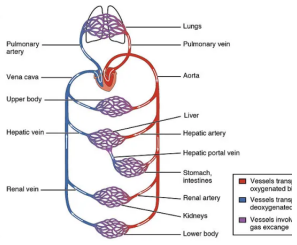
physiology

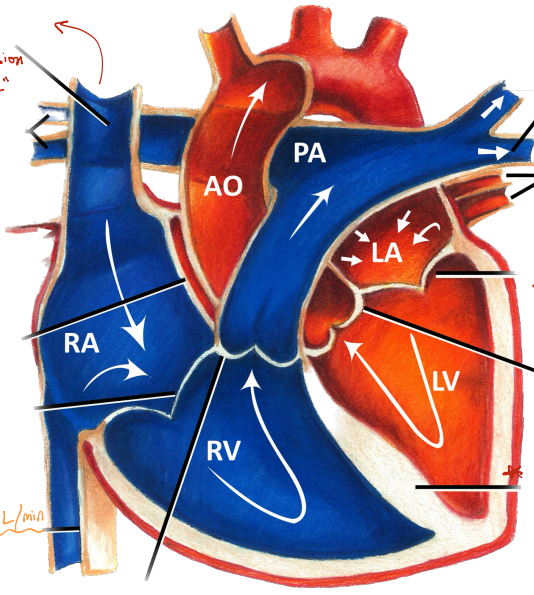
⚠ Heart Failure
- Dyspnea.
- Palpitations.
- Fatigue.
Triad

CARDIOVASCULAR SYSTEM

two circulations:
→ Peripheral circulation "systemic" (↑Resistance)
→ lesser circulation "pulmonary"
• the lung disease may affect the systemic circulation and vice versa.



* Pericardium lacks elastin to prevent distension "Not stretchable" ↳ tough collagen.



* two chambers for collecting blood: Rt. + Lt. Artia.
* two chamber for ejecting blood: Rt. + Lt. Ventricles.
* Valves → uni directional movement and prevention of backflow

⚠ If stenosis occured, narrowing, this will not fill the ventricles with blood appropriately, and blood might regurge.

* AV (Atrioventricular valves):-
↳ Rt. AV valve = tricuspid valve.
↳ Lt. AV valve = bicuspid valves.= Mitral valve
valve opens passively due to pressure difference.
P. Atria >> P. ventricle

* Valves:
Between lf. ventricle + Aorta → Semilunar Aortic Valve
Between Rt. ventricle + Pulmonary Artery → Semilunar pulmonary valve.

* Rt. atrium is seperated from lf. atrium by interatrial septum, same applies to ventricles, the interventricular septum. To prevent mixing of blood.
⚠ Rt. side → Deoxygenated Blood.
lt. side → Oxygenated Blood.

Volume ejected from the ventricle per minute
• Cardiac Output = Flow per unit time = Q = 5L/min

$$\frac{\Delta F}{R} = \frac{\Delta P}{TPR} = Q$$

Driving Force: is the difference in pressure that caused the blood to move "Arterial Pressure".

Resistance: Total Resistance that is faced by blood when flowing through arterioles + venules → in systemic circulation, and when flowing through pulmonary arteries → in the pulmonary circulation.

$\frac{\Delta P}{TPR}$ (total peripheral resistance)

$\frac{\Delta P}{PR}$ (pulmonary resistance)

⚠ Resistance in the periphery is 7 times greater than resistance in the Pulmonary.
↳ Meaning that the pressure needed to overcome the peripheral resistance is 7 times greater than in pulmonary.
because the pulmonary arteries are not as muscularized as the systemic counterparts. Thinner, less muscular vessels are more easily distended.

further info
* Reasons for Resistance:
1. Directly with Viscosity.
2. Directly with BV length.
3. Inversely with BV radius.

