الفسلجة
مرحلة ثانية

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CARDIOVASCULAR SYSTEM

Refractory Periods

Absolute refractory period (ARP)

The interval during which no AP can be produced, regardless of the stimulus intensity.

It lasts the upstroke till mid-repolarization at about -50 to -60 mV, (~0.25 to 0.30 sec).

Relative refractory period (RRP)

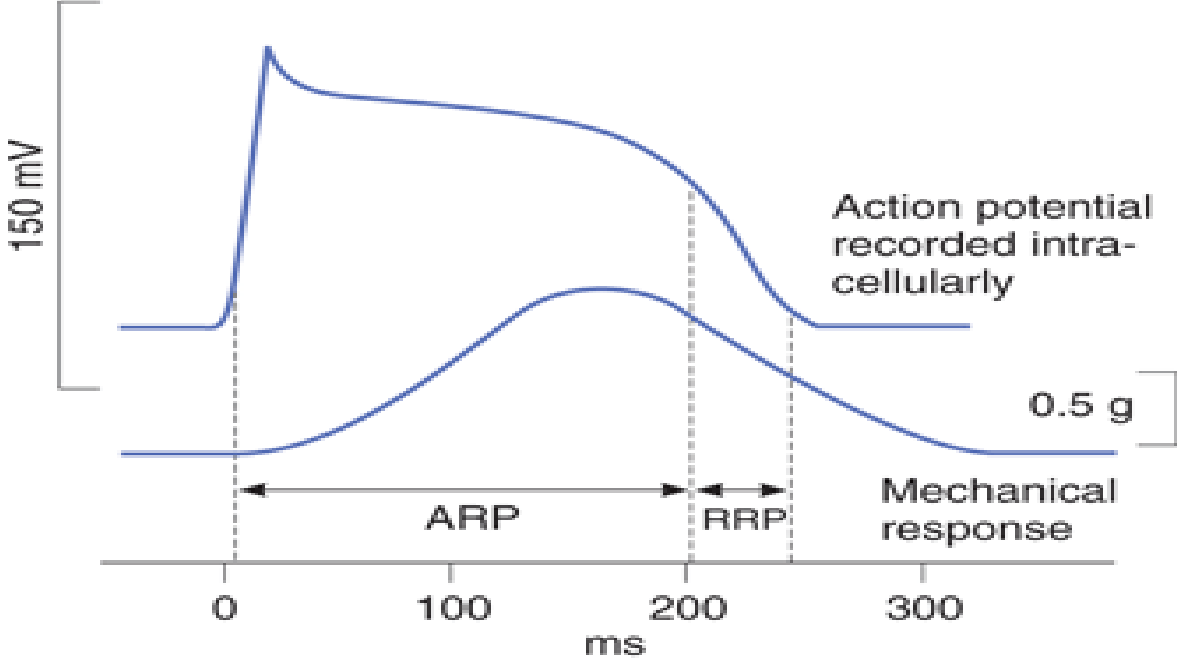
it is the interval during which the muscle can be excited only by a ***very strong excitatory signal***.

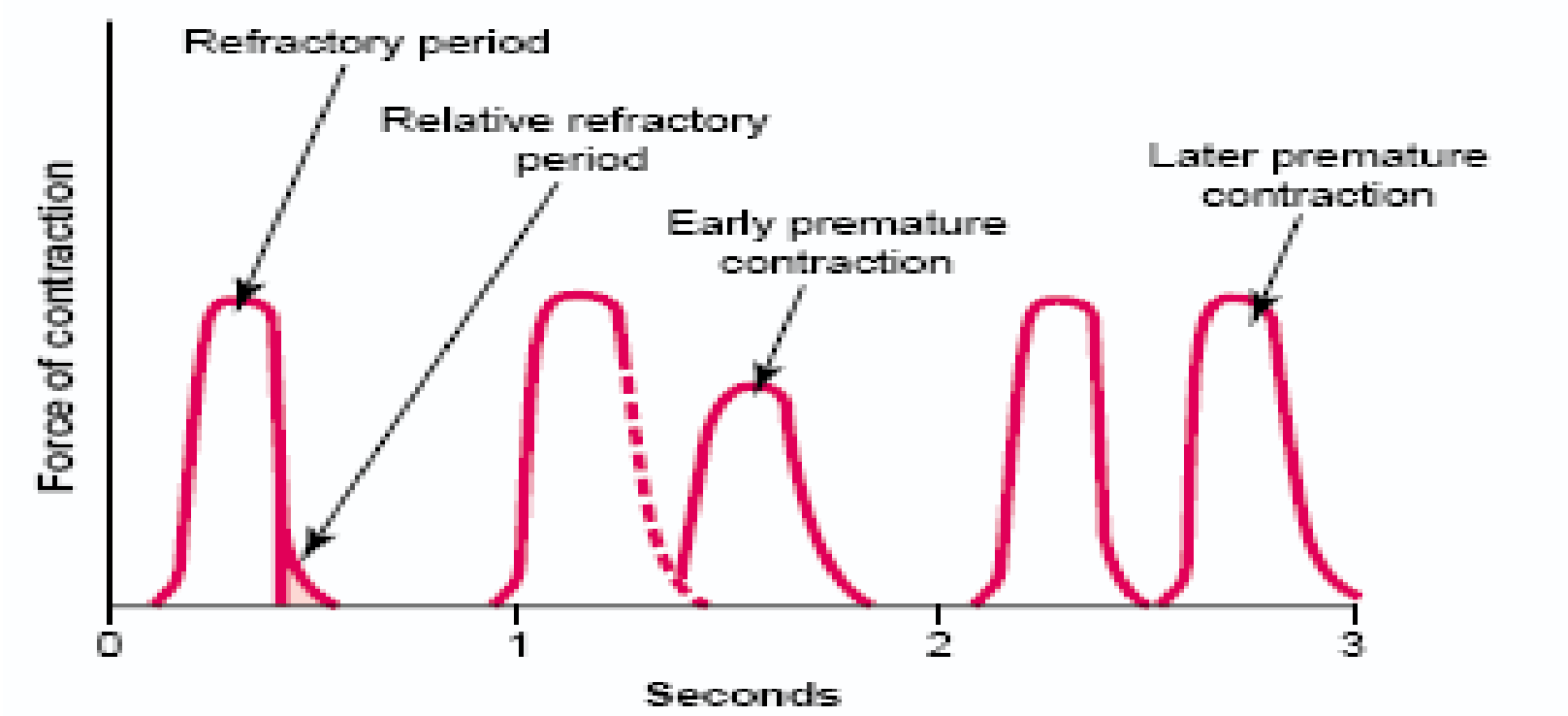
It lasts (~ 0.05 sec) from the end of **ARP** (mid-repolarization) till shortly before complete repolarization (phase 4).

