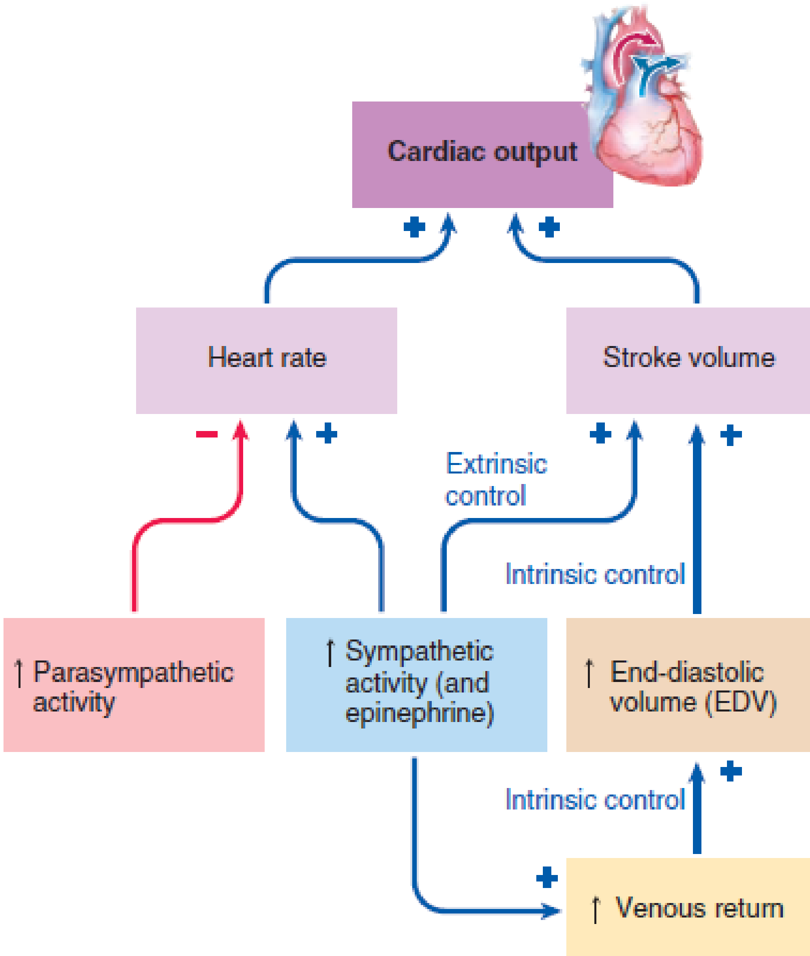

TIME FOR
RECAP

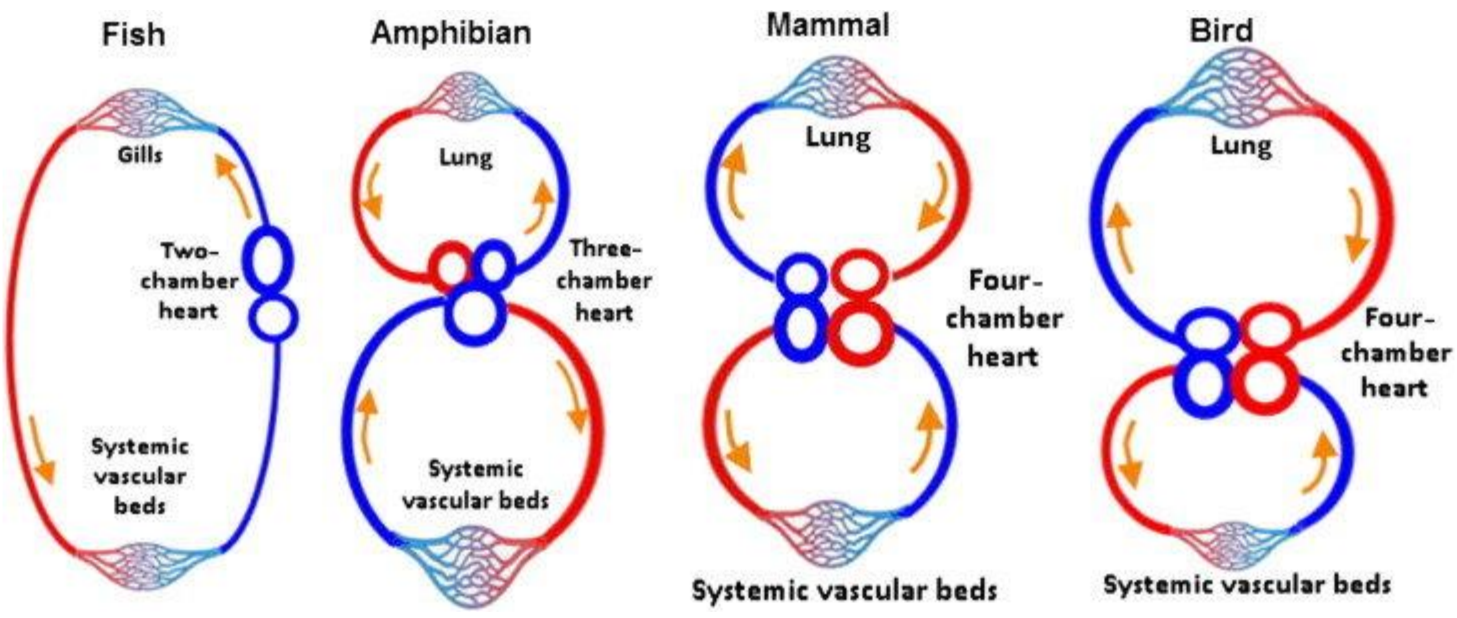


i. Cardiac output depends on the heart rate times the stroke volume.
ii. Heart rate is determined primarily by antagonistic regulation of autonomic influences on the SA node.
iii. Stroke volume is determined by the extent of venous return and by sympathetic activity.
iv. Increased end-diastolic volume, which occurs during exercise as skeletal muscles squeeze more blood into the heart, results in increased stroke volume.

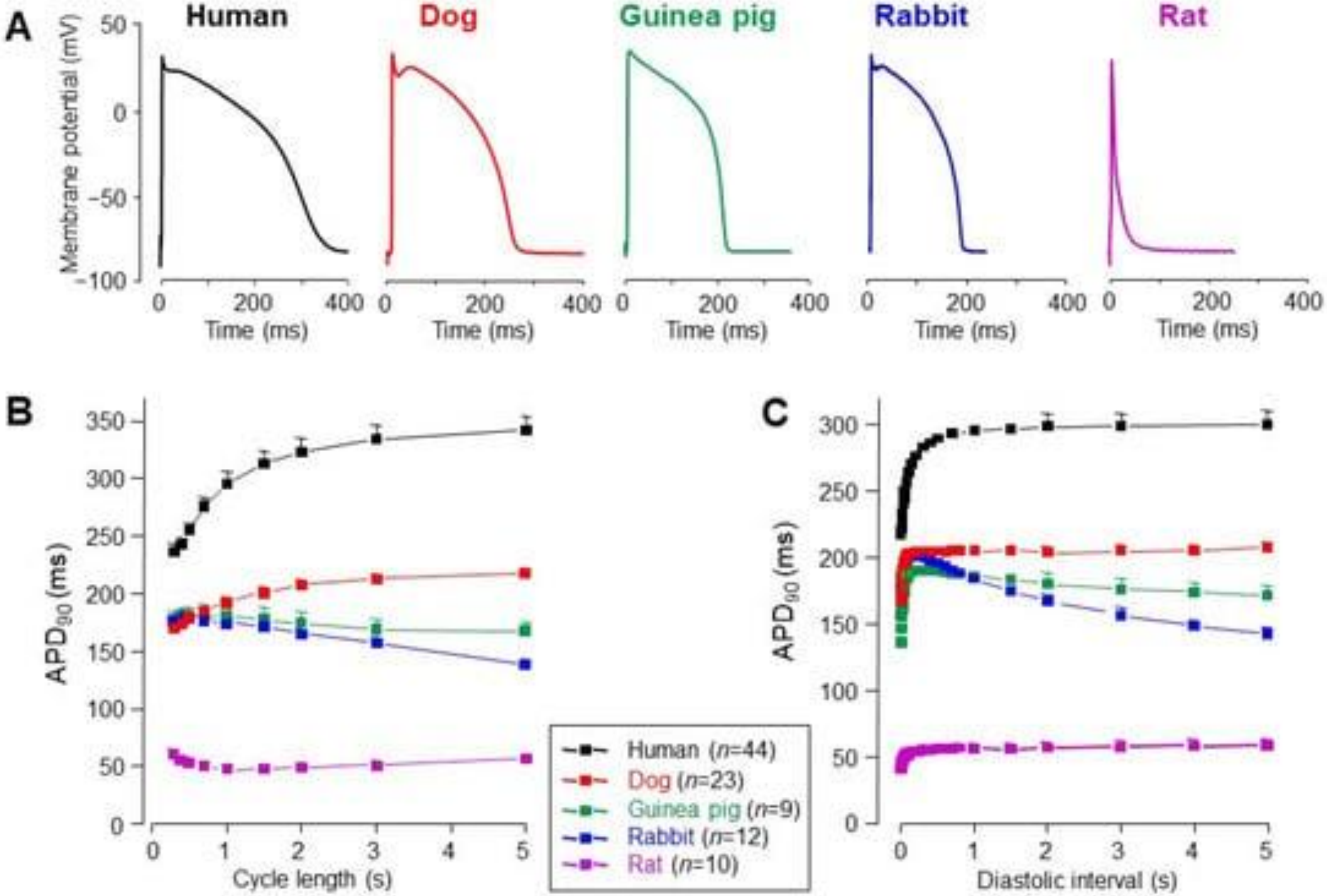
- ✓ Blood flow Q through vessels depends on the pressure gradient ΔP and inversely on vascular resistance R: $Q = \Delta P/R$.
- ✓ Pressure is dependent on many factors such as gravity;
- ✓ resistance depends on many factors, but blood vessel radius is the most important.

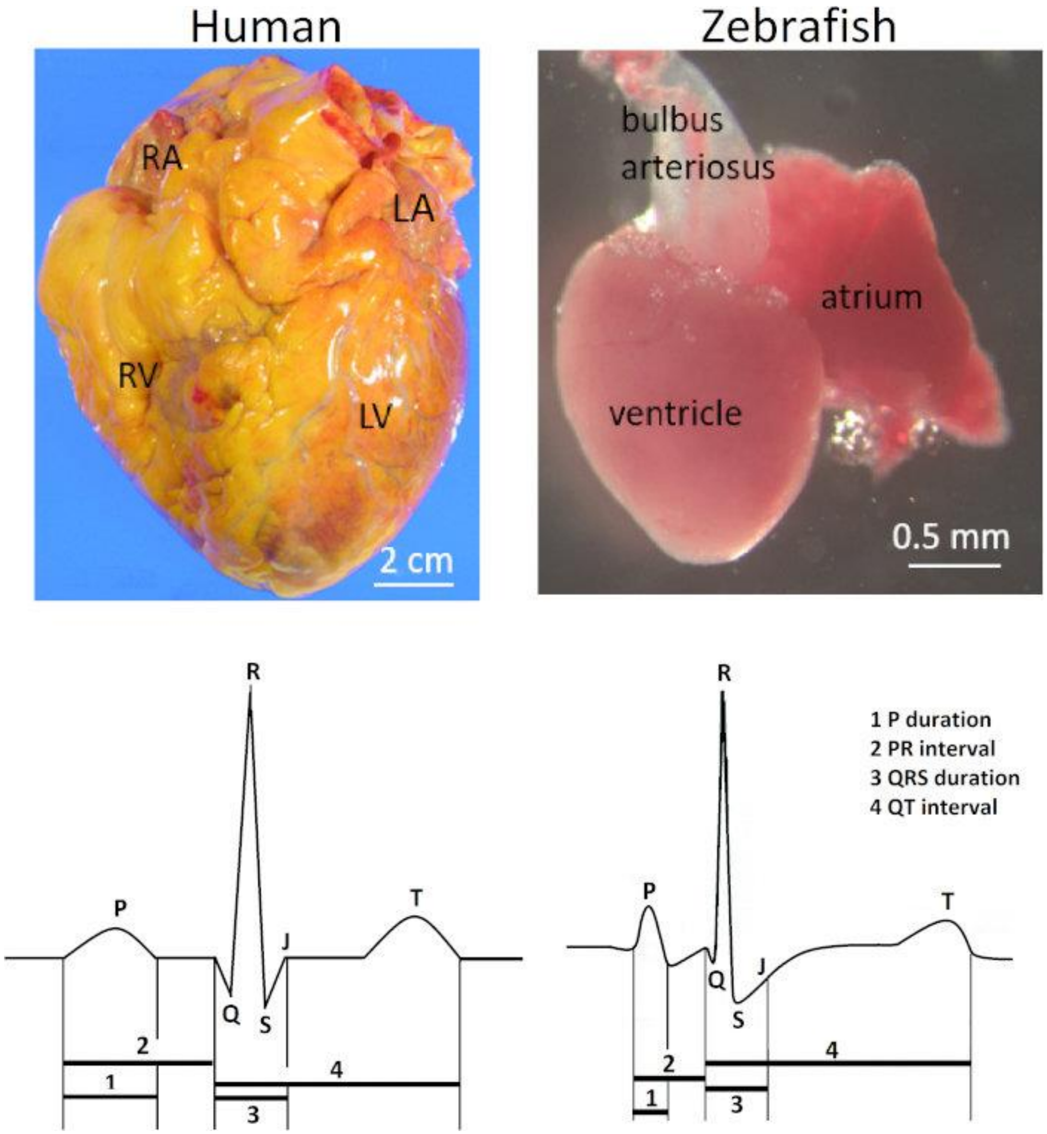
- ✓Circulatory fluids transport materials in a parallel manner, especially in closed systems, so that each organ gets a fair share of fluid.
- ✓Flow to respiratory organs may be in series for maximal gas exchange.
- ✓Circulatory fluids are driven by pressure and can transmit useful force, such as extending spider legs for jumping.

The vascular system evolved from one circuit to two separate circuits (pulmonary to the lungs and systemic to the rest of the body) in vertebrates, along with a change from a two-chambered heart to a four-chambered one.

