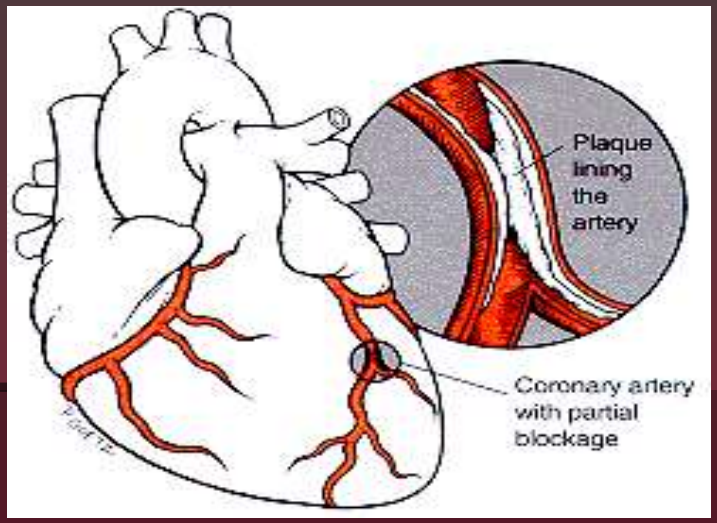
FARMAKOLOGI

OBAT ANTIANGINA



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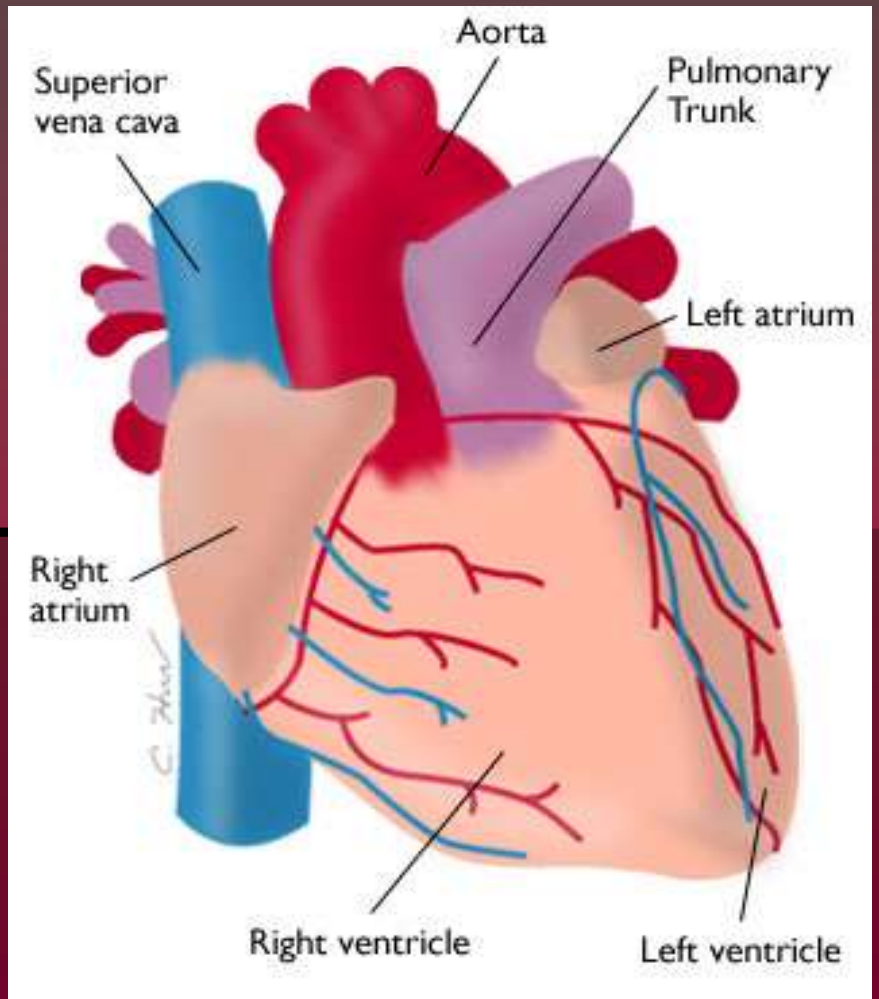
2020

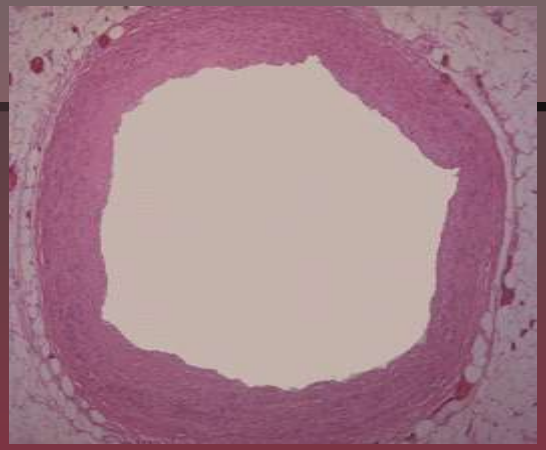
Arteri Koroner

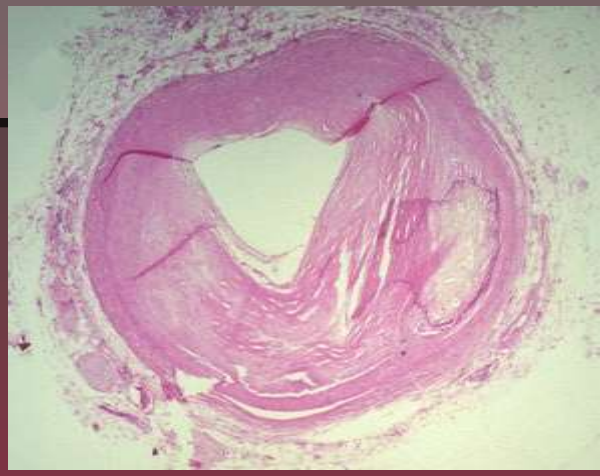
- Otot jantung mendapat suplai O2 dan nutrisi dari : Arteri koronaria kiri dan kanan
- Ventrikel kiri mendapat suplay dari A. koronaria kiri. Diameter arteri ini kecil, dan beresiko terjadinya obstruksi.

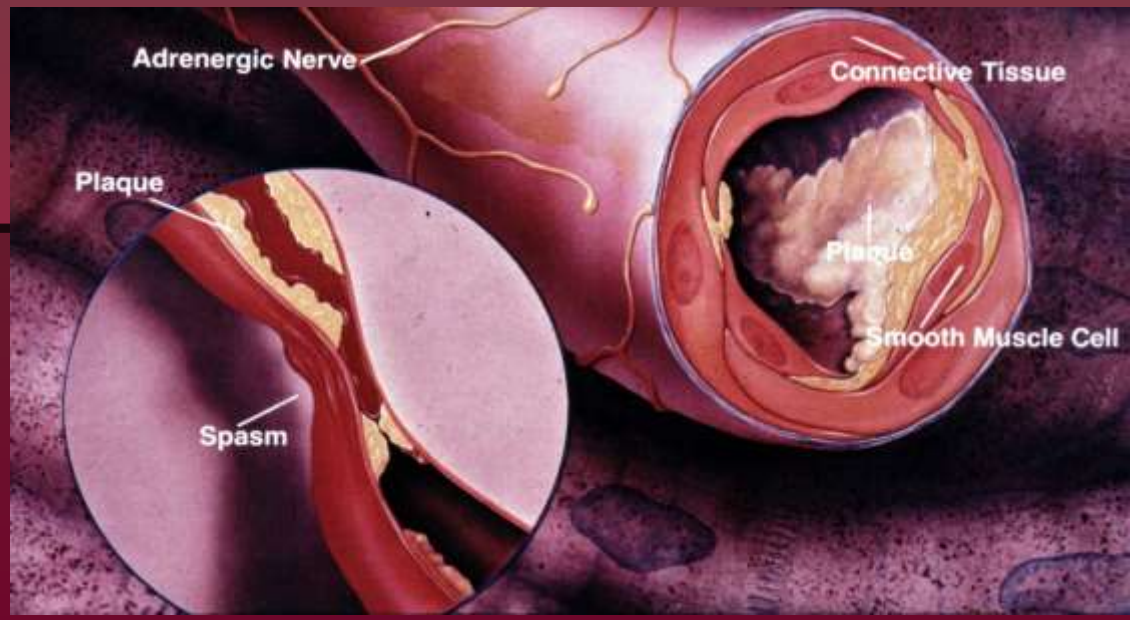


Pembentukan Plak

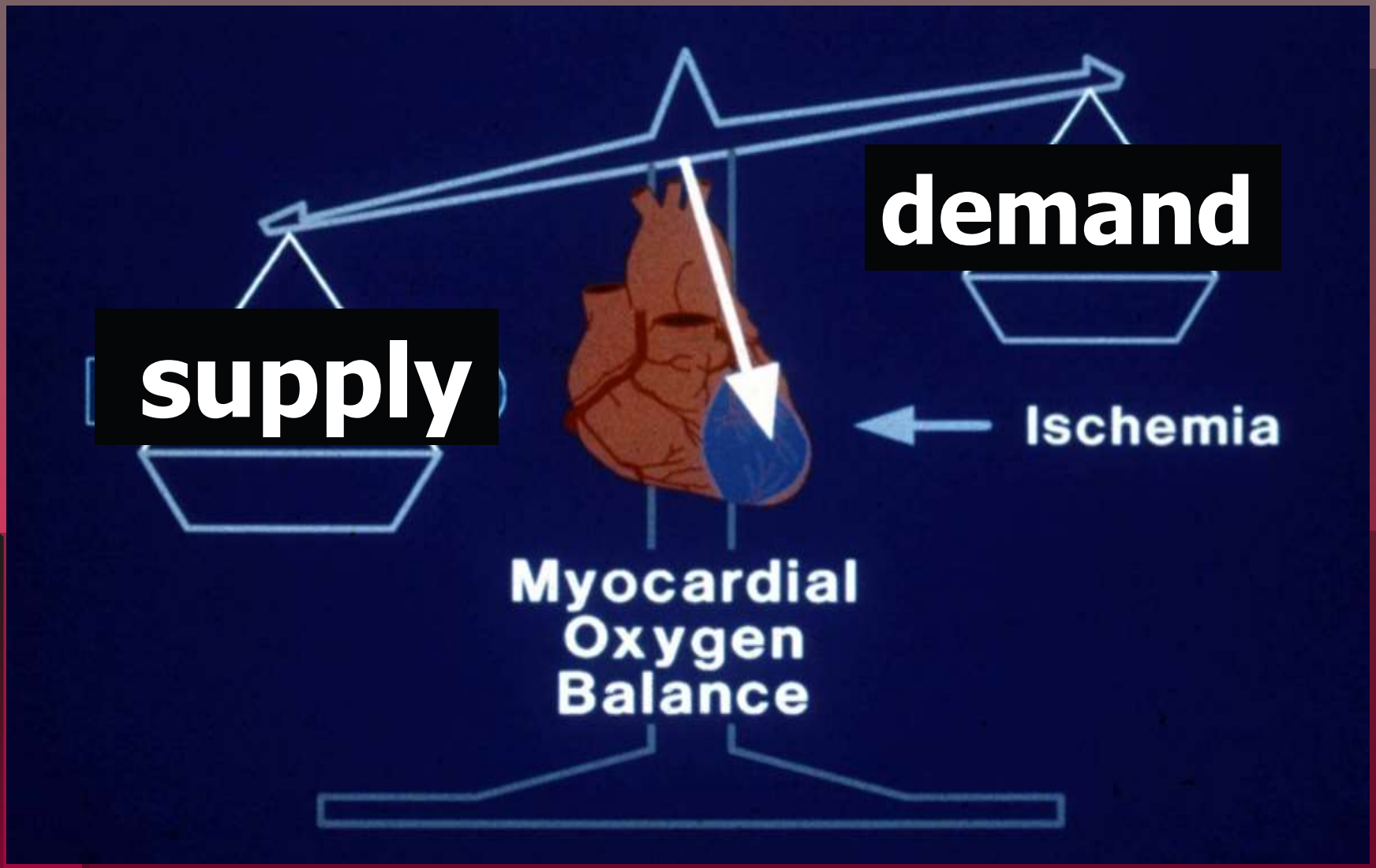
- Lesi dimulai dalam bentuk fatty streaks (usia 20 th)
  - Akumulasi foam sel yang berisi lipid di subendothel
- Fibrous Plaque
  - Makin membesar ke arah lumen arterial
  - Menurunkan aliran darah



