# *CPC CORE MODULE PHYSIOLOGY AND PATHOPHYSIOLOGY REVIEW*


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# EDUCATIONAL OBJECTIVES

1. The learner will describe physiological concepts relevant to anesthesia practice as outlined in the CPCA blueprint.

2. The learner will describe pathophysiological concepts relevant to anesthesia practice as outlined in the CPCA blueprint.

**Specific concepts/ideas:**

**Relate** the determinants of myocardial oxygen supply and demand to the pathophysiology of stable angina, unstable angina, variant angina, and microvascular angina.

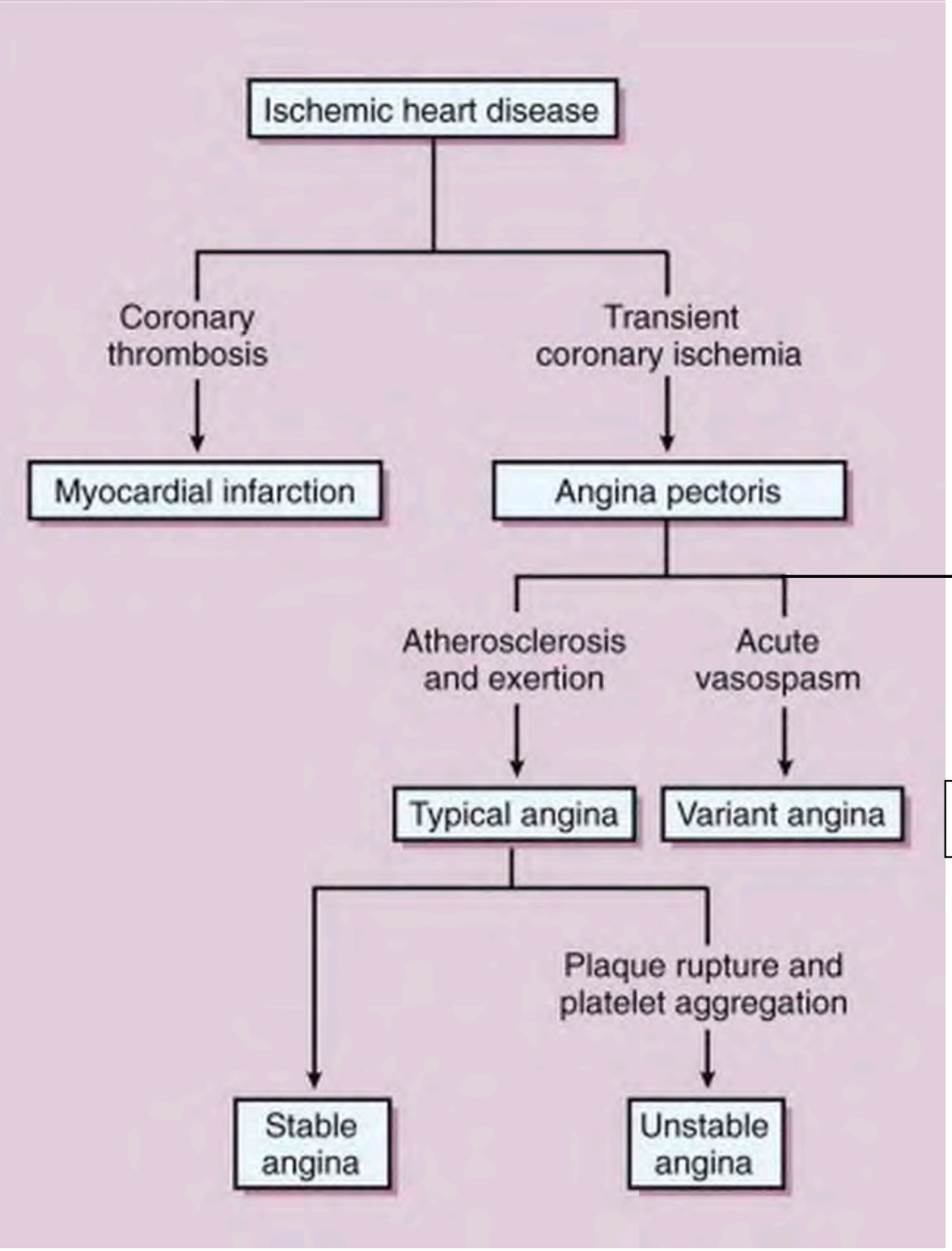
**Review** the pathophysiology of congestive heart failure, including the signs and symptoms, causes, maladaptive compensatory responses, and cardiac remodeling process.

**Review** the physiology of the renin-angiotensin-aldosterone system (RAAS) and the system's role in the pathophysiology of CHF..

**Describe** the normal values and determinants of cerebral blood flow, cerebral metabolism, intracranial pressure and cerebral perfusion pressure.

**Define** flow-metabolism coupling within the CNS.

- The determinants of myocardial oxygen supply and demand
- The pathophysiology of coronary artery disease




## Ischemic Heart Disease

- 18.2 million Americans*
- 30,000-40,000 people per million in Western world
- 1 in 7 deaths in the US

## Angina pectoris

- 9.4 million Americans (3.6% population)*
  - 3.5% of US male population
  - 3.7% (5.1 million) of US female population

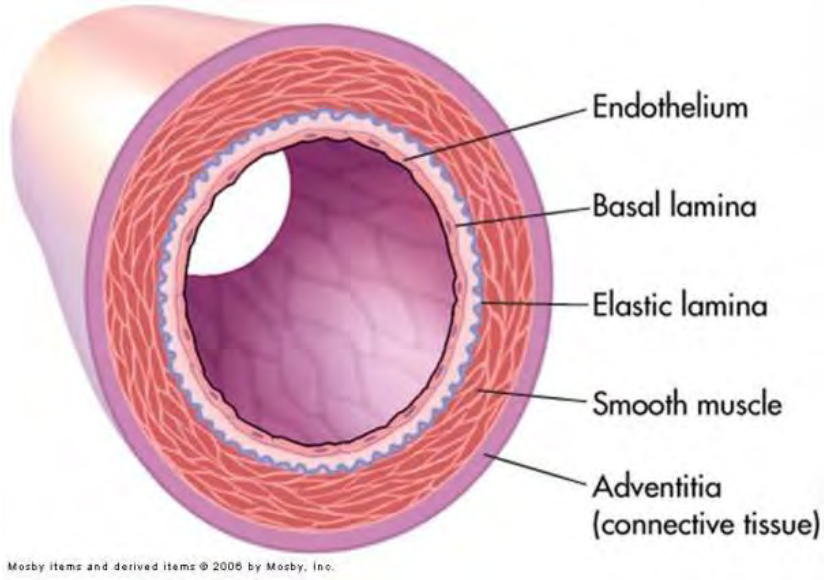
**Microvascular angina**

* AHA data (2019 update)
*Circulation* 139(10); Benjamin et al

# NORMAL CORONARY BLOOD FLOW

## At Rest

- Coronary blood flow is 70ml/min/100g
- ~5% the cardiac output
- % Oxygen extracted from myocardial tissue beds is VERY HIGH = 70%





## Intense Exercise

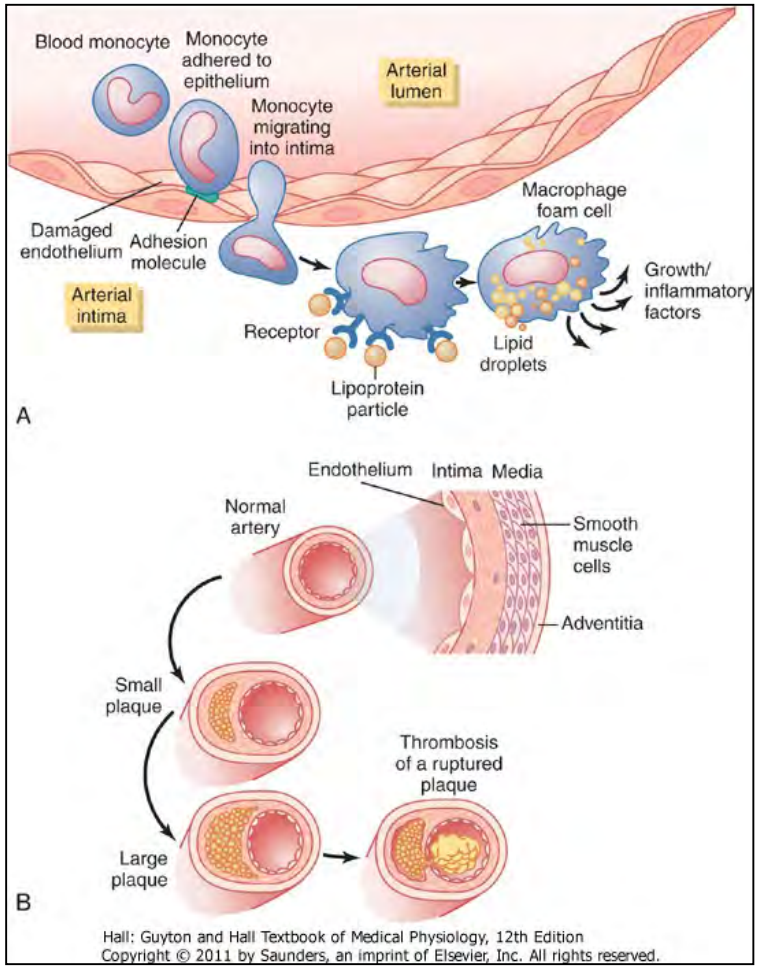
- Coronary blood flow increases 2-4 fold

(Supply)

- However cardiac demands increase proportionally higher
  - CO to the body increases 4-7 fold
    - Preload
    - Heart rate
    - Contractility

(Demand)

