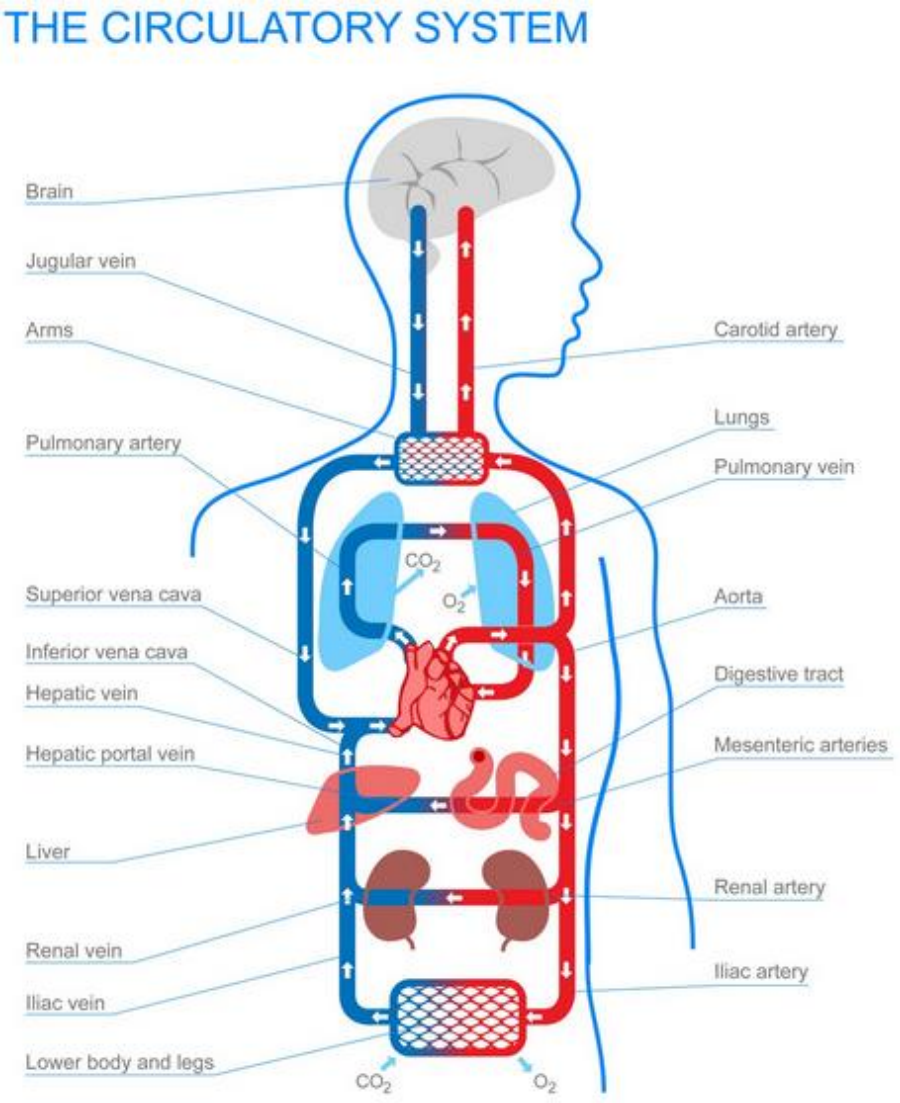
CARDIOVASCULAR & RESPIRATORY PHYSIOLOGY



From http://naturecure-siva.blogspot.com/[1]

MEDICAL SCIENCES FALL, 2015

IV. Higher Functions of the Cerebral Cortex

A. Electroencephalogram (EEG) and B. Sleep

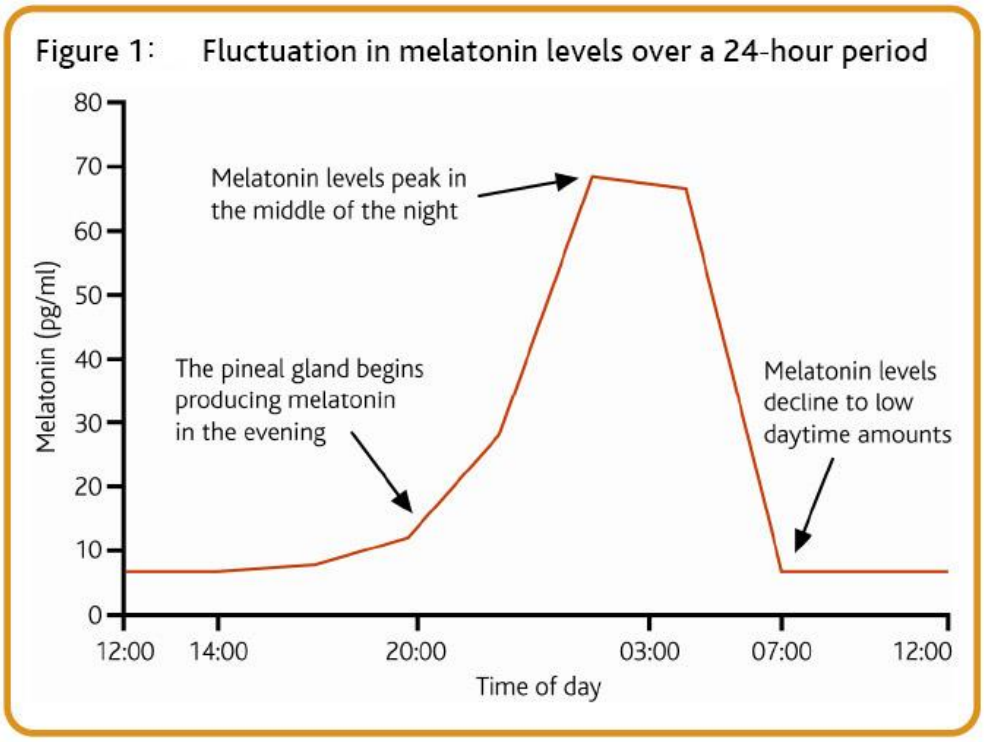
The pineal gland and melatonin

- Pineal body is tucked at the edge of the third ventricle in the brain, half-way between the hypothalamus and the cerebellum. It is classified as an endocrine structure because it releases melatonin

- Melatonin is derived from tryptophan

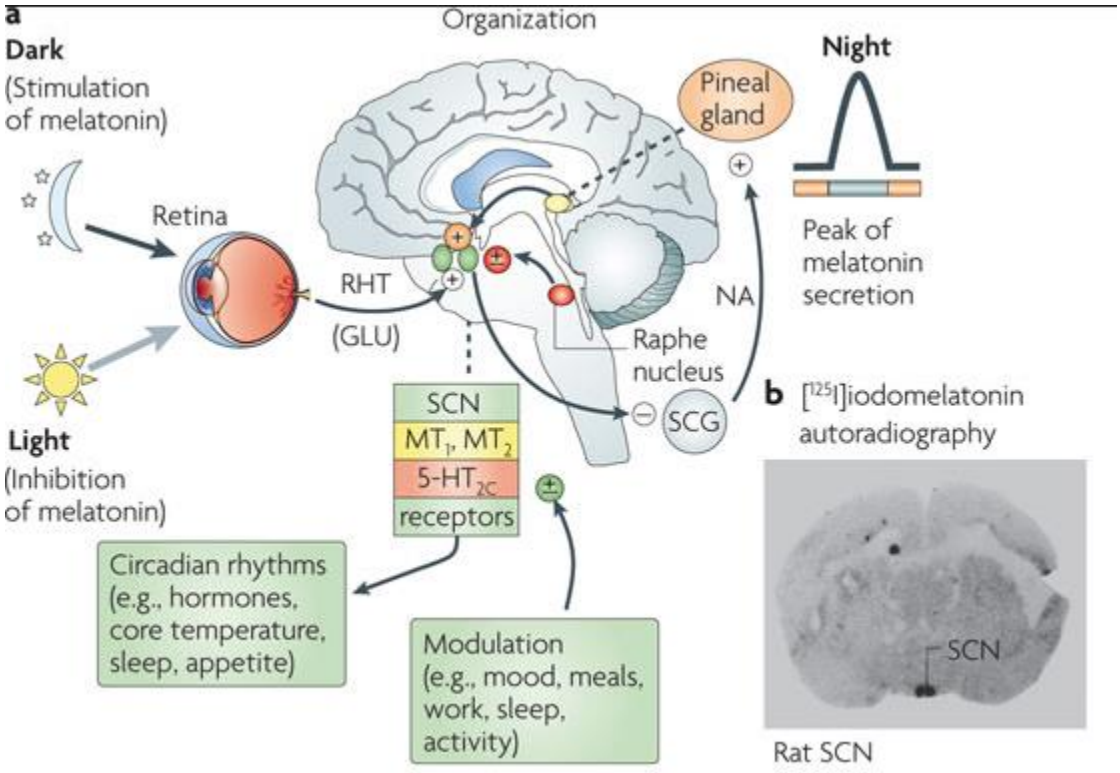
- Melatonin cyclic blood levels vary with the light-dark cycle

- Light—sensed at the suprachiasmatic nucleus in the brain, near the optic nerves—helps "entrain" melatonin to the light-dark cycle



From http://www.epgonline.org/images/insomnia/in-2211.jpg[2]

- Suprachiasmatic nuclear cells spontaneously generate the ~24 hour rhythm, and are then linked to the pineal to yoke melatonin levels as well:



From http://www.nature.com/nrd/journal/v9/n8/fig_tab/nrd3140_F1.html[169]

- Light resets the clock every day
- In the absence of external light or environmental cues, humans show a circadian rhythm in body temperature, melatonin levels, and cortisol levels of 24 hours and about 3-6 minutes (ca. 24.05 hours). This cycle—for all three markers—is
    - Identical from day to day, unchanged in old age, and virtually the same in all persons
- Melatonin and external light determine sleep onset/offset

Questions:

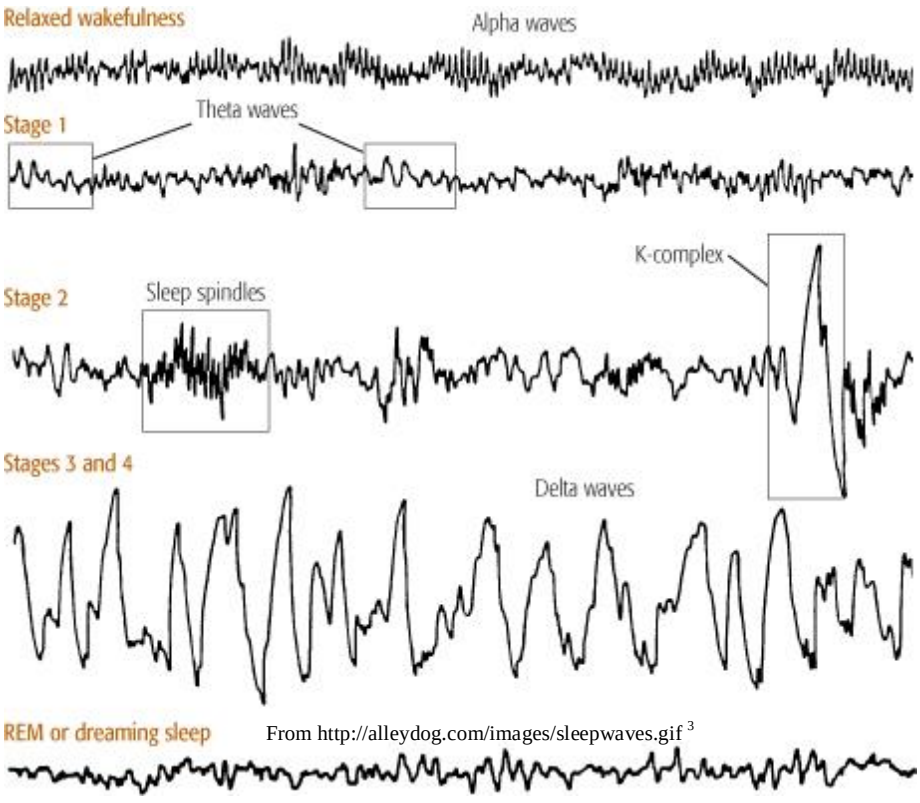
Question	Answer
A 73-y/o woman flies from Chicago to Paris, and for several days thereafter experiences insomnia, early waking, and excessive sleepiness. Why?	
Why does she also have difficulty concentrating?	

Question	Answer
Why is her return trip to Chicago much less difficult to tolerate?	
Why does the American Academy of Sleep Medicine recommend that middle and high schools start their school day after 8:30 AM?	
What are some consequences of inadequate sleep in teenagers?	

EEG

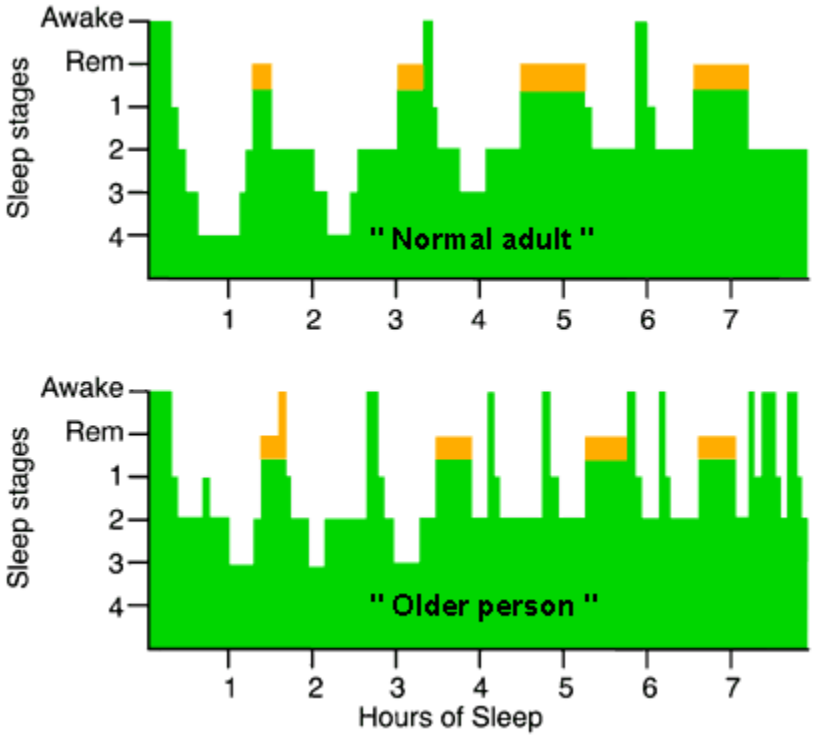
- Cortical evoked potentials in response to discrete stimuli can be studied—there are distinctive waveforms of relaxed wakefulness (alpha waves), alert wakefulness (beta waves), and various sleep stages

Sleep



From http://alleydog.com/images/sleepwaves.gif [3]

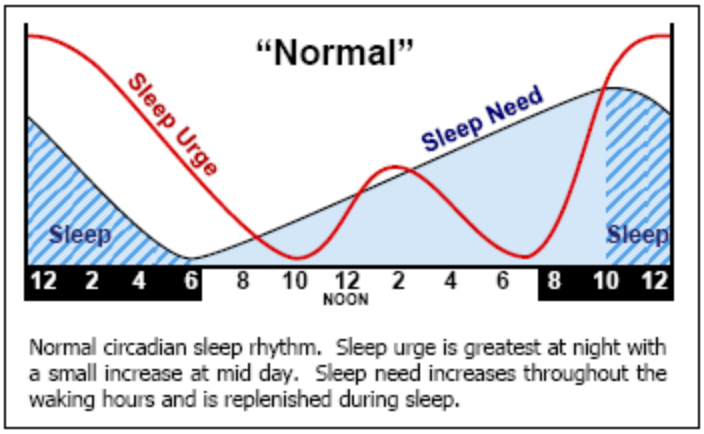
- EEG monitoring shows that sleep progresses in ordered stages, through several stages of non-rapid-eye-movement (non-REM) sleep, and through rapid-eye-movement (REM) sleep
    - REM is associated with dreaming
    - Non-REM is defined, roughly, in four stages
        - Stages 1 and 2 are light sleep
        - Stages 3 and 4 are deeper sleep ("slow-wave sleep" from EEG)
- Feeling refreshed after sleep requires:
    - Sufficient total amounts of both REM and Stages 3 and 4 of non-REM
    - Sufficient uninterrupted periods (at least 20-30 min at a time) of, especially, the deeper stages of sleep:



From http://www.healthandage.com/html/res/primer/pics/sleep.gif[4]

- Circadian rhythm ("clock-dependent alerting") and *sleep load* combine to create fluctuating daytime sleepiness:

From http://www.ride4ever.org/images/normalsleep.gif[5]



Normal circadian sleep rhythm. Sleep urge is greatest at night with a small increase at mid day. Sleep need increases throughout the waking hours and is replenished during sleep.

- Daytime sleepiness is now recognized as the primary symptom in sleep medicine

Question: What are some of the symptoms of excessive daytime sleepiness?

- Sleep stages, learning, and memory

Self-awareness question: Measure your current daytime sleepiness using the following scale (0 to 24):

Table 2 – Epworth daytime sleepiness scale

READ CAREFULLY: How likely are you to doze off or fall asleep, as opposed to simply feeling tired, in the following situations? Even if you have not done some of these things recently, try to imagine how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = No chance of dozing
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	( )
Watching TV	( )
Sitting in a public place (waiting room, cinema, theater, church, etc.)	( )
As a passenger in a car, bus, or train for an hour without a break	( )
Lying down to rest in the afternoon when circumstances permit	( )
Sitting and talking to someone	( )
Sitting quietly after a lunch without alcohol	( )
In a car, while stopped for a few minutes in traffic	( )
Total: _____	

From www.psychiatrymmc.com[14]

- Increased daytime sleepiness is associated with shortened sleep latency
- Sleep needs are constant ("sleep homeostasis")
    - Individual sleep needs vary from ca. 7 – 9 hours/night
    - Inadequate sleep causes sleep debt accumulation
    - Training and "practice" cannot change sleep need
    - Increased sleep debt decreases sleep latency and increases sleep efficiency
    - High sleep debt is a modern epidemic

Questions: Daytime sleepiness

Question	Answer
What is the treatment for inadequate time in bed?	
What are the effects of emotional stress or anxiety disorders on sleep?	
What is involved in the cognitive-behavioral therapy for insomnia?	
How, specifically, does clinical depression alter sleep?	
What is sleep apnea and how does it affect sleep and daytime sleepiness?	
What are some reasons why sleep needs and sleepiness increase during the 1st trimester of pregnancy?	
What are some of the factors that compromise sleep during the 3rd trimester of pregnancy?	

Practice Questions

1. Sleep latency testing is most accurately done in the early afternoon because
    a. circadian sleep urge reaches a secondary peak at that time
    b. fatigue and increased core temperature combine to reduce wakefulness drives
    c. melatonin is at a minimal level
    d. rising blood glucose after lunch suppresses brain activity
    e. sleep load is maximized at that time

2. Normal sleep in a 20-y/o is shown below. The total nightly duration of which stage of sleep declines most obviously between age 10 and age 80?

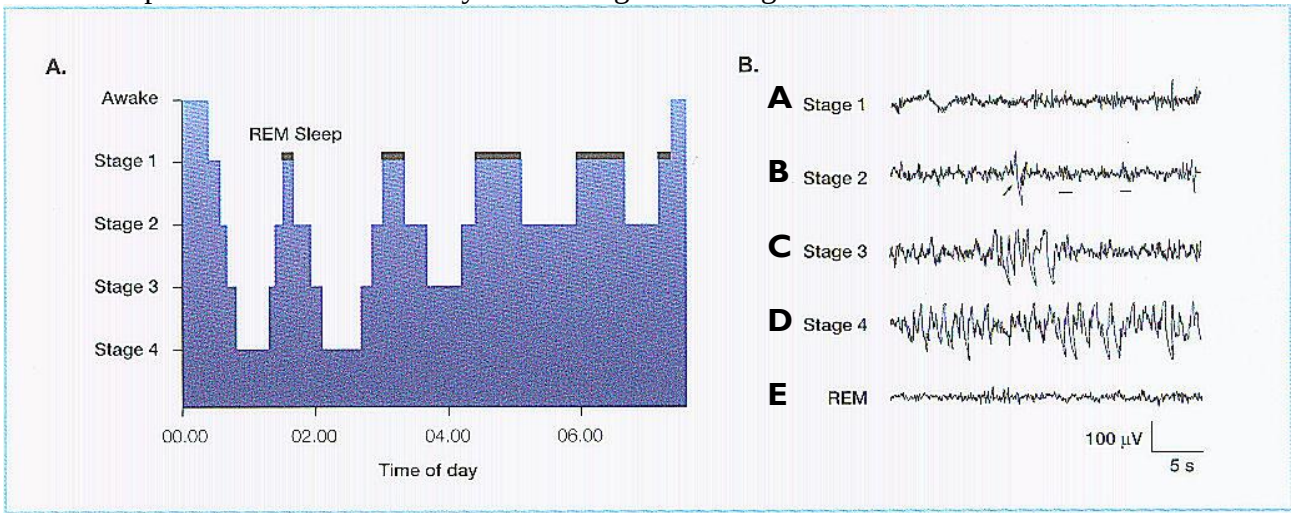


Figure 1. **Sleep stages: A. Hypnogram and B. Electroencephalogram.** Adapted with permission from Carskadon and Dement[7] and Kandel et al.[8] From http://www.mdpi.com/2075-163X/1/1/49/htm[176]

    a. A
    b. B
    c. C
    d. D
    e. E

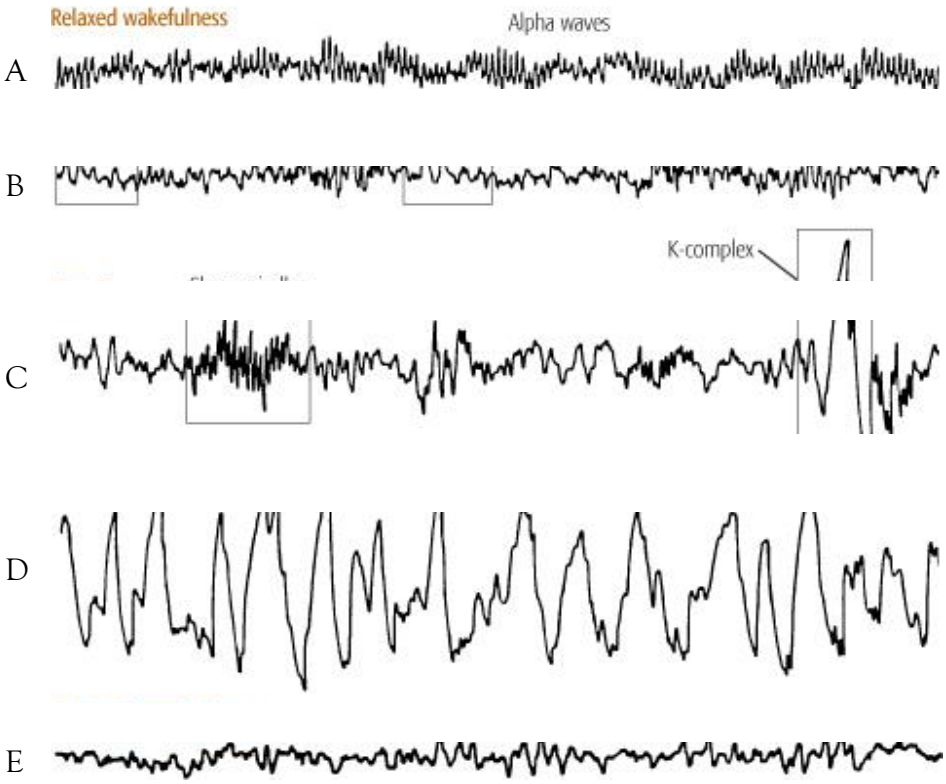
3. Recent evidence points to cyclical changes in temperature regulation as the defining factor in the circadian rhythm of body core temperature. Core temperature falls prior to the onset of sleep (at constant metabolic rate and under constant ambient conditions) because there is decreased
    a. sweating
    b. conduction of heat from core to skin
    c. skin blood flow
    d. Na^+ and Cl^- reabsorption in sweat glands
    e. α_1 stimulation of skin resistance vessels

4. A 44-y/o man's pituitary tumor has damaged the suprachiasmatic nucleus, resulting in
    a. a diurnal rhythm in body core temperature
    b. a chronic 3-5 hour "jet lag"
    c. disruption of the 24-h sleep-wake cycle
    d. homeostatic sleep drive decreasing at the same time each morning
    e. melatonin release in response to onset of darkness instead of in response to onset of daylight

5. Persons with bipolar affective disorder ("manic-depression") have abnormal circadian rhythms whether symptomatic or asymptomatic. These abnormalities include
    a. a 24.1 hour circadian cycle
    b. an increase in sleepiness in mid- to late afternoon
    c. mood changes with increased sleep deprivation
    d. rising body temperature in late evening
    e. sleep loss accumulation as sleep debt

From http://alleydog.com/images/sleepwaves.gif [3]

6. Which of the sleep EEG patterns shown below represents the time during which experiences of the previous day are first moved from hippocampal short-term memory into an initial pattern representation in the cortex?

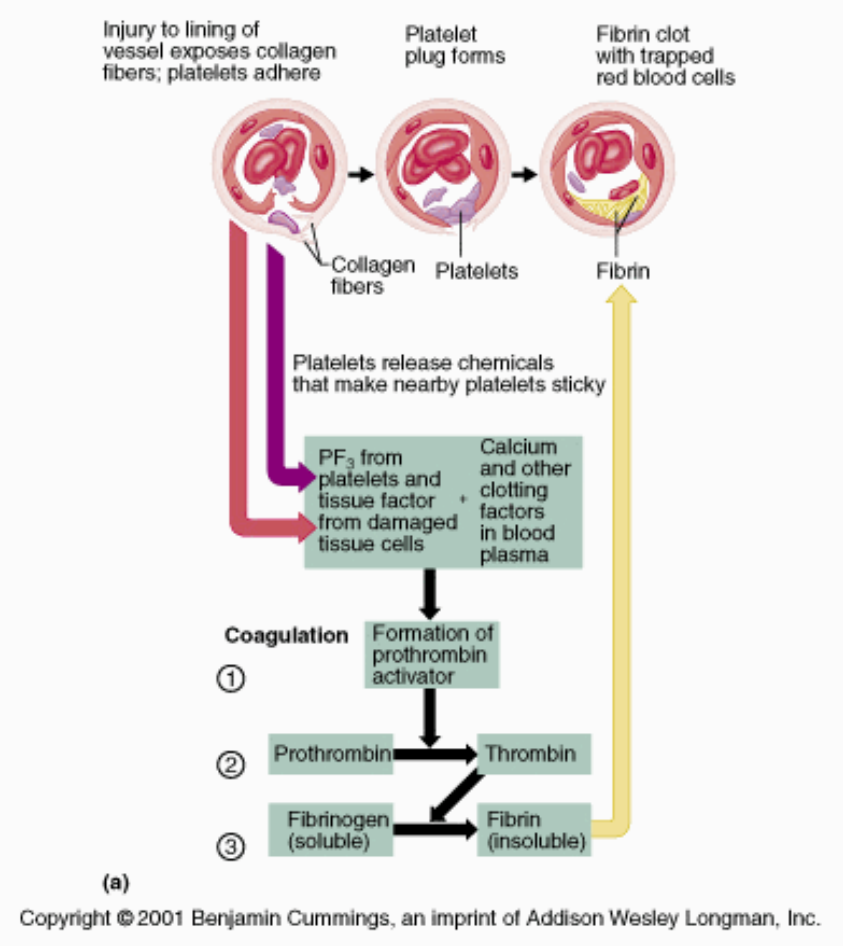


    a. A
    b. B
    c. C
    d. D
    e. E

Chapter 3: Cardiovascular Physiology

Hemostasis

- Cessation of bleeding has four components:
    - Vasoconstriction
    - Increased tissue pressure
    - Formation of platelet plug
    - Production of fibrin proteins from fibrinogen: this is a "blood clot"



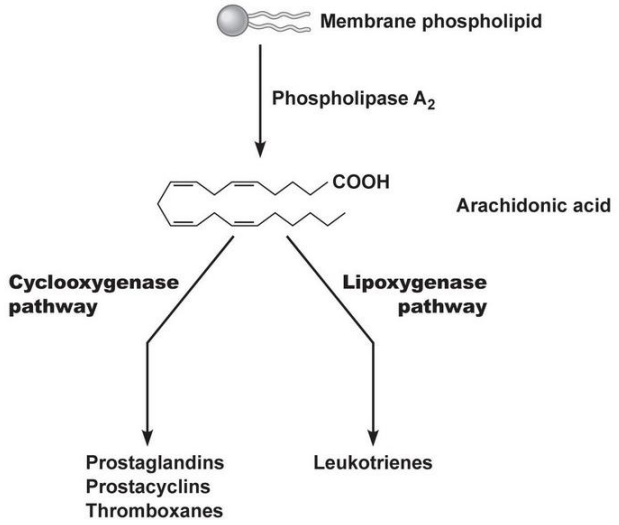
From www.legacy.owensboro.kctcs.edu[26]

Platelet activation

- Platelet adhesion is (usually) to damaged vessel walls, to prevent internal or external blood loss, in response to a variety of substances including exposed collagen

- Platelet stimulation by, for example, collagen, triggers the "platelet release reaction", which involves platelet discharge of

    - Thromboxane A_2, ADP, and serotonin, which contribute to platelet adhesion and aggregation

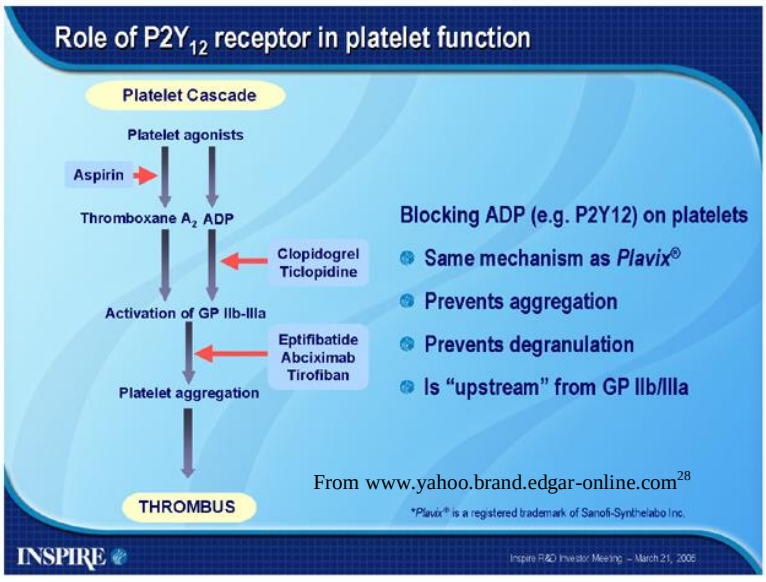


From http://droualb.faculty.mjc.edu/Course%20Materials/Physiology.htm[27]

    - Growth factors, which help the damaged vessel walls rebuild

    - Clotting factors, which contribute to activation of the coagulation cascade. These include platelet factor 3 (PF3) and a phospholipid binding surface for coagulation to proceed

Discussion question: Aspirin and other drugs block the cyclooxygenase pathway to prostaglandin synthesis. Aspirin therefore blocks platelet production of thromboxane A_2, which contributes to that portion of the platelet release reaction that clumps platelets together ("platelet aggregation and adhesion"). (Clopidogrel (Plavix®) blocks the activation of platelets by ADP):

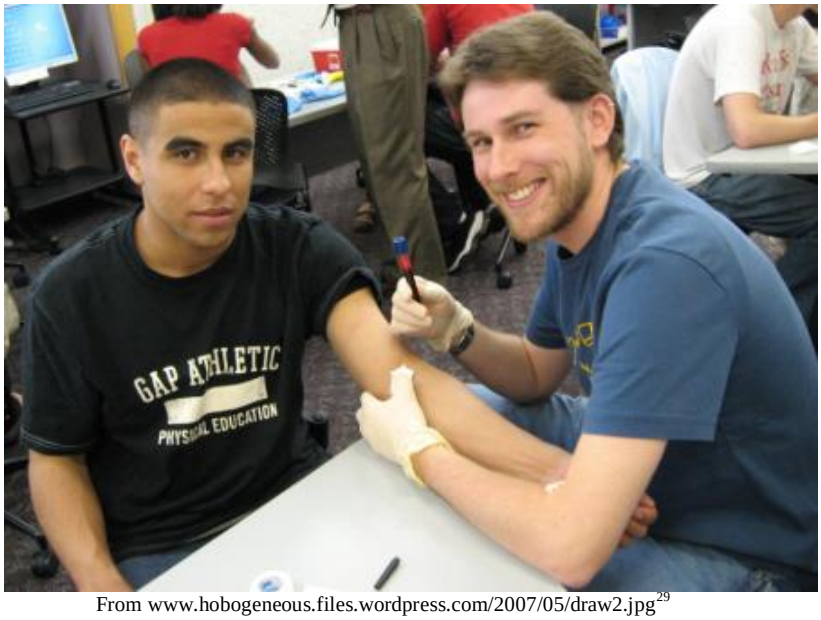


From www.yahoo.brand.edgar-online.com[28]

List some of the effects of aspirin. What are the pros and cons of aspirin use as a preventive medicine for heart attack?

- Platelet plugs can be sufficient to stop bleeding from very small wounds; larger wounds require the addition of a blood clot

Formation of an intravascular blood clot (or thrombus, which is a clot + trapped elements; a thrombus that is free and moving in circulation = an example of an embolus)

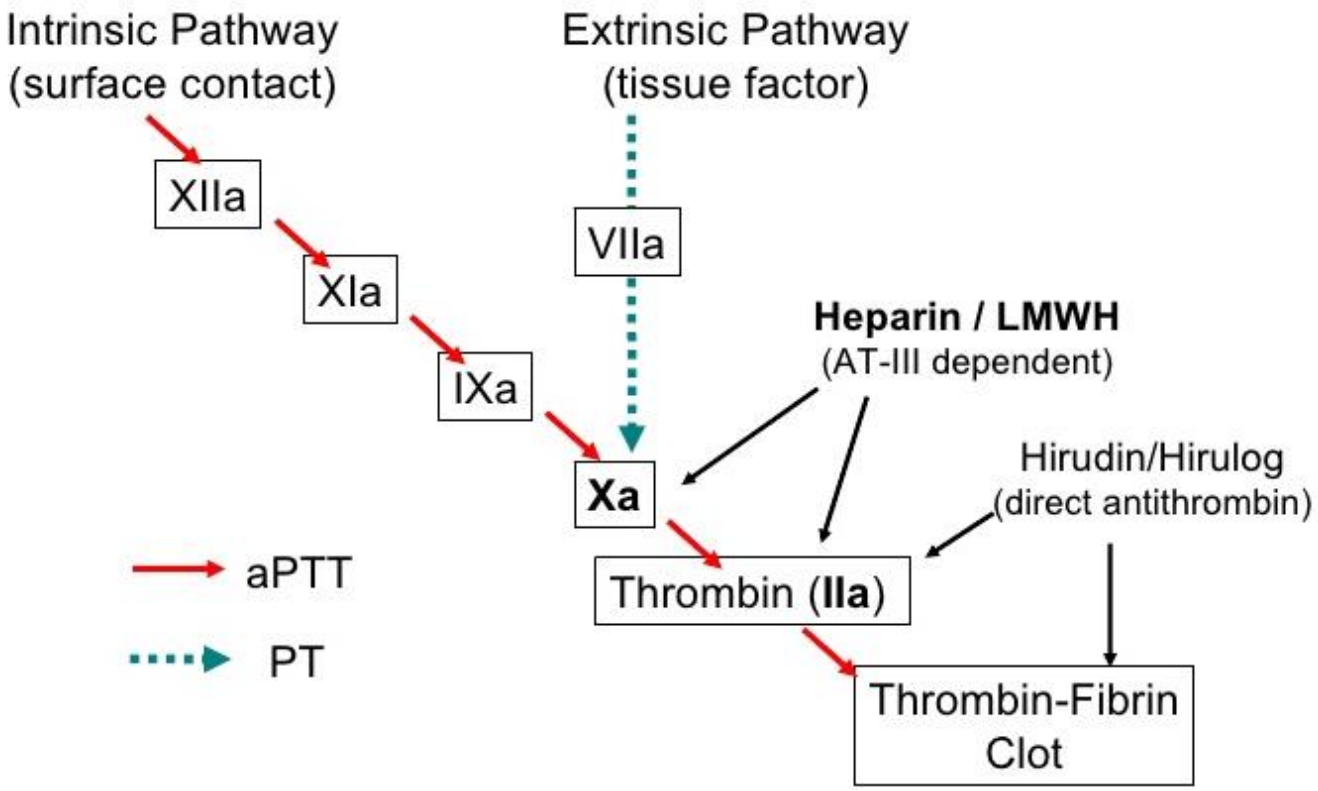


From www.hobogeneous.files.wordpress.com/2007/05/draw2.jpg[29]

- Conversion of fibrinogen to fibrin
    - Fibrinogen (3% of plasma proteins), although far less prevalent than albumin (~60%) or the globulins (~35%), is a soluble plasma protein essential for the formation of blood clots
    - Plasma vs. serum
        - Clot retraction in response to contraction of platelet actin and myosin

Question: What are some relative advantages and disadvantages of measuring a variable in *plasma* as opposed to *serum*?

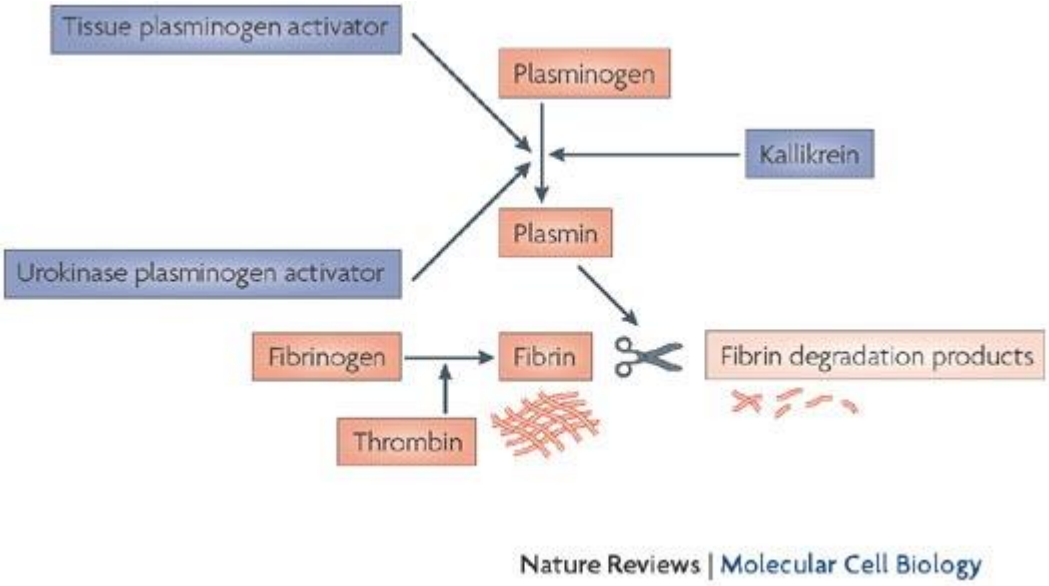
- The "intrinsic" pathway is slow and, although usually dependent upon contact with a negatively charged foreign surface, requires no elements except what is already in the blood
- The "extrinsic" pathway is very fast, requires additional factors from outside the blood, and is usually initiated by liberation of tissue thromboplastin from damaged vessel walls
- Usually, the extrinsic pathway initiates coagulation, while the intrinsic pathway primarily serves to amplify the coagulation cascade
- Intrinsic, extrinsic, and common clotting pathways are shown below:



From http://www.slideshare.net/iyerbk/enoxaparin-2782382[30]

- Intrinsic clotting pathway
  - Triggered by contact with damaged surface or even with a seemingly neutral foreign surface such as glass—negative charge is trigger
  - Requires Ca^{2+} at several steps
  - Intrinsic pathway is roughly estimated clinically by the "activated partial thromboplastin time" (aPTT)—key is initiation by surface factors
- Extrinsic clotting pathway
  - Requires tissue thromboplastin (Factor III, or tissue factor (TF)) from damaged tissues
  - Ca^{2+} is also required for the extrinsic pathway
  - Roughly estimated clinically by the "prothrombin time" (PT)—key is initiation by thromboplastin
  - The two tests (aPTT and PT) overlap to some extent, and can both be used to monitor therapy with anticoagulants

- Clot dissolution is carried out by plasmin, an enzyme that digests fibrin into "split products"



From http://www.nature.com/nrm/journal/v9/n8/images/nrm2455-i1.jpg[170]

- Antithrombin III

Questions: Practical facts about hemostasis

Topic	Mechanism or Comment; Question	Answer
Vitamin K	Fat-soluble vitamin; present in many green leafy vegetables; also a small but insufficient amount is synthesized in gastrointestinal tract; required for Ca^{2+} activation of several critical steps in coagulation. What can cause vitamin K deficiency?	
Coumadin® (warfarin)	Inactivates the cellular actions of vitamin K. It was discovered as the active ingredient in spoiled clover (1930's). 1) What symptom did the cows exhibit who ate this clover? 2) Why does Coumadin® use require repeated blood monitoring and adherence to a consistent diet?	
Hemophilia A	X-linked recessive disease that results in defective clotting factor VIII (or occasionally factor IX). Why don't persons with hemophilia bleed excessively from small cuts? What clinical clotting test would be most specific for detection of hemophilia?	
Thrombocytopenia	Low platelet count; caused by decreased production (e.g., bone marrow deficiencies) or excessive destruction (e.g., inflammatory illness, drug side effects) What are the signs and symptoms of thrombocytopenia?	
Heparin	Prevents blood clotting by activating antithrombin III and thereby inactivating thrombin; rapid acting but is inactive when given orally. What are the side effects of heparin? Is it really a "blood thinner"?	

Topic	Mechanism or Comment; Question	Answer
Tissue plasminogen activator (tPA)	Activates plasmin Why is tPA given during a heart attack? How do tPA and heparin/warfarin differ?	
von Willebrand disease	von Willebrand factor is a glycoprotein involved in both platelet adhesion and stabilization of factor VIII in clotting. Although there are three forms of vW disease, what general symptoms characterize all three?	
Activated partial thromboplastin time (aPTT)	Standard clinical test of clotting; platelet-poor plasma is incubated with surface activator, platelet factor 3, and phospholipids What does it test?	
Prothrombin time (PT)	Second standard clinical test of clotting function; thromboplastin and Ca^{2+} are added to blood; time to a clot is measured What does it test?	
Deep vein thrombosis (DVT)	Initiated by leukocytes adhering to vascular endothelium, with subsequent leukocyte release of tissue thromboplastin (=tissue factor or factor III). Which clotting pathway is activated? What are some appropriate preventive treatments?	
Atrial fibrillation → Atrial thrombus → thromboembolism → stroke	What might be some preventive measures, given that blood stasis, endothelial damage, and a hypercoagulable state are all involved?	

Practice Questions:

1. A lab technician realizes too late that the blood set aside for a serum sample is actually supposed to be used for a plasma sample. To convert the sample back to plasma, he would need to remove the clot and then do *at least* all of the following:
    a. add glucose, lactate, ADP, fibrinogen, and all of the products of the platelet release reaction
    b. add fluid volume and remove some platelets
    c. remove all of the metabolic byproducts of the fibrinogen→fibrin conversion and subtract some fluid
    d. remove from serum some serotonin, ADP, and thromboxane A_2, and add fibrinogen
    e. subtract some volume, platelets, and fibrinogen

2. (Adapted from www.cap.org) A 35-y/o woman injured in snowmobile accident is conscious at her arrival in the emergency room. She is taken to the operating room for open reduction of fractures of the left hip and femur. She receives two units of packed red blood cells intraoperatively. During the postoperative period, after her admission to the surgical intensive care unit, the patient's vital signs are stable and laboratory test results are obtained (Table 1, below).

Table 1

Laboratory findings

Test	Value	Reference range	Units
PT	12.5	10–13	seconds
aPTT	70	25–36	seconds
Fibrinogen	145	130–330	mg/dL
Hemoglobin	11	12–15	g/dL
Hematocrit	34	36–44	percent
WBC	9,000	4,000–10,000	per L
Platelet count	145,000	150,000–450,000	per L

From http://www.cap.org/apps/docs/cap_today/images/9_99table1.jpg[15]

She shows evidence for
    a. activation of extrinsic clotting factors
    b. fibrinogen depletion
    c. inhibition of the intrinsic clotting pathway
    d. plasmin activation
    e. vitamin K deficiency

3. A parent brings a conscious, curious 2-year old to the emergency room and explains, "I think he ate some of the mouse poison we were keeping under the kitchen cabinet". Your best indicator of warfarin (Coumadin®) poisoning is
    a. ↑ fibrinogen blood levels
    b. ↑ prothrombin time
    c. ↑ bleeding time from small cuts
    d. ↓ platelet count
    e. extensive bruising

4. After taking 325 mg aspirin, a 45-y/o man has a 50% increase in bleeding time from a very small skin wound, primarily due to reduction in platelet production of
    a. ATP
    b. diacylglycerols
    c. leukotrienes
    d. norepinephrine
    e. thromboxane A_2

5. A 47-y/o woman, previously healthy with normal blood tests, has lost 30 lbs unintentionally over 3 months, has loose stools 5/times per day, and little appetite. Her blood test results (normal in parentheses):

aPTT	46	(25 – 36) sec
fibrinogen	210	(130 – 330) mg/dL
hemoglobin	13.4	(12 – 15) g/dL
platelets	184,000	(150 – 450,000) per μL
PT	18	(10 – 13) sec

    She is most likely suffering from
    a. aspirin overdose
    b. hemophilia
    c. sample contamination with tissue thromboplastin
    d. thrombocytopenia
    e. vitamin K deficiency

6. A 56-y/o man arrives in the emergency room with chest pain and shortness of breath. Studies find a sizable clot in a major coronary artery. He is first (perhaps inappropriately) given intravenously a drug that inactivates thrombin, leading to
    a. ↑ activated partial thromboplastin time
    b. ↓ existing clot mass
    c. ↓ platelet activation
    d. ↓ prothrombin time
    e. slowing of the extrinsic but acceleration of the intrinsic clotting pathway

7. Persons A and B have platelet deficiencies. Person A has platelets unable to release ADP, while person B has platelets deficient in platelet factor 3 (PF_3). What problems will they manifest?

	Person A	Person B
a.	inadequate clotting	no platelet aggregates
b.	no apparent problems	slow platelet aggregation
c.	no platelet aggregation	no apparent problems
d.	accelerated platelet activation	slightly slowed clotting
e.	slow platelet aggregation	inadequate clotting

8. An apparently healthy 2-y/o boy taking no prescription drugs bleeds for 13 hours from a minor cut on his arm. Tests show elevated prothrombin time and aPTT, decreased platelet adhesion capacity, and normal fibrinogen levels. Most likely, he is suffering from
    a. accidental ingestion of warfarin in rat poison
    b. aspirin excess
    c. hemophilia
    d. vitamin K excess
    e. von Willebrand disease

9. Detailed blood testing in a 56-y/o woman finds high levels of fibrin split products, indicating prior use of
    a. heparin
    b. Coumadin® (warfarin)
    c. aspirin
    d. tPA
    e. vitamin K supplements

10. An 8-y/o boy has the following results from routine blood testing:

Red cell count (per µl)	5.2		[4.7 – 6.1]
Platelet count (per µl)	205,000		[150,000 – 400,000]
Platelet adhesion test (s)	98		[75 – 122]
Prothrombin time (s)	12.2		[11 – 13.5]
aPTT (s)	47	**H**	[25 – 35]
Fibrinogen (mg/dl)	288		[200 – 400]

    He is suffering from
    a. Coumadin® (warfarin) overdose
    b. hemophilia A
    c. von Willebrand disease
    d. vitamin K deficiency
    e. systemic inflammatory illness

11. In a 67-y/o man, elevated LDL cholesterol (176 (**H**)) interacts with coronary artery vascular endothelium to initiate local coagulation. This interaction will
    a. ↑ prothrombin time
    b. ↓ antithrombin III activity
    c. ↓ aPTT
    d. ↓ platelet ADP release
    e. ↓ vitamin K activity

12. A 14-y/o boy developed a deep vein thrombosis followed by a massive pulmonary embolus. Emergency treatment with tPA was effective. He was asymptomatic during subsequent treatment with warfarin (Coumadin®), but twice developed venous thrombosis when failing to take his medicine. His condition was traced to
    a. antithrombin III deficiency
    b. atrial fibrillation
    c. tissue thromboplastin deficiency
    d. vitamin K deficiency
    e. von Willebrand's disease

13. A 19-y/o woman has repeated nosebleeds requiring cauterization, and her menstrual periods last 10 - 12 days. Laboratory testing finds

Prothrombin time	11 s	
aPTT	28 s	
Hemoglobin	9 g/dl	**L**
Hematocrit	27%	**L**
Platelet count	202,000/μl	
Platelet aggregation time	203 s	**H**

    She is suffering from
    a. hemophilia A
    b. platelet receptor defect
    c. thrombocytopenia
    d. vitamin K deficiency
    e. von Willebrand's disease

14. Two sisters take a 16 hour plane flight to Singapore. Andrea has taken oral medication to inhibit vitamin K; Brielle has not. Shortly after the flight, Brielle develops chest pain and shortness of breath from a pulmonary embolus and is effectively treated. The drugs used to treat Andrea and Brielle are, respectively,
    a. aspirin; heparin
    b. clopidogrel (Plavix®); warfarin
    c. heparin; warfarin
    d. tPA; heparin
    e. warfarin; tPA

15. After falling from a chair, a 2-year old boy develops swelling of his right shoulder and upper arm. Hospital examination finds a hematoma of the right shoulder. Following aspiration of the hematoma he has profuse bleeding. Lab tests find

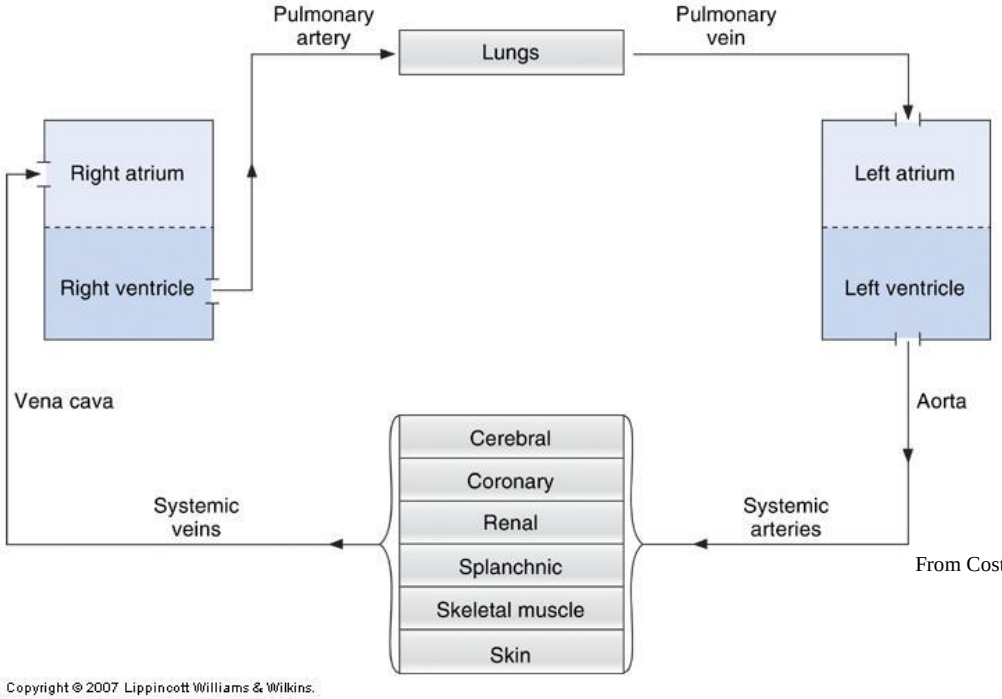
Hemoglobin	8 g/ml	**L**
Hematocrit	26%	**L**
Platelets	165,000/µl	
Platelet aggregation time	103 s	
Prothrombin time	12 s	
aPTT	60 s	**H**

His eventual diagnosis was
   a. fibrinogen deficiency
   b. hemophilia A
   c. thrombocytopenia
   d. von Willebrand's disease
   e. warfarin poisoning

I. Circuitry

- Need for cardiovascular system a consequence of increased size and complexity of organisms; system distributes energy substrates and oxygen to all body tissues
    - Insufficient nutrient delivery due to insufficient blood flow is called *ischemia*
- Removes waste products from tissues (e.g., CO_2); delivers hormones, other blood-borne mediators, moves white blood cells, platelets, antibodies to areas needing defense

Circuitry and directional flow through the cardiovascular system:



From Costanzo p. 69[31]

Questions:

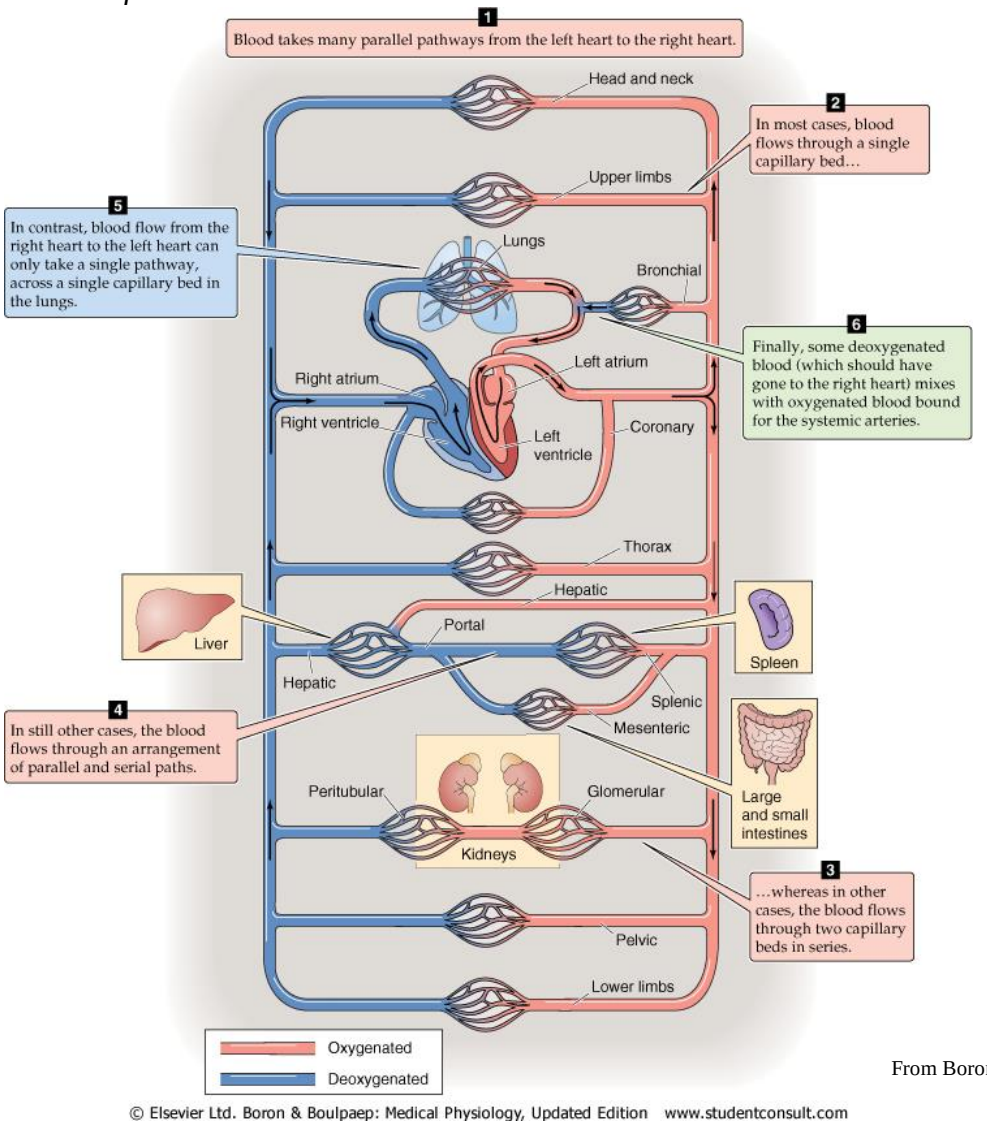
1. What organ—besides the heart—receives the entire cardiac output?

2. A rise in left atrial pressure will in turn raise pressure in what part(s) of the circulatory system?

3. A 20-y/o man exercises at a constant rate as the day grows warmer. Why does his cardiac output rise over time?

4. List at least five places in the circulatory system that have pressures higher than right atrial pressure.

Another view of the entire circuit:



From Boron p. 432[32]

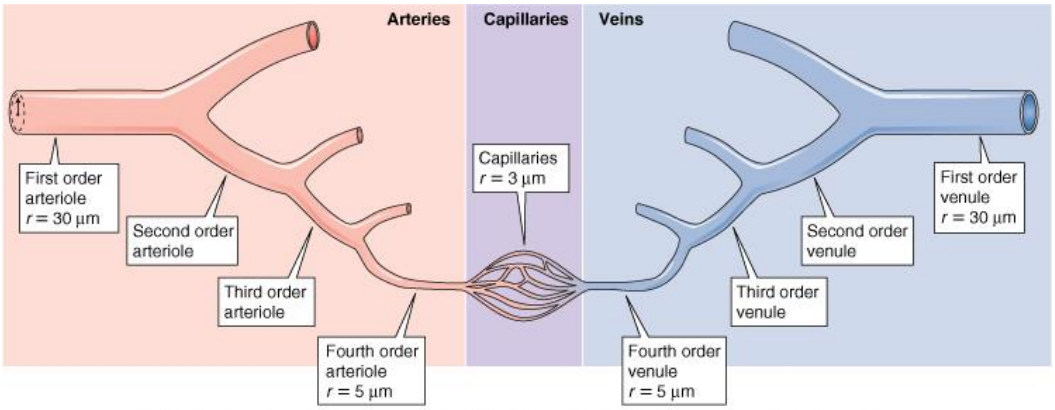
Question: Hepatic venous blood flow equals the sum of what other vessel blood flows?

Question: If the O_2 consumption by the bronchi increases, what effect does this have on the oxygenation of systemic arterial blood?

II. Hemodynamics

Text: Costanzo pp. 68 – 73

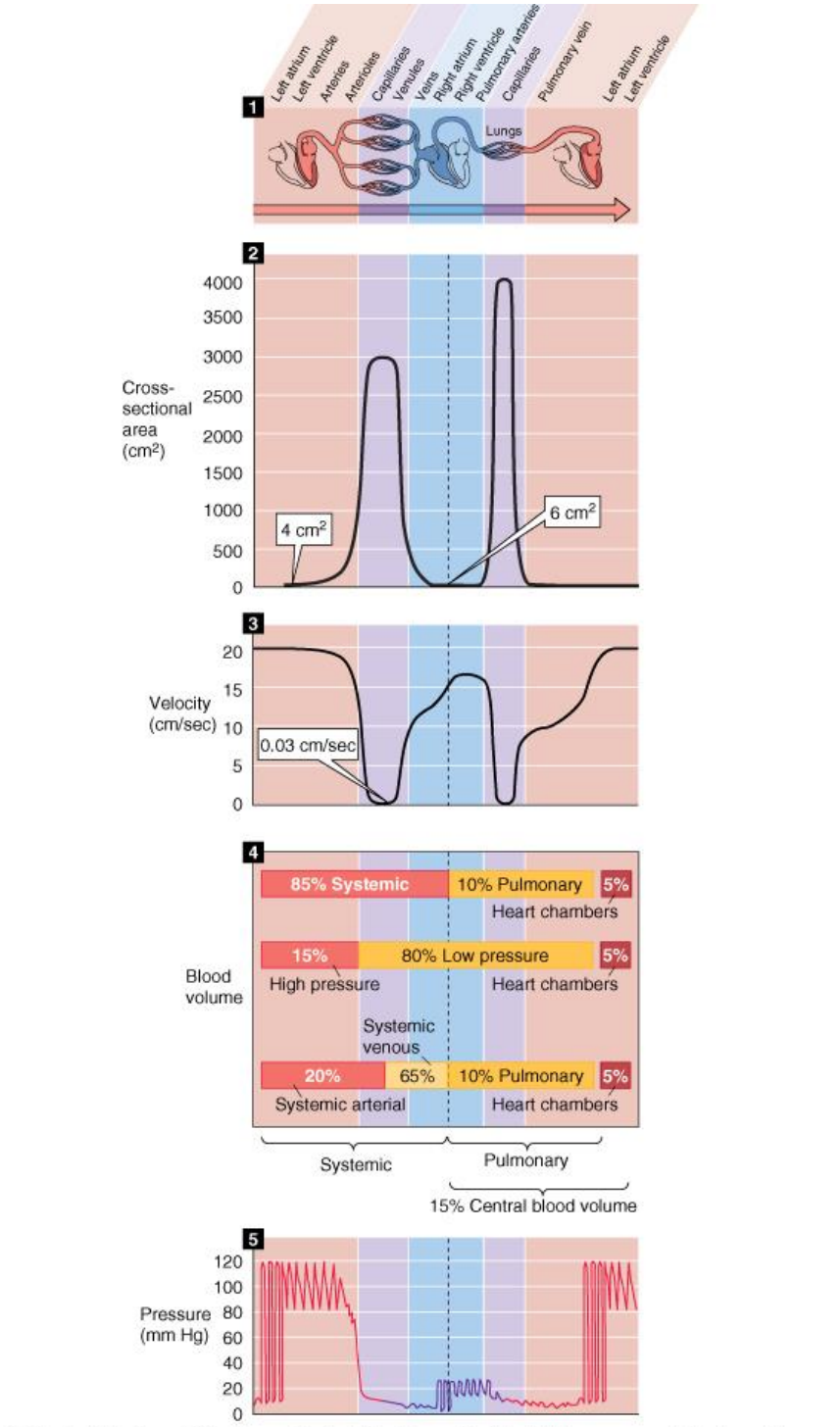
- Arteries: thick walled, high pressure
    - Site of formation of atherosclerotic plaques
- Arterioles: very much smaller, lower pressure, zone of highest resistance
    - Site of regulated resistance
        - Extensive autonomic (sympathetic) innervation
            - α_1 adrenergic receptors: splanchnic, skin, renal, skeletal muscle
            - β_2 adrenergic receptors: skeletal muscle
        - Site of action of nitric oxide (NO), other non-autonomic, locally active mediators



From Boron p. 469[33]

- Capillaries: thin wall, single cell layer; no innervation; no smooth muscle; small individually but largest total cross-sectional area
- Veins are thin-walled, low pressure, hold a very high proportion of the total blood volume, and are innervated by the sympathetics (α_1 adrenergic receptors)

- Velocity of blood flow is slowest in areas with largest cross-sectional area (capillary beds; Velocity = Total blood flow (Q) / Cross-sectional area)



Questions:

1. A congenital defect in the septum between the left and right ventricle causes a "left-to-right shunt"—blood flowing directly from the left ventricle to the right ventricle—in a newborn child. (A typical shunt fraction might be 15% of cardiac output (Q)). What problems will ensue?

2. How would the situation above differ if the shunt were right-to-left?

3. In diabetic retinopathy, damage to retinal capillary walls results in a) loss of capillaries, b) a decreased total capillary cross-sectional area, and c) increased total retinal blood flow. What problems will this cause?

Blood flow via Poiseuille's equation ($Q = \Delta P/R$)

- Equation can be used to understand how blood pressure is regulated, and affected by anti-hypertensive drugs, in the entire systemic (or pulmonary) circulation

---

$$Q = \Delta P / R$$

Where Q = flow or cardiac output (ml/min)
ΔP = pressure gradient (mm Hg)
R = resistance or total peripheral resistance (mm Hg/ml/min)

or

Cardiac output = (Mean arterial pressure – Right atrial pressure) / (Total peripheral resistance)

- Equation can also be used to understand how, in a single organ or tissue, blood flow to that organ or tissue varies with organ or tissue vascular resistance

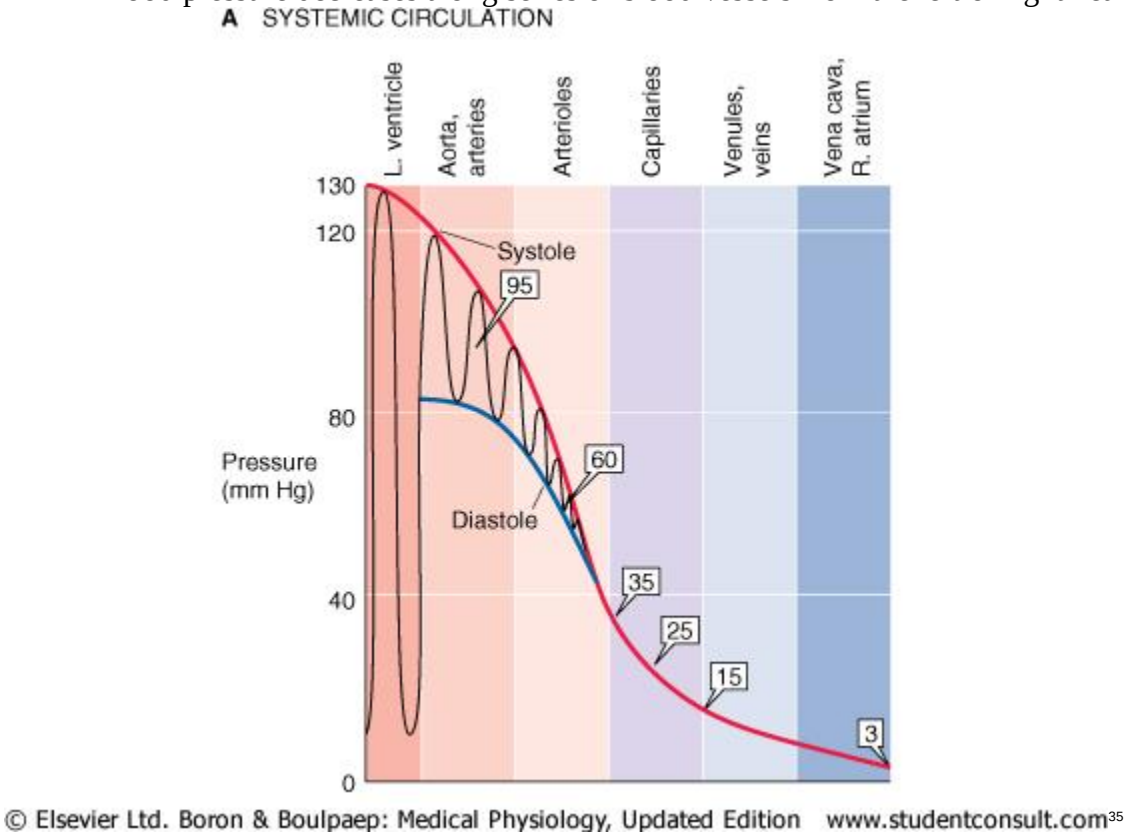
Blood flow to organ = ΔP across organ / Resistance within organ

Question: A teenager stung by a bee has substantial peripheral histamine release and widespread systemic arteriolar vasodilation. Total peripheral resistance falls by 50%, while cardiac output remains constant.