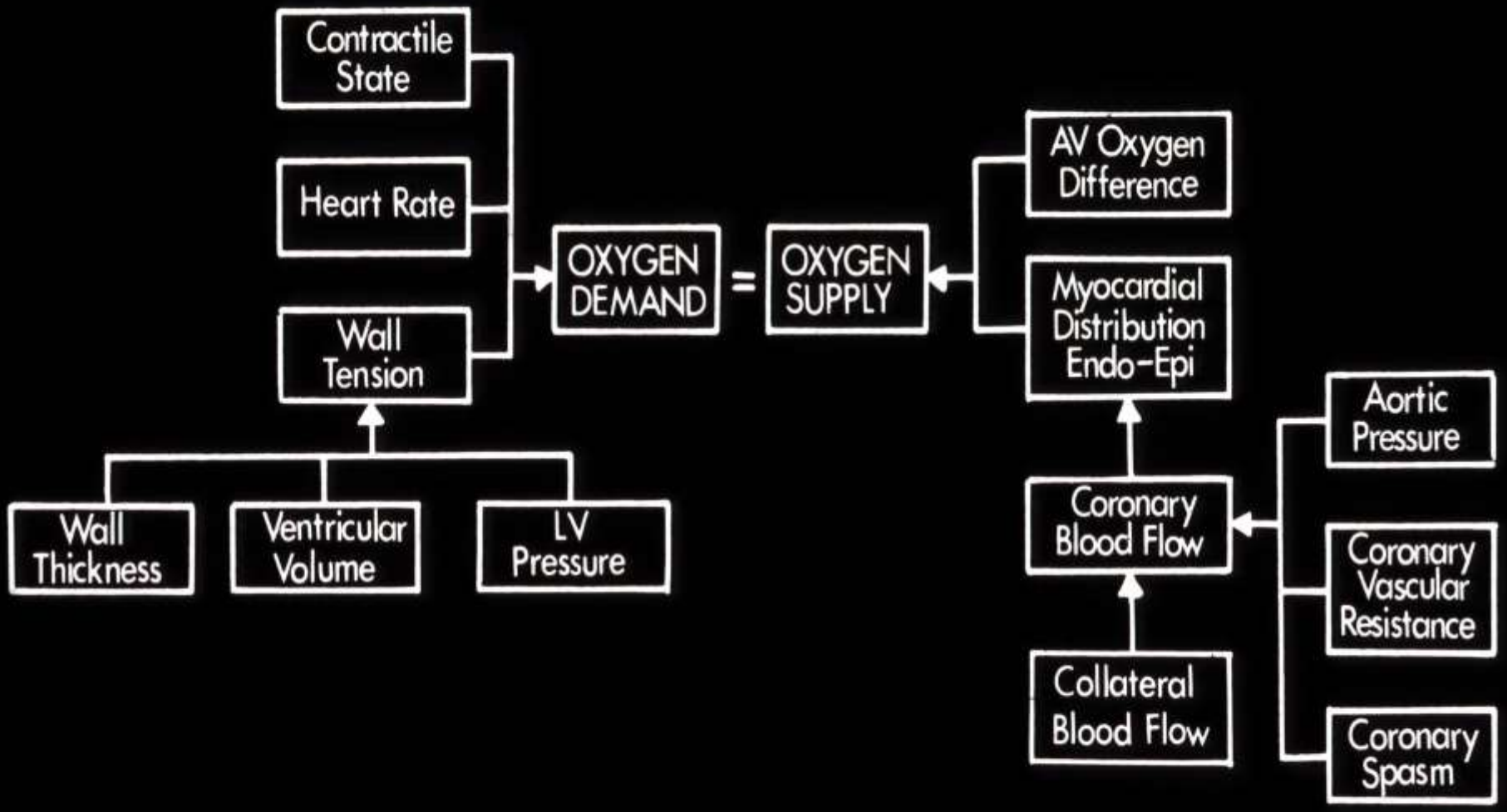


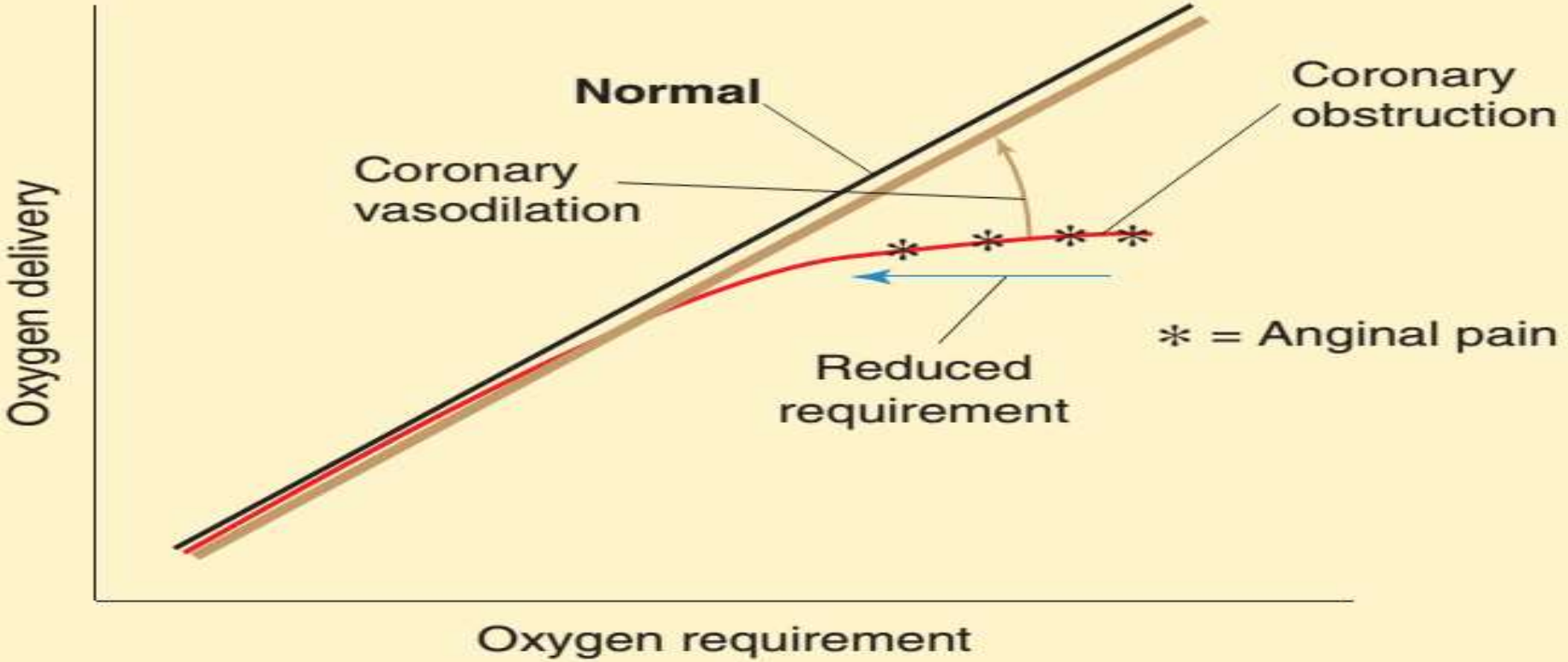


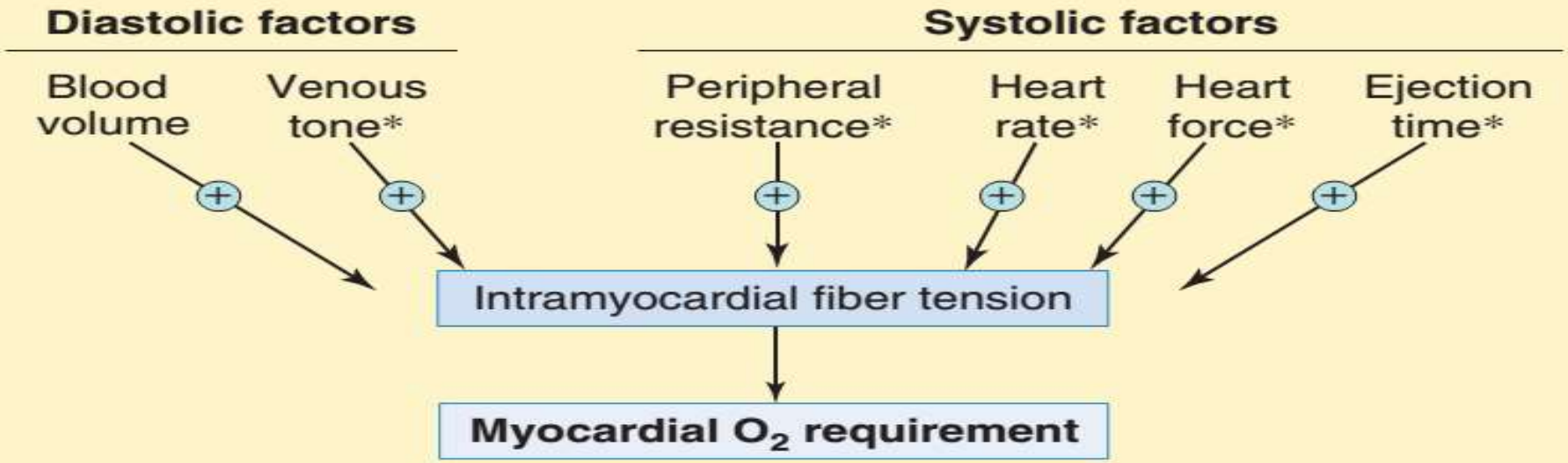
Patofisiologi Angina



Faktor-faktor yang mempengaruhi O_2 demand dan O_2 supply

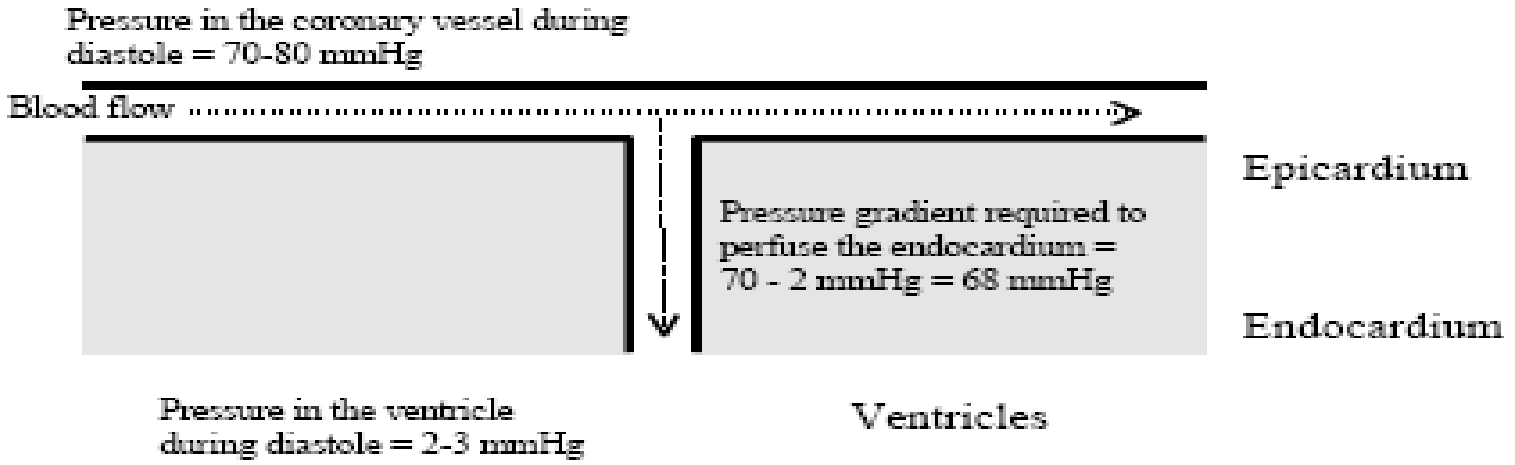



Normal
Coronary obstruction
Coronary vasodilation
* = Anginal pain
Reduced requirement
Oxygen delivery
Oxygen requirement

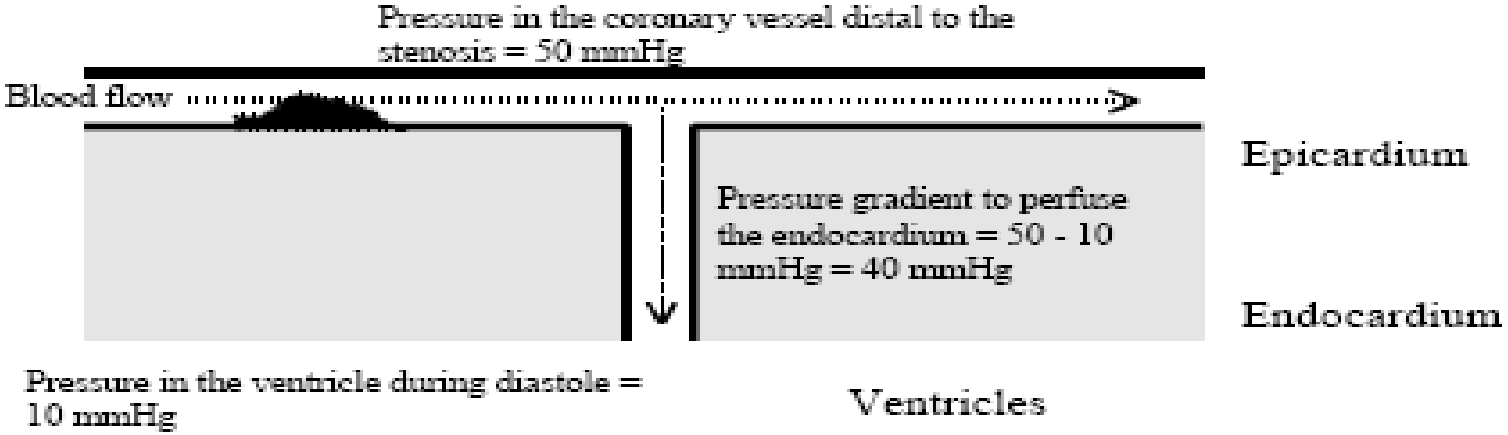

Diastolic factors
Systolic factors
Blood volume
Venous tone*
Peripheral resistance*
Heart rate*
Heart force*
Ejection time*
Intramyocardial fiber tension
Myocardial O_2 requirement

Mechanism of ischaemia

Normal heart:



Hear with a coronary atheroma



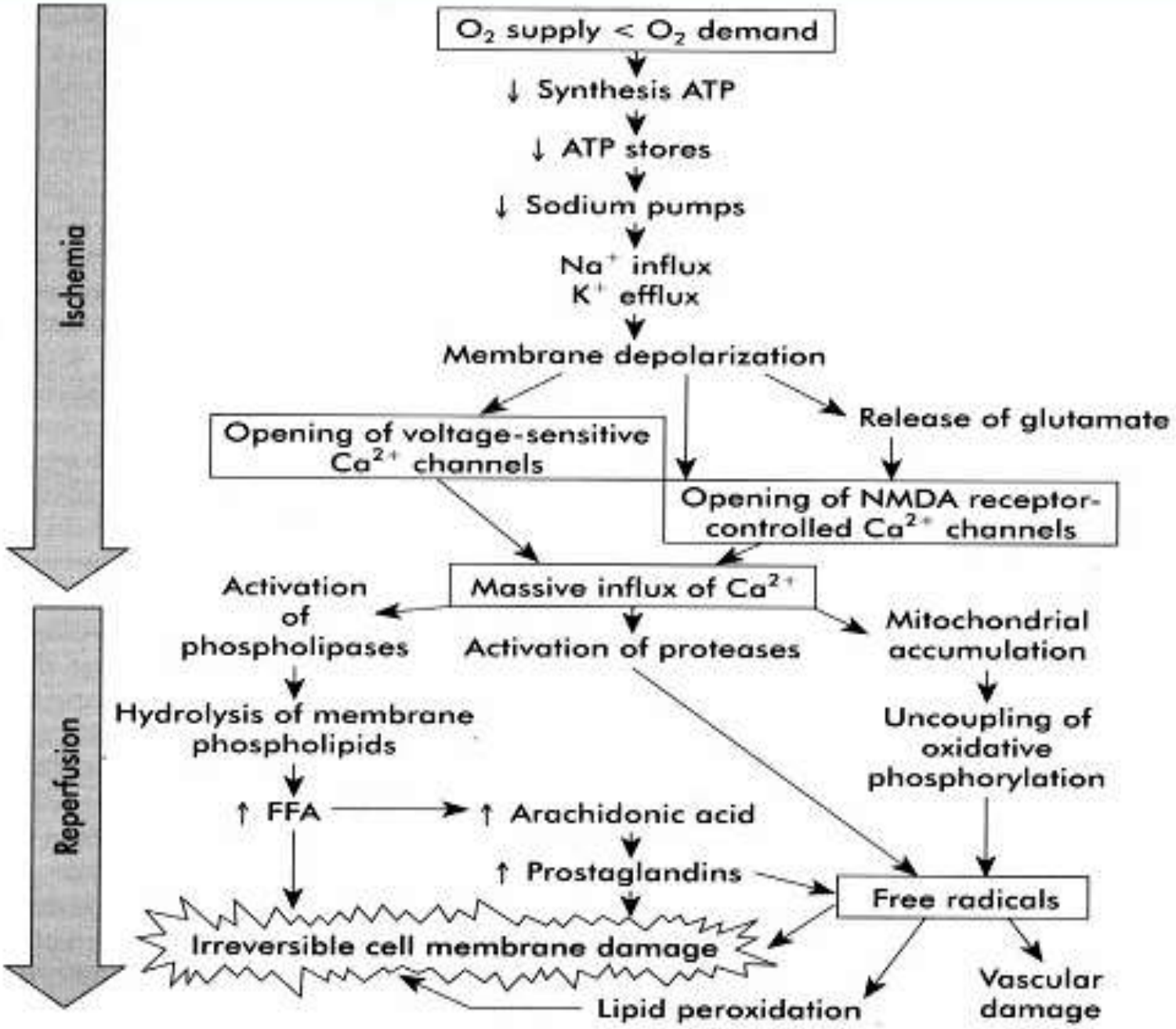
This pressure has increased because poor emptying of the heart leads to increased residual volume after systole (not all the blood is pumped out) which increases the ventricular diastolic pressure

