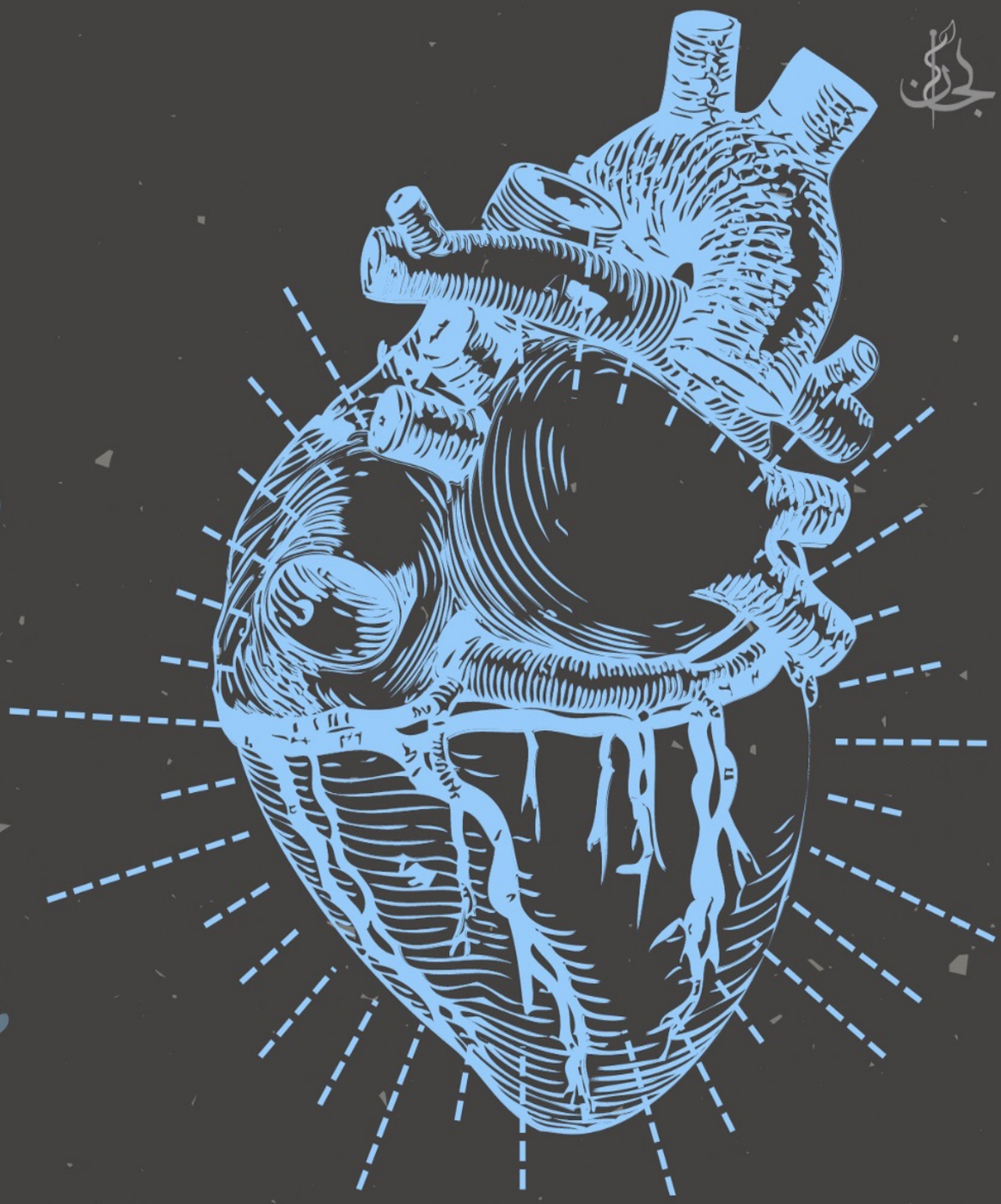
CVS



PHARMACOLOGY

WRITER: Doctor 018

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Beta Adrenergic Blockers

Note: Beta Blockers يُستخدموا للناس اللي عندهم خوف/رهاب المسرح They reduce Sympathatic Symptoms of anxiety.

