Cardiovascular Physiology and Pharmacology

Lecture overview:

Part I
Cellular cardiac physiology
Determinants of systolic function
Myocardial oxygen consumption and supply
Oxygen delivery

Part II
Inotropic drugs

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ST-utbildning
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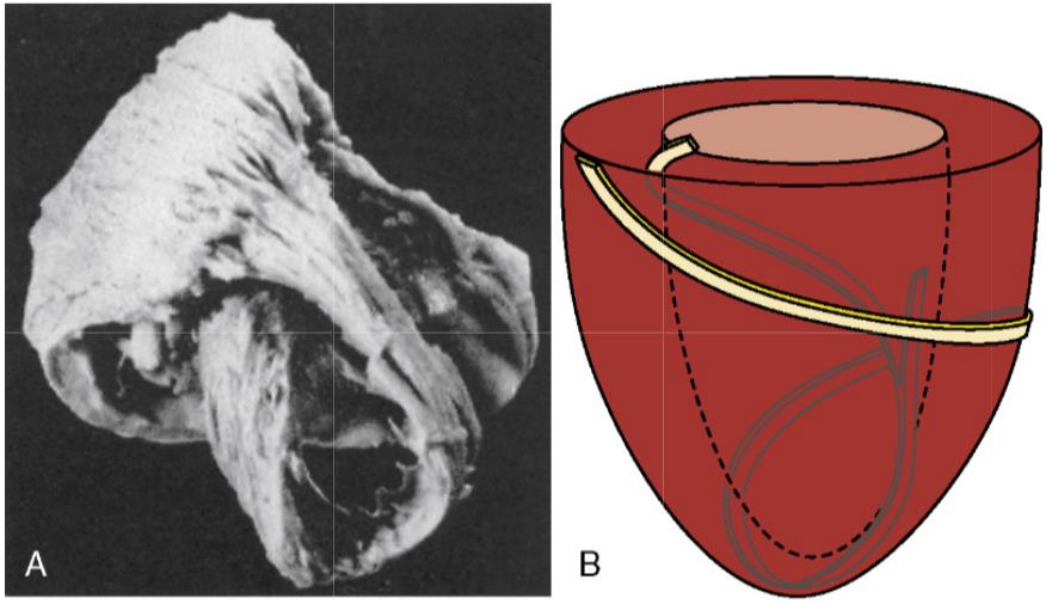
Gross Anatomy of LV



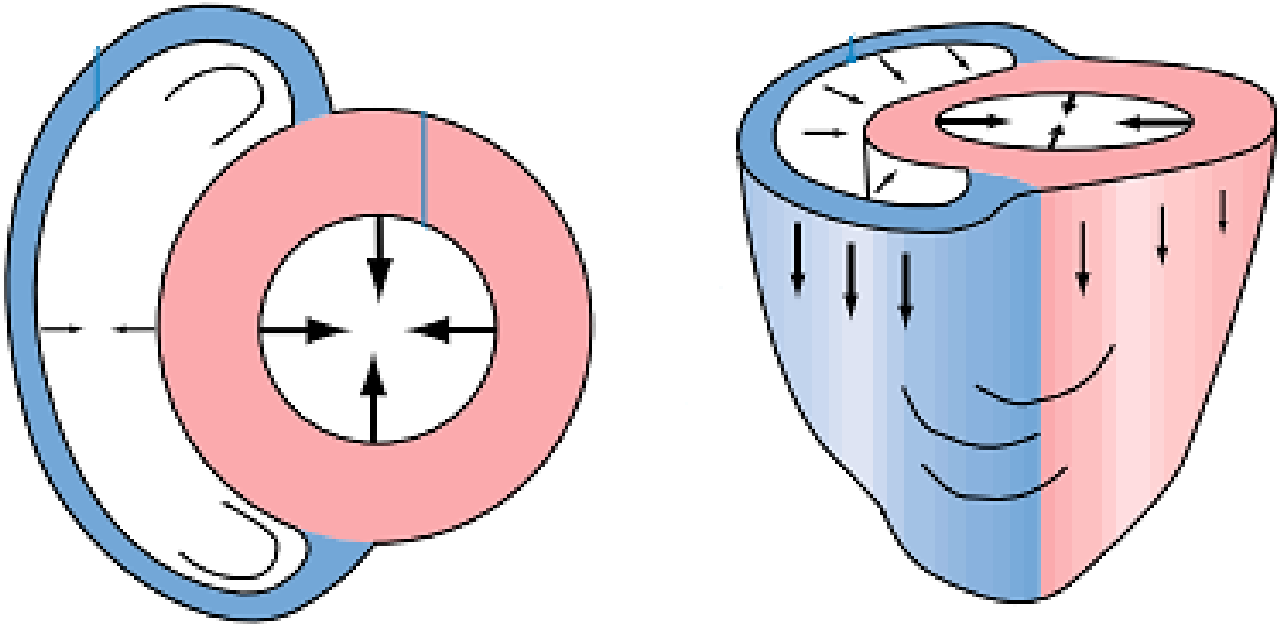
Ellipsoid shape

Different orientation of muscle bundles:
Subendocardial / subepicardial: helical
→ longitudinal shortening, „twisting“

Midmyocardium: spherical
→ radial shortening

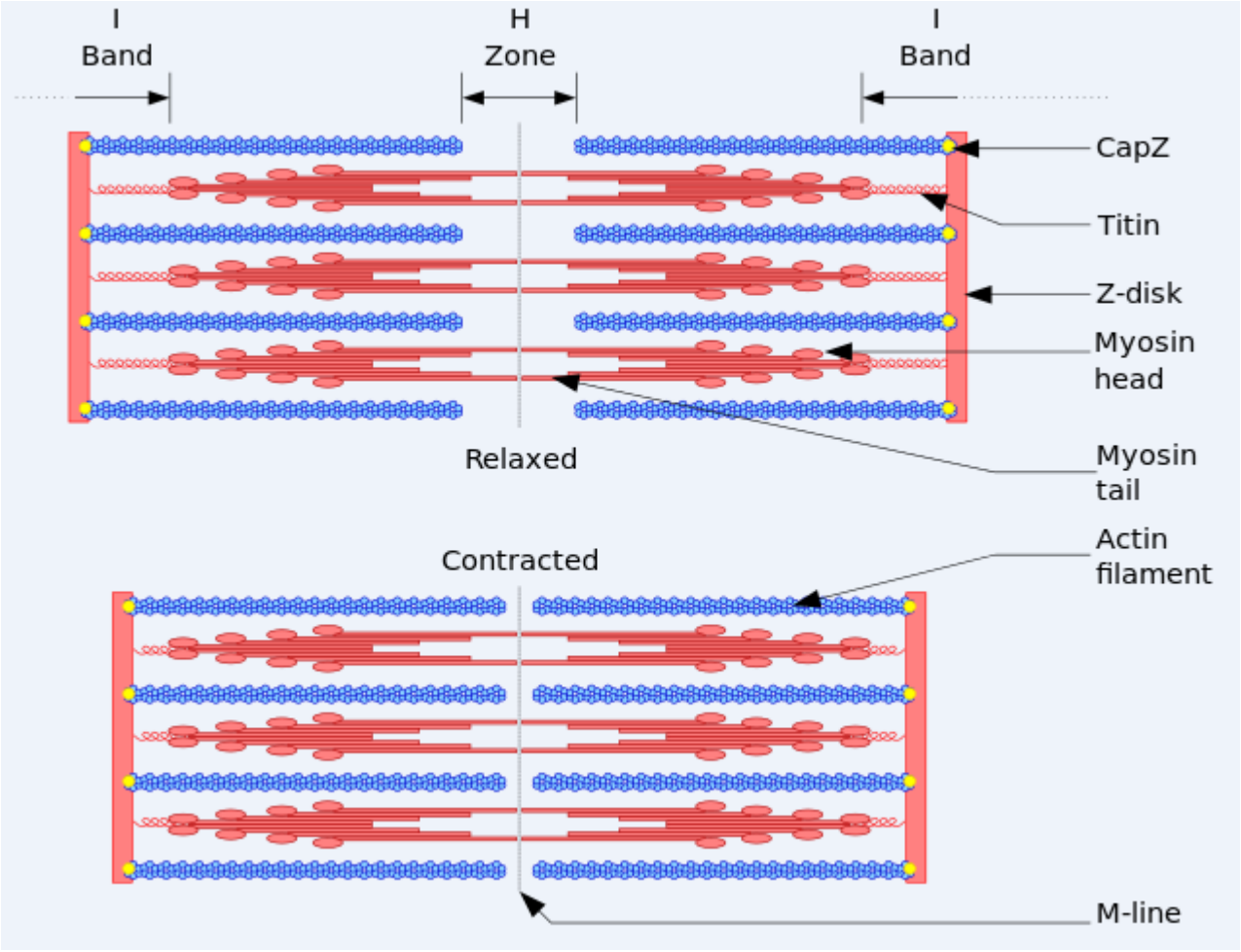
Differences to RV

Less wall thickness
Crescent shaped
Contracts in a peristaltic manner, „bellows-like“ action
Interventricular septum / LV provide a splint
Systolic interventricular dependence



Cardiac Myocyte Anatomy (1/3)

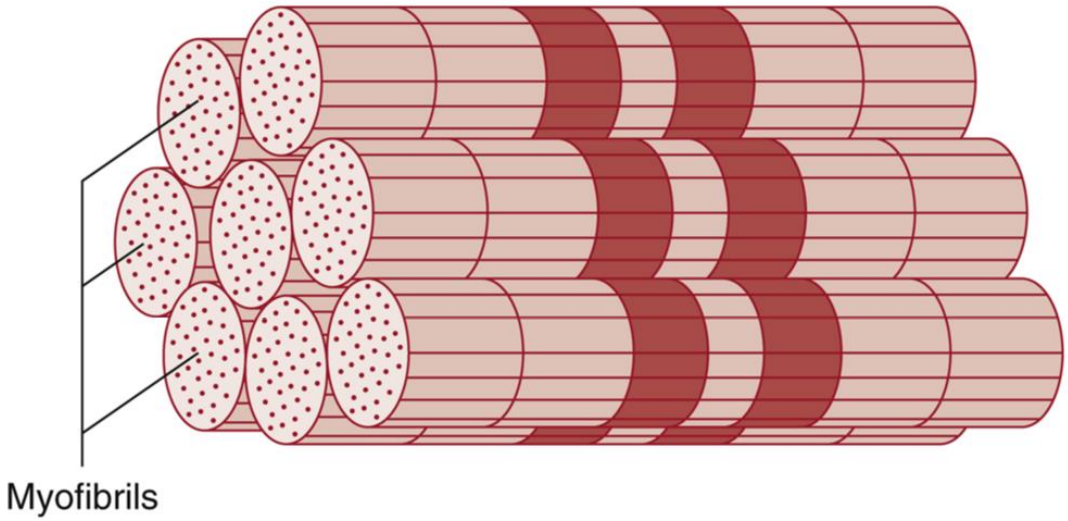
Sarcomere = basic unit of contraction



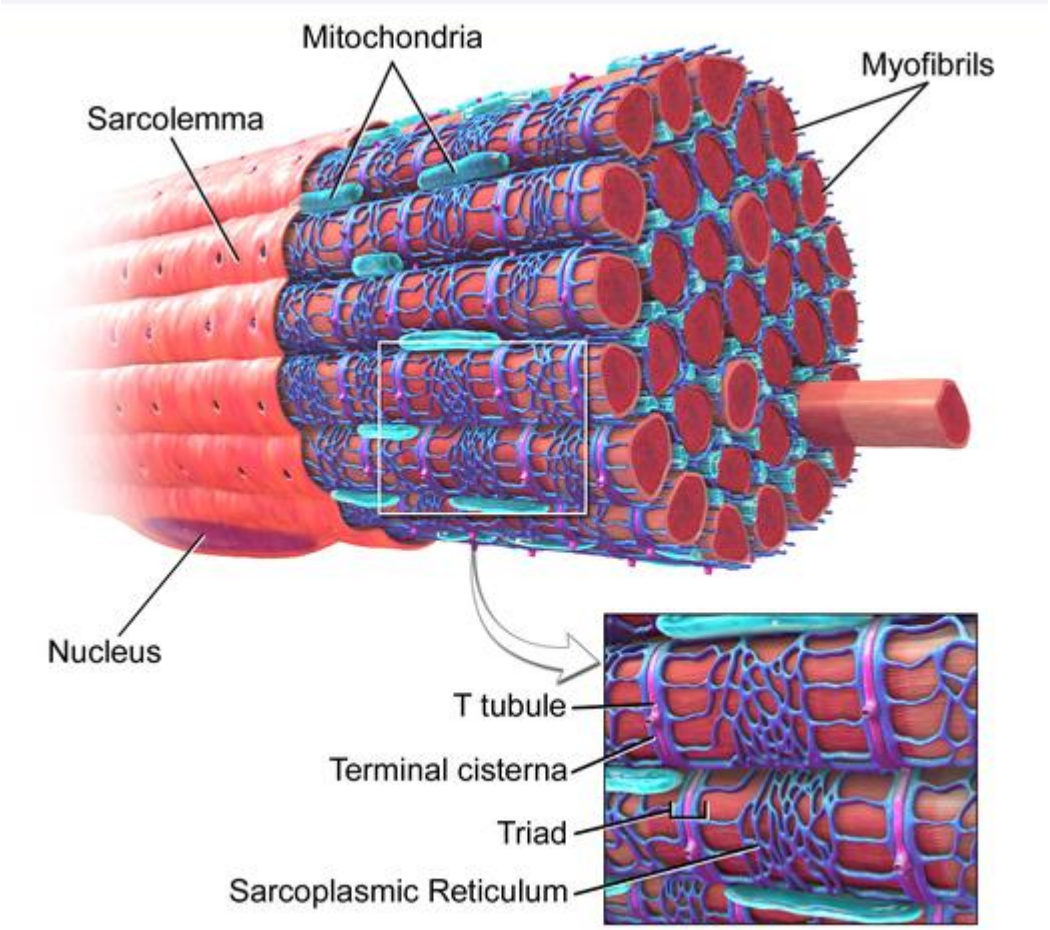
Cardiac Myocyte Anatomy (2/3)

Myofilaments:
thin (actin, tropomyosin, troponin complex)
thick (myosine, titin)

