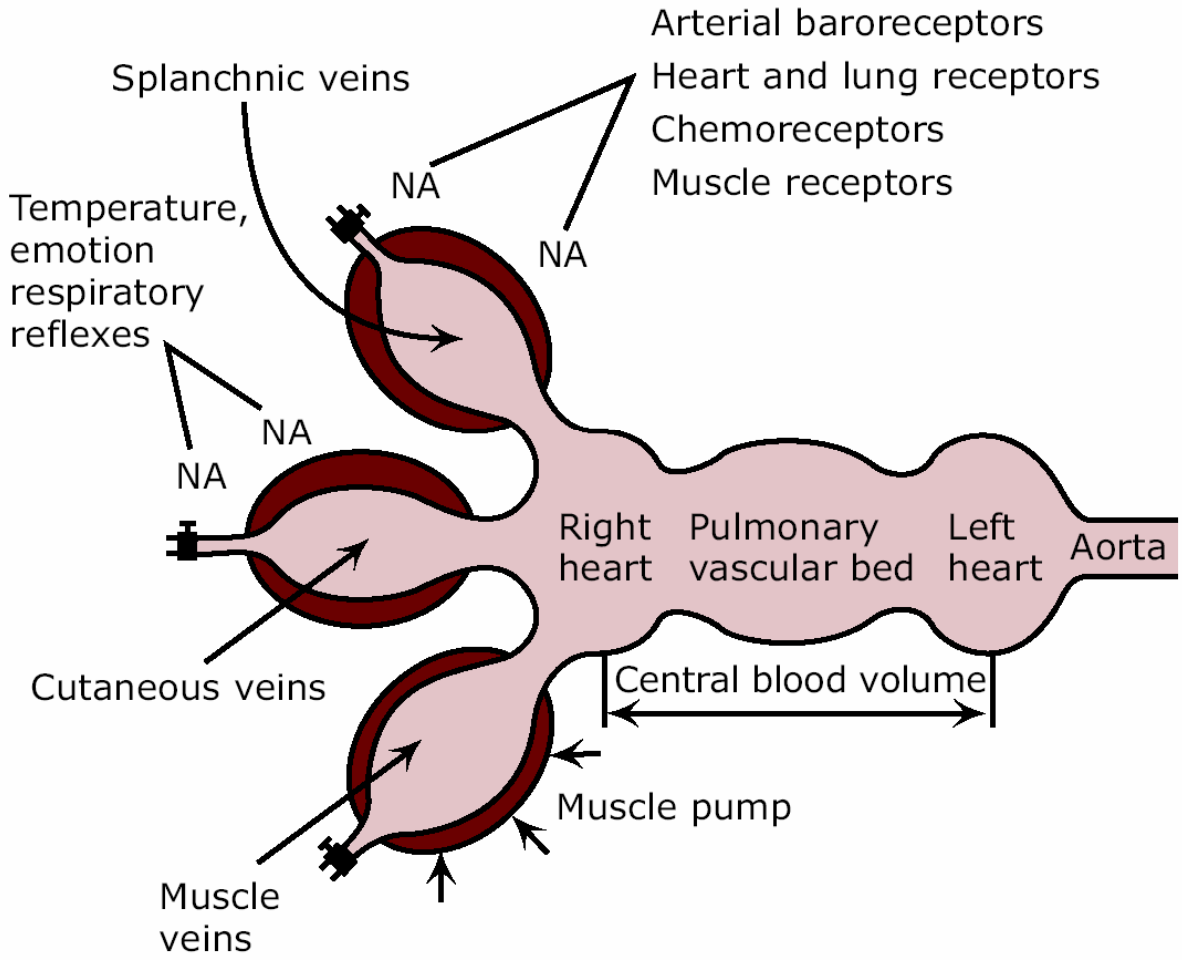


A-electrical stimulation of symp. fibers to muscle
B-elect. stim of adrenals
C-Epinephrine
D-Norepinephrine

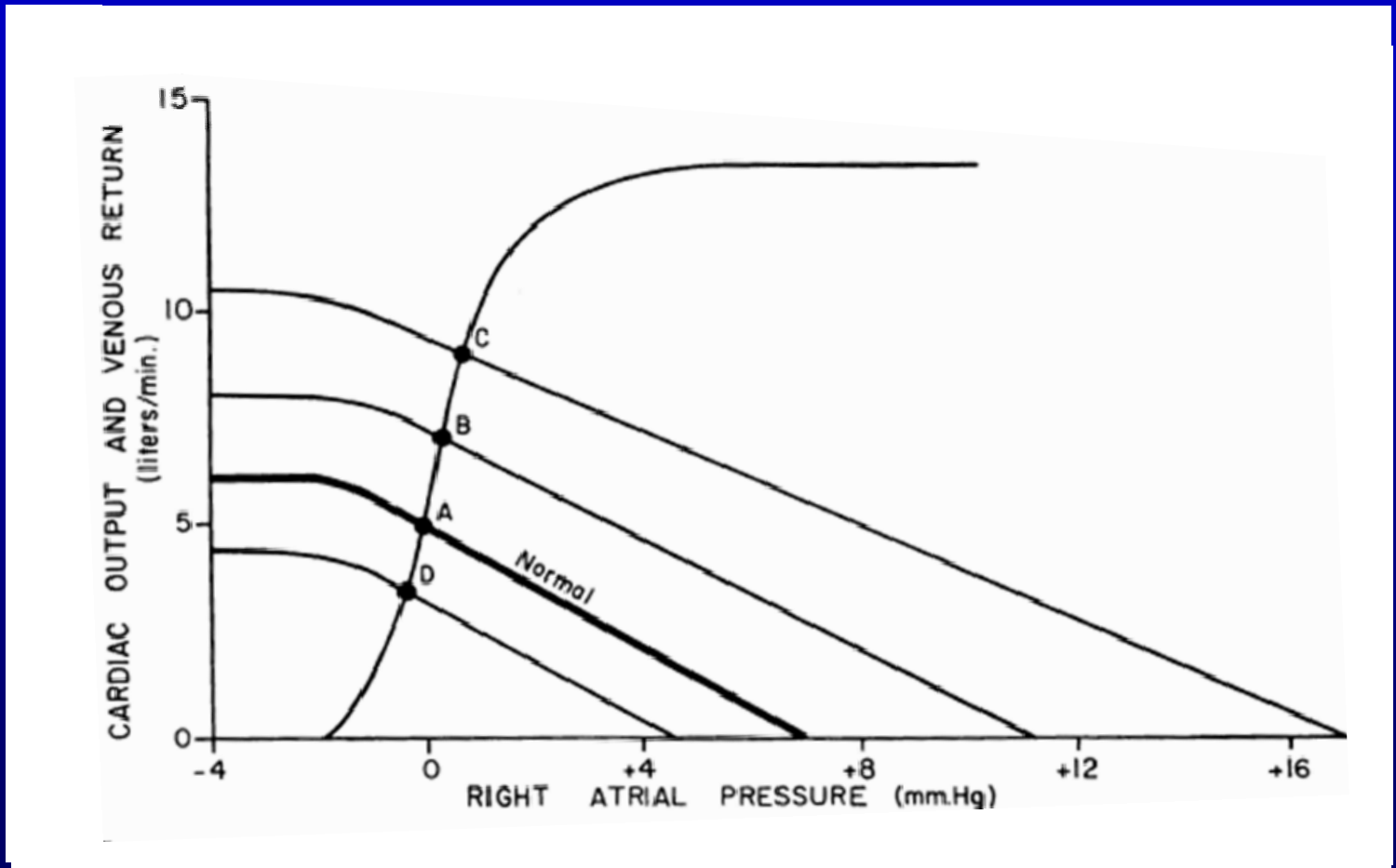
Effector: Venous tone (ZPFV)