- Prevent actions of catecholamines, so they are more effective during exertion/stress (that is why they may be preferred=>young people).
- Do not dilate coronary arteries, might constrict them (since we have blocked beta-adrenergic receptors, alpha-receptors will have a higher chance to bind to epinephrine and NE).
- Do not increase collateral blood flow.
- Cause subjective and objective improvement:
  1. Decreased number of anginal episodes.
  2. Decreased Nitroglycerin consumption.
  3. Enhanced exercise tolerance.
  4. Improved ECG.

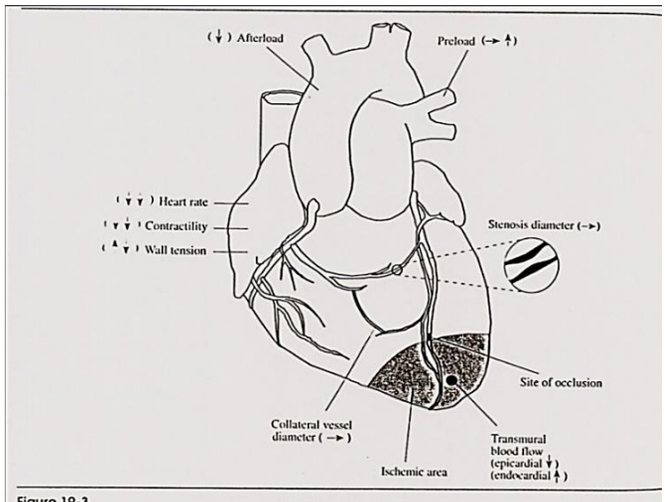


Figure 19-3
A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. For key, see Fig. 19-2.

Calcium Channel Blockers

- Particularly beneficial in vasospasm
- Can also affect platelets aggregation.
- May be dangerous in the presence of **heart failure** and in patients susceptible to **hypotension**.
- The figure below shows the chemical structures of several calcium channel-blocking drugs.

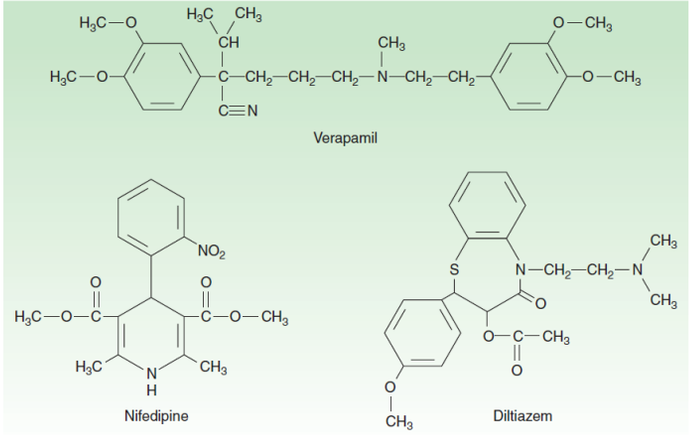
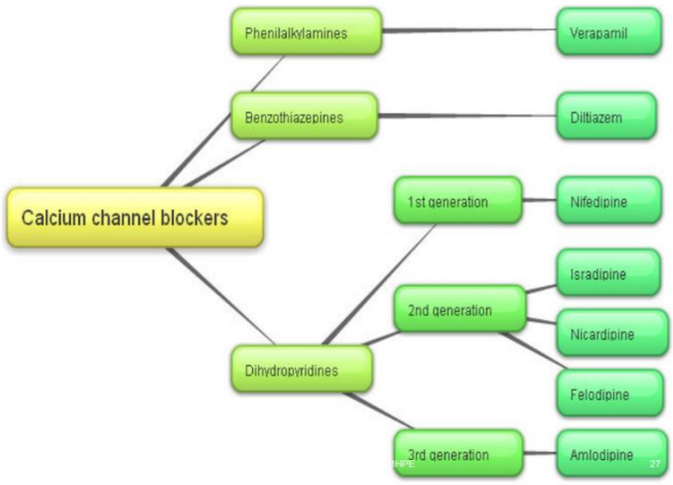


FIGURE 12–4 Chemical structures of several calcium channel-blocking drugs.