In myocardial ischaemia, the endocardium will be affected due to poor perfusion

The ischemic Cascade

Death cell: Apoptotic,

Necrotic

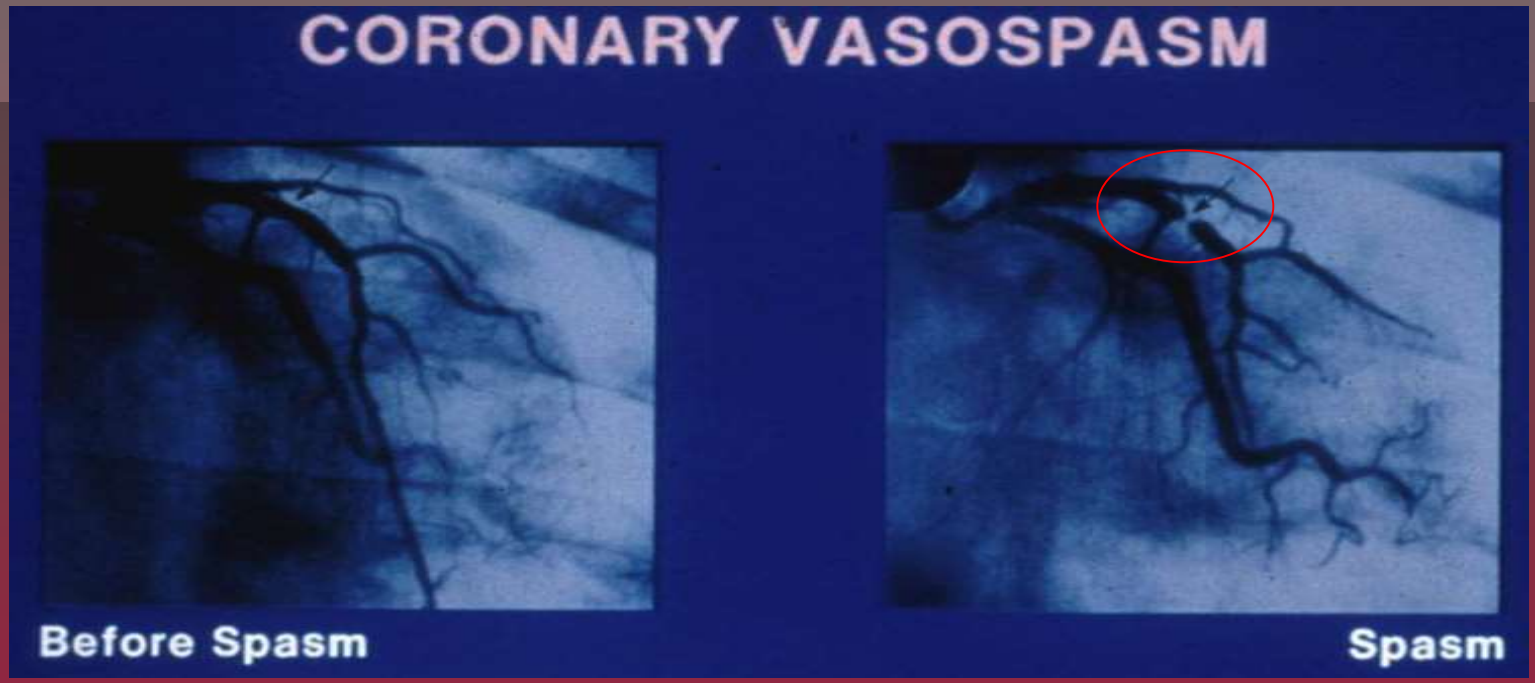


Ischemic/reperfusion injury.

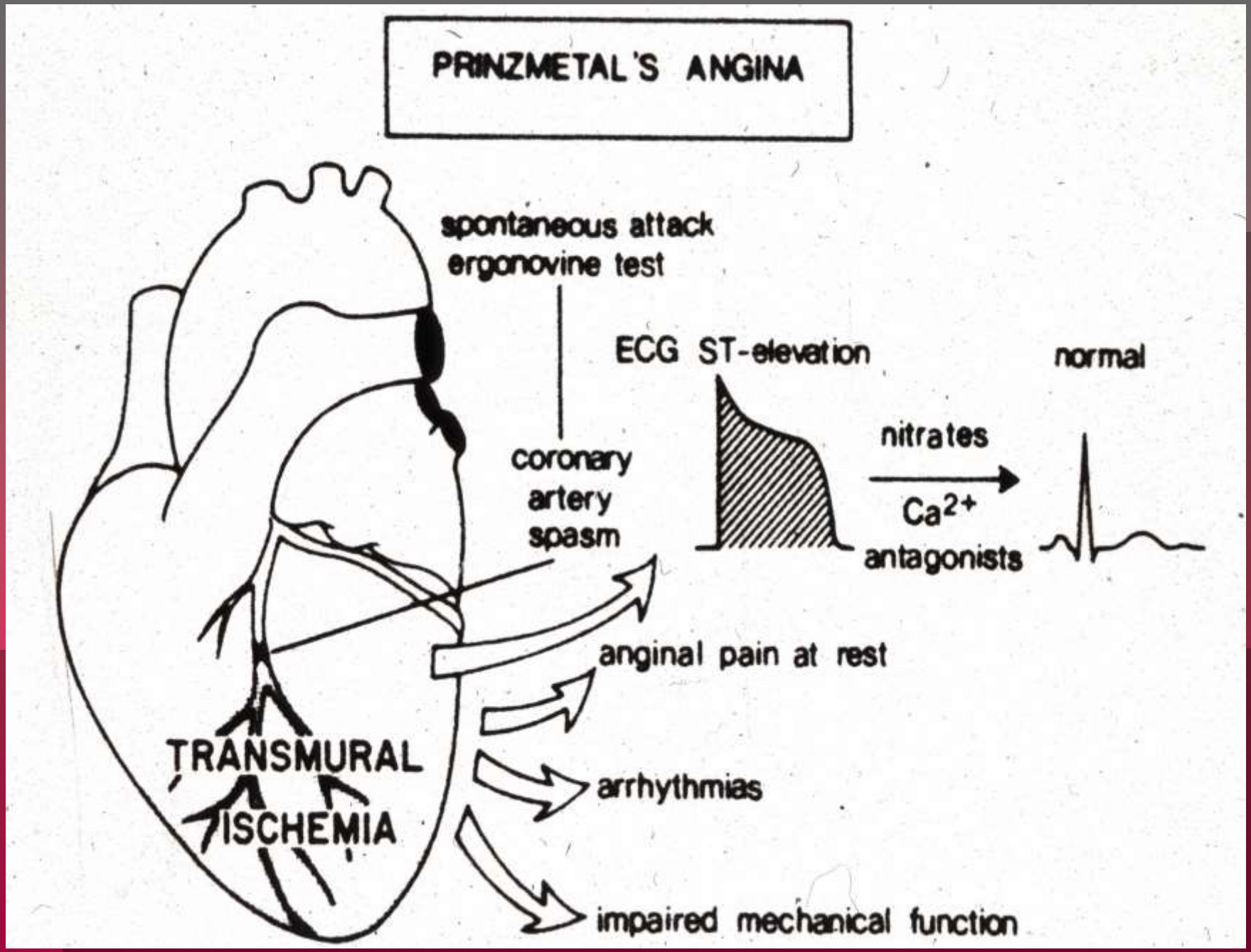
3 tipe Angina

1. **Klasik (exertional, typical, stable)**
   - Bentuk yang paling umum (90%)
   - Insufisiensi koroner disebabkan oleh sumbatan pembuluh darah (atherosclerosis)
   - Serangan terjadi saat beraktivitas berat (OR berat, kerja berat) ketika kebutuhan oxygen meningkat.
   - Nyeri hilang dg istirahat

2. Variant (Prinzmetal's) [rest angina]



- Insufisiensi koroner disebabkan oleh **vasospasm** (adanya atherosclerosis menyebabkan peningkatan tonus vasomotor)
- Serangan sering terjadi saat istirahat (mis. Saat tidur tengah malam)


PRINZMETAL'S ANGINA
spontaneous attack
ergonovine test
coronary
artery
spasm
ECG ST-elevation
normal
nitrates
Ca2+
antagonists
anginal pain at rest
TRANSMURAL
ISCHEMIA
arrhythmias
impaired mechanical function

3. Unstable angina (acute coronary syndrome)

- Masalah serius (impending MI)
- Disebabkan oleh atherosclerotic plaques, platelet aggregation pada fractured plaques & vasospasm

PRINSIP MANAGEMENT TERAPI ANGINA

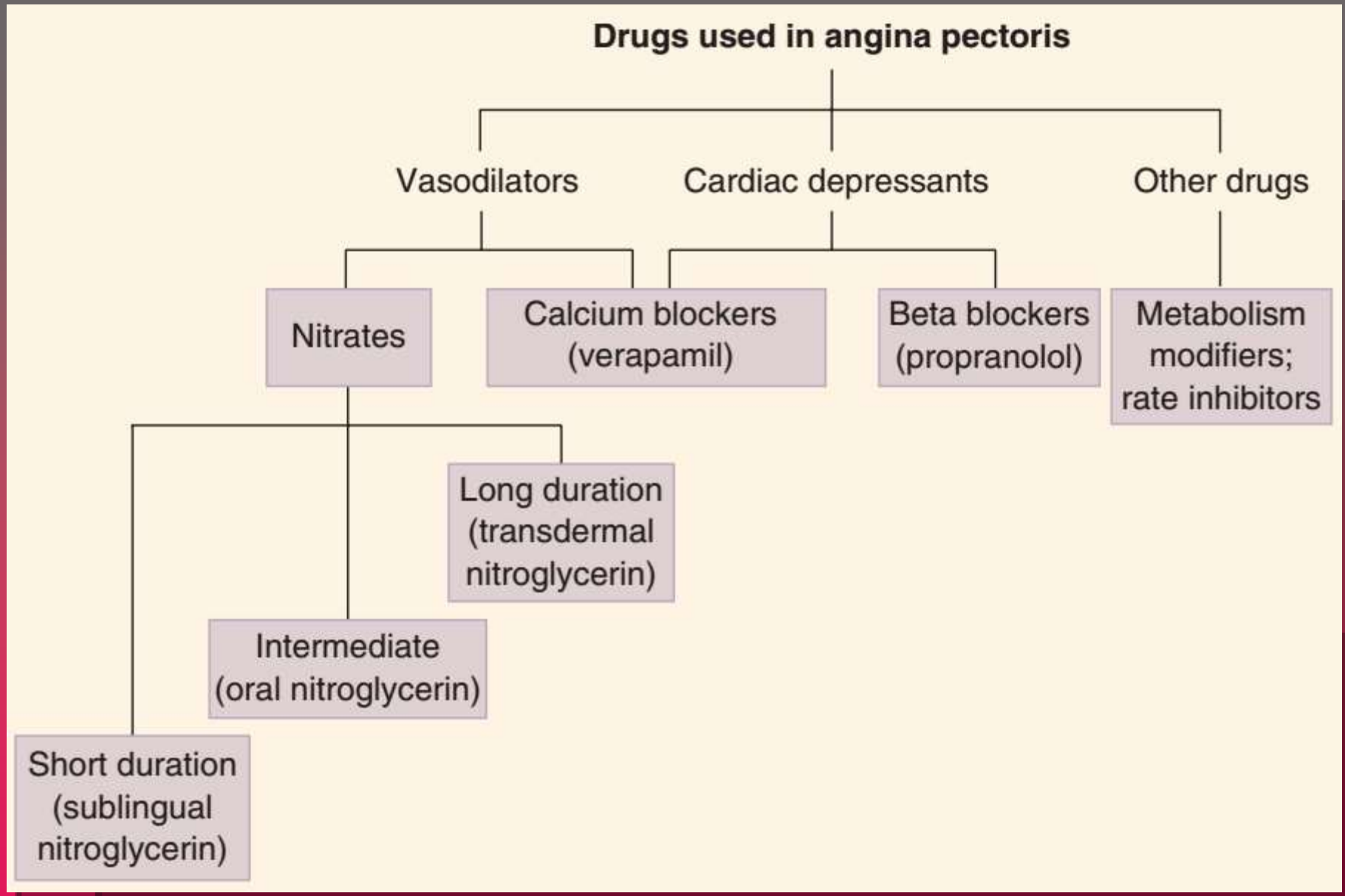
- **NITRAT ORGANIK**

  Nitrogliserin, ISDN
- **BETA BLOKER**

  Propanolol, labetolol,
- **CALCIUM ANTAGONIST**

  Nifedipin, Verapamil, Diltiazem

- me ↓ kebutuhan O2 : Beta bloker, nitrat, CCB (me ↓ HR, kontraktilitas, preload & afterload)
- me ↓ vasospasme : nitrat, CCB (angina varian & unstable)
- Metabolism modifier : Ranolazine
- Me↓ denyut jantung : Ivabradine
- me ↓ faktor resiko cardiac :
  - Kontrol : HT, DM, hiperlipidemi, hiperkoagulasi, trombogenesis
  - OR, ↓ BB, diet rendah lemak, stop rokok
  - Pemberian aspirin 75-80 mg/hari


Drugs used in angina pectoris
Vasodilators
Cardiac depressants
Other drugs
Nitrates
Calcium blockers (verapamil)
Beta blockers (propranolol)
Metabolism modifiers; rate inhibitors
Long duration (transdermal nitroglycerin)
Intermediate (oral nitroglycerin)
Short duration (sublingual nitroglycerin)

