

Special Circulations I and II

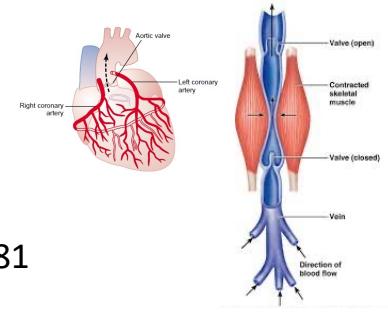
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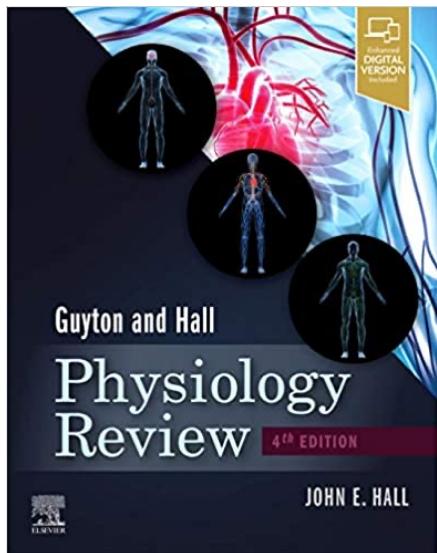
Fall 2024

Reference: Costanzo, 7th Ed., pp. 176-181



Outline:

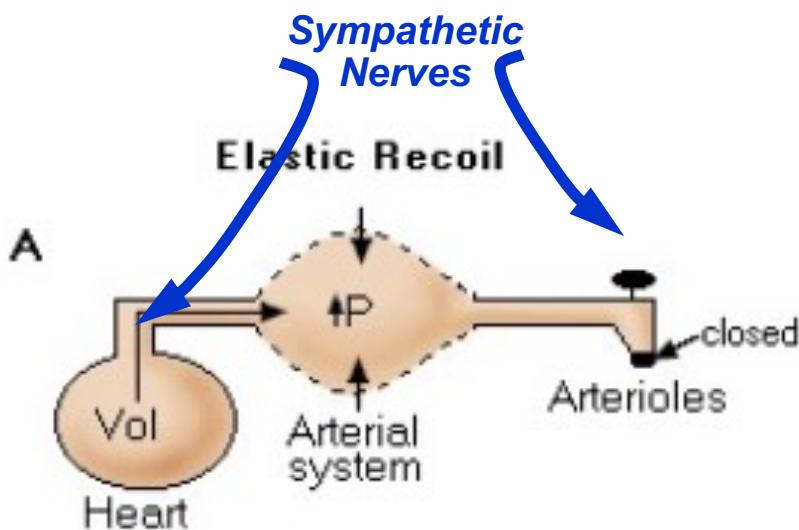
1. Define and describe the mechanisms of autoregulation of blood flow.
2. Identify how the theory of metabolic regulation of blood flow accounts for active hyperemia and reactive hyperemia.
3. Define the contribution of myogenic tone to blood flow regulation.
4. Identify the role of PO₂, PCO₂, pH, adenosine and K⁺ in the metabolic control of blood flow to specific tissues.
5. Define the synthetic pathway for nitric oxide, including substrate and the interplay between endothelium and vascular smooth muscle.
6. Define the interaction of a) intrinsic (local), b) neural and c) humoral control mechanisms and contrast their relative dominance in the skeletal muscle, coronary, cutaneous and cerebral vascular beds.
7. Identify the phasic flow of blood to the ventricular myocardium through an entire cardiac cycle. Contrast this cyclic variation in myocardial flow a) in the walls of the right and left ventricles and b) in the subendocardium and subepicardium of the left ventricle.
8. Define how arterio-venous O₂ difference and oxygen extraction in the heart is unique when compared with other body organs.
9. Define the mechanism whereby coronary blood flow is coupled to myocardial workload and identify stimuli that cause increases in coronary blood flow to occur.
10. Contrast the local and neural control of cerebral blood flow. Define the relative importance of O₂, CO₂ and pH in regulating cerebral blood flow.
11. Define the Cushing Reflex and the CNS ischemic pressor response.
12. Contrast local and neural control of cutaneous blood flow.
13. Define the unique characteristics of skin blood flow that are adaptive for body temperature regulation.



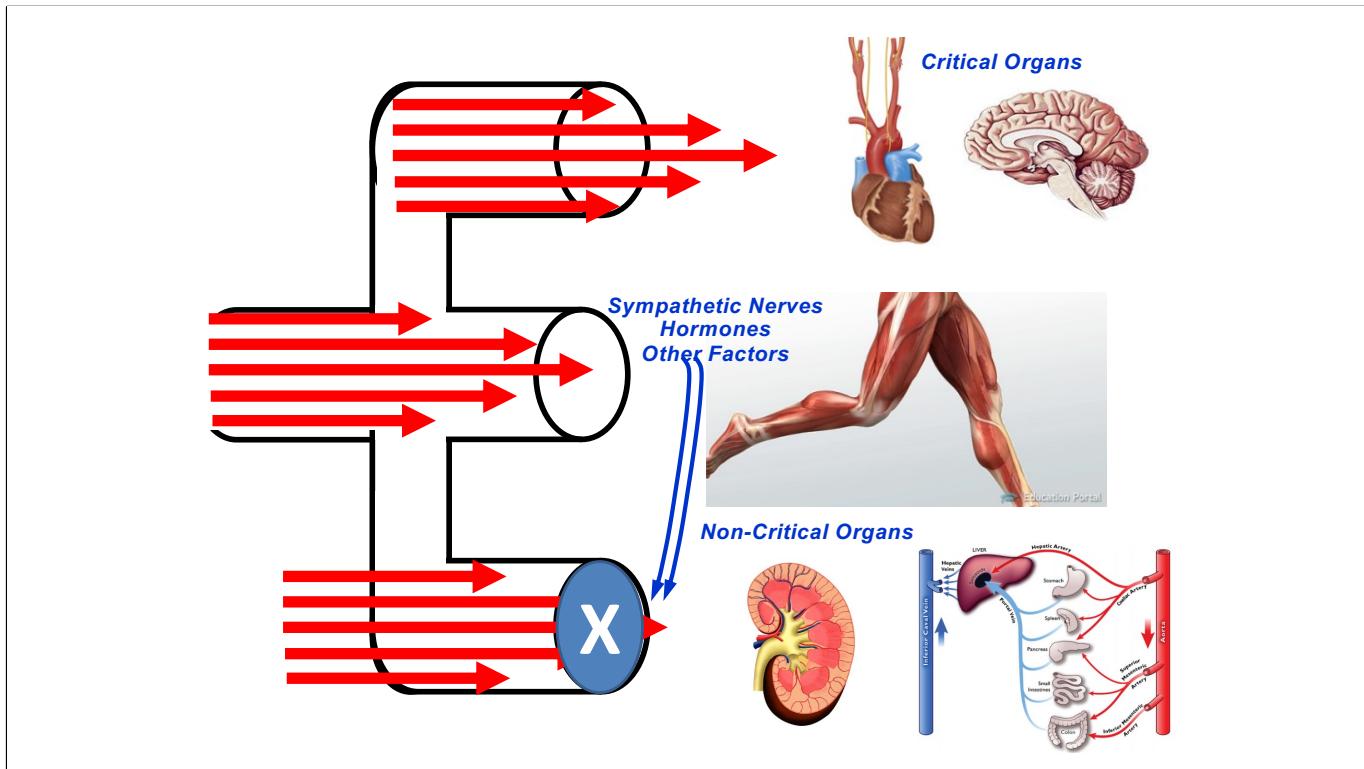
By the end of this session, you should be able to answer the following questions from Unit IV of Guyton and Hall *Physiology Review* 4th Ed.

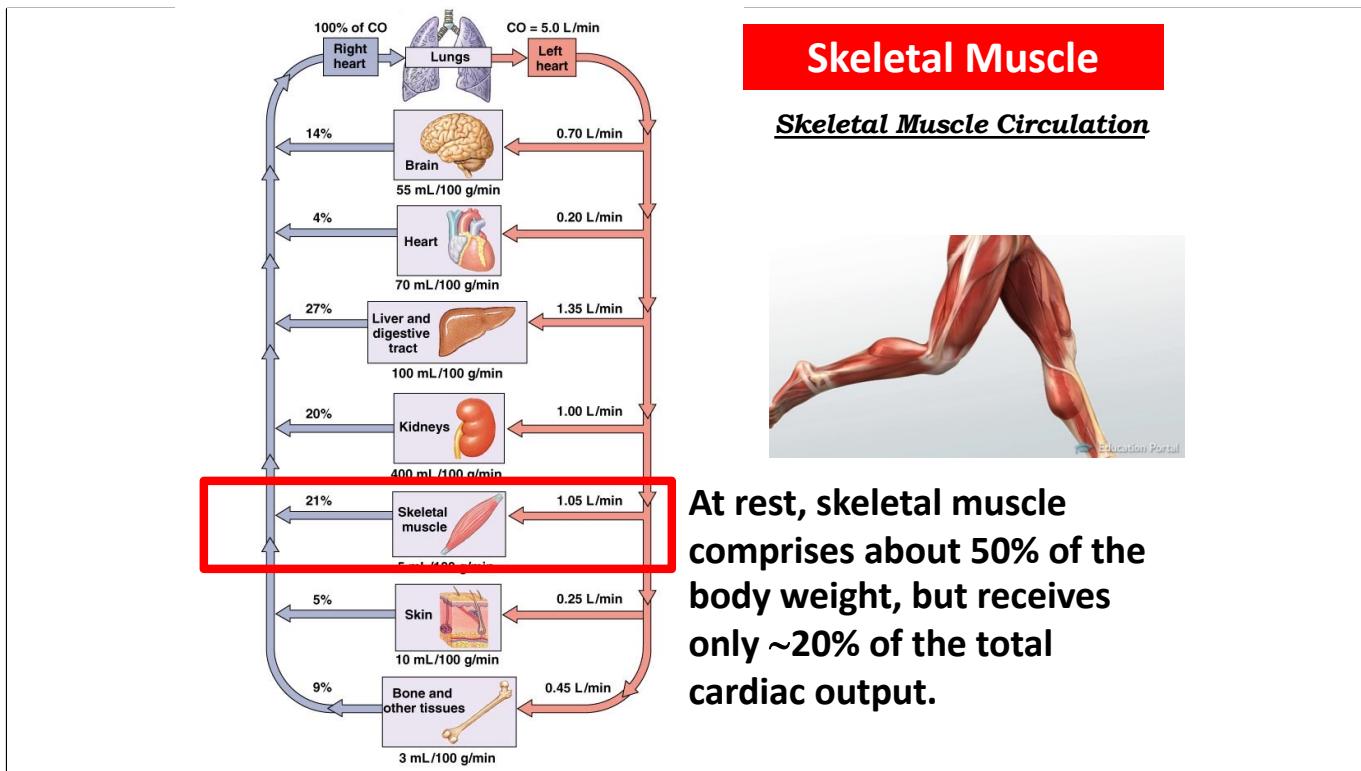
Questions: 7, 34, 43, 59, 89, 91, 92, 93

$$\text{Mean arterial pressure} = \text{Cardiac output} \times \text{Total peripheral resistance}$$



- Arterioles in the following vascular beds:
- Skeletal muscle
 - Coronary
 - Cutaneous
 - Cerebral





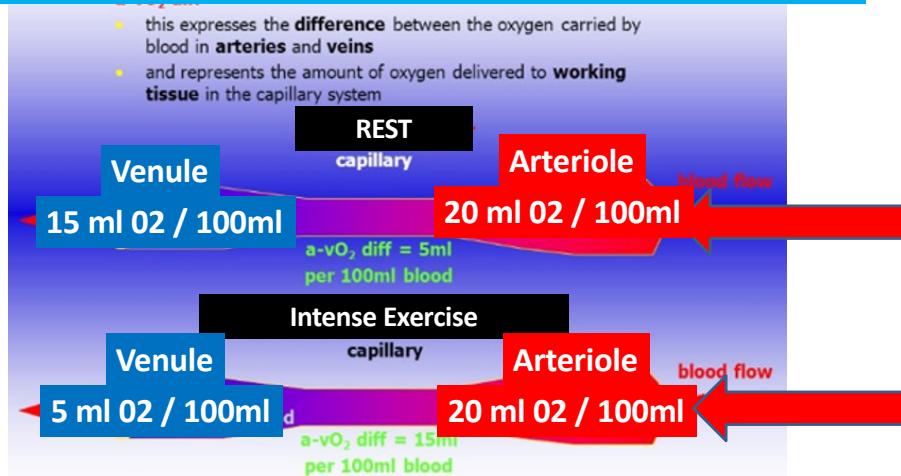
Skeletal Muscle

Skeletal Muscle Circulation



Skeletal Muscle Circulation

ARTERIO VENOUS OXYGEN DIFFERENCE

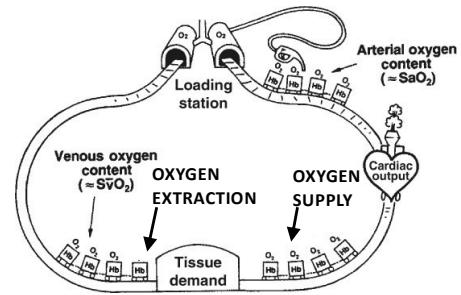


At rest, skeletal muscle comprises about 50% of the body weight, but receives only ~20% of the total cardiac output.

