

Antiarrhythmic Pharmacology

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Use the same reasoning chain for every antiarrhythmic.

A quick refresher - focus on the steps that explain the drug, then reconnect them to the full chain.

1 Target

Where does the drug act?

2 Action

What does it do there?

3 Tissue effect

What changes directly?

4 Body response

How does the body respond?

5 Uses and outcomes

Who benefits, and how?

6 Safety

What could go wrong, and why?

7 Pharmacokinetics

Does exposure change the prediction?

HOW TO USE IT IN THIS LECTURE

Each section highlights the one or two steps that do the most explanatory work.

Use the complete chain to connect mechanism, ECG effects, clinical use, and predictable toxicity.

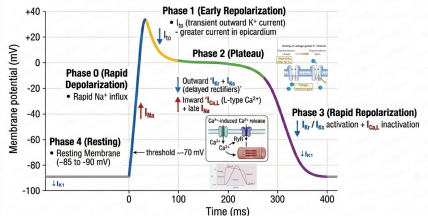
ACTION POTENTIAL: The Drug Target Map

To Know Antiarrhythmics, You Have to Know the Action Potential

Fast-response tissue

Atrial · ventricular · His–Purkinje

PHASE	CURRENT	EVENT
0	I_{Na}	Upstroke. Rate of rise sets conduction velocity.
1	I_{to}	Notch.
2	I_{CaL} vs I_K	Plateau. Ca^{2+} entry triggers contraction.
3	I_{Kr} , I_{Ks}	Repolarization. Major determinant of APD and QT.
4	I_{K1}	Stabilizes rest; also contributes to terminal repolarization.

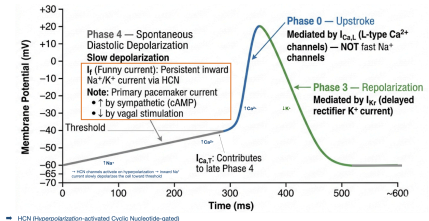


Fast response — atrial, ventricular, His–Purkinje

Slow-response tissue

SA node · AV node

PHASE	CURRENT	EVENT
0	I_{CaL}	Slow upstroke; sets nodal conduction velocity.
1	—	Absent: no notch.
2	—	Absent: no plateau.
3	I_K	Repolarization to maximum diastolic potential.
4	I_f , I_{CaT}	Spontaneous depolarization toward threshold.



Slow response — SA and AV node

Different tissue → different current → different pharmacologic target.

Every phase is a current.

TISSUE

CELL

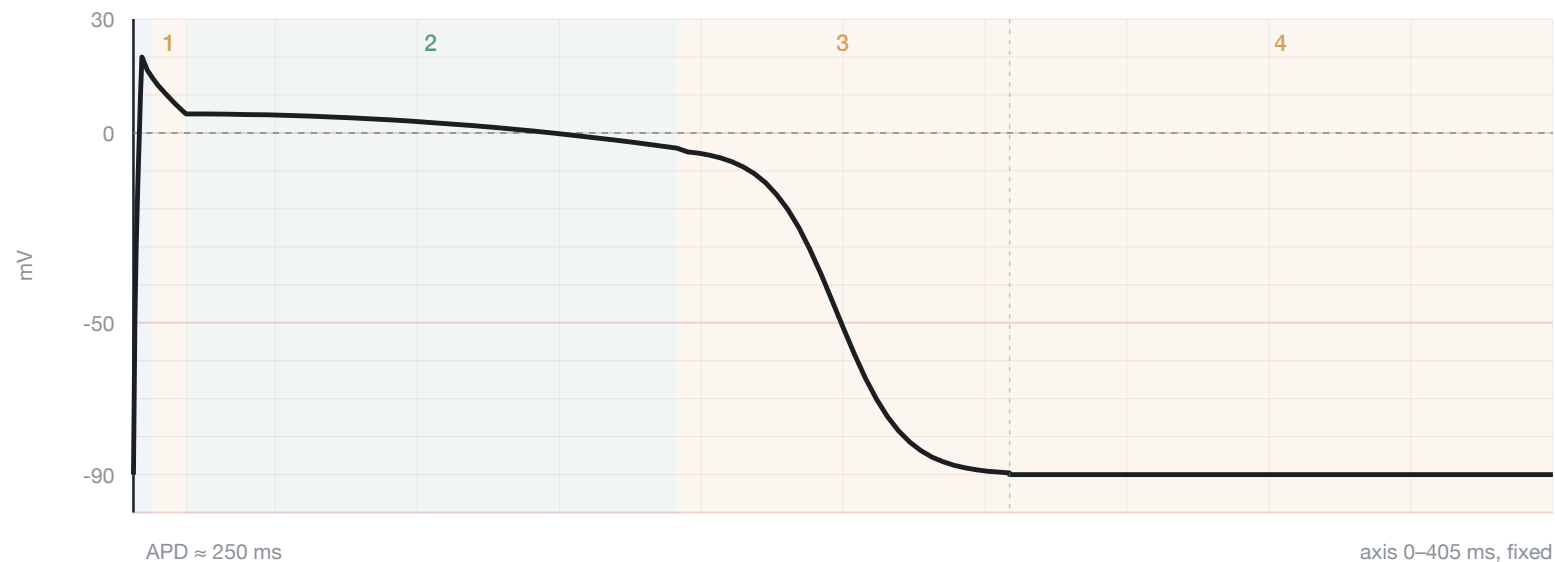
Fast response

Slow response

Ventricular

Atrial

Purkinje



Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Select a phase above. Note the stable phase 4: working myocardium has no automaticity unless disease depolarizes it. The axis is fixed across cell types here, so compare atrial, ventricular and Purkinje traces directly — atrial repolarizes first.

DOMINANT ION CURRENTS

PAUSE

Incoming stimulus before Phase 0

Before phase 0 · excitable cell

Nav1.5 is closed but available;
gap-junction charge approaches threshold.

EXTRACELLULAR

Nav1.5

Na⁺ CLOSED · AVAILABLE

CYTOPLASM

ADJACENT CELL

positive charge via gap junction

KEY TAKEAWAY

Working myocardium has a stable phase 4 and waits for a propagated stimulus.

Fast Na^+ current turns voltage into conduction.

TISSUE

CELL

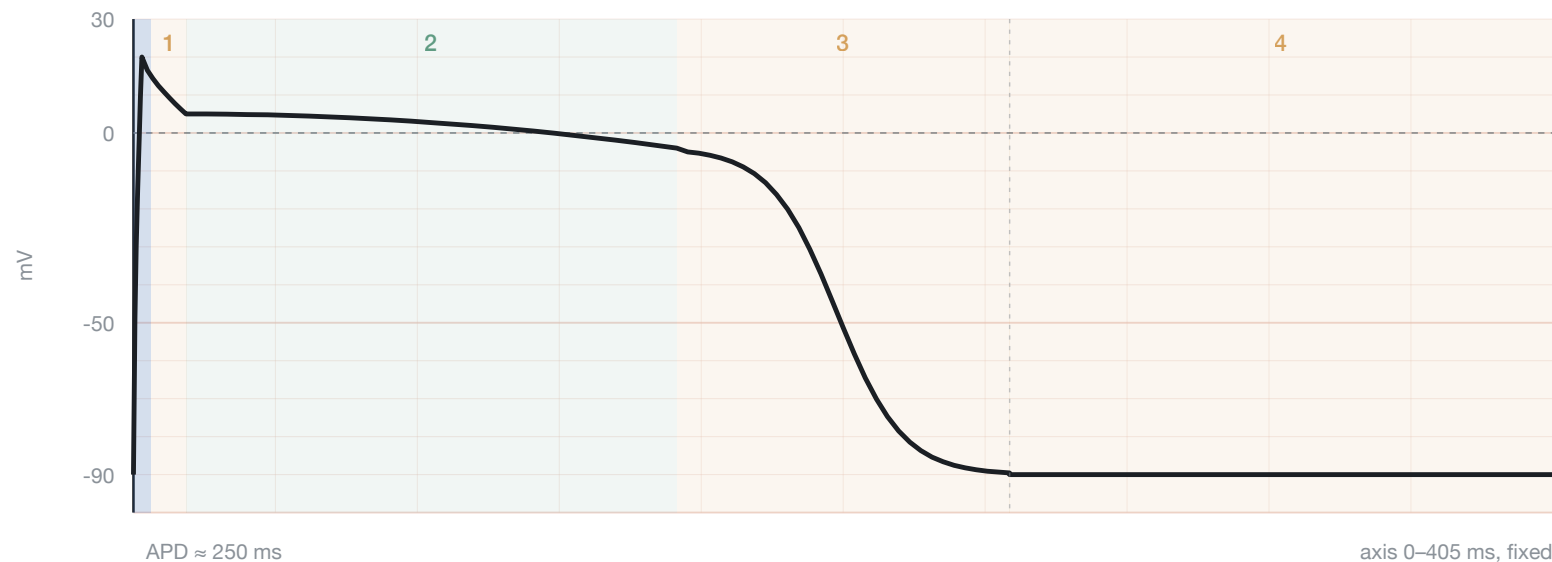
Fast response

Slow response

Ventricular

Atrial

Purkinje



DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 0 · fast upstroke

Gap-junction charge reaches threshold;
fast Na^+ channels then open.

EXTRACELLULAR

 I_{Na} Na^+ INWARD

CYTOPLASM

ADJACENT CELL

positive charge via gap junction

Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Phase 0 — upstroke

Positively charged ions entering from an adjacent cardiomyocyte through gap junctions depolarize the membrane to threshold and trigger fast Na^+ channels (Nav1.5) to open. The resulting large inward I_{Na} drives the membrane from about -90 mV toward $+20$ mV. The rate of rise sets conduction velocity, which is why blocking here

KEY TAKEAWAY

Phase-0 dV/dt is the bridge from sodium-channel availability to conduction velocity and QRS duration.

Transient outward K^+ current creates the phase-1 notch.

TISSUE

CELL

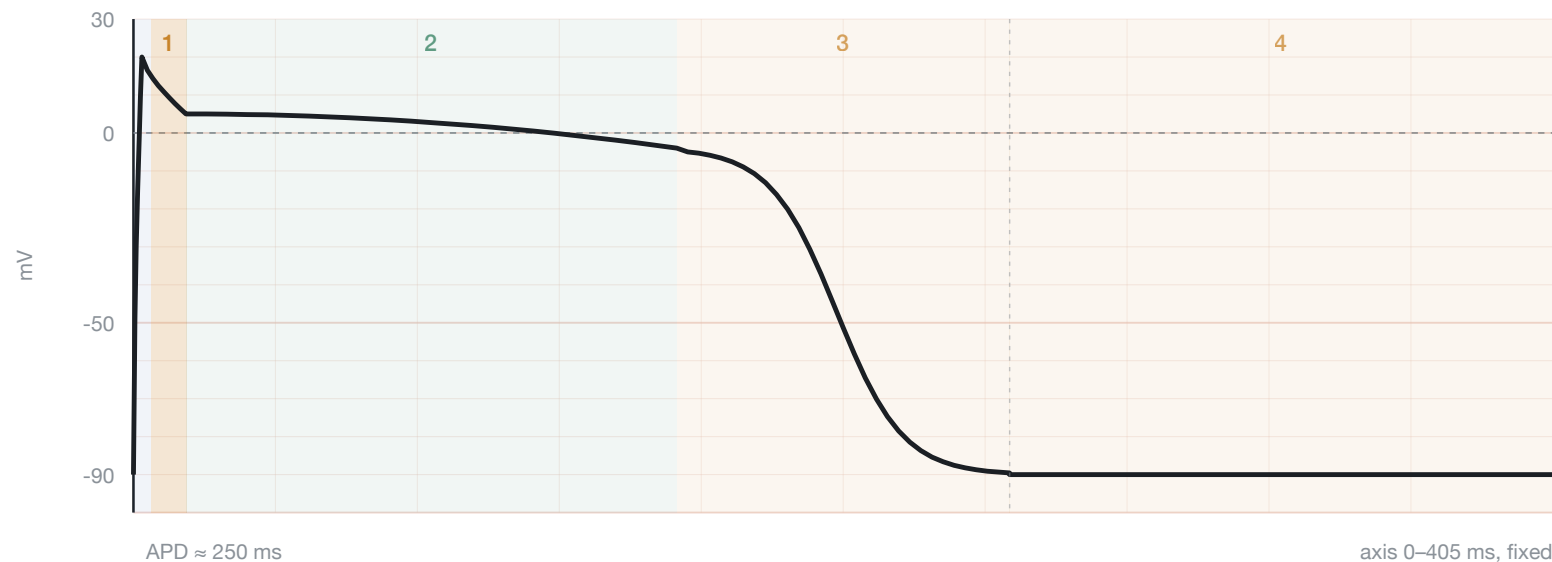
Fast response

Slow response

Ventricular

Atrial

Purkinje



DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 1 · early repolarization

Transient outward current creates the phase 1 notch.

EXTRACELLULAR

 I_{to} K^+ OUTWARD

CYTOPLASM

Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Phase 1 — early repolarization

Transient outward K^+ current (I_{to} , $Kv4.2/4.3$) produces the notch.

KEY TAKEAWAY

Brief I_{to} -mediated K^+ efflux produces early repolarization between the Na^+ upstroke and the phase-2 plateau.

The plateau is a balance, not a pause.

TISSUE

CELL

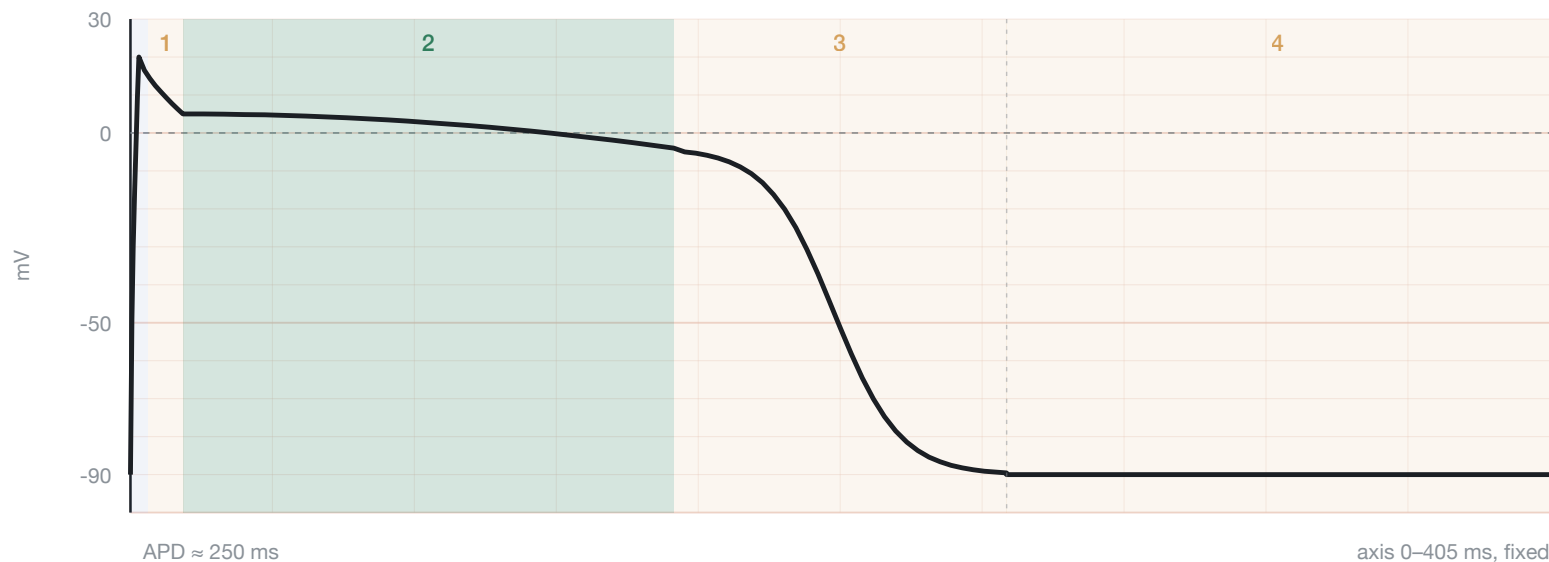
Fast response

Slow response

Ventricular

Atrial

Purkinje



Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Phase 2 — plateau

Inward L-type Ca^{2+} current is balanced against outward delayed rectifier K^+ current. This Ca^{2+} entry triggers SR Ca^{2+} release and contraction.

DOMINANT ION CURRENTS

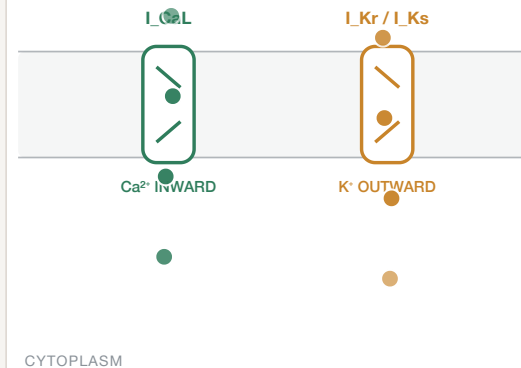
PAUSE

Synchronized with the highlighted phase

Phase 2 · plateau

Inward Ca^{2+} and outward K^+
nearly balance each other.

EXTRACELLULAR



KEY TAKEAWAY

During phase 2, inward I_{CaL} is balanced by outward potassium current; calcium entry couples excitation to contraction.

Repolarizing potassium currents set action-potential duration.

TISSUE

CELL

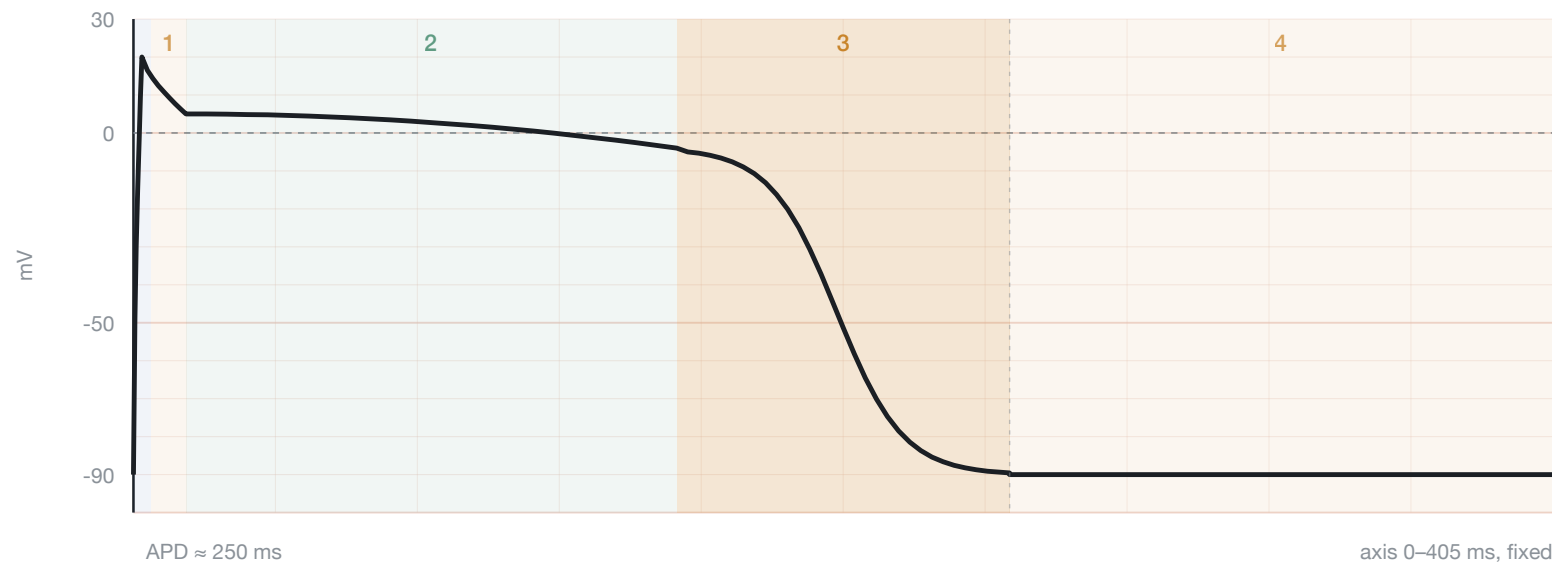
Fast response

Slow response

Ventricular

Atrial

Purkinje



DOMINANT ION CURRENTS

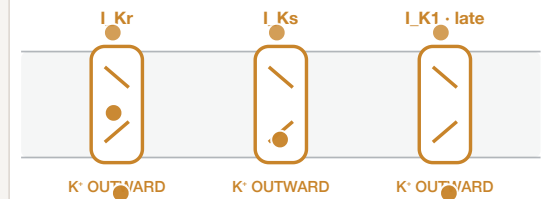
PAUSE

Synchronized with the highlighted phase

Phase 3 · repolarization

Ca²⁺ entry falls; outward K⁺ current returns the cell to rest.

EXTRACELLULAR



CYTOPLASM

Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Phase 3 — repolarization

K⁺ efflux dominates as Ca²⁺ conductance falls. I_{Kr} and I_{Ks} are major delayed rectifiers; I_{K1} contributes increasingly during terminal repolarization as the membrane returns to rest.

KEY TAKEAWAY

Phase 3 is the bridge from repolarizing-current block to longer APD and a longer QT.

Working myocardium normally waits.

TISSUE

CELL

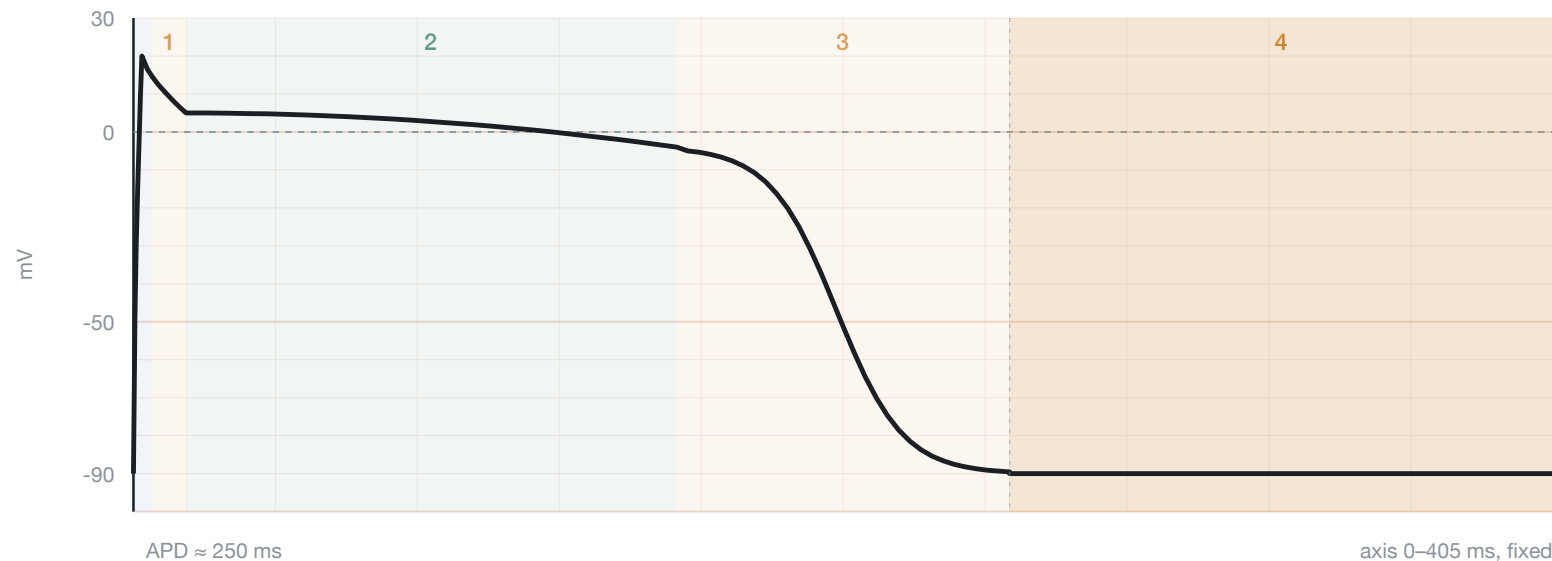
Fast response

Slow response

Ventricular

Atrial

Purkinje



Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Phase 4 — resting potential

Stable in working myocardium, held near E_K (≈ -91 mV) by inward-rectifier K^+ conductance. Inward and outward currents are balanced; the cell waits for an outside stimulus

DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 4 · stable rest

I_{K1} conductance clamps voltage near the K^+ equilibrium potential.

EXTRACELLULAR

 I_{K1} $K^+ \text{ NET } \approx 0$

CYTOPLASM

KEY TAKEAWAY

I_{K1} stabilizes the resting membrane potential; a new propagated stimulus is normally required to fire again.

Atrial myocardium repolarizes earlier.

TISSUE

CELL

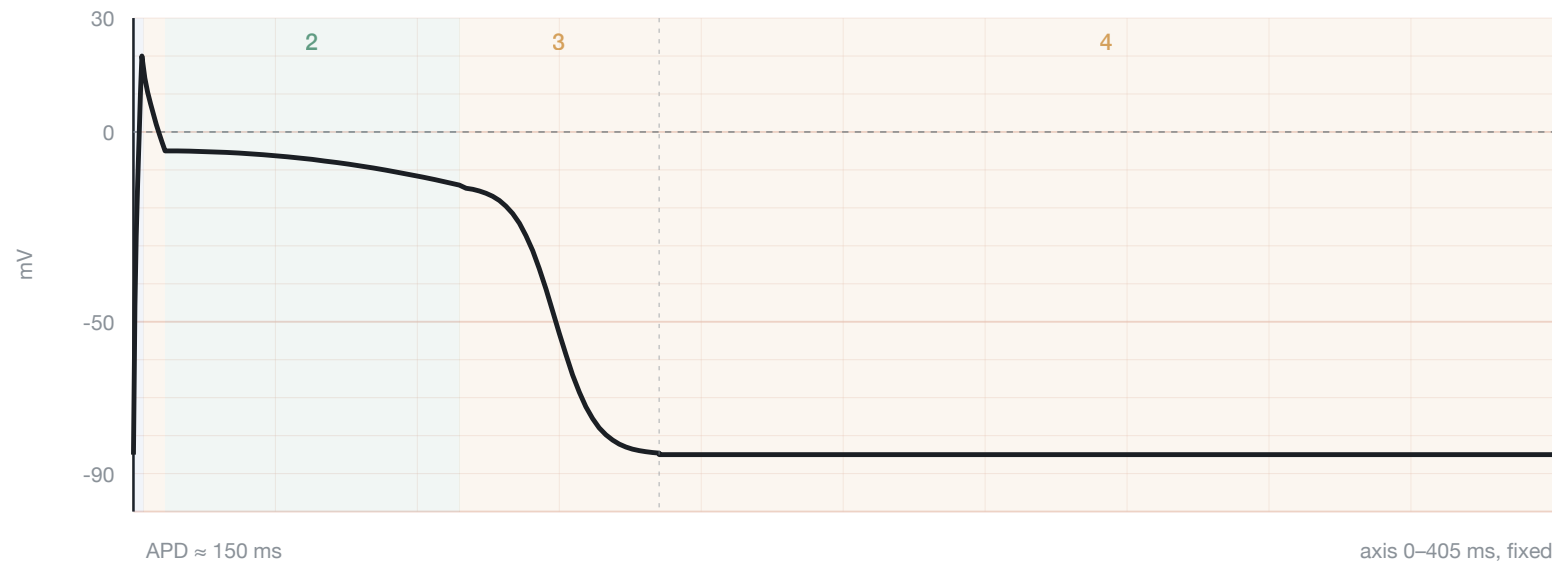
Fast response

Slow response

Ventricular

Atrial

Purkinje



Phase 0

Phase 1

Phase 2

Phase 3

Phase 4

Select a phase above. Note the stable phase 4: working myocardium has no automaticity unless disease depolarizes it. The axis is fixed across cell types here, so compare atrial, ventricular and Purkinje traces directly — atrial repolarizes first.