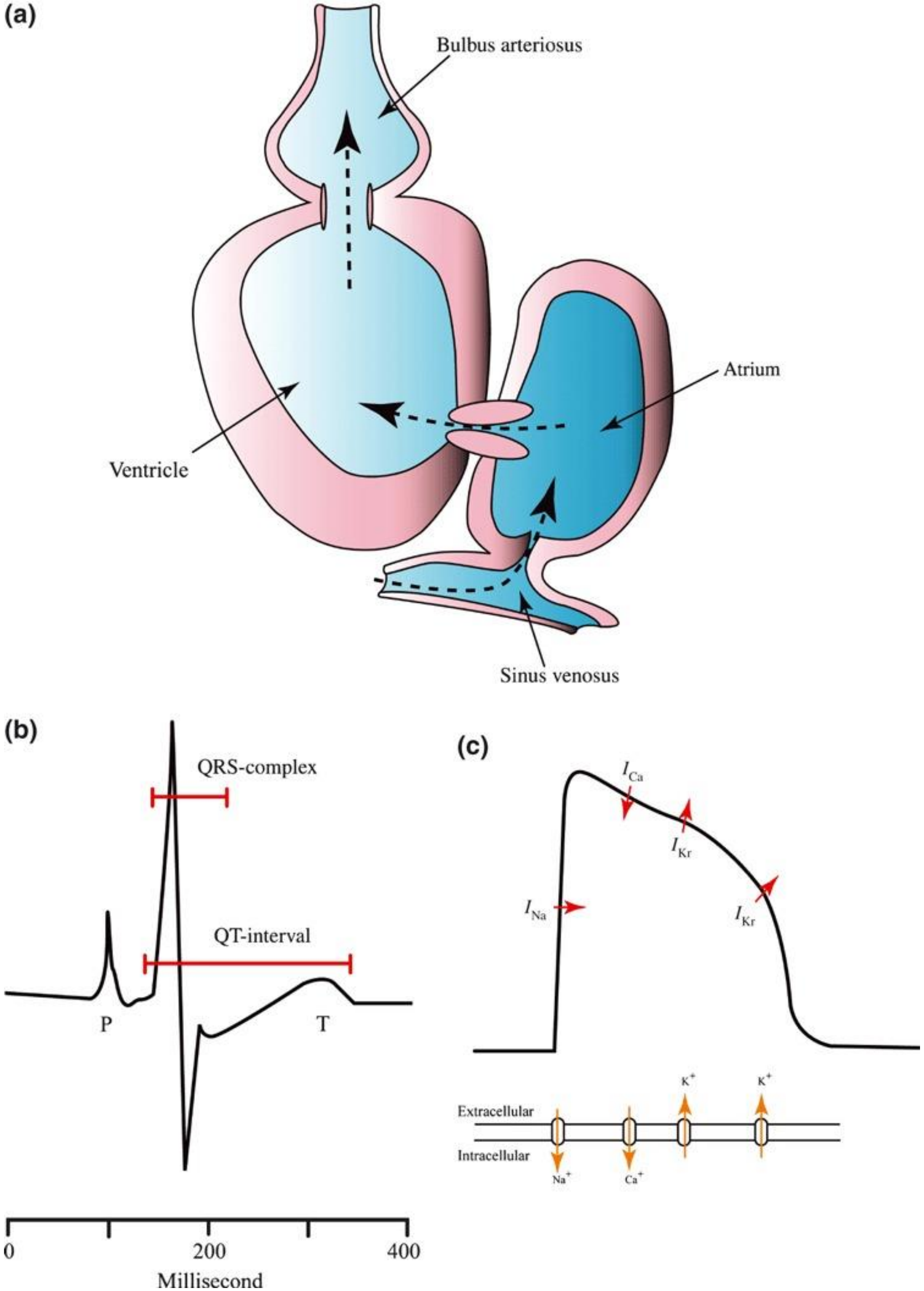


The zebrafish issue

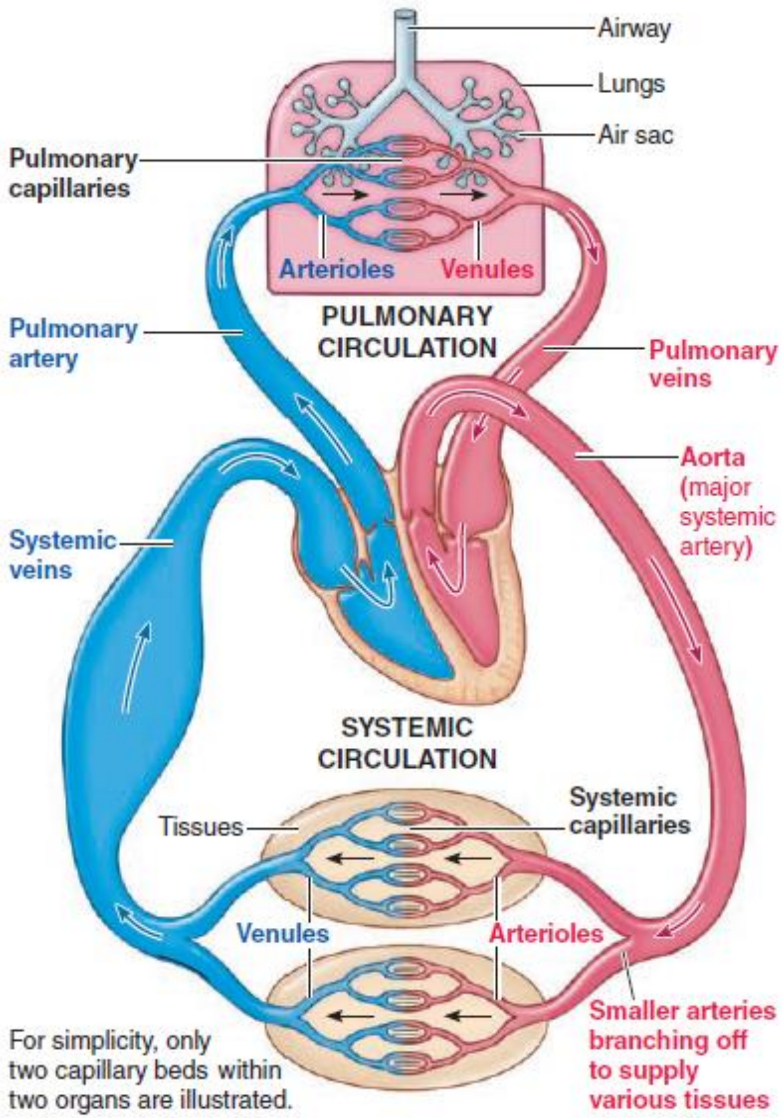

A
Human
Dog
Guinea pig
Rabbit
Rat
Membrane potential (mV)
50
0
−50
−100
0
200
400
Time (ms)
B
APD$_{90}$ (ms)
350
300
250
200
150
100
50
0
0
1
2
3
4
5
Cycle length (s)
Human (n=44)
Dog (n=23)
Guinea pig (n=9)
Rabbit (n=12)
Rat (n=10)
C
APD$_{90}$ (ms)
300
250
200
150
100
50
0
Diastolic interval (s)

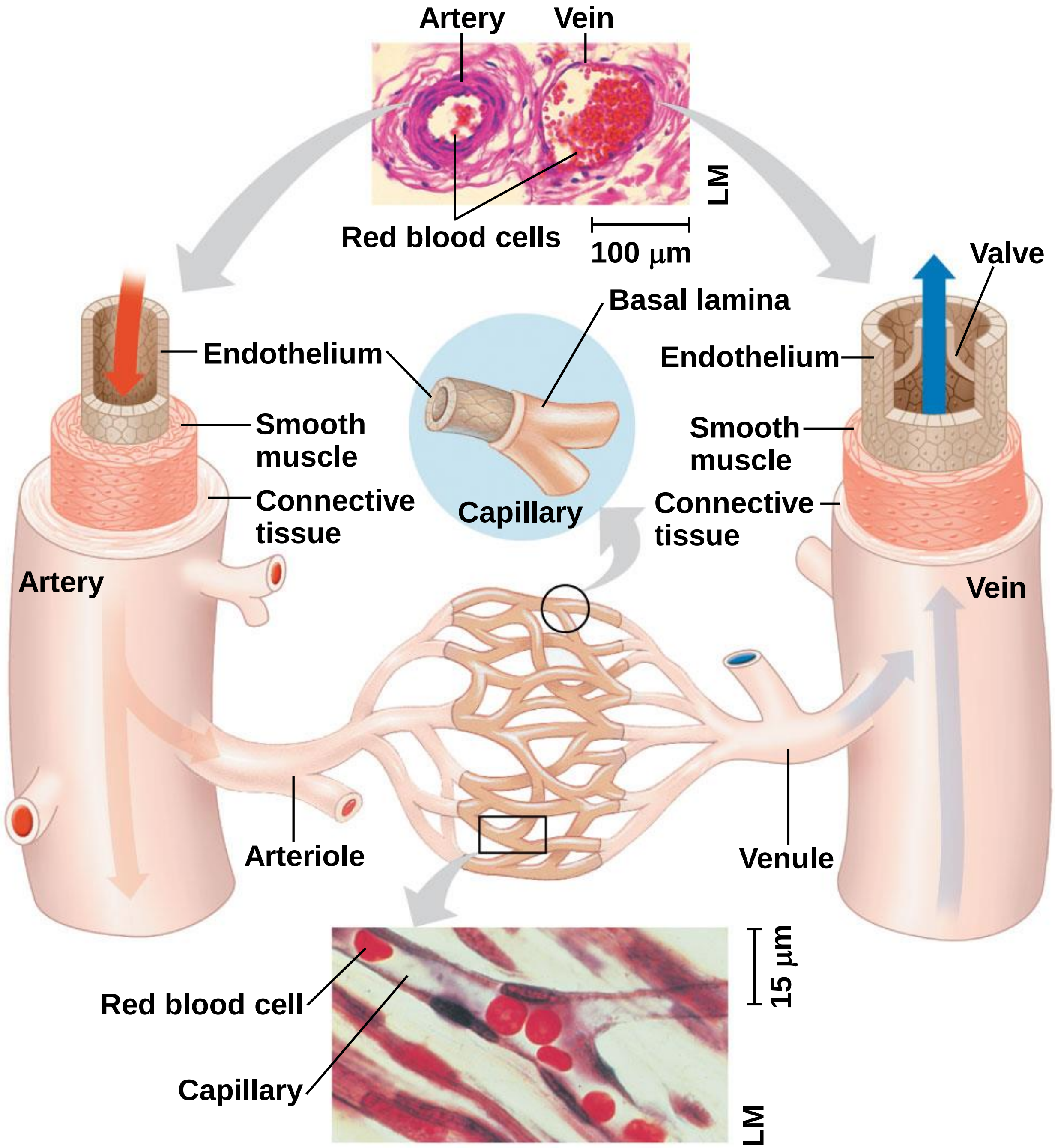


Human
Zebrafish
RA
LA
RV
LV
2 cm
bulbus
arteriosus
atrium
ventricle
0.5 mm
R
P
T
J
Q
S
1
2
3
4
1 P duration
2 PR interval
3 QRS duration
4 QT interval



(a)
Bulbus arteriosus
Atrium
Ventricle
Sinus venosus
(b)
QRS-complex
QT-interval
P
T
0
200
400
Millisecond
(c)
I_{Ca}
I_{Kr}
I_{Na}
I_{Kr}
K^+
K^+
Extracellular
Intracellular
Na^+
Ca^+


Airway
Lungs
Air sac
Pulmonary capillaries
Arterioles
Venules
PULMONARY CIRCULATION
Pulmonary artery
Pulmonary veins
Aorta (major systemic artery)
Systemic veins
SYSTEMIC CIRCULATION
Tissues
Systemic capillaries
Venules
Arterioles
Smaller arteries branching off to supply various tissues
For simplicity, only two capillary beds within two organs are illustrated.


Artery
Vein
Red blood cells
LM
100 µm
Valve
Basal lamina
Endothelium
Smooth muscle
Connective tissue
Artery
Capillary
Endothelium
Smooth muscle
Connective tissue
Vein
Arteriole
Venule
Red blood cell
Capillary
15 µm
LM

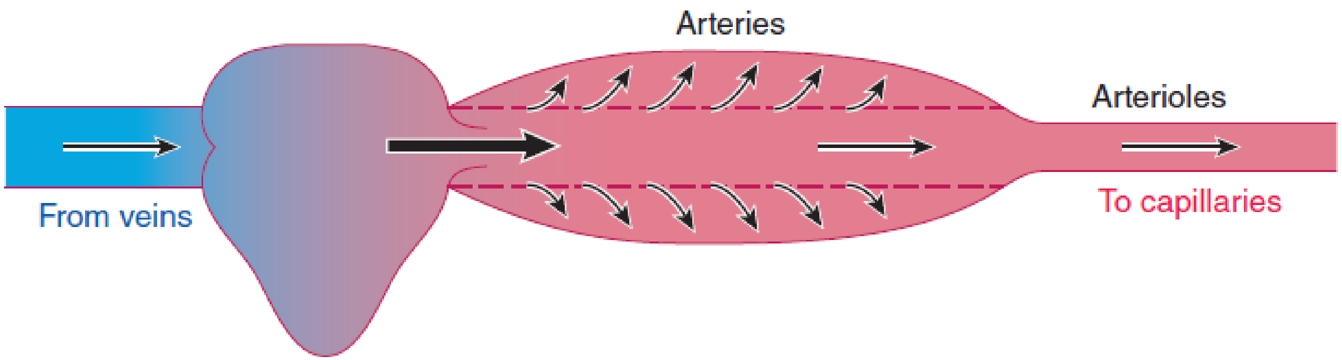
Circulatory Vessels: Arteries

1. A rapid-transit passageways for blood from the heart to the tissues;
2. A pressure reservoir to provide the driving force for blood when the heart is relaxing

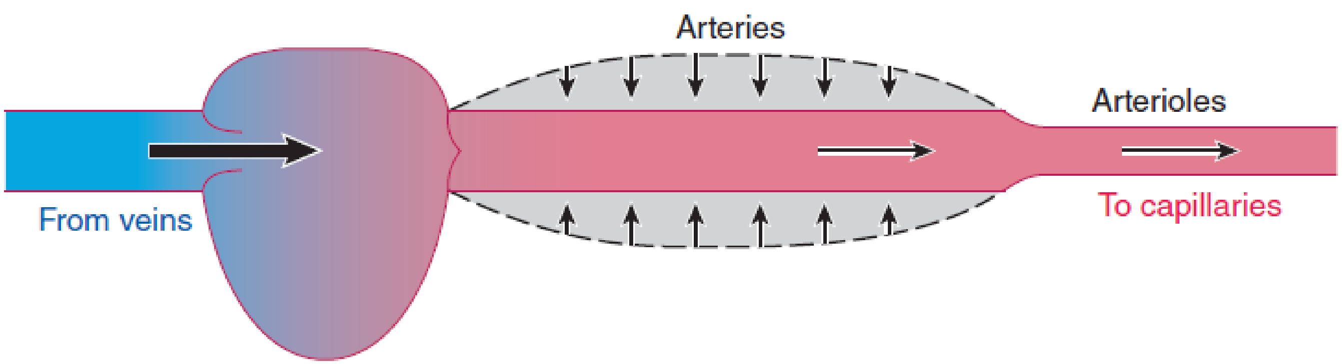
All vessels are lined with a layer of smooth, flattened endothelial cells.

Surrounding the arterial endothelial lining is a thick wall containing smooth muscle and two types of connective tissue fibers;

- *collagen fibers,* which provide tensile strength against the high driving pressure of blood ejected from the heart, and
- *elastin fibers,* which give the arterial walls elasticity so that they behave much like a balloon



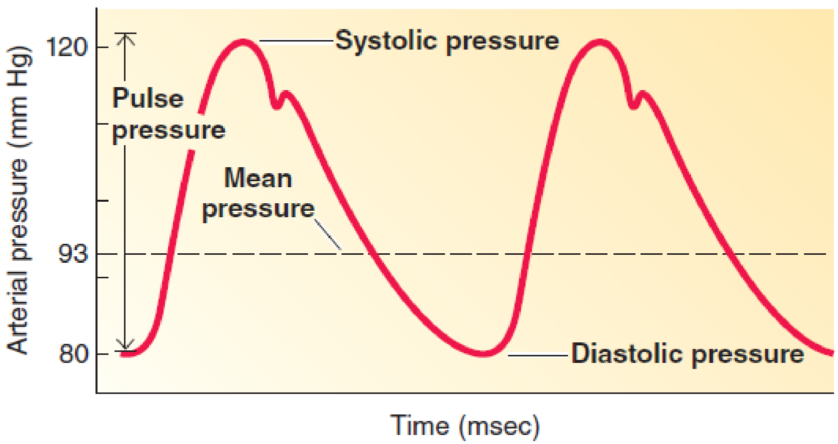
(a) Heart contracting and emptying



(b) Heart relaxing and filling

What are normal systolic and diastolic blood pressure values?

The maximum pressure exerted in the arteries when blood is ejected into them during systole, the **systolic pressure,** averages 120 mm Hg in humans. The minimum pressure within the arteries when blood is draining off into the remainder of the vessels during diastole, the **diastolic pressure,** averages 80 mm Hg in humans.



Integrated Cardiovascular Function

$$Q = C.O. = \Delta P/R \text{ or } \Delta P = C.O. \times R$$

Recall that a vertebrate can rapidly alter (1) cardiac output (C.O.) by varying heart rate and stroke volume, and (2) resistance (R) primarily by changing arteriole diameter.

1. Proper gas and heat transport. Because oxygen and heat balance are so crucial to short-term survival, proper blood flow for gas and heat transport is the first priority of the cardiovascular system

2. Arterial blood pressure.

Values in mammals are not very different:

- ✓ 130/95 for horses
- ✓ 110/80 for rabbits

Birds usually have higher values, such as 180/130 for starlings.

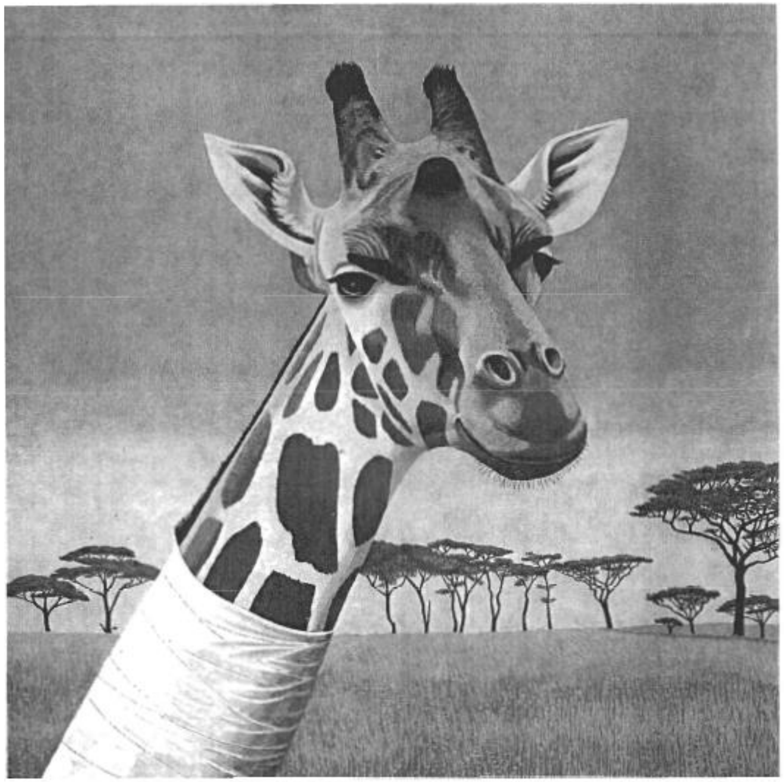
Ectotherms have lower pressures in general, such as 31/21 for frogs, 43/33 for trout, and 35/21 for lobster (open circulation).

There are significant exceptions to this:

- ✓ in an octopus can reach 75 mm Hg,
- ✓ in a jumping spider they can reach 400 mm Hg!