So ⇒ $R = \frac{8\eta L}{\pi r^4}$

Blood Flow = $Q = \frac{\Delta P}{R}$ "$Q \propto \frac{1}{R}$"

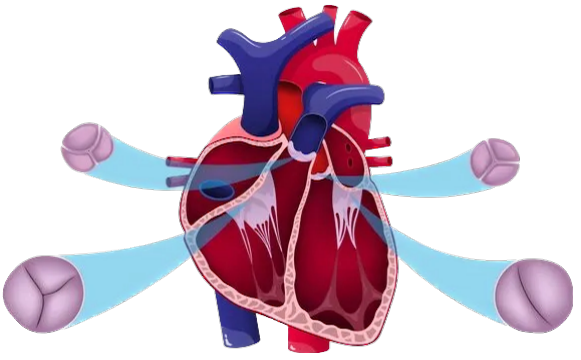
$TPR = R_1 + R_2 + R_3 + \dots$ توالي

Parallel resistance: $\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2}$ → Here blood flow in each one isn't equal to the other.

* When do valves open? Pressure-dependent changes lead to opening of the valve
P. lf. v. > P Aorta. → valve opens.
P. lf. v. < P Aorta → valve closes.
↳ Same applies to pulmonary valve.

* thickness of lf. ventricles (10–15 mm) >> Rt. ventricles (3–5 mm)
↳ Both greater than thickness of Atria. 2mm

• Main function of the ventricles is to eject blood, and to do that valves must be opened, so pressure in ventricle >> pressure in Aorta, the pressure of ventricles becomes greater as the ventricles contract due to the Electrical stimulation



* Sequence of Events.

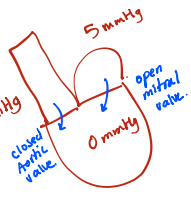
excitation contraction coupling
1. Electrical Stimulation
2. Mechanical Contraction. cardiomyopathy, carditis.
3. Increase of intraventricular pressure.
4. opening of the valve. • calcification. • stenosis
5. Ejection. No blood (diuretics, bleeding)

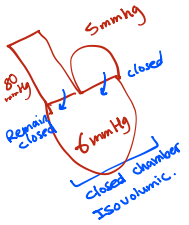
Abnormalities
Increased pressure in artery in a way that exceeds the pressure of the ventricle in a way that cannot be overcomed.
eg:

⚠ Failure of any of these steps → Haart failure.
⚠ Excitation contraction uncoupling. due to removal of T-tubules

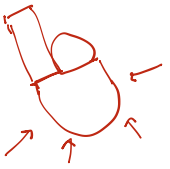
* AV valves are open → Filling phase.
* Semilunar valves are open → Ejection phase.
* Isovolumic → All 4 phases are closed. phase
⚠ No phase where all valves are opened.

↳ Papillary muscle + chorda tendinae → prevent the bulging of valve toward the atrin.





we want to make ejection by increasing the pressure in ventricle to exceed pressure in artery so the valve will open.
contraction due excitation.



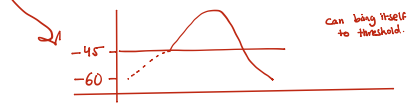
cycle → systole → contraction → emptying
diastole → relaxation → filling

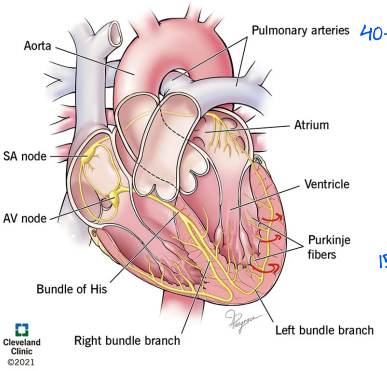
Electrical Behaviour

Transmission of Electric impulse

* The impulse is born in SA nodal cells.
  - small cells 3-5 μm.
  - they lack actin + myosin (non contractile).
  - can initiate the action potential by itself without the help of NS or Endorine system.

"Autorythmic cells that can get themselves to threshold, to a less negative potential".
↳ thus, they are called PACEMAKERS





70-80/min SA node 0.00
↓
40-60/min AV node 0.04 (delayed and captured for 0.12 seconds)
↓ this delay is decreased in sympathetic because there's an increase in conducting velocity
↓ this delay is increased in parasympathetic.
↓
AV bundle 0.16
↓
lt. + Rt. bundle branches
↓
15-40/min purkinje fibers. 0.19 * Highest conduction velocity
↓
Travel through the myocardium from inside to outside. 0.22

- Depolarization created in SA node is distributed as the following:

① ↳ Rt. + Lt. Atria → to contract → empty the content into the ventricle.