KEY TAKEAWAY

Atrial cells retain a fast Na^+ -dependent phase 0 and stable phase 4, but their shorter, less prominent plateau produces a shorter action potential than ventricular cells.

DOMINANT ION CURRENTS

PAUSE

Incoming stimulus before Phase 0

Before phase 0 · excitable cell

Nav1.5 is closed but available;
gap-junction charge approaches threshold.

EXTRACELLULAR

Nav1.5

Na⁺ CLOSED · AVAILABLE

ADJACENT CELL

positive charge via gap junction

CYTOPLASM

Nodal tissue runs on a different action potential.

TISSUE

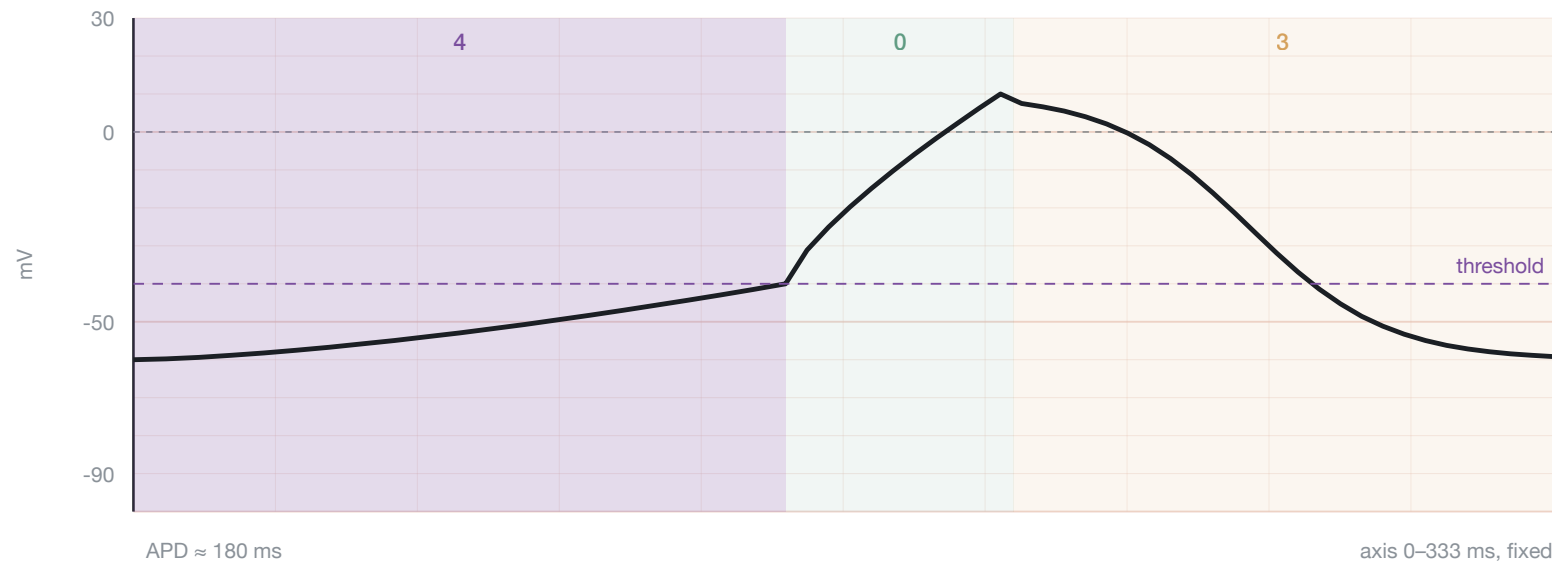
CELL

Fast response

Slow response

SA node

AV node



Phase 4

Phase 0

Phase 3

Select a phase above. Note that phases 1 and 2 are absent — nodal cells have no plateau, and phase 4 is not flat.

DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 4 · pacemaker drift

Funny current and Ca^{2+} entry move the nodal cell to threshold.

EXTRACELLULAR



CYTOPLASM

KEY TAKEAWAY

Changing the tissue changes both the phase-4 behavior and the current that carries phase 0.

The SA node never truly rests.

TISSUE

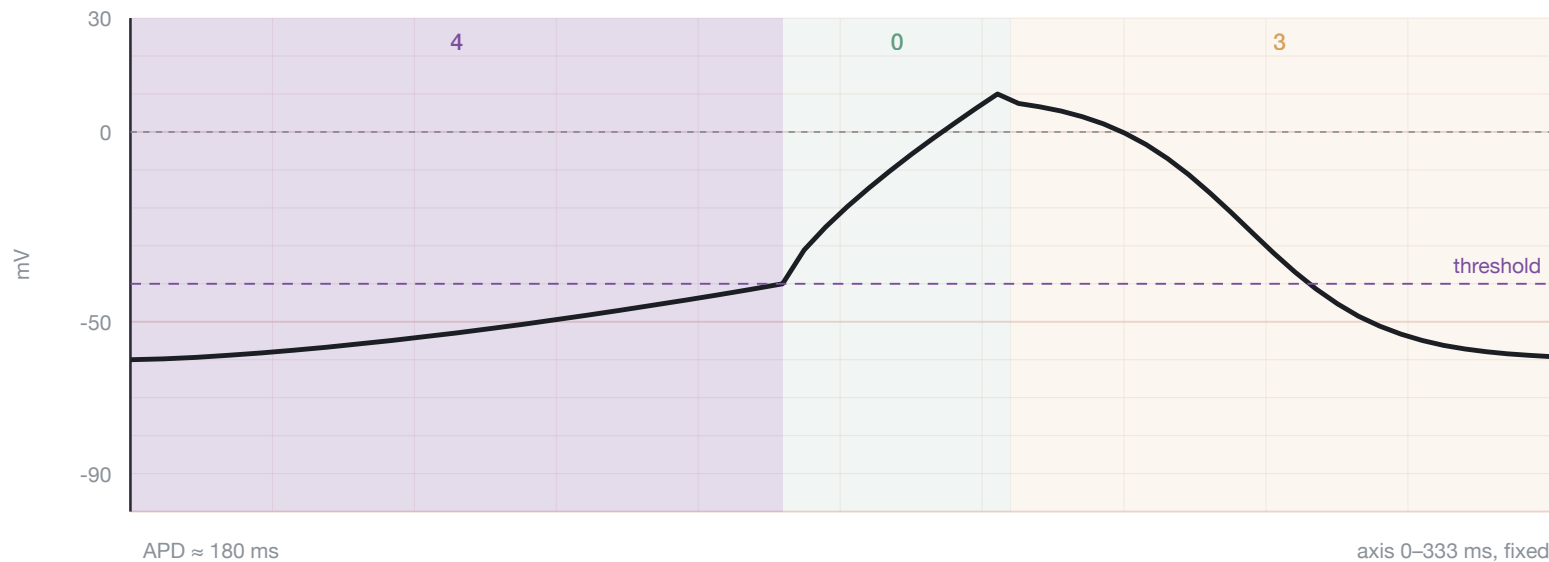
CELL

Fast response

Slow response

SA node

AV node



Phase 4

Phase 0

Phase 3

Phase 4 — spontaneous depolarization

The pacemaker potential. I_f (HCN channels, the "funny" current) carries inward Na^+ , drifting the membrane from about -60 mV up toward threshold. Ivabradine — Class 0 — blocks exactly this

DOMINANT ION CURRENTS

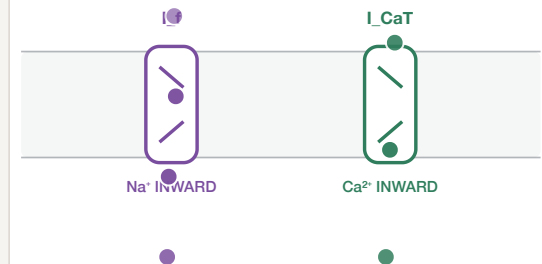
PAUSE

Synchronized with the highlighted phase

Phase 4 · pacemaker drift

Funny current and Ca^{2+} entry move the nodal cell to threshold.

EXTRACELLULAR



CYTOPLASM

KEY TAKEAWAY

Spontaneous phase-4 depolarization allows pacemaker tissue to reach threshold without an incoming propagated impulse.

Nodal phase 0 is carried by calcium.

TISSUE

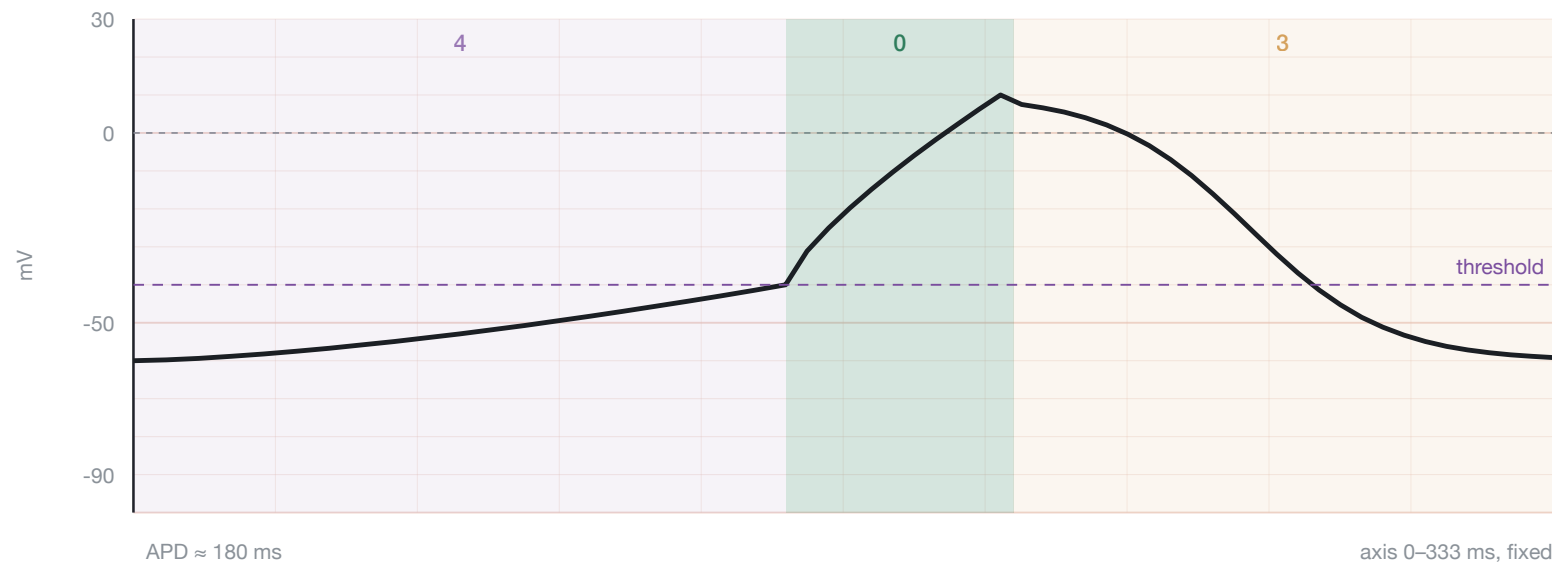
CELL

Fast response

Slow response

SA node

AV node



Phase 4

Phase 0

Phase 3

Phase 0 — slow upstroke

Ca^{2+} , not Na^{+} , carries the upstroke. It is slower and smaller than in fast-response tissue, which is why nodal conduction is slow and why Class IV agents act selectively here.

KEY TAKEAWAY

A calcium-dependent upstroke explains why nodal conduction is slow—and why fast sodium-channel block is not the dominant nodal strategy.

DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 0 · slow upstroke

L-type Ca^{2+} channels—not fast
 Na^{+} channels—carry the upstroke.

EXTRACELLULAR

 I_{CaL} Ca^{2+} INWARD

CYTOPLASM

Potassium current resets the pacemaker cell.

TISSUE

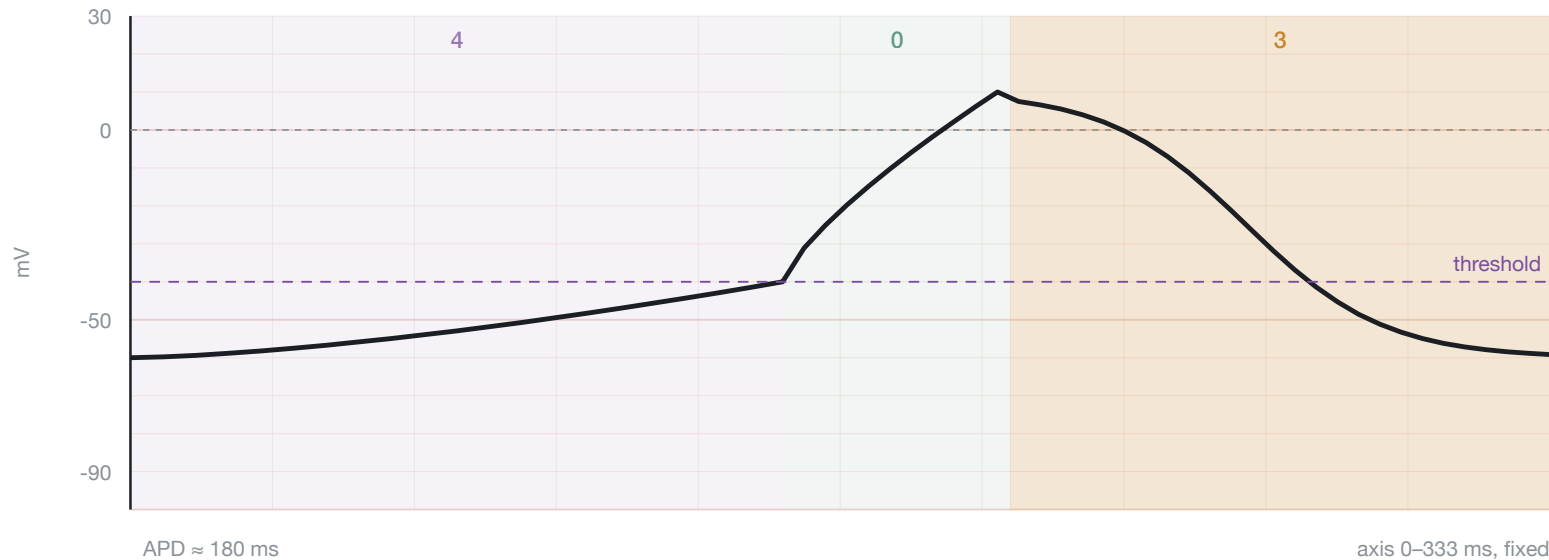
CELL

Fast response

Slow response

SA node

AV node



Phase 4

Phase 0

Phase 3

Phase 3 — repolarization

K^+ efflux returns the membrane to maximum diastolic potential, and phase 4 drift begins again. Vagal tone and adenosine open I_{KACH} here, hyperpolarizing the cell and slowing the next beat

KEY TAKEAWAY

Outward delayed-rectifier K^+ current repolarizes the SA-node cell toward its maximum diastolic potential, preparing the next spontaneous phase 4.

DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 3 · repolarization

Outward K^+ current returns the nodal cell to its most negative voltage.

EXTRACELLULAR

I_K

K^+ OUTWARD

CYTOPLASM

The AV node is a calcium-dependent gate.

TISSUE

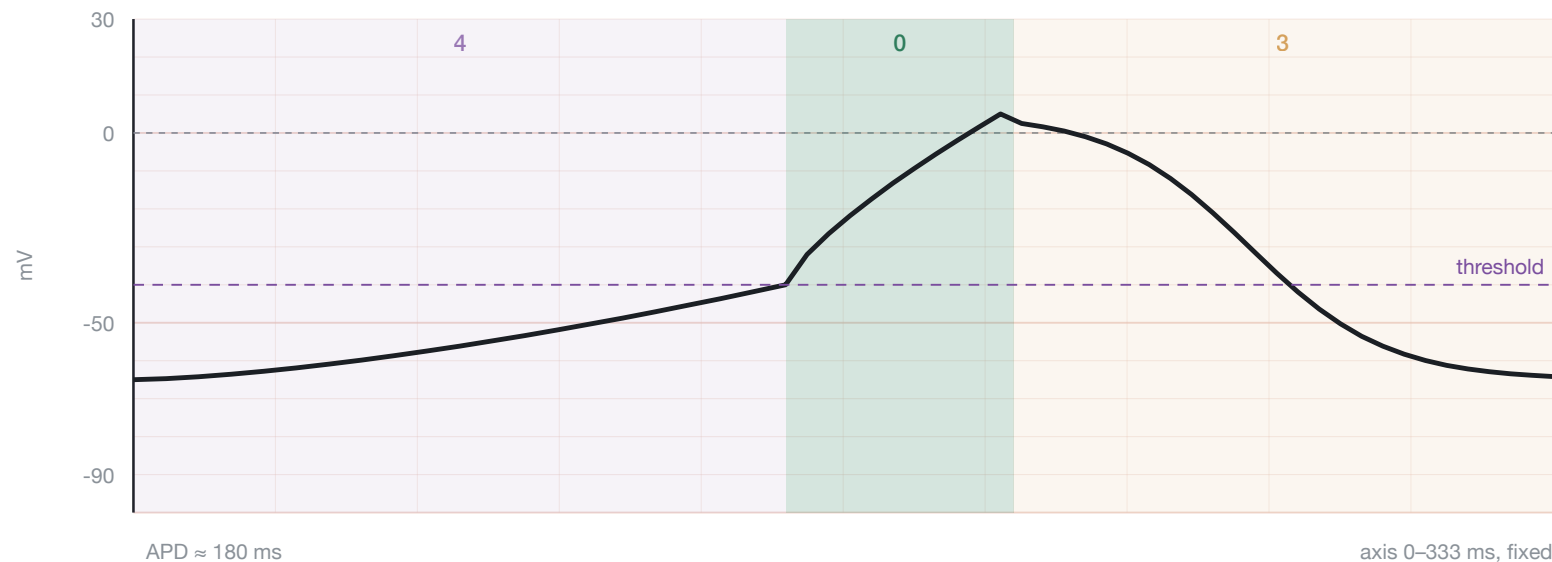
CELL

Fast response

Slow response

SA node

AV node



Phase 4

Phase 0

Phase 3

Phase 0 — slow upstroke

Ca^{2+} , not Na^{+} , carries the upstroke. It is slower and smaller than in fast-response tissue, which is why nodal conduction is slow and why Class IV agents act selectively here.

DOMINANT ION CURRENTS

PAUSE

Synchronized with the highlighted phase

Phase 0 · slow upstroke

L-type Ca^{2+} channels—not fast
 Na^{+} channels—carry the upstroke.

EXTRACELLULAR

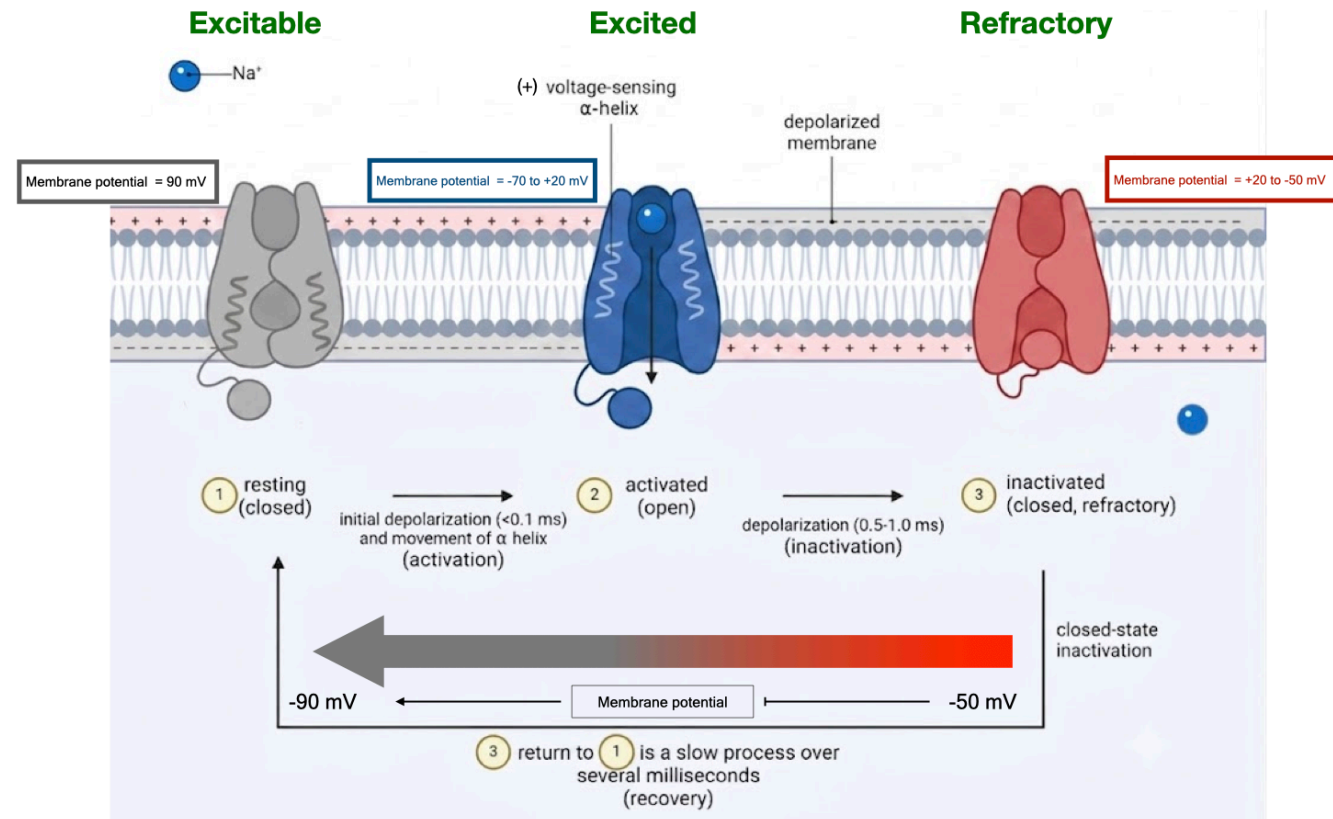
 I_{CaL} Ca^{2+} INWARD

CYTOPLASM

KEY TAKEAWAY

Its slow, calcium-dependent conduction makes the AV node both a physiologic filter and a high-value antiarrhythmic target.

FAST Na⁺ CHANNELS: Excitable, Excited, Refractory



The refractory clock is a channel-state cycle: available $\rightarrow$ open $\rightarrow$ inactivated $\rightarrow$ recovered and available again.

CORE DISTINCTION

Closed does not always mean ready: a resting channel is excitable; an inactivated channel is refractory.

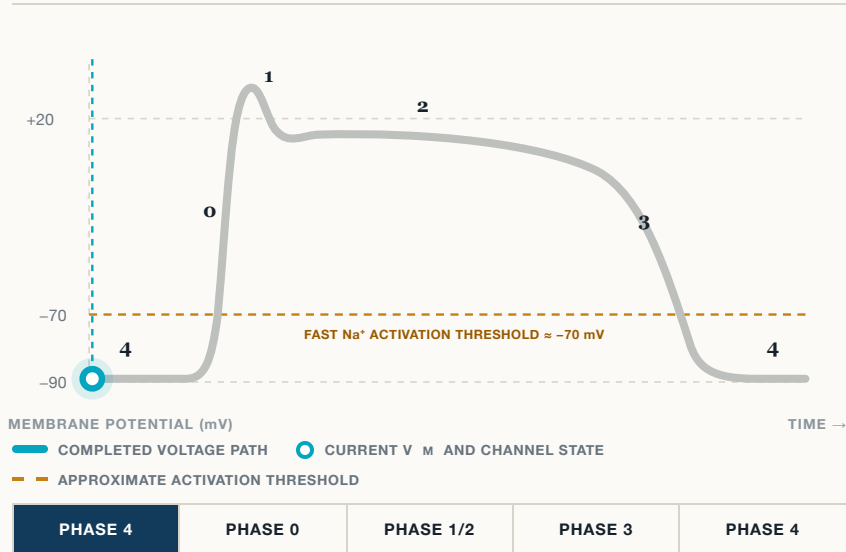
Fast Na⁺ channels set the refractory clock.



Core mechanism: Refractoriness is determined largely by how many fast Na⁺ channels have recovered from inactivation and can participate in the next action potential.

01 Ventricular action potential

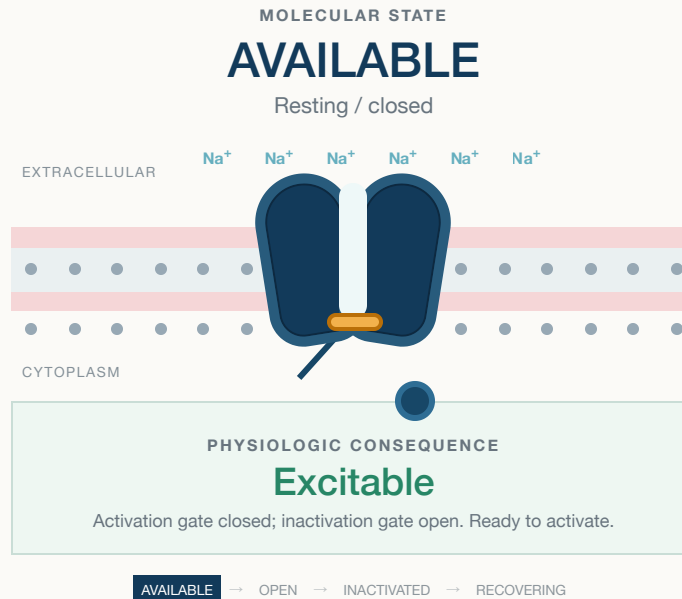
MEMBRANE VOLTAGE · SYNCHRONIZED CURSOR



Pause anywhere, then deliver a premature stimulus to test excitability.

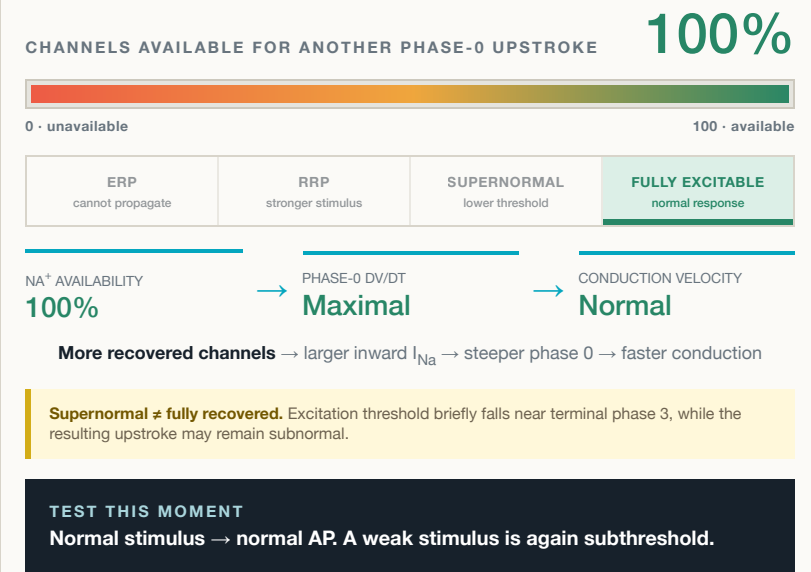
02 Fast Na⁺ channel state

MOLECULAR STATE FIRST · CONSEQUENCE SECOND



03 Recovery & refractoriness

AVAILABLE CHANNELS DETERMINE THE NEXT UPSTROKE



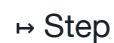
Play



Pause



Back



Step



Replay

Speed

1x



STIMULUS

Weak

Normal

Strong



Deliver premature stimulus

ERP, RRP, and why they are not the same as APD

KEY TAKEAWAY

The next impulse can propagate only after enough channels have recovered from inactivation.

