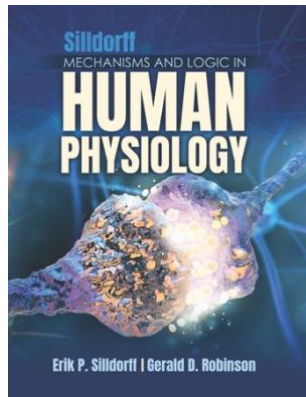


Chapter 9: Cardiovascular Physiology

Cardiac Function, Instructor Guide

Mechanisms and Logic in Human Physiology | Silldorff & Robinson | Kendall Hunt

Format: Left column = instructor narrative in the author's voice, drawn from lecture transcripts. Right column = structured causal chains, key distinctions, common student errors (red), and prediction prompts (gold italic). Sections without transcripts are written to match the established pedagogical voice.



Companion to **Mechanisms and Logic in Human Physiology** by Erik P. Silldorff and Gerald D. Robinson (Kendall Hunt Publishing). The half-year and full-year web subscriptions and the print version are available at <https://he.kendallhunt.com/product/mechanisms-and-logic-human-physiology-2>. For those teaching A&P more classically in a 2-semester sequence, the book is also packaged with Visible Body to support the anatomical portions of those courses (365-day subscriptions): <https://he.kendallhunt.com/product/mechanisms-and-logic-human-anatomy-and-physiology-visible-body-1>.

Cite as: Silldorff, E. P., & Robinson, G. D. (2026). Chapter 9 – Cardiovascular Physiology: An Instructor Guide for *Mechanisms and Logic in Human Physiology*. <https://doi.org/10.5281/zenodo.22738066>

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[Resource Hub](#)

Section 1: Vascular Circuits and the Heart as Hub

Instructor Narrative	Structured Outline / Causal Chain
The move: Establish the figure-eight layout first: two circuits in series with the heart at the crossing point, and the requirement that right and left output match over time. That equal-output constraint is what later explains heart failure, pulmonary hypertension, and edema. Why two circuits? Before we talk about how the heart works, one picture has to be established first: the cardiovascular system is a figure eight, with the heart sitting at the crossing point. Two separate pumps, the right heart and the left heart, drive blood through their own circuit simultaneously.	The Fundamental Design - Two circuits in series, pulmonary (gas exchange) and systemic (tissue delivery) - Outputs of right and left heart must be equal over time - Capillaries: the reason the rest of the system exists Causal Chain: Why Is the Left Ventricle So Large? Systemic circuit: greater collective vessel length and tone means higher resistance, which sets a higher pressure

The right heart takes in blood that has already completed its delivery run through the body, low in oxygen, high in CO₂, and sends it to the lungs to be reoxygenated. The left heart takes freshly oxygenated blood returning from the lungs and pressurizes it for delivery to everything else: brain, muscle, gut, skin. The systemic circuit covers all of it.

This design has one non-negotiable requirement: the output of both sides must be equal over time. If the right heart pumps more than the left, blood backs up in the lungs. If the left pumps more, it backs up in the systemic veins. That balance is the foundation for understanding heart failure, pulmonary hypertension, and edema.

Pressure differences explain the asymmetry

The two circuits are not symmetric, and that asymmetry is written in muscle mass. The left ventricle is about 70 to 75% of total heart mass. The right ventricle has a far thinner wall. This is not a design flaw, it is the consequence of resistance. The systemic circuit reaches your toes; its resistance is far higher than the pulmonary circuit, which is just the lungs. High resistance requires high pressure, and high pressure requires thick muscle. The atria look more symmetric because both operate under low pressure, their role is not to generate significant force but to complete ventricular filling.

The capillaries are the reason the rest of the system exists. Every artery, vein, and heart chamber is simply infrastructure in service of capillary exchange.

requirement. The thick left ventricular wall is the structure that meets it.

Key Definitions

- Arteries: carry blood away from the heart (regardless of O₂ content)
- Veins: carry blood toward the heart (regardless of O₂ content)
- Capillaries: site of all exchange, thin walls, gradient-driven diffusion

Common Errors

- **Error:** Oxygenated = arterial and deoxygenated = venous. False: pulmonary arteries carry deoxygenated blood; pulmonary veins carry oxygenated blood.
- **Error:** Assuming both sides pump the same volume at the same pressure. They pump the same volume; the pressure is dramatically different.

Prediction Prompt

- **Predict:** If the right coronary artery is blocked, which circuit suffers reduced output and why?

Section 2: Heart Structure, Cell Types, and Functional Syncytia

Instructor Narrative

***The move:** Separate the two cell populations first. Conducting cells set and distribute the rhythm; cardiomyocytes generate force. Keeping the two distinct is what later separates arrhythmia from pump failure.*

Two cell types, two jobs

Structured Outline / Causal Chain

Key Cell Types

- Nodal/conducting cells: spontaneously depolarize, non-contractile, set the rhythm
- Cardiomyocytes: stable RMP, contractile, require stimulus from conducting system

The heart has two fundamentally different cell populations and understanding why is essential to comprehension of heart control and function. Cardiomyocytes are the force generators, striated, aerobically equipped, contractile. They make up the vast majority of heart mass but remain electrically silent without the second population: the nodal and conducting cells that generate and distribute the stimulus. Think of the cardiomyocytes as an engine that will not start on its own. The conducting system is the ignition. Disease of the conducting system produces arrhythmias. Disease of the cardiomyocytes produces pump failure. Different problems, different solutions.

Cardiomyocytes: continuous aerobic demand

The histology tells you immediately this is a tissue that cannot afford to stop. Mitochondria occupy about 25% of cell volume, the highest of any cell type. That investment in aerobic ATP production reflects the non-negotiable requirement to keep beating without rest. Myoglobin supports this by binding oxygen intracellularly, maintaining a favorable diffusion gradient from capillary to mitochondrion. High capillary density completes the picture. This is slow-twitch physiology applied to a pump that never rests.

These cells are mononucleated, unlike skeletal muscle fibers, which form true syncytia by cell fusion. Each cardiomyocyte retains its own nucleus. What connects them is not fusion but the specialized junctions of the intercalated disk.

Gap junctions and desmosomes: solving two problems at once

Cardiomyocytes do not pull on tendons. They pull on each other. That creates two engineering problems the intercalated disk solves simultaneously. Gap junctions form cytoplasmic bridges between adjacent cells allowing depolarizing current to flow from one to the next, the domino effect. Desmosomes are the structural anchors that prevent contracting cells from tearing apart. Remove the gap junctions and the stimulus cannot propagate. Remove the desmosomes and the cells separate under mechanical stress. Both are lethal defects.

The fibrous skeleton then electrically separates the atrial and ventricular syncytia. Without this insulation, depolarization would

- Purkinje fibers: fast-response, large, many gap junctions, rapid conduction

Cardiomyocyte Aerobic Profile

- ~25% mitochondrial volume, highest of any cell type
- Myoglobin: O₂ store and diffusion facilitator (capillary → mitochondrion)
- Dense capillary network: minimizes diffusion distance
- Consequence: cannot tolerate ischemia, even brief hypoxia kills cells

Intercalated Disk

- Gap junctions: electrical coupling → stimulus propagation (domino effect)
- Desmosomes: mechanical coupling → cells cannot pull apart under contractile force

Causal Chain: Why Must Atria Contract Before Ventricles?

Ventricles must be filled before they generate ejection pressure → the final increment of filling comes from atrial contraction (the atrial "kick," ~25% of EDV) → if the atria and ventricles contracted together, atrial contraction could add nothing to ventricular volume and would instead drive blood backward into the veins. The atria must therefore empty into the ventricles first, and the sequential AV delay is what produces that order, and end-diastolic volume is maximized as a result

Common Errors

- **Error:** Calling cardiomyocytes a 'true syncytium.' They are a functional syncytium, connected, not fused. Each cell has its own nucleus.
- **Error:** Thinking fibrous skeleton is only structural. It also constitutes the electrical insulator that enforces sequential contraction.
- **Error:** Assuming gap junctions alone explain intercalated disk function. Desmosomes are equally essential for mechanical integrity.

Prediction Prompt

short-circuit from atria directly to ventricles, bypassing the AV node delay and destroying the sequential filling-then-ejection sequence.

- **Predict:** *If gap junctions were absent: what happens to stimulus propagation and the heartbeat? If desmosomes were absent: what happens during contraction?*

Section 3: The Specialized Conducting System

Instructor Narrative

The move: Present the AV delay as functional rather than a defect: it is the timing step that lets the atria finish filling the ventricles before ventricular contraction. Framed as a timing problem, the order of activation follows directly.

Why does the heart need a conducting system?

You need all ventricular cells to receive a stimulus in a specific order, fast enough to produce a coordinated squeeze, but with enough delay between atria and ventricles to allow filling before ejection. You cannot accomplish this by letting depolarization spread at random through the myocardium. You need preferential pathways, a wiring system.

Of the system's spontaneously excited cells, those of the SA node fire first because they depolarize fastest. They reach threshold before any other cell on every cycle. The stimulus they initiate spreads through internodal pathways to the AV node and simultaneously through the atrial syncytium, causing atrial contraction. The critical architectural feature is the fibrous skeleton: an electrical insulator between the atria and ventricles. The only way a stimulus crosses from atria to ventricles is through the AV node and the AV bundle. That single crossing point is where the essential delay occurs.

The delay is the functional feature

The AV node delays conduction adaptively, it has fewer gap junctions than other cardiac cells, slowing cell-to-cell current flow. The result is that the atria contract and drive blood into the ventricles before the ventricles receive their stimulus. Remove that delay and atria and

Structured Outline / Causal Chain

Conducting System Pathway

- SA node (right atrium): fastest intrinsic rate (60–100 bpm) → fires first
- Internodal pathways: carry stimulus to AV node; atrial syncytium depolarizes → initiates atrial contraction
- AV node (base of right atrium): adaptive delay (reduced gap junctions)
- AV bundle (bundle of His): only pathway through the fibrous skeleton
- Bundle branches: down the interventricular septum
- Purkinje fibers: endocardium → epicardium, apex upward
- Result: apex-to-base ventricular activation → blood driven toward the outflow tracts

Intrinsic Rates (Backup Hierarchy)

- SA node: 60-100 bpm
- AV node: 40-60 bpm
- Purkinje fibers: 15-40 bpm

Autonomic Innervation

- Both divisions innervate SA and AV nodes → heart rate control
- Sympathetic only → ventricular myocardium → contractility control
- At rest: parasympathetic dominant → HR ~70 bpm (below intrinsic ~100 bpm)

ventricles would contract simultaneously, losing the atrial contribution to ventricular filling.

Once through the AV bundle, the stimulus accelerates. Purkinje fibers are large cells with many gap junctions, specialized for rapid conduction. Bundle branches run down the septum to the apex, then Purkinje fibers sweep up the ventricular walls. This apex-to-base activation is essential because the arterial outflow tracts are at the top. A top-down contraction would push blood down into a dead end.

Backup pacemakers

Every conducting system cell can spontaneously depolarize (no stable resting potential), the SA node typically does it first and entrains all others. AV node intrinsic rate: 40 to 60 bpm. Purkinje fibers: 15 to 40 bpm. These are not failures of design; they are backup systems. The heart downgrades rather than stops. The autonomic nervous system modulates but does not initiate automaticity. Sympathetic fibers innervate the SA node, AV node, and ventricular myocardium. Parasympathetic fibers innervate predominantly the nodes. At rest, parasympathetic tone dominates, holding heart rate below the intrinsic SA node rate of ~100 bpm.

Causal Chain: AV Delay Is Adaptive

The AV bundle is the only structure that penetrates the insulating fibrous skeleton, so all atrium-to-ventricle conduction is funneled through the node-and-bundle route. Because the AV node conducts slowly (few gap junctions), a delay is imposed before the signal reaches the bundle → ventricles are stimulated only after the atria contract → atrial contribution to filling is preserved

Common Errors

- **Error:** Saying AV node 'blocks' the signal. It delays it, adaptively.
- **Error:** Thinking conducting cells contract to move blood. They are stimulus delivery cells, not force generators.
- **Error:** Assuming complete heart block means cardiac arrest. Ventricles run at Purkinje rate (~30 bpm), inefficient but viable.

