CVS MODULE
PHYSIOLOGY LECTURE (3)
PUMPING ACTION OF THE HEART

PRESENTED BY

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4. CONTRACTILITY

Definition:
It is the ability of the cardiac muscle to contract (i.e. to change the chemical energy into mechanical work; contraction).

The effect of various factors on contractility is called inotropism:
a +ve inotropic effect means an increase in contractility and a – ve inotropic effect means a decrease in contractility

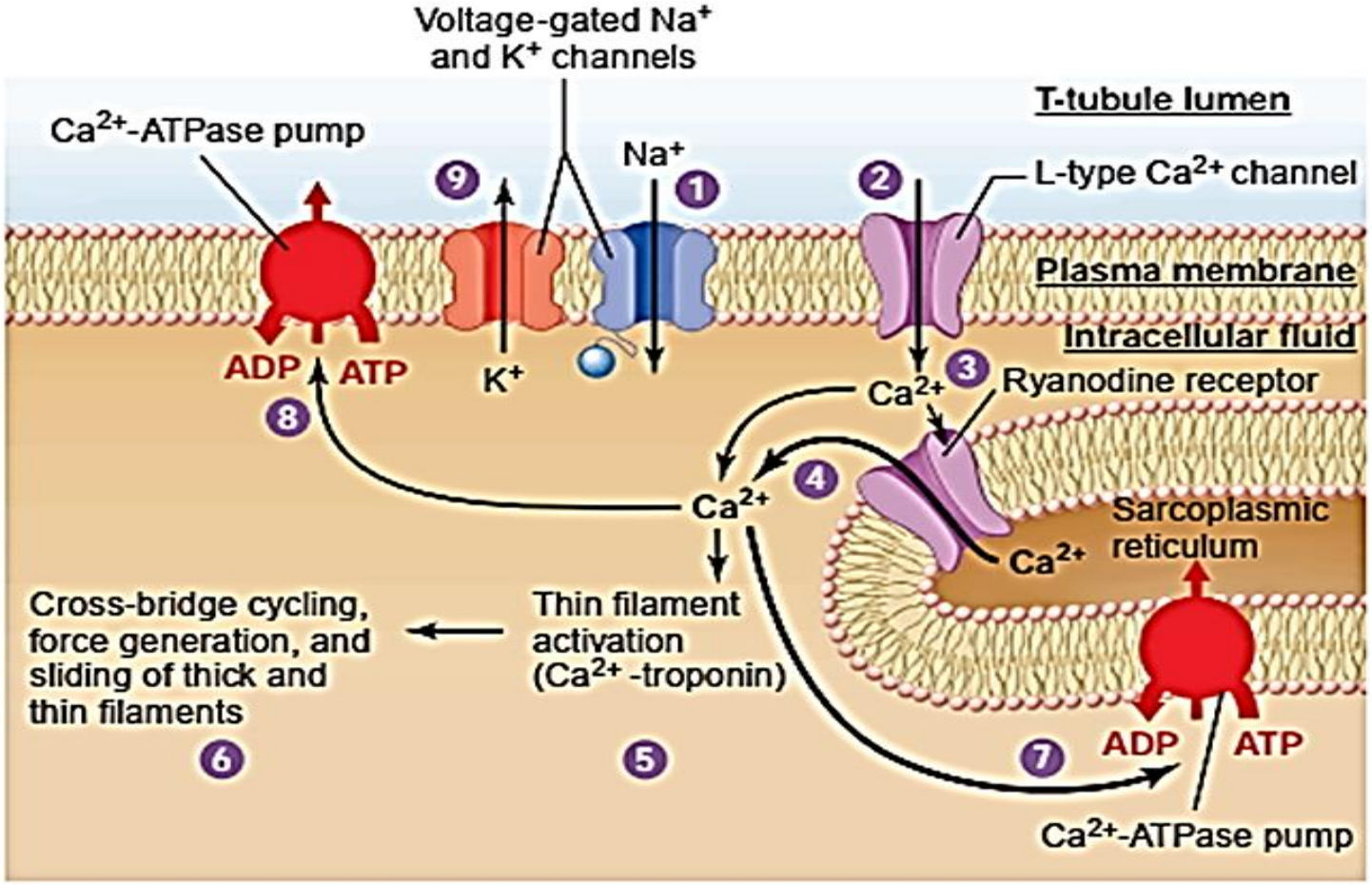
Myocardial Excitation-Contraction Coupling (ECC)