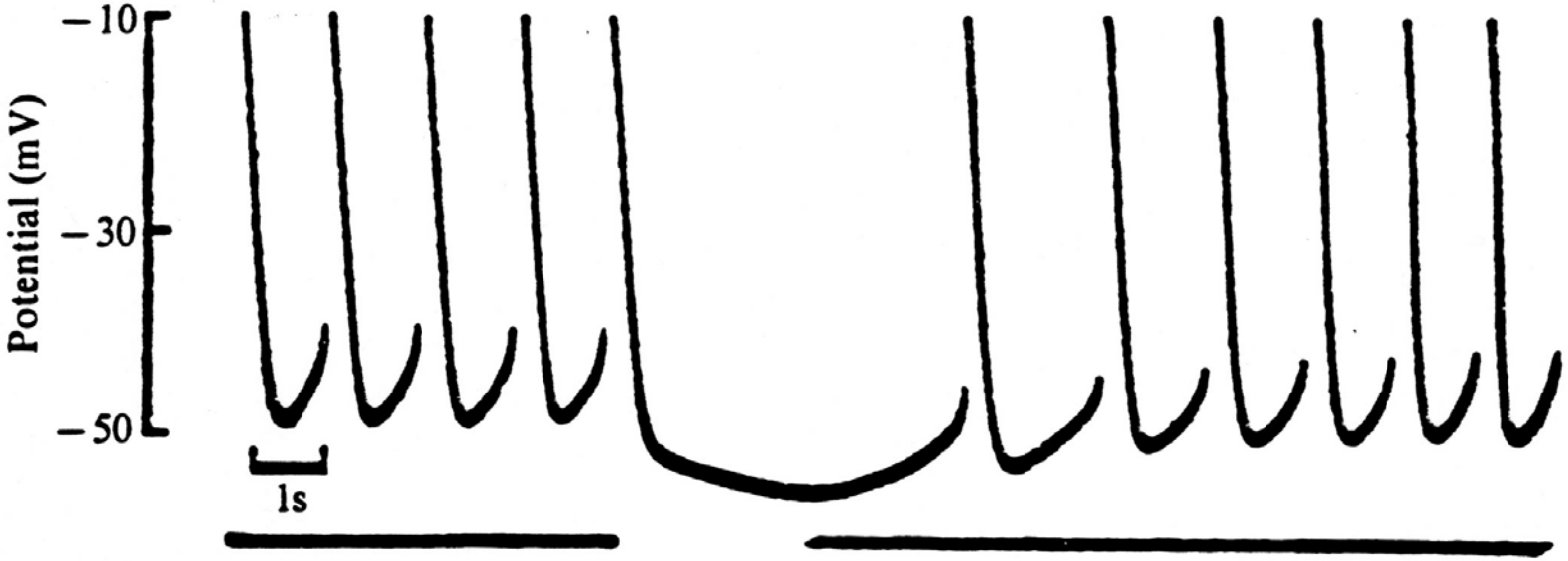
Venoconstriction



Sympathetic Stimulation of Peripheral Circulation Only



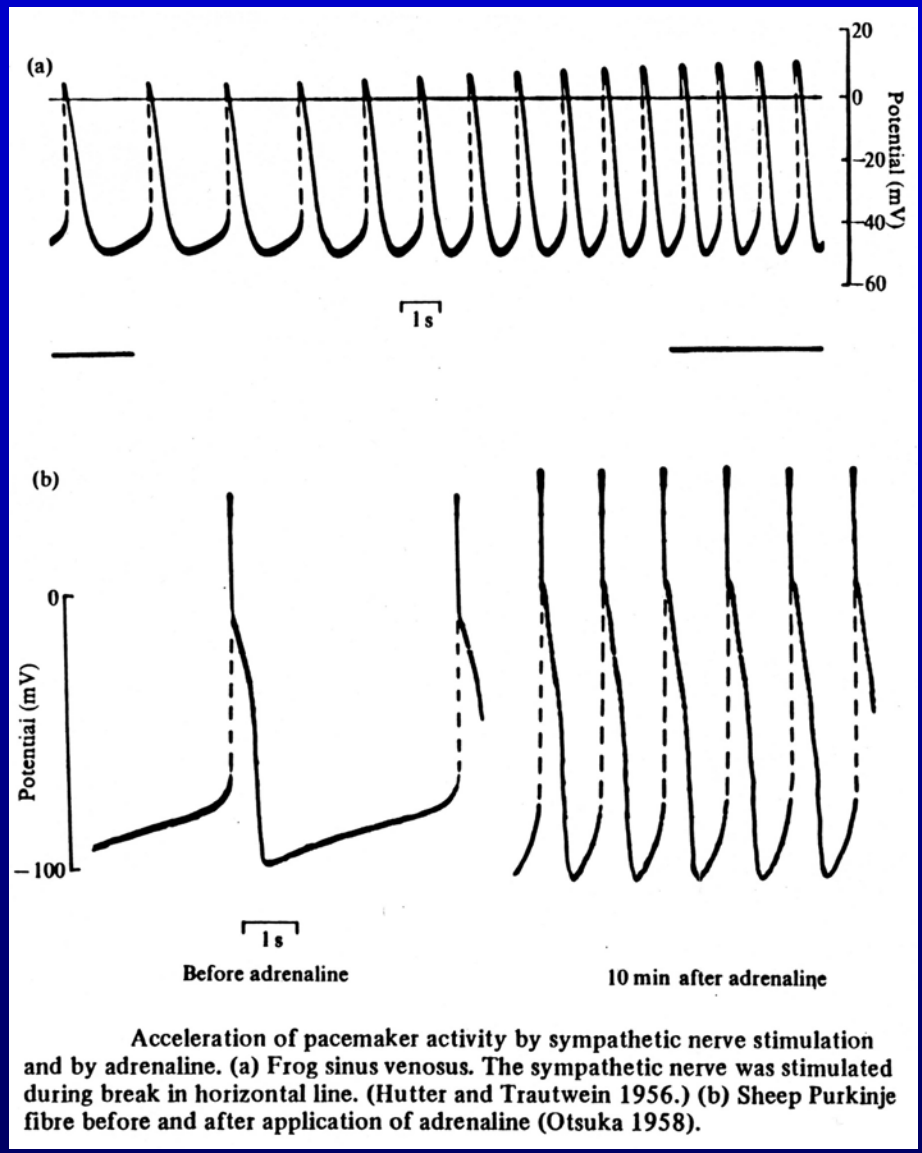
Effector: Heart Rate
Vagal Slowing



Membrane potentials recorded in frog sinus venosus during vagus nerve stimulation (indicated by interruption in horizontal line). (Hutter and Trautwein 1956.)