Prediction Prompt

- **Predict:** If the fibrous skeleton had a second conduction gap allowing direct atrial-to-ventricular conduction, what would happen to ventricular filling and ejection effectiveness?

Section 4: Nodal Cell Electrophysiology

Instructor Narrative

***The move:** Center the section on the prepotential slope. Once heart rate is expressed as the steepness of that slope, each autonomic input and drug effect can be predicted from how it changes the slope rather than memorized.*

The prepotential: why these cells are spontaneous

Structured Outline / Causal Chain

Nodal Action Potential Phases

- Phase 4 (prepotential): funny current (I_f), Na^+ in > K^+ out → slow depolarization
- Late phase 4: T-type Ca^{2+} channels open → additional depolarizing push

Most excitable cells in the body have a stable resting membrane potential. They remain at that potential until a stimulus arrives. The heart's nodal cells do not. They have a prepotential, a slow drift toward threshold built into their ion channel biology. Every time they repolarize at the end of an action potential, they immediately begin drifting toward the next one. There is no true rest. That is what makes them pacemakers.

The key current driving this drift is funny current, named because the channel carrying it behaves unusually. Almost all voltage-gated channels open when the membrane depolarizes. Funny channels do the opposite: they open when the membrane hyperpolarizes (i.e., they're "hyperpolarization-activated"). The act of repolarizing at the end of each action potential is itself the trigger for the next prepotential. The cycle is self-sustaining.

Funny channels carry a mixed current, mostly sodium influx, partially offset by potassium efflux. Because sodium dominates, the net current is depolarizing, driving the membrane slowly toward threshold. Near the end of the prepotential, T-type calcium channels open and add a small additional push that carries the membrane to the threshold of the L-type calcium channels.

The action potential: calcium up, potassium down

When the prepotential reaches threshold, L-type calcium channels open and calcium floods in. This causes the upswing of the nodal action potential, and it is calcium, not sodium, that depolarizes these cells. This distinguishes nodal cells from every other excitable cell we study. Then voltage-gated potassium channels open, potassium leaves, the cell repolarizes, and the funny channels reopen to begin the next cycle.

Why heart rate is controlled here

Funny channels are HCN channels: hyperpolarization-activated, cyclic nucleotide-gated. The cyclic nucleotide part is the key. Sympathetic output increases cyclic AMP, opens more funny channels, steepens the prepotential slope, and reaches threshold faster, faster heart rate. Parasympathetic output decreases cyclic AMP, reduces funny channel opening, and also increases potassium efflux to deepen hyperpolarization, both slow the heart rate. This mechanistic

- Phase 0 (upswing): L-type Ca^{2+} channels open $\rightarrow$ Ca^{2+} in $\rightarrow$ depolarization (not sodium)
- Phase 3 (repolarization): voltage-gated K^+ channels open $\rightarrow$ K^+ out $\rightarrow$ repolarization
- Repolarization reopens funny channels $\rightarrow$ next prepotential begins immediately

HCN Channel: Key to Rate Control

- H = hyperpolarization-activated (opens as membrane becomes more negative)
- C = cyclic nucleotide-gated (opened by cAMP in addition to voltage)
- Sympathetic (NE at beta-1 receptors) $\rightarrow$ $\uparrow$ cAMP $\rightarrow$ more HCN channels open $\rightarrow$ steeper prepotential $\rightarrow$ faster rate
- Parasympathetic (ACh at muscarinic receptors) $\rightarrow$ $\downarrow$ cAMP + $\uparrow$ K^+ efflux $\rightarrow$ flatter prepotential + deeper hyperpolarization $\rightarrow$ slower rate

Three Mechanisms for Heart Rate Change

- A: Alter prepotential slope (dominant mechanism, funny current)
- B: Alter depth of repolarization (parasympathetic K^+ effect $\rightarrow$ farther from threshold)
- C: Shift threshold of L-type Ca^{2+} channels (pharmacological, least common)

Causal Chain: Why Is SA Node the Pacemaker?

SA node: steepest prepotential slope $\rightarrow$ reaches threshold fastest $\rightarrow$ fires first $\rightarrow$ entrains all slower conducting system cells via gap junctions

Common Errors

- **Error:** Calling the prepotential a 'resting potential.' These cells are never at rest, the membrane potential is always changing.
- **Error:** Saying sodium drives the nodal action potential upswing. It is calcium (L-type channels). Sodium is not the upswing current here.

understanding explains why beta (adrenergic)-blockers slow the heart, why calcium channel blockers (like diltiazem) reduce both rate and contractility, and why ivabradine selectively slows heart rate by blocking only the funny channel.

- **Error:** Assuming AV node fires at the same rate as SA node. It is intrinsically slower (40-60 bpm) and is driven by SA node current.

Prediction Prompt

- **Predict:** If equal amounts of Na^+ and K^+ moved through funny channels, what would happen to the prepotential slope and heart rate?
- **Predict:** Diltiazem blocks L-type Ca^{2+} channels. Predict its effect on SA node firing rate and explain the mechanism.

Section 5: Cardiomyocyte Action Potential

Instructor Narrative

The move: Make the plateau the central concept: the depolarization before it establishes it, and the refractory period and repolarization after it are its consequences. The essential outcome is understanding why the prolonged plateau prevents twitch summation and tetanus.

A cell that depends on an external stimulus

Unlike nodal cells, cardiomyocytes have a genuine resting membrane potential, about negative 90 millivolts, and they stay there until depolarizing current arrives from an adjacent cell through gap junctions. These cells are excitable but not spontaneous. A cardiomyocyte with no input from the conducting system would remain completely silent. The rhythm is set by nodal cells and imposed on cardiomyocytes.

When current arrives from an adjacent cell it pushes the cardiomyocyte membrane to the threshold of its fast sodium channels. Those channels open rapidly, sodium floods in, and we get the sharp upswing characteristic of this action potential, familiar from skeletal muscle and neurons. But what happens next is unique to cardiac muscle.

Structured Outline / Causal Chain

Causal Chain: Cardiomyocyte Action Potential Phases

- Phase 4: stable RMP (~ -90 mV); requires external stimulus via gap junctions
- Phase 0: fast Na^+ channels open $\rightarrow$ rapid depolarization (upswing)
- Phase 1: brief K^+ leak $\rightarrow$ small notch
- Phase 2 (plateau): L-type Ca^{2+} in + slow K^+ out $\rightarrow$ balanced $\rightarrow \sim 0$ mV sustained
- Phase 2: Ca^{2+} influx $\rightarrow$ SR Ca^{2+} release $\rightarrow$ cytosolic Ca^{2+} rises and binds troponin $\rightarrow$ cross-bridges $\rightarrow$ tension rises here
- Phase 3: L-type Ca^{2+} channels close + fast K^+ channels open $\rightarrow$ rapid repolarization
- L-type Ca^{2+} channels close, ending Ca^{2+} influx $\rightarrow$ SERCA returns Ca^{2+} to the SR $\rightarrow$ cytosolic Ca^{2+} falls $\rightarrow$ tension falls

Plateau Function 1: Prevents Wave Summation

Plateau extends AP $\sim 100\times$ longer than skeletal muscle
AP $\rightarrow$ absolute refractory period spans plateau $\rightarrow$ tension

The plateau: the most important phase in cardiac electrophysiology

After the initial spike, the cardiomyocyte does not rapidly repolarize. Instead, it maintains depolarization for 200 to 300 milliseconds, the plateau. Two opposing currents are approximately balanced: calcium entering through L-type channels and potassium leaving through slow outward rectifying channels. These currents nearly cancel, holding the membrane potential near zero.

The calcium influx during the plateau is not incidental. It triggers calcium-induced calcium release from the sarcoplasmic reticulum, raising cytoplasmic calcium to drive cross-bridge formation and tension. The mechanical event, the heartbeat, occurs during the plateau. By the time the cell repolarizes, the contraction has already begun and is nearly complete.

Why the plateau defines cardiac muscle function

The plateau does two essential things. First, it extends the action potential so that tension rises and falls within the absolute refractory period. A cardiomyocyte cannot receive a second stimulus while generating its first, the channels responsible for depolarization are inactivated throughout the plateau. This prevents wave summation and tetanus. In skeletal muscle, summation is essential, it builds the sustained tension needed for most movements. In cardiac muscle it would be catastrophic: a tetanized heart cannot relax between beats, cannot refill, and cardiac output goes to zero. Every heartbeat is a single whole muscle twitch.

Second, the long refractory period protects against reentry arrhythmia. When a depolarization wave travels through the ventricular syncytium and circuits back to its origin, those cells are still refractory. The wave runs into a wall and dies. Shorten the plateau, as occurs with ischemia-induced K_{ATP} channel opening, and those cells may be excitable again when the wave returns. The result is circus movement: self-sustaining loops of depolarization producing tachyarrhythmia or, when disorganized, fibrillation.

rises and falls within one refractory period → second stimulus impossible before twitch ends → summation and tetanus cannot occur

Plateau Function 2: Prevents Reentry Arrhythmia

Depolarization circles ventricular syncytium → returns to origin while those cells are still refractory (in plateau) → wave extinguished → normal rhythm maintained

K_{ATP} Channels, Adaptive and Maladaptive

- Normal: open when ATP low → shorten plateau → reduce Ca^{2+} → fewer crossbridges cycle and less Ca^{2+} must be pumped back → ATP use falls
- Maladaptive: excessive opening (ischemia, commotio cordis) → shortened refractory period → reentry loops possible → tachyarrhythmia; if loops disorganize, fibrillation

Common Errors

- **Error:** Thinking that during the plateau the cell is 'resting.' The plateau phase is actually when the cell is maximally active, contracting and consuming ATP.
- **Error:** Assuming cardiac and skeletal muscle twitches work the same way. In skeletal muscle twitches must summate. In cardiac muscle summation must not occur.
- **Error:** Treating atrial and ventricular fibrillation as equally dangerous. Atrial fibrillation reduces performance; ventricular fibrillation stops cardiac output.

Prediction Prompt

- **Predict:** If the absolute refractory period is 250 ms, what is the theoretical maximum heart rate? Why would summation at that rate be catastrophic?
- **Predict:** A drug shortens the cardiomyocyte plateau by 30%. What happens to reentry arrhythmia risk and why?

Instructor Narrative	Structured Outline / Causal Chain
<i>The move: Start from the dipole principle and have students derive each wave rather than memorize the tracing. A derived waveform can be re-predicted when a variable changes; a memorized one cannot.</i> Start with the principle, not the waveform Students often try to memorize the ECG. That is exactly the wrong approach because a memorized waveform cannot be adjusted; change one variable and recall alone is insufficient. The right approach is to understand why the ECG exists at all, then every wave follows logically. The ECG is an extracellular recording. We are not measuring inside any individual cell, that would require a microelectrode inside the cell. Instead, we are comparing electrical charge densities in the interstitial fluid at two body surface locations. Body fluids are excellent conductors, so cardiac electrical events propagate outward and can be detected at the limbs or chest wall. A wave appears on the ECG only when a dipole exists, a separation of charge between two regions. That happens when some cells are depolarized and others are not. Depolarized cells have lost their outside-positive charge; resting cells retain it. When all cells in a chamber are in the same state, all resting or all depolarized, there is no charge difference and the trace is isoelectric. Isoelectric does not mean inactive. Following the waves The SA node fires. Atrial cells depolarize sequentially, some are depolarized, some are not, a dipole exists across the atria. This generates the P wave. When all atrial cells have depolarized, the trace goes isoelectric even though the atria are now contracting. The PR segment is electrically silent not because nothing is happening, but because all atrial cells are in the same depolarized state. Then atrial cells repolarize and ventricular cells begin depolarizing simultaneously. Ventricular depolarization dominates, ventricular mass is roughly ten times atrial mass, generating the large QRS complex. The ST segment is isoelectric with all ventricular cells depolarized and	Principle: When Does an ECG Deflection (Wave) Appear? - Any deflection from the isoelectric line → dipole present → some cells depolarized, some at rest - Isoelectric → no dipole → all cells same electrical state (all resting or all depolarized) - Critical: isoelectric does not mean the heart is mechanically inactive ECG Wave Sequence - P wave: atrial depolarization (partial = dipole = wave) - PR segment (isoelectric): all atrial cells depolarized → atria contracting - QRS: ventricular depolarization + buried atrial repolarization - ST segment (isoelectric): all ventricular cells depolarized → ventricles contracting - T wave: ventricular repolarization and ventricles relaxing - TP segment (isoelectric): all chambers repolarized → no contractions Why QRS Amplitude > P Wave Amplitude - Ventricular mass ~10x atrial mass → larger dipole current → larger deflection T Wave Direction - Inner cells depolarize first but have longest APs → repolarize last - Repolarization travels outer-to-inner (opposite of depolarization) - a reversed charge change traveling a reversed path → the two reversals cancel → dipole points same direction as during depolarization → upward T wave - T wave inversion = altered regional AP duration → suggests ischemia or disease

contracting. Then asynchronous ventricular repolarization generates the T wave.