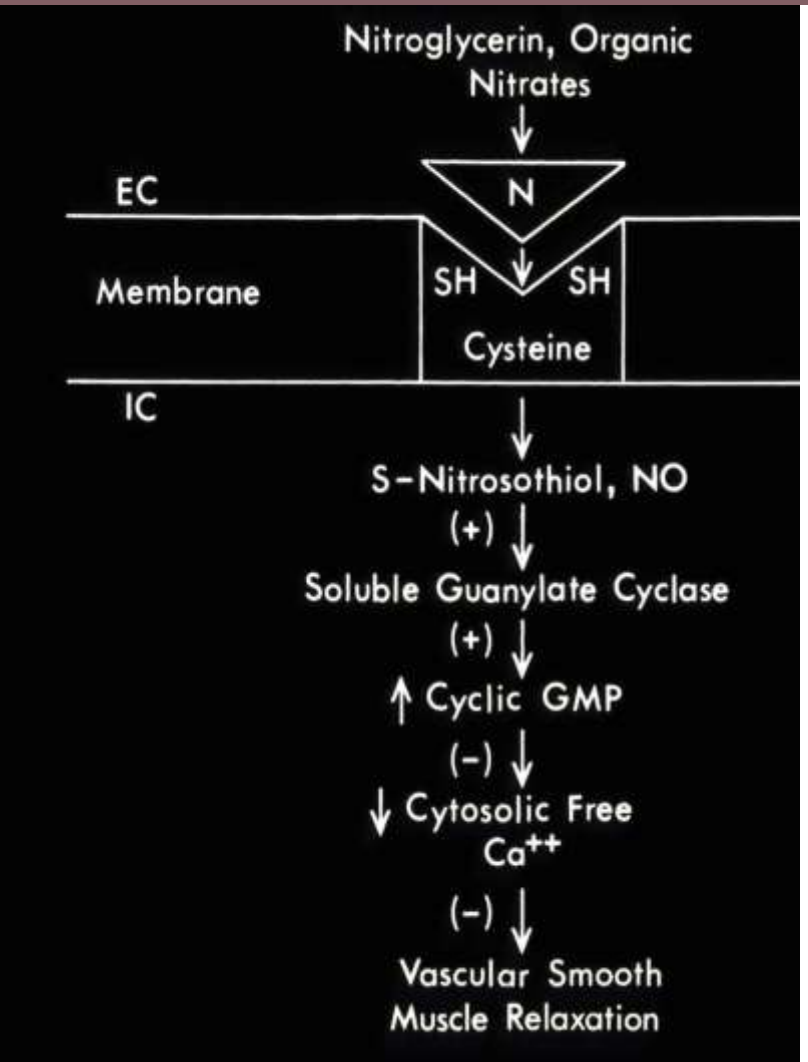
Tx Angina Stabil

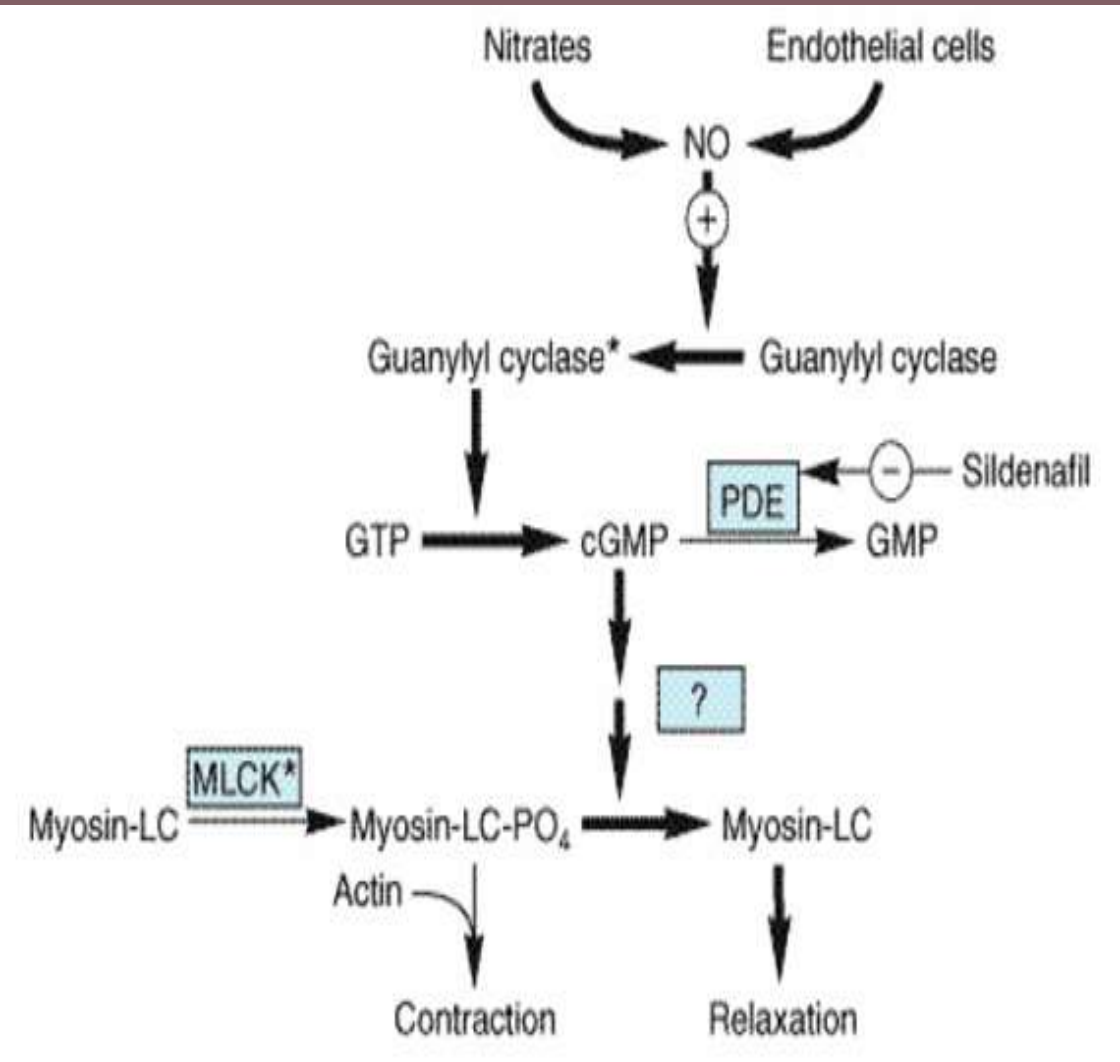
- **Serangan akut**

  glyceryl trinitrate (GTN) per sublingual atau spray.
- **Profilaksis jangka panjang**
  - Beta bloker, CCB, atau nitrat. Beta bloker : pilihan pertama (The National Service Framework)
  - Terapi kombinasi jk monoterapi tidak efektif

NITRAT ORGANIK

Mekanisme kerja - release NO





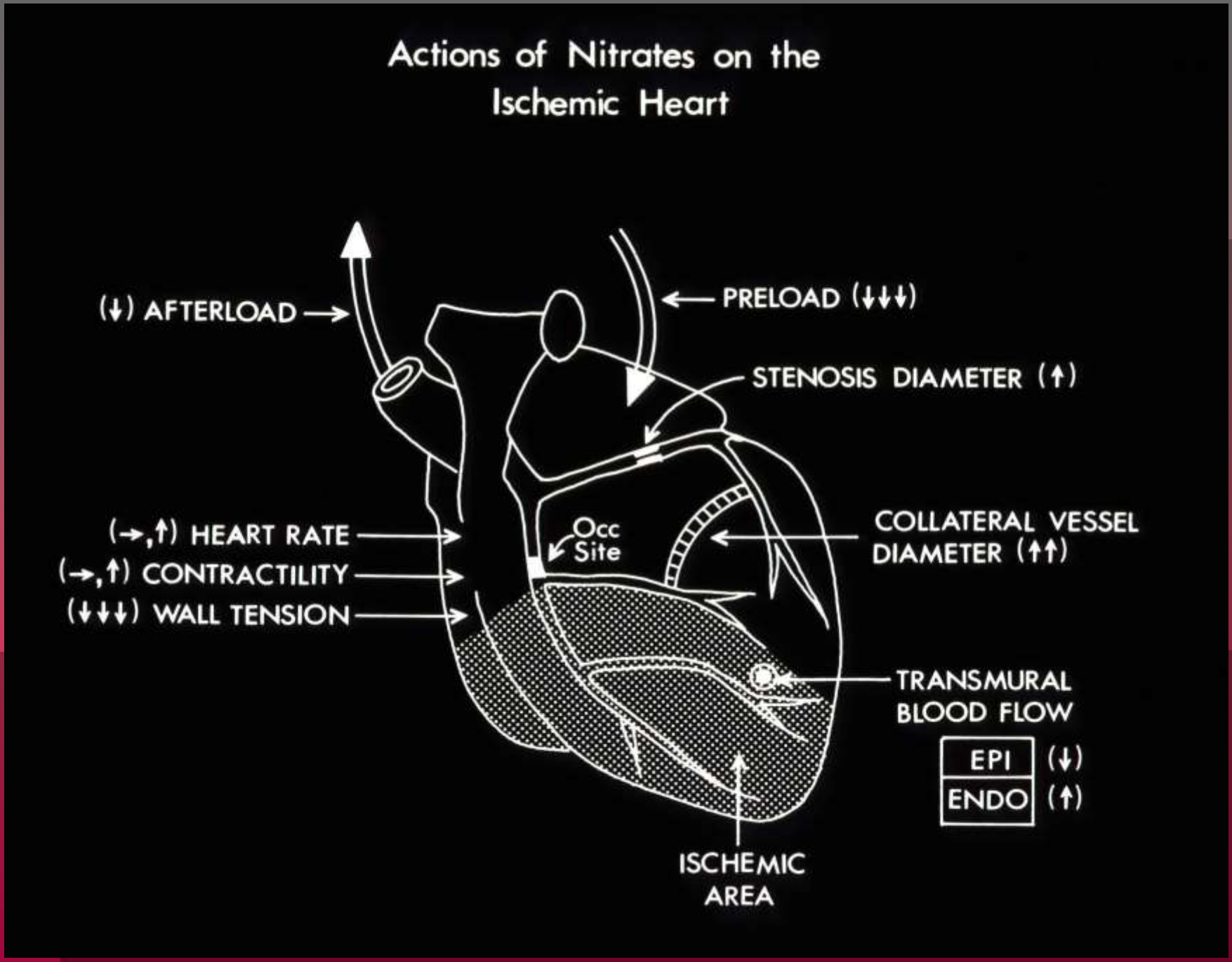
Efek Nitrat

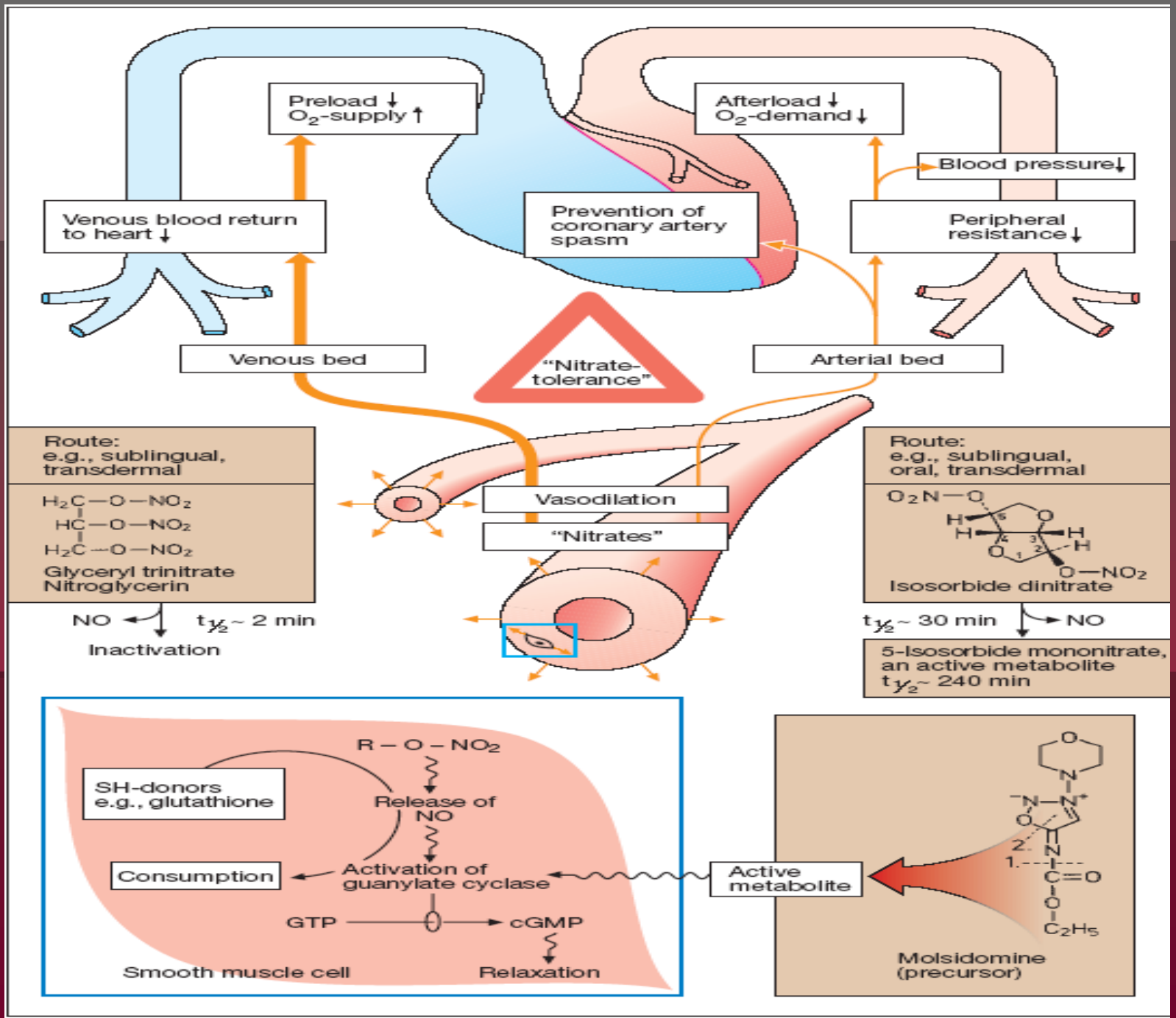
a. **Venodilatasi** – efek utama
   - ☺ Vena dilatasi → preload ↓ (decreased ventricular chamber size, end diastolic pressure, fiber tension) → kerja jantung ↓→ kebutuhan O_2 ↓
   - ☺ Pada dosis besar : afterload ↓ (arterial resistance) → dapat menyebabkan refleks takikardi

b. **Redistribusi aliran koroner**
   - ☺ Daerah subendocardial adalah yang paling iskemi
   - ☺ Nitrat organik secara selektif mampu me ↑ aliran darah ke daerah iskemik
   - ☺ Aliran koroner total tidak meningkat

c. **Menghilangkan vasospasme epikardial koroner pd angina vasospastik**

d. **Antiplatelet agregasi.** Akibat peningk cGMP


Actions of Nitrates on the Ischemic Heart
(↓) AFTERLOAD
PRELOAD (↓↓↓)
STENOSIS DIAMETER (↑)
(→,↑) HEART RATE
(→,↑) CONTRACTILITY
(↓↓↓) WALL TENSION
Occ Site
COLLATERAL VESSEL DIAMETER (↑↑)
TRANSMURAL BLOOD FLOW
EPI (↓)
ENDO (↑)
ISCHEMIC AREA


Preload ↓
O_2-supply ↑
Afterload ↓
O_2-demand ↓
Blood pressure ↓
Venous blood return to heart ↓
Prevention of coronary artery spasm
Peripheral resistance ↓
Venous bed
"Nitrate-tolerance"
Arterial bed
Route:
e.g., sublingual, transdermal
$H_2C—O—NO_2$
$HC—O—NO_2$
$H_2C—O—NO_2$
Glyceryl trinitrate
Nitroglycerin
NO
$t_{1/2}$ ~ 2 min
Inactivation
Vasodilation
"Nitrates"
Route:
e.g., sublingual, oral, transdermal
$O_2N—O$
$O—NO_2$
Isosorbide dinitrate
$t_{1/2}$ ~ 30 min
NO
5-Isosorbide mononitrate, an active metabolite
$t_{1/2}$ ~ 240 min
$R—O—NO_2$
SH-donors
e.g., glutathione
Release of NO
Consumption
Activation of guanylate cyclase
GTP
cGMP
Smooth muscle cell
Relaxation
Active metabolite
Molsidomine
(precursor)

Penggunaan Nitrat Organik

Sediaan :

- Utk serangan akut : sublingual (dosis kecil)
- Utk profilaksis jangka panjang : oral (dosis besar), dermal

TABLE 15–10. Nitrate Products

Product	Onset (min)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 min	5 μg/min
Sublingual/lingual	1–3	30–60 min	0.3 mg
PO	40	3–6 h	2.5–9 mg tid
Ointment	20–60	2–8 h	1/2–1 in
Patch	40–60	>8 h	1 patch
Erythritol tetranitrate	5–30	4–6 h	5–10 mg tid
Penterythritol tetranitrate	30	4–8 h	10–20 mg tid
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 h	2.5–5 mg tid
PO	20–40	4–6 h	5–20 mg tid
Isosorbide mononitrate	30–60	6–8 h	20 mg qd, bid[a]

FARMAKOKINETIK

- Mengalami First pass metabolism di hepar (high-capacity organic nitrate reductase)
- *Nitrogliserin Very short half life* 1-4 mnt

ES : sakit kepala, takikardia, hipotensi (dizziness, sinkope)

INDIKASI :

1. Tx akut angina (stable, vasospastic, unstable)
2. CHF dg IMA
3. Kontrol TD pd HT yg berhub dg tindakan pembedahan

Kontraindikasi

- hipotensi (<80 mmHg)
- acute infarction with low filling pressures
- hamil trimest I

Hati-hati pada :

- Anemia
- increased intracranial pressure
- severe aortic or mitral stenosis,
- cardiac tamponade,
- constrictive pericarditis
- coronary thrombosis.
- hypertrophic cardiomyopathy.
- Tx PDE inhibitor-tjd severe hipotensi

Toleransi Nitrat

= *penurunan efek nitrat akibat pemakaian jangka panjang*

- Dapat terjadi pada semua gol. Nitrat & tergantung dosis
- Dapat hilang setelah 24 jam stop minum obat
- Toleransi dapat dihindari dg :
  - ☺Menggunakan dosis efektif terkecil
  - ☺Interval antar dosis minimal 8 jam

BETA BLOKER

a. Mekanisme kerja

1) **Me ↓ kebutuhan O2**
melalui pe ↓ HR (t.u selama aktivitas), efek inotropik negatif & pe ↓ TD (t.u sistole) selama aktivitas.