So, the cardiac muscle ***can not be re-exited*** during the whole systole and early part of diastole.

Refractory period prevents waves summation

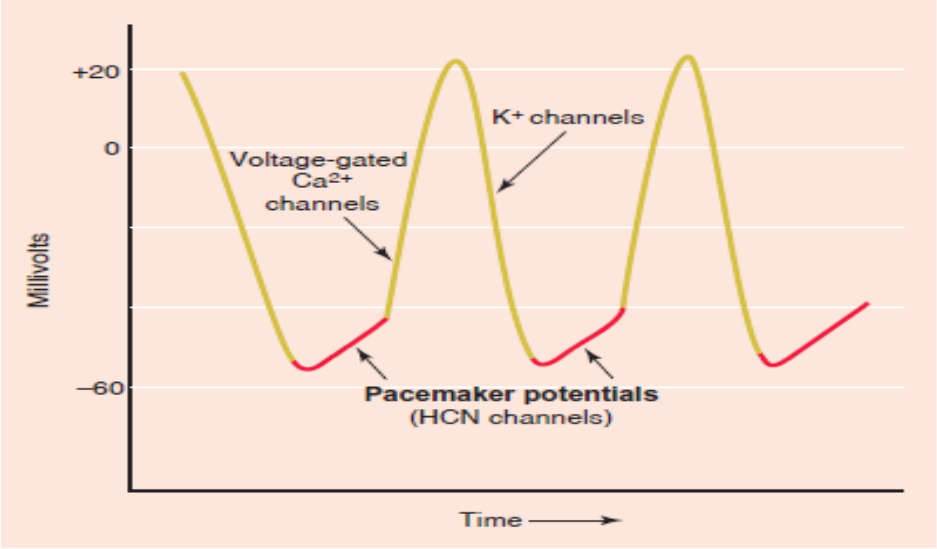
The long plateau phase of the myocardial action potential distinguishes it from the spike-like action potentials in axons and muscle fibers. The plateau phase is accompanied by the entry of Ca^{2+} , which begins excitation-contraction coupling (as described shortly). Thus, myocardial contraction accompanies the long action potential, and is completed before the membrane recovers from its refractory period. Summation and tetanus, as can occur in skeletal muscles, is thereby prevented from occurring in the myocardium by this long refractory period.


150 mV
Action potential recorded intra-cellularly
0.5 g
ARP
RRP
Mechanical response
0
100
200
300
ms


Refractory period
Relative refractory period
Early premature contraction
Later premature contraction
Force of contraction
0
1
2
3
Seconds

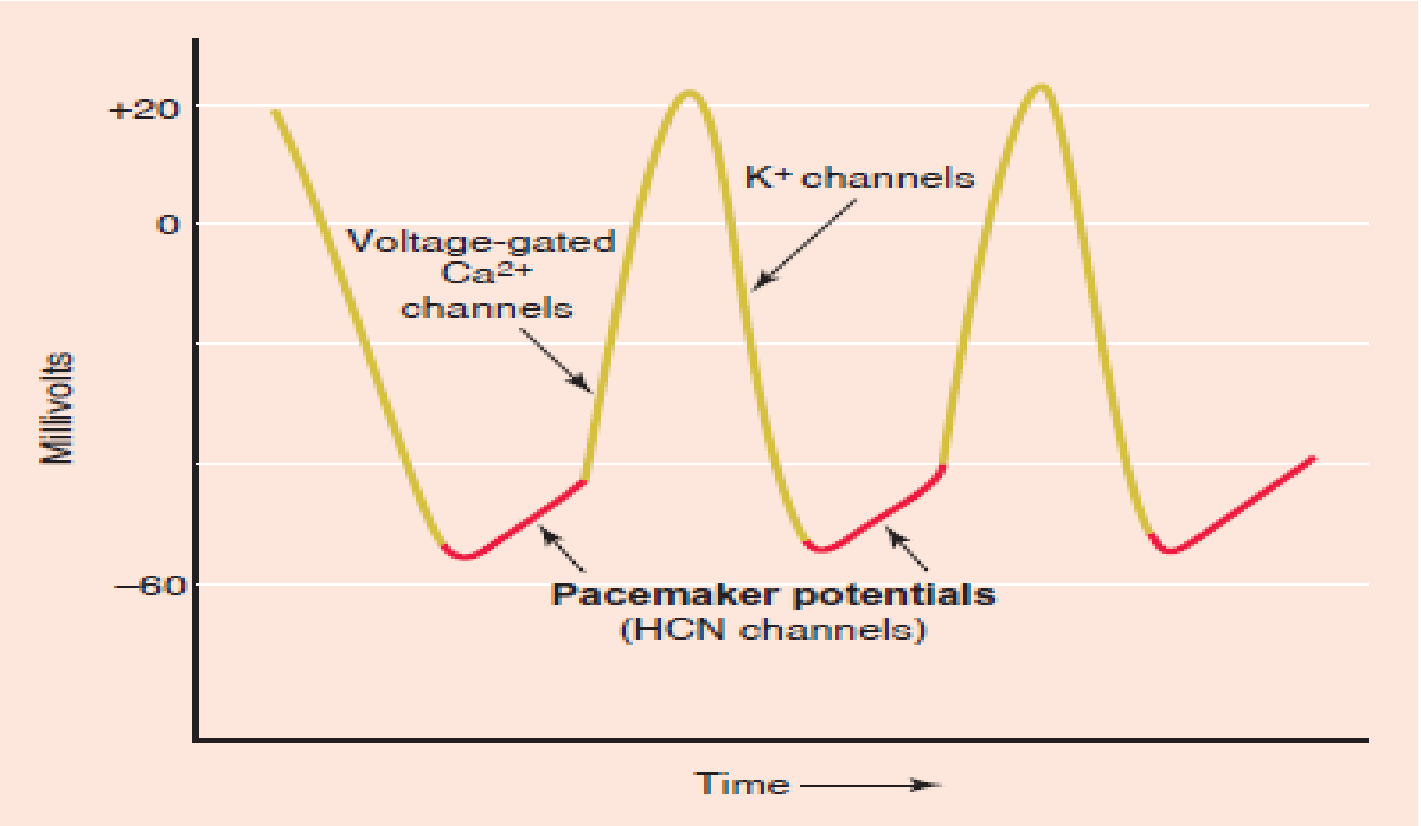
Pacemaker Potential

The cells of the SA node do not maintain a resting membrane potential in the manner of resting neurons or skeletal muscle cells. Instead, during the period of diastole, the SA node exhibits a slow *spontaneous depolarization* called the **pacemaker potential.** The membrane potential begins at about − 60 mV and gradually depolarizes to − 40 mV, which is the threshold for producing an action potential in these cells