The T wave direction, a teaching moment

Students expect the T wave to deflect opposite to the QRS because it is a repolarization event. It does not. Action potential duration is not uniform across the ventricular wall, innermost cells depolarize first but have the longest action potentials and repolarize last. Repolarization therefore travels in the opposite direction from depolarization, and the resulting dipole points the same direction as during depolarization, producing an upward deflection. T wave inversion indicates that this normal spatial heterogeneity of action potential duration has changed, suggesting ischemia or disease.

Causal Chain: PR Segment Is Isoelectric but Atria Contracting

All atrial cells fully depolarized, so there is no charge difference between regions and no dipole → no ECG wave. Meanwhile, Ca^{2+} influx during the plateau → SR Ca^{2+} release → cytosolic Ca^{2+} rises and binds troponin → crossbridges → atrial contraction occurring

Common Errors

- **Error:** Thinking ECG measures action potentials directly. It measures extracellular charge differences, population readout, not intracellular recording.
- **Error:** Assuming isoelectric = no cardiac activity. Isoelectric = uniform electrical state. PR and ST segments are isoelectric during active contraction.
- **Error:** Expecting T wave to deflect downward. It deflects upward due to reversed repolarization direction across the ventricular wall.

Prediction Prompt

- **Predict:** Left ventricular hypertrophy increases ventricular mass. How does this change the QRS complex and why?
- **Predict:** Why do limb lead ECGs show more movement artifact during exercise than chest leads?

Section 7: The Cardiac Cycle and the Wiggers Diagram

Instructor Narrative

The move: Build the Wiggers diagram from the ECG and the action potentials, one pressure trace and one valve event at a time, using the pressure gradient across each valve as the cause of every opening and closing. Derived this way, each feature follows from the one before it.

Deriving the Wiggers from first principles

Structured Outline / Causal Chain

Causal Chain: Wiggers Correlations

- Atrial depolarization (P wave) → initiates atrial contraction (during the PR segment) → active ventricular filling
- PR segment: atria contracting, ventricles being actively filled

The Wiggers diagram is not a figure to memorize. It is a logical consequence of everything we cover about electrical and mechanical events. If you understand those events, you can derive the diagram. If you only memorize it, none of the underlying mechanism is retained.

We begin with the ECG, the electrical map. Everything mechanical follows from it. The P wave tells us the atria are depolarizing and about to contract. During the PR segment, atria contract, pushing blood through the open AV valves into the ventricles, active filling, adding about 25% to the 75% that arrived passively during the preceding TP segment.

The QRS complex tells us the ventricles are depolarizing. Ventricular pressure rises almost immediately. When it exceeds atrial pressure, the pressure gradient across the AV valves reverses and those valves snap shut, the first heart sound. But the semilunar valves have not yet opened. The ventricle is contracting against a closed chamber. Volume cannot change because fluids are incompressible. This is isovolumic contraction, pressure rising, volume fixed.

Ejection and the arterial trace

When ventricular pressure exceeds arterial pressure, the semilunar valves are forced open and ejection begins. Ventricular volume falls, arterial pressure peaks at systolic pressure. Then the ventricle relaxes, ventricular pressure falls below arterial pressure, blood briefly reverses, and the semilunar valves close, the second heart sound. Isovolumic relaxation follows, pressure falls, volume fixed, until ventricular pressure falls below atrial pressure, AV valves open, and passive filling begins again.

The arterial pressure trace is easily measured clinically. Diastolic pressure is the lowest arterial pressure, occurring just before semilunar valves open. Systolic pressure is the peak during ejection. Mean arterial pressure lies one-third of the way up from diastolic, not halfway, because more time is spent in diastole than systole.

Volumes and ejection fraction

The ventricle reaches its maximum volume, end diastolic volume, about 130 ml at rest, at the end of active filling, just before the QRS. It does not eject all of this. End systolic volume is about 50 ml. Stroke volume is 80 ml. Ejection fraction, stroke volume divided by EDV, is

- Ventricular depolarization (QRS) → initiates ventricular contraction → ventricular pressure exceeds atrial pressure → AV valves close (S1) → isovolumic contraction begins
- Ventricular contraction continues (ST segment) → ventricular pressure exceeds arterial pressure → semilunar valves open (isovolumic contraction ends) → ejection begins
- Ventricular repolarization (T wave) → ventricle begins to relax → ventricular pressure falls below arterial pressure → semilunar valves close (S2) → isovolumic relaxation begins
- All chambers relaxed (TP segment) → ventricular pressure falls below atrial pressure → AV valves open (isovolumic relaxation ends) → passive ventricular filling begins

Valve Event Logic (Pressure Gradient Drives All Valve Motion)

- AV valves open: atrial pressure > ventricular pressure
- AV valves close: ventricular pressure > atrial pressure → S1
- Semilunar valves open: ventricular pressure > arterial pressure → ejection
- Semilunar valves close: arterial pressure > ventricular pressure → S2

Phases of the Cardiac Cycle

- Passive filling (TP): ~75% of ventricular fill, no active contraction
- Active filling (PR): atrial contraction adds ~25%
- Isovolumic contraction: all valves closed; pressure rises, volume fixed
- Ejection: semilunar valves open; volume falls, arterial pressure peaks
- Isovolumic relaxation: all valves closed; pressure falls, volume fixed

Key Volumes (Resting)

- EDV: ~130 ml (maximum ventricular volume)

normally 55 to 65%. It is the number cardiologists care about most because it integrates the effects of preload, contractility, and afterload into a single performance metric.

- ESV: ~50 ml (minimum ventricular volume)
- $SV = EDV - ESV = \sim 80 \text{ ml}$
- Ejection fraction = $SV/EDV = \sim 62\%$ (normal: 55-65%)

Blood Pressure Landmarks

- Diastolic: lowest arterial pressure, just before semilunar valves open
- Systolic: peak arterial pressure during ejection
- Pulse pressure = systolic - diastolic
- MAP = diastolic + $1/3 \times$ pulse pressure (not 1/2, more time in diastole)

Common Errors

- **Error:** Thinking valves are actively opened/closed by muscle. Valves respond passively to pressure gradients only.
- **Error:** Assuming the ventricle empties completely. ESV is always > 0 ; this reserve allows both increases and decreases in SV.
- **Error:** Confusing 'atrial' and 'arterial', they sound similar but are different pressures in different spaces.

Prediction Prompt

- **Predict:** At HR = 40 bpm with normal ESV, how does EDV compare to HR = 70 bpm? What principle explains this, and what is the cardiac output consequence?
- **Predict:** The 'lub' coincides with which ECG wave? The 'dub' with which wave? Explain the pressure gradient event causing each.

Section 8: Heart Sounds (Overview)

Instructor note: This section can be covered briefly in lecture or assigned as reading. The essential teaching point is the causal link between valve events and turbulent flow, not memorization of clinical auscultation details.

Instructor Narrative

Structured Outline / Causal Chain

The move: Establish that turbulent flow produces sound and laminar flow is silent. From that single distinction, both the normal heart sounds and murmurs can be predicted.

Turbulent flow generates the sounds

Heart sounds are not the sound of valves mechanically slamming shut like a door. They are the sounds initiated by turbulent blood flow (the swirling that occurs when blood changes direction rapidly or encounters a sudden change in chamber geometry) as well as the vibration of heart structures this causes. Laminar flow is silent. Any time you hear an abnormal heart sound, something is creating turbulence where there should not be any.

S1 occurs when AV valves close at the onset of ventricular systole, as blood swirls against the closing cusps. S2 occurs when semilunar valves close at the end of systole, as blood briefly reverses in the aorta and pulmonary trunk. S3 occurs in children and some adults during rapid passive filling, the sudden inrush of blood into the relaxed ventricle creates turbulence. S4 is pathological, occurring during active atrial filling into a stiff, non-compliant ventricle. Abnormal sounds called murmurs arise from valve stenosis (narrowed passage) or regurgitation (backflow through incomplete valve closure).

Heart Sounds, Cause and Timing

- S1 (lub): AV valves close → onset of isovolumic contraction; coincides with QRS
- S2 (dub): semilunar valves close → onset of isovolumic relaxation; coincides with T wave
- S3: rapid passive filling; normal in children; may indicate volume overload in adults
- S4: active filling into stiff ventricle → always pathological; precedes S1

Murmurs

- Stenosis: narrowed valve → turbulence through restricted opening
- Regurgitation: incompetent valve → backflow through incomplete closure

Common Errors

- **Error:** Thinking S1/S2 are caused by mechanical valve impact. They are caused by turbulent blood flow and subsequent vibrations.
- **Error:** Assuming S3 is always pathological. It is normal in children and high-output states such as during pregnancy and in well-conditioned athletes.

Section 9: Cardiodynamics, Controlling Cardiac Output

Instructor Narrative

The move: Treat $CO = HR \times SV$ as the organizing equation, with preload, contractility, and afterload as three separate determinants of stroke volume. The central task is keeping the three distinct, since students tend to conflate them.

The equation that ties everything together

Cardiac output equals the product of heart rate and stroke volume. Both variables are continuously adjusted to match blood flow to

Structured Outline / Causal Chain

Cardiac Output Framework

- $CO = HR \times SV$
- $SV = EDV - ESV$
- Three determinants of SV: preload, contractility, afterload

Preload → Frank-Starling

metabolic demand. Stroke volume is determined by three factors: preload, contractility, and afterload. Getting these three concepts sorted is the key to understanding everything from exercise physiology to drug mechanisms to heart failure.

Preload: filling determines force

Preload is the stretch on ventricular cardiomyocytes just before contraction, set by how much blood fills the ventricle during diastole, the end diastolic volume. The Frank-Starling mechanism: greater filling means greater stretch, more cross-bridges, harder contraction, more blood ejected, and lower end systolic volume (enhanced sensitivity to Ca^{2+} also aids elevated tension). Venous return, driven by central venous pressure, is what determines filling. Blood volume, venomotor tone, and the muscular pump during exercise all increase central venous pressure and therefore preload.

A lower heart rate also increases filling time and therefore EDV. This is why elite endurance athletes with resting heart rates of 40 bpm do not have lower cardiac output, they compensate with dramatically larger stroke volumes because the heart is given more time to fill and has adapted to generate a larger Frank-Starling response.

Contractility: force at a given preload

Inotropic agents change how strongly the heart contracts at any given filling volume, they shift the Frank-Starling curve upward. All positive inotropes converge on a common final pathway: increasing intracellular calcium during the plateau. Norepinephrine and epinephrine act through beta-adrenergic receptors, cAMP, and protein kinase A to phosphorylate L-type calcium channels (more calcium in during plateau) and phospholamban (removes SERCA inhibition, faster calcium removal, faster relaxation, important for maintaining diastolic filling time at high heart rates). Thyroxine increases beta-receptor expression and fast myosin ATPase isoforms for sustained long-term enhancement.