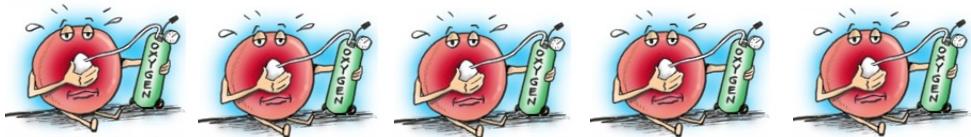
Thus, as blood transits the capillary bed of a RESTING individual it releases only 5-7 Vol% of the oxygen to the tissues.

If the oxygen requirements of the muscle change, oxygen supply can be appropriately altered in two ways:

- 1. changing the amount of oxygen extracted from the blood**
OR
- 2. changing the amount of blood supplied to the tissue**



Factors That Alter Oxygen Extraction



Holding blood flow constant, predict the effect of:
(Hint: think about how each impact metabolism)

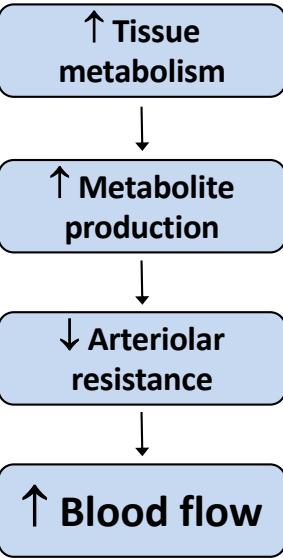
Tissue cooling on oxygen extraction ↓

Cooling = ↓ metab.

Tissue warming on oxygen extraction ↑

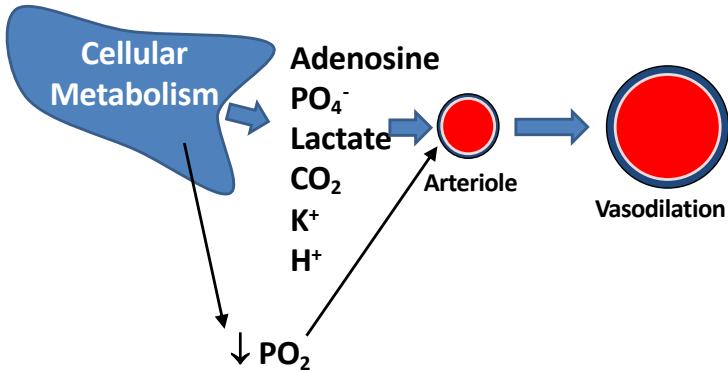
Catecholamines on oxygen extraction ↑

Thyroxin on oxygen extraction ↑



Factors That Alter Blood Supply

Metabolic Theory

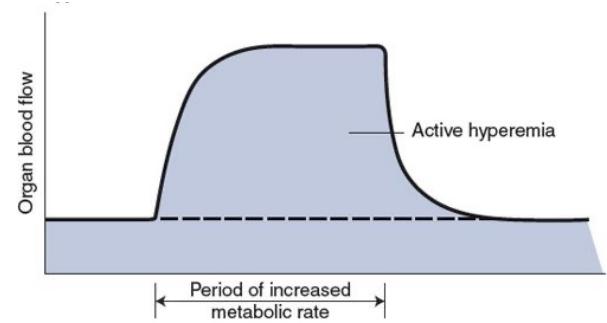
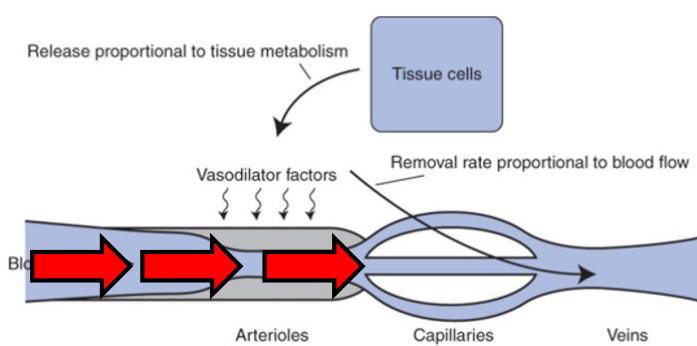


- Cells continually release metabolic byproducts, which ↑ with ↑ in tissue activity

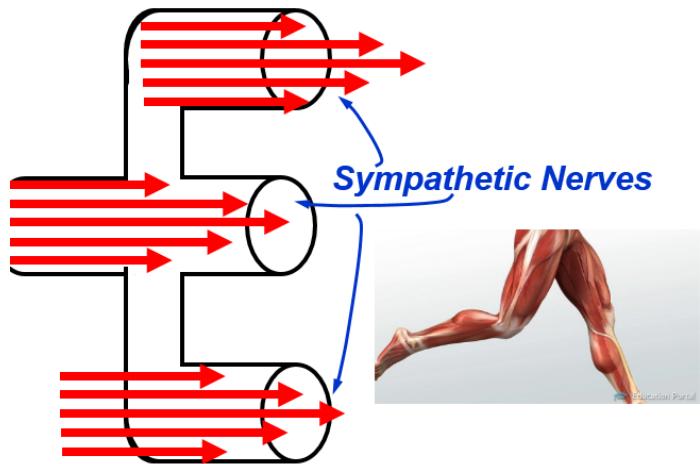
Active Hyperemia

more blood flow w/ ↑ activity

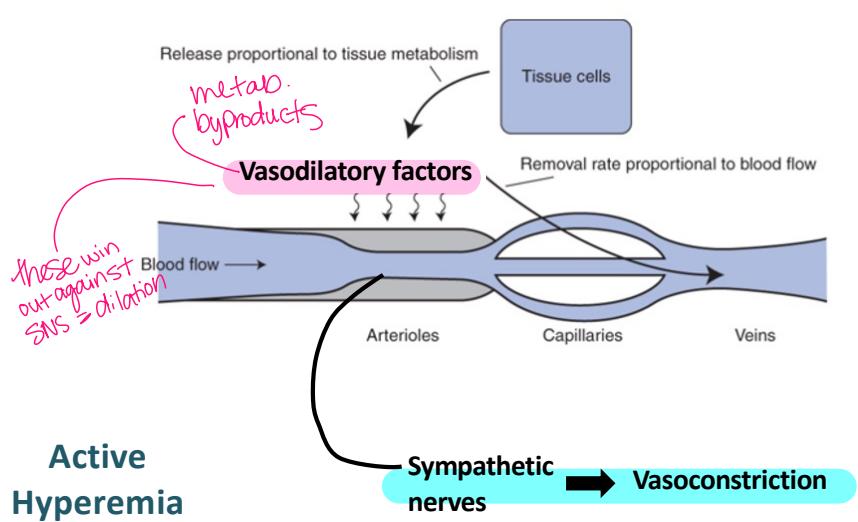
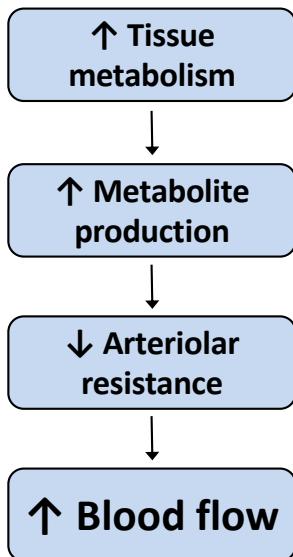
Factors That Alter Blood Supply: Active Hyperemia



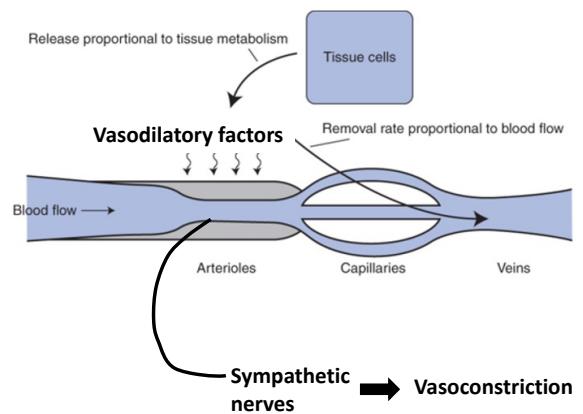
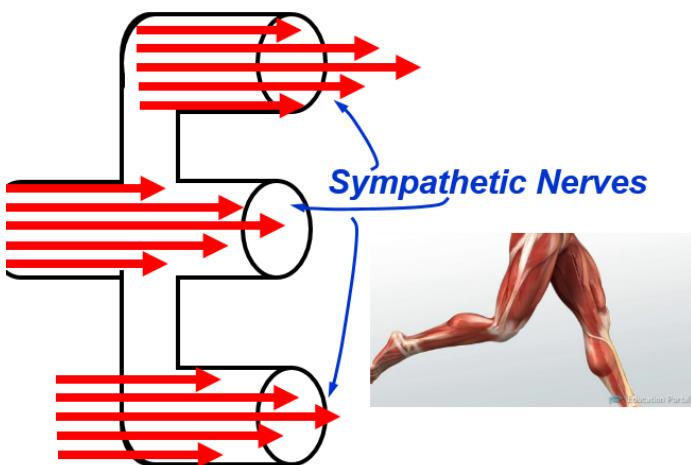
Resting skeletal muscle blood flow is controlled by resistance vessels with a high level of sympathetic nerve activity.



During exercise, control of flow shifts to the local level and is determined by local metabolic factors that override the nervous influences.



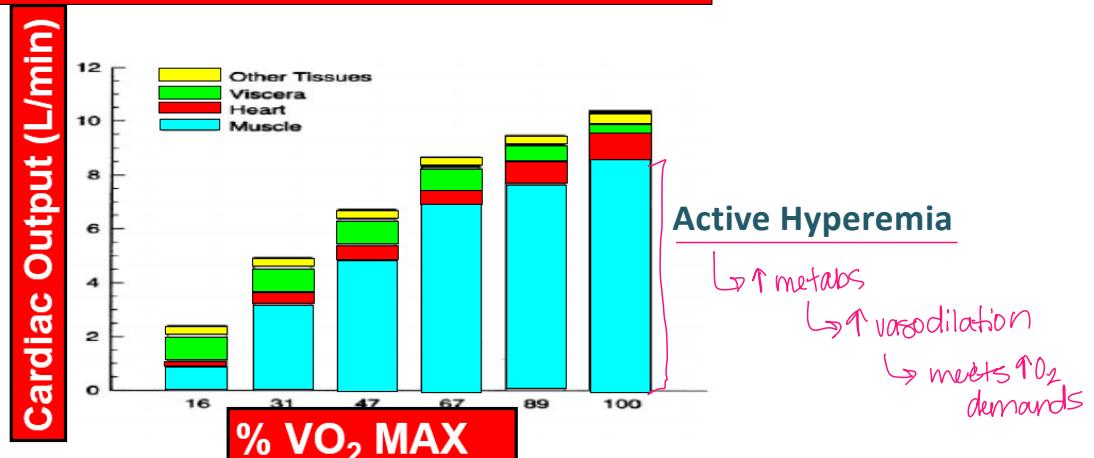
However, sympathetic activity is required to limit vasodilation so that blood pressure does not fall



Exercising muscle, while still comprising 50% of the body weight, may use up to 80% of the cardiac output (which may rise to 30 L/min).