Membrane depolarization initiates the process of excitation contraction coupling (ECC) as follows:

- ✓ Opening of the long lasting (L-type) Ca^{2+} channels present in the sarcolemma and T-tubules→ Ca^{2+} influx from ECF into cardiac muscle fibers.
- ✓ This Ca^{2+} is called **depolarizing Ca^{2+}**. Although its amount is normally very small, it is important.
- ✓ This Ca^{2+} is sensed by the Ca^{2+} release channel in the terminal cisterns of the sarcoplasmic reticulum (SR) → this triggers the release of large amount of Ca^{2+} from the sarcoplasmic reticulum (**activator Ca^{2+}**).
- ✓ Calcium binds to troponin C → allows sliding of actin over myosin → muscle contraction.

Muscle relaxation occurs by

- Active reuptake of Ca^{2+} back to the SR (by Ca^{2+} ATPase pump; SERCA)
- Extrusion of Ca^{2+} from the cell by Na^{+} /Ca^{2+} exchanger and Ca^{2+} ATPase pump.


Voltage-gated Na+ and K+ channels
T-tubule lumen
Ca2+-ATPase pump
Na+
L-type Ca2+ channel
Plasma membrane
Intracellular fluid
ADP
ATP
K+
Ca2+
Ryanodine receptor
Ca2+
Sarcoplasmic reticulum
Ca2+
Cross-bridge cycling, force generation, and sliding of thick and thin filaments
Thin filament activation (Ca2+ -troponin)
ADP
ATP
Ca2+-ATPase pump
1
2
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In the cardiac muscle, the Ca^{+2} required for contraction comes from TWO sources;

Intracellular;

From the **SR (major** source called **activator** Ca^{2+}).

Extracellular,

via voltage gated **(L-type) Ca^{2+} channels** called **depolarizing** Ca^{2+} **(although limited** source, but it is very **important** as it **promotes** more Ca^{2+} release from the SR).

Factors that affect cardiac contractility

These include : Mechanical, cardiac and extra-cardiac factors.

(A) Mechanical Factors

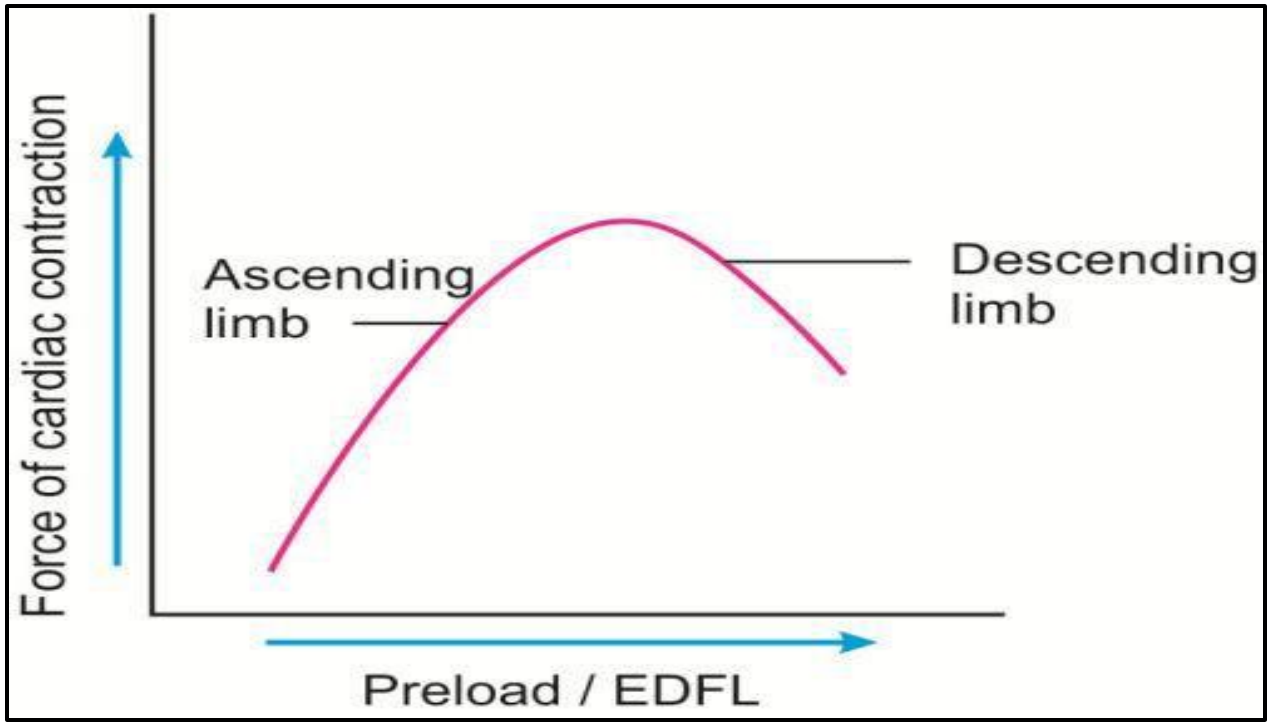
I. The Preload:

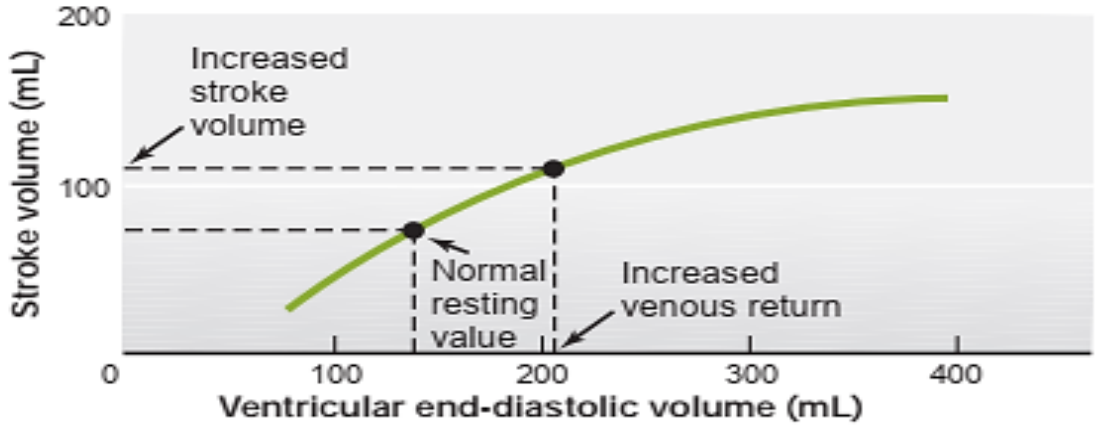
- ✓ In the intact heart, the level of preload is represented by the end-diastolic volume (EDV) (the volume of blood in the ventricles just before contraction).
- ✓ The preload determines the initial length of the resting muscle before contraction.
- ✓ It affects the tension developed in the muscle as well as the velocity of shortening and its extent.
- ✓ All these increase when EDV increases, resulting in a stronger ventricular contraction and a rise of intraventricular pressure which increases the stroke volume (SV).
- ✓ However, this occurs only up to a certain limit after which the peak ventricular performance is decreased.

Frank-Starling Mechanism of the Heart

- It **describes** the relation **between** the initial length of the muscle and the force (i.e. tension) generated in that muscle (i.e. **Length-Tension Relationship**).
- In the **cardiac** muscle: **Within limits**, the force of cardiac muscle contraction is **directly proportional** to the initial length of the muscle fibers.
- (i.e. the greater the initial length of cardiac muscle fiber, the greater is the force of contraction).
- The **initial length** of the cardiac muscle is determined by the **degree of diastolic filling** or **preload** (i.e. **EDV)** which in turn depends on the amount of venous return (VR) to the heart.
- This relationship between stroke volume and EDV is known as the **Frank–Starling mechanism** (also called ***Starling's law of the heart***).
- **Due to this law**, the heart is able to **pump any amount** of blood that it receives. But **overstretching** of cardiac muscle fibers → marked decrease in contractility.

Starling's Law of the heart





Significance of Starling's law of the heart

Starling's law allows heterometric autoregulation of myocardial contractility (= regulation of contractility by changing the length of the muscle fibers), which occurs in the following conditions:

1. In normal hearts → Allows the heart to pump excess blood returning to it from veins (i.e. matches the ventricular output to the changes in VR). e.g. during muscular exercise. Thus, prevents stagnation of blood in the heart and veins.