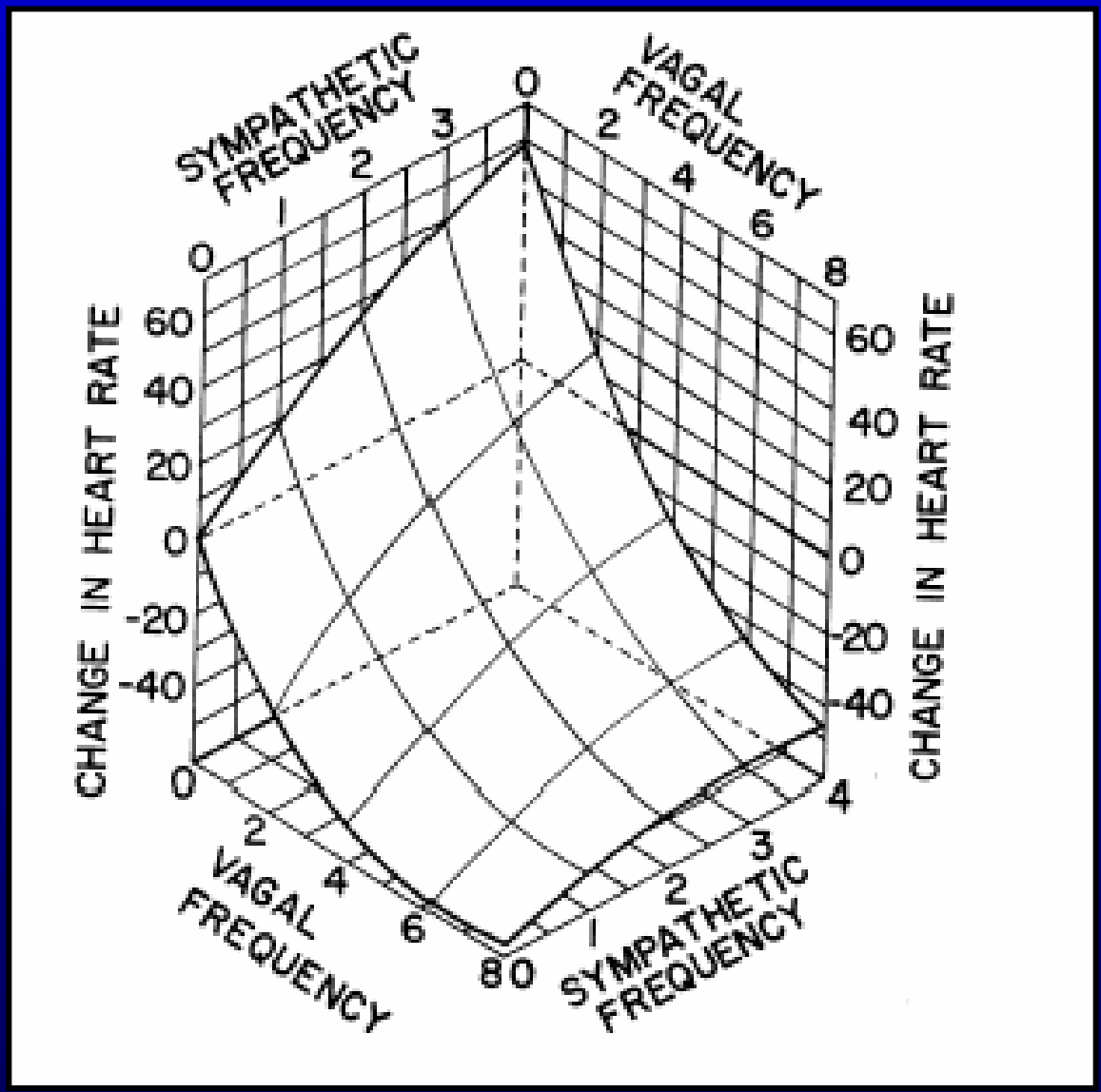
Effector: Heart Rate

Sympathetic Acceleration

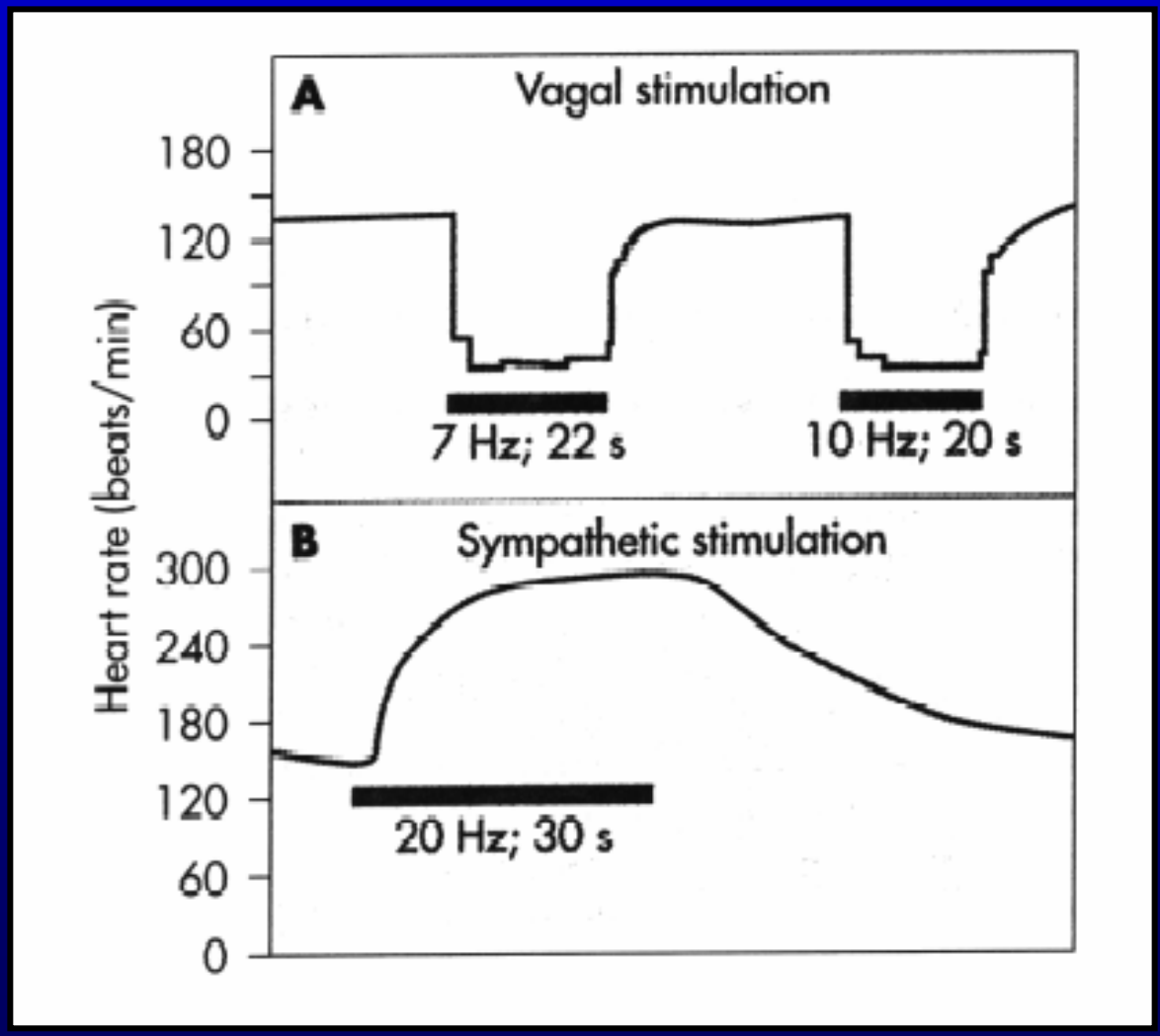


Acceleration of pacemaker activity by sympathetic nerve stimulation and by adrenaline. (a) Frog sinus venosus. The sympathetic nerve was stimulated during break in horizontal line. (Hutter and Trautwein 1956.) (b) Sheep Purkinje fibre before and after application of adrenaline (Otsuka 1958).