2) **Memperpanjang wkt diastole** → me ↑ wkt drh mengalir mel A.Coro naria → me ↑perfusi dae iskemi

b. Penggunaan:

- Hanya utk profilaksis angina stabil
- Tidak effektif (atau KI) utk angina variant (blok R/β2 arteri koroner R/α dominan- memperburuk spasme)
- Sering dikombinasi dg obat gol lain

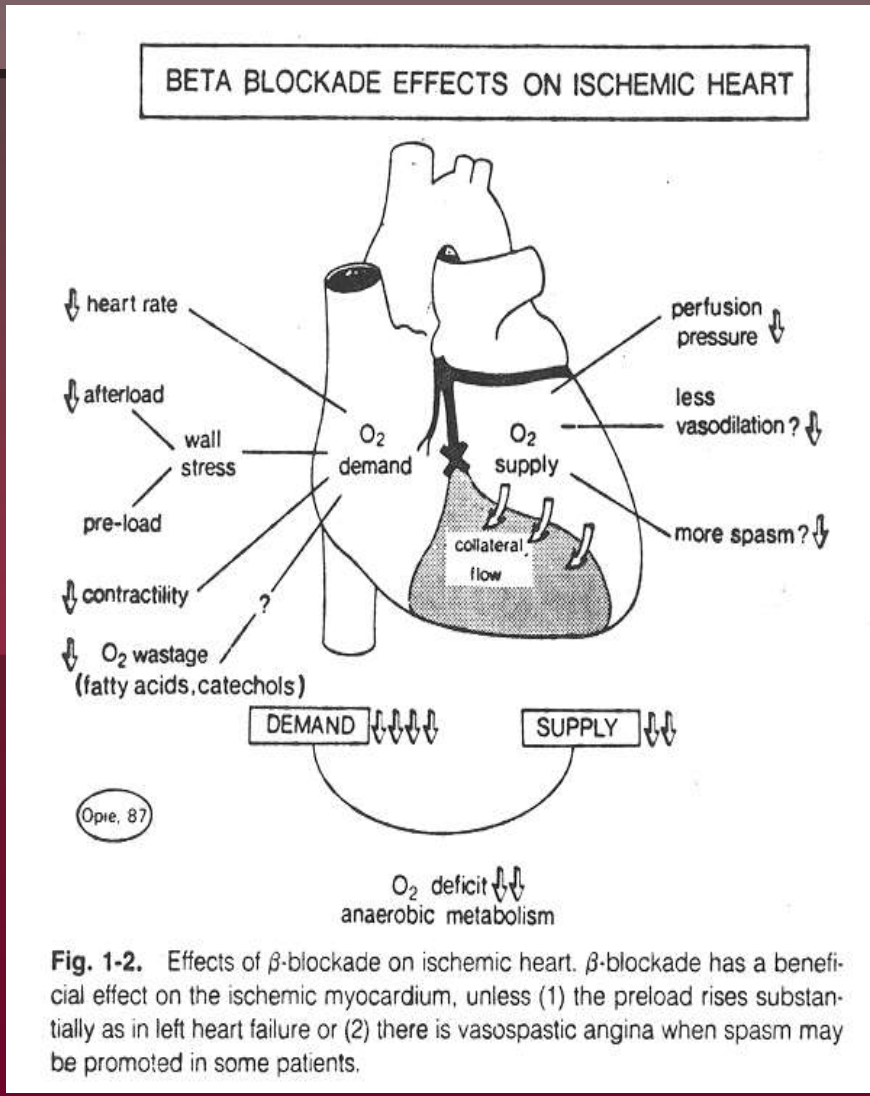


Fig. 1-2. Effects of β-blockade on ischemic heart. β-blockade has a beneficial effect on the ischemic myocardium, unless (1) the preload rises substantially as in left heart failure or (2) there is vasospastic angina when spasm may be promoted in some patients.

CALCIUM CHANNEL BLOCKER

- Non-Dihydropyridines
  - Block L-type Ca^{++} Channels
  - Slow cardiac nodal conduction
  - More cardiac effect
- Dihydropyridines
  - Block L-type Ca^{++} Channels
  - Relax vascular smooth muscle
  - Vasodilators

Non-Dihydropyridines

- Diltiazem (Cardizem)
- Verapamil (Calan)

Dihydropyridines

- Amlodipine (Norvasc)
- Felodipine (Plendil)
- Nicardipine (Cardene)
- Nifedipine (Procardia)

CALCIUM CHANNEL BLOCKER

Mekanisme Kerja :

blok calcium influx mel L-type channels pada otot jantung dan otot polos vasc, sehingga :

- Me ↓ kebutuhan O_2 - probably "most" important
  - Sinus and AV node blockers → Me ↓ HR
  - Pe ↓ calcium influx selama fase plateau aksi potensial → inotropik negatif → Me ↓ kontraktilitas
  - Pe ↓ Ca intrasel → vasodilatasi t.u arteri perifer→ Me ↓ afterload (↓TPR, BP)
- Dilatasi arteri / arteriol koroner (utk tx / preventif angina vasospastic)

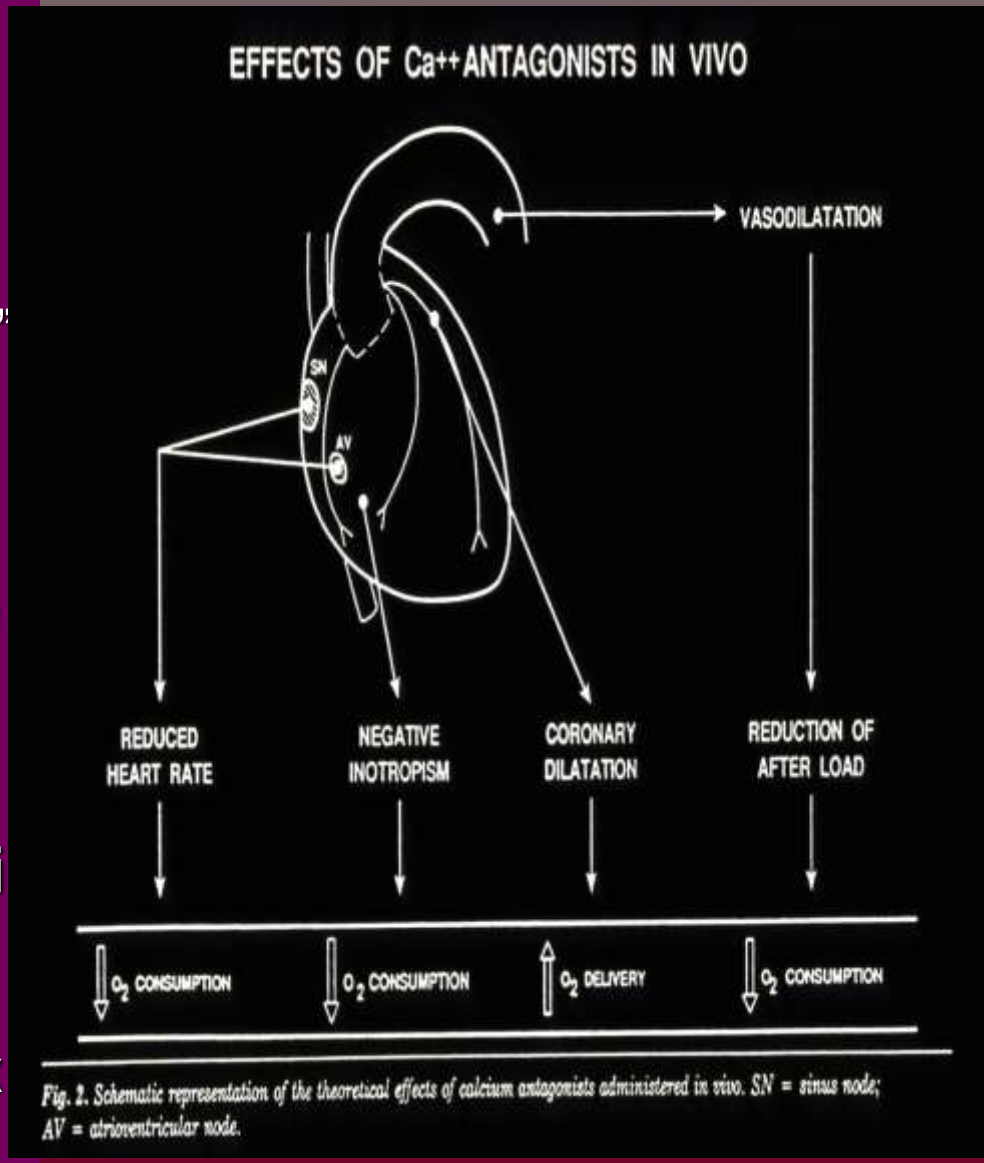
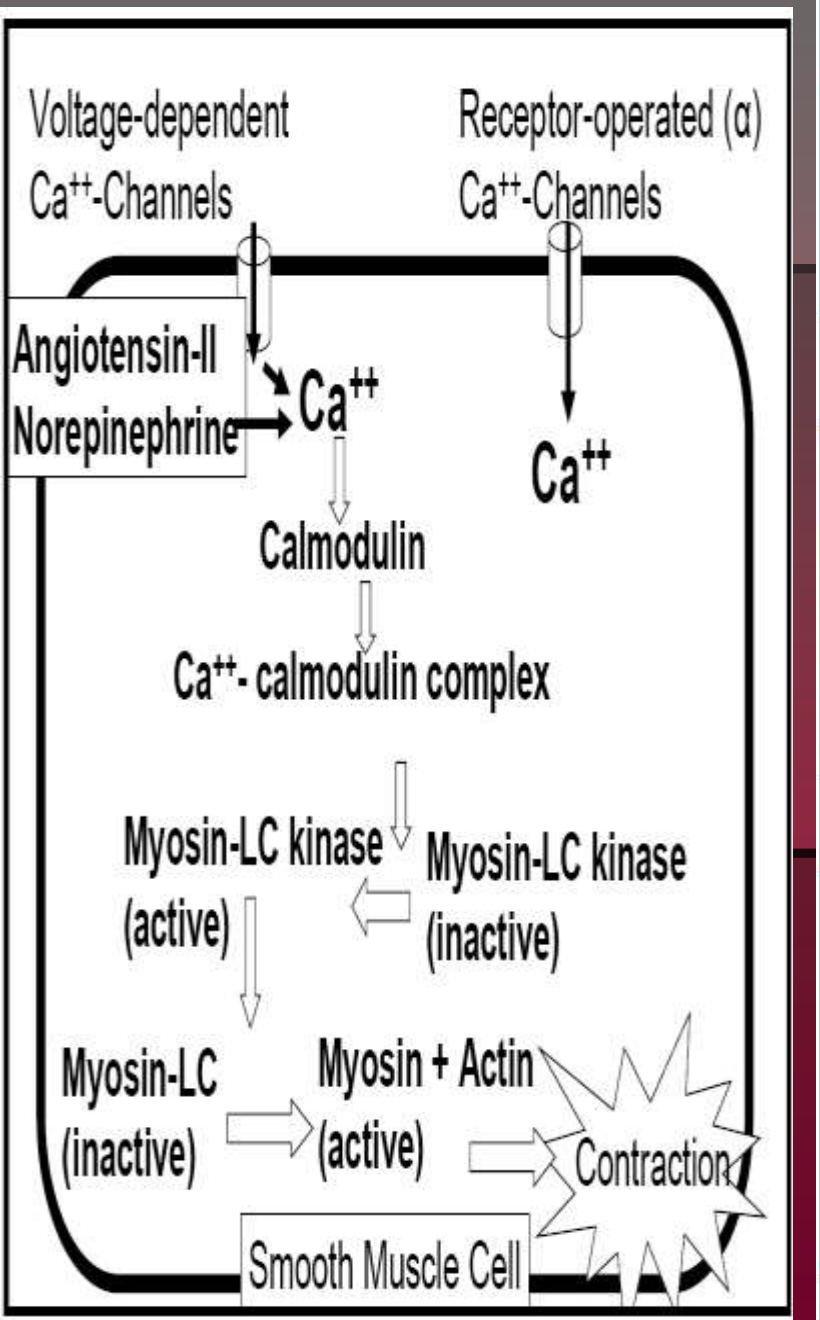
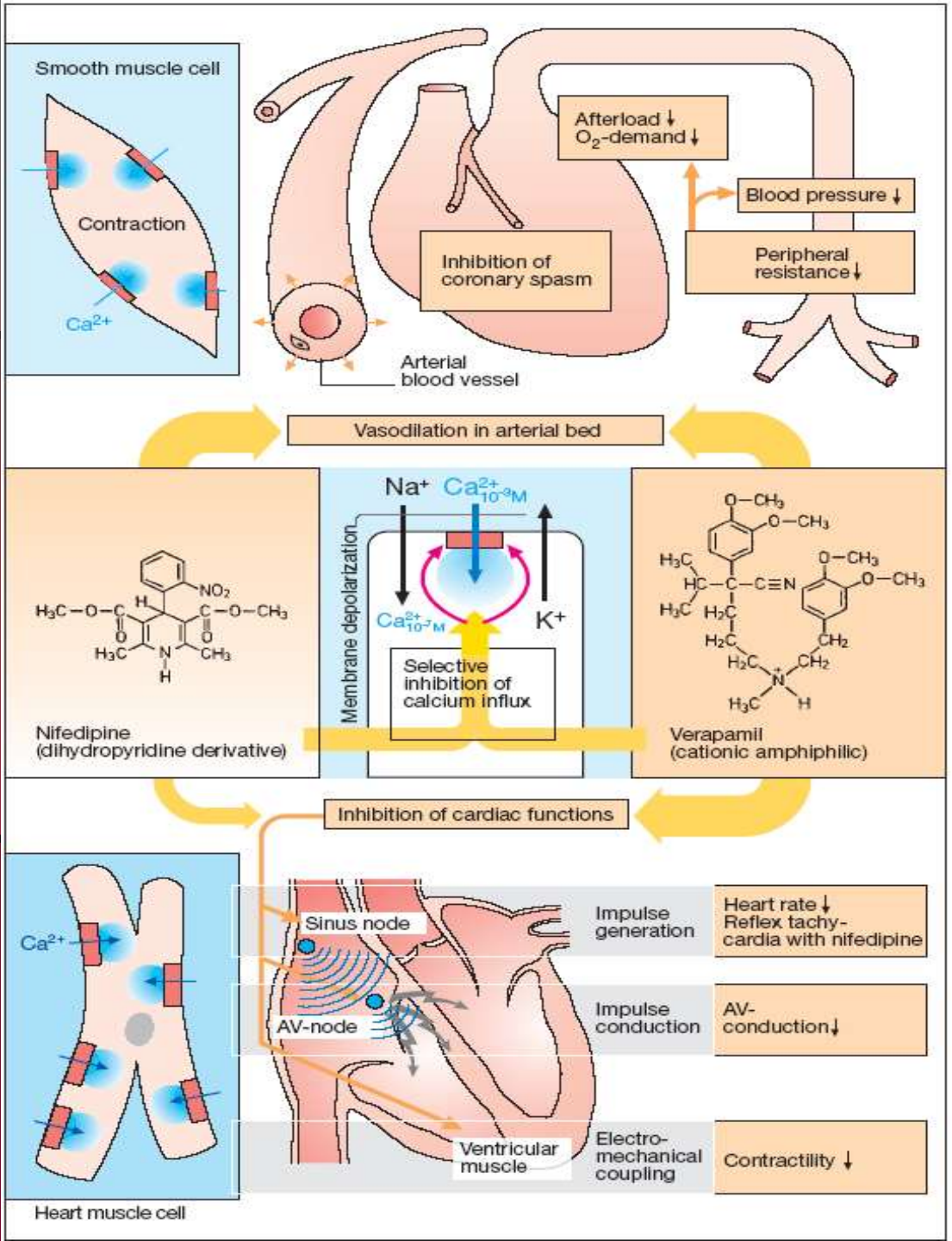
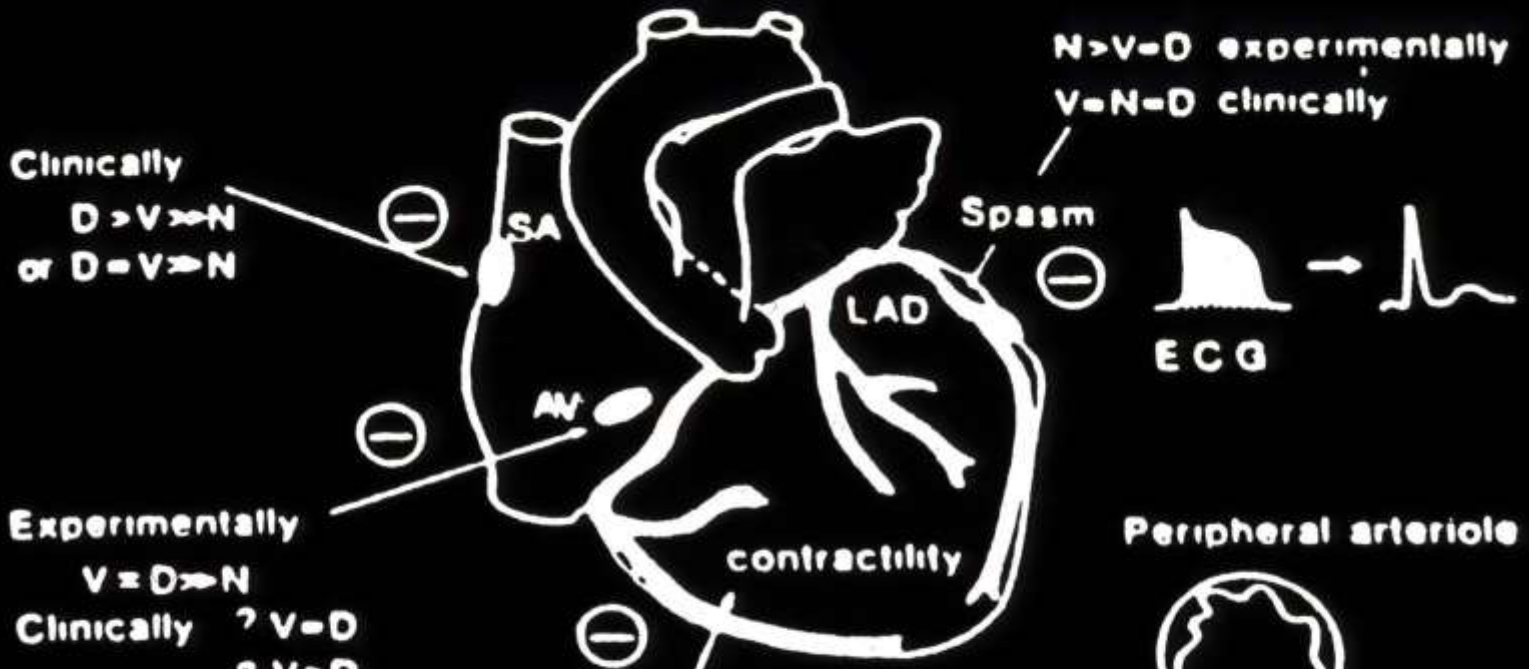