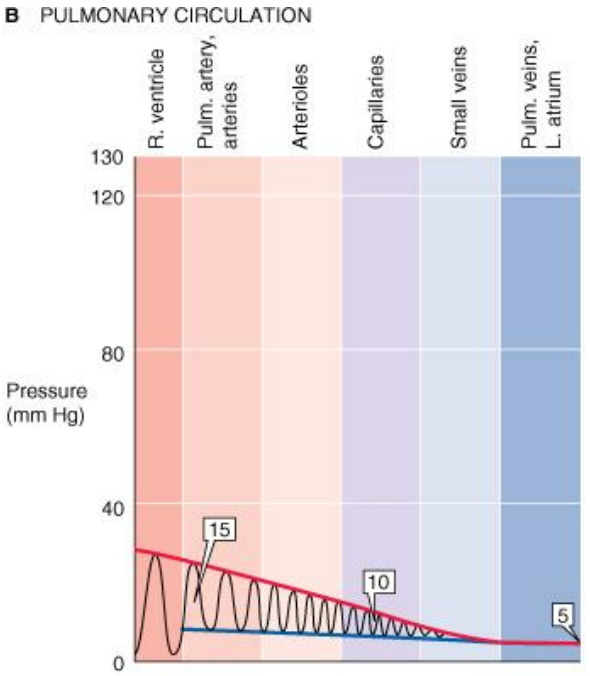
1. If the mean arterial blood pressure was 100 mmHg before the incident, what is it after the bee sting?

2. If vascular resistance within the brain remains constant, how has the bee sting altered brain blood flow? Will this person lose consciousness?

- Resistance in a blood vessel:
    - Is directly proportional to tube length
        - Tubes placed in series increase total resistance
    - Is directly proportional to blood viscosity
    - Is inversely proportional to tube radius—to the fourth power
        - Tubes placed in parallel decrease total resistance
- Total blood flow is the same at any level of the cardiovascular system (e.g., aorta vs. capillaries)
- Blood pressure decreases along series of blood vessels from the left or right heart:



[35]



Questions:

Anatomic Site	What is total blood flow (Q)?	What is the ΔP across this circuit?	What is a reasonable estimate for total vascular resistance (R) across this circuit?
Systemic Circulation			
Pulmonary Circulation			

Questions: The ΔP (pressure difference between one end and the other; "pressure drop")

- across the aorta is 1 mm Hg
- across all of the arteries is 10 mm Hg
- across all of the arterioles is 60 mm Hg
- across all of the capillaries is 15 mm Hg
- across all of the veins is 15 mm Hg

1) How does arteriolar resistance compare, quantitatively, with arterial resistance and venous resistance?

Questions (continued):

2) What is the ΔP across the entire systemic circulation?

3) Do atherosclerotic plaques significantly affect the total systemic resistance? Why or why not?

4) Blood pressure in a major artery leading into each of the limbs is as follows:

Left arm 124/82	Left leg 120/78
Right arm 122/80	Right leg 76/40

Is this patient healthy? Why or why not?

5) When cardiologists study how the coronary arteries are functioning during coronary angiography, they sometimes measure the "gradient" across a plaque detected in one of these vessels. The "gradient" refers simply to the ΔP—the change in pressure in this artery—from one side of the plaque to the other.

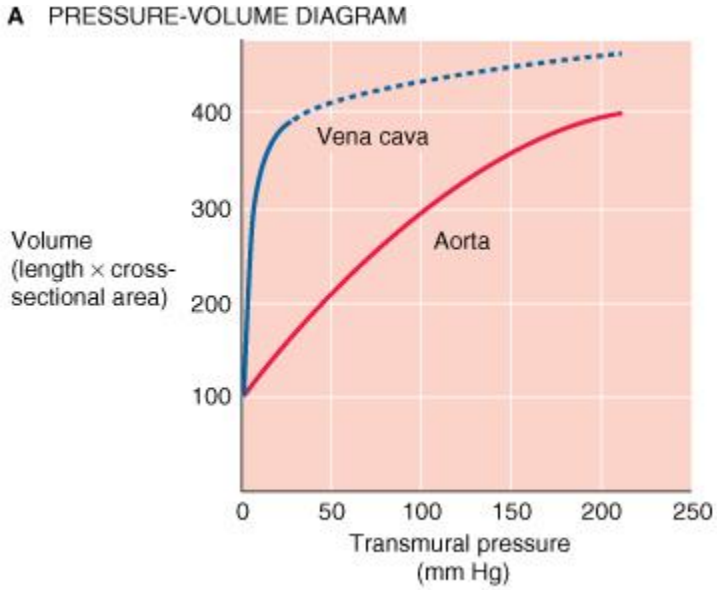
a) What is a normal ΔP across any small segment of a healthy coronary artery?

b) What can we infer from the magnitude of any measured gradient?

- Turbulent flow creates audible vibrations which can be heard with amplification (stethoscope)
    - In blood vessels: "bruits"
    - Turbulence increased by low blood viscosity (e.g., anemia) and high blood velocity (e.g., artery vs. vein, narrowed vessel)
- Blood vessels differ in compliance

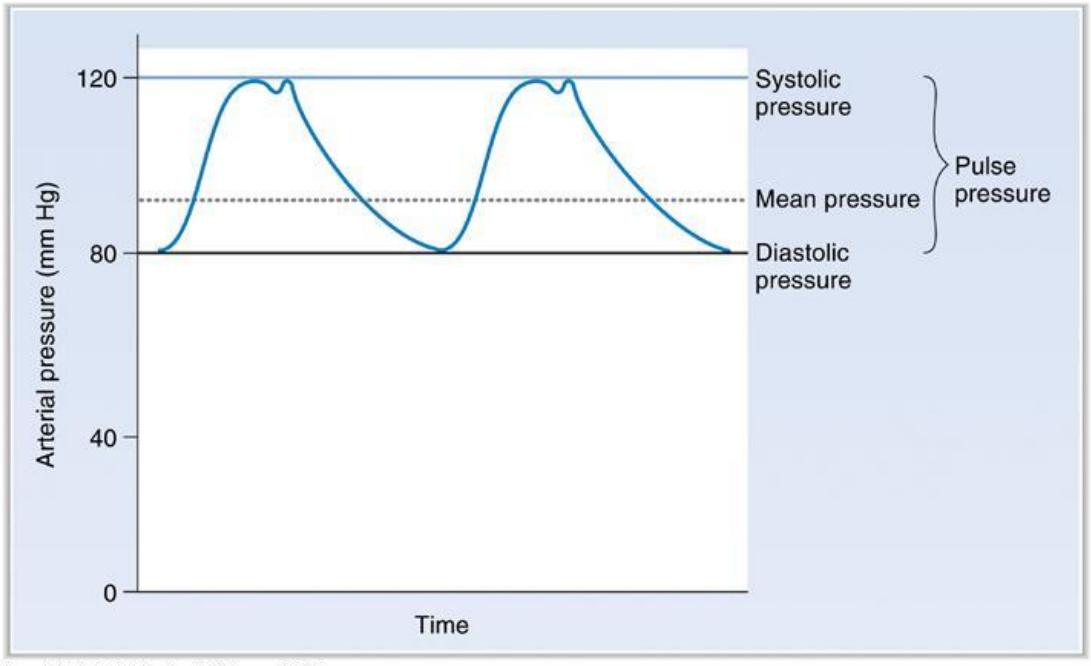
    Compliance (or capacitance) = Δ Volume / Δ Pressure

- Veins are more compliant than arteries, old arteries are less compliant than young arteries



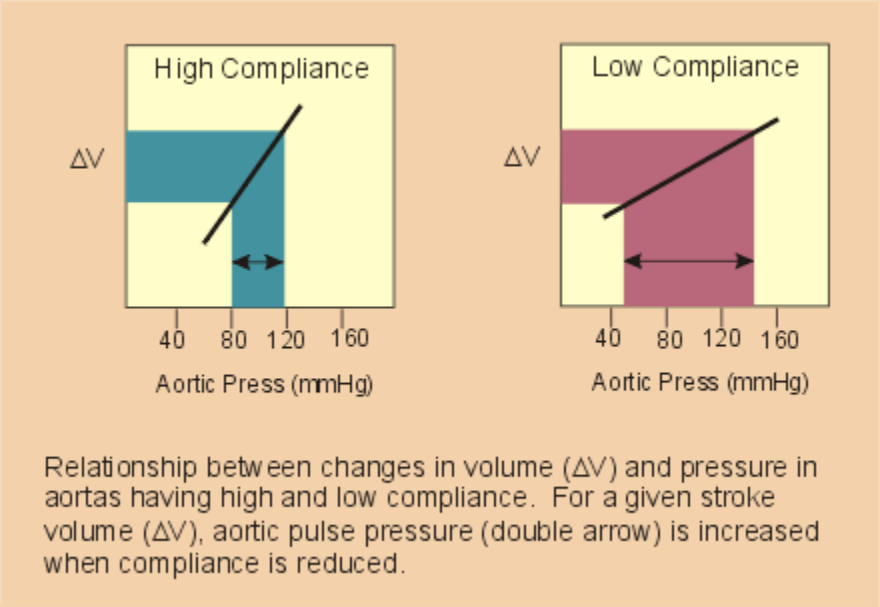
[37]

- Arterial pressure
    - As the heart pushes a single contraction's worth of blood into the aorta, pressure rises and then falls (this "pulsatile" pressure, the difference between the systolic and diastolic pressures, is the "pulse pressure")



From Costanzo p. 72[38]

- Stroke volume and aortic compliance (capacitance) are the two major determinants of pulse pressure



From http://www.cvphysiology.com/Blood%20Pressure/BP003_pulse_pressure.gif[39]

Questions:

1) How would you expect normal aging to affect aortic compliance and normal pulse pressure?

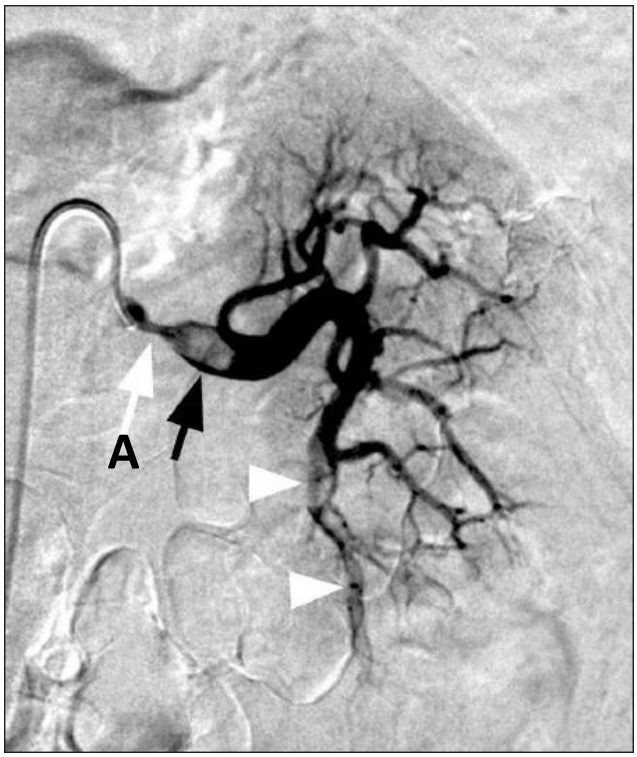
2) Does a change in aortic compliance alter mean aortic pressure? Why or why not?

3) A landmark 2001 study (Framingham) found a 2.5 × greater risk of heart attack, stroke, or heart failure in persons with "high normal" blood pressure (130-139 systolic, 85-89 diastolic) compared with blood pressure ≤ 120/80. What are some reasons why?

4) What are the risks of pathologically high venous pressure?

Practice Questions:

1. The figure below shows a blockage in the renal artery at the white arrow, A):



From http://www.clinicalimagingscience.org/articles/2011/1/1/images/JClinImagingSci_2011_1_1_11_76689_f2.jpg[16]

Such a lesion would typically give rise to

   a. a reduction in renal blood flow (l/min) before any reduction in pressure distal to the site
   b. a blood pressure gradient across the site
   c. vasoconstriction distal to the site
   d. decreased turbulence at the site
   e. reduced blood velocity (cm/s) at the site

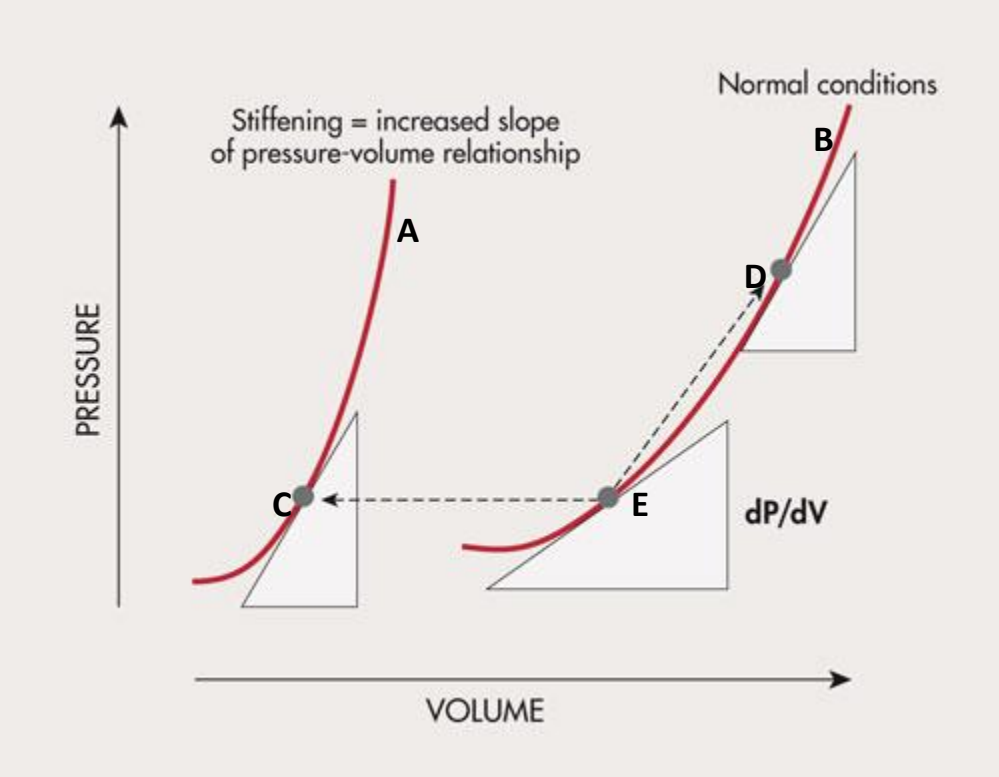
2. (Case from JAMA, 1922 (jama.ama-assn.org/cgi/reprint/78/20/1529[17])) "A 45-y/o man, on a day when he had been walking more than his custom, noticed that his left leg "began to play out on him." It felt "draggy," numb and painful. He quickly discovered that if he rested for a minute or two, the tired feeling and discomfort would disappear and he could resume comfortable walking. He learned, however, that precisely the same lameness reappeared on covering so much as a distance of two city blocks."

   In this person, it would be most probable to find

   a. ↑ total systemic resistance
   b. ↑ turbulent flow in the aorta
   c. ↓ cardiac output
   d. ↓ arterial pressure in the left leg
   e. systemic O_2 deficiency

3. A 59-year old woman with type 1 diabetes has lost 40% of the arterioles in her cerebral vasculature. If her systemic arterial pressure and brain blood flow are normal, which of the following must be true (as compared to normal)?
    a. ↑ ΔP across her brain
    b. ↑ resistance in her cerebral vasculature
    c. ↓ flow velocity in her cerebral capillaries
    d. ↓ vasoconstriction in her remaining arterioles
    e. ↑ cerebral capillary inlet pressure

4. The figure below shows the compliance curves of two different arteries. At which point is compliance greatest?



From http://www.nature.com/ajh/journal/v18/n1s/images/ajh2005287f2.jpg[18]

    a. A
    b. B
    c. C
    d. D
    e. E

5. The blood with the lowest oxygen content would be found in the
    a. glomerular capillaries
    b. left atrium
    c. portal vein
    d. pulmonary artery
    e. pulmonary vein

6. A 70-y/o woman has pulmonary artery pressure 76/48 (**H**) and a 20% loss of pulmonary blood flow. There is a rise in bronchial blood flow from 1% to 20% of cardiac output, and a 3-fold increase in bronchial metabolic rate. There is also
    a. ↑ systemic arterial pressure
    b. ↓ left atrial pressure
    c. decreased systemic arterial oxygen content
    d. decreased systemic venous pressure
    e. increased LV output

7. A 38-y/o woman with weight loss, bloody sputum, and fever is diagnosed with granulomatous vasculitis. There is a 30% loss of pulmonary capillaries; pulmonary arterial pressure is 21/8 and cardiac output remains stable at 5.3 l/min. She also has
    a. decreased systemic blood volume
    b. increased right atrial pressure
    c. LV hypertrophy
    d. rapid pulmonary capillary velocity
    e. systemic hypotension

8. A healthy 90-y/o man compares his lab results with those from age 20:

	Age 20	Age 90
Cardiac output (l/m)	5.8	5.4
Heart rate (b/m)	66	64
Systemic arterial pressure (mmHg)	118/70	130/64
Mean arterial pressure (mmHg)	86	86

    Aging has
    a. decreased aortic compliance
    b. decreased ejection fraction
    c. increased cardiac work
    d. increased total peripheral resistance
    e. increased stroke volume

9. In a diagnostic test of a patient with stress-induced chest pain, a catheter probe is advanced down the left anterior descending coronary artery. A blockage is detected when there is a sudden decrease in the coronary arterial
    a. flow
    b. flow velocity
    c. mean pressure
    d. pulse pressure
    e. turbulence

10. A 73 y/o woman presented to her family doctor with intermittent right calf pain for one month of duration, which she described as "aching sensation". Her pain was brought on by walking and was relieved by rest. She also had numbness in her right big toe. Resting arterial pressures were as follows:

Left arm	118/70
Right arm	116/68
Right ankle	84/50 **L**
Left ankle	120/72

Exercise exacerbated her symptoms because
    a. arterioles in the affected leg remain constricted
    b. increases in right ankle arterial pressure reduced flow
    c. more blood had to be diverted to other tissues, causing leg ischemia
    d. tissue flow demands exceeded vasodilatory capacity
    e. total leg blood flow is inadequate at rest and in exercise

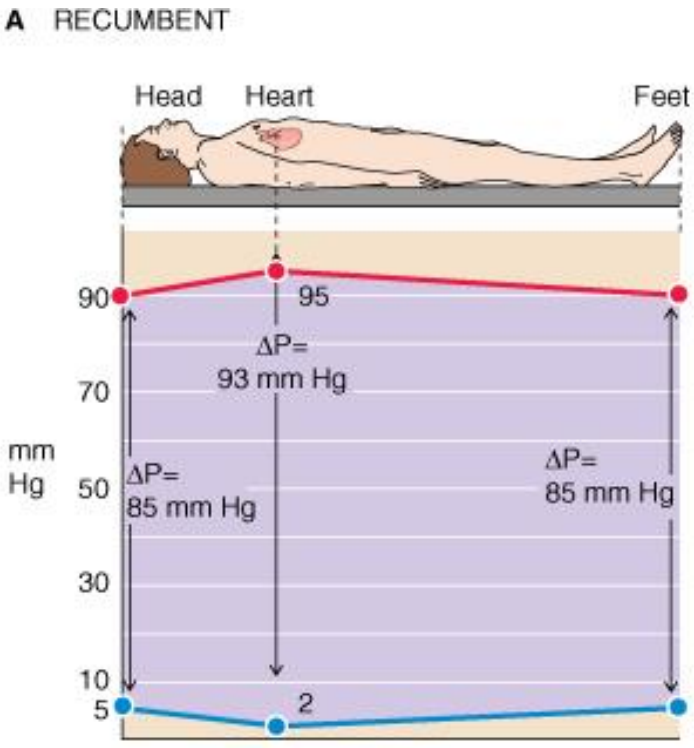
11. A deep vein thrombosis forms in a leg vein in a 36-y/o pregnant woman sitting for 19 hours on an airliner. When the clot breaks loose, the embolus eventually lodges in a
    a. cardiac chamber
    b. systemic vein
    c. vessel with lower mean flow velocity
    d. vessel with lower pressure
    e. vessel with smaller cross-sectional area

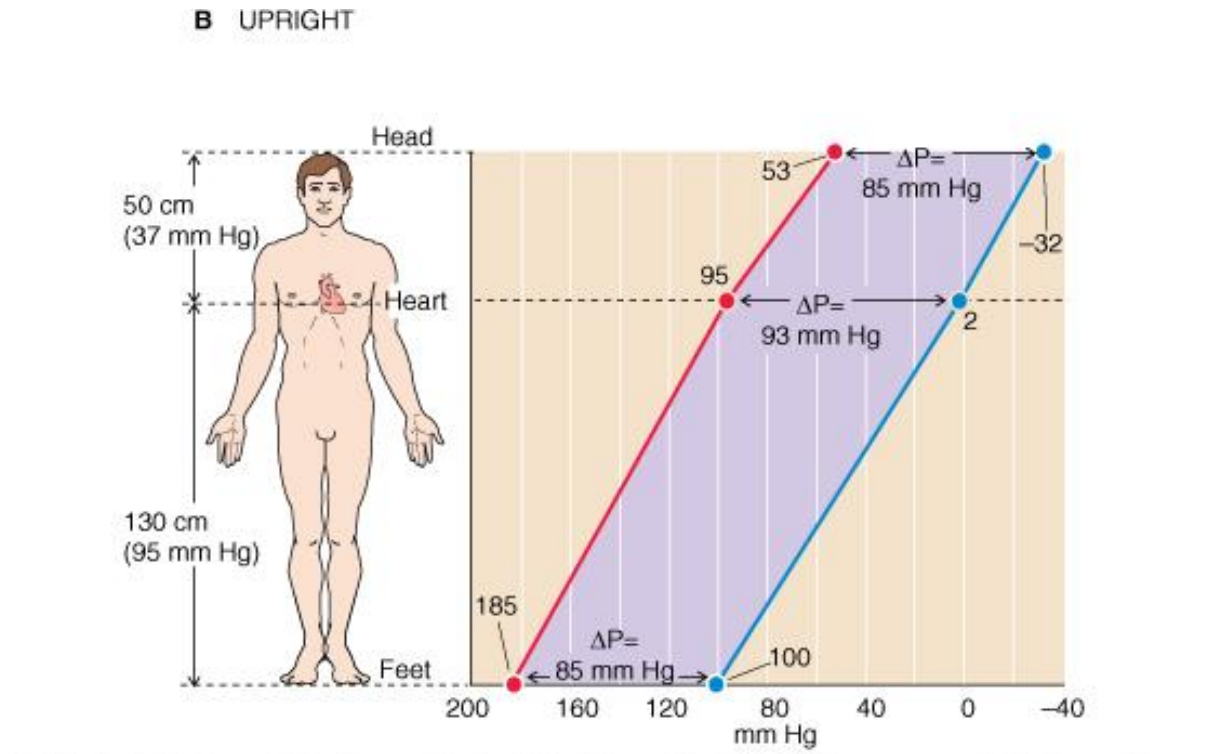
12. (Case from pathhsw5m54.ucsf.edu[175]) A term male infant had an echocardiogram showing right-to-left atrial shunting. He had increased pulmonary arterial pressure, right atrial pressure, and decreased right heart cardiac output. He also must have had abnormally high
    a. arterial blood oxygen content
    b. left ventricular systolic pressure
    c. pulmonary capillary pressure
    d. pulmonary vascular resistance
    e. pulmonary wedge pressure

13. Which of the following is equal in the systemic and pulmonary circulations?
    a. ΔP across the circuit
    b. arteriolar resistance
    c. blood volume
    d. mean arteriolar pressure
    e. total blood flow

Gravity creates a hydrostatic pressure difference when there is a difference in height

- Fluid (e.g., blood) always flows between two areas of different pressure
- Because all columns of blood in the body begin at the heart, blood pressures elsewhere in the body (e.g., in arteries in the feet or neck during standing) will have additional gravitational effects added or subtracted
    - The contraction of the heart generates pressure
    - The total intravascular pressure = BP from heart ± gravitational force
    - ΔP down the tube ("driving" pressure; "axial pressure gradient") determines flow down the tube
    - Transmural pressure = Total intravascular pressure – Extravascular (tissue) pressure
- Gravitational effects in the "tissue" compartment are not additive because cell membranes break up the column of fluid
- Venous valves similarly break up columns of fluid in veins and reduce cumulative gravitational effects





From Boron, p. 438[41]

Questions:

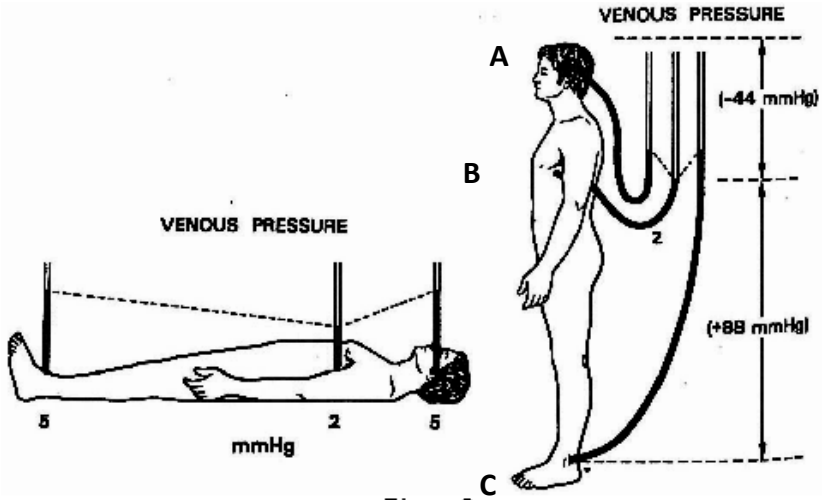
1. A person has external bleeding from a superficial leg vein. Why elevate the leg? Why apply pressure to the site?

2. During needle puncture of an arm vein, a deep arm artery is accidentally nicked. There is no external bleeding. What are the signs and symptoms—if any—of this wound? Why are elevation, cold, and pressure appropriate treatments?

3. Why do superficial leg veins expand in patients with failed venous valves? Why are support hose an effective treatment?

Practice questions

1. In the figure at right, below, it is apparent that

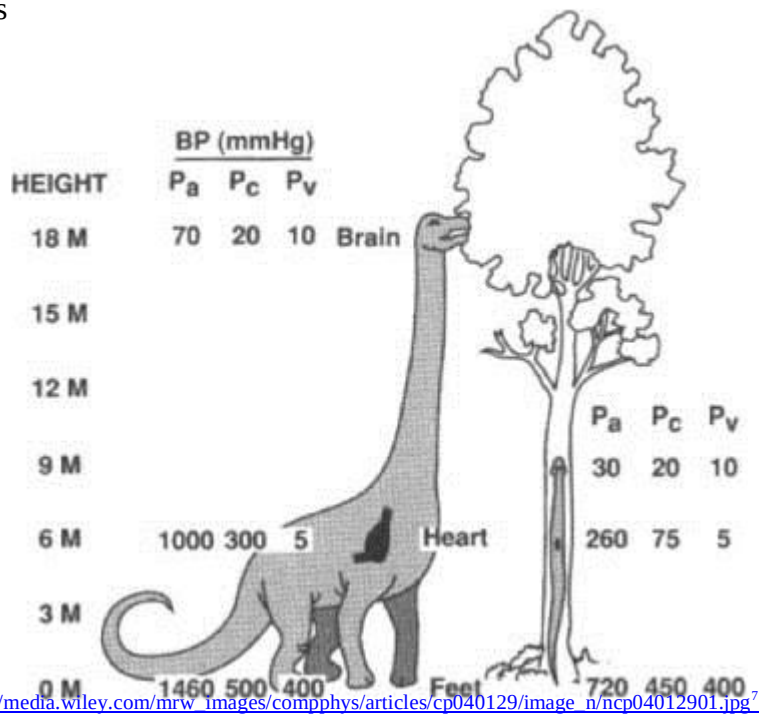


From http://rfumsphysiology.pbworks.com/f/ar8.bmp[6]

   a. atmospheric pressure is higher than total venous pressure at point A
   b. the difference between total arterial pressure and total venous pressure at point C is much larger than this same difference at points A or B
   c. tissue pressure will exceed total venous pressure at point C
   d. venous blood will flow from point A (-44 mmHg) to point B (0 mmHg) only due to venous valves
   e. venous valves are irrelevant to the difference in total venous pressure between points B and C

2. A 48-year old man has a chain-saw accident that causes an arterial injury in his lower leg that breaks the vessel wall and skin surface. While standing, the bleeding will continue until, at that site,
   a. axial arterial pressure equals axial venous pressure
   b. externally applied pressure matches total arterial pressure
   c. pressure applied to the site equals the axial arterial pressure
   d. that portion of the arterial pressure due to gravity equals lateral pressure placed on the artery
   e. total arterial pressure equals total venous pressure

3. The diagram of hypothetical pressure gradients for the terrestrial dinosaur, below, assumes



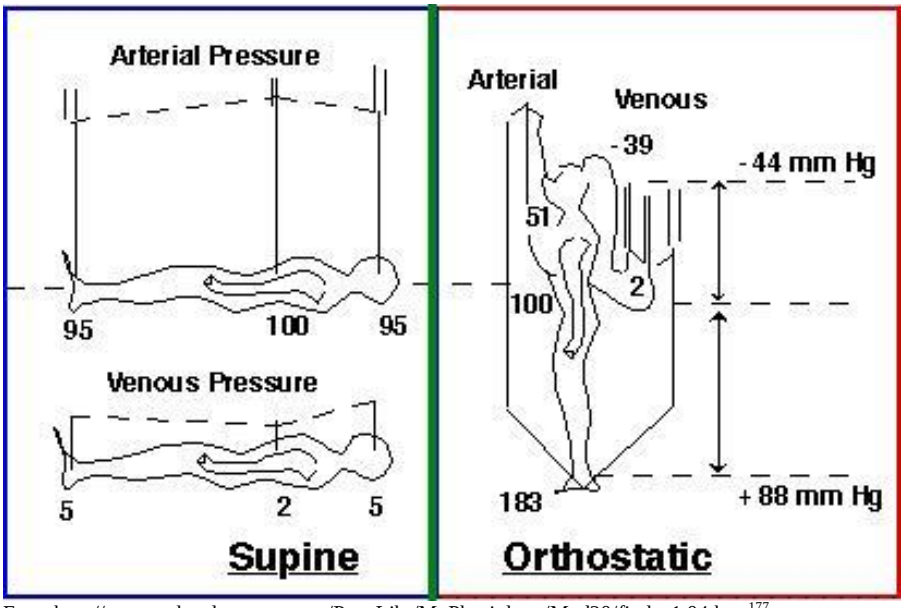
From http://media.wiley.com/mrw_images/compphys/articles/cp040129/image_n/ncp04012901.jpg[7]

   a. brain perfusion will decrease as the head is elevated
   b. gravity enhances axial pressure gradients
   c. tissue pressure will exceed venous pressure in the feet
   d. total arterial pressure in the brain is similar to that of humans
   e. varicose veins cannot occur in dinosaurs

4. In a 7-foot man, the distance from heart to foot is 143 cm (143 cm of H_2O = 105 mm Hg). If his blood pressure at heart level is 140/100 mm Hg, the total blood pressure (in mm Hg) in an artery in his foot while he is standing will be
   a. 140/100
   b. 223/183
   c. 245/205
   d. 283/243
   e. 35/(-5)

5. In a 25-y/o woman standing quietly, mean total aortic pressure is 95 mm Hg, while mean total systemic arterial pressure in the foot is 185 mm Hg. Why, then, does blood flow from the heart to the foot?
   a. gravitational effects on blood pressure are greater in arteries than in veins since venous valves break up columns of blood
   b. the arterial axial pressure gradient is +10 mm Hg between aorta and foot
   c. the transmural pressure in an artery in the foot is lower than the transmural pressure in the aorta
   d. total arterial pressure at heart level is higher than total venous pressure in the feet
   e. total arterial pressure in the heart is by definition unaffected by gravity

6. In a supine person shown in the left portion of the Figure,



From http://www.coheadquarters.com/PennLibr/MyPhysiology/Mod20/figdev1.04.htm[177]

   a. axial pressure gradients across the head and feet are equal
   b. axial pressure is equal at all sites
   c. perfusion of the head equals perfusion of the feet
   d. vascular resistances across the head and feet are equal
   e. venous pressure in the head is 95 mmHg

7. A 3-y/o girl has a surgical procedure to separate fused bones in the skull. During surgery she is seated upright. Special precautions are taken to avoid air embolism arising from
   a. decreased in right atrial pressure during upright posture
   b. low systemic arterial pressure that is characteristic in young children
   c. reduced arterial to venous delta P in the head
   d. subatmospheric cranial venous pressure
   e. venous pressure > arterial pressure in the head

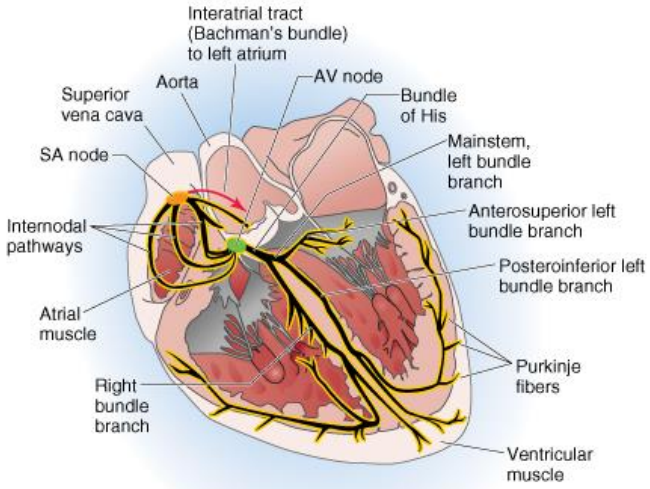
8. A 30-y/o man holds a chain saw overhead to cut a high tree branch. He then slips and cuts the radial artery in his wrist, exposing the cut artery to the atmosphere. The pressure gradient for blood loss from the cut artery--if his arm continues to be held overhead--equals the
   a. mean arterial pressure measured at heart level
   b. total arterial pressure at the wrist
   c. wrist tissue pressure
   d. ΔP between axial arterial pressure and axial venous pressure at the wrist
   e. ΔP between total arterial pressure and total venous pressure at the wrist

III. Cardiac Electrophysiology

Text: Costanzo pp. 73 – 78

Cardiac Action Potentials

Normal route of conduction in the heart



From Boron p. 505[42]

Conduction velocity in different cardiac tissues:

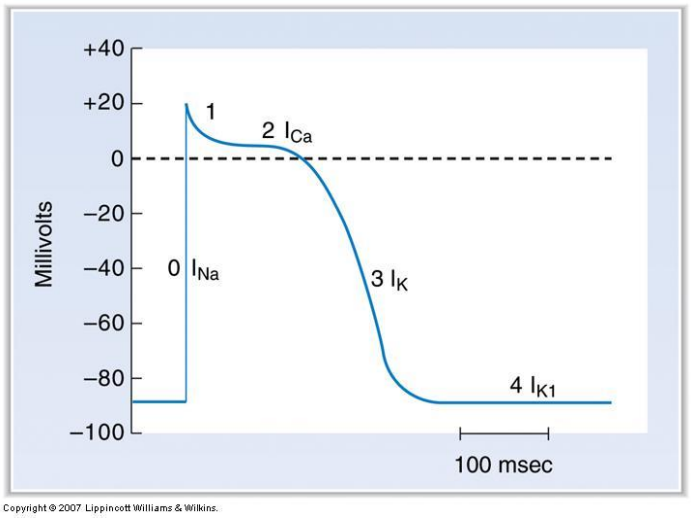
Tissue	Conduction Velocity (m/s)
SA node	0.05
Atrial pathways	1
AV node	0.05
Bundle of His	1
Purkinje system	4
Ventricular muscle	1

[SA = sinoatrial; AV = atrioventricular]

"Fast" cells: atria, ventricles, and Purkinje system

- Analogous to nerve and skeletal muscle, resting membrane potential is determined primarily by relatively high K^+ permeability. So resting membrane potential is stable at ~ -90 mV

- Abrupt depolarization (phase 0) is due to a transient, sudden, large increase in Na^+ permeability that creates an inward Na^+ current (I_{Na}) that depolarizes the membrane; brief peak in membrane potential is referred to as phase 1



From Costanzo p. 75[43]

- Long plateau phase (phase 2) in fast cells is due to a slow Ca^{2+} current (I_{Ca}; Na^+ permeability is back to normal)

- This slow Ca^{2+} is through L-type Ca^{2+} channels (dihydropyridine-type) and is linked to contractile force

- Return of potential to negative (phase 3) is due to closure of Ca^{2+} channels, opening of K^+ channels and a return to dominance of the K^+ permeability in the membrane potential; I_K dominates here

- Phase 4 is return to baseline, with K^+ permeability again predominant (I_{K1})

- All channels in ventricular muscle—Na^+, K^+, and Ca^{2+}—are voltage and time dependent:

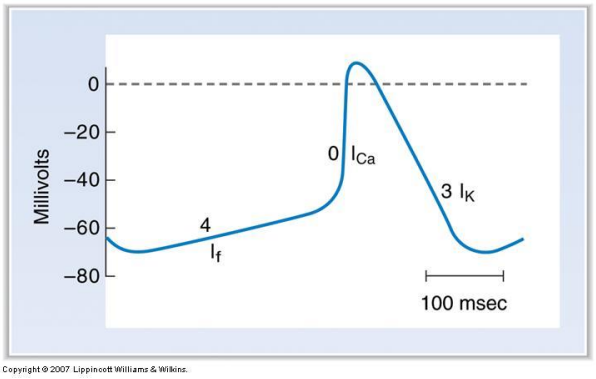
	Activation	Inactivation
Na^+	rapid	rapid
Ca^{2+}	rapid	slow
K^+	very slow	very slow and incomplete

"Slow" cells (SA and AV node)

- Slow cells show spontaneous but slow depolarization: a slow Na^+/K^+ "leak" termed I_f moves membrane potential toward new equilibrium potential of -15 mV

- Before this equilibrium potential is reached, an inward Ca^{2+} current is triggered

- The upstroke (phase "0" in this diagram) is due to this inward Ca^{2+} current (I_{Ca})



From Costanzo p. 76[44]

- Repolarization (phase 3) is due to decreased Ca^{2+} permeability and increased K^+ permeability (I_K)
- Leakiness of the Na^+/K^+ channel then returns as a voltage-gated phenomenon
- Automaticity is good for the pacemaker of the heart (sinoatrial (SA) node)
- Slow cells in the AV node, or even some slightly leaky cells in the His-Purkinje system, can serve as pacemakers if the SA node is damaged

Questions: Complete the following table:

Effect	Autonomic Division	What is the neuro-transmitter?	What receptor type is involved?	What is the cardiac cell target?	What membrane channel is targeted?	Which membrane current is affected
↑ Heart Rate	Sympathetic					
↓ Heart Rate	Parasympathetic					

Cardiac cell-to-cell conduction velocity

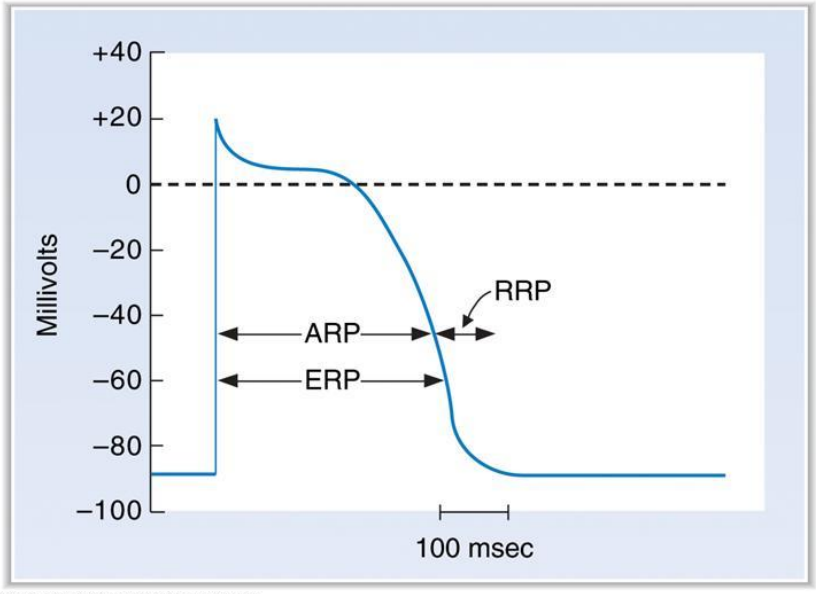
- Depends upon the size and rate of change of the inward current during the upstroke of the cardiac action potential (which is reflected by the slope of the initial depolarization voltage change, phase 0)
    - Spread is fastest in fast cells, slower in slow cells

- Conduction velocity is also faster in larger cells
- Purkinje system conducts the cardiac action potential around the ventricle using very large, fast cardiac cells

Question: Some congenital cardiac arrhythmias are caused by a loss-in-function mutation in the membrane K^+ channels that mediate phase 3 of the fast cell action potential. What change in fast cell action potential would be expected?

Excitability: the duration of cardiac cell refractory periods

- Absolute: no stimulus—no matter how great—can elicit an action potential, because I_{Na} and I_{Ca} are inactivated at positive voltage and must remain in an inactive/deactivated state for a fixed duration.
- Effective: slightly longer than absolute; no propagated action potential can be elicited (neighboring cells are refractory)
- Relative: supranormal inward current can elicit an action potential



From Costanzo p. 77[45]

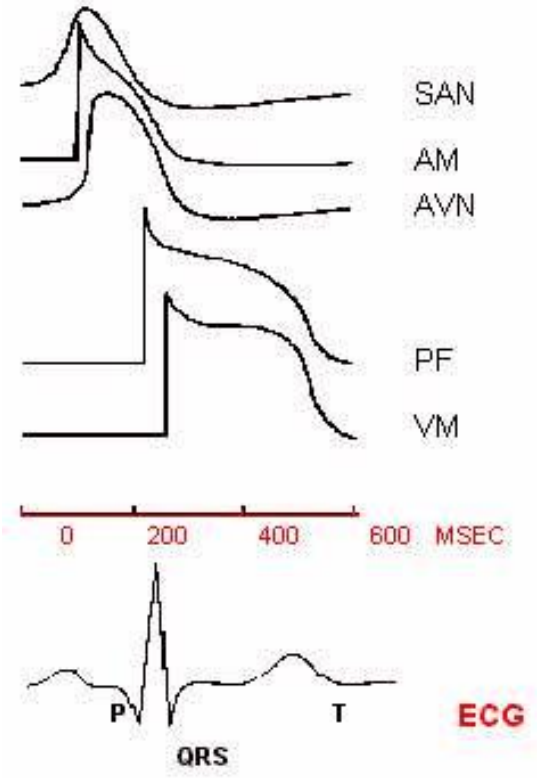
Questions: Some drugs used to treat cardiac arrythmias specifically block the fast Na^+ channels of fast cardiac cells. What effects would these drugs have on

1. Heart rate?

2. Conduction velocity in the atrioventricular node?

3. Conduction velocity in the ventricular muscle?

A view linking the ECG to individual slow and fast cell action potentials



From http://www.dchaos.com/portfolio/dchaos1/yse_fig11.jpg[46]

Practice Questions

1. A 67-y/o man is diagnosed with sinus bradycardia and episodic sinus pauses ("sick sinus syndrome"). His condition is due to
    a. "leaky" AV nodal [Na^+/K^+] channels
    b. early activation of atrial potassium channels
    c. gain-in-function mutation of atrial calcium channels
    d. inactivation of I_f at negative voltage
    e. SA nodal cells that lack sodium channels

2. A 71-y/o woman has a reentrant circuit in the ventricle, giving rise to episodes of ventricular tachycardia. Drug treatment decreases conduction velocity of ventricular cells by
    a. blocking fast Na^+ channels
    b. decreasing I_f
    c. reducing duration of K^+ currents
    d. increasing duration of Ca^{2+} currents
    e. using ventricular α_1-adrenergic receptor inhibitors

3. A 3 month old baby is resuscitated after cardiac arrest occurs while she is asleep. She is diagnosed with "Short QT syndrome", resulting from
    a. absence of ventricular fast Na^+ channels
    b. absence of a $[Na^+/K^+]$ channel in AV nodal cells
    c. early activating high-flux ventricular K^+ channels
    d. gain-in-function ventricular Na^+ and Ca^{2+} channels
    e. delayed and prolonged ventricular Ca^{2+} channel activation

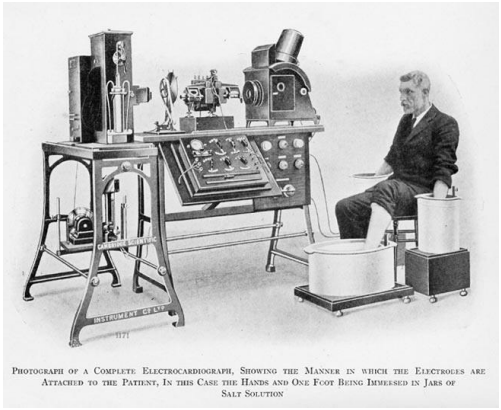
4. The cardiac cell membrane current activated at negative membrane voltage and inactivated at positive membrane voltage involves a
    a. Ca^{2+}/Na^+ channel
    b. Ca^{2+}/K^+ channel
    c. fast Na^+ channel
    d. Na^+/K^+ channel
    e. slow Na^+ channel

5. A 75-y/o man with Parkinson's disease is given atropine (a parasympathetic blocker) to reduce rigidity and tremor. A cardiac side effect of the drug will be
    a. ↑ AV nodal Ca^{2+} current
    b. ↑ heart rate and ↑ PR interval
    c. ↑ heart rate and ↑ ventricular contractility
    d. ↓ atrial contractility
    e. ↓ heart rate and AV nodal delay

6. Class IV antiarrythmic drugs are Ca^{2+} channel blockers. In Purkinje fibers, these drugs
    a. create "undershoot" during repolarization
    b. decrease action potential duration
    c. increase conduction velocity
    d. increase peak positive membrane voltage
    e. increase resting membrane potential

Electrocardiogram

- As in skeletal muscle, electrical events precede contractile events
- Unlike in skeletal muscle, cardiac cells transmit the action potential from one to another in a predictable, coherent pattern (measured as electrocardiogram [ECG or EKG])
- If skeletal muscle is relaxed, ECG is strongest electrical signal that can be recorded from the body surface
- Technique first developed by Willem Einthoven in 1903:

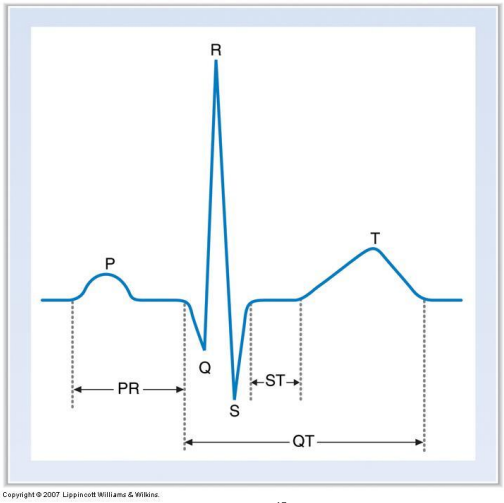


PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

From http://upload.wikimedia.org/wikipedia/commons/1/1c/Willem_Einthoven_ECG.jpg[47]

- Pattern of movement—from fast to slow cells and vice versa—creates the predictable pattern of electrical activity of the ECG
- A normal ECG does not ensure that cardiac pumping is adequate: only a measure of electrical, not contractile performance

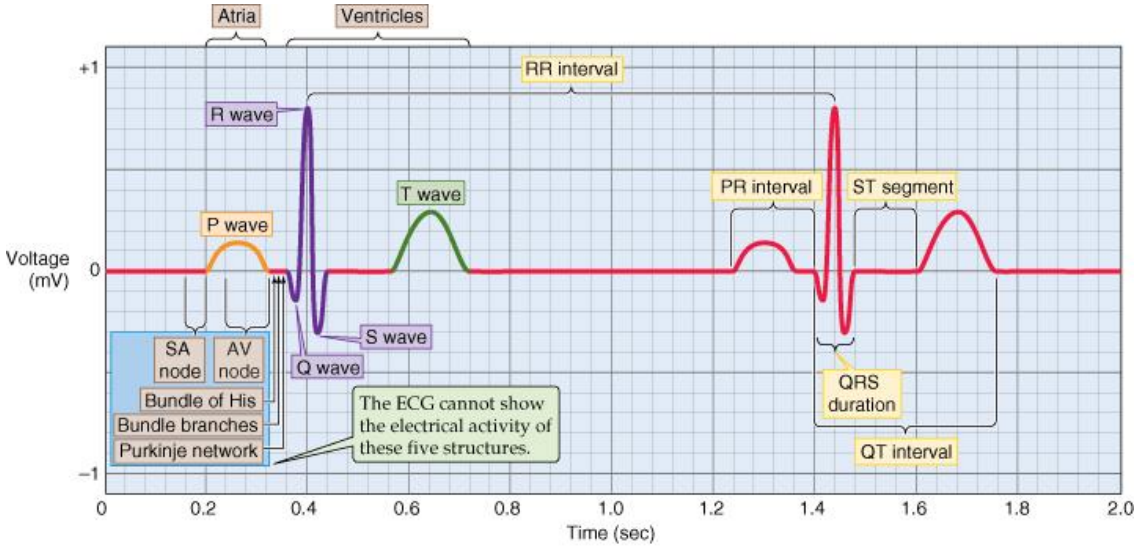
The normal ECG



From Costanzo p. 74[48]

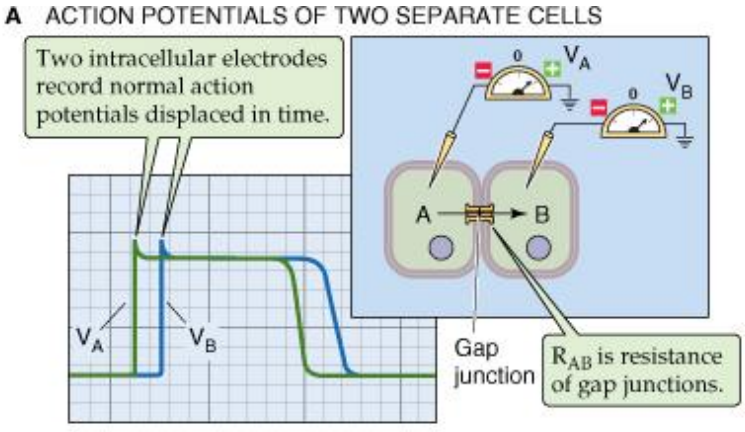
- P wave: atrial depolarization
- PR interval: AV nodal delay
- QRS complex: depolarization of the ventricles
- QT interval: entire period of ventricular depolarization and repolarization
- ST segment: period in which ventricles are depolarized
- T wave: ventricular repolarization

Another view of the ECG:



From Boron p. 515[49]

- Genesis of the T wave:



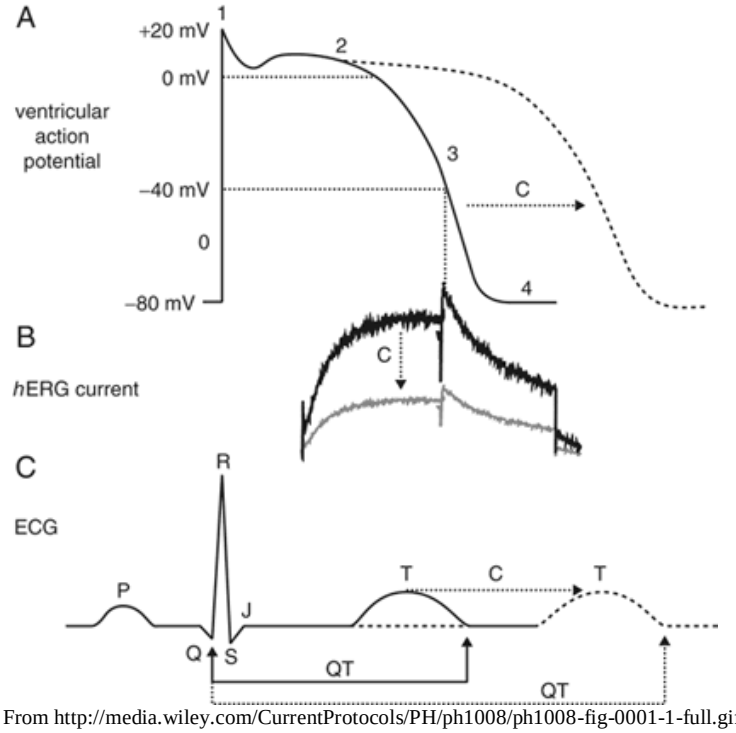
From Boron p. 518[50]

- T wave is positive (in most leads) because the last ventricular muscle cells to depolarize are the first to repolarize

- Anything (e.g., drugs, congenital defects in ion channels) that changes the duration of the ventricular fast cell action potential can affect the QT interval

- Alterations in the QT interval—for complex reasons—can lead to serious, even fatal, cardiac arrythmias

- Various drugs or congenital defects can delay the opening of K^+ channels that terminate the ventricular myocyte action potential:



From http://media.wiley.com/CurrentProtocols/PH/ph1008/ph1008-fig-0001-1-full.gif[51]

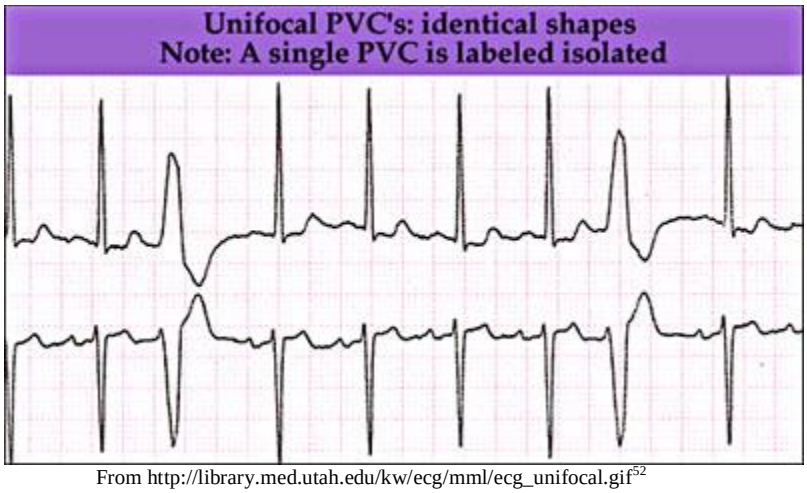
Questions: Draw abnormal ECG's to match their names and descriptions

Name of arrythmia	Description	How it looks
Ventricular fibrillation	Uncoordinated ventricular electrical activity	
First-degree AV block	Slowed AV nodal conduction	

Name of arrythmia	Description	How it looks
Atrial fibrillation	Uncoordinated atrial electrical activity	
Second-degree AV block	Some—but not all—P waves fail to be conducted to the ventricles	
Bundle-branch block	Ventricular depolarization wave is slowed	
Ventricular tachycardia	An organized loop passes rapidly around the ventricles; normal ventricular conduction system is not utilized	

Question: Define sinus tachycardia

Question: A premature ventricular contraction (PVC) occurs when the ventricles depolarize and then contract on their own, without receiving a stimulus from the atria via the AV node. An example is shown below:



From http://library.med.utah.edu/kw/ecg/mml/ecg_unifocal.gif[52]

1. Why is the PVC electrical signal different from the normal QRS?

2. Why does the next QRS after the PVC occur on the normal R-R interval?

3. Why are frequent, "multifocal" PVC's (arising from different foci in the ventricles) considered more ominous than occasional unifocal PVCs?

Question: Untreated atrial fibrillation is often associated with the formation of blood clots (thrombi) within the atrium. These clots can break loose and travel in the blood stream (emboli) until they lodge in a vessel

1. Why would such thrombi tend to form in a fibrillating—as opposed to a normally coordinated—atrium?

2. Where would an embolus originating in the right atrium tend to lodge, and what symptoms (if any) would result?

3. Where would an embolus originating in the left atrium tend to lodge, and what symptoms (if any) would result?

Autonomic Effects on the Heart and Blood Vessels

Three aspects of autonomic control of the heart:

1) Heart rate (= rate of SA nodal spontaneous depolarization; chronotropic effect)

2) Conduction velocity (mostly: at AV node; dromotropic effect)

    i. Sympathetically-induced ↑ Ca^{2+} inward current increases conduction velocity

    ii. Parasympathetically-induced ↓ Ca^{2+} inward current decreases conduction velocity

3) Strength or force of contraction (contractility)

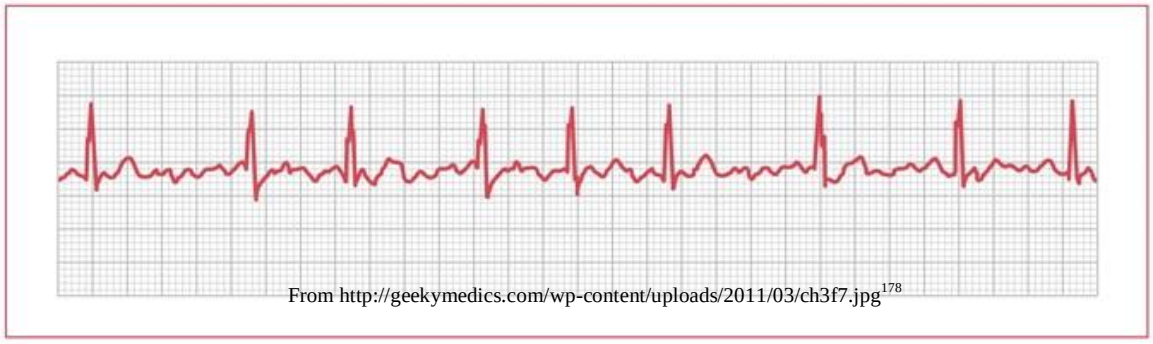
Sympathetics, not parasympathetics, innervate vascular smooth muscle

Autonomic Effects on the Heart and Blood Vessels

	Sympathetic		Parasympathetic	
	Effect	Receptor	Effect	Receptor
Heart rate	↑	β_1	↓	muscarinic
Conduction velocity (AV node)	↑	β_1	↓	muscarinic
Contractility	↑	β_1	↓ (atria)	muscarinic
Vascular smooth muscle				
Skin, splanchnic	Constriction	α_1		
Skeletal muscle	Constriction	α_1		
	Dilation	β_2		

Practice Questions:

1. A 56-y/o man is hot, anxious, sweaty, and is losing weight. He also experiences occasional palpitations and some weakness and fatigue. Tests show he is suffering from hyperthyroidism. His ECG is shown below:



From http://geekymedics.com/wp-content/uploads/2011/03/ch3f7.jpg[178]

The waveform above, with heart rate around 73 b/min, shows
   a. 1st degree AV block
   b. atrial fibrillation
   c. premature ventricular contractions
   d. ventricular fibrillation
   e. ventricular tachycardia

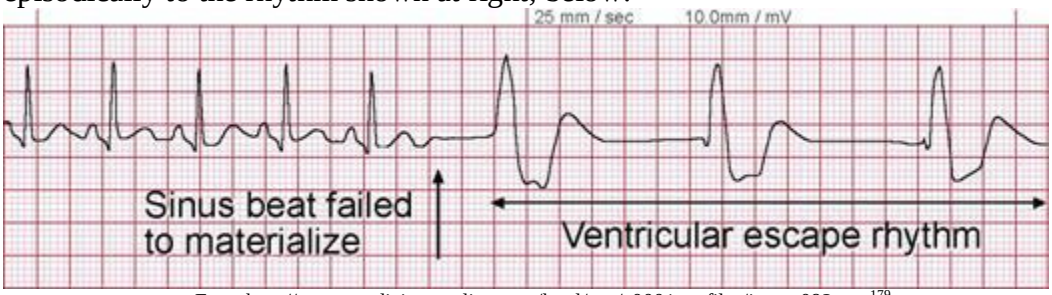
2. A 3-mo old child has Brugada syndrome, caused by a defect in the SCN5A channel. The result is reduced Na^+ current in cardiac cells. One predictable effect will be
   a. bradycardia
   b. increased QRS duration
   c. inverted T wave
   d. prolonged PR interval
   e. increased cardiac output

3. For a 30-y/o woman given a β_1-adrenergic agonist, a predictable effect prior to any reflex adjustments would be
    a. ↓ ejection fraction
    b. ↓ slow cell I_f
    c. ↑ slow cell I_{Ca}
    d. ↓ contractility
    e. ↑ mean systemic filling pressure

4. A 48-y/o woman with nervousness, fatigue, and a fast and irregular heartbeat is sweating and has frequent and loose bowel movements. She is losing weight despite eating more than usual. To reduce anxiety, heart rate, and cardiac contractility she is given a
    a. muscarinic agonist
    b. Na^+-K^+ ATPase inhibitor
    c. α_1- adrenergic antagonist
    d. α_2-adrenergic agonist
    e. β_1-adrenergic antagonist

5. In 1847, in England, a picnicker has feasted—unfortunately—on mushrooms containing muscarine. Among the cardiac effects are
    a. accelerated spontaneous depolarization of the AV node
    b. decreased Na^+/K^+ current in the SA node
    c. increased Ca^{2+} currents in the AV node
    d. loss of phase 0 of cardiac fast cell action potentials
    e. slowed ventricular muscle action potential conduction velocity

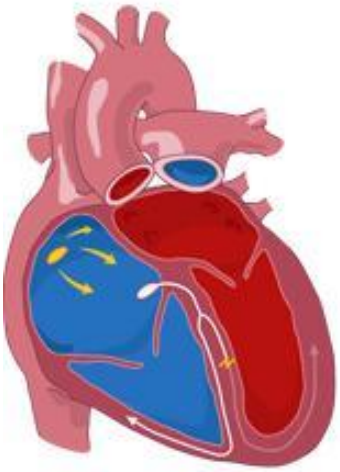
6. A 75-y/o man with normal heart rate 78 b/min has a heart rate <50 when he converts episodically to the rhythm shown at right, below:

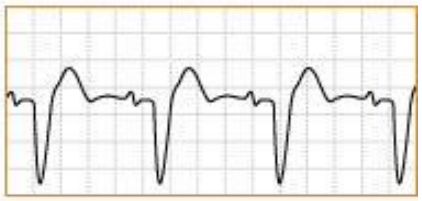


From http://www.medicine-on-line.com/html/ecg/e0001en_files/image092.png[179]

Which of the following is clear from the "ventricular escape rhythm"?
    a. cardiac output is reduced
    b. the atrial muscle is damaged
    c. the ventricular beats arise from multiple foci
    d. ventricular depolarization does not follow the normal pathway
    e. ventricular fast cells have abnormally long I_{Ca}

7. An asymptomatic 30-y/o man has the ECG shown in the Figure. His QRS wave is prolonged, indicating

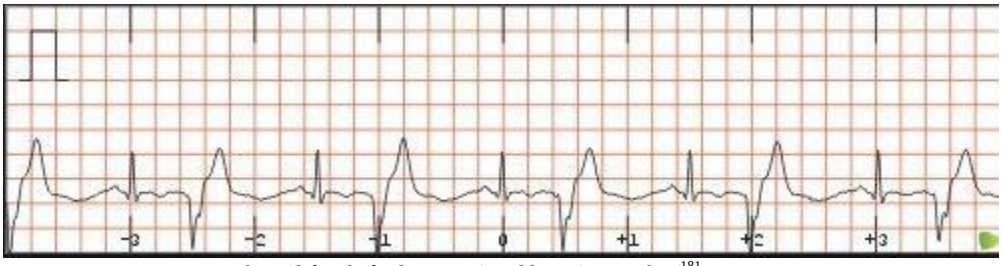




From http://nyp.org/health/block.html[180]

a. 1st degree AV block
b. 2nd degree AV block
c. an area of abnormally repolarizing ventricular fast cells
d. bundle branch block
e. reentry pathway likely due to unidirectional block

8. An active, asymptomatic 30-year old woman has the following ECG:

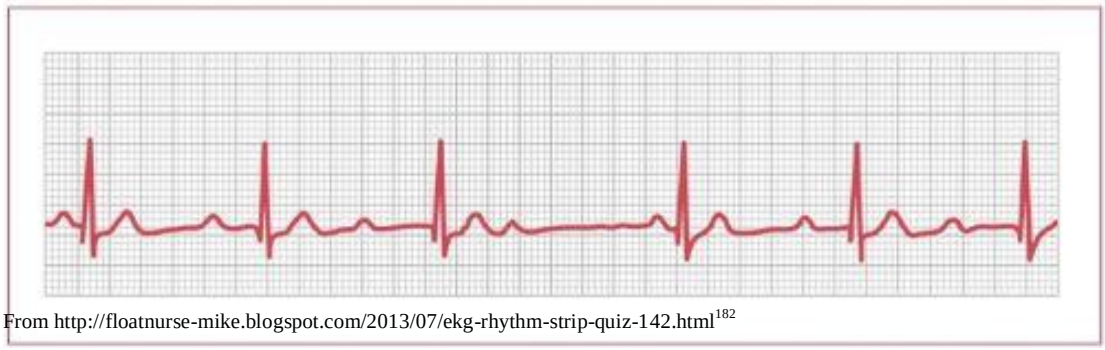


From http://lifeinthefastlane.com/ecg-library/pacemaker/[181]

This tracing shows

a. alternating atrial and ventricular pacemakers
b. a series of rapid, multifocal premature ventricular contractions
c. cessation of action of the SA node
d. each beat having a different ventricular site of origin
e. waxing and waning of 2nd degree AV block

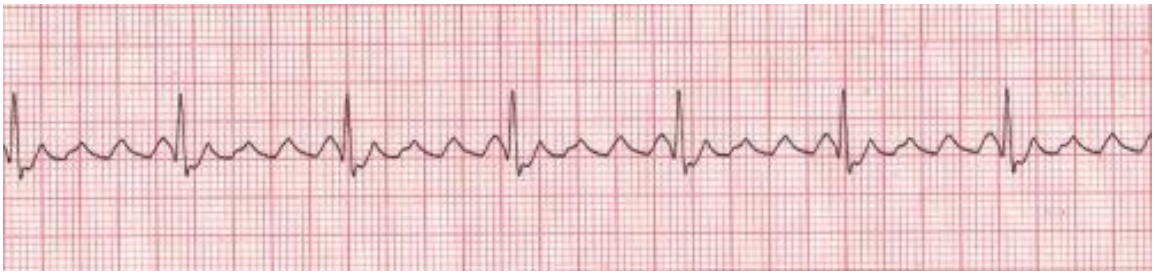
9. A 77-y/o man develops dizziness, light-headedness, shortness of breath, and occasional chest pain. His ECG is shown below. Atrial rate is 74 and the ventricular rate is 54 and irregular. His diagnosis is



From http://floatnurse-mike.blogspot.com/2013/07/ekg-rhythm-strip-quiz-142.html[182]

   a. 1st degree AV block
   b. 2nd degree AV block
   c. atrial fibrillation
   d. left bundle branch block
   e. SA nodal damage and the "sick sinus syndrome"

10. A 46-y/o woman with palpitations and exercise limitation has the ECG shown in the Figure. The R-R interval corresponds to a heart rate of 86 beats/min; the P-P interval to a rate of 300 beats/min. The two rhythms are unequal because of

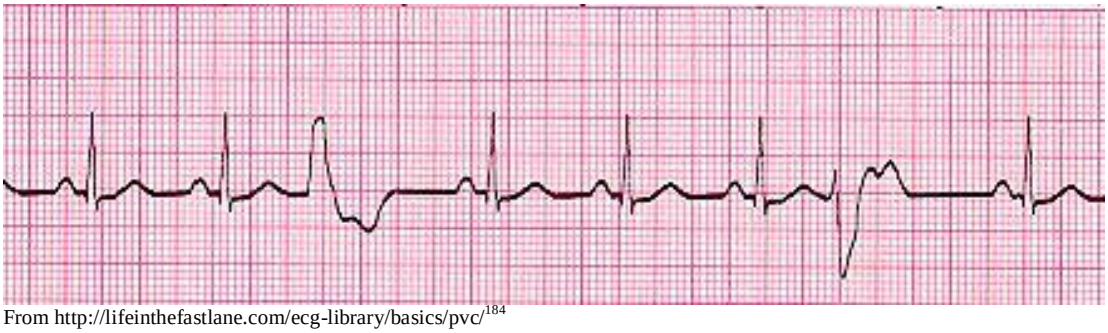


From http://www.practicalclinicalskills.com/ekg/Atrial-Flutter[183]

   a. 3rd degree AV block
   b. right bundle branch block
   c. SA nodal damage
   d. the AV nodal refractory period
   e. the presence of multifocal ventricular ectopic beats

11. A 4-y/o boy accidentally consumes a large dose of his father's metoprolol, a $ß_1$-adrenergic antagonist. Tests in the emergency room find
   a. decreased atrial contractility
   b. decreased LV end-diastolic volume
   c. increased PR interval
   d. increased slow cardiac cell I_f
   e. systemic vasodilation

12. A 43-y/o, asymptomatic man has the ECG shown below:

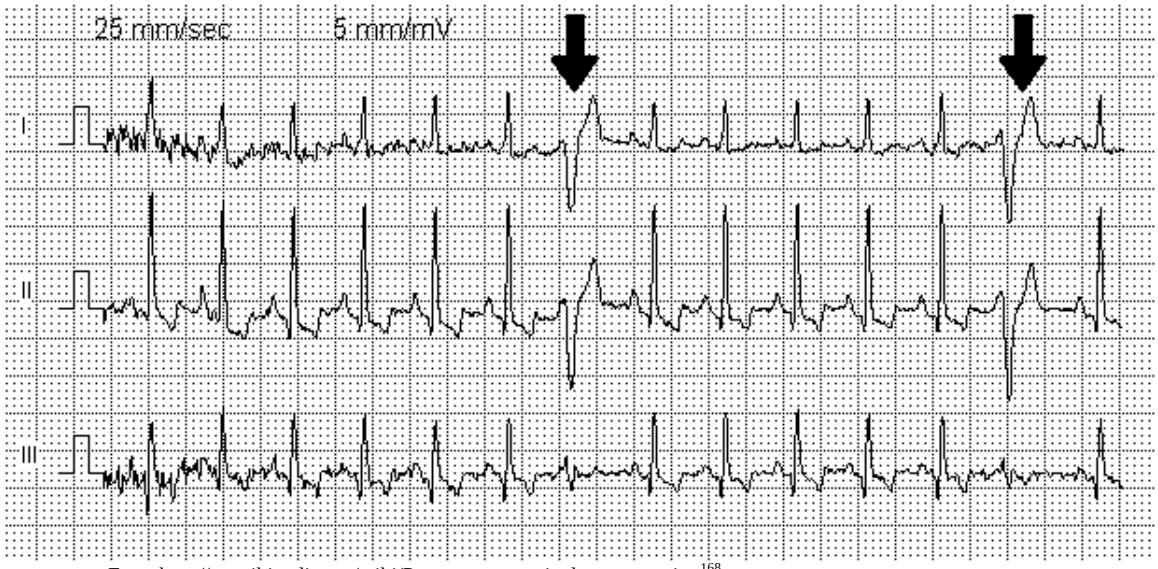


From http://lifeinthefastlane.com/ecg-library/basics/pvc/[184]

This tracing shows evidence for

a. a second AV conduction pathway
b. 3rd degree AV block
c. episodic right and left bundle branch block
d. brief, limited episodes of ventricular tachycardia
e. two different ventricular ectopic foci

13. Two contractions are identified with arrows below (shown are leads I, II, and III):



From http://en.wikipedia.org/wiki/Premature_ventricular_contraction[168]

These two contractions have

a. differ from each other in their ventricular conduction pathways
b. high stroke volume
c. initiation from the SA node
d. normal AV nodal delay
e. slow ventricular conduction

Cardiac Muscle and Cardiac Output

Structure

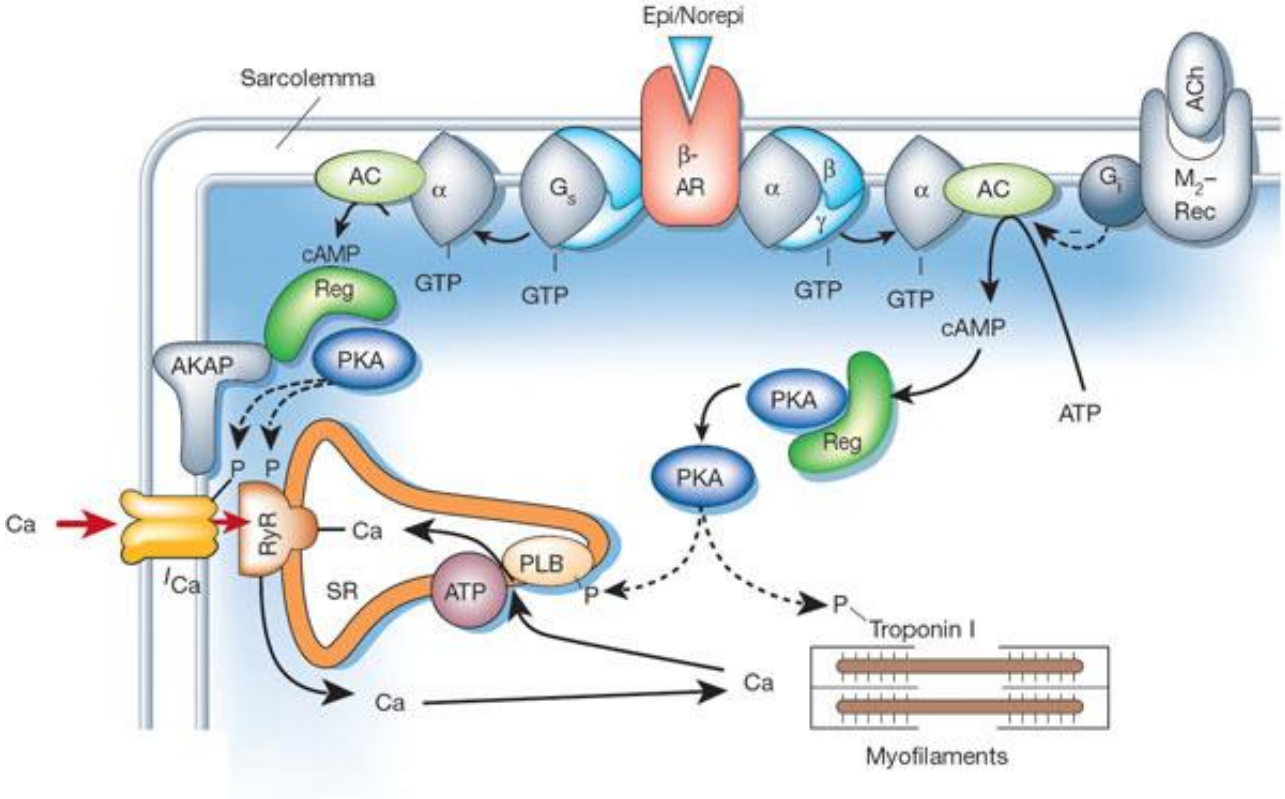
- Mitochondria are more numerous than even in slow-twitch, red skeletal muscle
    - Very high aerobic capacity, very low anaerobic capacity
    - Although cardiac muscle is omnivorous, it prefers to eat
        - Free fatty acids
        - Lactate; does not require glucose

Question: Why is occlusion of a coronary artery so immediately deadly?