$\dot{V}_{O_2} \text{ max}$ = function of work

Blood Flow Redistribution During Exercise



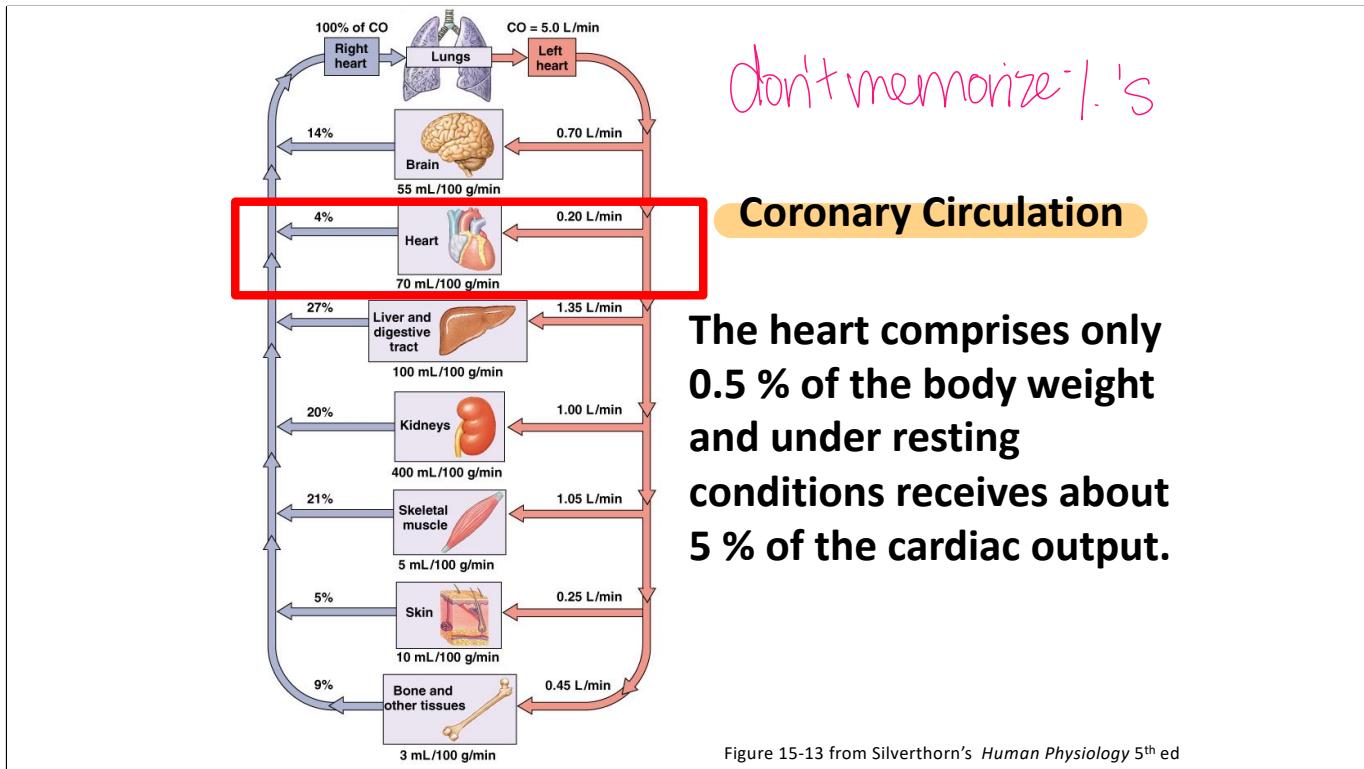
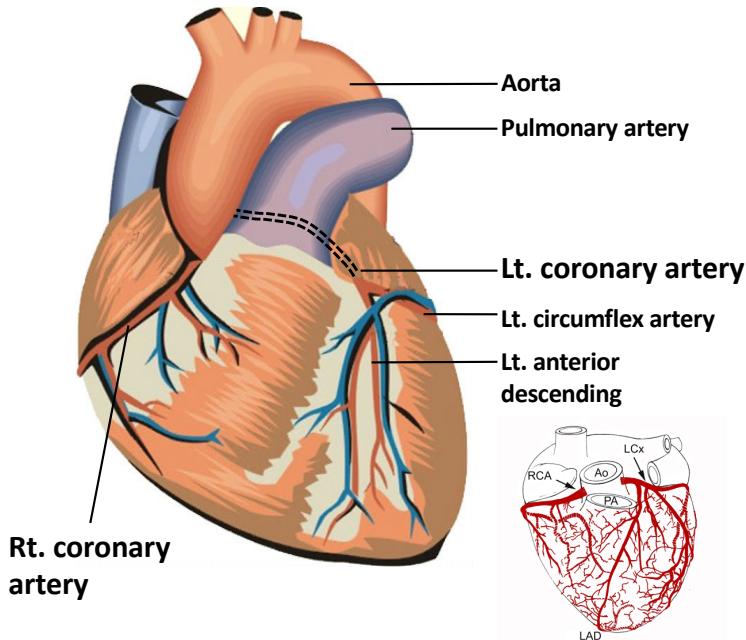


Figure 15-13 from Silverthorn's *Human Physiology* 5th ed

Coronary Anatomy



- Entire myocardial blood supply is derived from the left and right coronary arteries
- Left/right coronary arteries originate at the aortic root
- Generally, the right coronary supplies the right heart and the left coronary supplies the left heart
- Cardiac muscle has a dense capillary network and muscle fibers that are small in diameter - *heart needs lots of O₂*
& ↓ diameter = quick diffusion
- Coronary veins empty into the right atrium via the coronary sinus

- Entire myocardial blood supply is derived from the rt and lt coronary arteries.
- They originate at root of aorta behind cusps of aortic valves
- Generally, rt coronary supplies rt ventricle and atrium and left coronary supplies left ventricle and atrium
- Lt main divides into Lt circumflex and LAD
- Lcx sends branches to Lt atrium and ventricle
- LAD descends to the apex and sends branches to supply the intervent septum and portion of rt as well as lt ventricle.
- Arteries branch and penetrate into tissue forming a very dense capillary network that facilitates O₂ diffusion into cardiac cells, which have a high energetic demand
- Blood is then drained outward from myocardium to converge on epicardial veins which empty into the rt atrium via the coronary sinus.
- Other cardiac channels called thebesian veins drain capillary beds from the ventricular wall and drain directly into the ventricles.

Coronary Blood Flow Cycle

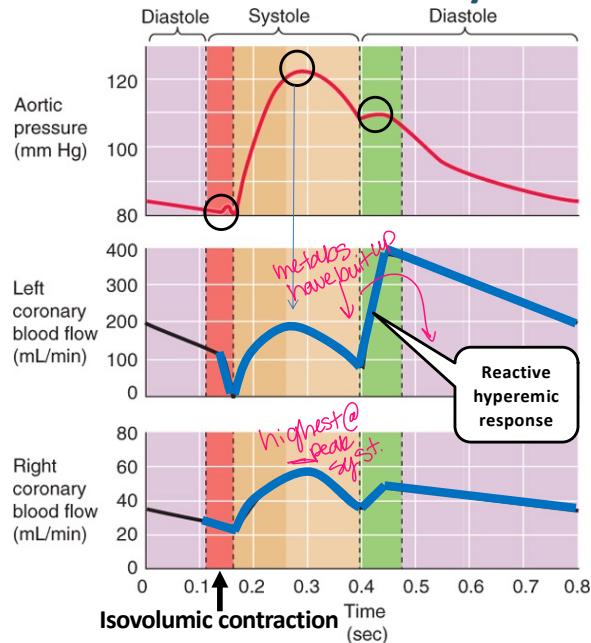


Figure 24-4 from Boron and Boulpaep's *Medical Physiology* 2nd ed

Early Systole:

Aortic Pressure lowest point

Left coronary arteries compress as myocardium contracts against a closed aortic valve

Mid Systole:

LV pressure rises, causing aortic pressure to increase, which drives left coronary flow to overcome compression of the artery

Early Diastole:

Diastolic pressure is at its peak

As compression of the left coronary artery decreases, left coronary blood flow reaches its peak

Late Diastole:

Myocardium relaxed

Aortic Pressure falling so coronary flow decreases

Most myocardial blood flow occurs during diastole

Pulsatile nature of coronary blood flow measured in the left coronary artery. Flow is lower during systole because of mechanical compression of intramuscular coronary vessels. Flow is maximal early in diastole as the heart is relaxing, and then it falls as aortic pressure declines.

Coronary Blood Flow Cycle Summary

Left coronary flow is greater than right coronary flow due to the fact that the mass and the work output of the left ventricle is greater than that of the right.

Total coronary flow is determined by the oxygen needs of the myocardium.

Peak **left** coronary flow occurs early in **diastole**, while peak **right** coronary flow occurs during **systole**.

Again, since left coronary flow is greater than right coronary flow, **total** coronary flow is greater during **diastole** than systole.



Vasomotion as a Basis for Coronary Reserve

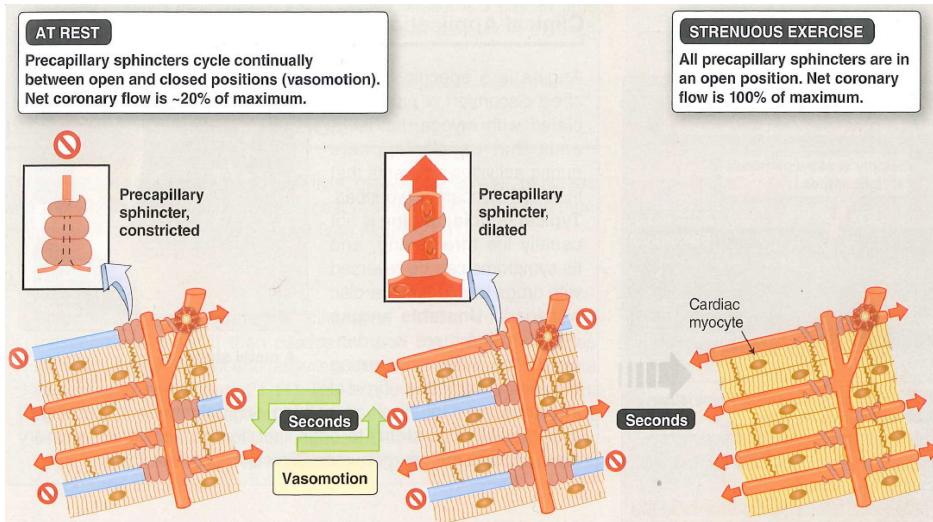
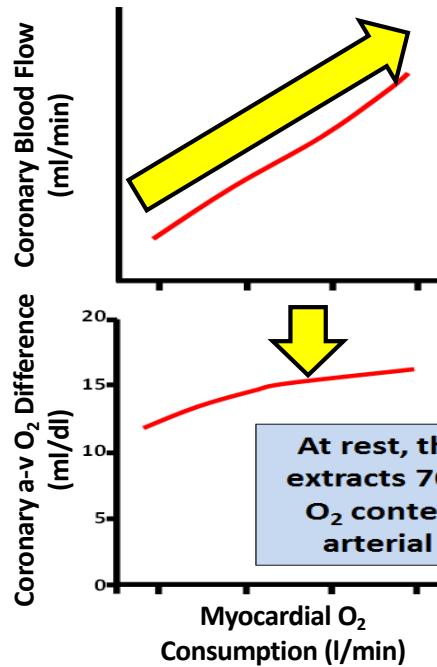


Figure 21-8 from Preston and Wilson's *Physiology*

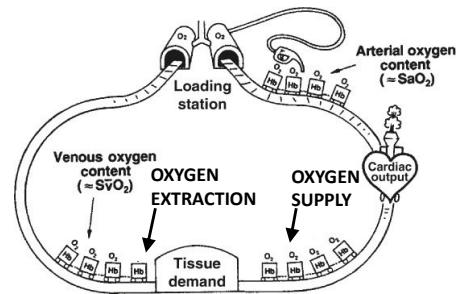
- Precapillary sphincters are comprised of smooth muscle cells
- Contraction/relaxation is regulated by local metabolite concentration
- At rest, only a small number of sphincters are relaxed
- During maximal exercise, all sphincters are open
- This allows coronary blood flow to rise to maximal levels

Myocardial Oxygen Supply: Blood Flow vs. Oxygen Extraction

↑ work
= ↑ O₂ consumption
= ↑ blood flow
= ←→ O₂ extraction



At rest, the heart extracts 70-80% of O₂ content from arterial blood

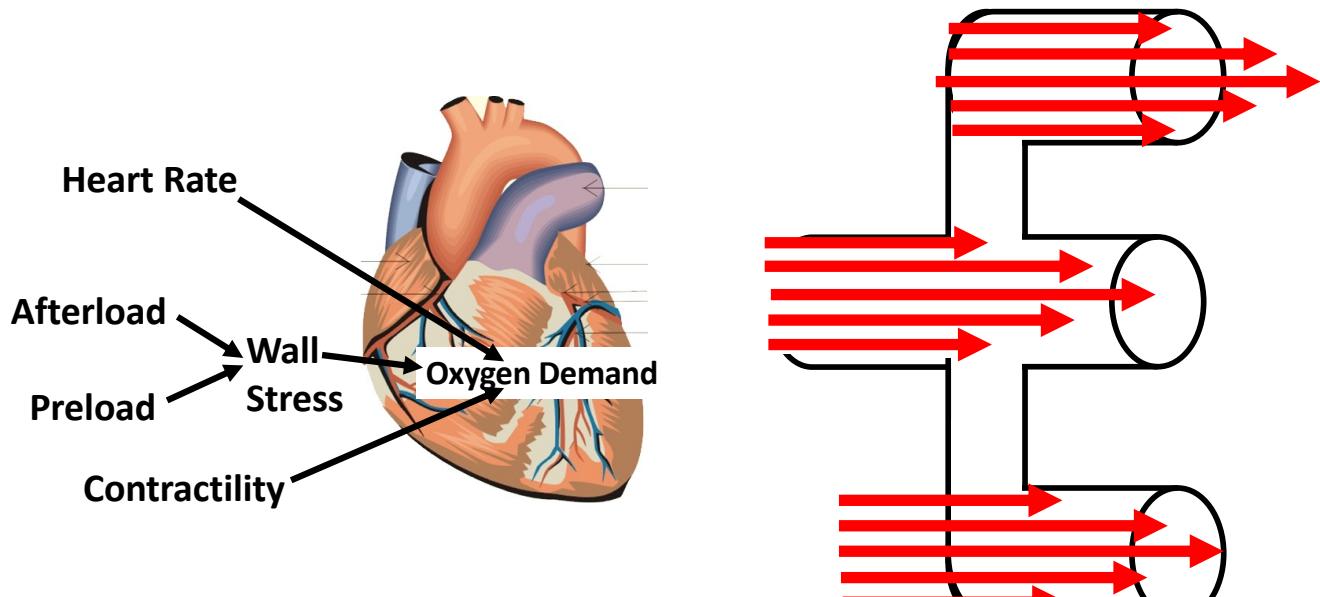


How is the rising cardiac O₂ demand met as workload increases?