Fig. 2. Schematic representation of the theoretical effects of calcium antagonists administered in vivo. SN = sinus node; AV = atrioventricular node.


Voltage-dependent
Ca++-Channels
Receptor-operated (α)
Ca++-Channels
Angiotensin-II
Norepinephrine
Ca++
Ca++
Calmodulin
Ca++- calmodulin complex
Myosin-LC kinase
(active)
Myosin-LC kinase
(inactive)
Myosin-LC
(inactive)
Myosin + Actin
(active)
Contraction
Smooth Muscle Cell


Smooth muscle cell
Contraction
Ca2+
Afterload ↓
O2-demand ↓
Blood pressure ↓
Inhibition of coronary spasm
Peripheral resistance ↓
Arterial blood vessel
Vasodilation in arterial bed
Na+
Ca2+ 10-3M
Membrane depolarization
Ca2+ 10-7M
K+
Selective inhibition of calcium influx
Nifedipine
(dihydropyridine derivative)
Verapamil
(cationic amphiphilic)
Inhibition of cardiac functions
Ca2+
Heart muscle cell
Sinus node
AV-node
Ventricular muscle
Impulse generation
Impulse conduction
Electro-mechanical coupling
Heart rate ↓
Reflex tachy-cardia with nifedipine
AV-conduction ↓
Contractility ↓

Ca^{2+} ANTAGONISTS : COMPARATIVE PROPERTIES



RATIO NEG INOTROPIC TO VASCULAR EFFECT : V>D>N

Dihydropyridine

INDIKASI

- Angina akut (stable, vasospastic)
- Hipertensi –vascular selective

EFEK SAMPING

- Dizzines, flushing, headache
- Transient hypotension
- Peripheral edema

FARMAKOKINETIK

- Formulasi = oral immediate release, extended release
- First pass metabolism di hati

Non Dihydropyridine

VERAPAMIL

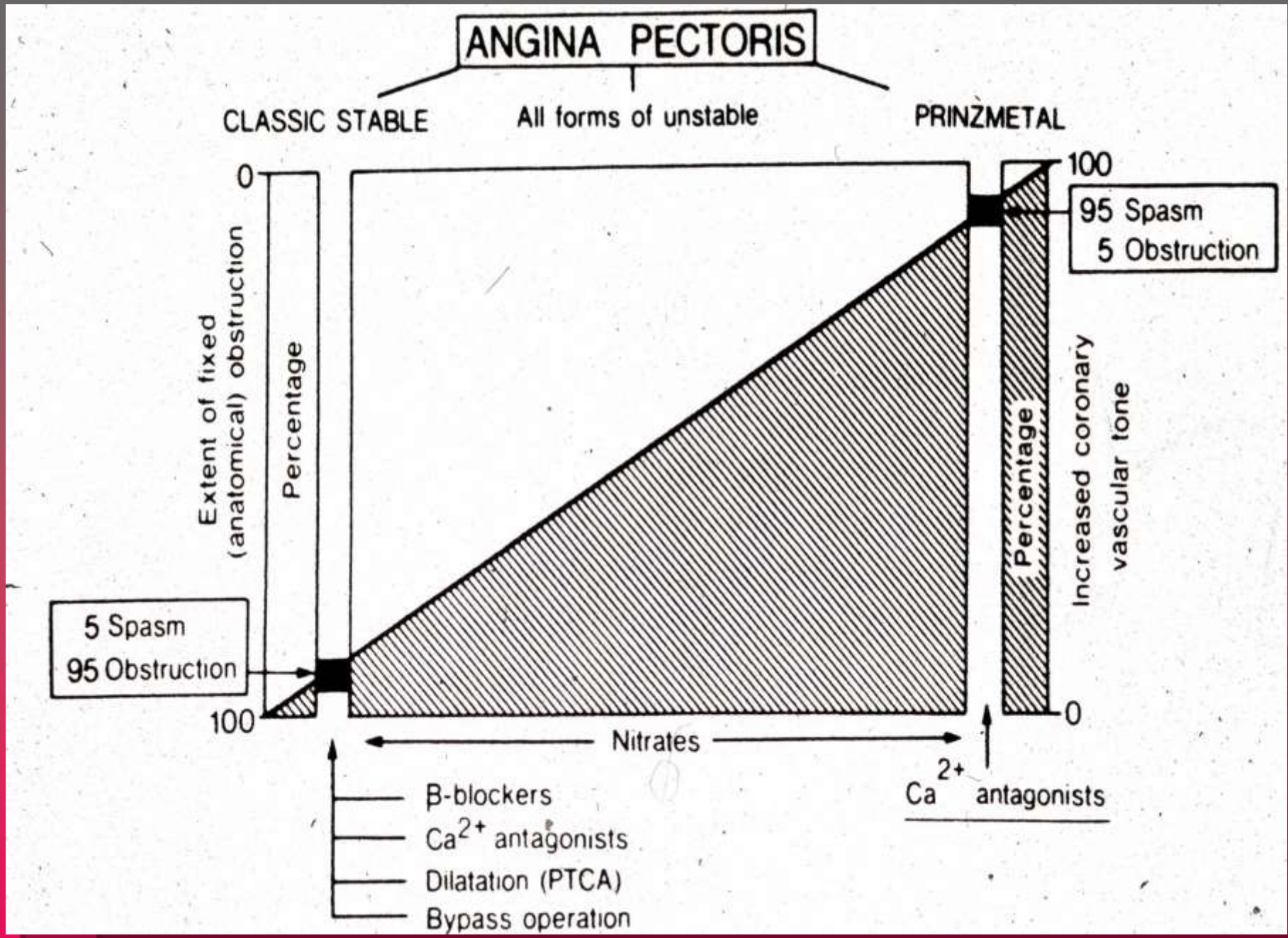
- More cardiac selective
- Indikasi :
  - Angina stable, vasospastic
  - HT
  - Ggn irama jantung PSVT (DOC profilaksis)
  - Kontrol ventricular rate pd pasien Atrial Fibrilasi kronik
- KI :
  - Hipotensi berat, CHF berat
  - AV blok derajat 2,3
  - Syok kardiogenik
- ES : konstipasi, bradikardi, AV blok, asistole

DILTIAZEM

- Cardiac & vascular
- Indikasi :
  - Angina stable , vasospastic
  - HT
  - Kontrol ventricular rate pd pasien Atrial Fibrilasi kronik
- KI :
  - Hipotensi berat, CHF berat
  - AV blok derajat 2,3
  - IMA
  - Laktasi
- ES : konstipasi, bradikardi, AV blok, asistole

VIII. COMPARISON OF OVERALL CARDIOVASCULAR EFFECTS OF NITRATES, BETA BLOCKERS AND CALCIUM CHANNEL BLOCKERS IN ANGINA

	NITRATES	BETA BLOCKERS	CALCIUM BLOCKERS
Endo/Epi	↑↑	↑	↑
Collateral	↑↑	→	↑↑
Wall Tension	↓↓	→↑	↓
Heart Rate	↑(reflex)	↓↓	↑↓ (reflex)
Contractility	↑(reflex)	↓↓	↓→↑(reflex)
Cardiac Work	↓↓	↓↓	↓↓


ANGINA PECTORIS
CLASSIC STABLE
All forms of unstable
PRINZMETAL
0
100
Extent of fixed (anatomical) obstruction
Percentage
5 Spasm
95 Obstruction
100
95 Spasm
5 Obstruction
Percentage
Increased coronary vascular tone
0
Nitrates
β-blockers
Ca2+ antagonists
Dilatation (PTCA)
Bypass operation
Ca2+ antagonists

Useful Drug Combinations

Nitrate + β blocker

- Mekanisme kerja beda - additive efficacy
  - Nitrat & Beta Blockers sama2 me ↓ kebutuhan O2 miokard mel mekanisme berbeda
  - Nitrat & Beta Blockers sama2 me ↑ aliran drh subendocardial mel mekanisme yg berbeda
- β blocker dpt mencegah reflex tachycardia & efek inotropic positif yg disebabkan oleh nitrat
- Nitrat mencegah coronary vasospasm akibat Beta Blockers.
- Nitrates dpt me ↓ peningkatan end-diastolic volume (EDV) yg disebabkan oleh β blockers dg jln me ↑ kapasitas vena

Useful Drug Combinations

- CCB + β blocker + Nitrate
  - Different mechanisms of action - additive efficacy
  - CCB may cause improvement if there is a vasospastive component to the angina
  - β blocker can prevent reflex tachycardia caused by nitrate or dihydropyridine type CCB (& further lower HR & BP)

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers Alone	Combined Nitrates and β Blockers or Calcium Channel Blockers
Heart rate	*Reflex increase*	**Decrease**	**Decrease**
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic pressure	**Decrease**	*Increase*	**Decrease**
Contractility	*Reflex increase*	**Decrease**	No change or decrease
Ejection time	**Reflex decrease**	*Increase*	No change
Net myocardial oxygen requirement	**Decrease**	**Decrease**	**Decrease**

[a]Undesirable effects (effects that increase oxygen requirement) are shown in *italics*; major beneficial effects are shown in **bold**.