Excitation-contraction coupling in cardiac muscle

- T-tubules (which are essentially just extensions of the cell membrane) spread action potential deep into the tissue
- Ca^{2+} enters cell during plateau phase of action potential
- Ca^{2+} entry triggers Ca^{2+} release from SR (Ca^{2+}-induced Ca^{2+} release)
- Ca^{2+} binds to troponin C, I and T, moving tropomyosin out of the way for cross-bridge formation
    - Troponins I and T, specific to cardiac muscle, are a useful blood marker for myocardial infarction
- Magnitude of tension developed is proportional to $[Ca^{2+}_i]$
- Relaxation after calcium reuptake into SR

- Ca^{2+} movements during excitation-contraction coupling in cardiac muscle:



From http://www.nature.com/nature/journal/v415/n6868/images/415198a-f6.2.jpg[53]

Legend: AC, adenylyl cyclase; ACh, acetylcholine; AKAP, A kinase anchoring protein; β-AR, β-adrenergic receptor; M_2-Rec, M_2-muscarinic receptor; PLB, phospholamban; Reg, PKA regulatory subunit; SR, sarcoplasmic reticulum.

- Norepinephrine (NE) and epinephrine (Epi) increase Ca^{2+} influx across the membrane during the action potential
- Bind at β_1 receptor, activate G proteins, adenylate cyclase, and cAMP
- Result is increased Ca^{2+} release from the SR during a contraction, and greater contractile force ("contractility")
- NE and Epi increase SR sensitivity to ↑ $Ca^{2+}{}_i$
- NE and Epi also increase SR reuptake of Ca^{2+} between beats
    - Phospholamban, an SR membrane protein, inhibits Ca^{2+} reuptake into the SR
    - NE and Epi inhibit phospholamban, increasing SR Ca^{2+} reuptake between beats
    - Increases rate of relaxation between beats

Questions: Complete the following table of autonomic and associated drugs that influence cardiac ventricular excitation-contraction coupling:

Drug	**Action/Class**	**Does ventricular contractility ↑ or ↓?**	**Why does contractility ↑ or ↓?**
Verapamil, diltiazem	Ca^{2+} channel blocker (L-type)		
Propranolol			
Dobutamine (β_1 agonist)			
Acetylcholine			

Contractility ("inotropism")

- Defined as cardiac muscle force development at a given muscle length
- Only defined and definable under matched conditions
    - Fixed or constant cardiac filling time (heart rate)
    - Fixed or constant afterload (pulmonary or systemic arterial pressure)
    - Fixed or constant pre-set muscle stretch conditions ("preload")
- Various factors and reflexes usually preclude direct comparisons under matched conditions, but the contractility concept is still useful
- Positive or negative inotropic effects are substitute terms for increased or decreased contractility

- While stroke volume (ml blood ejected from the ventricle per beat) is a useful method for estimating force, the "ejection fraction" is functionally important and a better index, overall, of contractility.
    - Ejection fraction = (Stroke volume / End diastolic volume (EDV))
    - Ejection fraction = ((EDV – End systolic volume) / EDV)
- Normal ejection fraction: ca. 50% at rest, ca. 80% in maximal dynamic exercise

Questions: How do each of the following affect cardiac contractility and the ventricular ejection fraction? Consider each at fixed heart rate and without other reflex adjustments—and then consider other possible reflex adjustments.

Condition	What is the autonomic effect—if any?	How do contractility and ejection fraction change?	What other reflex adjustments would be expected that would complicate contractility measurements?
Emotional stress			
Metoprolol			
Exercise			
Dobutamine			
Post-myocardial infarction			

One important drug class that affects contractility

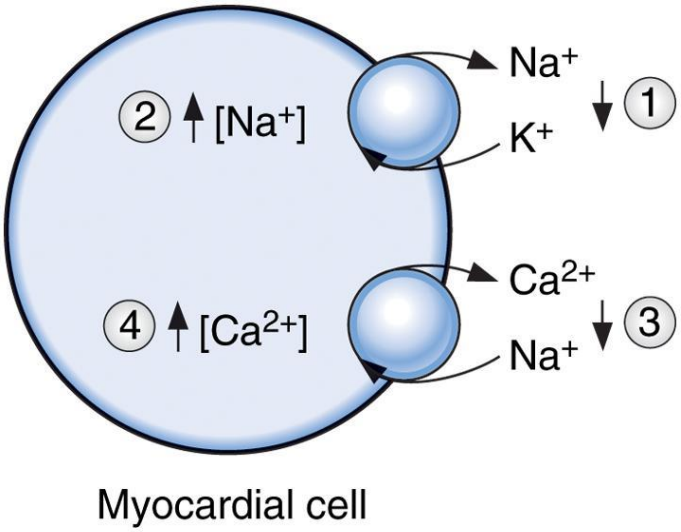
- Cardiac glycosides (e.g., digitalis)

Mechanism of action of cardiac glycosides:

i. Inhibition of Na^+-K^+ ATPase

ii. Consequently, intracellular Na^+ increases

iii. Na^+-Ca^{2+} exchange diminishes (because Na^+ gradient is decreased), allowing Ca^{2+} levels to increase inside the cell



From Costanzo p. 80[54]

Questions: Definitions in your own words:

Term	Definition
Preload	
Afterload	
Contractility	

Term	Definition
Stroke volume	
Ejection Fraction	
Cardiac output	
Cardiac chamber Compliance	

Practice Questions

1. Two women are running on adjacent treadmills in Washington DC. Their data:

	Hillary	Condoleezza
Heart rate (b/min)	150	180
End-systolic volume (mL)	50	80
Systolic pressure (mm Hg)	180	200
Diastolic pressure (mm Hg)	80	90
End-diastolic volume (mL)	150	160

Ejection fractions for the two women are

	Hillary	Condoleezza
a.	66%	50%
b.	33%	50%
c.	66%	90%
d.	80%	70%
e.	25%	33%

2. A 41-year old woman with hypertension (blood pressure 156/116) is treated with an α_1-antagonist. Blood pressure falls to 122/86, while heart rate is unchanged at 72 b/min and cardiac output remains 4.6 L/min. The drug has clearly changed cardiac
    a. afterload
    b. ejection fraction
    c. end-diastolic volume
    d. filling time
    e. preload

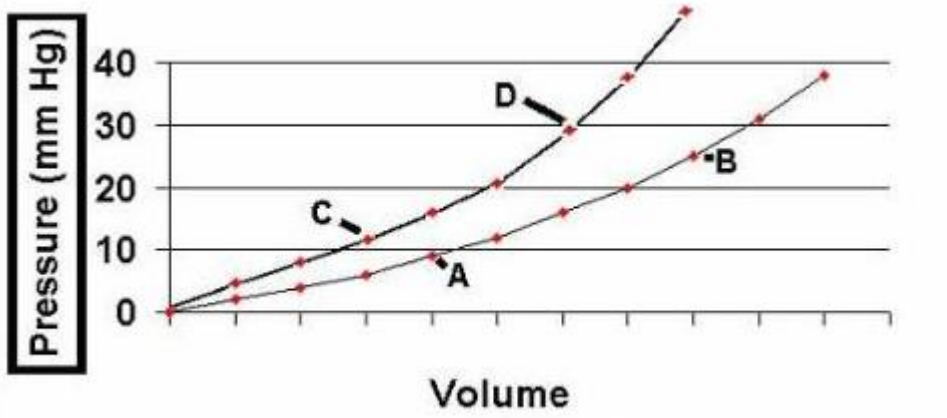
3. During a stressful exam for a 24-y/o student, cardiac output increases from 6 to 6.4 l/min, and heart rate increases from 62 to 114 beats/min. Mean blood pressure is constant at 98 mmHg. There *must* be a concomitant
    a. increased aortic compliance
    b. increased stroke volume
    c. increased total peripheral resistance
    d. decreased left atrial pressure
    e. decreased pulse pressure

4. A 31-y/o woman with blood pressure 112/72 before pregnancy develops blood pressure 146/94 after the second trimester. She is treated with a drug that directly leads to reductions in heart rate, cardiac contractility, and plasma aldosterone levels; it's a (an)
    a. ACE inhibitor
    b. angiotensin receptor blocker
    c. calcium-channel blocker
    d. diuretic
    e. β_1- adrenergic antagonist

5. A 7-y/o boy is admitted to the emergency room with palpitations, chest pressure, and shortness of breath. Cardiac ejection fraction is 78% (**H**), and toxicology tests indicate accidental ingestion of
    a. Ca^{2+}-channel blockers
    b. muscarine
    c. Na^{+}-K^{+} ATPase inhibitors
    d. β_1-adrenergic antagonists
    e. β_2-adrenergic agonists

6. In the pre-colonial era, extracts containing ouabain were used by Komba tribesmen in East Africa to poison the tips of hunting arrows. A sufficiently concentrated ouabain dart can bring down a hippopotamus, probably as the result of cardiac arrest. Ouabain is a Na^{+}-K^{+} ATPase inhibitor, and in low doses the drug is still used in France and Germany to
    a. decrease afterload
    b. increase preload
    c. increase ejection fraction
    d. decrease heart rate
    e. decrease pulse pressure

7. The figure below shows LV end-systolic and end-diastolic volumes and pressures in a highly active 57-y/o woman (points A and B) and her sedentary sister (points C and D).



From http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v03/030268r00.HTM[167]

Training has
   a. decreased heart rate
   b. decreased LV afterload
   c. decreased LV preload
   d. increased LV compliance
   e. increased LV contractility

8. An 85-y/o man has fatigue, shortness of breath, and exercise intolerance. Cardiac function tests find

Stroke volume (ml)	54	**L**
Heart rate (b/m)	102	**H**
LV EDV (ml)	218	**H**
LV ESV (ml)	164	**H**
Blood pressure (mmHg)	124/74	

He also exhibits decreased
   a. LV contractility
   b. LV end-diastolic pressure
   c. myocardial energy demands
   d. pulmonary venous pressure
   e. right atrial pressure

9. A 23-y/o woman with myotonic dystrophy has skeletal muscle weakness and cardiac problems due to a congenitally defective protein kinase. In the cardiac muscle cell, the defective protein kinase reduces the rate of relaxation during diastole, due to
   a. increased cAMP
   b. increased membrane calcium flux with the action potential
   c. increased SR calcium reuptake
   d. increased phospholamban activity
   e. increased SR calcium sensitivity

Length-tension relationship of the ventricles

- Describes effect of resting muscle length on force of subsequent contraction; similar to that seen in skeletal muscle

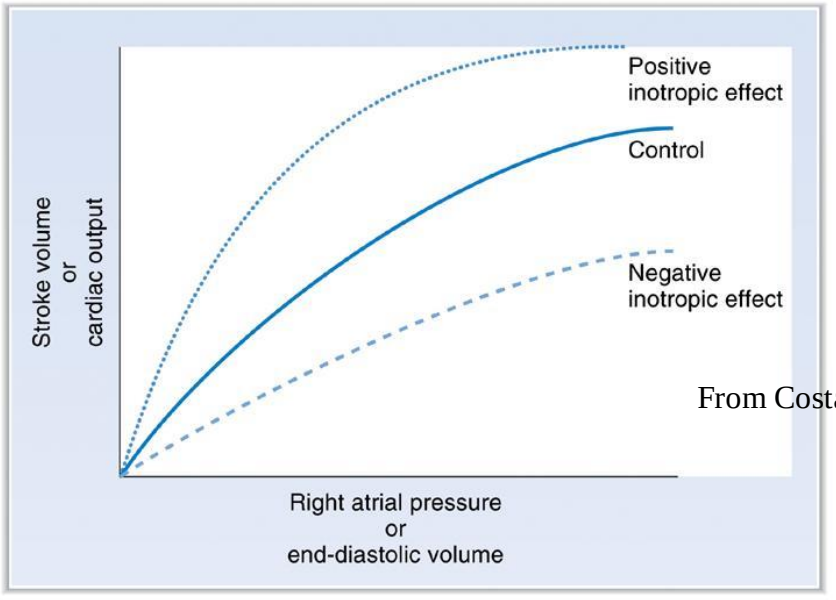
- Units converted from the linear (skeletal muscle) to the three-dimensional heart

Table 22-4. EQUIVALENT UNITS FOR CONVERTING BETWEEN A THREE-DIMENSIONAL HEART AND A LINEAR MUSCLE FIBER

ISOLATED MUSCLE = LINEAR		CARDIAC VENTRICLE = HOLLOW ORGAN	
Parameter	**Units**	**Parameter**	**Units**
Length	mm	Volume	ml
Extent of shortening	mm	Stroke volume	ml
Velocity of shortening	mm/s	Velocity of ejection	ml/s
Load	gram	Pressure	mm Hg
or Force	dyne		
or Tension	$dyne/cm^2$		

From © Elsevier Ltd. Boron & Boulpaep, Medical Physiology, Updated Edition. www.studentconsult.com, p. 547[55]

The cardiac length-tension relationship ("Frank-Starling curve")



From Costanzo p. 81[56]

A more clinical cardiac length-tension relationship ("Frank-Starling curve")

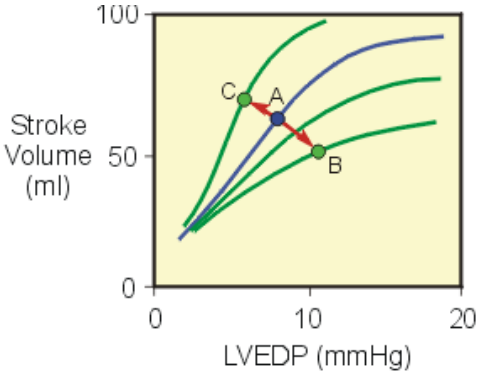


Figure 1. Effects of changes in inotropy on Frank-Starling curves. A shift from A to B occurs with decreased inotropy, and from A to C with increased inotropy.

From http://www.cvphysiology.com/Cardiac%20Function/CF010_Frank-Starling_inotropy.gif[57]

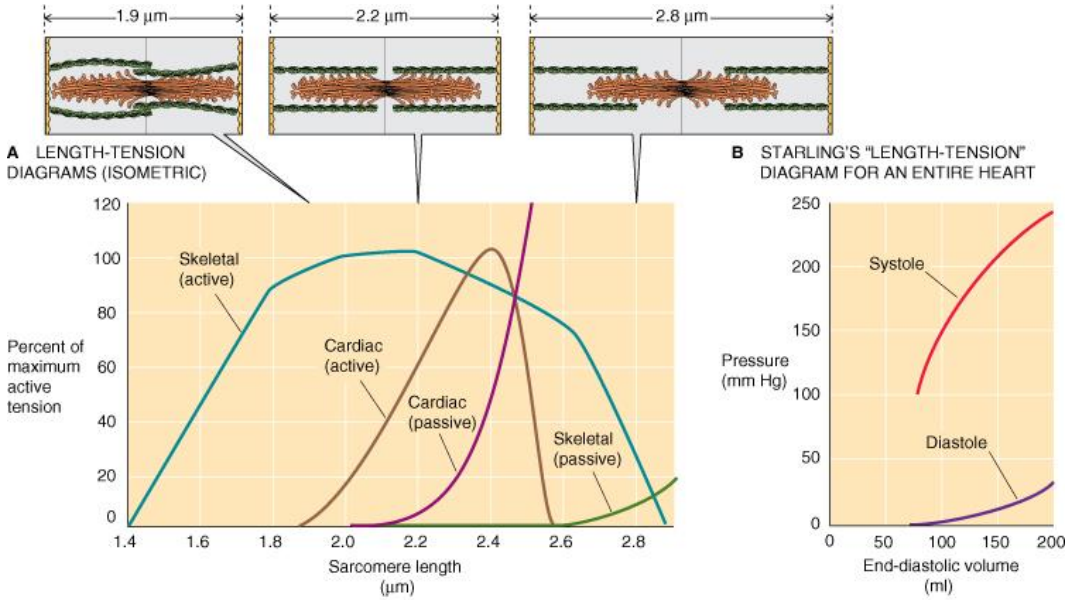
Ventricular Pressure-volume loops

- Pressure-volume loops are one way to look at how the heart behaves under conditions of varying preload, afterload, and contractility

- Loops relate changes in ventricular volume to corresponding changes in pressure throughout the cardiac cycle (diastole and systole)

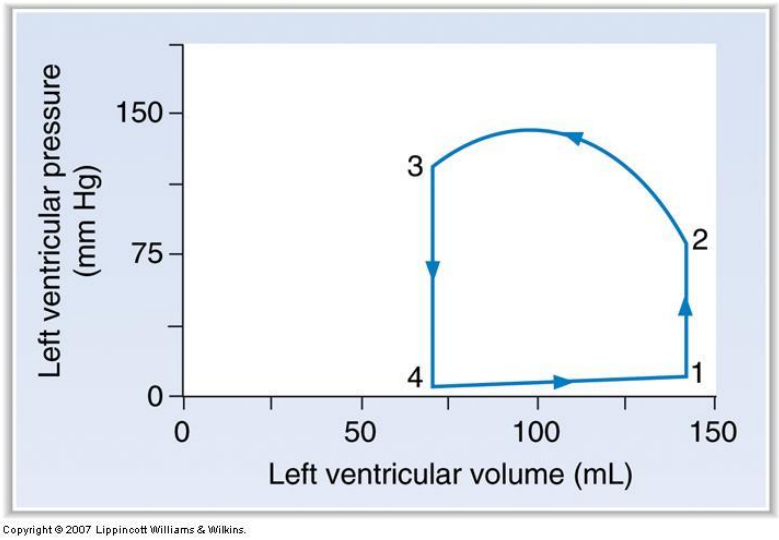
- Loops reflect the realistic situation: a ventricle begins a contraction at a given volume of filling, develops tension, but valves opening (and closing) determine much of the subsequent pattern of volumes and pressure.

    - For the left ventricle, loop will move between diastolic and systolic pressure-volume relations of the chamber



From Boron p. 546[58]

- During diastole, the mitral valve is open between the left atria and the left ventricle, and the ventricle is filling
- During systole, the mitral valve is closed, and the ventricular pressure rises
- Before peak isometric tension can be reached, however, the aortic valve opens and blood is ejected into the aorta, and ventricular volume falls



From Costanzo p. 82[59]

- "Isovolumetric" contraction is just cardiac isometric contraction
- When pressure in the ventricle falls below aortic pressure, the aortic valve closes, and pressure falls at constant volume (isovolumetric relaxation)

Question: Match events with numbers or line segments in the Costanzo diagram above

*Isovolumetric contraction*_____ and *Isovolumetric relaxation*_____

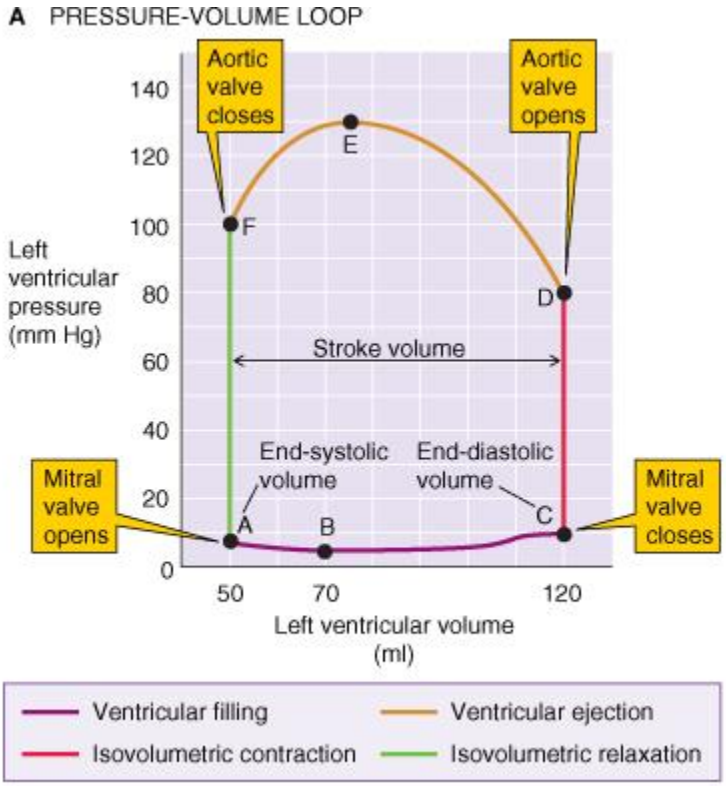
*Stroke volume*_____, *End-diastolic volume*_____, *End-systolic volume*_____

*Ejection fraction*_____; *Peak intraventricular systolic pressure*_____

Aortic valve opens at_____; *Aortic valve closes* at_____; *Preload*_____

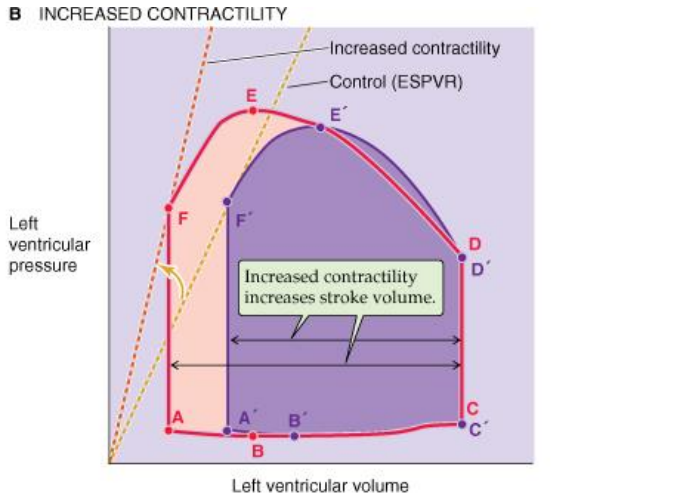
Mitral valve opens at_____; *Mitral valve closes* at_____; *Afterload*_____

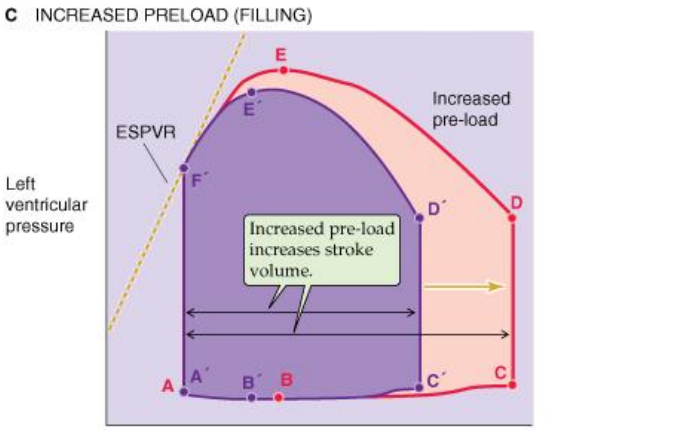
Another view of a ventricular pressure-volume loop:

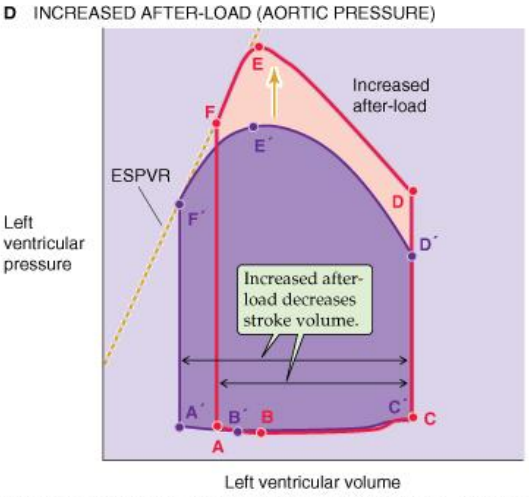


From Boron p. 542[60]

Pressure-volume loops under conditions of varying contractility, preload, and afterload:

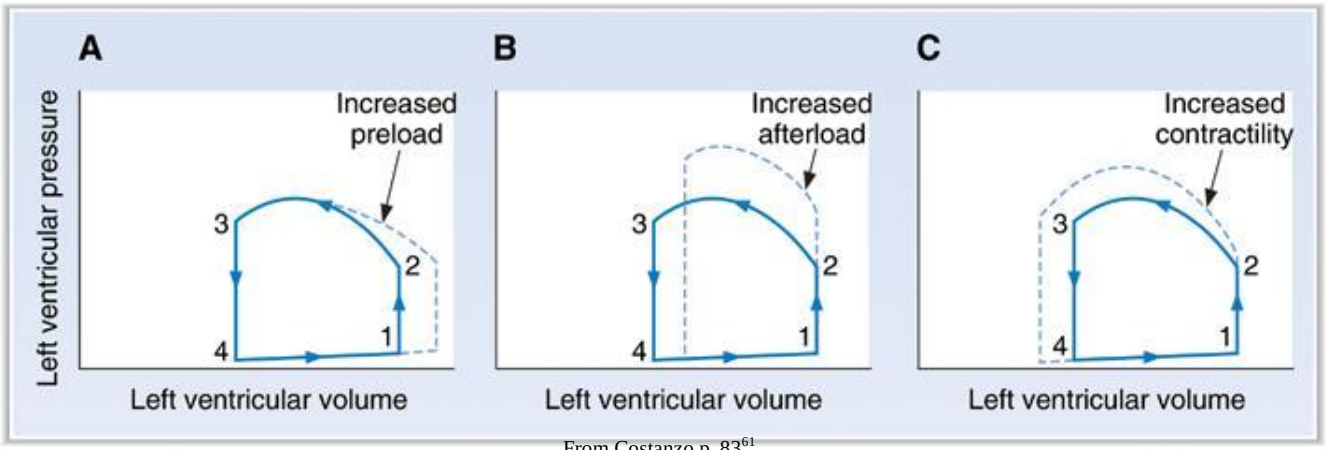






From Boron p. 551[8]

Costanzo's figure showing ventricular pressure-volume loops under conditions of varying preload, afterload, and contractility:



From Costanzo p. 83[61]

Questions:

1. After a major loss of blood, the cardiac preload may be markedly diminished below normal. Explain how under these conditions the heart may still be able to manage a normal cardiac output

2. How can a heart maintain a normal stroke volume under conditions of increased afterload, while maintaining normal preload? How can the heart hope to accomplish these changes long-term?

3. In terms of cardiac preload, contractility, and afterload, explain how emotional stress, exercise, and drugs that are β_1-agonists (e.g., dobutamine) increase the cardiac output

Practice Questions

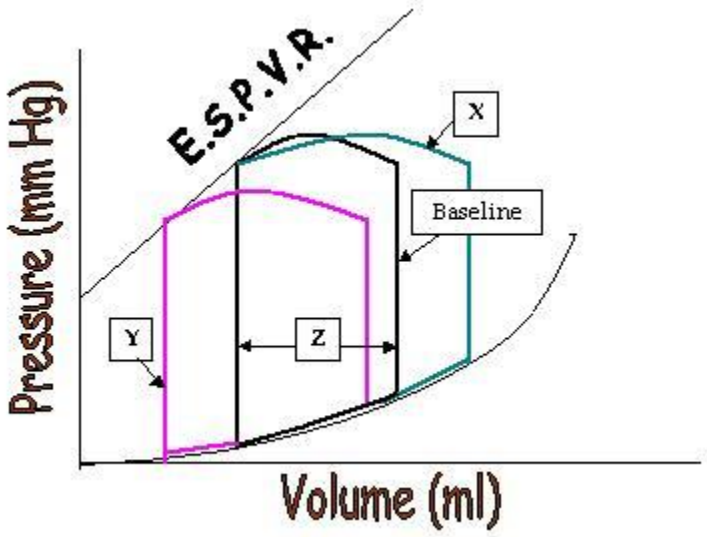
1. A 16-y/o girl has episodic heart palpitations during exercise. At rest, her lab results include

Heart rate (b/m)	90	
LV end-diastolic volume (ml)	122	
LV end-systolic volume (ml)	38	**L**
Ejection fraction (%)	69	**H**
Systemic systolic/diastolic press (mmHg)	115/75	

   Her symptoms are a result of
   a. decreased SR sensitivity to Ca^{2+}
   b. gain-in-function phospholamban gene mutation
   c. defective troponin T
   d. increased tonic sympathetic nervous system activity
   e. up-regulation of cardiac M2 receptors

2. The extreme hyperglycemia seen in untreated type 1 diabetes, devastating as it is, is not especially demanding for cardiac muscle because for the heart,
   a. coronary arterial collaterals can increase blood flow during glucose deprivation
   b. facilitated glucose uptake is insulin-independent
   c. free fatty acids and ketone bodies are preferred energy substrates
   d. large amounts of glucose, stored as glycogen, are available for use
   e. only small amounts of insulin are required to sustain heart muscle

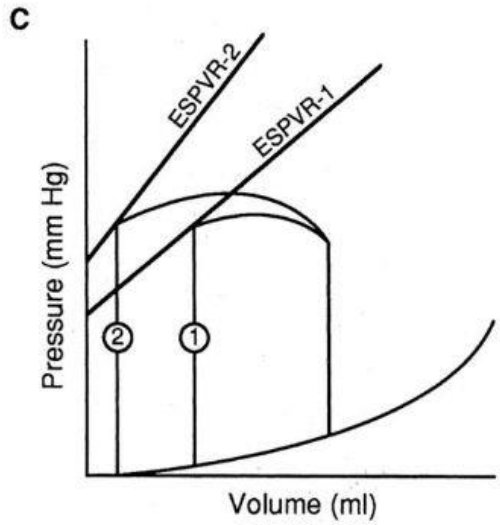
3. In the Figure below, movement from the LV flow-volume loop marked Y to that marked X would occur with



From http://www.brown.edu/Courses/Bio_281-cardio/cardio/Exam99.htm[9]

a. decreased afterload
b. decreased contractility
c. decreased blood volume
d. increased heart rate
e. increased preload

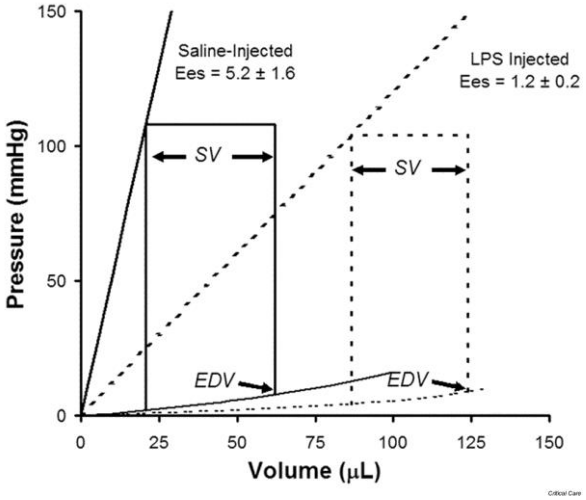
4. Treatment with what drug will cause a shift from loop 1 to loop 2?



From http://www.brown.edu/Courses/Bio_281-cardio/cardio/handout1.htm[10]

a. acetylcholine
b. α_1- agonist
c. β_1-agonist
d. M_2-antagonist
e. stimulation of myocardial cell Na^+ - K^+ ATPase

5. The figure below shows the effects of lipopolysaccharide (LPS) injection on the rat heart:

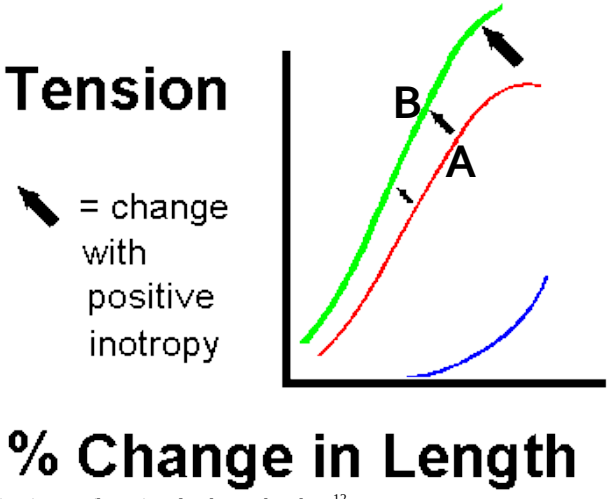


From http://openi.nlm.nih.gov/detailedresult.php?img=2374637_cc6213-1&req=4[11]

For the heart, LPS has

a. ↑ afterload
b. ↑ contractility
c. ↓ ejection fraction
d. ↓ heart rate
e. ↓ preload

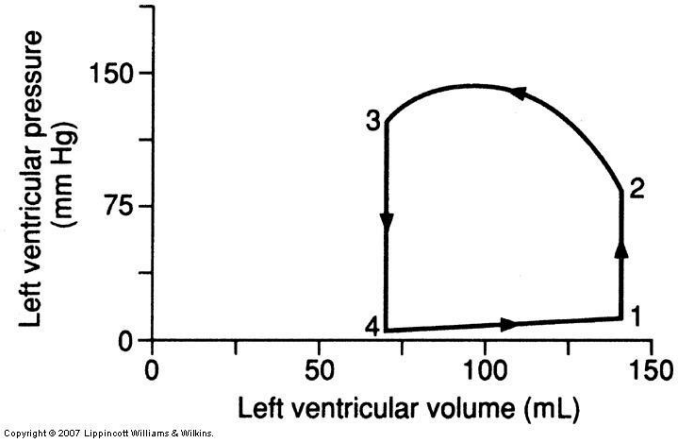
6. For the cardiac length-tension curve below, which of the following will cause the shift from line A to line B represented by the arrows?



From http://www.anaesthetist.com/icu/organs/heart/Findex.htm#phys.htm[12]

a. metoprolol
b. increased preload
c. decreased afterload
d. dobutamine
e. increased left-ventricular end-diastolic pressure

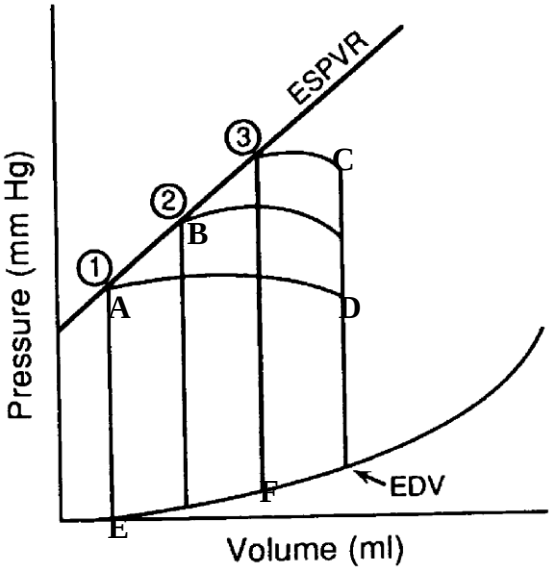
7. If an intravenous infusion of atropine (a muscarinic antagonist) begins to have an effect at point 4, the most immediate reduction will be in



From http://www.anaesthetist.com/icu/organs/heart/Findex.htm#phys.htm[13]

a. afterload
b. pressure at point 3
c. the LV pressure difference between points 2 and 3
d. there will be no changes
e. volume at point 1

8. For the left ventricular flow-volume loops shown below, an increase in afterload will move the point of opening of the mitral valve from which point to which point?



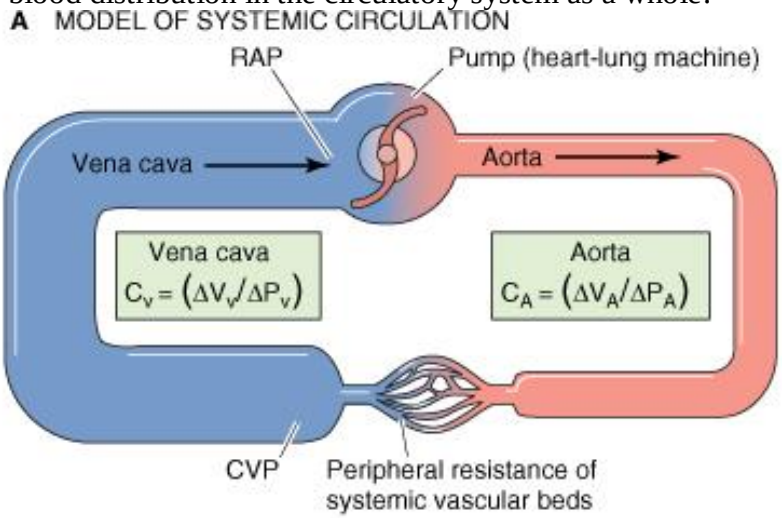
From http://www.brown.edu/Courses/Bio_281-cardio/cardio/BIO281V1.htm[19]

a. from A to B
b. from D to C
c. from E to F
d. from D to A
e. it does not move; it remains at point D

Cardiac and vascular function curves or

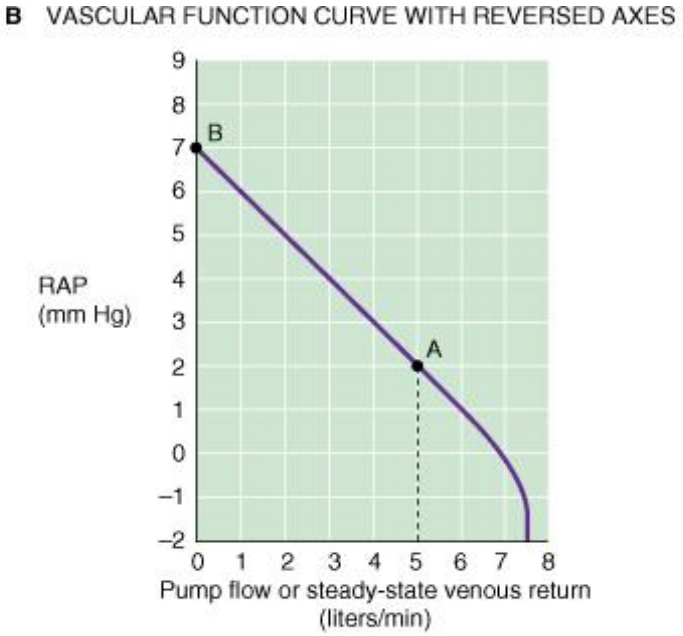
Coupling of the heart's forward output (cardiac output) to venous return

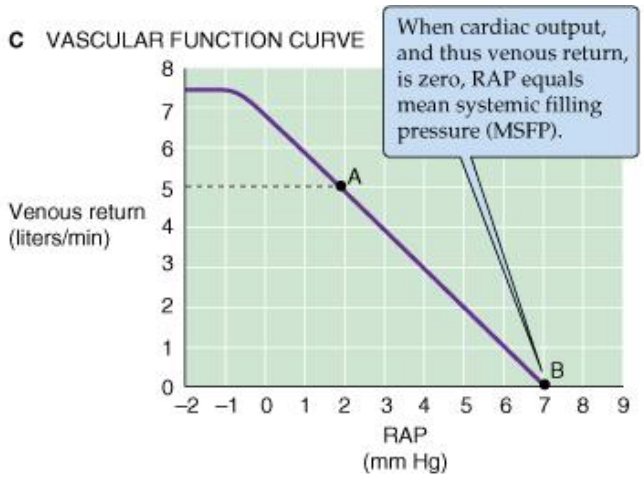
- Cardiac output always = venous return in the steady state
- To understand the relationship between cardiac output and venous return, we need to consider blood distribution in the circulatory system as a whole:



From Boron p. 570[62]

Graphically



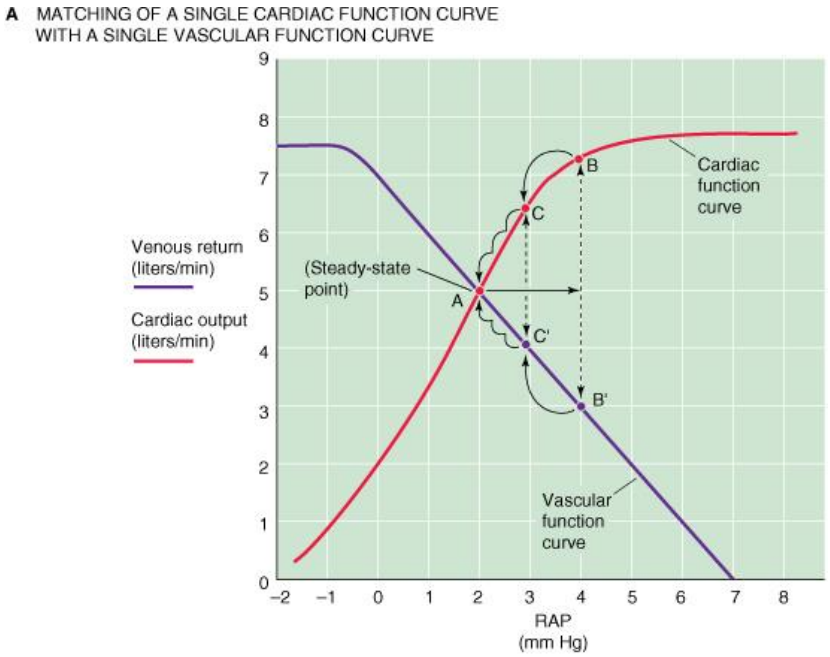


From Boron p. 570[63]

- We also know that the cardiac length-tension curve relates cardiac output to end-diastolic volume (≈ right atrial pressure, given a constant cardiac filling time (constant heart rate))

- Placing both curves on the same graph lets us simultaneously consider how both venous return and cardiac output are related to right atrial pressure

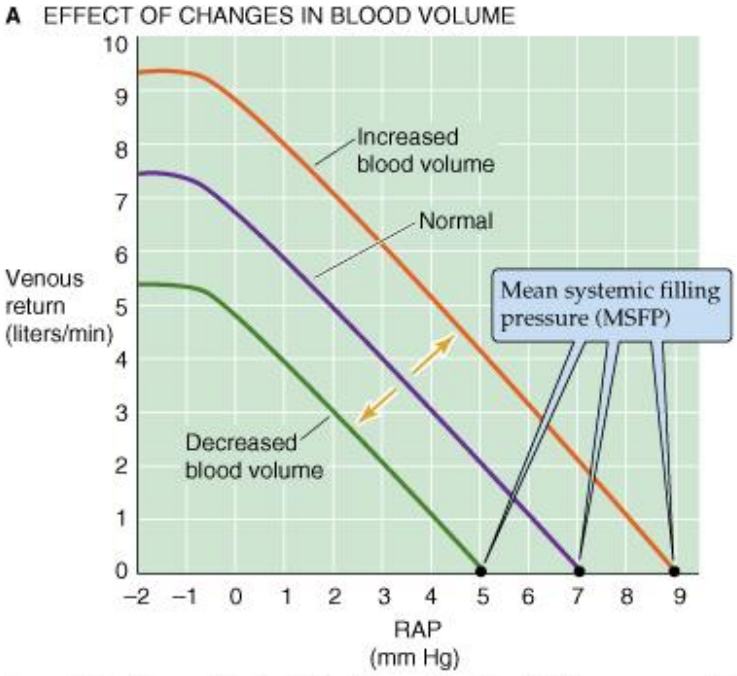
- Since in the steady state, cardiac output must = venous return, the steady-state operating point of the cardiovascular system is at the intersection of the two curves



Legend: Point A is the single right atrial pressure at which venous return and cardiac output match. A transient increase in RAP from 2 to 4 mm Hg causes an initial mismatch between cardiac output (*point B*) and venous return (*point B*'), which eventually resolves (B'C'A and BCA). From Boron p.573[64]

Increased or decreased blood volume

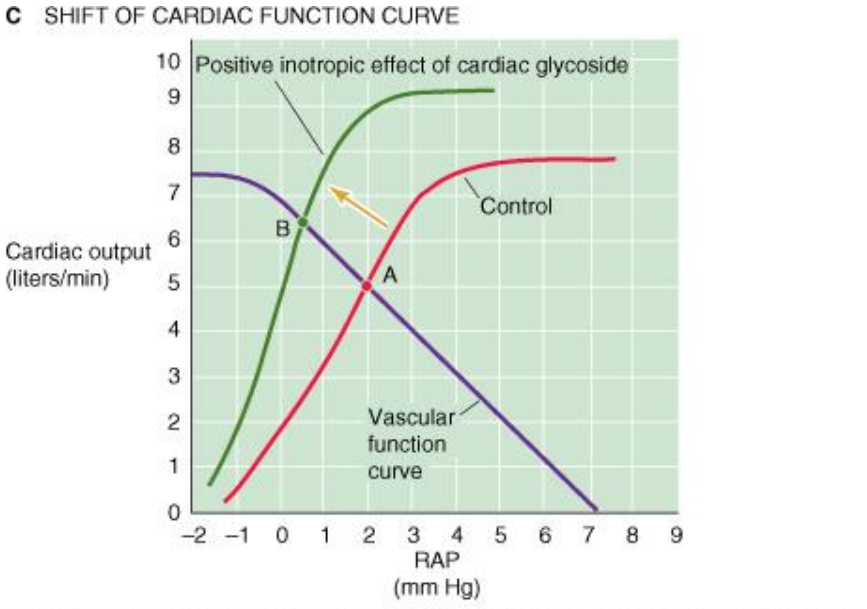
- Alter the mean systemic filling pressure and displace the vascular function curve



From Boron p. 571[65]

Factors that alter cardiac contractility

- Alter the slope of the cardiac function curve (Frank-Starling relationship; cardiac length-tension relationship)



From Boron p. 573[66]

Questions: Complete the following table of factors that alter blood volume or cardiac ventricular contractility, and their impact on cardiac output and right-atrial pressure. Consider heart rate to be constant under all conditions, and consider only primary responses, not reflex adjustments to those responses. Note: drawing a graph may help

Factor	**Cardiac Contractility, ↑,↓, or =**	**Blood Volume, ↑, ↓, or =**	**Cardiac Output, ↑, ↓, or =**	**Right Atrial Pressure, ↑, ↓, or =**
Post-myocardial infarction				
Hemorrhage				
Dobutamine				
Metoprolol				
Blood transfusion				

Cardiac work and cardiac output

- External work performed by the heart is called the stroke work
- Stroke work is roughly = stroke volume × aortic pressure
- Stroke work represents only external work, and ignores isometric components of contraction
- *Total* cardiac work is most closely related to mean wall tension × mean fractional time spent in systole
    - Mean wall tension increases with increasing aortic pressure
    - Mean fractional time spent in systole increases with heart rate

- Rough estimate for total cardiac work—and for cardiac oxygen consumption—is the "rate-pressure product": heart rate × mean arterial pressure

Question: What are some of the adaptations to regular endurance exercise that reduce the risk of coronary ischemia?

Measuring cardiac output

- Based on the conservation of mass (of oxygen): a classic method that uses what is easily measured, and based on measurements in a "steady-state".

- Systemic tissues use oxygen (~250 ml/min at rest), removing it from the blood; lungs add 250 ml/min at rest.

- By conservation of mass (of O_2),

$$\text{Cardiac output} = \frac{O_2 \text{ consumption}}{[O_2]_{\text{pulmonary vein}} - [O_2]_{\text{pulmonary artery}}}$$

The equation is solved as follows:

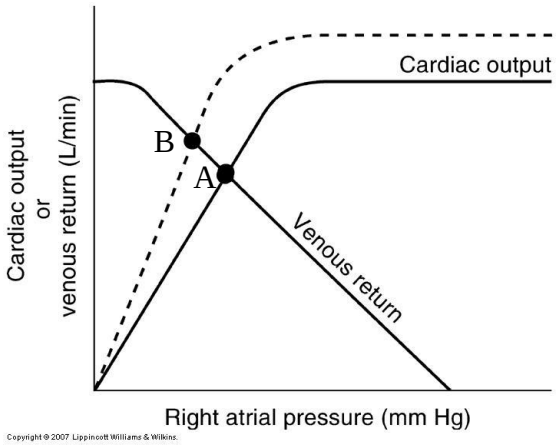
1. O_2 consumption for the whole body is measured
2. Pulmonary venous $[O_2]$ is measured in a peripheral artery
3. Pulmonary arterial $[O_2]$ is measured in systemic mixed venous blood

Note: O_2 consumption is in units of ml O_2/min
O_2 content in blood is in units of ml O_2/ml *blood*

Question: A 62-y/o man in the intensive care unit has a oxygen consumption of 280 ml O_2/min and a pulmonary vein O_2 content of 0.20 ml O_2/ml blood. His pulmonary arterial O_2 content is 0.06 ml O_2/ml blood. What is his cardiac output in liters/min?

Practice Questions

1. Movement from point A to point B as shown below would occur most directly in response to what change?



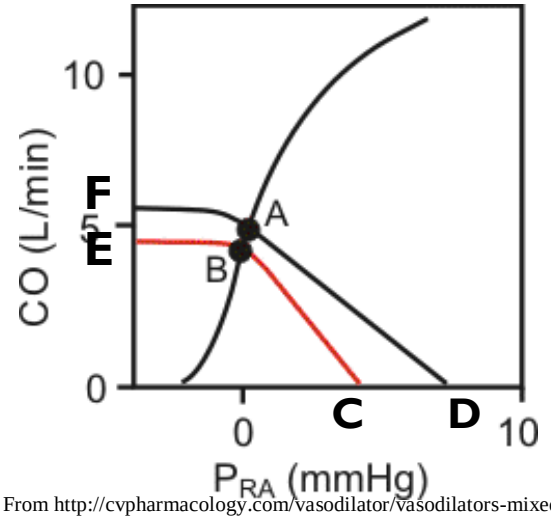
From http://users.atw.hu/blp6/BLP6/HTML/C0199780323045827.htm[20]

   a. ↑ myocardial intracellular [Na^+]
   b. infusion of 1 liter normal saline
   c. hemorrhage
   d. prolonged bed rest
   e. treatment with muscarinic antagonist

2. As a unit, the systemic veins, as compared to the systemic arteries, have
   a. greater blood volume
   b. higher blood velocity
   c. lower compliance
   d. much higher overall vascular resistance
   e. β_2- rather than α_1-adrenergic innervation

3. A 52-y/o man with a history of chronic systemic arterial hypertension has a normal resting cardiac output and heart rate. Medications are keeping his mean arterial blood pressure normal as well. However, his resting pulse pressure is abnormally large, showing that he has
   a. a significant cardiac arrhythmia
   b. chronic left ventricular dysfunction
   c. high stroke volume
   d. low stroke volume
   e. reduced aortic compliance

4. A 19-y/o man is wounded with a knife, and loses about 1½ units of blood, thereby directly lowering his mean systemic filling pressure from



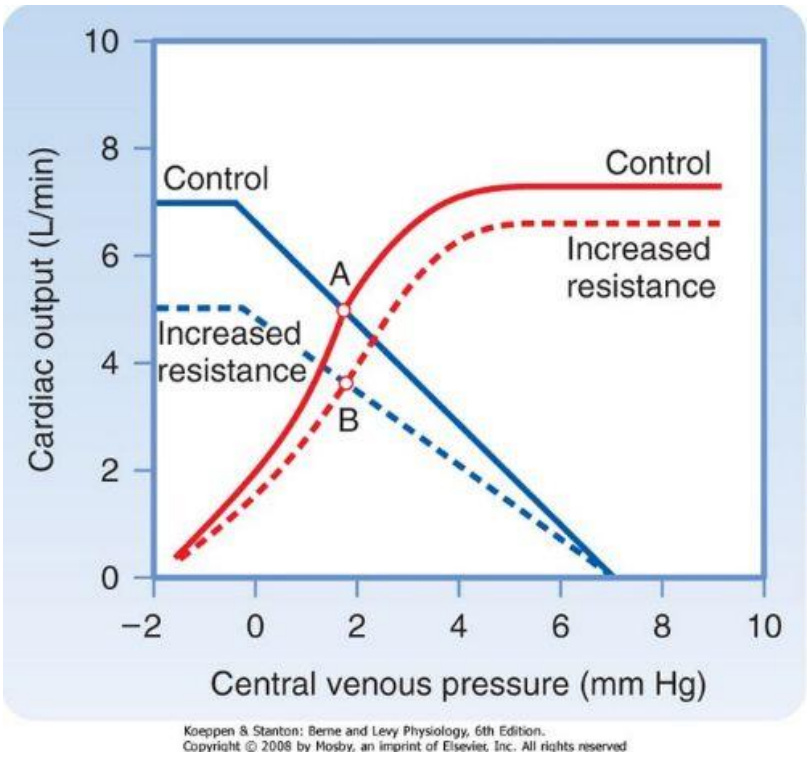
From http://cvpharmacology.com/vasodilator/vasodilators-mixed%20cardiac-sys%20funct%20curves.gif[21]

   a. A to B
   b. A to F
   c. B to E
   d. D to C
   e. F to E

5. Aging reduces the cardiac contractility increase seen with dobutamine stimulation, possibly by causing an increase in
   a. adenyl cyclase activity
   b. cAMP
   c. phospholamban activity
   d. SR Ca^{2+} reuptake
   e. SR sensitivity to ↑ Ca^{2+}

6. A 67-y/o woman develops a sudden, severe renal ischemia that triggers a blood pressure rise from 116/76 to 184/120 mm Hg over a period of only two days. This in turn will—at constant preload, heart rate, and stroke volume—cause which of the following changes in flow-volume characteristics of the left ventricle?
   a. decreased contractility
   b. decreased ejection fraction
   c. decreased end-systolic volume
   d. increased isovolumetric contraction
   e. increased peak end-diastolic pressure

7. Over a 15-year period, a 45-y/o woman has developed hypertension (blood pressure 148/94 (**H**)). Graphically her cardiac and vascular function curves have moved from intersection point A to point B (Figure). This change is associated with



From http://users.atw.hu/blp6/BLP6/HTML/C0199780323045827.htm[2]

a. increased mean systemic filling pressure
b. decreased stroke volume
c. decreased total peripheral resistance
d. increased central venous pressure
e. lung congestion

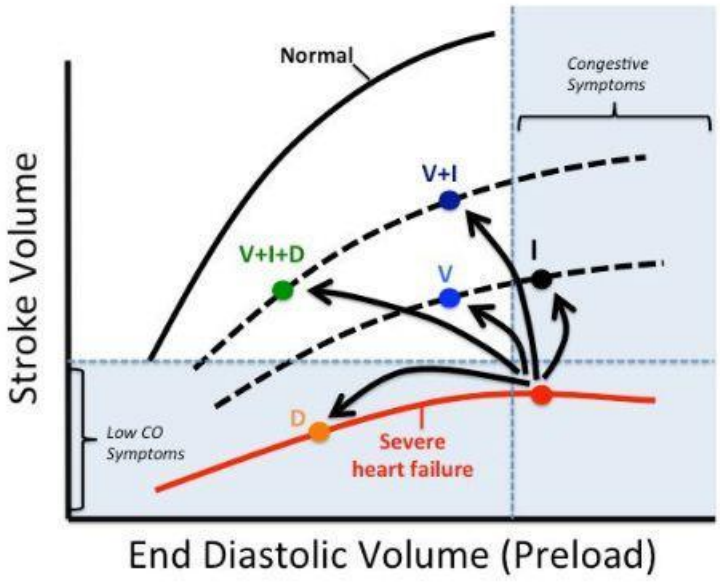
8. An 88-y/o man with cough, swollen ankles, and severe fatigue has the following lab data:

Arterial pressure (mmHg)	104/84	
Heart rate (b/min)	98	
Cardiac output (l/min)	4.3	**L**
Stroke volume (ml)	48	**L**
End-diastolic volume (ml)	196	**H**

His left ventricle has

a. ↑ afterload
b. ↑ compliance
c. ↑ contractility
d. ↑ ejection fraction
e. ↑ preload

9. An 86-y/o woman with cough, shortness of breath while supine, and ankle edema is treated with three drugs. The drugs (V+I+D) cause a shift on the figure below from the red dot to the green dot:

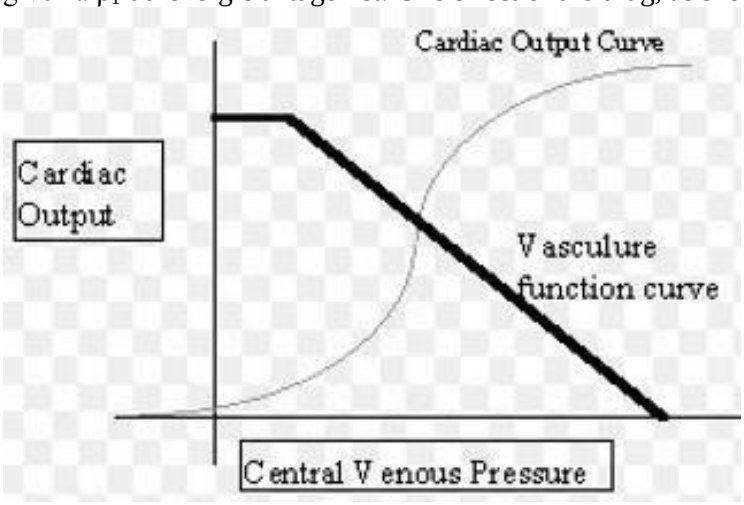


From http://www.cram.com/flashcards/symptoms-17-dyspnea-orthopnea-and-edema-4706908[185]

From this figure we can conclude that this combination of drugs has

a. ↓ preload and afterload
b. ↓ blood volume and ↑cardiac contractility
c. ↓ total systemic resistance and ↑cardiac output
d. ↑ ejection fraction and ↑mean systemic filling pressure
e. ↑ heart rate and ↓stroke volume

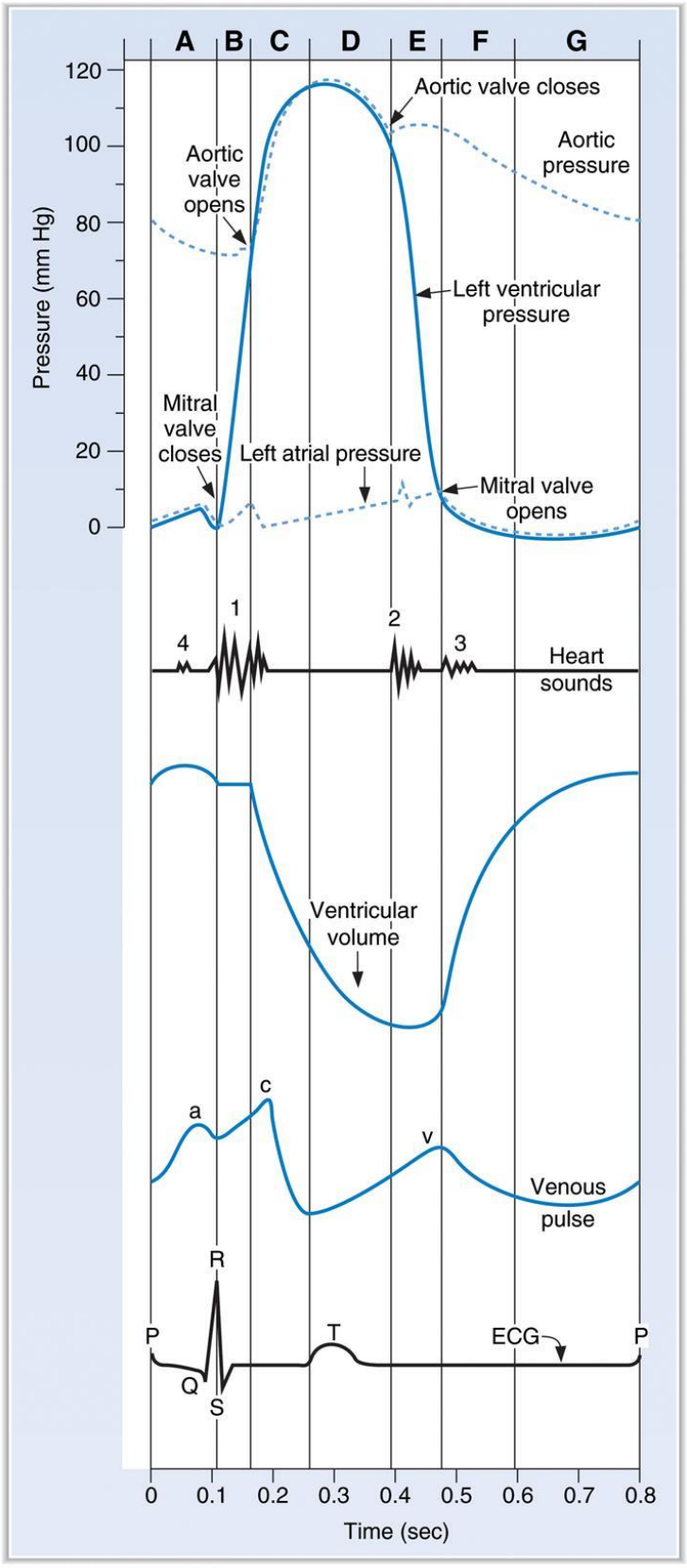
10. A 70-y/o man with hypertension (mean arterial pressure 180/104) and high risk for heart attack is given a β_1-adrenergic antagonist. One effect of the drug, as shown on the figure below, will be to



a. shift the vascular function curve to the left
b. shift the vascular function curve to the right
c. increase his central venous pressure
d. increase his cardiac output
e. decrease the slope of the vascular function curve