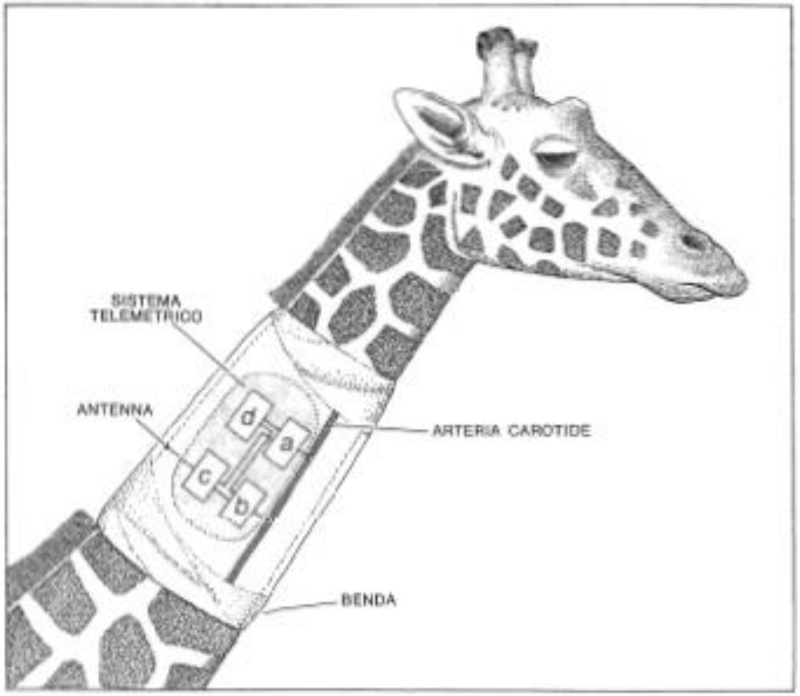
LE SCIENZE

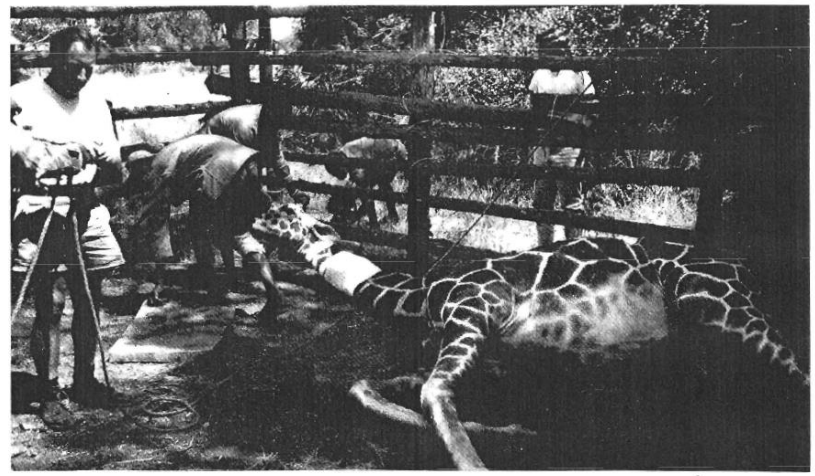
edizione italiana di **SCIENTIFIC AMERICAN**

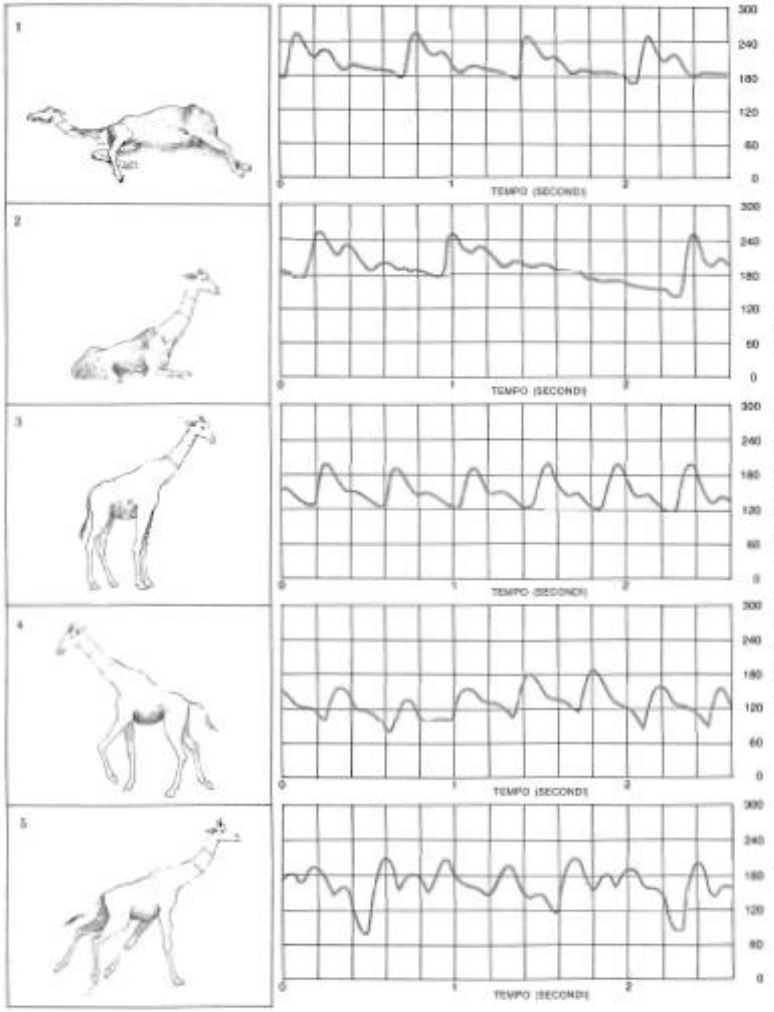


La fisiologia della giraffa

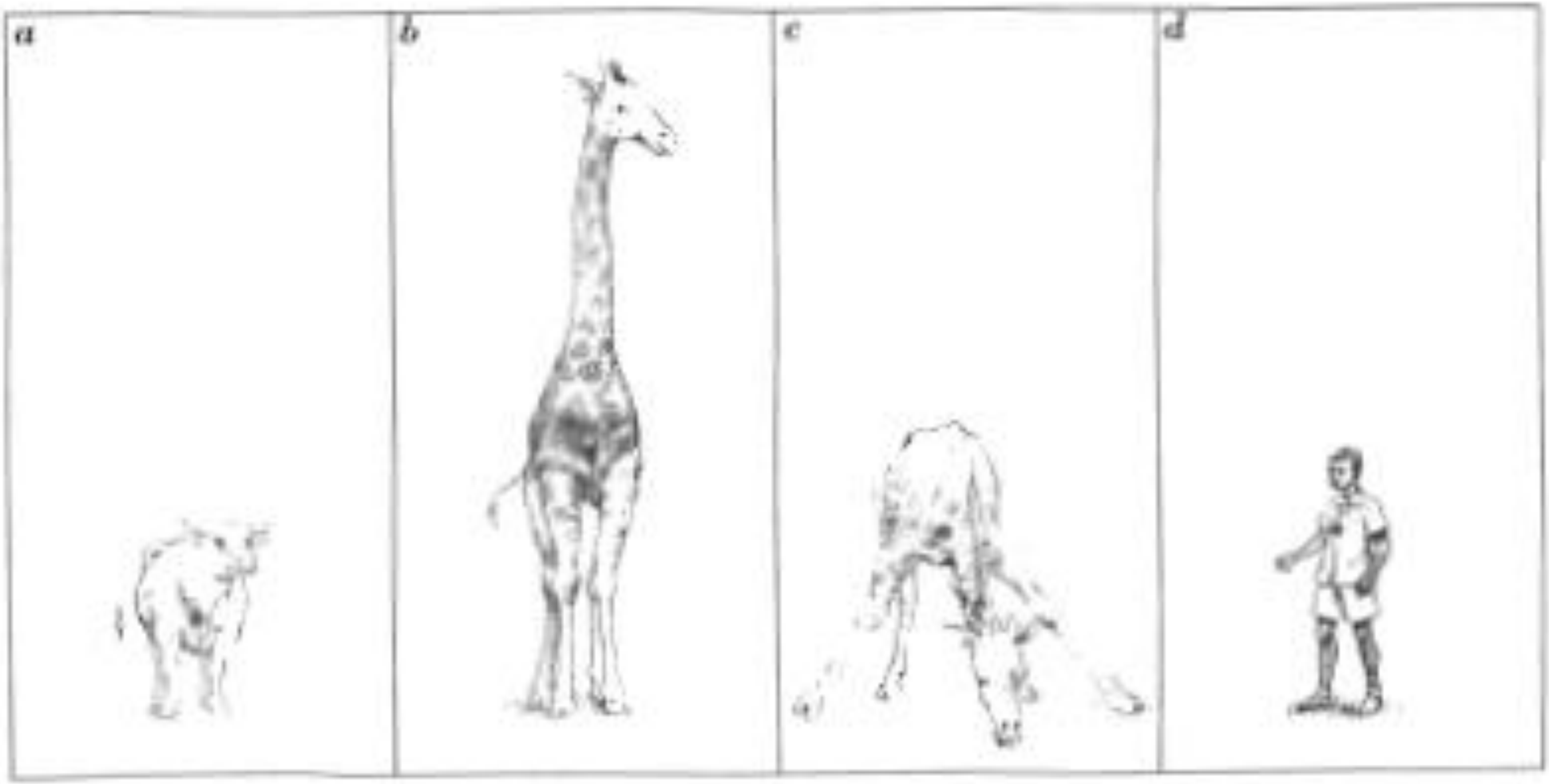
Lire Mille
Febbraio 1975
Numero 78


SISTEMA
TELEMETRICO
ANTENNA
d
a
c
b
ARTERIA CAROTIDE
BENDA

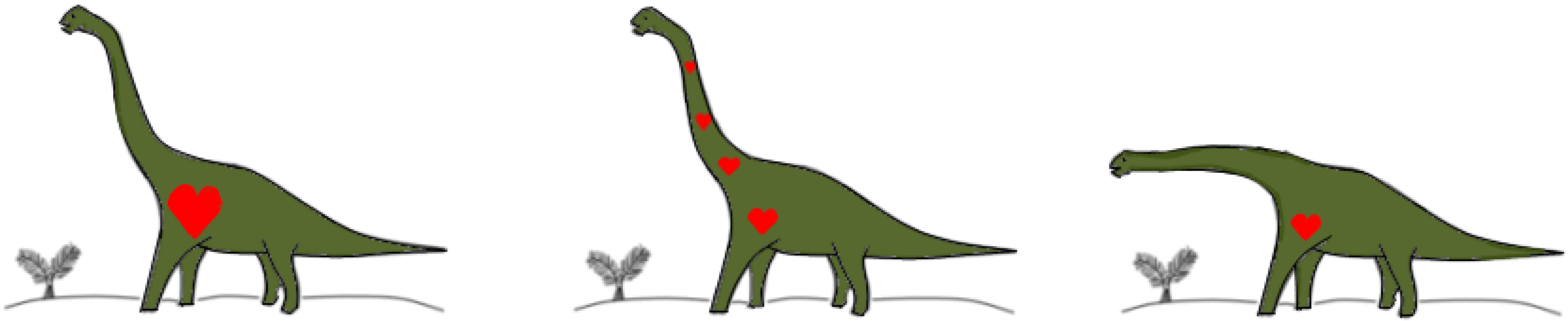




1
2
3
4
5
TEMPO (SECONDI)
0
1
2
300
240
180
120
60
0
PRESSIONE ARTERIOSA MEDIA DELL'ORGANISMO (MILLIMETRI DI MERCURIO)


a
b
c
d

Proposed Solutions to the Brachiosaurus' Extreme Blood Pressure Problem



The Brachiosaurs had a massive, strong heart weighing at least 1.6 tons.

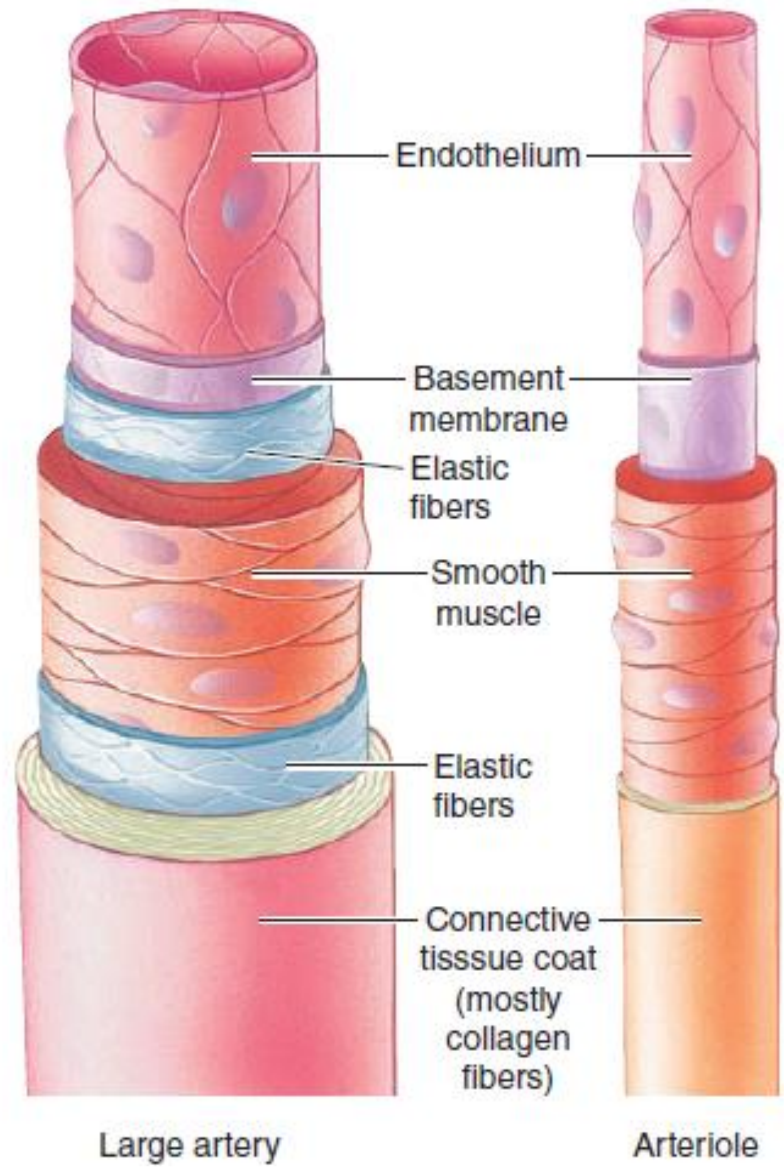
The Brachiosaurus had hearts in its neck to reach the height in a series of steps.

The Brachiosaurus never lifted its head above its shoulders.

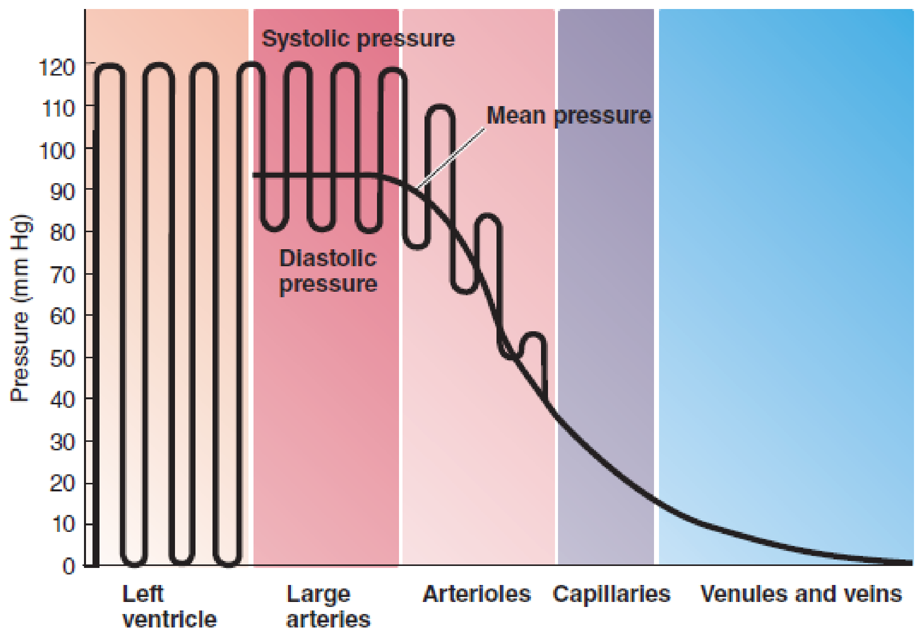
Circulatory Vessels: Arterioles

The radii (and, accordingly, the resistances) of arterioles supplying individual organs can be adjusted independently to accomplish two major functions:

- To variably distribute the cardiac output among the systemic organs, depending on the body’s momentary needs
- To help regulate bodywide arterial blood pressure.

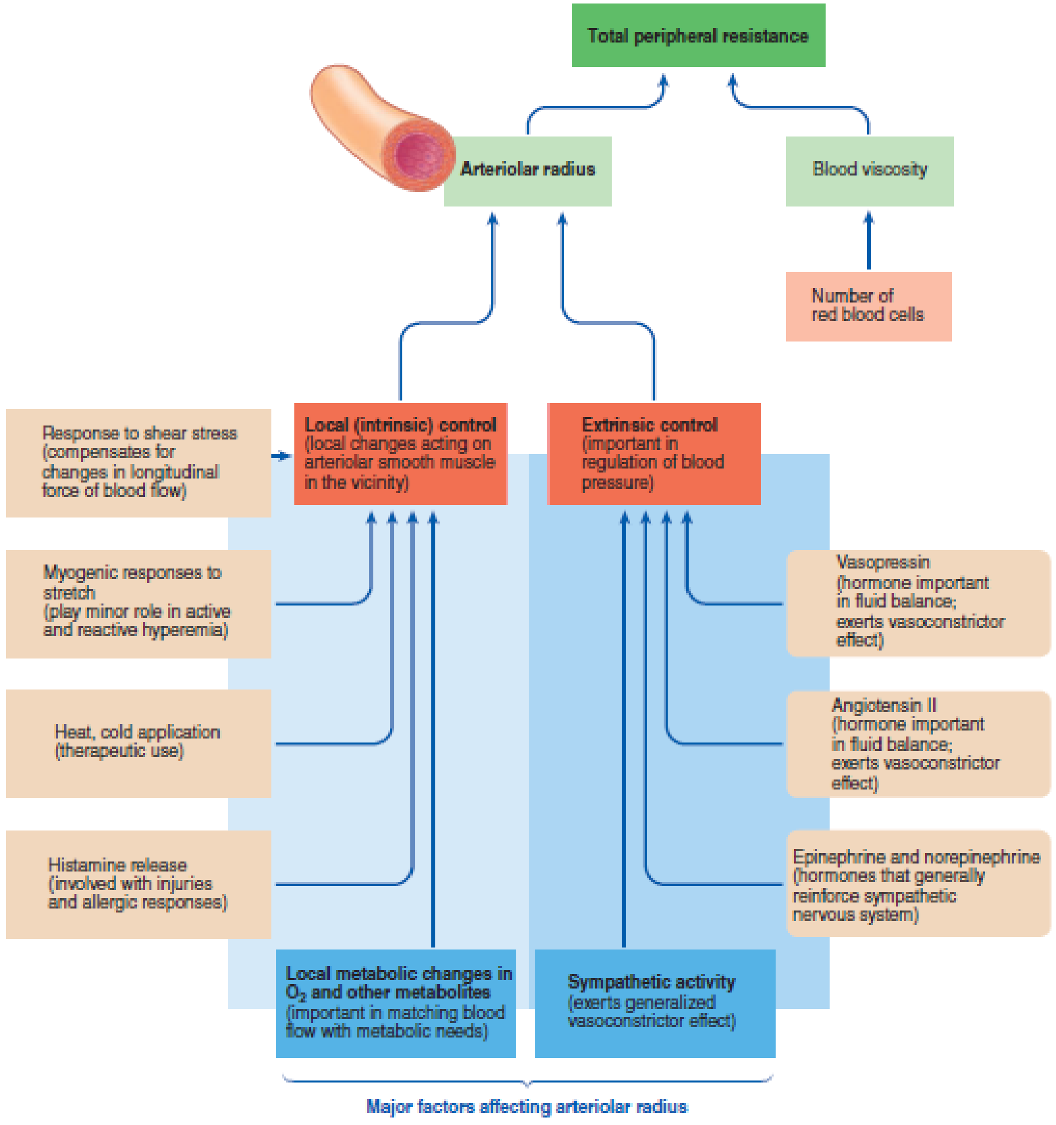


In contrast to the low resistance of the arteries, the high degree of arteriolar resistance causes a marked drop in local pressure as the blood flows through these vessels and the pressure energy dissipates.