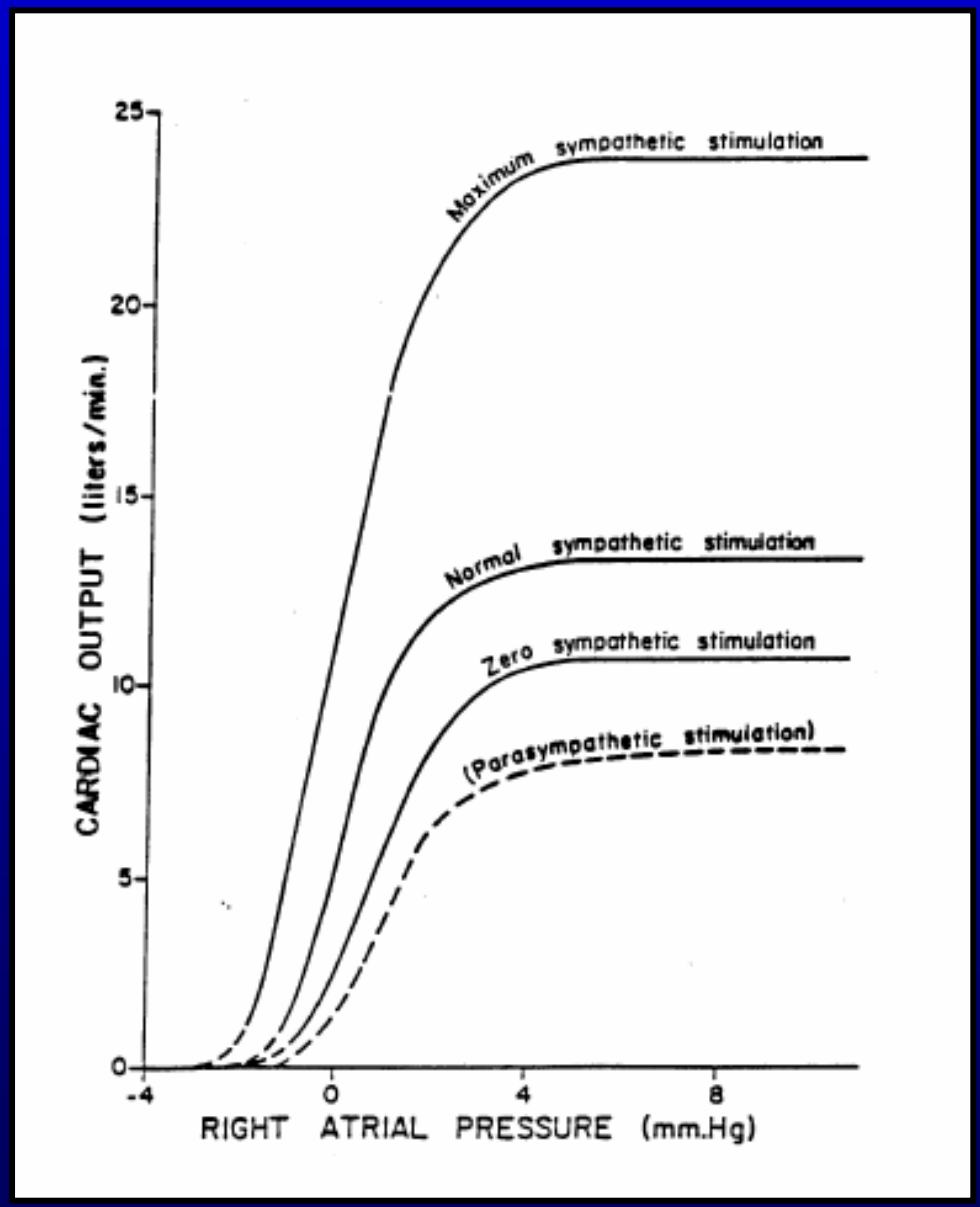
Effector: Heart Rate



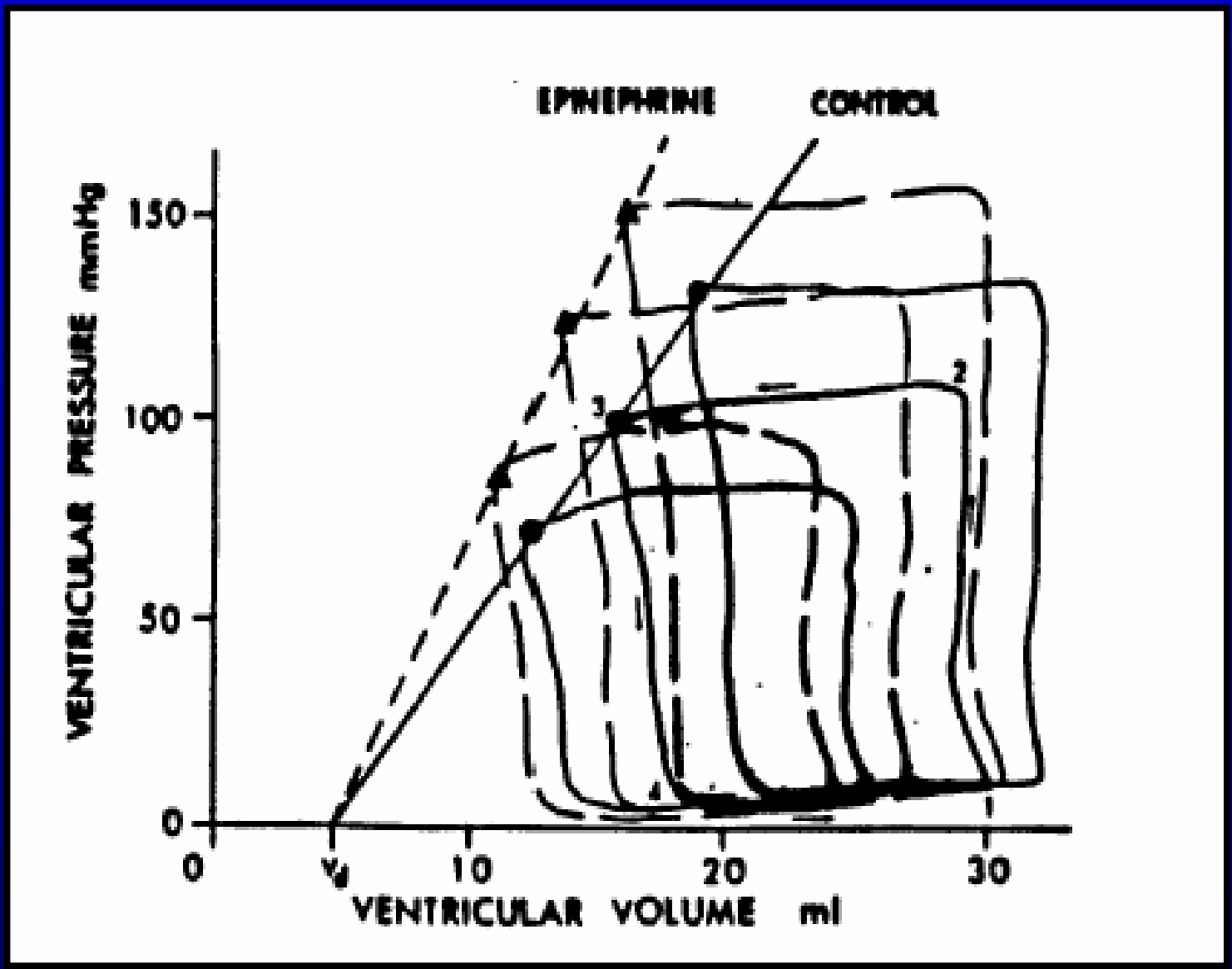
Dynamics of HR Control

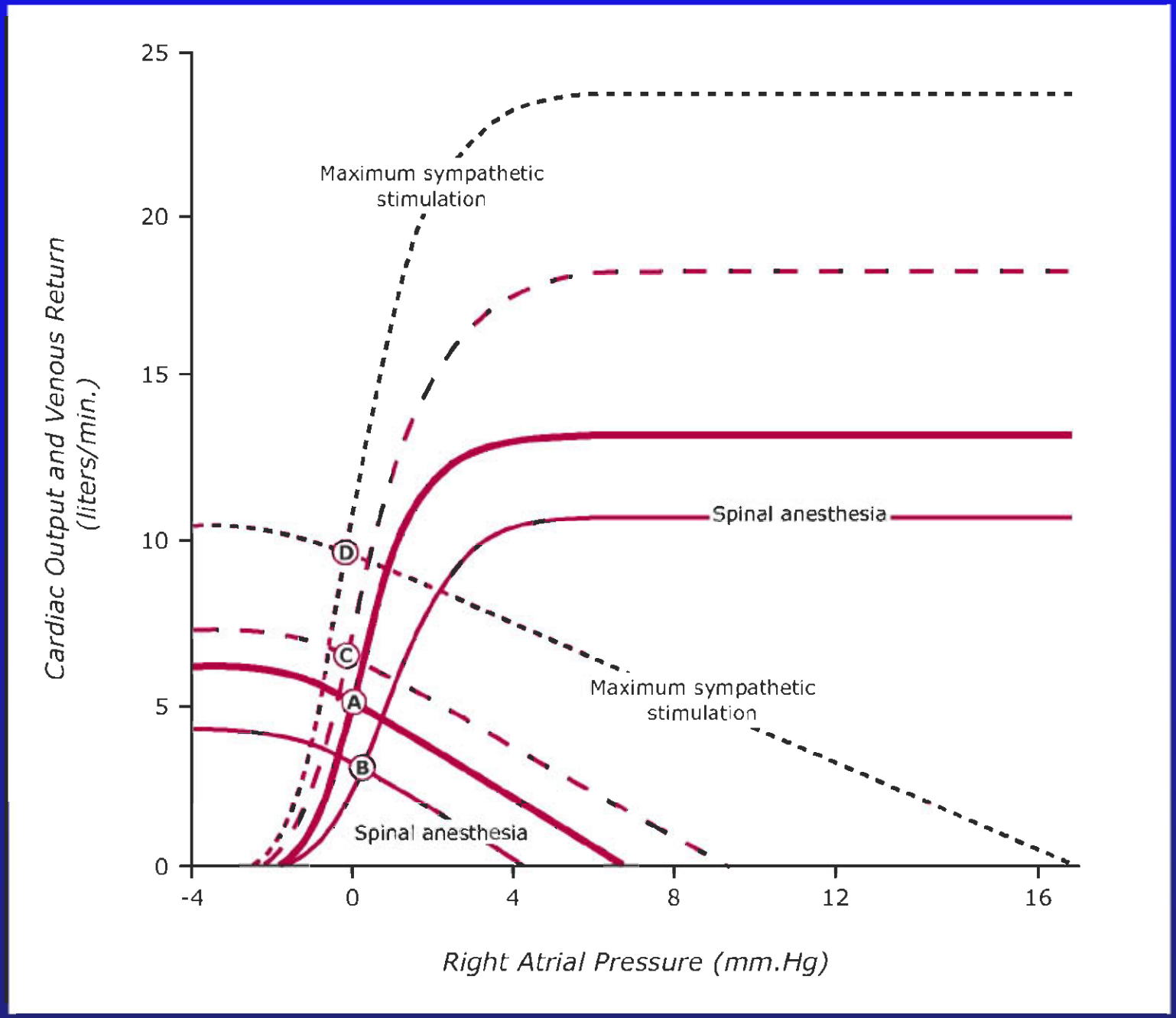


Effector: Contractility

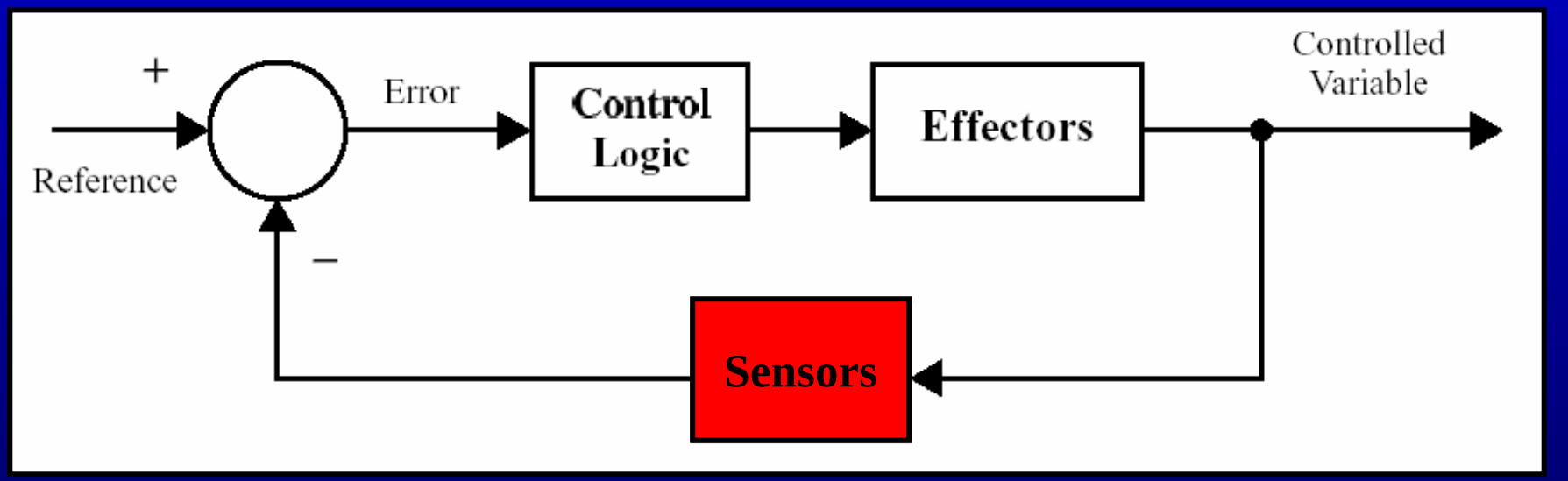


Contractility Increase