The figure beside lists the main calcium channel blockers.



Having said all of this, let us now talk about the properties of several recognized voltage-activated calcium channels.

The professor mentioned the first three types and their sites.

Notice that the calcium channel blockers that we have already mentioned act on type "L calcium channels"

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_v1.1$–$Ca_v1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_v1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, -aga-IIIA
T	$Ca_v3.1$–$Ca_v3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_v2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] -CTX-GVIA, -aga-IIIA, Cd^{2+}
P/Q	$Ca_v2.1$	Neurons	Long, high threshold	-CTX-MVIIC, -aga-IVA
R	$Ca_v2.3$	Neurons, sperm[2]	Pacemaking	SNX-482,[26] -aga-IIIA

The Effect of calcium channel blockers on our cardiovascular system is shown beside.

Notice that the drug's effect on the heart rate and contractility is variable (depends on the position of the patient).

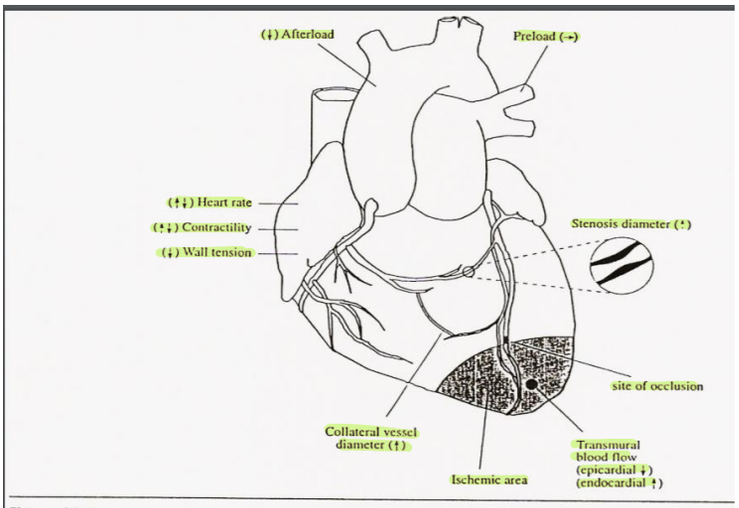


Figure 19-4
A schematic drawing indicating the major actions of the calcium antagonists on the ischemic heart and coronary circulation. For key, see Fig. 19-2.

Side effects of calcium channel blocker include:

1) Hypotension.
2) Headache.
3) Dizziness.
4) Flushing (especially in short acting drugs like Nifedipine).
5) Peripheral edema.

So that they are relatively very safe Drugs.

Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
Amlodipine	65–90	30–50	Angina, hypertension
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
Isradipine	15–25	8	Hypertension
Nicardipine	35	2–4	Angina, hypertension
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nimodipine	13	1–2	Subarachnoid hemorrhage
Nisoldipine	< 10	6–12	Hypertension
Nitrendipine	10–30	5–12	Investigational
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

The table beside shows the effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.

Make sure you understand it.

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	***Reflex[1] increase***	**Decrease**	**Decrease**
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic volume	**Decrease**	**Increase**	**Non or decrease**
Contractility	***Reflex[1] increase***	**Decrease**	**Non**
Ejection time	**Decrease**	**Increase**	**Non**

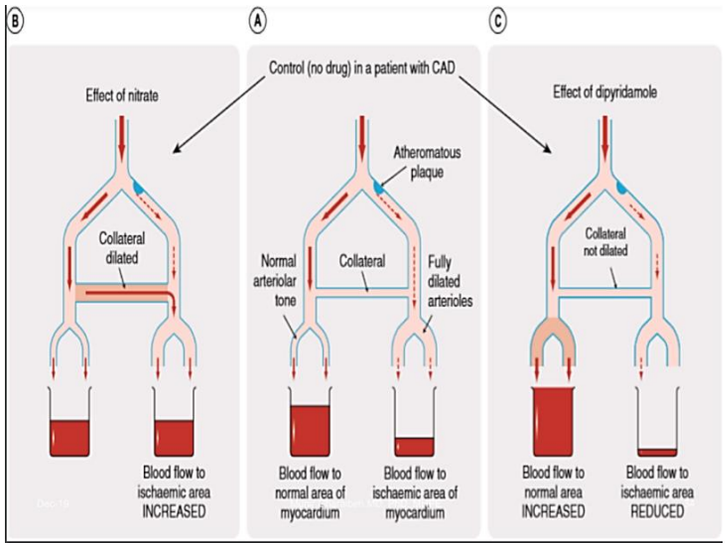
Due to tachycardia.