2. In denervated (i.e. transplanted) heart → it is considered the main mechanism to adjust the pumping capacity of the heart.

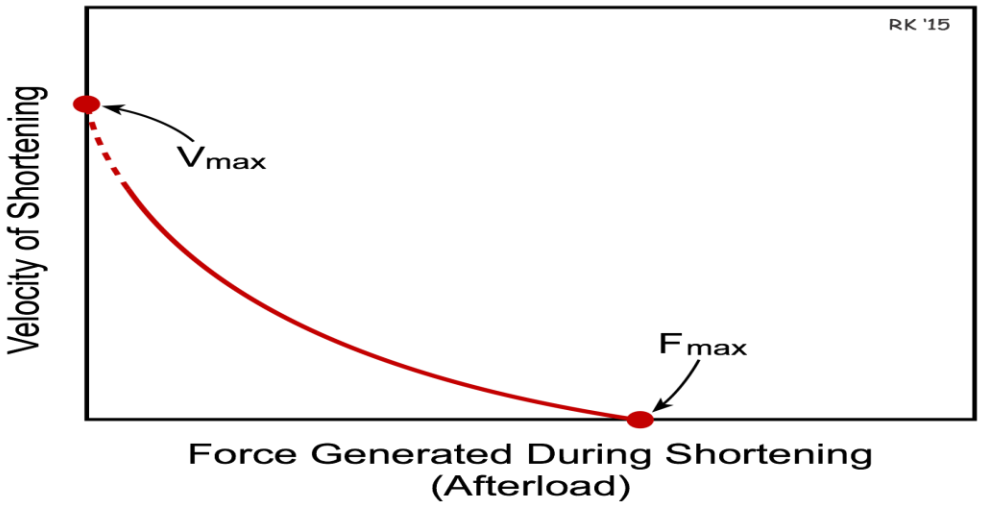
II. The Afterload

- The afterload is the load that the muscle faces when it begins to contract.
- It is the arterial pressures against which the ventricles pump.
- Changes in afterload affect mainly the velocity of shortening of the cardiac muscle.
- Effect of afterload on velocity of shortening (Force-Velocity curve):

✓ The initial velocity of shortening is inversely proportional to the magnitude of afterload.

✓ At zero afterload, maximal velocity of shortening (V max) is achieved.

✓ While, at critical afterload, the velocity of shortening becomes zero and the muscle contracts isometrically.



(B) Cardiac (or intrinsic) Factors

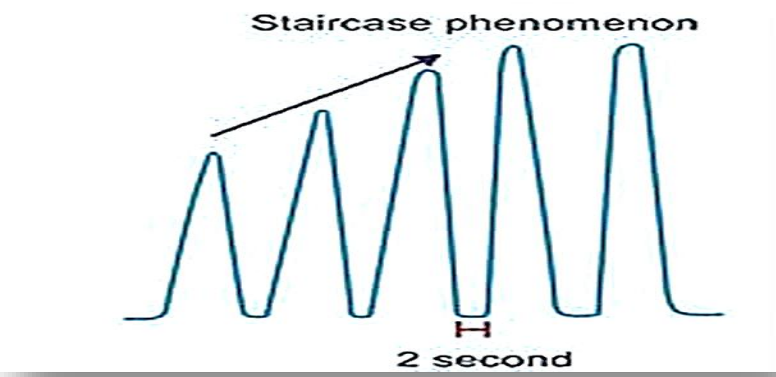
(1) The myocardial mass:

A significant injury (or loss) of the functioning ventricular mass (e.g. due to ischemia or necrosis) decreases the force of myocardial contractility. This also occurs in cases of heart failure.

(2) The heart rate:

Normally, there is a **Force-Frequency relationship** in the heart. i.e. the force of cardiac contractility is affected by the frequency of stimulation (heart rate).

An increase in the frequency of stimulation causes a proportional increase in the force of contraction (like the staircase or treppe phenomenon) and vice versa.