An arrhythmia begins when impulse generation or propagation goes wrong.

First ask what created the impulse. Then ask what allows it to continue.

01 Impulse generation

Why did a cell fire?

Automaticity

Spontaneous phase-4 depolarization reaches threshold without a preceding action potential; when a site outside the normal dominant pacemaker fires first, it acts as an **ectopic pacemaker**.

Triggered activity

A preceding action potential is required: an EAD interrupts repolarization; a DAD follows it.

02 Impulse propagation

Why did the wavefront conduct—or fail?

Conduction delay or block

The impulse slows, becomes decremental, or fails to traverse a region of tissue.

Reentry

A wavefront returns to previously activated tissue after that tissue has recovered excitability.

Initiation and maintenance can differ. An ectopic or triggered beat may start an arrhythmia that is then sustained by reentry.

The fastest pacemaker wins the race.

3 · Automaticity where it shouldn't be

The dominant pacemaker repeatedly resets slower pacemakers; rapid activation also produces transient post-overdrive suppression.

A latent pacemaker escapes when the leader fails.

1 · The pacemaker race

3 · Automaticity where it shouldn't be

Whoever reaches threshold first wins — and resets everyone else

Three pacemakers drift toward threshold at once. The fastest arrives first, and its impulse resets the others before they reach threshold. This panel isolates pacemaker capture by timing. Rapid activation can also produce post-overdrive suppression through electrogenic pump currents. Slow the SA node and watch what happens.

SA NODE INTRINSIC RATE



75 bpm

CONDUCTION SYSTEM

- All intact
- Sinus node fails
- Sinus + AV junction fail

DOMINANT PACEMAKER	AV junction
RESULTING RATE	45 bpm
RHYTHM	Junctional escape rhythm

Nothing new started — something stopped. The junction is not firing faster than usual; it is firing at its own intrinsic rate because the faster pacemaker above it is no longer

SA node

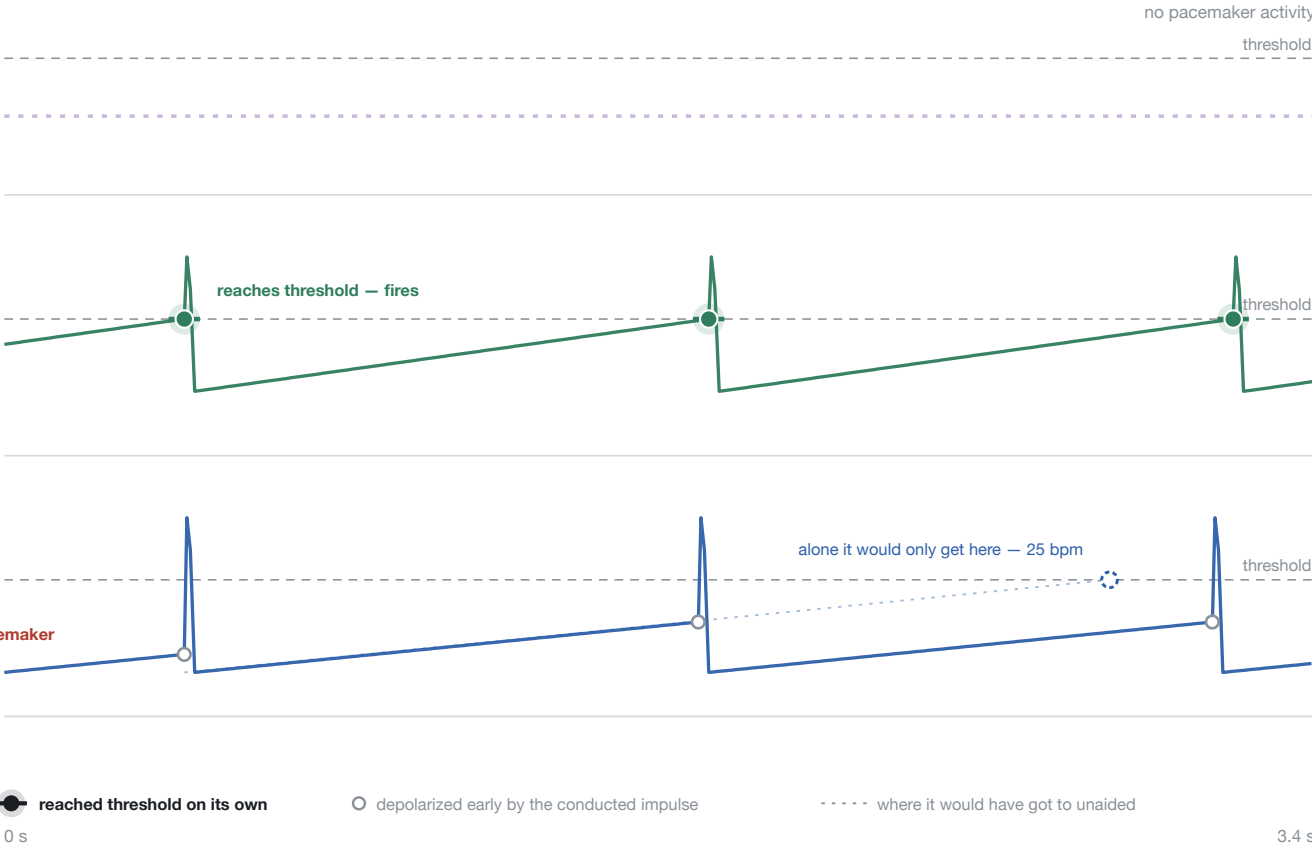
not firing

AV junction

intrinsic 45 bpm
♦ dominant
phase 4 18.8 mV/s

Purkinje

intrinsic 25 bpm
phase 4 13.3 mV/s
reset by dominant pacemaker



KEY TAKEAWAY

An escape rhythm is protective: nothing fired too early; a slower backup finally reached threshold.

Working myocardium can acquire automaticity.

1 · The pacemaker race

3 · Automaticity where it shouldn't be

Automaticity where there should be none

Working myocardium sits quietly at its resting potential and waits to be told. Depolarize it far enough — by any of several mechanisms — and it starts to drift on its own. This is *abnormal* automaticity, and it is not confined to the ventricle.

TISSUE

Atrial

Ventricular

Purkinje

CAUSE OF DEPOLARIZATION

Healthy

Ischemia / infarction

Hyperkalemia

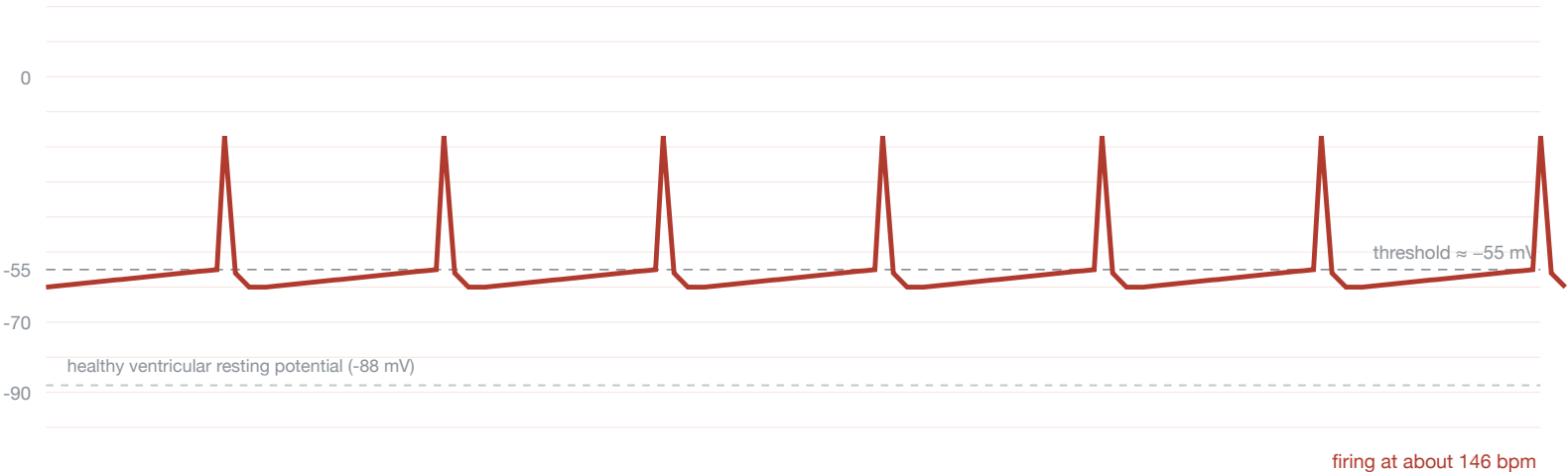
Chamber stretch

RESTING MEMBRANE POTENTIAL



-60 mV

[↗ Sites of abnormal automaticity](#)

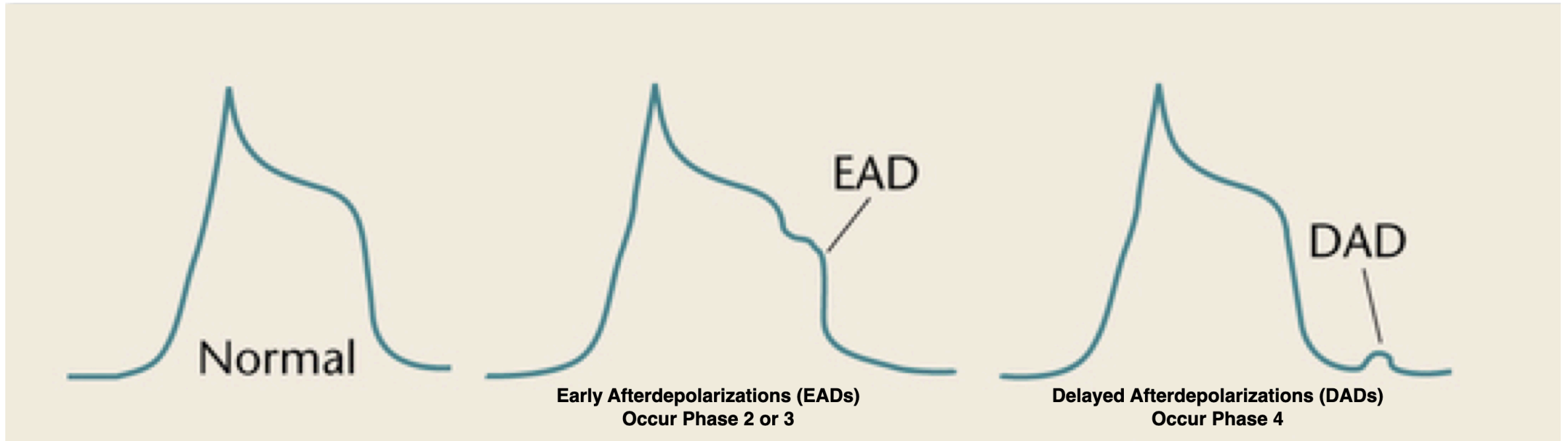


SPONTANEOUS ACTIVITY present, accelerating	NAV1.5 AVAILABLE 8%	UPSTROKE CARRIED BY Ca ²⁺ (slow-response-like)	RESULTING RHYTHM automatic VT, 146 bpm
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KEY TAKEAWAY

Depolarizing the resting potential can create spontaneous phase-4 drift while reducing fast-Na⁺-channel availability.

Triggered activity depends on a preceding action potential.



The first discriminator is timing relative to repolarization—not the size or shape of the afterdepolarization.

CORE DISTINCTION

EAD means before repolarization is complete; DAD means after the membrane has returned to rest.

An EAD interrupts repolarization.

SHOW

CONDITION

Normal AP

EAD

DAD

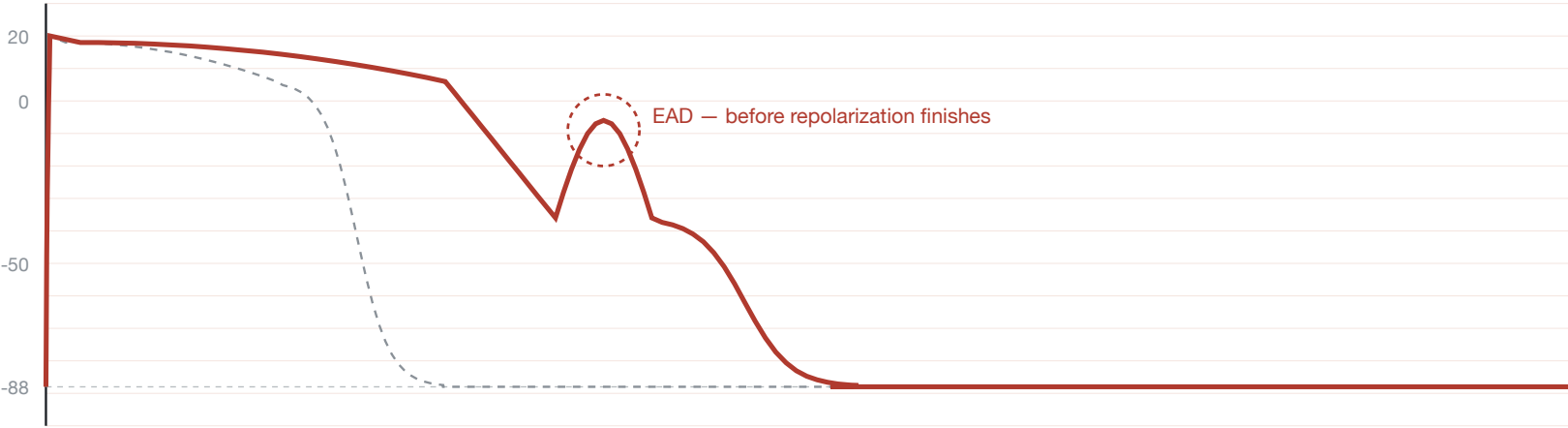
Compare

QT-prolonging drug

Hypokalemia

Bradycardia

Congenital LQT



TIMING phase 2–3	CARRIED BY net inward; often I_{CaL}	WORSE WHEN slow rates, pauses	PRODUCES torsades de pointes
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QT-prolonging drug. Many acquired long-QT drugs reduce I_{Kr} /hERG-mediated outward current. Repolarization and the QT interval lengthen, reducing repolarization reserve; this extra time can permit inward current —often I_{CaL} —to reactivate before the membrane returns to rest. Note that the hump interrupts repolarization — the membrane never got back to rest. If it reaches threshold it produces a triggered beat, and on a substrate of long QT with dispersion across the wall, that beat starts torsades.

KEY TAKEAWAY

Reduced repolarization reserve allows net inward current—often involving L-type Ca^{2+} current—to reverse the falling membrane voltage.

A DAD follows completed repolarization.

SHOW

CONDITION

Normal AP

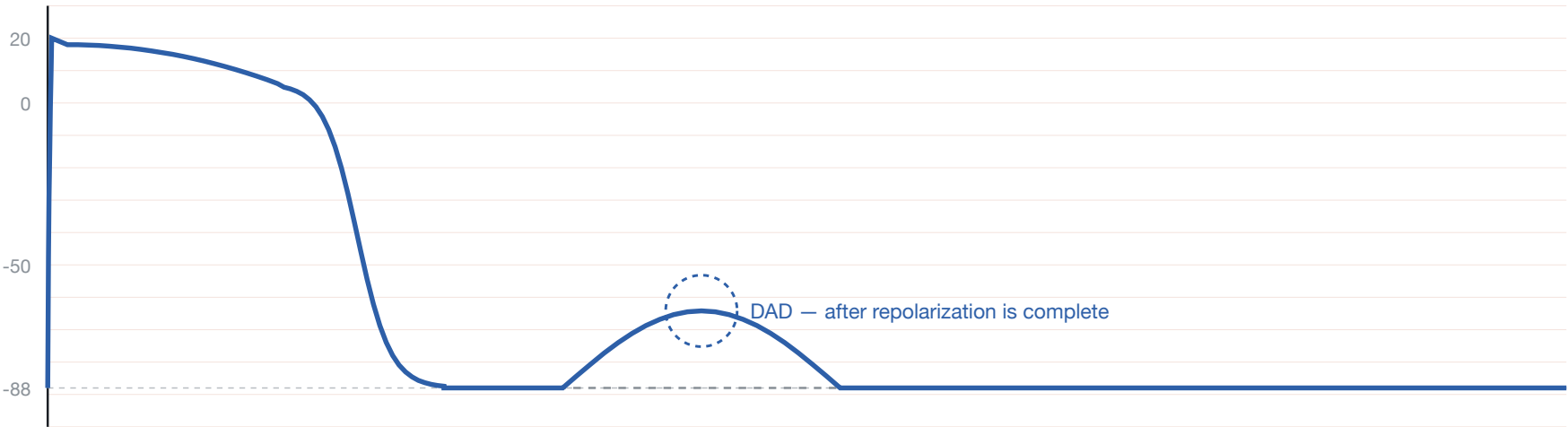
EAD

DAD

Compare

Catecholamines

Reperfusion



TIMING phase 4	CARRIED BY NCX transient inward	WORSE WHEN fast rates, catecholamines	PRODUCES ectopy, bidirectional VT
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Catecholamines. β_1 stimulation raises cAMP, increasing I_{CaL} and SR Ca^{2+} loading. This is why DAD-mediated arrhythmias are often exercise- and stress-triggered. The membrane has completed repolarization before the DAD appears; this is therefore a calcium-loading problem rather than fundamentally a QT-duration problem.

KEY TAKEAWAY

SR Ca^{2+} overload drives spontaneous Ca^{2+} release; forward-mode NCX then produces a transient inward current.

Timing separates EAD from DAD.

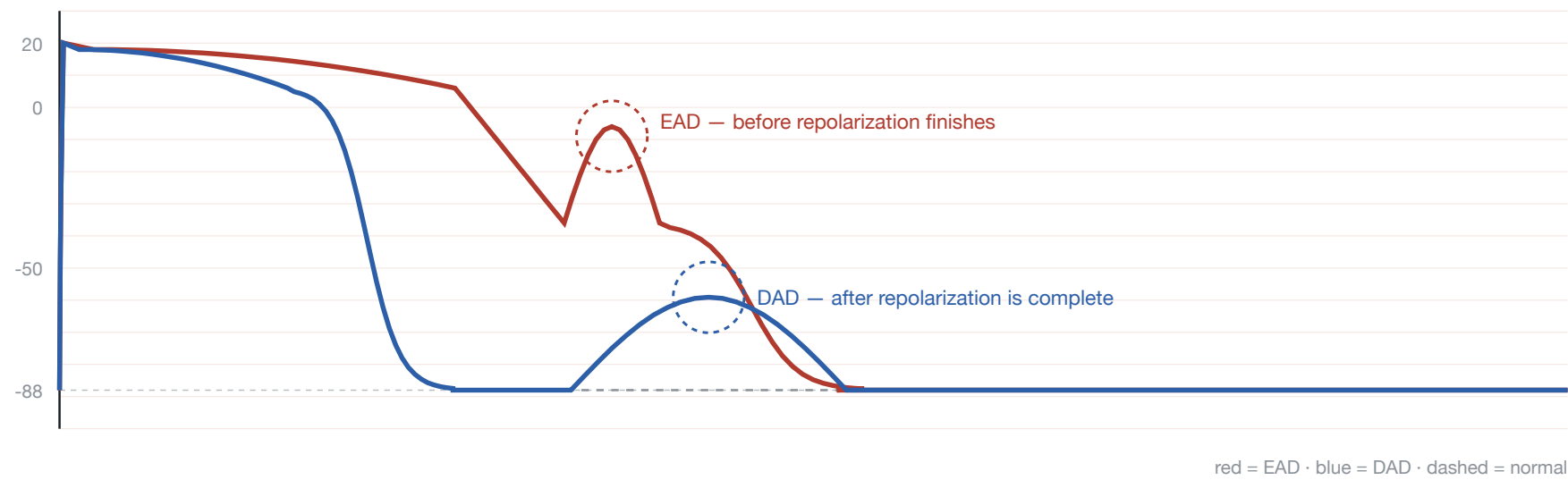
SHOW

Normal AP

EAD

DAD

Compare



TIMING see below	CARRIED BY I_{CaL} vs NCX	WORSE WHEN opposite directions	PRODUCES torsades vs ectopy
--	--	--	---

One difference in timing, two different mechanisms. The EAD arrives before repolarization is complete and is favored by prolonged or unstable repolarization. The DAD arrives after repolarization is finished and requires intracellular calcium loading.

KEY TAKEAWAY

EAD: incomplete repolarization and slow-rate vulnerability. DAD: completed repolarization and intracellular Ca^{2+} loading.

Reentry needs all three.

1 Two pathways

Anatomically or functionally distinct

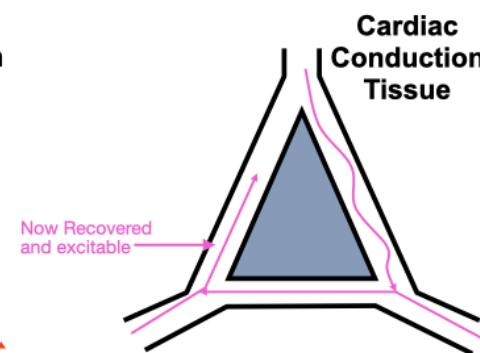
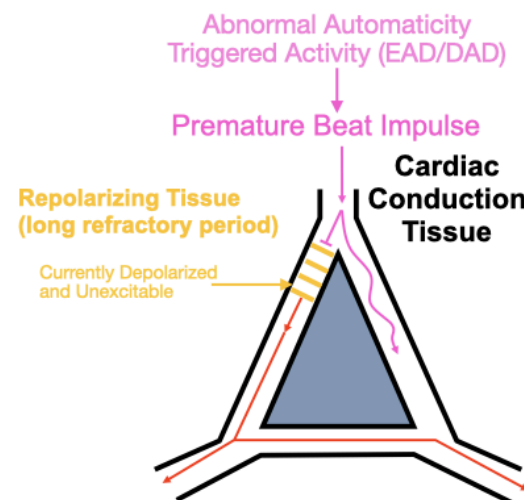
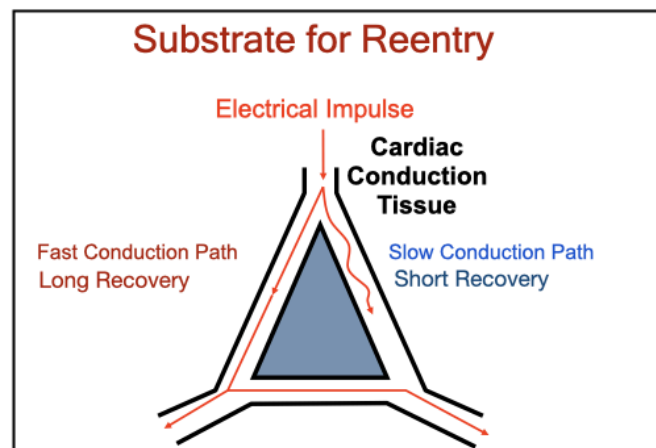
2 Unidirectional block

One pathway blocks in one direction

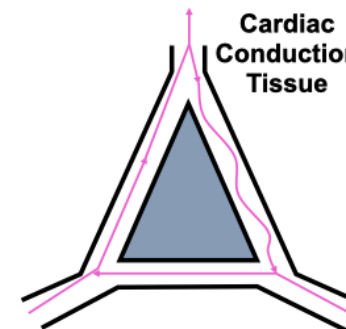
3 Sufficient delay

The returning pathway recovers in time

Two ways to interrupt it. Depress conduction enough to cause propagation failure—or **extend refractoriness** so the returning wavefront encounters tissue that is still inexcitable.



Re-exciting the heart with every lap



A circuit alone does not create reentry.

Part 1 — Building the circuit one condition at a time

Color shows how far each segment has recovered. Watch *where* the impulse dies in the first two configurations, then watch what changes when the block is added.

Two pathways only

Limbs α and β both conduct normally, in both directions.

NO REENTRY

+ Slow conduction in α

α conducts slowly. Both limbs still conduct in both directions.

NO REENTRY

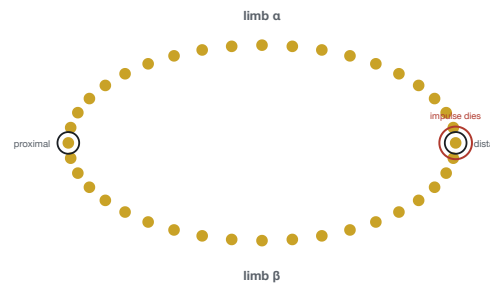
+ Unidirectional block in β

A block mid-way along β stops antegrade conduction but still passes retrograde.

REENTRY SUSTAINS

► Play

t = 21 ms



■ active wavefront ■ refractory — blocks any impulse ■ partially recovered — will conduct again ■ fully excitable

t = 20 ms — The two wavefronts meet head-on. Each runs into tissue the other has just depolarized — both are extinguished.

No reentry — the wavefronts annihilate each other. Both limbs conduct equally, so the two impulses arrive at the distal junction together and each meets tissue the other has just depolarized. A circuit that conducts symmetrically cannot circulate, however many pathways it contains.

KEY TAKEAWAY

With symmetric bidirectional conduction, opposing wavefronts collide and extinguish one another.

Slow conduction alone only moves the collision.

Part 1 — Building the circuit one condition at a time

Color shows how far each segment has recovered. Watch *where* the impulse dies in the first two configurations, then watch what changes when the block is added.

Two pathways only

Limbs α and β both conduct normally, in both directions.

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α conducts slowly. Both limbs still conduct in both directions.

NO REENTRY

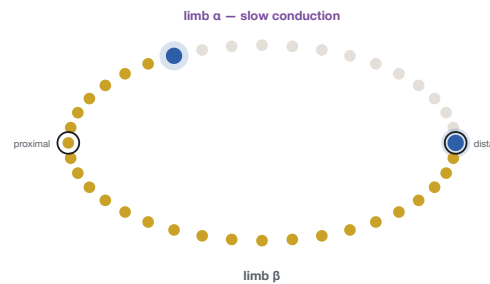
+ Unidirectional block in β

A block mid-way along β stops antegrade conduction but still passes retrograde.

REENTRY SUSTAINS

■ Pause

t = 21 ms



■ active wavefront ■ refractory — blocks any impulse ■ partially recovered — will conduct again ■ fully excitable

t = 20 ms — The wavefront reaches the distal junction and turns back up β , travelling retrograde.

No reentry — delay alone only moves the collision. The fast β wavefront rounds the distal junction and starts back up α , meeting the slow α wavefront head-on at t = 40 ms. Slow conduction has changed *where* they meet, not *whether* they meet. Watch the green band trailing each wavefront: recovery is happening, but there is no route that lets an impulse reach it.

KEY TAKEAWAY

Delay changes where the wavefronts meet; it does not by itself create a circulating impulse.

Unidirectional block lets the impulse return.

Part 1 — Building the circuit one condition at a time

Color shows how far each segment has recovered. Watch *where* the impulse dies in the first two configurations, then watch what changes when the block is added.

Two pathways only

Limbs α and β both conduct normally, in both directions.

NO REENTRY

+ Slow conduction in α

α conducts slowly. Both limbs still conduct in both directions.