Myofibril: myofilaments in parallel and sarcomeres in series

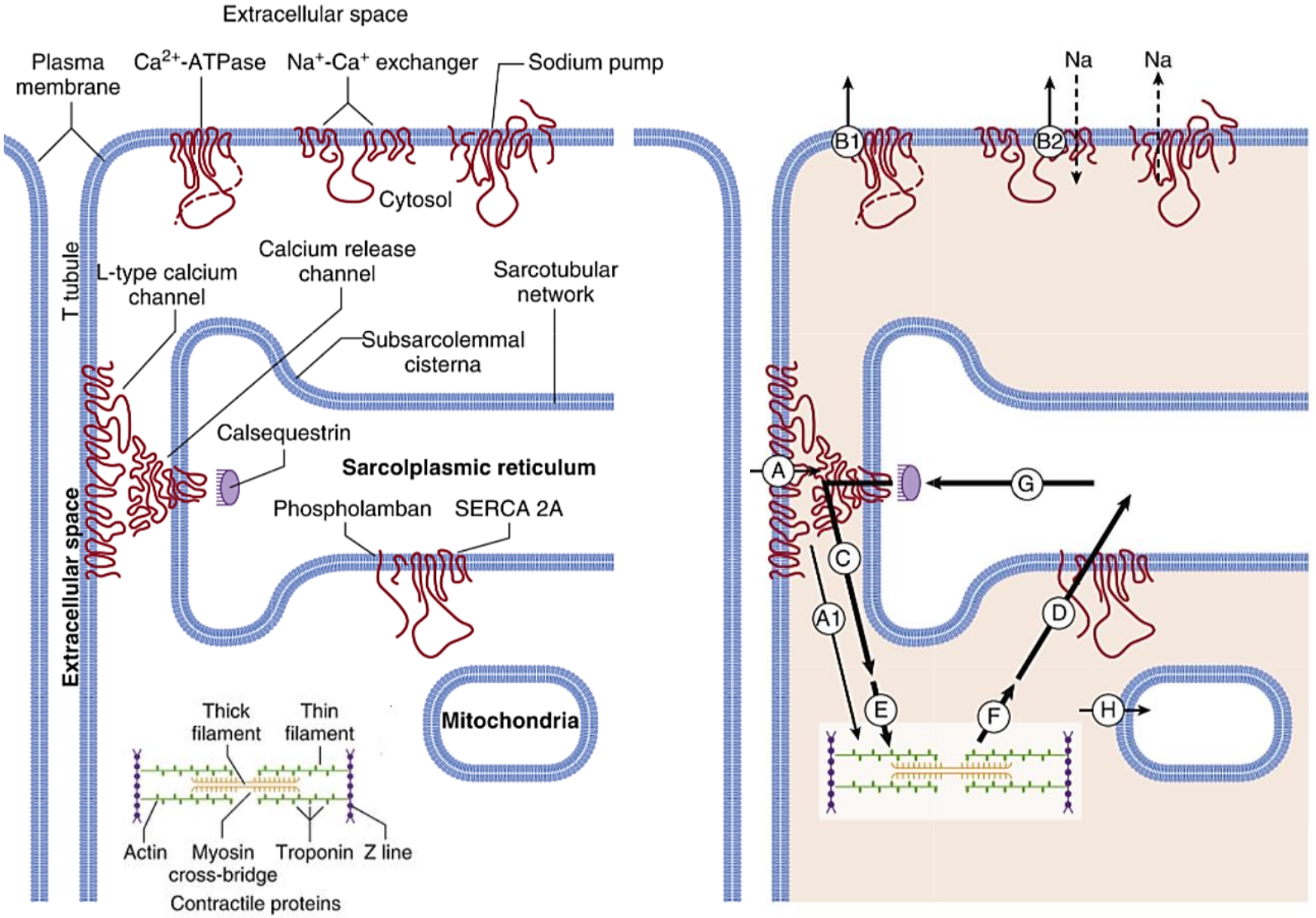


Cardiac Myocyte Anatomy (3/3)

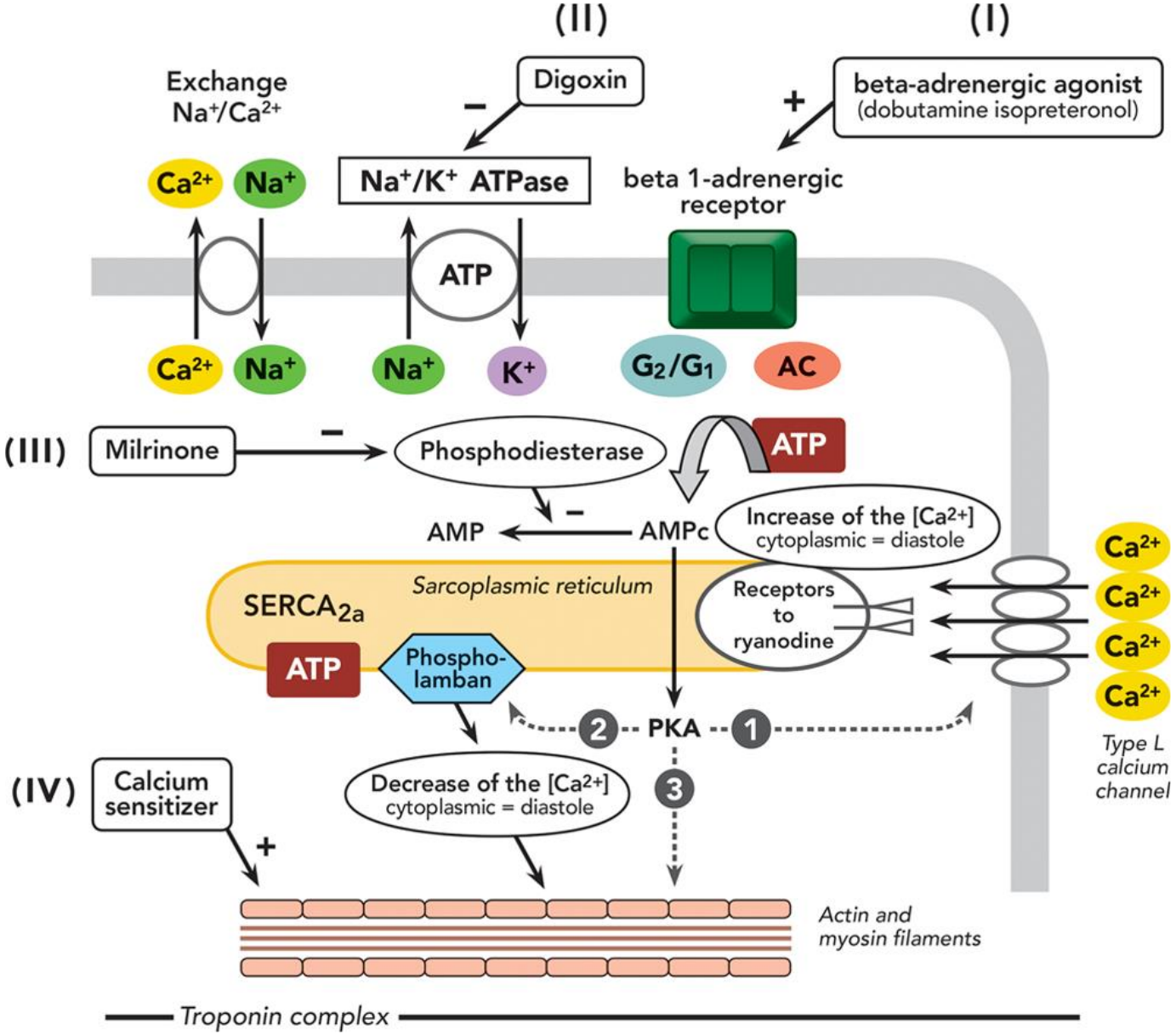


Cardiac myocyte is engineered for contraction and relaxation, not for protein synthesis

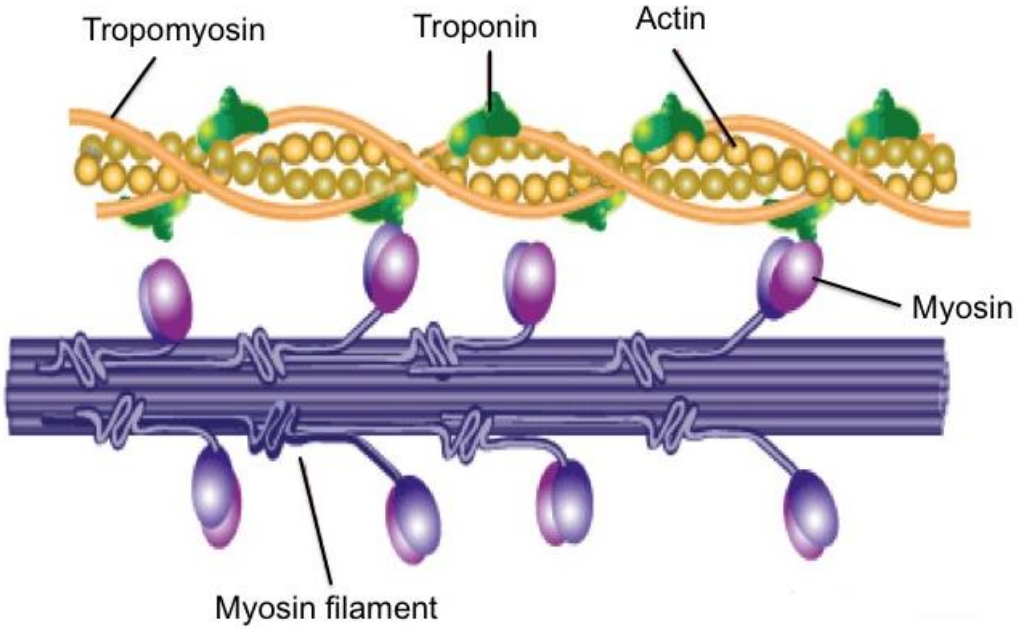
Excitation-Contraction Coupling

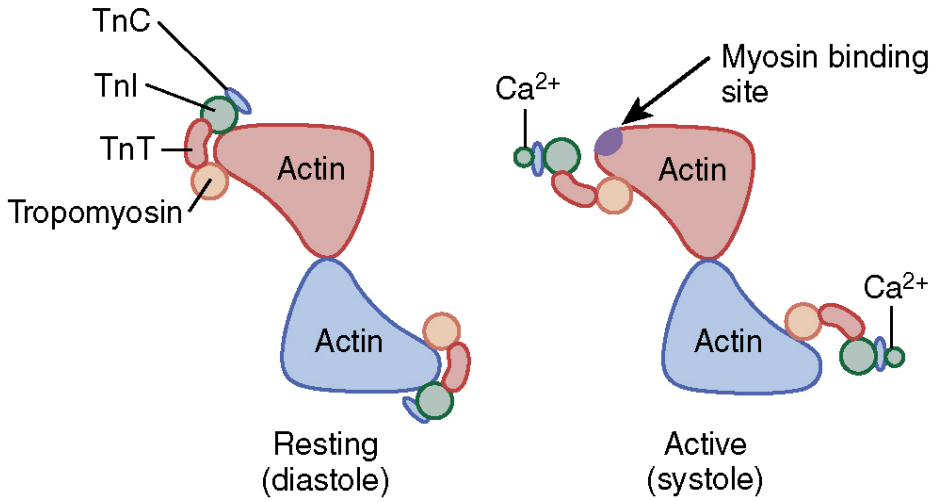


Inotropic Drugs

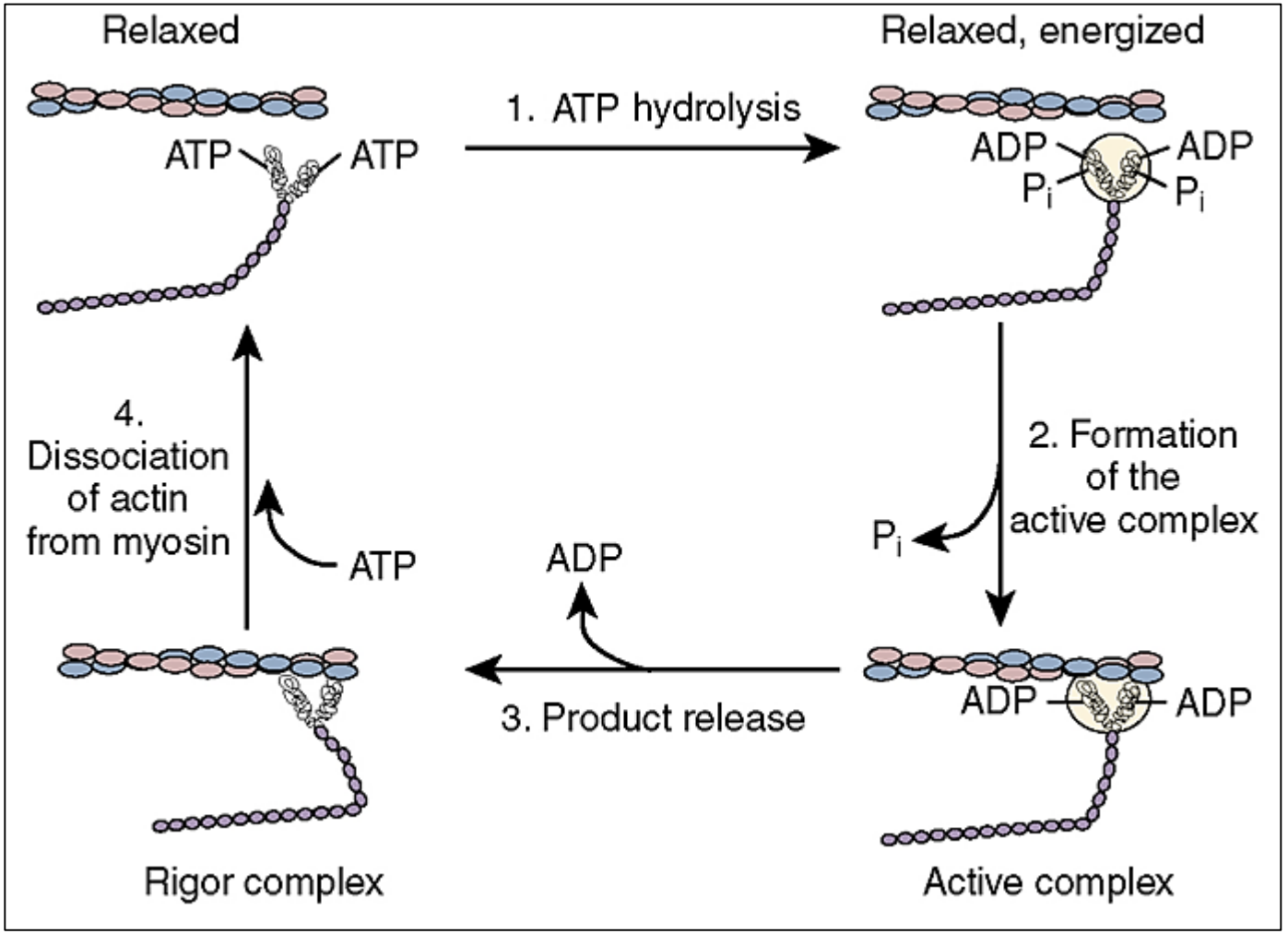


Calcium-Myofilament Interaction

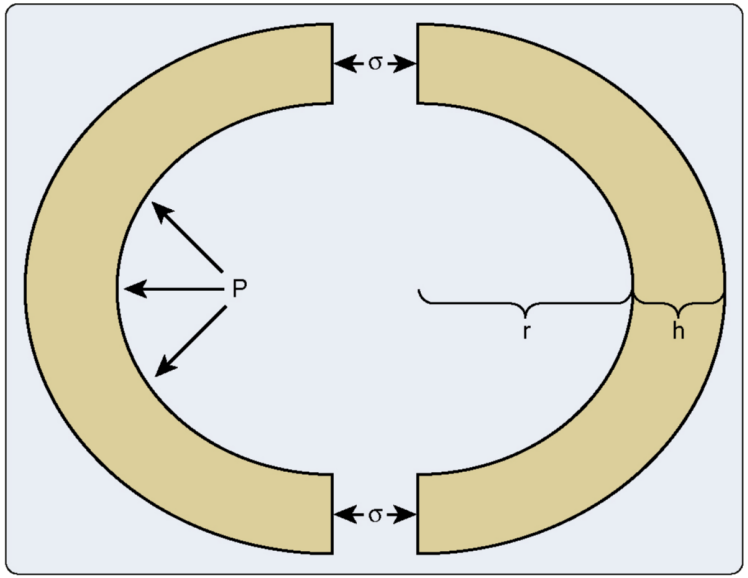




Myosin-Actin Interaction



Laplace's Law



$$\sigma = Pr/2h$$

$$\text{Wall stress} = \frac{\text{Pressure radius}}{2\ (\text{Wall thickness})}$$