Afterload: the resistance to ejection

Afterload is the resistance the ventricle must overcome to drive blood into the arterial circuit, primarily arterial blood pressure. Higher arterial pressure means the semilunar valves are more difficult to open, isovolumic contraction is prolonged, less time is available for ejection,

Venous return increases $\rightarrow$ EDV rises $\rightarrow$ sarcomere stretch increases $\rightarrow$ (two effects: greater thin/thick filament overlap and increased myofilament Ca^{2+} sensitivity) $\rightarrow$ more crossbridges engaged per beat $\rightarrow$ greater tension and stroke work $\rightarrow$ ventricle ejects a larger stroke volume from the larger starting volume $\rightarrow$ ESV essentially unchanged $\rightarrow$ SV rises ($\text{SV} = \text{EDV} - \text{ESV}$, with EDV up and ESV $\sim$ constant)

- Drivers of increased preload: $\uparrow$ blood volume, muscular pump (exercise), venoconstriction, $\downarrow$ HR (longer fill time)

Causal Chain: Contractility (Inotropy)

- Positive inotropes: NE, epinephrine, thyroxine
- Mechanism: $\uparrow$ cAMP $\rightarrow$ activates protein kinase A $\rightarrow$ phosphorylates L-type Ca^{2+} channels $\rightarrow \uparrow \text{Ca}^{2+}$ influx $\rightarrow$ more crossbridges at same EDV $\rightarrow \downarrow \text{ESV} \rightarrow \text{SV}$ rises
- Also: PKA phosphorylates phospholamban $\rightarrow$ removes SERCA inhibition $\rightarrow$ faster Ca^{2+} removal $\rightarrow$ faster relaxation $\rightarrow$ preserves filling time at high HR
- Net: upward shift of Frank-Starling curve

Afterload

$\uparrow$ arterial BP (hypertension) $\rightarrow$ semilunar valve harder to open $\rightarrow$ isovolumic contraction prolonged $\rightarrow$ less time for ejection $\rightarrow$ SV falls $\rightarrow$ pressure work rises while volume work falls $\rightarrow$ O_2 consumed per ml ejected rises $\rightarrow$ cardiac efficiency falls

Heart Rate Control

- Rate set at SA node, both ANS divisions active simultaneously
- Sympathetic (NE): $\uparrow$ cAMP $\rightarrow$ steeper prepotential $\rightarrow$ faster rate (+chronotropy)
- Parasympathetic (ACh): $\downarrow$ cAMP + $\uparrow$ K^+ efflux $\rightarrow$ shallower slope + deeper hyperpolarization $\rightarrow$ slower rate

and stroke volume falls. The heart does more pressure work and less volume work, it consumes more oxygen while moving less blood. Chronically elevated afterload drives left ventricular hypertrophy and eventually pathological remodeling and failure.

Heart rate control: the autonomic balance

Heart rate is set exclusively at the SA node by the balance between sympathetic and parasympathetic output, like driving with one foot on the gas and one on the brake, adjusting speed by changing the balance. At rest, parasympathetic tone dominates, holding heart rate below the intrinsic SA node rate of ~100 bpm. During exercise, sympathetic output rises and parasympathetic falls, steepening the prepotential slope. Key inputs are baroreceptors sensing arterial pressure, chemoreceptors sensing $O_2/CO_2/pH$, and atrial stretch receptors (Bainbridge reflex) during exercise. Contractility is altered separately at the ventricular myocardium by sympathetic innervation, there is minimal parasympathetic innervation of the ventricles.

- Bainbridge reflex: atrial stretch during exercise $\rightarrow \uparrow$ sympathetic $\rightarrow \uparrow$ HR
- Contractility: sympathetic only $\rightarrow$ ventricular beta-receptors (+inotropy)

Common Errors

- **Error:** Thinking low heart rate always means lower cardiac output. Athletes have low HR and normal CO because SV is proportionally larger.
- **Error:** Confusing preload and contractility. Preload changes EDV (stretch mechanism). Contractility changes force at a given EDV. Independent mechanisms.
- **Error:** Defining afterload as only blood pressure. Afterload = total resistance to ejection; BP is the dominant component, but vascular resistance contributes.
- **Error:** Thinking sympathetic stimulation only affects heart rate. It also increases contractility via ventricular beta-receptors.

Prediction Prompt

- **Predict:** A denervated heart (no ANS input) still increases CO during exercise. What mechanism allows this and why does EDV rise dramatically?
- **Predict:** Diltiazem blocks L-type Ca^{2+} channels. What happens to contractility? What happens to SA node firing rate? Are the mechanisms the same?
- **Predict:** A patient has hypertension and an ejection fraction of 45%. Explain mechanistically why high afterload reduces ejection fraction.

Section 10: Pressure-Volume Loops

The move: Teach the pressure-volume loop as the Wiggers diagram with time removed. Have students trace it counterclockwise and read the enclosed area as ventricular work before any clinical case is introduced.

A different view of the same cycle

The Wiggers diagram shows cardiac events across time. The pressure-volume loop shows the same events from the ventricle's perspective, with time removed, replaced by the relationship between pressure and volume. The loop is traversed counterclockwise through one complete cardiac cycle.

Start at the bottom left: minimum volume (ESV), low pressure, AV valve about to open. Move rightward as filling occurs, passive then active, reaching EDV at the right edge. Ventricles contract: AV valves close, pressure rises steeply while volume stays fixed, isovolumic contraction, the vertical right edge. When pressure exceeds aortic pressure, the semilunar valve opens and we move leftward across the top as blood ejects. Pressure peaks then falls. Semilunar valve closes, isovolumic relaxation, the vertical left edge. Pressure falls until AV valve opens again and filling restarts.

The width of the loop equals stroke volume. The height indicates peak systolic pressure. The area enclosed is proportional to ventricular work performed and therefore oxygen consumed. This is why the loop is clinically powerful: you can assess efficiency, not just output.

Increased preload: the Frank-Starling loop

When preload increases, more filling, larger EDV, the loop shifts rightward. Frank-Starling ensures a stronger contraction, higher peak pressure, and lower ESV. The loop gets wider. Area increases proportionally, more work but more output. The work-to-output ratio stays favorable. This is the adaptive response to exercise, increased blood volume, or slow heart rate.

Increased afterload: the hypertensive loop

Higher arterial pressure means the semilunar valve is more difficult to open. The loop becomes taller and narrower. The ventricle spends more energy on pressure work and less on volume work. Stroke volume falls. The loop area may actually increase even though less blood is moved, more oxygen consumed per milliliter ejected. This is

Loop Traversal (Counterclockwise)

- Bottom left: ESV, AV valve opens
- Bottom (rightward): passive then active filling → EDV
- Right vertical edge: isovolumic contraction, pressure rises, volume fixed
- Top (leftward): ejection, volume falls, pressure peaks
- Left vertical edge: isovolumic relaxation, pressure falls, volume fixed
- Bottom left: AV valve opens → next cycle

What the Loop Tells You

- Width = stroke volume (EDV - ESV)
- Height = peak systolic pressure
- Right edge = diastolic pressure (semilunar opens here)
- Area = ventricular work = O₂ consumed

Increased Preload

- Loop shifts rightward (larger EDV)
- Frank-Starling → greater tension → ventricle ejects more from the larger starting volume; ESV essentially unchanged (ESPVR fixed by contractility)
- Wider loop = larger SV (SV = EDV - ESV, widening because EDV rose, not because ESV fell)
- Area increases proportionally: more stroke work and more output (efficiency maintained)

Increased Afterload (Hypertension)

- Isovolumic contraction must reach higher pressure before semilunar opens
- Loop becomes taller and narrower
- Less ejection time → SV falls
- Area may increase despite reduced SV → more O₂ consumed per ml ejected
- Cardiac efficiency falls: pressure work up, volume work down

Common Errors

the definition of reduced cardiac efficiency. You want your loop short and wide, not tall and narrow. Chronically, this drives hypertrophy and eventually failure, particularly dangerous in already weakened hearts where the added pressure demands work the ventricle cannot perform.

- **Error:** Thinking larger loop area is always better. In hypertension, larger area with smaller SV means the heart works harder for less output.
- **Error:** Traversing the loop clockwise. Always follow it counterclockwise.
- **Error:** Confusing left and right ventricular loops. Both have the same SV; the left loop is much taller (higher pressures) with a much larger area.

Prediction Prompt

- **Predict:** Compare O_2 consumption of left and right ventricles using loop area. What does this predict about distribution of coronary blood flow?
- **Predict:** A hypertensive patient maintains normal SV despite increased afterload. What must have compensated and how?

Section 11: Blood Pressure, Framework and Factors (Transition to Vascular)

Instructor note: This section bridges cardiac and vascular content. Blood pressure is a direct consequence of cardiac output; vascular determinants (resistance, vessel tone) are developed in Sections 12 through 18.

Instructor Narrative	Structured Outline / Causal Chain
The move: Reduce blood pressure control to $BP = CO \times TPR$ together with the arterial reservoir model, then trace every intervention as a change in one of those terms. Blood pressure as a balance Solving Poiseuille's law for the whole systemic circuit gives us the essential equation: flow for the entire circuit is cardiac output, the driving pressure gradient is essentially mean arterial pressure because venous pressure is near zero, and total resistance is total peripheral resistance, so rearranging $Q = \Delta P/R$ yields blood pressure equals cardiac output multiplied by total peripheral resistance. There are two possible controls only: change how much the heart outputs, or	Core Equation • $BP = CO \times \text{Total Peripheral Resistance (TPR)}$ • $BP = HR \times SV \times TPR$ Arterial Reservoir Model CO (input) greater than arteriolar runoff (output) $\rightarrow$ arterial volume rises $\rightarrow$ BP rises Runoff greater than CO $\rightarrow$ arterial volume falls $\rightarrow$ BP falls Determinants of Central Venous Pressure • Blood volume (long-term: renal Na^+/H_2O regulation) • Ven constriction (sympathetic $\rightarrow$ compresses venous reservoir)

change how much resistance the vessels offer. Both are in continuous use.

Think of the arterial circuit as a pressurized reservoir. Input is cardiac output. Output is runoff, blood draining through arterioles into capillaries, governed by arteriolar resistance. If input exceeds runoff, volume and pressure rise. If runoff exceeds input, pressure falls. You can watch this during a single cardiac cycle: pressure rises during ejection, falls during diastole as runoff drains the reservoir without new input.

Central venous pressure is the upstream driver of venous return, and is itself determined by blood volume, venomotor tone, and the muscular pump during exercise. All three feed into cardiac output through the Frank-Starling mechanism. Blood volume is the longest-acting lever, regulated over hours to days by renal handling of sodium and water, which is why the kidneys are central to long-term blood pressure control.

The key principle: blood pressure is maintained by continuous, simultaneous adjustment of cardiac output and vascular resistance, integrated by the autonomic nervous system receiving input from baroreceptors and chemoreceptors. Understanding why any intervention raises or lowers blood pressure is simply a matter of tracing its effect through this framework.

- Muscular pump (exercise → squeezes veins → ↑ venous return)
- All three → ↑ CVP → ↑ venous return → ↑ EDV → Frank-Starling mechanism → ↑ SV → ↑ CO → ↑ BP

Causal Chain: Autonomic Inputs

- Baroreceptors (aortic arch, carotid sinus): sense wall stretch = pressure
- Chemoreceptors: sense O₂, CO₂, pH
- High BP → ↑ arterial wall stretch → ↑ baroreceptor firing → baroreceptor reflex → ↓ sympathetic, ↑ parasympathetic → ↓ HR, ↓ CO, ↓ TPR (vasodilation) → ↓ BP
- Low O₂/High CO₂ → ↑ chemoreceptor firing → ↑ sympathetic → ↑ HR, ↑ contractility → ↑ CO → ↑ BP

Common Errors

- **Error:** Thinking MAP is halfway between systolic and diastolic. It is 1/3 of the way up from diastolic because more time is spent in diastole.
- **Error:** Assuming blood pressure is controlled only by the heart. TPR is equally important and is the dominant long-term lever.

Prediction Prompt

- **Predict:** A patient loses 1 liter of blood (hemorrhage). Trace from baroreceptor detection through the cardiovascular response that attempts to restore blood pressure.
- **Predict:** An athlete has HR = 42 bpm and normal resting BP. What must be true about their SV and what mechanism explains it?