# ATHEROSCLEROTIC PLAQUE FORMATION



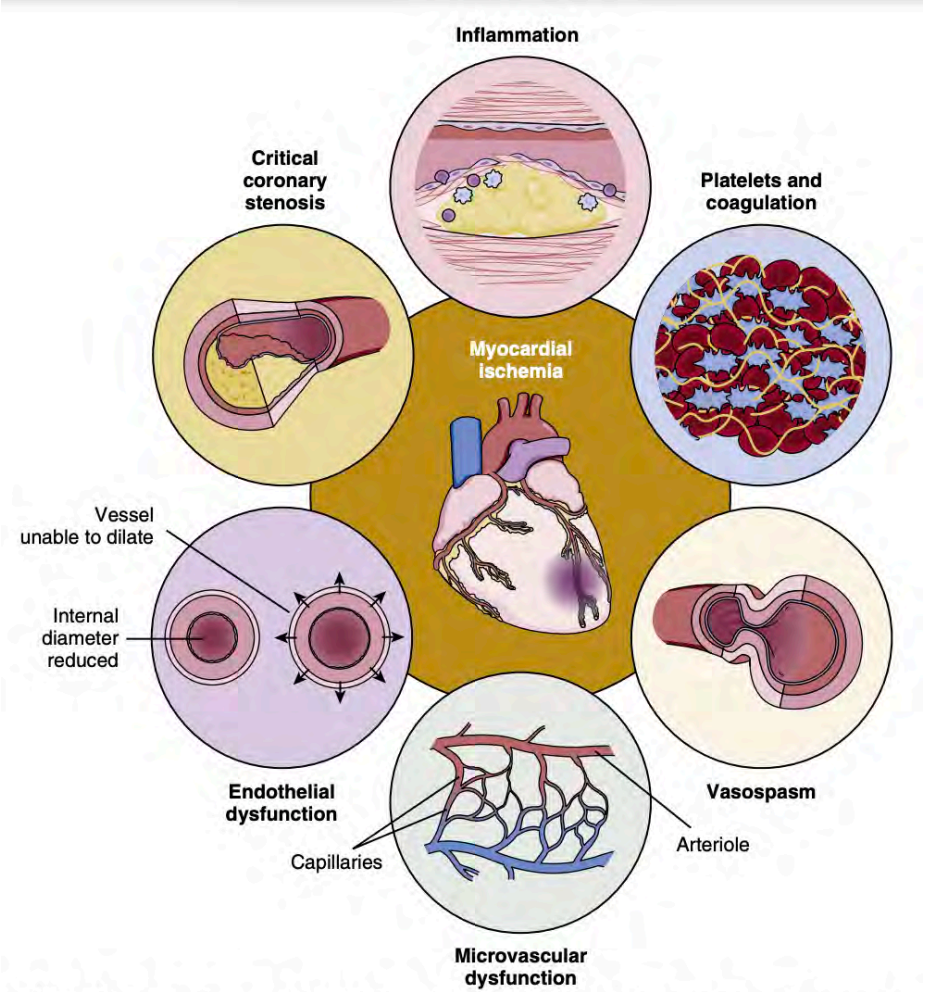
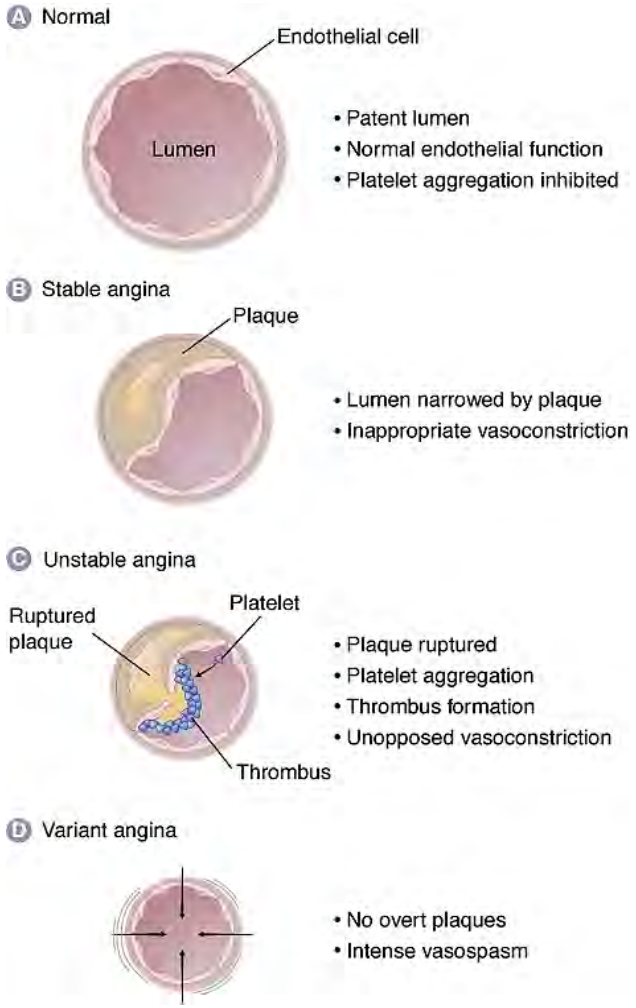
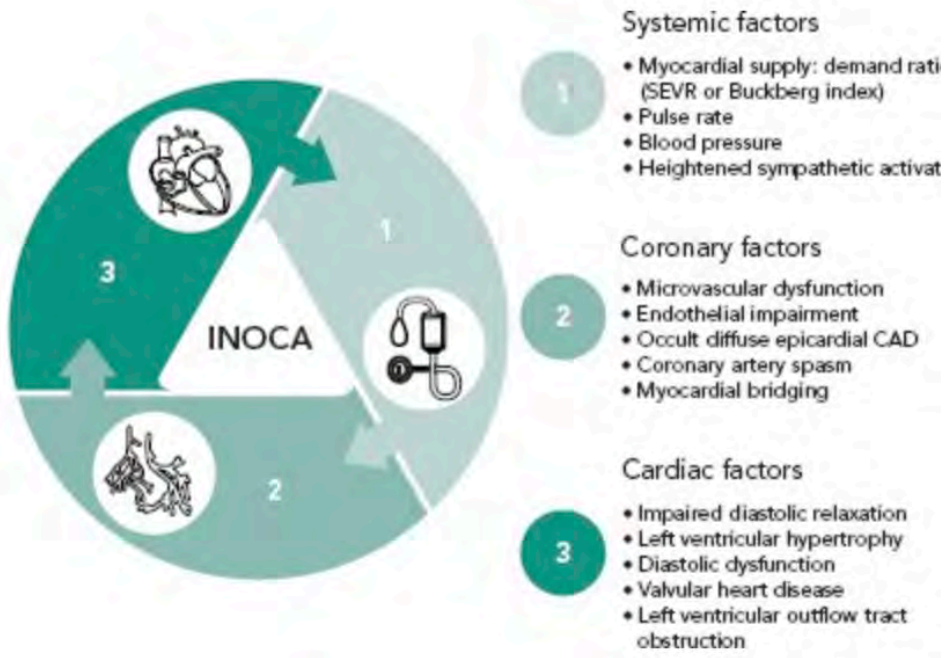



**FIGURE 40.1 Pathophysiology of ischemic heart disease.** The notion that ischemic heart disease is synonymous with critical stenoses of epicardial coronary arteries is overly simplified. The potential contributors to ischemic heart disease are multiple.

*Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine* *12th edition*

# ANGINA PATHOPHYSIOLOGY: SYSTEMIC AND CORONARY FACTORS




Ford and Berry, Interv Cardiol. 2019
doi: 10.15420/icr.2019.04.R1

Golan et al., *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, 3rd ed., 2012

# VASOSPASTIC/VARIANT ANGINA

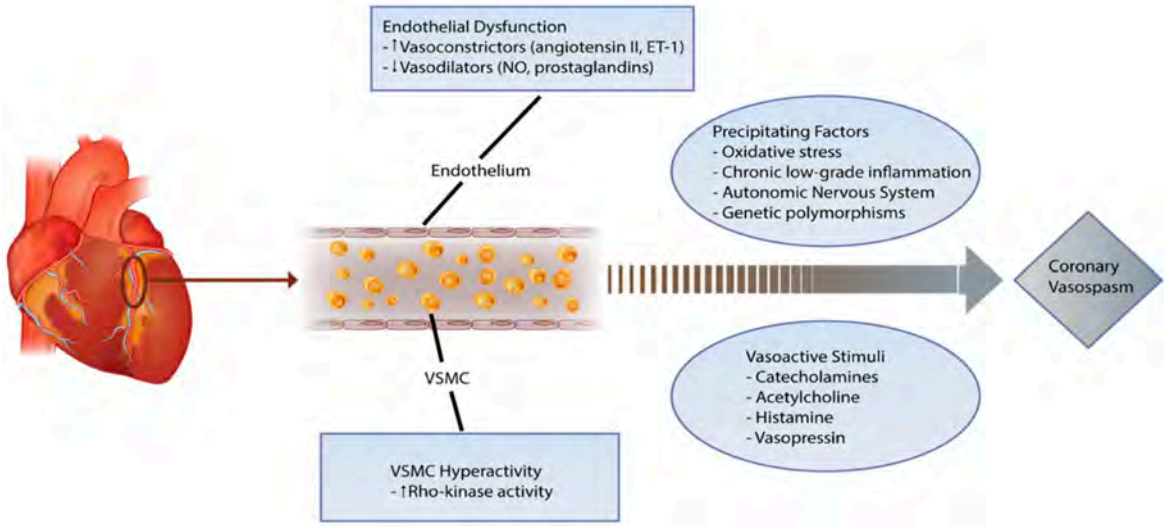



Figure 1: **Coronary Vasospastic Angina: A Review of the Pathogenesis, Diagnosis, and Management** Rehan, Weaver and Yong (2022) https://doi.org/10.3390/life12081124

# SUMMARY: CORONARY BLOOD FLOW CONTROL

Duration of diastole (heart rate)

Systolic compressive forces

Pressure gradient between diastolic blood pressure & left ventricular end diastolic pressure

- Perfusion pressure to the left ventricle = DBP – LVEDP

Metabolic

- Local flow adjusts to meet local nutritional needs

Circulating hormones/autocrine/paracrine factors produced within the arterial wall esp. endothelium

Nervous system modulation (autonomic tone)

Auto-regulation (myogenic response)

# CORONARY BLOOD FLOW
# POISEUILLE'S LAW

$$\text{Blood Flow} = \frac{\Delta P \, r^4 \, \pi}{\eta \, L \, (8)}$$

$\Delta$ = Change

P = Pressure

r = Radius of vessel

$\pi$ = constant (3.14)

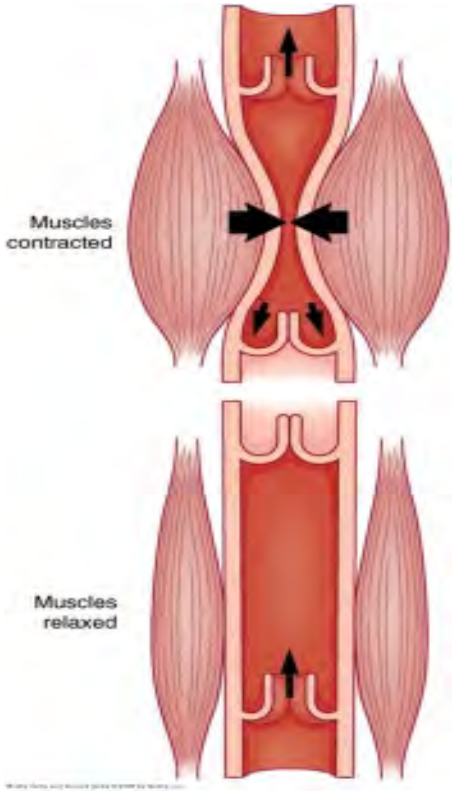
$\eta$ = Viscosity of blood

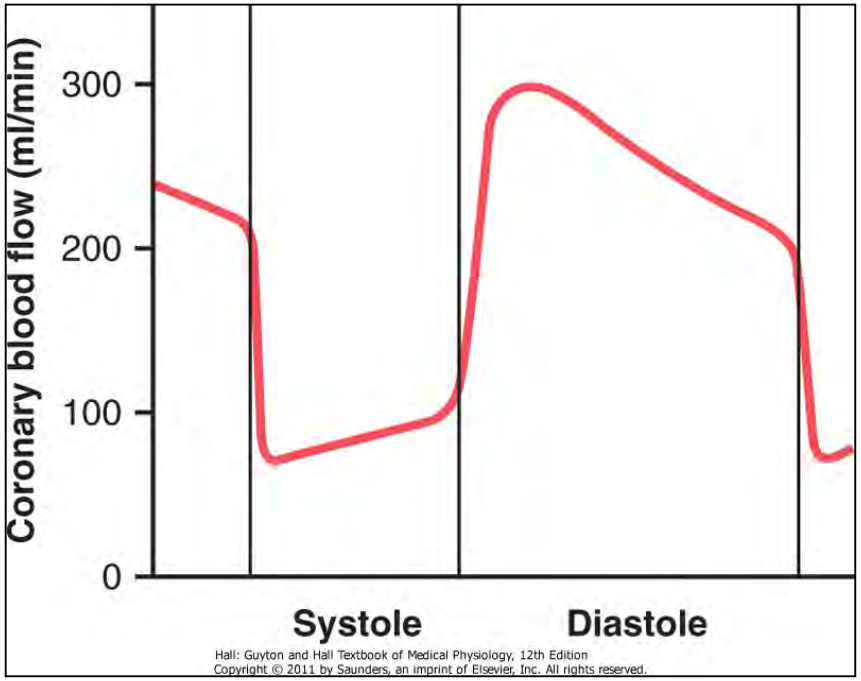
L = Vessel length

# The coronary arteries to the L ventricle fill during diastole

Systolic contraction impedes coronary arterial filling because of the increase in intramural pressure