⚠ Filling of ventricles:
↳ 80% ↳ passive due to difference in pressure
↳ 20% ↳ active due to atrial contraction.

② ↳ To AV node ↳ to AV bundles (Bundle of His) → Lt. bundle branch. Rt. bundle branch → Purkinje fibers.
to carry the electric impulse into the wall of the septum and walls of ventricles.

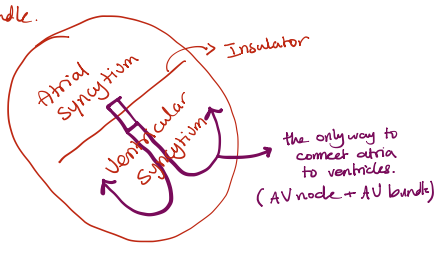
- We want the atria to be contracted at the same time so that it empties the blood into ventricles
- But the atria and the ventricles shouldn't contract at the same time, because that will lead to closure of the AV valve and the blood will go from lt. atrium to pulmonary veins, because of the atrial overfilling without enough time for emptying.
- Significance of AV Delay.
  It gives enough time for contraction of atria + emptying the content of blood into ventricles. (ventricles haven't contracted yet, so the have a great capacity to accomodate the blood)

WHY?
"AV nodal cells contain few gap junctions and they are small" → ↑ Resistance
⚠ $R \propto \frac{1}{r^2}$
Also the RMP is more negative, harder to reach threshold
→ this all contributes to the slow conduction.

HOW?

* Cardiac Muscle Cells
↳ Between them { - Desmosome → adhere cells together. → prevent detachment when contraction occurs.
- Gap junctions → allows conduction of electrical impulse (depolarization)
"communication between 2 adjacent cells with very low resistance"
"Syncytium" → in atria + in ventricles
intercalated discs

BUT Atria + Ventricles are seperated by an electrical insulator so that prevents the conduction of electrical impulse, keeping it limited to be conducted through the AV bundle.



* ↑ gap junction ∝ ↑ fast conduction velocity.
↓ gap junction ∝ ↓ slow conduction velocity
No gap junctions → No communication "Skeletal muscles"

Skeletal Muscles	Cardiac Muscles
• Cells are isolated from each other "No syncytium"	• cells are connected with each other via gap junctions "Syncytium"
• Need a neurogenic stimulation	• Myogenic autorythmic stimulation arises within the muscle itself.
• Short action potential 2-3 msec.	• Action potential is longer
• T-tubules are longer (No calcium from outside).	• T-tubules are shorter + broader (ECM + extrinsic Ca^{2+}).
• More abundant SR Ca^{2+} (intrinsic)	• plenty of mitochondria → FFA 65% source of energy.
	• Ca^{2+} is intrinsic + extrinsic
	T tubules function is questionable as Calcium might directly enter from ECM.

* Ions distribution inside + outside the cells.

This occurs because each ion wants to get into equilibrium by bringing the membrane potential to its equilibrium.

Na^+ 140	Ca^{2+} 10^{-3}	K^+ (in all cells)
↓ 14	10^{-7}	
+61	+122	-92

the more K^+ out making the resting membrane potential more negative.
« hyperkalemia »

2 forces:
- chemical force opposing the movement.
- Electrical force driving the movement.
→ Electro-chemical gradiant

when they are equal → net movement is zero. → Electro-chemical equilibrium.

So when the inside is positive enough, the chemical force will be able to neutralize/equalize the Driving force (electrical).

When is it positive enough? when we reach sodium equilibrium potential

$E_{Na^+} = -61 \log \frac{Na^+_{in}}{Na^+_{out}} = +61$

Equilibrium isn't reached because of the membrane impermeability

* $Flow = \frac{DF}{R}$

$R = \frac{1}{g(\text{conductance})}$

$\therefore I_{current\ Na^+} = DF \times g_{Na^+}$

DF → How far the equilibrium potential for that ion is from membrane potential.

$\therefore$ So $I_x = (E_{membrane} - E_x) \times g_x$.