NO REENTRY

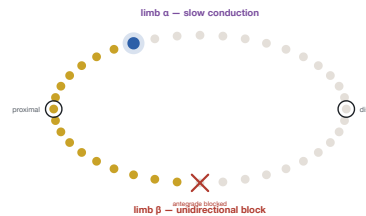
+ Unidirectional block in β

A block mid-way along β stops antegrade conduction but still passes retrograde.

REENTRY SUSTAINS

■ Pause

t = 21 ms



■ active wavefront ■ refractory — blocks any impulse ■ partially recovered — will conduct again ■ fully excitable

t = 10 ms — The β wavefront reaches the block and stops. Conduction here is blocked in the antegrade direction only — the tissue beyond it is never depolarized, and stays fully excitable.

Reentry sustains. The β wavefront is stopped at the block at t = 10 ms, so the tissue beyond it is never depolarized and stays fully excitable. Meanwhile the α wavefront takes until t = 58 ms to crawl to the distal junction, turns retrograde into β , and reaches the block from the far side at t = 70 ms — where it passes straight through, because the block is antegrade-only. By t = 80 ms it is back at the proximal junction, which recovered long ago. The loop closes and repeats every 80 ms. Compare with the previous configuration: same slow conduction, same circuit. The block did not create the delay — it removed the oncoming wavefront that was cancelling it.

KEY TAKEAWAY

The blocked antegrade limb stays excitable, then conducts retrograde after the delayed wavefront reaches it from the far side.

Wavelength determines the excitable gap.

Part 2 — Wavelength and the excitable gap

Hypothetical teaching circuit: the circular path is fixed at 12 cm so one variable can be changed at a time; real reentry pathways vary in size and geometry. Wavelength ($\lambda = CV \times ERP$) is the length occupied by the advancing wavefront and its refractory tail. Whatever path remains is the excitable gap.

CHANGE WAVELENGTH λ

- Shorten λ

Reset

+ Lengthen λ

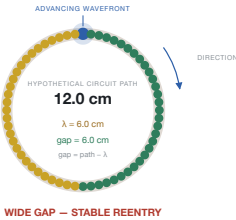
SET THE EXCITABLE GAP

Wide gap

Narrow gap

Critical margin

No gap



■ advancing wavefront ■ wavelength λ — refractory tail ■ excitable gap — recovered tissue

Wavelength = Conduction velocity × Effective Refractory Period

MODEL CIRCUIT PATH	WAVELENGTH λ	EXCITABLE GAP	STABILITY
12.0 cm	6.0 cm	6.0 cm	Stable

Wide gap — stable reentry in this teaching model. Wavelength occupies 6.0 cm of the 12.0 cm path, leaving a 6.0 cm excitable gap. The returning wavefront reaches recovered tissue with a generous margin.

KEY TAKEAWAY

λ = conduction velocity × ERP; whatever part of the circuit is not occupied by wavelength is recovered tissue.

Close the excitable gap and reentry terminates.

Part 2 — Wavelength and the excitable gap

Hypothetical teaching circuit: the circular path is fixed at 12 cm so one variable can be changed at a time; real reentry pathways vary in size and geometry. Wavelength ($\lambda = CV \times ERP$) is the length occupied by the advancing wavefront and its refractory tail. Whatever path remains is the excitable gap.

CHANGE WAVELENGTH λ

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SET THE EXCITABLE GAP

Wide gap

Narrow gap

Critical margin

No gap



■ advancing wavefront ■ wavelength λ — refractory tail ■ excitable gap — recovered tissue

Wavelength = Conduction velocity × Effective Refractory Period			
MODEL CIRCUIT PATH	WAVELENGTH λ	EXCITABLE GAP	STABILITY
12.0 cm	12.0 cm	0.0 cm	Terminated

No excitable gap — reentry terminates. Wavelength now equals the 12.0 cm circuit length, so the returning wavefront encounters tissue that is still refractory from its previous pass.

KEY TAKEAWAY

When wavelength reaches the circuit length, the returning wavefront meets its own refractory tail.

PR, QRS, and QT make the drug effect visible.

Measure this tracing

Choose an interval, then click the strip once at its start and once at its end. Check your answer, then move to the next.

PR

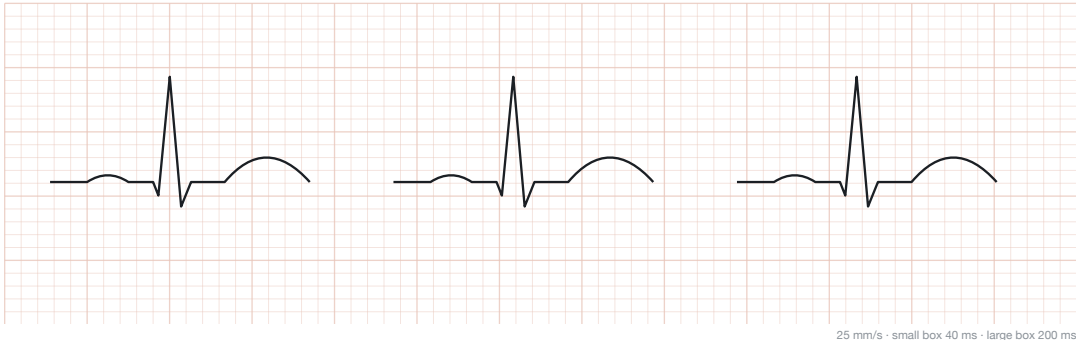
QRS

QT

CLEAR MARKS

CHECK ANSWERS

NEW TRACING



Click the strip twice to place a start and an end marker. Tolerance is ± 20 ms for PR and QT, ± 16 ms for QRS.

PR — place two markers	QRS — place two markers	QT — place two markers	
RATE 72 bpm	RR INTERVAL 833 ms	YOUR QTC (BAZETT) —	CLINICAL READ —

Case. Routine pre-operative tracing. Measure all three intervals, then check.

KEY TAKEAWAY

Read each interval as a tissue-level clue: PR reflects atrioventricular conduction, QRS reflects ventricular depolarization, and QT spans ventricular depolarization through repolarization.

The class label is the starting point—not the mechanism.

Lei modernized Vaughan–Williams map: read across from target → electrophysiologic effect → ECG clue → representative agents.

The Ila/Ild/Ile extensions are not standard Step 1 nomenclature. Real drug behavior still depends on state, kinetics, secondary targets, rate, and substrate.

CLASS	SUBCLASS / GROUP	DOMINANT TARGET	ELECTROPHYSIOLOGIC EFFECT	ECG CLUE	REPRESENTATIVE AGENTS
I Na ⁺	Ia Ib Ic	Nav1.5 State preference + recovery kinetics	Fast-tissue conduction ↓ Post-repolarization refractoriness ↑ Ia also delays repolarization	QRS ↑ Ia: QT ↑	Ia procainamide, quinidine, disopyramide Ib lidocaine, mexiletine Ic flecainide, propafenone
II Signals	Ila β antagonists Ild vagal/ACh → M ₂ Ile adenosine → A ₁	G-protein signaling G _s and G _i pathways	Pacemaker drive ↓ AV conduction ↓; nodal ERP ↑	PR ↑ Rate often ↓	Ila metoprolol, propranolol, esmolol Ild digoxin Ile adenosine
III K ⁺	I_{Kr}-directed Multichannel	Repolarizing K⁺ currents I _{Kr} -directed versus multiple K ⁺ currents and secondary targets	Ventricular APD ↑ ERP ↑	QT ↑	I_{Kr}-directed dofetilide, sotalolol, ibutilide Multichannel amiodarone, dronedarone
IV Ca ²⁺	L-type blockers	L-type Ca²⁺ channels Nodal phase 0	AV nodal conduction ↓ nodal ERP ↑	PR ↑	Verapamil diltiazem

Classification is orientation, not explanation. Sotalolol also blocks β receptors, ibutilide also enhances a slow inward current, and the multichannel drugs differ substantially in efficacy and safety.

Class I begins with a moving target.

CLASS



Nav1.5

The fast Na^+ channel changes conformation every beat. A drug's effect therefore depends on **when it binds** and **whether it leaves before the next impulse**.

01

Channel stateResting · open ·
inactivated

02

Binding kineticsAssociation +
dissociation

×

03

Activation rateHow often the channel
cycles

×

→

RESULT**Channels available
next beat**Phase-0 dV/dt ·
conduction ·
refractoriness

“Sodium-channel blocker” is not yet an explanation. State preference and recovery from block are what make Ia, Ib, and Ic behave differently.

The channel cycles; the drug follows the state.

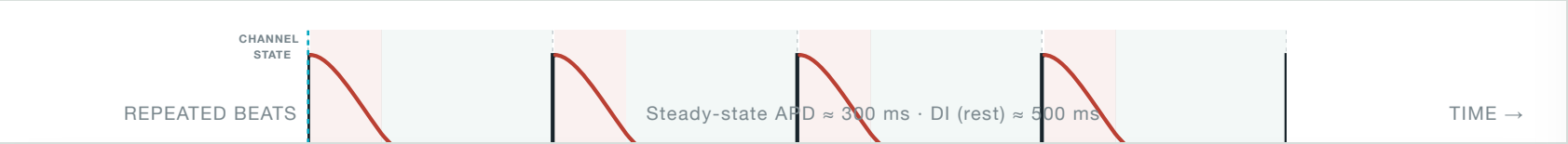
State-dependent binding: channel conformation changes drug access and affinity; functional recovery from block then competes with the interval before the next activation.

SCHEMATIC MODEL · VALUES ARE QUALITATIVE

01 Binding and unbinding follow the channel-state cycle

REPEATED ACTIVATION · FAVORED-STATE UPTAKE · DIASTOLIC RECOVERY FROM BLOCK

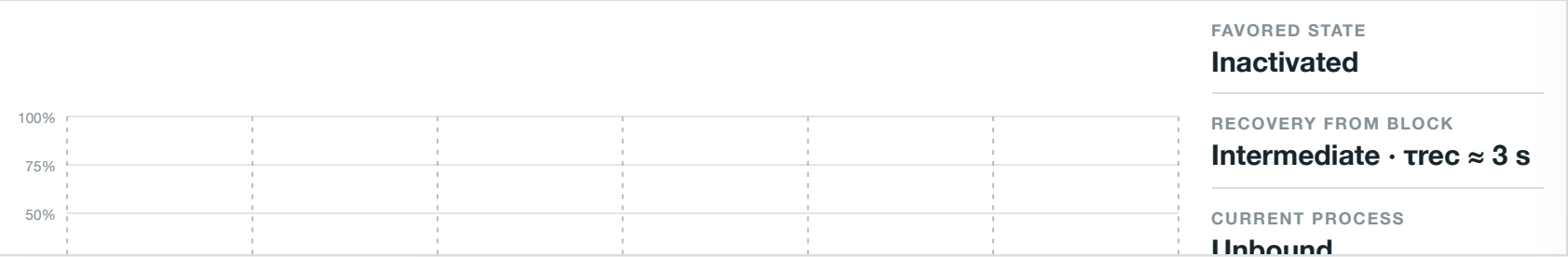
-- Rest — Open — Inactivated — Drug-bound



02 Model occupancy across successive beats

BINDING DURING THE FAVORED STATE · RECOVERY FROM BLOCK AT REST

$\approx 0\%$ MODEL DRUG-BOUND

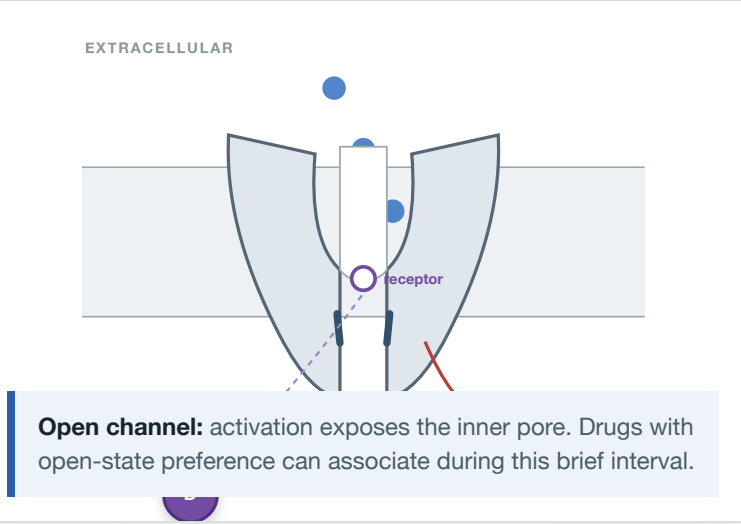


03 Channel + drug

CONFORMATION · RECEPTOR
ACCESS · OCCUPANCY

CHANNEL STATE

**OPEN ·
ACTIVATED**



MODEL OCCUPANCY $\approx 0\%$

$\rightarrow$

MODEL-UNBLOCKED NAV1.5 $\approx 100\%$

$\rightarrow$

PHASE-0 UPSTROKE RESERVE **Preserved**

$\rightarrow$

EXPECTED TISSUE EFFECT

Conduction preserved

ANIMATION

▶ Play

↪ Step state

↺ Reset

FAVORED STATE

Open

Inactivated

Open + inactivated

RECOVERY FROM BLOCK

Fast

Intermediate

Slow

PACING CONDITION

60

75

150 bpm

The pore is open, but this profile favors another state; little additional binding occurs here.

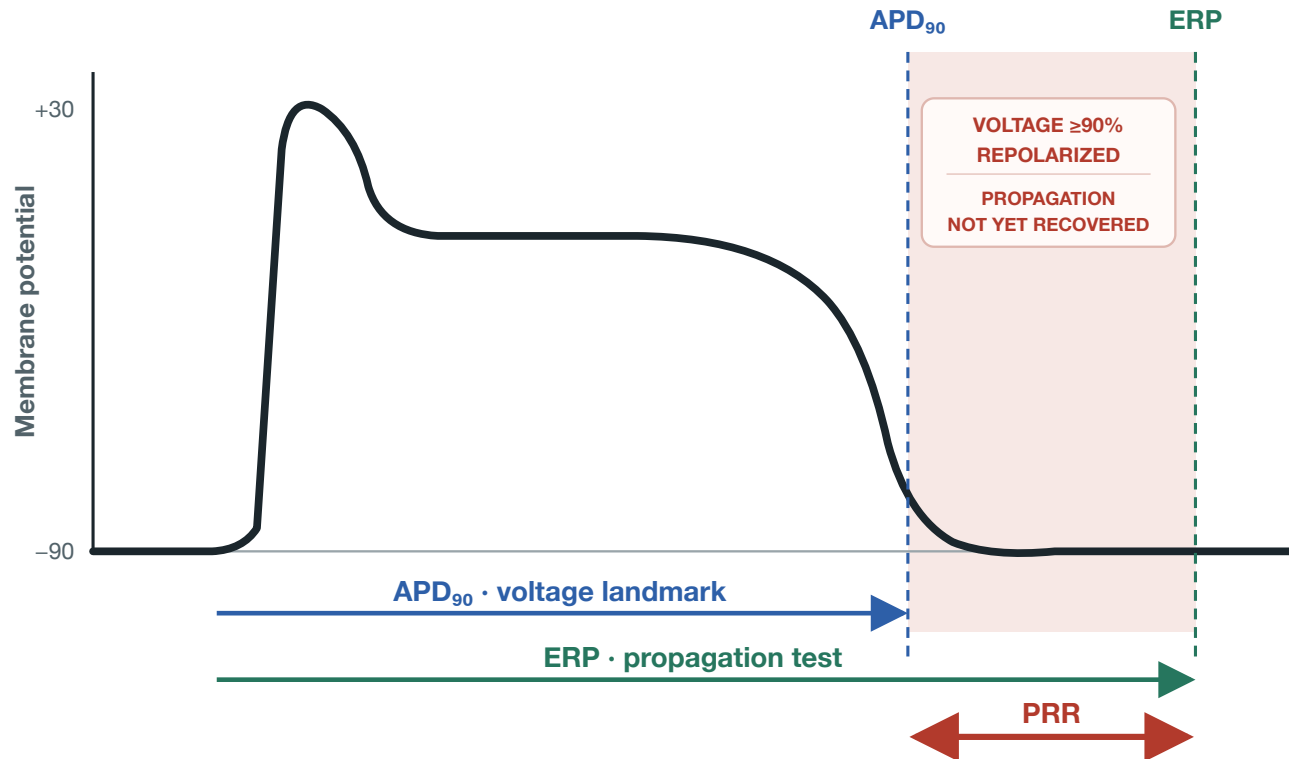
KEY TAKEAWAY

State preference determines when block develops; dissociation determines how much block survives to the next beat.

Voltage can recover before excitability does.

The membrane-voltage clock and the channel-availability clock can separate.

ERP > APD₉₀



APD₉₀ is a standardized 90%-repolarization landmark—not a claim that the final 10% of repolarization is complete.

1 APD₉₀: measure voltage

The membrane has completed 90% of its return toward resting potential. This defines a reproducible action-potential duration.

2 PRR: voltage is not enough

With Class I block, a sufficient fraction of Nav1.5 channels can remain **drug-associated and unavailable**. A premature impulse may therefore fail to propagate despite substantial repolarization.

3 ERP ends when propagation returns

ERP is defined operationally with a premature-stimulus test. It ends only when enough available fast Na⁺ current has recovered to support a propagated response.

KEY RELATIONSHIP

PRR is the positive interval ERP – APD₉₀: the voltage clock reaches its 90% landmark before propagation recovers.

A premature stimulus—not the voltage trace—defines ERP.

CLASS I · ELECTROPHYSIOLOGIC EFFECT

Test excitability after voltage has recovered

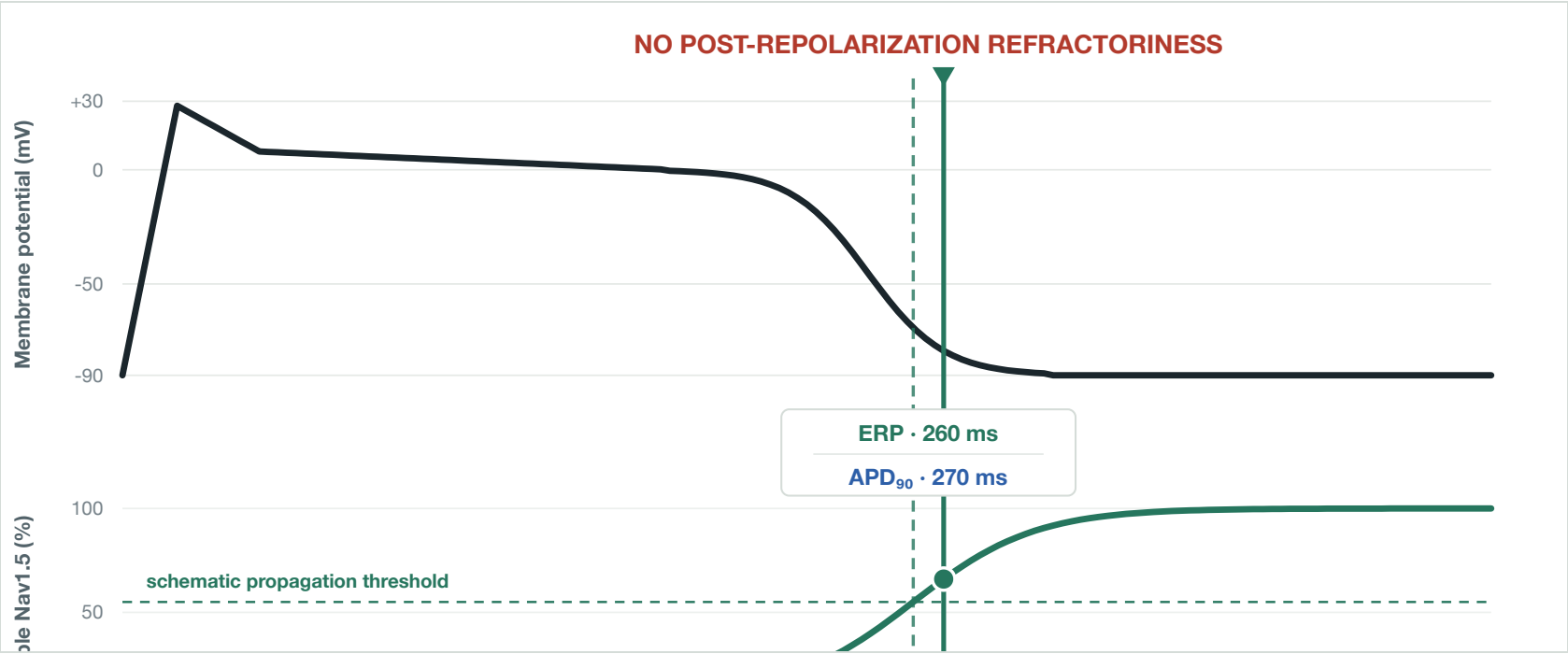
Qualitative teaching model. The displayed timing and channel-availability threshold are illustrative, not universal physiologic constants.

RECOVERY CONDITION

- No drug-associated delay
- Delayed recovery from Na⁺-channel block

PLACE THE PREMATURE STIMULUS

- At APD₉₀
- At ERP



Premature stimulus

270 ms

WHEN ERP OUTLASTS APD₉₀

PRR = ERP – APD₉₀

APD ₉₀ 270 ms	ERP 260 ms
PRR none	AVAILABLE NAV1.5 66%

PREMATURE-STIMULUS TEST

Propagated response returns

Enough unblocked, available fast Na⁺ channels have recovered to support the next phase-0 upstroke and tissue propagation.

APD₉₀ A voltage measurement: time from activation until

KEY TAKEAWAY

Without a drug-associated delay, excitability has recovered by APD₉₀ and no positive PRR interval remains.

Class Ia changes two currents—and therefore two clocks.

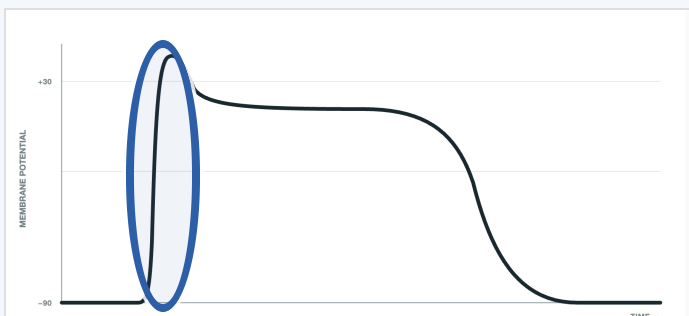
Procainamide · quinidine · disopyramide. The subclass shares a dual-current pattern, but the agents are not pharmacologically interchangeable.

Modernized V-W: open-state Nav1.5 · intermediate recovery · often K⁺ block

TARGET 01 · FAST ACTIVATION

Peak Na⁺ current

State-dependent Nav1.5 block develops during repeated activation and recovers on an intermediate clock.



Phase 0 · fast Na⁺-dependent upstroke

Cell phase-0 dV/dt and excitability ↓

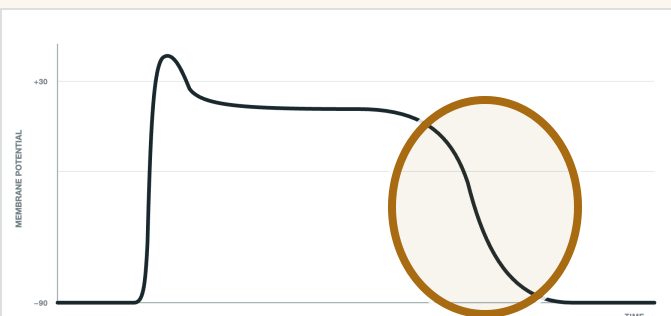
“Ia” describes a kinetic and current pattern, not moderate Na⁺-block potency. ∇

ventricular conduction ↓

TARGET 02 · REPOLARIZATION

Repolarizing K⁺ currents

Channel contribution differs by agent; NAPA is an important repolarization-delaying metabolite of procainamide.



Phase 3 · K⁺-dependent repolarization

Cell phase-3 recovery slows

APD and ERP ↑ together

NET CLASS 1A PHENOTYPE

Conduction slows while refractoriness lengthens.

- QRS widening
- repolarization/JT and QT prolongation
- ERP rises through two mechanisms
- reentry may become unsustainable
- conduction block and torsades remain the tradeoffs

Class 1a favors the open state and recovers on an intermediate clock.

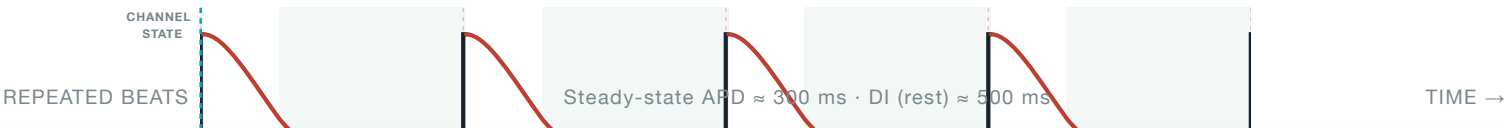
State-dependent binding: channel conformation changes drug access and affinity; functional recovery from block then competes with the interval before the next activation.

SCHEMATIC MODEL · VALUES ARE QUALITATIVE

01 Binding and unbinding follow the channel-state cycle

REPEATED ACTIVATION · FAVORED-STATE UPTAKE · DIASTOLIC RECOVERY FROM BLOCK

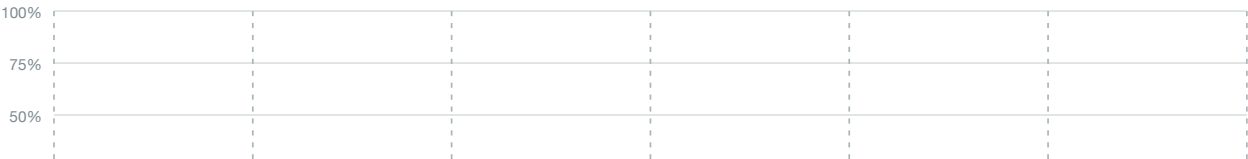
-- Rest — Open — Inactivated — Drug-bound



02 Model occupancy across successive beats

BINDING DURING THE FAVORED STATE · RECOVERY FROM BLOCK AT REST

$\approx 0\%$ MODEL DRUG-BOUND



FAVORED STATE
Open

RECOVERY FROM BLOCK
Intermediate · $\tau_{rec} \approx 3$ s

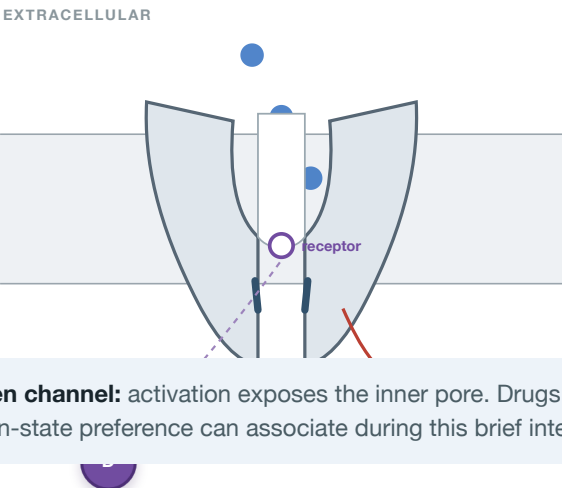
CURRENT PROCESS
Unbound

03 Channel + drug

CONFORMATION · RECEPTOR ACCESS · OCCUPANCY

CHANNEL STATE

OPEN · ACTIVATED



MODEL OCCUPANCY $\approx 0\%$



MODEL-UNBLOCKED NAV1.5 $\approx 100\%$



PHASE-0 UPSTROKE RESERVE **Preserved**



EXPECTED TISSUE EFFECT

Conduction preserved

ANIMATION

Play $\rightarrow$ Step state $\hookrightarrow$ Reset

FAVORED STATE

Open Inactivated Open + inactivated

RECOVERY FROM BLOCK

Fast **Intermediate** Slow

PACING CONDITION

60 **75** 150 bpm

Activation opens access: association accelerates while the pore is open.