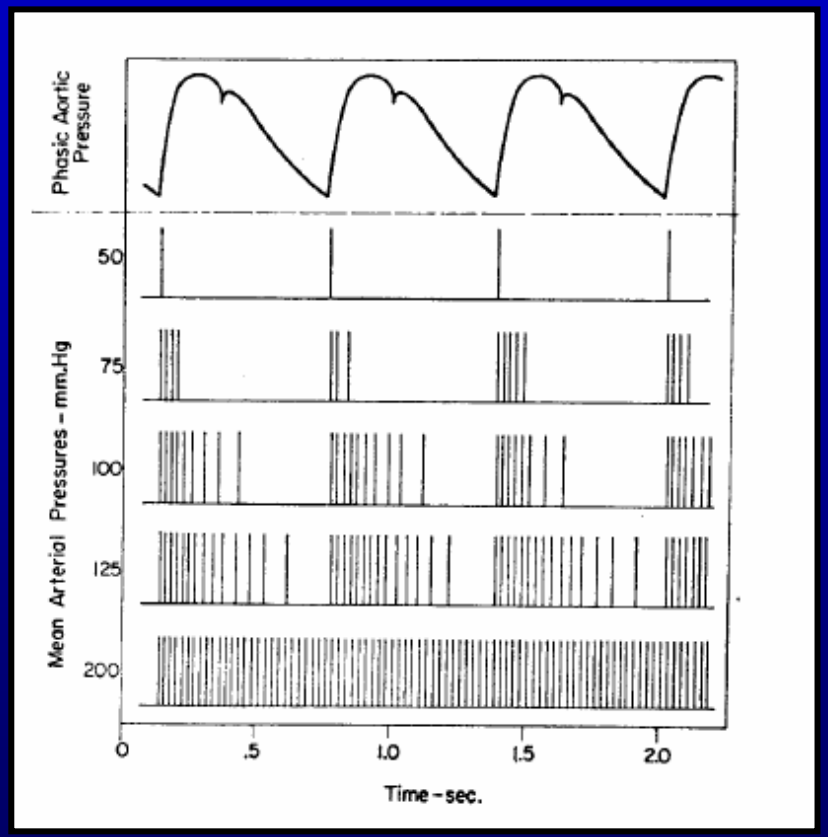


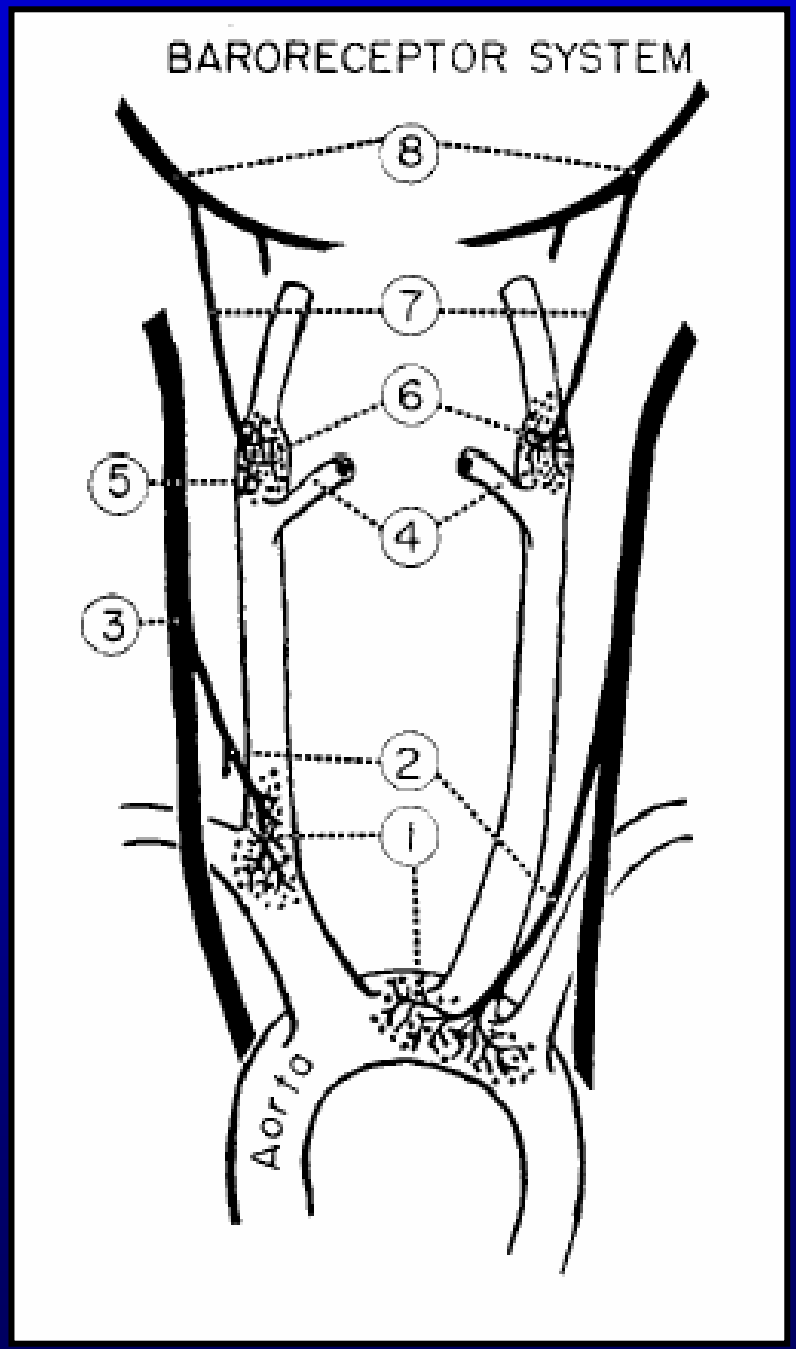

Cardiac Output and Venous Return
(liters/min.)
25
20
15
10
5
0
-4
0
4
8
12
16
Right Atrial Pressure (mm.Hg)
Maximum sympathetic
stimulation
Spinal anesthesia
Maximum sympathetic
stimulation
Spinal anesthesia
D
C
A
B