The spontaneous depolarization of the pacemaker potential is produced by the opening of a type of channel that, strangely, opens in response to hyperpolarization. When first discovered, the ion current through this strange channel was called a **“funny current.”** The hyperpolarization (approaching − 60 mV) stimulus that opens this channel occurs at the end of the preceding action potential. Once opened, this channel is permeable to both Na + and K + . Because the electrochemical gradient is greater for the entry of Na + than for the exit of K + , the entry of Na + predominates and produces a depolarization. The spontaneous,
automatic depolarization of the pacemaker occurs during diastole, so it can be termed a **diastolic depolarization.**

When the diastolic depolarization reaches threshold (about–40mV), it causes the opening of voltage-gated Ca 2 + channels in the plasma membrane of the pacemaker cells. It is the inward diffusion of Ca 2 + that produces the upward phase of the action potential. The inward current of Ca 2 + also results in contraction of these myocardial cells. Repolarization is produced by the opening of voltage-gated K + channels and the outward diffusion of K + .

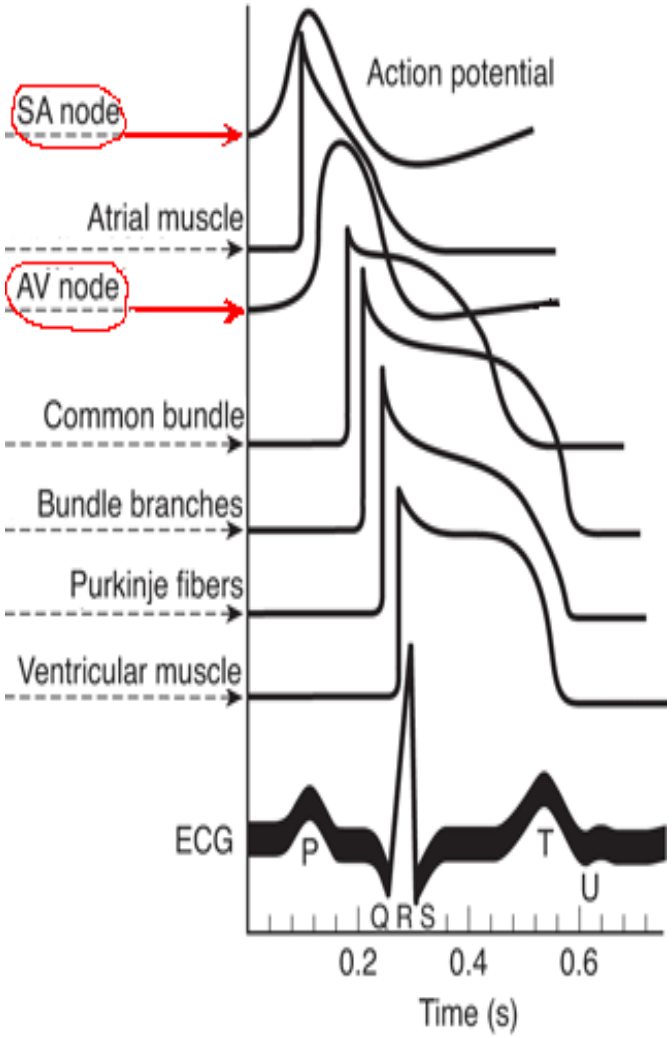


SA node normally discharges most rapidly. Therefore, ***is the normal cardiac pacemaker.***

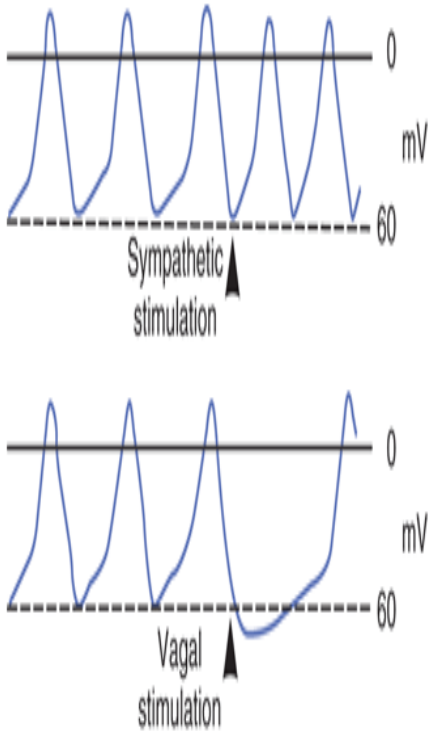
Its rate of discharge determines heart rate. However, "latent pacemakers" are present in other portions of the conduction system, When?

Atrial and ventricular muscle fibers *do not have prepotentials*, and they discharge spontaneously only when injured or abnormal.

Recorded extracellularly, the summed electrical activity of all the cardiac muscle fibers is the **electrocardiogram** (**ECG**).



The diastolic depolarization occurs faster in response to epinephrine and norepinephrine. This is because these catecholamines stimulate the β 1 -adrenergic receptors, causing the production of cAMP within the pacemaker cells. The cAMP, like hyperpolarization, keeps the pacemaker channels open. This is why the cardiac pacemaker channels are termed **HCN channels (for *hyperpolarizationactivated cyclic nucleotide-gated channels*).** Pacemaker HCN channels opened by cAMP (formed in response to catecholamine stimulation) allow for a faster rate of diastolic depolarization, resulting in a faster heart rate. In summary, the hyperpolarization resulting from the previous action potential causes the opening of HCN channels, and this action is augmented by cAMP as a second messenger of catecholamine stimulation. Opening of HCN channels produces a diastolic depolarization, primarily caused by an inward Na + current through these channels. When the diastolic depolarization reaches threshold, it stimulates the opening of voltage-gated Ca 2+ channels in the plasma membrane, producing the action potential that causes the heartbeat.