KEY TAKEAWAY

Repeated activation exposes the favored state; incomplete recovery between beats produces use-dependent block.

First current: peak Na^+ block slows phase 0 and conduction.

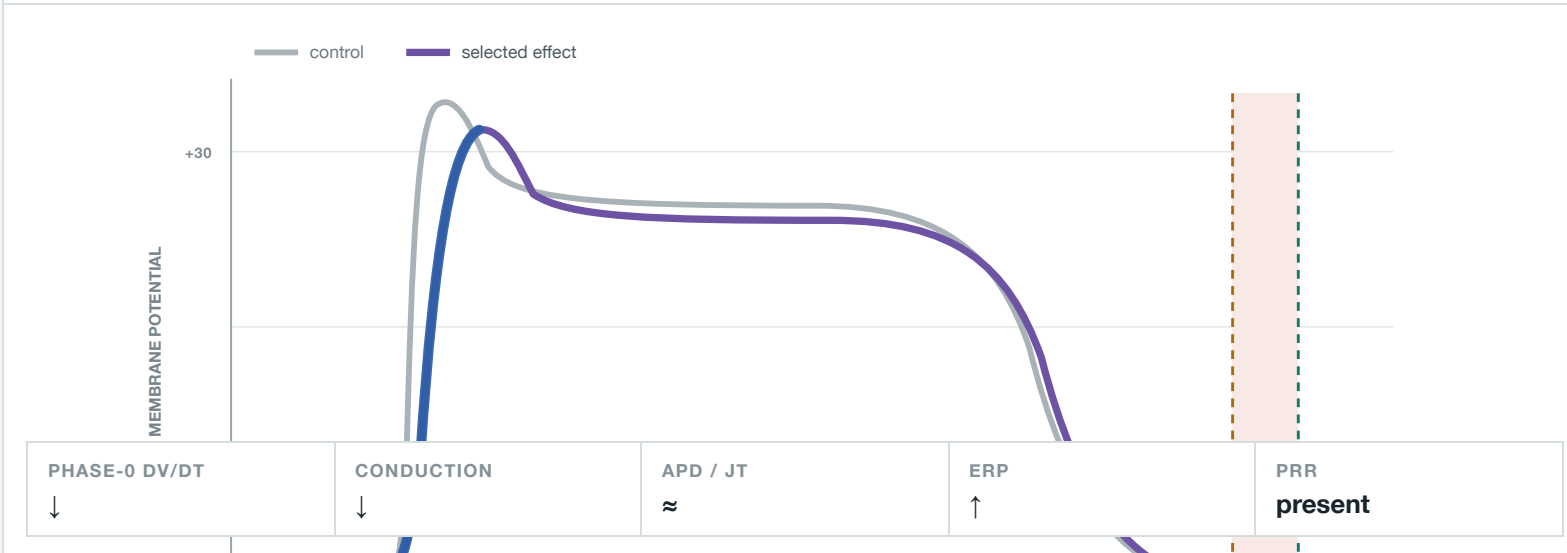
Class Ia has two electrophysiologic levers: peak Na^+ -current block slows fast-tissue activation, while K^+ -current block delays repolarization.

QUALITATIVE TEACHING MODEL · NOT TO SCALE

01 Ventricular action potential + recovery clocks

SEPARATE EACH TARGET, THEN COMBINE THEM

SELECTED VIEW
 Na^+ target isolated



02 Surface ECG footprint

ACTIVATION AND REPOLARIZATION LEAVE DIFFERENT CLUES



Na^+ target isolated: the slower phase-0 upstroke reduces conduction reserve and widens QRS. Drug-associated recovery from block can extend ERP after APD without directly delaying repolarization.

Na^+ TARGET
peak I_{Na} ↓

+

K^+ TARGET
repolarizing I_{K} unchanged

→

RECOVERY CLOCKS
PRR after APD

→

NET TISSUE EFFECT
conduction slows; reentry may block

BUILD THE MECHANISM

Control **Na^+ target only** K^+ target only Class Ia · both

Peak Na^+ -current block: phase-0 dV/dt and conduction fall. The repolarization waveform changes little, but recovery from block can create PRR.

KEY TAKEAWAY

The Na^+ branch lowers phase-0 dV/dt, widens QRS, and can extend ERP beyond APD through delayed recovery from block.

Second current: K⁺ block delays phase 3 and repolarization.

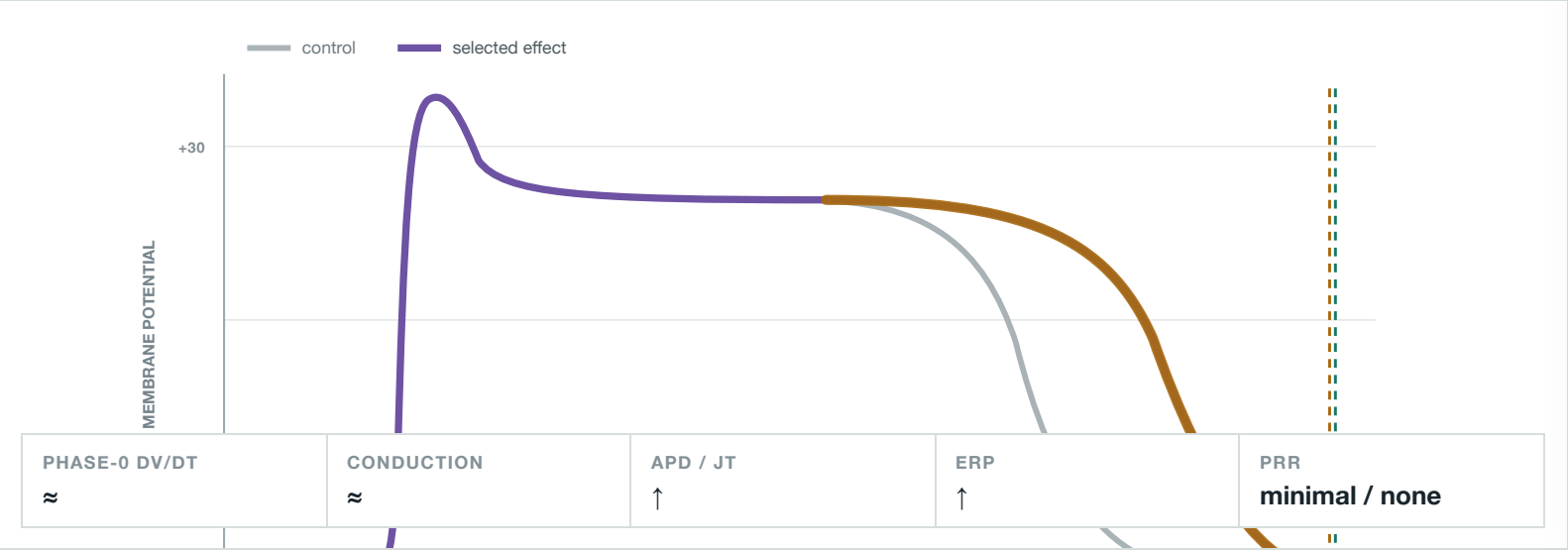
Class 1a has two electrophysiologic levers: peak Na⁺-current block slows fast-tissue activation, while K⁺-current block delays repolarization.

QUALITATIVE TEACHING MODEL · NOT TO SCALE

01 Ventricular action potential + recovery clocks

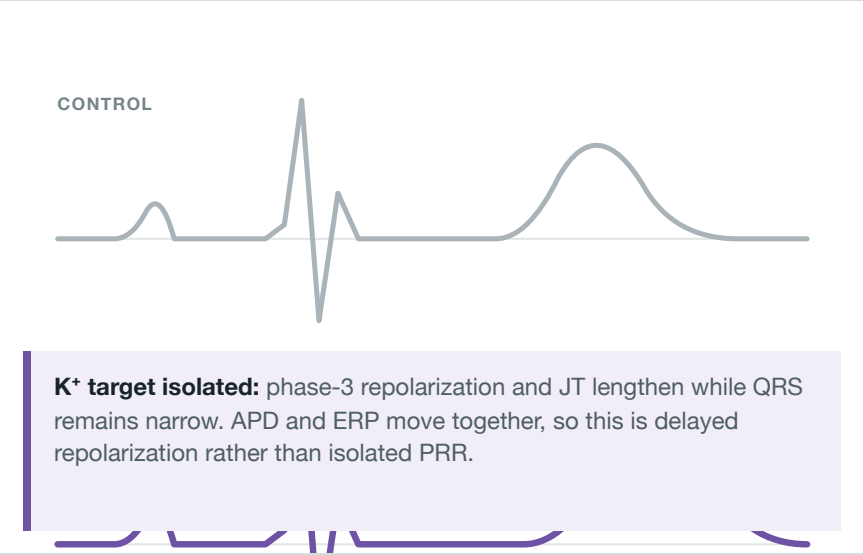
SEPARATE EACH TARGET, THEN COMBINE THEM

SELECTED VIEW
K⁺ target isolated



02 Surface ECG footprint

ACTIVATION AND REPOLARIZATION LEAVE DIFFERENT CLUES



BUILD THE MECHANISM

Control Na⁺ target only **K⁺ target only** Class 1a · both

Repolarizing K⁺-current block: APD, JT, QT, and ERP lengthen together. This can close a reentrant excitable gap —and can facilitate EADs and torsades.

KEY TAKEAWAY

The K⁺ branch lengthens APD, JT, QT, and ERP together; this is delayed repolarization, not isolated PRR.

Class 1a combines conduction slowing with delayed repolarization.

Class 1a has two electrophysiologic levers: peak Na^+ -current block slows fast-tissue activation, while K^+ -current block delays repolarization.

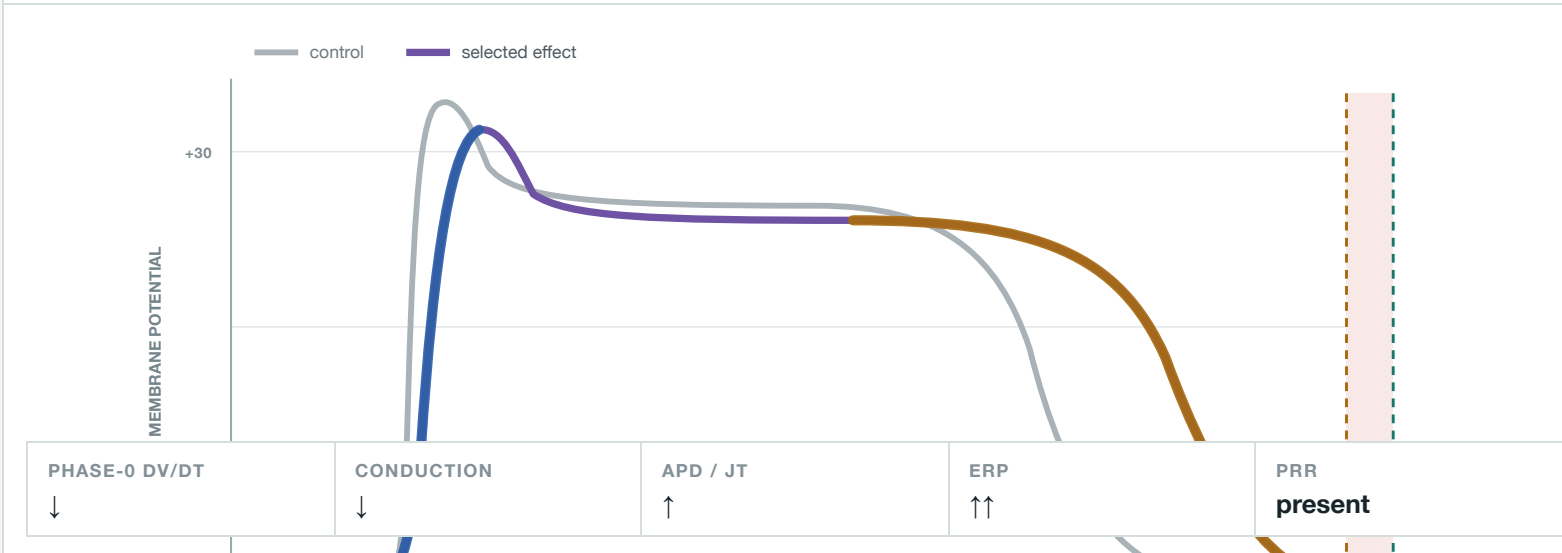
QUALITATIVE TEACHING MODEL · NOT TO SCALE

01 Ventricular action potential + recovery clocks

SEPARATE EACH TARGET, THEN COMBINE THEM

SELECTED VIEW

Class 1a · both targets



02 Surface ECG footprint

ACTIVATION AND REPOLARIZATION LEAVE DIFFERENT CLUES



Combined Class 1a effect: peak Na^+ -current block widens QRS, while delayed repolarization lengthens JT and usually QT. QT includes depolarization; JT isolates the repolarization component.

Na^+ TARGET
peak I_{Na} ↓

+

K^+ TARGET
repolarizing I_{K} ↓

→

RECOVERY CLOCKS
APD ↑ + PRR

→

NET TISSUE EFFECT
reentry becomes less sustainable

BUILD THE MECHANISM

Control

Na^+ target only

K^+ target only

Class 1a · both

Both targets are active: conduction slows while repolarization and refractoriness lengthen. The result can interrupt reentry, but the same QT prolongation creates torsades risk.

KEY TAKEAWAY

Expect QRS widening, repolarization/JT prolongation, QT prolongation, and a larger increase in ERP than either branch alone.

Procainamide is an acute option when the wide-complex rhythm is stable.

Procainamide is the clinically relevant acute Class 1a agent. Its usefulness depends on rhythm stability and on which pathway is carrying the tachycardia.

MONITORED IV THERAPY · DEFIBRILLATOR AVAILABLE

USE 01 · AHA 2025 · CLASS 2B

Stable wide-complex tachycardia

IV procainamide may be considered while the rhythm and blood pressure are continuously monitored.

If stable Obtain a 12-lead ECG, establish IV access, and treat with expert support.

If unstable **Synchronized cardioversion.** Do not delay electricity for a drug infusion.

2025 AHA infusion 20–50 mg/min; stop for rhythm suppression, hypotension, QRS increase >50%, or 17 mg/kg total. Maintenance: 1–4 mg/min. **Avoid with prolonged QT or CHF.**

CONTRAINDICATIONS AND CAUTIONS

Stable rhythm permits monitored drug therapy; instability, long-QT polymorphic VT, or torsades demands a different pathway.

WHY IT CAN WORK

It acts on myocardium and the accessory pathway—not selectively on the AV node.

Peak Na⁺ block
conduction and excitability ↓

+

Refractoriness ↑
APD prolongation + recovery from block

→

USE 02 · AF GUIDELINE · CLASS 1

Stable pre-excited AF

IV procainamide or ibutilide is recommended as an alternative to elective cardioversion.

Avoid **AV-nodal blockers:** adenosine, β-blockers, verapamil, diltiazem, digoxin, and IV amiodarone.

If unstable **Electrical cardioversion.**

One subclass, three toxicity signatures.

Shared electrical toxicity; distinct noncardiac signatures. Identify the mechanism first, then attach the adverse effect to the individual drug. **QT · QRS · BLOOD PRESSURE · ELECTROLYTES**

AGENT	DISTINGUISHING PHARMACOLOGY	TOXICITY SIGNATURE	CONTRAINDICATIONS AND CAUTIONS
Procainamide	Parent drug + active NAPA ; both accumulate when renal clearance falls.	Drug-induced lupus with prolonged exposure; ANA positivity; neutropenia/agranulocytosis and other blood dyscrasias; IV hypotension.	Interrupt loading for hypotension or marked QRS widening. Avoid complete heart block, prolonged QT/torsades, and CHF.
Quinidine	Prominent K ⁺ -current block plus antimuscarinic and α-blocking effects; P-glycoprotein inhibition.	Cinchonism: tinnitus, headache, visual disturbance. Diarrhea, thrombocytopenia, and torsades.	Rarely used as a routine antiarrhythmic. Can raise digoxin exposure; QT risk may be greatest at slower rates.
Disopyramide	Strong antimuscarinic action and pronounced negative inotropy.	Dry mouth, urinary retention, constipation, blurred vision; heart-failure worsening; torsades.	Avoid systolic HF, glaucoma, and urinary retention. A specialist niche remains in symptomatic obstructive HCM with an AV-nodal blocker.
Shared Class Ia hazards	Excess Na⁺ block: QRS widening, AV block, conduction failure. Excess repolarization delay: QT prolongation, EADs, and torsades—especially with bradycardia, hypokalemia, renal dysfunction, or interacting QT-prolonging drugs.		

Class 1b block is greatest in depolarized ventricular tissue.

Lidocaine · mexiletine. Class 1b drugs preferentially bind activated and inactivated Nav1.5 channels and dissociate rapidly after repolarization.

Activated / inactivated-state binding · rapid dissociation

PROPERTY 01 · STATE PREFERENCE

Preference for inactivated channels

Lidocaine and mexiletine preferentially bind Nav1.5 channels in the inactivated state.

×

PROPERTY 02 · RECOVERY KINETICS

Rapid dissociation after repolarization

When Nav1.5 channels enter the resting state, lidocaine and mexiletine dissociate rapidly.

=

NET CLASS 1B PHENOTYPE

More block in depolarized tissue

Peak Na⁺ current falls, which can slow or prevent propagation. Clinically, Class 1b drugs are used for ventricular arrhythmias and are largely ineffective against atrial arrhythmias, although their

Well-polarized tissue

near -90 mV

 **Most channels return to the available state**

During diastole in normally functioning, well-polarized tissue, Nav1.5 channels rapidly return to the resting state, causing Class 1b drugs to dissociate quickly.

Little drug-associated block remains at slower rates.

Depolarized / ischemic tissue

less negative rest

 **More channels remain inactivated**

Ischemia causes extracellular K⁺ to accumulate, making the resting potential less negative. Nav1.5 channels therefore spend more time in the high-affinity inactivated state, allowing Class 1b block to accumulate and become more pronounced—especially during rapid activation.

Depolarized, rapidly activated ventricular tissue retains more block.

Class 1b favors inactivated channels but recovers quickly at rest.

State-dependent binding: channel conformation changes drug access and affinity; functional recovery from block then competes with the interval before the next activation.

SCHEMATIC MODEL · VALUES ARE QUALITATIVE

01 Binding and unbinding follow the channel-state cycle

REPEATED ACTIVATION · FAVORED-STATE UPTAKE · DIASTOLIC RECOVERY FROM BLOCK

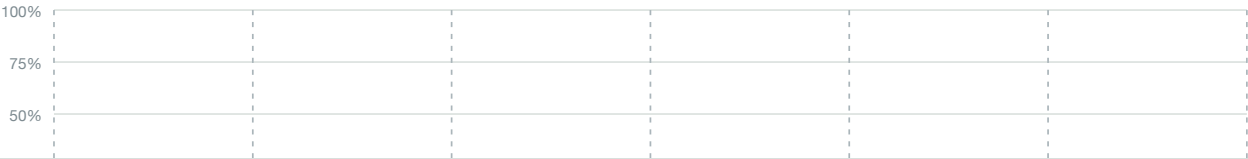
-- Rest — Open — Inactivated — Drug-bound



02 Model occupancy across successive beats

BINDING DURING THE FAVORED STATE · RECOVERY FROM BLOCK AT REST

≈0% MODEL DRUG-BOUND



FAVORED STATE
Inactivated

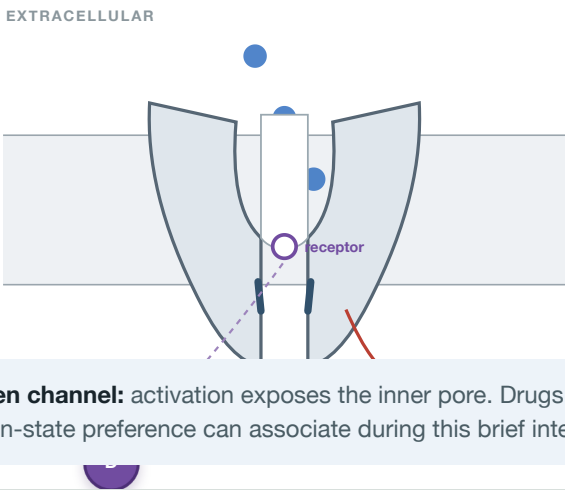
RECOVERY FROM BLOCK
Fast · $\tau_{rec} \approx 0.3$ s

CURRENT PROCESS
Unbound

03 Channel + drug

CONFORMATION · RECEPTOR ACCESS · OCCUPANCY

CHANNEL STATE
OPEN · ACTIVATED



MODEL OCCUPANCY ≈0%

MODEL-UNBLOCKED NAV1.5 ≈100%

PHASE-0 UPSTROKE RESERVE **Preserved**

EXPECTED TISSUE EFFECT

Conduction preserved

ANIMATION

▶ Play ➞ Step state ↺ Reset

FAVORED STATE

Open **Inactivated** Open + inactivated

RECOVERY FROM BLOCK

Fast Intermediate Slow

PACING CONDITION

60 **75** 150 bpm

The pore is open, but this profile favors another state; little additional binding occurs here.

KEY TAKEAWAY

Well-polarized tissue clears most use-dependent block between ordinary beats; depolarization and rapid activation leave less recovery reserve.

When refractoriness outlasts repolarization

Repolarization can finish before excitability returns. The interval between APD₉₀ and ERP is post-repolarization refractoriness (PRR).



Lidocaine terminates the loop only when the vulnerable limb fails to propagate.

CARDIOVASCULAR PHARMACOLOGY · CLASS IB

Lidocaine: breaking the reentry circuit

INTERACTIVE TEACHING MODEL

First pass · 4 steps · about 1 minute

CHOOSE YOUR LEVEL OF DETAIL

Four ideas first. Optional details pause playback so you can study.

First pass

4 steps

Deep dive

8 steps

01
An impulse keeps circling→ **02**
The vulnerable limb loses readiness→ **03**
The wave hits unrecovered tissue→ **04**
Block reverses as rate slows

01 · A REPEATING CIRCUIT

An impulse gets trapped in a loop

0 / 18 s
in this step

One direction is blocked at first. The impulse takes the other route and returns when tissue ahead is ready to fire again.

VENTRICULAR TISSUE · SCHEMATIC

Before lidocaine

THE MAIN IDEA

The impulse comes back.

Normally, an impulse activates ventricular tissue and stops. Here, it finds a route around the injured core.

The slow limb gives tissue ahead time to recover. The returning impulse activates it.

KEY TAKEAWAY

Selective slowing is not enough: termination occurs when the returning wavefront reaches repolarized tissue that still lacks sufficient Na^+ -channel availability.

Lidocaine is used for acute ventricular arrhythmias.

IV · rapid onset. Lidocaine is used in acute ventricular arrhythmias, especially when ischemic or rapidly activated myocardium is part of the substrate.

ACUTE CARE · VENTRICULAR ARRHYTHMIAS

THERAPEUTIC USE

Acute ventricular arrhythmias

VF or pulseless VT

After defibrillation and CPR, lidocaine may be considered when VF or pulseless VT remains unresponsive to shocks.

Other acute ventricular arrhythmias

May be used for recurrent ventricular arrhythmias, including polymorphic VT without QT prolongation, while ischemia and other causes are treated.

Not an atrial or AV-nodal drug

It is not a general treatment for AF, AVNRT, or AVRT.

ADVERSE EFFECTS

Neurologic toxicity often appears first

Early warning symptoms

Perioral numbness, tinnitus, dizziness, drowsiness, tremor, and confusion.

Severe toxicity

Seizures, unconsciousness, and respiratory depression; bradycardia, conduction block, hypotension, or cardiovascular collapse can follow.

Exposure rises in low-flow states

Liver disease, shock, and severe heart failure reduce clearance and increase toxicity risk.

MONITOR

Continuous ECG, blood pressure, and neurologic status during IV therapy.

CLINICAL SEQUENCE

Defibrillation and CPR remain primary in VF or pulseless VT.

SURFACE ECG

PR and QRS may change little at therapeutic exposure; toxicity or vulnerable tissue can produce conduction slowing.

Mexiletine provides oral Class Ib therapy.

Oral Class Ib therapy. Mexiletine is reserved for selected ventricular arrhythmias and selected patients with LQT3. **CHRONIC ORAL THERAPY · SPECIALIST SELECTION**

THERAPEUTIC USE

Selected ventricular disorders

Life-threatening ventricular arrhythmias

Used for documented ventricular arrhythmias such as sustained VT when the arrhythmia is judged life-threatening.

Selected LQT3 patients

Blocking pathologic late I_{Na} can shorten QT when the SCN5A variant is responsive.

Do not suppress asymptomatic PVCs

Use for lesser ventricular arrhythmias is discouraged, and antiarrhythmic therapy

ADVERSE EFFECTS

GI and neurologic effects commonly limit treatment

Gastrointestinal

Nausea, vomiting, heartburn, and upper abdominal distress are common and dose related.

Neurologic

Lightheadedness, tremor, paresthesias, and impaired coordination can require dose reduction or discontinuation.

Cardiac

Mexiletine can worsen ventricular arrhythmias and is contraindicated in

ADMINISTRATION

Taking doses **with food or an antacid** can reduce gastrointestinal intolerance.

MONITOR

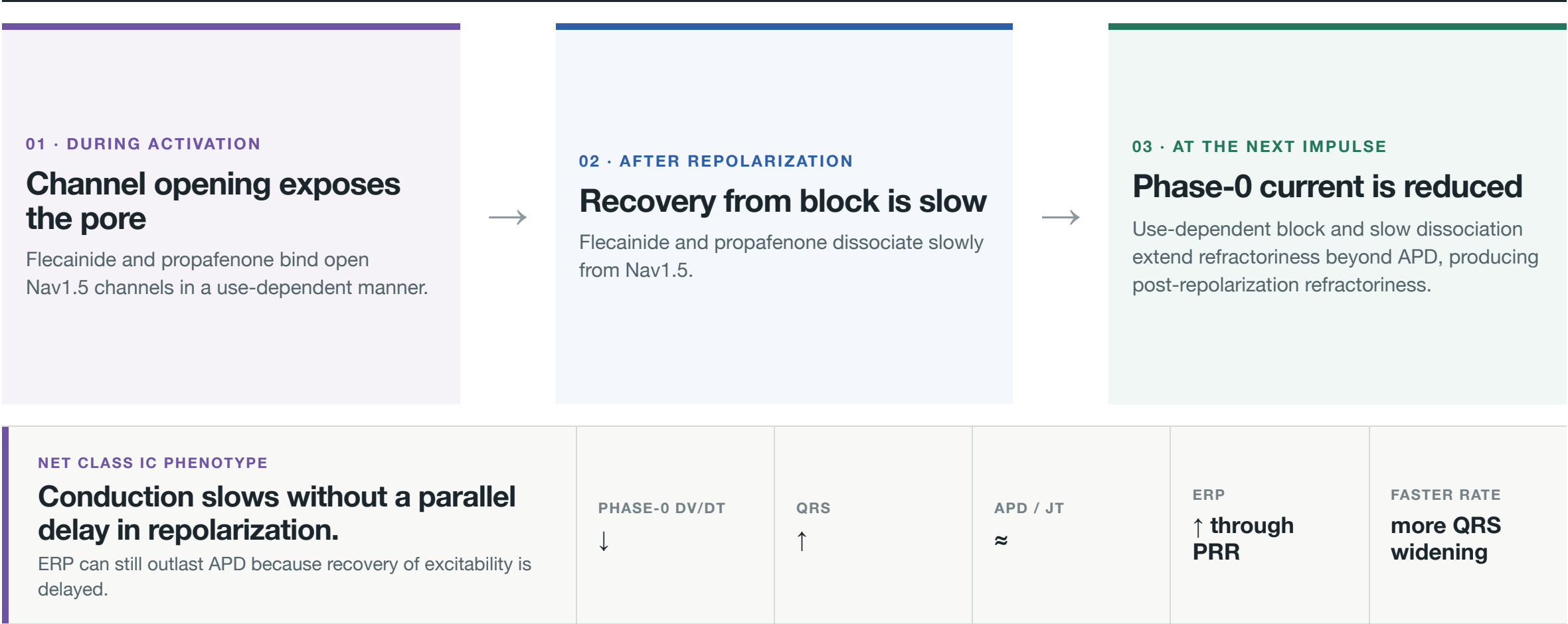
Initiate life-threatening-arrhythmia therapy in the hospital; follow rhythm, ECG intervals, adverse effects, and hepatic status.