Regulation of Coronary Blood Flow

- 1. Local control:** primarily regulated via changes in cardiac tissue metabolism
- 2. Extrinsic control:** sympathetic innervation (mainly), small parasympathetic dilation
- 3. Mechanical compression:** results from coronary arterial compression during cardiac contraction

Local control: Active Hyperemia Maintains Myocardial Oxygen Supply



What is O₂ content?

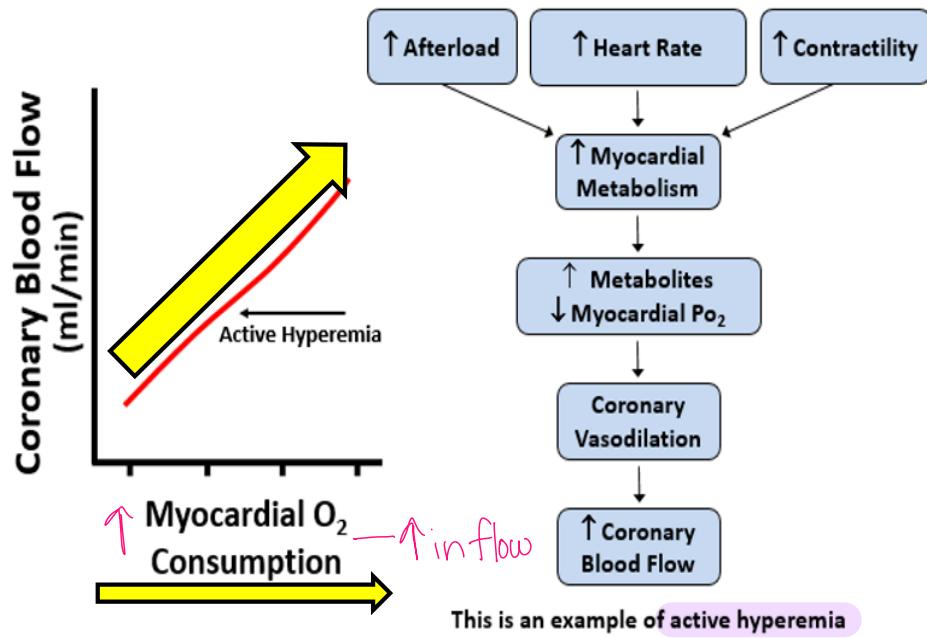
Oxygen consumption by the heart is principally required for contraction, with requirements for maintaining basal metabolism comprising only 10–20% of total oxygen

Consumption

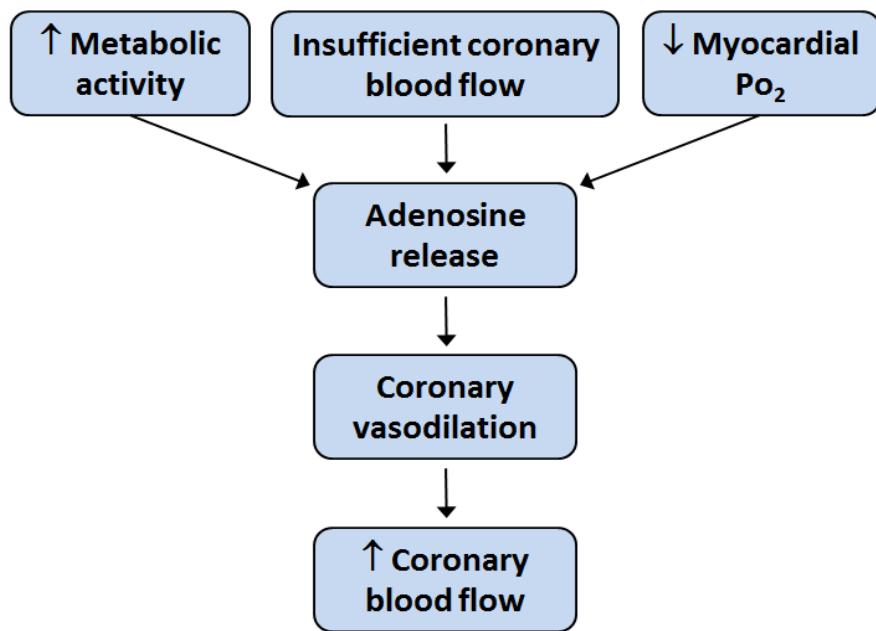
Increases in HR reduce coronary perfusion cause diastole is shortened and diastole when blood flow to myocardium occurs.

During exercise, dogs n horses can increase hematocrit and thus total O₂ content via splenic contraction

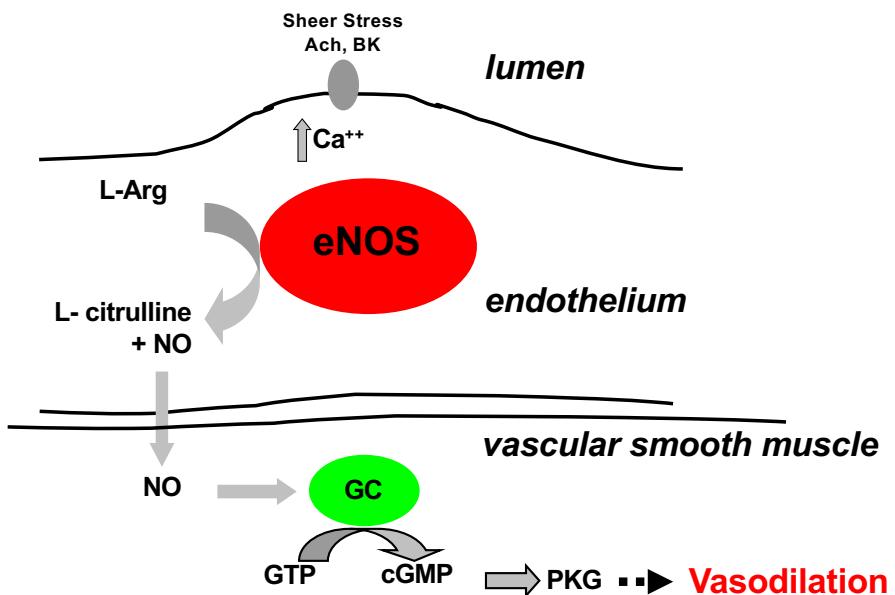
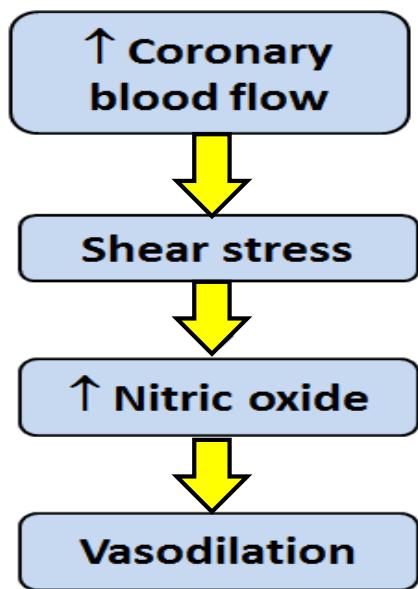
Local Control: Active Hyperemia



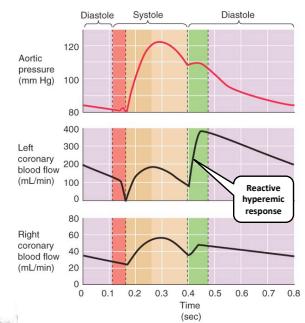
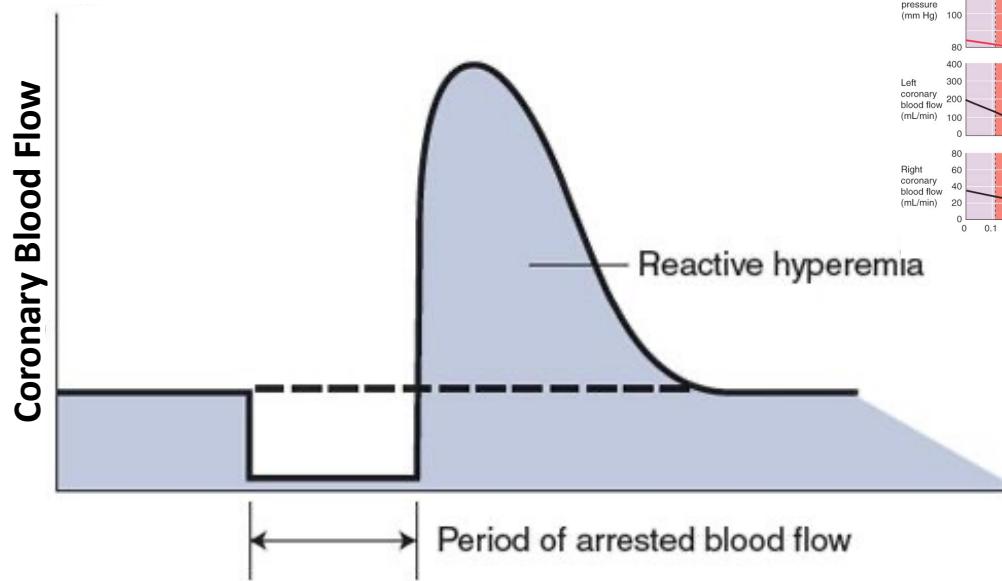
Local Control: Adenosine Hypothesis



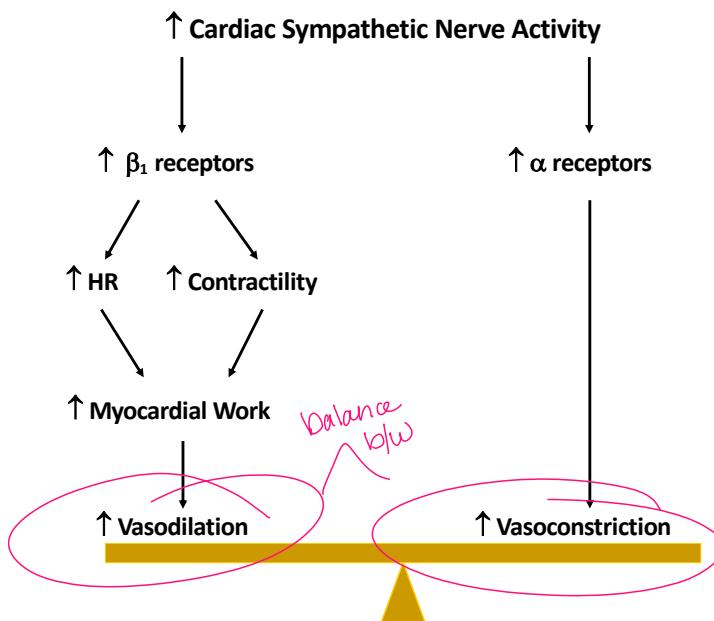
Local Control: Nitric Oxide and Coronary Vasodilation



Local Control: Reactive Hyperemia



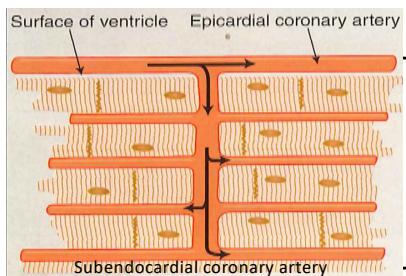
Extrinsic Control: Role for Sympathetic Nerves



release of nitric oxide, induced by the shear stress of increased coronary flow

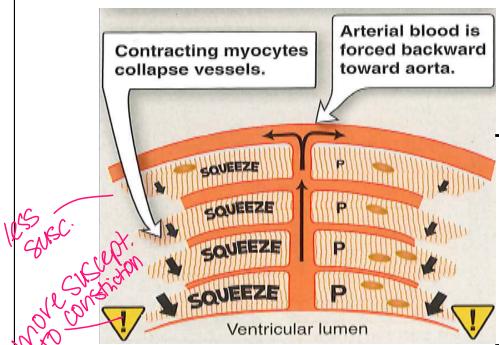
opposes α adrenergic vasoconstriction limiting the potential reduction in myocardial perfusion during augmented sympathetic drive

Mechanical Compression and Left Ventricular Myocardial Blood Flow



Diastole

During **DIASTOLE** the epicardial coronary vessels (those that run along the outer surface of the heart) and subendocardial vessels (those that run along the internal surface of the heart) remain patent.