Sympathetic stimulation

↓

Release of noradrenaline

↓

Binds to β1 receptors

↓

Increased cAMP

↓

Opening of L-type Ca2+ channels

↓

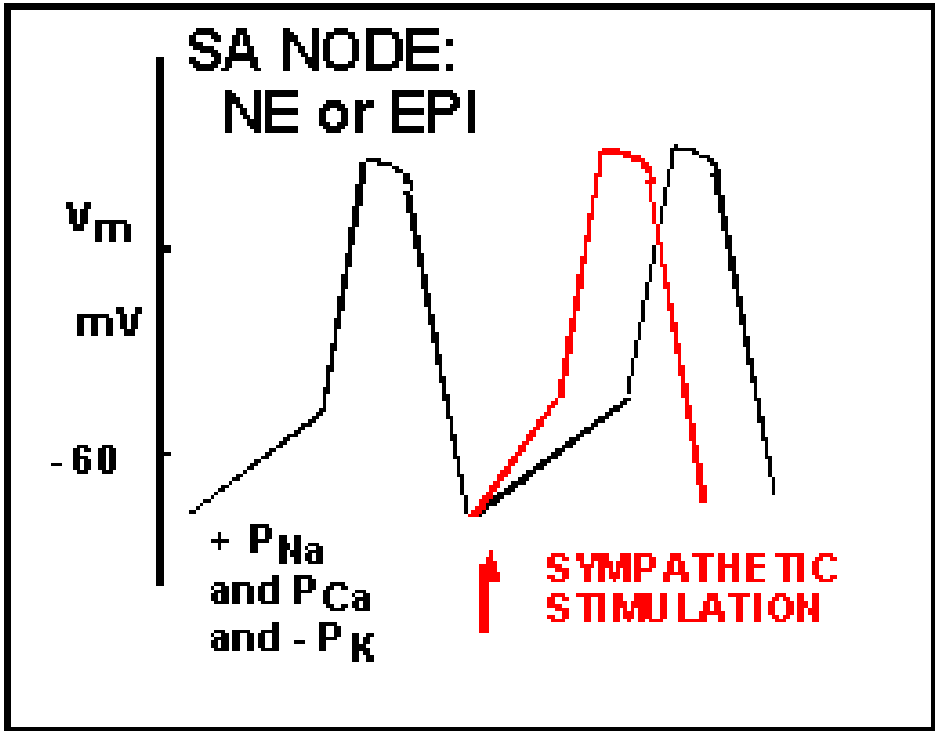
Increased Ca2+ influx

↓

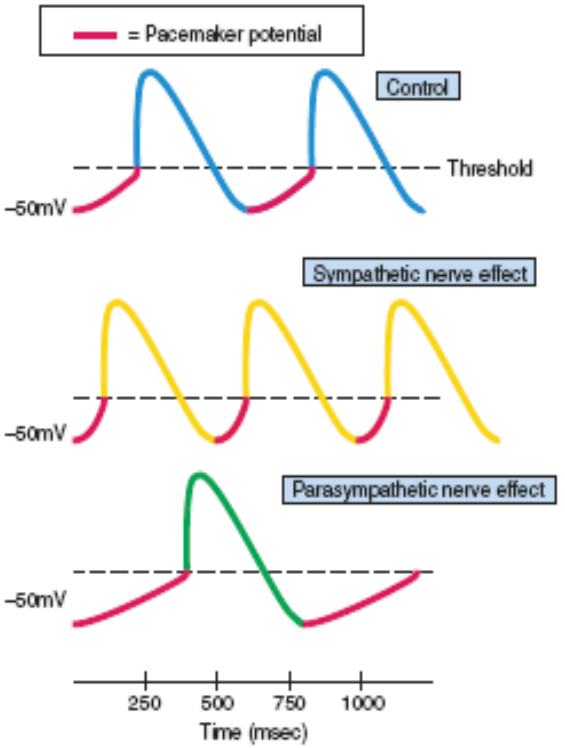
Reduced pre-potential slope

↓

Increased rate of impulse generation



On the other hand, the rate of diastolic depolarization is slowed by the action of parasympathetic axons, primarily because ACh released by these axons causes the opening of separate K + channels. The movement of K + out of the pacemaker cells slows the time required for the diastolic depolarization to reach threshold, thereby slowing the heart rate. In these ways, sympathetic and parasympathetic nerves modify the rate of the automatic diastolic depolarization, and thereby regulate the cardiac rate.



Vagal stimulation

Release of acetylcholine

Ach binds to M2 muscarinic receptor

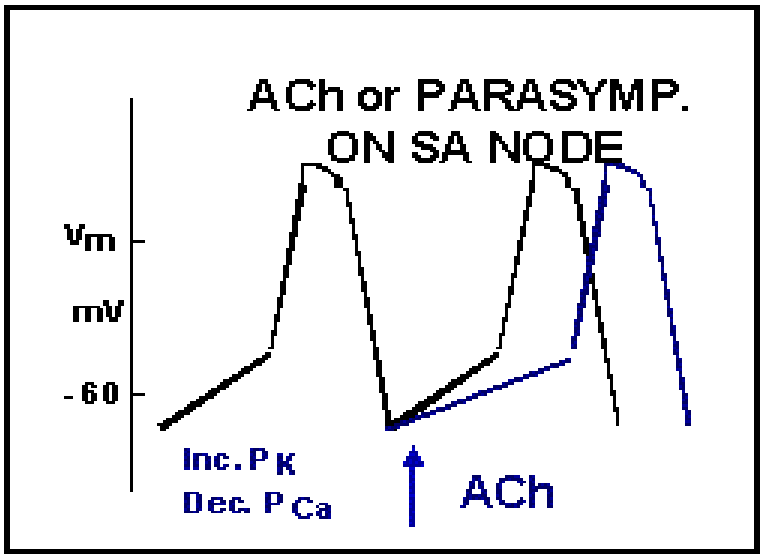
βγ subunit of G-protein act on K^+ channels

Reduced cAMP

Opening of K^+ channels

Reduced Ca2+ influx

Decreased pre-potential slope



See Fig 12.10 !!!!