So according to this, K^+ conductance is the greatest of all

* cells across the body have different membrane potentials due to differences in conductance of ions and that will lead to driving the membrane potential close to the potential that is of the most conducted ion.

* In the case of cardiac cells, they have high conductance to K^+ ions, that's why it tends to leak the most and causing the membrane potential to reach the threshold.

NOT Important ⚠ if potassium exceeds a lot inside the cell, this will cause accumulation of positive charge. This will lead to switching to slow response action potential, this will lead to low conductance + arrythmias.
Solution: Hemodialysis

But more negative MP → ↓ K^+ conductance

Ninja Nerd Video.

Electrophysiology

- It can intrinsically depolarizes itself = Automaticity
  - Increase / Decrease HR
  - Increase / Decrease Contractility

Myocardium

1/ Non-contractile (Nodal cells) << Contractile

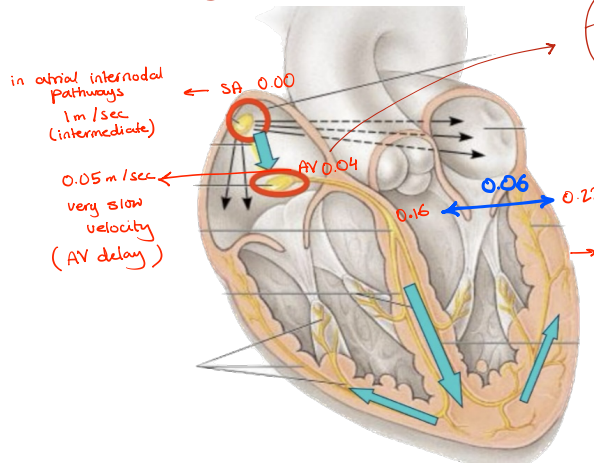
Non-contractile (Nodal cells)
→ Intrinsically depolarize

- SA node
- AV node
- AV bundle "Bundle of His"
- Bundle branches Rt. + lf.
- Purkinje Fibers

Set a Rhythm

Contractile
Containing:
- Actin, myosin troponin & tropomyosin.
- Sarcoplasmic Reticulum.

give the force + contractility



the pacemaker ⇒ SA node. in RA superiorly
sets the rhythm
making 60-80 b/min.
Normal rhythm / without any extrinsic effect

* Now, it moves the electric impulses to LA. via Backmans Bundle to activate LA.

* SA node is supplying the RA via the internodal pathway
  ⇓
  will converge to form AV node
  ⇓
  that then completes through the interventricular septum, acting as the conductor between atria + ventricles.

AV node is going to delay the conduction of impulse for about 0.12 second.
(As if it is holding the depolarization)

WHY?
→ To give time for the atria to contract and push the blood towards ventricles before ventricles contract.
→ AV nodal cells have fewer gap junctions
→ they have smaller diameter
→ RMP is more negative.

⇓
to bundle of HIS
- Rt. myocardium ← RBB → Purkinje fibers
- LBB → lf. myocardium → Purkinje fibers

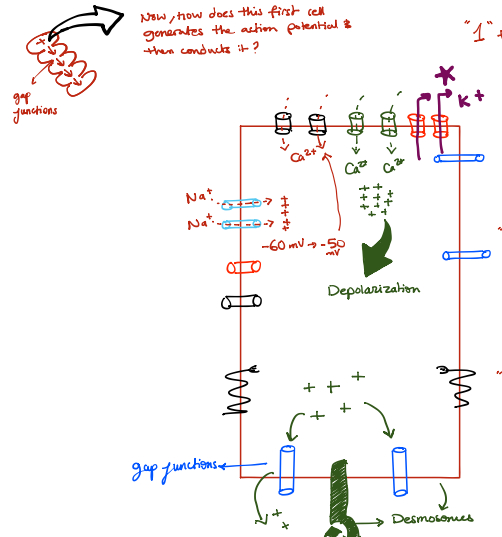
get the myocardium to contract.

this all happened due to the generation of an action potential in SA nodal cells that was transmitted to the contractile cells.

How do these nodal cells work?
And How do they communicate with contractile cells?

SA nodal cells

Now, how does this first cell generates the action potential & then conducts it?