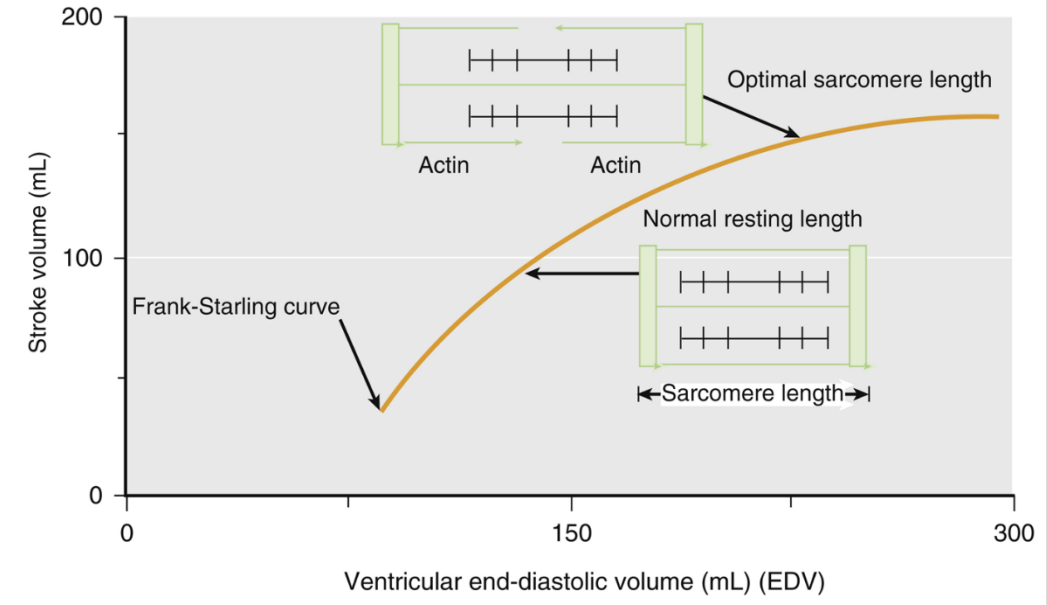
Increase in wall stress: myofilaments require more energy to develop this degree of enhanced tension → greater O_2 demand

Wall stress not uniformly distributed → greatest subendocardial

Facilitates the conversion of the contractile behavior of the individual sarcomeres in vitro into global chamber function in vivo

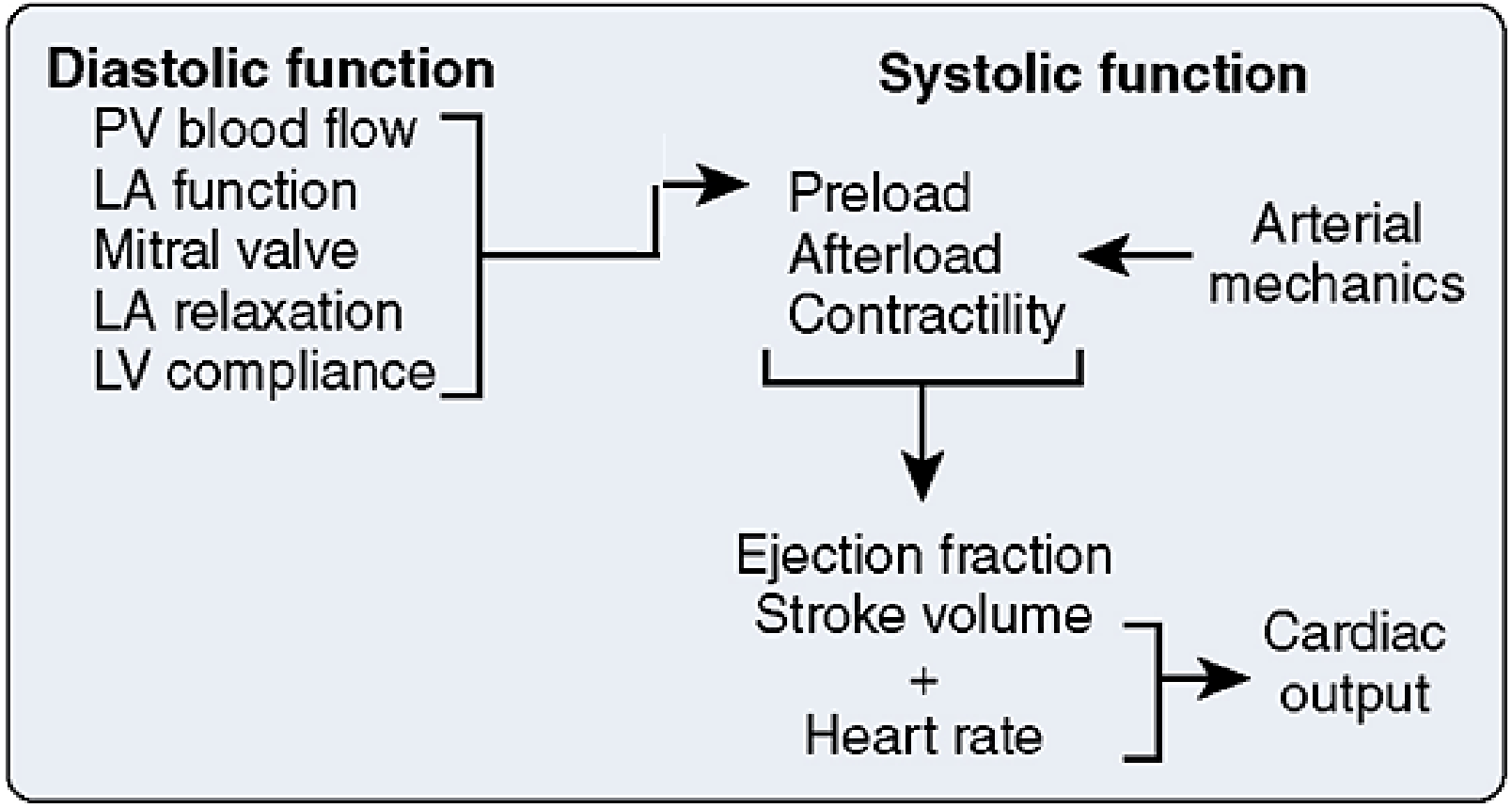
Frank-Starling Relationship

Length-tension relationship



Related to:
Increased Ca^{2+} sensitivity of troponin C
Decrease in spacing between thick and thin filaments → increased number of cross-bridges
Titin-induced elastic recoil

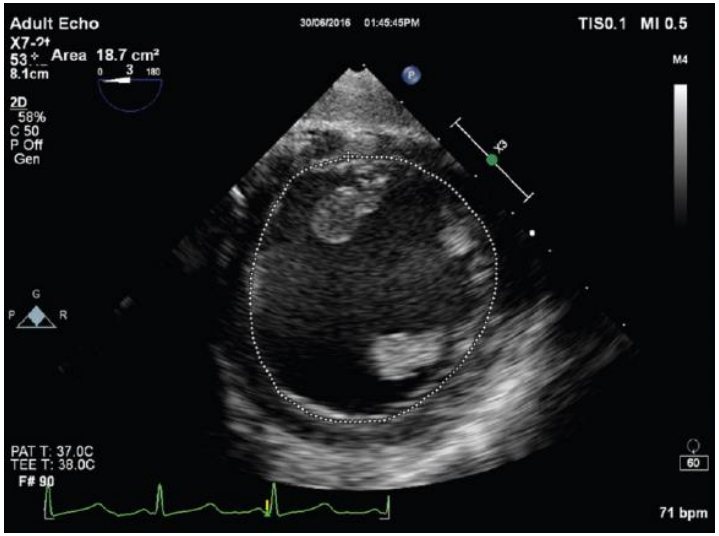
Determinants of Pump Performance

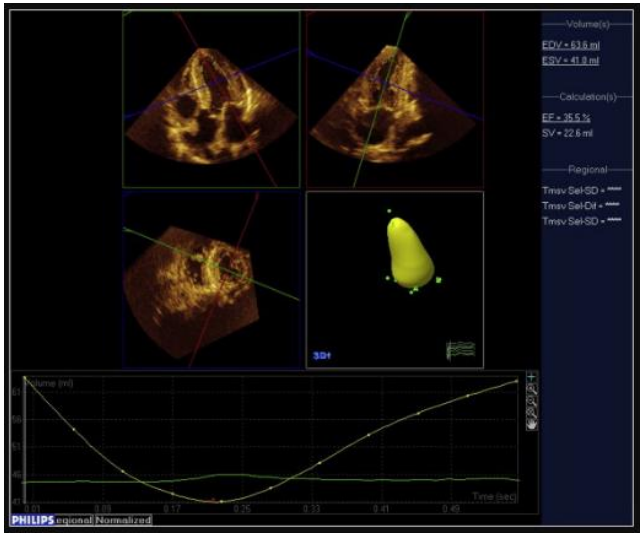


Preload (1/3)

Definition:
- Sarcomere length immediately before contraction
- Ventricular load at the end of diastole before contraction

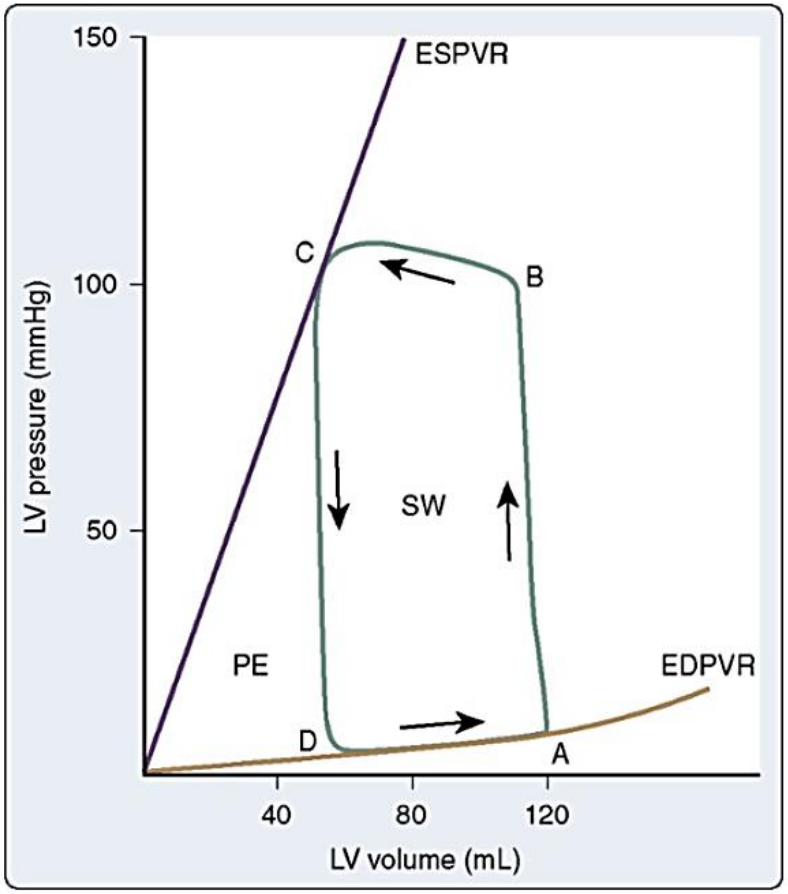
Measurement:
Sonomicrometry, conductance catheter technique → invasive
Radionuclide angiography, dynamic MRI → noninvasive
2D TEE, real-time 3D TEE





Pressure-Volume Diagram

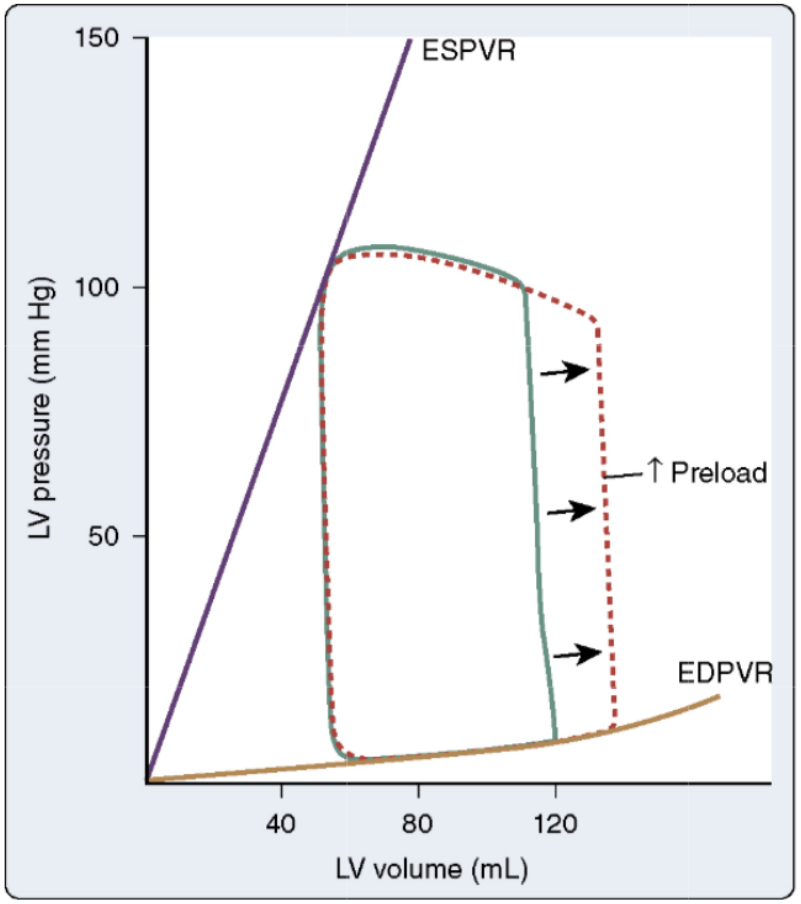
Measurement:
Catheter in LV chamber

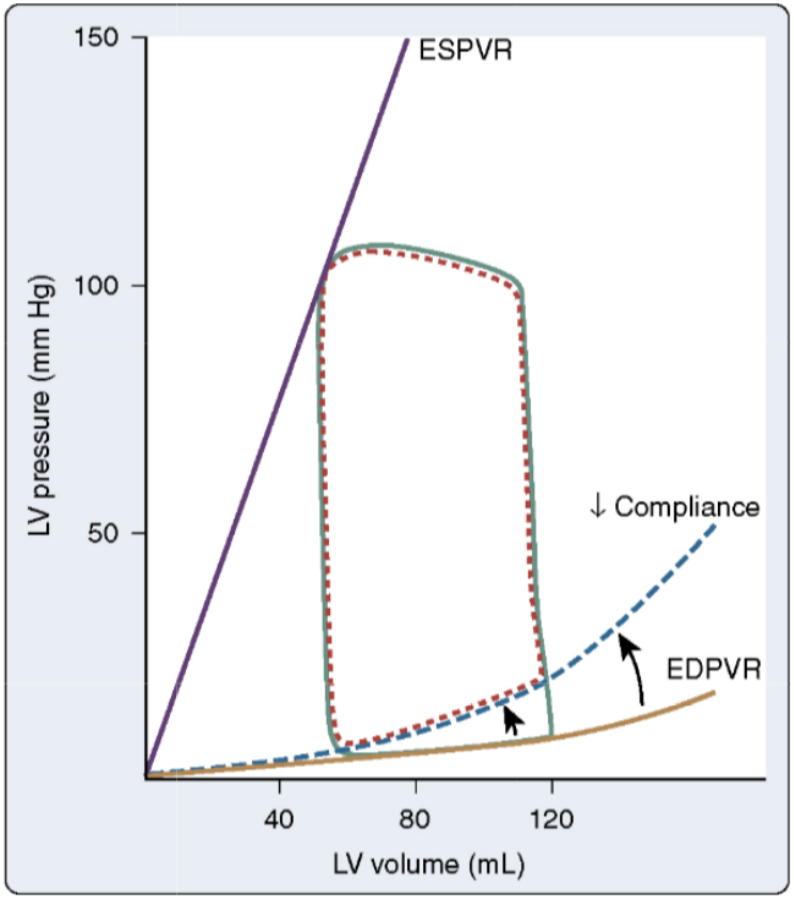


Steady-state left ventricular (LV) pressure-volume diagram. The cardiac cycle proceeds in a time-dependent counterclockwise direction (arrows). Points A, B, C, and D correspond to LV end-diastole (closure of the mitral valve), opening of the aortic valve, LV end-systole (closure of the aortic valve), and opening of the mitral valve, respectively. Segments AB, BC, CD, and DA represent isovolumic contraction, ejection, isovolumic relaxation, and filling, respectively. The LV is constrained to operate within the boundaries of the end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR, respectively). The area inscribed by the LV pressure-volume diagram is stroke work (SW; kinetic energy) performed during the cardiac cycle. The area to the left of the LV pressure-volume diagram between ESPVR and EDPVR is the remaining potential energy (PE) of the system. The sum of SW and PE is pressure-volume area.