Staircase (Treppe) Phenomenon:

Increasing the frequency of stimulation of cardiac muscle results in gradual increase in force of contractions that occur over the first few contractions. This continues till a new higher steady state is reached and this higher level of force of contraction is maintained as long as the high frequency of stimulation is maintained. This is called staircase phenomenon.

Explanation:

Increasing the frequency of stimulation (tachycardia) → increases the number of depolarization → increases the intracellular Ca^{2+} content and its availability to the contractile proteins → ↑ force of contraction. Thus, tachycardia causes a +ve inotropic effect while bradycardia exerts a –ve inotropic effect.

(3) The cardiac inotropic state

- This is the level of myocardial contractility independent of the cardiac loading conditions.
- It is determined by the quantity of Ca^{2+} delivered to the contractile proteins and is affected by the heart rate and integrity of the myocardial mass as well as by the extra-cardiac factors.

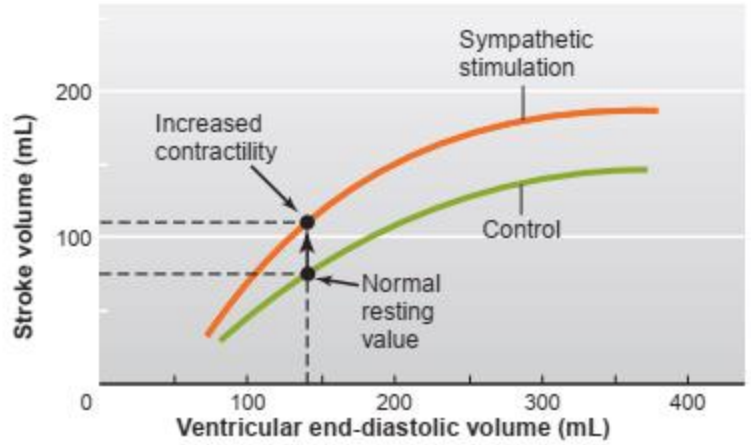
The major determinants of cardiac performance include:

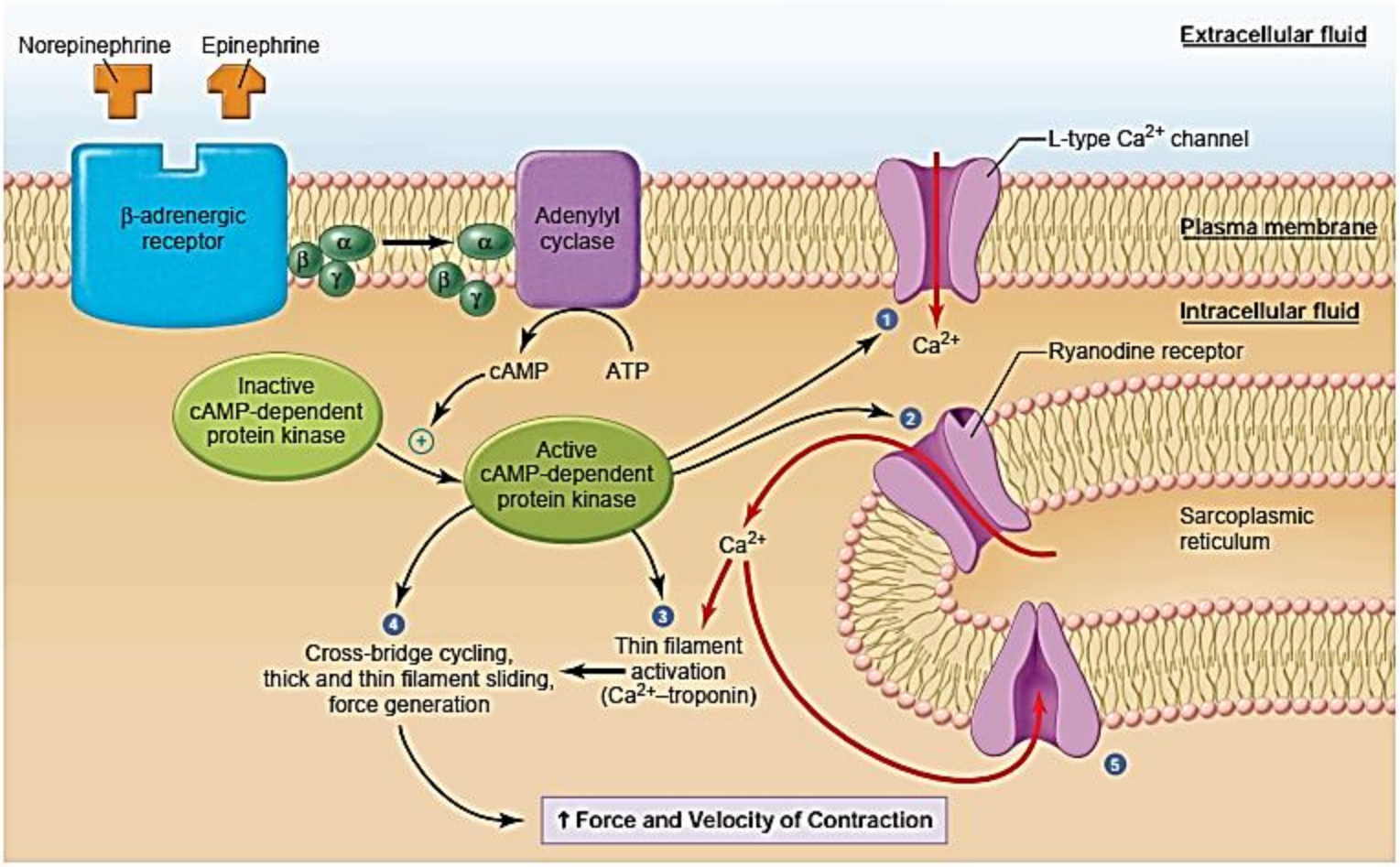
✓ The initial length of the cardiac muscle (the preload).
✓ The afterload.
✓ The frequency of the heart contraction.
✓ The cardiac inotropic state.