V. Cardiac cycle

- ECG useful event marker for pressure and volume events
- Venous pulse curve represents changes in the jugular venous pressure and is in relative terms
- Ventricular volume is that blood volume within the ventricle at a given moment, with units the curve could provide end-diastolic, end-systolic, and stroke volumes
- Pressures indicate that this information is from the left heart, but qualitatively similar data would obtain from the right heart
- Heart sounds are detected with stethoscope from the chest surface, and represent periods of increased turbulence in cardiac blood flow
    - S_1 ("lub")—caused by closure of mitral and tricuspid valves—has two components
    - S_2 ("dub")—caused by closure of aortic and pulmonic valves—also has two components
    - S_3 and S_4 are much less audible
- These heart sounds are normal; additional turbulence, especially during periods of normally laminar flow, are termed murmurs and indicate the presence of disease or damage
- Note minimal difference between left atrial and ventricular pressures during ventricular diastole, indicating that the mitral valve can open normally
- Left ventricular pressure and aortic pressure are very similar during ventricular systole, indicating that the aortic valve can open fully
- Aortic pressure curve is very similar to the systemic arterial pressure curve seen in the brachial artery



From Costanzo p. 89[67]

Questions: Match the portions of the cardiac cycle with the letter (identifier) provided in the preceding figure

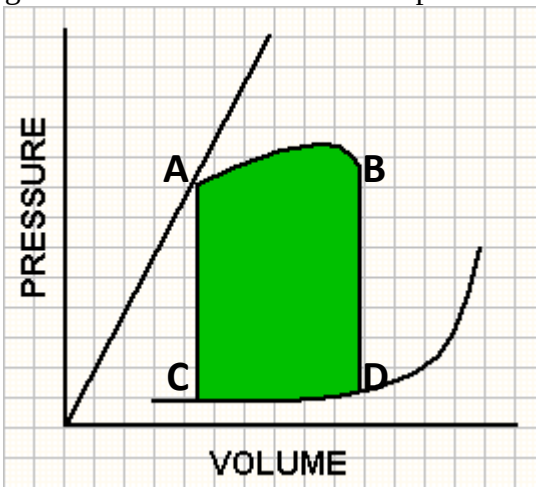
Cardiac Cycle Phase	Description/Details	Identifier
Rapid ventricular ejection	Rapid reduction of ventricular volume; ventricular pressure slightly exceeds aortic pressure; c wave in jugular pulse is due to tricuspid bulging into right atrium; T wave marks end of this phase	
Reduced ventricular filling (diastasis)	Slower filling of ventricle; this time reduced when heart rate is increased; aortic pressure continues to fall due to runoff to the periphery	
Isovolumetric ventricular contraction	QRS marks initiation of ventricular contraction, which quickly generates sufficient pressure to close mitral valve, which ends ventricular filling; mitral and tricuspid valve closure creates the first heart sound (S_1); splitting of this sound can be heard because the mitral closes fractionally earlier	
Rapid ventricular filling	Mitral valve opens and the heart begins to fill rapidly; turbulent inflow can create a third heart sound (S_3); v peak on jugular venous pulse corresponds to pressure buildup behind the tricuspid valve, which is relieved by AV valve opening	
Atrial systole	Initiated by P wave; adds only fractionally to ventricular end-diastolic volume (patients with atrial fibrillation may notice only small decrements in exercise capacity); creates the "a" wave on jugular venous pulse curve; fourth heart sound (S_4) from stretching ventricle during final fill	
Isovolumetric ventricular relaxation	Closure of semilunar (aortic and pulmonic) valves creates the second heart sound (S_2); these too will be split in time slightly during inspiration (complex physiology), and may be split further when one of the valves is damaged, etc. Bump in aortic pressure is called the dicrotic notch or incisura	
Reduced ventricular ejection	Falling ventricular pressure allows aortic pressure to exceed ventricular, but inertia of blood flow in aortic valve keeps valve open, and ventricle continues to empty; runoff from aorta to periphery causes aortic pressure to fall	

Practice Questions:

1. An 82-y/o man has atrial fibrillation, fatigue, shortness of breath, and episodic faintness. He also has reduced blood volume. It is *certain* that he has
   a. ↑ heart rate
   b. ↓ cardiac contractility
   c. ↓ mean arterial pressure
   d. ↓ mean systemic filling pressure
   e. ↓ stroke volume

2. The QRS complex of the ECG marks the beginning of
   a. isovolumetric contraction
   b. rapid ventricular filling
   c. reduced ventricular filling
   d. rapid ventricular ejection
   e. isovolumetric relaxation

3. A right ventricular flow-volume loop is shown below:



From http://crashingpatient.com/wp-content/images/part1/pressure%20volume%20loop.gif[166]

At point A, there is
   a. mitral valve closure
   b. pulmonary valve closure
   c. pulmonary valve opening
   d. tricuspid valve closure
   e. tricuspid valve opening

4. A 33-y/o woman with chest pain, fatigue, and dizziness is diagnosed with restrictive cardiomyopathy, a disorder of left ventricular diastolic function that results in increased
    a. cardiac output
    b. LV end-diastolic pressure
    c. stroke volume
    d. LV end-diastolic volume
    e. pulse pressure

5. A cardiologist detects an abnormal "fixed split" in the second heart sound in a 7-y/o boy with exercise intolerance, indicating that something is abnormal at the
    a. aortic pressure minimum (ca. 80 mmHg in health)
    b. time of mitral valve opening
    c. beginning of isovolumetric relaxation
    d. end of isovolumetric contraction
    e. time of the QRS wave on the ECG

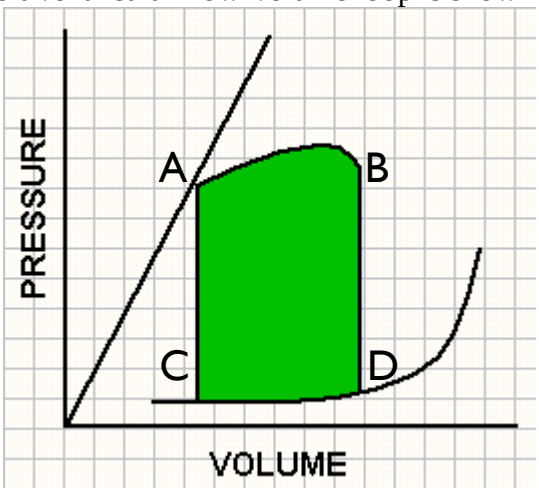
6. A 33-y/o man with pericarditis develops chest pain, difficulty breathing, and light-headedness. Lab tests show:

Test	**Result**	
Heart rate (b/m)	114	**H**
Cardiac output (l/m)	4.4	**L**
Stroke volume (ml/b)	39	**L**
Arterial blood press (mmHg)	98/74	**L**
End-diastolic volume (ml)	154	

The diagnosis of *cardiac tamponade* is supported by the clear evidence above for
    a. atrial fibrillation
    b. increased afterload
    c. low ejection fraction
    d. reduced preload
    e. ventricular ischemia

7. A medical student is listening to heart sounds in a 40-y/o man with hypertension (blood pressure 148/100). The first heart sound ("lub") is coincident with
    a. opening of the aortic valve
    b. the P wave on the ECG
    c. opening of the mitral valve
    d. closing of the tricuspid valve
    e. the T wave on the ECG

8. A left ventricular flow-volume loop is shown below:

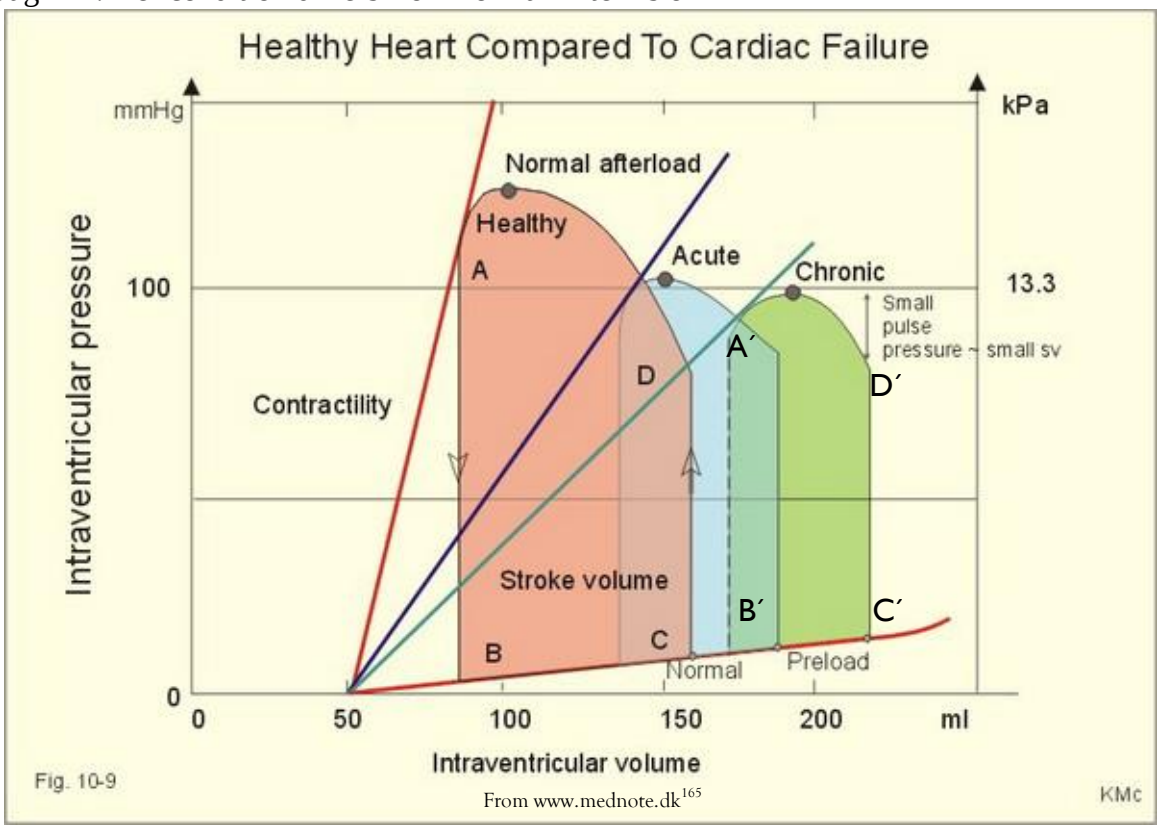


From www.crashingpatient.com[187]

At point D, there is
   a. aortic valve opening
   b. aortic valve closure
   c. pulmonary valve opening
   d. mitral valve closure
   e. mitral valve opening

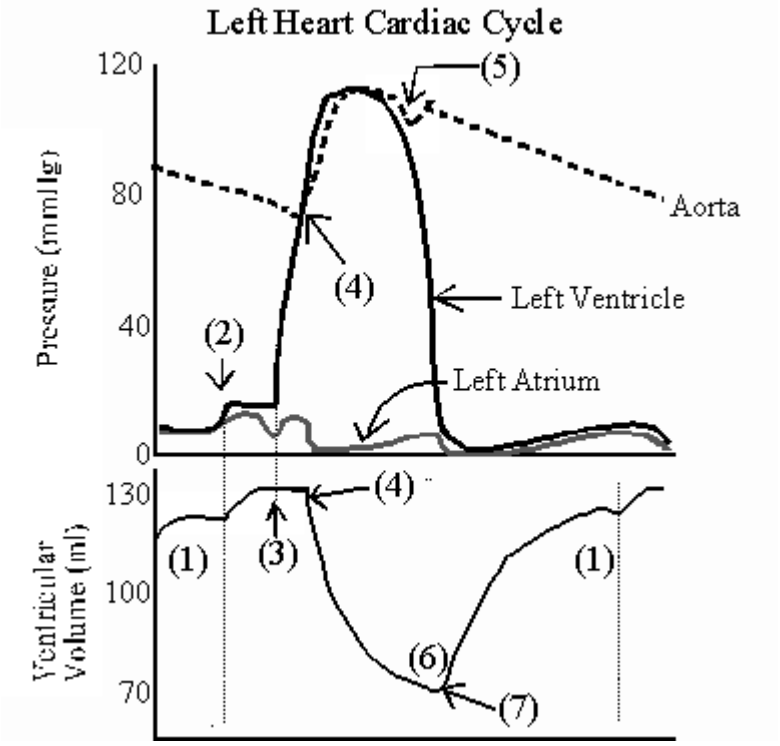
9. What cardiac event marks the beginning of isometric relaxation?
   a. aortic valve closure
   b. mitral valve opening
   c. mitral valve closure
   d. T wave
   e. rapid ventricular ejection

10. A 74-y/o woman with shortness of breath upon exertion and ankle swelling has heart function corresponding to the "chronic" condition shown below as it intersects points A´ through D´. Her condition differs from normal in terms of



a.↑ afterload
b.↑ ejection fraction
c.↑ stroke volume
d.↓ contractility
e.↓ preload

11. The cardiac cycle is shown below:



From http://webanatomy.net/anatomy/cardiac_cycle_quiz.htm[164]

The first heart sound ("lub") occurs at approximately point

a. 1
b. 2
c. 3
d. 4
e. 5

Cardiac Valvular Disease

Murmurs

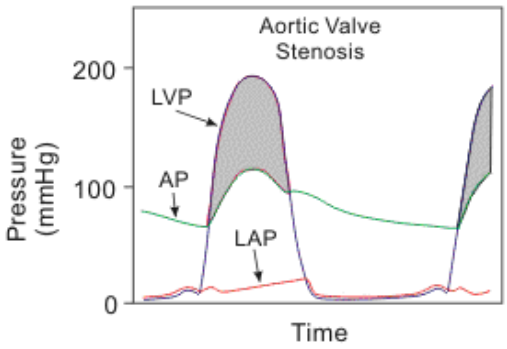
- Due to turbulent flow, at abnormal times in the cardiac cycle

Valvular stenosis

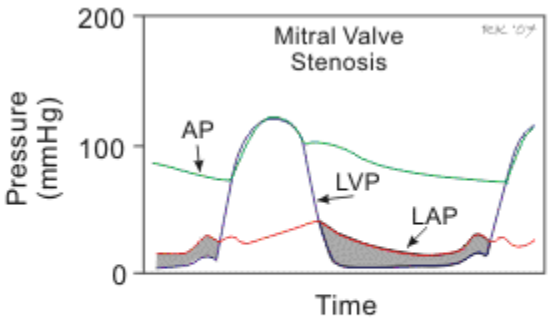
- Valve is unable to open fully, partially blocks outflow during systole
    - Creates turbulent flow and murmur during systole
    - Requires abnormally large pressure gradient between chambers separated by a stenotic valve
        - Increased pressure demand increases work for the cardiac chamber "pushing against" the stenosis

- Increased pressure demand may lead to hypertrophy of the involved chamber and eventual heart failure

Aortic stenosis and mitral stenosis:



During ventricular ejection, LVP exceeds AP (gray area, pressure gradient generated by stenosis). *Abbreviations:* LAP, left atrial pressure; LVP, left ventricular pressure; AP, aortic pressure.

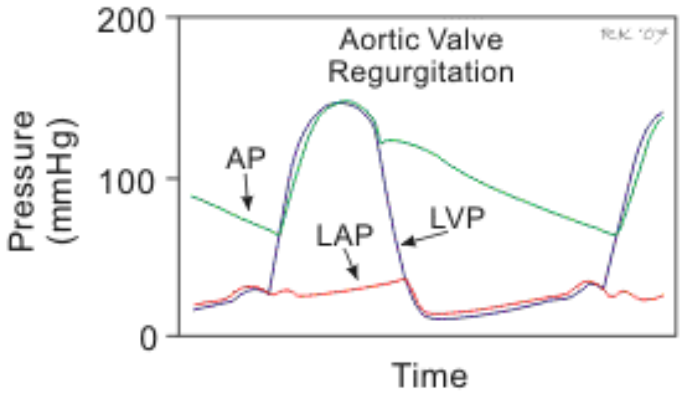


During ventricular filling (diastole), LAP exceeds LVP (gray area, pressure gradient generated by stenosis). *Abbreviations:* LAP, left atrial pressure; LVP, left ventricular pressure; AP, aortic pressure.

From http://www.cvphysiology.com/Heart%20Disease/HD004%20aortic%20stenosis.gif[68]

Valvular regurgitation ("insufficiency")

- Valve is unable to close fully when required to do so, allowing backflow
- Backflow reduces effective cardiac output
- For aortic regurgitation, backflow causes
  - Rapid two-way runoff from the aorta, resulting in low diastolic pressures
  - Rapid filling (inappropriately) of the ventricle, increasing preload, stroke volume, and systolic pressure
  - Very high pulse pressures
  - Ventricular and perhaps atrial dilation

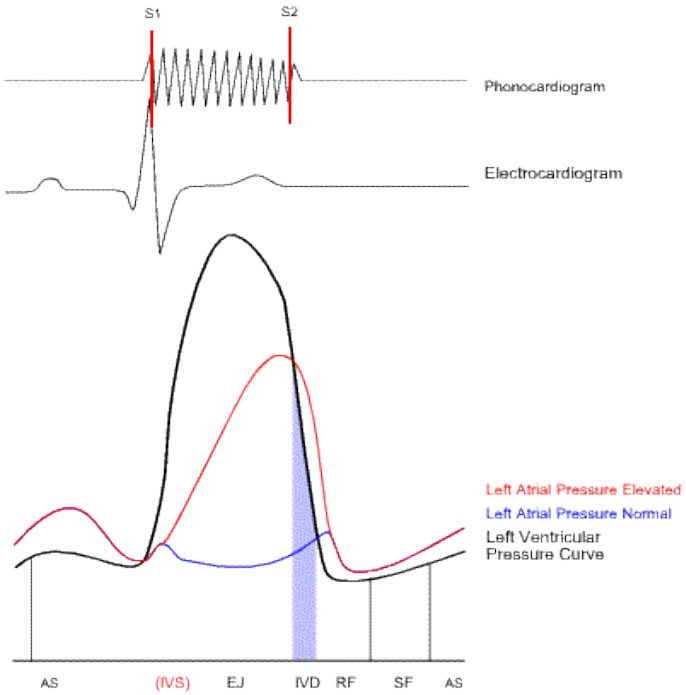


During ventricular relaxation, blood flows backwards from aorta into the ventricle. Aortic systolic pressure increases, aortic diastolic pressure decreases, and pulse pressure increases; LAP increase. *Abbreviations:* LAP, left atrial pressure; LVP, left ventricular pressure; AP, aortic pressure.

From http://www.cvphysiology.com/Heart%20Disease/HD005%20aortic%20regurgitation.gif[69]

Mitral regurgitation

- Backflow elevates atrial pressure during ventricular systole
- Reduced forward cardiac output
- Atria may eventually dilate, reducing the pressure reaching the pulmonary capillary bed
- Systolic murmur
- Pulmonary edema results from high pressure in pulmonary capillary bed
- Mitral prolapse is very common (3 – 5% of the population) and usually benign, but can progress to mitral regurgitation



From http://auscultation.com/Human/Heart/MitralRegurgitation/Images/MitralRegurgitation_pressure.gif[70]

Questions: Valvular stenoses:

Valve	**↑ Pressure gradient?—between which chambers or areas?**	**Is there a hypertrophied or dilated chamber? If so, which one?**	**Is there a murmur—and if so, when does it occur in the cardiac cycle?**
Aortic			
Mitral			
Pulmonic			
Tricuspid			

Questions: Valvular regurgitations:

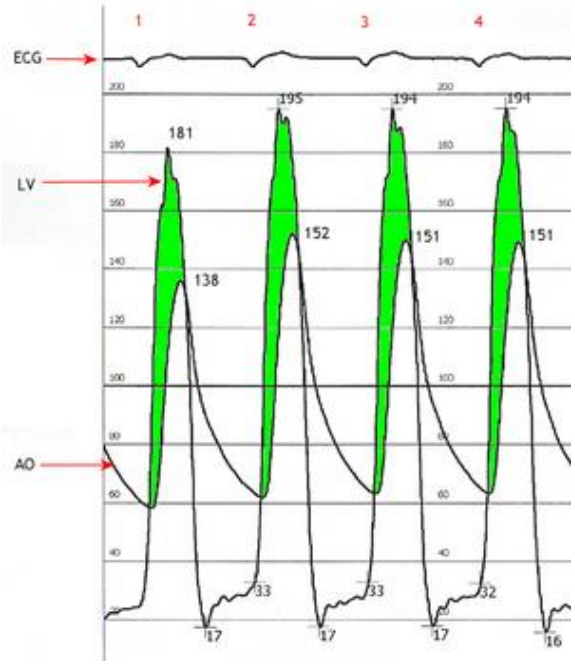
Valve	Is there ↑ pressure—and if so, where does it occur?	Is there a murmur—and if so, when does it occur?
Aortic		
Mitral		
Pulmonic		
Tricuspid		

Practice Questions:

1. A 38-y/o man has cough, evidence for lung congestion, P_{aO2} = 66 mmHg, P_{aCO2} = 40 mmHg, and systolic murmur. These signs and symptoms would be most directly caused by the uncompensated effects of
    a. ↓ aortic compliance
    b. pulmonic regurgitation
    c. excess angiotensin II receptor inhibition
    d. mitral regurgitation
    e. tricuspid regurgitation

2. The second heart sound ("dub") is heard at the
    a. approximate mid-point of reduced ventricular ejection
    b. beginning of isovolumetric relaxation
    c. peak of aortic pressure
    d. end of isovolumetric contraction
    e. opening of the mitral valve

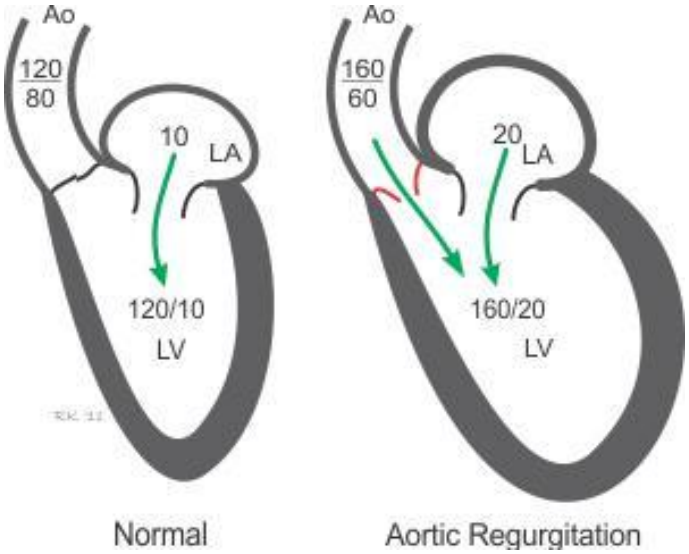
3. Based on the numbers shown in the pressure tracing from the left ventricle (LV) and aorta (AO), what are some predicted signs and symptoms?



From http://upload.wikimedia.org/wikipedia/commons/3/3e/Aortic_Stenosis_-_Hemodynamic_Pressure_Tracing.png[163]

a. ↑ ADH, ↑ renal H_2O retention
b. cardiac hypertrophy, inadequate coronary perfusion
c. ↑ systemic venous congestion, ankle edema
d. cyanosis and fatigue due to ischemic systemic tissues
e. pulmonary hypertension, right ventricular failure

4. A 51-y/o man has severe fatigue due to aortic regurgitation as shown below:

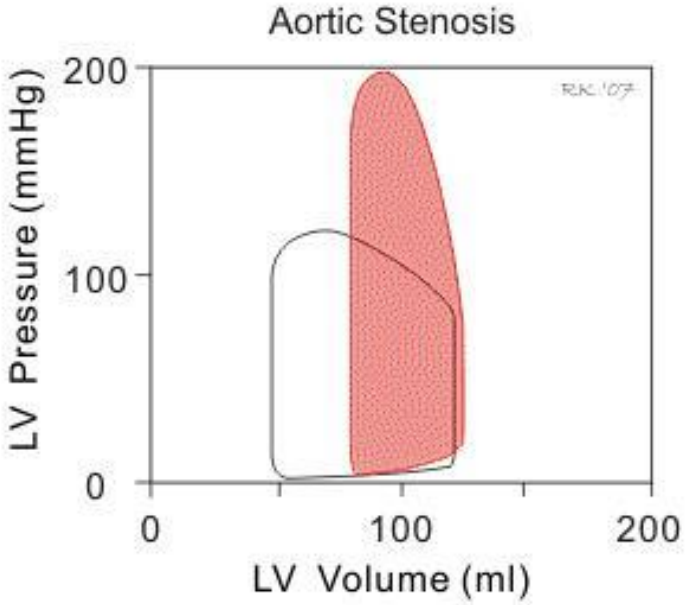


From http://www.cvphysiology.com/Heart%20Disease/HD005.htm[162]

As his disease progresses, he develops
   a. decreased aortic compliance
   b. more severe systolic murmur
   c. decreased LV end-diastolic pressure
   d. pulmonary edema
   e. systemic hypertension

5. A 37-y/o woman with active pulsing of the neck veins, reduced urine output, ankle edema, and fatigue has systolic murmur and increased right atrial pressure at S2. Peak right ventricular pressure is 22 mmHg; pulmonary artery pressure is 21/9. She has
   a. pulmonic stenosis
   b. pulmonic regurgitation
   c. tricuspid regurgitation
   d. right-to-left intracardiac shunt
   e. tricuspid stenosis

6. A 30-y/o man with shortness of breath, cough, fatigue, and episodic chest pain has blood pressure 115/75, heart rate 115 (**H**), and normal systemic arterial oxygenation. His left-ventricular pressure-volume curve is shown as the red shaded area in the figure. He also has (as compared with normal)



From http://www.cvphysiology.com/Heart%20Disease/HD009b.htm[161]

   a. decreased afterload
   b. increased preload
   c. increased ejection fraction
   d. decreased cardiac contractility
   e. systolic murmur

VI. Regulation of Arterial Blood Pressure

- Control system could send constant flow to every organ at all times

- Or it could generate a constant blood pressure to each organ, then let each organ decide how much blood it needs by adjusting local resistance which will then affect local blood flow

- Of course if every organ wants high flow at the same time, central pressure will fall and there will be significant problems

- But the cardiovascular system works via managing a central, regulated blood pressure, typically abbreviated as the "mean arterial pressure" (MAP)

- Hypertension—high MAP—presents long-term health risks but does not compromise organ blood flow or flow regulation in the short term

Recall Flow = ΔP / R

- Rearranged, this is, for the entire systemic circulation, CO × TSR = MAP, where CO is cardiac output, TSR is total systemic (peripheral) resistance, and MAP is mean arterial pressure

- Control systems for MAP must manipulate either CO or TSR (or both)

    - Since CO is the product of heart rate and stroke volume, either or both may be altered by reflexes that control blood pressure

    - Since TSR is set by arteriolar diameter, regulation of the constriction or dilation of the systemic arterioles is a major player in blood pressure regulation

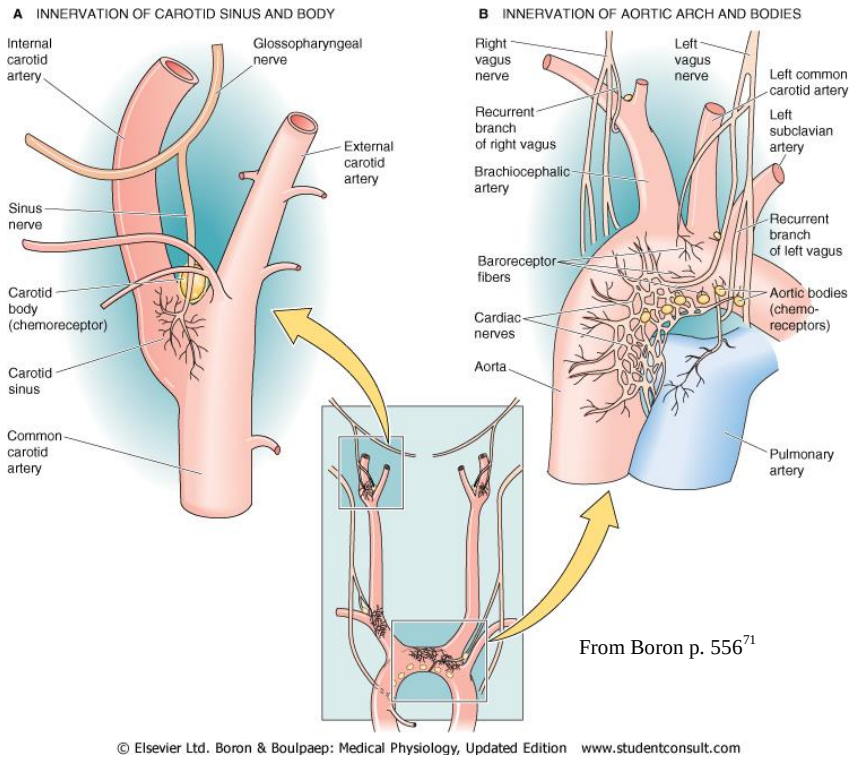
    - Since the autonomic nervous system directly affects heart rate, stroke volume (via cardiac contractility), and arteriolar resistance, rapid adjustments in blood pressure via neural mechanisms utilize the autonomic nervous system

Immediate, neural reflex control of blood pressure: the baroreceptor reflex ("baroreflex")

- Negative feedback system

- Responsible for minute-to-minute blood pressure regulation

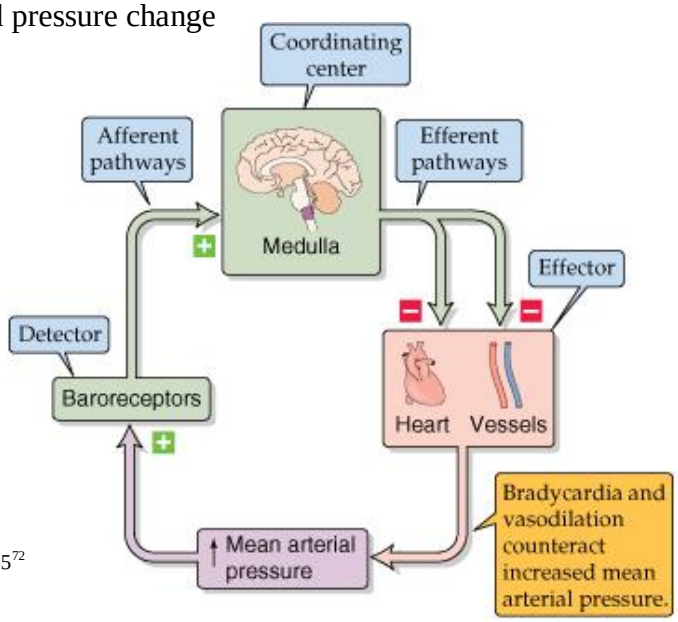
- Detector is stretch receptors in the wall of the carotid sinus (and aortic arch)



From Boron p. 556[71]

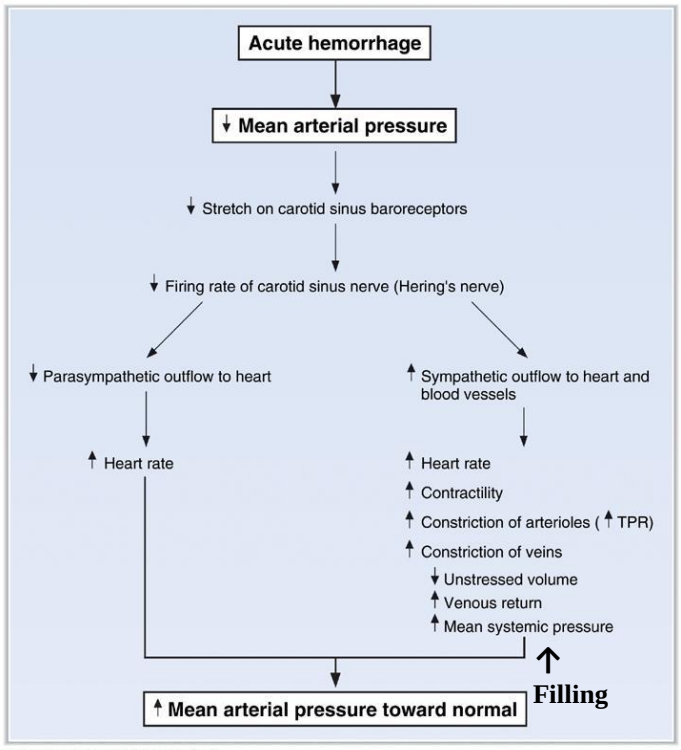
- Information goes via the carotid sinus nerve (cranial nerve (CN) IX) to the cardiovascular or "vasomotor" center in the brainstem (medulla)

- Cardiovascular center coordinates an appropriate autonomic response to counter the initial blood pressure change



From Boron p. 555[72]

- Baroreceptors happily adjust to slow changes in "set point" (normally ~100 mmHg): they do not cause and do not counter gradually developing hypertension

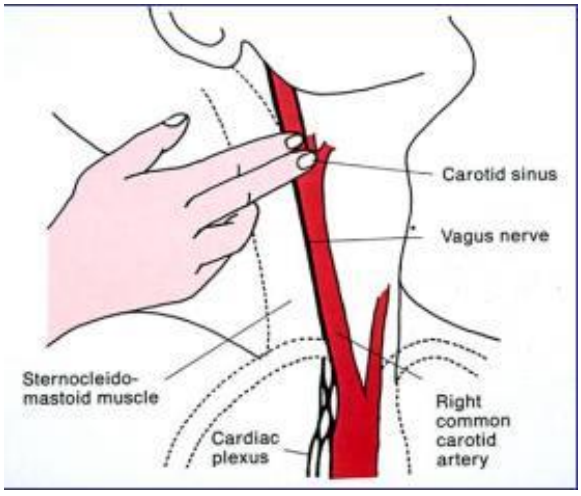


From Costanzo p. 91[73]

Questions: Understanding the autonomic reflex responses to a sudden blood pressure decrease

Autonomic Response	What is the effect on heart rate?	What is the effect on stroke volume?	What is the effect on total systemic resistance?
↑ Contractility			
↑ Constriction of arterioles			
↑ Constriction of veins			
↑ Mean circulatory filling pressure			
↑ Venous return			

Question: A cardiologist administers "carotid sinus massage" to correct a cardiac arrhythmia. She does this by putting external pressure on the baroreceptors at the bifurcation of the common carotid artery. What is happening that could suppress a cardiac arrhythmia?



From http://www.pohai.org.tw/ped/contents/D5/G/Arrhythmia/Treatment%20of%20arrhythmia.files/slide0063_image007.jpg[171]

Practice Questions

1. An 82-year old man suffers from carotid sinus hypersensitivity. Even mild physical stimulation of the carotid sinus results in cardioinhibitory actions including sinus bradycardia, atrioventricular block, or even asystole. This response can be abolished with
    a. acetylcholine
    b. alpha-1 adrenergic blocker
    c. M2 receptor blocker
    d. non-selective beta blocker
    e. selective beta-1 blocker

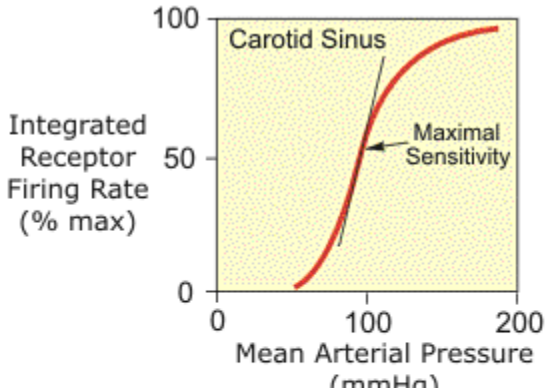
2. A 24-y/o graduate student stands up immediately after donating blood. His blood pressure falls to 88/50 (**L**), causing carotid sinus baroreceptor actions that
    a. increase cardiac M2 receptor stimulation
    b. decrease cardiac contractility
    c. increase mean systemic filling pressure
    d. decrease venous resistance
    e. decrease SA nodal I_f

3. A 74-y/o man suffers a stroke. During the ensuing week he has reduced carotid baroreceptor sensitivity, resulting in
    a. orthostatic hypotension
    b. systemic hypertension while supine
    c. systemic arteriolar dilation
    d. pulmonary arteriolar vasodilation
    e. increased pulse pressure

4. A 28-y/o man is kicked in the neck, stretching the carotid sinus and causing reflex
    a. ↑ RV contractility
    b. ↓ muscarinic cardiac tone
    c. arteriolar constriction
    d. cardiac β_1-stimulation
    e. venodilation

5. Carotid sinus massage will trigger
    a. ↑ muscarinic stimulation of ventricular contractility
    b. ↑ venoconstriction
    c. ↓ cardiac work
    d. ↓ P-R interval on the ECG
    e. ↓ R-R interval on the ECG

6. The carotid sinus baroreceptor reflex sensitivity of a healthy 20-y/o is shown below:



From http://cvphysiology.com/Blood%20Pressure/BP012.htm[160]

If hypertension develops in this person by age 50, the curve shown above will be
   a. displaced to a lower mean pressure
   b. flattened in slope around same mean pressure
   c. shifted to a higher mean pressure
   d. steepened in slope around same mean pressure
   e. unchanged

7. A 52-y/o man and his 20-y/o son have resting blood pressures 152/94 and 122/64, respectively. Both have heart rate 62 b/m and cardiac output 5.6 l/m. They differ primarily in
   a. Δ carotid sinus nerve activity per unit Δ blood pressure
   b. Δ MAP during sudden standing ("tilt tolerance"; "orthostatic hypotension")
   c. baroreceptor sensitivity
   d. baseline parasympathetic activity
   e. set point of baroreceptors

8. Compared with controls, patients with fibromyalgia often have syncope when they suddenly stand up (orthostatic hypotension). When a patient with fibromyalgia is suddenly tilted upright, which of the following changes might account for their orthostatic hypotension?
   a. ↑ cardiac vagal stimulation
   b. ↑ circulating epinephrine
   c. ↑ SV/EDV
   d. ↑ SA nodal [Na^+/K^+] current
   e. ↑ skeletal muscle sympathetic nerve activity

Slower, hormonal control of blood pressure: the renin-angiotensin system

- Regulates blood pressure by altering blood volume

    1. Blood plasma is in equilibrium with other fluids outside of cells (extracellular fluid [ECF])

    2. Any factor that alters ECF volume will alter plasma volume

    3. The kidney regulates the ECF volume by regulating excretion of Na^+ and H_2O

    4. Therefore, blood pressure can be regulated by altering how much Na^+ and H_2O is excreted (or "retained") by the kidney

    5. Kidney's responses are relatively slow (hours to days), unlike the baroreflex

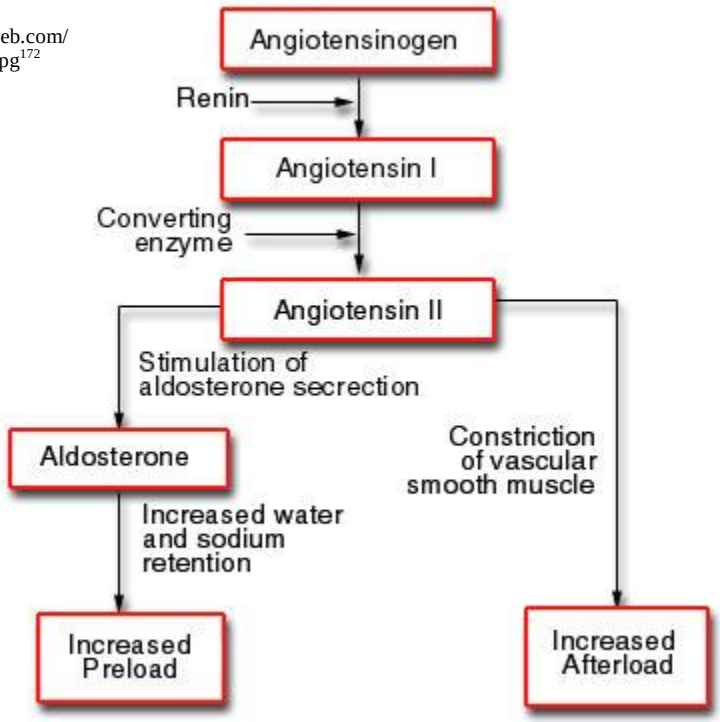
- Baseline activity of this reflex contributes to normal blood pressure; increased activity is implicated in hypertension

- Initiating step is a fall in the blood pressure detected by the kidney ("renal perfusion pressure")

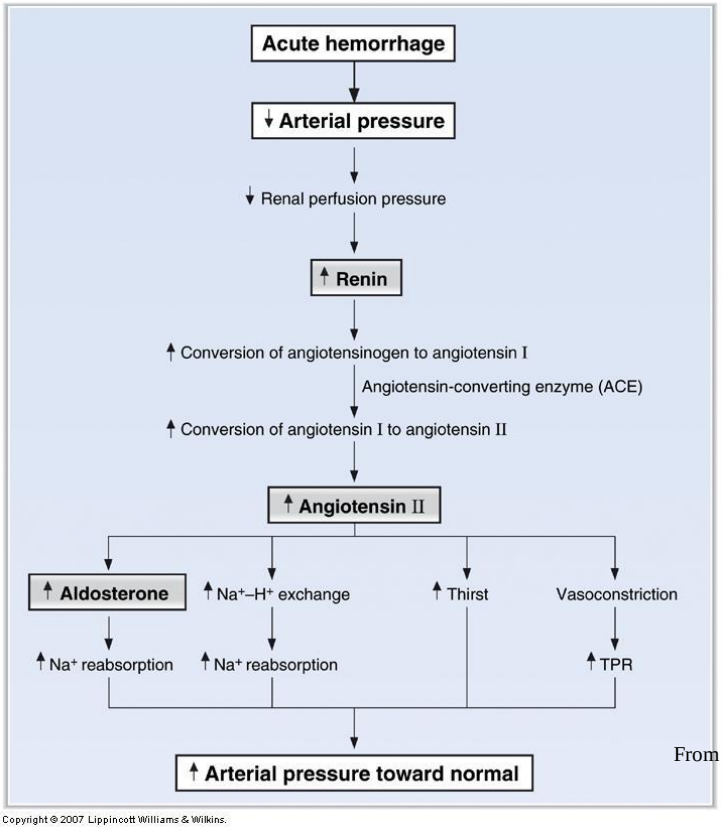
- Any change, or any defect, in renal perfusion pressure from factors inside or outside the organ (e.g., stenosis of a renal artery) will activate this reflex. Some of these can cause systemic hypertension

- Renin is an enzyme, released from specialized cells in the kidney

From http://www.gcrweb.com/HeartDSS/charts/fig4.jpg[172]

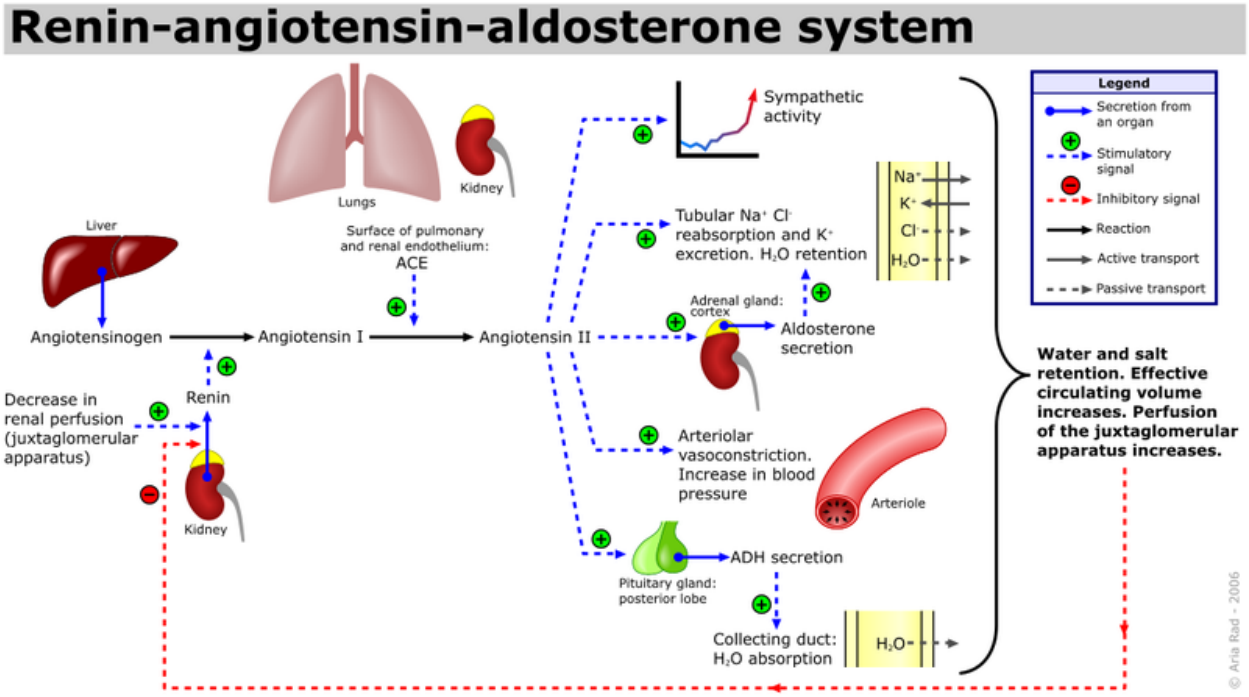


- Regulation of blood pressure by the renin-angiotensin system:

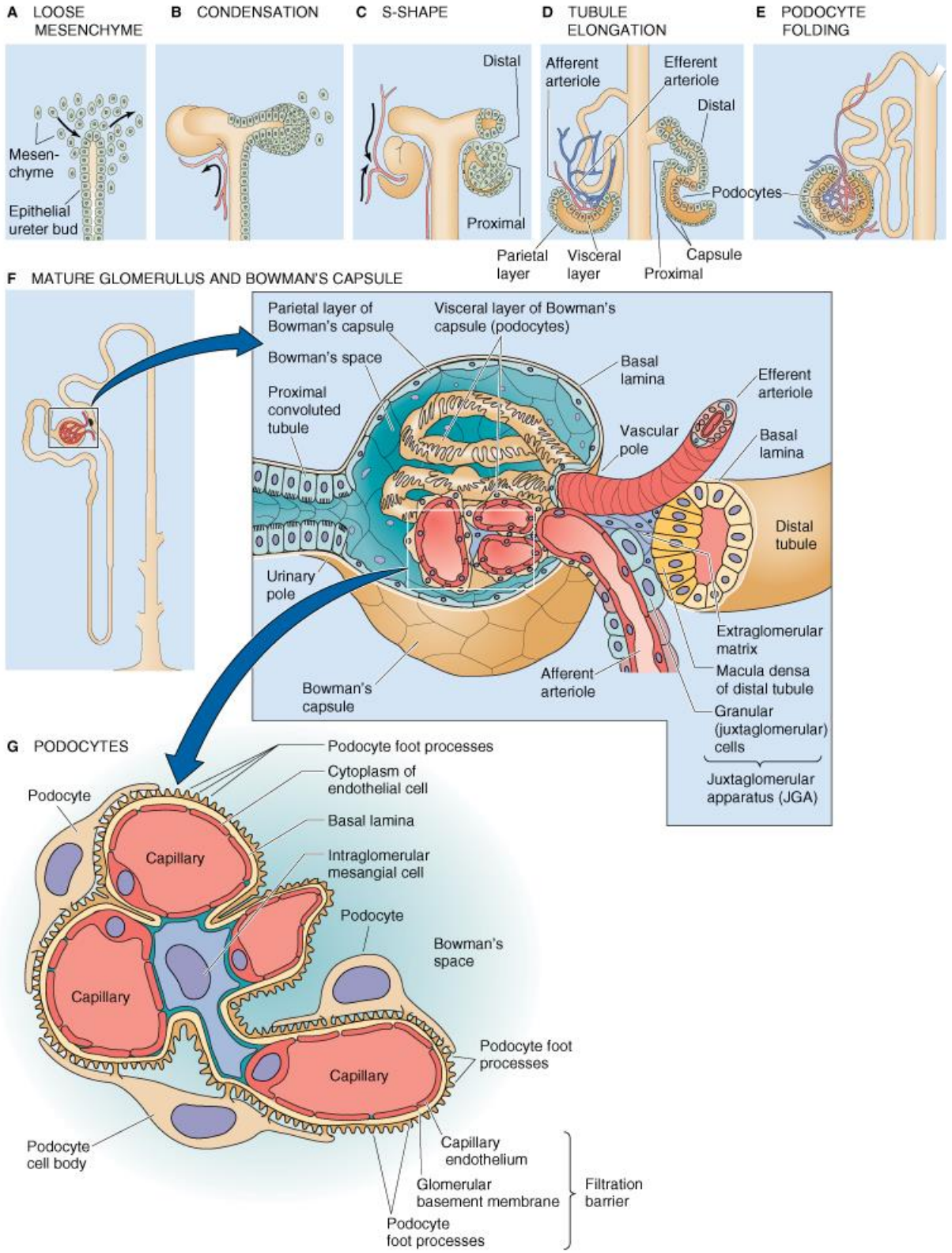


From Costanzo p. 93[74]

From https://upload.wikimedia.org/wikipedia/commons/thumb/a/a2/Renin-angiotensin-aldosterone_system.png/800px-Renin-angiotensin-aldosterone_system.png[173]



- The juxtaglomerular apparatus (JGA):



From Boron p. 1068[75]

- "↓ Effective circulating volume" includes two factors that can cause renin release from the juxtaglomerular apparatus (JGA)
    - Increased sympathetic outflow to the JGA
    - Decreased blood pressure, locally, at the JGA
- Renin converts angiotensinogen (inactive) to angiotensin I (inactive)
- Angiotensin converting enzyme (ACE) is present within lung capillary endothelial cells and converts angiotensin I (inactive) to angiotensin II (active)
- Angiotensin II has two major effects:
    1. Vasoconstriction of systemic arterioles
    2. Stimulation of aldosterone secretion from the adrenal
        - Aldosterone acts on the kidney to increase Na^+ retention (and, therefore, indirectly, H_2O retention).

Questions: Reducing the activity of the renin-angiotensin system for treatment of hypertension:

Intervention	**What is its effect on renin levels? (↑, ↓, =)**	**What is its effect on angiotensin I levels? (↑, ↓, =)**	**What is its effect on angiotensin II levels? (↑, ↓, =)**	**What is its effect on aldosterone levels? (↑, ↓, =)**

Review questions:

a) Draw graphically a combined curve of cardiac output and venous return

b) Then draw another curve corresponding to reduced cardiac contractility

c) What is the response of the renin-angiotensin system to the decline in cardiac contractility? Why?

d) Draw a line showing the effects of activation of the renin-angiotensin system on the combined cardiac output/venous return curves. In terms of the whole body, what is good and what is bad about this response?

Practice Questions

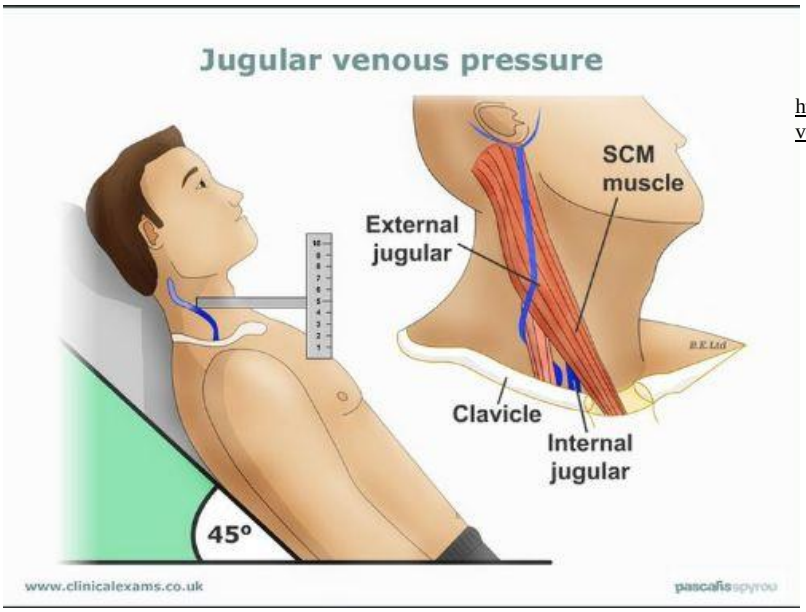
1. In 1799, William Withering recorded that use of the dried leaf of the digitalis plant would be effective for dropsy (edema) when "brisk diuresis of several quarts of urine often heralded the patient's recovery". This "brisk diuresis" arises from a drug-induced decline in
    a. ACE
    b. carotid baroreceptor stretch
    c. cerebral perfusion pressure
    d. renal perfusion pressure
    e. renin

2. We now know that in cardiac cells, digitalis
    a. ↑ Na^+/K^+ ATPase activity
    b. ↑ intracellular $[Ca^{2+}]$
    c. ↓ intracellular $[Na^+]$
    d. blocks muscarinic receptors
    e. stimulates β_1 adrenergic receptors

3. A 24-y/o woman with a history of multiple episodes of unexplained fainting is studied during sudden postural changes on a tilt-table. When the table abruptly shifts her posture from supine to upright, she has this *abnormal* baroreceptor reflex response to the tilt:
    a. ↓ cardiac vagal tone
    b. ↑ I_f
    c. ↑ heart rate
    d. systemic venodilation
    e. α_1 adrenergic stimulation

4. An asymptomatic 50-y/o man has blood pressure 158/114, increased plasma and ECF volume, normal plasma osmolarity, and normal or low levels of renin and angiotensin II. A potential cause of his condition is
    a. ACE overactivity in the pulmonary vascular endothelium
    b. excess adrenal aldosterone production
    c. generalized fall in systemic arteriolar resistance
    d. hyperfunction of the baroreceptor reflex
    e. obstruction of the renal artery

5. The pressure illustrated in the figure is increased in which of the following conditions?



From http://www.clinicalexams.co.uk/jugular-venous-pressure.asp[159]

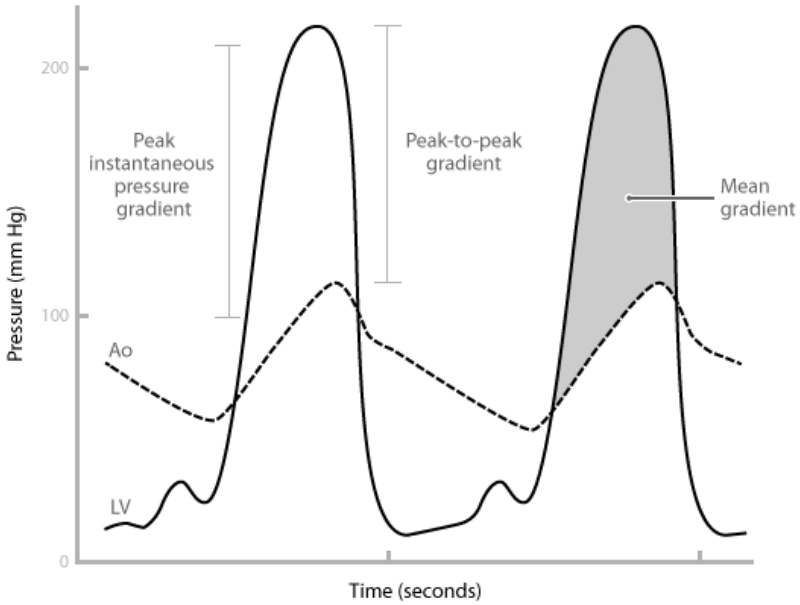
   a. hemorrhage
   b. hyperaldosteronism
   c. systemic arterial hypotension
   d. treatment with angiotensin II receptor antagonists
   e. upright posture

6. A 47-y/o woman with blood pressure 157/110 has plasma renin 11.6 ng/ml/hr (**H**) and angiotensin II 345 pg/ml (**H**). As a direct result of these, she has
   a. ↑ cardiac contractility
   b. ↑ cardiac I_f
   c. ↑ cardiac output
   d. ↑ systemic arteriolar resistance
   e. ↓ aldosterone

7. A 65-y/o man is given an angiotensin receptor blocking drug, lowering his blood pressure from 150/96 to 122/84. The drug also directly
   a. ↑ thirst
   b. ↑ aldosterone
   c. ↓ renal Na^+ excretion
   d. ↓ renin
   e. ↓ total peripheral resistance

8. A 77-y/o woman in congestive heart failure is treated with a β_1-adrenergic antagonist, which directly
    a. ↑ ACE activity
    b. ↑ cardiac I_f
    c. ↑ renal Na^+ and H_2O reabsorption
    d. ↓ aldosterone
    e. ↓ renin

9. A 51-y/o woman with shortness of breath on exertion, fatigue, and chest tightness has the following LV and aorta (Ao) pressures:



From http://pie.med.utoronto.ca/TEE/TEE_content/assets/applications/synopsis/cas/cas-fig8.png[158]

Compared with a healthy person, she has a (an)
    a. ↑ cardiac O_2 demand
    b. ↓ angiotensin II
    c. ↓ LV hypertrophy
    d. ↑ coronary vessel ΔP during diastole
    e. diastolic murmur

10. [From http://www.ncbi.nlm.nih.gov[157]] A 48-year-old man was hospitalized after a traffic accident, in shock with blood pressure 70/40 mmHg and complete occlusion of the right renal artery. Three days later his blood pressure rose to 260/156 mm Hg, with increased
    a. carotid sinus baroreceptor sensitivity
    b. cardiac contractility
    c. inhibition of angiotensin-converting enzyme
    d. renal Na^+ excretion
    e. systemic arteriolar constriction

Other factors in blood pressure regulation

- Cerebral ischemia
    - Chemoreceptors in or near the cardiovascular center respond to ↓ local pH
    - Cerebral ischemia—via either low MAP or increased intracranial pressure that locally compresses blood vessels—allows local CO_2 to accumulate and pH to fall
    - Chemoreceptor response is to stimulate the medullary cardiovascular center to increase sympathetic outflow to blood vessels and the heart
    - This central response is sometimes called the Cushing reflex or Cushing reaction
- Peripheral chemoreceptors
    - Specialized carotid body is near but very different function from the carotid sinus baroreceptor
    - Carotid body organ is a chemoreceptor; glomus cells within it have very high metabolic rate
    - Glomus cells of carotid body are responsive to locally ↓ P_{O2}, ↑ P_{CO2}, ↓ pH of arterial blood
    - Stimulation of carotid body by these "chemical" changes in arterial blood stimulates the medullary cardiovascular center to ↑ sympathetic outflow to heart and blood vessels
- Low-pressure baroreceptors (1): Direct effects and antidiuretic hormone (ADH)
    - Sensory endings in low-pressure central vessels (atria, primarily; also pulmonary vein and vena cava)
        - Respond to falling pressure within these vessels by triggering an *increase* in vasoconstrictor outflow to the kidney
            - Sensory information via vagus nerve (CN X) to medullary cardiovascular center → ↑ renal afferent arteriolar constriction
        - Renal vasoconstriction will in turn decrease glomerular filtration rate and the rate of fluid loss
        - Afferent fibers also project to the hypothalamus, to neurons that synthesize antidiuretic hormone [ADH; also called vasopressin or arginine vasopressin (AVP)]

        - ADH is transported down the axons of these hypothalamic neurons to the posterior pituitary where it enters the blood

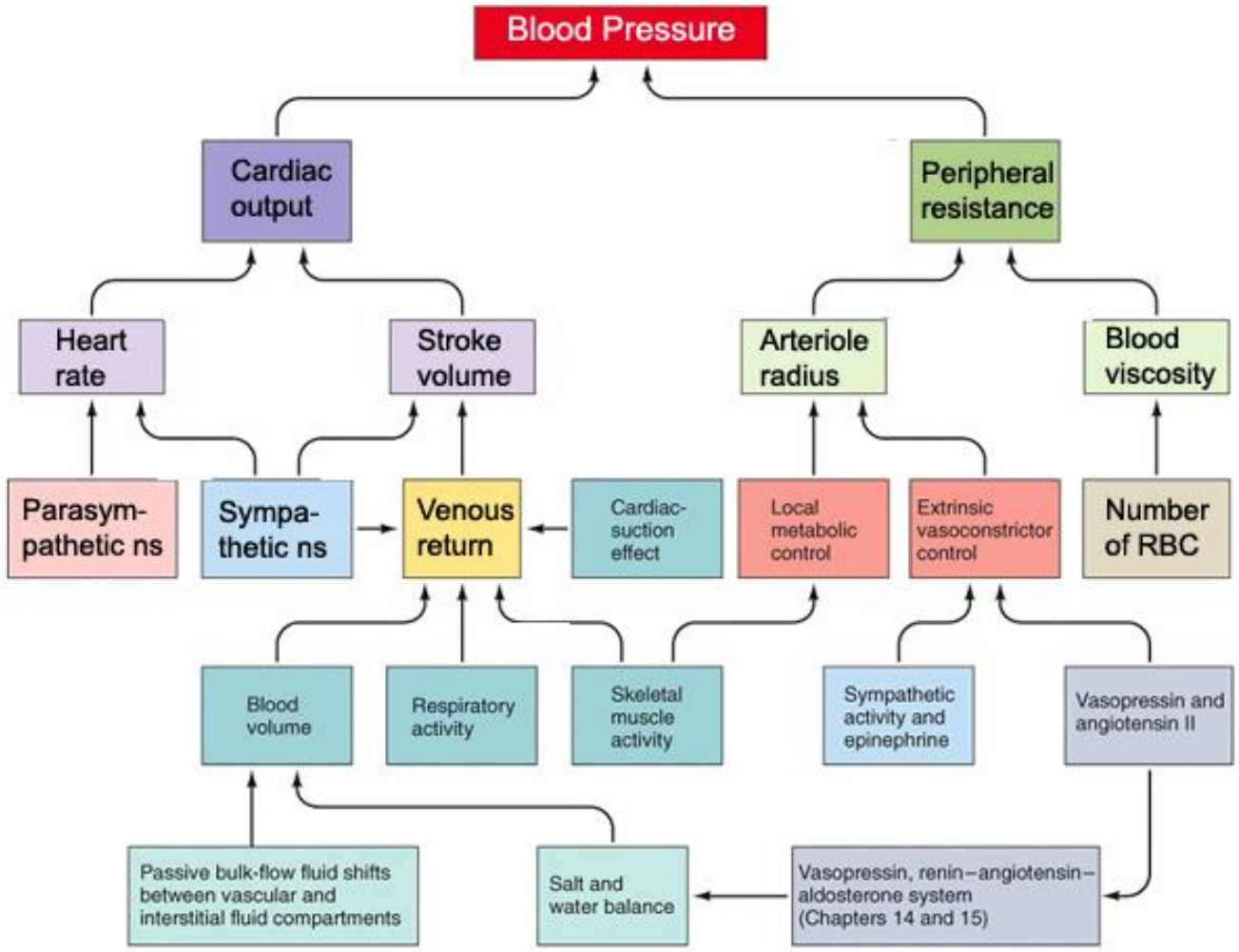
- Effects of ADH—released in response to falling "central venous pressure"—include
    - Vasoconstriction (V_1 receptors on systemic arterioles)
    - Water retention at the distal tubule and collecting ducts of the kidney, which increases blood volume (V_2 receptors)

- Low pressure baroreceptors (2): atrial natriuretic peptide (ANP) responds to ↑ pressure
    - Hormone released directly from atrial myocytes: stimulus is stretch
    - ANP is a hormone that reduces blood pressure: it relaxes systemic arterioles; increases renal Na^+ and H_2O excretion; inhibits renin secretion

Questions: Review of blood pressure control. Consider each portion of the response in isolation and without influence from other responses or reflex adjustments.

Question	Cardiac response	Renal response	Vascular response
What is the effect of ANP release from the atrial myocytes?			
What is the effect of stimulation of carotid body chemoreceptor stimulation by ↓ P_{O2}?			
What is the effect of AVP (ADH) release from the posterior pituitary?			
What is the effect of increased circulating angiotensin II?			
What is the effect of increased circulating aldosterone?			