When the repolarization phase of an action potential in a pacemaker cell is followed by a certain level of hyperpolarization, the HCN channels in the plasma membrane will be opened and a new pacemaker potential will begin. Before that, however, the action potentials produced by the pacemaker cells will spread from myocardial cell to myocardial cell through the gap junctions that connect them. Thus, action potentials will spread from the SA node through the atria and, by means of conducting tissue, into the ventricles.

two other regions in the heart,

the AV node and Purkinje fibers, can potentially serve as pacemakers but are normally suppressed by action potentials originating in the SA node. This is because their rate of spontaneous depolarization is slower than that of the SA node. Thus, the potential pacemaker cells are stimulated by action potentials from the SA node before they can stimulate themselves through their own pacemaker potentials. If action potentials from the SA node are prevented from reaching these areas (through blockage of conduction), they will generate pacemaker potentials at their own rate and serve as sites for the origin of action potentials; they will function as pacemakers.

A pacemaker other than the SA node is called an ectopic pacemaker, or alternatively, an ectopic focus. From this discussion, it is clear that the rhythm set by such an ectopic pacemaker is usually slower than that normally set by the SA node.

Conducting Tissues of the Heart

Action potentials that originate in the SA node spread to adjacent myocardial cells of the right and left atria through the gap junctions between these cells. Because the myocardium of the atria is separated from the myocardium of the ventricles by the fibrous skeleton of the heart, however, the impulse cannot be conducted directly from the atria to the ventricles.

Specialized conducting tissue, composed of modified myocardial cells, is thus required. These specialized myocardial cells form the ***AV node, bundle of His,*** **and** ***Purkinje fibers.***

Once the impulse has spread through the atria, it passes to the **atrioventricular node (AV node),** which is located on the inferior portion of the interatrial septum. From here, the impulse continues through the **atrioventricular bundle,** or bundle of His, beginning at the top of the interventricular septum. This conducting tissue pierces the fibrous skeleton of the heart and continues to descend along the interventricular septum. The atrioventricular bundle divides into right and left bundle branches, which are continuous with the Purkinje fibers within the ventricular walls. Within the myocardium of the ventricles, the action potential spreads from the inner (endocardium) to the outer (epicardium) side. This causes both ventricles to contract simultaneously and eject blood into the pulmonary and systemic circulations.

FACTORS AFFECTING AUTORHYTHMICITY

i) *Autonomic nerve stimulation*

ii) *Temperature:* may contribute to the tachycardia associated with fever.

iii) *Hormones*

iv) *Drugs :* Digitalis depresses nodal tissue and exerts an effect like that of vagal stimulation, particularly on the AV node.

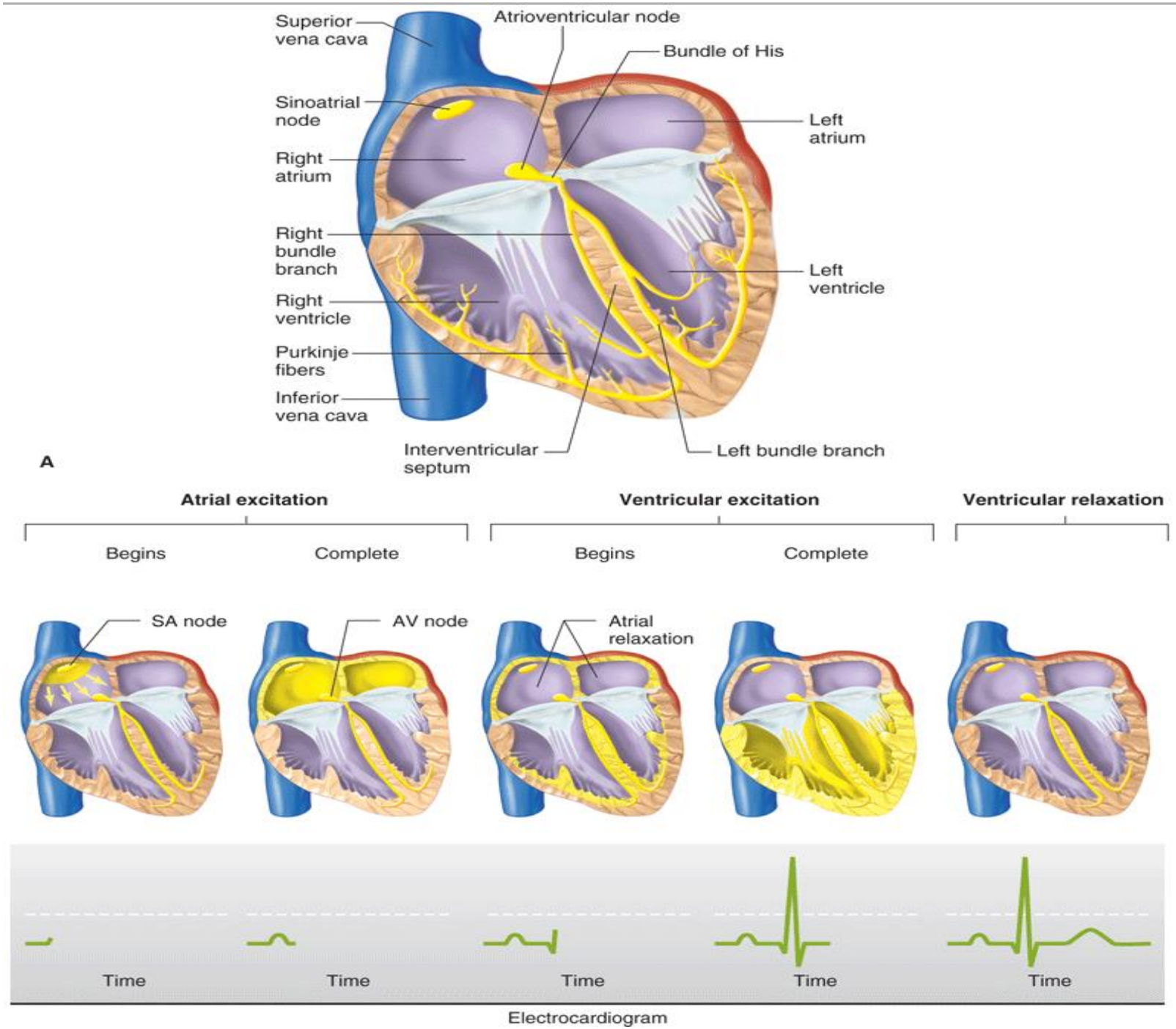
v) *Ions-*

a) K^+→ increased K^+ in ECF → decreased RMP → hyperpolarisation→ reduced heart rate

→ diastolic arrest

Conduction of the Impulse

Action potentials from the SA node spread very quickly—at a rate of 0.8 to 1.0 meter per second (m/sec)—across the myocardial cells of both atria. The conduction rate then slows considerably as the impulse passes into the AV node. Slow conduction of impulses (0.03 to 0.05 m/sec) through the AV node accounts for over half of the time delay between excitation of the atria and ventricles. After the impulses spread through the AV node, the conduction rate increases greatly in the atrioventricular bundle and reaches very high velocities (5 m/sec) in the Purkinje fibers. As a result of this rapid conduction of impulses, ventricular contraction begins 0.1 to 0.2 second after the contraction of the atria.