(C) Extra-cardiac (Extrinsic) Factors

(1) Nervous Factors:

- Sympathetic Stimulation → ↑ contractility (+ve inotropic effect) through stimulation of β1 adrenergic receptors → formation of cyclic AMP. cAMP activates protein kinase A→ phosphorylation (activation) of L- type calcium channels →more Ca^{2+} influx from ECF and more Ca^{2+} release from SR.
- Vagal Stimulation (on atria ONLY): → ↓ contractility (-ve inotropic effect) due to decreased cAMP.




Norepinephrine
Epinephrine
Extracellular fluid
β-adrenergic receptor
α
β
γ
Adenylyl cyclase
L-type Ca^{2+} channel
Plasma membrane
Intracellular fluid
1
Ca^{2+}
Ryanodine receptor
cAMP
ATP
Inactive cAMP-dependent protein kinase
+
Active cAMP-dependent protein kinase
2
Sarcoplasmic reticulum
Ca^{2+}
3
4
Cross-bridge cycling, thick and thin filament sliding, force generation
Thin filament activation (Ca^{2+}–troponin)
5
↑ Force and Velocity of Contraction

(2) Physical Factors:

- Moderate rise of body temperature → ↑ contractility.

(Due to increased metabolism and decreased viscosity of myocardial structures and increased Ca^{2+} influx).

- Hypothermia→ ↓ contractility.

(3) Chemical Factors

(A)Hormones:

Catecholamines, glucagon and thyroid hormones all exert a +ve inotropic effect.

(B) Blood gases:

- Moderate hypoxia (O_2 lack) and hypercapnia (CO_2 excess) increase the cardiac contractility through stimulating the chemoreceptors.
- On the other hand, severe hypoxia and hypercapnia directly depress the cardiac muscle and decrease the contractility. This is usually due to insufficient blood supply → inhibits ATP production which is the source of energy of muscle contraction.

(C) Effect of ions (Na^+, K^+ & Ca^{2+}):

Na^+:

Excess Na^+ (i.e. Hypernatremia) →↓ contractility (a – ve inotropic effect) as it favors Na^+ influx and Ca^{2+} efflux by the Na^+- Ca^{2+} exchanger.

K^+

Hyperkalaemia→↓ contractility (a – ve inotropic effect) and may stop the heart in diastole.
On the other hand, hypokalaemia produces +ve inotropic effect.

Ca^{2+}

Excess Ca^{2+} (i.e. Hypercalcemia) →↑ contractility (a +ve inotropic effect) as a result of more calcium influx into the cardiac muscle fibers. It prolongs the systole on the expense of diastole and the heart may stop in systole (Ca^{2+} rigor). So, I.V. Ca^{2+} injections should be given very slowly.