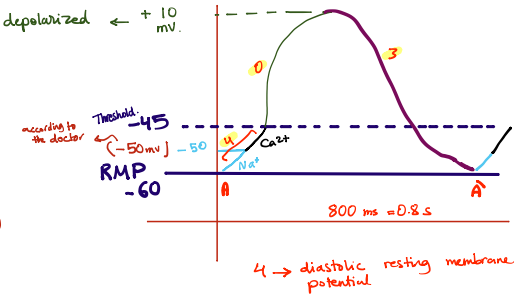


"1" * Funny Na+ channels Leaky channels → Allow flow of Na+ → No stable membrane potential → the inside becomes slightly positive.
made +10 mV difference.
→ SA nodal cells are the most leaky to Na+, enabling them to reach threshold faster than other cells, that's why they're the main pacemaker.

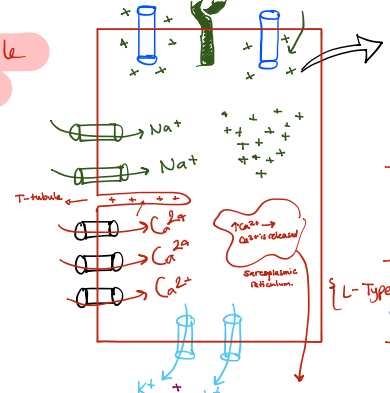
* K+ channels causes leakage of K+ to the outside bringing the MP to -60 mv.
→ it is not stable
So the Funny leaky Na+ will start working. So it will immediately start another AP.

"2" * T-Type Ca2+ channels activated at -55 mv.
→ membrane potential becomes less negative.
+5 mv difference → threshold is auto generated.

"3" * L Type Ca2+ channels
Ca2+ will flow inside very powerfully until reaching +10 mV
→ the actual depolarization.
+55 mv difference



Contractile Cells



brings the cell from the RMP to threshold stimulating the opening of voltage gated Na^+ channels.

- Na^+ flows inside the cell very fast causing the MP to reach +10 mv and then deactivate.

- This will trigger the opening of {L-Type} Ca^{2+} channels + K^+ channels

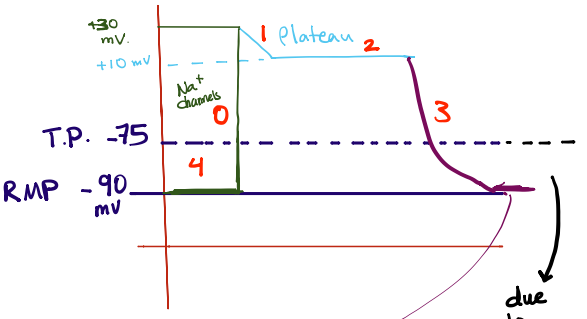
- K^+ channels will efflux K^+ more than influx of Ca^{2+} causing the MP to drop to 0 mv.

this will reactivate Ca^{2+} to flow → this will equalize & neutralize the efflux of K^+.

- K^+ is going out → Plateau

repolarization

Muscle Contraction as a unit → Functional Syncytium → Ejection of Blood.



⚠ Not immediately as it has to wait until the positive ions from nodal cells kak again through gap junctions.

due to leakage of ⊕ through gap junctions.
= stimulation from conduction system.

* Ca^{2+} channels will close
less ↓Ca^{2+} is coming in.
more ↑K^+ is going to.

* Ca^{2+} should return back to sarcoplasmic reticulum & ECM.

- Also, calcium in the cell is shunted back into the sarcoplasmic reticulum or out of cell to prevent any further prolonged contraction

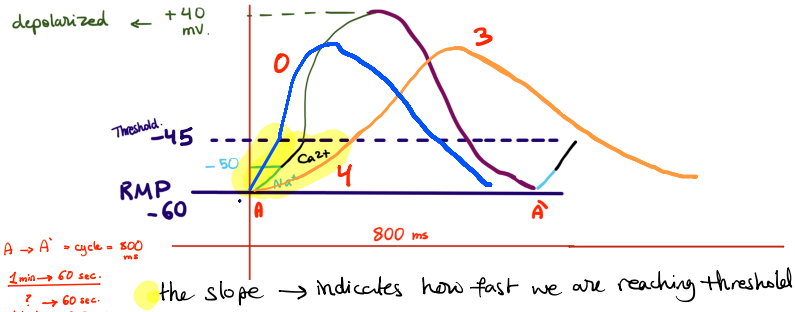
(i) Into SR:
- ATP dependent Ca++/H+ exchanger
- Na+/ Ca++ exchanger via secondary active transport