Systole

During **SYSTOLE** the subendocardial coronary vessels are compressed due to the high intraventricular pressures → blood flow in the subendocardium nearly stops.

Subendocardial regions are more susceptible to ischemic injury when coronary heart disease or reduced aortic pressure is present

Figure 21-10 from Preston and Wilson's Physiology

How does coronary blood flow ↑ to **REST** meet ↑ oxygen demand?

↑ O₂ demand



Metabolic vasodilation

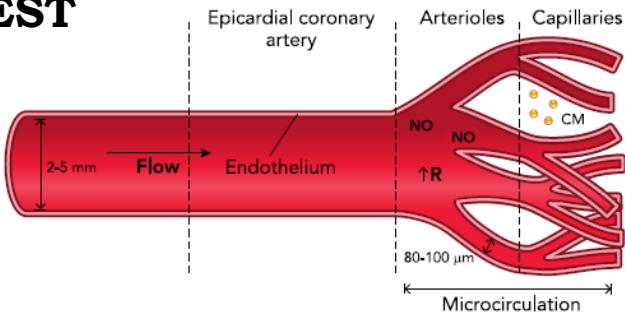


Flow-mediated vasodilation

↑ flow → ↑ NO

↳ vasodilation
(flow mediated)

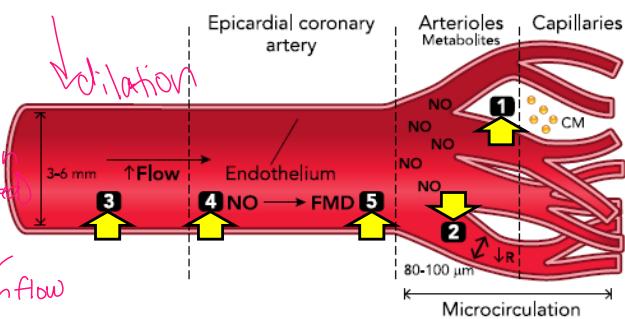
↓
Stims further
increases in flow



↑ O₂ demand

↓
Vasodilation

3 ↑ Flow
4 NO → FMD
5 ↓ R



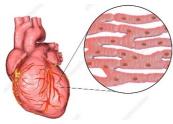
Top: at rest, arterioles display a high level of resting tone, which determines the basal blood flow through the upstream arteries.

Bottom: during times of increased oxygen demand, cardiac myocytes (CM) release vasoactive metabolites (1), which leads to a drop in arteriolar resistance (2). The decreased arteriolar resistance elicits increased flow in upstream arteries (3), causing increased NO release and oxygen delivery to downstream capillaries (4), as well as FMD in the artery (5), further increasing flow.



If the oxygen requirements of the skeletal muscle change, oxygen supply can be appropriately altered by either:

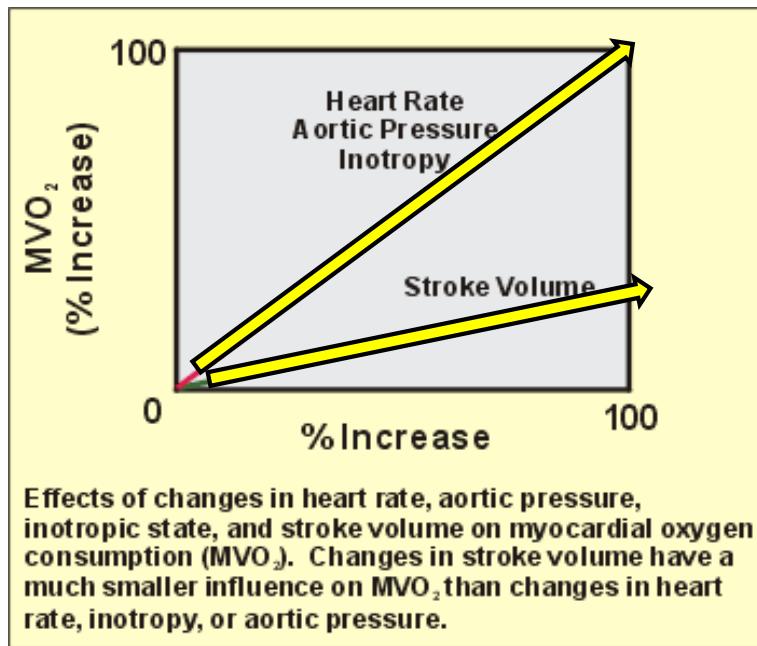
- ↑ skeletal muscle oxygen extraction
- ↑ skeletal muscle oxygen delivery (i.e., skeletal muscle blood flow)



If the oxygen requirements of the cardiac muscle change, oxygen supply can be appropriately altered only by:

- ↑ coronary oxygen delivery (i.e., coronary blood flow)

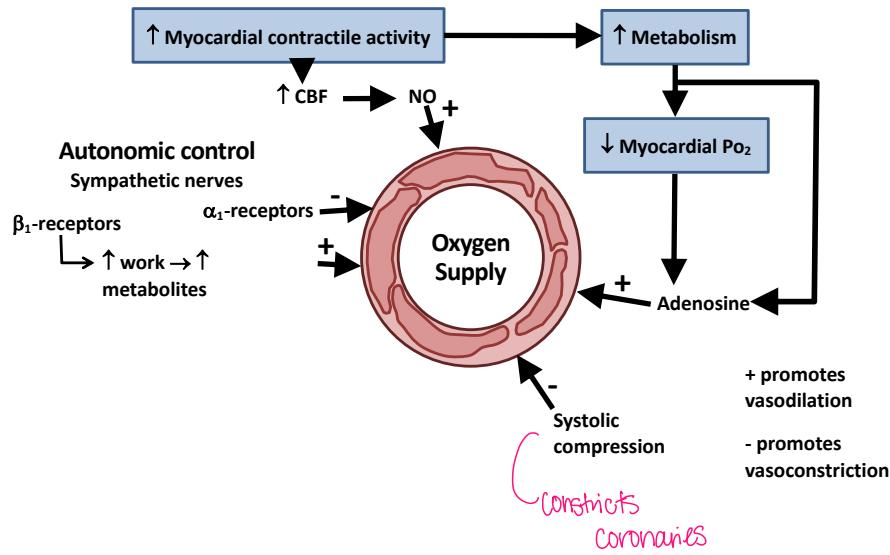
Myocardial Oxygen Consumption, Work and Coronary Blood Flow



This relationship indicates that a 100% increase in ventricular volume (V) increases wall tension (T) by only 26%. In contrast, increasing intraventricular pressure (P) by 100% increases wall tension (T) by 100%. For this reason, wall tension, and therefore MVO₂, is far less sensitive to changes in ventricular volume than pressure (see figure). In summary, increasing [heart rate](#) (HR), [aortic pressure](#) (AP), and [inotropy](#) (Ino) increase MVO₂ about 4-times more than an equivalent percent change in [stroke volume](#) (SV).

These findings have implications for the treatment of patients with [coronary artery disease](#) (CAD). For example, drugs that decrease afterload, heart rate, and inotropy are particularly effective in reducing MVO₂ and relieving anginal symptoms. CAD patients should avoid situations that lead to large increases in afterload such as lifting heavy weights, which causes large increases in arterial pressure. It is very important that hypertensive CAD patients are fully complying with their anti-hypertensive medications because hypertension dramatically increases MVO₂ due to increased afterload. CAD patients can also be encouraged to participate in exercise programs such as walking that utilize preload changes to augment cardiac output by the [Frank-Starling mechanism](#). It is important to minimize adrenergic activation in CAD patients because sympathetic activation of the heart and vasculature increases heart rate, inotropy, and systemic vascular resistance, all of which lead to significant increases in oxygen demand by the heart.

Summary of Control of Coronary Blood Flow

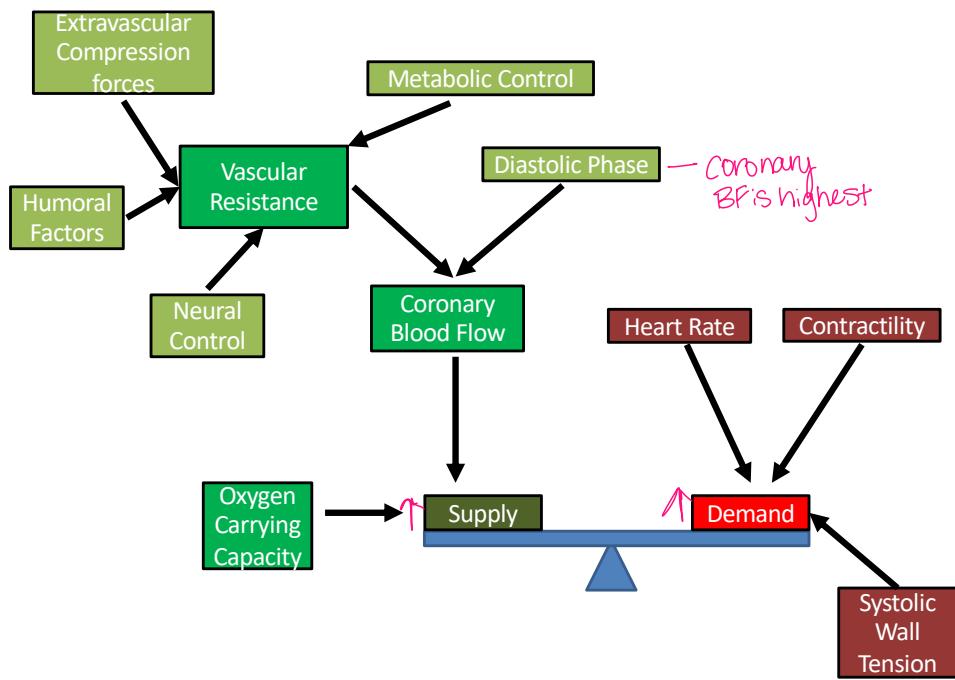


Coronary blood flow is primarily regulated by changes in tissue metabolism.

Adenosine has been shown to be important in dilating the coronary vessels when the myocardium becomes hypoxic or when cardiac metabolism increases during increased cardiac work.

Experimental studies have shown that inhibiting adenosine formation, enhancing its breakdown to inosine, or blocking vascular adenosine receptors impairs coronary vasodilation under these conditions. In addition, nitric oxide has been shown to be important in coronary vessels, particularly in producing flow-dependent vasodilation. Finally, there is also some evidence that prostaglandins play a role in regulating coronary blood flow.

Summary of Coronary Circulation

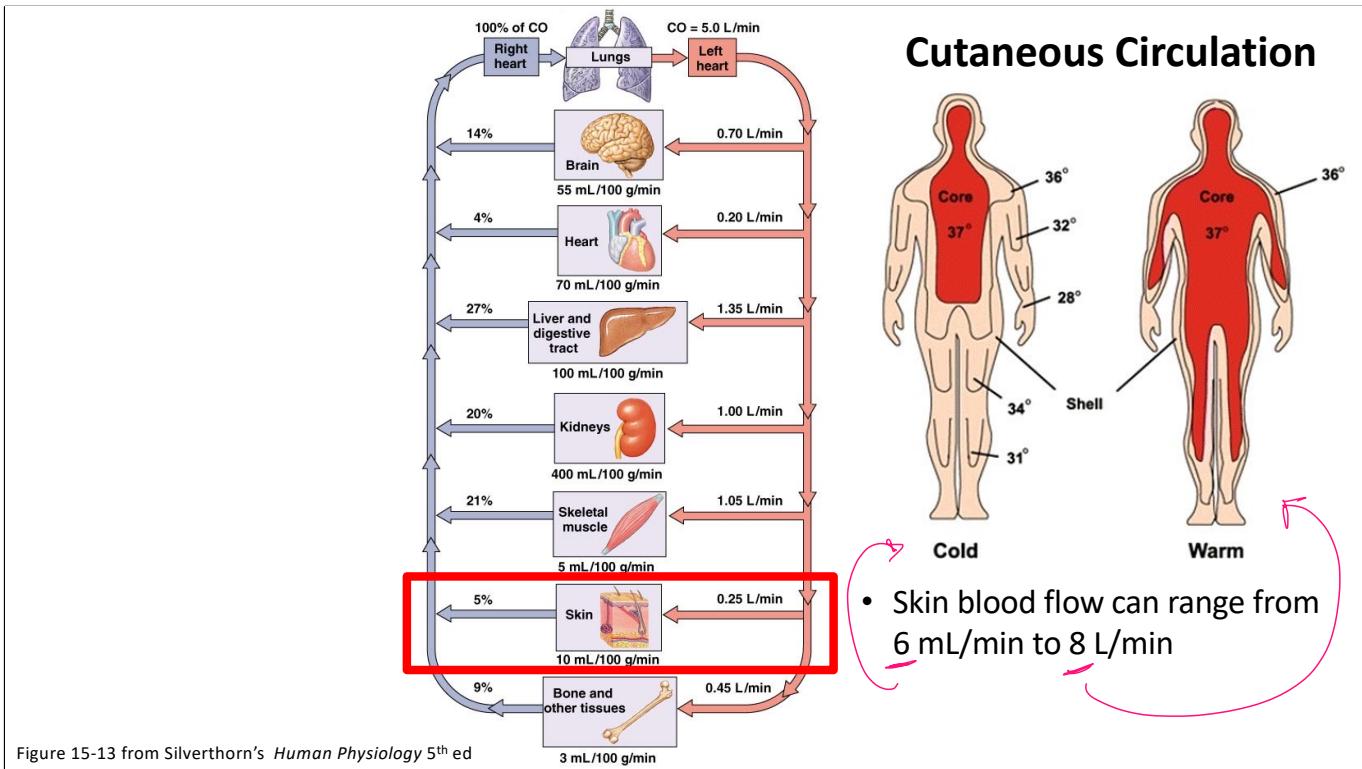


During the cardiac cycle, when does the highest coronary blood flow per gram of left ventricular myocardium occur.