Superior vena cava
Atrioventricular node
Bundle of His
Sinoatrial node
Left atrium
Right atrium
Right bundle branch
Left ventricle
Right ventricle
Purkinje fibers
Inferior vena cava
Interventricular septum
Left bundle branch
A
Atrial excitation
Begins
Complete
Ventricular excitation
Begins
Complete
Ventricular relaxation
SA node
AV node
Atrial relaxation
Time
Time
Time
Time
Time
Electrocardiogram

Conduction Speeds in Cardiac Tissue.	
Tissue	**Conduction Rate (m/s)**
SA node	0.05
Atrial pathways	1
AV node	0.05
Bundle of His	1
Purkinje system	4
Ventricular muscle	1

Excitation-Contraction Coupling in Heart Muscle

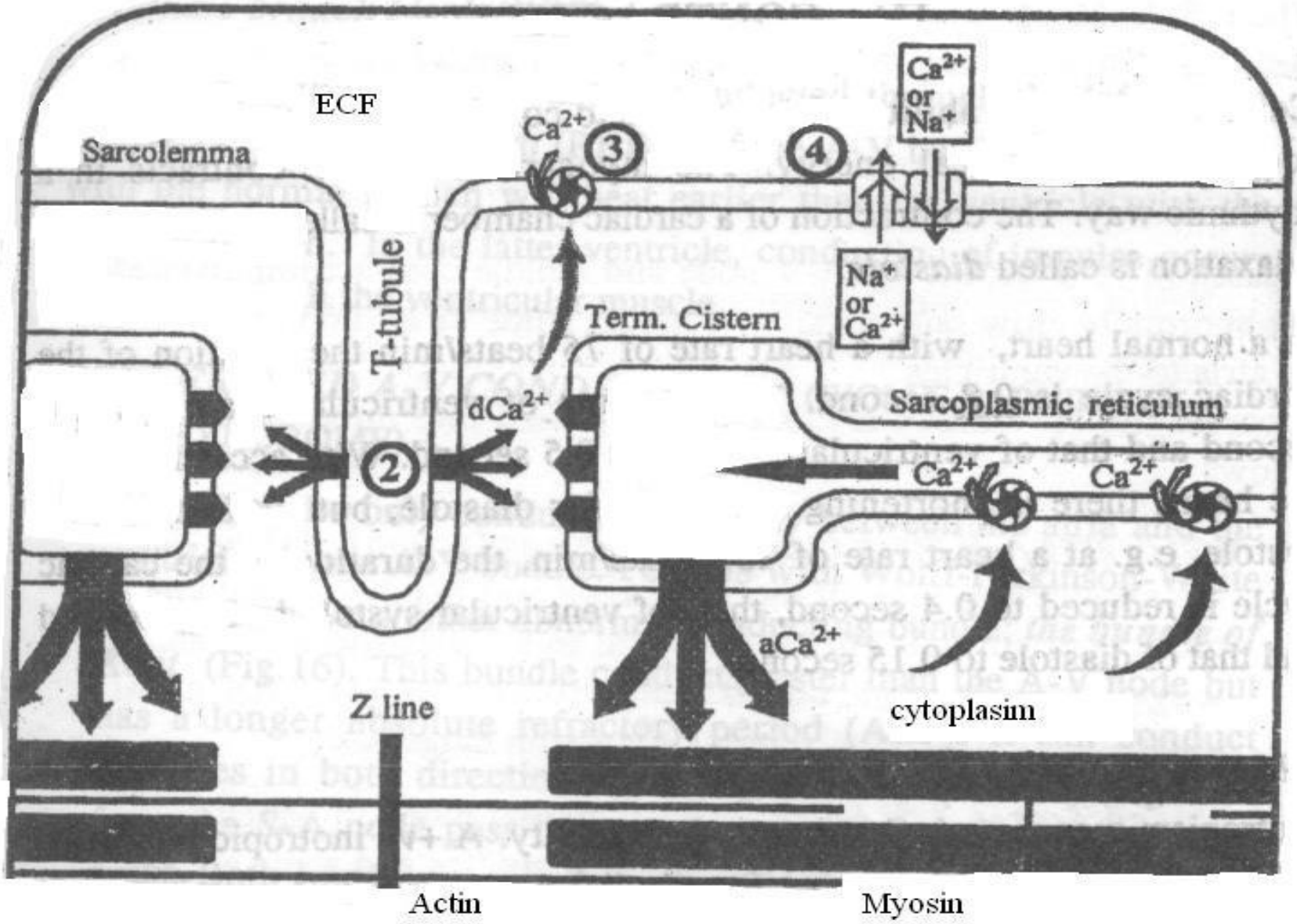
The mechanism of excitation-contraction coupling in myocardial cells, involving ***Ca 2 + - stimulated Ca 2 + release***.