A summary of blood pressure control:



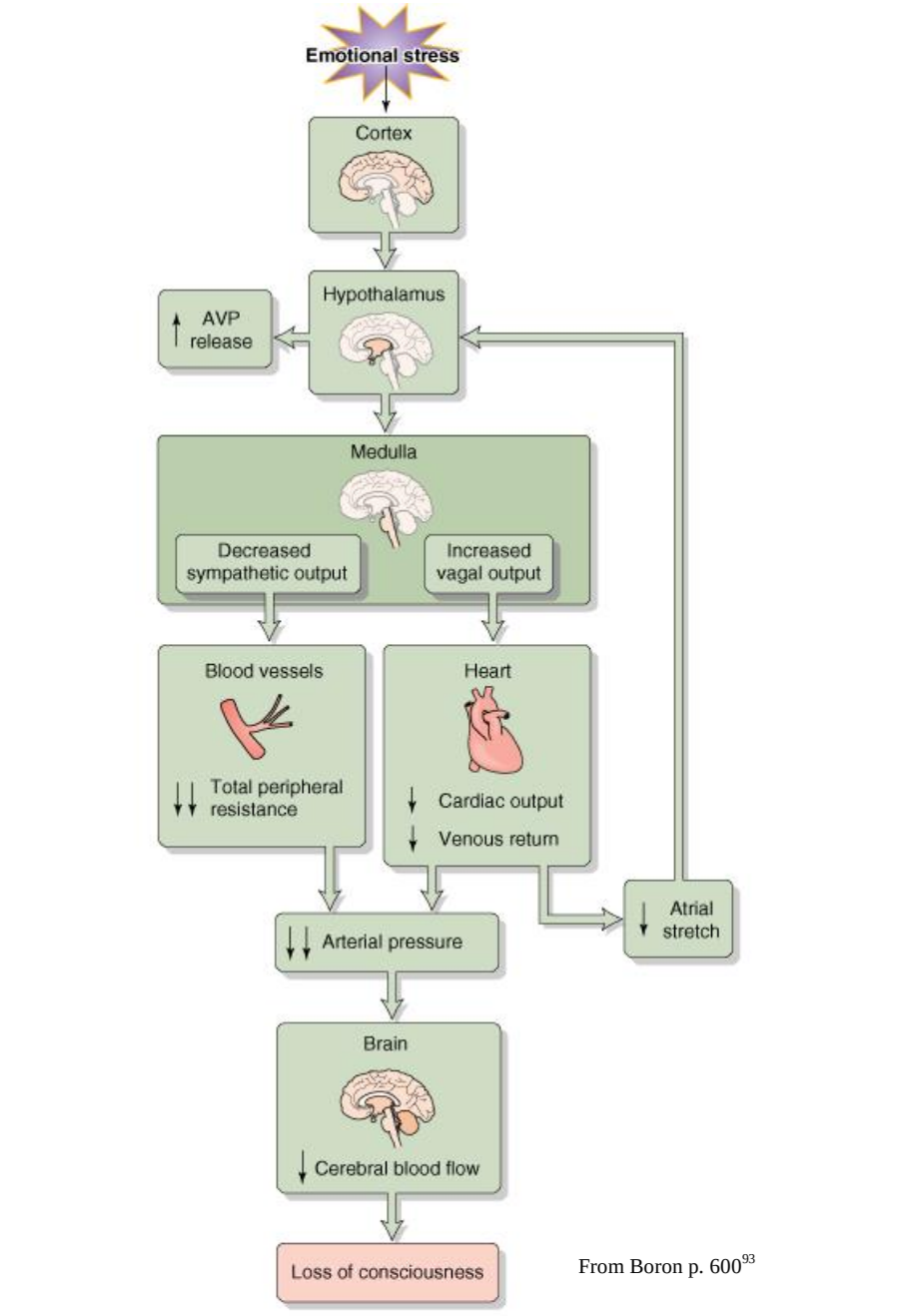
From www.colorado.edu/intphys/Class/IPHY3430-200/image/figure1034.jpg[92]

Question: Certain emotional stresses lead to a "pre-programmed" response from the vasomotor center, commonly known as vasovagal syncope, that includes

1. Extremely powerful vagal (parasympathetic) stimulation of the heart
2. Withdrawal of sympathetic outflow to the heart and blood vessels
3. Temporary suspension of baroreceptor influence upon the cardiovascular center in the brainstem

A. Describe the changes in heart rate, cardiac output, and blood pressure during the response

B. Explain why fainting is more common in persons who are upright, hypoglycemic, and dehydrated



From Boron p. 600[93]

Questions: Explain how the following treatments for hypertension exert their actions

Treatment	Heart Rate	Contractility	Blood Volume	TSR (TPR)
Diuretics				
Ca^{2+}-channel blockers				
ACE inhibitors				
Angiotensin II receptor antagonists				
β_1-blockers				
α_1-blockers				
Central anti-sympathetics				
Psychological stress reduction				
Stimulators of nitric oxide release				
ANP analogues (theoretical)				

Practice Questions:

1. For a resting, supine woman,
    a. ANP release is greater than when upright
    b. right atrial pressure is higher than ankle venous pressure
    c. stroke volume is lower than when upright
    d. the axial pressure gradient from aorta to ankle is negative
    e. total carotid artery pressure is lower than when upright

2. A 44-y/o woman with blood pressure 144/92 is given a drug that increases her renal excretion of Na^+ and H_2O, but has no direct effect on angiotensin II blood levels or actions. The drug is a (an)
    a. ACE inhibitor
    b. aldosterone receptor antagonist
    c. angiotensin receptor blocker
    d. ADH receptor agonist (V_1 and V_2)
    e. ANP receptor antagonist

3. The direct effects of treating a 33-y/o woman with hypertension result in the following:

	Before treatment	After treatment
Blood pressure (mmHg)	150/104	114/76
Heart rate (b/min)	68	68
Stroke volume (mL/beat)	80	80
Ejection fraction (%)	54	54
Angiotensin II (pg/mL)	42	42
ADH (pg/mL)	2.2	2.2

    She is being treated with a (an)
    a. Ca^{2+}-channel blocker
    b. central antisympathetic agent
    c. diuretic
    d. α_1 antagonist
    e. β_1 blocker

4. An obese 43-y/o man has blood pressure 116/76. When sleeping, he experiences repeated episodes of airway closure (sleep apnea) that lead to sudden arousals and restoration of normal breathing. After a typical apneic episode, his arterial P_{O2} is 62 (**L**), P_{CO2} is 51 (**H**), and blood pressure is 188/124 (**H**). His nocturnal hypertension could be most directly treated with
    a. ANP receptor antagonists
    b. abolishing feedback from atrial low pressure baroreceptors
    c. denervation of the carotid sinus baroreceptor
    d. inactivation of the carotid body
    e. V1 receptor antagonists

5. A 38-year old woman with high-renin systemic hypertension (166/116) is treated with medication X that lowers her blood pressure to 118/82. Before and 6-months after treatment measurements are made (**H** indicates above normal, **L** below normal):

	Before Treatment	6-Months after Treatment
Cardiac output (L/min)	6.3	5.6
Stroke volume (mL/beat)	90	80
Heart rate (b/min)	70	70
Angiotensin II (pg/mL)	96 **H**	4 **L**
Renin (ng/mL/hr)	4.8 **H**	7.7 **H**

   Medication X is a (an)
   a. ACE inhibitor
   b. angiotensin II receptor blocker
   c. central antisympathetic drug
   d. diuretic
   e. β_1-antagonist

6. How does vasovagal syncope affect cerebral vascular resistance?
   a. decrease
   b. increase
   c. initial decrease, followed by substantial increase
   d. initial increase, followed by substantial decrease
   e. no effect

7. A 16-y/o girl takes a rest after a busy day. Which of the following will increase when she moves from the upright to the supine posture?
   a. antidiuretic hormone (ADH)
   b. atrial natriuretic peptide (ANP)
   c. renal vasoconstriction
   d. V1 receptor stimulation
   e. V2 receptor stimulation

8. A 50-y/o woman is undergoing cerebral endoscopy for removal of a brain tumor. During fluid irrigation of the site, there is a sudden rise in intracranial pressure, resulting in ischemia of the medullary cardiovascular center and
   a. increased atrial natriuretic peptide (ANP)
   b. hyperventilation
   c. reflex cardiac parasympathetic stimulation
   d. increased right atrial pressure
   e. systemic arteriolar vasoconstriction

9. After exercise-induced heat exhaustion, a 30-y/o man is hospitalized and accidentally given excessive intravenous isotonic fluid, resulting in
    a. ↑ ADH
    b. ↑ cardiac contractility
    c. ↑ heart rate
    d. ↓ mean systemic filling pressure
    e. ↓ plasma renin

10. A 33-y/o woman with cough, shortness of breath, and systolic murmur has left atrial pressure 13 mm Hg (**H**), which has directly resulted in
    a. ↑ V_1 receptor stimulation
    b. ↑ ANP
    c. ↓ renal H_2O excretion
    d. ↑ renin
    e. ↑ ADH

11. A 54-y/o woman has shortness of breath, chest discomfort, atrial fibrillation, heart rate 120 (**H**) and arterial blood pressure 240/120. Renin is 26 ng/L (**H**), aldosterone 218 mg/L (**H**), and there is also elevated
    a. ACE
    b. ADH
    c. ANP and renal fluid loss
    d. cardiac contractility
    e. total systemic resistance

12. A 41-y/o woman is given antihypertensive drug X. Her lab results are as follows:

	Baseline	w/Drug X
Blood pressure	158/98	120/80
Heart rate	82	68
Ejection fraction	53%	41%
Systemic resistance (arbitrary units)	7.5	6.4
Supine plasma renin	2.3	1.8

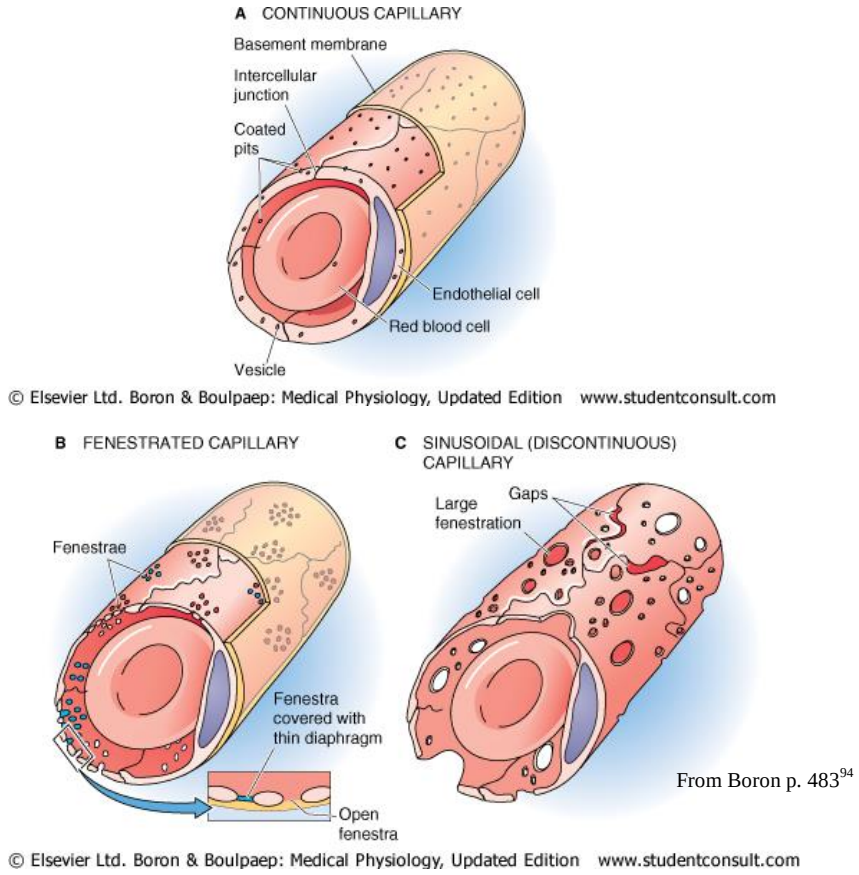
    These changes could all be direct effects of a (an)
    a. ACE inhibitor
    b. central antisympathetic
    c. V_1 and V_2 antagonist
    d. α_1-blocker
    e. β_1-blocker

VII. Microcirculation and lymph

Text: Costanzo pp. 94 – 97

Exchange of nutrients occurs at the capillary level

- Entry of blood into capillary beds is regulated at arterioles and precapillary sphincters
- Capillaries have only endothelial cells in their walls, and readily permit diffusion of O_2 and CO_2
- Small hydrophilic substances (e.g., glucose, amino acids; anything smaller than plasma proteins) can move by *diffusion* through intercellular clefts and fenestrations between endothelial cells



From Boron p. 483[94]

- Brain: tightest junctions; liver and intestine: loosest junctions ("sinusoids") permit protein movement

Water movement across capillary walls

- While small solute movement is via diffusion, water moves both transcellularly (through aquaporins) and paracellularly (through intercellular clefts and fenestrations)

- Water flow is therefore faster than by diffusion: movement is by *convection*
    - *Solvent drag* is the flux of solute along swept along in the bulk movement of the solvent
- The forces that determine fluid movement between capillary and interstitial space:
    - Hydrostatic pressure (blood pressure in capillaries; fluid pressure in interstitial space)
    - Oncotic pressure (osmotic forces due to protein concentration differences, in plasma and interstitial fluid)

Plasma Osmolarity	**Osmotic pressure**
Total osmolarity = 280 mOsmol/L	*1 mOsmol exerts ≈ 20 mm Hg osmotic pressure*
Na^+ 140 K^+ 4 Cl^- 105 HCO_3^- 25 Pr^- ≈1 Glucose 5 280	Total osmotic pressure of plasma = 20 × 280 = 5600 mm Hg All osmotically active particles are the same in plasma and interstitial fluid except for plasma proteins, which have a concentration of about 1.2 mOsmoles/L Proteins exert about 1.2 × 20 = 24 mm Hg Osmotic (or oncotic) pressure

---

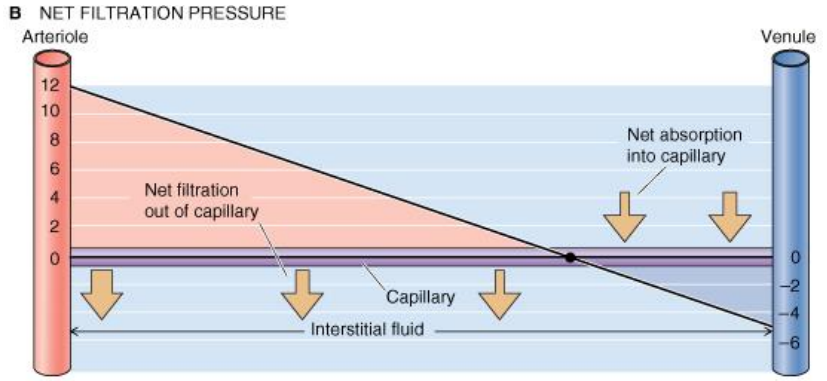
- The "Starling" equation:

$$\text{Fluid movement} = K_f [(P_c - P_i) - (\pi_c - \pi_i)]$$

where K_f = hydraulic conductance

P is hydrostatic pressure in capillary (P_c) and interstitium (P_i)
π is oncotic pressure in capillary (π_c) and interstitium (π_i)

- Net fluid movement out of capillaries is called "filtration"; movement in is called "absorption"
    - For an average capillary, there is filtration at the arterial end, and absorption at the venular end:



From Boron p. 494[95]

- P_i and π_i are normally close to zero
- P_c is can be elevated in a tissue if a) venous pressure leaving that tissue is elevated, b) arterioles and precapillary sphincters leading to the tissue relax (vasodilation), or c) gravity ↑ pressure in areas below the heart
- A normal slight net filtration [filtration > absorption] is returned to the circulation via the lymphatics (unidirectional; carry protein and fluid)

- Net bulk flow of water and solute into the interstitial fluid is called *edema*
  - Edema causes oxygen diffusion problems when it occurs in the lung, because diffusion distance is increased; edema *per se* is largely inconsequential—a sign rather than a symptom—when it occurs in other tissues

Questions: Factors affecting filtration and/or absorption in capillaries (Hint: the liver makes plasma proteins, requires adequate dietary protein to carry out this task)

Condition	**How are P_c or P_i altered from normal?**	**How are π_c or π_i altered from normal?**	**What change in net filtration or net absorption occurs?**	**Result**
Prolonged standing				
Protein-calorie malnutrition				
Mitral regurgitation				

Condition	How are P_c or P_i altered from normal?	How are π_c or π_i altered from normal?	What change in net filtration or net absorption occurs?	Result
Right heart failure due to lung disease				
Excessive plasma protein loss via kidneys				
Post-hemorrhage				
Liver failure				

Practice Questions

1. Which of the following conditions would be *least* likely to result in pulmonary edema?
    a. hemorrhage
    b. LV failure
    c. mitral regurgitation
    d. mitral stenosis
    e. protein-calorie malnutrition

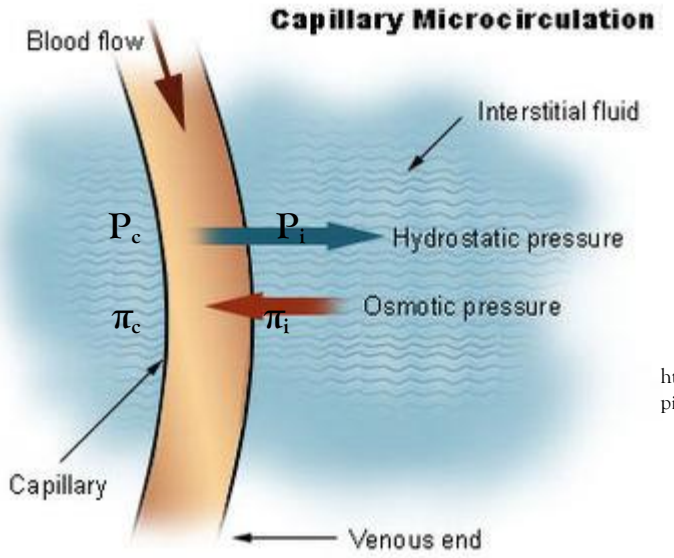
2. A 60-y/o man with poor appetite and unintentional weight gain has proteinuria (4.7 g protein in urine/day) and hypoalbuminemia, which result in
    a. edema
    b. hypotension
    c. hypoventilation
    d. polycythemia
    e. tachycardia

3. For a 57-y/o man with alcoholism, peritoneal edema (ascites) has developed, in response to an increase in portal vascular resistance in the liver. In the splenic and mesenteric capillaries, the rise in hepatic portal vascular resistance has
    a. $\uparrow P_c$
    b. $\uparrow P_i$
    c. $\uparrow \pi_c$
    d. $\uparrow \pi_i$
    e. $\downarrow P_i$

4. [Adapted from http://www.im.org/toolbox/curriculum/[156]]

    A middle-aged man who looks older than his stated age is in acute distress. He cannot answer any questions because of his extreme shortness of breath. He is restless and prefers to sit up in bed. BP is 90/70, pulse 120 (**H**), O_2 saturation 83% (**L**). Jugular venous pressure is elevated at 12 mmHg and left atrial pressure is 14 (**H**). His shortness of breath is due to
    a. pulmonary edema
    b. renal protein loss
    c. right heart hypertrophy
    d. severe ECF volume contraction
    e. tricuspid valve regurgitation

5. In the figure below showing a portal capillary, what abnormal value explains why peritoneal edema ("ascites") develops in persons with portal hypertension?



From http://commons.wikimedia.org/wiki/File:Capillary_microcirculation.svg[155]

    a. decreased P_i
    b. decreased π_i
    c. increased P_c
    d. increased π_c
    e. increased π_i

6. Right heart failure will most directly cause, at either the arterial or venous end of the systemic capillaries, increased
    a. capillary colloid osmotic pressure at the arterial end
    b. capillary colloid osmotic pressure at the venous end
    c. capillary hydrostatic pressure at the arterial end
    d. interstitial colloid osmotic pressure at the venous end
    e. capillary hydrostatic pressure at the venous end

7. A 17-y/o man loses 2.2 units (1.0 liters) of blood after a motorcycle accident. In response, there will be a rapid increase in
    a. brain blood flow
    b. capillary absorption
    c. hematocrit
    d. capillary oncotic pressure
    e. skin blood flow

VIII. Special Circulations

Text: Costanzo pp. 97 – 100

- Recall that local arteriolar resistance determines individual organ blood flow as "perfusion pressure" (MAP) is similar throughout the systemic circulation

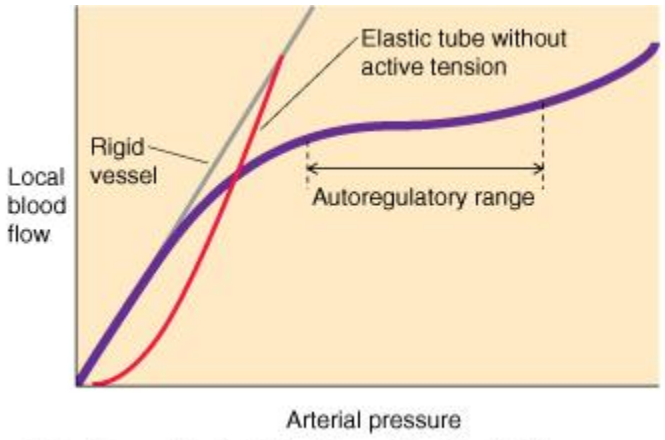
- Blood flow = $\Delta P/R$; or, Blood flow = MAP/R, for each organ or tissue

What regulates local flow?

- Many organs maintain constant flow despite fairly large fluctuations in MAP

- Constant flow despite MAP variations means that R in the organ adjusts with MAP

- The process, called autoregulation, is local, autonomous (does not require neural or endocrine mechanisms), and not immediate



From Boron p. 502[96]

- Two factors account for autoregulation
    - "Myogenic": stretch of vascular smooth muscle triggers reflex contraction
    - "Metabolic": increased blood flow during a period of increased MAP washes out vasodilator metabolites
        - Vasodilator metabolites act directly from interstitial fluid on neighboring vascular smooth muscle cells
        - There are numerous vasodilator metabolites, including at least the following:

Table 20-8. LOCAL METABOLIC CHANGES THAT CAUSE VASODILATION IN THE SYSTEMIC CIRCULATION

CHANGE	MECHANISM*
↓ PO_2	↓ $[ATP]_i$, ↑ adenosine release, ↑ PGI_2 release, ↑ NO release
↑ PCO_2	↓ pH_o
↓ pH	↓ pH_o
↑ $[K^+]_o$	Transient hyperpolarization → closes voltage-gated Ca^{2+} channels
↑ $[lactic\ acid]_o$	Probably ↓ pH_o
↓ $[ATP]_i$	Opens K_{ATP} channels
↑ $[ATP]_o$	Activates purinergic receptors P_2
↑ $[ADP]_o$	Activates purinergic receptors P_2
↑ $[Adenosine]_o$	Activates purinergic receptors P_1

* The subscript *i* refers to intracellular levels, and the subscript *o* refers to interstitial levels.

From ©Elsevier Ltd. Boron & Boulpaep: Medical Physiology, Updated Edition www.studentconsult.com, p. 501[97]

- In the pulmonary circulation, the effects of P_{O2}, P_{CO2}, and pH on arteriolar diameter are the reverse of what is seen in the systemic circulation.

- Metabolic regulation probably accounts for both active and reactive hyperemia

There are many other vasoactive compounds, of unknown overall importance for control of the circulation

- Tend to be involved in long-term, not short-term regulation
- May only have local importance
- These compounds can be amines, peptides, or proteins; derivatives of arachidonic acid, or even gases (NO). *Italicized* names below are produced by the endothelial cell:

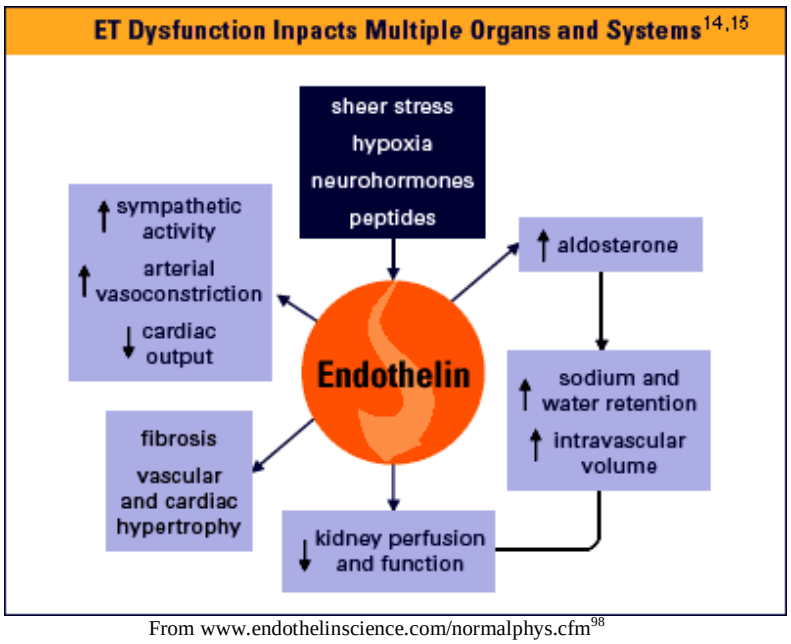
Table 23-3. VASOACTIVE COMPOUNDS

VASOCONSTRICTORS	VASODILATORS
Epinephrine (through α_1 receptors)	Epinephrine (through β_2 receptors)
Serotonin	Histamine
Angiotensin II	ANP
Antidiuretic hormone (ADH)	Bradykinins
Endothelin	*PGI_2 (Prostacyclin)*
	Nitric oxide (NO)

ANG II, angiotensin II; ANP, atrial natriuretic peptide; AVP, arginine vasopressin; NO, nitric oxide; PGE_2, prostaglandin E_2.

From ©Elsevier Ltd. Boron & Boulpaep: Medical Physiology, Updated Edition www.studentconsult.com, p. 501[97]

- Balance of vasodilator and vasoconstrictor compounds allows normal microvascular function: e.g., excess endothelin causes pathological changes:



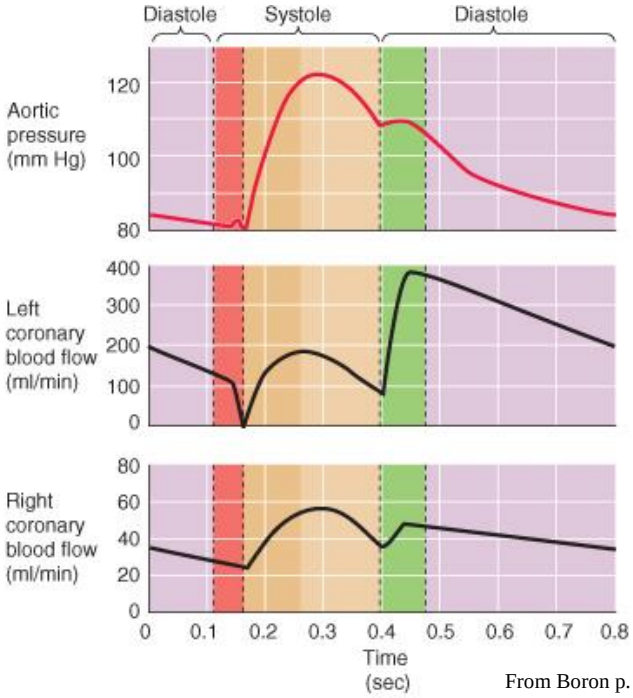
From www.endothelinscience.com/normalphys.cfm[98]

Coronary blood flow

- Autonomic nerves have relatively little influence on the coronary vasculature
- Local factors, linked to metabolic activity, are the primary regulators of the coronary circulation. Major local regulatory factors are ↓ P_{O2} (hypoxia) and adenosine
- If cardiac workload is maintained constant, coronary circulation will exhibit autoregulation. Active hyperemia will occur when workload is increased.

Question: Coronary blood flow and myocardial O_2 demand and utilization are linearly related over the entire range. What does this relationship suggest regarding myocardial oxygen extraction at rest and during increased energy demand?

- Nitric oxide and prostaglandins are critical for ↑ coronary vasodilator capacity in exercise training
- Pressure changes during the cardiac cycle affect coronary flow



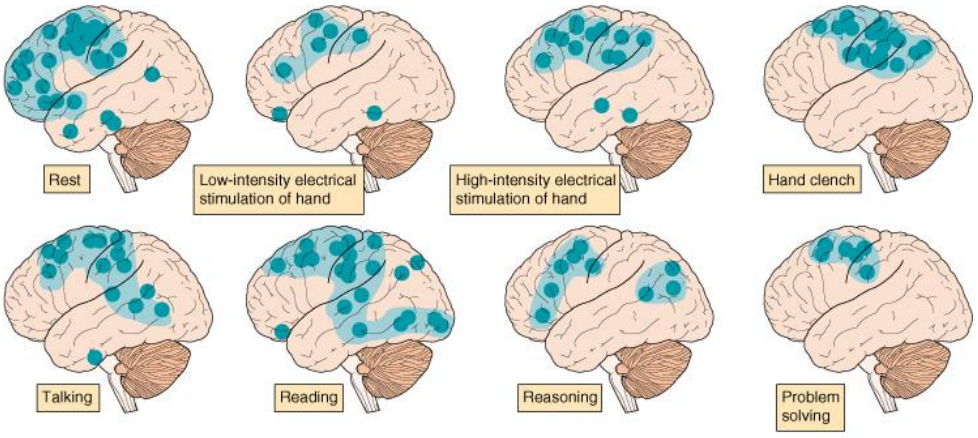
From Boron p. 582[99]

Questions: Coronary artery blood flow**:**

Question	Answer
List the major factors that influence *myocardial oxygen demand* and *myocardial oxygen supply*.	
Explain why persons with aortic stenosis have such inadequate coronary arterial perfusion.	
Why is an exercise test ("stress test")—as opposed to just testing at rest—often used to determine the presence of coronary ischemia?	

Cerebral circulation

- The brain receives constant total blood flow, because total brain metabolic rate is always about the same despite regional variations with different brain activities



From Boron p. 579[100]

- The brain maintains constant blood flow (autoregulates) over a mean arterial pressure range from ~60 to ~180 mmHg. Outside of that range, brain blood flow is a linear function of arterial pressure

- Autonomic control of vessels is fairly weak

- ↑ P_{CO2} vasodilates the brain, but P_{CO2} normally is fairly constant and is not important for blood pressure autoregulation of brain blood flow

- Local blood-borne vasoactive substances usually cannot cross the blood-brain barrier

Questions: The cerebral circulation is little influenced by the autonomic nervous system. As one example, consider donation of a unit of blood while supine. After quickly standing up,

1. How is blood pressure changed compared to the pre-donation baseline, and why?

2. What is the baroreflex response to this blood pressure change?

3. What changes in cerebral blood flow would occur if cerebral arterioles were under control of this baroreflex response to decreased mean arterial pressure?

4. What is the actual cerebrovascular—and cerebral blood flow—response to this blood pressure change?

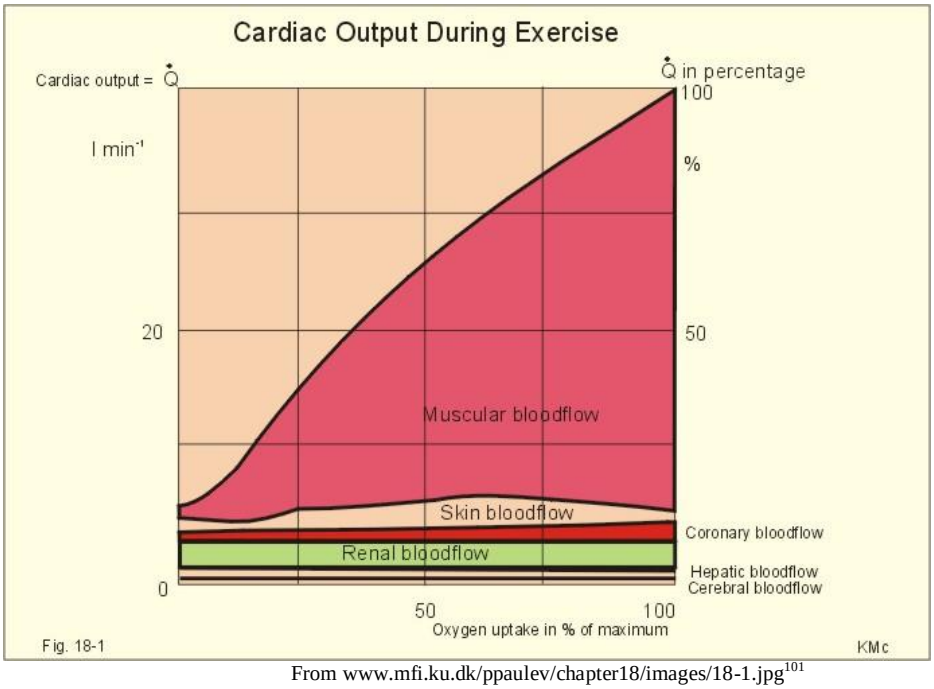
Skeletal muscle circulation

- Major component of total systemic resistance due to large mass

- Sympathetic innervation: α_1-adrenergic (constrictor), β_2 (dilator)

    - α_1-adrenergic (constrictor) is dominant physiologically, but β_2 (dilator) can be dominant if selective β_2 agonist drugs are used

- Increased skeletal muscle activity causes vasodilation: influence of local metabolites (K^+, low P_{O2}, adenosine, lactate, etc.) dominate neural influences



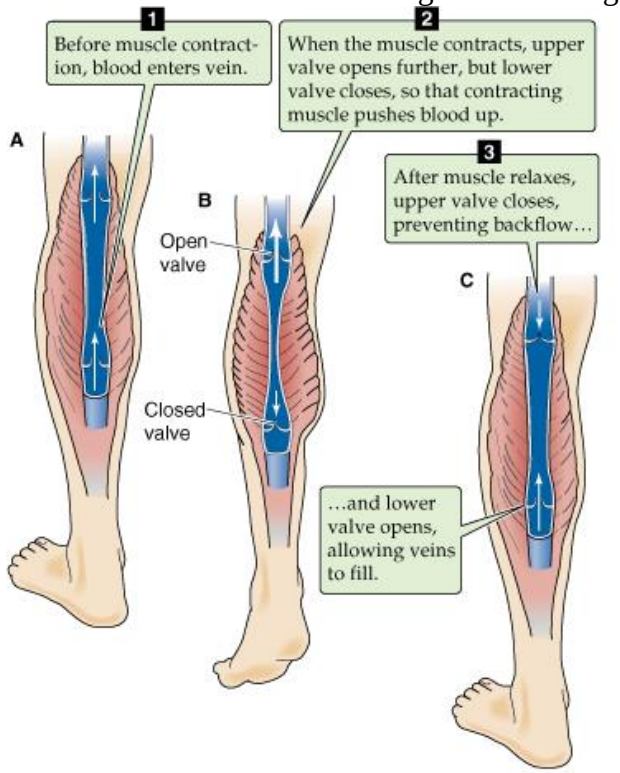
From www.mfi.ku.dk/ppaulev/chapter18/images/18-1.jpg[101]

Question: A 23-year old woman compares data taken at rest and during demanding exercise on an elliptical exercise machine. She finds the following:

	Cardiac output (l/min)	Mean arterial pressure (mmHg)
Rest	5	100
Severe exercise	15	110

How has her total systemic resistance—in arbitrary units—changed with exercise? Why?

- Compression and relaxation of skeletal muscle changes flow during rhythmic exercise



From Boron p. 586[102]

- "Muscle pump" is a major contributor to venous return (= cardiac output) during dynamic exercise

- After occlusion of muscle, blood flow increases above baseline ("reactive hyperemia")

Skin ("cutaneous") circulation

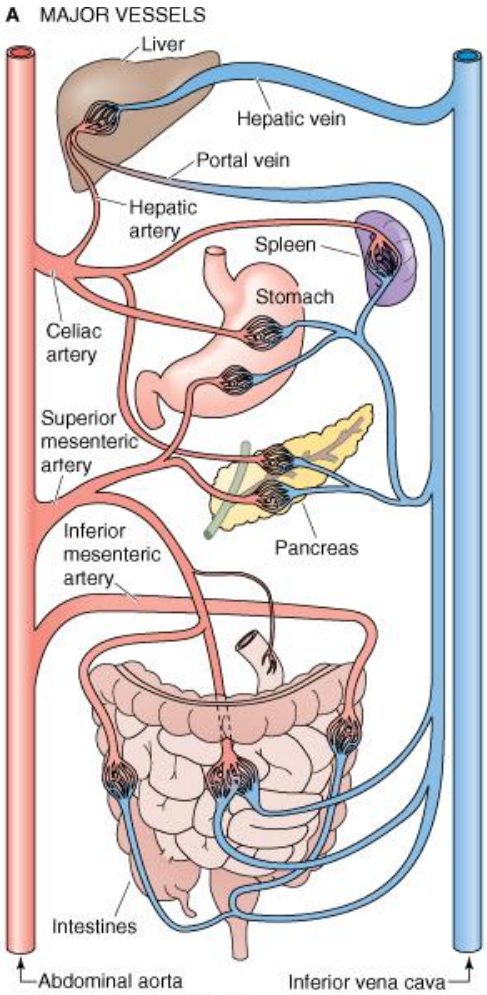
- Extensive sympathetic (α_1) innervation is dominant

- Temperature regulation requirements are a major controller

- Sign of shock is pale, cold skin

Splanchnic circulation

- Includes blood flow to stomach, small and large intestine, spleen, pancreas, and liver



From Boron p. 587[103]

- ↑↑ Following a meal
    - Factors include ↑ gut metabolic activity, ↑ in local vasodilator hormones
- ↓↓ During exercise
    - Sympathetic vasoconstriction
    - ↑ Vascular resistance in exercise helps maintain blood pressure
    - Movement of blood volume out of splanchnic vessels also aids venous return during exercise

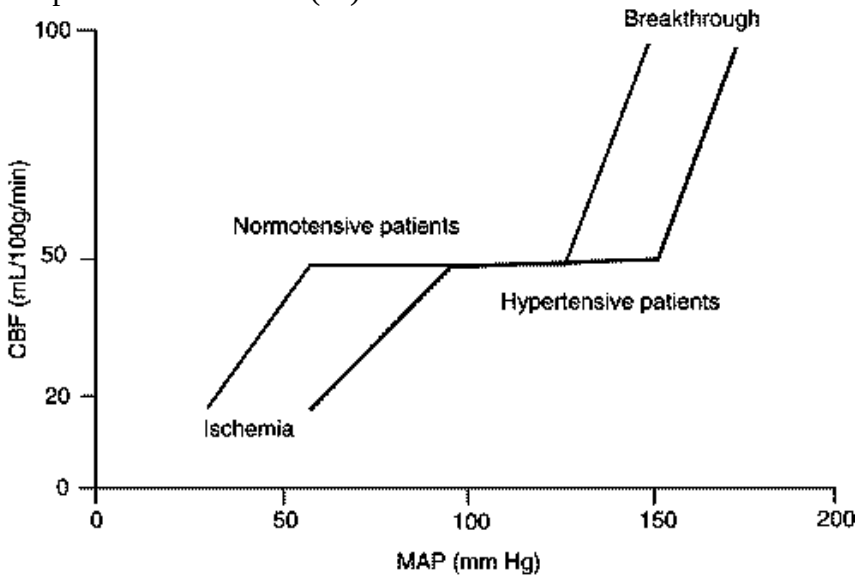
Questions: Splanchnic circulation and hemorrhage.

Question	Answer
What is the response of the splanchnic circulation to hemorrhage?	
What physiological factors would give rise to the splanchnic circulatory response to hemorrhage?	
How does this response aid survival?	
What are some possible deleterious effects of the splanchnic circulatory response to hemorrhage?	

Practice Questions:

1. An 81-y/o man suffers an ischemic stroke. His blood pressure and heart rate are labile, and he has weakness and loss of feeling in his left arm. His cerebral blood flow is normal (750 ml/min), and remains stable although blood pressure oscillates between 100/60 and 150/110. The stable cerebral perfusion is a positive prognostic factor, showing that cerebral arteriolar smooth muscle has appropriately
    a. ↓ Ca^{2+} influx with ↑ MAP
    b. ↑ α_1-adrenergic stimulation with ↓ MAP
    c. ↓ Ca^{2+} influx with ↓ local pH
    d. vasodilated when local P_{O2} increases
    e. ↓ β_2-adrenergic stimulation as local [ADP] rises

2. Cerebral blood flow (CBF) as a function of mean arterial pressure is shown below. If a 60-y/o man with chronic hypertension (160/108 mmHg) loses considerable blood after a knife wound, causing an arterial pressure reduction to 65 mmHg, there will be—as compared to normal—a (an)



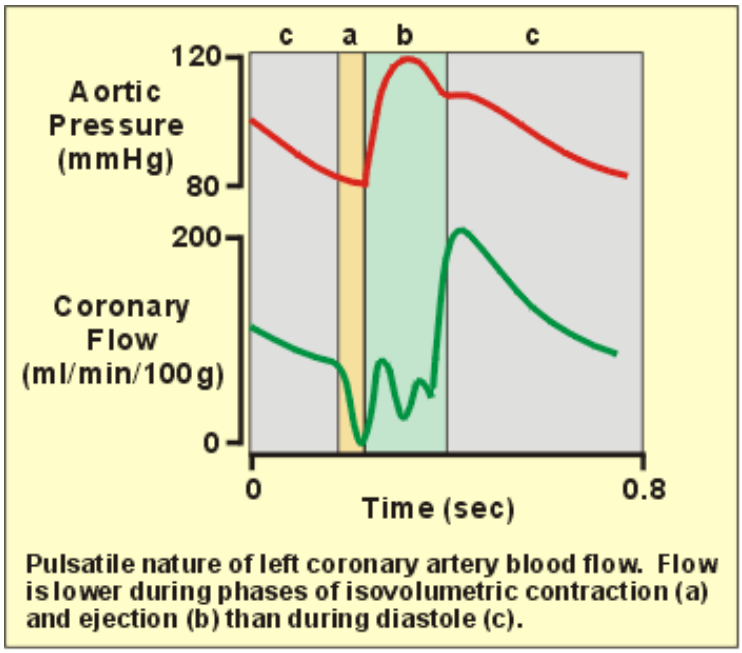
From http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/figures/3041F06.gif[23]

   a. ↑ cerebral blood flow (CBF)
   b. ↑ total systemic resistance
   c. ↓ cerebral vascular resistance
   d. ↓ cerebral vasodilation
   e. ↓ reactive hyperemia

3. A 53-y/o man without a history of hypertension develops a severe headache, nausea, and is taken to the emergency room after losing consciousness. A CT scan reveals a severe intracranial hemorrhage. Blood pressure is 234/172. The stimulus that results in hypertension is
   a. ↑ central venous pressure and ↑ atrial stretch
   b. ↑ P_{O2} at the carotid body chemoreceptor
   c. ↑ pressure at the juxtaglomerular cells
   d. ↑ stretch of the carotid sinus
   e. ↓ pH at the medullary cardiovascular center

4. A 40-y/o woman visits Mt. Everest base camp at 17,400 ft altitude. Her arterial P_{O2} is 102 at sea level, 47 on Everest. The expected cardiovascular result of the reduced P_{O2} is
    a. ↑ ADH with ↑ renal water retention and systemic vasoconstriction
    b. ↑ ANP, renal Na^+ and water loss, and systemic vasodilation
    c. ↑ heart rate, ejection fraction, and total systemic resistance
    d. ↑ α_1 adrenergic, unchanged β_1 adrenergic activity
    e. profound pulmonary vascular vasodilation

5. Why is coronary flow higher during phase **c** than during phase **b**?



Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).

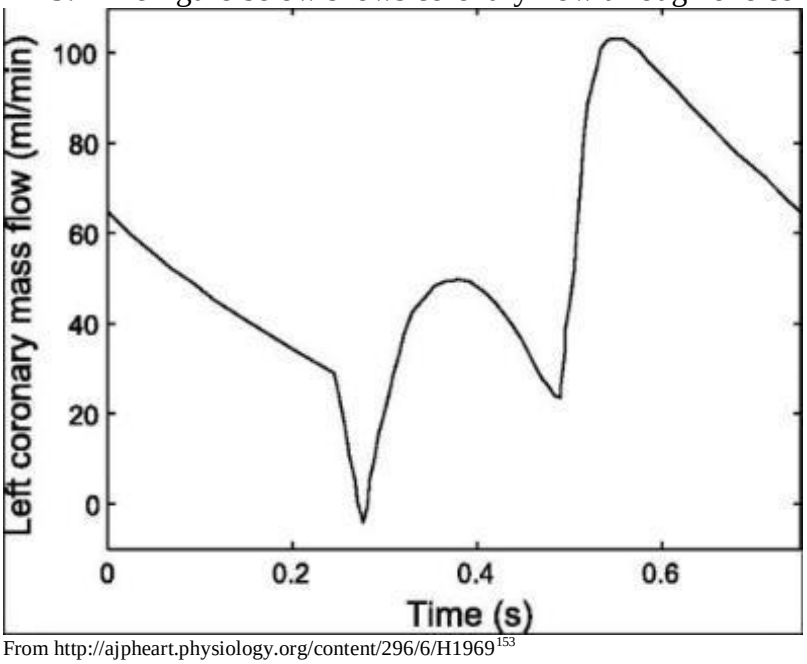
From http://www.cvphysiology.com/Blood%20Flow/BF001.htm[154]

    a. ↑ myocardial rate-pressure product
    b. ↑ cardiac workload
    c. ↓ coronary vascular resistance
    d. ↓ dilator molecules (e.g., ↑ P_{CO2}) in cardiac tissue
    e. ↓ sympathetic α_1 stimulation of coronary vasculature

6. An 80-y/o woman has an episode of dizziness, sudden severe headache, and weakness and numbness in her right arm. Evidence for an occlusion in the carotid artery includes
    a. ↑ ΔP across the entire cerebral circulation
    b. ↓ cerebral venous pressure
    c. ↑ jugular venous pressure
    d. turbulent flow in the carotid artery
    e. ↓ total cerebral vascular resistance

7. A 66-y/o woman has a portal venous pressure of 17 mmHg (**H**), due to
    a. a partial occlusion of the mesenteric artery
    b. ↑ angiotensin II
    c. ↑ intrahepatic vascular resistance
    d. systemic hypertension
    e. ↓ renal vascular resistance

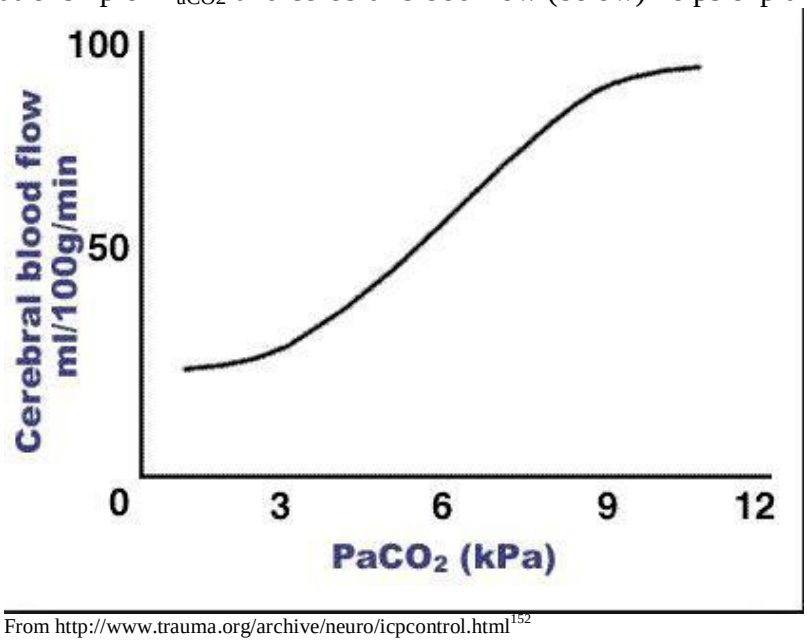
9. The figure below shows coronary flow through one complete cardiac cycle:



From http://ajpheart.physiology.org/content/296/6/H1969[153]

Minimum and maximum flows correspond to, respectively,
    a. isovolumetric contraction; rapid ventricular filling
    b. P wave; QRS wave
    c. rapid ventricular ejection; reduced ventricular ejection
    d. mitral valve opening; mitral valve closing
    e. minimum aortic pressure; maximum aortic pressure

10. The relationship of P_{aCO2} and cerebral blood flow (below) helps explain



From http://www.trauma.org/archive/neuro/icpcontrol.html[152]

a. carotid body chemoreceptor regulation of cerebral blood flow
b. dizziness during hyperventilation
c. ↓ intracranial pressure during 5% CO_2 breathing
d. metabolic autoregulation of cerebral blood flow
e. myogenic autoregulation of cerebral blood flow

11. A 19-y/o man with hypertrophic cardiomyopathy (a hypertrophied heart with abnormal myocytes) is treated with a Ca^{2+}-channel blocker and β_1 blocker. Resting data before and after drug treatment:

	Before	After
Blood pressure	150/100	132/82
Heart rate	80	72
Stroke volume	90	100
Arterial O_2 content	20	20

What other effect was seen?

a. ↑ coronary venous O_2 content
b. ↑ diastolic left coronary flow
c. ↓ aortic blood flow velocity
d. ↓ coronary blood flow
e. increased coronary O_2 extraction

12. The figure below shows the effect of exercise training on maximal coronary blood flow in rats. The changes seen result from
    a. ↑ coronary arteriolar sensitivity to NO
    b. ↑ exercise rate-pressure product
    c. ↓ myocardial lactic acid production
    d. ↓ resting and exercise heart rate
    e. ↓ LV wall tension in exercise

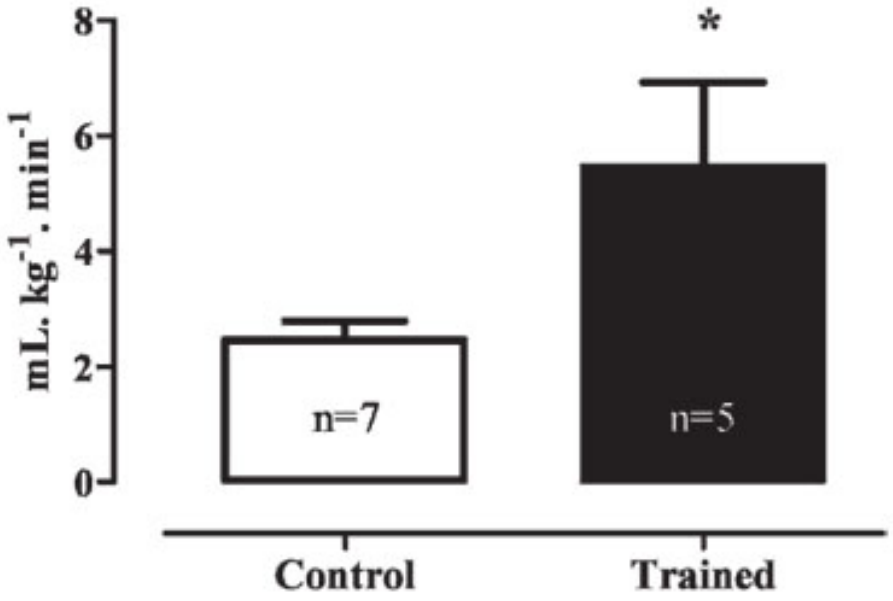


Figure 1 - Coronary blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$). The values are represented as the means ± SEMs; (*) $p<0.05$ compared with the control group. The number of animals (n) is indicated in the figure.

From http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322011001200017[151]

IX. Integrative Cardiovascular Function in Postural Change and Exercise

Text: Costanzo pp. 100 – 104

Postural changes ("gravity"; the effects of standing vs. supination)

- High venous compliance causes increased venous pooling in the legs when standing
- Blood moves from the central veins to the leg veins; loss of central venous pressure
- Dizziness, lightheadedness after sudden standing is termed orthostatic hypotension

Questions (review): Cardiovascular responses to supination and standing

Variable	What change occurs when moving from supine to upright posture?
Blood volume in the legs	
Pressure in the central veins (central venous pressure)	
Stroke volume (immediate effect, prior to reflex adjustments)	
Cardiac output (immediate effect, prior to reflex adjustments)	
Mean arterial pressure (immediate effect, prior to reflex adjustments)	
Baroreceptor activity (in response to alterations in mean arterial pressure)	
TSR (TPR) (in response to change in baroreceptor activity)	

Exercise

- Isometric exercise:
    - No relaxation phase in skeletal muscle: muscle blood flow is reduced, reducing nutrient delivery and accelerating fatigue
- Regulation of blood pressure during exercise:
    - "Central command": activation of motor cortex causes parasympathetic withdrawal (begins with mild exercise of any form)
    - "Muscle chemoreflex": metabolic changes within working muscle provide afferent feedback to vasomotor center, causing sympathetic activation
    - Central command and muscle chemoreflex reset arterial baroreceptor set point
- Sympathetics constrict skin, splanchnic regions, renal, and inactive muscle

Review questions: Summary of the effects of acute rhythmic, dynamic exercise

Variable	**Response to Exercise (↑↓)**	**Major causal factor(s)**
Heart rate		
Stroke volume		
Cardiac output		
Arterial pressure		
Pulse pressure		
Total peripheral resistance		
A – V O_2 difference		
Cerebral blood flow		
Skeletal muscle blood flow		
Skin blood flow		
Splanchnic blood flow		

Cardiovascular effects of chronic dynamic exercise

- Adaptations within the heart:
    - Increased ventricular volume at constant wall thickness
    - Increased vagal tone and decreased β-adrenergic responsiveness
        - Decreased resting and exercise heart rate
            - Decreased cardiac energy demands at any fixed exercise level
            - Decreased coronary flow requirement at any fixed exercise level
    - Increased coronary arteriolar vasodilatory capacity
        - Increased responsiveness to adenosine and NO-mediated vasodilation
        - Enhanced work capacity prior to ECG abnormality or angina
- Adaptations in the systemic vasculature
    - Primarily within trained skeletal muscle
        - Increased capillary density
        - Increased maximal muscle blood flow
        - Together with changes within the skeletal muscle cells, these changes increase fatigue resistance
            - Intramuscular adaptations: ↑ glycogen, ↑ Kreb's cycle enzyme content, ↑ mitochondrial density
                - ↑ Fat, ↓ carbohydrate utilization, ↓ lactate production
- Effects on resting blood pressure may or may not be significant
- Effects secondary to chronic activity may benefit the arteries—including the coronary arteries—by indirectly reducing risk factors for atherosclerosis development
    - Increased HDL cholesterol
    - Weight loss
    - Increased insulin sensitivity and improved glucose tolerance

Practice Questions

1. A 38-y/o man completes a 6-month endurance exercise program. The training has increased his
   a. cardiac β_1-adrenergic responsiveness
   b. coronary flow requirement at a fixed exercise intensity
   c. coronary arteriolar responsiveness to endothelin
   d. leg muscle capillary density
   e. resting coronary blood flow

2. A sedentary 50-y/o women with chest pain on exertion has blood pressure 146/100. Six months of endurance exercise training increases her
   a. HDL cholesterol
   b. insulin resistance
   c. maximal cardiac rate-pressure product
   d. resting coronary blood flow
   e. resting SA nodal I_f

3. Data is taken from a 22-y/o woman during a constant-speed 2 hour run on a 82°F day:

	First 15 min	Last 15 min
HR	168	183
Cardiac output (L/m)	17.5	19.7
Blood pressure	176/82	154/74
Core temperature (°C)	37.0	39.2

What is the major physiological mechanism accounting for the changes seen?
   a. ↑ cardiac preload
   b. ↑ β_2-adrenergic stimulation of active muscle arterioles
   c. ↑ β_2-adrenergic stimulation of inactive muscle arterioles
   d. ↓ cardiac contractility
   e. ↓ α_1-adrenergic stimulation of skin arterioles

4. A 71-y/o woman, after a major heart attack, completes 6 months of vigorous endurance exercise training. One effect of the training is
   a. ↑ coronary flow at rest
   b. ↑ coronary vasodilator capacity
   c. ↓ maximal muscle blood flow
   d. ↓ resting cardiac parasympathetic activity
   e. ↓ skeletal muscle mitochondrial density

Chapter 4: Respiratory Physiology

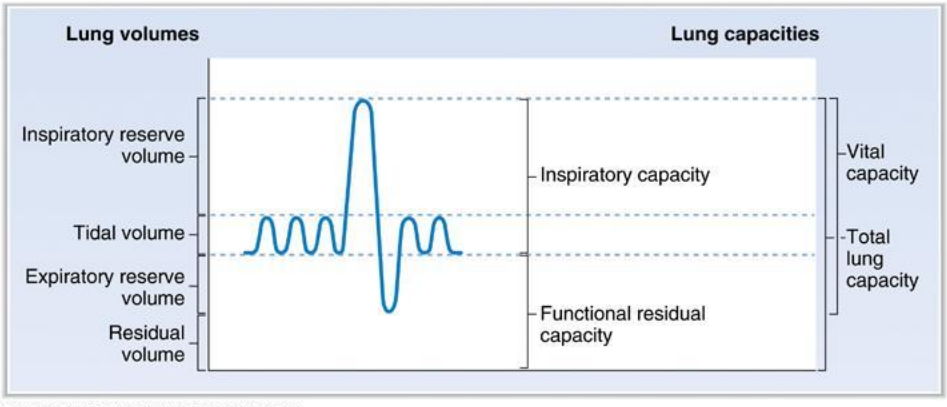
Overview

- Respiratory system maintains homeostasis by supplying oxygen (O_2) and getting rid of metabolically-produced carbon dioxide (CO_2)
- "External" respiration is concerned with the mechanics and control of breathing, gas diffusion and exchange in the lung, and transport of gases in the blood (usually considered physiology)
- "Internal" respiration is concerned with oxygen utilization within the cell
- Secondary roles of the lungs and external respiration include acid-base balance, defense against inhalation of particulates, and endocrine functions of the pulmonary capillary endothelium

I. Lung volumes and capacities

Text: Costanzo pp. 119-121

- Effective gas exchange requires sufficient ability to move bulk amounts of gas
- The volume inspired or expired with each breath is termed the tidal volume (V_T)
- The volumes that can be inspired or expired beyond the tidal volume are termed the inspiratory and expiratory reserve volumes
- Some air remains in the lung after a maximal expiration; this residual volume cannot be measured directly by spirometry
- The vital capacity (VC; or forced vital capacity (FVC)), the most clinically important lung capacity, is the difference between maximal inspiration and maximal expiration



From Costanzo p. 120[104]

- The functional residual capacity (FRC)—the volume of air remaining in the lung at the end of a normal expiration—represents the balance point of lung elastic recoil and chest wall recoil. The FRC is an important reference point in discussions of the mechanics of breathing

Dead space

- In a healthy person, about 150 ml of each 500 ml breath are from the conducting airways. This is the anatomic dead space
- So ~350 ml of each 500 ml breath enters and exits the alveoli
- Hence, the alveolar volume is about 350 ml in an average resting tidal volume
- O_2 and CO_2 only exchange between the body and the atmosphere from the alveolar space
- The total volume of air breathed in and out in one minute is termed the minute ventilation (V_E)
- V_E equals the volume of each breath (tidal volume, V_T) multiplied by the frequency of breathing in breaths per minute (f)
- Alveolar ventilation, V_A, equals the alveolar volume (V_A) × f

Questions: Lung volumes and capacities, and dead space and alveolar ventilation.

Question	Answer
If functional residual capacity (FRC) is 2 L, residual volume (RV) is 1 L, and total lung capacity is 6 L, what is the vital capacity (VC)?	
What is the dead space/tidal volume ratio (V_D/V_T) in a healthy person at rest?	
During a 3000 m run, a healthy person has minute ventilation (V_E) of 125 L/m, and breathing frequency of 50 breaths/m. If V_D remains 150 ml, what is the dead space/tidal volume ratio (V_D/V_T)?	
A person with lung disease has minute ventilation (V_E) of 8 L/m, breathing frequency 20 breaths/m, and alveolar ventilation (V_A) of 2 L/m. What is his or her dead space volume (V_D)?	

- All areas of the lung that receive air but do not exchange gas with the blood are part of the physiologic dead space
    - Physiologic dead space is measured by assuming that all of the CO_2 gas expired from the lung comes from the gas-exchanging (alveolar) space of the lung
- In certain lung diseases the physiologic dead space will be larger than the anatomic dead space; this represents a "pathophysiologic" dead space
    - If disease reduces the ability of a portion of the alveolar space to exchange gas with blood, that space will now contribute to the (patho)physiologic dead space
    - Physiologic dead space can be determined by a conservation of mass equation stating that all of the CO_2 expired from the mouth came from the alveolar space within the lung
    - This calculation requires a measurement of the CO_2 fraction of an expired gas sample, which is a mixture of dead space gas and alveolar space gas. This gas mixture, called mixed expired gas, has a CO_2 partial pressure designated P_{ECO2}
    - The alveolar CO_2 partial pressure is designated P_{ACO2}, and is in equilibrium with the arterial P_{CO2}, which is designated P_{aCO2}
    - It is usually easier in a lung disease patient to measure arterial blood P_{CO2} than it is to estimate the CO_2 pressure in the alveolar gas
    - The mass conservation equation becomes

$$V_D = V_T \times \frac{P_{aCO2} - P_{ECO2}}{P_{aCO2}}$$

where V_D is physiological dead space, V_T is tidal volume, P_{aCO2} is arterial P_{CO2}, and P_{ECO2} is mixed expired P_{CO2}

Question: 24 hours after hip replacement surgery, a 78-year old man develops cyanosis and shortness of breath. His mixed expired P_{CO2} is 10 mmHg, and is arterial P_{CO2} is 60 mm Hg. If his tidal volume is increased to 0.6 liters/breath, what is his physiologic dead space in liters?

II. Mechanics of breathing

Text: Costanzo pp. 121-128

- The lungs have to work properly in a mechanical sense for ventilation to be effective in terms of both volumes and flow rates

- Lung mechanics must provide cost-efficient breathing with minimal respiratory muscle work and fatigue

- Numerous diseases (e.g., emphysema, asthma, cystic fibrosis and other pulmonary fibrotic diseases) seriously impair the mechanics of breathing

Ventilatory muscles

- The inspiratory muscles include, in order of importance, the 1) diaphragm, 2) external intercostals, and 3) accessory muscles (including scalenes, sternocleidomastoids, and neck and back muscles)

    - Diaphragm is innervated by the phrenic nerves, from cervical roots C3 – C5

    - Contraction of the diaphragm moves the abdominal contents downward

    - Contraction of the external intercostals moves the ribs outward

    - At rest in health, only inspiratory muscles (that increase lung volume) are active; expiration is passive

    - When all respiratory muscles are inactive (end of expiration during quiet breathing), lung volume returns spontaneously to the functional residual capacity (FRC). FRC represents the balance point of chest wall and lung

    - Efficient work by the diaphragm allows the work of breathing to be negligible in health at rest. In some lung diseases, the work of breathing can become a significant cause of energy expenditure and muscle fatigue

- Expiratory muscles are inactive at rest in healthy persons

    - Active during exercise and during lung diseases that increase the work of breathing (e.g., asthma, emphysema)

    - Expiratory muscles include abdominal and internal intercostal muscles

Questions: Ventilatory muscle function.

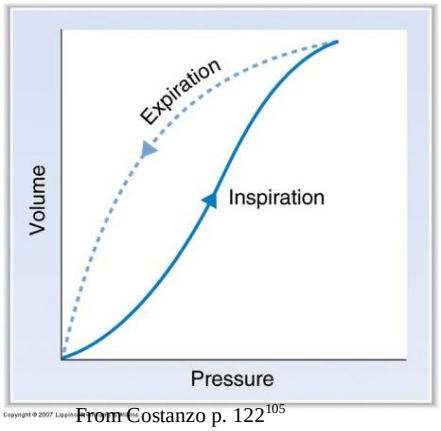
Question	Answer
What would be one method for measurement of inspiratory and expiratory muscle strength?	
A "sniff nasal-inspiratory force" test (SNIF) is used to measure severity of amyotropic lateral sclerosis (ALS). Why is this test used to assess disease severity?	
A 25-y/o man has severe phrenic nerve damage from a traumatic accident. What will be the consequences for his ventilatory function?	
Asthma increases the resistance to airflow during both inspiration and expiration. How will demands on the respiratory muscles change during a severe asthma attack?	
What are some symptoms of respiratory muscle fatigue?	
What are some conditions that might be improved by inspiratory and expiratory muscle strength training?	

Lung compliance

- Compliance (= distensibility) of any structure is defined as the volume change (ΔV) per unit pressure change (ΔP)

- Compliance = $\Delta V / \Delta P$ (the slope of a pressure-volume curve)

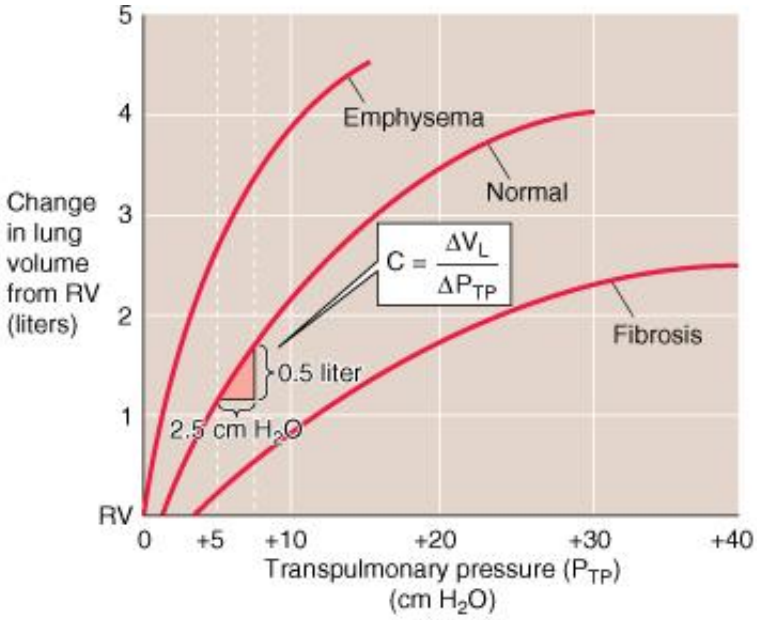
- The compliance curve for lungs (considered separately from the chest wall) is shown below:



From Costanzo p. 122[105]

- Inspiration and expiration follow different curves (hysteresis) because of surface tension forces in the lungs
- For lung compliance, the pressure term is the pressure difference between the alveolus (the alveolar pressure) and the pressure outside the lung (the intrapleural pressure, since outside the normal lung we find the intrapleural space)
    - This pressure difference is called the transpulmonary pressure

- Some lung diseases change the compliance of the lung:



From Boron p. 634[106]

Questions: Effects of abnormal lung compliance and functional residual capacity (FRC) in fibrosis and emphysema

Question	Emphysema	Fibrosis
How does lung compliance change?		
How does the lung compliance change *per se* affect the work of inspiration?		
How does the lung compliance change *per se* affect the work of expiration?		
How does functional residual capacity (FRC) change?		
How does the FRC change *per se* affect the work of inspiration?		
How does the FRC change *per se* affect the work of expiration?		