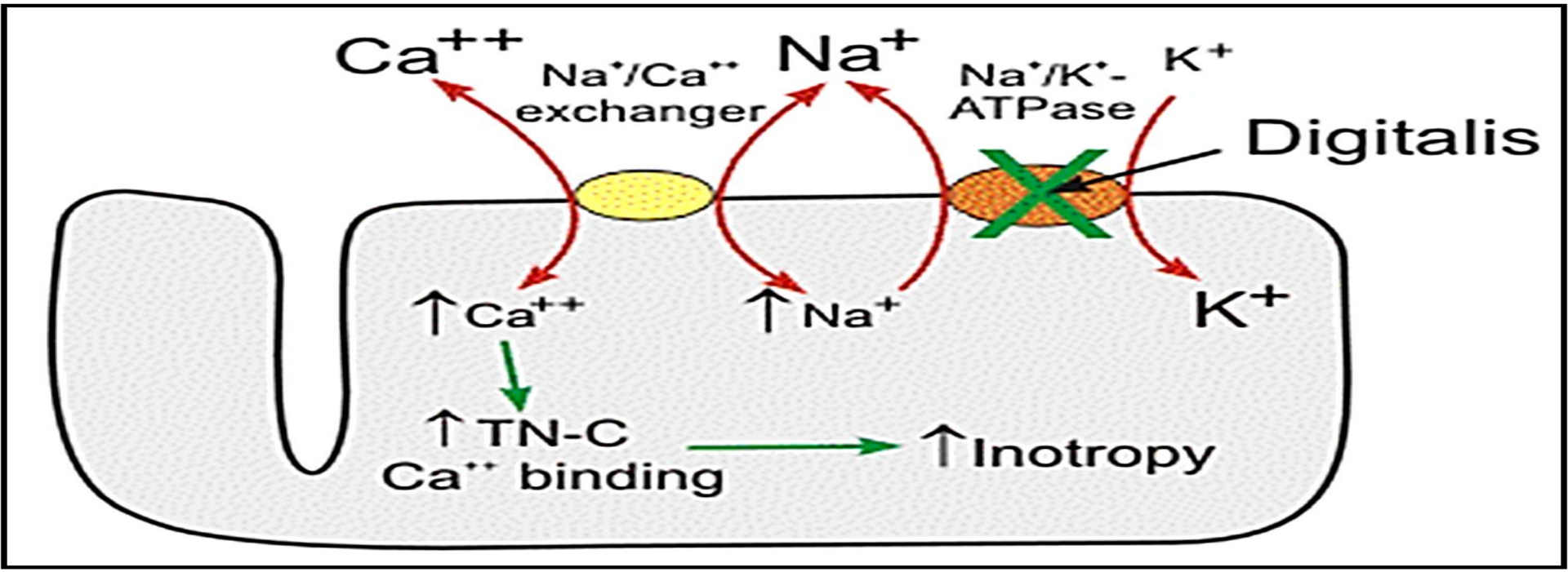
On the other hand, hypocalcemia has a little (or no) –ve inotropic effect, since lowering of the serum Ca^{2+} level causes fatal tetany before affecting the heart.

(D) Acetylcholine → ↓ contractility (–ve inotropic effect)**.**

(E) Drugs: e.g.

Digitalis → ↑ contractility **(+ve inotropic effect)**.

<u>Mechanism:</u> (via inhibition of Na^+- K^+ pump in sarcolemma) →↑ intracellular Na^+ concentration→ stimulates Na^+- Ca^{+2} exchanger → ↑ Ca^{2+} influx and Na^+ efflux → ↑ intracellular Ca^{2+} concentration → **(+ve)** inotropic effect.



Xanthines (e.g. Caffeine & Theophylline):

These drugs inhibit breakdown of cAMP (through inhibiting phosphodiesterase enzyme) → ↑ **intracellular cAMP** →↑contractility (+ ve inotropic effect).

Calcium channel blockers:

Inhibits L-type Ca^{+2} channels → ↓ Ca^{+2} influx into the cardiac muscle fibers → ↓ Contractility (- ve inotropic effect).


Thank
You