(ii) Out of cell:
- ATP dependent Ca++/H+ exchanger
- Na+/ Ca++ exchanger via secondary active transport

Notice how important the extracellular Ca^{2+} is for the contraction of myocardium, unlike skeletal muscles.

Slow Response Action Potential.

SRAP (in AV node + SA node)



A → A` = cycle = 800 ms

1 min → 60 sec.
? → 60 sec.
1 beat → 0.8 sec.
60 / 0.8 = x
x = 75 beat/min

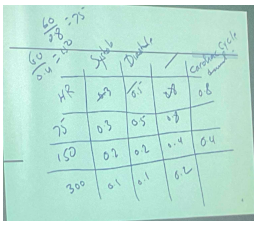
the slope → indicates how fast we are reaching threshold.
if the slope increased → sympathetic
if the slope decreased → parasympathetic.

Normal cardiac cycle = 0.8 sec. when HR = 75 b/min
systole = 0.3 diastole = 0.5

{NE + adrenergic receptors} * this is with sympathetic stimulation, making it easier + faster to reach threshold.
→ the period between each and every cycle is lesser. → cardiac cycle = 0.4 sec
↳ Tachy Cardia.

HR = 150 b/min (60 / 0.4)
systole = 0.2
Diastole = 0.2
↳ if decreased cardiac perfusion is lessened.

→ sympathetic → ↑HR → ⊕ chronotropic effect by increasing I_{Na+} / $I_{Ca^{2+}}$ in SA node.
↳ ⊕ Dromotropic ← (conducting velocity of AV node).
↳ ↑Ca^{2+} / + Contractility → ⊕ inotropic.



{Ach Muscarinic Receptors} * this is with parasympathetic stimulation.
takes more time to reach threshold.
→ The period between each and every cycle is greater. ⇒ each cardiac cycle = 1.2 sec.
↳ Bradycardia. bp = 60 / 1.2 = 50 bp / min

vagus only on SA node + AV node.
- ⊖ve chronotropic
- ⊖ve dromotropic

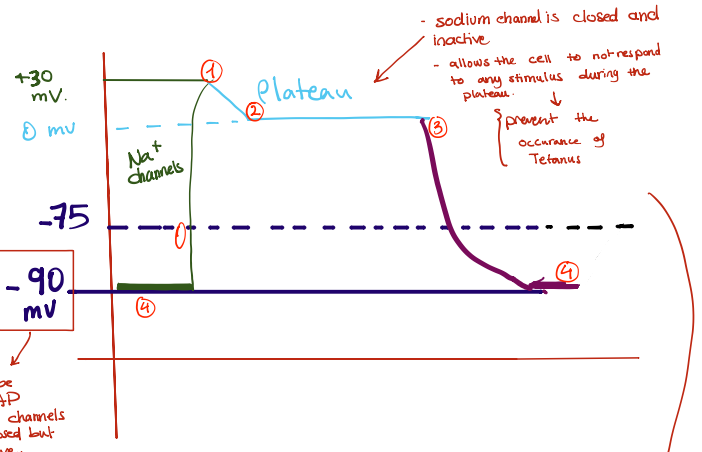
→ that is due to ↓I_{Na+} ↓$I_{Ca^{2+}}$ and ↑↑I_{K4} that will cause the membrane potential to be more negative making it harder to reach threshold.

- No effect on inotropic effect as the vagus nerve doesn't reach the ventricles to affect their conductance towards Ca^{2+} → thus no effect on contractility

← So, as a conclusion, phase 4 might be modified by sympathic or parasympathetic stimulation.

Fast Response Action Potential.

FRAP (cardiac muscle).