Dipyridamole

there is nothing much written about this drug in the slides. For further info refer to the last page in this sheet

Adenosine will produce maximal coronary dilation

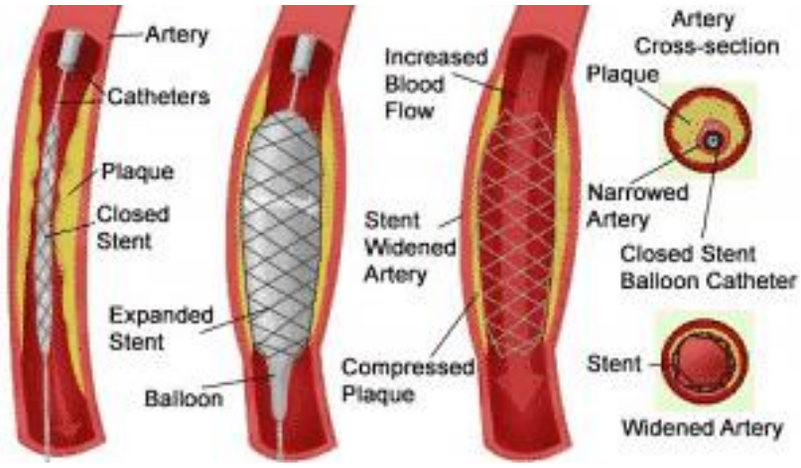
- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme
- **Thought** to be a good coronary dilator.
- Still used as an antiplatelet drug (in Transient ischemic attacks), but **not** better than aspirin. It could be given to patients who cannot tolerate aspirin due to gastric irritation.
- Increases the blood flow to the **normal** area i.e. "Coronary Steal Phenomenon" as shown **beside**.



Therefore, nitrates pre-treatment can be used. Nitrates increase coronary blood flow to ischemic areas by supporting that epicardial vessel dilation.

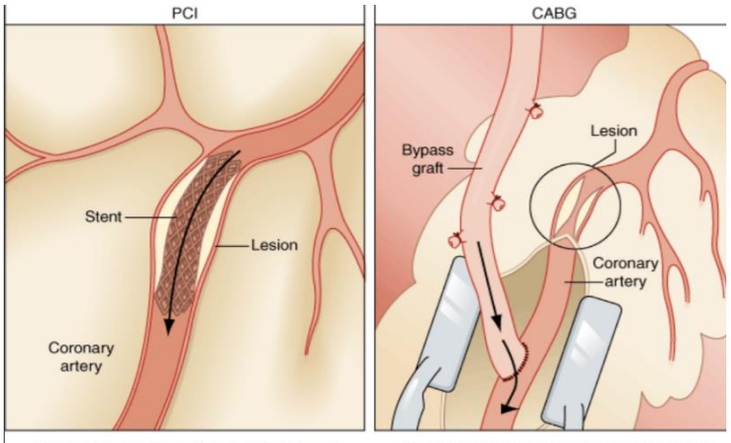
Other agents that are used to treat Angina include:

- Angiotensin converting-enzyme inhibitor (ACEI)
- Anticoagulants and/or Thrombolytic Therapy
- Cholesterol Lowering Agents (They have anti-inflammatory effect)
- Surgery
- **Angioplasty** (the procedure is shown in the figure below)



Extra

Percutaneous Coronary Intervention (**PCI**, formerly known as angioplasty with stent) is a non-**surgical procedure** that uses a catheter (a thin flexible tube) to place a small structure called a stent to open up blood vessels in the heart that have been narrowed by plaque build-up, a condition known as atherosclerosis.



Stent addresses the existing lesion but not future lesions.

Bypass grafting addresses the existing lesion and also future culprit lesions.