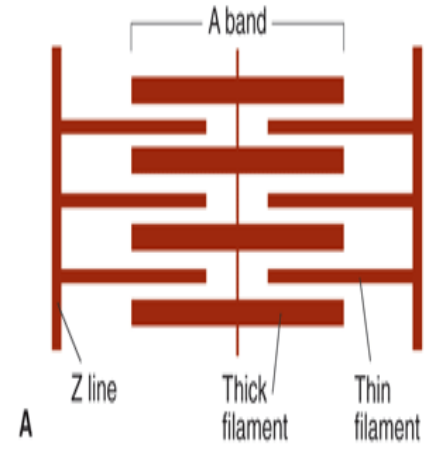
In summary, the depolarization of action potentials, conducted along the sarcolemma and transverse tubules, briefly opens voltage-gated Ca 2 + channels in the plasma membrane. This allows some Ca 2 + to diffuse into the cytoplasm from the extracellular fluid, as a brief “puff” of Ca 2 + . This extracellular Ca 2 + stimulates the opening of Ca 2 + release channels in the sarcoplasmic reticulum, which had previously accumulated a high concentration of Ca 2 + by active transport. In response to the stimulus of extracellular Ca 2 + , a far greater amount of Ca 2 + diffuses out of the sarcoplasmic reticulum, binds to troponin, and stimulates contraction. These events occur where the transverse tubule (containing voltage-gated Ca 2+ channels) forms a *signaling complex* with the sarcoplasmic reticulum (containing Ca 2+ -release channels).

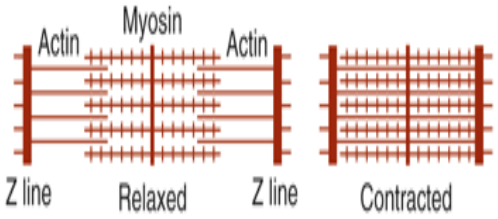
There are about 20,000 signaling complexes in a myocardial cell, which are activated simultaneously by the action potential depolarization to stimulate contraction

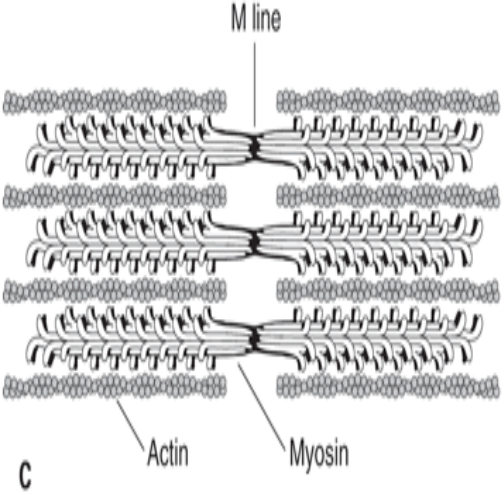
During the repolarization phase of the action potential, the concentration of Ca 2 + within the cytoplasm is lowered by

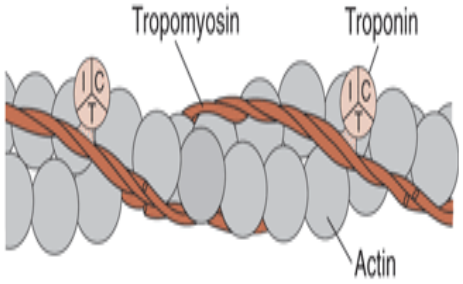
(1) active transport of Ca 2 + back into the sarcoplasmic reticulum by a Ca 2 + -ATPase pump.
(2) (2) extrusion of Ca 2 + through the plasma membrane into the extracellular fluid by a Na + -Ca 2 + exchanger. This exchanger is a secondary active transport carrier; it pumps Ca 2 + out of the cytoplasm against its concentration gradient in exchange of Na + , which moves down its concentration gradient into the cell. That is, the “downhill” movement of Na + into the cell powers the “uphill” extrusion of Ca 2 + . These two mechanisms lower the cytoplasmic Ca 2 + concentration, thereby allowing the myocardium to relax during repolarization

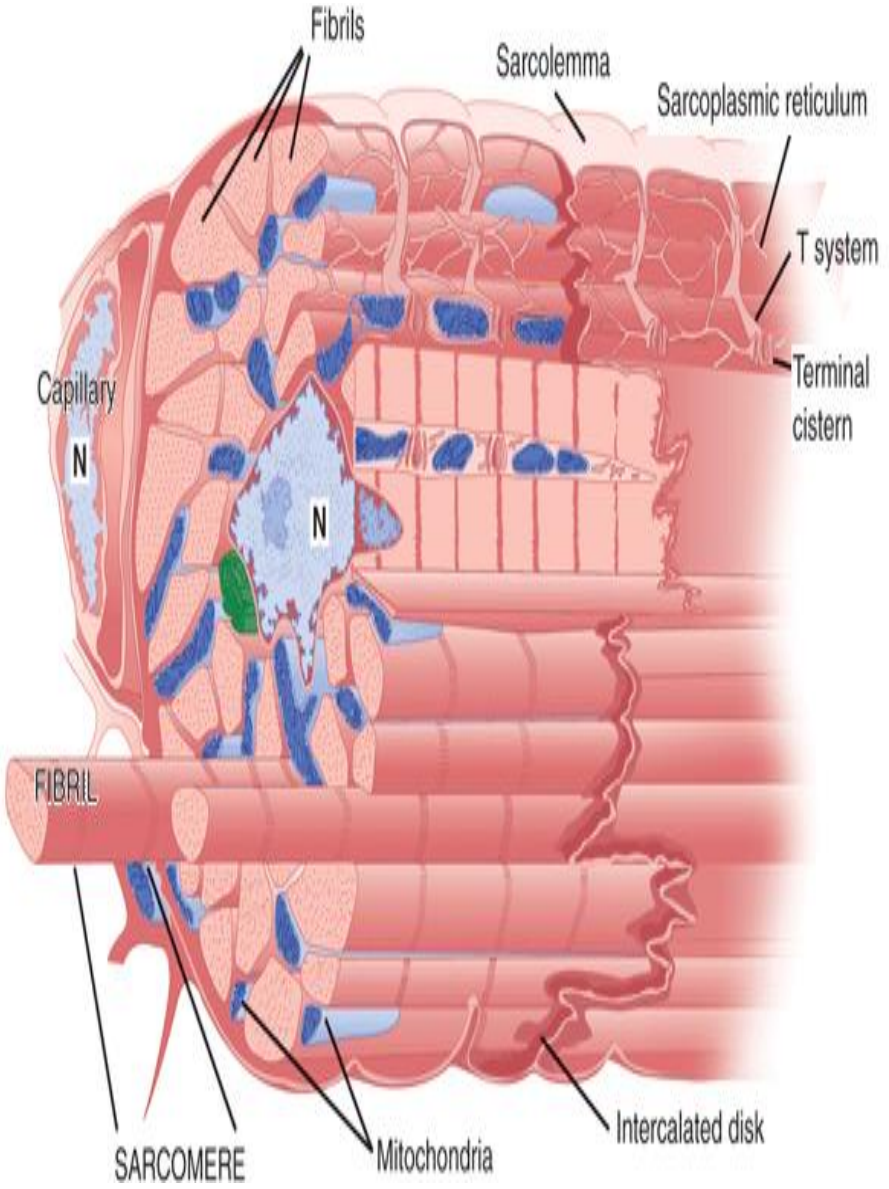

ECF
Sarcolemma
T-tubule
Term. Cistern
Sarcoplasmic reticulum
Ca2+
or
Na+
Na+
or
Ca2+
Ca2+
3
4
2
dCa2+
Ca2+
Ca2+
aCa2+
Z line
cytoplasim
Actin
Myosin