Sensors

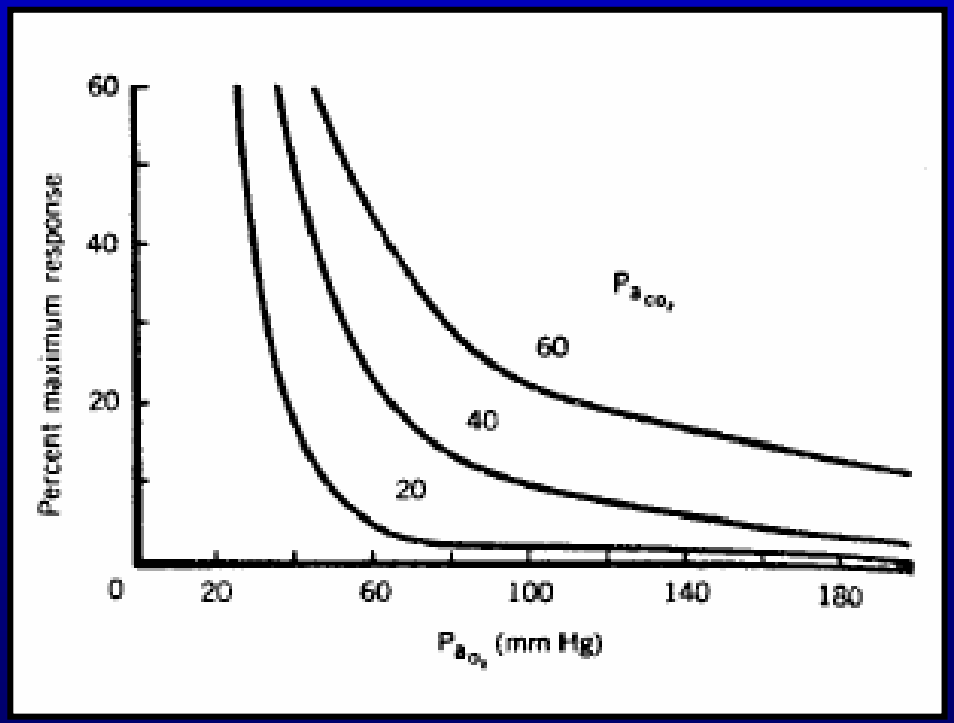

+
Reference
Error
Control Logic
Effectors
Controlled Variable
–
Sensors

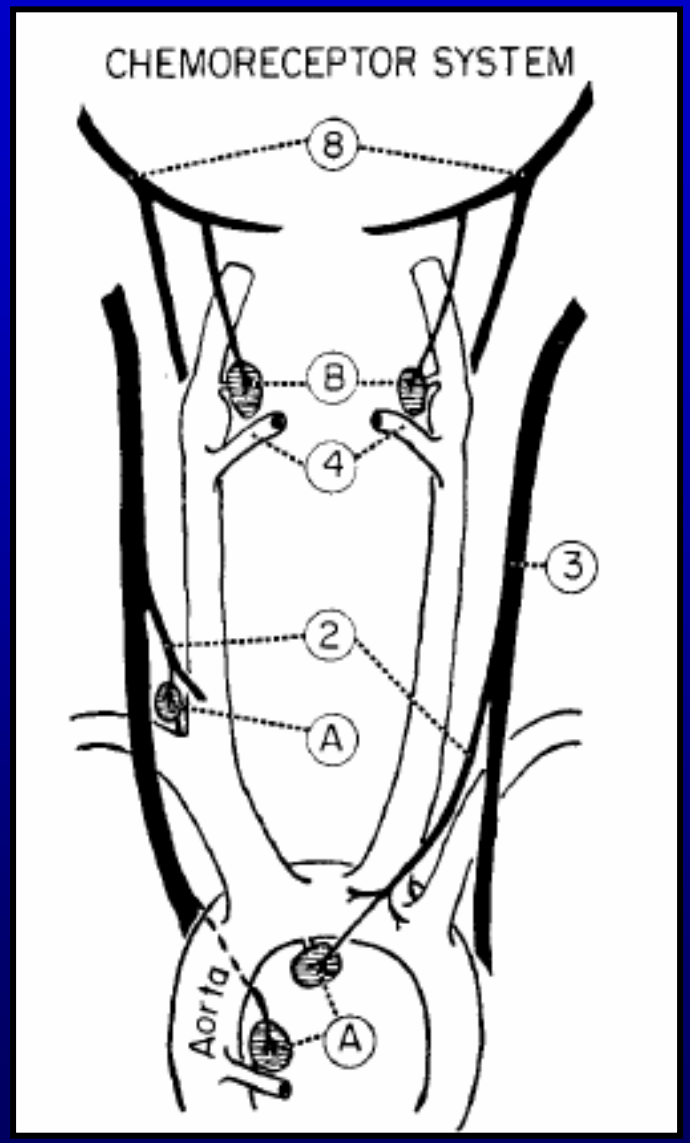
Sensor: Pressure





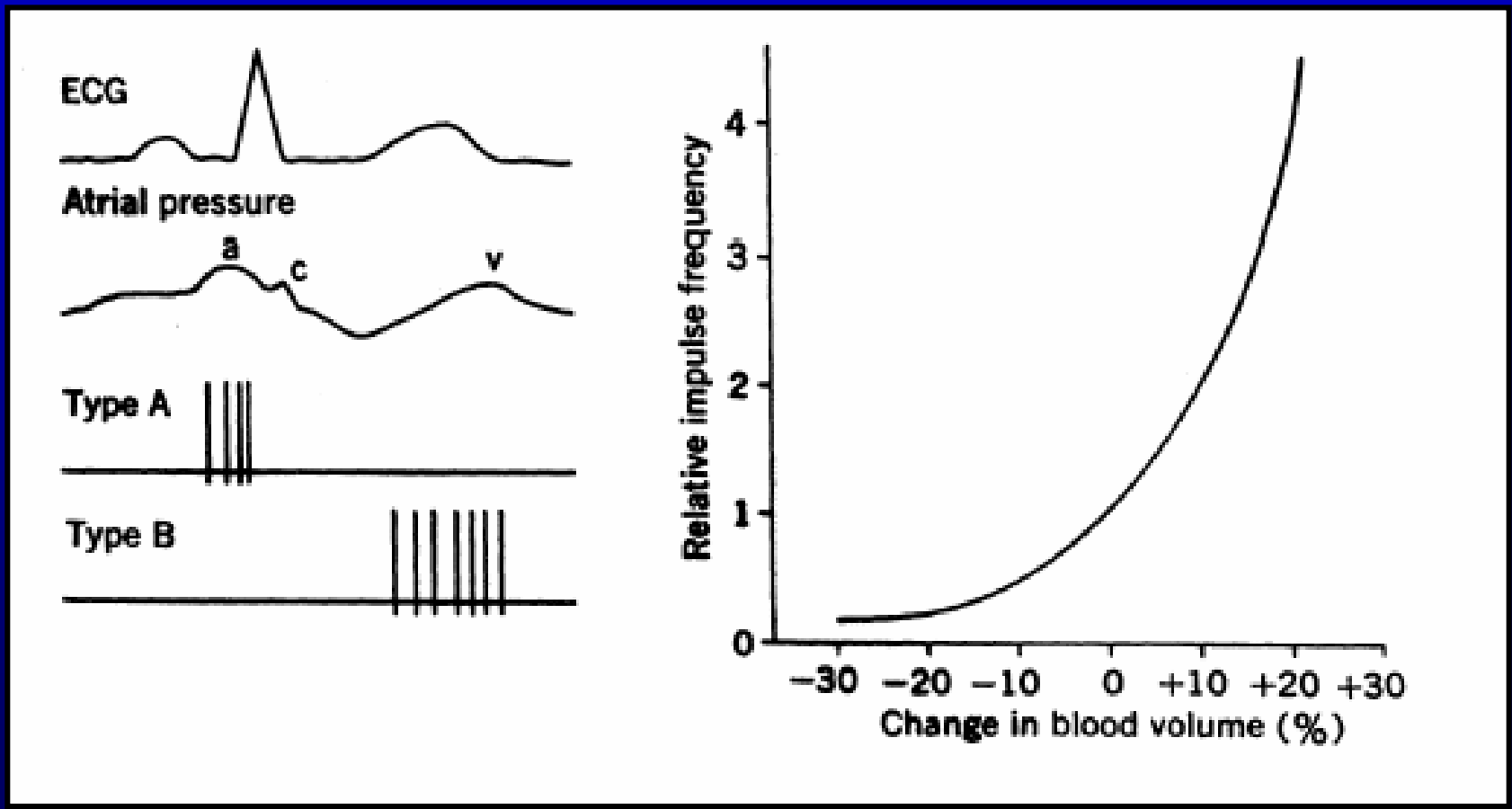
Sensor: Blood Gases





Sensor: Volume

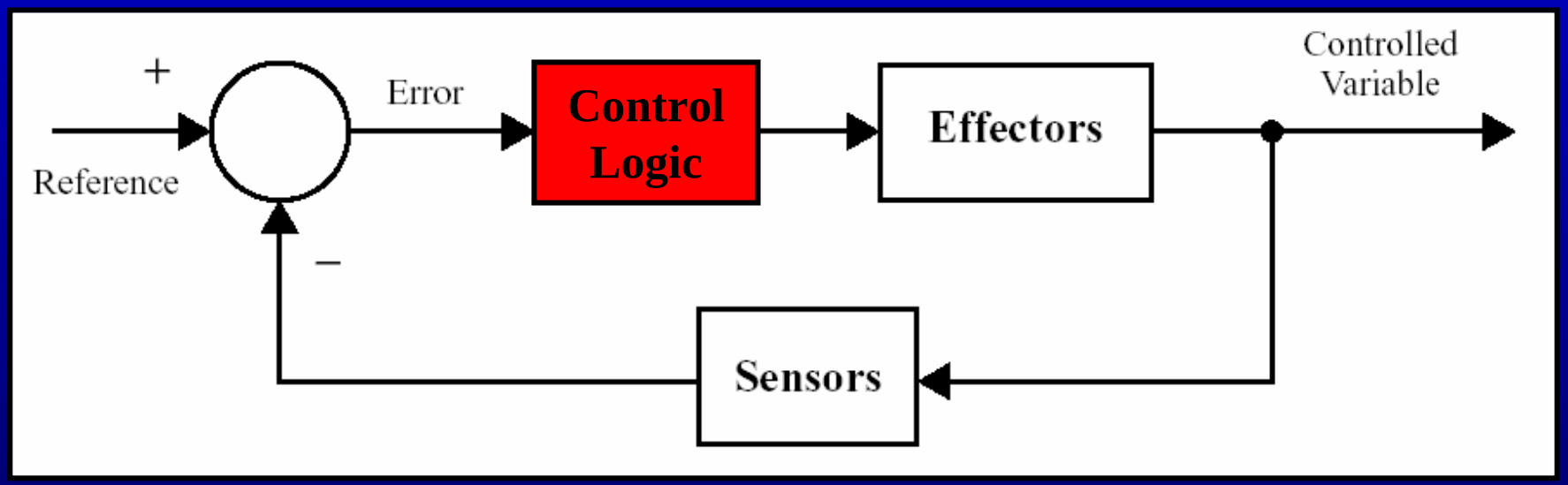
Atrial stretch receptors



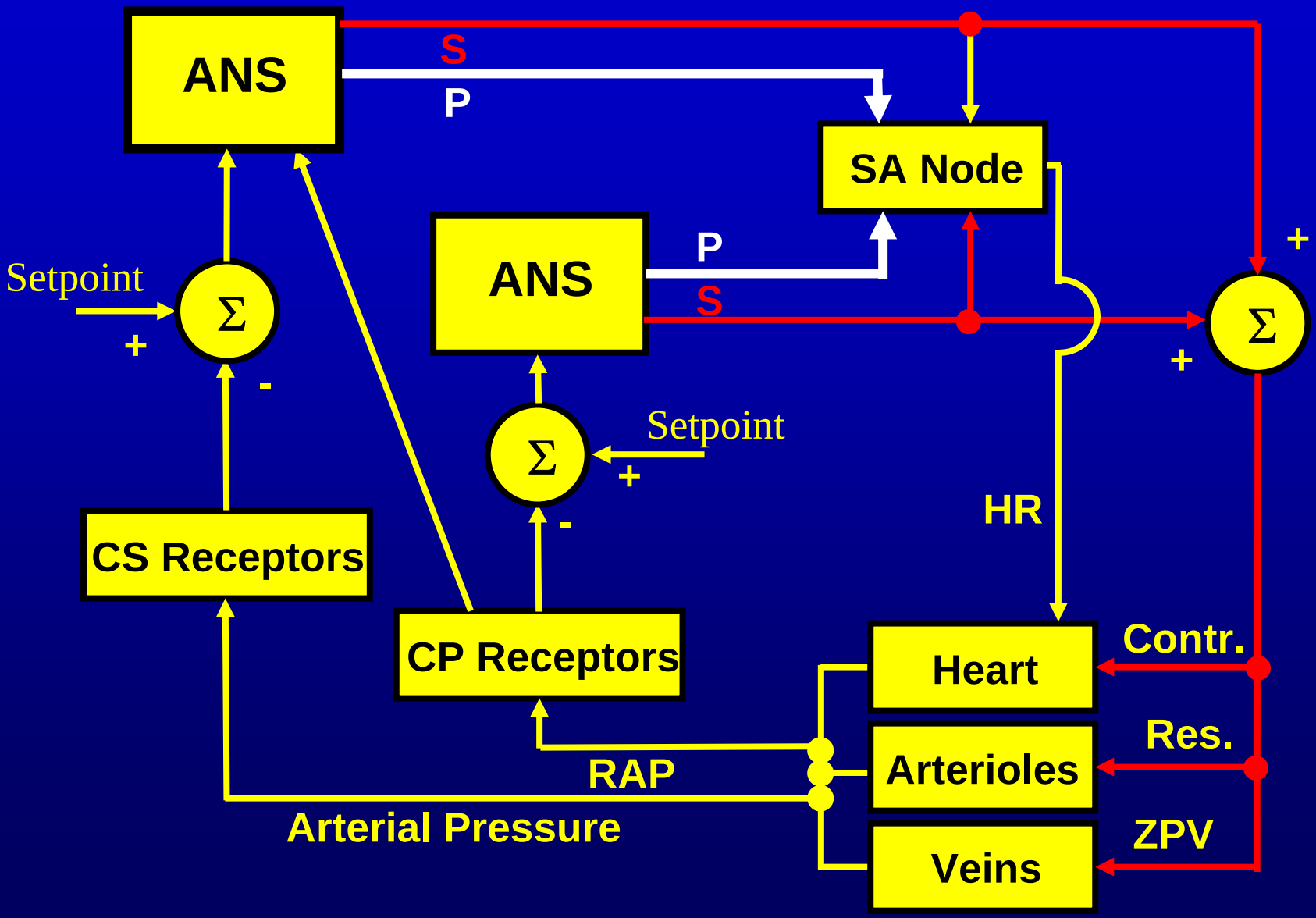
Sensors of internal and external environment

- Pain
- Temperature
- Environmental stimuli interpreted by cortex (real or imagined)
  - Anxiety
  - Anger
  - Fear
  - etc.