Section 12: Poiseuille's Law, Pressure, Flow, and Resistance

The move: State the causal sequence first, the heart pressurizes blood, pressure drives flow, and resistance opposes it, then establish that resistance varies with the fourth power of vessel radius as the central quantitative point.

The heart generates pressure. Pressure drives flow. Resistance opposes it.

That single sequence organizes the whole of cardiovascular function; everything else elaborates it. The heart is a pressure pump: it does not push blood directly, it pressurizes it, and pressure gradients do the pushing. Poiseuille's law is the equation that captures this: flow equals the pressure gradient divided by the resistance. Three variables. Everything that follows in hemodynamics is a consequence of manipulating one or more of them.

The pressure gradient, delta (Δ) P, is the difference in pressure between two points along a vessel. Flow always moves from high to low pressure. As blood travels through the vascular circuit, friction with vessel walls dissipates energy and pressure falls continuously. This is not a design flaw, it is the thermodynamic cost of moving fluid through pipes. The key consequence is that P1 always exceeds P2 in any flowing system, and the ΔP that drives flow across the entire systemic circuit is essentially mean arterial pressure, since venous pressure returning to the right heart is near zero.

The practical point is often left implicit: we do not control blood flow to individual tissues by adjusting blood pressure. Blood pressure would have to double to double flow to a muscle, and that would cause a stroke. Instead, we adjust flow tissue by tissue by locally adjusting resistance, constricting or dilating the vessels that supply each capillary bed. The pressure stays approximately constant; the resistance is what moves.

Laminar flow and the parabolic profile

Poiseuille's law describes laminar flow, fluid moving in concentric layers at different speeds. The slowest layer is right at the vessel wall, where friction is greatest. The fastest layer is in the center, farthest from the wall. The resulting velocity profile is parabolic. Laminar flow makes no sound. This matters clinically: turbulent flow *does* make

Poiseuille's Law

- $Q = \Delta P / R$
- Q = flow (cardiac output for whole circuit)
- ΔP = pressure gradient ($P_1 - P_2$; blood pressure for whole circuit ~ 100 mmHg)
- R = resistance (total peripheral resistance for whole circuit)
- Flow and ΔP : directly proportional
- Flow and R : inversely proportional

Resistance Equation

- $R = 8L\eta / \pi r^4$
- L (length): directly proportional, fixed anatomically
- η (viscosity): directly proportional, largely determined by hematocrit; slow to change
- r (radius): inversely proportional to the fourth power, dominant variable
- 50% reduction in radius = 16-fold increase in resistance
- Radius is under dynamic smooth muscle control, the physiologically relevant lever

Causal Chain: How Exercise Increases Muscle Blood Flow Without Dangerous Hypertension

Skeletal muscle metabolism rises $\rightarrow$ O_2 falls, CO_2 and metabolites rise in interstitium $\rightarrow$ local arterioles dilate, increasing radius $\rightarrow$ resistance falls steeply (fourth power of radius) $\rightarrow$ flow to active muscle rises dramatically; meanwhile arterioles in inactive beds constrict $\rightarrow$ net total peripheral resistance falls substantially $\rightarrow$ (at the same time) cardiac output rises several-fold ($\uparrow HR$, $\uparrow SV$) $\rightarrow$ since $MAP = CO \times TPR$, the large rise in CO and the large fall in TPR nearly offset $\rightarrow$ mean arterial pressure rises only modestly rather than dangerously

Laminar vs Turbulent Flow

- Laminar: concentric layers, parabolic profile, fastest in center, silent

sound, which is why a stethoscope can detect abnormal flow through narrowed valves or partially occluded arteries.

The resistance equation: what matters most

Resistance equals the product of η , vessel length, and blood viscosity (η) divided by the product of π and vessel radius to the fourth power. Resistance is directly proportional to length and viscosity, longer pipe, more friction; thicker fluid, more resistance. Resistance is inversely proportional to radius, but the exponent is what makes radius the dominant factor. Raising radius to the fourth power means a 50% reduction in radius increases resistance 16-fold. Not twice. Not four times. *Sixteen*. And unlike length, which is anatomically fixed, and viscosity, which changes slowly with hematocrit, radius can change dramatically in seconds through smooth muscle contraction and relaxation. This is why radius is the most physiologically relevant variable, it is the one that's routinely employed to regulate flow.

During exercise, cardiac output can increase four to five-fold yet blood pressure rises only modestly. For Poiseuille's law to balance, total resistance must fall by a similar factor. That fall is achieved by dilating the arterioles supplying active skeletal muscle, driven by the local metabolic environment, while simultaneously constricting arterioles supplying non-essential tissues like the GI tract. Blood flow is redistributed, not simply increased everywhere.

Turbulence adds resistance

Turbulent flow disrupts the orderly laminar blood layers and dramatically increases resistance, more than Poiseuille's equation predicts for laminar flow alone. Turbulence occurs when velocity is high, vessels are large, viscosity is low, or geometry, such as at bifurcations or around atherosclerotic plaques, is irregular. Blood flow through the aorta is normally turbulent during peak ejection, but this vessel's enormous radius keeps overall resistance low. At sites of atherosclerotic narrowing, turbulence adds resistance on top of the reduced radius effect, a compounding problem that explains why even partial coronary or peripheral artery occlusion is so physiologically limiting.

- Turbulent: layers disrupted, mixing, noise (bruits, Korotkoff sounds), increased resistance
- Turbulence occurs: high velocity, large vessels, low viscosity, irregular geometry, bifurcations, plaques
- Aorta: normally turbulent during peak ejection, large radius compensates

Series and Parallel Resistance

- Series: resistances add ($R_t = R_1 + R_2 + R_3 \dots$)
- Parallel: total resistance falls as pathways added ($R_t = R_{\text{each}} / \text{number of vessels}$)
- Capillary beds: tiny individual resistance but enormous parallel number $\rightarrow$ low total resistance

Common Errors

- **Error:** Thinking blood pressure is how we regulate local blood flow. Blood pressure is the constant driving force; resistance is what we adjust for local control.
- **Error:** Treating radius to the fourth as equivalent to other factors affecting resistance. The fourth power relationship makes radius changes massively more impactful than changes in L or viscosity.
- **Error:** Assuming turbulent flow only occurs in diseased vessels. The aorta has normal turbulence as do some other arteries; bifurcations are common sites of turbulence in healthy vessels.

Prediction Prompt

- **Predict:** Cardiac output increases 5-fold during maximal exercise. Blood pressure rises only slightly. What must have happened to total peripheral resistance and where specifically did this change occur?
- **Predict:** An atherosclerotic plaque reduces coronary artery radius by 30%. By what factor does resistance increase and what is the flow consequence at resting blood pressure?

Section 13: Blood Vessel Structure and Function

Instructor Narrative

***The move:** Have students derive each vessel's function from its wall composition rather than memorizing a table. Each wall layer is present in proportion to the mechanical demand placed on that vessel type.*

Structure follows function, read the wall

Every blood vessel type has a wall composition that directly reflects its functional role in the circuit. You do not need to memorize a table if you understand the functional logic. Large arteries must absorb the pressure surge of each ventricular ejection and maintain downstream flow between beats, that requires elastic recoil, which is why the aorta and its major branches are rich in elastin. Muscular arteries and arterioles must redirect flow between tissues, that requires thick smooth muscle layers capable of dramatic constriction and dilation. Capillaries must exchange, that requires a single endothelial cell layer with essentially no structural barrier between blood and interstitium. Veins must accommodate variable return flow without pressure rising too high, that requires compliance, which is the inverse of elasticity.

All vessels share three wall layers: the tunica intima, which is the endothelial lining and its basement membrane; the tunica media, which is smooth muscle and elastic tissue in varying proportions; and the tunica externa, which is collagen providing structural strength. Capillaries are the exception, they are the tunica intima alone, just endothelium and basement membrane.

Elastic arteries and the Windkessel effect

The heart is an intermittent pump. It ejects blood during systole and not during diastole. If the arteries were rigid pipes, flow to the tissues would spike during systole and stop entirely during diastole. That is not what happens. The elastic walls of the large arteries stretch during ejection, storing volume and energy, and then recoil during diastole, pushing that stored blood forward. This converts pulsatile ejection into continuous flow. It also prevents systolic pressure from reaching dangerous peaks and keeps diastolic pressure from falling to zero. This is the Windkessel effect, named for the pressurized air chamber

Structured Outline / Causal Chain

Vessel Wall Layers

- Tunica intima: endothelium + basement membrane (all vessels)
- Tunica media: smooth muscle + elastic tissue (variable proportions)
- Tunica externa: collagen for structural strength
- Capillaries: tunica intima only, no media, no externa

Vessel Type Functions

- Elastic arteries (aorta, large branches): Windkessel effect, dampen pulsatile flow, maintain diastolic pressure
- Muscular arteries: broad-scale flow distribution to organs and limbs
- Arterioles: local flow control, the resistance vessels, most smooth muscle relative to lumen
- Capillaries: exchange, thin wall, large surface area, slow velocity
- Venules: collect capillary outflow, some exchange capacity
- Veins: high compliance reservoir, 66% of blood volume at rest

Causal Chain: Windkessel Effect

Property: large arteries are elastic (stretch and recoil).

Systolic branch: ventricular ejection → arteries stretch, storing part of the volume → systolic pressure peak dampened.

Diastolic branch: ejection stops → arteries recoil → stored volume driven forward → diastolic pressure maintained.

Combined result: pulsatile ejection → continuous flow at the capillaries

in old fire engines that smoothed out the intermittent hand-pump output into a continuous stream.

Arterial stiffening with age or atherosclerosis counteracts this effect. Vessel walls cannot stretch and recoil, so systolic pressure spikes higher and diastolic pressure falls lower. Pulse pressure widens. This is why isolated systolic hypertension is so common in the elderly and why widened pulse pressure is a marker of vascular disease.

Arterioles: the resistance vessels

By the time blood reaches the arterioles, the pulsatility generated by cardiac ejection has been largely damped by the elastic arteries. Arterioles are where the remaining pressure drops most steeply and where local flow control actually happens. Their walls are disproportionately muscular relative to their tiny lumens. When smooth muscle in the arteriolar wall contracts, radius falls, resistance rises to the fourth power of that radius change, and flow to the downstream capillary bed falls. When it relaxes, the opposite occurs. These are the spigots of the circulatory system.

Veins: compliance and the venous reservoir

Veins are thin-walled and highly compliant. They distend easily with increased volume and do not recoil. At rest, veins contain about 66% of total blood volume, they act essentially as a reservoir. During exercise, when cardiac output jumps from 5 to 20 or 25 liters per minute, the venous side must accommodate dramatically increased return flow without pressure rising much. Compliance allows this. If veins were as stiff as arteries, the pressure rises during exercise would disrupt capillary filtration-reabsorption balance and produce edema in working muscles. Venous valves prevent backflow in the limbs where gravitational forces would otherwise cause pooling.

Arterial Stiffening Consequences

- Elastin replaced by collagen with age/atherosclerosis
- Cannot store volume during systole or recoil during diastole
- Systolic pressure spikes higher, diastolic pressure falls lower
- Pulse pressure widens, clinical marker of vascular disease

Venous Compliance

- Compliance = $\Delta\text{Volume} / \Delta\text{Pressure}$ (inverse of elastance)
- High compliance: large volume change with small pressure change
- Essential: accommodates exercise-driven increases in venous return without raising capillary back-pressure
- Venous valves: prevent backflow in limbs against gravity

Pressure Profile Across the Circuit

- Aorta: highest, pulsatile (~120/80 mmHg systemic)
- Muscular arteries: high, losing pulsatility with distance
- Arterioles: steepest pressure drop, highest resistance zone
- Capillaries: low (~25-35 mmHg inflow, ~10 mmHg outflow), non-pulsatile
- Veins: very low (~5-10 mmHg), near zero at right atrium

Common Errors

- **Error:** Thinking elastin makes arteries stiff. Elastin gives them elastance, the ability to stretch and recoil. Collagen is what makes them stiff.
- **Error:** Assuming veins are just passive return tubes. They are the major blood volume reservoir and actively participate in venous return regulation via venoconstriction (reducing their compliance).