- Redistributes blood flow from the subendocardial to the subepicardial layers
- Compresses the arterioles, venules and capillaries
- Perfusion pressure to the left ventricle = DBP – LVEDP



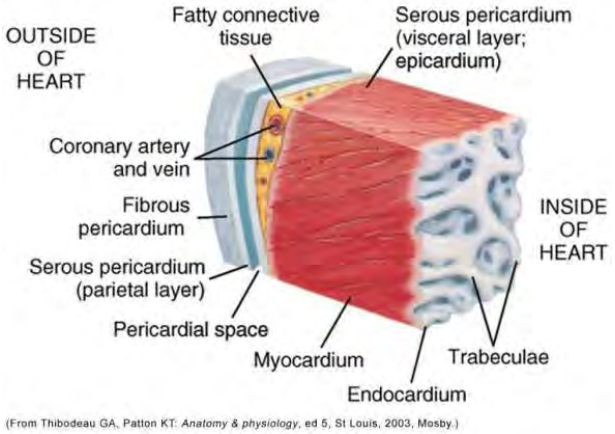
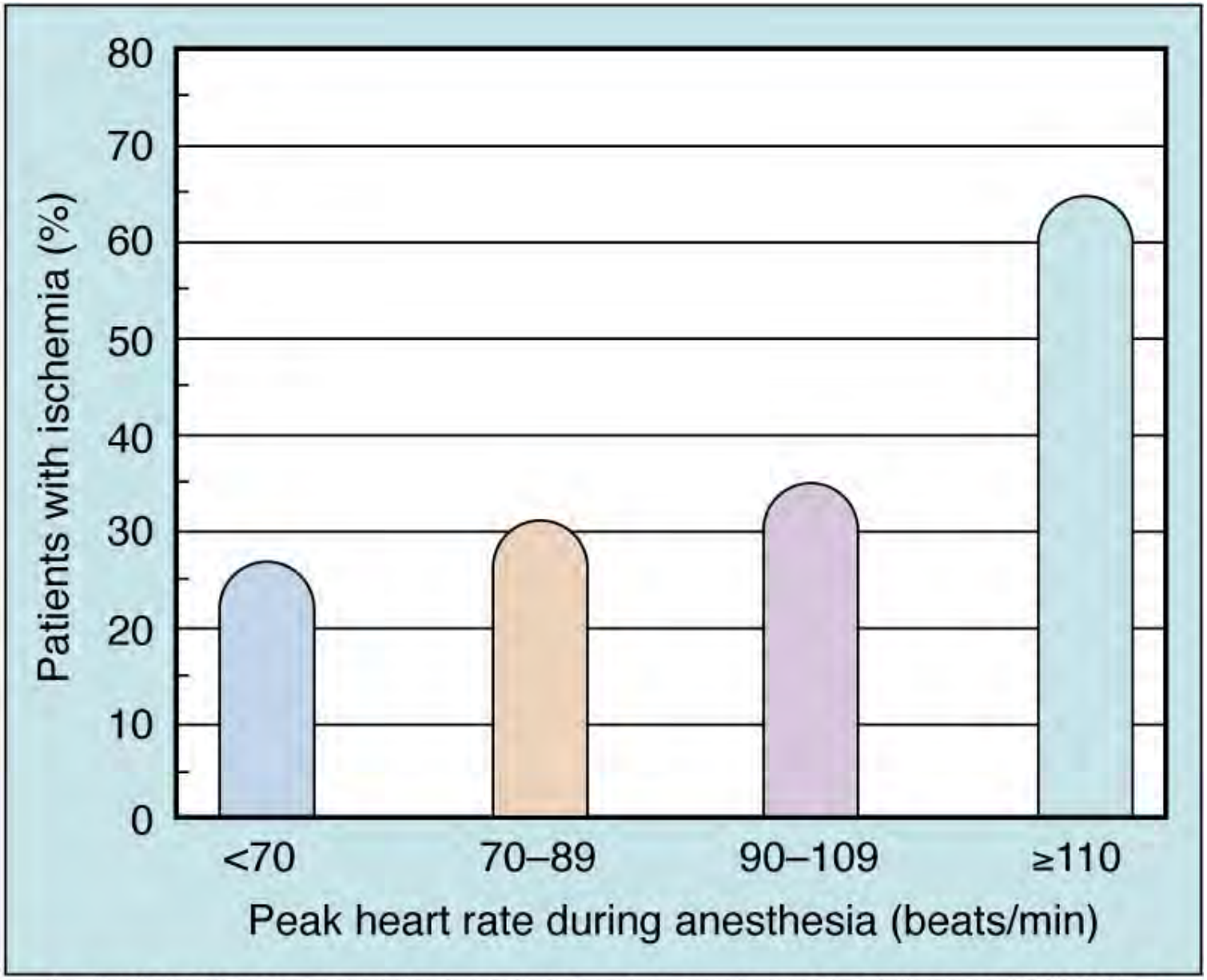




Figure 21-4 Phasic flow of blood through the coronary capillaries of the human left ventricle during cardiac systole and diastole (as extrapolated from measured flows in dogs).




(From Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988;68:676-680, with permission.)

Fig. 25-1. The incidence of myocardial ischemia rises with increases in heart rate, with the greatest effect at heart rates greater than 110 beats/min.

# PRACTICE QUESTIONS

**Based on the pathophysiology of variant angina, which of the following treatments might exacerbate a patient's symptoms?**

a. A calcium channel blocker like amlodipine

b. A beta-blocker such as propranolol

c. A vasodilator such as nitroglycerin

d. A volatile agent such as sevoflurane

**Which of the following has the greatest impact on coronary blood flow?**

a. The systolic pressure

b. The diastolic pressure

c. The mean arterial pressure

d. The radius of the vessel

- *The Renin-Angiotensin Aldosterone System*
- *The Pathophysiology of Heart Failure*

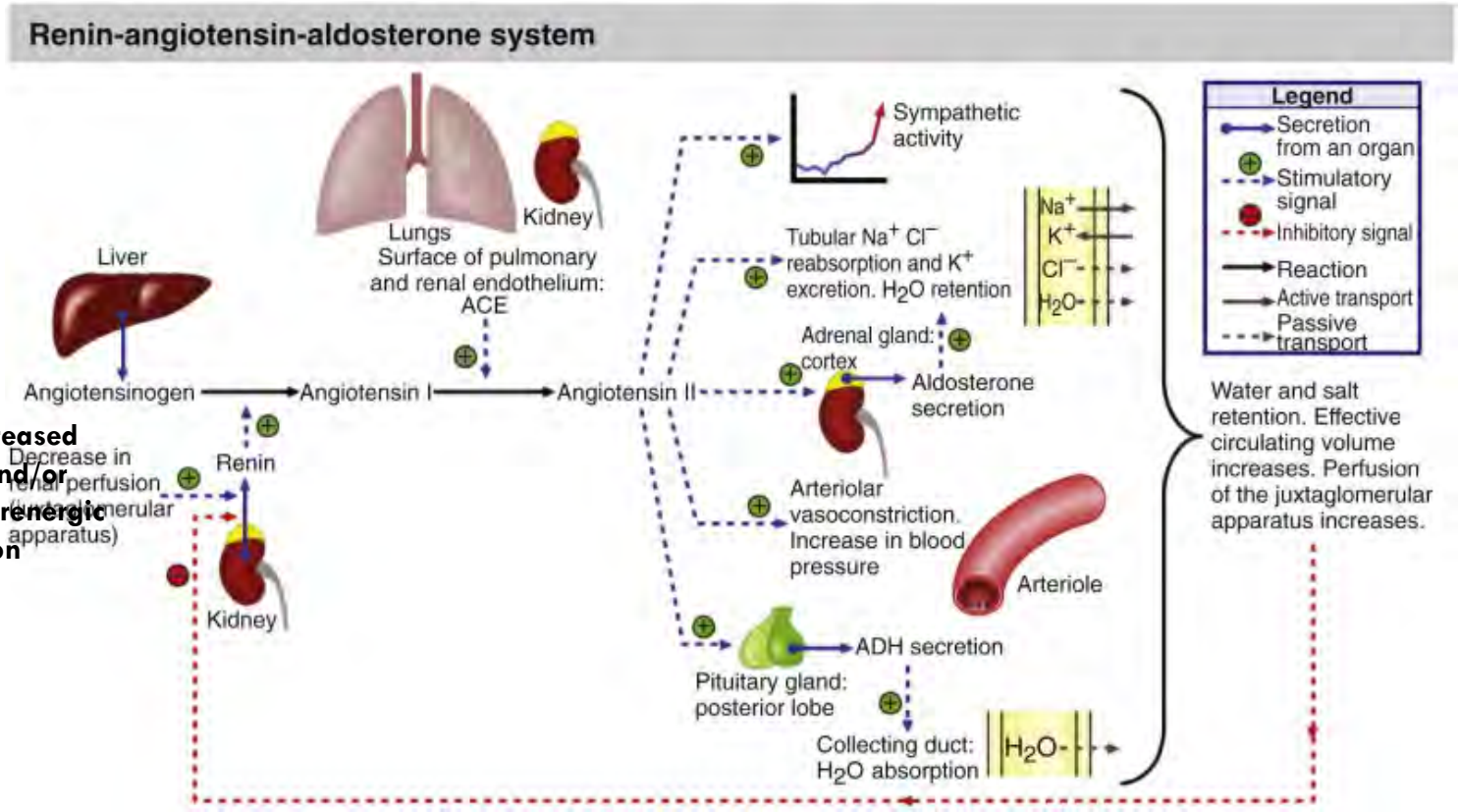
# SCENARIO 1: HEALTHY BUT DEHYDRATED CARDIOVASCULAR SYSTEM

A 34-year-old CRNA works 12 hours in the OR caring for 2 ASA IV patients. One of her patients codes and requires short periods of CPR before they stabilize. She is so busy and engrossed in her work that she skips lunch, takes only two small breaks, drinks two cups of coffee, and eats a stale turkey sandwich. She runs 3 miles in 90-degree heat when she gets home to decompress before eating dinner. After her run, she noticed she had a headache, and it occurred to her she did not drink any water all day and had not urinated for the past 8 hours. How is she able to function for such a long period of time without water?