- sodium channel is closed and inactive
- allows the cell to not respond to any stimulus during the plateau. → prevent the occurrance of Tetanus

→ to be FRAP sodium channels are closed but active.
→ high conductance of K^+

Cardiac cells * $\frac{DV}{DT}_{\text{voltage, time}} = 0$ → equal to slope = at this point no chance to reach threshold

* The cardiac cells aren't autorhythmic as their RMP will stay = -90 mV → no net movement across the membrane.
* The cell itself cannot bring itself to threshold. → stable RMP
* They reach threshold upon stimulus from the conducting systems, and if one cell was stimulated the others will be stimulated as well due to syncytium (because of gap junctions)
* Fast Sodium channels are closed but active.
* Notice, here is no depolarization wave.

Note :- Ventricles → Ejection → ~~Filling~~ → ~~Relaxation~~

They are inhibited when there's tetanus.
sustained contraction without relaxation.
* This is more in skeletal muscles because the duration of Action Potential is very short.

⚠ Meanwhile, ventricles donot tetanize because that will interfere with their relaxation, thus filling & ejection.
If tetanus occured heart will lose its function.
So, ventricles aren't allowed to have summation of contraction, that's why there's plateau.

⚠ In ventricular fibrillation, there's no enough time for relaxation + filling due to extremely high rate.
Mainly happen before MI, حدث قبل النوبة
from ischemic foci acting as ectopic pacemakers.
So, death might occur due to electrical problems

⚠
- SA node → pacemaker → 70 - 80 bp/min
- If sinus sick syndrome occur → ectopic pacemaker which is AV node → 40 - 60 bp/min.
- If SA + AV nodes were blocked → Purkinje fiber will act as ectopic pacemakers → 15 - 40 bp/min.

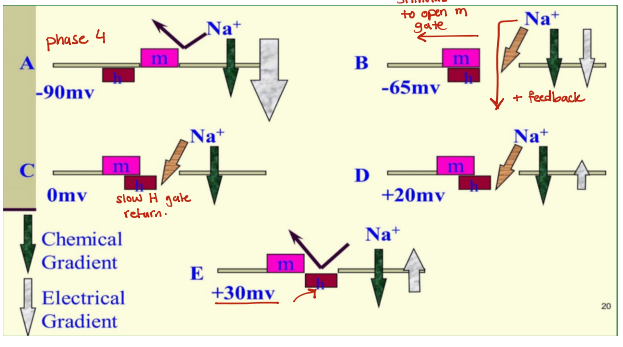
But the risk is, as we said before, when there's an ectopic focus, especially in myocardial cells "as you know myocardial cells have no rhythmic activity" → this will lead to having 300 bp/min → Ventricular fibrillation ← cause HF.

→ Atrial fib. isn't as dangerous as that of ventricles.

In phase 4 → at rest, no conductance for sodium
In phase 0 → the conductance for sodium increases by opening fast Na^+ channels
In phase 1 → K^+ channels are opened causing their efflux (Na^+ channels are closed)
In phase 2 (plateau) → maintained depolarization due to opening of both:
slow + voltage-gated ← 1 L-Type Ca^{2+} channels
2 K^+ channels causing inflow.
} → They're balanced + equalized.
In phase 3 → Ca^{2+} channels close + K^+ channels remain open.

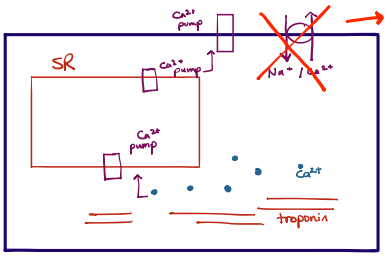
→ Sodium channels are closed + inactive → Refractory period
- in vivo → Absolute Refractory Period
- in vitro → can be relative refractory period if there was an extrinsic stimulus

- A graph illustrating how the voltage-gated Na^+ channels are opened and closed (+30 mv)



⇒ to achieve relaxation, Ca^{2+} should dissociate from troponin and return back to ECM and SR

→ Ca^{2+} pump on SR
→ Ca^{2+} pump on sarcolemma.
→ Ca^{2+} / Na^+ exchange → secondary active transport



→ Digoxin
so the Ca^{2+} will stay inside the cell, this drug is used in patients with HF + problems in contractability.