- A. When aortic pressure is highest
- B. When left ventricular pressure is highest
- C. At the beginning of isovolumic contraction
- D. When aortic blood flow is highest
- E. At the beginning of diastole

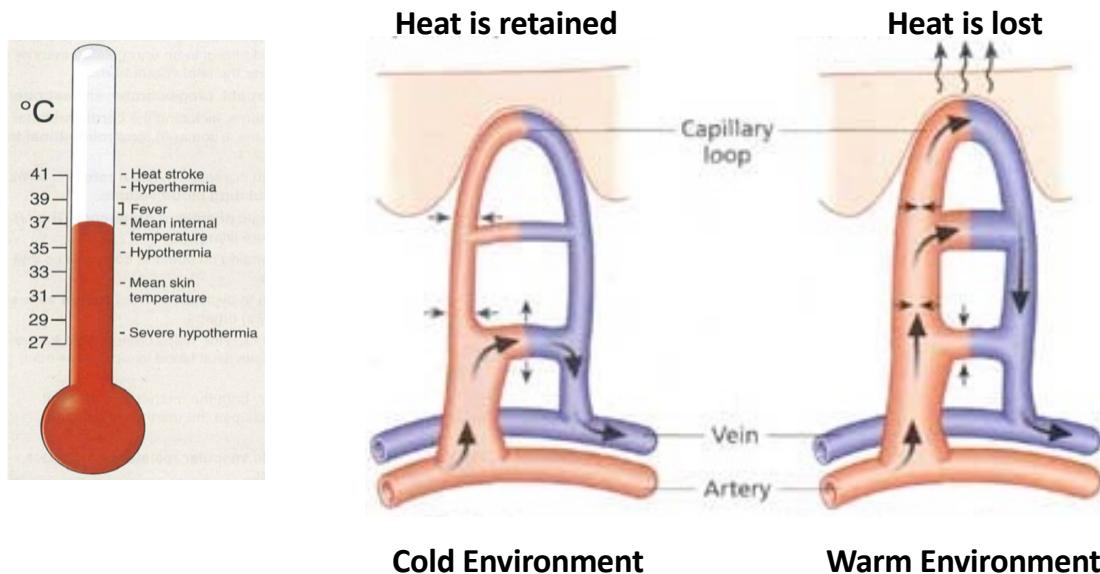
Answer: E

Explanation: Blood flow through the coronary vessels of the left ventricle is determined by the ratio of perfusion pressure to vascular resistance. The perfusion pressure is directly related to the aortic pressure at the ostia of the coronaries. Myocardial vascular resistance is significantly influenced by the contractile activity of the ventricle. During systole, when the ventricle is contracting, vascular resistance increases substantially. Flow is highest just at the beginning of diastole because, during this phase of the cardiac cycle, aortic pressure is still relatively high and vascular resistance is low due to the fact that the coronary vessels are no longer being squeezed by the contracting myocardium.



Cutaneous Circulation

The primary function of the skin circulation is to help maintain body temperature, plus provide nutrients



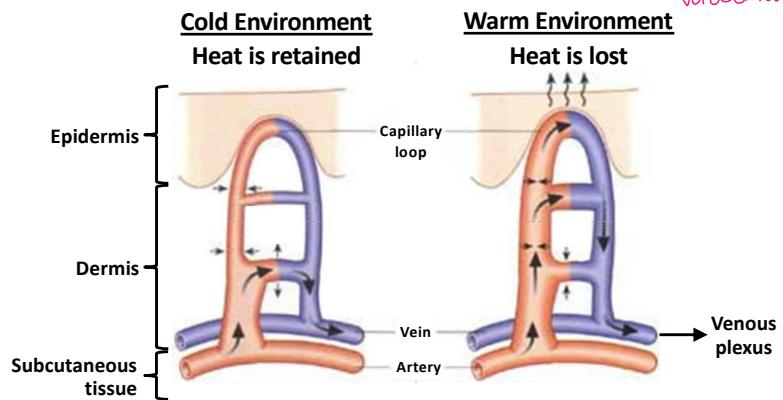
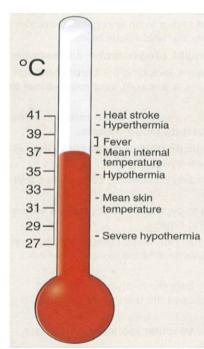
The primary function of the skin circulation is to help maintain body temperature.

Blood vessels constrict to prevent heat loss and dilate to facilitate transfer of heat from the body core to the body surface.

The skin comprises 4% to 5% of the total body weight and receives about 2% of the cardiac output.

The arterio-venous oxygen difference is small (3 Vol%), indicating that most of the blood flow is non-nutrient flow.

Why do we care about skin blood flow? → huge ability to vasodilate



- % of cardiac output comprised by skin blood flow: at rest (~2%),
- during severe cold (<1%)
- during severe heat stress (~60%)
- Thus, skin vasculature has an enormous vasodilatory capacity!

Apical skin- present in nose, lips, ears, hands and feet

Non-apical skin- everywhere else

Blood vessels only reach dermis...epidermis does not have blood supply

INTERNAL

Central Thermoreceptors

EXTERNAL

Cutaneous Thermoreceptors

Skin temperature (°C)	Cold receptor range (%)	Warmth receptor range (%)
10	100	0
20	50	0
30	0	0
40	0	100
50	0	50

The Body's Thermoreceptors

- The setpoint for core body temperature is 37°C
- Heating or cooling the hypothalamic preoptic area elicits the appropriate behavior
- Damage to the preoptic area (i.e., stroke, MS) leads to temperature fluctuations and impaired response to thermal stress
- Thermoregulatory control center neural output is regulated:
 - Primarily by central thermoreceptors, BUT
 - Preoptic area integrates input from peripheral thermoreceptors
 - Thermoregulatory responses occur mostly through the sympathetic nervous system

The body possesses two diverse groups of thermosensors. Central thermoreceptors monitor internal body temperature, whereas skin thermoreceptors provide information about the external thermal environment.

1. Central: Thermoreceptors that monitor internal temperature are located in the hypothalamus, spinal cord, and viscera, but the sensors that have the greatest influence on thermoregulatory control center output are in the **preoptic area of the hypothalamus**. Warmth-sensitive preoptic neurons are tonically active at normal body temperature. A rise in internal temperature (as reflected by the temperature of blood bathing the preoptic area), increases their firing rate, whereas cooling decreases firing rate.

2. Skin: There are four primary skin thermoreceptor types. Two mediate nociceptive responses to painfully cold or hot stimuli and are discussed elsewhere (see 16·VII·B). The other two, comprising distinct populations of cold and warmth receptors, are involved in thermoregulation.

a. Cold: **Cold receptors** mediate neutral, cool, and cold sensations (5°–45°C). Cold temperatures are believed to be sensed by TRPM8, one of the transient receptor-potential (TRP) channel family (see 2·VI·D) that mediates a depolarizing receptor potential

when active. Afferent firing rate increases as a consequence.

b. Warmth: Heat sensation involves **warmth receptors** that are activated from 30°–50°C. Heat reception also involves TRP channels (TRPV3 and TRPV4) that are active at neutral and warm temperatures.

Thermoregulatory Response Mediators

- **Skeletal muscle**
- **Brown adipose tissue**
- **Sweat gland**
- **Blood vessels**

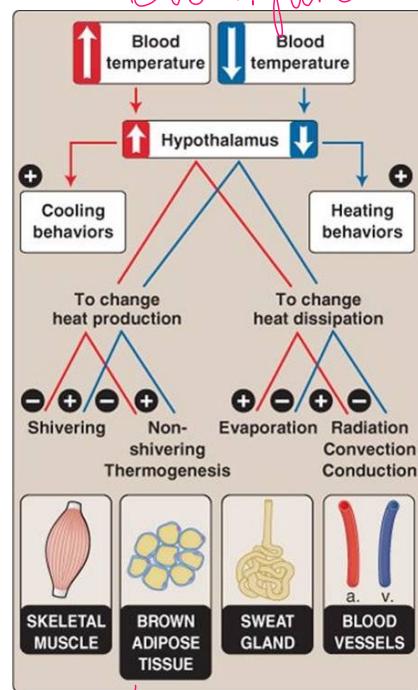


Figure 38-4 from Preston and Wilson's Physiology

Cold stress initiates pathways that increase tissue insulation and increase metabolic rate via shivering and nonshivering thermogenesis (heat production). Conversely, heat stress reduces tissue insulation and initiates sweating. The primary thermoregulatory effectors are the skin blood vessels, sweat glands, skeletal muscles, and brown adipose tissue.

1. Muscles: Shivering is a rapid, cyclical contraction of skeletal muscles that liberates heat but produces minimal force. Muscle contractions always produce large amounts of heat because force production is only 20% efficient. The remaining 80% of expended energy is liberated as heat. Shivering muscles do not perform meaningful work, and, thus, almost all of the energy used is liberated as heat. Shivering is unique in that it is mediated by the somatic motor pathways rather than the SNS, but the response is initiated by the preoptic area.

2. Nonshivering thermogenesis: Nonshivering thermogenesis is a SNS-mediated increase in metabolic rate in muscle and other tissues designed to liberate heat. In brown fat, SNS stimulation activates an uncoupling protein (**thermogenin**) in the inner mitochondrial membrane. Thermogenin is a pore-forming protein that allows H⁺ to cross the inner mitochondrial membrane without generating adenosine triphosphate. Thus, oxidative phosphorylation becomes

uncoupled. Infants rely on brown adipose tissue for heat production, but this pathway is less important in adults.

3. Sweat glands: There are three sweat gland types, but only **eccrine sweat glands** produce sweat that mediates evaporative cooling during heat stress. Sweating is initiated by SNS cholinergic nerves, but the glands are stimulated by adrenergic compounds (e.g., epinephrine, norepinephrine) also. Sweating can dehydrate the body and cause a hypertonic volume contraction. Even small fluid loss (2% body weight) can decrease work performance and allow internal temperatures to rise during heat stress.

4. Skin blood vessels: Heat loss or gain is most effectively regulated at the level of the skin. To dissipate heat, blood flow is brought in close proximity to the body's surface, whereas to conserve heat, blood flow is shunted away from the body's surface. Glabrous skin contains deep arteriovenous anastomoses that allow blood to bypass surface capillary beds. Hairy (nonglabrous) skin does not have arteriovenous anastomoses but does have deep and superficial capillaries. The most efficient heat transfer with the environment occurs when blood is shunted through these surface capillaries. Postganglionic adrenergic nerves constrict cutaneous arteries, veins, and anastomoses, acting via α -adrenergic receptors. Removing the constrictor influence and then actively dilating vessels increases blood flow through the cutaneous vasculature. The vasodilation mechanism is less understood but involves nitric oxide and cholinergic sympathetic nerves. These vasomotor changes allow skin blood flow to change from <6 mL/min to 8 L/min. During heat stress, venous volume increases also to provide additional time for heat transfer. Heart rate and CO increase, and other vascular beds (e.g., renal and splanchnic), vasoconstrict to facilitate the skin blood flow increase.

5. Behavior: Thermoregulatory behaviors can decrease or even eliminate thermal stress. These behaviors are driven by the preoptic area but can be overridden or modified by other areas of the brain. Conscious behavioral responses to cold stress involve increasing insulation (e.g., putting on a coat), increasing physical activity to increase metabolic rate, or seeking an external heat source. Heat stress-related behaviors include drinking fluids to facilitate sweating, removing clothing, seeking shade, or turning on a fan.