**Renin-angiotensin-aldosterone system**

**Sympathetic nervous system**

# RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



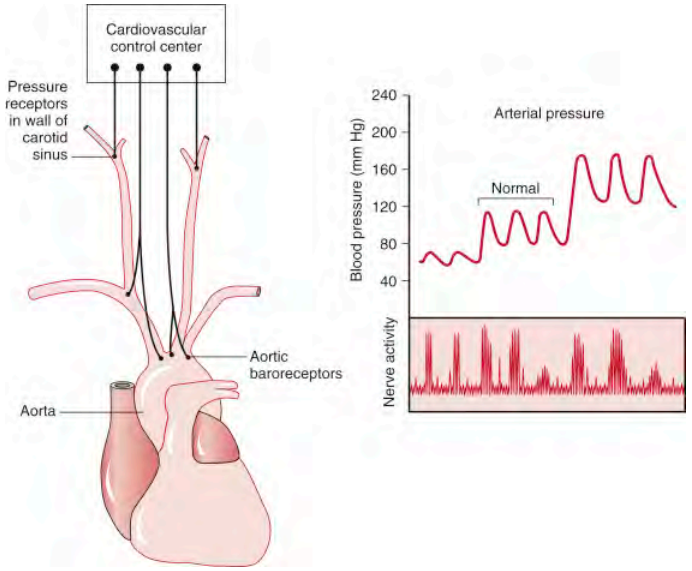

**Also Decreased $Na^+$ $Cl^-$ And/or Beta-1 adrenergic stimulation**

Meltzer, Pharmacology and Physiology for Anesthesia, Chapter 32 Figure 32-3

# SYMPATHETIC NERVOUS SYSTEM

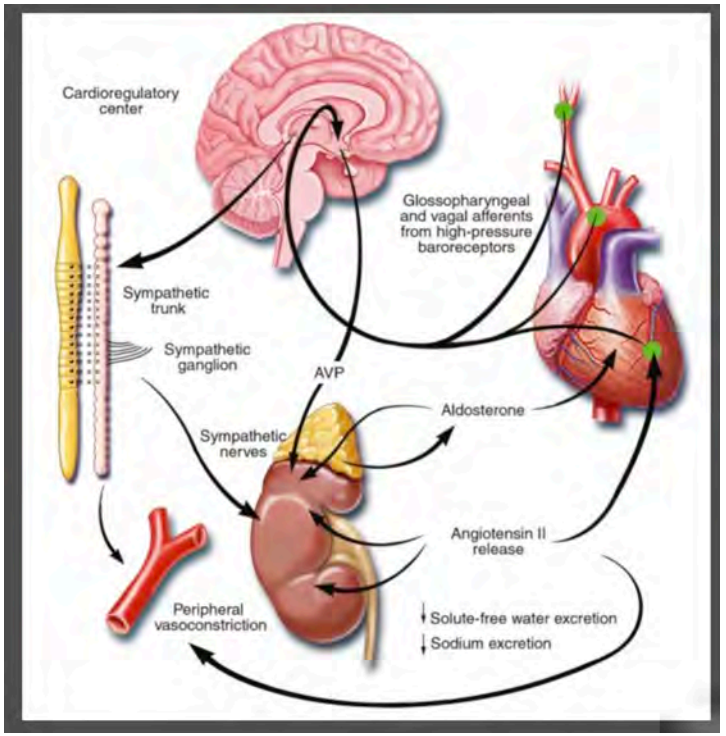
## 1) Low BP (arterial under-filling)

Baroreceptors in the left ventricle, carotid sinus, and aortic arch fire




## 2) SNS activity during "fight or flight" at work and while exercising

- Efferent SNS signals generated
  - Vasopressin released (antidiuretic hormone)
  - Peripheral and renal vasoconstriction (alpha-1)
  - Increased heart rate and contractility (Beta-1)
  - **Increases renin release (Beta- 1)which in turn further increases vasoconstriction (angio II release) and fluid retention (aldosterone release)**




Braunwald's Heart Disease Figure:22-6

# WHAT MEDIATORS OPPOSE THE SNS AND RAAS?

Atrial Natriuretic Peptide

Brain Natriuretic Peptide

C-type Natriuretic Peptide

Also:

Bradykinin

Substance P

Adrenomedulllin

VIP, etc.….

***Neprilysin Breaks down natriuretic Peptides**

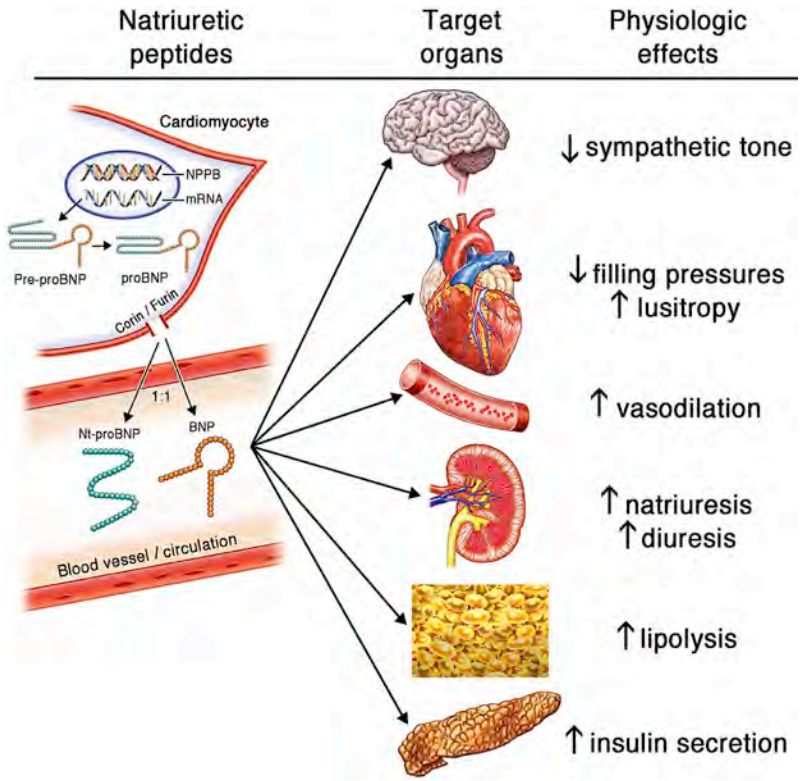
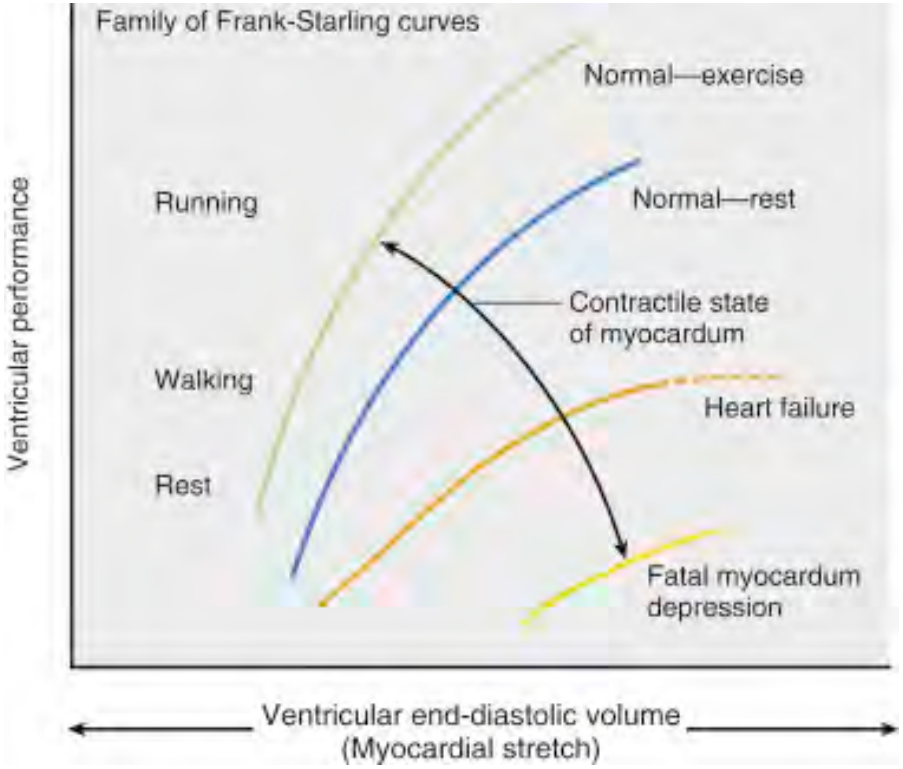



Image: **JACC: Heart Failure** Volume 3, Issue 7, July 2015

# FRANK STARLING CURVE IN DIFFERENT PHYSIOLOGIC STATES

MILLER'S ANESTHESIA CHAPTER 20-5



# SCENARIO 2:

A 59 year old patient was recently diagnosed with Stage B heart failure following a myocardial infarction 6 months ago. His ejection fraction and exercise tolerance are mildly decreased and his ECG shows left ventricular hypertrophy. How is his body compensating for the decrease in myocardial performance following the MI?

**Renin-angiotensin-aldosterone system**

**Sympathetic nervous system**

# HEART FAILURE

**Heart is unable to pump adequate blood to meet the metabolic demand of the body**

Inadequate tissue perfusion

**Table 1** Predominant clinical situations for systolic and diastolic heart failure

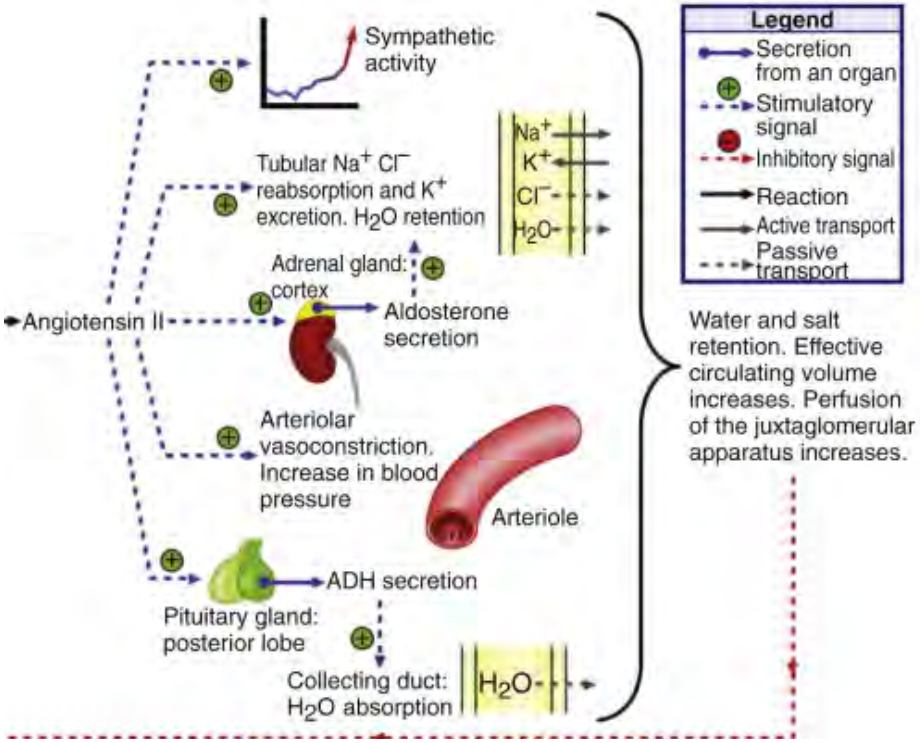
| Systolic heart failure | Diastolic heart failure |
|---|---|
| Coronary artery disease | Diabetes mellitus |
| Arterial hypertension | Arterial hypertension |
| Valvular heart disease (Volume load) | Valvular heart disease (pressure load) |
| Arrhythmia | Hypertrophic cardiomyopathy |
| Inflammatory diseases | Restrictive cardiomyopathy |
| Idiopathic cardiomyopathy | Constrictive pericarditis |
| Toxic cardiomyopathy (alcohol) | Amyloidosis (storage disease) |