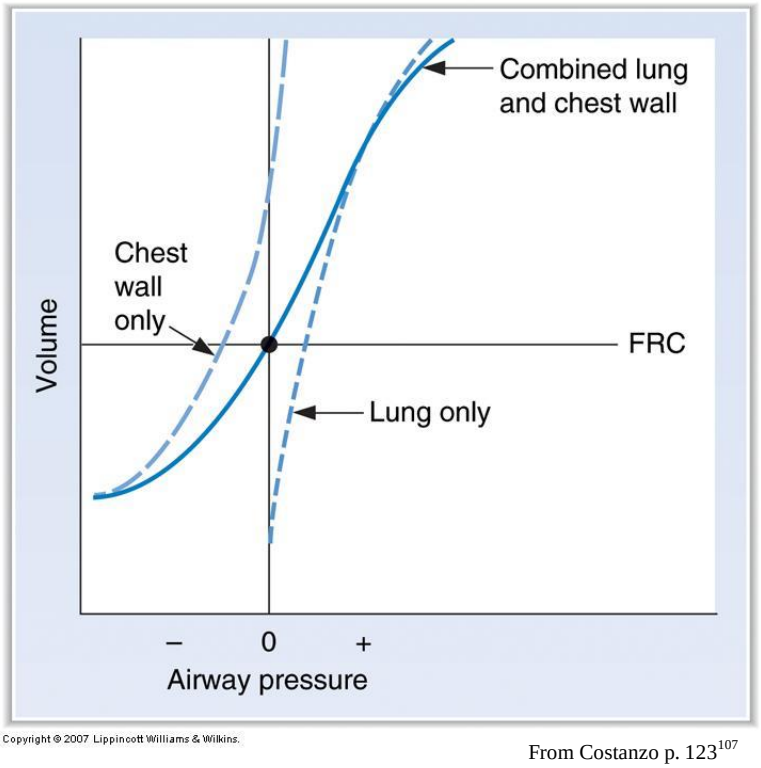
Compliance of the lungs and chest wall

- The compliance of the lung and chest wall together is what matters in practical terms; the non-compressibility of the liquid in the intrapleural space keeps the lung (recoiling inward) and the chest wall (recoiling outward) together

- The opposing elastic recoil of lung and chest wall create a slightly subatmospheric pressure within the intrapleural space

- When no respiratory muscle force is placed on the lung-chest wall system, lung and chest wall recoils balance. This occurs at the functional residual capacity (FRC)

- We can consider then a pressure volume curve for the lung, for the chest wall, or for the combination of the two:



From Costanzo p. 123[107]

- Transmural pressure can be considered for any structure or combination of structures as the pressure across the structure

- Zero transmural pressure—for the lung in isolation—allows that structure to become very small; conversely, for the chest wall, volume increases

    - Zero transmural pressure for the lung—chest wall combination is at the point where no respiratory muscles are active. This is the functional residual capacity (FRC)

Practice Questions:

1. An 80-y/o woman with dry cough and fatigue has the following pulmonary function measurements:

Vital capacity (L)	3.2	**L**
Total lung capacity (L)	4.7	**L**
Residual volume (L)	1.5	
Functional residual capacity	2.0	**L**

   From the above, we can be most certain that her illness involves
   a. ↑ anatomic dead space
   b. ↓ alveolar ventilation
   c. ↑ lung elastic recoil
   d. ↑ physiologic dead space
   e. ↓ tidal volume

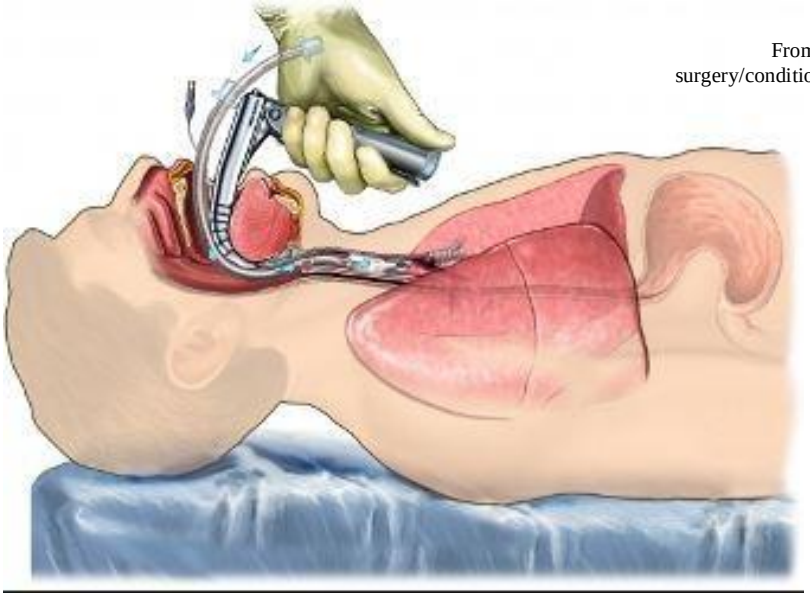
2. A mechanically ventilated 4-y/o girl in intensive care has $V_D/V_T = 0.42$. This measurement (determined as $P_{aCO2} - P_{ECO2})/P_{aCO2}$) assumes that
   a. alveolar and arterial P_{CO2} are equal
   b. inspired and expired P_{CO2} are equal
   c. mixed expired P_{CO2} equals alveolar P_{CO2}
   d. P_{CO2} is increased in physiologic dead space
   e. total dead space <physiologic dead space

3. [Adapted from http://www.ccmtutorials.com[91]]

   In critical care, two patients have a minute ventilation of 10 liters/minute: patient A is taking 50 breaths of 200 ml tidal volume; patient B is taking 20 breaths of 500 ml tidal volume. Both have V_D/V_T of 0.75 because
   a. patient A has abnormally small anatomic dead space
   b. patient A has fibrotic lung disease and decreased lung compliance
   c. patient B has a greater functional residual capacity
   d. patient B has greater physiologic dead space
   e. they have the same functional residual capacities

4. After a severe head injury, a 59-y/o woman with normal lungs is placed on a ventilator. V_T is set at 200 ml. To maintain normal P_{aCO2}
   a. breathing frequency will have to be very high
   b. end-inspiration should be set at the FRC
   c. minute ventilation should be maintained at 6 l/min
   d. mixed-expired CO_2 should be set at normal values
   e. physiologic dead space must be < 150 ml

5. A healthy 30-y/o man has resting V_T 500 ml, anatomic dead space 150 ml, and breathing frequency 20/min. After an auto accident, he requires surgery with mechanical ventilation after intubation (Figure). If the external volume of the tube past the mouth is 150 ml, then maintaining normal alveolar ventilation at the same breathing frequency will require a

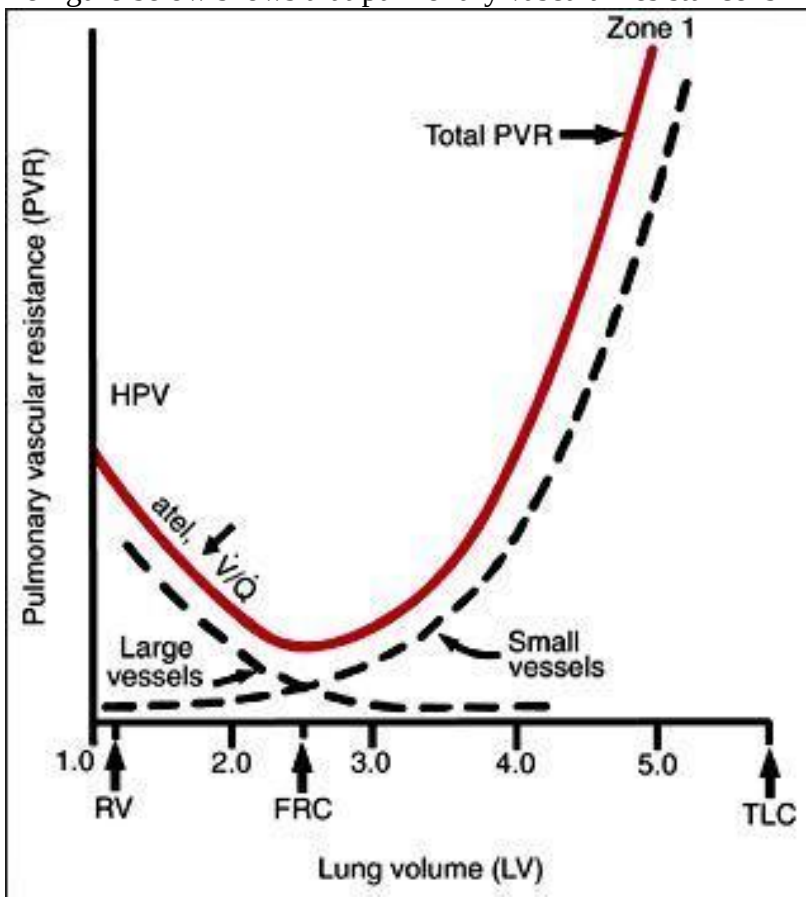


From http://uvahealth.com/services/plastic-surgery/conditions-treatments/112024[150]

   a. decrease in tidal volume from 500 to 350 ml
   b. doubling of dead space ventilation
   c. doubling of minute ventilation
   d. doubling of tidal volume
   e. 150 ml increase in alveolar volume (V_A)

6. Measurements in a healthy 34-y/o woman find $P_{intrapleural}$ = -35 mmHg, $P_{alveolar}$ = -30 mmHg, and P_{airway} = -28 mmHg, evidence that these measurements were taken
   a. at FRC
   b. at residual volume
   c. during forceful expiration
   d. during forceful inspiration
   e. during tidal breathing

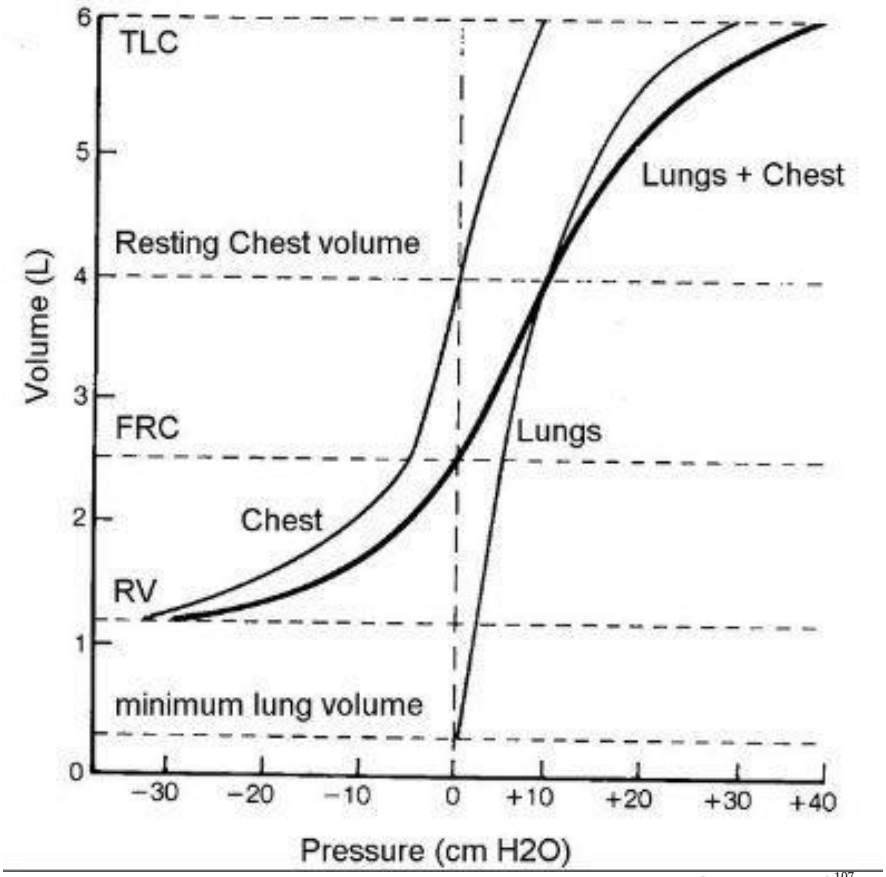
7. The figure below shows that pulmonary vascular resistance is minimized when



From http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v02/020515r00.HTM[149]

a. diaphragm length is minimal
b. expiratory muscle effort is maximal
c. large pulmonary vessels have their lowest resistance
d. lung recoil and chest wall recoil are balanced
e. small pulmonary vessels have their lowest resistance

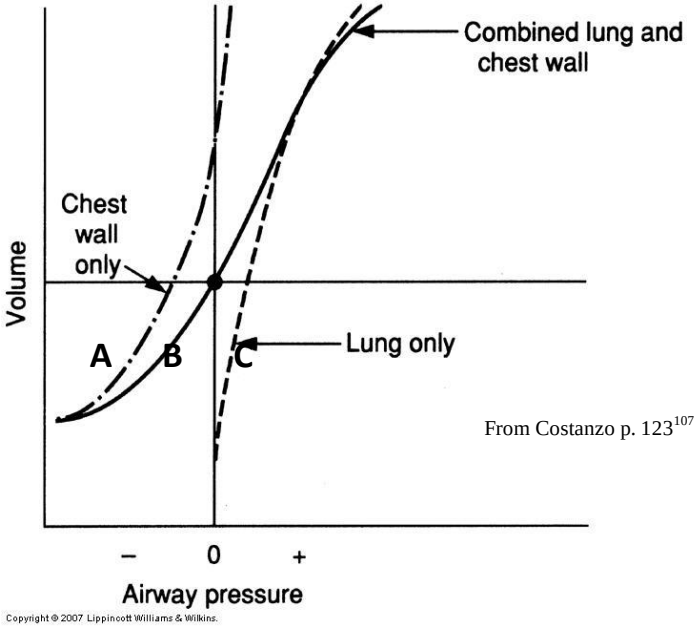
8. The figure below shows that



From From Costanzo p. 123[107]

a. chest wall compliance is always higher than lung compliance
b. compliance of (lungs + chest) is always greater than lung compliance alone
c. lung recoil and chest wall recoil balance at FRC
d. minimum lung volume increases if lung compliance decreases
e. resting chest wall volume is reached at maximal inspiration

9. In the figure below, lung disease reduces FRC and reduces the slopes of curves B and C:



From Costanzo p. 123[107]

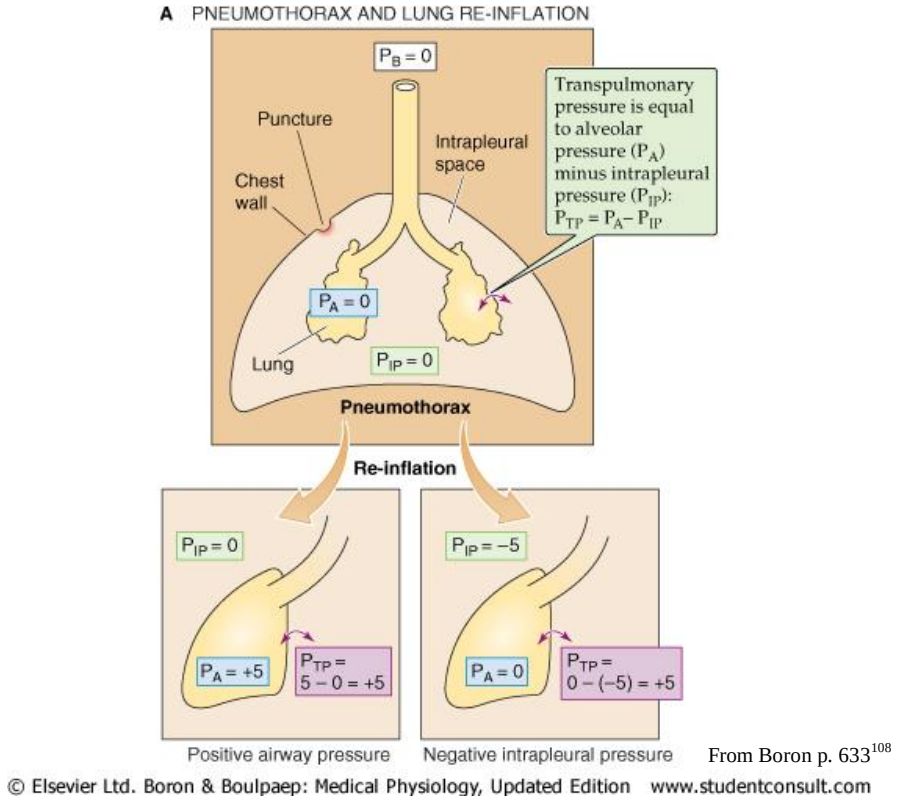
What is another effect of this lung disease?

a. ↑ anatomic dead space
b. ↑ FVC
c. ↑ V_T
d. ↓ FEV_1/FVC
e. ↓ lung $\Delta V/\Delta P$

Pneumothorax

Question: If a puncture wound allows air to enter the intrapleural space, the resulting pneumothorax allows the lung and the chest wall to separate and move to their respective equilibrium volumes. What are these volumes? What are the signs and symptoms of a pneumothorax?

Question: Describe two methods for lung re-inflation after pneumothorax (each would work in theory although only one is typically used in practice)



Question: *Tension* pneumothorax occurs when air under tension accumulates in the intrapleural space. How is this possible? What would be some consequences for cardiac and pulmonary function?

Surface tension of alveoli and surfactant

- Another factor that affects lung compliance: lack of surfactant makes the lungs stiff and hard to inflate (low compliance)

- Principle: a wetted surface of tissue resists stretch from both elastic forces (within the tissue itself) and from surface tension (the force required to stretch a surface of water molecules, since the water molecules are attracted to each other)

Surface tension (force)←←Water→→Surface tension (force)
Elastic force←←Tissue→→Elastic force

- On large surfaces, tissue elastic recoil dwarfs surface tension, so surface tension is negligible

- But on small surfaces (e.g., alveolar walls, very small airways), surface tension contributes significantly to the force required for stretch

- If the liquid on these surfaces is mostly just water (+electrolytes, isosmotic), they are very hard to stretch, especially at low lung volume when these surfaces are small

- Type II pneumocytes, between weeks 24 and 35 of gestation, begin to manufacture a soap-like molecule that moves to water surfaces and reduces surface tension of wetted surfaces in the lung alveoli and small airways

    - Molecule (a complex lipoprotein that contains dipalmitoyl phosphatidylcholine [DPPC] in its lipid portion) is called pulmonary surfactant

- Incidence of neonatal respiratory distress syndrome rises to ~75% in premature infants born before 30 weeks' gestation

Questions: Effects of lack of surfactant in the neonate: the neonatal respiratory distress syndrome

Lung Compliance	**Work of Breathing**	**Respiratory Muscle Fatigue**	**Collapse of Alveoli (Atelectasis)**	**Oxygen Levels in Blood**

- Testing for surfactant development can be done by checking the amniotic fluid lecithin:sphingomyelin ratio; > 2:1 reflects mature surfactant

- Prenatal surfactant development is strongly stimulated late in gestation by cortisol, a "glucocorticoid" hormone from the adrenal cortex

- Cortisol in fetal blood is 2/3 fetal, 1/3 maternal in origin

- Cortisol upregulates fatty acid synthase and phosphocholine transferase, key regulatory enzymes in the fetal production of surfactant

- Exogenous glucocorticoids are given to the mother if fetal respiratory distress is predicted

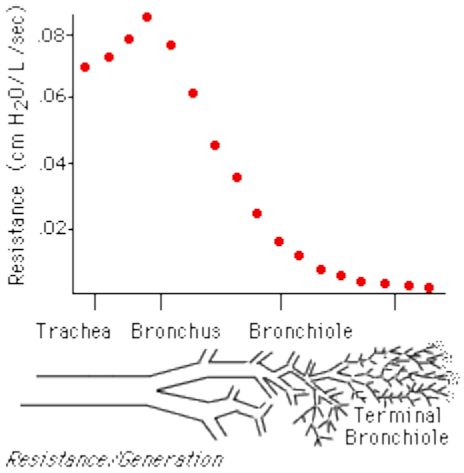
Airways resistance

- Airway flow and ΔP follow Poiseuille ($\text{Airflow} = \Delta P / R$), where R is airways resistance

- Analogous to blood vessels, resistance R varies with radius to the fourth power

- Bulk of airways resistance resides in the medium-sized bronchi in the conducting airways

- The factors that change airways R are those factors that alter radius of these medium-sized bronchi:



From http://oac.med.jhmi.edu/res_phys/Encyclopedia/AirwayResistance/AirwayResistGen.GIF[109]

Factors that affect tube (medium-sized bronchi) radius

1. Dilation or constriction of bronchial smooth muscle

    a. Constriction

        i. Parasympathetic stimulation (via the vagus nerve)

        ii. Airway irritants or allergens (includes histamine; various antigens that stimulate production of eicosanoids like thromboxanes and leukotrienes)

        iii. Nonadrenergic, noncholinergic stimulants (e.g., substance P, neurokinin A & B; airway cooling and drying)

        iv. Repeated stimuli for constriction is often accompanied by increased mucus production, smooth muscle hypertrophy, and chronic airway inflammation

    b. Dilation

        i. Sympathetic stimulation

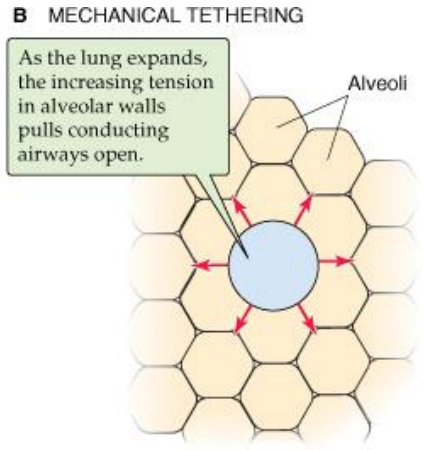
            1. Circulating epinephrine at the bronchial smooth muscle β_2 receptor; aerosolized β_2 agonists are highly effective

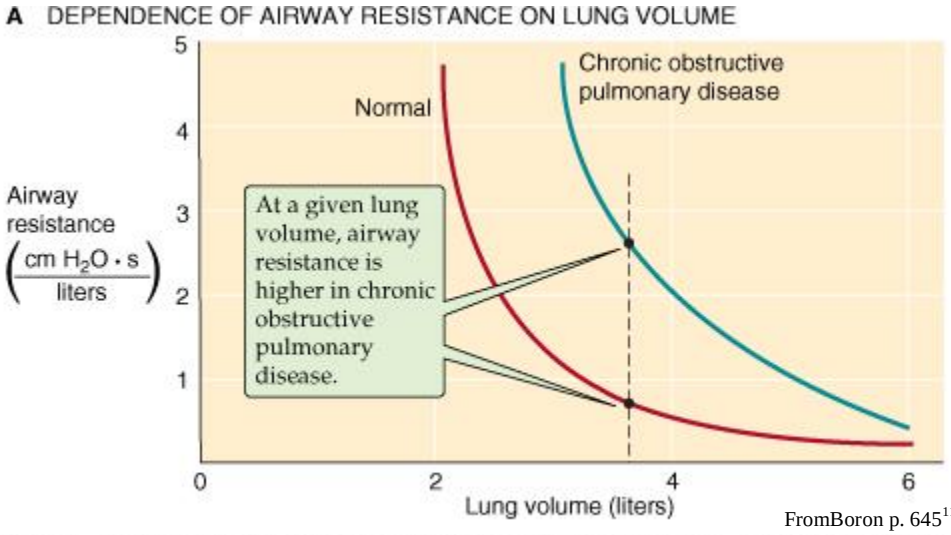
            2. Direct neural effects (norepinephrine) and circulating norepinephrine are relatively weak, due to low potency of norepinephrine at the β_2 receptor

Question: Why does exercise dilate the bronchi?

Question: Why does exercise-induced, non-allergic asthma typically occur only *after* several minutes of exercise?

2. Lung volume: Radial traction pulls airways open, so airways resistance falls as lung volume increases





FromBoron p. 645[110]

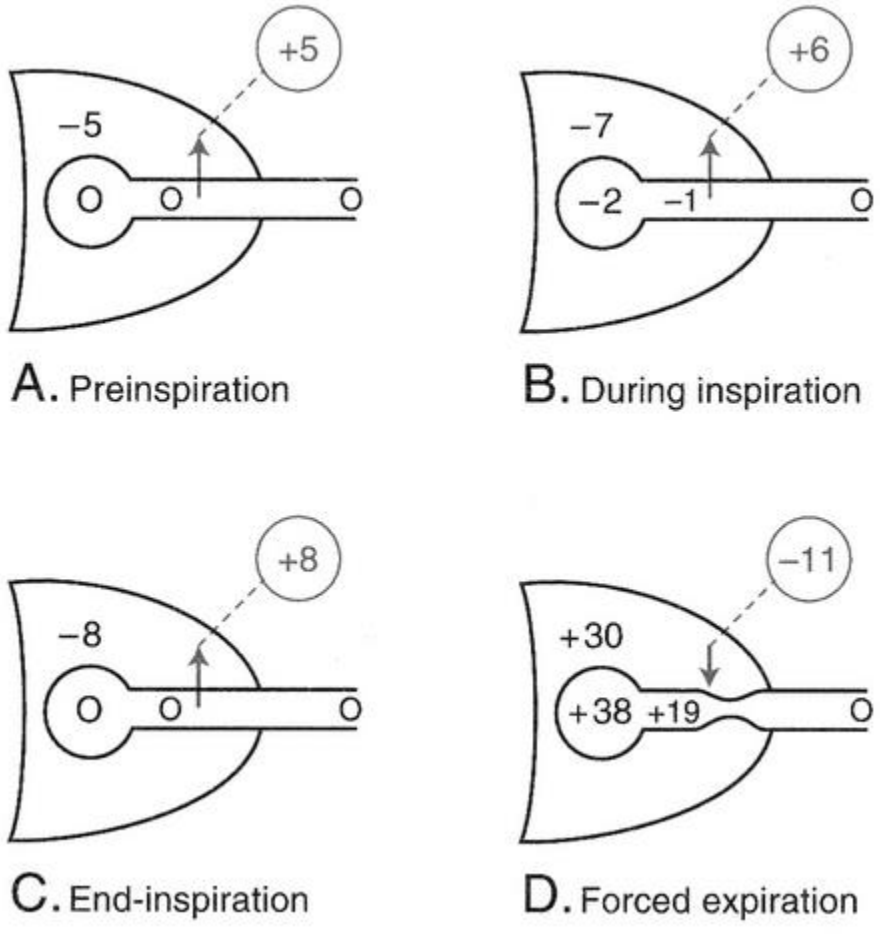
a. Pulmonary fibrosis increases radial traction forces, keeps airways open

b. Emphysema causes loss of alveolar septa, which reduces forces during inspiration that pull airways open

3. In all lungs, airways tend to collapse during expiration (not inspiration), due to several factors and forces on the intermediate-sized airways. This is called "dynamic compression of the airways"

a. Never a problem in quiet breathing in health; can only be seen in forced expiration to a very low lung volume

b. In severe chronic obstructive lung disease, airways collapse is very obvious even during normal expiration



From http://a-vet-to-be.blogspot.com/2012/04/alveolar-ventilation-and-gas-diffusion.html[111]

Three factors in dynamic airways compression

a. Lung volume—larger lung volumes dilate airways

b. Lung compliance

   I. *Decreased* lung compliance stiffens the lung, holding airways open

   II. *Increased* compliance involves loss of elastic recoil and results from loss of supporting lung tissue, increasing exposure of medium-sized airways to intrapleural pressure and allowing those airways to collapse

c. Airways resistance—as airways congestion or edema increases, the rise in resistance increases the pressure drop down the airways

Questions: Airways resistance.

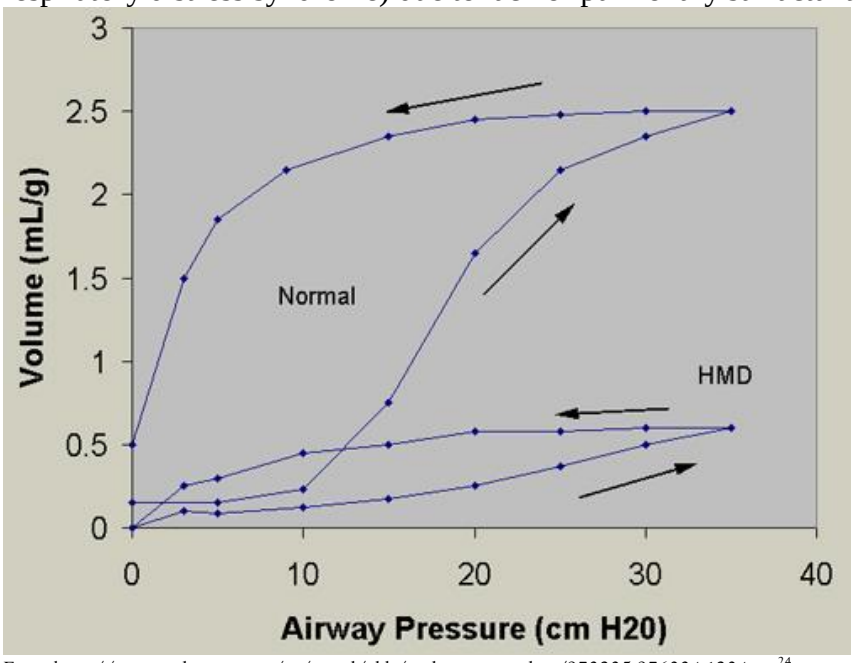
Question	Answer
If the radius of an airway falls to 50% of the initial value, how much and in what direction will the resistance of that airway change?	
What are the pros and cons (for the work of breathing) of the chronic hyperinflation seen in persons with emphysema?	
At FRC in a healthy person, what are the intrapleural, alveolar, and airway pressures?	
Why is the change in airways resistance after inhaling methacholine (a synthetic acetylcholine analogue) used as a standard clinical test for asthma?	

Practice Questions:

1. As lung volume is increased during inspiration, there is normally a concomitant
    a. ↑ intrapleural pressure toward 0 mmHg
    b. ↑ lung compliance
    c. ↓ airways resistance
    d. ↓ chest wall volume
    e. ↓ lung recoil force

2. A 62-y/o woman who has smoked 2 packs of cigarettes a day for 42 years has 70% loss of alveolar septa and elastic tissue, causing
    a. ↑ alveolar ventilation
    b. ↑ expiratory muscle activity
    c. ↑ work of inspiration
    d. ↓ (more negative) intrapleural pressure at FRC
    e. ↓ lung volume at FRC

3. The figure below shows lung pressure-volume curves from a neonate with healthy lungs, and from an infant who died from hyaline membrane disease (HMD; aka infant respiratory distress syndrome) due to lack of pulmonary surfactant:



From http://img.medscape.com/pi/emed/ckb/pediatrics_cardiac/973235-976034-1204.jpg[24]

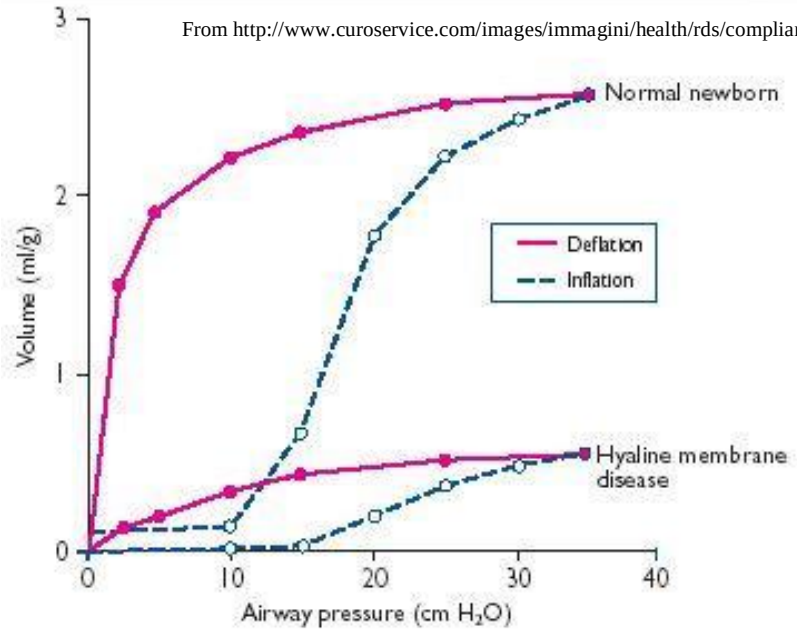
Neonates with HMD would be expected to suffer from
    a. ↑ work of expiration
    b. ↓ lung compliance
    c. a flattened diaphragm at mechanical disadvantage
    d. hyperventilation
    e. lung hyperinflation

4. Airways collapse on expiration is enhanced by
    a. increased airway radius
    b. increased lung airway tethering
    c. increased lung volume
    d. less negative intrapleural pressures
    e. β_2-agonist treatment

5. A healthy 16-y/o girl experiences chest tightness, cough, wheezing, and fatigue shortly after running a cross-country race. In theory, immediate symptom relief would be most likely via
    a. breathing cool, dry air
    b. inhalation of an M_3 agonist
    c. inhalation of a β_2-antagonist
    d. intravenous infusion of epinephrine
    e. norepinephrine released from sympathetic neurons

6. The lung pressure-volume curves shown below contrast normal neonates with those suffering from lack of pulmonary surfactant:

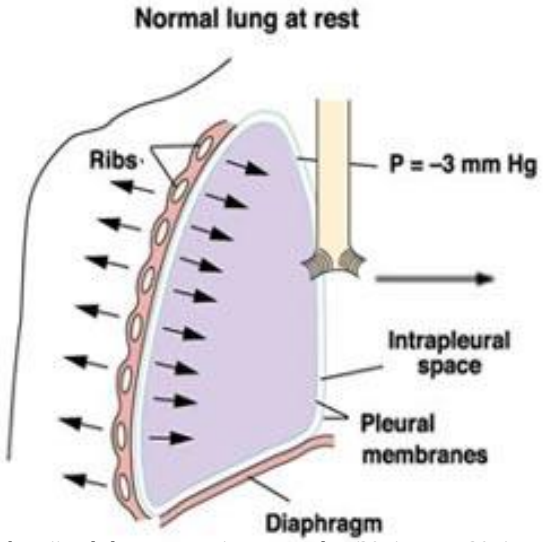
From http://www.curoservice.com/images/immagini/health/rds/compliance_1.gif[25]



The figure shows that
    a. abolition of surface tension forces in the lungs decreases lung compliance
    b. inflation of normal lungs requires work to overcome surface tension forces
    c. surfactant decreases the work of inspiration but increases the work of expiration
    d. surfactant deficiency causes intrapleural pressure to become less negative
    e. surfactant-free lungs are excessively compliant

7. Airways collapse on expiration is enhanced by
    a. increased expiratory effort
    b. increased lung volume
    c. increased lung $\Delta V/\Delta P$
    d. more negative intrapleural pressures
    e. β_2-agonist treatment

8. For a lung illustrated below, intrapleural pressure becomes most negative during

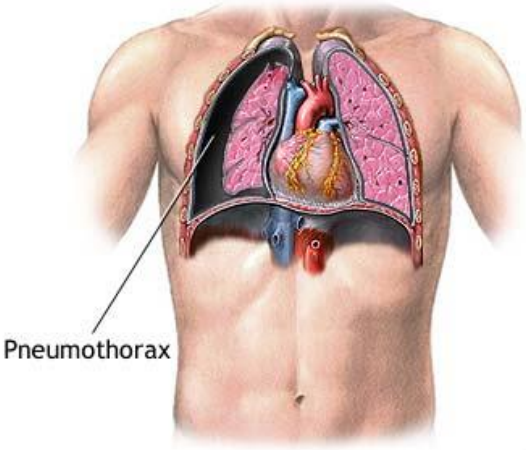


From http://mededsys-rcp.com/courses_online/302/images_302/27.jpg[76]

    a. emphysema, when lung compliance ↑
    b. forced expiration
    c. maximal inspiration
    d. positive pressure breathing
    e. uncomplicated pneumothorax

9. During which of the following will intrapleural pressure be higher than atmospheric pressure?
    a. at FRC, with no muscle force involved
    b. forced expiration
    c. normal inspiratory effort with the airway closed
    d. spontaneous, uncomplicated pneumothorax
    e. normal inspiration with an open airway.

10. The “chest tube” for treatment of a pneumothorax (below) has the purpose of



From http://www.mybwmc.org/sites/all/modules/adam/graphics/images/en/15206.jpg[77]

a. allowing transpulmonary pressure to reach zero mmHg
b. elevating airway pressure above alveolar pressure
c. equalizing transpulmonary pressure with alveolar pressure
d. lowering intrapleural pressure below alveolar pressure
e. matching intrathoracic pressure with intrapleural pressure

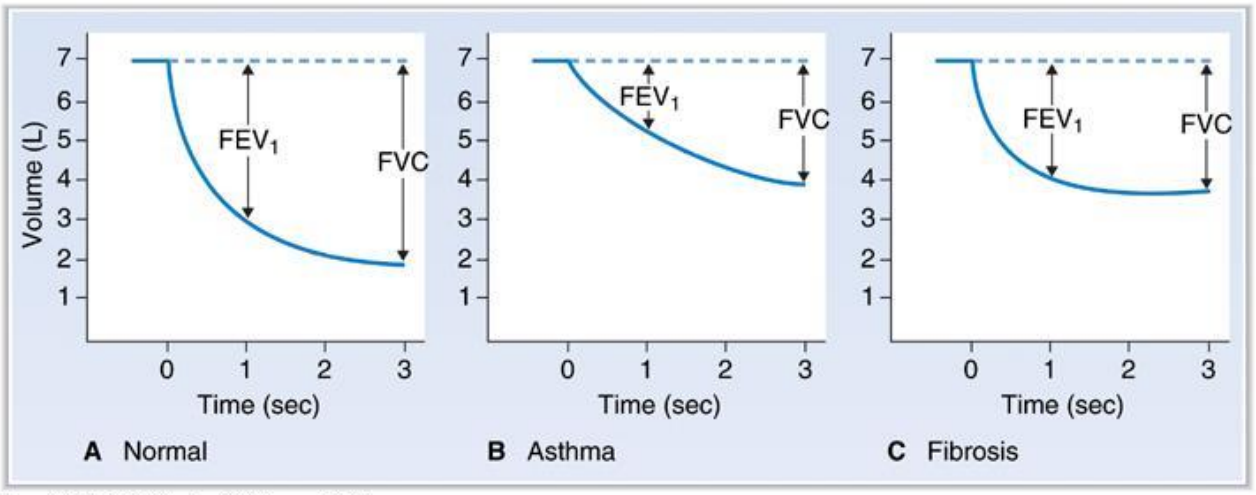
11. A 66-y/o man was referred to the outpatient clinic with a 2-year history of exertional breathlessness. He had worked as an engineer for 20 years where he did a significant amount of welding but always wore a face shield. Clinical, radiological and histological features were consistent with a diagnosis of pulmonary siderosis from inhalation of iron compounds, with associated fibrosis. His condition is associated with an increase in
    a. expiratory muscle strength
    b. functional residual capacity
    c. inspiratory work
    d. lung compliance
    e. vital capacity

Pulmonary function tests

- Forced vital capacity (FVC)
- Forced expiratory volume in 1 sec (FEV_1)
- FEV_1 in healthy persons is close to 80% of the FVC

$$FEV_1 / FVC = 0.8$$

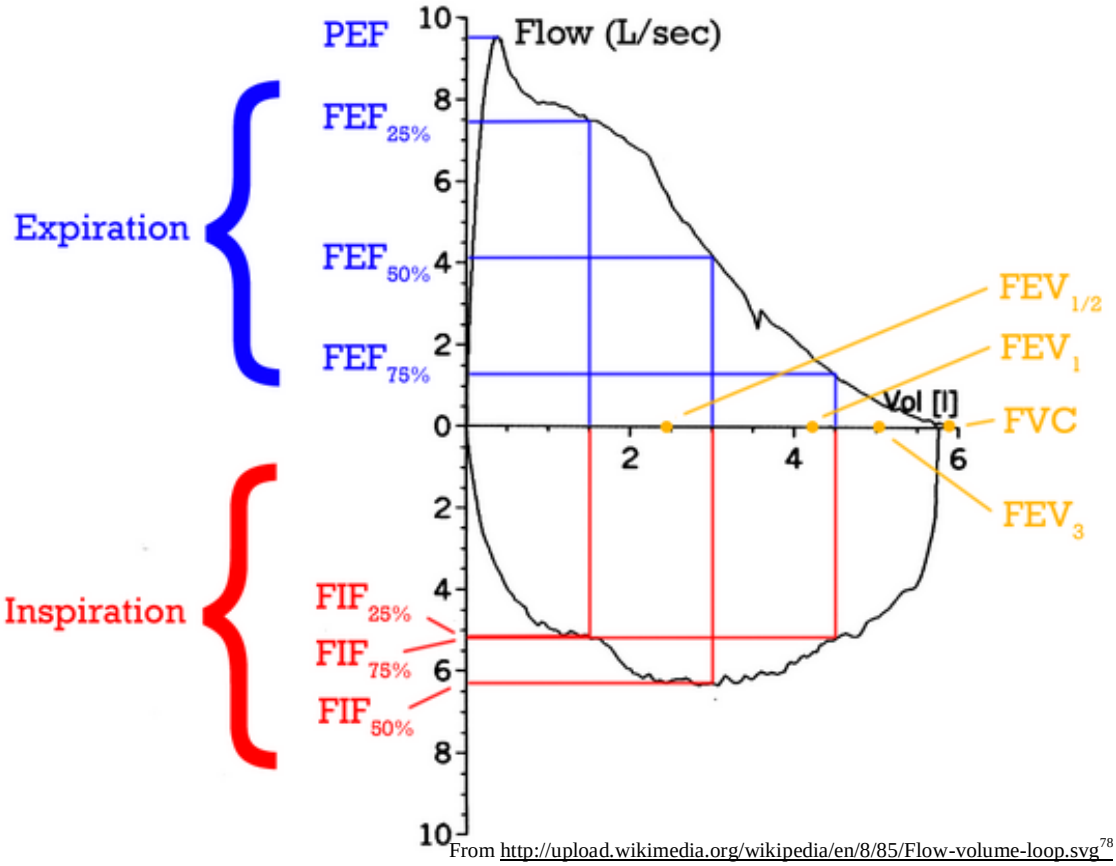
- Because FEV_1 (and, especially, FEV_1 as a % of FVC) are primarily measurements of flow rate, they are reduced in diseases that reduce the maximal rate of airflow in the lung during forced expiration
    - These diseases are generically termed "obstructive" lung diseases
- In contrast, FVC itself is strictly a measure of total volume of air moved, irrespective of flow rate. FVC is reduced by diseases that physically limit the ultimate range of motion of the lungs or chest wall, such as the fibrotic lung diseases
    - These diseases are termed "restrictive" lung diseases
- Many, if not most, lung diseases have elements of both obstruction and restriction:



From Costanzo p. 121[112]

The "flow-volume loop"

- Examines volumes and flow rates during both maximal forced inspiration and expiration
- Flow-volume loops typically plot flow rate as a function of lung volume



From http://upload.wikimedia.org/wikipedia/en/8/85/Flow-volume-loop.svg[78]

Question: Draw flow-volume loops, during maximal inspiration and expiration, for

- Asthma (assume it is an obstructive [on both inspiration and expiration] and restrictive disease)

- COPD (assume it is an obstructive disease with distinct dynamic airways compression on expiration

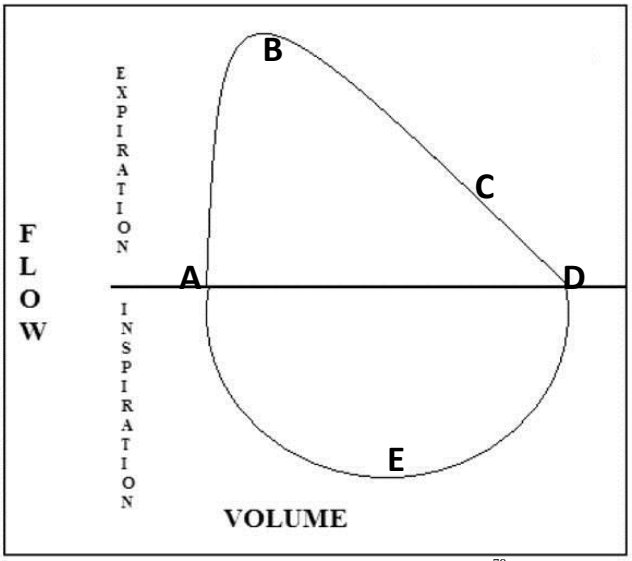
- A purely restrictive lung disease (e.g., pulmonary fibrosis)

Note: On all three graphs, plot flow rate as a function of absolute, not relative, lung volume.

Practice Questions:

1. A 54-y/o woman with shortness of breath during exercise has evidence for restrictive lung disease, that result being
    a. $FEV_1 = FEV_2 = FEV_3$
    b. $FEV_1/FVC = 58\%$
    c. FVC = 60% of normal
    d. Peak expiratory flow rate = 105% of normal
    e. [lung + chest wall] $\Delta V/\Delta P$ = 133% of normal

2. The residual volume is found at what point in the flow-volume loop below?

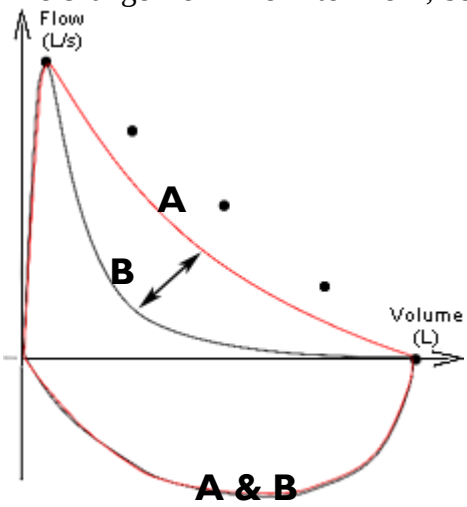


From http://ccforum.com/content/figures/cc3516-6.jpg[79]

Critical Care

    a. A
    b. B
    c. C
    d. D
    e. E

3. The change from line A to line B, below, could be caused by what condition?



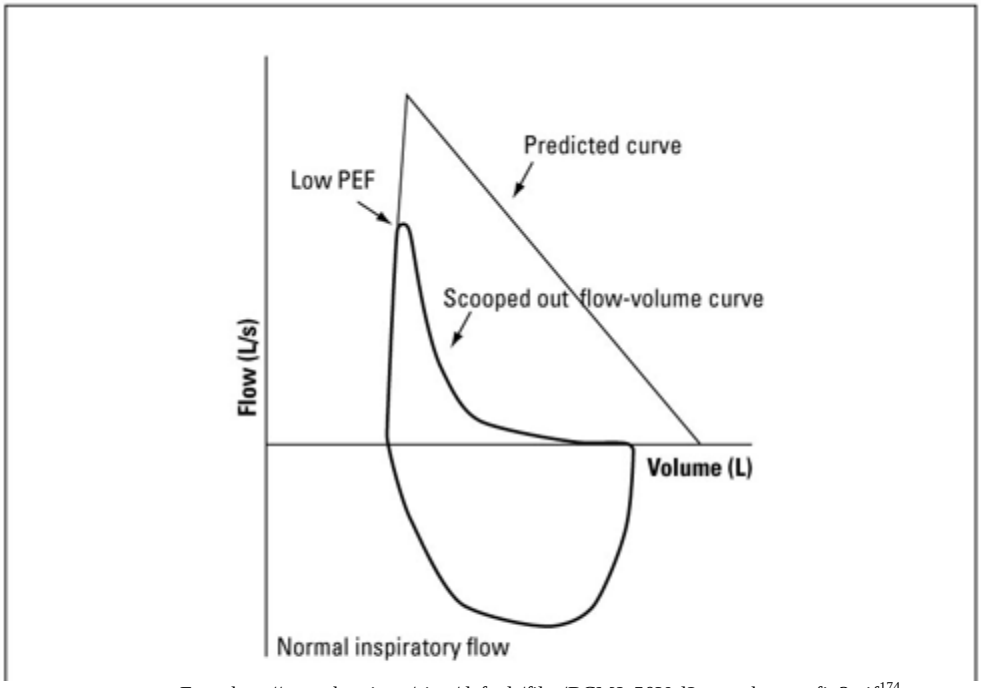
From http://www.spirometrie.info/img/reversible.png[80]

   a. asthma
   b. emphysema
   c. fibrotic lung disease
   d. fixed external obstruction
   e. simple pneumothorax

4. A 23-y/o woman runs every morning, but after a 20 minute run, she becomes short of breath, particularly on cold mornings. Tests find exaggerated airway constriction after methacholine challenge, and post-exercise
   a. ↑ bronchial β_1 responsiveness
   b. ↑ D_{LCO}
   c. ↓ FRC
   d. ↓ lung $\Delta V/\Delta P$
   e. ↓ peak expiratory flow rate

5. A 60-y/o man with α_1-antitrypsin deficiency has shortness of breath and cyanosis. Vital capacity is 4.7 liters (**L**), total lung capacity is 7.7 liters, and FRC is 3.8 liters (**H**). FEV_1/FVC is 38% (**L**). His respiratory function differs from normal because it involves
   a. loss of lung elastic recoil
   b. obstructive but not restrictive lung disease
   c. ↑peak expiratory flow rate but ↓peak inspiratory flow rate
   d. ↑reliance on the diaphragm to generate inspiration
   e. restrictive but not obstructive disease

6. The figure below shows the flow-volume loop in a healthy person and as measured in a person suffering from emphysema:



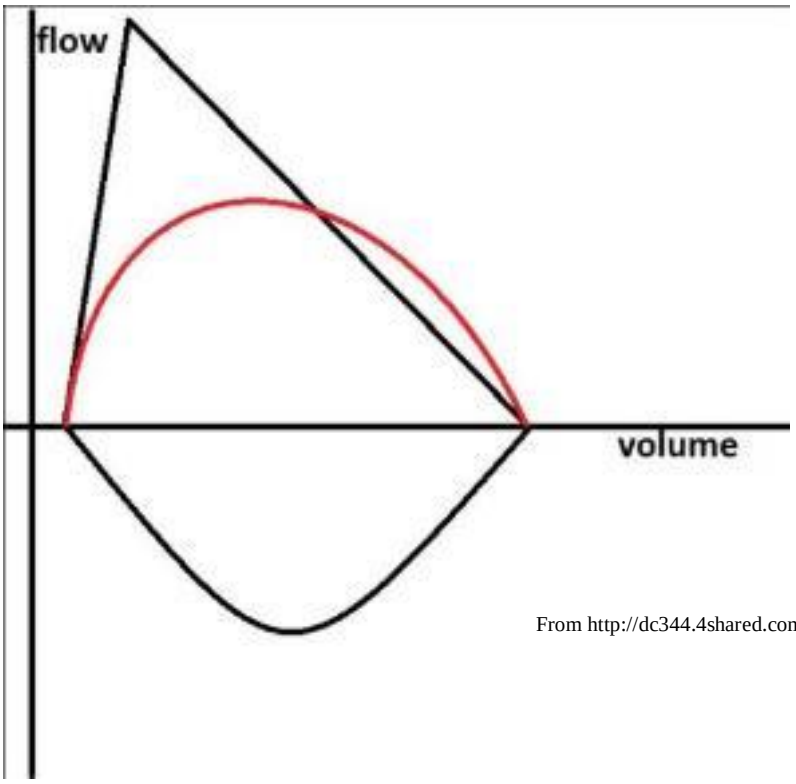
From http://www.bcmj.org/sites/default/files/BCMJ_50Vol2_nonpharma_fig3.gif[174]

PEF: peak expiratory flow

The "scooped out" flow-volume curve arises in part from emphysema causing

a. decreased airways resistance
b. more negative intrapleural pressure
c. positive alveolar pressure during inspiration
d. reduced airway tethering
e. restrictive lung disease

7. A 33-y/o woman has the expiratory portion of her flow-volume loop shown in red, below; the black lines represent the normal response:



From http://dc344.4shared.com/doc/RC3PP6I8/preview.html[81]

Her results indicate

   a. asthma with significant air trapping
   b. decreased lung compliance
   c. diffuse parenchymal lung disease with fibrosis
   d. reduced peak flow rate with normal vital capacity
   e. restrictive lung disease

8. An 8-y/o boy having a severe asthma attack will show
   a. ↑ (less negative) intrapleural pressure during a typical inspiration
   b. ↑ work of inspiration and ↓ work of expiration
   c. ↓ activation of accessory muscles of inspiration
   d. ↓ $FEV_{1.0}$
   e. ↓ (more negative) intrapleural pressure during a typical expiration

III. Gas exchange

Text: Costanzo pp. 128 – 130

Overview

- In respiratory diseases, the body may have difficulty getting sufficient O_2 to the tissues, or have difficulty removing CO_2 adequately
- These problems can occur at several levels:
    - Insufficient breathing ("hypoventilation")
    - At the interface of alveolar air with blood, the diffusional surface of the lung
    - In the matching of air flow ("V") with blood flow ("Q") within the lung ("V/Q mismatch")
    - To understand where the problem may lie, gas partial pressures may be measured at various sites
    - Gas diffusion is always in the direction of a partial pressure gradient

Gas partial pressure

- Atmosphere (total barometric pressure at sea level: 760 mm Hg) contains lots of O_2 (21%) and very little CO_2 (0.03%)
- Partial pressure is calculated as gas percentage × total pressure; partial pressures represent the pressures of individual gases in the atmosphere
- Partial pressures are designated as P_{O2}, P_{CO2}, etc.

Question: What are the following partial pressures in atmospheric air? (P_{bar} is total barometric pressure)

1. P_{O2} in Bloomington (P_{bar} = 740 mm Hg)

2. P_{CO2} in Bloomington

3. P_{O2} at the top of Pike's peak (P_{bar} = 440 mm Hg)

4. P_{O2} at the top of Mt. Everest (P_{bar} = 200 mm Hg)

Partial pressures of O_2

- Humidified tracheal air: P_{O2} = 150 because water vapor (P_{H20} = 47 mm Hg at body temperature) displaces all other gases, slightly reducing the P_{O2}

- Alveolar gas: P_{O2} = 100 because a) some O_2 enters the pulmonary capillary blood, b) ventilation is not infinite, and c) some added CO_2 displaces O_2

- Systemic arterial blood: P_{O2} = 100 because blood passing through pulmonary capillaries becomes equilibrated (in terms of oxygen partial pressure) with gas in the alveoli

    - About 2% of the cardiac output bypasses the lungs, creating a "physiologic shunt" and contributing to a normal, slight reduction in arterial P_{O2} vs. alveolar P_{O2}

- Mixed venous blood: P_{O2} = 40 because O_2 has diffused into tissues, lowering the O_2 remaining in the blood

Partial pressures of CO_2

- P_{CO2} in tracheal gas is zero; alveolar P_{CO2} is 40: CO_2 diffuses from pulmonary capillary blood into the alveoli

- Systemic arterial P_{CO2} is also 40, as gas partial pressures equilibrate in the pulmonary capillary

- Mixed venous P_{CO2} is 46; CO_2 produced in tissues is added to systemic capillary blood

O_2 partial pressures from atmosphere to the tissues

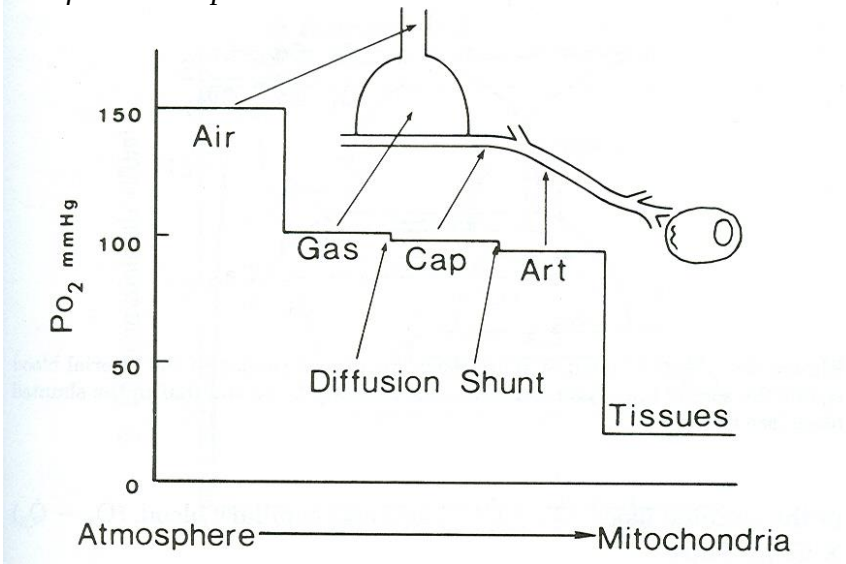


Figure 5.2. Scheme of O_2 transfer from air to tissues showing the depression of arterial P_{O_2} caused by diffusion and shunt.

From West JB. *Respiratory Physiology—the Essentials*. 5th edition, Williams & Wilkins, 1995, p. 55[114]

- In the absence of diffusion defects, ventilation/perfusion mismatching, or shunt, the alveolar P_{O2} will equal the arterial P_{O2}. Alveolar $P_{O2} \approx$ Arterial P_{O2} in health

Dissolved gases

- The amount of gas dissolved in a liquid (e.g., plasma) at a given partial pressure will depend entirely upon solubility of that particular gas in plasma. In the equation below, kO_2 is the solubility constant of O_2 in blood:

Equation 28–1

$$[O_2]_{Dis} = kO_2 \cdot PO_2$$

Equation 28–2

$$[O_2]_{Dis} = \frac{0.003 \text{ ml } O_2}{100 \text{ ml blood} \cdot \text{mm Hg}} \cdot 100 \text{ mm Hg}$$
$$= 0.3 \text{ ml } O_2/100 \text{ ml blood}$$

- Dissolved O_2 in plasma is very small; sufficient O_2 transport is only possible because of hemoglobin – O_2 binding

- CO_2 is more soluble than O_2; even its carriage in blood involves more than the simple dissolved fraction

Diffusion of gases

- For all gases, irrespective of solubility, diffusion is always from higher to lower partial pressure

Question: Fluids A and B are separated by a membrane that only allows diffusion of O_2 between A and B

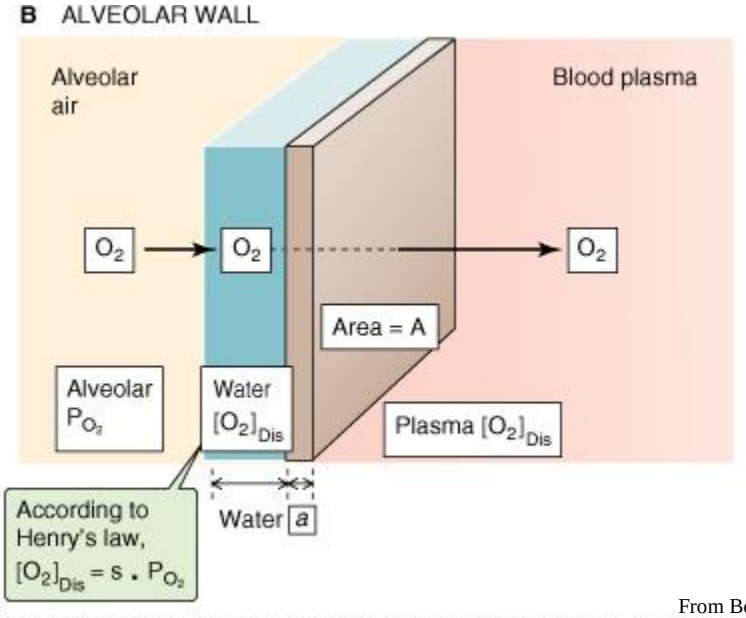
	Fluid A	Fluid B
P_{O2} (mmHg)	200	100
Hemoglobin (g/L)	0	15
Total oxygen content (mL O_2 / 100 mL blood)	0.6	20.0

Will there be O_2 movement between in the two fluids? If so, in which direction?

- Diffusion between two fluids will of course cease when the partial pressures are equal

- Diffusion of gases is most often a consideration—because it is most often a problem—between alveolar gas and pulmonary capillary blood

- Rate of gas transfer across a surface is proportional to surface area, gas solubility, and partial pressure difference, and inversely proportional to surface thickness



From Boron p. 686[116]

- Diffusional exchange is most often a problem for O_2, because the solubility constant for CO_2 through tissue sheets is 20 × as great as for O_2

Diffusion and perfusion limited gas exchange between alveolus and capillary

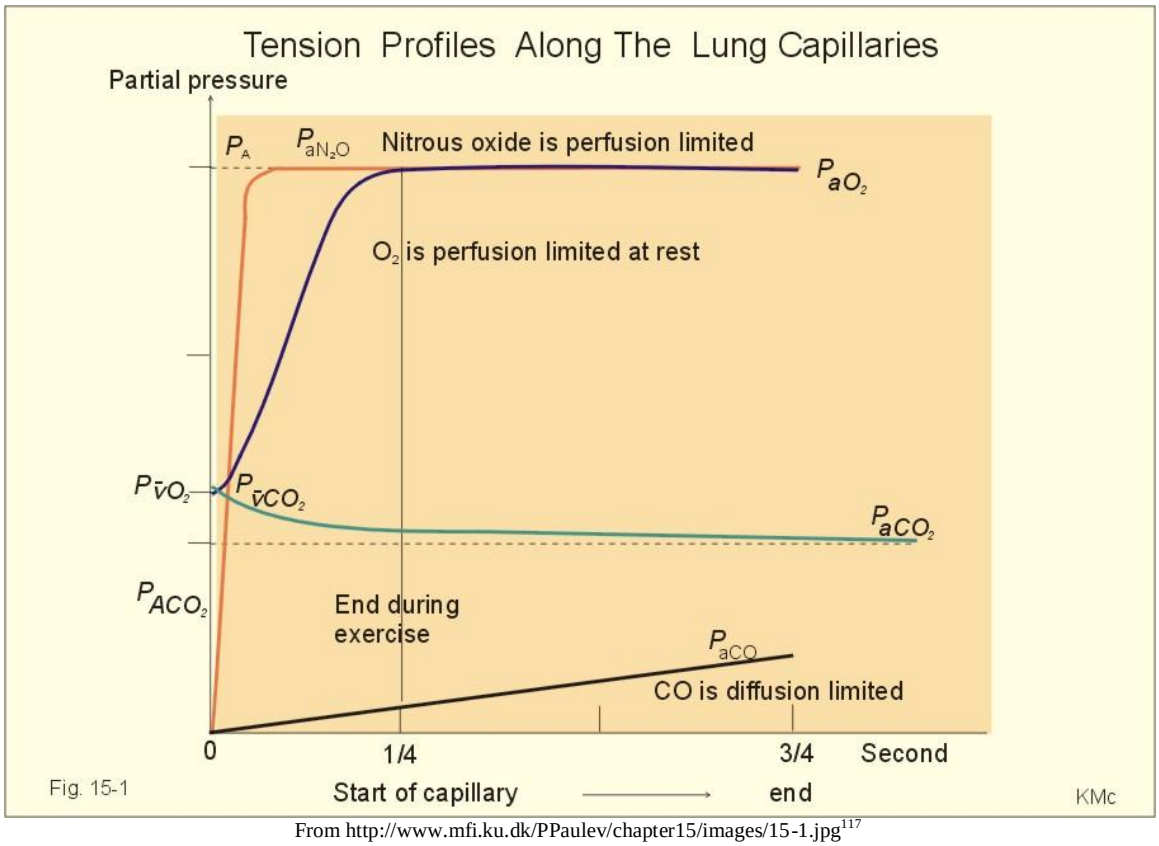
- A rule-of-thumb to help understand how various gases enter the blood from the alveoli

- A central issue is that a unit of pulmonary capillary blood has a finite "residence time" in the pulmonary capillary

- If, in that time, partial pressure of a gas between alveolus and that unit of blood becomes equal, there can be no more diffusion of that gas

- The total amount of gas moving from alveolus to blood, in this situation, would be increased if the blood moved faster

- Transfer of such gases is said to be subject to so-called "perfusion limitation"



From http://www.mfi.ku.dk/PPaulev/chapter15/images/15-1.jpg[117]

- For gases that do not reach equilibrium in partial pressure between alveolus and capillary during capillary blood transit, enhanced diffusion would increase gas exchange
- Transfer of such gases are said to be subject to so-called "diffusion limitation"
- Some gases—such as O_2—may be perfusion limited in health, diffusion limited in certain diseases

Question: On a graph of capillary residence time (x) vs. gas partial pressure (y), show graphically how greater exercise intensity, and greater tissue membrane thickness, each contribute to the severity of an O_2 "diffusion problem" in lung disease

CO diffusion (capacity)

- CO partial pressure in arterial blood rises so slowly—due to avid Hb–CO binding—that movement of this gas is always diffusion limited

- To calculate the diffusion capacity of the lung: a small amount of CO is inhaled in a single breath

- The alveolar P_{CO} is measured; the capillary P_{CO} is negligible and is ignored

- The diffusion equation is simplified:

$$\text{Gas transfer rate} = (\text{Area} / \text{Thickness}) \times \text{Diffusion constant} \times (P_1 - P_2)$$

Since area, thickness, and the diffusion constant cannot be measured for the lung, they are lumped together as "diffusing capacity for the lung", D_L

$$\text{Gas transfer rate} = D_L \times (P_1 - P_2)$$

Since P_1 is alveolar P_{CO} (P_{ACO}), and P_2 is pulmonary capillary P_{CO}, we can ignore the latter since it is so small; the result is

$$\text{Gas transfer rate} = D_L \times P_{ACO}$$

Finally, the gas transfer rate can be measured by determining the CO fractions in a single inspired breath (containing CO), and the next expired breath (containing a little less CO, since some entered the blood)

$$D_L = [\text{Net } CO \text{ transfer (mL/min)}] / P_{ACO}$$

Questions: Conditions that alter lung diffusing capacity, and the reasons why

Condition	D_{LCO}	Mechanism
Emphysema		
Age		
Exercise		

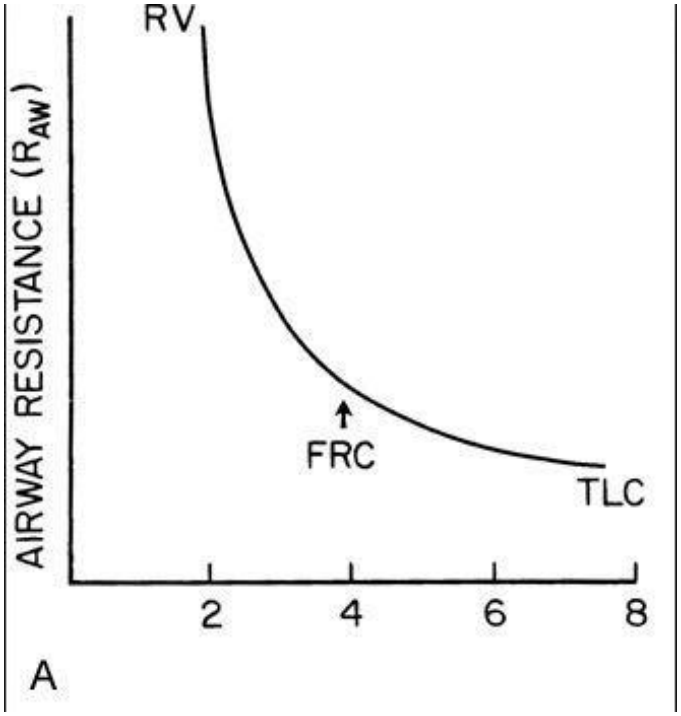
Condition	D_{LCO}	Mechanism
Pulmonary edema		
Pulmonary hypertension w/obliteration of small pulmonary arteries		
Pneumothorax		
Body size		
Pulmonary fibrosis		
Low blood volume in pulmonary capillaries		

Practice Questions

1. A disoriented 37-y/o man suffering from carbon monoxide poisoning is placed in a hyperbaric chamber at 3 atmospheres pressure of 42% oxygen, resulting in an estimated arterial P_{O2} of
    a. impossible to determine without knowing arterial P_{CO}
    b. 2250 mmHg
    c. 900 mmHg
    d. 760 mmHg
    e. 600 mmHg

2. A 65-y/o man with an 80 pack-year smoking history has chronic lung hyperinflation: residual volume and functional residual capacity are each increased by 1.4 liters. He also has increased
    a. airway collapse on inspiration
    b. FEV_1/FVC
    c. likelihood of inadvertent hyperventilation
    d. lung recoil
    e. reliance on accessory inspiratory muscles

3. A 58-y/o woman with chronic inflammatory bronchitis has cough, shortness of breath, and cyanosis. Her vital capacity and total lung capacity are normal. She has lost roughly 25% of her alveolar septa. As compared with the normal curve below, her airways resistance during inspiration at a lung volume of 5 liters is

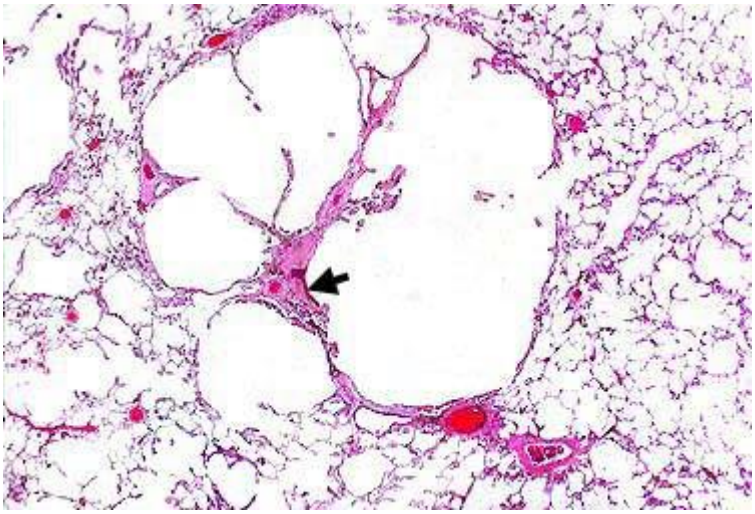


From http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v03/030090r00.HTM[82]

    a. decreased because the lung volume is on a steeper portion of the lung compliance curve
    b. increased due to airways collapse on inspiration
    c. increased due to reduced airway tethering
    d. reduced due to increases in lung compliance
    e. reduced because FRC is increased

4. A 28-y/o man working as a sandblaster develops cough, fever, and cyanosis. Test results find $FEV_1/FVC = 0.52$ (**L**), $P_{aO2} = 66$ (**L**), and $V_D/V_T = 0.48$ (**H**). Total lung capacity remains normal; residual volume is 2.7 liters (**H**). He has
    a. chronic lung hyperinflation
    b. loss of lung elastic recoil
    c. obstructive and restrictive lung disease
    d. obstructive lung disease only
    e. restrictive lung disease only

5. The image below shows a histologic section of lung of a patient with centroacinar emphysema:

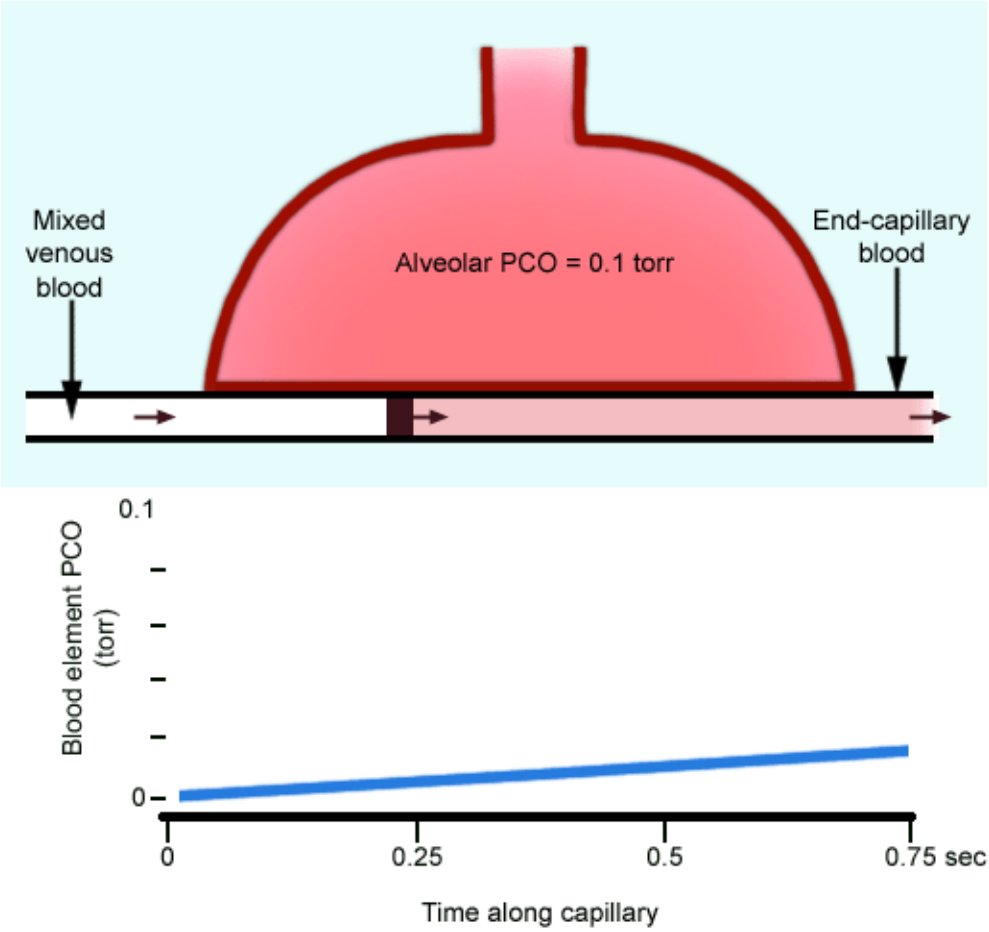


From: http://www.pharmacology2000.com/respiratory_anesthesiology/pulmonary_assessment/emphysema3.jpg[83]

The loss of alveolar walls contributes to *all but one* of the following problems:
    a. ↑ work of breathing
    b. ↓ FRC
    c. ↓ mechanical advantage of the diaphragm
    d. ↓ surface area for O_2 diffusion
    e. dynamic compression of airways on expiration

6. A 28-y/o electrical engineer was driving home from work one evening when he experienced sudden stabbing pain in his right lateral axillary region. He began to feel out of breath and both his respiratory rate and heart rate increased dramatically. The emergency room physician, after viewing a chest radiograph, diagnosed the condition as a spontaneous pneumothorax, and further tests showed
    a. ↓ airways resistance
    b. ↓ chest wall volume
    c. ↓ P_{aO2}
    d. ↓ V_D/V_T
    e. more negative intrapleural pressure

7. As illustrated in the figure below, what is assumed when CO is used to estimate lung diffusing capacity?

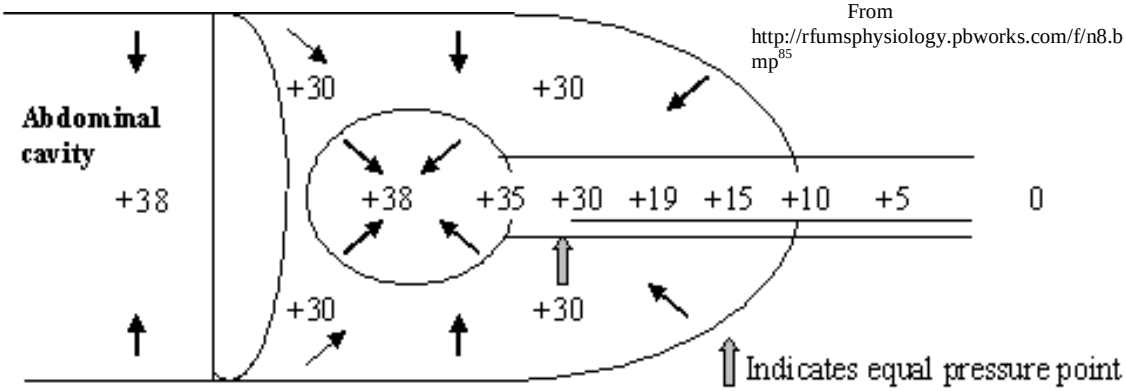


From http://alexandria.healthlibrary.ca/documents/notes/bom/unit_2/17no6.gif[84]

a. CO is perfusion limited
b. CO will not bind to hemoglobin
c. exercise will not change capillary residence time
d. P_{aCO} is zero
e. P_{ACO} is zero

8. A 34-y/o man, after being seriously injured in a car wreck, experiences an episode of severe sepsis that generates widespread clotting in the lung and plugging of numerous pulmonary arterioles. There is an increase in
    a. $f \times V_A$
    b. P_{aO2}
    c. P_{ECO2}
    d. V_A/V_T
    e. V_D/V_T

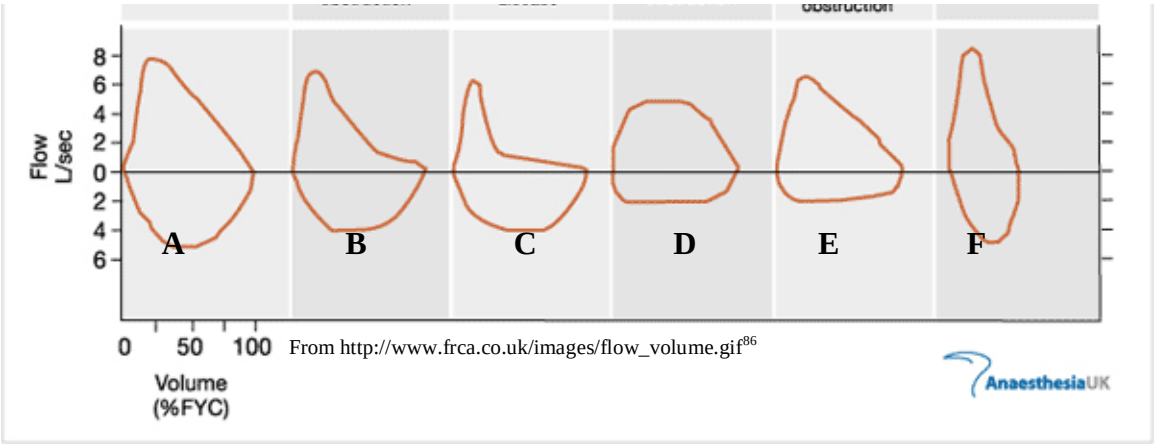
9. In a 35-y/o woman with asthma, what factor will move the "equal pressure point" in the figure below closer to the mouth?