Blood Flow to the Apical Skin

- Apical skin is the thick skin found on nose, lips, ears, hands and feet
- Very high surface-to-volume ratio that favors heat loss
- Play a critical role in temperature regulation
- Unique feature are A-V anastomosis, which is non-nutritive flow
- Densely innervated with sympathetic vasoconstrictor nerves
- Glomus bodies begin shunt blood away from skin when exposed to cooler temperatures

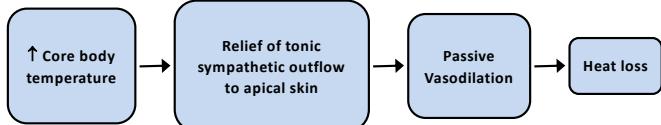
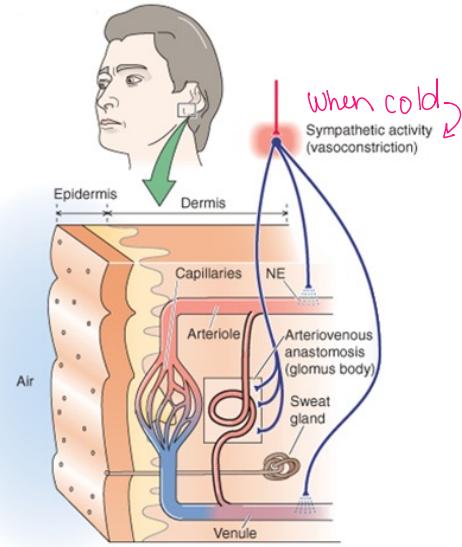


Figure 24-8 from Boron and Boulpaep's *Medical Physiology* 2nd ed

Apical skin- present in nose, lips, ears, hands and feet

Capillaries only reach dermis...epidermis does not have blood supply

Apical Skin The apical skin at the extremities of the body has a very high surface-to-volume ratio that favors heat loss. Circulation to these apical regions has an unusual feature—arteriovenous (a-v) anastomoses called **glomus bodies**. (These glomus bodies are unrelated to the glomus cells of the peripheral chemoreceptors.) Glomus bodies are tiny nodules found in many parts of the body, including the ears, the pads of the fingers and toes, and the nail beds. As the afferent arteriole enters the connective tissue capsule of the glomus body, it becomes a vessel with a small lumen and a thick, muscular wall comprising multiple layers of myoepithelioid cells. These vessels—which have a rich sympathetic innervation—connect with short, thin-walled veins that eventually drain into larger skin veins. The a-v anastomoses, which are involved in heat exchange, are in parallel with the capillaries of the skin, which are involved in nutrient exchange.

The anastomotic vessels are under neural control, rather than the control of local metabolites, and play a critical role in temperature regulation. In these apical regions, blood flow is under the control of

sympathetic fibers that release norepinephrine and thereby constrict the arterioles, anastomotic vessels, and venules. Therefore, the increase in sympathetic tone that occurs in response to decreases in core temperature elicits vasoconstriction in the a-v anastomoses, a fall in blood flow, and a reduction in heat loss. Maximal sympathetic stimulation can completely obliterate the lumen of an anastomotic vessel, thus greatly reducing total blood flow to the skin. On the other hand, when the core temperature rises, the withdrawal of sympathetic tone leads to passive vasodilation; there is no active vasodilation. Thus, sympathetic tone to the vasculature of apical skin is substantial at rest.

Blood Flow to the Non-Apical Skin (Hairy Skin)

Surface BV

- Skin everywhere BUT the palms, soles, and skin of the ears, nose, and lips.
 - No A-V anastomosis, but has superficial capillaries
 - Sympathetic nerves release either:
 - Norepinephrine → vasoconstriction
 - Acetylcholine → vasodilation
- Tonic sympathetic tone at rest

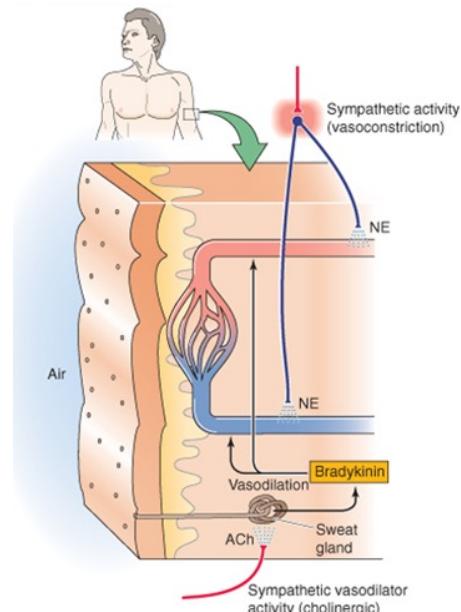
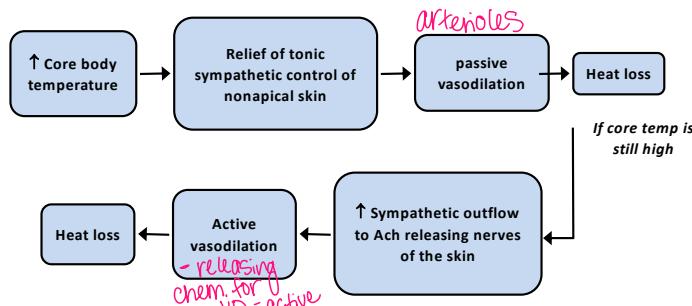


Figure 24-8 from Boron and Boulpaep's Medical Physiology 2nd ed

Nonapical Skin The body uses a very different approach for regulating blood flow in nonapical skin. One important difference is that the vasculature of this skin almost completely lacks a-v anastomoses. A second important difference is that there are two types of sympathetic neurons innervating the vessels of the skin. Some release *norepinephrine* and some release *acetylcholine*.

Vasoconstriction occurs in response to the release of norepinephrine. In contrast to the situation in *apical* skin, blockade of sympathetic innervation to *nonapical* skin in a thermoneutral environment produces little change in skin blood flow, demonstrating little vasoconstrictor activity at rest.

Vasodilation in nonapical skin occurs in response to sympathetic neurons that release acetylcholine. Indeed, blockade of sympathetic innervation to the nonapical skin in a warm environment produces vasoconstriction and a decrease in skin blood flow, demonstrating neurally directed vasodilation before the blockade.

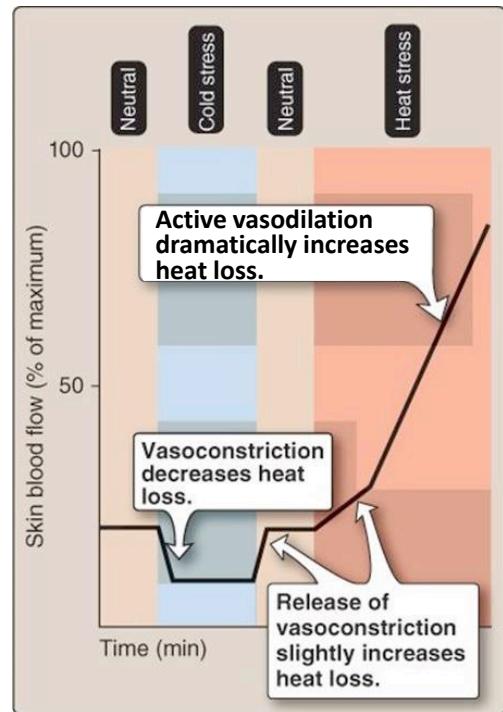


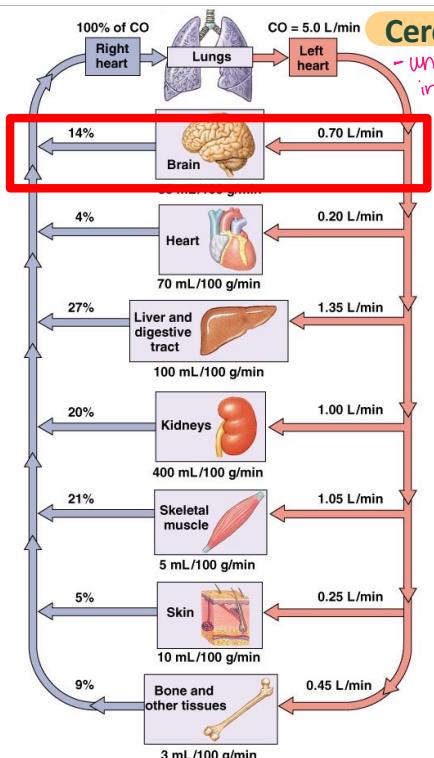
Figure 38-5 from Preston and Wilson's *Physiology*

Blood Flow to the Non-Apical Skin

- Most skin in the body is non-apical skin
- The most efficient heat transfer with the environment is when blood is shunted through these surface capillaries

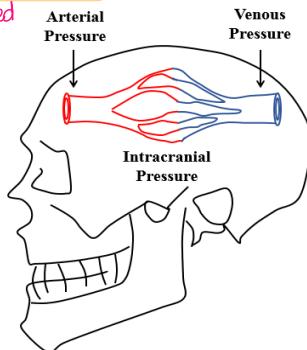
➤ During heat stress:

- Blood volume in skin veins ↑
- Heart rate and cardiac output ↑
- Renal and splanchnic blood flow ↓



Cerebral Circulation

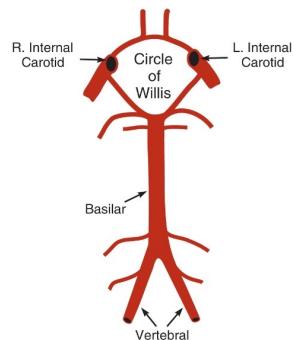
• b/c enclosed
• hard shell



The brain comprises about 2.5% of the total body weight and receives 15 % of the cardiac output.

Oxygen extraction is relatively high, however, with venous oxygen levels approximating 13 Vol%, an AV oxygen difference of 7 Vol%.

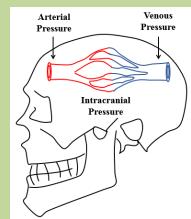
Features of the Cerebral Circulation



➤ 20% of resting oxygen consumption

➤ Highly oxidative

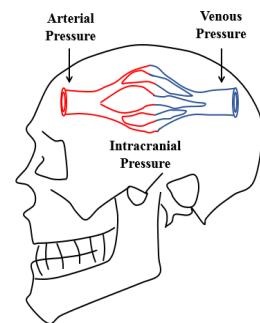
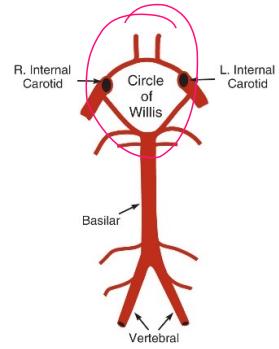
- Intolerant of ischemia (~25% ↓ blood flow causes lightheadedness)
- Shuts down with anoxia



➤ Complete interruption of blood flow for >4-5 min can cause organ failure and death

Cerebral Vasculature

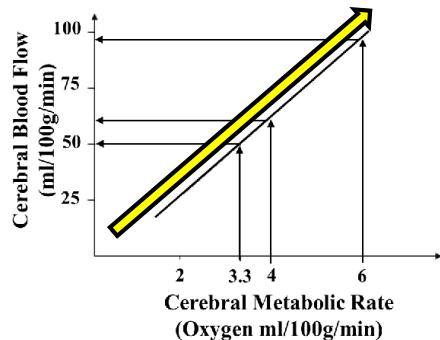
- The brain circulation is supplied by four principal arteries
- Interconnecting arterial vessels at the brainstem provides a safety mechanism for cerebral perfusion
- Blood-brain-barrier and cerebral capillaries:
 - Rarely form pinocytotic vesicles
 - No fenestrations
 - Adjacent endothelial cells are fused
 - O₂ and CO₂ (lipid soluble) readily cross
 - Many transporters for glucose, fatty acids, etc.



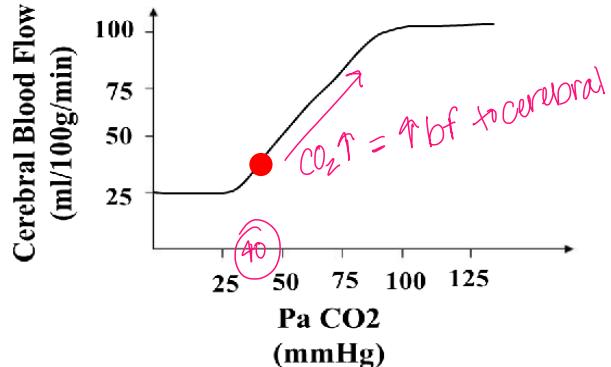
Major cerebral arteries perfusing the brain. This view is of the ventral surface of the brain and brainstem. The carotid and vertebral arteries are the major source of cerebral blood flow and are interconnected through the Circle of Willis and basilar artery. Smaller branches from these vessels perfuse different brain regions. L, left; R, right.