SURFACE ECG

Intervals often change little; QT can shorten in responsive LQT3 patients.

Class Ic block carries into the next beat.

Flecainide · propafenone. Class Ic drugs produce use-dependent Nav1.5 block that recovers slowly between beats. **Activated/open-state access · slow recovery from block**



Slow recovery leaves fewer channels available for the next impulse.

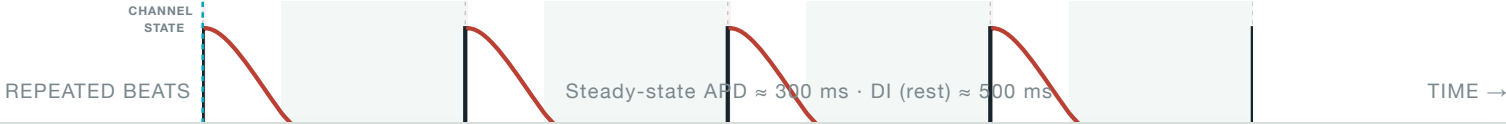
State-dependent binding: channel conformation changes drug access and affinity; functional recovery from block then competes with the interval before the next activation.

SCHEMATIC MODEL · VALUES ARE QUALITATIVE

01 Binding and unbinding follow the channel-state cycle

REPEATED ACTIVATION · FAVORED-STATE UPTAKE · DIASTOLIC RECOVERY FROM BLOCK

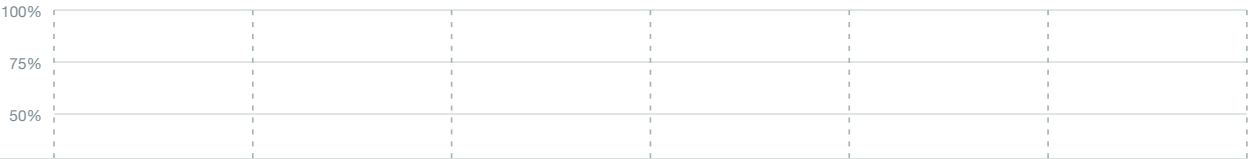
-- Rest — Open — Inactivated — Drug-bound



02 Model occupancy across successive beats

BINDING DURING THE FAVORED STATE · RECOVERY FROM BLOCK AT REST

≈0% MODEL DRUG-BOUND



FAVORED STATE
Open

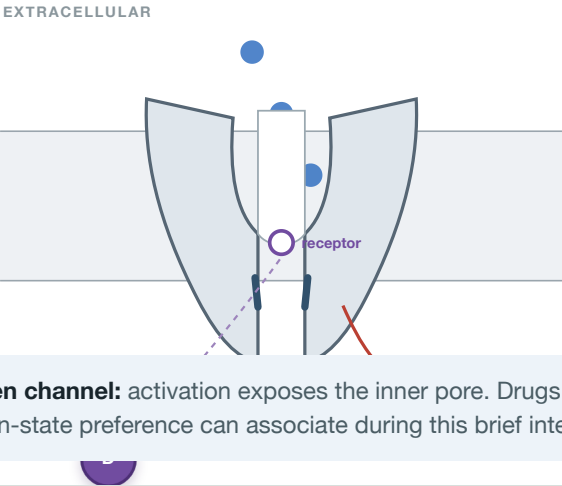
RECOVERY FROM BLOCK
Slow · $\tau_{rec} \approx 15$ s

CURRENT PROCESS
Unbound

03 Channel + drug

CONFORMATION · RECEPTOR ACCESS · OCCUPANCY

CHANNEL STATE
OPEN · ACTIVATED



MODEL OCCUPANCY ≈0% → MODEL-UNBLOCKED NAV1.5 ≈100% → PHASE-0 UPSTROKE RESERVE **Preserved** → EXPECTED TISSUE EFFECT **Conduction preserved**

ANIMATION

▶ Play

↪ Step state

↺ Reset

FAVORED STATE

Open

Inactivated

Open + inactivated

RECOVERY FROM BLOCK

Fast

Intermediate

Slow

PACING CONDITION

60

75

150 bpm

Activation opens access: association accelerates while the pore is open.

KEY TAKEAWAY

At an ordinary rate, persistent drug-associated channel unavailability lowers baseline conduction reserve.

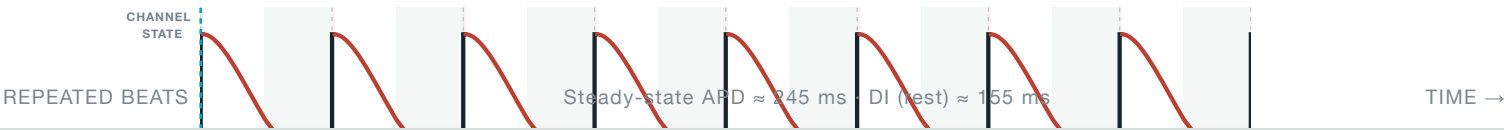
Faster activation magnifies Class Ic conduction slowing.

State-dependent binding: channel conformation changes drug access and affinity; functional recovery from block then competes with the interval before the next activation.

SCHEMATIC MODEL · VALUES ARE QUALITATIVE

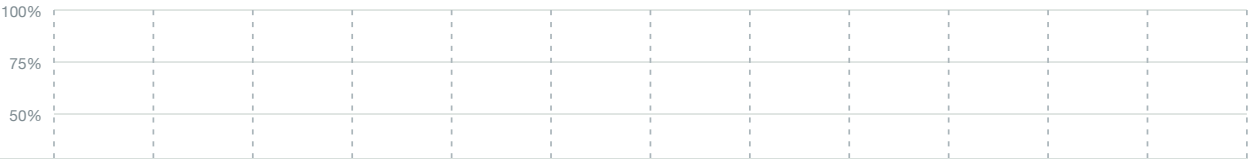
01 Binding and unbinding follow the channel-state cycle
REPEATED ACTIVATION · FAVORED-STATE UPTAKE · DIASTOLIC RECOVERY FROM BLOCK

-- Rest — Open — Inactivated — Drug-bound



02 Model occupancy across successive beats
BINDING DURING THE FAVORED STATE · RECOVERY FROM BLOCK AT REST

≈0% MODEL DRUG-BOUND



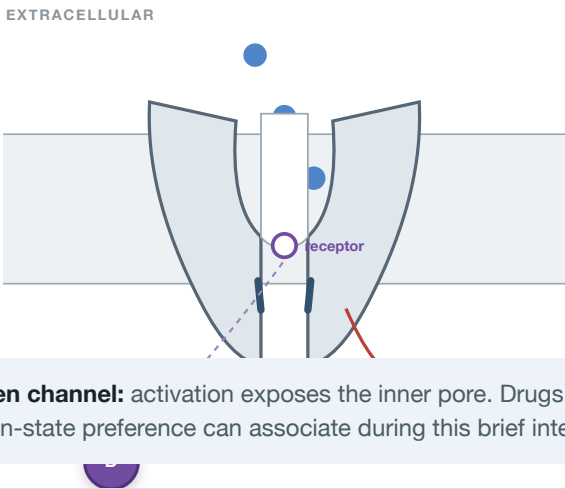
FAVORED STATE
Open

RECOVERY FROM BLOCK
Slow · $\tau_{rec} \approx 15$ s

CURRENT PROCESS
Unbound

03 Channel + drug
CONFORMATION · RECEPTOR ACCESS · OCCUPANCY

CHANNEL STATE
OPEN · ACTIVATED



Open channel: activation exposes the inner pore. Drugs with open-state preference can associate during this brief interval.

MODEL OCCUPANCY ≈0% → MODEL-UNBLOCKED NAV1.5 ≈100% → PHASE-0 UPSTROKE RESERVE Preserved → EXPECTED TISSUE EFFECT Conduction preserved

ANIMATION

▶ Play

→ Step state

↺ Reset

FAVORED STATE

Open

Inactivated

Open + inactivated

RECOVERY FROM BLOCK

Fast

Intermediate

Slow

PACING CONDITION

60

75

150 bpm

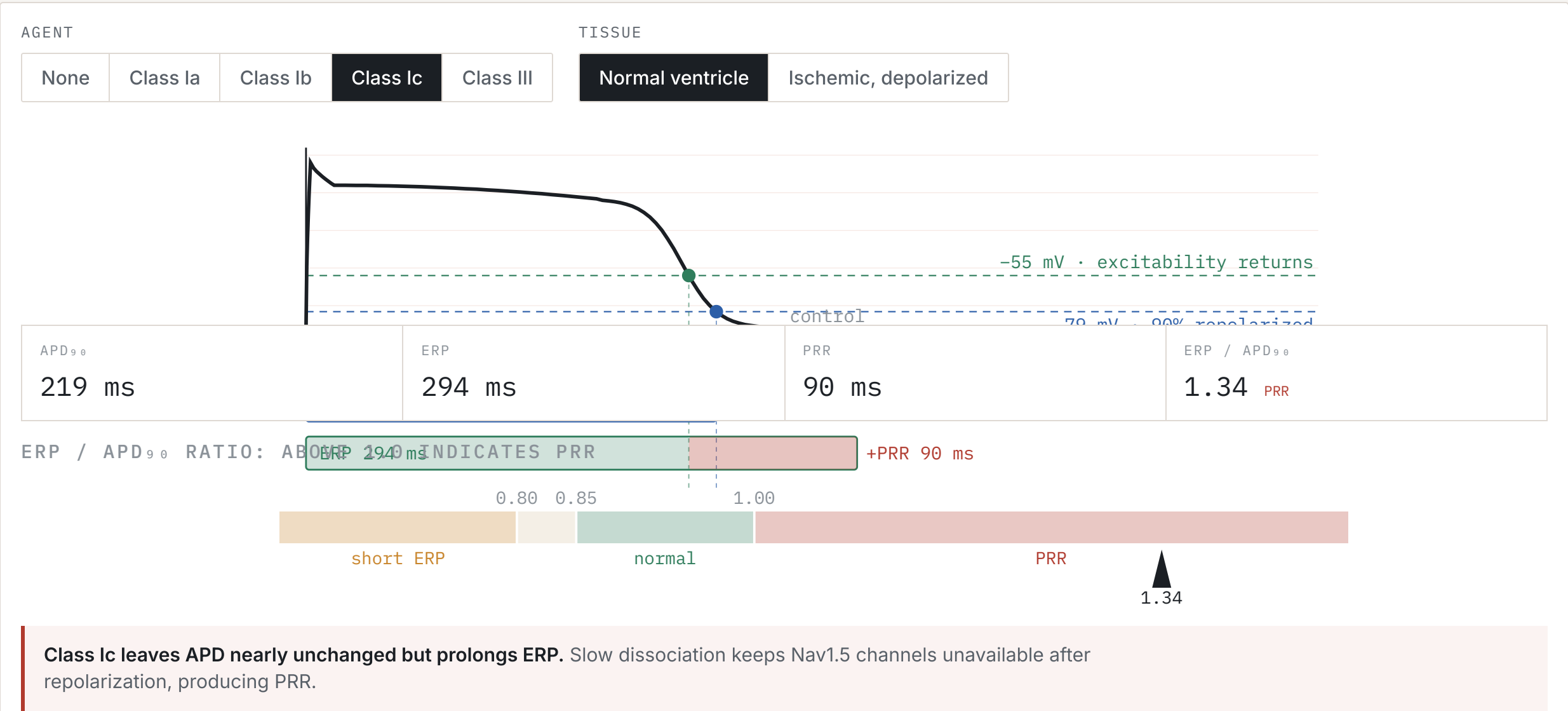
Activation opens access: association accelerates while the pore is open.

KEY TAKEAWAY

Repeated channel opening and a shorter resting interval allow more block to persist, so QRS widening can increase as heart rate rises.

When refractoriness outlasts repolarization

Repolarization can finish before excitability returns. The interval between APD₉₀ and ERP is post-repolarization refractoriness (PRR).



Class Ic requires a suitable substrate before the first dose.

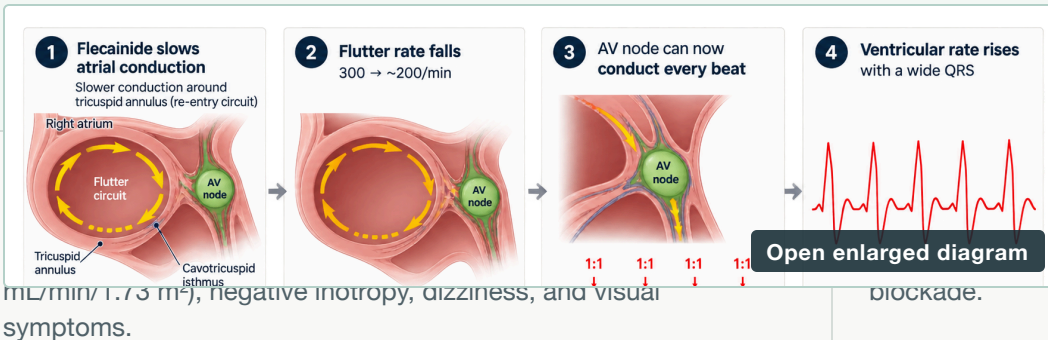
Flecainide · propafenone. These drugs can maintain sinus rhythm in selected patients with atrial fibrillation after the ventricular substrate has been assessed.

RHYTHM CONTROL · CONTRAINDICATIONS AND CAUTIONS

WHEN CLASS IC IS REASONABLE

Use after excluding a high-risk ventricular substrate

- AF rhythm control when there is **no prior MI**, significant structural heart disease, ventricular scar or fibrosis, or HFrEF.
- A selected pill-in-the-pocket strategy only after the first dose has proved safe and effective with monitoring.
- Give an **AV-nodal blocking drug** first to reduce the risk of atrial flutter with 1:1 AV conduction.



WHEN CONDUCTION SLOWING BECOMES DANGEROUS

Avoid after MI or with significant structural heart disease

- Scar creates nonuniform conduction; Class Ic can slow a vulnerable pathway enough to promote ventricular reentry.
- QRS widening can become more pronounced during tachycardia because block is use dependent.
- **CAST-I** showed that suppressing ventricular ectopy with encainide or flecainide after MI **increased arrhythmic death and cardiac arrest**.

ECG READOUT

PR ↑ · QRS ↑

QT may rise because QRS is longer; this is not primarily a repolarization-delaying class.

CONTRAINDICATIONS AND CAUTIONS

Flecainide and propafenone are atrial rhythm-control drugs for carefully selected patients—not drugs for suppressing ectopy in a scarred ventricle.

Flecainide: one action, two outcomes.

Class 1c · Medical education

Study

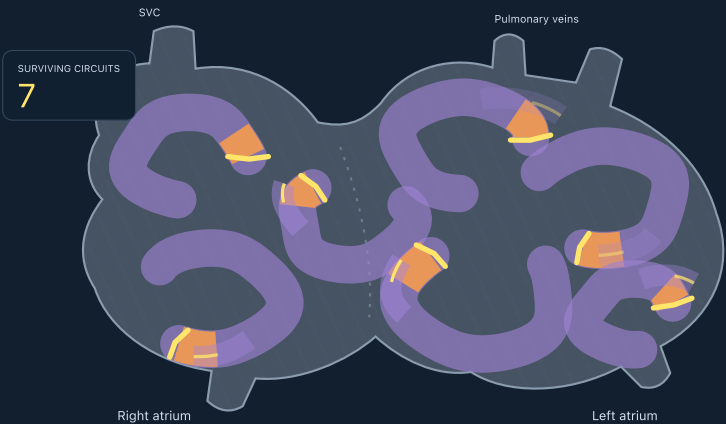
ACT 1 / RELATIVELY NORMAL ATRIUM

Multiple wavelets sustain atrial fibrillation

01 / 20

ATRIAL ACTIVATION · SCHEMATIC SUPERIOR VIEW

Before flecainide



Active wavefront Recently activated Refractory Excitable Repolarized, not recovered

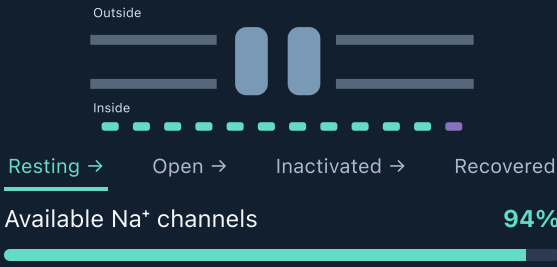
ILLUSTRATIVE SURFACE ECG · TIME EXPANDED

Atrial fibrillation

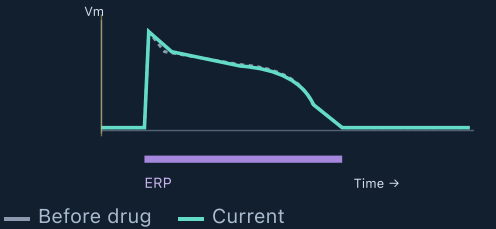


Na_v1.5

SAME TARGET



ACTION POTENTIAL & EXCITABILITY



ATRIAL BALANCE · SELECTED MODEL

Conduction velocity	Baseline
Functional ERP / recovery	Baseline
Wavelength λ	Short

WHAT TO NOTICE

Several shifting fronts split, collide, and re-enter. Many short-lived daughter waves and multiple surviving circuits keep the atria active.

PAUSE & PREDICT

What would happen if each circulating wave required more recovered tissue?

▶ Play

↺ Restart

← Previous

Next →

Speed

1x

✓

Show mechanism labels

Class II changes nodal signaling rather than fast- Na^+ conduction.

Classical Class II means beta-blockers. The modernized map also groups adenosine and vagal M_2 signaling by their effects on nodal G-protein pathways.

SLOW-RESPONSE TISSUE · RECEPTOR SIGNALING

SYMPATHETIC DRIVE

Beta-blockers

β_1 / G_s

Norepinephrine $\uparrow \beta_1/\text{G}_s$ signaling, raising cAMP and directly increasing I_f . The steeper phase-4 slope accelerates SA-node firing, while PKA-dependent Ca^{2+} current $\uparrow$ AV-node conduction.

Block this receptor signal

DIRECT INHIBITORY SIGNAL

Adenosine

A_1 / G_i

Adenosine lowers cAMP support and opens GIRK channels. This hyperpolarizes the membrane potential, causing a brief pause in AV-node conduction.

Activates this receptor signal

VAGAL INHIBITORY SIGNAL

Digoxin

M_2 / G_i

Digoxin increases vagal signaling, lowering cAMP and increasing K^+ conductance. Nodal cells hyperpolarize, slowing AV-node conduction and increasing refractoriness.

Increases vagal influence

SA NODE

phase-4 slope $\downarrow$ · rate $\downarrow$

+

AV NODE

$I_{\text{Ca,L}}$ support $\downarrow$ · conduction $\downarrow$ · ERP $\uparrow$

→

SURFACE ECG

PR may increase · QRS usually unchanged

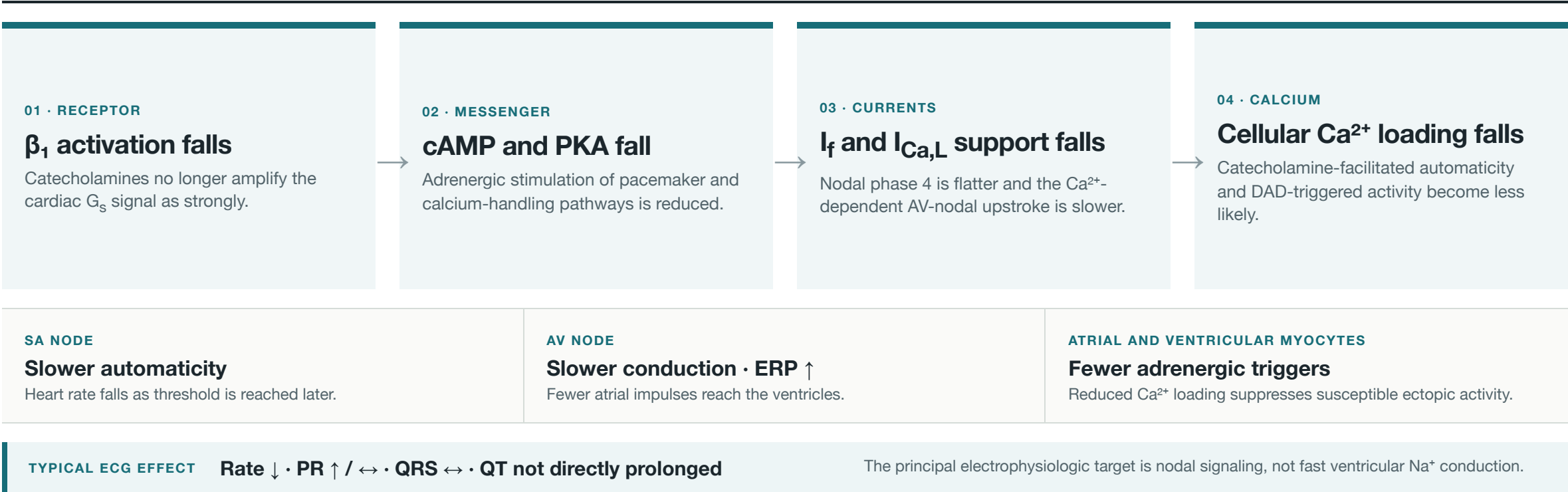
ORGANIZING PRINCIPLE

Beta-blockers remove sympathetic drive · adenosine and digoxin slow nodal signaling through G_i pathways.

Beta-blockers remove adrenergic amplification.

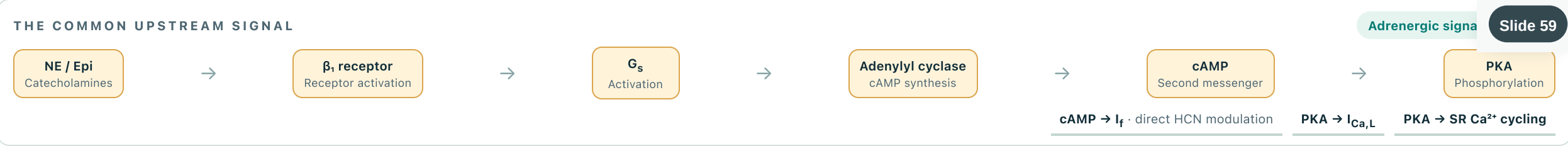
Metoprolol · esmolol · propranolol · nadolol. The antiarrhythmic effect begins by blocking cardiac adrenergic signaling.

ONE UPSTREAM ACTION · THREE ELECTRICAL EFFECTS



MECHANISTIC ANCHOR

Less β₁/G_s signaling slows sinus automaticity, slows AV-nodal conduction, and reduces catecholamine-dependent calcium loading.



Choose the beta-blocker by the clinical task.

Beta-blockers are most useful when **AV-nodal transmission or sympathetic drive** is part of the problem.

INDICATIONS · AGENT SELECTION · ADVERSE EFFECTS

AGENT PATTERN	WHERE IT FITS	WHAT DISTINGUISHES IT	IMPORTANT ADVERSE EFFECTS
Metoprolol β₁-selective · oral or IV	AF/flutter rate control; AV-node-dependent SVT; adrenergic or ischemic rhythm contexts.	Common cardiac-selective reference. Selectivity is dose dependent rather than absolute.	Bradycardia, AV block, hypotension, fatigue; can worsen acute decompensated HF.
Esmolol β₁-selective · IV · ultrashort acting	Acute monitored rate or rhythm control when rapid titration and rapid offset are useful.	Minutes-long effect allows close bedside adjustment.	Hypotension and bradycardia; infusion-site reactions and excessive nodal depression.
Propranolol · nadolol nonselective β blockade	Selected congenital long-QT and catecholaminergic polymorphic VT settings under specialist care.	Nadolol is long acting; propranolol has central and membrane-stabilizing effects at higher exposure.	Bronchospasm plus nodal effects; caution with reactive-airway disease and hypoglycemia risk.

Contraindications & cautions Avoid severe bradycardia or advanced unpaced AV block. Use cautiously in shock or acute decompensated HF. Other nodal depressants add to the effect.

Avoid abrupt withdrawal when possible.

THERAPEUTIC USE AND ADVERSE EFFECTS

The shared antiadrenergic mechanism supports rate control, nodal rhythm treatment, and suppression of catecholamine-driven triggers; agent and patient context determine safety.

Adenosine briefly blocks the AV node.

Adenosine activates A₁ receptors. It briefly suppresses AV-nodal excitability rather than directly blocking a calcium-channel pore.

SECONDS-LONG SIGNAL · LASTING CIRCUIT TERMINATION

01 · RECEPTOR

A₁ activates G_i

cAMP/PKA support falls; G-protein-gated K⁺ current increases.

02 · AV NODE

The nodal gate closes briefly

GIRK-mediated hyperpolarization moves the membrane away from threshold, preventing I_{Ca,L} opening and briefly blocking conduction.

03 · CIRCUIT

AVNRT or orthodromic AVRT stops

The induced transient AV block prevents the circulating wavefront from completing its required nodal limb, terminating reentry.

04 · RECOVERY

Conduction returns within seconds

The drug clears, sinus rhythm returns, and AV-nodal conduction resumes within seconds.

USE

Regular AV-node-dependent SVT

Acute termination after vagal maneuvers; it may also reveal underlying atrial activity.

EXPECTED TRANSIENT EFFECTS

Flushing · chest pressure · dyspnea

Brief AV block and a strong sense of apprehension are common; bronchospasm can occur.

DO NOT GENERALIZE THE NODAL STRATEGY

Irregular wide-complex rhythm or pre-excited AF

AV-nodal blockade can be dangerous when an accessory pathway conducts to the ventricle.

BLOOD HALF-LIFE **<10 seconds**

Caffeine and other methylxanthines antagonize; dipyridamole potentiates.

CIRCUIT ENDPOINT

Adenosine clears within seconds, but an AV-node-dependent tachycardia remains terminated because the circulating wavefront has already been extinguished.

The fast pathway wins.

A sinus impulse enters both functional pathways. The **fast pathway reaches the His bundle first**. The slower wavefront meets already activated tissue and dies out.

- **Fast conduction**
Longer refractory period: recovery takes more time.
- **Slow conduction**
Shorter refractory period: available again sooner.

WATCH FOR

The fast wavefront moves ahead, but its purple refractory afterglow lasts longer.



Digoxin slows the AV node through vagal signaling.

Digoxin has two mechanisms with different clinical consequences. Vagal nodal slowing and positive inotropy coexist at therapeutic concentrations. Higher exposure does not produce a clean mechanism switch; it progressively raises direct myocardial effects and toxicity risk.