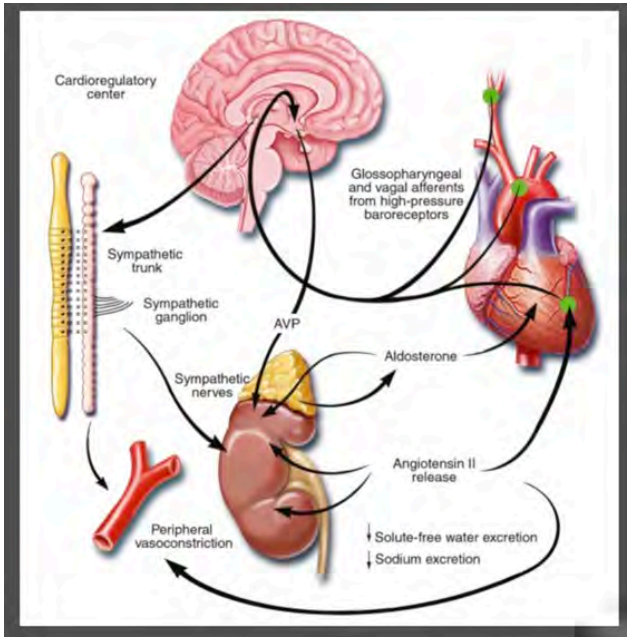
# HEART FAILURE: RIGHT VS. LEFT

**Table 2** Predominant clinical situations for left-sided and right-sided heart failure

| Left-sided heart failure | Right-sided heart failure |
|---|---|
| Coronary artery disease | Coronary artery disease (right ventricle MI) |
| Hypertension | COPD |
| Myocarditis | Pulmonary hypertension |
| Heart valve disease | Pulmonary valve stenosis |
| Tachycardiomyopathy | Pulmonary embolism |
| | Tricuspidal regurgitation |
| | Pneumothorax |
| | Pericardial effusion |

# IN THE CONTEXT OF A FAILING HEART… WHAT IS THE IMPACT OF CHRONIC SNS AND RAAS ACTIVATION IN THE SHORT TERM?

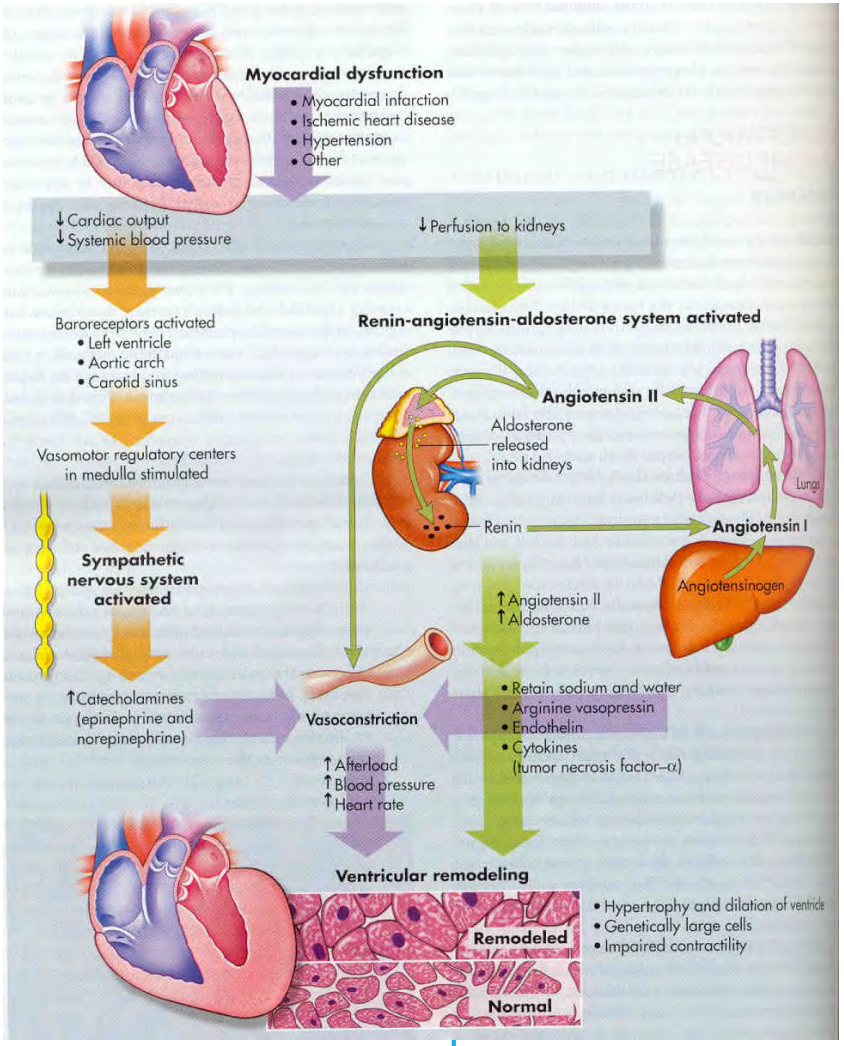


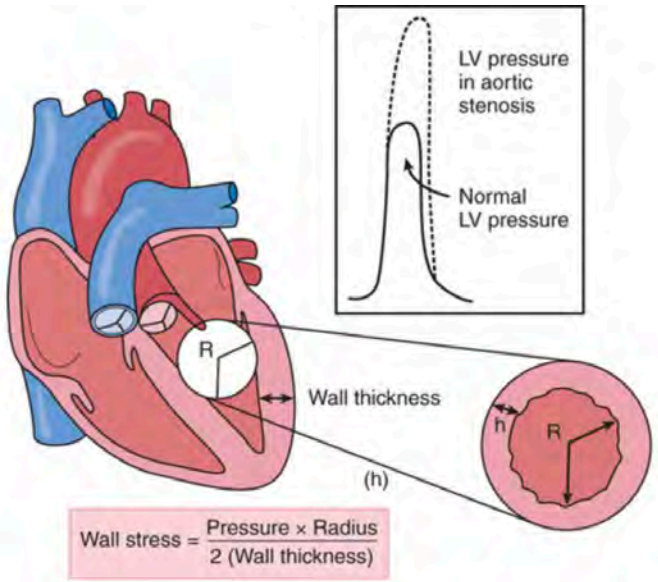
IN THE CONTEXT OF A FAILING HEART…

CHRONIC SNS AND RAAS ACTIVATION RESULTS IN ENHANCED MYOCARIDAL DYSFUNCTION + VENTRICULAR AND VASCULAR REMODELING =

DISEASE PROGRESSION



**Law of La Place**



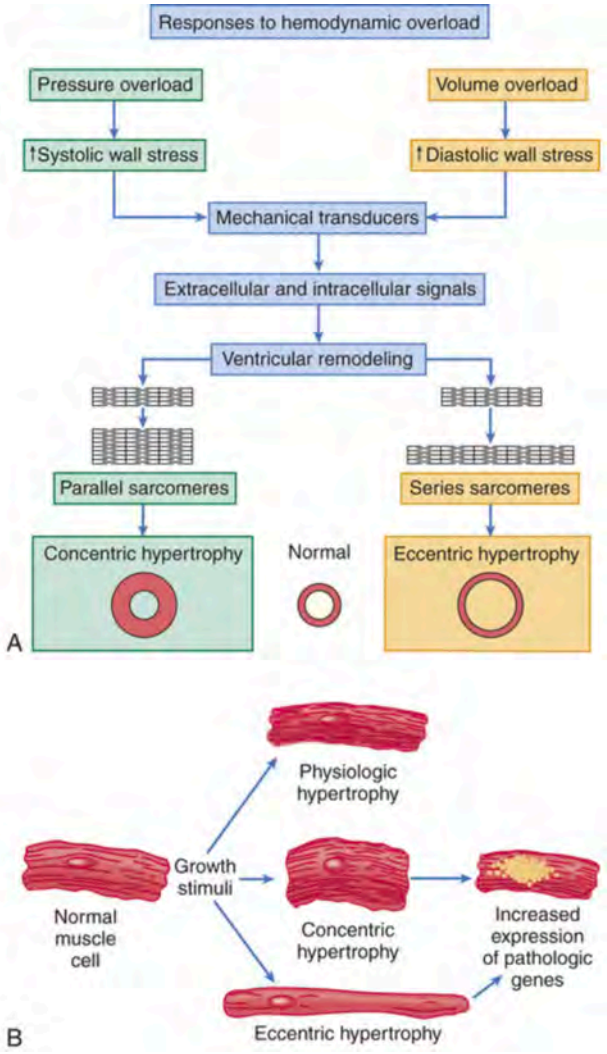

If 1) pressure inside the ventricle

or 2) radius of the ventricle increase

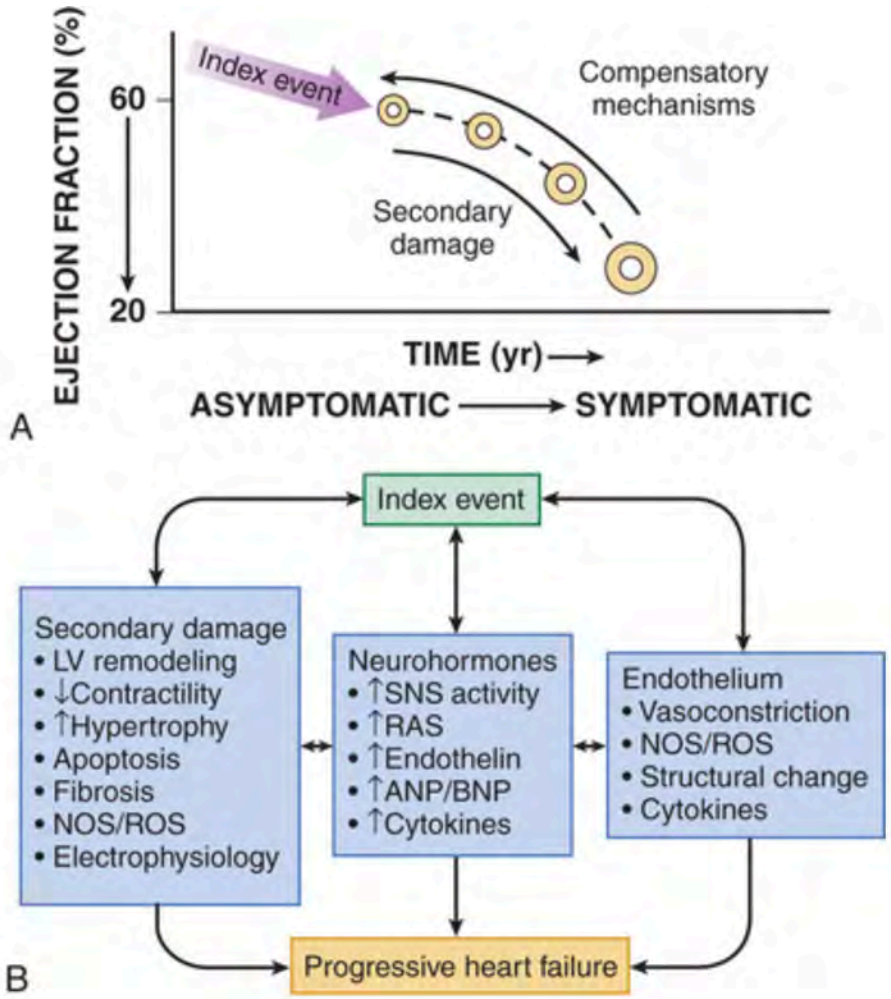
Wall stress increases and the wall has to generate more force to contract.