Unstable Angina

- Pasien dg recurrent ischemic episodes at rest
- Recurrent thrombotic occlusions
- Platelet aggregation
- Tx:
  - Antiplatelet agent (aspirin dan/ CPG)
  - Antikoagulan i.v. (heparin, lovenox)
  - Traditional anti angina : nitroglycerin, β blockers; CCBs in refractory patients.
  - ACE inhibitor
  - Statin agent
  - Tx Reperfusi dg trombolitic

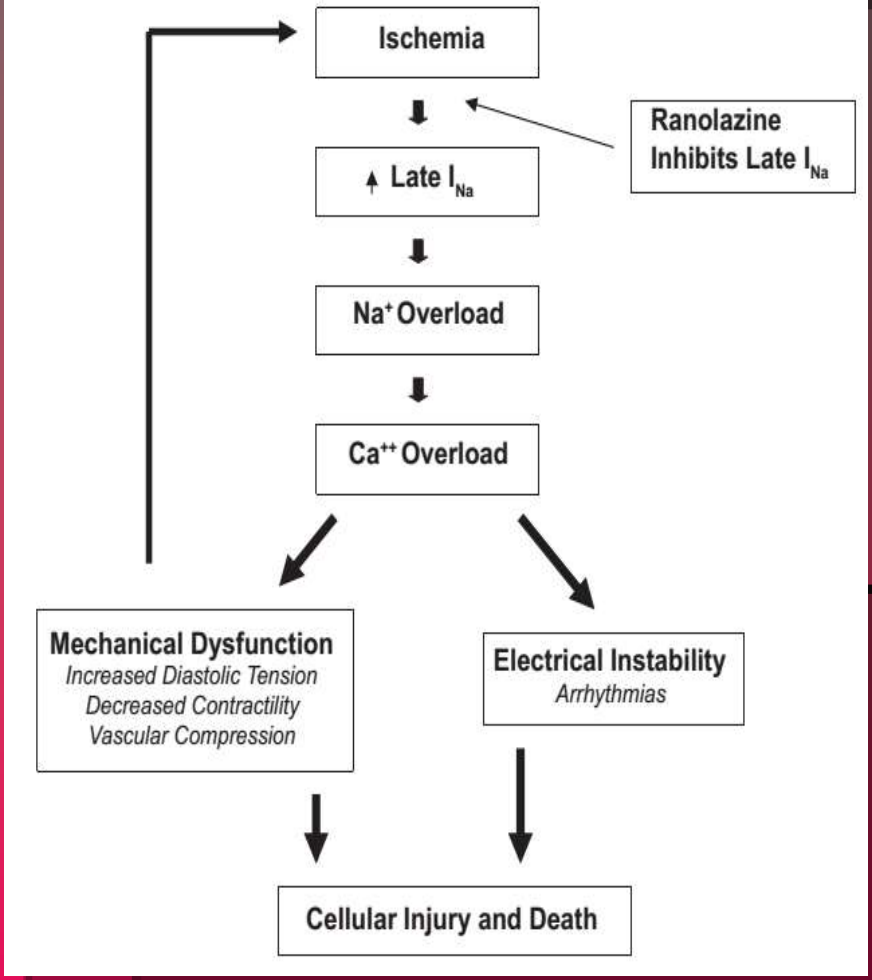
TABLE 1. **Contraindications and Cautions for Fibrinolysis as Treatment for Patients With ST-Segment Elevation Myocardial Infarction**

Absolute contraindications
Any previous ICH
Known structural cerebrovascular lesion (eg, arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 mo, except for acute ischemic stroke within 3 h
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Severe closed-head or facial trauma within 3 mo
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP ≥180 mm Hg or DBP ≥110 mm Hg)
History of ischemic stroke more than 3 mo previously, dementia, or known intracranial pathology not included in contraindications
Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk previously)
Recent (within 2-4 wk) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase: previous exposure (>5 d previously) or previous allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

CPR = cardiopulmonary resuscitation; DBP = diastolic blood pressure; ICH = intracerebral hemorrhage; INR = international normalized ratio; SBP = systolic blood pressure.

From *J Am Coll Cardiol*,[4] with permission from Elsevier.

Ranolazine



FD :

- Blok *late Na plateau current* → me↓ Na influx selama depolarisasi ventrikel
- Na intrasel << → ggn Na/Ca exchanger → Ca ↓ → kontraktilitas ↓ → iskemia ↓

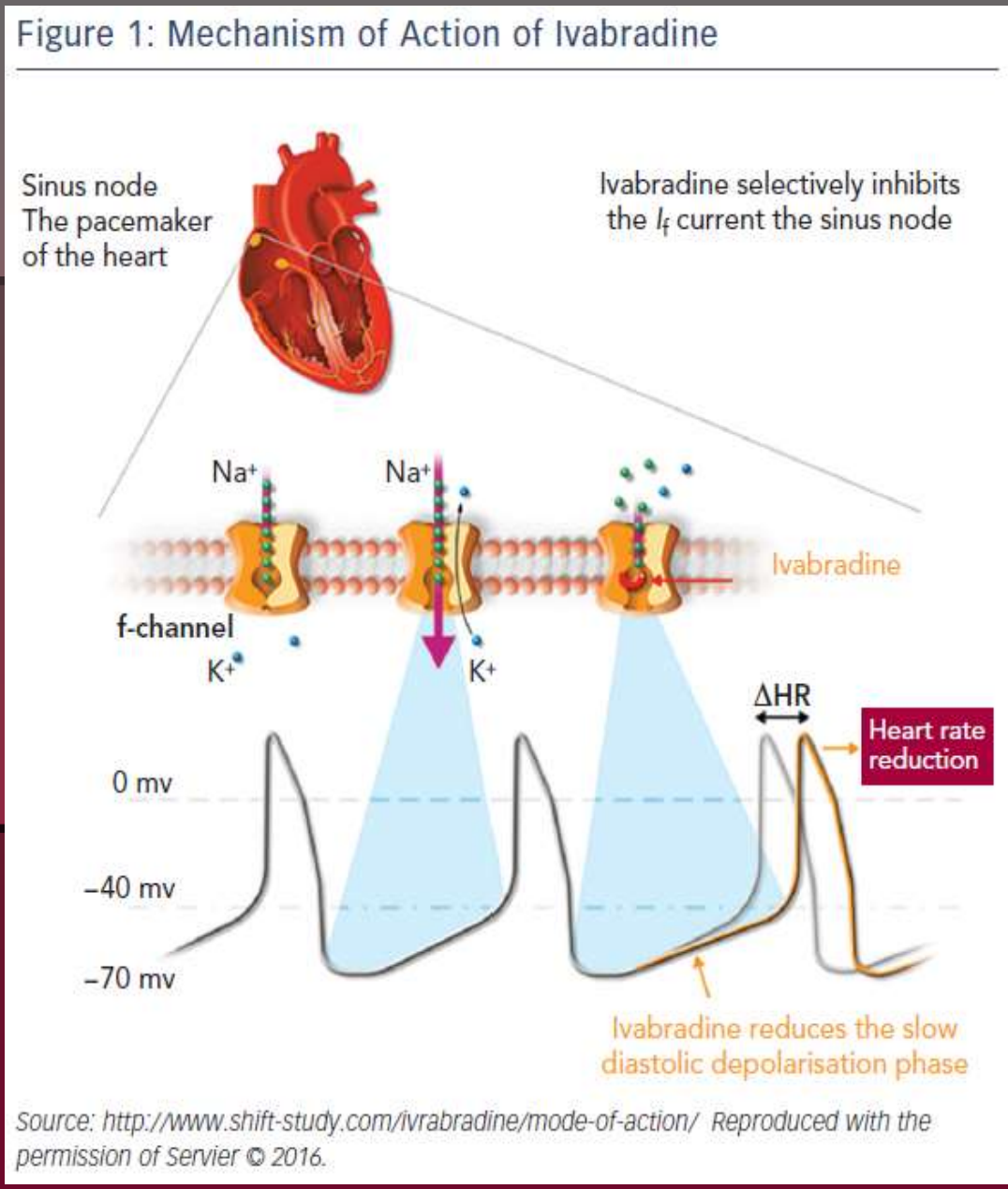
ES = prolongation QT (arritmia)

Bukan 1st tx, hanya adjuvant dr traditional agent, atau sbg 2nd choice ketika tdk toleran dg traditional agent

IVABRADIN

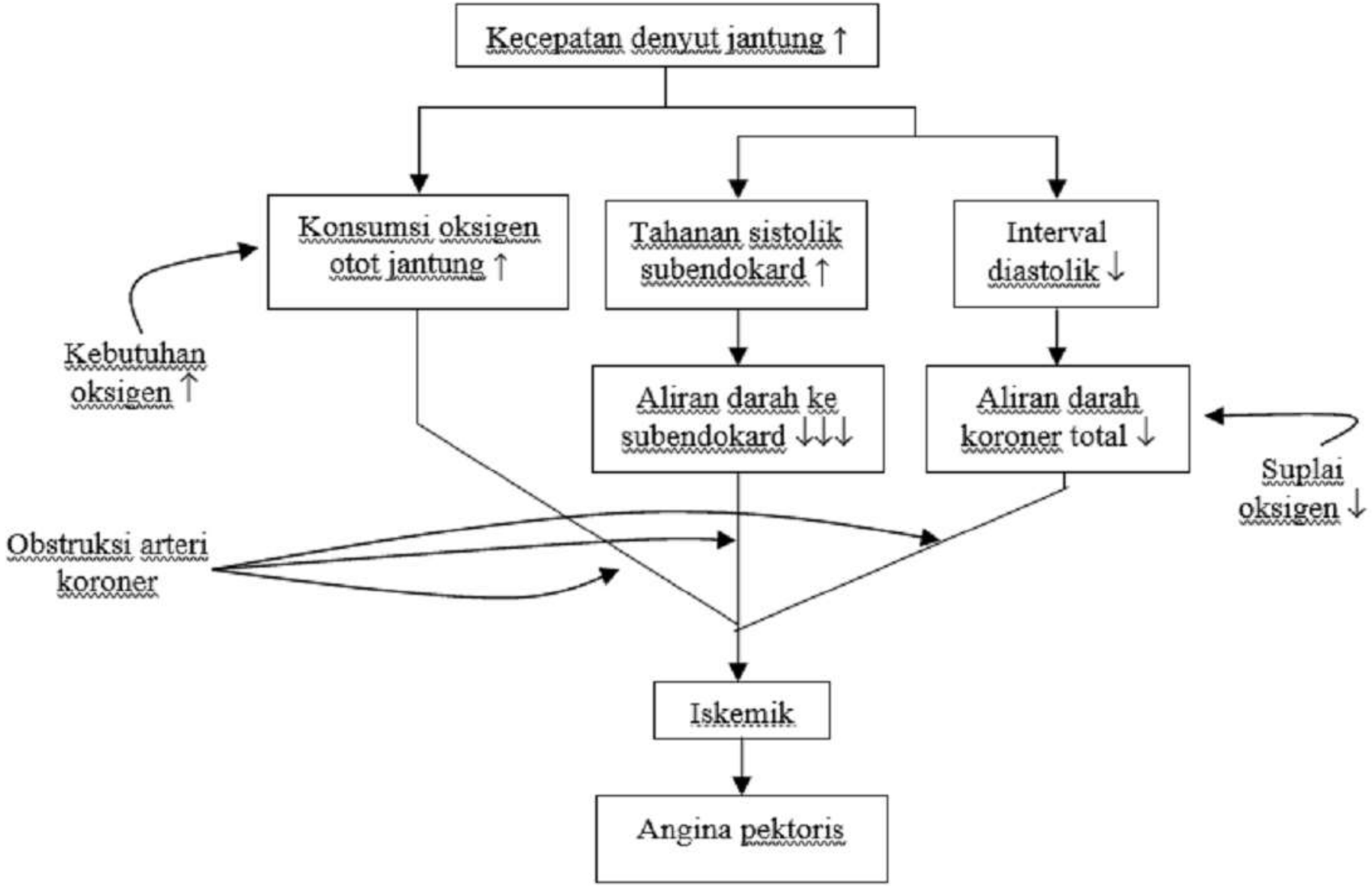
Farmakodinami = menghambat secara selektif dan spesifik arus di kanal *f* pada SA node → pe↓ arus *f* → me↓ depolarisasi diastolik spontan → peningkatan lama fase diastolik → pe↓ kecepatan denyut jantung

Figure 1: Mechanism of Action of Ivabradine



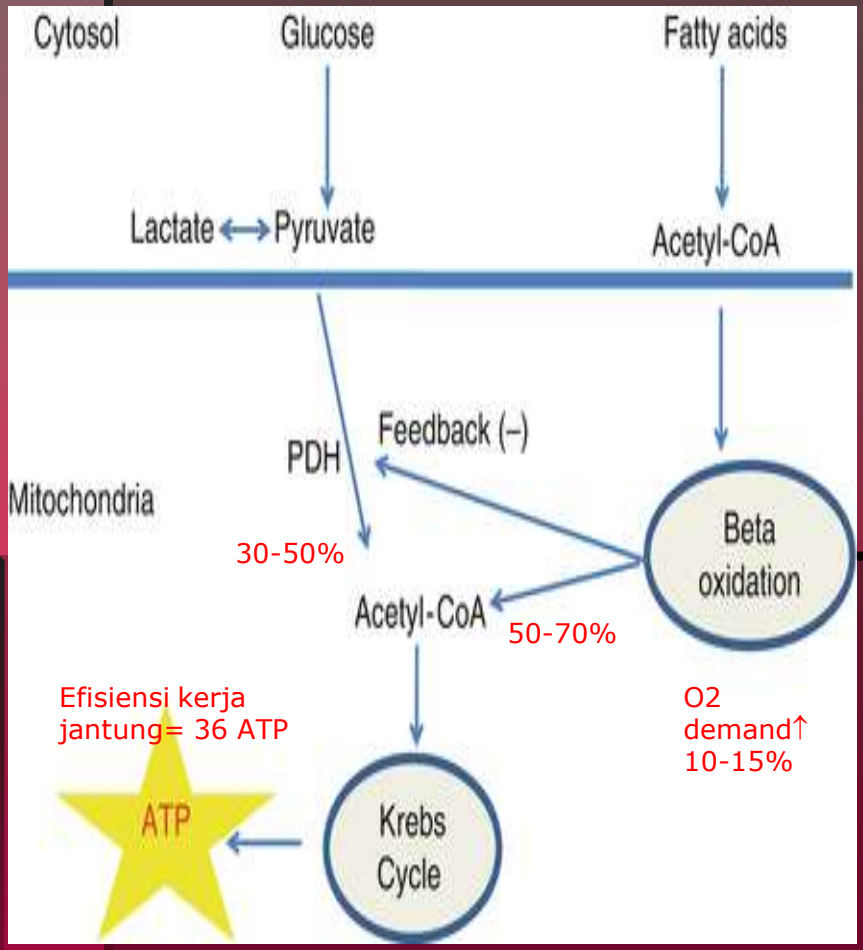
Source: http://www.shift-study.com/ivrabradine/mode-of-action/ Reproduced with the permission of Servier © 2016.