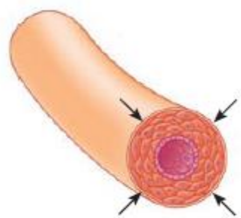


Regulation of Blood Pressure

- Blood pressure is determined by cardiac output and peripheral resistance due to constriction of arterioles
- **Vasoconstriction** is the contraction of smooth muscle in arteriole walls; it increases blood pressure
- **Vasodilation** is the relaxation of smooth muscles in the arterioles; it causes blood pressure to fall

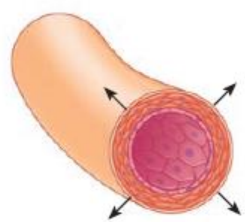

Total peripheral resistance
Arteriolar radius
Blood viscosity
Number of red blood cells
Local (intrinsic) control (local changes acting on arteriolar smooth muscle in the vicinity)
Extrinsic control (important in regulation of blood pressure)
Response to shear stress (compensates for changes in longitudinal force of blood flow)
Myogenic responses to stretch (play minor role in active and reactive hyperemia)
Heat, cold application (therapeutic use)
Histamine release (involved with injuries and allergic responses)
Local metabolic changes in O_2 and other metabolites (important in matching blood flow with metabolic needs)
Sympathetic activity (exerts generalized vasoconstrictor effect)
Vasopressin (hormone important in fluid balance; exerts vasoconstrictor effect)
Angiotensin II (hormone important in fluid balance; exerts vasoconstrictor effect)
Epinephrine and norepinephrine (hormones that generally reinforce sympathetic nervous system)
Major factors affecting arteriolar radius

(b) Normal arteriolar tone



Caused by:
↑ Myogenic activity
↑ Oxygen (O_2)
↓ Carbon dioxide (CO_2) and other metabolites
↑ Endothelin
↑ Sympathetic stimulation
Vasopressin; angiotensin II
Cold

(c) Vasoconstriction (increased contraction of circular smooth muscle in the arteriolar wall, which leads to increased resistance and decreased flow through the vessel)



Caused by:
↓ Myogenic activity
↓ O_2
↑ CO_2 and other metabolites
↑ Nitric oxide
↓ Sympathetic stimulation
Histamine release
Heat

(d) Vasodilation (decreased contraction of circular smooth muscle in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel)

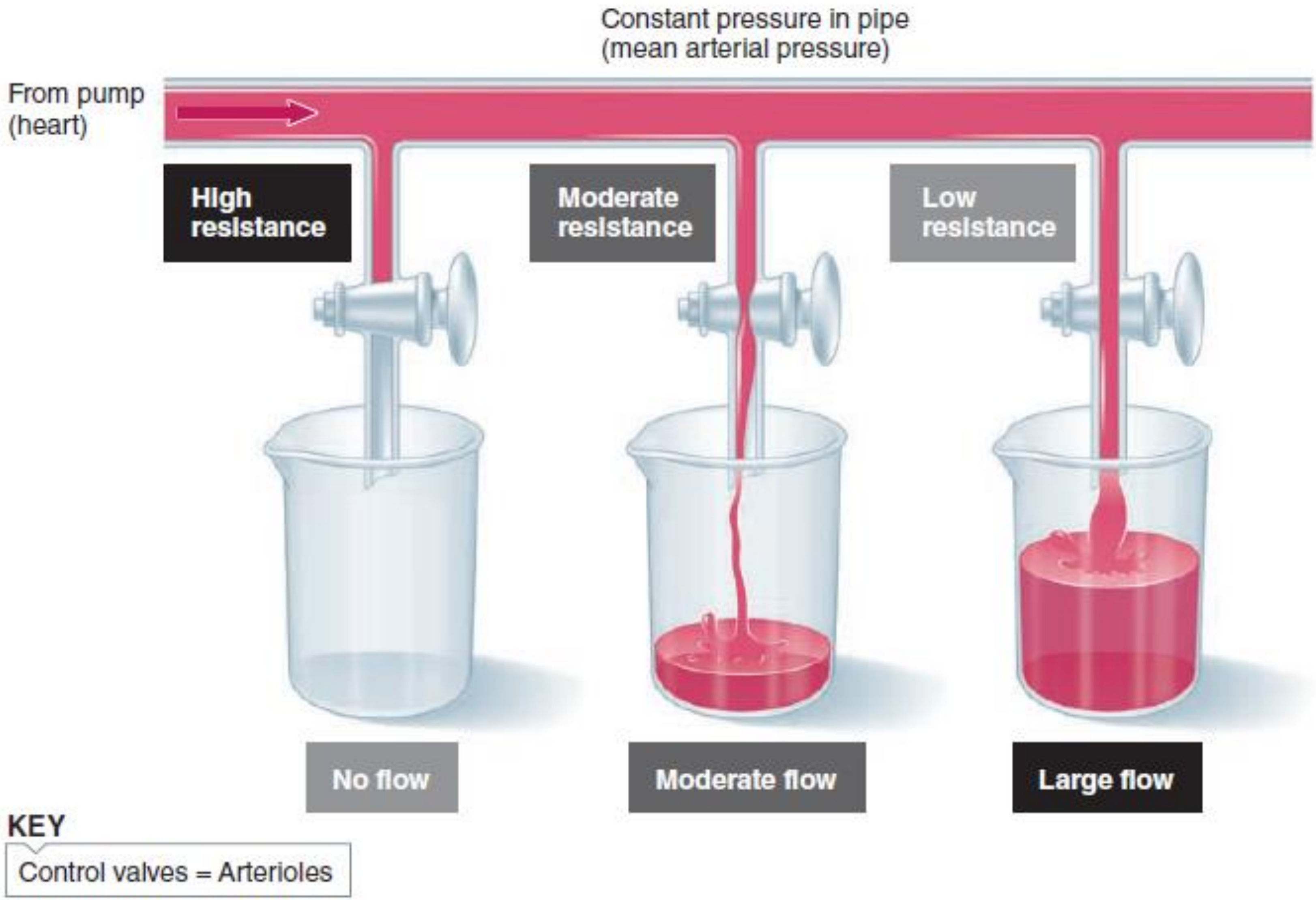
For the entire systemic circulation, re-arranging $Q = \Delta P/R$ and using C.O. for flow Q gives us the following equation:

$$\Delta P = \text{C.O.} \times R$$

i. Q: Looking at the circulatory system as a whole, flow through all the vessels in either the systemic or pulmonary circulation is equal to the cardiac output, C.O.
ii. ΔP: The pressure gradient (ΔP) for the entire systemic circulation is the mean arterial pressure. ΔP equals the difference in pressure between the beginning and the end of the systemic circulatory system. Because the beginning pressure is the mean arterial pressure as the blood leaves the left ventricle at an average of 93 mm Hg (in humans) and the end pressure in the right atrium is about 0 mm Hg, ΔP = 93 mm Hg (that is, 93 minus 0).
iii. R: By far the greatest percentage of the total resistance offered by all the systemic peripheral vessels (total peripheral resistance) is due to arteriolar resistance.

Mean arterial pressure = cardiac output × total peripheral resistance

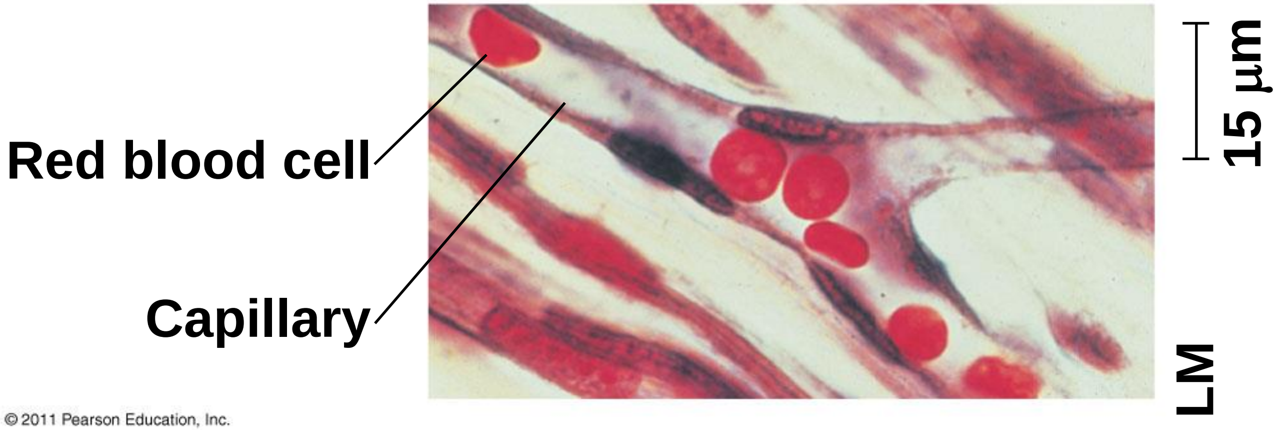
The extent of total peripheral resistance offered collectively by all the systemic arterioles influences the mean arterial blood pressure immensely.

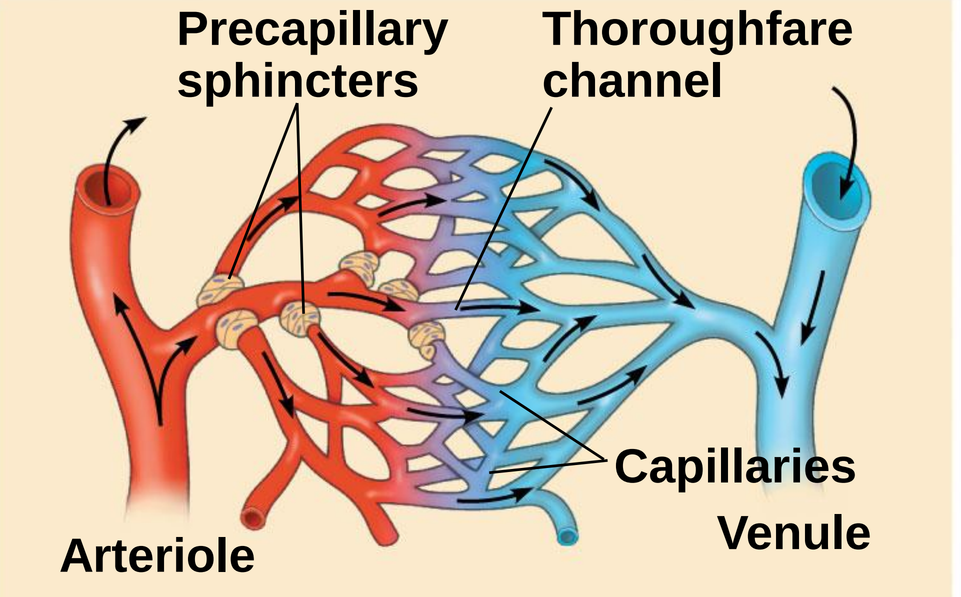

Constant pressure in pipe
(mean arterial pressure)
From pump
(heart)
High
resistance
Moderate
resistance
Low
resistance
No flow
Moderate flow
Large flow
KEY
Control valves = Arterioles

Circulatory Vessels: Capillaries

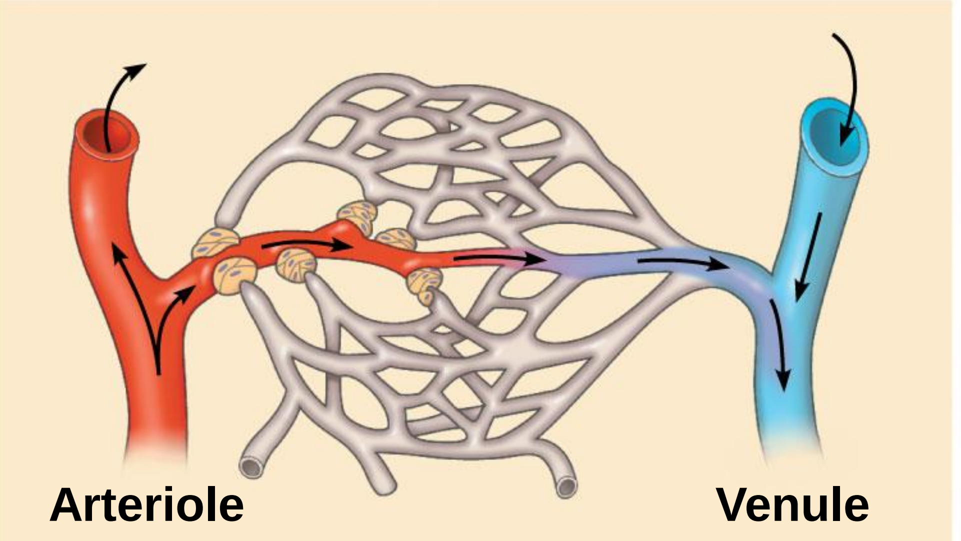
Are the ultimate functional units of circulation.

As the sites for exchange of materials between the blood and tissues, they have thin walls, the endothelium plus its basal lamina to accomplish their primary function: to enhance diffusion.





(a) Sphincters relaxed



(b) Sphincters contracted

Capillary exchange

- Movement of substances between blood and interstitial fluid
- 3 basic methods:

1. Diffusion
2. Transcytosis
3. Bulk flow

Diffusion

- Most important method
- Substances move down their concentration gradient
  - O_2 and nutrients from blood to interstitial fluid to body cells
  - CO_2 and wastes move from body cells to interstitial fluid to blood
- Can cross capillary wall through intracellular clefts, fenestrations or through endothelial cells
  - Most plasma proteins cannot cross
  - Except in sinusoids – proteins and even blood cells leave
  - Blood-brain barrier – tight junctions limit diffusion

Diffusion follows Fick's law

$$\text{Rate of diffusion } (Q) = \frac{\Delta C \times A \times D}{\Delta X}$$

ΔX

Diffusing molecules have only a short distance to travel between the blood and surrounding cells because of the following factors:

a. Capillary walls are very thin (1 µm in thickness). Capillaries are composed of only a single layer of flattened endothelial cells—essentially the lining of the other vessel types. No smooth muscle or connective tissue is present.

b. Each capillary is so narrow that red blood cells have to squeeze through single file. Consequently, oxygen does not have to travel far from hemoglobin inside those cells to leave the capillary (or vice versa).

c. Because of extensive capillary branching, it is estimated that no cell is farther than 0.1 mm 4/1,000 inch) from a capillary.

A

Because capillaries are distributed in such incredible numbers (estimates range from 10 to 40 billion capillaries), a tremendous total surface area (A) is available for exchange (an estimated 600 m2).

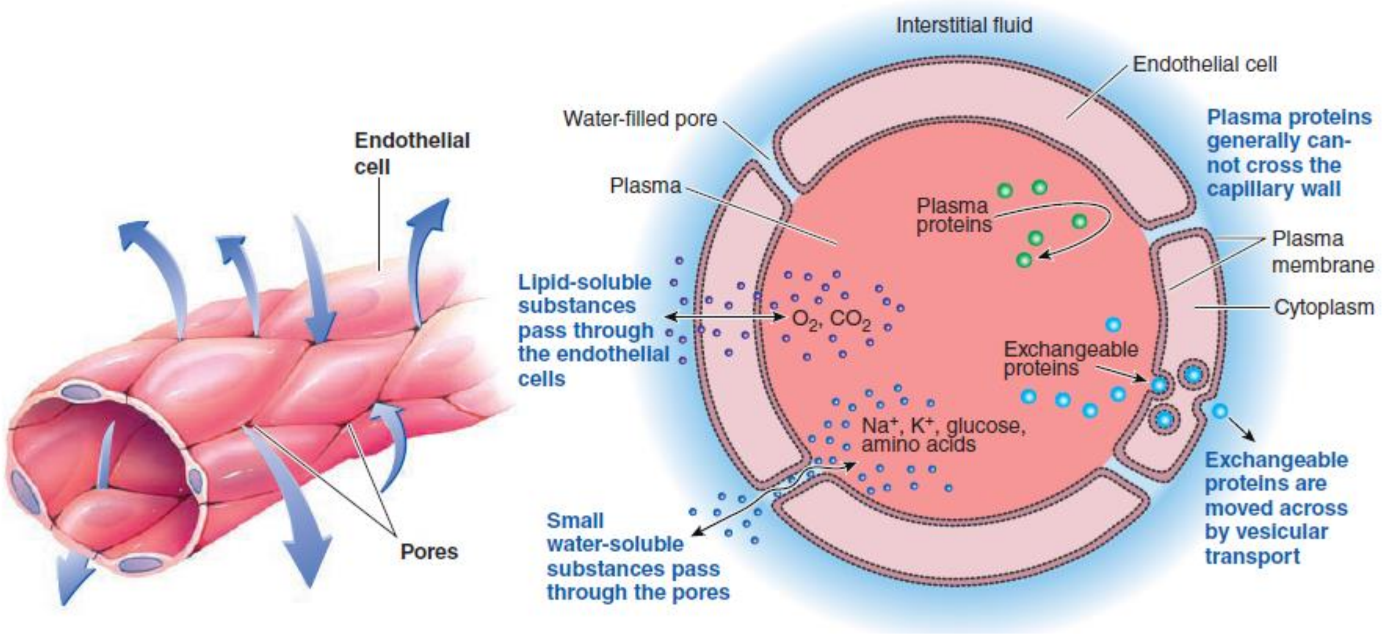
Generally, tissues that are more metabolically active have a greater density of capillaries (vascularization). Muscles, for example, have a small volume of blood is exposed to an extensive surface area.

If all the capillary surfaces of a human were stretched out in a flat sheet and the volume of blood contained within the capillaries were spread over the top, this would be roughly equivalent to spreading a cup of paint over the floor of a high-school gymnasium.