Preload (2/3)

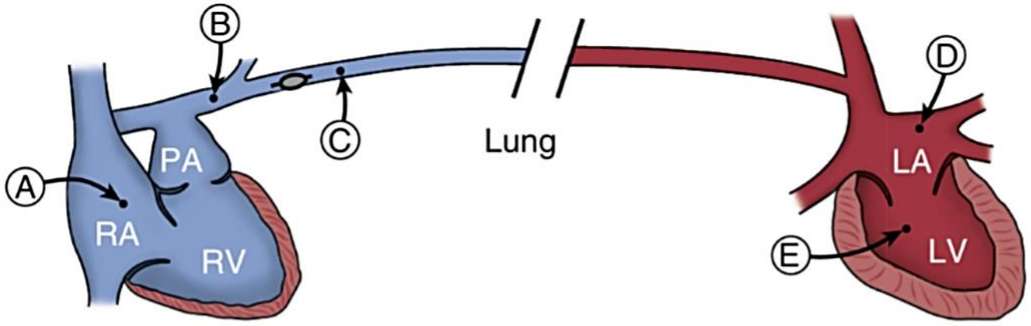
Measurement:
Catheter in LV chamber

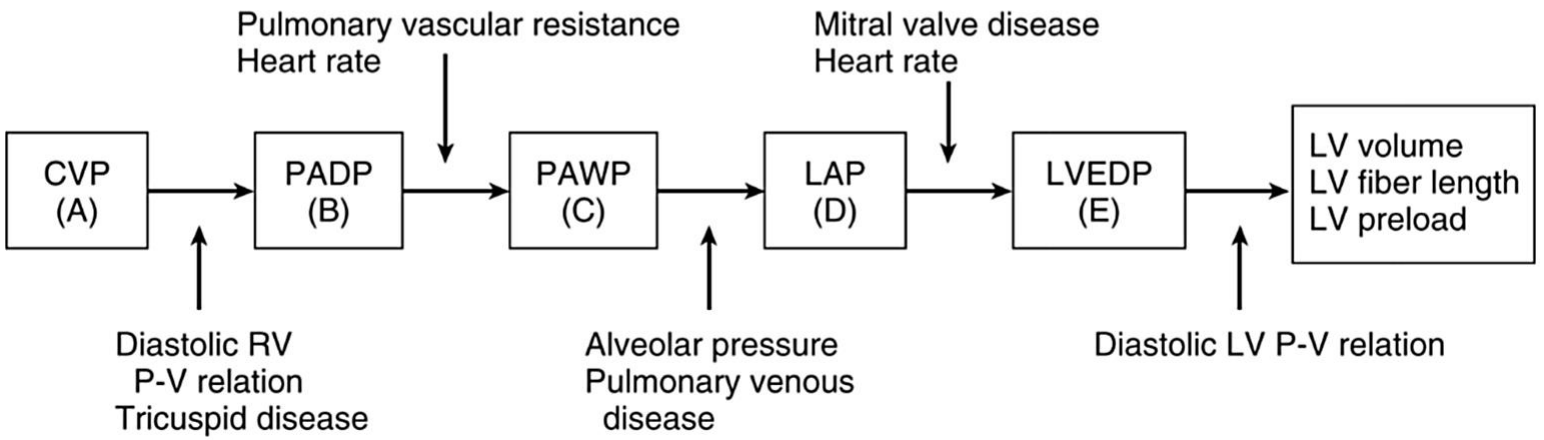




Preload (3/3)

Measurement:
Pressure „upstream“ from LV chamber to estimate LVEDV





Afterload (1/3)

Definition:

- The tension which needs to be generated in the myocardium before shortening will occur
- End load / systolic load on the ventricle after contraction has begun
- External resistance to emptying

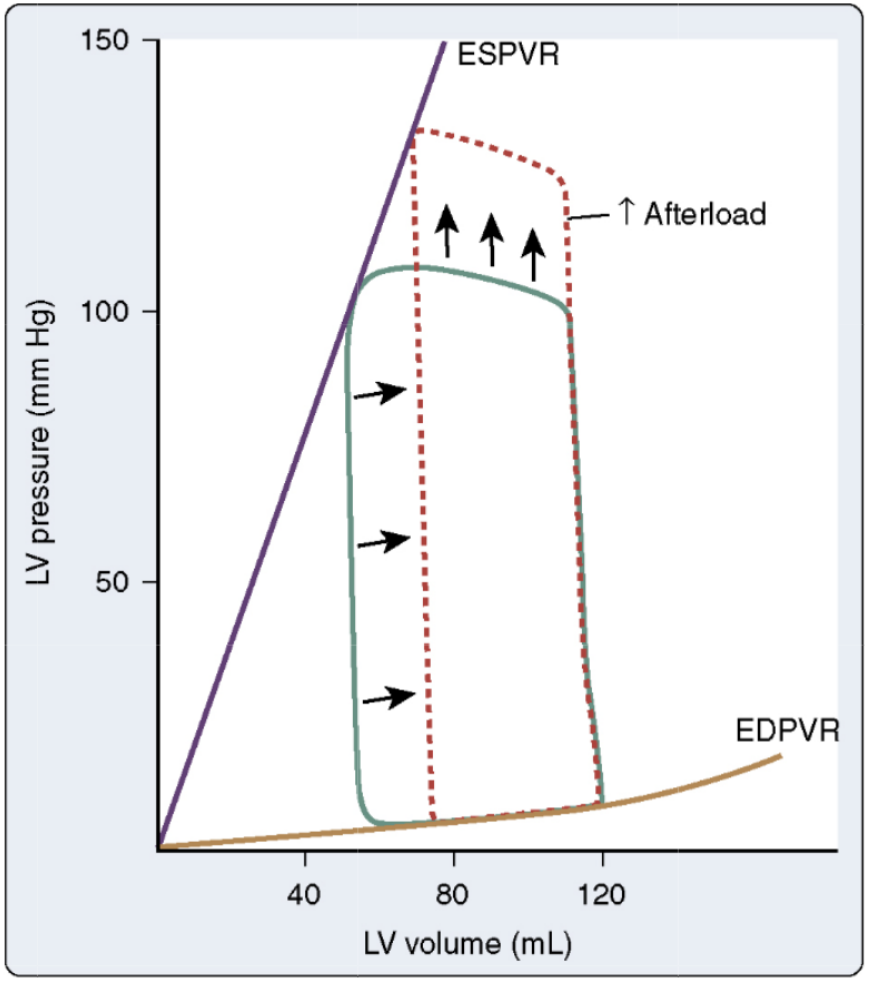
Four major components:

- Physical properties of arterial blood vessels (e.g. diameter, elasticity)
- LV end-systolic wall stress (pressure development, geometric changes)

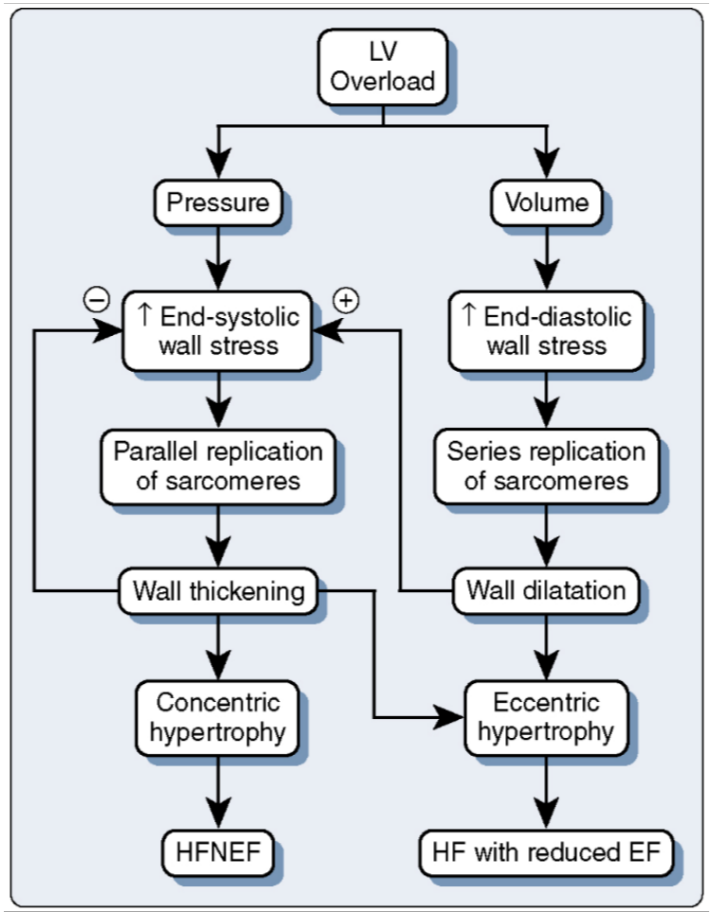
$$\text{Wall stress} = \frac{\text{Pressure radius}}{2\ (\text{Wall thickness})}$$

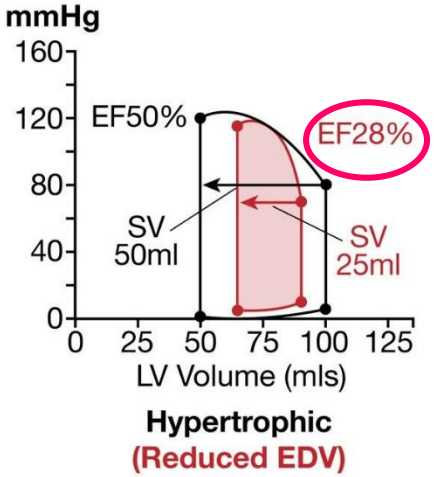
- Total arterial resistance (arteriolar smooth muscle tone)
- Physical properties of blood (e.g. rheology, viscosity, density)

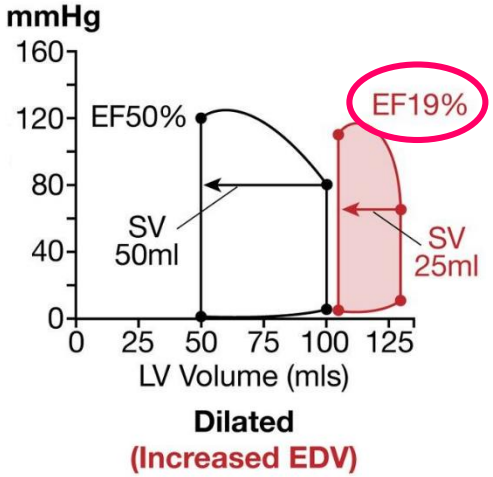
Afterload (2/3)



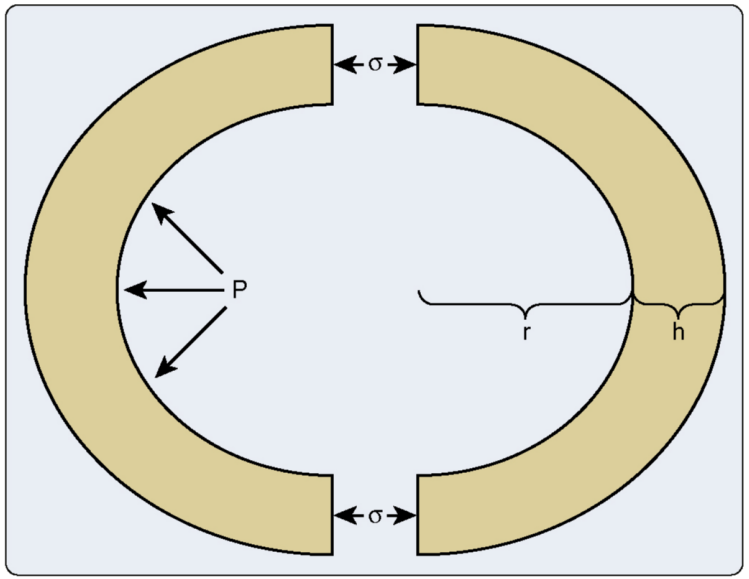
Afterload (3/3)







$$\text{Wall stress} = \frac{\text{Pressure radius}}{2\ (\text{Wall thickness})}$$

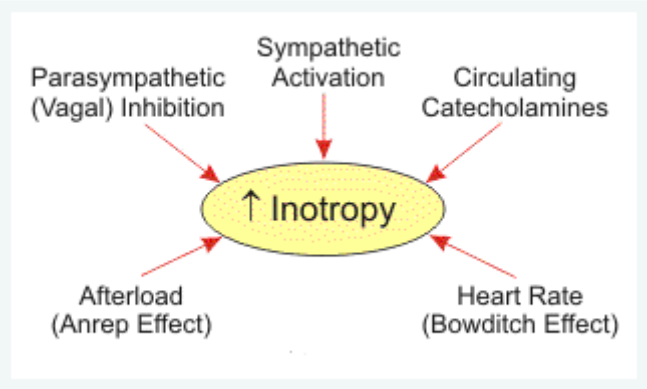


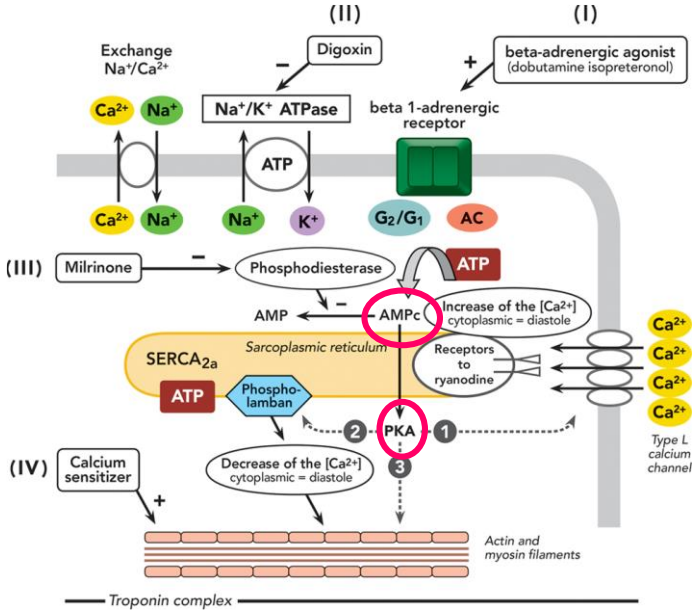
Contractility (1/5)

Definition:
The intrinsic ability of the myocardium to contract (length independent activation)

Mechanism:
↑increased Ca^{++} influx during AP
↑increased Ca^{++} release by SR
↑increased Ca^{++} sensitivity of troponin C

Regulating factors:





Contractility (2/5)

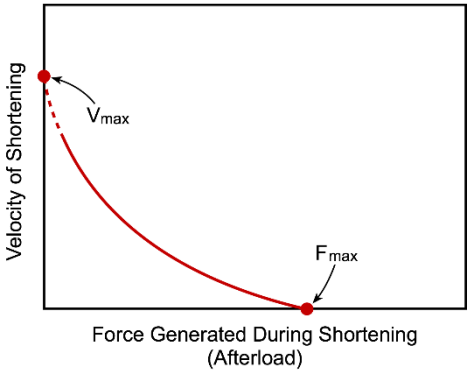
Indices of LV-contractility:

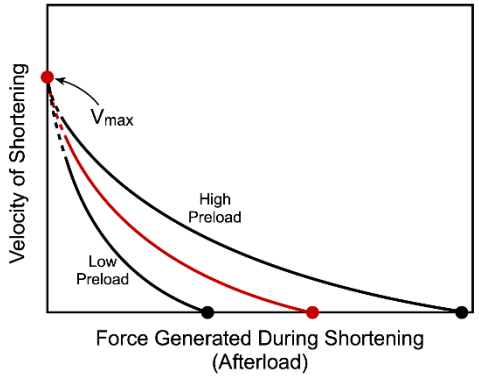
Pressure-Volume Analysis
End-systolic pressure-volume relation (E_{es}) ←
Stroke work—end-diastolic volume relation (M_{sw}) ←
Isovolumic Contraction
dP/dt_{max} ←
$dP/dt_{max}/50$
$dP/dt_{max}/P$
dP/dt_{max}/end-diastolic volume relation (dE/dt_{max})
Ejection Phase
Stroke volume
Cardiac output
Ejection fraction
Fractional area change
Fractional shortening
Wall thickening
Velocity of shortening
Ventricular Power
PWR_{max} ←
PWR_{max}/EDV^2

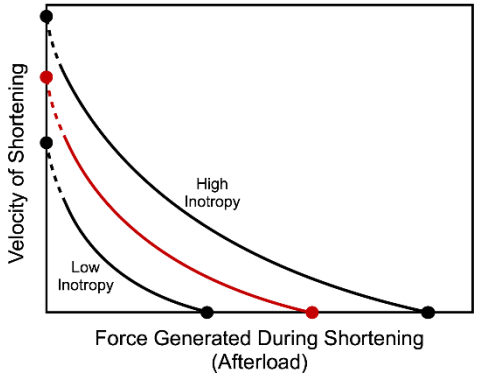
Contractility (3/5)

Mechanisms that can alter force generation are:
Changes in preload: length-dependent
Changes in inotropy: length-independent

Force-velocity relationship:



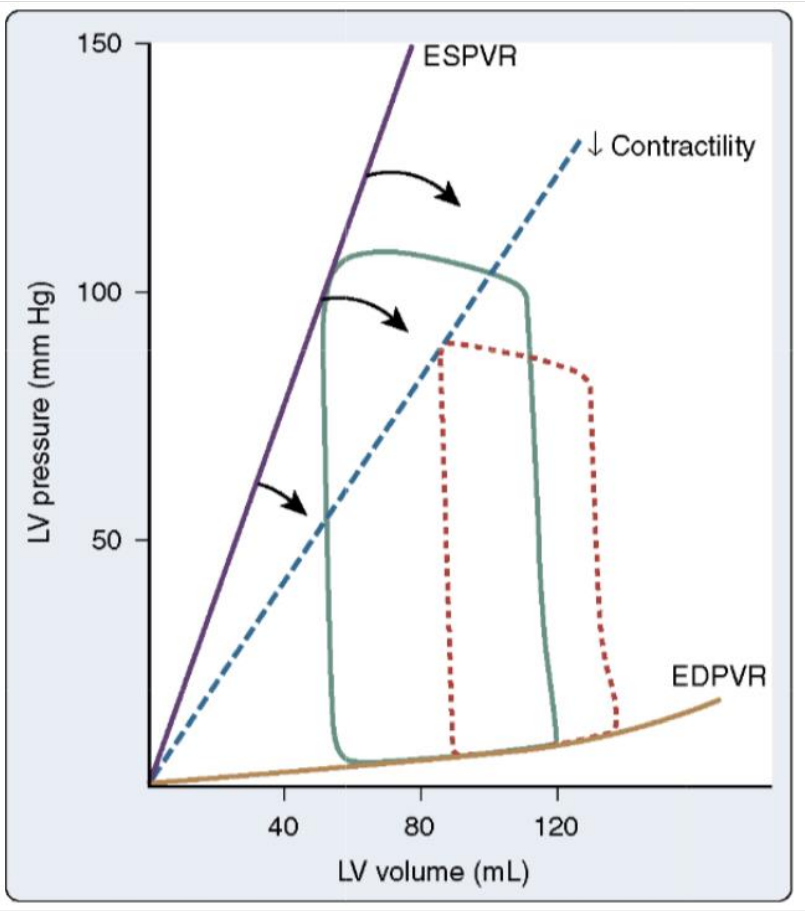




↑velocity of fiber shortening →
↑rate of ventricular pressure development →
↑maximal dP/dt (rate of pressure change) during isovolumetric contraction

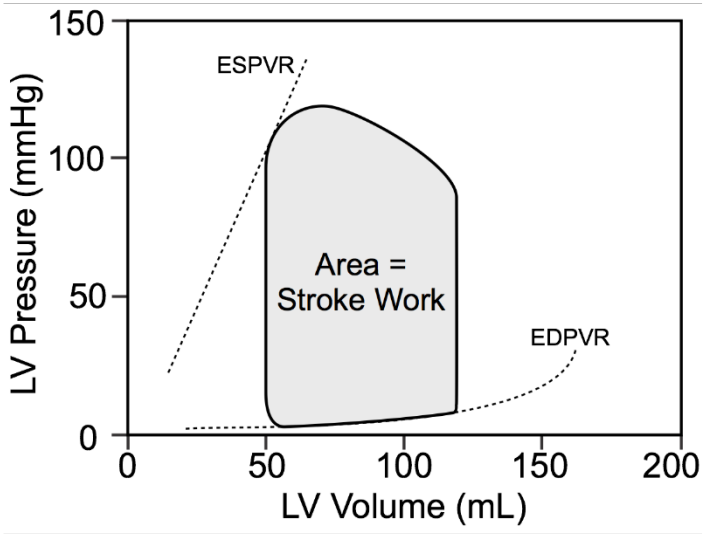
Contractility (4/5)

End-systolic pressure-volume relation = maximal pressure developed at any given LV-volume



Contractility (5/5)

Stroke work (Nm) = pressure (N/m²) x volume (m³)

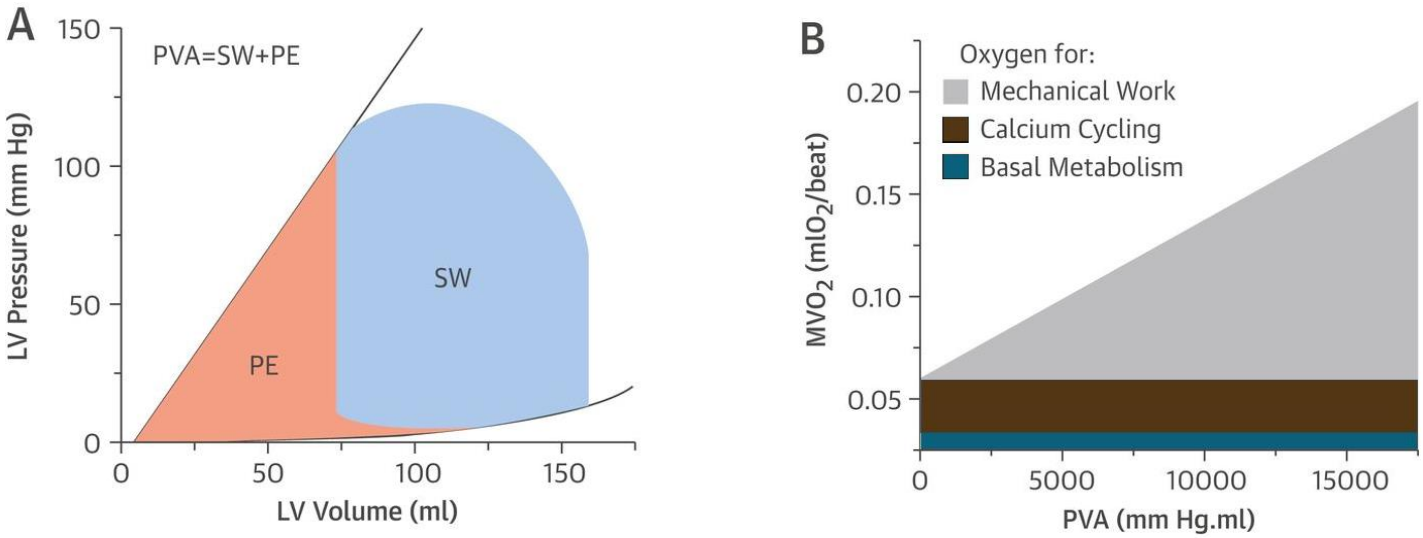


SW = MAP x SV
SW = (mmHg x ml) / 7500 = Joule

Cardiac power (Nm/s) = pressure (N/m²) x flow (m³/s)

CP = MAP x SV x HR
CP = (mmHg x liter/min) / 451 = Watt

Cardiac Work



Pressure-volume area (PVA) represents total mechanical energy generated by ventricular contraction

Stroke work = external work, kinetic energy
Potential energy = internal work, contributes to inefficiency

PVA linearly related to MVO2 (myocardial oxygen consumption)

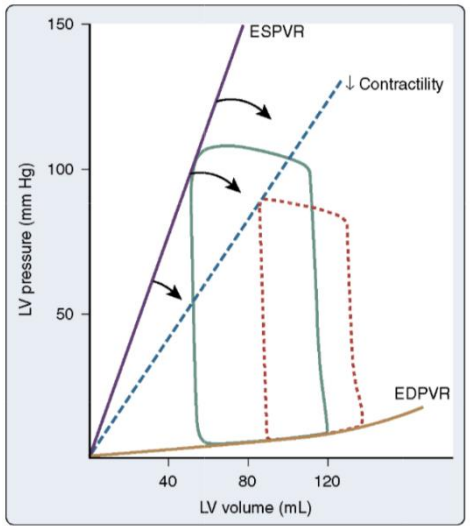
Cardiac efficiency = SW/PVA
Cardiac efficiency = SW/MVO_2

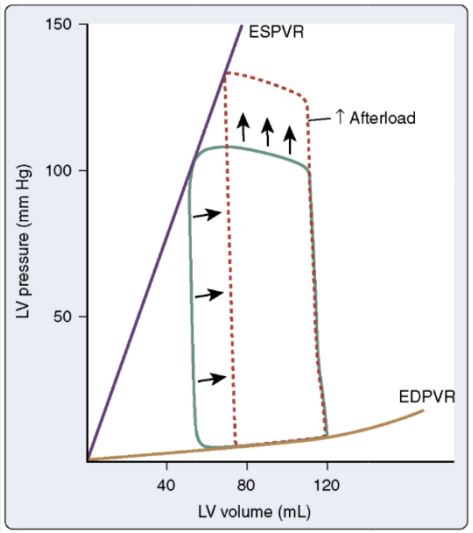
Cardiac efficiency

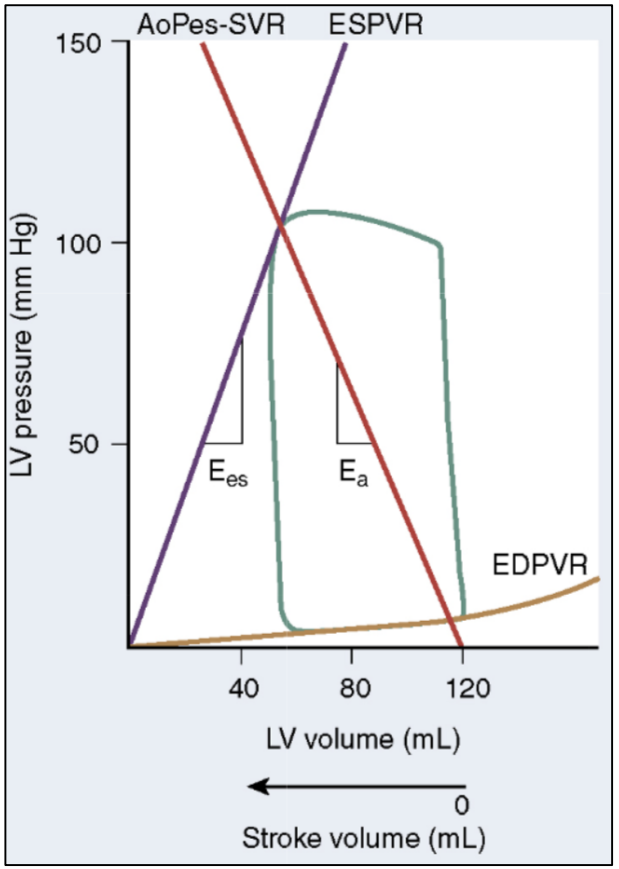
Coupling = transfer of kinetic energy / stroke work between two elastic chambers (LV and arterial circulation)

Coupling = LV elastance / arterial elastance

Ideal couling: Ees / Ea $\geq$ 1





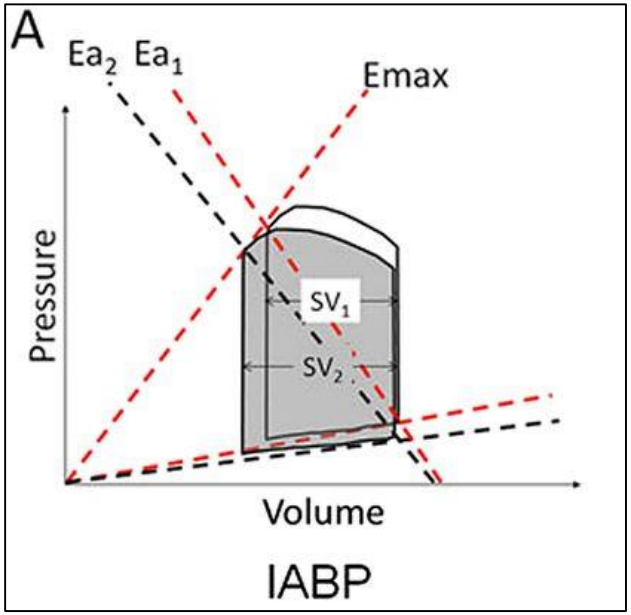


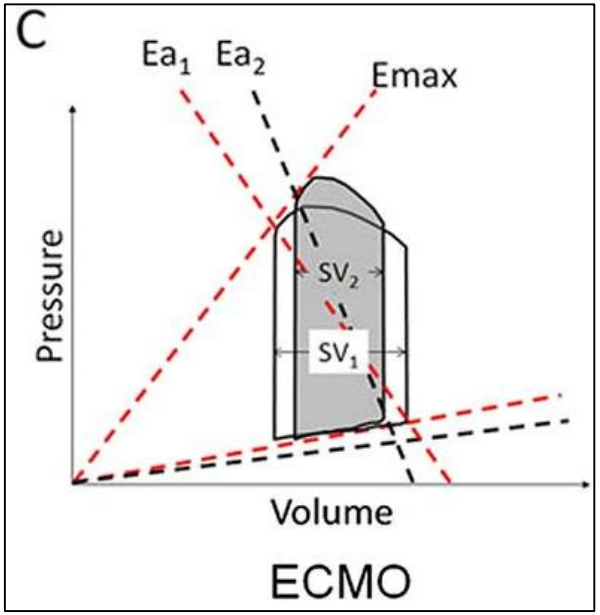
Cardiac efficiency

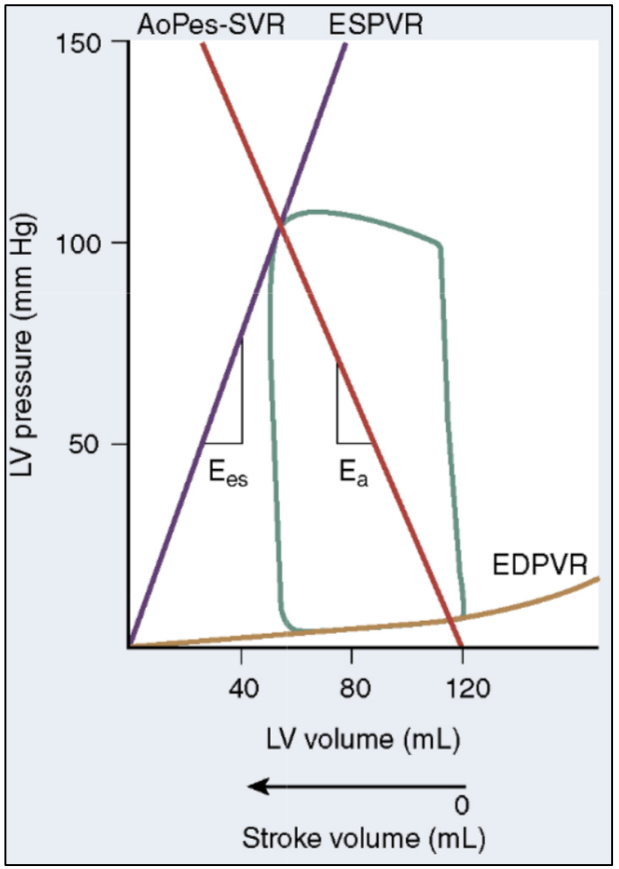
Coupling = transfer of kinetic energy / stroke work between two elastic chambers (LV and arterial circulation)