Coronary artery bypass grafting (CABG) is a type of surgery that improves blood flow to the heart. It's used for people who have severe coronary heart disease (CHD).

Newer Antianginal Drugs

- Metabolic modulators: ranolazine
- Direct bradycardic agents: Ivabradine
- Potassium channel activators: Nicorandil
- Rho-kinase inhibitors: Fasudil
- Sulfonylureas: Glibenclamide → used in treatment of DM.
- Thiazolidinediones.
- Vasopeptidase inhibitors
- Nitric oxide donors: L- arginine
- Capsaicin → [الشطة] ↳ not real drugs
- Amiloride
  - ↳ diuretics causes your body to get rid of extra salt and water while also preventing the kidneys from getting rid of too much potassium

Extra:

Special Coronary Vasodilators

Many vasodilators can be shown to increase coronary flow in the absence of atherosclerotic disease. These include **dipyridamole** and **adenosine.** In fact, dipyridamole is an extremely effective coronary dilator, but it is not effective in angina because of coronary steal (see below). Adenosine, the naturally occurring nucleoside, acts on specific membrane-bound receptors, including at least four subtypes (A1, A2A, A2B, and A3). Adenosine, acting on A2A receptors, causes a very brief but marked dilation of the coronary resistance vessels and has been used as a drug to measure maximum coronary flow **("fractional flow reserve," FFR)** in patients with coronary disease. The drug also markedly slows or blocks atrioventricular (AV) conduction in the heart and is used to convert AV nodal tachycardias to normal sinus rhythm.

Regadenoson is a selective A2A agonist and has been developed for use in stress testing in suspected coronary artery disease and for imaging the coronary circulation. It appears to have a better benefit-to-risk ratio than adenosine in these applications. Similar A2A agonists (binodenoson, apadenoson) are investigational. Adenosine receptor ligands are also under investigation for anti-inflammatory and antinociceptive and other neurological applications.

Coronary steal is the term given to the action of nonselective
coronary arteriolar dilators in patients with partial obstruction of a portion of the coronary vasculature. It results from the fact that in the absence of drugs, arterioles in ischemic areas of the myocardium are usually maximally dilated as a result of local control factors, whereas the resistant vessels in well-perfused regions are capable of further dilation in response to exercise. If a potent arteriolar dilator is administered, only the vessels in the well perfused regions are capable of further dilation, so more flow is diverted ("stolen") from the ischemic region into the normal region. Dipyridamole, which acts in part by inhibiting adenosine uptake, typically produces this effect in patients with angina. In patients with unstable angina, transient coronary steal may precipitate a myocardial infarction. Adenosine and Regadenoson are labelled with warnings of this effect.

CASE STUDY ANSWER

The case described is typical of coronary artery disease in a patient with hyperlipidaemia. Her hyperlipidaemia should be treated vigorously to slow progression of, and if possible, reverse, the coronary lesions that are present *Coronary angiography* is not indicated unless symptoms become much more frequent and severe; revascularization may then be considered. Medical treatment of her acute episodes of angina should include sublingual tablets or sublingual **Nitroglycerin** spray 0.4–0.6 mg. Relief of discomfort within 2–4 minutes can be expected. To prevent episodes of angina, a **β blocker** such as metoprolol should be tried first. If contraindications to the use of a β blocker are present, a medium- to long-acting **calcium channel blocker** such as verapamil, diltiazem, or amlodipine is likely to be effective. Because of this patient's family history, an antiplatelet drug such as low-dose **aspirin** is indicated. Careful follow-up is mandatory with repeat lipid panels, repeat dietary counselling, and lipid-lowering therapy.

25:16

Heart Failure (HF)

Definition: The heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements.

It is usually characterized by:

- Decreased CO
- Increased TPR (a compensatory mechanism)
  Progression to congestive heart failure (CHF) is accompanied by peripheral and pulmonary edema.