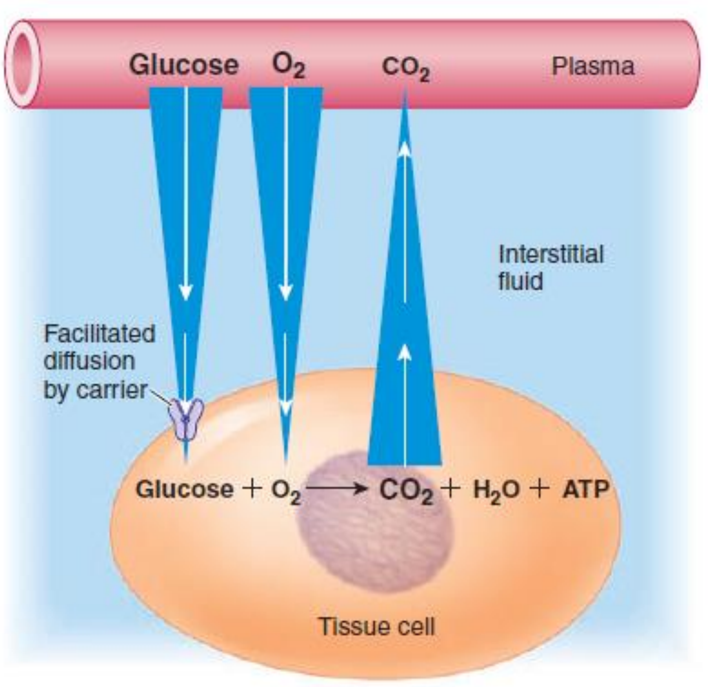
D

Diffusion across capillary walls also depends on the walls' permeability to the materials being exchanged.

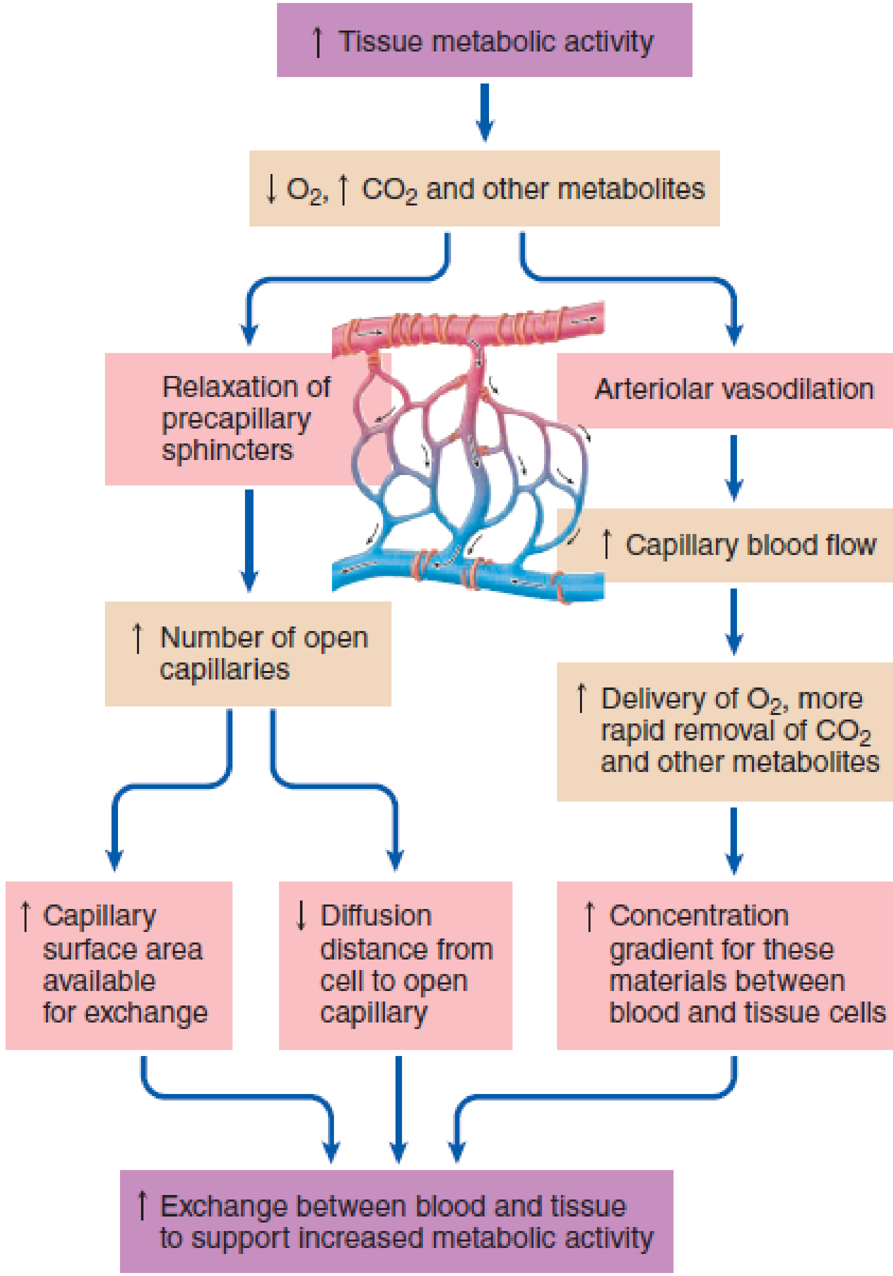
In most capillaries, narrow, water-filled pores are present at the junctions between the cells.

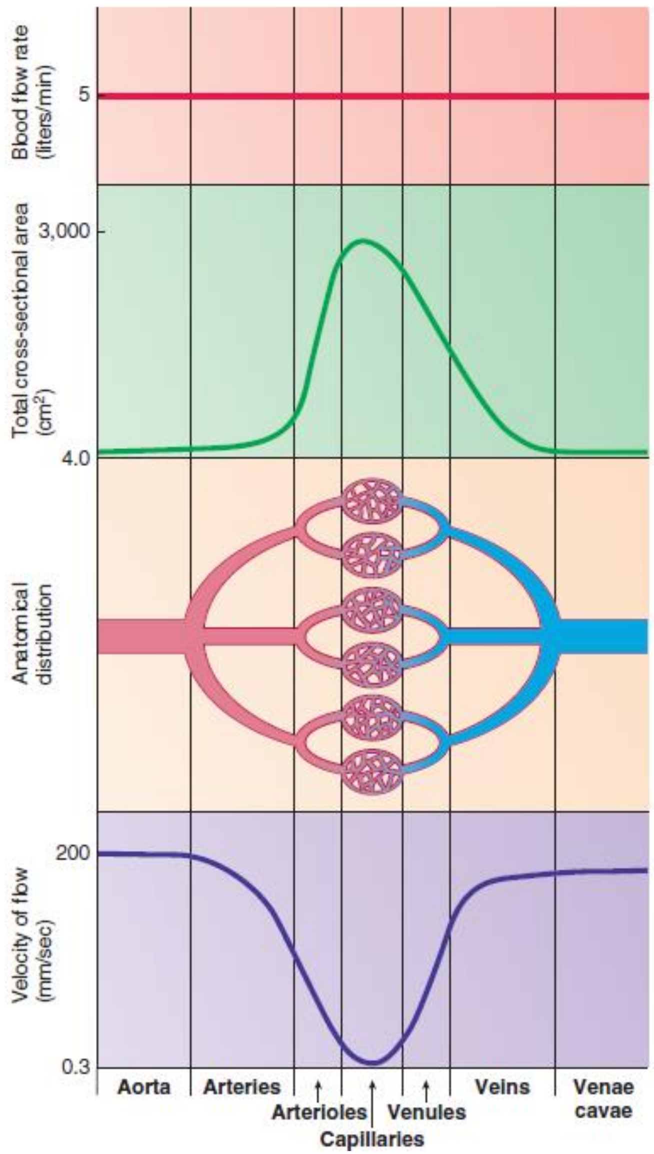


ΔC



Glucose
O2
CO2
Plasma
Interstitial fluid
Facilitated diffusion by carrier
Glucose + O2 ⟶ CO2 + H2O + ATP
Tissue cell


↑ Tissue metabolic activity
↓ O_2, ↑ CO_2 and other metabolites
Relaxation of precapillary sphincters
Arteriolar vasodilation
↑ Capillary blood flow
↑ Number of open capillaries
↑ Delivery of O_2, more rapid removal of CO_2 and other metabolites
↑ Capillary surface area available for exchange
↓ Diffusion distance from cell to open capillary
↑ Concentration gradient for these materials between blood and tissue cells
↑ Exchange between blood and tissue to support increased metabolic activity



Blood flow rate (liters/min)
5
Total cross-sectional area (cm²)
3,000
4.0
Anatomical distribution
Velocity of flow (mm/sec)
200
0.3
Aorta
Arteries
Arterioles
Capillaries
Venules
Veins
Venae cavae

Bulk flow

- Passive process in which large numbers of ions, molecules, or particles in a fluid move together in the same direction
- Based on pressure gradient
- Diffusion is more important for solute exchange
- Bulk flow more important for regulation of relative volumes of blood and interstitial fluid

Bulk flow

i. When moving from the bloodstream into the interstitium, bulk flow is termed filtration, which is favored by blood hydrostatic pressure and interstitial fluid oncotic pressure.

ii. When moving from the interstitium into the bloodstream, the process is termed reabsorption and is favored by blood oncotic pressure and interstitial fluid hydrostatic pressure.

The Starling Principle holds that extracellular fluid movements between blood and tissues are determined by differences in hydrostatic pressure and colloid osmotic (oncotic) pressure between plasma inside microvessels and interstitial fluid outside them.

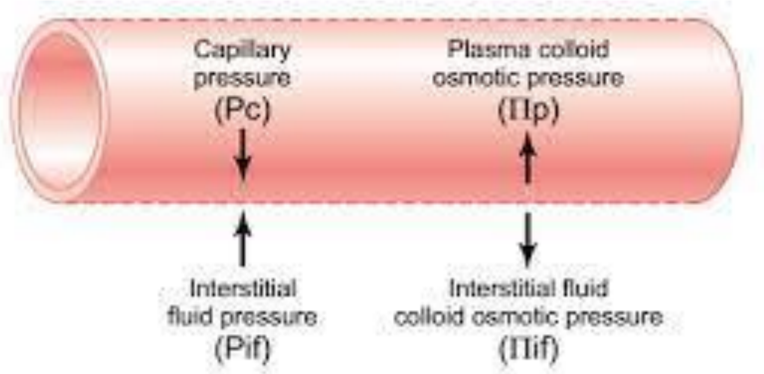
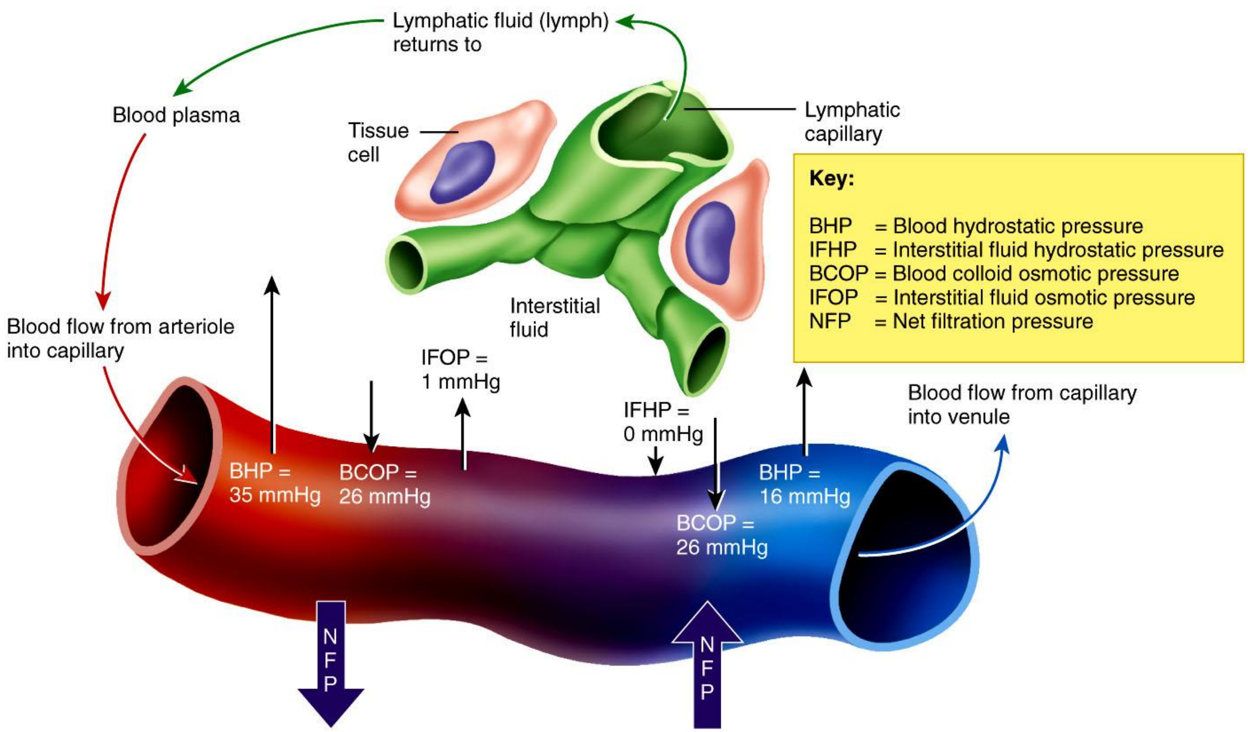


Figure 16–5

Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane, tending to move fluid either outward or inward through the membrane pores.



Net filtration art arterial end of capillaries (20 liters per day)

Net reabsorption at venous end of capillaries (17 liters per day)

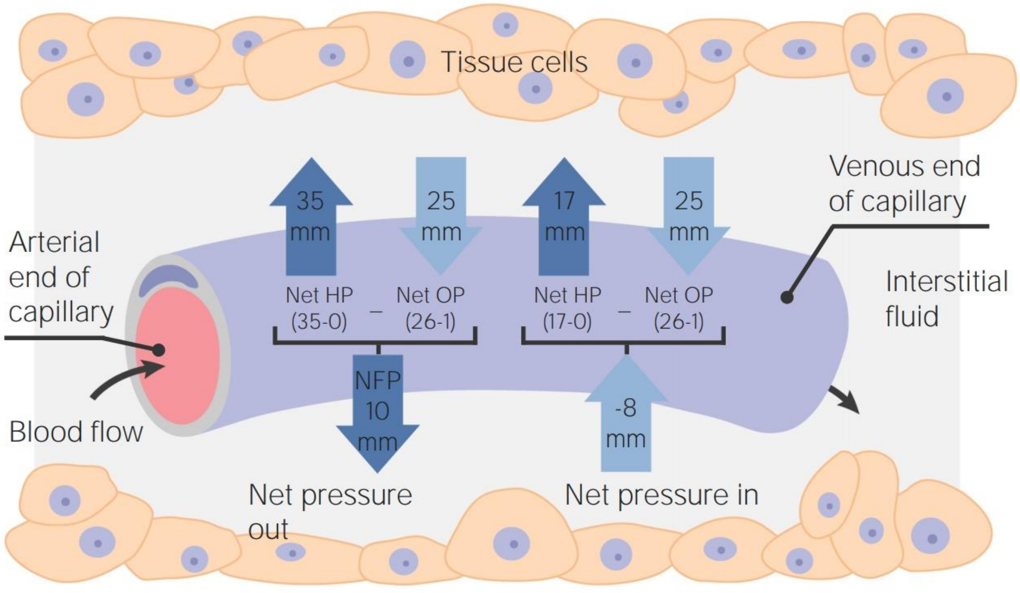
Net filtration pressure (NFP) = (BHP + IFOP) – (BCOP + IFHP)

(BHP + IFOP): Pressures promoting filtration

(BCOP + IFHP): Pressure promoting reabsorption

	Arterial end	Venous end
	NFP = (35 + 1) – (26 + 0) = 10 mmHg	NFP = (16 + 1) – (26 + 0) = – 9 mmHg
Result	Net filtration	Net reabsorption