- **Error:** Treating arterioles as too small to matter. They generate more total resistance than any other vessel type and are the primary site of local flow control.

Prediction Prompt

- **Predict:** Atherosclerosis reduces arterial elastance. Predict what happens to systolic pressure, diastolic pressure, pulse pressure, and the Windkessel effect. What is the clinical consequence for the heart?
- **Predict:** During exercise, venous return increases dramatically. Why does venous pressure not rise proportionally, and why does this matter for capillary exchange?

Section 14: Capillary Varieties and Precapillary Sphincters

Instructor Narrative	Structured Outline / Causal Chain
The move: Connect each capillary type to the exchange requirement of the tissue where it is found. Present continuous, fenestrated, and sinusoidal capillaries in terms of the permeability each tissue requires rather than as a list to memorize. Not all capillaries are created equal Capillary walls vary quite dramatically in structure and function, matched to local exchange requirements, and they exhibit a spectrum of permeability tuned to the exchange requirements of each perfused tissue. All capillaries are a single layer of endothelial cells on a basement membrane. The differences among them are in the size and number of gaps between cells and in the continuity of the basement membrane itself. Continuous capillaries are found in most tissues, brain, muscle, lung. Their endothelial cells are joined by tight junctions with only small paracellular clefts. Small hydrophilic solutes and water can pass through these clefts. The brain is the sealed extreme: there, tight junctions close these clefts, forming the blood-brain barrier. Lipophilic solutes, oxygen, CO₂, steroid hormones, diffuse directly through the	Capillary Varieties • Continuous: small paracellular clefts; water and small solutes pass; proteins reflected ($\sigma \approx 1$); location: muscle, brain, lung • Fenestrated: larger pores + diaphragm; high water/small solute flux; proteins still mostly reflected; location: kidney, intestine, endocrine glands • Sinusoidal (discontinuous): gaps in endothelium and basement membrane; proteins and cells pass freely ($\sigma = 0$); location: liver, bone marrow, spleen Reflection Coefficient (σ) • $\sigma = 1$: protein completely reflected (continuous capillary), oncotic pressure maintained • $\sigma = 0$: protein freely permeable (sinusoid), no oncotic gradient possible • σ between 0 and 1: partial reflection (fenestrated), intermediate oncotic effect

lipid bilayer and are not limited by pore size at all. Large solutes like plasma proteins are reflected, meaning they cannot get through and stay trapped in the vascular space. That trapping is not incidental; it develops oncotic pressure, which drives reabsorption of filtered fluid back into the capillary.

Fenestrated capillaries have larger pores, often spanned by protein diaphragm meshes, allowing much higher flux of water and small solutes while still mostly excluding proteins. They are found where large volumes need to move quickly, kidney glomeruli, intestinal mucosa, endocrine glands. The glomerular capillary is the extreme example: its filtration coefficient is hundreds of times higher than a muscle capillary, enabling the 150 to 200 liters of filtrate produced per day.

Sinusoidal capillaries have gaping holes in both the endothelial layer and the basement membrane. Large solutes and even whole cells pass freely. The liver has sinusoids because plasma proteins are synthesized in hepatocytes and must readily enter the bloodstream, that requires a capillary with no barrier to macromolecules. Bone marrow also has capillaries of this kind because red and white blood cells are produced there and must enter circulation without squeezing through tight junctions.

Precapillary sphincters: gating flow into the bed

Not all capillary beds are perfused simultaneously. There is not enough blood volume to fill every capillary in the body at once. Rings of smooth muscle called precapillary sphincters sit at the entrances to capillary beds (best characterized in the mesenteric circulation), and they open and close in response to the local metabolic environment. When cells in a tissue are hypoxic, oxygen low, CO₂ high, metabolites accumulating, these signals dilate both the supplying arteriole and the precapillary sphincters, opening the capillary bed to maximum perfusion. When tissue metabolic demand is momentarily met, the sphincters constrict, perfusion falls to a minimum or zero, and blood is shunted through the thoroughfare channel that bypasses the capillary network.

This creates a dynamic, oscillating perfusion pattern called vasomotion. Individual capillary beds cycle between perfused and unperfused states over the course of minutes. The result is that at any

Why Each Capillary Type Exists

- Continuous: most tissues, selective small solute exchange; preserve protein oncotic gradient
- Fenestrated (kidney): 150-200 L/day of filtrate requires extremely high K_f
- Fenestrated (intestine): massive post-prandial nutrient uptake
- Sinusoidal (liver): plasma proteins made in hepatocytes must enter blood
- Sinusoidal (bone marrow): RBCs and WBCs made outside bloodstream must enter circulation

Causal Chain: Precapillary Sphincters and Vasomotion

Tissue hypoxic: O₂ ↓, CO₂ ↑, metabolites ↑ → arteriole and sphincters dilate → capillary bed opens → exchange meets metabolic need → O₂ restored, metabolites cleared → dilator signals withdrawn, basal tone resumes → sphincters constrict → bed closes → cycle repeats

- At rest: <10% of total capillary volume perfused at any instant
- Thoroughfare channel: allows arteriole-to-venule flow while capillaries are unperfused
- Vasomotion: oscillating perfusion/non-perfusion cycle, matched to local metabolic demand

Common Errors

- **Error:** Thinking all capillaries are equally permeable. Capillary type is precisely matched to tissue function, the kidney could not work with continuous capillaries. Neither could the liver.
- **Error:** Assuming capillaries are all perfused all the time. At rest, the vast majority are not. This is normal and adaptive, not a failure of perfusion.
- **Error:** Confusing diffusion limitation and flow limitation. Small solute exchange is flow-limited (equilibrium reached quickly, more flow = more delivery). Large solute exchange is diffusion-limited (permeability is the bottleneck).

given instant, only about 10% or less of the body's total capillary volume is perfused. This is not a system operating at a fraction of capacity, it is a system precisely matching blood flow to current metabolic demand, capable of rapidly opening capillary beds when demand rises and just as rapidly closing them when demand falls.

Prediction Prompt

- **Predict:** *Diabetes mellitus causes microvascular rarefaction (loss of capillaries). Predict the consequences for diffusional exchange as capillary surface area falls and diffusion distance rises. What downstream tissue effects would result?*
- **Predict:** *A patient has sinusoidal capillaries replaced by continuous capillaries in the liver due to fibrosis. What happens to plasma protein entry into blood and to oncotic pressure systemically?*

Section 15: Pressure, Flow, and Velocity Across the Circuit

Instructor Narrative

The move: *Overlay the pressure, velocity, and cross-sectional area graphs and have students justify each curve from first principles. The inverse relationship between velocity and total cross-sectional area is the least intuitive, so concentrate on it.*

Three graphs that summarize the hemodynamic sequence

If you overlay three graphs, blood pressure, flow rate, and flow velocity, across the anatomical sequence from aorta to vena cava, you can read the entire logic of the vascular circuit. Each graph has a different shape, and understanding why each looks the way it does is much more useful than just trying to memorize their differences.

Pressure starts highest at the aorta and falls continuously with distance from the heart due to frictional energy loss. It is pulsatile in the large arteries because of the intermittent nature of cardiac ejection, but that pulsatility is progressively damped by arterial elasticity. The steepest pressure drop occurs at the arterioles, the resistance vessels, which is both expected from their high resistance and adaptive for the capillaries downstream. Capillaries cannot tolerate high transmural pressures. Their walls are just a single cell layer; excessive pressure would rupture them or drive excessive filtration. The arteriolar pressure drop is protection. By the time blood

Structured Outline / Causal Chain

Pressure Across the Circuit

- Highest in aorta (~100 mmHg mean systemic)
- Pulsatile in large arteries, damped progressively by arterial elastance
- Steepest fall at arterioles, highest resistance, most energy dissipated here
- Capillary inflow: ~25-35 mmHg; capillary outflow: ~10-15 mmHg
- Veins: very low (~5 mmHg); vena cava: near zero
- Arteriolar pressure drop is protective, prevents capillary rupture

Flow Rate Across the Circuit

- Mean flow must be equal across all segments
- Pulsatile in large arteries (systole/diastole); continuous at capillaries
- Cardiac output = flow rate through any segment of the circuit

Velocity Across the Circuit

reaches the capillaries, pressure has fallen to about 25 to 35 mmHg at the inlet and continues to decrease along the capillary length.

Flow rate, the total volume moving through any given vascular segment per unit time, must normally match the total moving through any other segment in the system in the same interval. For example, if more blood flowed through arteries than veins per minute, blood would be pooling somewhere between them with detrimental consequences. Arterial flow may vary with each heartbeat due to the pulsatile ejection, but the mean values must match in these vessels, as in other vascular sections, from aorta to vena cava.

Velocity, how fast individual fluid elements are moving, is the most counterintuitive of the three because it is inversely proportional to total cross-sectional area. The aorta is a single large vessel with a relatively small cross-sectional area, so velocity there is high, about 40 cm per second at rest. The capillaries collectively have an enormous total cross-sectional area because there are billions of them. Velocity there falls to less than 1 mm per second. This low velocity is not a problem; it is what allows adequate transcapillary diffusion time for nutrients and wastes. Blood traverses a capillary in less than a second, yet gas and solute equilibration is essentially complete in that time precisely because velocity is so slow. Then blood coalesces back into veins and the vena cava, cross-sectional area falls, and velocity rises again for the return trip to the heart.

- Velocity = flow / total cross-sectional area ($v \propto 1/A$)
- Aorta: small CSA → high velocity (~40 cm/s at rest)
- Arteries: branching increases total CSA → velocity falls
- Capillaries: enormous total CSA (billions of capillaries) → very low velocity (<1 mm/s)
- Veins and vena cavae: CSA falls as vessels coalesce → velocity rises again

Derivation Chain: Why Is Capillary Velocity So Low?

Billions of capillaries in parallel → enormous total cross-sectional area → by velocity = flow / area, velocity must be very low → slow velocity allows diffusion equilibration within <1 second capillary transit time → tissue homeostasis maintained

Common Errors

- **Error:** Confusing flow rate and velocity. Flow rate (L/min) is equal across all segments. Velocity (cm/s) is inversely proportional to cross-sectional area and differs enormously between segments.
- **Error:** Thinking slow capillary velocity is a problem. It is what enables diffusion-based exchange.
- **Error:** Assuming pressure falls linearly across the circuit. The steepest drop is at the arterioles, not distributed evenly.

Prediction Prompt

- **Predict:** If total capillary surface area is 1000 times that of the aorta and aortic velocity is 500 mm/s at peak systole, what is capillary blood velocity? What would happen to diffusional exchange if this velocity were 10 times higher?
- **Predict:** During exercise, cardiac output increases 5-fold or more. Capillary cross-sectional area also increases as more capillary beds open. Predict what happens to capillary transit time and why this matters for gas exchange.