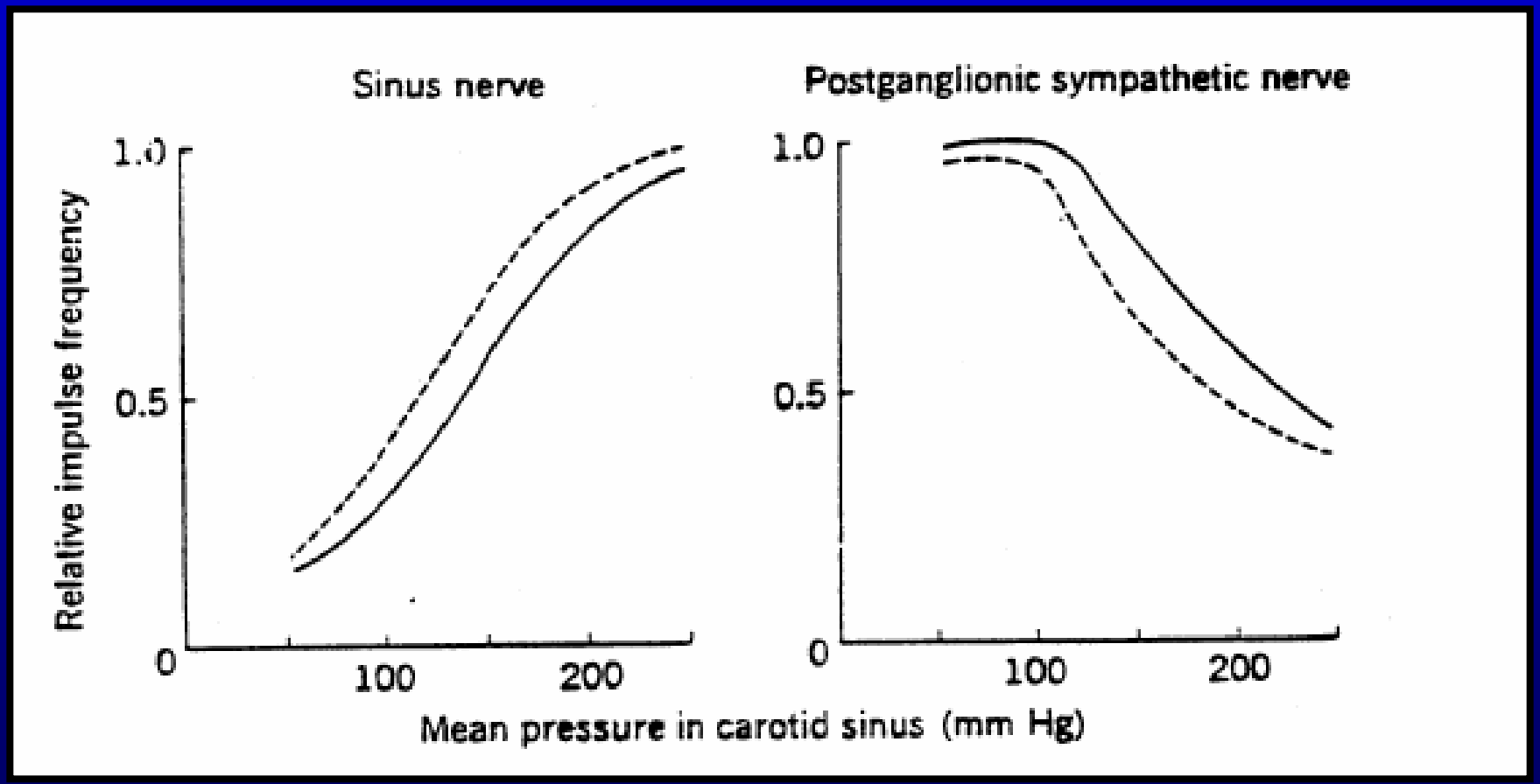
Control Logic



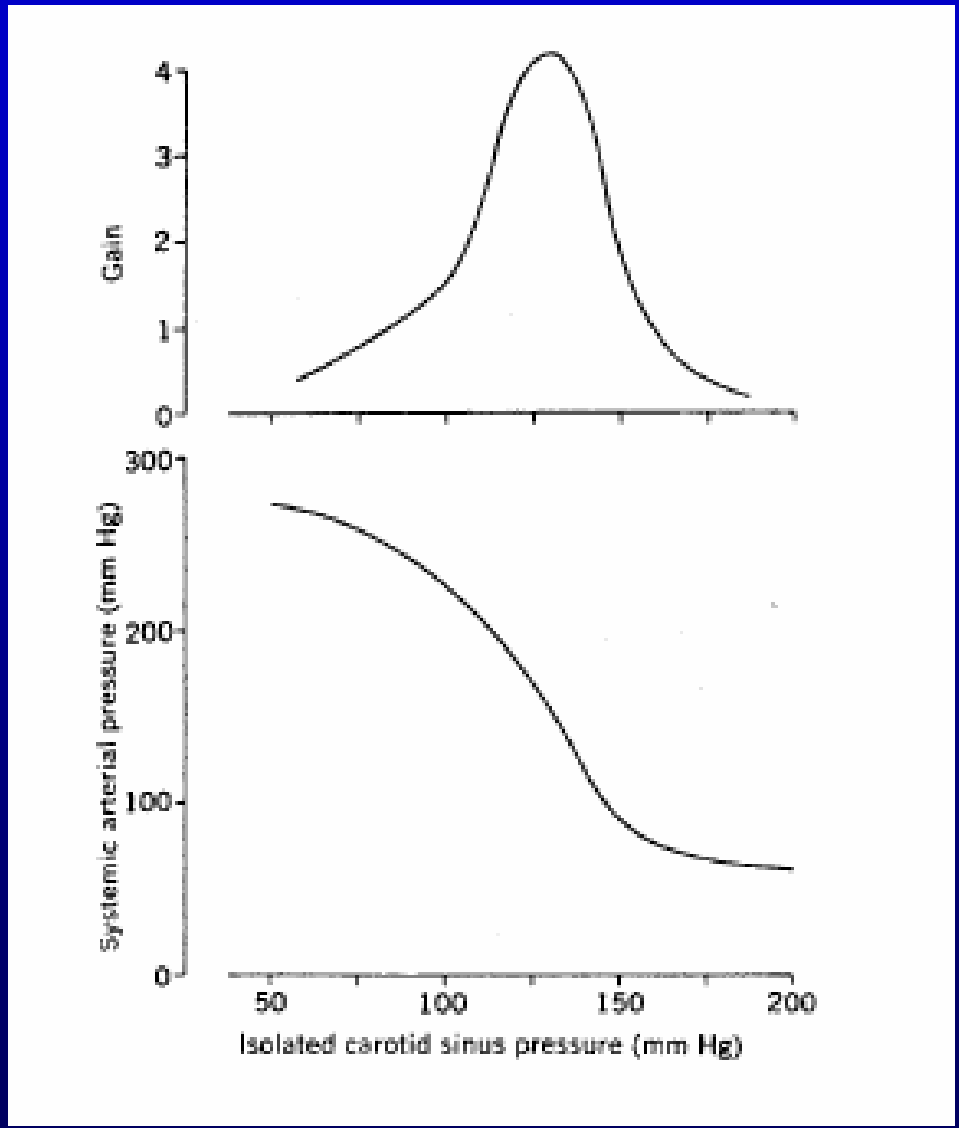
Control System



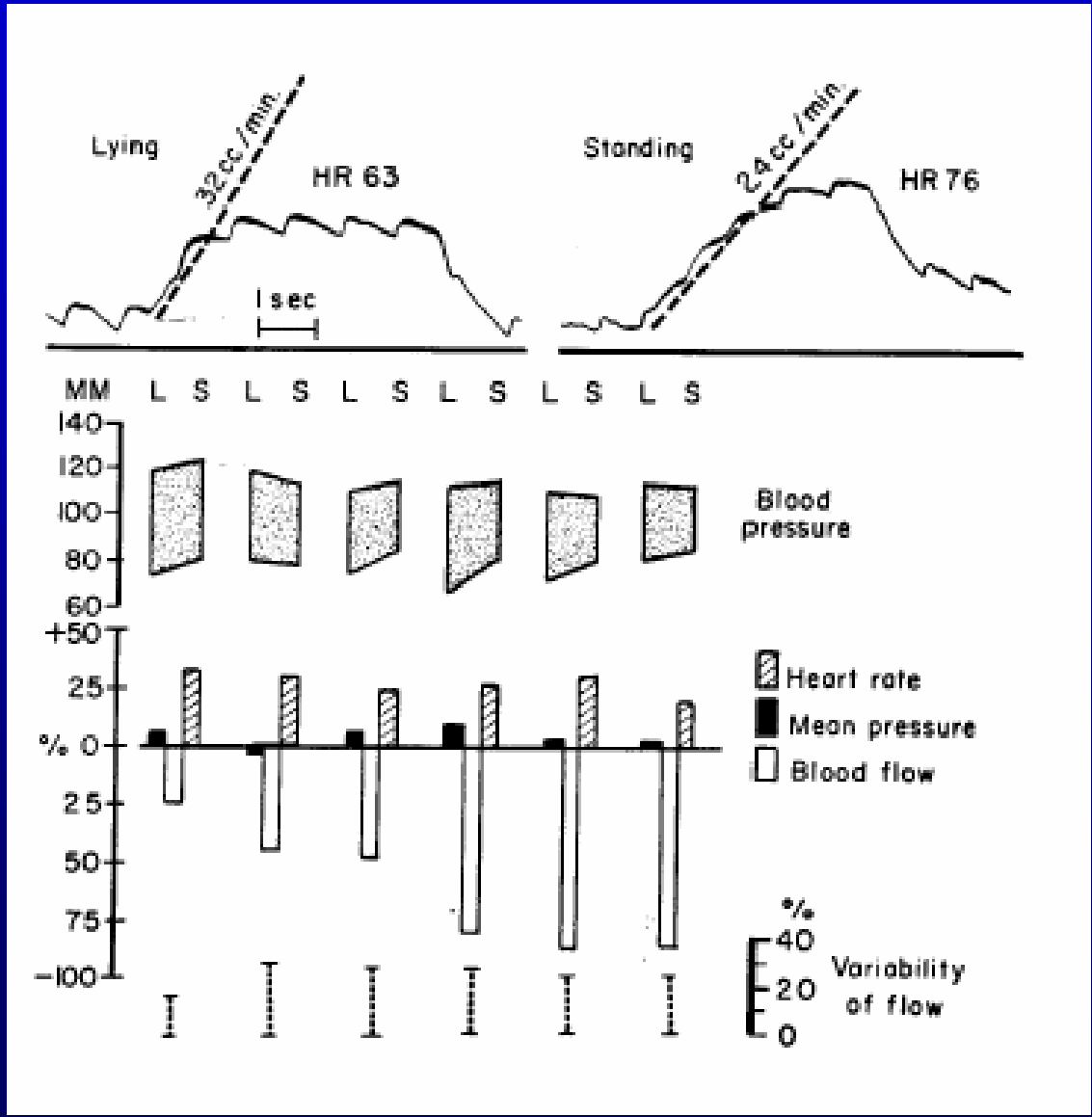
Central Control Logic: Baroreceptor Reflex