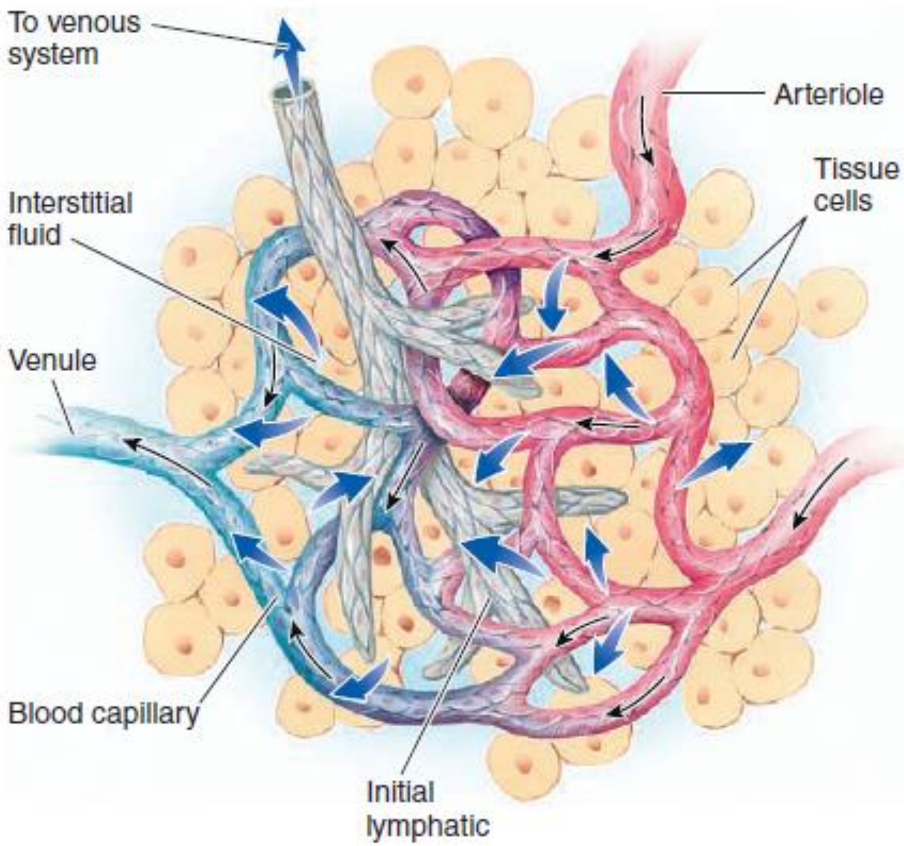
Figure 21.07 Tortora - PAP 12/e

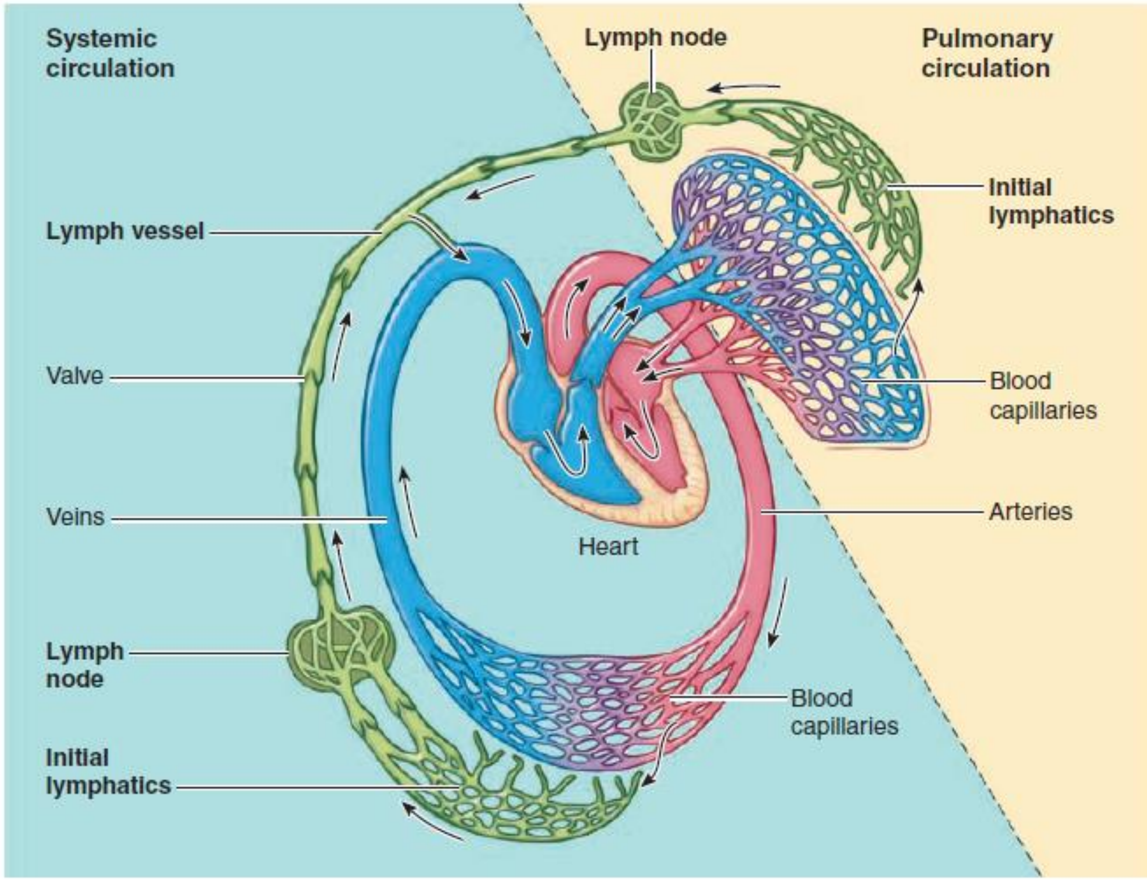


- Nearly as much reabsorbed as filtered
  - At the arterial end, net outward pressure of 10 mmHg and fluid leaves capillary (filtration)
  - At the venous end, fluid moves in (reabsoprtion) due to -9 mmHg
  - On average, about 85% of fluid filtered is reabsorpbed
  - Excess enters lymphatic capillaries (about 3L/ day) to be eventually returned to blood

Fluid Return by the Lymphatic System

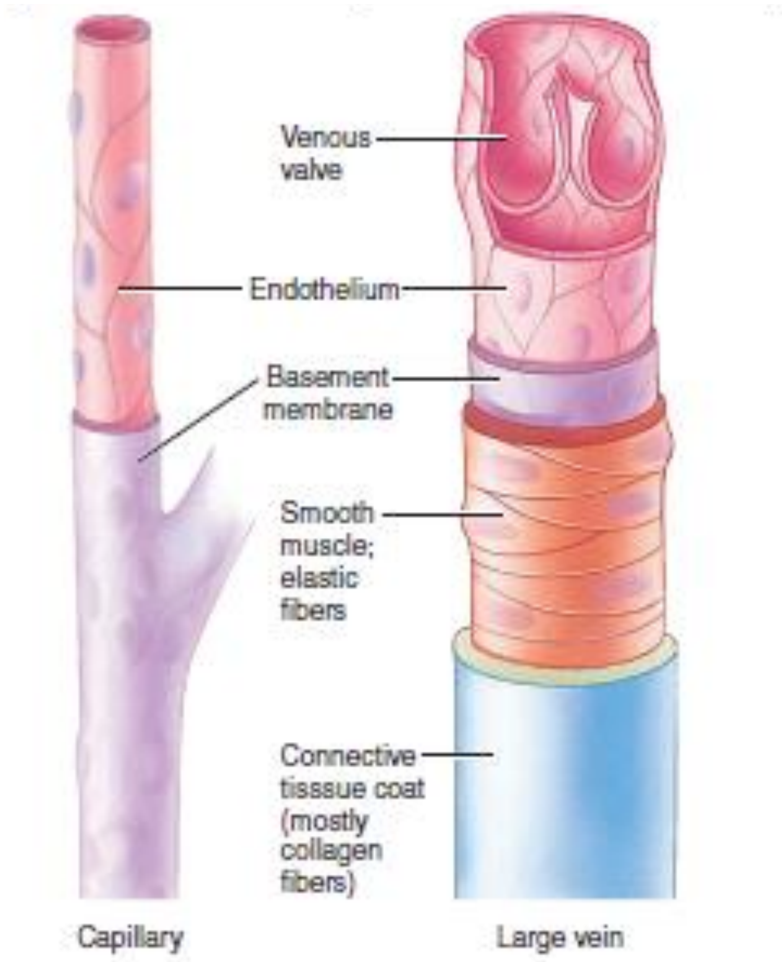
The **lymphatic system** returns fluid that leaks out from the capillary beds



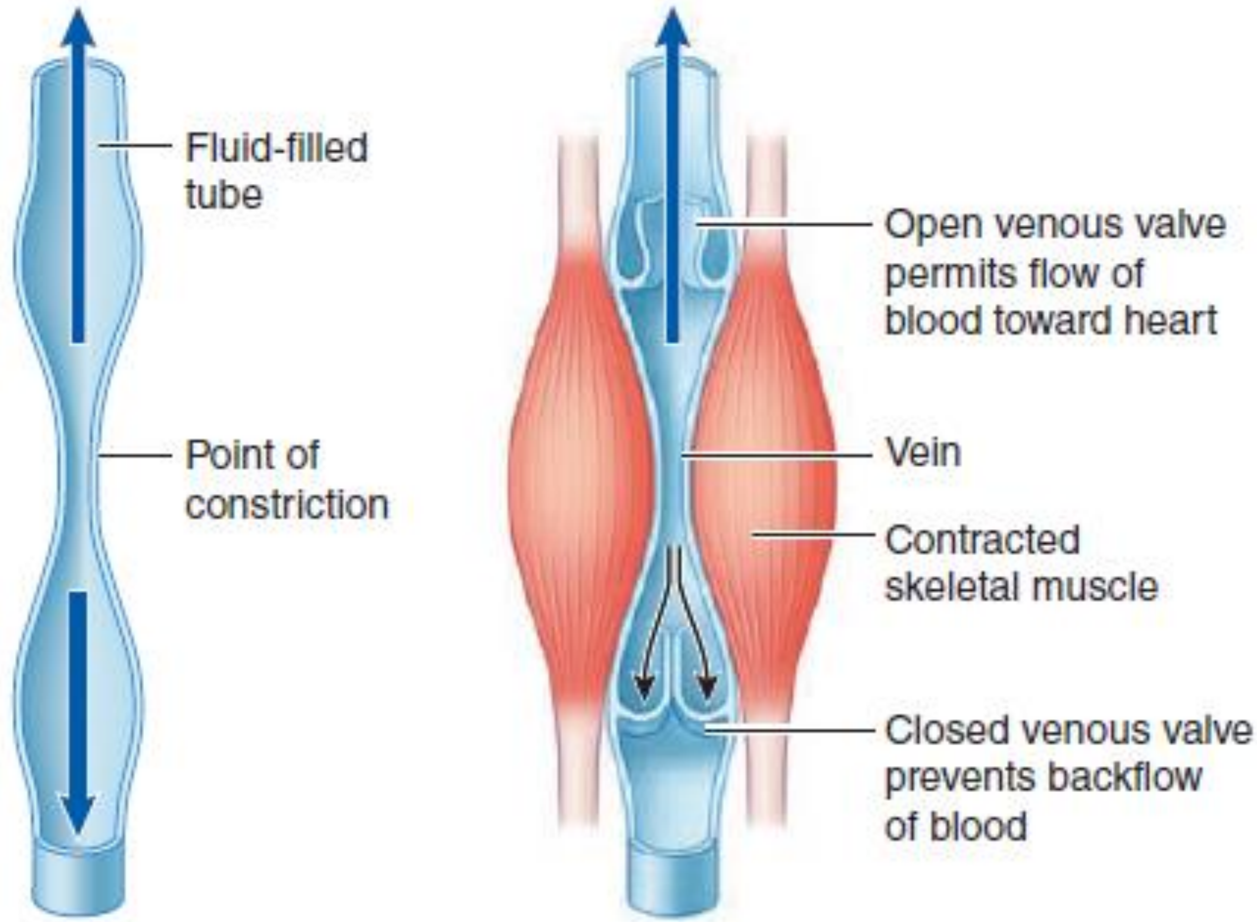


- ✓Fluid, called lymph, reenters the circulation directly at the venous end of the capillary bed and indirectly through the lymphatic system
- ✓The lymphatic system drains into veins in the neck
- ✓Valves in lymph vessels prevent the backflow of fluid

Circulatory Vessels: Venules and Veins



- ✓ Veins have large radii, so they offer little resistance to flow.
- ✓ The total cross-sectional area of the venous system gradually decreases as smaller veins converge into progressively fewer but larger vessels, the velocity of blood flow *increases* as the blood approaches the heart despite the lower pressure



(a) Fluid moving in both directions on squeezing a fluid-filled tube

(b) Action of venous valves, permitting flow of blood toward heart and preventing backflow of blood

Blood Distribution

- Largest portion of blood at rest is in systemic veins and venules
    - Blood reservoir
- Venoconstriction reduces volume of blood in reservoirs and allows greater blood volume to flow where needed

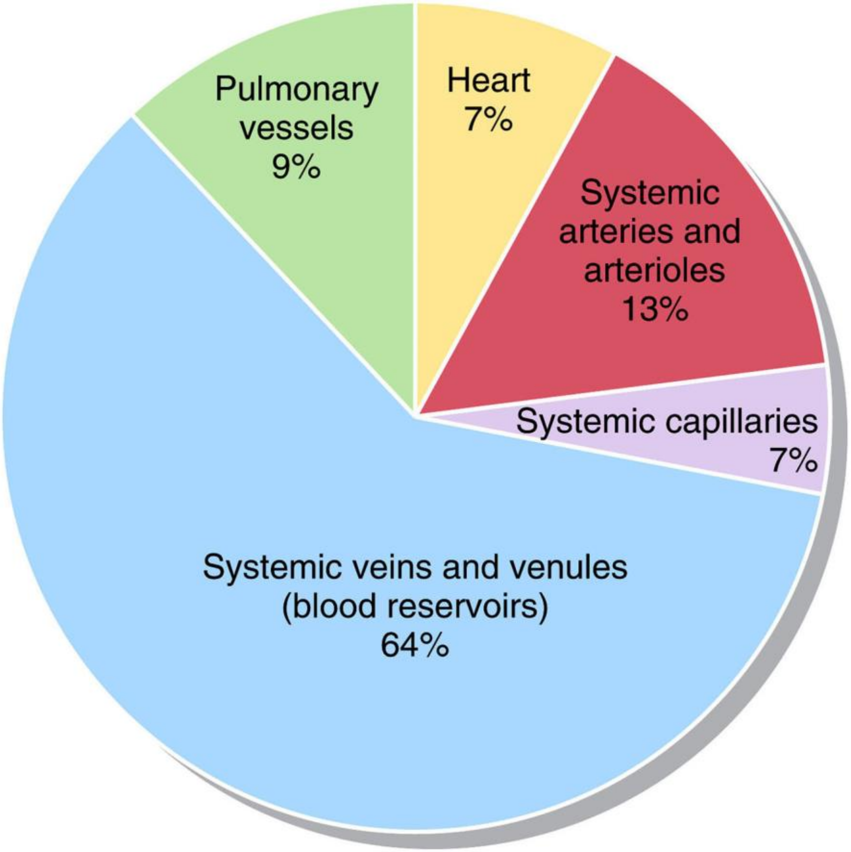
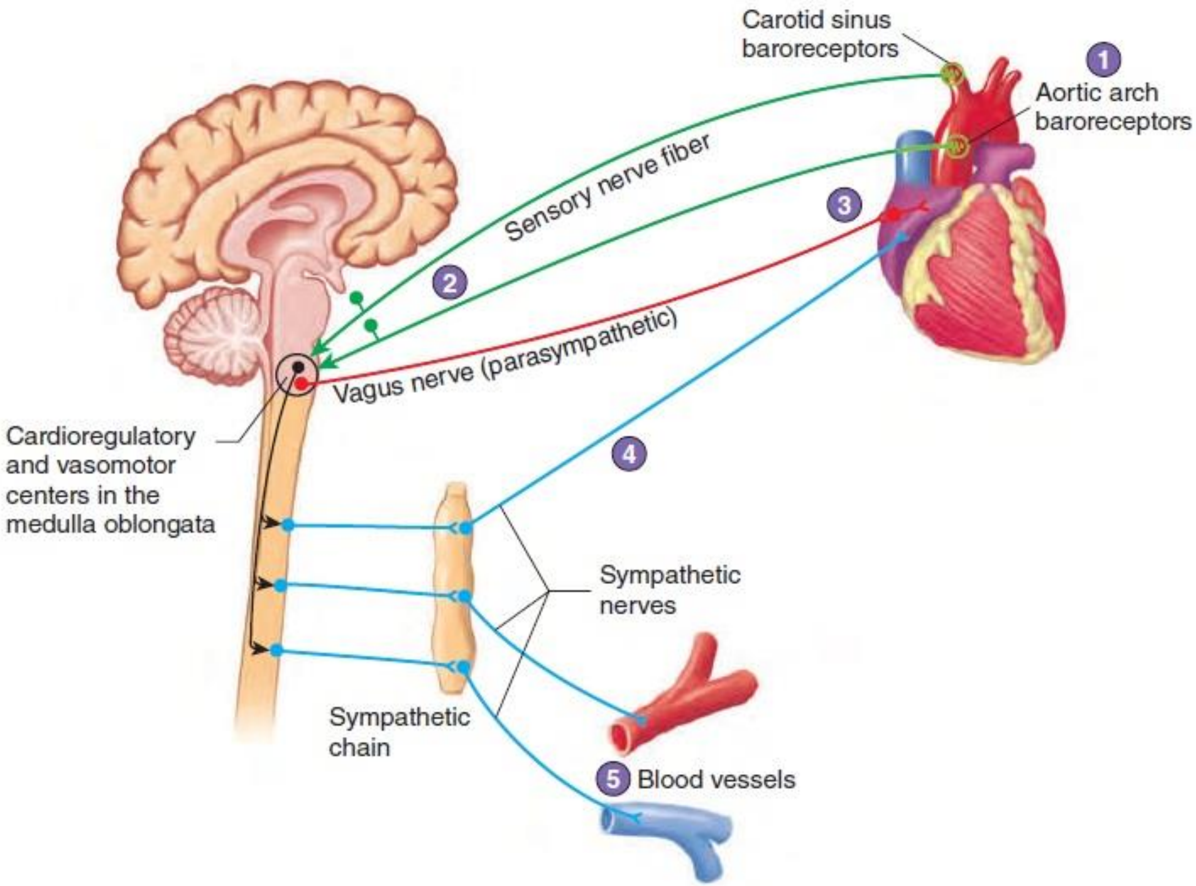


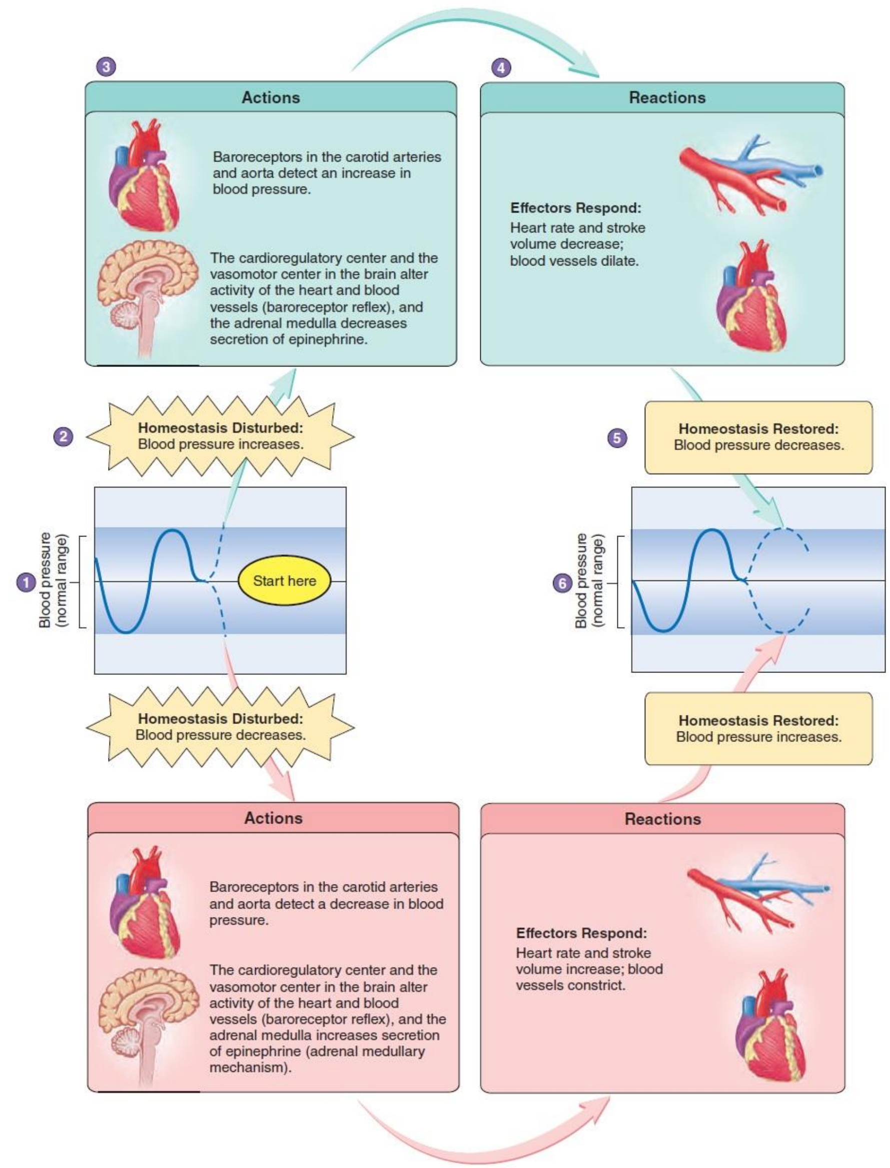
Figure 21.06 Tortora - PAP 12/e

REGULATION OF ARTERIAL PRESSURE

Baroreceptor reflexes

1. Baroreceptors in the carotid sinus and aortic arch monitor blood pressure.
2. Sensory nerves conduct action potentials to the cardioregulatory and vasomotor centers in the medulla oblongata.
3. Increased parasympathetic stimulation of the heart decreases the heart rate.
4. Increased sympathetic stimulation of the heart increases the heart rate and stroke volume.
5. Increased sympathetic stimulation of blood vessels increases vasoconstriction.