Penurunan Heart rate pada angina stabil

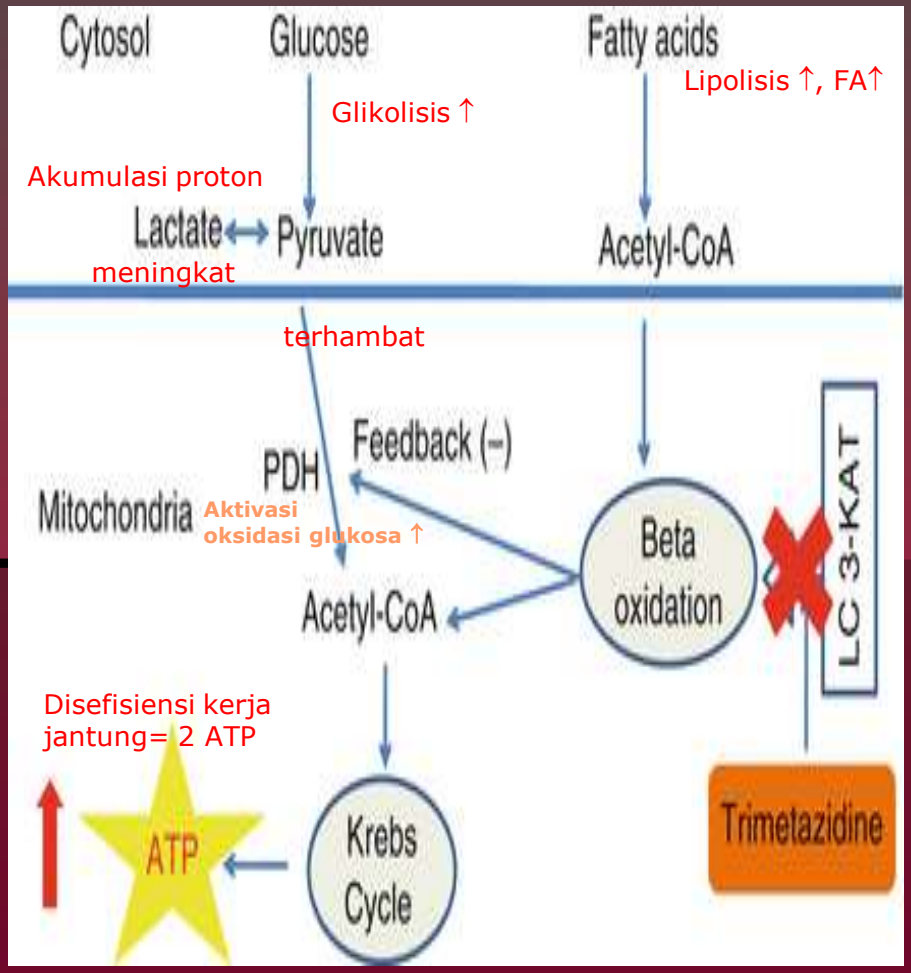


Trimetazidine

Normal condition



Ischemia condition



Trimetazidine

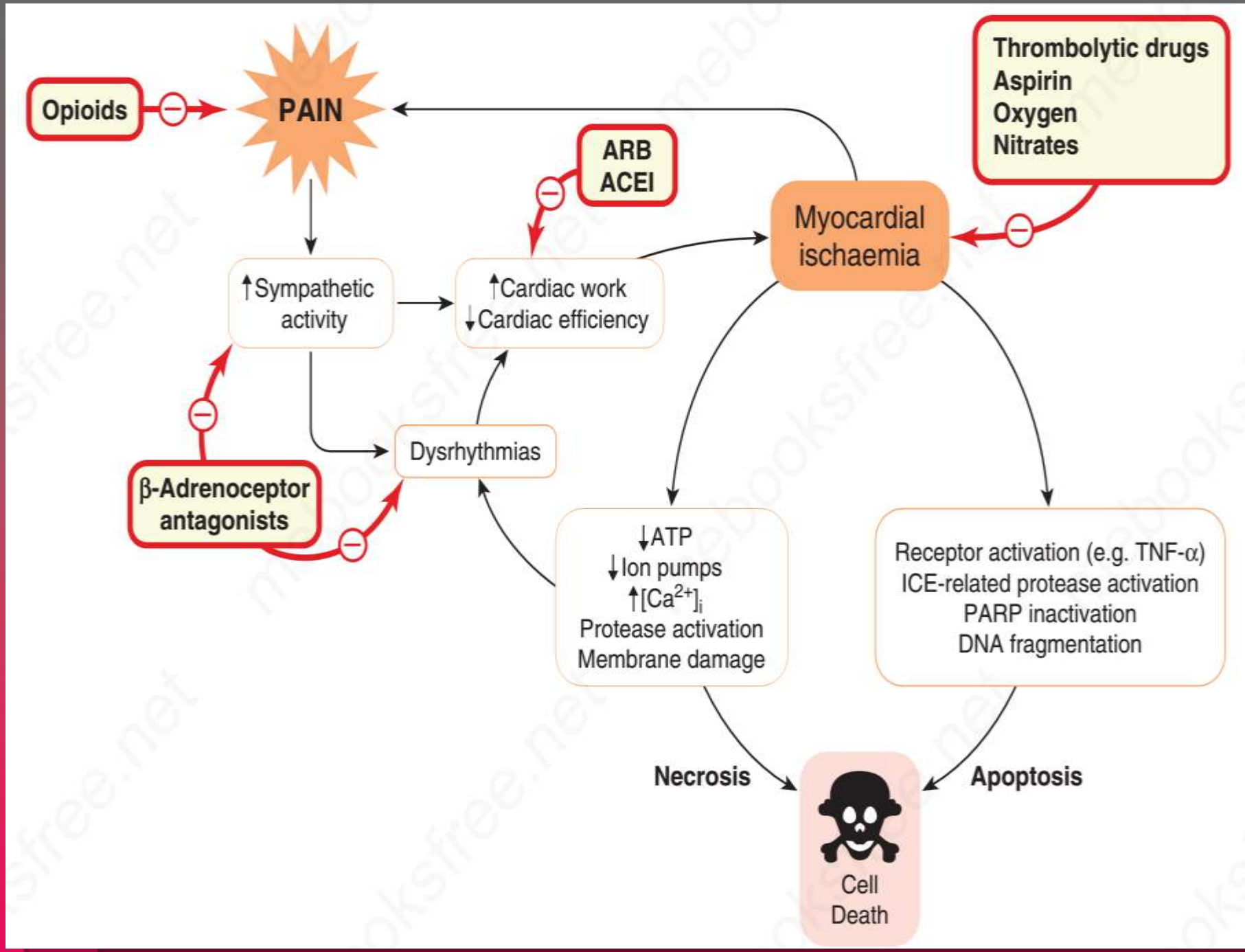
- Metabolic modulator agent
- Blok enz β-oxidative (long-chain 3-ketoacyl CoA thiolase (LC 3-KAT) → hamb oksidasi asam lemak (FAO)→ aktivitas PDH (piruvat dehydrogenase) ↑→ oksidasi gluk (GO)↑→ 36 ATP-efisiensi kerja jantung↑

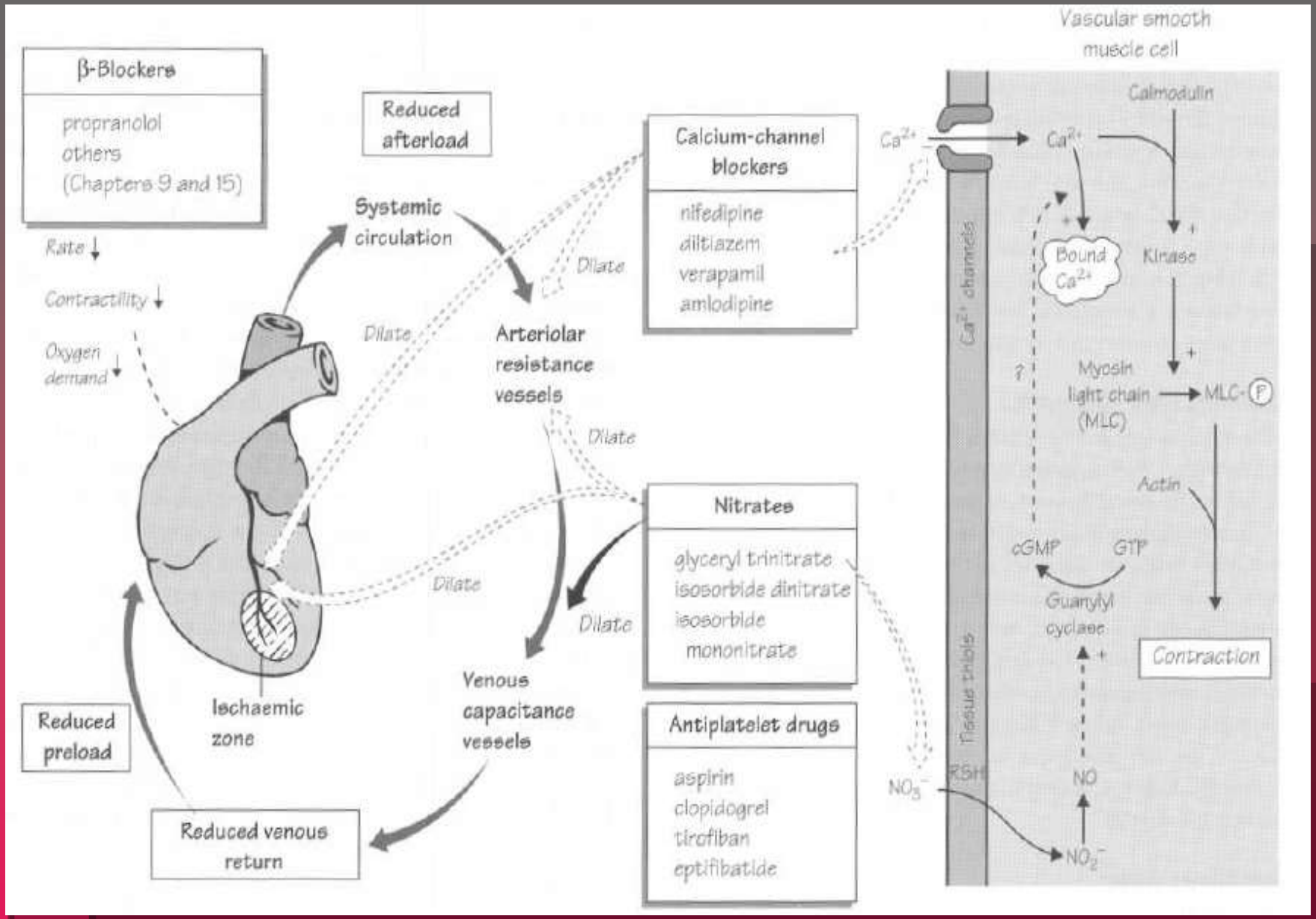
Infark Miokard Akut (IMA)

Tatalaksana : MONA (AHA)

- Morfin : menurunkan nyeri dan kecemasan

  nyeri → HR↑, inotropik↑, sistolik↑→O2 demand↑
- Oksigen : jk SpO2 < 90%
- Nitrogliserin : coroner dilatasi, perfusi ↑, preload↓, afterload↓
- Aspirin 160-325 mg p.o


Opioids
PAIN
Thrombolytic drugs
Aspirin
Oxygen
Nitrates
ARB
ACEI
Myocardial ischaemia
↑Sympathetic activity
↑Cardiac work
↓Cardiac efficiency
Dysrhythmias
β-Adrenoceptor antagonists
↓ATP
↓Ion pumps
↑[Ca2+]i
Protease activation
Membrane damage
Receptor activation (e.g. TNF-α)
ICE-related protease activation
PARP inactivation
DNA fragmentation
Necrosis
Apoptosis
Cell Death


β-Blockers
propranolol
others
(Chapters 9 and 15)
Rate ↓
Contractility ↓
Oxygen demand ↓
Reduced afterload
Systemic circulation
Dilate
Dilate
Arteriolar resistance vessels
Dilate
Dilate
Dilate
Venous capacitance vessels
Ischaemic zone
Reduced preload
Reduced venous return
Calcium-channel blockers
nifedipine
diltiazem
verapamil
amlodipine
Nitrates
glyceryl trinitrate
isosorbide dinitrate
isosorbide mononitrate
Antiplatelet drugs
aspirin
clopidogrel
tirofiban
eptifibatide
Vascular smooth muscle cell
Calmodulin
Ca2+
Ca2+
Ca2+ channels
Bound Ca2+
Kinase
Myosin light chain (MLC)
MLC-P
Actin
cGMP
GTP
Guanylyl cyclase
Contraction
Tissue thiols
RSH
NO3−
NO
NO2−

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Short-acting nitrates				
Nitroglycerin, sublingual (SL)	Releases nitric oxide (NO), increases cGMP (cyclic guanosine monophosphate), and relaxes vascular smooth muscle	Acute angina pectoris • acute coronary syndrome	Rapid onset (1 min) • short duration (15 min)	Tachycardia, orthostatic hypotension, headache
Isosorbide dinitrate (SL): like nitroglycerin SL but slightly longer acting (20–30 min)				
Intermediate-acting nitrates				
Nitroglycerin, oral	Like nitroglycerin SL • active metabolite dinitroglycerin	Prophylaxis of angina	Slow onset • Duration: 2–4 h	Same as nitroglycerin SL
Isosorbide dinitrate and mononitrate, oral: like nitroglycerin oral				
Pentaerythritol tetranitrate and other oral nitrates: like nitroglycerin oral				
Long-acting nitrate				
Transdermal nitroglycerin	Like nitroglycerin oral	Prophylaxis of angina	Slow onset • long duration of absorption: 24 h • duration of effect: 10 h (tachyphylaxis)	Same as nitroglycerin SL • loss of response is common after 10–12 h exposure to drug
Ultrashort-acting nitrite				
Amyl nitrite	Same as nitroglycerin SL	Obsolete for angina • some recreational use	Volatile liquid, vapors are inhaled • onset seconds Duration: 1–5 min	Same as nitroglycerin SL

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Calcium channel blockers				
Verapamil	Blocks L-type Ca^{2+} channels in smooth muscle and heart • decreases intracellular Ca^{2+}	Angina (both atherosclerotic and vasospastic), hypertension • AV-nodal arrhythmias; migraine	Oral, parenteral Duration: 6–8 h	Constipation, pretibial edema, flushing, dizziness • Higher doses: cardiac depression, hypotension
Diltiazem: like verapamil; shorter half-life				
Nifedipine	Dihydropyridine Ca^{2+} channel blocker; vascular > cardiac effect	Angina, hypertension	Oral • slow-release form Duration: 6–8 h	Like verapamil • less constipation, less cardiac effect
Amlodipine, felodipine, nicardipine, nisoldipine: like nifedipine but longer acting				
Beta blockers				
Propranolol	Blocks sympathetic effects on heart and blood pressure • reduces renin release	Angina, hypertension, arrhythmias, migraine, performance anxiety	Oral, parenteral Duration: 6 h	See Chapter 10
Atenolol, metoprolol, other β blockers: like propranolol; most have longer duration of action				
Other antianginal drugs				
Ranolazine	Blocks late Na^+ current in myocardium, reduces cardiac work	Angina	Oral Duration: 10–12 h	QT prolongation on ECG • inhibits CYP3A and 2D6
Ivabradine	Blocks pacemaker Na^+ current (I_f) in sinoatrial node, reduces heart rate	Heart failure; investigational in angina	Oral, administered twice daily	Excessive bradycardia
Drugs for erectile dysfunction				
Sildenafil, tadalafil, vardenafil	Block phosphodiesterase 5 • increase cGMP	Erectile dysfunction in men	Oral Duration: hours	Interaction with nitrates • priapism

TERIMA KASIH