MYOCYTE INOTROPY · VAGAL NODAL SLOWING

WORKING MYOCYTE · DIRECT DRUG EFFECT

Na⁺/K⁺-ATPase inhibition



Contractility increases

Excess cellular Ca²⁺ also contributes to DADs and ventricular ectopy during toxicity.

AV NODE · INDIRECT VAGAL EFFECT

Vagal M₂/G_i signaling increases



Ventricular rate can fall in AF

High sympathetic tone weakens its rate-control effect; onset is slow, and exercise or other non-resting heart rates are controlled less reliably.

WHERE IT FITS

Selected AF rate control, especially with HF symptoms

Use alone when other agents are unsuitable or as an adjunct when additional resting rate control is needed.

TOXICITY

Gastrointestinal, neurologic, visual, and arrhythmic

Renal impairment, interacting drugs, low body mass, and hypokalemia increase risk. Toxicity can produce bradycardia, AV block, atrial tachycardia with block, junctional rhythms, PVCs, or VT.

CONTRAINDICATIONS AND CAUTIONS

Narrow therapeutic margin

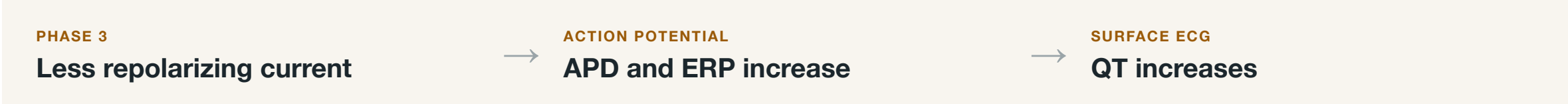
Adjust to kidney function and clinical context. When a level is checked for AF, a target below 1.2 ng/mL is reasonable.

CLINICAL DISTINCTION

Use vagal M₂ signaling to explain rate control; use Na⁺/K⁺-ATPase inhibition to explain inotropy and much of the toxicity.

Class III contains two pharmacologic strategies.

Dofetilide · ibutilide · sotalol · amiodarone · dronedarone. Each can prolong repolarization, but they do not reach that endpoint in the same way. **SHARED ENDPOINT · DIFFERENT PHARMACOLOGY**



FOCUSED REPOLARIZATION BRANCH

IKr-directed drugs

Dofetilide is the selective IKr reference. Sotalol blocks IKr and also provides nonselective β-blockade. Ibutilide also enhances a slow inward, predominantly Na⁺ current.

Dofetilide · ibutilide · sotalol

QT and torsades risk are central to dosing and monitoring.

BROAD ELECTROPHYSIOLOGIC BRANCH

Multichannel drugs

Amiodarone and dronedarone affect potassium, sodium, calcium, and adrenergic pathways. Their clinical effects and adverse-effect profiles extend beyond QT prolongation.

Amiodarone · dronedarone

Related pharmacology does not mean interchangeable clinical use.

IKR-DIRECTED BRANCH Reduced reserve prolongs repolarization; trigger and heterogeneity determine torsades	AMIODARONE Broad rhythm activity · substantial organ toxicity	DRONEDARONE Atrial rhythm control · narrow patient selection
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Selective IKr block lengthens phase 3 and the QT interval.

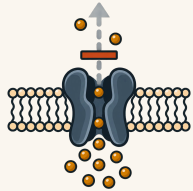
Dofetilide is the cleanest example. Sotalol shares the IKr effect but adds β -blockade.

REPOLARIZATION RESERVE HELPS DETERMINE SAFETY

01 · TARGET

IKr is inhibited

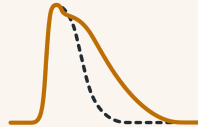
Less rapid delayed-rectifier K⁺ current leaves the cell during phase 3.



02 · VOLTAGE

Phase 3 slows

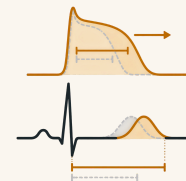
Ventricular repolarization takes longer, especially when repolarization reserve is already reduced.



03 · TIMING

APD, ERP, and QT increase

The longer refractory period can prevent a premature impulse from completing a reentry circuit.



04 · EXCESS EFFECT

EADs can trigger torsades

Long pauses and marked, nonuniform repolarization prolongation create the vulnerable setting.



THERAPEUTIC EFFECT

Refractoriness lengthens with repolarization, making reentry less likely to continue.

PROARRHYTHMIC EFFECT

Too little repolarization reserve permits early afterdepolarizations and polymorphic VT.

Torsades risk rises with: bradycardia or pauses low K⁺ or Mg²⁺ renal accumulation baseline QT prolongation other QT-prolonging drugs

MECHANISM AND LIABILITY

A longer ERP can interrupt reentry, but excessive or heterogeneous prolongation permits early afterdepolarizations and torsades.

Dofetilide shows reverse-use dependence.

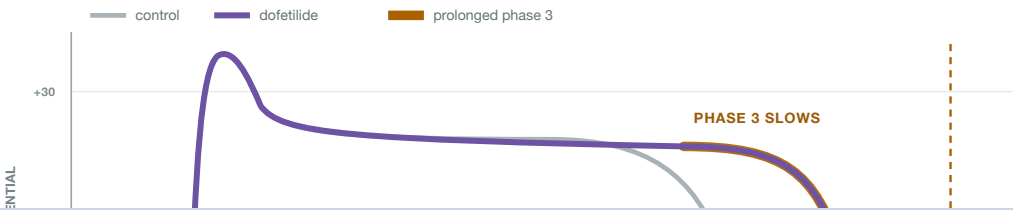
IKr block leaves less outward K⁺ current during phase 3. APD, ERP, and QT increase; reverse-use dependence means these drug effects are larger at slower heart rates.

QUALITATIVE TEACHING MODEL · COMPARE RATES WITHIN EACH DRUG

01 Ventricular action potential

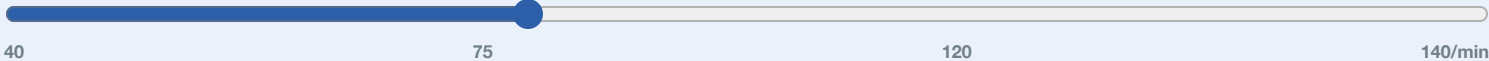
SELECTED VIEW
Dofetilide · 75/min

CONTROL AND SELECTED DRUG AT THE SAME RATE



HEART RATE

75/min



Move toward bradycardia: dofetilide produces progressively more APD and QT prolongation.

IKR DURING PHASE 3

↓↓

APD

↑

ERP

↑

SURFACE QT

↑

RATE RESPONSE

clear reverse-use

APD₉₀ ↑

PRIMARY TARGET

IKr ↓↓

PHASE 3

net outward current ↓

RECOVERY CLOCK

APD and ERP ↑

SURFACE ECG

QT ↑; more at slow rates

COMPARE IKR-DIRECTED DRUGS

Dofetilide

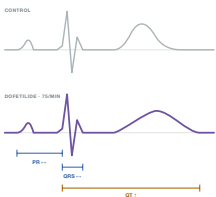
Sotalolol

Ibutilide

Dofetilide at 75/min: selective IKr block prolongs phase 3. Drag toward a slower rate to see the APD and QT effect increase.

02 Corresponding ECG effect

REPOLARIZATION CHANGES WHILE QRS REMAINS NARROW



Dofetilide: phase-3 prolongation lengthens the ST–T portion of the beat and therefore QT; PR and QRS change little.

ORAL · SELECTIVE IKR BLOCK

Dofetilide has no clinically relevant β -blocking effect.

Its rate-dependent APD and QT prolongation provides the clearest example of reverse-use dependence in this comparison.

Refractoriness defeats reentry.

Follow a Class III drug from ion channel to atrial rhythm.

Selective IKr block

Pure Class III reference • Can convert AF/flutter and maintain sinus rhythm.

ORAL • CONVERSION + MAINTENANCE

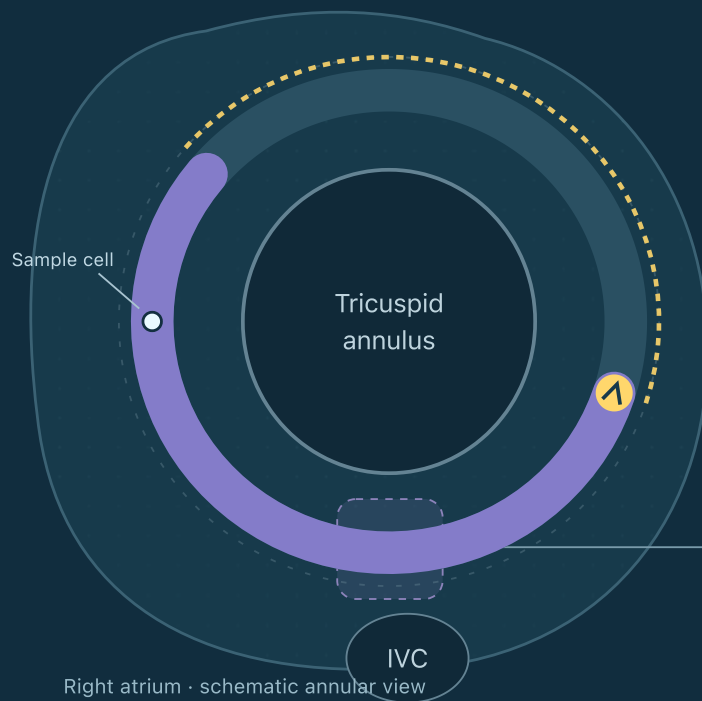
01 • TISSUE SCALE

Right atrium • CTI-dependent substrate

Counterclockwise macroreentry

1 circulating wavefront

REENTRY



CIRCUIT LENGTH

Fixed anatomy

EXCITABLE GAP

44%

of schematic circuit

● Activation front ● Refractory wake ○ Recovered / excitable

The CTI lies between the tricuspid annulus and IVC. Purple tissue cannot yet support a returning

02 • CELLULAR SCALE

Atrial myocyte action potential

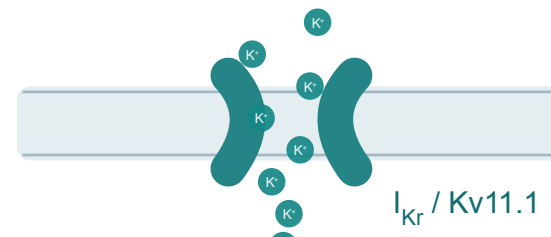
-- Before drug

— Current state



Sample cell: Refractory. Phase 0 preserved; phase 3 repolarizes.

Extracellular



Outward K⁺: normal

K⁺ efflux contributes to phase-3 repolarization.

Other repolarizing currents remain.

The clinical task determines the Class III drug.

The important differences are **what each drug is used for** and the adverse effects that accompany that choice.

INDICATIONS · NON-TORSADES TOXICITY

DRUG	PRIMARY INDICATION	IMPORTANT ADVERSE EFFECTS	CONTRAINDICATIONS AND CAUTIONS
Dofetilide oral · atrial rhythm control	Conversion and maintenance of sinus rhythm in highly symptomatic AF/AFL; an option in HFrEF.	Relatively little extracardiac toxicity. Headache, chest pain, and dizziness are reported most often.	Start or restart in hospital for ≥3 days. Dose by QT and CrCl; contraindicated if CrCl <20 mL/min. Check major drug interactions.
Ibutilide IV · acute conversion	Rapid conversion of recent-onset AF or atrial flutter; more effective for flutter. Not used for maintenance.	Prolonged repolarization can trigger EAD-mediated ventricular ectopy. Nonsustained monomorphic VT is reported, but its specific mechanism is uncertain. Hypotension, bradycardia or AV block, nausea, and headache.	Give only with continuous ECG monitoring and resuscitation capability. Avoid when LVEF ≤40%.
Sotalol oral · atrial or ventricular	Maintenance of sinus rhythm in selected symptomatic AF/AFL; treatment of documented life-threatening VT.	Bradycardia and AV block; fatigue, dizziness, dyspnea or bronchospasm, hypotension, and worsening heart failure.	Dose by kidney function. Avoid significant bradycardia or AV block, bronchospasm, and decompensated HF; generally avoid in HFrEF.

Shared issue: all three can cause clinically important QT-related proarrhythmia; their indications and other adverse effects remain distinct.

CLINICAL DISTINCTION

Dofetilide: atrial rhythm control · ibutilide: acute conversion · sotalol: selected atrial or ventricular arrhythmias.

Repolarization reserve protects phase 3—until it is spent.

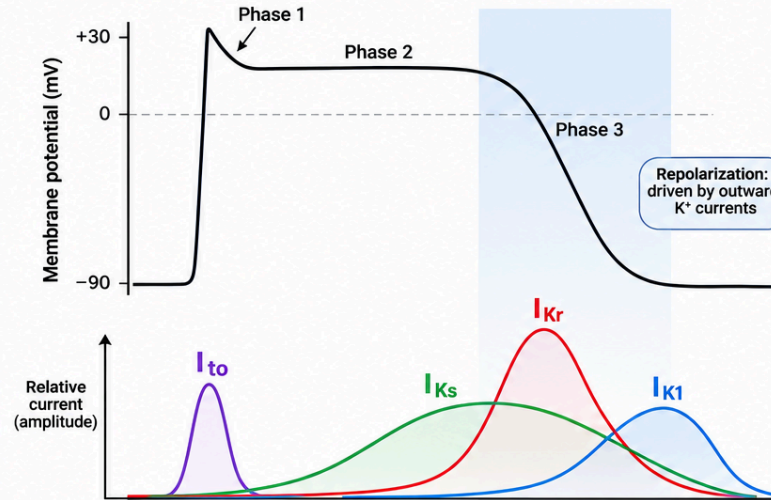


Any one hit is often tolerated. Repolarization reserve is the spare capacity supplied by overlapping repolarizing K⁺ currents.

Torsades becomes possible when enough redundancy is lost and repolarization becomes markedly prolonged and nonuniform.

Repolarization reserve

Multiple, **overlapping outward K⁺ currents** provide **redundant** repolarizing charge so action potential duration (APD) is preserved if any single current is lost or blocked.



Key repolarizing K⁺ currents

Primary phase 3 currents

- I_{Kr}** (Kv11.1 / hERG, KCNH2; MiRP1/KCNE2)
 - Rapidly inactivates in plateau, then surges in phase 3
 - Principal determinant of terminal repolarization
 - Main target in acquired long QT
- I_{Ks}** (Kv7.1 / KvLQT1, KCNQ1; MinK/KCNE1)
 - Activates slowly; accumulates through plateau → phase 3
 - "Safety-factor" current when I_{Kr} is compromised
 - ↑ with β-adrenergic/cAMP-PKA; stronger at faster rates
- I_{K1}** (Kir2.x, KCNJ2/12/4)
 - Suppressed at plateau; conducts outward in late phase 3
 - Governs final repolarization and stabilizes resting potential

Contributory / conditionally important

- I_{to}** (Kv4.x / KCNIP2, Kv1.4)
 - Phase 1 notch current
 - Independent contributor to reserve & beat-to-beat variability
 - More prominent when I_{Ks} is inhibited
 - Underlies transmural repolarization gradients

AGENT

None

I_Kr blocker

Class Ia

Amiodarone

CO-PRESCRIBED NON-CARDIAC DRUG

None

Ondansetron

Azithromycin

Haloperidol

Methadone

SERUM K⁺

4.2 mmol/L

HEART RATE

75 bpm

TRIGGER

DELIVER A PAUSE

PVC + compensatory pause · long RR in AF
dropped beat · sinus pause · after cardioversion

APD ₉₀	QT	QTC (BAZETT)	POST-PAUSE QT	REPOL. RESERVE	DISPERSION	MODEL PATTERN
343 ms	403 ms	450 ms	—	71%	raised	heterogeneous recovery

PIN THIS SCENARIO

CLEAR

pin one, change something, and compare without scrolling

Build a scenario and watch all three consequences

The controls stay pinned above. Read left to right: prolongation and trigger, modeled reserve, then one illustrative regional-dispersion hypothesis.

VENTRICULAR ACTION POTENTIAL — TREATED AGAINST CONTROL

RHYTHM STRIP

REPOLARIZING CAPACITY

Each row shows how much of one outward K⁺ current remains. The bottom bar is the combined reserve—not a torsades score.

CONTRIBUTION TO PHASE 3 · CAPACITY LEFT	
I_Kr 46% share	62% lost
I_Ks 28% share	intact
I_K1 18% share	intact
I_to 8% share	intact

ILLUSTRATIVE TRANSMURAL MODEL

This wedge-style teaching model compares regional repolarization endpoints. It does not assert that intact human hearts contain a discrete M-cell layer or a universal transmural gradient.

— Epicardium — Midmyocardial phenotype — Endocardium — dashed control

ACTIVATION AT 0 ms · RETURN TO REST

RAISED SPREAD

Amiodarone acts in atria, ventricles, and the AV node.

Amiodarone is not a selective potassium-channel blocker. Its Class III label captures only one part of its electrophysiology.

BROAD CARDIAC ELECTROPHYSIOLOGY

K⁺ CURRENTS APD, ERP, and QT increase	NA⁺ CHANNELS Fast-tissue conduction slows	CA²⁺ CHANNELS Nodal current decreases	ADRENERGIC EFFECTS Sinus rate and AV conduction slow
--	--	--	--

ATRIAL RHYTHM CONTROL

Maintains sinus rhythm when other options narrow

- Effective maintenance of sinus rhythm in AF; commonly used when HFrEF limits other options.
- Calcium-channel and antiadrenergic effects also slow sinus and AV-nodal activity.
- QT often lengthens, but torsades is less common than with selective IKr block.

VENTRICULAR RHYTHM CONTROL

Broad electrical effects reach scar-related reentry

- IV and oral formulations have roles in selected ventricular arrhythmias.
- Amiodarone or lidocaine may be considered for VF/pulseless VT that persists despite defibrillation.
- K⁺-current block lengthens ERP while Na⁺-channel block can slow conduction.
- Reentry terminates when the returning wavefront meets tissue that remains

REENTRY BALANCE ERP ↑ while conduction may slow	SURFACE ECG Rate ↓ · PR ↑ · QT ↑ · QRS ↔ / mildly ↑	STRUCTURAL HEART DISEASE A common rhythm-control option when HFrEF limits alternatives
---	---	--

Closing the excitable gap.

How **amiodarone** interrupts myocardial reentry, from ion channels to rhythm.

Established tissue-effect model Scar-related monomorphic VT. Time and geometry are simplified; this is not an acute IV onset simulation or a guarantee of conversion.

01 / MYOCARDIAL CIRCUIT

Before amiodarone



A circuit is necessary, but not sufficient.

Leading wavefront Refractory tail Recovered / excitable

Surface ECG · conceptual

Sinus rhythm

BUILD THE SUBSTRATE

01 / 14

A path around a scar

Viable myocardium surrounds a fixed, nonconducting scar. The narrow isthmus conducts slowly. A circuit alone does not create a circulating impulse.

02 / The timing relationship

Relative units*

Circuit travel time 100

Effective refractory period (ERP) 64

Activation · 0 Same time scale · 140

ERP ends before the wavefront returns: tissue recovers and reentry can continue.

Recovery margin: 36.0 relative units

03 / Cellular action potential

Ventricular myocyte

Before drug Current state

mV | 0

The amiodarone paradox

Amiodarone can markedly prolong QT, yet torsades occurs much less often than with selective IKr blockers.

QT duration and torsades propensity reflect different electrophysiologic features.

WHY TORSADES IS LESS COMMON

Inward-current suppression	Na ⁺ - and L-type Ca ²⁺ -channel effects can reduce early afterdepolarizations and triggered beats.
Weak reverse-use dependence	Chronic amiodarone prolongs repolarization more consistently across rates, so slow rates and pauses amplify the effect less.
Repolarization pattern	Experimental tissue models often show less dispersion than selective IKr block. Surface QT-dispersion findings are inconsistent.

THE DISTINCTION

QT records repolarization duration.
Torsades also needs a vulnerable substrate and an initiating beat. Amiodarone can lengthen QT while opposing EAD formation and pause amplification.

Amiodarone can still cause torsades. Bradycardia, low K⁺ or Mg²⁺, and other QT-prolonging drugs increase risk.

AGENT

None

I_Kr blocker

Class Ia

Amiodarone

None

Ondansetron

Azithromycin

Haloperidol

Methadone

CO-PRESCRIBED NON-CARDIAC DRUG

None

Ondansetron

Azithromycin

Haloperidol

Methadone

SERUM K⁺

4.2 mmol/L

HEART RATE

75 bpm

TRIGGER

DELIVER A PAUSE

PVC + compensatory pause · long RR in AF
dropped beat · sinus pause · after cardioversion

APD₉₀

381 ms

QT

441 ms

QTC (BAZETT)

493 ms

POST-PAUSE QT

—

REPOL. RESERVE

61%

DISPERSION

low

MODEL PATTERN

QT prolongation

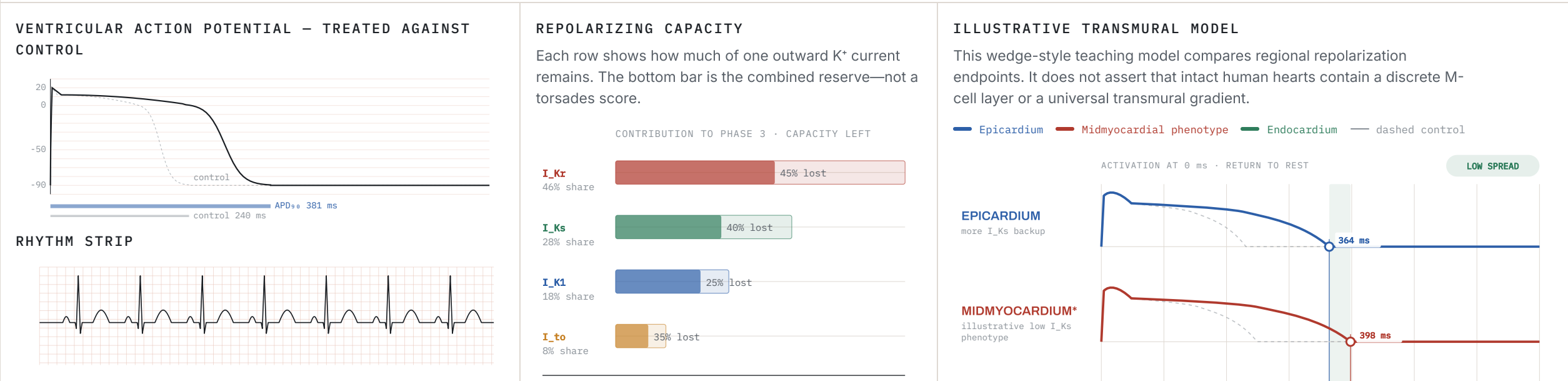
PIN THIS SCENARIO

CLEAR

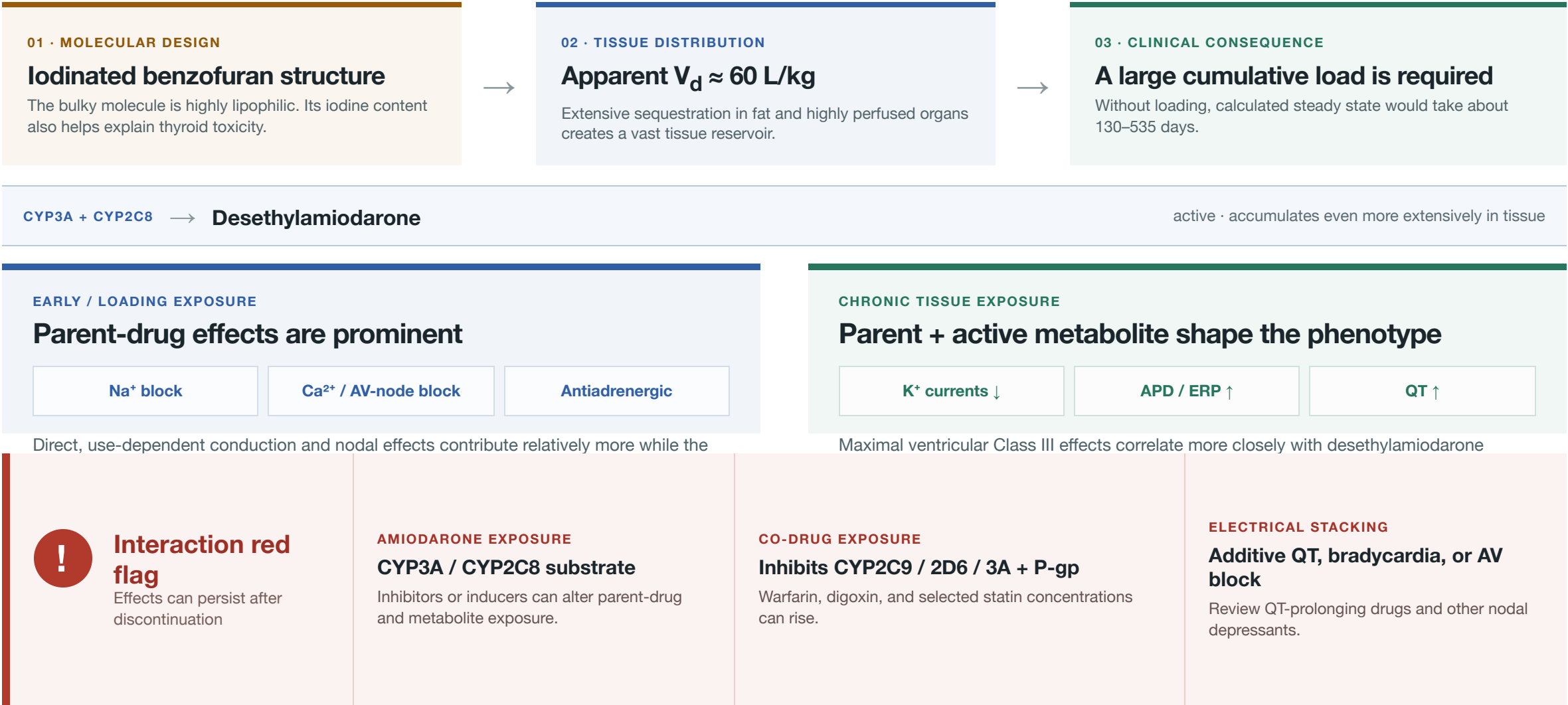
pin one, change something, and compare without scrolling

Build a scenario and watch all three consequences

The controls stay pinned above. Read left to right: prolongation and trigger, modeled reserve, then one illustrative regional-dispersion hypothesis.



Amiodarone pharmacokinetics reshape its cardiac effects.



TIME CHANGES THE PHENOTYPE

Loading builds a vast tissue reservoir; parent drug and active metabolite then sustain evolving electrophysiologic effects, interactions, and toxicity.

Amiodarone toxicity and monitoring

Scheduled surveillance and symptom-triggered evaluation address different parts of amiodarone toxicity.