Coupling = LV elastance / arterial elastance

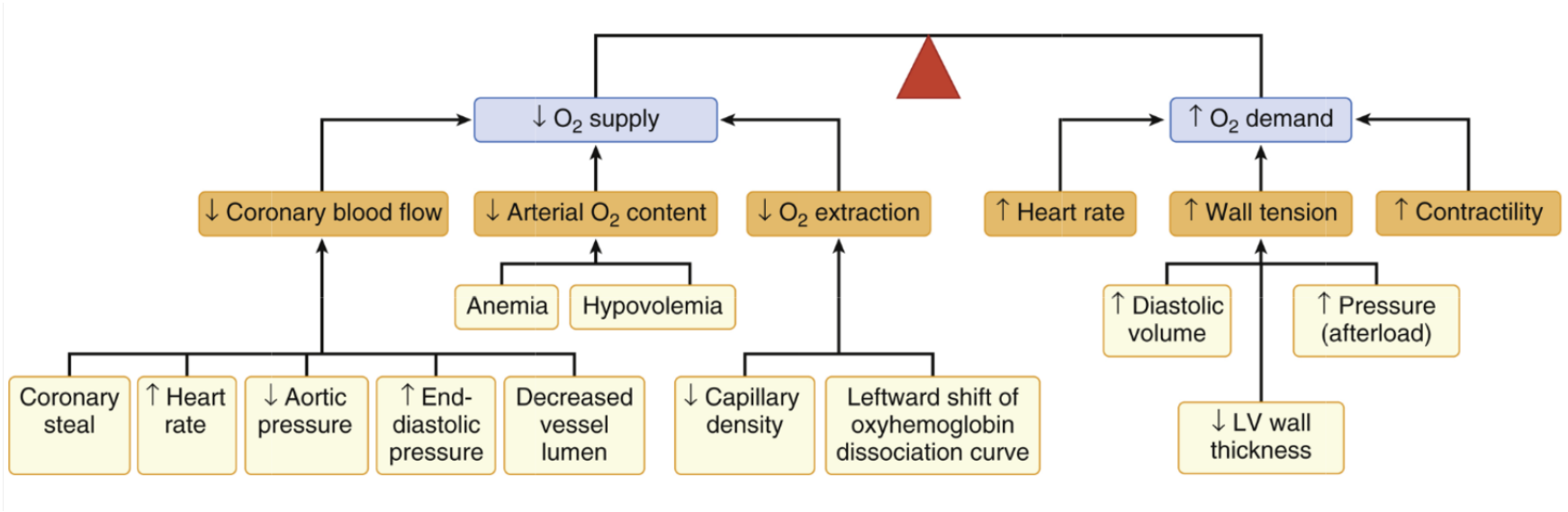
Ideal couling: Ees / Ea ≥ 1

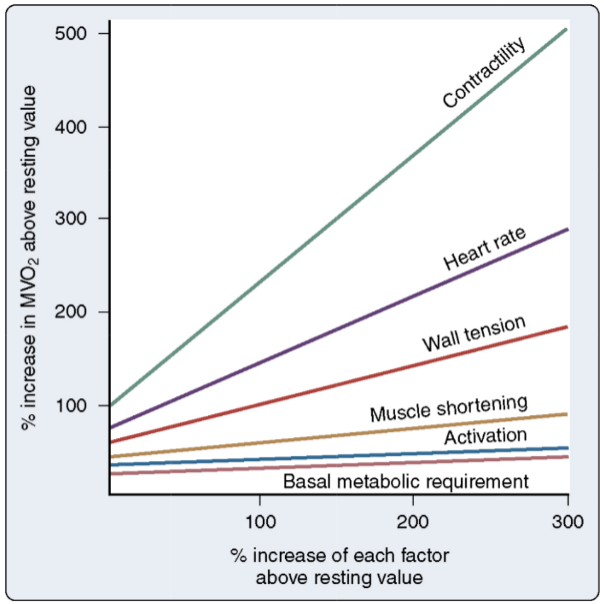






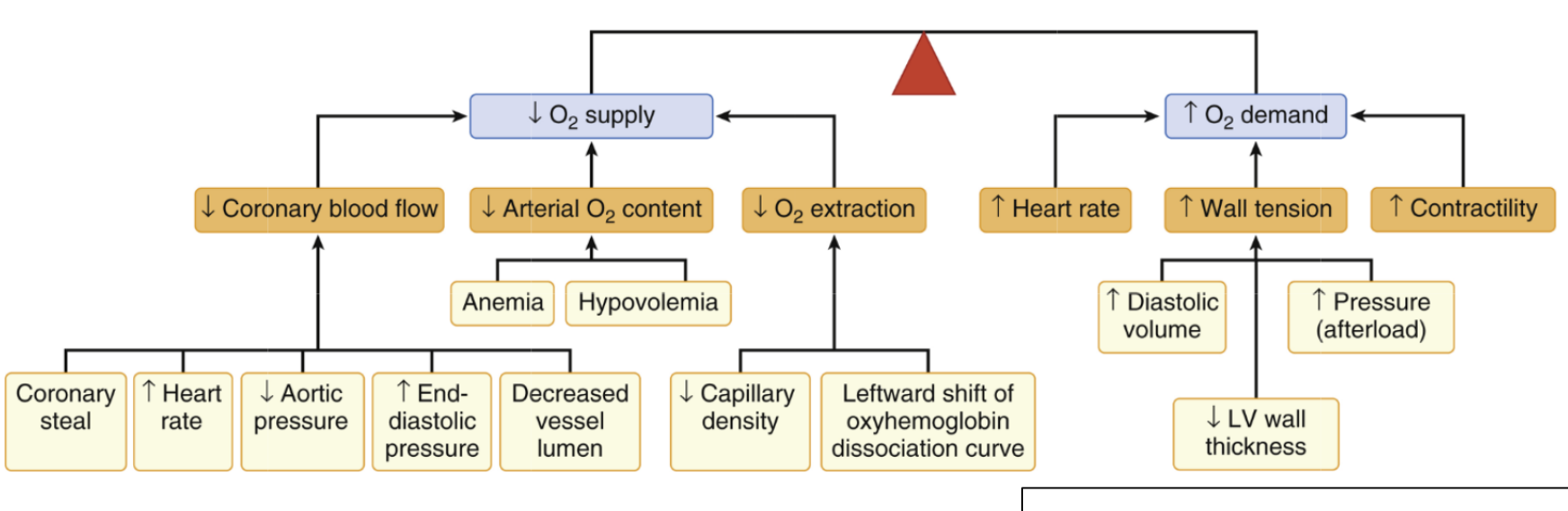
Myocardial Oxygen Supply and Demand



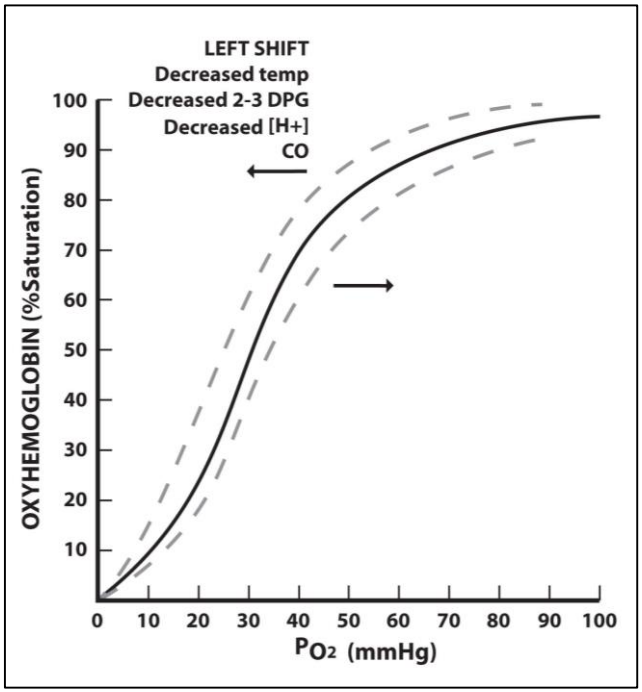


$$\text{Wall stress} = \frac{\text{Pressure radius}}{2\ (\text{Wall thickness})}$$

Myocardial Oxygen Supply and Demand

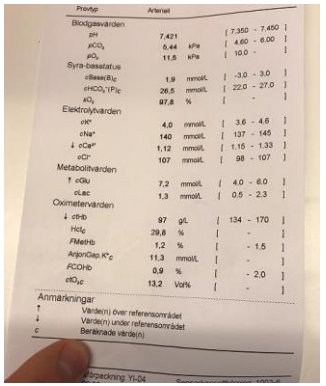


Bohr effect:
The affinity of hemoglobin for oxygen is reduced by a reduction in pH.



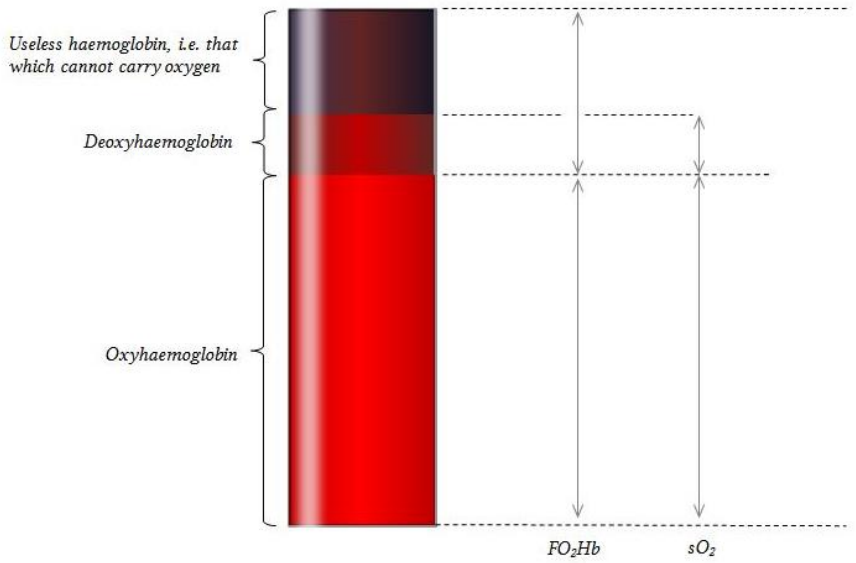
Oxygen Content (CaO_2)

$$CaO_2 = (1.39 \times Hb \times sO_2) + (0.23 \times pO_2)$$

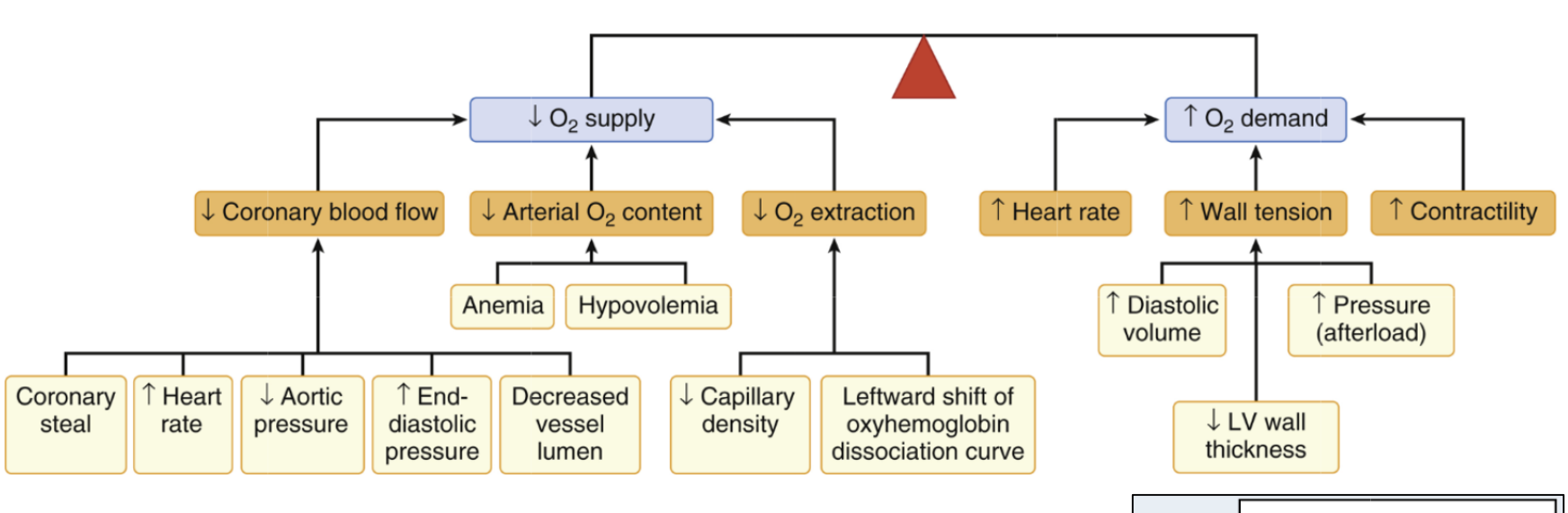


1 mol Hb: 64500 g
1 mol O_2: 22400 ml
89600 $ml O_2$ / 64500 gHb
1.39 $ml O_2$ / gHb

Functional saturation = sO_2
Fractional saturation = FO_2Hb

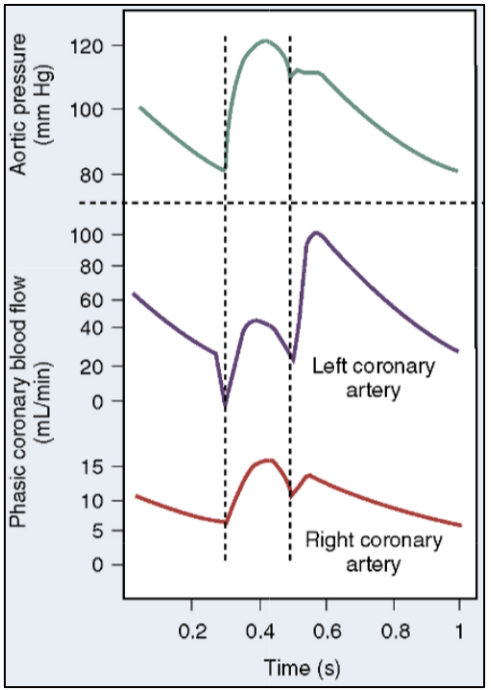


Myocardial Oxygen Supply and Demand



Coronary perfusion pressure (CPP)
= aortic diastolic pressure – LVEDP

	Heart Rate 75/min	Heart Rate 200/min
Duration, each cardiac cycle	0.80	0.30
Duration of systole	0.27	0.16
Duration of action potential	0.25	0.15
Duration of absolute refractory period	0.20	0.13
Duration of relative refractory period	0.05	0.02
Duration of diastole	0.53	0.14