The thicker the wall the more wall stress normalizes - compensation

Braunwald's Heart Disease 11th Ed. 2018




**Ventricular remodeling leads to progressive heart failure**

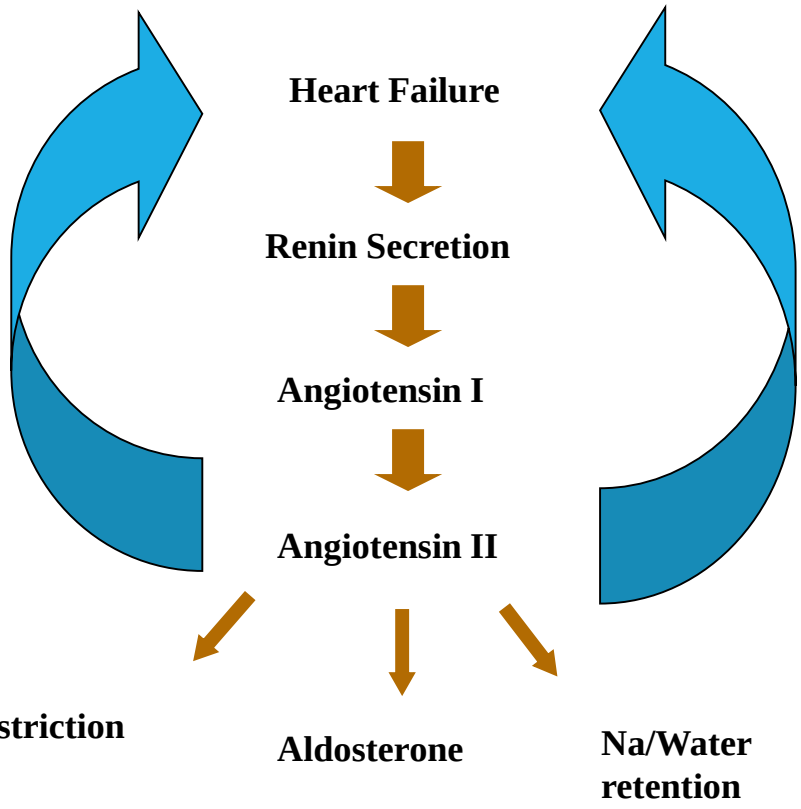



Braunwald's Heart Disease 11th Ed. 2018

# A VICIOUS CYCLE

Too much Afterload

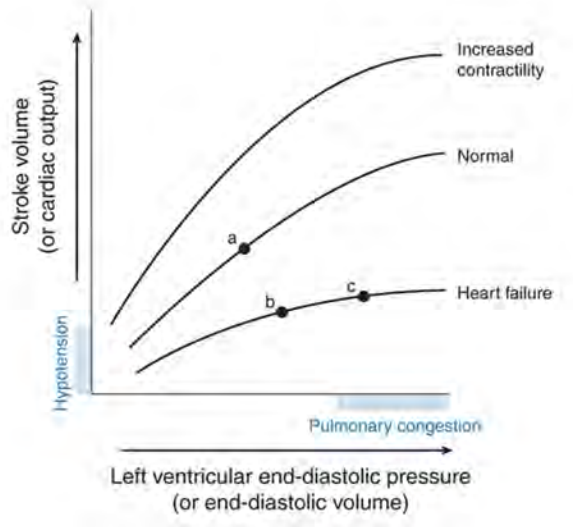
(systemic vascular resistance/LV systolic wall stress)

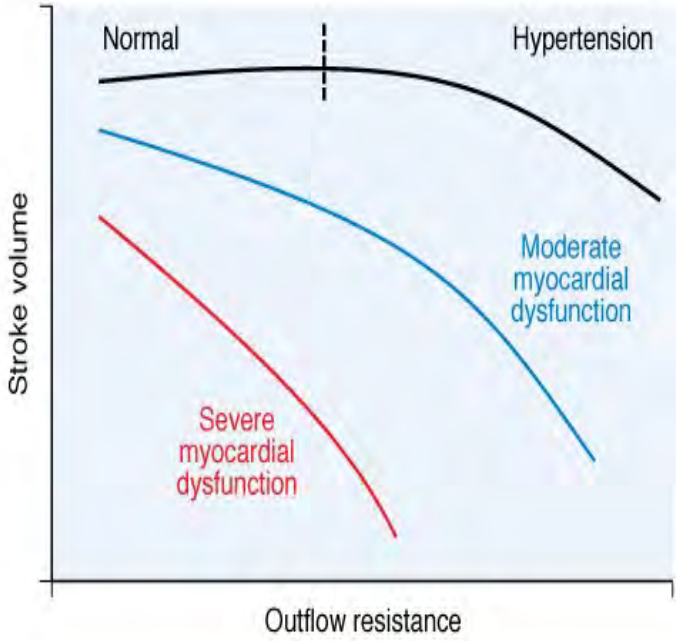



Too much Preload

(the stretch of the LV myocytes at end diastole)

# FRANK STARLING CURVE IN DIFFERENT PHYSIOLOGIC STATES




Goodman and Gilman, 12th ed., 2011

# PRACTICE QUESTIONS

**Which of the following best describes a patient with left-sided systolic heart failure?**

a. Relatively preload-dependent and afterload-dependent
b. Relatively preload-independent and afterload-independent
c. Relatively preload-dependent and afterload-independent
d. Relatively preload-independent and afterload-dependent

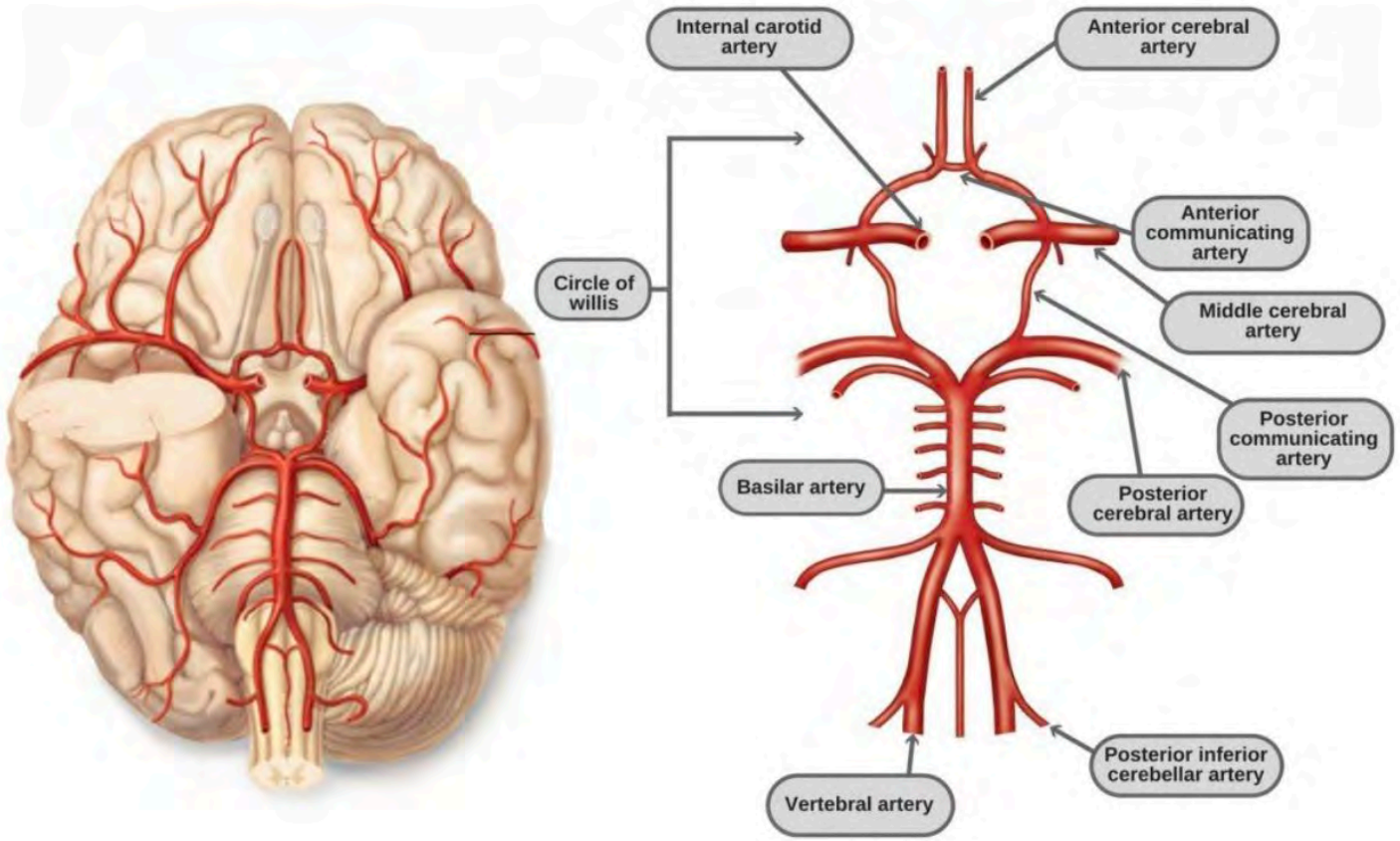
Which of the following mediators counteracts the harmful impacts of angiotensin II signaling in heart failure?