Control of Cerebral Blood Flow

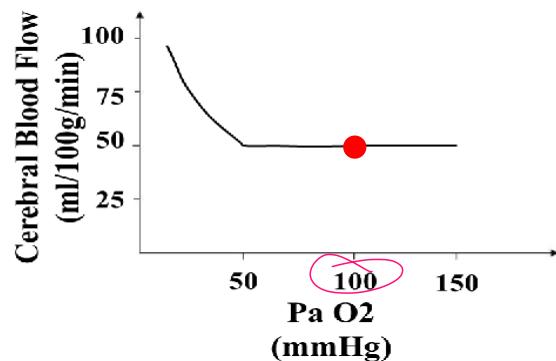
- Cerebral blood flow is tightly coupled to oxygen consumption
- Regional cerebral blood flow changes as neurons become more or less active
- Normally ↑ metabolic activity → ↑ blood flow → tissue expansion
- The rigid cranium constrains cerebral blood flow and volume
- ↑ cerebral blood flow that accompany ↑ activity are matched by opposing changes in less active brain areas



Effect of Carbon Dioxide and Oxygen on Cerebral Blood Flow



Normal PCO₂ of arterial blood ≈ 40 mmHg



Normal PO₂ of arterial blood ≈ 95 mmHg

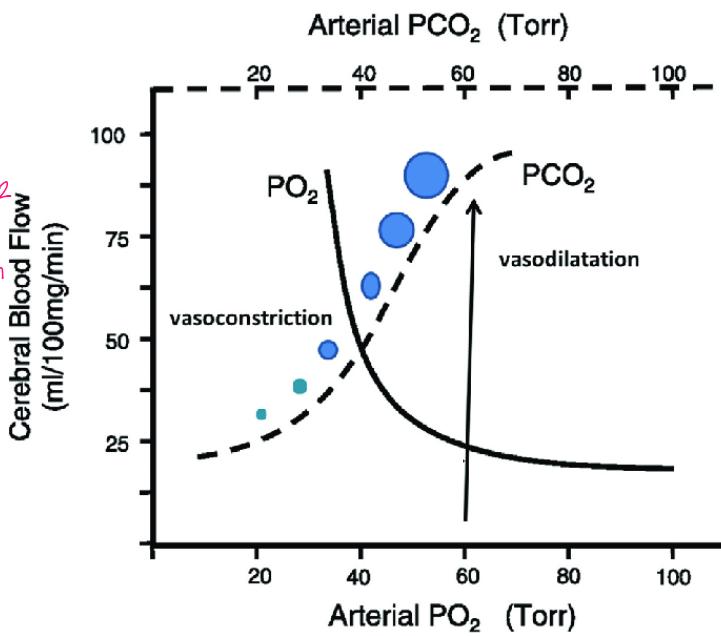
CO₂ = more potent regulator of CBF

Case: Dr. Sheldon Cooper, PhD suddenly realizes that his World of Warcraft account was hacked and all of his virtual possessions were virtually stolen. This causes him to hyperventilate and then become lightheaded.

Why did he become lightheaded? blowing off CO_2
Why is he breathing into a paper bag?
 -inhale back some exhaled CO_2 Cerebral constriction

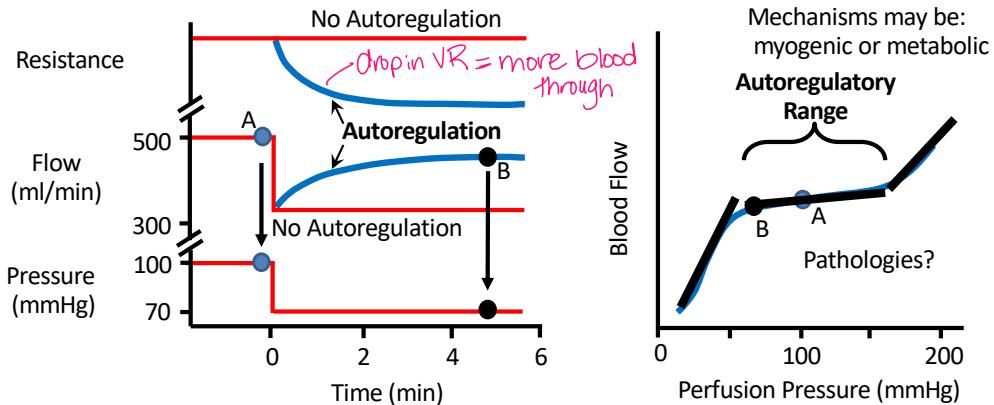


Effects of Arterial PO_2 and PCO_2 on Cerebral Blood Flow



Intrinsic Control Examples: Autoregulation of Blood Flow

Autoregulation is the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure.



The autoregulatory range is the range of pressure over which there is little if any change in blood flow. Nature of these curves may be different for each organ.

Circulations w/ "flat" curves

- 1) Cerebral
- 2) Renal
- 3) Coronary

Stretch-induced contraction is thought to protect capillaries from surges in arterial pressure

Figure 7-3 from Klabunde's Cardiovascular Physiology Concepts 2nd Ed

Autoregulation of blood flow. The left panel shows that decreasing perfusion pressure from 100 to 70 mm Hg at point A results in a transient decrease in flow. If no autoregulation occurs, resistance remains unchanged and flow remains decreased. With autoregulation (red line), the initial fall in pressure and flow are followed by a decrease in vascular resistance, which causes flow to increase to a new steady-state level despite the reduced perfusion pressure (point B). The right panel shows steady-state, autoregulatory flows plotted against different perfusion pressures. Points A and B represent the control flow and autoregulatory steady-state flow, respectively, from the left panel. The autoregulatory range is the range of pressures over which flow shows little change. Below or above the autoregulatory range, flow changes are approximately proportional to the changes in perfusion pressure. The autoregulatory range as well as the flatness of the autoregulatory response curve varies among organs.

NEW NOTES

Regulation of GFR

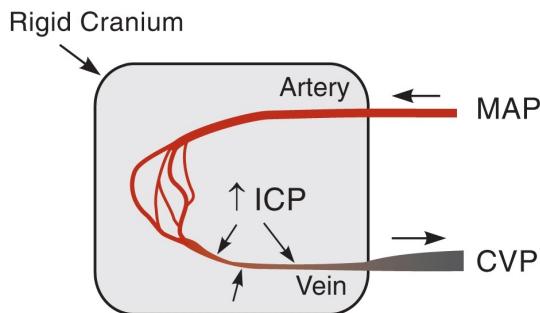
One would think that changes in the systemic blood pressure would cause changes in the pressure in the glomerular capillaries (P_{GC}) and thus, changes in the GFR. In healthy individuals, this does not occur because of **renal autoregulation**. Renal autoregulation involves feedback mechanisms **intrinsic to the kidney** that cause either dilation or constriction in the **afferent arteriole** so as to counteract blood pressure changes and keep a steady GFR. For instance, if the mean arterial pressure

increases, renal autoregulation causes the afferent arteriole to constrict, preventing the pressure increase from being transmitted to the glomerular capillaries, and keeping the GFR from increasing. As shown in the graph, renal autoregulation normally operates to keep GFR steady over a wide range of blood pressures. Note, however, that renal autoregulation is disrupted in chronic kidney disease.

If blood pressure drops too low due to excessive fluid loss, then the **sympathetic nervous system** will override renal autoregulation. Sympathetic nerves innervate the afferent arteriole, causing smooth muscle contraction. The sequence of events is as follows: loss of ECF volume (due to hemorrhage, diarrhea or dehydration) causes a drop in mean arterial pressure (MAP). Decreased MAP is detected by arterial baroreceptors, which leads to sympathetic nervous system activation, afferent arteriole constriction, and decreased GFR.

Effect of Intracranial Pressure on Cerebral Blood flow

Intracranial Pressure (ICP)- Pressure in the fluid-filled space between the cranium and the brain tissue.



$$\text{CPP} = \text{MAP} - \text{ICP}$$

Cerebral perfusion pressure (CPP) is based upon gradient between MAP and Intracranial pressure

ICP increased by:

- intracranial bleeding
- cerebral edema
- tumor

Increased ICP:

- collapses veins
- decreases effective CPP
- reduces blood flow

For the brain to remain adequately perfused, MAP must be maintained higher than ICP

Figures 7-10 from Klabunde's Cardiovascular Physiology Concepts 2nd Ed

Effects of intracranial pressure (ICP) on cerebral blood flow. ICP is the pressure within the rigid cranium (gray area of figure). Increased ICP decreases transmural pressure (inside minus outside pressure) of blood vessels (particularly veins), which can cause vascular collapse, increased resistance, and decreased blood flow. Therefore, the effective cerebral perfusion pressure (CPP) is mean arterial pressure (MAP) minus ICP. CVP, central venous pressure.



Cushing's Reflex — last ditch effort from the brain

Hypotensive shock (BP <60 mmHg) or cerebral occlusion (stroke, head trauma, tumor) leads to decreased brain perfusion

→

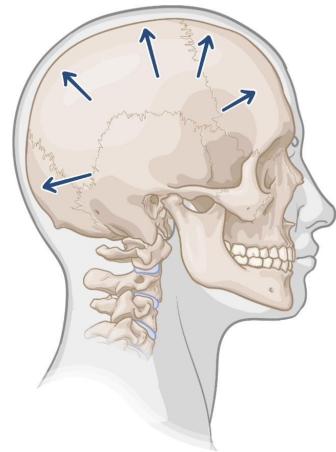
hypoxia (and increased CO₂) to pons and medulla powerfully activates sympathetic autonomic control centers → → severe rise in blood pressure (>200 mmHg)

→

last ditch effort by body to restore cerebral blood flow

→

increases microvasculature pressure. (blood flow improves, but increased hydrostatic pressure exacerbates cerebral edema and increases intracranial pressure).



$$\text{CPP} = \text{MAP} - \text{ICP}$$

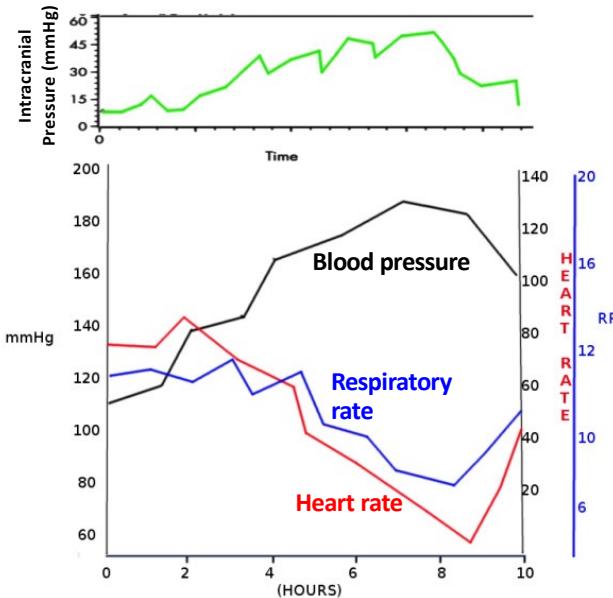
Untreated, most patients will die within hours of event

Cushing's Reflex

- ↑↑ ICP
 - Severe and life-threatening
- ↓ CBF → ↑ CO₂
 - Vasomotor center of brain
- Sympathetic response → vasoconstriction
 - ↑ MAP to ↑ CPP
- Baroreceptors in aortic arch and carotid arteries
 - Reflex bradycardia

Cushing's Triad:

- Hypertension
- Bradycardia
- Irregular respirations



Untreated, most patients will die within hours of event

The Cushing reflex is a physiological nervous system response to acute elevations of intracranial pressure (ICP), resulting in the Cushing triad of widened pulse pressure (increasing systolic, decreasing diastolic) bradycardia, and irregular respirations. In the first stage of the Cushing reflex, blood pressure and heart rate rise in response to sympathetic activation to overcome increases in ICP. This sympathetic response allows for brain perfusion as long as the ICP is not too high to overcome. For the brain to remain adequately perfused, mean arterial pressure (MAP) must be maintained higher than ICP. In the second stage of the Cushing reflex, hypertension continues to be present, but the patient becomes bradycardic rather than tachycardic. This is widely believed to occur because of increased blood pressures lead to activation of baroreceptors in the aortic arch, triggering parasympathetic activation and resultant bradycardia.

A 2-year-old boy is mauled by a black bear while hiking with his family in the Appalachian mountains. A claw puncture wound to the skull compressed the underlying brain tissue. Which of the following occurs in response to an increased intracranial pressure?

- A. Blood pressure and heart rate increase
- B. Blood pressure and heart rate decrease
- C. Blood pressure increases and heart rate decreases
- D. Blood pressure decreases and heart rate increases
- E. Blood pressure and heart rate remain constant

Answer: C

Explanation: If intracranial pressure is rapidly elevated, cerebral blood flow is reduced. The increase in intracranial pressure stimulates the vasomotor center and produces an increase of systemic blood pressure called the Cushing reflex that may lead to a restoration of cerebral blood flow. The increased blood pressure induces bradycardia mediated by the baroreceptor reflex.