Section 16: Capillary Exchange, Diffusion and the Starling Forces

Instructor Narrative	Structured Outline / Causal Chain
The move: Separate diffusion from bulk flux at the outset, then treat every edema case as a change in one identifiable Starling term. Two mechanisms, one purpose Everything the cardiovascular system does is in support of substances moving across capillary walls. Transcapillary passage occurs via two distinct mechanisms, diffusion for gases and small solutes, and bulk flux for water and accompanying solutes. Transport of these substances obeys different laws and is driven by different forces. Diffusion is governed by Fick's law. For lipophilic solutes like oxygen and CO₂, the equation includes lipid solubility, lambda (λ), because these molecules diffuse directly through the endothelial cell membranes without needing a pore. For hydrophilic solutes like glucose and ions, λ is zero for transcellular movement, so we substitute a permeability term P that reflects the size and number of paracellular pores. Either way, the factors that determine diffusion rate are the same: larger surface area drives more diffusion, a steeper concentration gradient drives more diffusion, and greater diffusional distance slows it. These are not equations to memorize, they are logical relationships to reason from. The clinical implication is important: small solute delivery is flow-limited, not diffusion-limited. Equilibration between plasma and interstitium happens so fast that the capillary transit time is not the bottleneck, blood flow rate is. Double the flow, double the delivery. This is why exercise-induced vasodilation in skeletal muscle is so effective at increasing oxygen delivery: it increases flow, not diffusion capacity. Bulk flux and the Starling equation Water and dissolved small solutes also move across the capillary wall driven by the sum of hydrostatic and oncotic pressures, the Starling forces. Blood hydrostatic pressure, P_c, is the pressure of blood against the capillary wall from the inside. It drives fluid outward: filtration. Blood oncotic pressure, π_c, is the osmotic pressure due to	Diffusive Flux (Fick's Law) - Lipophilic solutes (O₂, CO₂): $J_{diff} = -DA\lambda(\Delta C/\Delta x)$ - Hydrophilic solutes (glucose, ions): $J_{diff} = -DAP(\Delta C/\Delta x)$ - D = diffusion coefficient (molecule size, temperature, viscosity) - A = capillary surface area, more capillaries = more exchange λ = lipid solubility (for membrane-crossing solutes) - P = capillary permeability (pore size and number for hydrophilic solutes) ΔC = concentration gradient, the driving force Δx = diffusional distance, inversely proportional to rate Small Solute Exchange Is Flow-Limited - Equilibration between plasma and ISF occurs within <1 second of capillary transit - Rate-limiting step is delivery by blood flow, not diffusion capacity - Therefore: vasodilation (more flow) directly increases O₂ delivery Starling Forces (Bulk Flux) $J_{bulk} = K_f \times [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$ - K_f = filtration coefficient (wall leakiness × surface area) - P_c = blood hydrostatic pressure → filtration - P_i = interstitial hydrostatic pressure → usually ~0 (reabsorptive when positive, filtrative when negative) π_c = blood oncotic pressure (plasma proteins) → reabsorption

trapped plasma proteins. Because proteins are reflected by most capillary walls and concentrated inside relative to the interstitium, they exert an inward osmotic pull: reabsorption. Interstitial hydrostatic pressure is usually near zero. Interstitial oncotic pressure is small in most tissues but not negligible. Bulk flux varies depending on a capillary's state of perfusion but is always dependent on the existing Starling forces:

In a perfused capillary, blood hydrostatic pressure dominates along most of the length, producing net filtration, fluid moves outward into the interstitium. This filtered fluid is not lost, it bathes the cells, facilitates diffusion of solutes, and is collected by lymphatic vessels and returned to the bloodstream. The lymphatic system is not a backup drainage system; it is an essential component of fluid homeostasis without which progressive edema would develop even in normal physiology.

When arterioles and precapillary sphincters constrict and a capillary becomes unperfused, blood hydrostatic pressure in that capillary falls. Now the oncotic pressure dominates and reabsorption occurs along its length, even filtered fluid from neighboring perfused capillaries is taken back up. This oscillation between filtration and reabsorption is normal and continuous. Filtration wins slightly overall, producing the small net lymph flow that is essential to tissue fluid homeostasis.

Applied: when the balance shifts

Hypertension raises P_c above normal, filtration forces increase, more fluid exits capillaries, lymph flow rises, and if lymphatics cannot keep up, edema develops. Liver failure reduces plasma protein production, π_c falls, oncotic reabsorptive force diminishes, filtration dominates throughout, and edema develops. This pitting edema is characteristic of liver failure patients. The mechanism is entirely different from hypertensive edema, but the outcome is similar because both conditions shift the Starling balance toward net filtration exceeding lymphatic capacity.

- π_i = interstitial oncotic pressure (small, filtrative)
- σ = reflection coefficient (1 = fully reflected; 0 = freely permeable)

Normal Balance

- Perfused capillary: P_c dominates $\rightarrow$ net filtration along most of length
- Unperfused capillary: P_c falls $\rightarrow \pi_c$ dominates $\rightarrow$ net reabsorption
- Overall: filtration slightly exceeds reabsorption $\rightarrow$ 4-8 L/day lymph flow
- Lymphatics: essential return pathway for excess interstitial fluid and proteins

Causal Chain: Edema from Hypertension

Arterial BP rises $\rightarrow \uparrow P_c$ in capillaries $\rightarrow$ net filtration increases $\rightarrow$ lymphatics may not keep up $\rightarrow$ interstitial fluid accumulates $\rightarrow$ edema

Causal Chain: Edema from Liver Failure

Liver fails to produce plasma proteins $\rightarrow \pi_c$ falls $\rightarrow$ reabsorptive oncotic force reduced $\rightarrow$ net filtration increases throughout $\rightarrow$ edema, accumulating first in the lower extremities (dependent regions, where the weight of the venous blood column raises capillary hydrostatic pressure)

Common Errors

- **Error:** Thinking reabsorption occurs at the venous end of every capillary. This classical model is oversimplified. Filtration dominates along most of a perfused capillary; reabsorption occurs primarily in unperfused capillaries when P_c falls.
- **Error:** Assuming edema always means the same thing. The mechanism differs: hypertension raises P_c ; liver failure lowers π_c ; capillary leak raises K_f . Different problems, same outcome.
- **Error:** Treating lymphatics as relatively unimportant. Without lymphatic return, even normal filtration would produce progressive edema.

Prediction Prompt

- **Predict:** Nephrotic syndrome causes massive protein loss in urine. Predict the effect on π_c , the Starling balance, and the clinical consequence. Where would edema appear first and why?
- **Predict:** Pulmonary hypertension raises capillary pressure in the lungs. What happens to filtration across pulmonary capillaries and what is the clinical danger? Use Fick's law to explain why this is particularly harmful in the lung.

Section 17: Local Blood Flow Control

Instructor Narrative

***The move:** Organize the section around one principle: every product of increased metabolism acts as a vasodilator. Have students derive the list of metabolic vasodilators from that principle rather than memorizing it.*

The Fåhræus-Lindqvist effect: reduced viscosity in microvessels

We already established that blood viscosity, determined largely by hematocrit, directly contributes to resistance. Normal hematocrit raises blood viscosity to about 2.5 times that of plasma alone. That is a significant resistance burden. But here is where physics provides an adaptive benefit: in vessels smaller than about 0.3 millimeters, red blood cells preferentially migrate toward the center of the vessel, leaving a peripheral zone that is essentially plasma alone. Plasma has much lower viscosity than whole blood. Because resistance to flow is generated primarily at the fluid-wall interface, and because that interface is now plasma rather than whole blood, the effective viscosity, and therefore resistance, drops significantly in precisely the vessels where resistance is already highest.

This is called anomalous viscosity, or the Fåhræus-Lindqvist effect. Blood does not behave like a simple Newtonian fluid, its viscosity depends on the vessel size. In microvessels, the very property that

Structured Outline / Causal Chain

Fåhræus-Lindqvist Effect

- Blood is a cellular suspension, not a simple Newtonian fluid
- In vessels <0.3 mm: red blood cells migrate axially (toward center)
- Peripheral zone becomes plasma-only (low viscosity)
- Resistance is generated at the fluid-wall interface
- Plasma at wall $\rightarrow$ lower effective viscosity $\rightarrow$ lower resistance in microvessels
- Result: anomalous viscosity, effective viscosity falls in smallest vessels

Causal Chain: Myogenic Autoregulation

$\uparrow$ Perfusion pressure $\rightarrow$ flow would rise (passive pressure-flow effect) and vessel is distended $\rightarrow$ stretch-sensitive Ca^{2+} channels open in smooth muscle $\rightarrow \uparrow$ intracellular $\text{Ca}^{2+} \rightarrow$ vasoconstriction $\rightarrow$ resistance rises $\rightarrow$ the resistance increase offsets the higher pressure $\rightarrow$ flow returns to the autoregulated level

creates the viscosity problem also provides the mechanism to mitigate it. It is an elegant physical consequence of blood being a cellular suspension rather than a simple solution.

Myogenic autoregulation: matching perfusion pressure to flow

Here is a problem that most courses skip: the perfusion pressure driving blood flow to the coronary arteries is much higher than the perfusion pressure at your fingertips, simply because the coronary arteries are close to the pressure source while your fingers are at the end of a long vascular tree. If flow were purely a function of driving pressure, tissues close to the heart would be chronically over-perfused and distant tissues under-perfused. That is not what happens, because vessel walls sense transmural pressure and respond intrinsically.

When transmural pressure rises, meaning more blood is pushing outward on the vessel wall, smooth muscle in the arteriolar wall opens stretch-sensitive calcium channels, intracellular calcium rises, and the vessel constricts. Resistance then increases, flow returns to the autoregulated level. When transmural pressure falls, the opposite occurs: the vessel dilates, resistance falls, and flow is maintained. This myogenic reflex operates continuously and locally, without any neural input. It is the reason tissues at different distances from the heart all receive appropriate perfusion at normal blood pressure.

Endothelial nitric oxide: the shear-driven vasodilator

Shear stress is the frictional force that flowing blood exerts along the endothelial lining. It is directly proportional to flow velocity and viscosity. High shear, as occurs in constricted vessels, threatens to damage the endothelium. The endothelial cells respond by releasing nitric oxide, which diffuses to adjacent smooth muscle cells and causes vasodilation. Vasodilation increases vessel radius, reduces velocity, and therefore reduces shear. This is a protective feedback loop: the tissue at risk initiates the response that reduces the insult. Exercise chronically increases NO production and upregulates nitric oxide synthase expression, which is thought to be a major mechanism behind the cardiovascular protective effects of regular physical activity.

↓ Perfusion pressure → flow would fall and vessel is stretched less → stretch-sensitive Ca^{2+} channels close → ↓ intracellular Ca^{2+} → vasodilation → resistance falls → the resistance drop offsets the lower pressure → flow restored

- Operates without neural input, intrinsic to vessel wall
- Compensates for pressure differences between tissues at different distances from heart
- Keeps tissue perfusion matched to need, not to driving pressure

Endothelial NO and Shear Stress

Flow high relative to vessel caliber (e.g. a constricted or narrowed segment, or elevated flow through a given vessel) → wall shear stress rises → NOS activation in endothelial cells → NO synthesis and release → NO diffuses to smooth muscle → activates guanylate cyclase → cGMP rises → decreases intracellular free Ca^{2+} (reducing contraction) and activates K^+ channels (hyperpolarizing the membrane) → smooth muscle relaxes → vasodilation → radius increases → wall shear stress falls steeply as the vessel widens → shear returns toward baseline, attenuating the original stimulus (protective negative feedback)

- Exercise: chronically upregulates NOS expression → lower vascular resistance, lower BP
- Viagra (sildenafil): blocks PDE that degrades cGMP → prolongs NO vasodilation

Metabolic Vasodilators (Logic Not Memorization)

- Low O_2 → dilator (tissue needs more oxygen delivery)
- High CO_2 → dilator (tissue needs more CO_2 removal)
- High H^+ (acidosis) → dilator (metabolic waste accumulating)
- Lactate → dilator (anaerobic shift indicates inadequate perfusion)
- High K^+ (interstitial) → dilator (active repolarizing cells = high metabolism)

Metabolic control: the logic of the local environment

The most powerful and direct local flow control mechanism is the metabolic environment itself. Every product of increased cellular metabolism is a vasodilator. Low oxygen, high CO₂, elevated H⁺, lactate, adenosine, and elevated interstitial potassium, all are vasodilatory signals generated when cells are working harder than their current blood supply can support. You do not need to memorize a list. The logic is the same for all of them: these are metabolic distress signals, and the vascular response to metabolic distress is *always* to increase flow. Do not memorize the details, derive them from the principle.

This is the basis of active hyperemia: blood flow to a tissue rises in proportion to its metabolic activity. During exercise, skeletal muscle flow can increase more than tenfold above resting levels, not because blood pressure changed, but because the metabolic environment drove local vasodilation. Reactive hyperemia is the rebound overshoot in flow after a period of occlusion: when flow is restored, the accumulated metabolic distress signals cause a transient vasodilation that raises flow above resting level until the metabolites are cleared.