MONITORING: 2023 AF GUIDELINE · OCCURRENCE VARIES WITH EXPOSURE

ADVERSE EFFECT	BASELINE	FOLLOW-UP	ACTION IF TOXICITY OCCURS
THYROID Hypo- or hyperthyroidism Approx. 2–24%	TSH T4 and T3 if TSH abnormal	3–6 months then every 6 months	Hypothyroid: thyroid replacement; reassess dose. Hyperthyroid: antithyroid therapy ± β-blocker/corticosteroid.
LIVER Hepatotoxicity LFT elevation 15–30%; clinical injury <3%	AST and ALT	3–6 months then every 6 months	Reduce or stop if >3× normal, or double an elevated baseline. Stop for clinical liver injury.
CARDIAC QT prolongation; bradycardia and AV block Bradycardia 2–4%; torsades ≈0.7%	ECG	Annually	Correct K ⁺ /Mg ²⁺ /Ca ²⁺ and remove interacting QT or nodal drugs. Reduce or stop for symptomatic block; pace if needed.
LUNG · MOST FEARED Interstitial pneumonitis/fibrosis Approx. 1–2%; fatal in ≈10% of cases	Chest X-ray Routine CT not recommended	CXR for unexplained cough or dyspnea CT when indicated	Withdraw amiodarone when feasible and evaluate promptly; corticosteroids may be required.
EYE Corneal microdeposits (>90%); rare visual toxicity Visual halos/blur ≤10%; optic neuropathy <1%	No routine baseline exam	Ophthalmology for visual abnormalities	Prompt ophthalmology. Consider stopping for optic neuropathy/neuritis; corneal microdeposits alone do not require it.
SKIN AND NERVE			



INTERACTION RED FLAG

Check interactions before treatment and whenever another drug starts, stops, or changes dose.

LONG PERSISTENCE

Exposure continues for weeks to months after discontinuation

MEAN APPARENT
TERMINAL HALF-
LIFE

58 days

REPORTED
RANGE

15–142
days

High lipophilicity, tissue accumulation, and the active metabolite desethylamiodarone allow toxicity and interactions to outlast therapy.

ACT ON SYMPTOMS

Evaluate new cough or dyspnea, visual

LONG PERSISTENCE

Exposure continues for weeks to months after discontinuation, so toxicity and interactions can outlast therapy.

Dronedarone is a narrower atrial rhythm-control drug.

Dronedarone retains amiodarone-like multichannel actions, but its pharmacokinetics and clinical role are substantially narrower.

DIRECT COMPARISON WITH AMIODARONE

FEATURE	DRONEDARONE	AMIODARONE
STRUCTURE AND PERSISTENCE	Noniodinated and less lipophilic Elimination t½ 13–19 hours	Iodinated and highly lipophilic Terminal t½ measured in weeks
RHYTHM-CONTROL EFFICACY	Less effective at preventing recurrent AF	More effective for maintaining sinus rhythm
CLINICAL ROLE	Selected paroxysmal or persistent AF in a patient who is in sinus rhythm	Broader atrial rhythm control and selected ventricular arrhythmias
LOADING AND PERSISTENCE	400 mg twice daily with meals; no loading regimen	Loading is often required; effects and interactions can persist for months
ORGAN BURDEN	Less tissue accumulation and no iodine-related thyroid load; liver or lung toxicity remains possible	Cumulative pulmonary, thyroid, hepatic, ocular, skin, and neurologic toxicity

WHERE IT FITS

Selected nonpermanent AF

Use to reduce AF-related hospitalization and help maintain sinus rhythm when there has been no recent decompensated heart failure or severe LV dysfunction.

BOXED-WARNING CONTRAINDICATIONS

Permanent AF or high-risk heart failure

Permanent AF: increased risk of death, stroke, and heart-failure hospitalization.

Recently decompensated symptomatic HF or NYHA class IV: increased mortality.

RHYTHM SURVEILLANCE Check at least every 3 months. If AF recurs, cardiovert if appropriate. If AF is permanent, discontinue dronedarone.	EXPECTED ECG EFFECTS Rate ↓ · PR ↑ · QT ↑	INTERACTION SCREEN CYP3A substrate and inhibitor · P-glycoprotein inhibition
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PATIENT SELECTION

Compared with amiodarone, dronedarone has less tissue persistence and lower rhythm-control efficacy, with a much narrower eligible population.

Class IV depresses calcium-dependent nodal conduction.

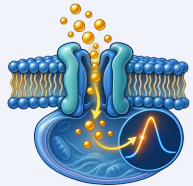
Verapamil and diltiazem act directly at the L-type Ca^{2+} channel. Their antiarrhythmic target is slow-response nodal tissue, where repeated rapid activation increases block.

SLOW-RESPONSE TISSUE · DIRECT CHANNEL BLOCK

01 · NODAL CURRENT

Phase 0 depends on $I_{\text{Ca,L}}$

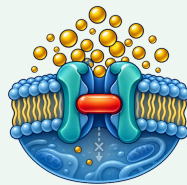
The AV-nodal upstroke is calcium dependent, not fast- Na^+ dependent.



02 · DRUG TARGET

L-type Ca^{2+} channels are blocked

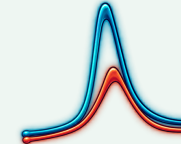
Open and inactivated channels are favored, producing frequency-dependent block.



03 · NODAL EFFECT

Phase-0 upstroke slows

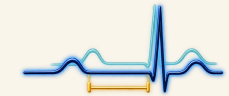
AV conduction ↓ while nodal ERP ↑.



04 · SURFACE ECG

PR ↑ · QRS usually ↔

Ventricular rate falls when the AV node is filtering an atrial rhythm.



WHEN THE AV NODE IS IN THE CIRCUIT

AVNRT or orthodromic AVRT can terminate

A transient nodal block prevents the circulating wavefront from completing the loop.

WHEN THE AV NODE IS DOWNSTREAM

AF or atrial flutter usually persists

More atrial impulses are filtered, so the ventricular response slows.

ORGANIZING PRINCIPLE

Verapamil and diltiazem produce frequency-dependent nodal $I_{\text{Ca,L}}$ block; the rhythm determines whether that effect terminates reentry or slows the ventricular response.

The same AV-nodal block produces two different endpoints.

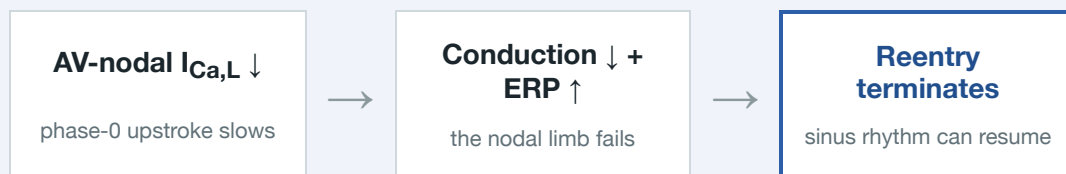
The target does not change; the rhythm anatomy does. Decide whether the AV node sustains the rhythm or merely transmits it.

ONE NODAL ACTION · TWO CLINICAL ENDPOINTS

01 · CIRCUIT INTERRUPTION

AVNRT and orthodromic AVRT

The AV node is a required limb of the reentrant loop.

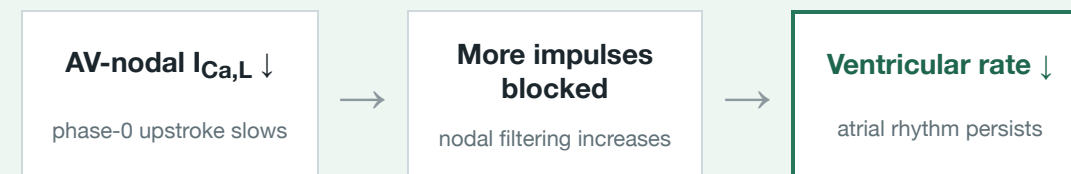


Why it works: one failed pass is enough because the circulating wavefront cannot complete its required nodal path.

02 · VENTRICULAR RATE CONTROL

Atrial fibrillation and flutter

The atrial rhythm is generated upstream from the AV node.



What it does not do: it does not directly terminate fibrillation or the macroreentrant flutter circuit.

! PRE-EXCITED AF IS THE EXCEPTION AV-nodal blockade leaves the accessory pathway available and can accelerate ventricular conduction.

The AV nodal gate.

How diltiazem and verapamil terminate AVNRT or slow the ventricular response in AF and flutter.

Medical education Interactive lesson · offline

▶ Play

← Back

Next →

↺ Restart

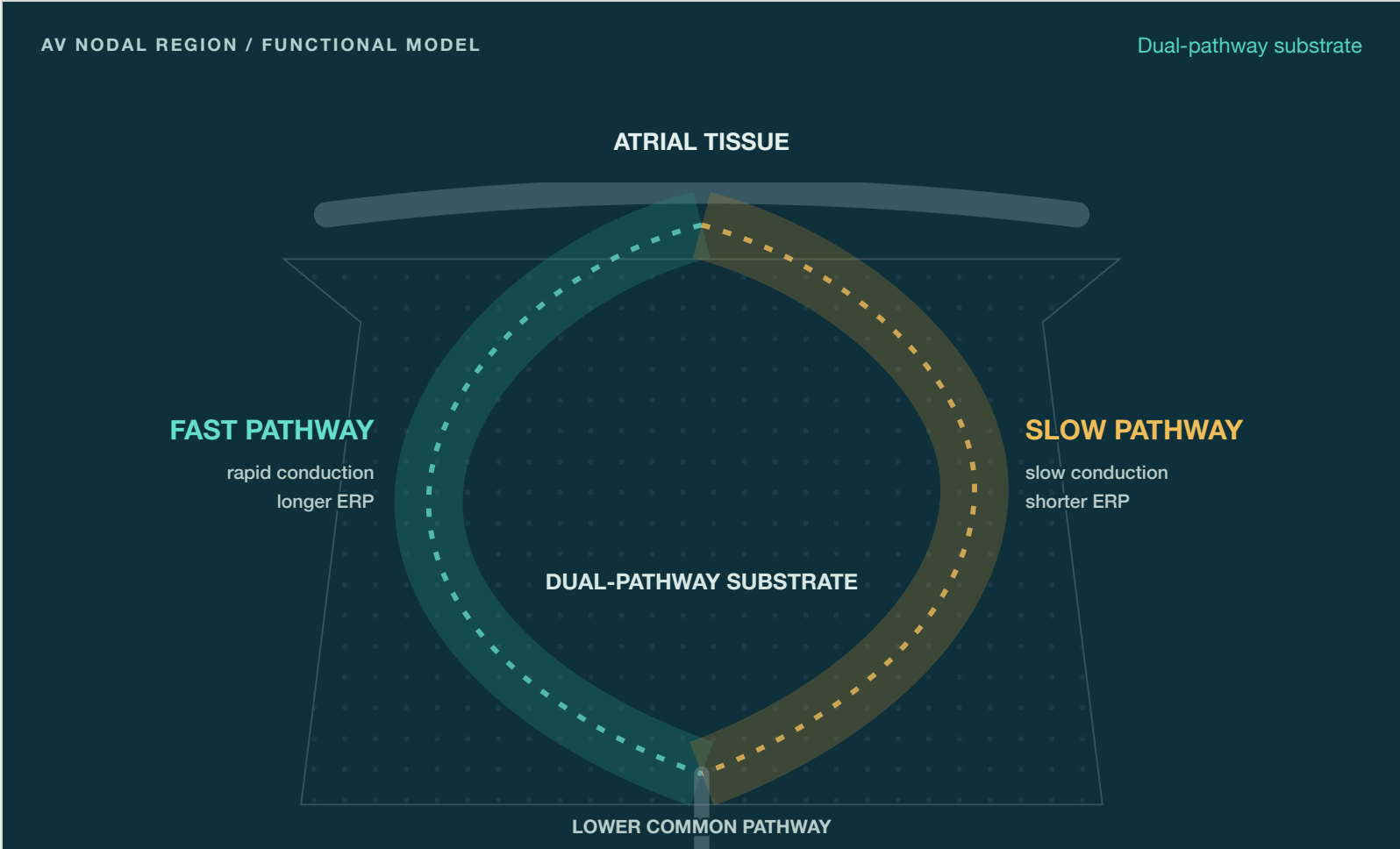
RHYTHM

AVNRT

AF

Atrial flutter

Pre-excited AF

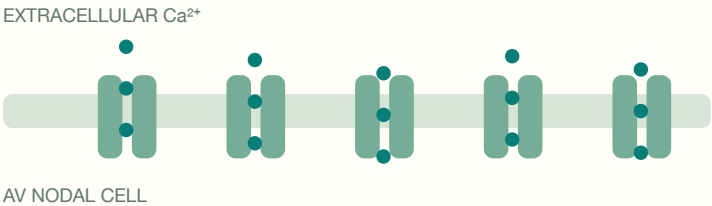


01 / DUAL-PATHWAY SUBSTRATE 1 of 7

The fast and slow pathways have different conduction and recovery.

The fast pathway conducts quickly but has a longer refractory period. The slow pathway conducts more slowly and recovers sooner.

AV nodal cell · L-type Ca^{2+} channels Baseline



Use non-DHP calcium-channel blockers when the AV node is the intended target.

Class IV means the non-dihydropyridines verapamil and diltiazem. Choose them only when slowing or transiently blocking the AV node is the intended strategy.

INDICATIONS · AGENT SELECTION · CONTRAINDICATIONS AND CAUTIONS

CLINICAL TASK	WHAT CLASS IV DOES	AGENT DISTINCTION	CONTRAINDICATIONS AND CAUTIONS
STABLE REGULAR PSVT Acute termination AVNRT or orthodromic AVRT	IV verapamil or diltiazem can terminate AV-node-dependent SVT when vagal maneuvers and adenosine are ineffective or unsuitable.	Diltiazem: bolus plus titratable infusion. Verapamil: effective bolus; greater concern for hypotension and negative inotropy.	Use only when the rhythm diagnosis is secure. Avoid in hypotension or HFrEF.
AF OR ATRIAL FLUTTER Ventricular rate control the atrial rhythm persists	Slower conduction and longer nodal refractoriness allow fewer atrial impulses to reach the ventricles.	Diltiazem: commonly titrated for acute rate control. Either: oral maintenance when ventricular function and blood pressure permit.	For acute AF rate control, guideline use requires EF >40%. Do not use for long-term rate control when LVEF is <40%.
SHARED ADVERSE EFFECTS Excess nodal and hemodynamic depression	Bradycardia · PR prolongation · AV block · hypotension · edema.	Verapamil: constipation is prominent. Diltiazem: infusion-site reactions can occur.	Avoid second- or third-degree AV block or sick-sinus syndrome without a functioning pacemaker.
THREE SITUATIONS TO AVOID Before IV Class IV therapy	01 Wide-complex tachycardia of unknown origin If it is VT, verapamil can cause hemodynamic collapse.	02 Pre-excited AF As with all AV-nodal blockers, accessory-pathway conduction can accelerate.	03 With a β-blocker Avoid concurrent IV use: additive nodal suppression and negative inotropy can cause collapse.

Proarrhythmia mechanisms

Match the rhythm to the electrophysiologic failure. The same drug can be safe in one substrate and proarrhythmic in another.

DRUG EFFECT · MODIFYING CONDITIONS · RHYTHM

PRIMARY DISTURBANCE	HOW PROARRHYTHMIA DEVELOPS	COMMON SETTING	ECG OR RHYTHM CONSEQUENCE
FAST-TISSUE CONDUCTION Excess Na ⁺ -channel block	Uneven conduction slowing creates functional block and permits reentry. Atrial slowing can organize AF into flutter.	Class IA or IC · rapid rate · structural scar · high concentration	QRS widens Monomorphic VT or rapid 1:1 flutter
REPOLARIZATION RESERVE Outward K ⁺ current falls	APD prolongation and repolarization dispersion permit EAD-triggered beats.	Class IA · IKr blockers · sotalol · bradycardia · low K ⁺ or Mg ²⁺	QT lengthens Pause-dependent torsades
CALCIUM HANDLING Intracellular Ca ²⁺ overload	Spontaneous calcium release activates inward NCX current and produces DADs.	Digoxin toxicity · renal accumulation · hypokalemia	Triggered ectopy Atrial tachycardia with block or bidirectional VT
NODAL CONDUCTION Excess AV-nodal depression	Stacked nodal effects slow conduction or stop it. Long pauses can add a torsades trigger when QT is prolonged.	β-blocker + IV non-DHP CCB · digoxin · adenosine	Rate falls and PR lengthens Bradycardia or AV block
PRE-EXCITED AF The AV node is bypassed	Nodal blockade leaves the accessory pathway available for rapid antegrade conduction.	Any AV-nodal blocker given during pre-excited AF	Very rapid irregular WCT Possible ventricular fibrillation
MULTIPLE HITS MATTER	Drug concentration, rate, electrolytes, interactions, ventricular function, and scar determine how much safety margin remains.		

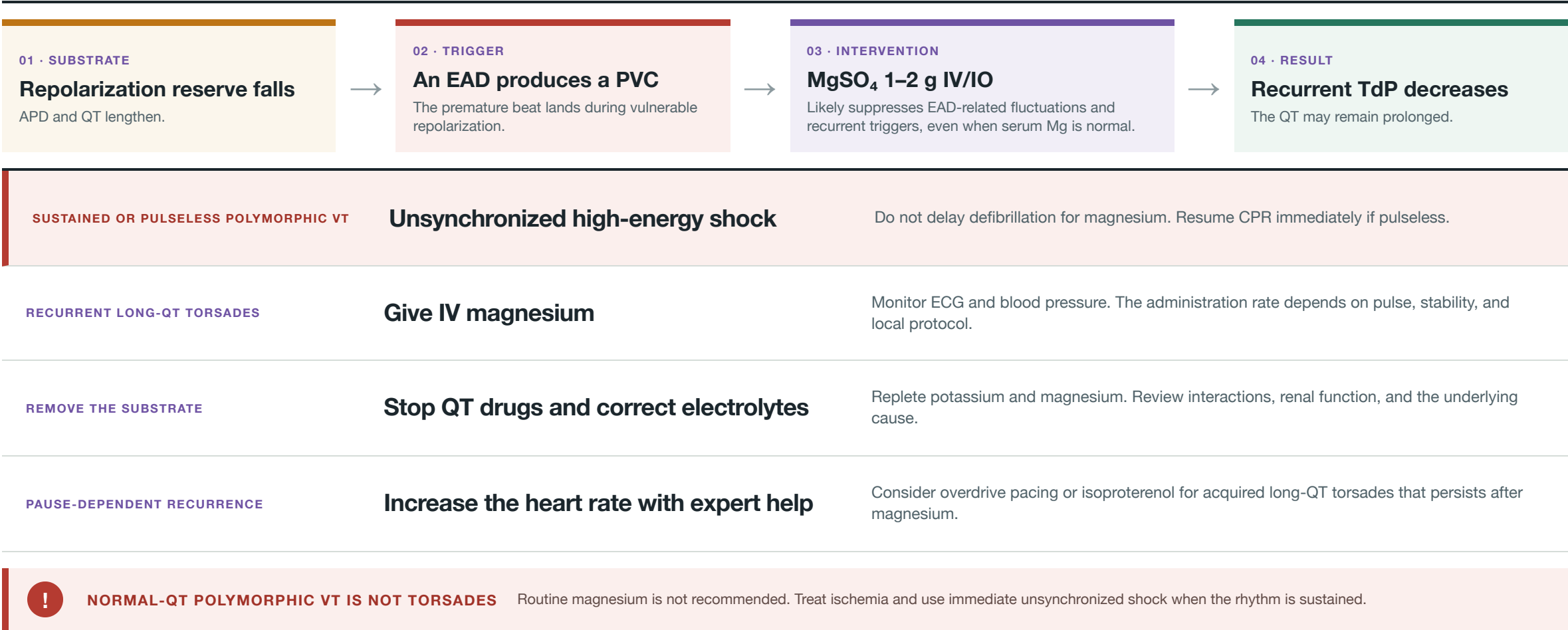
RISK IS MULTIPLICATIVE

A drug creates the electrophysiologic change. Rate, electrolytes, concentration, and substrate determine whether it becomes an arrhythmia.

Magnesium suppresses recurrent long-QT torsades

Torsades is polymorphic VT in the setting of a known or suspected long QT. Magnesium suppresses recurrent triggers, while sustained polymorphic VT requires electricity.

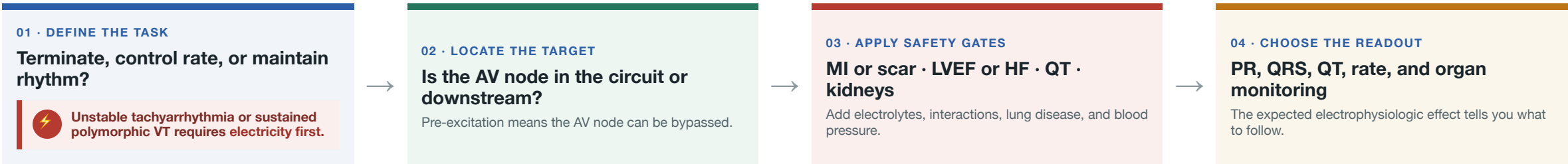
RECOGNIZE LONG QT BEFORE CHOOSING THE DRUG



Choosing an antiarrhythmic

The diagnosis names the rhythm. The patient substrate determines which mechanisms are safe.

STABILITY · TASK · ANATOMY · SUBSTRATE · MONITORING



Case: Name the clinical task

One decision at a time. Each build reveals only the information needed for the next safety gate.

COACHED CASE · 1 OF 4

PATIENT

72-year-old with symptomatic persistent AF

Now in sinus rhythm after cardioversion

INITIAL PRESENTATION

Sinus rhythm · HR 68 bpm · BP 118/72 mm Hg

Despite adequate rate control, AF caused limiting fatigue and exertional dyspnea. Symptoms improved after cardioversion, so maintenance of sinus rhythm is being considered.

3 clues still hidden

NO DECISIONS REVEALED YET Commit before advancing

DECISION 1

What is the clinical task?

The patient is hemodynamically stable and already in sinus rhythm.

- A

Acute conversion
- B

Ventricular rate control
- C

Maintain sinus rhythm

Pause for a commitment. Advance to reveal the reasoning.

REASONING RULE Name the task before naming a drug.

Case: Narrow the drug list

One decision at a time. Each build reveals only the information needed for the next safety gate.

COACHED CASE · 2 OF 4

PATIENT

72-year-old with symptomatic persistent AF

Now in sinus rhythm after cardioversion

INITIAL PRESENTATION

Sinus rhythm · HR 68 bpm · BP 118/72 mm Hg

Despite adequate rate control, AF caused limiting fatigue and exertional dyspnea. Symptoms improved after cardioversion, so maintenance of sinus rhythm is being considered.

VENTRICLE AND HEART FAILURE

Prior anterior MI · LVEF 30%

Heart-failure hospitalization 3 weeks ago

RENAL AND PROARRHYTHMIC SCREEN

CrCl 18 mL/min · QTc 492 ms

K⁺ 3.2 mmol/L

3 clues still hidden

REASONING RULE

Test efficacy first, then apply history and laboratory safety gates.

TASK

Maintain sinus rhythm after cardioversion

DECISION 2

Narrow the list in three steps

1

CLINICAL TASK

Identify ineffective drugs

2

MEDICAL HISTORY

Identify contraindications

3

ECG AND LABS

Identify unsafe drugs

Click the two drugs that do not serve long-term AF rhythm maintenance.

Procainamide CLICK TO CLASSIFY	Mexiletine CLICK TO CLASSIFY
Flecainide CLICK TO CLASSIFY	Propafenone CLICK TO CLASSIFY
Dofetilide CLICK TO CLASSIFY	Sotalol CLICK TO CLASSIFY
Dronedarone CLICK TO CLASSIFY	Amiodarone CLICK TO CLASSIFY

Case: Choose among the remaining drugs

One decision at a time. Each build reveals only the information needed for the next safety gate.

COACHED CASE · 3 OF 4

PATIENT

72-year-old with symptomatic persistent AF

Now in sinus rhythm after cardioversion

INITIAL PRESENTATION

Sinus rhythm · HR 68 bpm · BP 118/72 mm Hg

Despite adequate rate control, AF caused limiting fatigue and exertional dyspnea. Symptoms improved after cardioversion, so maintenance of sinus rhythm is being considered.

VENTRICLE AND HEART FAILURE

Prior anterior MI · LVEF 30%

Heart-failure hospitalization 3 weeks ago

RENAL AND PROARRHYTHMIC SCREEN

CrCl 18 mL/min · QTc 492 ms

K⁺ 3.2 mmol/L

AFTER ELECTROLYTE CORRECTION

K⁺ 4.2 mmol/L · QTc 458 ms

CrCl remains 18 mL/min. Current drugs: metoprolol, warfarin, digoxin.

All case data revealed

TASK

Maintain sinus rhythm after cardioversion

THREE-STEP SCREEN

Amiodarone remains; correct K⁺ and Mg²⁺ first

DECISION 3

Which drug remains a practical option?

Electrolytes have been corrected. Renal function and ventricular substrate remain limiting.

A

Dofetilide

B

Sotalolol

C

Amiodarone, if rhythm control remains warranted

Pause for a commitment.

Advance to reveal the reasoning.

REASONING RULE

A remaining option still needs an interaction and monitoring plan.

COACHING CUE

Use the corrected electrolyte value, renal limits, and ventricular substrate to identify the remaining drug option.

Case: Build the safety plan

One decision at a time. Each build reveals only the information needed for the next safety gate.

COACHED CASE · 4 OF 4

PATIENT

72-year-old with symptomatic persistent AF

Now in sinus rhythm after cardioversion

INITIAL PRESENTATION

Sinus rhythm · HR 68 bpm · BP 118/72 mm Hg

Despite adequate rate control, AF caused limiting fatigue and exertional dyspnea. Symptoms improved after cardioversion, so maintenance of sinus rhythm is being considered.

VENTRICLE AND HEART FAILURE

Prior anterior MI · LVEF 30%

Heart-failure hospitalization 3 weeks ago

RENAL AND PROARRHYTHMIC SCREEN

CrCl 18 mL/min · QTc 492 ms

K⁺ 3.2 mmol/L

AFTER ELECTROLYTE CORRECTION

K⁺ 4.2 mmol/L · QTc 458 ms

CrCl remains 18 mL/min. Current drugs: metoprolol, warfarin, digoxin.

All case data revealed

TASK Maintain sinus rhythm after cardioversion RESOLUTION	THREE-STEP SCREEN Amiodarone remains; correct K⁺ and Mg²⁺ first
--	---

Amiodarone remains an option, not an automatic answer

Class IC	Exclude	Prior MI, scar, and HFrEF
Dronedarone	Exclude	Recent decompensated heart failure
Dofetilide and sotalol	Exclude	Creatinine clearance remains below labeled limits
Amiodarone	Consider	Only if the rhythm-control benefit still justifies cumulative risk

INTERACTIONS Warfarin and digoxin exposure can rise	FOLLOW-UP ECG plus thyroid, liver, lung, eye, skin, and neurologic monitoring
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INDEPENDENT PRACTICE

Five additional coached cases are available outside the lecture sequence.

Open student cases

What matters most for Step 1?

- | | | |
|----|---|--|
| 01 | Start with cell physiology. | Separate fast-response atrial, ventricular, and Purkinje tissue from slow-response SA and AV nodal tissue. |
| 02 | Map each current to an action-potential phase. | Fast cells: Na ⁺ phase 0, Ca ²⁺ phase 2, and K ⁺ phase 3. Nodal cells: Ca ²⁺ phase 0 and spontaneous phase 4. |
| 03 | Predict the ECG effect from the target. | AV-nodal slowing lengthens PR; Na ⁺ -channel block widens QRS; delayed repolarization lengthens QT and raises torsades risk. |
| 04 | Reason by class—not just drug name. | Distinguish IA, IB, and IC; connect II and IV to the AV node; connect III to longer action-potential duration and refractoriness. |
| 05 | Recognize the defining vignette patterns. | Amiodarone toxicity, flecainide after MI, adenosine-sensitive SVT, digoxin toxicity, torsades, and pre-excited AF. |
| 06 | Study in a mechanism-first sequence. | Master channels, tissue, refractory periods, reentry, and ECG; then class signatures; then mechanism-based vignettes. De-emphasize exact doses and detailed prescribing. |

CORE APPROACH

Connect target → tissue → action-potential phase → conduction or refractoriness → ECG → one defining clinical or toxicity pattern.