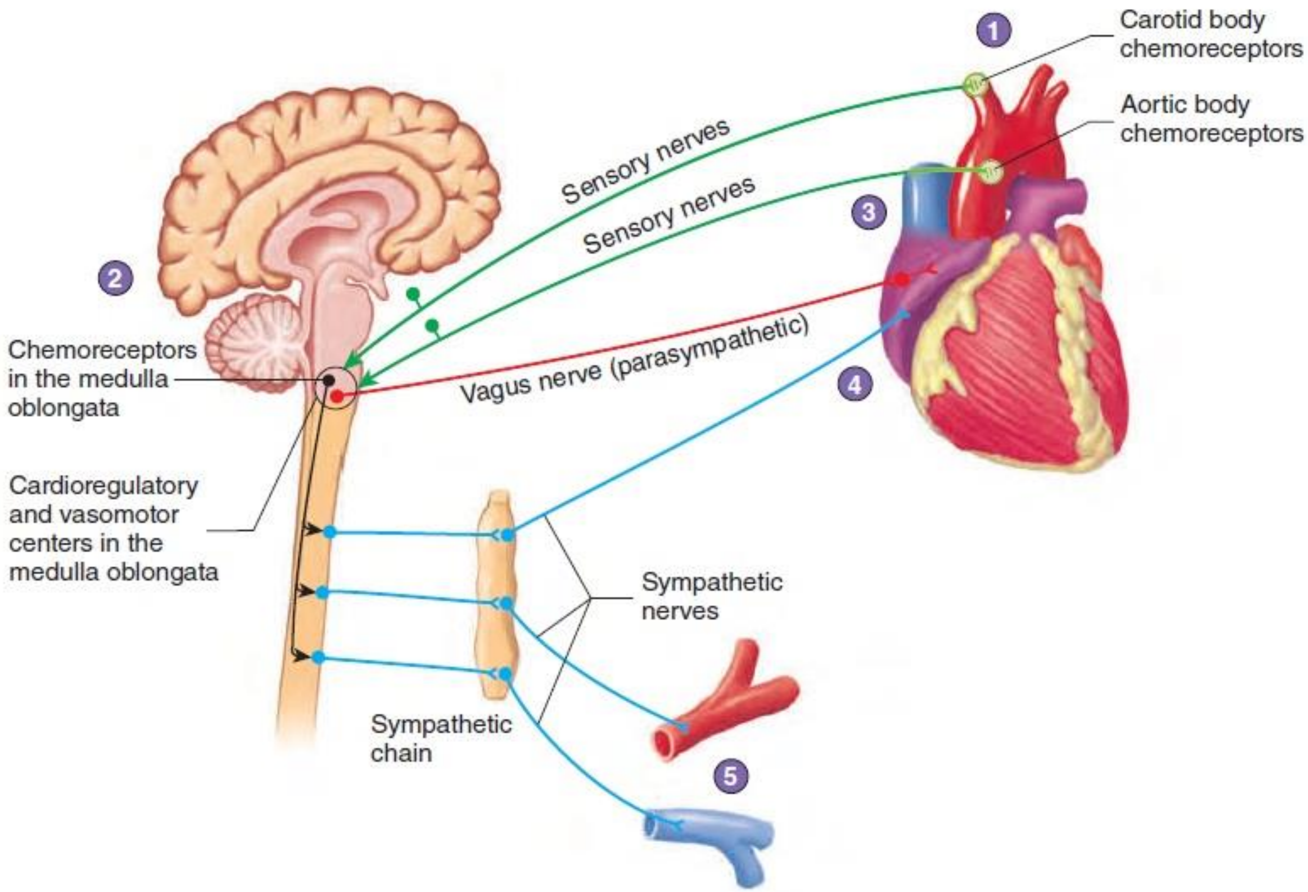



3
Actions
Baroreceptors in the carotid arteries and aorta detect an increase in blood pressure.
The cardioregulatory center and the vasomotor center in the brain alter activity of the heart and blood vessels (baroreceptor reflex), and the adrenal medulla decreases secretion of epinephrine.
4
Reactions
Effectors Respond:
Heart rate and stroke volume decrease; blood vessels dilate.
2
Homeostasis Disturbed:
Blood pressure increases.
5
Homeostasis Restored:
Blood pressure decreases.
1
Blood pressure (normal range)
Start here
6
Blood pressure (normal range)
Homeostasis Disturbed:
Blood pressure decreases.
Homeostasis Restored:
Blood pressure increases.
Actions
Baroreceptors in the carotid arteries and aorta detect a decrease in blood pressure.
The cardioregulatory center and the vasomotor center in the brain alter activity of the heart and blood vessels (baroreceptor reflex), and the adrenal medulla increases secretion of epinephrine (adrenal medullary mechanism).
Reactions
Effectors Respond:
Heart rate and stroke volume increase; blood vessels constrict.

REGULATION OF ARTERIAL PRESSURE

Chemoreceptor reflexes

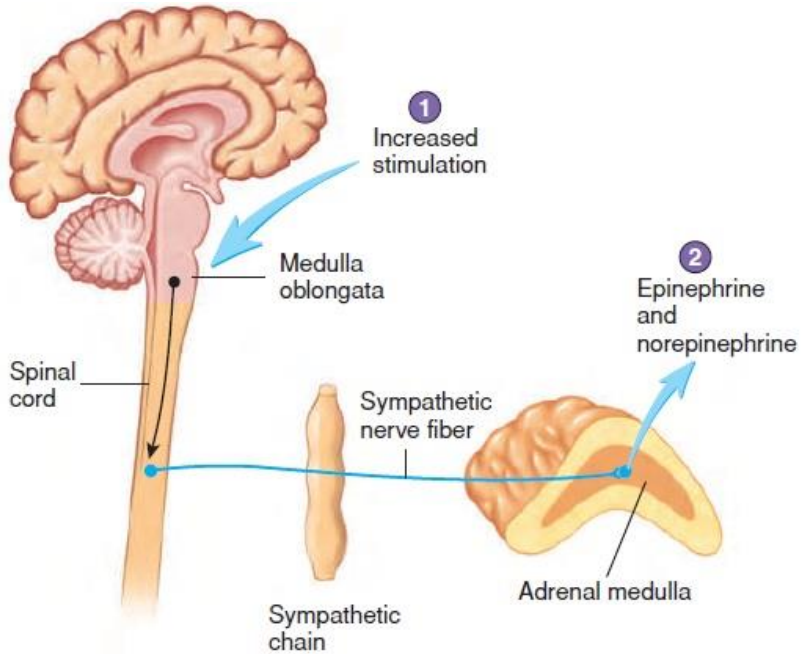
1. Chemoreceptors in the carotid and aortic bodies monitor blood O_2, CO_2, and pH.
2. Chemoreceptors in the medulla oblongata monitor blood CO_2 and pH.
3. Decreased blood O_2, increased CO_2, and decreased pH decrease parasympathetic stimulation of the heart, which increases the heart rate.
4. Decreased blood O_2, increased CO_2, and decreased pH increase sympathetic stimulation of the heart, which increases the heart rate and stroke volume.
5. Decreased blood O_2, increased CO_2, and decreased pH increase sympathetic stimulation of blood vessels, which increases vasoconstriction.



REGULATION OF ARTERIAL PRESSURE

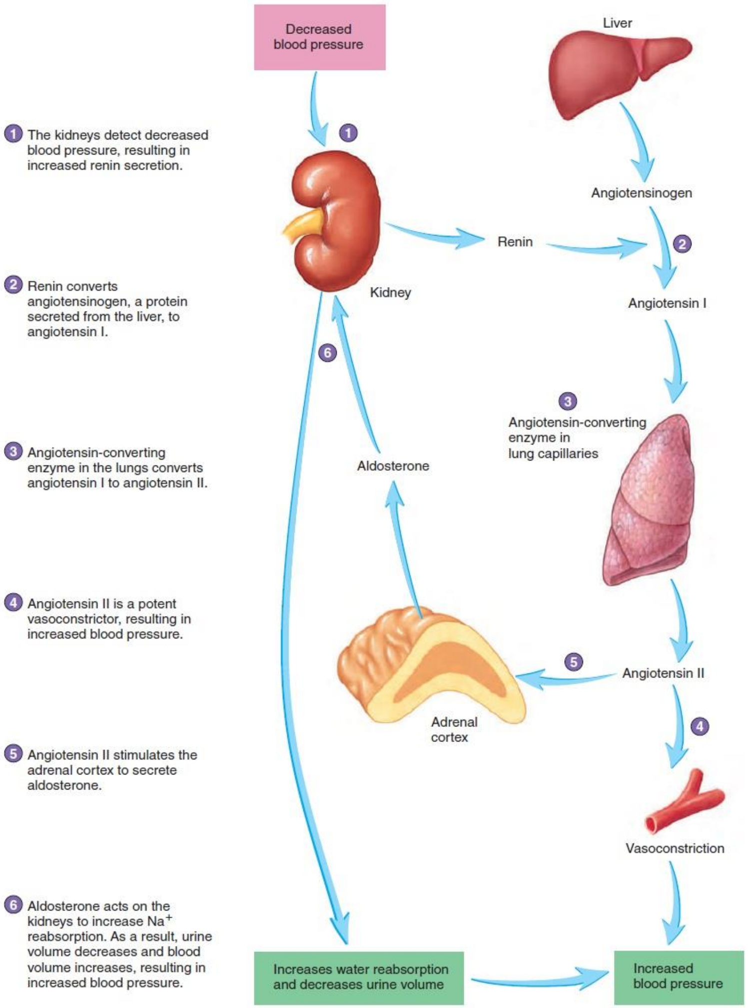
Hormonal Mechanisms

1. The same stimuli that increase sympathetic stimulation of the heart and blood vessels cause action potentials to be carried to the medulla oblongata.
2. Descending pathways from the medulla oblongata to the spinal cord increase sympathetic stimulation of the adrenal medulla, resulting in secretion of epinephrine and some norepinephrine.



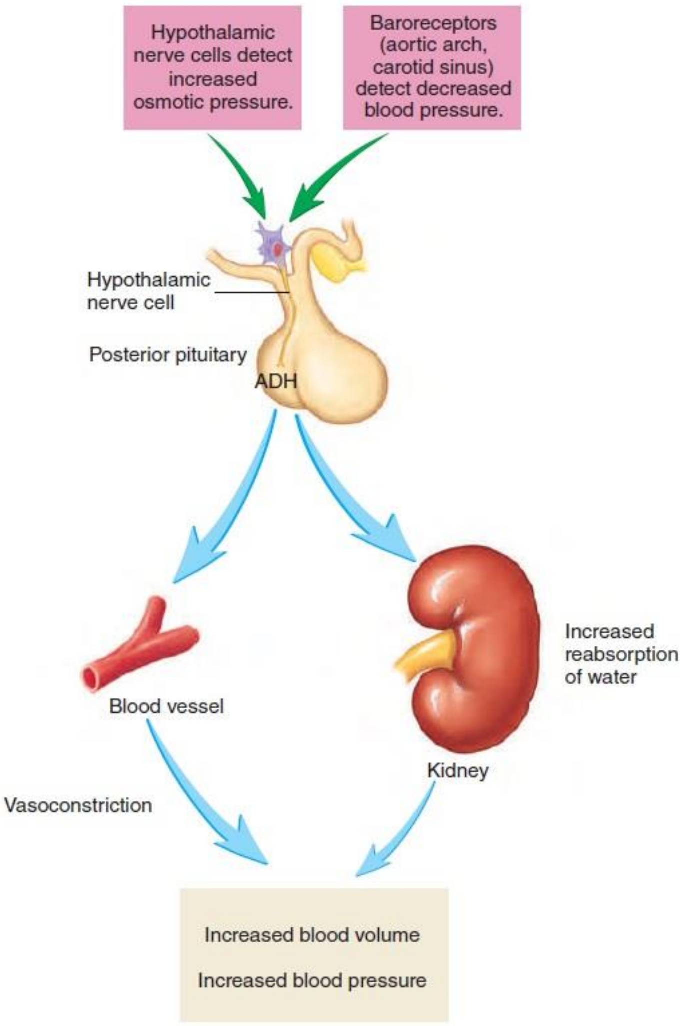
REGULATION OF ARTERIAL PRESSURE

Renin-Angiotensin-Aldosterone Mechanism



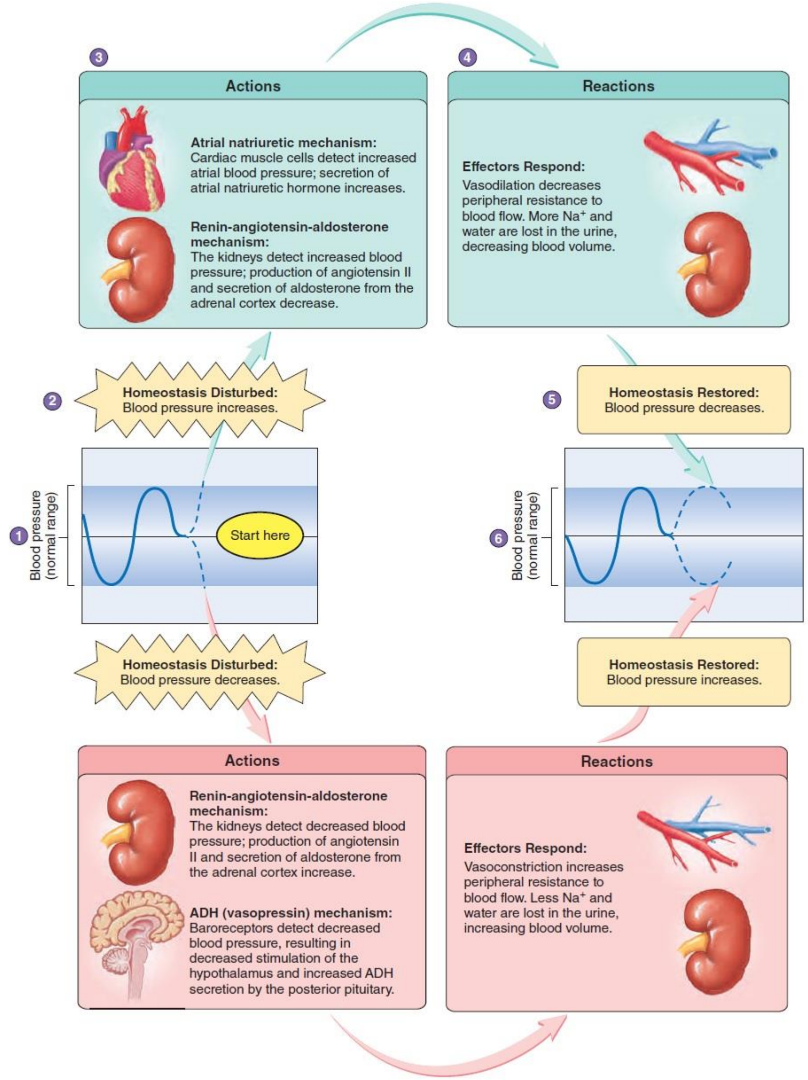
REGULATION OF ARTERIAL PRESSURE

Antidiuretic Hormone Mechanism



REGULATION OF ARTERIAL PRESSURE

Atrial Natriuretic Mechanism



THE ENVIRONMENT AND BLOOD PRESSURE

Blood pressure (BP) is affected by many environmental factors including ambient temperature, altitude, latitude, noise, and air pollutants