a. Renin
b. Aldosterone
c. Atrial Natriuretic Peptide
d. Epinephrine

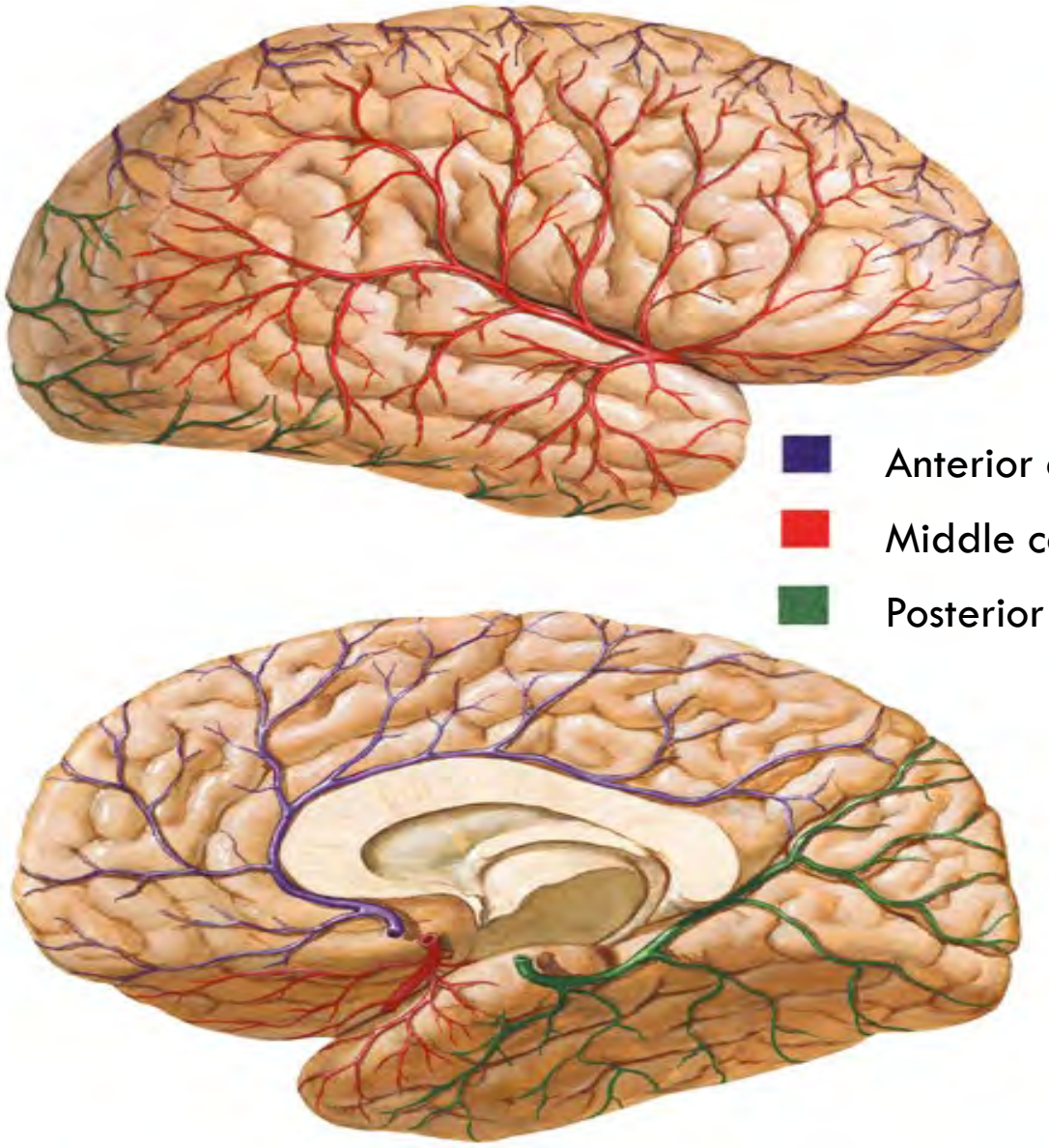
- *Cerebral Hemodynamics*
- *Intracranial pressure and the Determinants and Cerebral Blood Flow and Metabolism*

# CIRCLE OF WILLIS

IMAGE: HTTPS://WWW.BIOSTASIS.COM/THE-CIRCLE-OF-WILLES-IN-CRYONICS-PERFUSION/

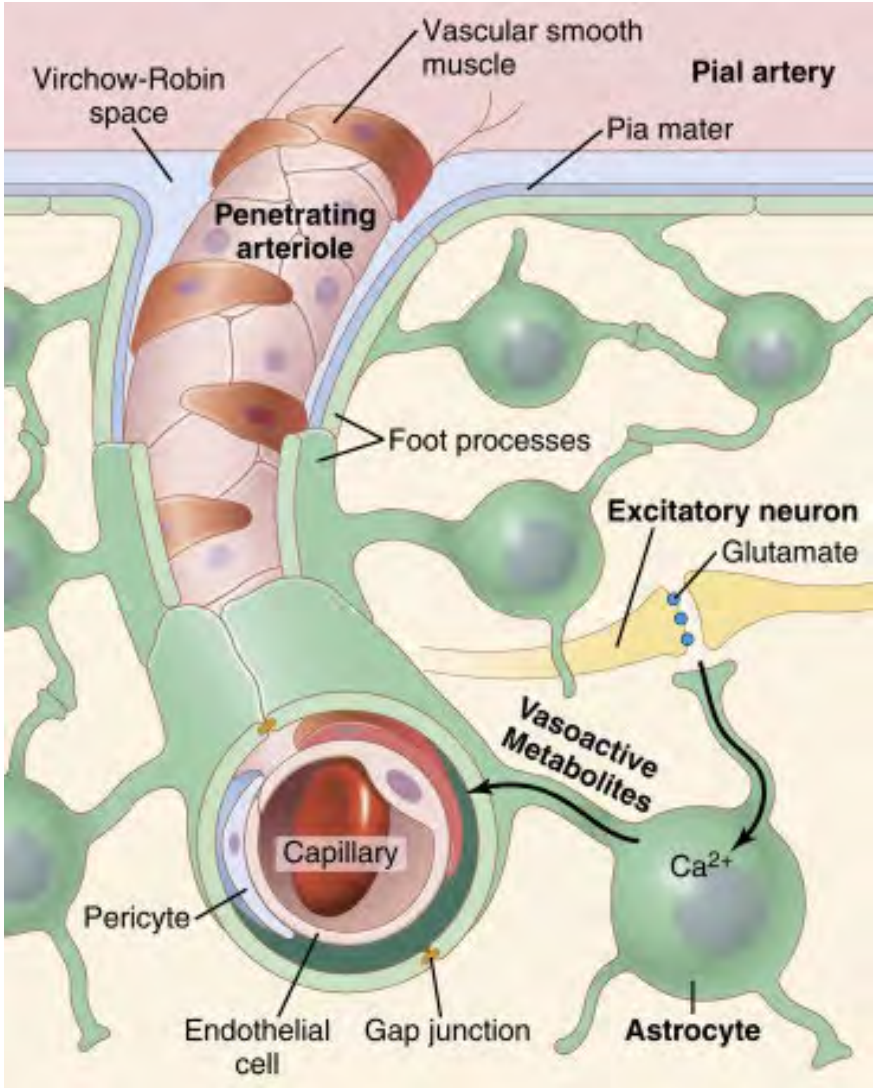


# Color Illustration of Territories of the Cerebral Arteries



# CEREBRAL MICROCIRCULATION

## FIGURE 62-1 GUYTON AND HALL



# CEREBRAL BLOOD FLOW VS CEREBRAL BLOOD VOLUME

Parallel but not 1:1 relationship

- CBV = 3-5ml/100g brain tissue

We care about flow because it influences total cerebral blood volume

Consider not only arterial flow (and tone) but also venous drainage (and tone)

# INTRACRANIAL PRESSURE

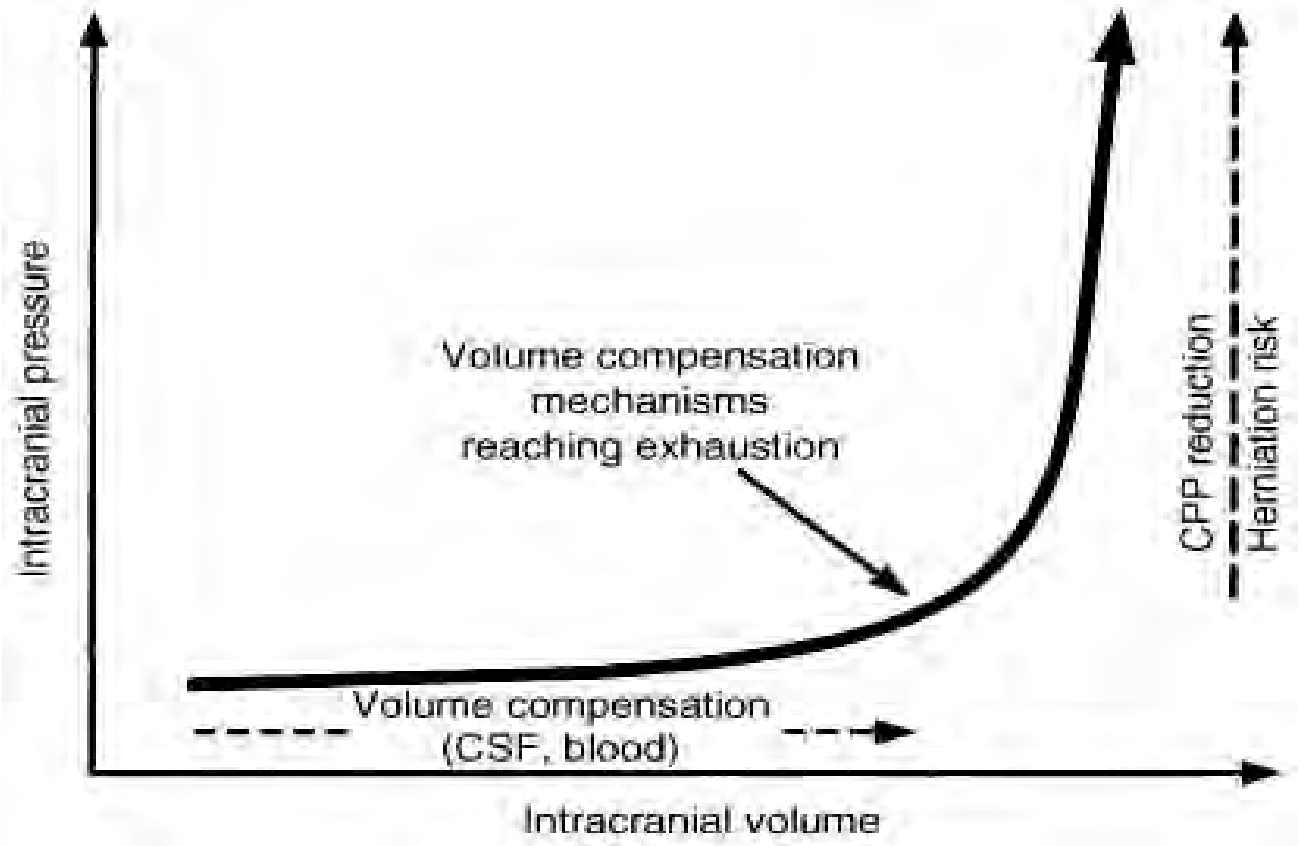
Normal pressure 8-12 mmHg

Rigid cranial vault fixed volume

- Brain (cellular and ICF) (80%)
- Blood (arterial and venous)(12%)
- CSF (8%)

# ICP – INTRACRANIAL PRESSURE

**FIGURE 53-3** MILLER 6TH EDITION 2128



# INTRACRANIAL ELASTANCE

Determined by the change in ICP after a change in intracranial volume – compensatory mechanisms include:

1. Initial displacement of CSF from cranial to spinal compartment
2. Increased CSF absorption
3. Decreased CSF production
4. Decreased CBV (primarily venous)

# CEREBRAL PERFUSION PRESSURE (CPP)

Mean Arterial Blood Pressure (MAP) – ICP (or central venous pressure whichever is greater)

CPP = MAP – max(ICP, CVP)

Normal is 80-100mmHg

Example, MAP (93) – ICP (10) → 83 mmHg

# CEREBRAL BLOOD FLOW

Normal Adult 50ml/100g/min =750ml/mi

- Brain is ~1500 g

Blood flow closely linked with metabolism

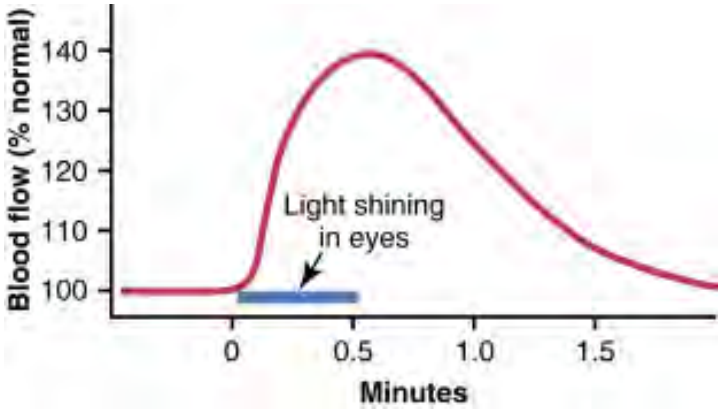
1. Level of arousal
2. Metabolic by-products from astrocytes & neurons
3. Blood Viscosity
4. Temperature
5. Concentration of $CO_2$ and $H^+$ ions
6. $O_2$