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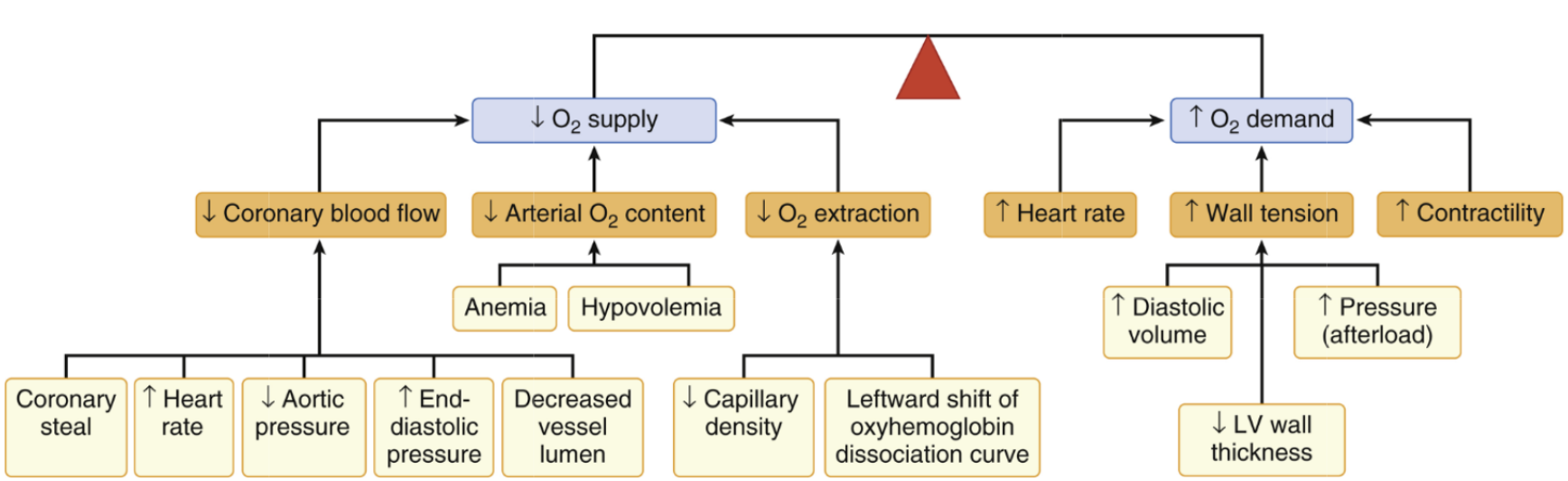
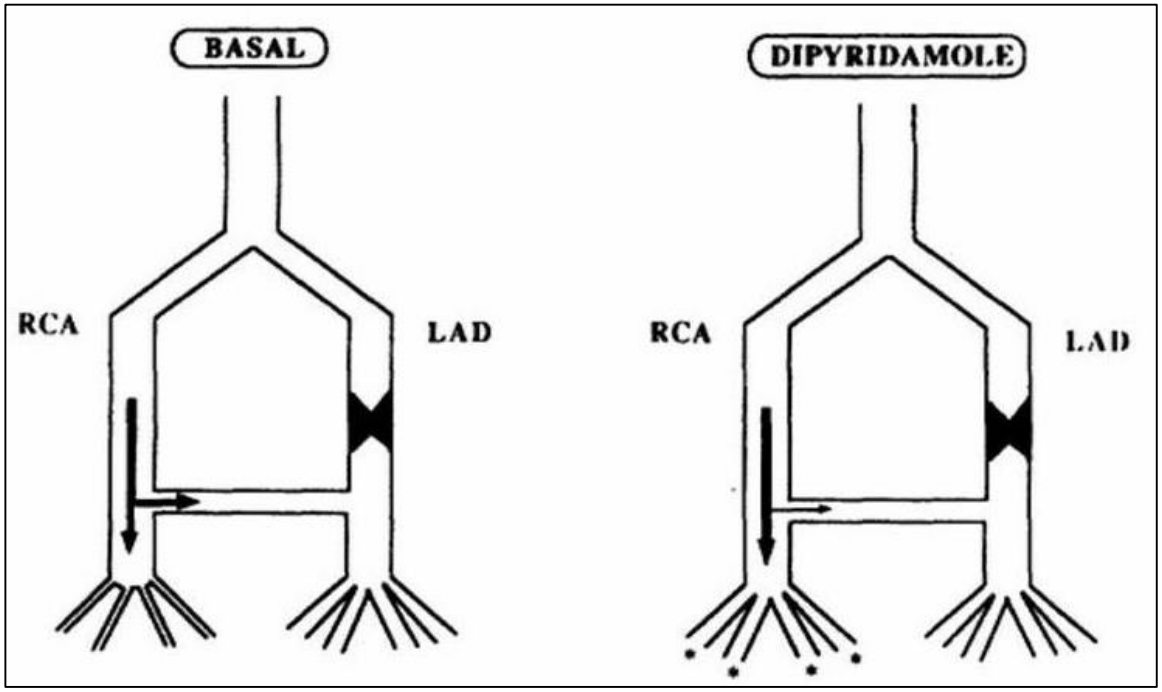




Ohm‘s Law

$U = R \times I$

CPP = coronary vascular resistance × coronary blood flow

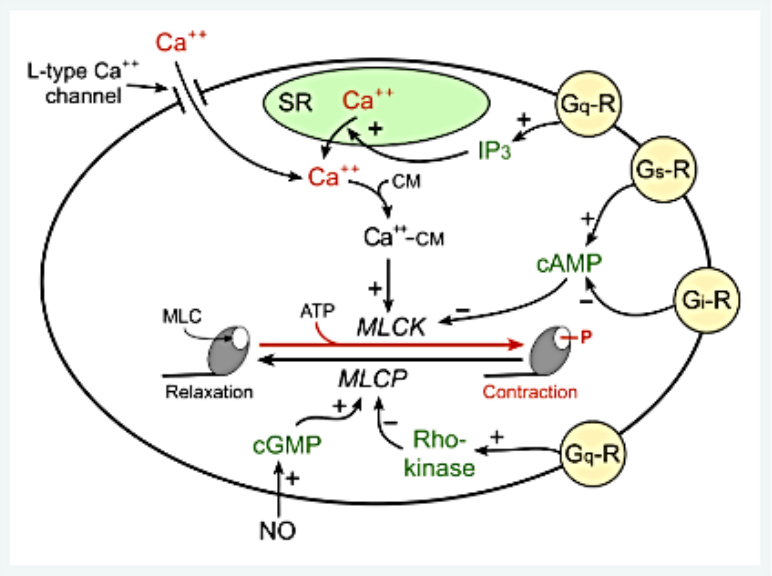
$$\frac{CPP}{CVR} = \text{CBF}$$

$MAP - CVP = SVR \times CO$

$$SVR = \left(\frac{MAP - CVP}{CO}\right) \times 80$$

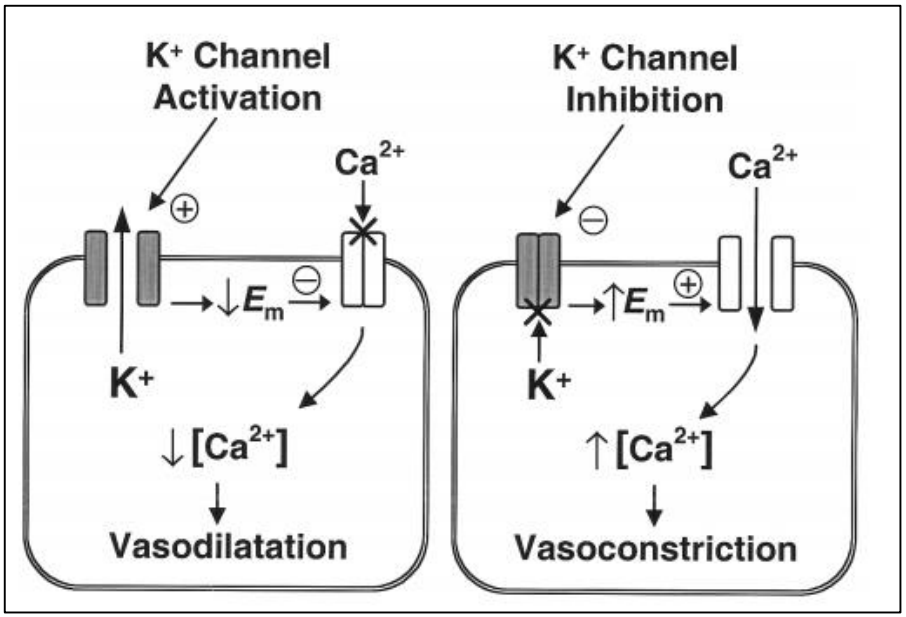
Normal range: 800 -1500 dyne·sec/cm^5

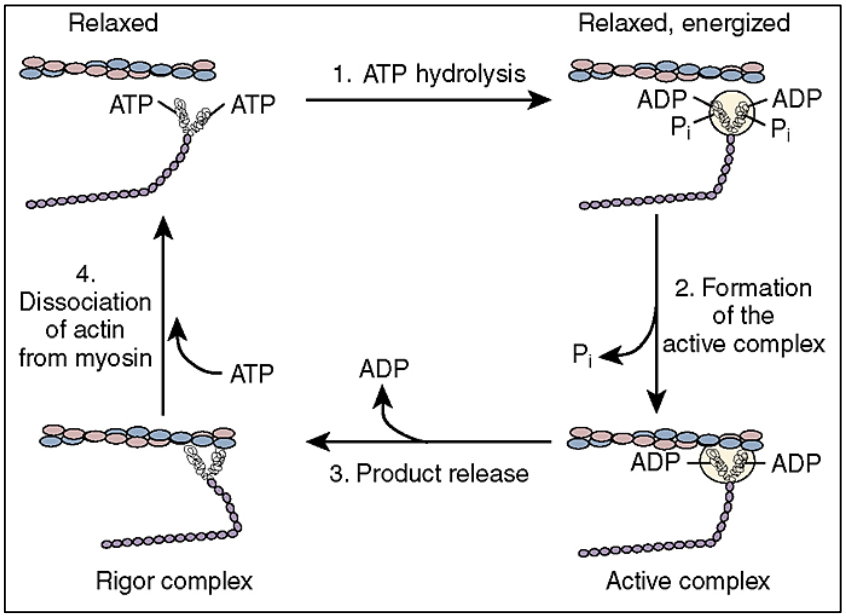
Systemic Vascular Resistance



G-protein Linked Vascular Receptors and their Biological Agonists

G-protein	2nd Messenger	Receptor	Biological Agonist
Gs	↑cAMP	β_2	Epinephrine
		A_2	Adenosine
		IP	Prostacyclin
Gi	↓cAMP	α_2	Norepinephrine/ Epinephrine
Gq	↑IP_3 & ↑Rho-kinase	α_1	Norepinephrine/ Epinephrine
		ET_A	Endothelin-1
		AT_1	Angiotensin II
		V_1	Vasopressin





Oxygen Delivery (DO_2)

$CaO_2 = (1.39 \times Hb \times sO_2) + (0.23 \times pO_2)$

$DO_2 = CO \times CaO_2$

$DO_2 = [SV \times HF] \times [(1.39 \times Hb \times sO_2) + (0.23 \times pO_2)]$

Hypoxia:

„The condition in which there is an insufficient supply of oxygen to the tissues to maintain normal cellular function. It may be generalized or regional.“

Classification of Hypoxia

$DO_2 = [SV \times HF] \times [(1.39 \times Hb \times sO_2) + (0.23 \times pO_2)]$

Hypoxemic hypoxia:
→ abnormal reduction in pO_2

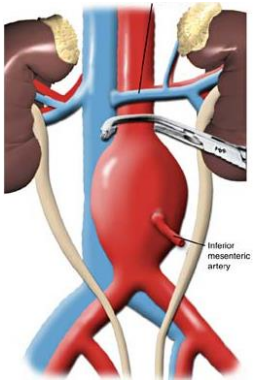
Anemic hypoxia:
→ failure of oxygen-carrying capacity of blood

Ischemic hypoxia:
→ failure of perfusion

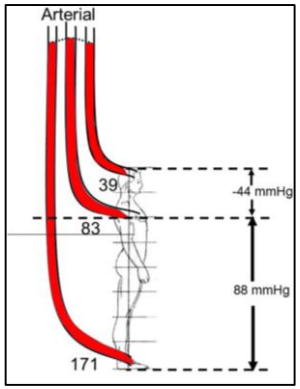
Histotoxic hypoxia:
→ failure of oxidative phosphorylation

Blood Pressure

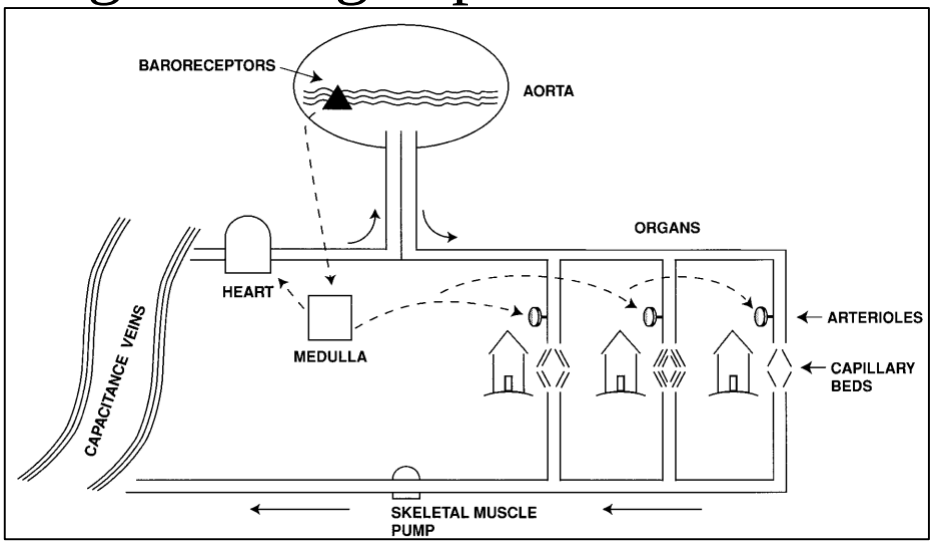
Blood pressure is a determinant but not an indicator of tissue perfusion



Autoregulation



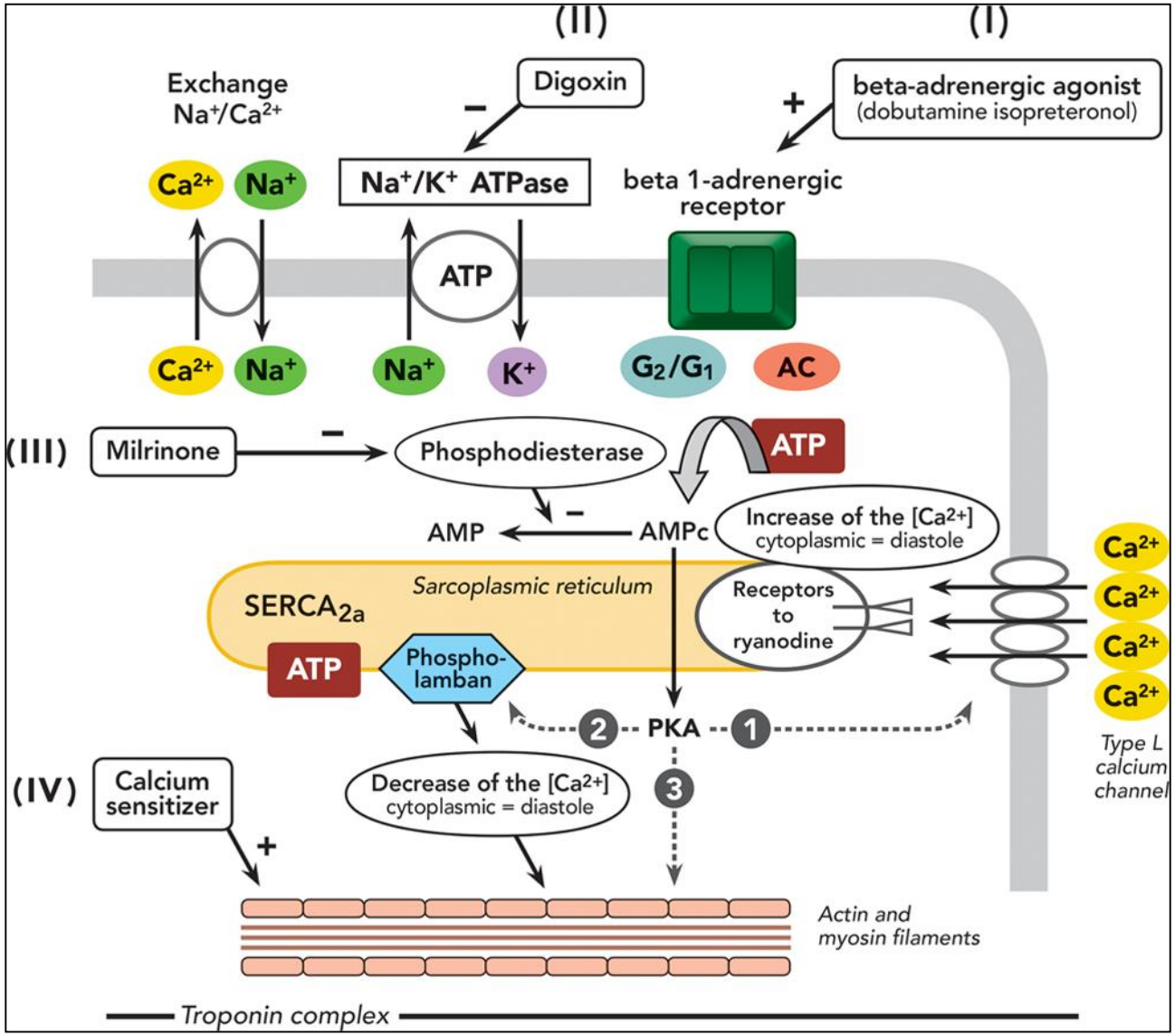
Regional organ perfusion – local resistance