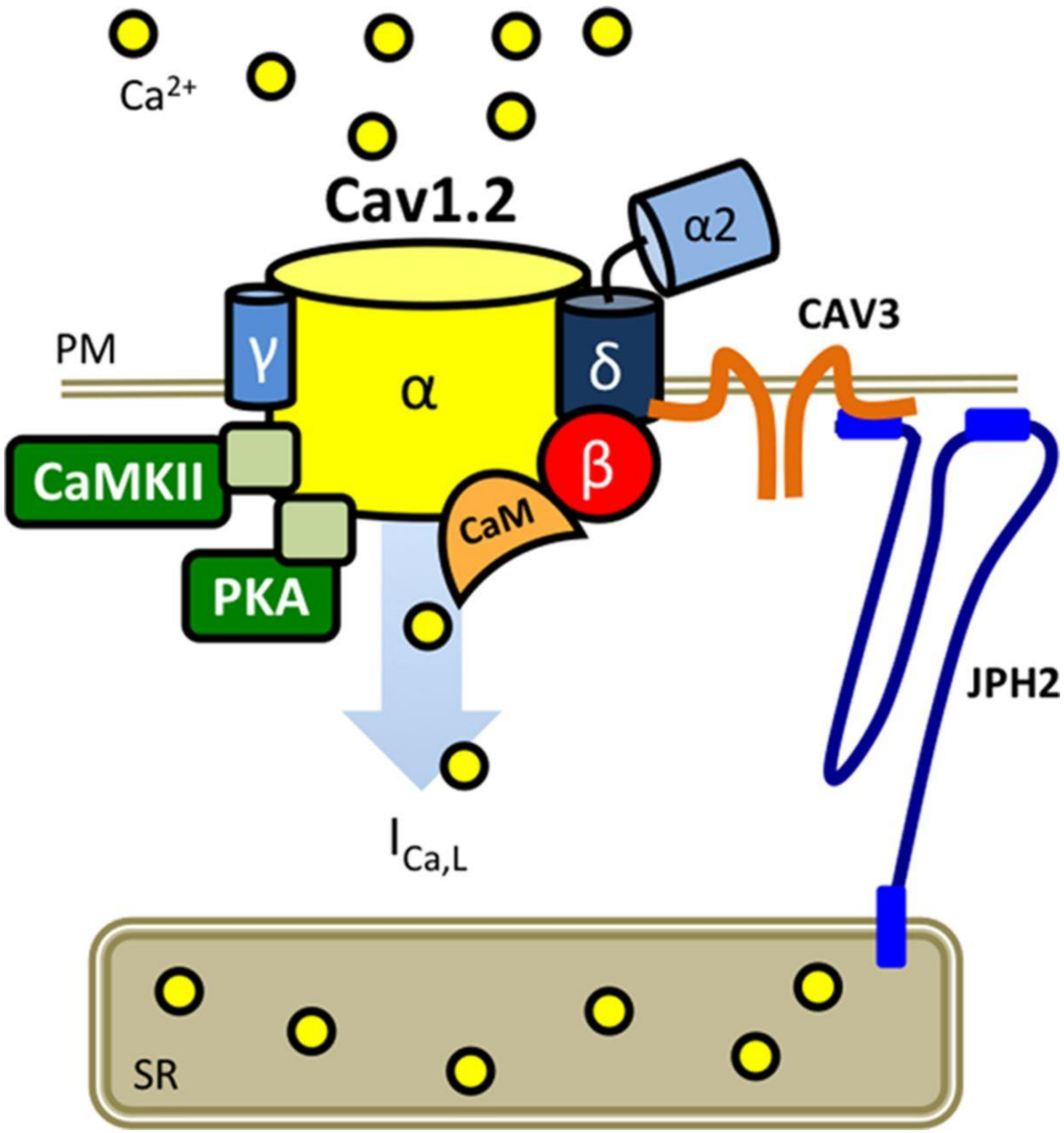
TABLE. Common Environmental Factors and Blood Pressure

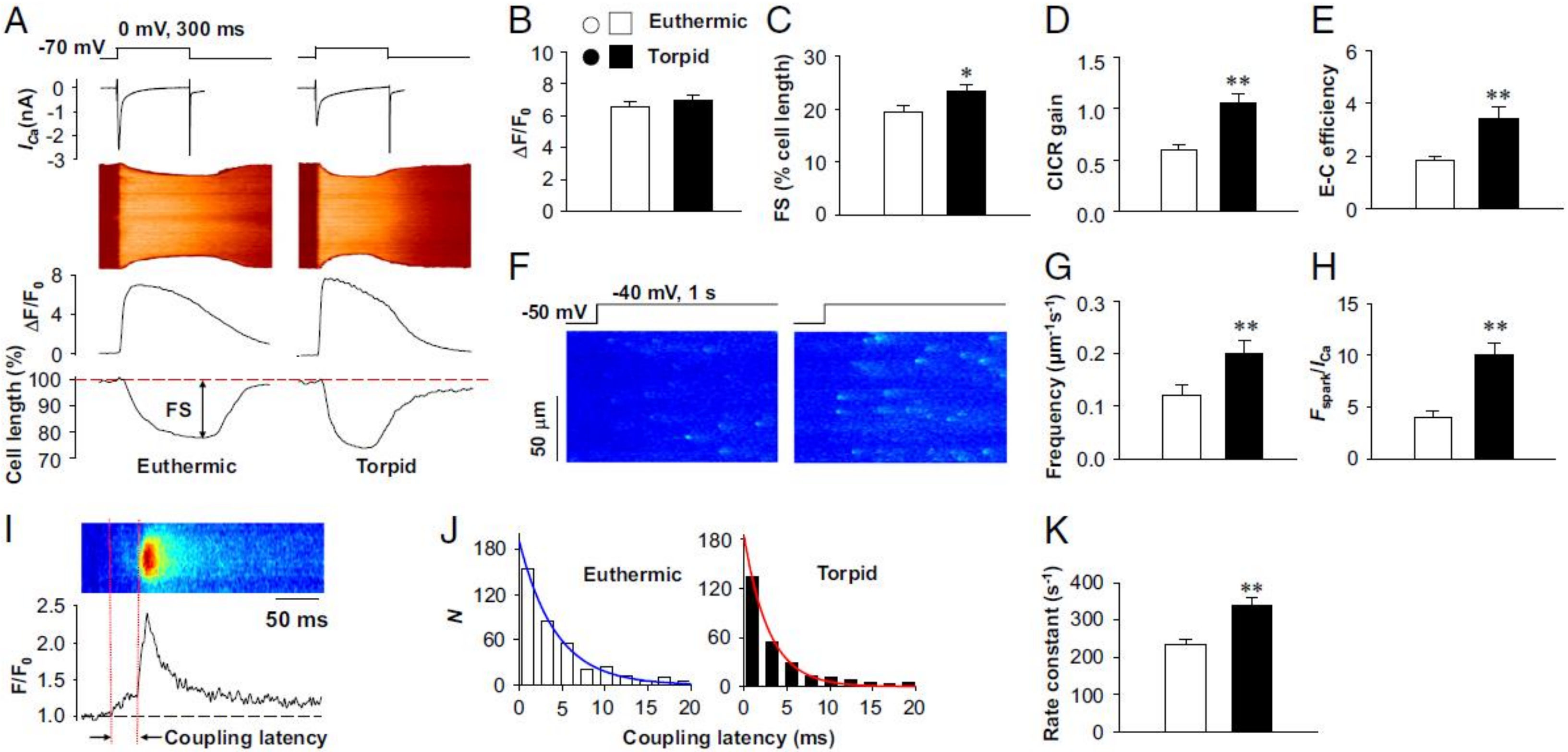
Factor	BP Effect	Putative Mechanisms
Temperature	Most common overall effect: inverse association	Direct thermoregulation-mediated vasoconstriction
Cold	Colder outdoor/indoor ambient temperature related to higher BP Colder temperatures elevate BP variability and aortic pulse pressure	HPAA and SNS activation, sodium/volume retention Impaired endothelial-dependent vasodilatation
Heat	Acute heat stress and sauna treatment lower BP	Reverse of cold mechanisms (above)
Nighttime BP	Hotter days associated with higher nocturnal BP	
Nighttime temperature	Hotter nighttime temperature associated with higher daytime BP	Possibly reduced sleep duration or quality
Season Winter	Most common overall effect: winter season related to higher BP Reduced temperature may be primarily responsible; however, winter season may have some added independent effects	Cold-induced mechanisms likely primarily responsible; however, additional chronic alterations may play additive roles: lower vitamin D levels, reduced activity, and weight gain
Geography	Most common overall effect: higher altitude (>2500 m) and latitude raise BP	Altitude-induced hypoxemia leading to chemo-reflex activation along with compensatory responses causing increased SNS and adrenal activity. Long-term acclimatization may lead to differing responsible responses
Altitude	Ascent to higher altitudes raises BP (variable interindividual responses noted) May be affected by race, acclimatization, rate of climb, or duration of exposure. Long-term population studies are limited in ability to determine effect and show heterogeneous results on chronic BP levels due to many confounding variables	Other associated factors such as colder temperatures and stress may also play a role. Long-term increases in red blood cell mass may contribute
Latitude	Higher prevalence of hypertension in higher latitudes	Effects of lower temperatures and UV light/vitamin D levels Perhaps ancient retained evolutionary changes promoting salt/water retention that are maladaptive to the colder climate with available salt
Loud noises	Most common overall effect: exposure to loud noises raises BP Numerous conditions implicated (ambient, occupational, traffic, airports)	Acute SNS activation, HPAA activation Potentially sleep disruption for nocturnal noise
Air pollutants	Most common overall effect: exposure to PM raises BP	Acute activation of the SNS via pulmonary autonomic reflexes rapidly raises BP in minutes. Possibly PM constituents reaching the systemic vasculature and promoting vasoconstriction
Ambient PM	Short- and long-term PM exposures related to higher BP	
Indoor PM	Biomass, cooking, and personal-level higher PM exposures raise BP	Chronic exposures likely alter vascular tone via endothelia dysfunction or reduced arterial compliance (reduced nitric oxide and higher endothelins) due to PM-mediated systemic inflammation and oxidative stress
SHS	SHS exposure raises BP	Baroreceptor sensitivity may also be impaired by PM inhalation

Abbreviations: BP, blood pressure; HPAA, hypothalamic pituitary adrenal axis; PM, particulate matter; SHS, secondhand smoke; SNS, sympathetic nervous system.

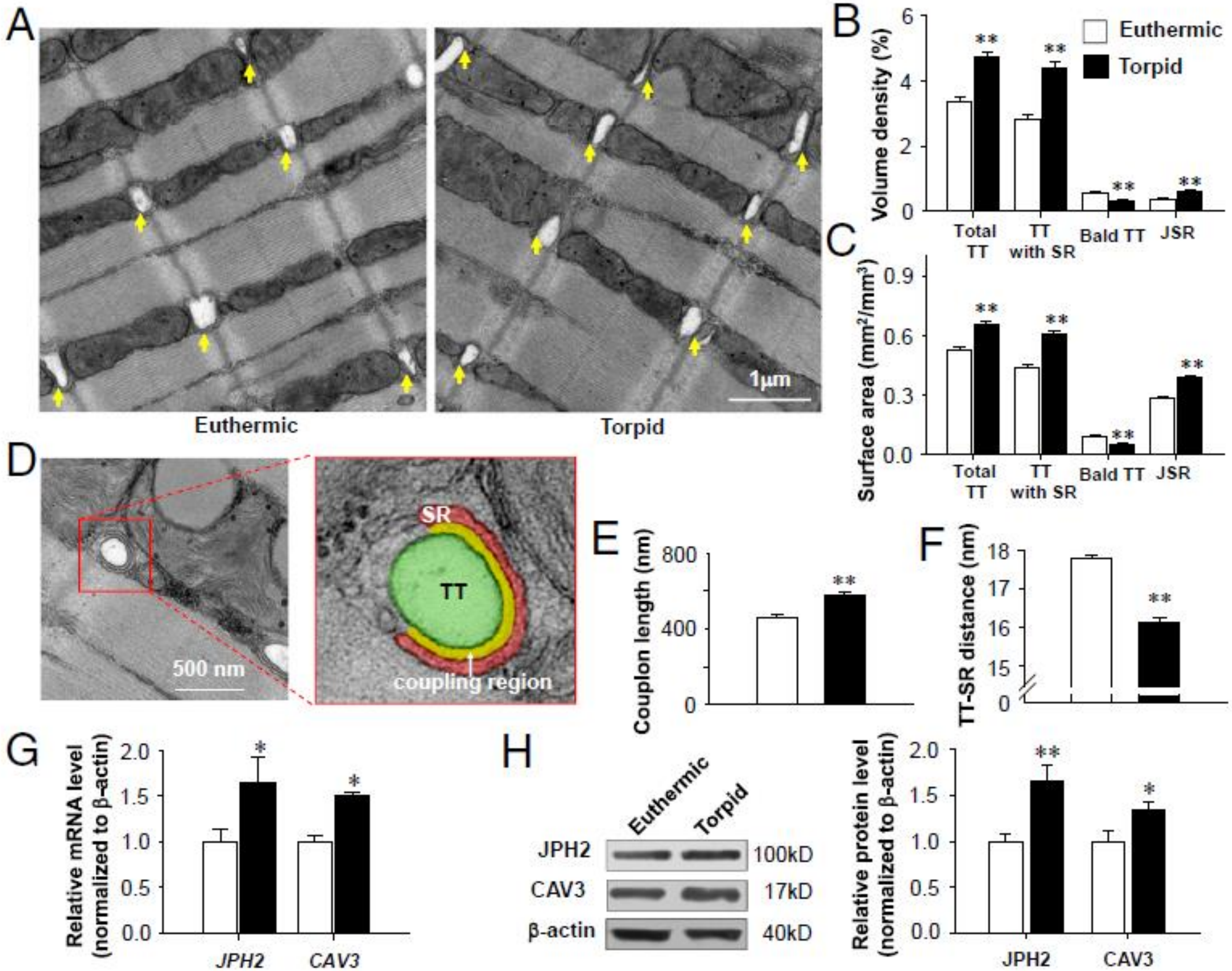
As an adaptation for coping with the harsh, inclement weather of the winter months, arctic ground squirrels hibernate for about eight months out of the year.

Their chosen hibernacula have coverage provided by vegetation, rather than open, windswept burrows.

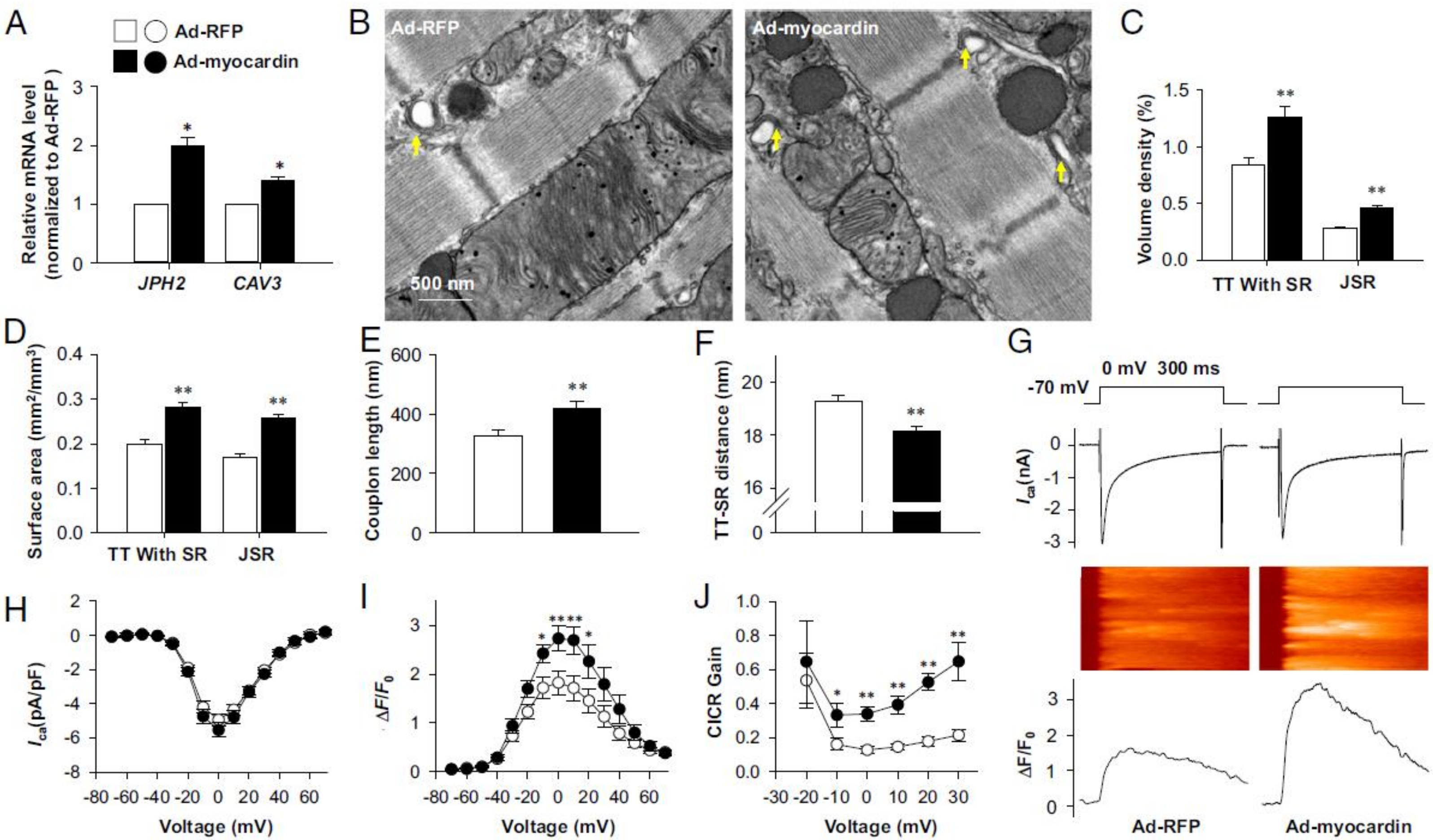

Ca^{2+}
Cav1.2
α2
CAV3
PM
γ
α
δ
β
CaMKII
CaM
PKA
JPH2
$I_{Ca,L}$
SR



A
0 mV, 300 ms
-70 mV
I_{Ca}(nA)
ΔF/F0
Cell length (%)
FS
Euthermic
Torpid
B
Euthermic
Torpid
ΔF/F0
C
FS (% cell length)
D
CICR gain
E
E-C efficiency
F
-40 mV, 1 s
-50 mV
50 μm
G
Frequency (μm-1s-1)
H
F_{spark}/I_{Ca}
I
50 ms
F/F0
Coupling latency
J
N
Euthermic
Torpid
Coupling latency (ms)
K
Rate constant (s-1)



A
B
C
D
E
F
G
H
Euthermic
Torpid
1μm
Volume density (%)
Surface area (mm²/mm³)
Total TT
TT with SR
Bald TT
JSR
500 nm
SR
TT
coupling region
Couplon length (nm)
TT-SR distance (nm)
Relative mRNA level (normalized to β-actin)
JPH2
CAV3
β-actin
100kD
17kD
40kD
Relative protein level (normalized to β-actin)


A
Ad-RFP
Ad-myocardin
Relative mRNA level (normalized to Ad-RFP)
JPH2
CAV3
B
Ad-RFP
Ad-myocardin
500 nm
C
Volume density (%)
TT With SR
JSR
D
Surface area (mm²/mm³)
TT With SR
JSR
E
Couplon length (nm)
F
TT-SR distance (nm)
G
0 mV 300 ms
-70 mV
Ica(nA)
ΔF/F0
Ad-RFP
Ad-myocardin
H
Ica(pA/pF)
Voltage (mV)
I
ΔF/F0
Voltage (mV)
J
CICR Gain
Voltage (mV)