- Adenosine (ATP breakdown product) → dilator (ATP being consumed rapidly)
- Heat → dilator (elevated temperature signals active metabolism)
- Principle: all indicate ↑ metabolism → all signal need for ↑ blood flow

Active vs Reactive Hyperemia

- Active hyperemia: ↑ metabolism → metabolite accumulation → vasodilation → ↑ flow proportional to activity
- Reactive hyperemia: vessel occluded → metabolites accumulate and arterioles dilate maximally → on release of the occlusion, transient flow overshoot above resting level → metabolites cleared → flow returns to baseline

Common Errors

- **Error:** Memorizing the list of metabolic vasodilators without understanding the unifying principle. All of them signal increased metabolism and inadequate perfusion. The logic is the same.
- **Error:** Confusing myogenic autoregulation with metabolic control. Myogenic responds to pressure (stretch); metabolic responds to chemical environment. Both act on smooth muscle but through different mechanisms.
- **Error:** Thinking NO is only involved in pathology. It is a continuous physiological regulator of vascular tone and a key mediator of exercise-induced vasodilation.

Prediction Prompt

- **Predict:** A coronary artery is completely occluded for 5 minutes then reopened. Describe the expected flow pattern immediately after reopening (reactive hyperemia) and the mechanisms driving it.
- **Predict:** A patient with poorly controlled diabetes has peripheral neuropathy affecting vascular smooth muscle innervation. How would myogenic

autoregulation and metabolic control be affected and what clinical consequence would result?

Section 18: Extrinsic Control of Blood Flow, Sympathetic and Hormonal

Instructor note: This section builds directly on the autonomic control introduced in Sections 3, 4, and 9. The emphasis here is the vascular side, how the same neurotransmitters produce different effects in different vessel beds based on receptor subtype.

Instructor Narrative	Structured Outline / Causal Chain
The move: Frame local (intrinsic) control as regulating flow to match tissue metabolism and extrinsic control as maintaining systemic arterial pressure, then use receptor subtype to explain how one transmitter produces opposite effects in different vascular beds. Local vs extrinsic control: different purposes Local control, myogenic, endothelial, and metabolic, serves the individual tissue. Its function is to match perfusion to local metabolic demand regardless of what is happening elsewhere in the body. Extrinsic control, sympathetic nervous system and hormonal, serves the system. Its function is to maintain adequate driving pressure for all tissues simultaneously and redistributing flow during system-level challenges like exercise, hemorrhage, or fight-or-flight. These two modes of control do not conflict, they are superimposed. Sympathetic constriction can narrow an arteriole at the system level while local metabolite-driven dilation acts to dilate it. Which effect dominates depends on the magnitude of each signal. During hemorrhage, sympathetic constriction typically dominates everywhere except the heart and brain, those tissues are protected by particularly strong local autoregulation that overrides extrinsic constriction. Norepinephrine and receptor subtypes Sympathetic nerve fibers release norepinephrine at vascular smooth muscle. The effect depends entirely on which adrenergic receptor subtype is expressed on the target smooth muscle. Most arterioles and veins express alpha-adrenergic receptors, norepinephrine binding causes vasoconstriction, raises resistance, and reduces runoff from	Local vs Extrinsic Control - Local: serves individual tissue, matches perfusion to local metabolic demand - Extrinsic: serves the system, maintains driving pressure and global redistribution - Both active simultaneously; the stronger signal dominates in a given bed, until systemic pressure is threatened, when extrinsic control overrides local dilation in most beds (heart and brain protected) to defend driving pressure Causal Chain: Sympathetic Vascular Effects - Neurotransmitter: norepinephrine (NE) at all vascular synapses - Alpha-receptors (most arterioles, veins): NE → vasoconstriction → ↑ resistance → ↑ BP - Beta-2 receptors (skeletal muscle arterioles): NE/epinephrine → vasodilation → ↑ muscle flow - Venous alpha-receptors: venoconstriction (reduces compliance) → ↑ venous return → ↑ CO (Frank-Starling) Epinephrine: Concentration-Dependent Effects - Low-moderate (exercise): preferential beta-2 binding → skeletal muscle dilation, ↓ TPR, ↑ CO

the arterial circuit. This is how sympathetic activation raises blood pressure: it increases total peripheral resistance by constricting most vascular beds simultaneously.

Arterioles supplying skeletal muscle express predominantly beta-2 receptors, here, norepinephrine and especially epinephrine cause vasodilation. During exercise and the fight-or-flight response, this preferentially opens flow to working muscle even while sympathetic tone is causing constriction elsewhere. This is the mechanism of blood flow redistribution during exercise: alpha-receptor-mediated constriction in the gut and skin, beta-receptor-mediated dilation in muscle. The same sympathetic signal produces opposite effects in different beds based on receptor identity.

Epinephrine: concentration-dependent effects

Circulating epinephrine from the adrenal medulla has dose-dependent effects. At moderate concentrations typical of exercise, it preferentially binds the high-affinity beta-2 receptors on skeletal muscle vasculature, vasodilation dominates in those beds, total peripheral resistance actually falls, and cardiac output can rise without resulting in dramatic hypertension. At high concentrations typical of severe stress or hemorrhage, epinephrine now also occupies alpha receptors throughout the vascular tree, widespread vasoconstriction dominates, total peripheral resistance increases dramatically, and blood pressure spikes. The same hormone produces opposite systemic hemodynamic effects depending on its concentration.

- High (severe stress, hemorrhage): alpha-receptor occupation → widespread constriction, ↑ TPR, blood pressure spikes
- Same hormone, opposite systemic effects, receptor affinity and density determine outcome

Common Errors

- **Error:** Assuming sympathetic activation always causes vasoconstriction. In skeletal muscle, sympathetic-released epinephrine causes vasodilation via beta-2 receptors.
- **Error:** Thinking extrinsic and local control are in opposition. They are superimposed and complementary, local control finetunes individual beds while extrinsic control maintains system-level pressure.
- **Error:** Treating blood pressure control as purely a cardiac issue. Vascular resistance (TPR) is an equally powerful lever and the dominant long-term determinant.

Prediction Prompt

- **Predict:** During hemorrhage, sympathetic output rises dramatically. Trace the vascular responses in: (a) skeletal muscle, (b) gut, (c) brain. Which overrides the other in each case and why?
- **Predict:** A patient takes a non-selective beta-blocker that also blocks beta-2 vascular receptors. During exercise, what happens to skeletal muscle blood flow and why is this problematic for exercise capacity?

Section 19: Lymphatics, Edema, and Blood Pressure Measurement

Instructor note: Lymphatics and sphygmomanometry are written in voice-matched style from chapter content. Edema is an applied integration of Starling forces developed in Section 16.

The move: Present lymphatic return as an essential part of the circulation rather than an auxiliary system, and build the edema logic directly on the Starling balance from Section 16 so it extends familiar material rather than introducing a new principle.

The lymphatic system: essential, not optional

Filtration dominates over reabsorption in most perfused capillaries under normal conditions. That means interstitial fluid is continuously produced. If it were to simply accumulate, every tissue would become progressively edematous. This does not occur because blind-ended lymphatic capillaries permeate essentially every tissue, collecting the excess interstitial fluid and returned solutes and carrying them, as lymph, through progressively larger lymphatic vessels until they empty into the subclavian veins at the base of the neck.

Lymph vessels are exceptionally permeable, far more so than blood capillaries, and they absorb not only water and small solutes but also interstitial proteins that managed to escape the vascular space. This protein removal is critical. Proteins that accumulate in the interstitium raise interstitial oncotic pressure, which would tip the Starling balance toward even more filtration. Lymphatic drainage prevents that amplification. The system is self-stabilizing as long as lymphatics can match the filtration rate.

Edema: when Starling balance is disrupted

Edema, swelling due to interstitial fluid accumulation, develops when filtration exceeds the capacity of lymphatics to drain. Any factor that increases filtration or impairs drainage can produce it. Hypertension raises P_c and drives more filtration. Liver failure reduces plasma protein production, lowering π_c and reducing the oncotic pull back into capillaries. Nephrotic syndrome causes protein loss in urine with the same effect. Inflammatory conditions increase capillary permeability, K_f rises and proteins leak through, raising interstitial oncotic pressure and reducing the reabsorptive gradient. Filariasis, parasitic worm infestation of lymphatics, blocks drainage directly. These are all edema by different mechanisms, and understanding Starling forces allows you to diagnose the mechanism from the clinical context rather than memorizing a disease list.

Lymphatic System

- Blind-ended capillaries in all tissues collect excess interstitial fluid
- Exceptionally permeable: absorb water, small solutes, and interstitial proteins
- Protein removal critical: prevents interstitial protein accumulation that would amplify filtration
- Lymph vessels coalesce → thoracic duct and right lymphatic duct → subclavian veins
- Net lymph flow: 4-8 L/day (a volume exceeding total plasma volume)
- Without lymphatics: progressive edema even under normal physiological conditions

Edema, Mechanisms by Starling Factor

- Hypertension: $\uparrow P_c \rightarrow \uparrow \text{filtration} \rightarrow \text{exceeds lymphatic capacity}$
- Liver failure: $\downarrow \text{protein production} \rightarrow \downarrow \pi_c \rightarrow \downarrow \text{reabsorption} \rightarrow \text{net filtration rises}$
- Nephrotic syndrome: protein loss in urine $\rightarrow \downarrow \pi_c \rightarrow \downarrow \text{reabsorption} \rightarrow \text{net filtration rises}$ (same mechanism as liver failure)
- Inflammation / capillary leak: $\uparrow K_f (\uparrow \text{permeability}) \rightarrow \text{protein enters ISF} \rightarrow \uparrow \pi_i \rightarrow \uparrow \text{filtration}$
- Filariasis: lymphatic blockage → drainage fails regardless of Starling balance
- Common feature: filtration > lymphatic drainage capacity

Causal Chain: Lymphedema from Lymphatic Blockage

Lymphatics blocked (filariasis, tumor, surgery) → interstitial fluid accumulates → proteins also accumulate → interstitial oncotic pressure rises → filtration further increases → progressive massive edema (elephantiasis in extreme cases)

Sphygmomanometry

- Cuff inflated above systolic pressure: artery occluded, no flow, no sound

Sphygmomanometry: measuring blood pressure non-invasively

The sphygmomanometer works by exploiting turbulent flow. A cuff is inflated around the upper arm to a pressure exceeding systolic blood pressure, completely occluding the brachial artery, no flow, no sound. The cuff pressure is then slowly released. When cuff pressure falls just below systolic pressure, blood can spurt through the narrowed artery during peak systole but is occluded again during diastole. That intermittent turbulent flow makes the characteristic rapping sounds, Korotkoff sounds, heard through the stethoscope with each succeeding heartbeat. The observed cuff pressure at hearing the first Korotkoff sound equals systolic pressure. As cuff pressure continues to fall, sounds persist as long as the cuff is partially occluding the artery and creating turbulence. When cuff pressure falls below diastolic pressure, the artery is no longer occluded at any point in the cardiac cycle, flow is laminar throughout the cycle, sounds disappear, and the cuff pressure at the last sound equals diastolic pressure.

- Cuff pressure falls below systolic: turbulent flow during peak systole → first Korotkoff sound = systolic BP
- Cuff between systolic and diastolic: intermittent turbulence with each systole → continuing sounds
- Cuff below diastolic: artery open throughout cycle, laminar flow, sounds disappear = diastolic BP
- Korotkoff sounds = turbulent flow in brachial artery

Common Errors

- **Error:** Thinking lymphatics are a backup system that only activates in disease. They are essential to normal fluid homeostasis and continuously active.
- **Error:** Assuming all edema has the same mechanism. Always identify which Starling force is altered: P_c (hypertension), π_c (liver/kidney), K_f (inflammation), or drainage (lymphatic blockage).
- **Error:** Confusing Korotkoff sounds with heart sounds. They originate in the brachial artery from turbulent flow, not from valve closure.

Prediction Prompt

- **Predict:** A patient develops edema after surgery that removed inguinal lymph nodes. Which Starling factor is primarily affected and what is the mechanism? Why would the edema be limited to one lower extremity?
- **Predict:** Explain why a patient with both severe hypertension and liver failure would have more severe edema than either condition alone. Which Starling forces are affected in each condition?