# NEURONAL ACTIVITY (METABOLISM) AND LOCAL CEREBRAL BLOOD FLOW (FIGURE GUYTON CH. 62)

"Flow-metabolism coupling"

- Metabolic by-products (glial, neuronal, vascular)

CBF to localized brain regions change up to 100-150% within seconds in response to local neuronal activity changes (sensory input/arousal)



# $PACO_2$ & $H^+$ INFLUENCE CEREBRAL BLOOD FLOW

$CO_2 + H_20 =$ carbonic acid

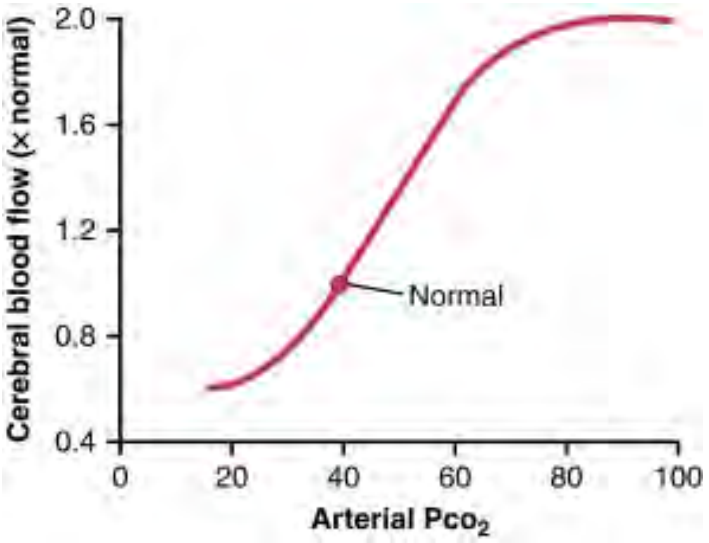
Carbonic acid disassociates & releases $H^+$

$H^+$ ions cause proportional cerebral vasodilation

Each 1 mmHg change in $PaCO_2$

- CBF changes approximately 1-2ml/100g/min
- CBV changes 0.5ml/100g brain tissue

Effect lasts ~ 6hrs and then in will return to normal despite maintenance of altered $CO_2$ levels (bicarb transport)




Guyton 62-2

# BRAIN METABOLISM

Only 2% of total body mass, 15-20% of total body metabolism and cardiac output

Cerebral Metabolic Rate ($CMRO_2$) = 3-3.8ml/100g/min = 50ml/min of $O_2$

Pediatric patients higher $CMRO_2$ = 5.2ml/100g/min (mean age 6 yr)

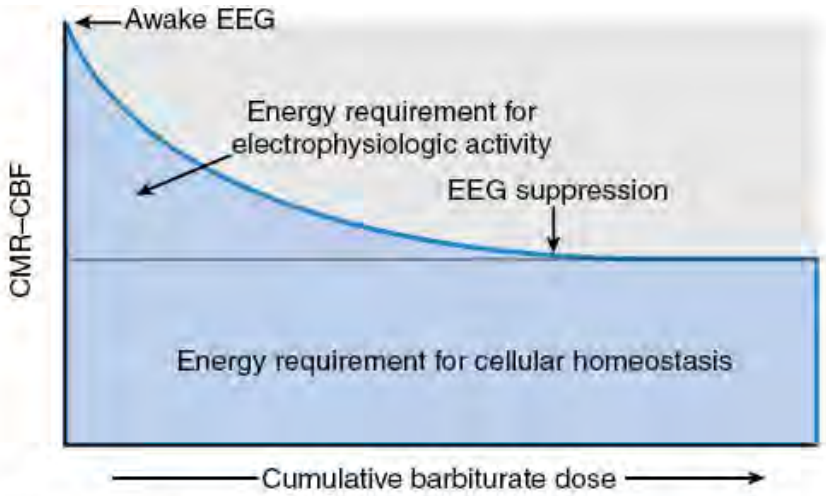



**Figure 13-1** Interdependency of cerebral electrophysiologic function and cerebral metabolic rate (CMR). Administration of various anesthetics, including barbiturates, results in a dose-related reduction in the CMR of oxygen ($CMRO_2$) and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrophysiologic silence. At this point, the energy utilization associated with electrophysiologic activity has been reduced to zero, but the energy utilization for cellular homeostasis persists unchanged. Additional barbiturate causes no further decrease in CBF or $CMRO_2$.

# BRAIN METABOLISM

Brain not capable of much anaerobic metabolism (high metabolism coupled with low local glycogen and oxygen stores)

Brain glucose consumption 5.5mg/100g/min

# CBF AND OXYGEN CONCENTRATION

Except for cases of intense brain activity $O_2$ utilization by brain tissue remains within narrow range ( a few % points around ***3.5mlO2/100gm brain tissue***)

If $PO_2$ of brain tissue drops below 30mmHg (35-45mm Hg normal) or $PaO_2$ drops below 50-60mmHg CBF increases

# AUTO-REGULATION OF CBF & ARTERIAL BLOOD PRESSURE

CBF auto-regulated really well between MAP of 70-150mmHG

Cerebral vasculature adjusts to changes in CPP/MAP after 1-3 minutes

HTN will shift auto-regulatory range to higher minimum values and maximums of 180-200mmHg

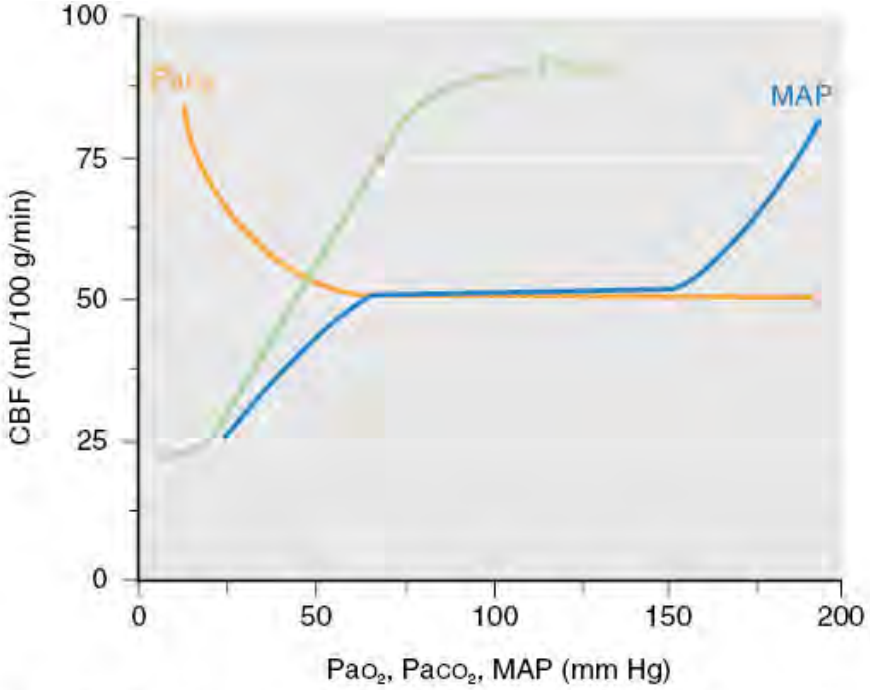



**Figure 13-4** Changes in cerebral blood flow (CBF) caused by independent alterations in $Paco_2$, $Pao_2$, and mean arterial pressure (MAP).

# THE SYMPATHETIC NERVOUS SYSTEM AND CBF

Under normal conditions, SNS innervation has little influence on CBF

Neither transection of these nerves or mild to moderate stimulation causes much change - the auto-regulation mechanism overrides

May shift the auto-regulation curve to the right

- SNS minor role unless sudden extreme BP rise (stroke prevention) or hemorrhagic shock

# TEMPERATURE AND CBF

CBF changes 5-7% per 1 degree C change

Hypothermia decreases CBF and $CMRO_2$

Hyperthermia opposite effect

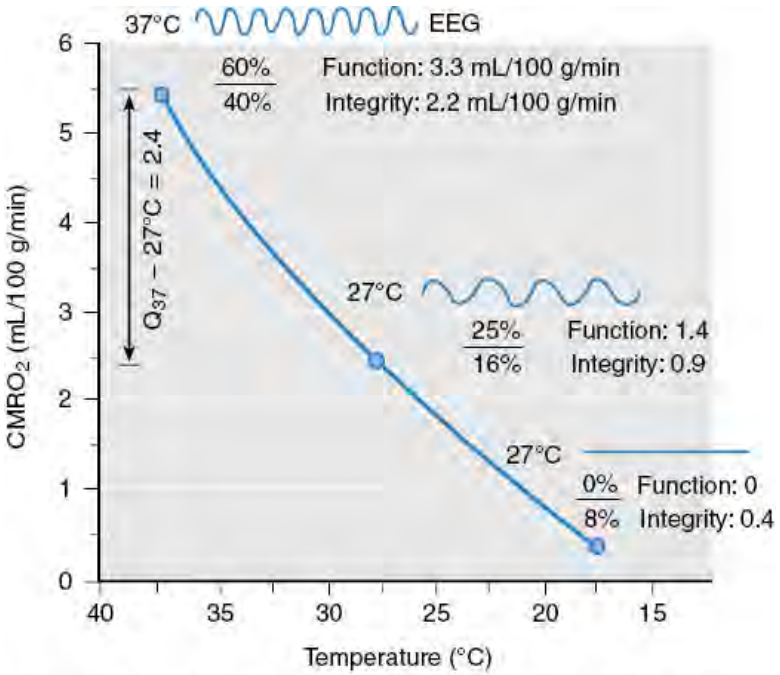



**Figure 13-3** Effect of temperature reduction on the cerebral metabolic rate of oxygen ($CMRO_2$). Hypothermia reduces both of the components of cerebral metabolic activity identified in Figure 13-1: that associated with neuronal electrophysiologic activity ("Function") and that associated with maintenance of cellular homeostasis ("Integrity"). This is in contrast to anesthetics that alter only the functional component. The ratio of CMR at 37°C to that at 27°C, the $Q_{10}$ ratio, is shown in the graph.

*(Adapted from Michenfelder JD: Anesthesia and the Brain: Clinical, Functional, Metabolic, and Vascular Correlates. New York, Churchill Livingstone, 1988.)*

# PRACTICE QUESTIONS

A patient has a blood pressure of 140/80 (100) mm Hg, HR of 60 beats per minute, central venous pressure of 16 mm Hg and an intracranial pressure of 14 mm Hg. What is his estimated cerebral perfusion pressure?

a. 64
b. 66
c. 84
d. 86

Blood (arterial and venous) makes up what % of cranial volume?

a. 5%
b. 8%
c. 12%
d. 20%

# PRACTICE QUESTIONS

A patient's temperature increases from 36 degrees C to 41 degrees C. Approximately how much will cerebral blood flow increase?

a. No change would be expected
b. 5%
c. 25%
d. 100%
e. 200%

A patient's $PaCO_2$ increases from 25mmHg to 50mmHg within a 5-minute period of time. What is the predicted *short-term* (1-2 hours) impact on cerebral blood flow?

a. Cerebral blood flow will stay the same
b. Cerebral blood flow will approximately double
c. Cerebral blood flow will decrease by approximately 50%
d. Cerebral blood flow will decrease by approximately 150%