From http://rfumsphysiology.pbworks.com/f/n8.bmp[85]

a. ↑ expiratory muscle force
b. ↓ lung elastic tissue
c. ↓ lung volume
d. less negative intrapleural pressure
e. β_2 agonists

10. Among the flow-volume loops below, the loop at the far left (A) is normal, while the loop at far right (F) involves



From http://www.frca.co.uk/images/flow_volume.gif[86]

a. airway inflammation and smooth muscle hypertrophy
b. an obstruction external to the thorax
c. elevated FRC
d. exaggerated airways collapse on expiration
e. increased elastic fibers in the alveolar walls

11. A 64-y/o woman with emphysema has total lung capacity 9 L, functional residual capacity 5.5 liters, tidal volume 0.5 L, and vital capacity 4.0 L. What is her residual volume?
    a. 1.5 L
    b. 3.0 L
    c. 3.5 L
    d. 4.5 L
    e. 5 L

12. A 23-y/o woman runs every morning, but after a 20 minute run, she becomes short of breath, particularly on cold mornings. Tests find exaggerated airway constriction after methacholine challenge, and post-exercise
    a. ↑ bronchial β_1 responsiveness
    b. ↑ D_{LCO}
    c. ↓ FRC
    d. ↓ lung $\Delta V/\Delta P$
    e. ↓ peak expiratory flow rate

Hypoventilation and hyperventilation

- Refers to the relative amount of minute ventilation, relative to the body's rate of production of CO_2 and consumption of O_2

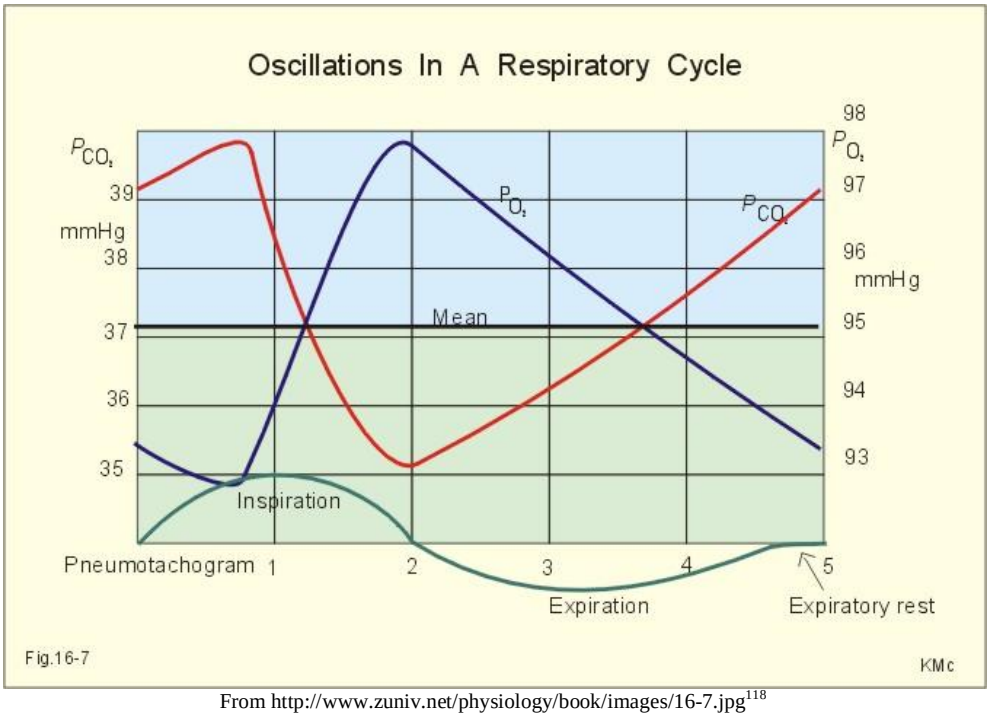
- Always defined relative to the metabolic needs of the body to receive O_2 and remove CO_2

- If ventilation increases in proportion to increased CO2 production or O2 consumption, this is termed *hyperpnea*, not hyperventilation

- If ventilation falls (assuming O_2 consumption and CO_2 production are constant), alveolar P_{CO2} will rise and alveolar P_{O2} will fall:

  Alveolar P_{CO2} = Constant × [Rate of CO_2 production] / [Alveolar ventilation]

- Breath-by-breath changes in alveolar P_{O2} and P_{CO2} reflect these same effects of ventilation increase and decrease on amounts of these gases in the alveoli and in the blood:



From http://www.zuniv.net/physiology/book/images/16-7.jpg[118]

Questions: Causes and effects of ventilation changes

Condition	ΔP_{O2}	ΔP_{CO2}	Comments
Mild exercise			
Opioid (e.g., heroin) overdose			
Suffocation			
Panic attack (panic disorder)			
Pain			
Severe asthma attack			
Respiratory muscle weakness			

- Ventilation is one of several factors that influences arterial P_{O2}; other factors include
    - Variations in inspired P_{O2}
    - Diffusion
    - Shunt
    - Mismatching of ventilation and perfusion (V/Q mismatch)
- Because CO_2 is a) rarely found in increased levels in inspired gas, b) much more diffusible than O_2, c) relatively unaffected by shunt, and d) relatively unaffected by V/Q mismatch—
    - The only significant cause of increased or decreased arterial P_{CO2} (hypercapnia and hypocapnia, respectively) is the presence of hypoventilation or hyperventilation
- CO_2 combines with water in plasma to form carbonic acid:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

  Therefore, ventilation changes can create, or compensate for, acid-base disturbances
- Because P_{CO2} changes dramatically alter cerebral vascular resistance, changes in ventilation alter brain blood flow
    - Hyperventilation → dizziness, fainting
    - Brain surgery → control ventilatory support to manage brain blood flow and intracranial pressure

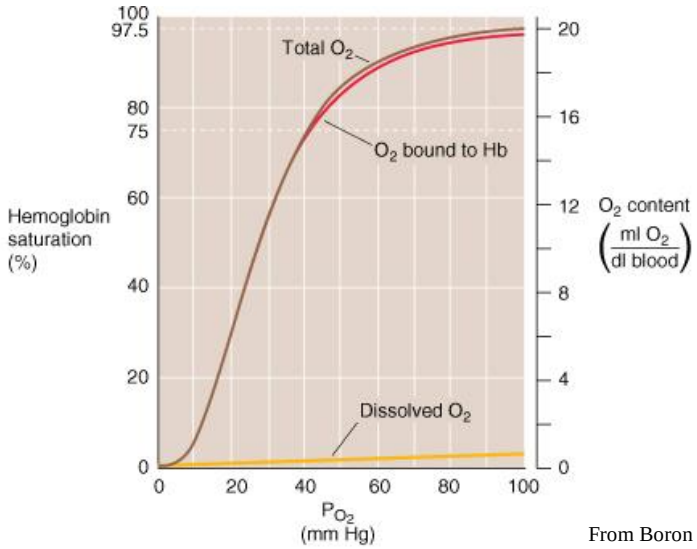
IV. Oxygen transport

Text: Costanzo pp. 130-135

- At a P_{O2} of 100 mm Hg in blood, more than 98% of the O_2 in blood is carried on hemoglobin
- Hemoglobin's iron-containing ferrous-state (Fe^{2+}) porphyrins ("heme moieties"), which are the O_2 binding sites, can be 100% O_2 saturated
- Ferric state—Fe^{3+}—does not bind O_2 (methemoglobin)

- We will distinguish hemoglobin saturation (O_2 saturation) from O_2 capacity, O_2 content, and P_{O2}

The association of O_2 with hemoglobin, as a function of P_{O2}, is non-linear



From Boron p. 674[119]

- O_2 capacity of blood: the maximum amount of O_2 that can be bound to hemoglobin
    - Depends upon hemoglobin concentration
    - Reduced in anemia, increased in polycythemia

- O_2 content of blood is the sum of the O_2 bound to hemoglobin, and the O_2 dissolved in the plasma

$$O_2 \text{ content} = (O_2 - \text{binding capacity} \times \%\ \text{saturation}) + \text{dissolved } O_2$$

where

O_2 content = amount of O_2 in blood (mL O_2/100 mL blood)

O_2 binding capacity = maximal amount of O_2 bound to hemoglobin at 100% saturation (mL O_2/100 mL blood)

% saturation = % of heme groups bound to O_2 (%)

Dissolved O_2 = unbound O_2 in blood (mL O_2/100 mL blood)

More quantitatively,

$$C_{aO2} = (S_{aO2} \times Hb \times 1.34) + .003\ (P_{aO2})$$

where C_{aO2} is arterial O_2 content in mL O_2 / 100 mL blood

S_{aO2} is % heme groups bound to O_2

Hb is hemoglobin concentration in g/100 mL blood

1.34 ml O_2 is the oxygen carrying capacity of one gram of hemoglobin

P_{aO2} is the arterial P_{O2} in mmHg

.003 "converts" arterial P_{O2} in mmHg to an O_2 content in mL O_2 / 100 mL blood

Questions: At rest, a person has normal minute ventilation and normal diffusion of oxygen from the alveolus into the pulmonary capillary. While these remain normal over a one-year period, during that time the person develops severe anemia, with hemoglobin falling from normal to 50% of normal. Complete the following table, and explain any changes from normal:

Condition	**What is alveolar P_{O2} ?**	**What is arterial P_{O2} ?**	**What is your estimate of total O_2 in blood?**
Healthy			
Anemia			

Questions: Complete the following table for systemic arterial blood:

Condition	**What is the effect on arterial P_{O2}?**	**What is the effect on O_2 capacity?**	**What is the effect on O_2 content?**	**What is the effect on O_2 saturation?**
Hypoventilation				
Anemia				

Condition	What is the effect on arterial P_{O2}?	What is the effect on O_2 capacity?	What is the effect on O_2 content?	What is the effect on O_2 saturation?
Polycythemia				
Pulmonary edema				

Practice Questions

1. A 60-y/o man with an 84 pack-year smoking history has cough, excessive sputum production, and fatigue. Tests find

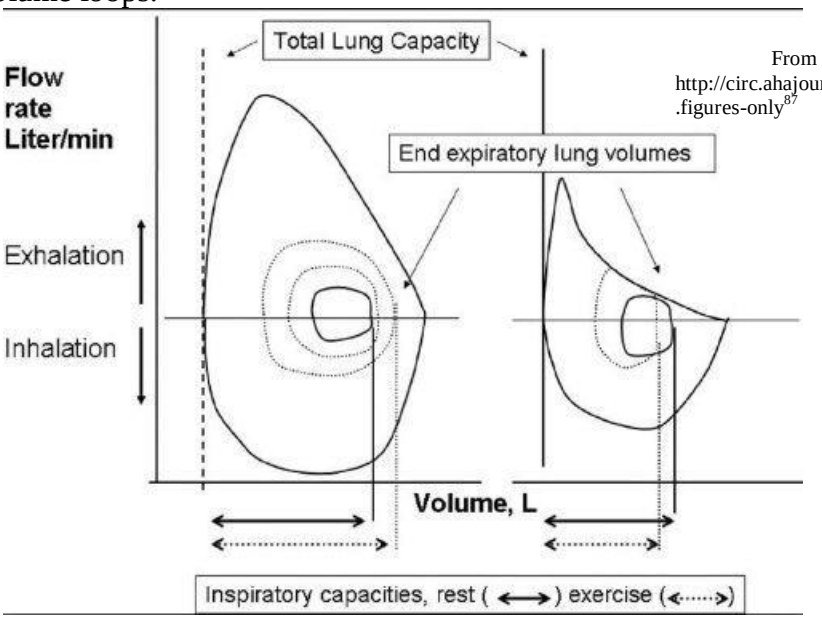
Hemoglobin (g/dl)	9.6	**L**
P_{AO2} (mm Hg)	103	
P_{aO2} (mm Hg)	64	**L**
P_{aCO2} (mm Hg)	40	
pH_a	7.40	

   Compared with normal, he has reduced arterial
   a. O_2 capacity only
   b. O_2 content only
   c. O_2 content and capacity only
   d. O_2 saturation, content, and capacity
   e. O_2 saturation only

2. In the emergency room, a 40-y/o man with dizziness and tachycardia has P_{AO2} 125 (**H**), P_{aO2} 122 (**H**), P_{aCO2} 21 (**L**), and arterial pH 7.53 (**H**). D_{LCO} and lung recoil are normal. He is suffering from
   a. acute, severe asthma attack
   b. heroin overdose
   c. panic attack
   d. pulmonary embolus
   e. simple pneumothorax

3. A 27-y/o man with 15 pet tropical birds develops hypersensitivity pneumonitis ("Bird fancier's disease"). He has reduced FEV_1 and FVC, normal FEV_1/FVC, decreased total lung capacity, normal P_{aO2} at rest, decreased P_{aO2} on exercise challenge, and
   a. ↓ D_{LCO}
   b. dynamic compression of airways during inspiration
   c. hypoventilation
   d. obstructive lung disease
   e. ↑ residual volume

4. Two 50-year old women, one healthy and one with emphysema, begin exercise stress tests together. Their tidal breathing at rest (solid line) and exercise-induced increases in tidal volume and flow rates (dotted lines) are shown below, along with their maximal flow-volume loops:



From http://circ.ahajournals.org/content/122/2/191.figures-only[87]

Pulmonary function in the woman with emphysema differs from the healthy woman in terms of

a. decreased breathing frequency during matched exercise
b. expiratory dynamic airway compression during exercise
c. greater resting and exercise tidal volumes
d. increased inspiratory capacity at rest and in exercise
e. relative hyperventilation during exercise

5. A 47-y/o woman with shortness of breath and cyanosis has P_{AO2} 102, P_{aO2} 57 (**L**), and mixed venous P_{O2} 31 (**L**) at rest. She is primarily suffering from

a. decreased pulmonary shunt
b. slow pulmonary capillary transit
c. diffusion limited O_2 transfer
d. perfusion limited O_2 transfer
e. hypoventilation

6. A 50-year old man develops chest pain, dyspnea, anxiety, fatigue, and cyanosis after a fall from a ski lift. A tension pneumothorax is diagnosed, which also causes

a. hypotension due to reduced venous return
b. ↑ lung volume at FRC
c. more positive (alveolar - intrapleural) pressure on the affected side
d. subatmospheric intrapleural pressure on the affected side
e. ↓ transpulmonary pressure on the unaffected side

7. A 15-y/o girl with dizziness, sleepiness, and exhaustion has P_{aO2} = 103 mmHg, arterial pH = 7.37, P_{aCO2} = 40 mmHg, and low arterial O_2 content = 10.4 vol%. A realistic diagnosis
    a. iron-deficiency anemia
    b. hypoventilation
    c. reduced lung diffusing capacity (D_{LCO})
    d. mitral regurgitation
    e. low cardiac output

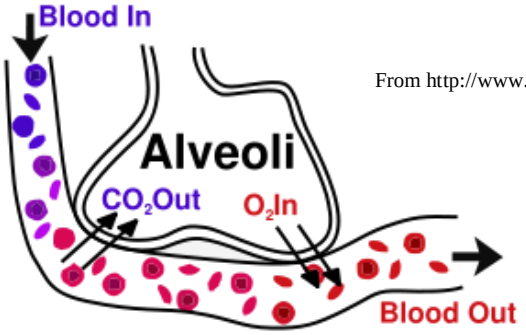
8. Inhalation of gas G causes alveolar P_G to reach 3.7 mmHg. If mixed venous P_G is 0.0 mmHg, and rises to 2.5 mmHg during transit through an average pulmonary capillary, it is correct to say that transfer of gas G into blood is
    a. diffusion limited
    b. lower than pulmonary CO diffusing capacity
    c. perfusion limited
    d. neither diffusion nor perfusion limited
    e. perfusion limited at rest; diffusion limited in exercise

10. Twin40-y/o brothers are seen in the emergency room. Patient A has arterial pH 7.51, P_{aCO2} 24, P_{aO2} 86, Sa_{O2} 96%, and hemoglobin 9.5. Patient B has arterial pH 7.39, P_{aCO2} 41, P_{aO2} 64, Sa_{O2} 89%, and hemoglobin 16.4. Which patient is has more total oxygen in the blood?
    a. A
    b. B
    c. impossible to determine from the information given
    d. they are equally low in blood O_2 content
    e. they are equally low in blood O_2 capacity

11. For a 66-y/o woman with P_{AO2} = 100 mmHg and P_{ACO2} = 40 mmHg, a P_{aO2} of 56 mmHg indicates the presence of
    a. diffusion defect or shunt only
    b. hypoventilation or diffusion defect only
    c. hypoventilation, shunt, or diffusion defect
    d. it can indicate only hypoventilation
    e. hypoventilation or shunt only

12. During open-heart surgery, mixed venous blood of a 67-y/o man is routed through a membrane gas exchanger to oxygenate the blood to arterial levels. What must the composition of the exchanger fluid be for sufficient oxygenation of blood, if equilibrium is attained between blood and exchanger fluid and no liquid or cells cross the membrane?
    a. O_2 content = 20 vol%
    b. P_{O2} = 100 mmHg
    c. dissolved O_2 = 2 vol%
    d. hemoglobin = 15 gm/dL, O_2 content = 15.5 vol%
    e. O_2 capacity = 20 vol%

13. For the alveolar-capillary combination pictured below,

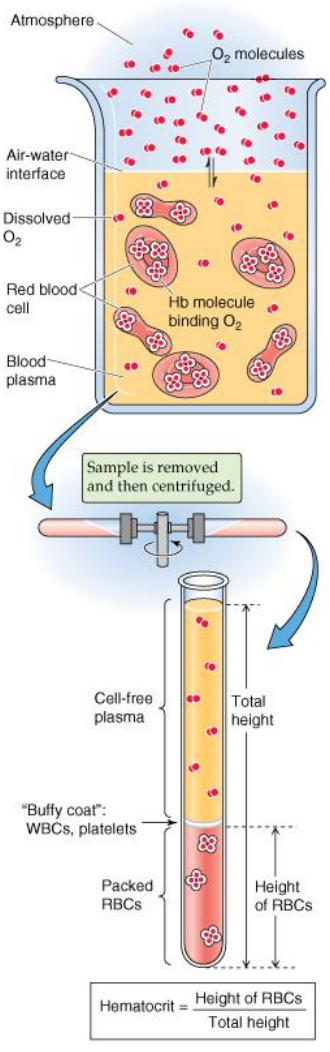


From http://www.vgate.net.au/SOB/alveoli.html[88]

Perfusion-limited gas exchange means for O_2 that

a. capillary O_2 content = alveolar O_2 content as blood exits
b. capillary O_2 content > alveolar O_2 content as blood exits
c. [O_2 In] ceases before blood exits the capillary
d. [O_2 In] equals [CO_2Out] within the capillary
e. [O_2 In] exceeds [CO_2Out]

Red cell indices

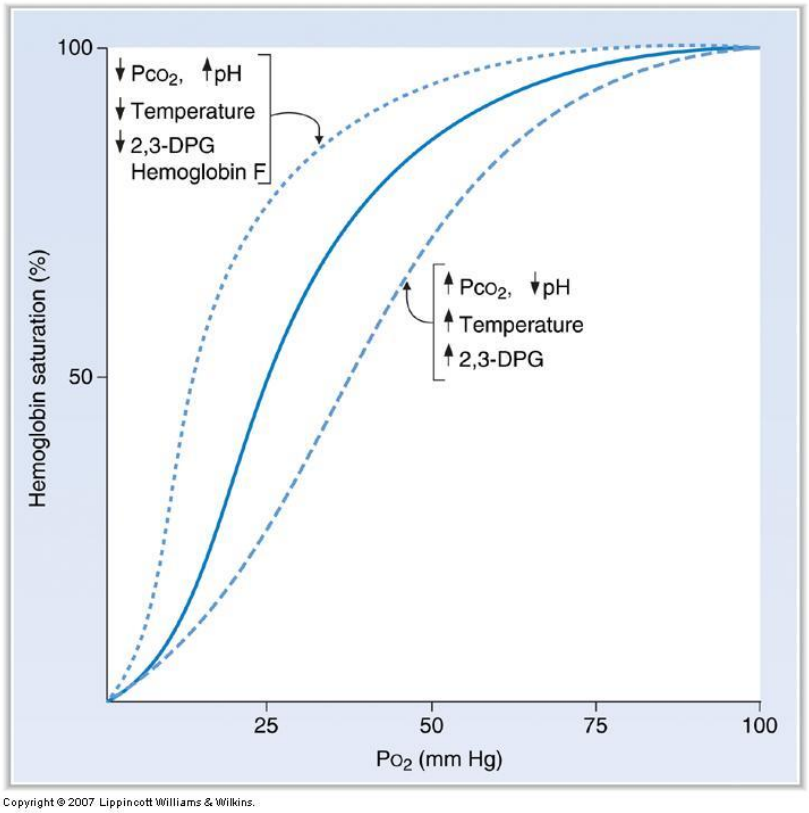


From Boron p. 674[120]

- Hematocrit is the % by volume of red blood cells in blood
- Hemoglobin concentration and hematocrit are usually linearly related
- Certain forms of anemia dissociate hemoglobin from hematocrit: red blood cells may have abnormally high or abnormally low amounts of hemoglobin per cell
- The complete blood count (CBC) details all basic structural aspects of the red and white blood cells
- For red blood cells, these include the basics (hemoglobin concentration and hematocrit) as well as the mean volume of the red cells (mean corpuscular volume, MCV) and the mean corpuscular hemoglobin (MCH)
- In the differential diagnosis of the anemias, for example, a vitamin B_{12} deficiency "pernicious anemia") increases the MCV (= "macrocytic anemia")
- An iron-deficiency anemia, in contrast, lowers the MCV

Changes in the hemoglobin-O_2 dissociation curve

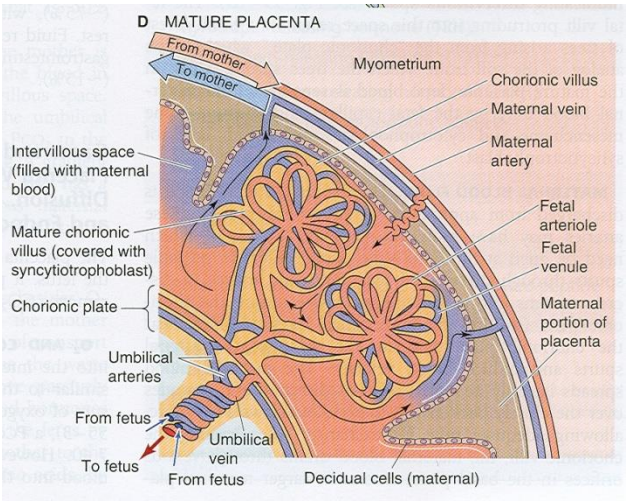
- Fetal hemoglobin
    - Adult form—two α, two β chains : $\alpha_2\beta_2$; this is HbA
    - Fetal form—replace β chains with γ chains: $\alpha_2\gamma_2$; this is HbF
    - HbF binds the glycolytic metabolite 2,3 diphosphoglycerate (2,3 DPG) less avidly than HbA
    - 2,3 DPG binding reduces the affinity of Hb for O_2
- Several other local biochemical changes right-shift and left-shift the curve, facilitating loading and unloading of O_2 from hemoglobin. Right-shifting is caused by
    - Increased temperature
    - Increased P_{CO2}
    - Increased acidity (decreased pH)
    - Increased 2,3-DPG
- Exercise provokes all the changes that cause right-shifting of the curve



From Costanzo p. 132[121]

- P_{50} is a rule of thumb to track changes in hemoglobin-O_2 affinity

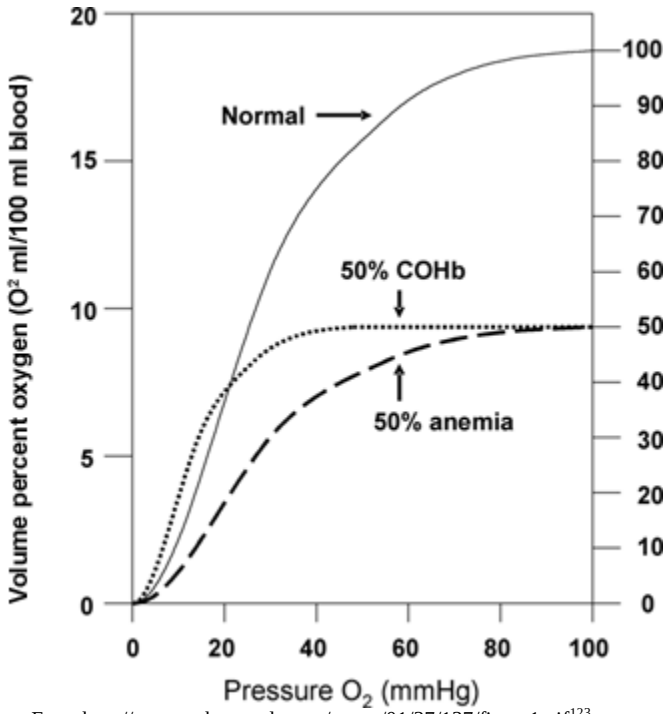
Question: Explain how O_2 moves between mother and fetus, and draw a graph showing how left-shifted fetal hemoglobin (HbF) facilitates fetal oxygenation



From ©Elsevier Ltd. Boron & Boulpaep: Medical Physiology, Updated Edition www.studentconsult.com, p. 1179[122]

Carbon monoxide poisoning

- Hb has 200× greater affinity for CO than for O_2



From http://www.cyberounds.com/assets/01/37/137/figure1.gif[123]

- CO also left-shifts the remaining O_2-hemoglobin binding sites, making it difficult to unload what little O_2 may remain

- A routine clinical measurement is "pulse oximetry", a small device that fits over a fingertip and measures heart rate (pulse) and redness of the nailbed; nailbed redness is linearly related to Hb – O_2 saturation but Hb –CO is equally red

Questions (and answers)**:** From the "World-Class Quiz in Pulmonary Medicine and Physiology" (http://www.lakesidepress.com/WCQ2001/1-30.htm) by: Lawrence Martin, MD, Chief, Division of Pulmonary and Critical Care Medicine, Mt. Sinai Medical Center, Cleveland, OH 44106[124]

1. (Degree of difficulty 2/5) Which patient is more hypoxemic, and why?

Patient A: pH 7.48, P_{aCO2} 34 mm Hg, P_{aO2} 85 mm Hg, S_{aO2} 95%, Hemoglobin 7 gm%

Patient B: pH 7.32, P_{aCO2} 74 mm Hg, P_{aO2} 55 mm Hg, S_{aO2} 85%, Hemoglobin 15 gm%

Hint: Be specific -- this is not a question you guess at.

2. (Degree of difficulty 3/5) True or False:

The P_{O2} in a cup of water open to the atmosphere is always higher than the arterial P_{O2} in a healthy person (breathing room air) who is holding the cup.

3. (Degree of difficulty 3/5) State which of the following situations would be *expected* to lower a patient's arterial P_{O2}. There may be none, one, or more than one correct answer.

a) anemia
b) carbon monoxide poisoning
c) an abnormal hemoglobin that holds oxygen with half the affinity of normal hemoglobin
d) an abnormal hemoglobin that holds oxygen with twice the affinity of normal hemoglobin
e) lung disease with intra-pulmonary shunting.

4. (Degree of difficulty 2/5) In the following completion statement about carbon monoxide, there may be none, one, or more than one correct response.

Carbon monoxide:

a) shifts the oxygen dissociation curve to the left
b) lowers the P_{aO2}
c) lowers the arterial oxygen content
d) is always elevated in the blood of cigarette smokers

5. (Degree of difficulty 3/5) Which statement is *most correct* about obtaining arterial blood gas in a patient with an acute asthma attack?

a) Anyone coming to the emergency department with an acute asthma attack should have an arterial blood gas at the start of therapy.
b) Peak flow or similar test of expiratory effort should be the guide, with a PF < 50% that doesn't improve with medication being one reasonable criterion to obtaining a blood gas.
c) Blood gases should be obtained in any patient using accessory breathing muscles, irrespective of the peak flow.
d) As long as pulse oximetry is adequate and the patient is alert, an arterial blood gas should not be necessary.

6. (Degree of difficulty 2/5) A physically-fit subject goes jogging for two miles. After 7 minutes and end of the first mile, her respiratory rate has doubled. She feels fine and anticipates no difficulty in completing the second mile. At the one mile point, based on your understanding of pulmonary physiology, you would expect her arterial blood to show:

a) Normal P_{CO2} and pH
b) Low P_{CO2} and high pH
c) High P_{CO2} and low pH
d) Low P_{CO2} and low pH

7) (Degree of difficulty 2/5) Which of the following changes will *most increase* arterial oxygen delivery?

a) P_{aO2} from 70 to 95 mm Hg
b) cardiac output from 4 to 5 L/min
c) hemoglobin from 9 to 10 grams%
d) atmospheric pressure from 1 to 2 atmospheres
e) arterial pH from 7.30 to 7.50

Causes of hypoxia and hypoxemia

- Hypoxia is a general term meaning lack of available oxygen for tissues, due to any sort of problem

- Hypoxemia is more specific, and refers to an abnormally low level of oxygen in the systemic arterial blood

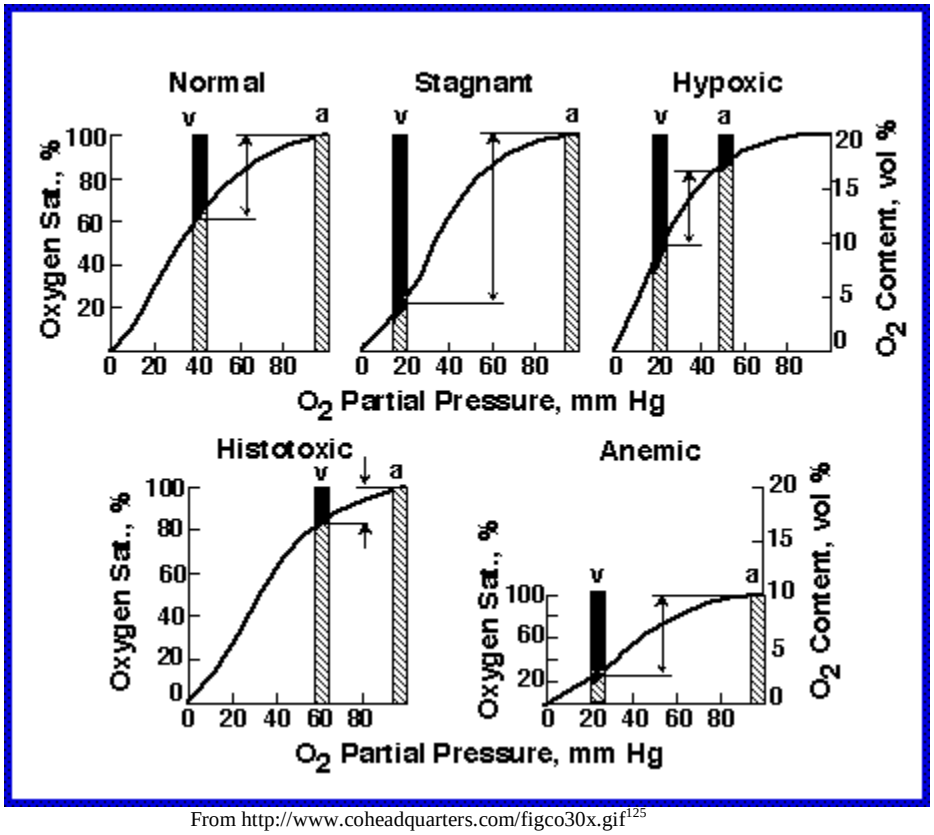
- The P_{O2} difference between the alveoli (P_{AO2}) and the systemic arterial blood (P_{aO2}) is called the A – a gradient. The normal A – a gradient is about 5 mmHg

Questions: Some causes of hypoxemia:

Causes	**P_{aO2}**	**A – a gradient**
High altitude		
Hypoventilation		
Diffusion defect (e.g., fibrosis, pulmonary edema)		
↑ Pulmonary shunt (pathophysiologic shunt)		
V/Q mismatch		

Questions: Some classic causes of hypoxia:

Cause	**What is the matching figure (next page) and what about the condition creates "hypoxia"?**
↓ Cardiac output	
Anemia	
Exposure to high altitude	
Cyanide poisoning	



From http://www.coheadquarters.com/figco30x.gif[125]

V. CO_2 transport in blood

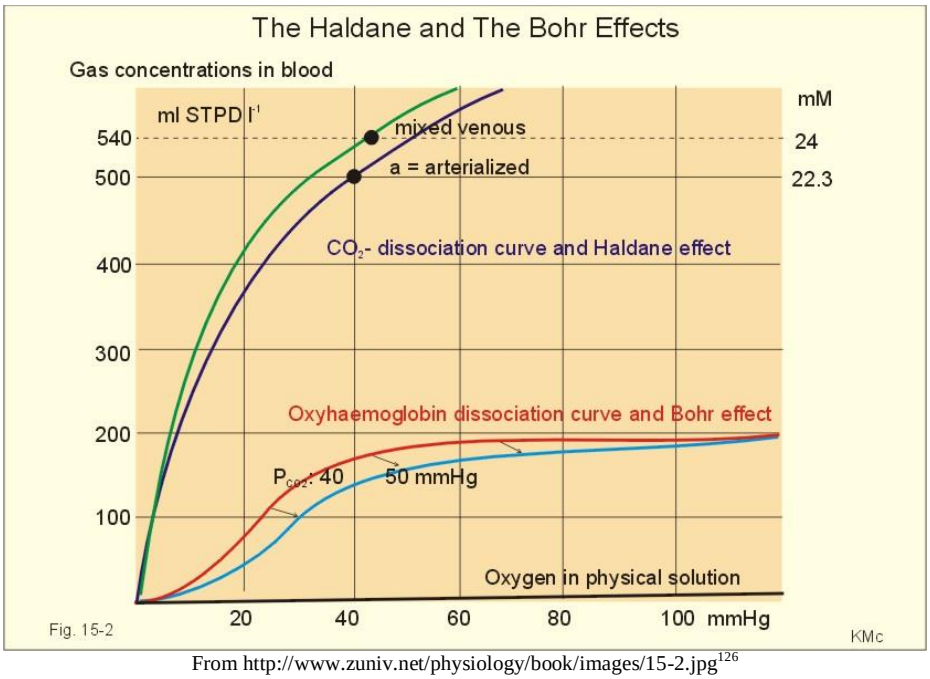
Text: Costanzo pp. 135-136

- Never really goes wrong; tissues add CO_2, lungs remove CO_2, it's okay
- But the CO_2 story is an intimate part of the acid-base balance story
- CO_2 is carried in blood in three forms
    - Dissolved, which is "free" in solution (small amount)
    - Directly attached to hemoglobin ("carbaminohemoglobin") (small amount)
    - "As bicarbonate": CO_2 is hydrated in blood to form carbonic acid (thanks to the enzyme carbonic anhydrase). Carbonic acid then almost entirely dissociates:

$$\begin{array}{c} Pr^- \\ + \\ CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \\ \downarrow\uparrow \end{array}$$

HPr

- The sum of the three forms of CO_2 carriage in blood yields a blood P_{CO2}—CO_2 content curve that is much more steep and linear than the P_{O2}—O_2 content curve



From http://www.zuniv.net/physiology/book/images/15-2.jpg[126]

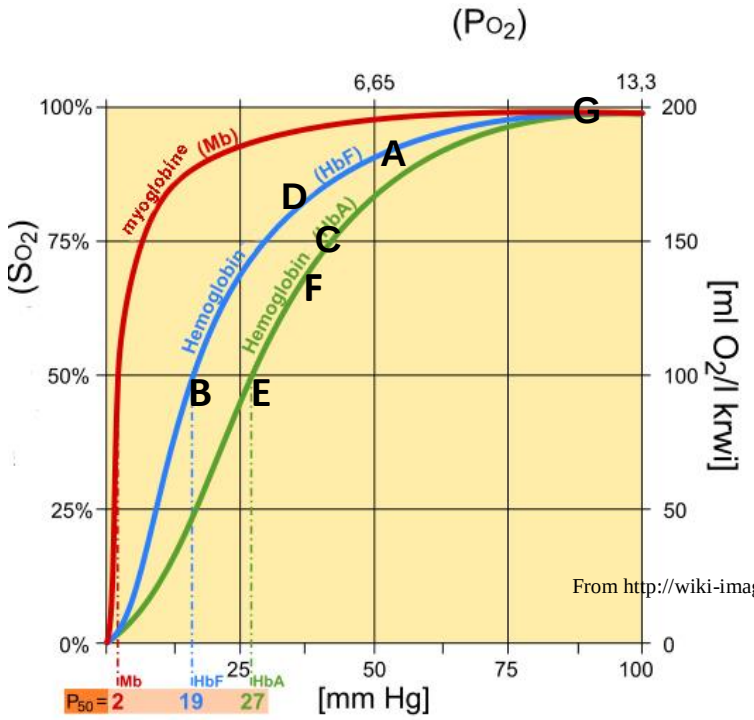
Clinical convention: "Total CO_2" or just "CO_2" from the hospital lab

- 90% of CO_2 is carried in the blood in the "form" of HCO_3^-
- Labs measure and report total CO_2, which is the total of HCO_3^- (90%), and dissolved CO_2, and the small amount of existing H_2CO_3. Carbaminohemoglobin doesn't get counted
- So doctors interpret the lab result of "total CO_2" or "CO_2" as really HCO_3^-
- Other acids in the body (e.g., lactic acid, ketoacids) are buffered by HCO_3^-, so HCO_3^- levels are best used as one measure of overall acid-base status
- "Total CO_2" or "CO_2" is listed as an electrolyte, along with Na^+, K^+, and Cl^-

Question: A 68-year old woman with severe emphysema has a disease exacerbation and is hospitalized. Is the hospital lab's venous "CO_2" result an appropriate test for the presence of hypoventilation? Please explain why or why not, and provide a better test (if there is one)

Practice Questions

1. Movement of O_2 from maternal to fetal blood during gestation follows which path in the figure below?



From http://wiki-images.enotes.com/a/a3/Hb.jpg[89]

   a. G to F
   b. A to C
   c. E to D
   d. C to D
   e. F to G

2. A 28-y/o woman of average size is taken to the emergency room with extreme shortness of breath. Pulmonary function tests show FEV_1/FVC = 42% (54% of normal) and V_T = .20 L/breath; breathing frequency is 11/min. The arterial blood gas results are
   a. P_{aO2} = 102, P_{aCO2} = 54
   b. P_{aO2} = 66, P_{aCO2} = 40
   c. P_{aO2} = 70, P_{aCO2} = 58
   d. P_{aO2} = 96, P_{aCO2} = 27
   e. P_{aO2} =124, P_{aCO2} = 31

3. If a fetus's hemoglobin F was suddenly changed to hemoglobin A, there would be
   a. ↑ O_2 content at any given O_2 sat
   b. ↑ O_2 content at any P_{O2}
   c. ↑ O_2 saturation at any P_{O2}
   d. ↑ P_{O2} for any equivalent O_2 content
   e. ↓ hematocrit required for transport of any given O_2 content

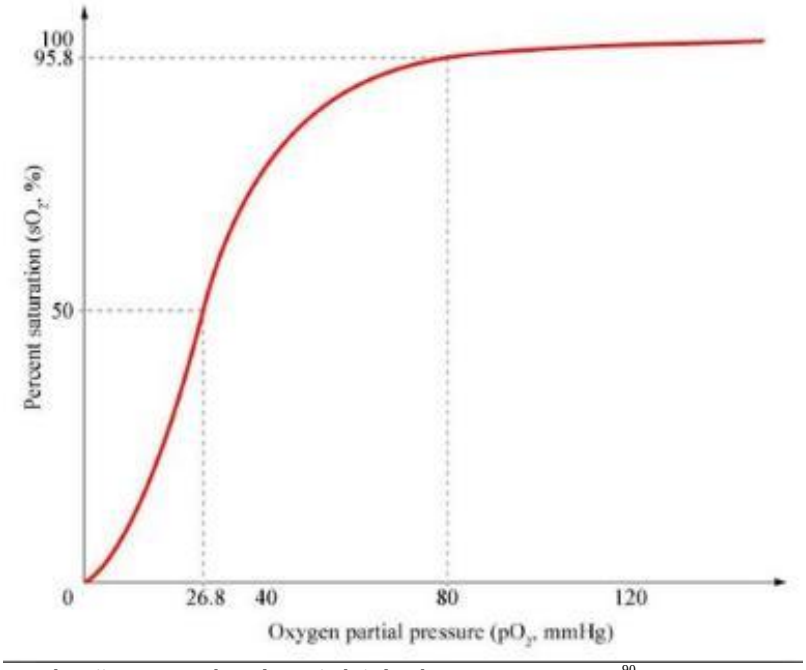
4. Which of the following clinical conditions will reduce "total CO_2" (which is reported routinely as an electrolyte):
    a. diabetic ketoacidosis
    b. hypoventilation
    c. polycythemia
    d. severe asthma
    e. V/Q mismatch

5. A 4-y/o girl was brought to the emergency department after a period of unresponsiveness with poor respiratory effort. Her appearance was described as "pale with cherry red lips." Temperature was 36.6°C, blood pressure 90/56, respiratory rate 32/min, and heart rate 119. P_{aO2} was 99, P_{aCO2} 41, hemoglobin 13, and venous COHb level was 22.2% (normal, 0.1% to 2.0%). What else was normal?
    a. arterial O_2 capacity
    b. arterial O_2 content
    c. arterial O_2 saturation
    d. mixed venous P_{O2}
    e. P_{50}

6. A 35-y/o man who works in an underground parking garage develops carbon monoxide-induced polycythemia. He has P_{aCO} 0.8 mmHg (**H**), P_{aO2} 102, carboxyhemoglobin 14% (**H**), and hemoglobin 17.5 (**H**). He has
    a. ↑ O_2 content and ↑O_2 capacity
    b. ↓ O_2 content and ↓O_2 capacity
    c. ↑ O_2 content and ↓O_2 capacity
    d. ↓ O_2 content and ↑O_2 capacity
    e. ↓ O_2 saturation, ↓O_2 content, and ↓O_2 capacity

7. Five patients are in the intensive care unit. The most hypoxemic patient is the one with
    a. pH 7.51, P_{aO2} 75, S_{aO2} 91%, hemoglobin 10 gm%
    b. P_{aO2} 722, S_{aO2} 99%, hemoglobin 7 gm%
    c. pH 7.24, P_{aO2} 124, S_{aO2} 98%, hemoglobin 12
    d. P_{AO2} 102, P_{aO2} 68, pH 7.33, S_{aO2} 89%, hemoglobin 14
    e. pH 7.32, P_{aO2} 150, S_{aO2} 86%, hemoglobin 16

8. Based on the figure below, derived from a normal adult, which of the following will increase the P_{50}?



From http://commons.wikimedia.org/wiki/File:Hb_saturation_curve.png[90]

   a. ↑ 2,3 DPG
   b. ↑ pH
   c. substitution of hemoglobin F for hemoglobin A
   d. ↓ P_{CO2}
   e. ↓ temperature

9. A previously healthy 41-y/o man develops hemochromatosis with hemoglobin 20 g/dl (**H**) and hematocrit 62% (**H**). P_{AO2} is 99, P_{aO2} 96, P_{aCO2} 39, and arterial pH 7.41. He has increased
   a. (A – v) O_2 difference
   b. A – a O_2 gradient
   c. arterial O_2 content and capacity
   d. arterial O_2 saturation and capacity
   e. D_{LCO}

10. A 44-y/o man with pulmonary sarcoidosis has dyspnea, cough, wheezing, and chest pain. Tests find

Vital capacity (L)	4.1	**L**
P_{AO2} (mmHg)	99	
P_{aCO2} (mmHg)	40	
P_{aO2} (mmHg)	65	**L**
D_{LCO}	4.7	**L**
Lung compliance	8.7	**L**
P_{aO2} on 100% O_2	703	

The sarcoidosis has resulted in

a. diffusion limited O_2 transfer
b. ↑ intrapulmonary shunt
c. hypoventilation
d. obstructive lung disease
e. perfusion limited CO_2 exchange

11. A 37-y/o woman with fibrotic lung disease, shortness of breath, and mild cyanosis has P_{AO2} 58 (**L**), P_{aO2} 57 (**L**), and mixed venous P_{O2} 31 (**L**) at rest. She is primarily suffering from

a. hypoventilation
b. increased pulmonary shunt
c. loss of alveolar surface area
d. O_2 diffusion limitation
e. O_2 perfusion limitation

12. A war criminal takes cyanide rather than face trial. A first effect of the drug is

a. ↑ hypoxic pulmonary vasoconstriction
b. ↓ (A – v) O_2 difference
c. ↓ arterial O_2 content
d. ↓ P_{aO2}
e. ↓ P_{AO2}

14. A 38-year old man with cough, shortness of breath, fatigue and abnormal breath sounds has P_{AO2} 98, P_{aO2} 58 (**L**), P_{ACO2} 40, and P_{aCO2} 40. P_{aO2} is 705 during 100% O_2 breathing, suggesting that he has

a. hypoventilation
b. left-to-right shunt
c. low D_{LCO}
d. pulmonary embolus
e. right-to-left shunt

VI. Pulmonary Circulation

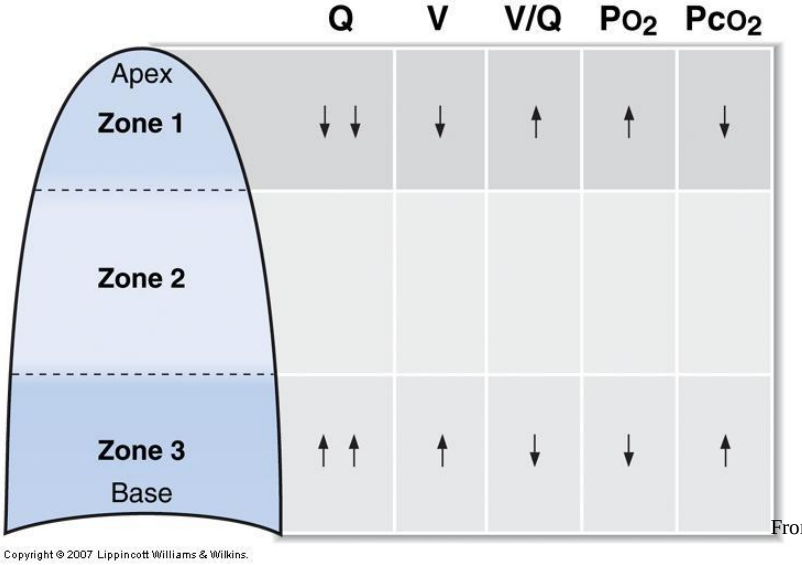
- Low pressure, low resistance (mean pulmonary arterial pressure is ~15 mmHg)

- No important autonomic neural (sympathetic or parasympathetic) influences on vessel caliber

- There are neuroendocrine/hormonal/peptide factors that can be manipulated to alter pulmonary vascular resistance. While useful in treatment of primary pulmonary hypertension, their *physiological* significance is unknown.

    - Prostacyclin—vasodilator
    - Nitric oxide—vasodilator
    - Endothelin 1—vasoconstrictor

- Regional blood flow is gravitationally dependent—regional flow varies on the basis of hydrostatic pressure differences



From Costanzo p. 138[127]

- Zone 1: Lowest flow. If alveolar pressure > capillary pressure at the arterial and venous ends of the capillaries, capillaries are compressed and no flow is possible (e.g., after hemorrhage, during positive pressure ventilation)

- Zone 2: Medium flow. Capillary pressure at the arterial end > alveolar pressure > capillary pressure at the venous end of the capillary: Blood flow is driven by the difference between *arterial* and *alveolar* pressure

- Zone 3: Highest flow. Capillary hydrostatic pressure throughout the capillary > alveolar pressure: Blood flow is driven by the arterial – venous pressure difference, as in most capillary beds

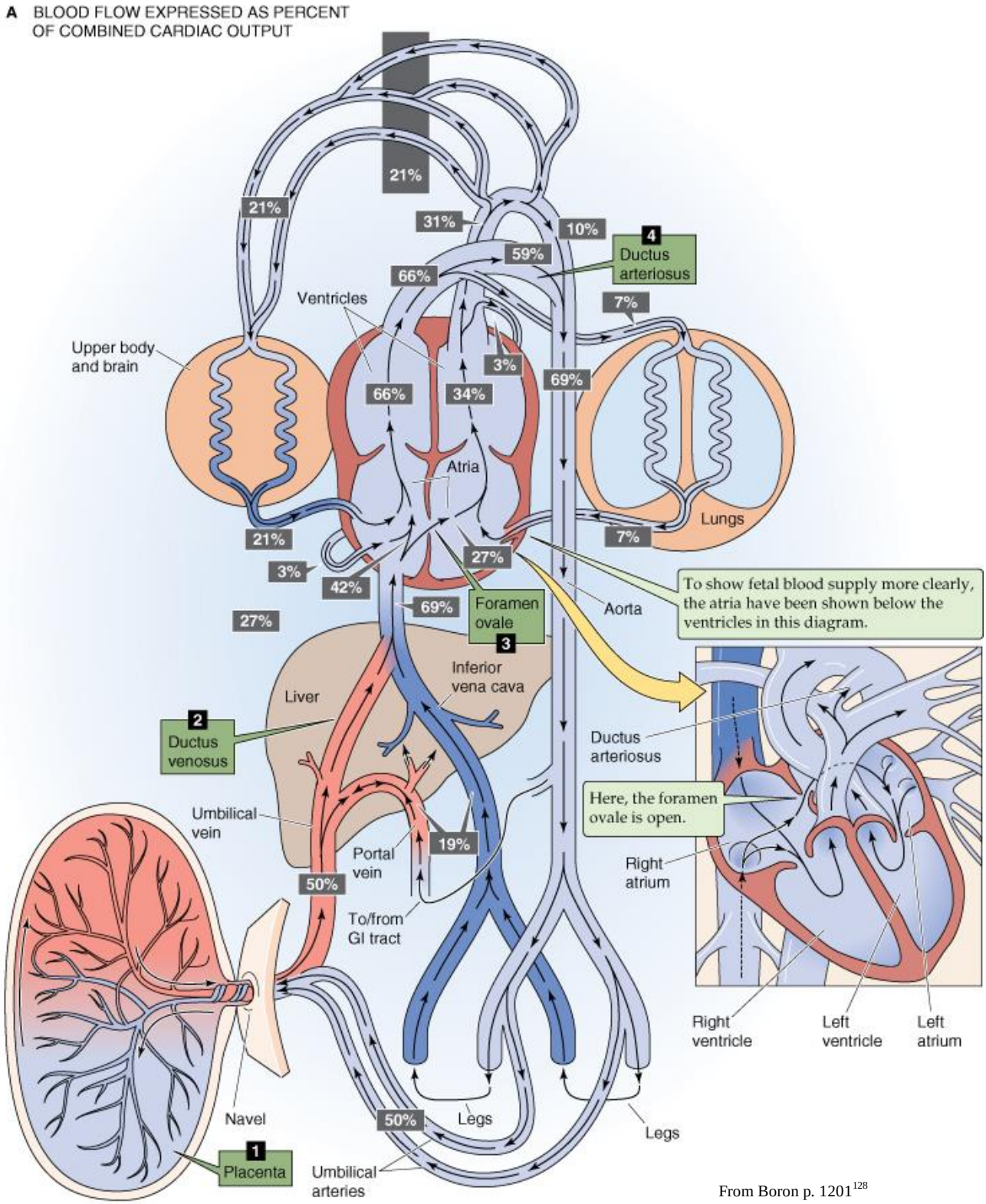
- Aside from posture, the major local controller of lung blood flow is alveolar hypoxia
    - Alveolar hypoxia causes nearby pulmonary arterioles to constrict ("hypoxic pulmonary vasoconstriction")
    - Hypoxia in the blood has little effect on pulmonary arteriolar caliber
    - The effects of low P_{O2} in alveolar gas on pulmonary arterioles is opposite that in systemic arterioles
    - Hypoxic pulmonary vasoconstriction is useful for locally matching ventilation (V) and blood flow (Q) in health

Question: What is the effect of chronically decreased P_{AO2} on the heart?