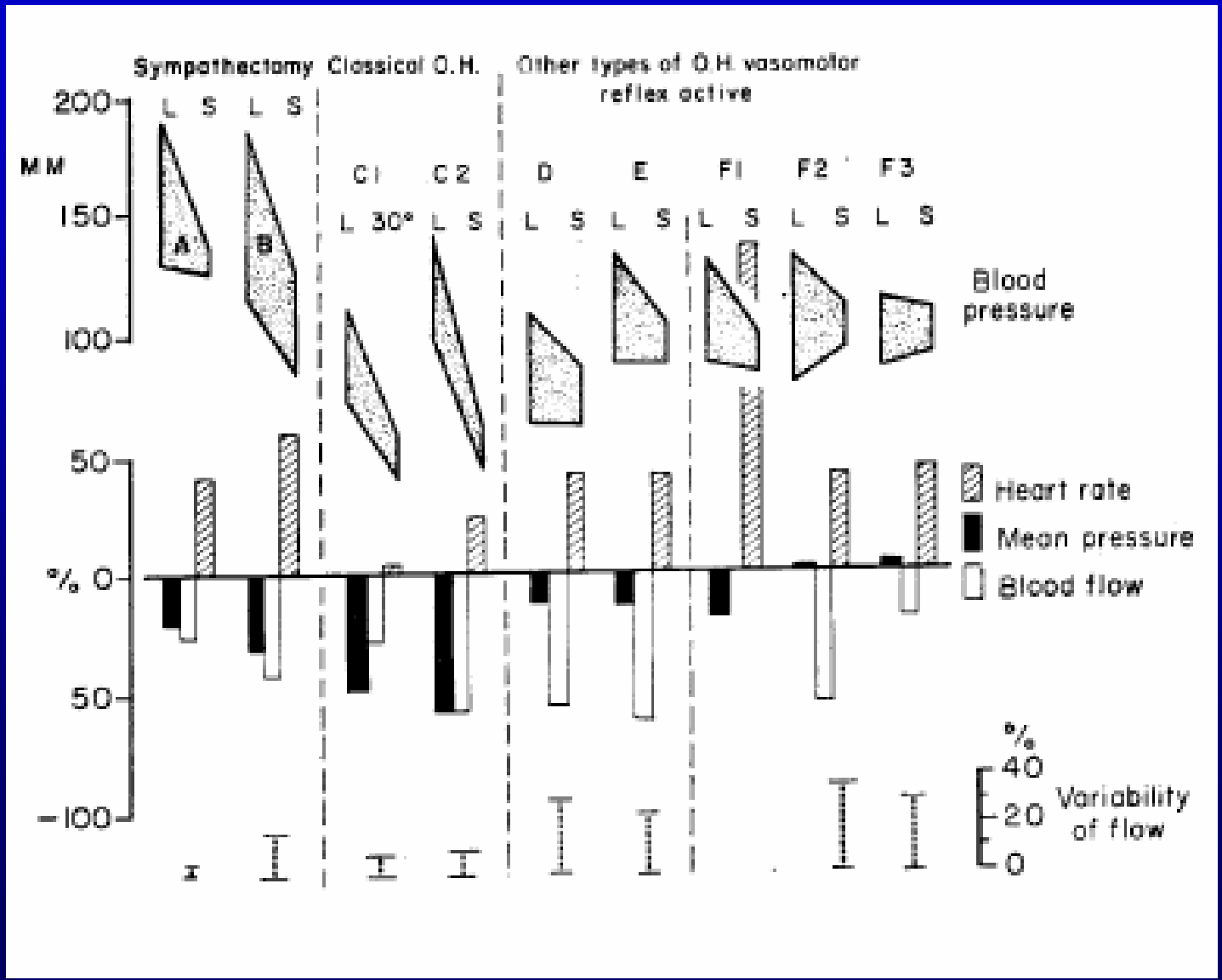
Baroreceptor Reflex



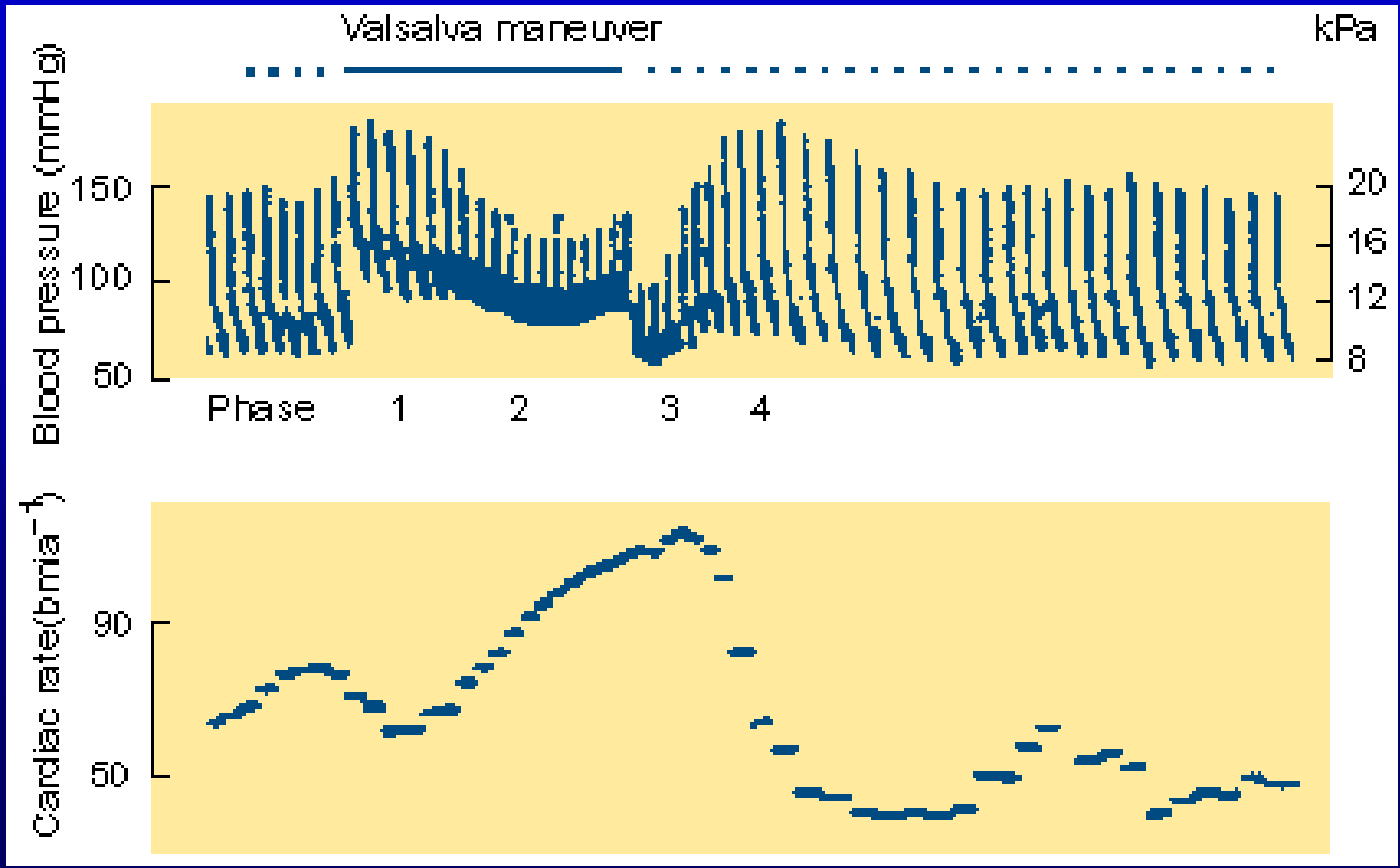
Baroreceptor and Standing



Control Failures



Valsalva Maneuver



Other Control Mechanisms

- Circulating blood volume : renal/hormonal controls
- Remodeling of CV components (hypertrophy, atrophy)
- Up- and down-regulation of receptors