Causes of Congestive Heart Failure:

- Mechanical causes:

  Pressure overload causes, which include:

  - ✓ Hypertension
  - ✓ Aortic valve stenosis
  - ✓ Pulmonary hypertension

  Volume overload causes:

  - ✓ Valvular regurgitation
  - ✓ Shunts
  - ✓ Increased blood volume

- Impaired cardiac filling:
  - ✓ Pericardial disease (constriction or tamponade)
  - ✓ Restrictive heart disease (endo- or myocardial)
  - ✓ Ventricular hypertrophy
  - ✓ Ventricular aneurysm

- Myocardial failure:

  Primary causes include:
  - ✓ Loss of functioning muscle (due to infarction)
  - ✓ Cardiomyopathy
  - ✓ Myocarditis

  Secondary:

  - ✓ Dysdynamic heart failure (response to chronic overload)
  - ✓ Drug-induced Like :-Doxorubicin
  - ✓ Involvement in systemic disease, such as hypothyroidism (where we have overall slowing of metabolism and other body functions)

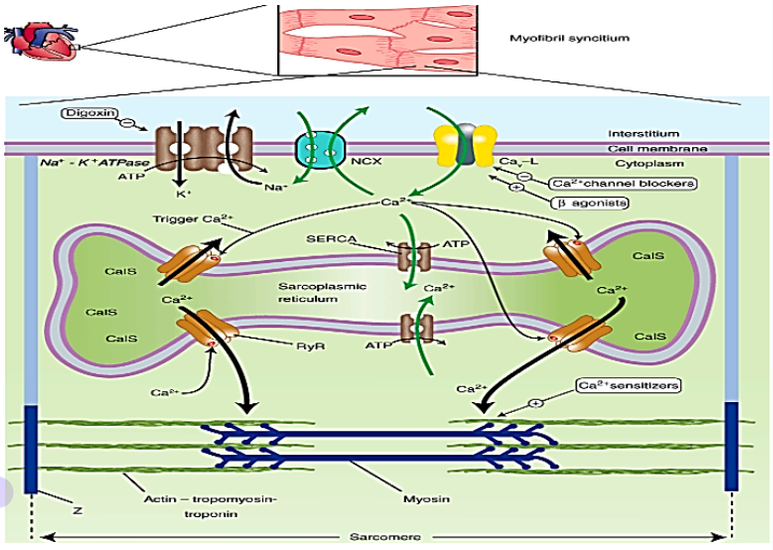
Cardiac output is the major factor contributing in the development of heart failure. It is determined by many factors including: (remember CO=SV x HR)

- Contractility
- Heart rate
- Afterload (ejection tension), it is the pressure that the heart must work against to eject the blood.
- Preload (end diastolic volume), increasing the venous return increases the preload which in turn increases CO.

This diagram shows the mechanism of myocardium contraction, contraction depends on the availability of extracellular calcium as well as intracellular calcium that is released from the sarcoplasmic reticulum (SR). Therefore, in treating HF we try to increase the availability of calcium for the cell.

Note :

In HF We Do not give the patients Ca^{++} because They will not benefit from it.



Mechanisms of HF

In general, we have reduction in the intrinsic myocardial contractility. It could be due to:

- Depletion of NE norepinephrine in heart muscle
- Decreased myosin ATPase activity
- Decreased ATP and other high energy phosphate compounds
- Decreased beta receptors density (due to downregulation after chronic exposure to high levels of catecholamines)
- Abnormal calcium binding (the major contributing factor) could be due to:
  - ✓ Less calcium stored in the SR
  - ✓ More calcium is stored in mitochondria
  - ✓ Lesser amounts of calcium are released from the SR upon excitation
  - ✓ Lesser reuptake of calcium back into the SR after the end of contraction
  - ✓ Slow and abnormal reuptake of calcium into the mitochondria leading to slow relaxation, instead of being reuptaken into SR.

The doctor said that they have proven that they are increasing not decreasing

قال رسول الله ﷺ :

أَلَا أُخْبِرُكَ بِأَحَبِّ الكَلَامِ إلى اللهِ؟ قُلتُ: يا رَسُولَ اللهِ، أَخْبِرْنِي بِأَحَبِّ الكَلَامِ إلى اللهِ، فَقالَ: إنَّ أَحَبَّ الكَلَامِ إلى اللهِ: سُبْحَانَ اللهِ وَبِحَمْدِهِ.

رواه أبو ذر الغفاري رضي الله عنه

صحيح مسلم