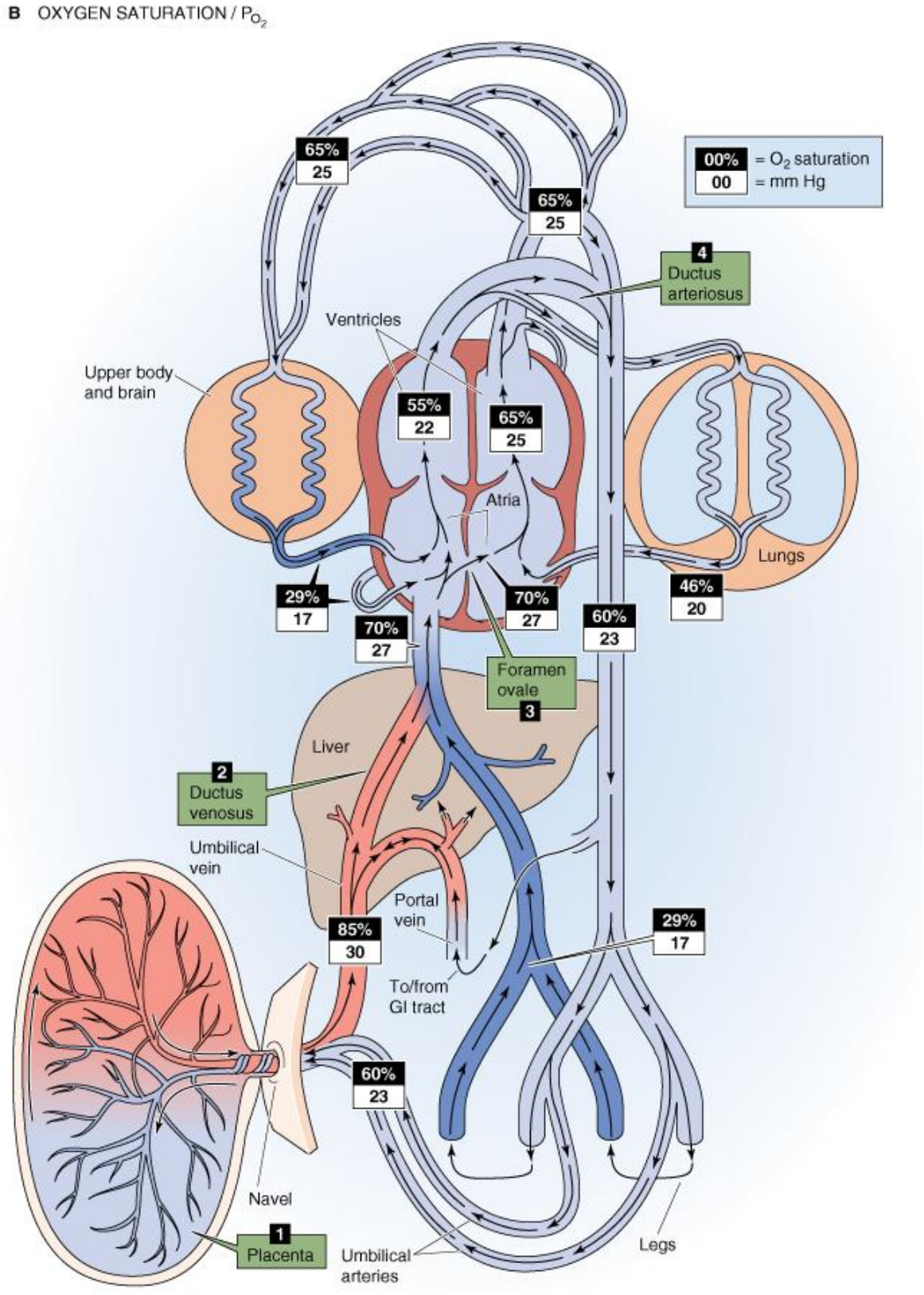
Question: What are the predicted pulmonary arterial pressures—and explain any changes from normal—during

1. Health
2. Climbing on Mt. Everest at 26,000 feet
3. Emphysema
4. Fetal life
5. The transition from fetal to neonatal life: the first few breaths

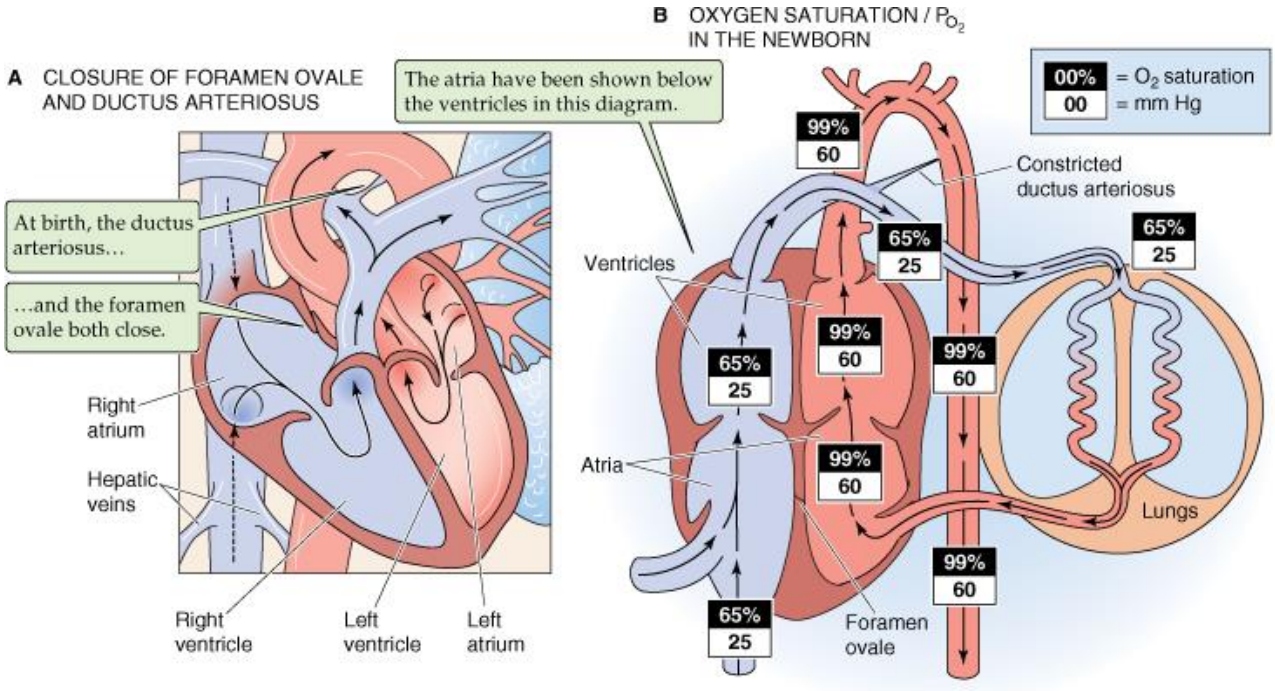
- Hypoxic pulmonary vasoconstriction is a major factor that determines flows and pressures in the fetal circulatory system:



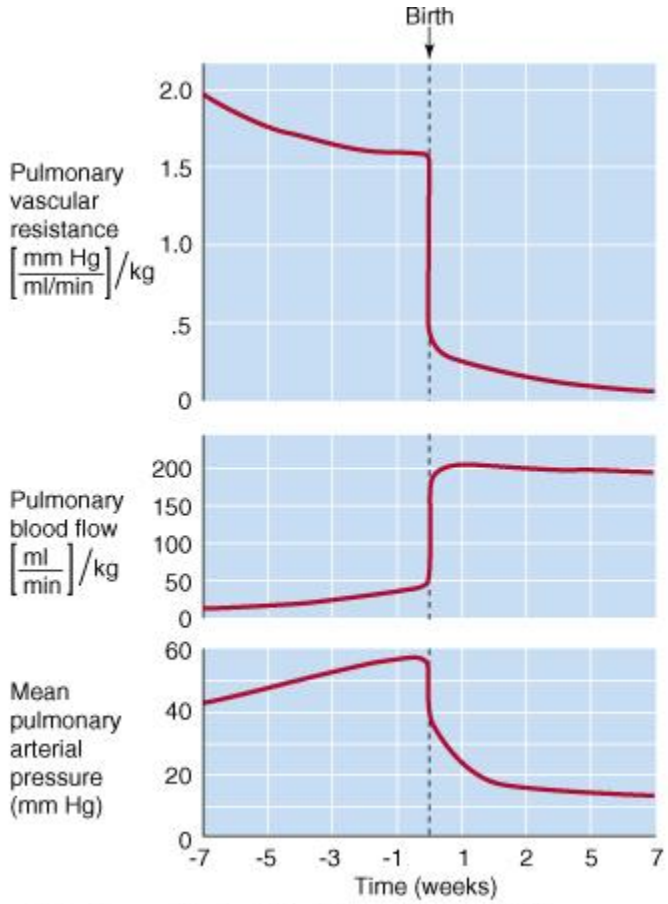
From Boron p. 1201[128]



From Boron p. 1202[129]



From Boron p. 1205[130]



From Boron p. 1204[131]

Shunts

- A channeling of blood, in this instance across the heart or lungs such that either
    - Systemic mixed venous blood is added directly to the systemic arteries (right-to-left shunt), or
    - Blood in the left atrium or ventricle moves to the right side of the heart (left-to-right shunt)

Questions: Characteristics of intracardiac left-to-right and right-to-left shunts

Condition	How does the shunt affect P_{aO2}?	Given that the shunt is present, how will breathing 100% O_2 influence arterial P_{O2}?	What is the effect of the shunt on left ventricular forward cardiac output?	What symptoms are caused by the presence of the shunt?
Left-to-right shunt				
Right-to-left shunt				

Right-to-left shunts

- In certain congenital conditions (e.g., Tetralogy of Fallot), the right-to-left shunt can reach 50%

Left-to-right shunts

- Common due to higher left-sided cardiac pressures; often due to congenital conditions

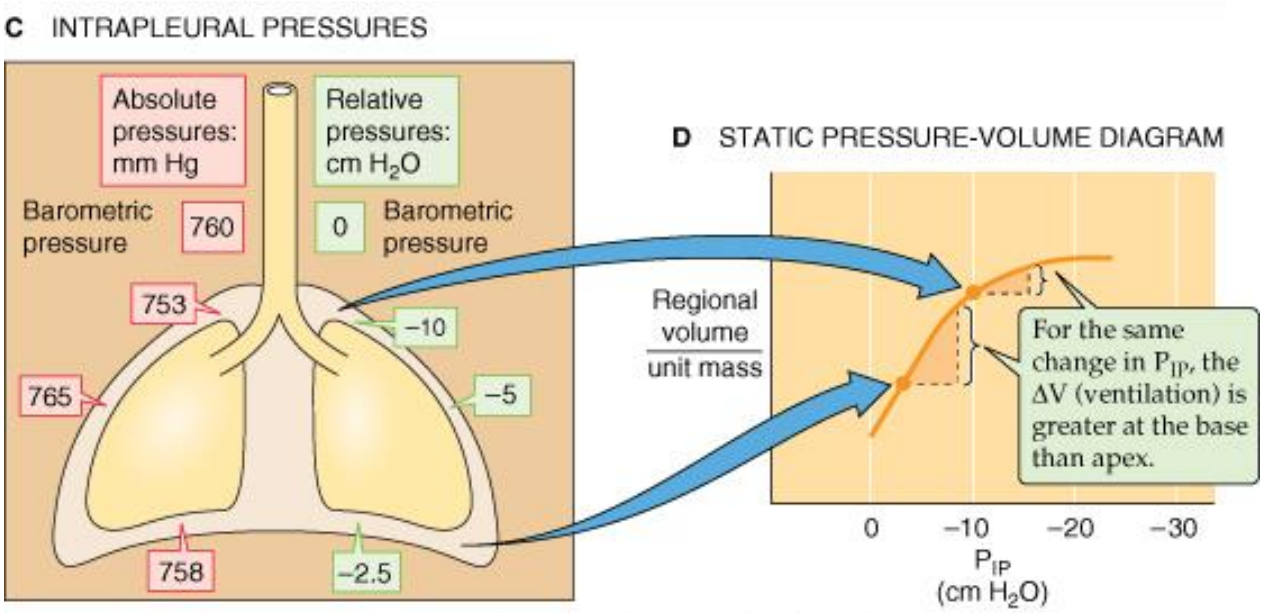
VII. Ventilation/Perfusion (V/Q) defects

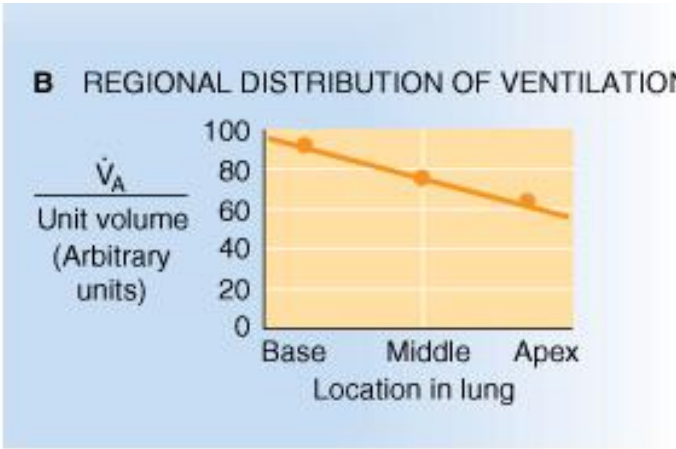
- For gas exchange to occur in the lung, air (alveolar ventilation, V) must reach blood flow (cardiac output, or perfusion, Q))
- The normal overall V/Q of the lung is about 0.8, providing effective, if imperfect, gas exchange

- If pulmonary capillary blood and alveolar gas don't meet in the proper proportions in any part of the lung, that's local V/Q mismatch

- Areas of local V/Q mismatch contribute to systemic arterial hypoxemia (if V/Q is too low), and to increases in physiological dead space (if V/Q is too high)

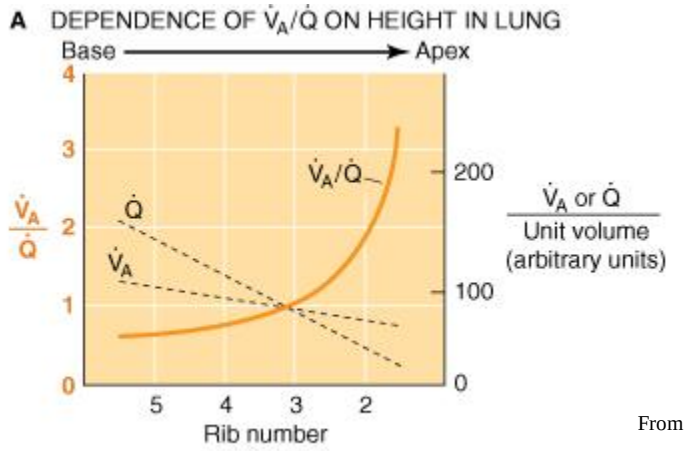
- In the normal lung, we know that gravitational effects account for Q increases from the gravitational top to bottom of the lung. Gravitational effects account for a greater V at the bases as well, but the regional differences for ventilation are not as great as they are for perfusion:





From Boron p. 707[132]

- Relatively higher Q than V at the bases of the lung create the normal profile of V/Q from bases to apices:



From Boron p. 715[133]

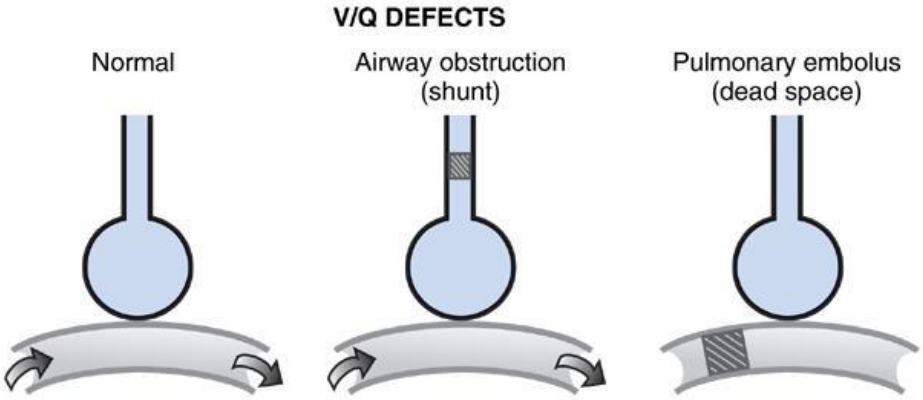
Questions: Extreme forms of V/Q mismatching

Condition	**What is the V/Q of the affected area?**	**Is there an increase in physiologic dead space?**	**Is there an increase in right-to-left shunt?**	**What changes would be expected in P_{aO2}?**
Pulmonary embolus blocking artery into one lung lobe				
Dislodged dental work blocking airway into one lung lobe				

Question: In terms of the oxygenation of arterial blood, areas of high V/Q cannot compensate for areas of low V/Q. Why?

Question: During 100% O_2 breathing, what is the approximate P_{aO2} in a) a healthy person, b) a person with V/Q mismatch such that regional V/Q ranges from 0.2 to 5.0, and c) a person with a 15% intrapulmonary shunt?

Table of extreme V/Q defects:

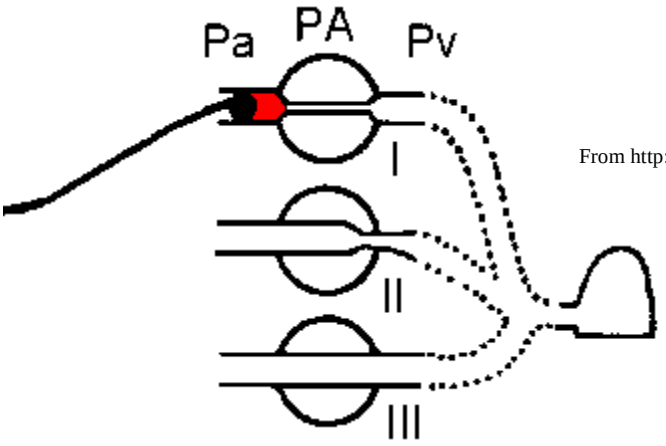


V/Q	0.8	0	
$P_{A_{O_2}}$	100 mm Hg	–	150 mm Hg
$P_{A_{CO_2}}$	40 mm Hg	–	0 mm Hg
Pa_{O_2}	100 mm Hg	40 mm Hg	–
Pa_{CO_2}	40 mm Hg	46 mm Hg	–

From Costanzo p. 139[134]

Practice Questions:

1. The figure below shows three lung "zones":

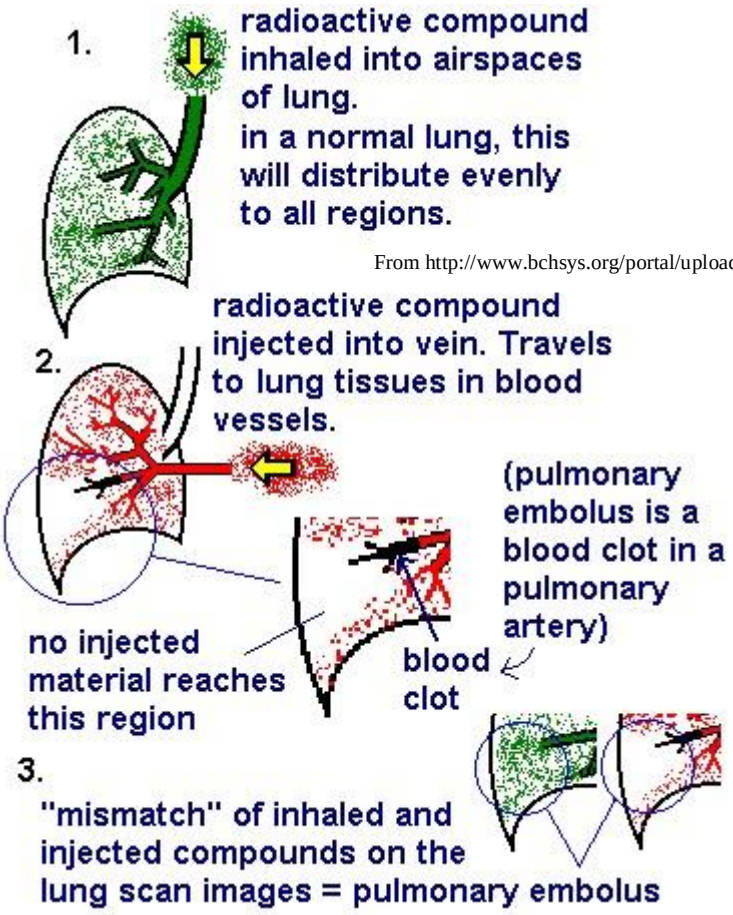


From http://www.creaghbrown.co.uk/anae/P14.gif[136]

A 65-y/o man briefly requires positive-pressure breathing due to an acute lung injury. This form of mechanically-assisted ventilation will

a. convert zone II into an additional area of zone III
b. elevate both P_a and P_A
c. eliminate gravitational effects on V/Q
d. eliminate zone II
e. increase the size of zone I

2. The principle of the "V/Q lung scan" is illustrated below:



From http://www.bchsys.org/portal/upload/page/391nucsdiag2.jpg[137]

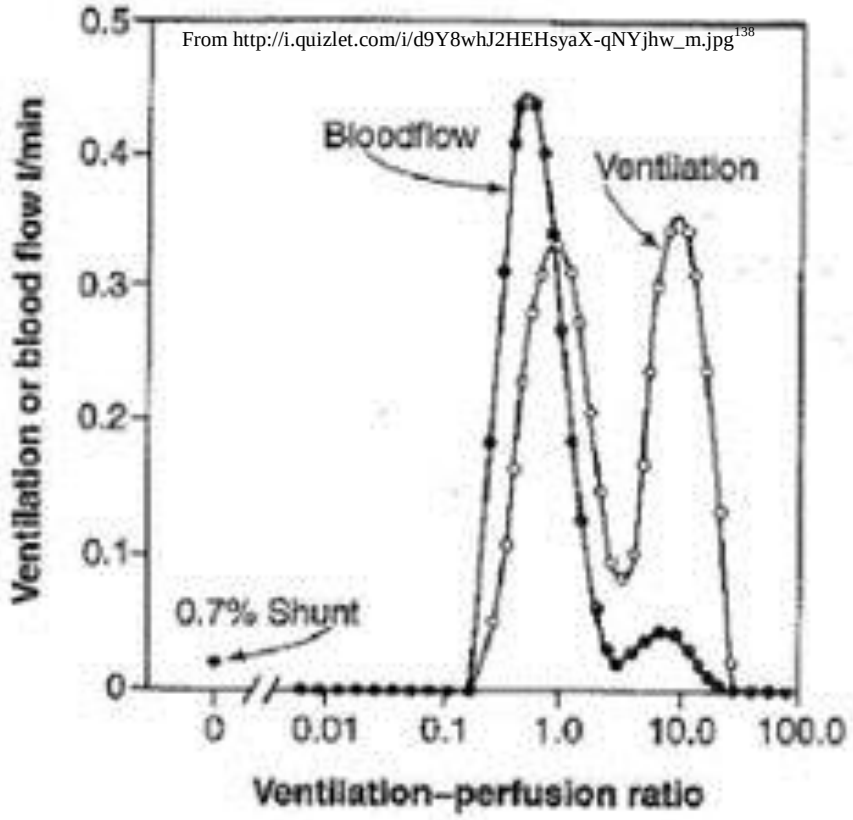
Evidence for a pulmonary embolus would be supported by finding

a. ↑ P_{aO2}
b. ↑ V_D/V_T
c. ↓ P_{aCO2}
d. ↓ V/Q
e. perfusion-limited O_2 transfer

3. A 44-y/o man has fatigue, sleepiness, constipation, weight gain and chills. Tests find thyroid hormone (T_3) levels 32% of normal (L), P_{AO2} 79 (L), P_{aO2} 75 (L), P_{aCO2} 50 (H), and D_{LCO} 70% normal (L). It is *certain* that he is suffering from

a. ↑ local V/Q mismatch
b. ↑ pulmonary shunt
c. ↓ V/Q
d. hypoventilation
e. O_2 diffusion limitation

4. A 67-y/o man with shortness of breath, chest pain stethoscope, and rapid, shallow breathing has the following lab test results:



The tests indicate the presence of
   a. ↑ (patho)physiologic dead space
   b. blockage of a major airway
   c. depressed arterial P_{CO2}
   d. diffusion-limited CO_2 exchange
   e. perfusion-limited O_2 exchange

5. A 72-y/o woman with shortness of breath and cyanosis has alveolar P_{O2} 105 mmHg, systemic arterial P_{O2} 55 mmHg (**L**), P_{CO2} 40 mm Hg, hemoglobin 13 g/dL, and cardiac output 5.1 L/min. While breathing 100% O_2, arterial P_{O2} rises to 145 mm Hg. She is suffering from
   a. ↑ physiologic dead space
   b. elevated V/Q
   c. hypoventilation
   d. left-to-right shunt
   e. right-to-left shunt

6. A 12-y/o girl suffering from cholera has fecal volume 15 x normal, and fecal K^+ and HCO_3^- losses each 6 x normal. Her diarrhea will cause
    a. ↑ P_{aCO2}
    b. ↑ V_D/V_T
    c. ↓ hematocrit
    d. ↓ P_{aO2}
    e. ↓ total CO_2

7. A 31-y/o woman, in her 21st week of pregnancy, developed headache, dizziness, palpitations, and severe fatigue. Her vital signs included pulse rate 90, blood pressure 100/80, and respirations 20. Tests found P_{AO2} 98, P_{aCO2} 40, hemoglobin 12.5, P_{aO2} 96. Pulse oximetry measures arterial O_2 saturation as 97%. Arterial O_2 content was 11.4 (**L**). She was suffering from
    a. ↑ pulmonary shunt
    b. CO poisoning
    c. left-to-right shunt
    d. pulmonary diffusion defect
    e. severe anemia

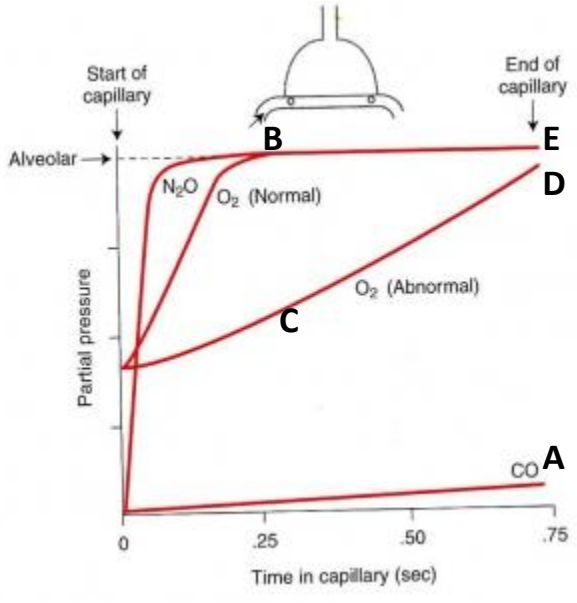
8. A healthy 24-y/o woman, swimming at maximal effort for 5 min, has P_{AO2} 115 mmHg, and P_{aCO2} 24 mmHg, indicating that this exercise leads to
    a. decreased D_{LCO}
    b. enlargement of physiologic shunts
    c. hyperventilation relative to CO_2 production
    d. decreased lung diffusional surface area
    e. lung diffusion limitation for CO_2

9. During the normal respiratory cycle, when does alveolar P_{CO2} reach its highest value?
    a. end of expiration
    b. end of inspiration
    c. it is constant throughout the cycle
    d. mid-expiration
    e. mid-inspiration

10. Which of the following are the blood and alveolar gases of a person during a panic attack?

	P_{AO2}	P_{aO2}	P_{ACO2}	D_{LCO}	O_2 Sat
a.	100	100	25	normal	98%
b.	125	123	30	normal	100%
c.	125	123	40	normal	98%
d.	75	70	25	decreased	90%
e.	75	70	50	increased	90%

11. At what point in the figure below is found the P_{aO2} of a person performing severe exercise despite severe pulmonary fibrosis with alveolar-capillary membrane thickening?



From http://studydroid.com/imageCards/0c/il/card-13194878-back.jpg[139]

a. A
b. B
c. C
d. D
e. E

12. A 44-y/o woman with fatigue and pale skin has blood pressure 157/87 (**H**), heart rate 105 (**H**), respiratory rate 12, and arterial P_{O2} 104. Hemoglobin is greatly reduced at 4.5 g/dL. Her A – a O_2 gradient is normal, and she has reduced arterial
    a. O_2 capacity
    b. O_2 content
    c. O_2 content and capacity
    d. O_2 saturation
    e. O_2 saturation and capacity

13. A 65-y/o man sleeps while a faulty space heater increases ambient P_{CO} to 1 mmHg in the house, causing a substantial
    a. ↑ A – a O_2 gradient
    b. ↓ arterial O_2 capacity
    c. ↓ arterial O_2 content
    d. ↓ P_{aO2}
    e. ↓ P_{AO2}

14. A 44-y/o woman with a hypersensitivity pneumonitis has $FEV_{1.0}$/FVC 62% of normal (**L**), vital capacity 50% of normal (**L**), D_{LCO} 48% of normal (**L**), P_{AO2} 102, P_{aO2} 58 (**L**), and dyspnea on exertion. Her disease is most accurately described as causing
    a. O_2 perfusion limitation, obstruction, and restriction
    b. obstruction and restriction
    c. obstruction and restriction with diffusion defect
    d. obstruction with diffusion defect
    e. restriction with O_2 perfusion limitation

15. A 76-y/o man is breathing 40% O_2, providing him an inspired P_{O2} at sea level of
    a. 10 mmHg
    b. 40 mmHg
    c. 100 mmHg
    d. 160 mmHg
    e. 300 mmHg

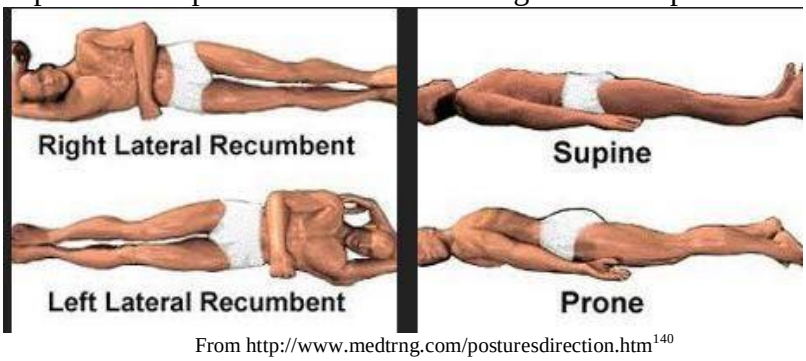
16. A 40-y/o man with shortness of breath on exercise and arterial O_2 saturation 91% (**L**) has D_{LCO} 14.6 (**L**) and pulmonary arterial pressure 46/32 (**H**). P_{AO2} is 100 and P_{ACO2} is 40. These results suggest a disease process that causes
    a. ↓ hemoglobin and ↓ hematocrit
    b. hypoventilation
    c. increased FRC
    d. loss of pulmonary capillary surface area
    e. polycythemia and increased blood viscosity

17. A 50-y/o man has breathlessness, non-productive cough and cyanosis. Pulmonary artery pressure is 78/35 (**H**), P_{AO2} 98, P_{aO2} 50 (**L**), P_{aCO2} 39, pH 7.45, and HCO_3^- 27. Breathing 100% O_2 results in P_{AO2} 710, P_{aO2} 80 (**L**), P_{aCO2} 40, pH 7.44, and HCO_3^- 27. These results indicate
    a. ↑ V_D/V_T
    b. ↓ cardiac output
    c. hypoventilation
    d. hypoxic pulmonary vasoconstriction
    e. right-to-left shunt

18. An 11-y/o boy suffering from a severe asthma attack is placed on positive pressure ventilation to maintain sufficient alveolar ventilation. Another effect of positive pressure ventilation is
    a. ↑ physiologic dead space
    b. ↑ right-to-left shunt
    c. ↓ FRC
    d. ↓ P_{aO2}
    e. ↓ pneumothorax risk

19. A 75-y/ woman with shortness of breathing, dizziness on exertion, and ankle swelling has P_{AO2} 52 (L), P_{ACO2} 54 (H), pulmonary arterial pressure 48/36 (H), and tachycardia. She also predictably has associated
    a. ↓ arterial O_2 capacity
    b. hyperventilation
    c. pulmonary arteriolar dilation
    d. right heart failure
    e. systolic murmur

20. A person with pneumonia in the left lung should be placed in which posture?



From http://www.medtrng.com/posturesdirection.htm[140]

    a. right lateral recumbent to maximize blood flow to the healthy lung
    b. right lateral recumbent to minimize ventilation in the healthy lung
    c. supine to maximize flow to the bases of the lungs
    d. left lateral recumbent to maximize V/Q in the diseased lung
    e. left lateral recumbent to minimize blood flow to the diseased lung

21. A 3-week old infant has an anomalous distal origin of the innominate artery. The artery is compressing the trachea and causing airway obstruction. One result is
    a. cyanosis
    b. ↑ overall lung V/Q
    c. ↑ P_{aO2}
    d. ↑ (patho)physiologic dead space
    e. ↓ P_{50}

VIII. Control of breathing

Overview

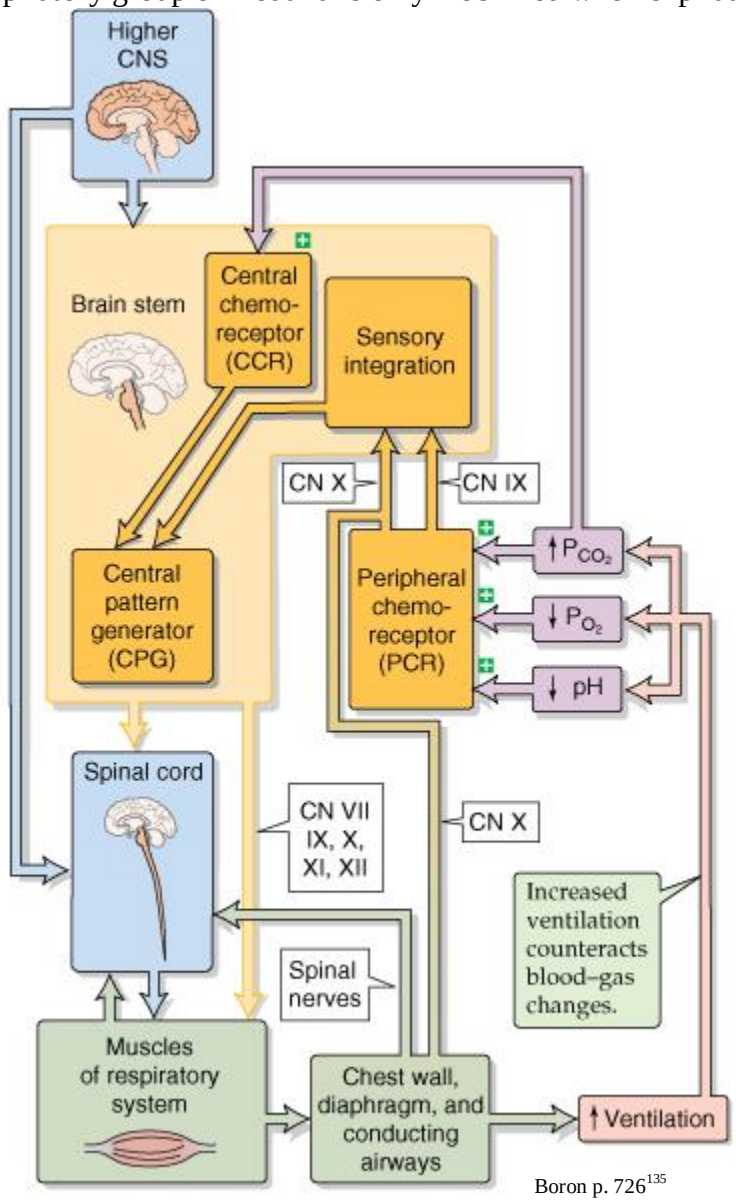
- Relatively few disorders arise from "pure" disruptions of the control of breathing

- Unlike the heart, which as cardiac muscle has auto-rhythmicity independent of neural input, the respiratory muscles are skeletal muscles that rely on somatic neural input

    - Disruptions in somatic neural input (e.g., spinal cord injury) can lead to respiratory failure

The control system

- Includes a central pattern generator in the brainstem (medullary respiratory center)
- Dorsal respiratory group in the medullary respiratory center generates inspiration
- Ventral respiratory group of medulla is only mobilized when expiration must be active



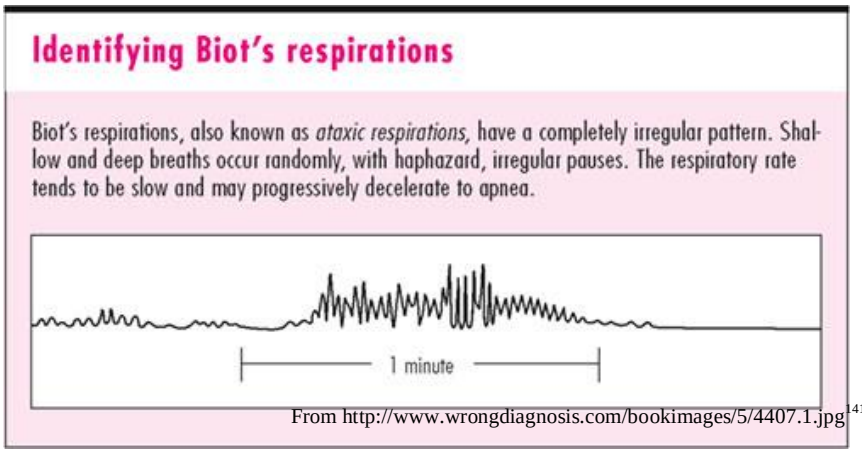
Boron p. 726[135]

- The apneustic and pneumotaxic centers have mostly historical significance; in general, neural groups in the pons modify the central pattern generator
- Cranial nerves IX (glossopharyngeal) and X (vagus) feed information to this center from lung mechanoreceptors (X) and peripheral chemoreceptors (IX and X)

- The respiratory pattern can be disrupted voluntarily (e.g., breath-holding), or by altered higher CNS or peripheral input (e.g., anxiety, apnea during sleep)

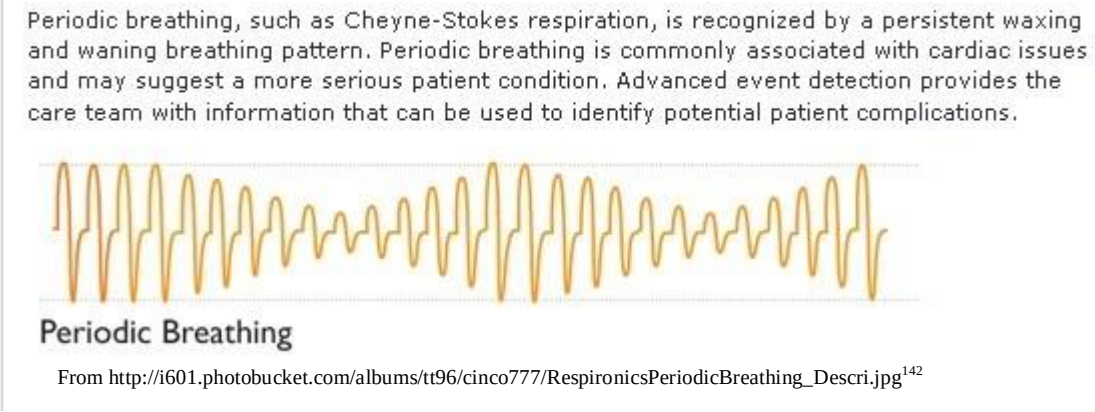
- There are a variety of recognizable abnormal respiratory patterns, including

Ataxic breathing: Irregular inspirations, usually due to medullary lesions



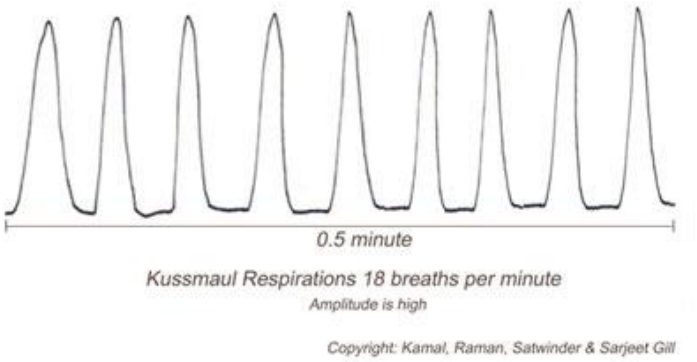
From http://www.wrongdiagnosis.com/bookimages/5/4407.1.jpg[141]

Cheyne-Stokes respiration: Cycles of waxing and waning tidal volume; may be seen during sleep at high altitude or in patients with congestive heart failure:



From http://i601.photobucket.com/albums/tt96/cinco777/RespironicsPeriodicBreathing_Descri.jpg[142]

Kussmaul breathing: Deep, rapid breathing seen in metabolic acidosis (e.g., diabetic ketoacidosis)



From http://s3.amazonaws.com/readers/healthmad/2006/09/12/2327_5.jpg[143]

Control of breathing: the central chemoreceptor

- Chemoreceptors provide negative feedback that modifies ventilation, keeping arterial P_{O2}, P_{CO2}, and pH constant
- The central chemoreceptor, located just under the ventral surface of the medulla, stimulates ventilation in response to increased arterial blood P_{CO2}
- CO_2–but not H^+—from arterial blood can cross the blood-brain barrier and stimulate the central chemoreceptors
- The direct stimulus to the central chemoreceptor is ↓ pH of the brain extracellular fluid

Control of breathing: the peripheral chemoreceptors

- The peripheral chemoreceptors, located in the carotid (and aortic) bodies, respond to all of the following by increasing ventilation:
    - Primary response: to reduced arterial P_{O2} (only site) [P_{O2} must fall below ≈ 60 mmHg to increase ventilation]
    - Less important response: to increased arterial P_{CO2} and decreased arterial pH
    - Increased P_{aCO2} and decreased pH_a amplify the ventilatory response to hypoxia
- Tiny carotid bodies (2 mg each) have the highest relative blood flow of any organ
- Although the carotid bodies respond to falling P_{O2}, the increase in ventilation is roughly linear in response to falling arterial O_2 saturation. (However, CO poisoning, which does not alter P_{O2}, does not elicit a ventilatory response).

Questions: Central and peripheral chemoreceptors

Ventilatory stimulus	What is the central chemoreceptor response?	What is the peripheral chemoreceptor response?
Exposure to high altitude		
Lung diffusion defect		

Ventilatory stimulus	What is the central chemoreceptor response?	What is the peripheral chemoreceptor response?
Mild exercise		
Diabetic ketoacidosis		
Acute hypoventilation in respiratory failure		

Peripheral inputs modify respiratory control

- Vagal input modifies brainstem-generated breathing patterns

    1. Lung stretch receptors (in airway smooth muscle) limit tidal volume (leading to increased breathing frequency); slow adapting.

    2. Irritant receptors (between airway epithelial cells), stimulated by various noxious substances, also limit tidal volume while increasing breathing frequency. Carried by C fibers; rapid adapting.

    3. Juxtacapillary (J) receptors, in alveolar walls, are stimulated when capillaries are engorged, leading to rapid, shallow breathing (e.g., during pulmonary edema), bronchoconstriction, and increased mucus production. Rapid adapting.

Control of breathing: sleep and sleep apnea

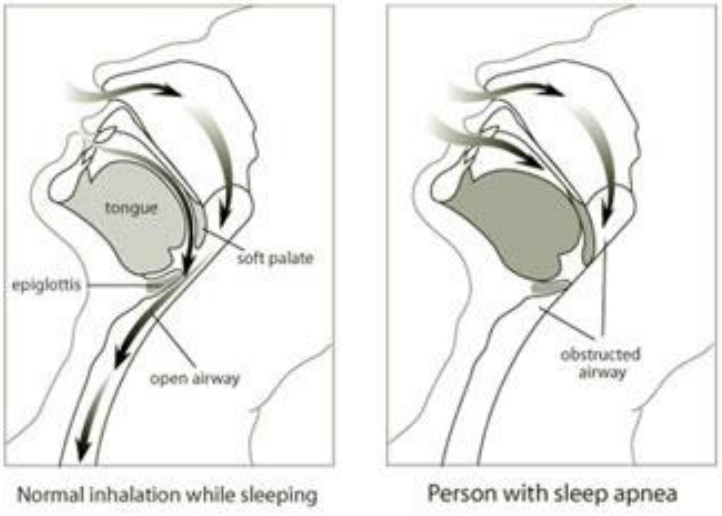
Overview

- Sleep is, overall, a depressant of breathing

- Drugs that depress the brain stem (alcohol, opioids) also depress breathing

    - Sleep and other brain depressants increase the risk of respiratory failure

- Sleep apneas occur because depression of the respiratory center allows either spontaneous cessation of breathing ("central apnea") or airflow obstruction ("obstructive apnea")



From http://ezsleepapneaappliance.com/normal-breathing-image.jpg[144]

- Obstructive apnea is caused by airway closure when sleep-induced reduction in pharyngeal muscle tone closes the oropharynx, during inspiration and usually during supination

- Apneic episode begins when upper airway collapses at the end of the previous expiration

- Obesity contributes to risk for obstructive apnea by increasing compressive factors that contribute to airway closure

- Further inspiratory effort only closes the airway more tightly

- Falling P_{aO2} and rising P_{aCO2}, in response to lack of breathing, stimulate the respiratory center and the brain, provoking arousal from sleep

- Arousal increases pharyngeal muscle tone and changes posture, ending the apneic episode

Question: During sleep lab testing, airflow at the mouth, chest wall motion, and arterial O_2 saturation are monitored. How do these findings differ during a 45 second period of *obstructive* as compared with *central* apnea? How would one distinguish between these two forms of apnea?

Sighs, yawns, coughs, and sneezes

- A *sigh* is exaggerated breath, may open closed (atelectatic) alveoli; may stimulate release of surfactant

- *Yawns* are exaggerated sighs, are even more effective than a sigh for opening alveolar areas that are atelectatic. Before sleep and upon awakening, yawns may serve to minimize anticipated or accumulated atelectasis.

- *Coughs* are airway scratches that help rid the tracheobronchial tree of accumulated unwanted debris. Pressure is built behind a closed glottis, and when the glottis is suddenly opened, very rapid airflow helps dislodge unwanted material.

- *Sneezes* occur in response to irritation of nasal receptors. Always preceded by a large inspiration, a sneeze, unlike a cough, involves forced airflow through the nasal passages, helping dislodge material from the nasal mucosa.

IX. Integrated responses of the Respiratory System

Text: Costanzo pp. 141-142

Exercise

- A rise in ventilation during exercise is essential due to increased consumption of O_2, and increased production of CO_2

- In health, the rise in ventilation matches the rise in O_2 consumption and CO_2 production during mild to moderate exercise

Description of the ventilatory response to mild and moderate dynamic exercise

- Ventilation increases match metabolism increases, allowing arterial P_{O2} and P_{CO2} to remain unchanged

- In persons with heart or lung disease, the rise in O_2 consumption and CO_2 production is the same as in healthy persons, assuming that the same amount of work is being carried out

- In persons with symptomatic heart disease, work will be limited by a cardiac or cardiovascular symptom, such as chest pain, faintness, or cardiac arrhythmia. Characteristically, this limitation will occur at a low level of ventilation or demand on the ventilatory system

- In lung disease patients, respiratory symptoms (“shortness of breath”) will limit exercise, often at a relatively low heart rate

Questions: Ventilatory responses to a matched level of moderate exercise in healthy persons and in persons with lung disease

Parameter	Response in Healthy Persons	Response in Persons with Lung Disease, as compared with Response in Healthy persons
O_2 consumption		
CO_2 production		
Ventilation		
Arterial P_{O2} and P_{CO2}		
Arterial pH		
Mixed venous P_{O2} and P_{CO2}		
Pulmonary blood flow or Cardiac output		
V/Q		

Erythropoietin (EPO)

- Hormone—essentially a growth factor like a cytokine—formed in fibroblast-like cells (type I interstitial cells) in the renal cortex

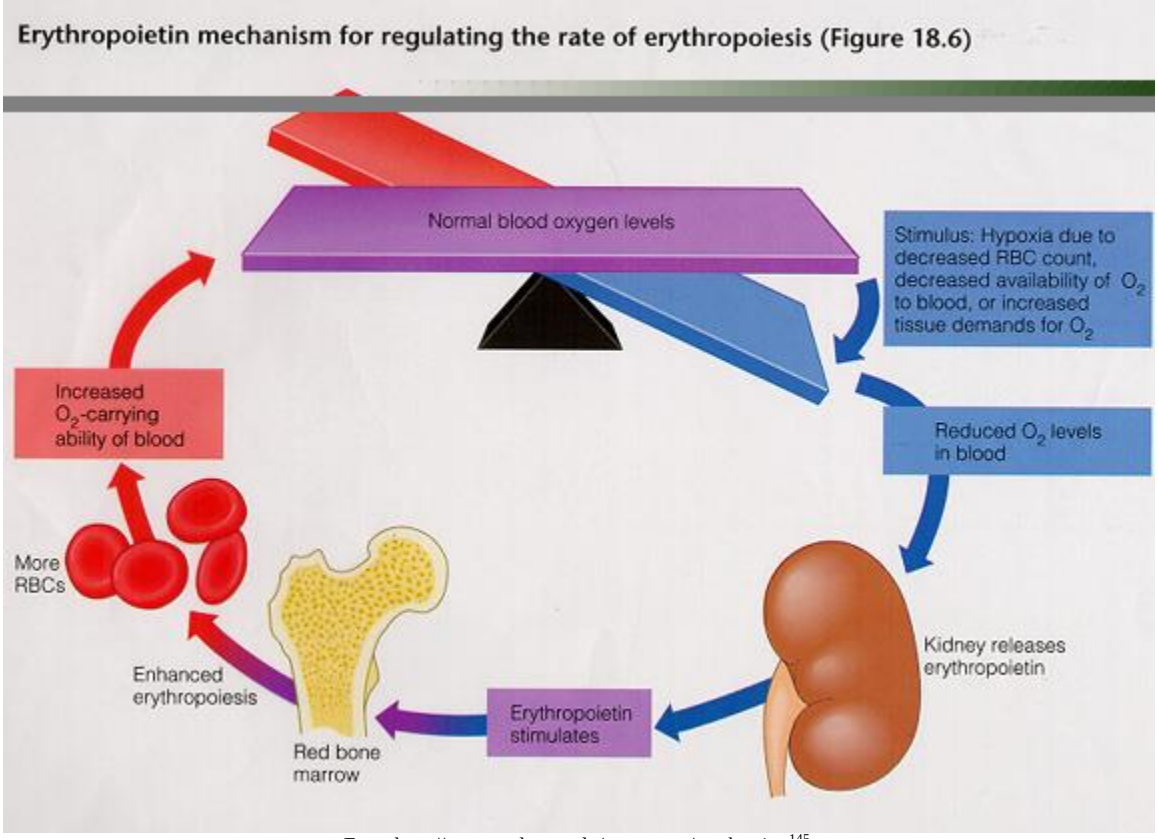
- Action in bone marrow: stimulates production of proerythroblasts and development of red cells from progenitor cells

- Stimulus for synthesis is a decrease in *local, tissue* P_{O2} in renal cortex: EPO synthesis increases in

    - anemia

    - with decreasing renal blood flow

- with declining systemic arterial P_{O2}
- conditions that result in increased affinity of Hb for O_2



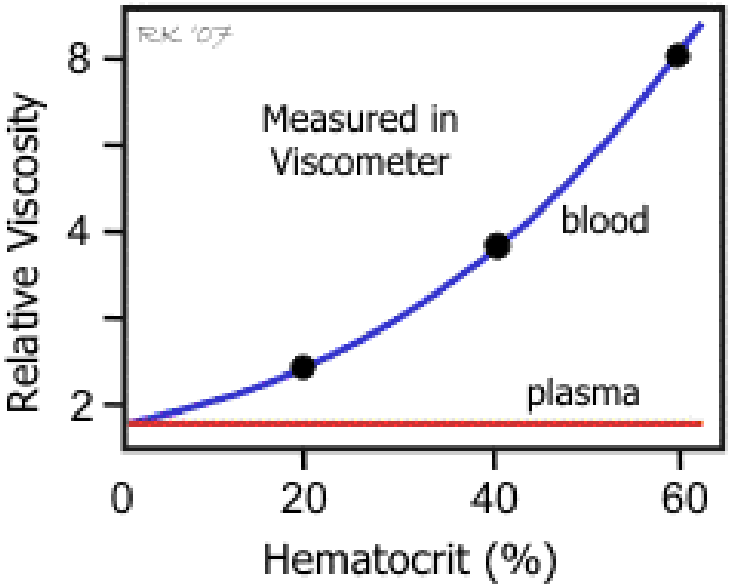
From http://www.tarleton.edu/~anatomy/erythro.jpg[145]

- Males have higher hematocrit than females; due to independent effect of testosterone on bone marrow production of red blood cells

Questions: Erythropoietin

Question	Answer
What is the mechanism for hematocrit changes during residence at high altitude?	
What is the result of EPO "doping" in competitive endurance athletes?	

Question	Answer
What are some representative diseases that may require exogenous EPO treatment?	
What are some problems associated with excessive endogenous production, or exogenous administration, of EPO?	
What are some conditions that should result in elevated endogenous levels of EPO?	



From http://www.cvphysiology.com/Hemodynamics/H011%20Viscosity-Hct.gif[146]

Practice Questions

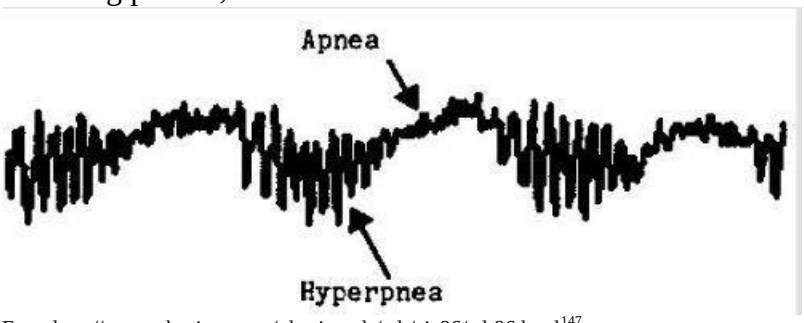
1. A 7-y/o boy, playing outside in Beijing during a smog alert, develops shortness of breath, reduced tidal volume, and increased breathing frequency due to ozone-induced stimulation of

a. central chemoreceptors
b. intrapulmonary irritant receptors
c. juxtacapillary (J) receptors
d. peripheral chemoreceptors
e. lung stretch receptors

2. A 30-y/o man has minute ventilation 9.5 l/m (**H**), due in part to central chemoreceptor stimulation induced by

a. lactic acidosis
b. acute high altitude exposure
c. idiopathic pulmonary fibrosis with decreased lung diffusing capacity
d. rebreathing (inspiring from a bag of expired gas)
e. severe anemia

3. A 77-y/o woman with swollen ankles, shortness of breath, and fatigue has the following breathing pattern, which is termed



From http://www.physionet.org/physiotools/edr/cic86/edr86.html[147]

a. ataxic respiration
b. Biot's breathing
c. Cheyne-Stokes breathing
d. Kussmaul's breathing
e. obstructive sleep apnea

4. A 55-y/o man with shortness of breath on exertion and cyanosis at rest breathes 100% O_2 during a clinical test. His arterial P_{O2} is 62 (**L**) on room air, and 105 on 100% O_2, indicating the presence of

a. anemia
b. hypoventilation
c. right-to-left shunt
d. reduced CO diffusing capacity
e. V/Q mismatch

5. A 13-y/o girl has a hemoglobinopathy characterized by decreased 2,3 DPG affinity for hemoglobin. One consequence is

a. carotid body chemoreceptor stimulation
b. central chemoreceptor stimulation
c. polycythemia
d. hypoventilation
e. ↑ V/Q

6. A 46-y/o man has had a patent foramen ovale all of his life. This defect contributes to his abnormally
   a. ↑ erythropoietin
   b. ↑ pulmonary artery pressure
   c. ↑ V/Q
   d. ↓ hematocrit
   e. ↑ maximal left-heart cardiac output

7. A 57-y/o woman with shortness of breath on exertion, chest pain, and easy fatigue has the following test results:

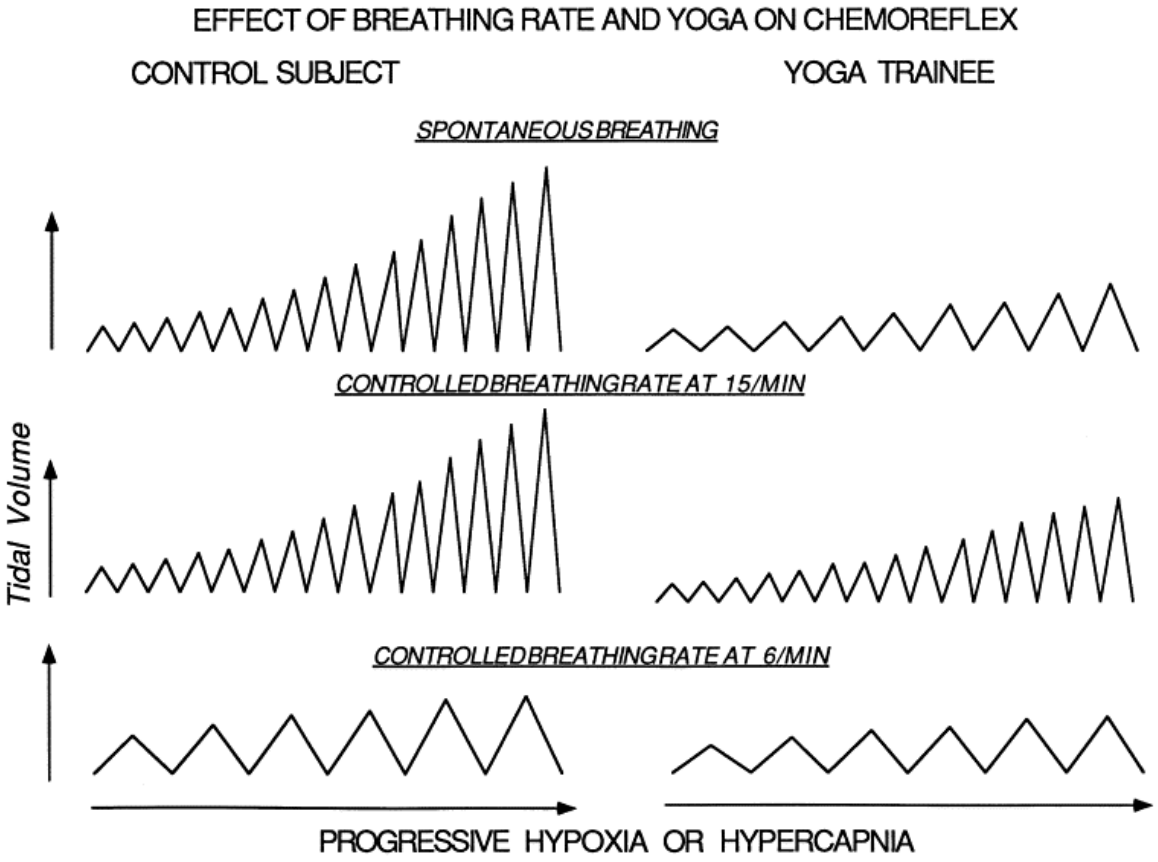
Test	Result
P_{aO2} (air)	56 (**L**)
P_{aCO2} (air)	40
Cardiac output	5.2
P_{aO2} (100% O_2)	157 (**L**)
P_{aCO2} (100% O_2)	41

   She has
   a. hypoventilation
   b. low CO diffusing capacity
   c. pulmonary diffusion defect
   d. pulmonary shunt
   e. V/Q mismatch

8. Prime conditions for partial upper airway obstruction during sleep (snoring) include
   a. prone posture, obesity, expiration, positive airway pressure
   b. prone posture, obesity, inspiration, positive airway pressure
   c. supine posture, obesity, expiration, reduced pharyngeal muscle tone
   d. supine posture, obesity, inspiration, increased pharyngeal muscle tone
   e. supine posture, obesity, inspiration, negative airway pressure

9. A 67-y/o man is hospitalized; hemoglobin is 9 (**L**) and hematocrit 29% (L). Erythropoietin levels are 1.5 mU/ml (**L**). Mean red cell volume is 90 fL. The most probable diagnosis is, at this point,
   a. chemotherapy-induced bone marrow toxicity
   b. excessive red cell destruction (hemolytic anemia)
   c. iron deficiency
   d. renal failure
   e. vitamin B_{12} deficiency

10. A study of a yoga-trained 45-y/o woman finds the following:



From http://ars.els-cdn.com/content/image/1-s2.0-S1566070201002673-gr5.gif[148]

Assuming that the trainee has normal metabolic rate, we can say that she must have

a. ↑ P_{aO2}
b. ↑ P_{aCO2}
c. higher mean V/Q
d. less sensitive lung mechanoreceptors
e. greater central chemoreceptor sensitivity

11. Which of the following conditions is *least* likely to result in increased endogenous erythropoietin production?

a. infusion of packed red cells into a healthy person
b. chronic CO-hemoglobin saturation = 13%
c. iron deficiency anemia
d. residence at 14,000 ft altitude
e. sickle-cell anemia

12. Normal results from a stress test on a healthy 24-y/o woman:

	Rest	Maximal exercise
Cardiac output (l/min)	5.5	19.5
Ventilation (l/min)	6.0	94.0
Heart rate (b/min)	65	204
Stroke volume (ml/beat)	84	96
P_{aO2} (mmHg)	100	105
P_{aCO2} (mmHg)	40	33

What increased demand was met by increased V/Q?

a. ↑ pulmonary diffusion defect
b. decreased mixed venous P_{O2}
c. exercise-induced ↑ V_D/V_T
d. increased pulmonary shunt fraction of cardiac output
e. increased ventilatory stimulus from P_{CO2}

13. Which of the following persons would be expected to have normal or low blood levels of endogenously produced erythropoietin?

a. person A with low hemoglobin and hematocrit
b. person B with $P_{aO2} = 62$
c. person C in chronic renal failure
d. person D, a heavy smoker, with long-term 10-12% carboxyhemoglobin
e. person E, with bilateral renal artery stenosis and mean arterial pressure 112/72

14. A 12-y/o boy has a patent ductus arteriosus. One result is

a. ↓ lung capillary transit time
b. ↓ mean lung V/Q
c. cyanosis
d. low forward systemic cardiac output
e. pulmonary diffusion defect

Sources

Note: Required texts are the Costanzo *Physiology* and Boron & Boulpaep *Medical Physiology* as listed below:

Required:

1. Costanzo L., *Physiology* 4th Ed. [Board Review Series] (2007), Lippincott Williams & Wilkins, ISBN # 0 – 781773113.

2. Boron W.F., and Boulpaep E.L. (eds), *Medical Physiology, A Cellular and Molecular Approach* 2nd Ed. (2009), Saunders, ISBN # 978-1-4160-3115-4

1. http://naturecure-siva.blogspot.com/
2. http://www.epgonline.org/images/insomnia/in-2211.jpg
3. http://alleydog.com/images/sleepwaves.gif
4. http://www.healthandage.com/html/res/primer/pics/sleep.gif
5. http://www.ride4ever.org/images/normalsleep.gif
6. http://rfumsphysiology.pbworks.com/f/ar8.bmp
7. http://media.wiley.com/mrw_images/compphys/articles/cp040129/image_n/ncp04012901.jpg
8. Boron p. 551
9. http://www.brown.edu/Courses/Bio_281-cardio/cardio/Exam99.htm
10. http://www.brown.edu/Courses/Bio_281-cardio/cardio/handout1.htm
11. http://openi.nlm.nih.gov/detailedresult.php?img=2374637_cc6213-1&req=4
12. http://www.anaesthetist.com/icu/organs/heart/Findex.htm#phys.htm
13. http://www.anaesthetist.com/icu/organs/heart/Findex.htm#phys.htm
14. www.psychiatrymmc.com
15. http://www.cap.org/apps/docs/cap_today/images/9_99table1.jpg
16. http://www.clinicalimagingscience.org/articles/2011/1/1/images/JClinImagingSci_2011_1_1_11_76689_f2.jpg
17. http://www.jama.ama-assn.org/cgi/reprint/78/20/1529
18. http://www.nature.com/ajh/journal/v18/n1s/images/ajh2005287f2.jpg
19. http://www.brown.edu/Courses/Bio_281-cardio/cardio/BIO281V1.htm
20. http://users.atw.hu/blp6/BLP6/HTML/C0199780323045827.htm
21. http://www.pathwaymedicine.org/cardiovascular-function-integration
22. http://users.atw.hu/blp6/BLP6/HTML/C0199780323045827.htm
23. http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/figures/3041F06.gif
24. http://img.medscape.com/pi/emed/ckb/pediatrics_cardiac/973235-976034-1204.jpg
25. http://www.curoservice.com/images/immagini/health/rds/compliance_1.gif
26. www.legacy.owensboro.kctcs.edu
27. http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_5%20Fall%202011.htm
28. www.yahoo.brand.edgar-online.com
29. www.hobogeneous.files.wordpress.com/2007/05/draw2.jpg
30. http://www.slideshare.net/iyerbk/enoxaparin-2782382

31. Costanzo p. 69
32. Boron p. 432
33. Boron p. 469
34. Boron p. 468
35. Boron p. 471
36. Boron p. 471
37. Boron p. 475
38. Costanzo p. 72
39. http://www.cvphysiology.com/Blood%20Pressure/BP003_pulse_pressure.gif
41. Boron p. 438
42. Boron p. 505
43. Costanzo p. 75
44. Costanzo p. 76
45. Costanzo p. 77
46. http://www.dchaos.com/portfolio/dchaos1/yse_fig11.jpg
47. http://upload.wikimedia.org/wikipedia/commons/1/1c/Willem_Einthoven_ECG.jpg
48. Costanzo p. 74
49. Boron p. 515
50. Boron p. 518
51. http://media.wiley.com/CurrentProtocols/PH/ph1008/ph1008-fig-0001-1-full.gif
52. http://library.med.utah.edu/kw/ecg/mml/ecg_unifocal.gif
53. http://www.nature.com/nature/journal/v415/n6868/images/415198a-f6.2.jpg
54. Costanzo p. 80
55. Boron p. 547
56. Costanzo p. 81
57. http://www.cvphysiology.com/Cardiac%20Function/CF010_Frank-Starling_inotropy.gif
58. Boron p. 546
59. Costanzo p. 82
60. Boron p. 542
61. Costanzo p. 83
62. Boron p. 570
63. Boron p. 570
64. Boron p. 573
65. Boron p. 571
66. Boron p. 573
67. Costanzo p. 89
68. http://www.cvphysiology.com/Heart%20Disease/HD004%20aortic%20stenosis.gif
69. http://www.cvphysiology.com/Heart%20Disease/HD005%20aortic%20regurgitation.gif
70. http://auscultation.com/Human/Heart/MitralRegurgitation/Images/MitralRegurgitation_pressure.gif
71. Boron p. 556
72. Boron p.555
73. Costanzo p. 91
74. Costanzo p. 93
75. Boron p. 1068
76. http://mededsys-rcp.com/courses_online/302/images_302/27.jpg
77. http://www.mybwmc.org/sites/all/modules/adam/graphics/images/en/15206.jpg

78. http://upload.wikimedia.org/wikipedia/en/8/85/Flow-volume-loop.svg
79. http://ccforum.com/content/figures/cc3516-6.jpg
80. http://www.spirometrie.info/img/reversible.png
81. http://dc344.4shared.com/doc/RC3PP6I8/preview.html
82. http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v03/030090r00.HTM
83. http://www.pharmacology2000.com/respiratory_anesthesiology/pulmonary_assessment/emphysema3.jpg
84. http://alexandria.healthlibrary.ca/documents/notes/bom/unit_2/17no6.gif
85. http://rfumsphysiology.pbworks.com/f/n8.bmp
86. http://www.frca.co.uk/images/flow_volume.gif
87. http://circ.ahajournals.org/content/122/2/191.figures-only
88. http://www.vgate.net.au/SOB/alveoli.html
89. http://wiki-images.enotes.com/a/a3/Hb.jpg
90. http://commons.wikimedia.org/wiki/File:Hb_saturation_curve.png
91. http://www.ccmtutorials.com
92. www.colorado.edu/intphys/Class/IPHY3430-200/image/figure1034.jpg
93. Boron p. 600
94. Boron p. 483
95. Boron p. 494
96. Boron p. 502
97. Boron p. 501
98. www.endothelinscience.com/normalphys.cfm
99. Boron p. 582
100. Boron p. 579
101. www.mfi.ku.dk/ppaulev/chapter18/images/18-1.jpg
102. Boron p. 586
103. Boron p. 587
104. Costanzo p. 120
105. Costanzo p. 122
106. Boron p. 634
107. Costanzo p. 123
108. Boron p. 633
109. http://oac.med.jhmi.edu/res_phys/Encyclopedia/AirwayResistance/AirwayResistGen.GIF
110. Boron p. 645
111. http://a-vet-to-be.blogspot.com/2012/04/alveolar-ventilation-and-gas-diffusion.html
112. Costanzo p. 121
114. West JB. *Respiratory Physiology—the Essentials* 5th ed., Williams & Wilkins, 1995, p. 55
115. Boron p. 672
116. Boron p. 686
117. http://www.mfi.ku.dk/PPaulev/chapter15/images/15-1.jpg
118. http://www.zuniv.net/physiology/book/images/16-7.jpg
119. Boron p. 674
120. Boron p. 674
121. Costanzo p. 132

122. Boron p. 1179
123. http://www.cyberounds.com/assets/01/37/137/figure1.gif
124. "World-Class Quiz in Pulmonary Medicine and Physiology" (http://www.lakesidepress.com/WCQ2001/1-30.htm) by: Lawrence Martin, MD, Chief, Division of Pulmonary and Critical Care Medicine, Mt. Sinai Medical Center, Cleveland, OH 44106
125. http://www.coheadquarters.com/figco30x.gif
126. www.octc.kctcs.edu
127. Costanzo p. 138
128. Boron p. 1201
129. Boron p. 1202
130. Boron p. 1205
131. Boron p. 1204
132. Boron p. 707
133. Boron p. 715
134. Costanzo p. 139
135. Boron p. 726
136. http://www.creaghbrown.co.uk/anae/P14.gif
137. http://www.bchsys.org/portal/upload/page/391nucsdiag2.jpg
138. http://i.quizlet.com/i/d9Y8whJ2HEHsyaX-qNYjhw_m.jpg
139. http://studydroid.com/imageCards/0c/il/card-13194878-back.jpg
140. http://www.medtrng.com/posturesdirection.htm
141. http://www.wrongdiagnosis.com/bookimages/5/4407.1.jpg
142. http://i601.photobucket.com/albums/tt96/cinco777/RespironicsPeriodicBreathing_Descri.jpg
143. http://s3.amazonaws.com/readers/healthmad/2006/09/12/2327_5.jpg
144. http://ezsleepapneaappliance.com/normal-breathing-image.jpg
145. http://www.tarleton.edu/~anatomy/erythro.jpg
146. http://www.cvphysiology.com/Hemodynamics/H011%20Viscosity-Hct.gif
147. http://www.physionet.org/physiotools/edr/cic86/edr86.html
148. http://ars.els-cdn.com/content/image/1-s2.0-S1566070201002673-gr5.gif
149. http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v02/020515r00.HTM
150. http://uvahealth.com/services/plastic-surgery/conditions-treatments/112024
151. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322011001200017
152. http://www.trauma.org/archive/neuro/icpcontrol.html
153. http://ajpheart.physiology.org/content/296/6/H1969
154. http://www.cvphysiology.com/Blood%20Flow/BF001.htm
155. http://commons.wikimedia.org/wiki/File:Capillary_microcirculation.svg
156. http://www.im.org/toolbox/curriculum/
157. http://www.ncbi.nlm.nih.gov
158. http://pie.med.utoronto.ca/TEE/TEE_content/assets/applications/synopsis/cas/cas-fig8.png
159. http://www.clinicalexams.co.uk/jugular-venous-pressure.asp
160. http://cvphysiology.com/Blood%20Pressure/BP012.htm

161. http://www.cvphysiology.com/Heart%20Disease/HD009b.htm
162. http://www.cvphysiology.com/Heart%20Disease/HD005.htm
163. http://upload.wikimedia.org/wikipedia/commons/3/3e/Aortic_Stenosis_-_Hemodynamic_Pressure_Tracing.png
164. http://webanatomy.net/anatomy/cardiac_cycle_quiz.htm
165. www.mednote.dk
166. http://crashingpatient.com/wp-content/images/part1/pressure%20volume%20loop.gif
167. http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v03/030268r00.HTM
168. http://en.wikipedia.org/wiki/Premature_ventricular_contraction
169. http://www.nature.com/nrd/journal/v9/n8/fig_tab/nrd3140_F1.html
170. http://www.nature.com/nrm/journal/v9/n8/images/nrm2455-i1.jpg
171. http://www.pohai.org.tw/ped/contents/D5/G/Arrhythmia/Treatment%20of%20arrhythmia.files/slide0063_image007.jpg
172. http://www.gcrweb.com/HeartDSS/charts/fig4.jpg
173. https://upload.wikimedia.org/wikipedia/commons/thumb/a/a2/Renin-angiotensin-aldosterone_system.png/800px-Renin-angiotensin-aldosterone_system.png
174. http://www.bcmj.org/sites/default/files/BCMJ_50Vol2_nonpharma_fig3.gif
175. http:// pathhsw5m54.ucsf.edu
176. http://www.mdpi.com/2075-163X/1/1/49/htm
177. http://www.coheadquarters.com/PennLibr/MyPhysiology/Mod20/figdev1.04.htm
178. http://geekymedics.com/wp-content/uploads/2011/03/ch3f7.jpg
179. http://www.medicine-on-line.com/html/ecg/e0001en_files/image092.png
180. http://nyp.org/health/block.html
181. http://lifeinthefastlane.com/ecg-library/pacemaker/
182. http://floatnurse-mike.blogspot.com/2013/07/ekg-rhythm-strip-quiz-142.html
183. http://www.practicalclinicalskills.com/ekg/Atrial-Flutter
184. http://lifeinthefastlane.com/ecg-library/basics/pvc/
185. http://www.cram.com/flashcards/symptoms-17-dyspnea-orthopnea-and-edema-4706908