A band
Z line
Thick filament
Thin filament
A

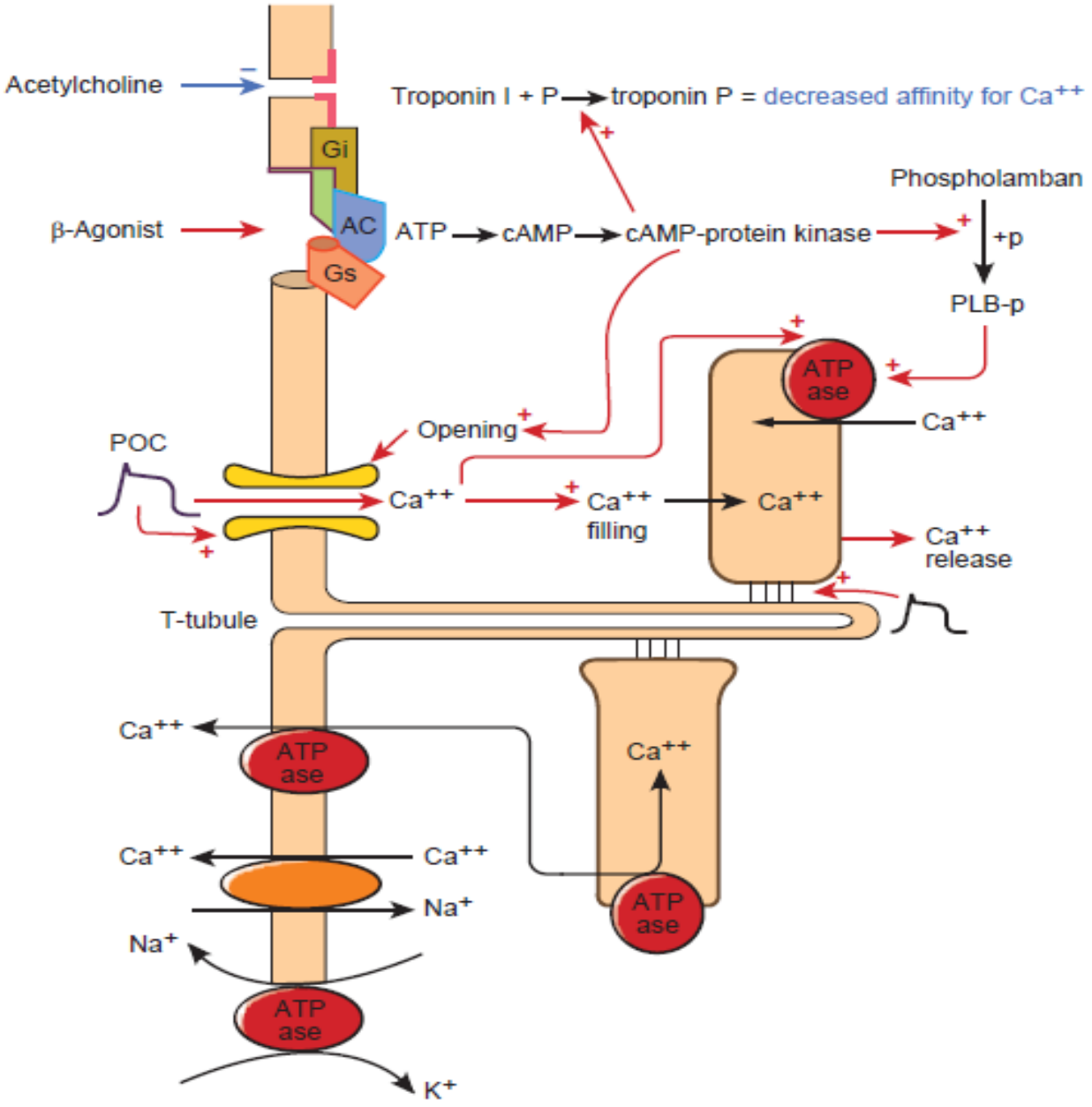

Actin
Myosin
Actin
Z line
Relaxed
Z line
Contracted
B


M line
Actin
Myosin
C


Tropomyosin
Troponin
I
C
T
I
C
T
Actin
D


Fibrils
Sarcolemma
Sarcoplasmic reticulum
T system
Terminal cistern
Capillary
N
N
FIBRIL
SARCOMERE
Mitochondria
Intercalated disk

People with congestive heart failure are often treated with the drug **digitalis.** Digitalis binds to and inactivates the Na+/K+-ATPase pumps in the plasma membrane of myocardial cells. This reduces the ability of these pumps to extrude Na+ from the cytoplasm, producing a rise in the cytoplasmic Na+ concentration. This reduces the difference in Na+ concentration between the inside and outside of the cells, so that the diffusion of Na+ into the cells is decreased. The decreased diffusion of Na+ into the cells then reduces the ability of the Na+- Ca2+ exchangers to extrude Ca2+. Thus, reduced Na+/Ca2+ exchange produces a rise in the intracellular Ca2+ concentration, which then causes more Ca2+ to be taken into the sarcoplasmic reticulum. Finally, it is this increased amount of Ca2+ in the sarcoplasmic reticulum that is responsible for the increased strength of myocardial contraction when a person takes digitalis.


Acetylcholine
Troponin I + P → troponin P = decreased affinity for Ca++
Gi
Phospholamban
β-Agonist
AC
ATP → cAMP → cAMP-protein kinase
+p
Gs
PLB-p
ATP ase
Ca++
Opening
POC
Ca++
Ca++ filling
Ca++
Ca++ release
T-tubule
Ca++
ATP ase
Ca++
Ca++
Ca++
Na+
Na+
ATP ase
ATP ase
K+