Inotropic Drugs - Overview

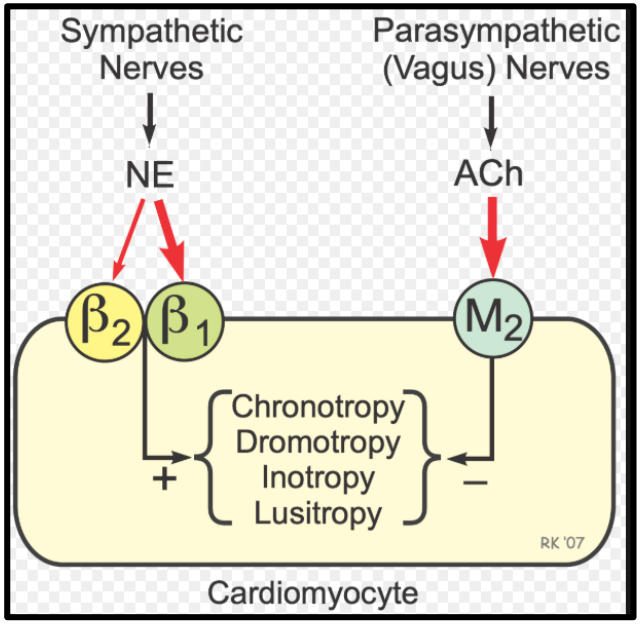
- Calcium
- Catecholamines:
  - Dopamine
  - Dobutamine
  - Adrenaline
  - Noradrenaline
  - Isoprenaline
  - Ephedrine
- Cardiac glycosides: Digoxin
- Posphodiesterase III inhibitors: Milrinone
- Calcium sensitizers: Levosimendan
- Cardiac myosin activators: Omecamtiv Mecarbil

Inotropic Drugs – Mechanism of Action



Adrenergic and Cholinergic Receptors

Organ	Sympathetic stimulation	Parasympathetic stimulation
Heart	↑ heart rate β_1 (and β_2) ↑ force of contraction β_1 (and β_2) ↓ conduction velocity	↓ heart rate ↓ force of contraction ↑ conduction velocity
Arteries	constriction (α_1) dilatation (β_2)	dilatation



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Arteries	constriction (α_1) dilatation (β_2)	dilatation

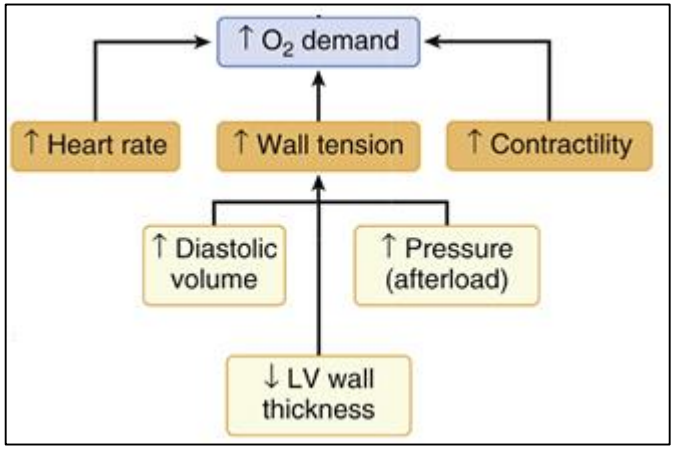
Inotropic Agent	α 1	β 1	β 2	DA- 1	SVR	CO	HR	BP
Epinephrine (Adrenaline)	++++	++++	+++		↑	↑	↑	↑
Norepinephrine (Noradrenaline)	+++	+++	+	zero	↑	+/-	↑	↑↑
Dobutamine	+	++++	++	zero	↓	↑	↑	+/-
Dopamine	++	++++	++	+++	↑	↑	↑	↑
Ephedrine	+	+++	++	zero	↑	↑	↑	↑
Phenylephrine	+++	zero	zero	zero	↑	+/-	+/-	↑
Isoprenaline	zero	++++	++++	zero	↓	↑	↑	↓
Levosimendan	-	-	-	-	↓	↑	↑	↓
Milrinone	-	-	-	↑	↓	↑	↑	↓
Vasopressin	-	-	-	-	↑	+/-	↓	↑↑

Potential Adverse Effects

Intracellular Ca^{2+} overload
→ arrythmias, coronary vasoconstriction, decreased myofilament sensitivity to Ca^{2+}

Hypotension
→ decreased coronary perfusion

Myocardial O_2 supply / demand imbalance



Dobutamine (Dobutrex, 1978)

Positive inotropic effect with weak vasodilating effect
Synthetic catecholamine: racemic mixture of two enantiomers
No effect on diastolic function (lusitropy)

Dosage: 2-10-15 μg/kg/min

Dose activity:
<3 μg/kg/min: usually no effect on BP or BP drop
5-10 μg/kg/min: β_1 effect, increased CO
>10 μg/kg/min: α_1 effect

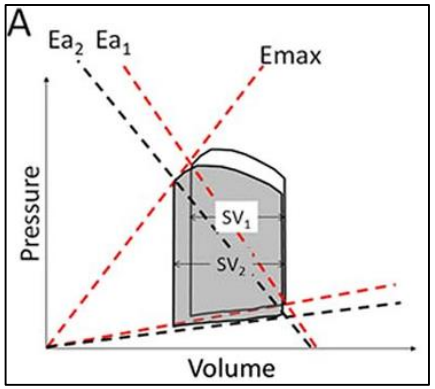
Adrenoceptors	(+) stereoisomer	(-) stereoisomer	Racemate
Alpha-1	High affinity but no agonist activity; thus this stereoisomer acts as a *competitive alpha-antagonist*	High affinity and potent partial agonist activity; thus this stereoisomer acts as a partial agonist	The net result is moderate partial agonist activity

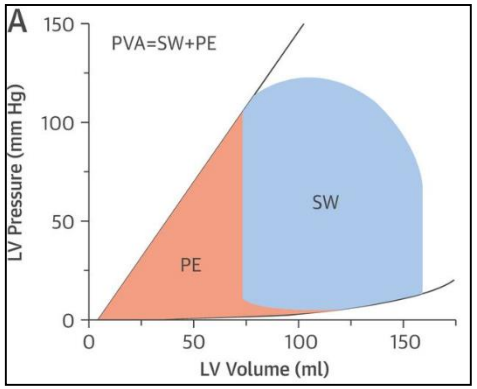
Milrinone (Corotrop, 1987)

Positive inotropic and vasodilating effect → inodilator:
→ decreased afterload → unloading the left ventricle →
→ decreased LVEDV → decreased wall stress
→ no increase in MVO_2
→ increased cardiac efficiency (SW/PVA)

$$\text{Wall stress} = \frac{\text{Pressure radius}}{2\ (\text{Wall thickness})}$$

Little chronotropic effect
Positive lusitropic effect
Pulmonary vasodilation





Dosage:
Loading 50 μg/kg over 10 minutes, maintenance 0.375-0.75 μg/kg/min.
Hemodynamic improvement within 5-15 minutes. Half-life 2-3 hours.

Dosage activity:
<0.375 μg/kg/min: usually moderate effect on circulation
0.5-0.75 μg/kg/min: increased CO

Applied Physiology

American Physiological Society | Journal of Applied Physiology

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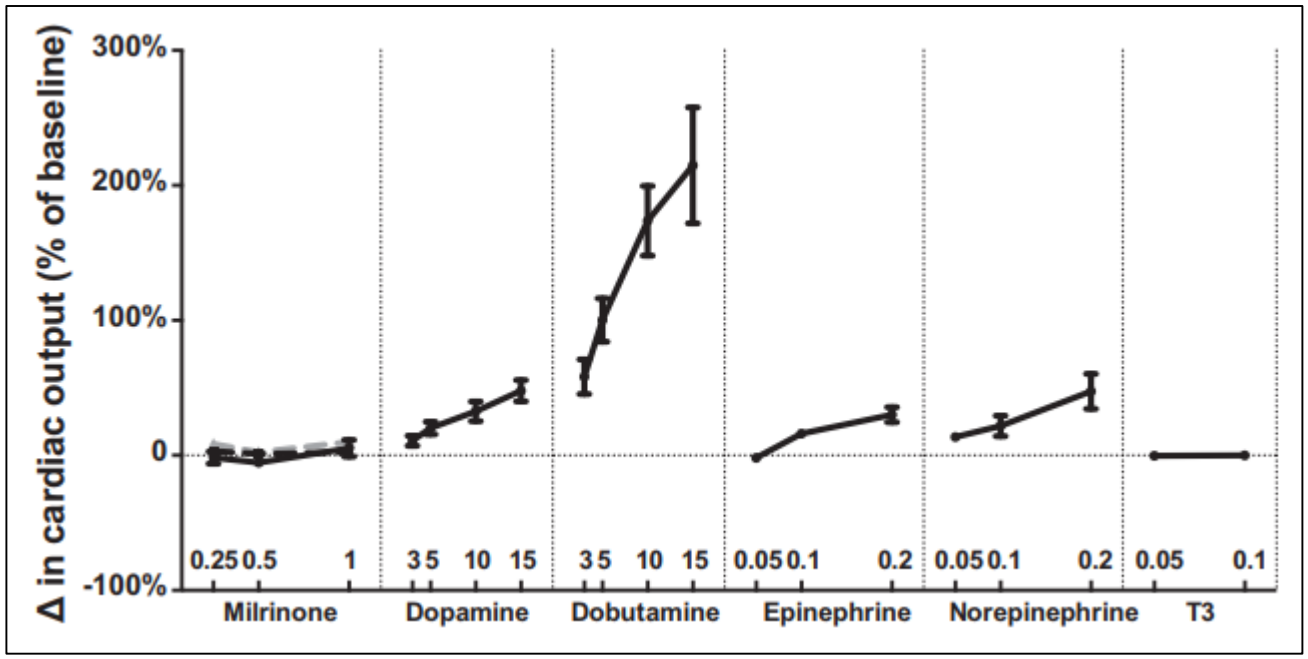
J Appl Physiol (1985). 2016 Jul 1; 121(1): 7–14.
Published online 2016 May 5. doi: 10.1152/japplphysiol.00058.2016

PMCID: PMC5504386
PMID: 27150829

Effects of commonly used inotropes on myocardial function and oxygen consumption under constant ventricular loading conditions

Elizabeth S. DeWitt,[1,*] Katherine J. Black,[1,*] Ravi R. Thiagarajan,[1] James A. DiNardo,[2] Steven D. Colan,[1] Francis X. McGowan,[3] and John N. Kheir[1]

Isolated working rodent hearts under constant ventricular loading conditions (constant left atrial pressure and aortic blood pressure)



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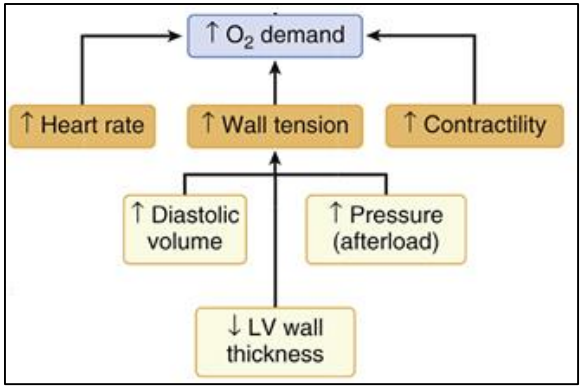
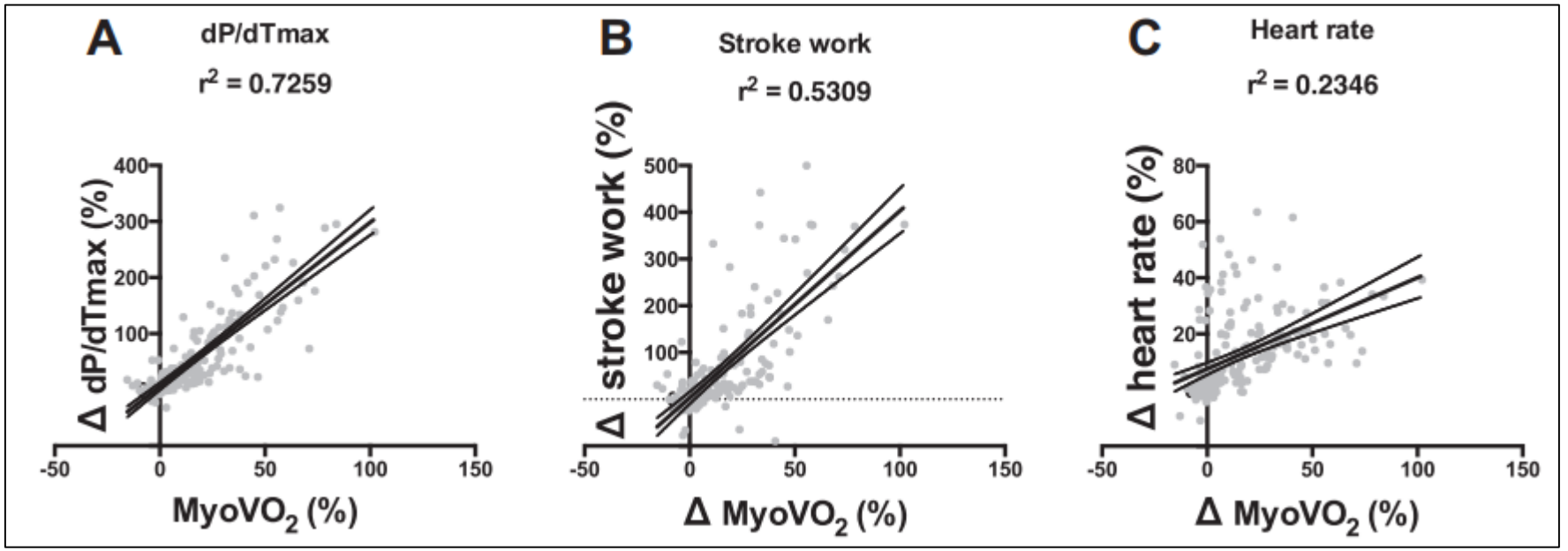


"Thus our data support the notion that milrinone's effects may be primarily or even exclusively that of arterial and venodilation, thus lowering myocardial afterload and enhancing performance."



Levosimendan (Simdax, 2000)

Positive inotropic and vasodilating effect → inodilator

Same effect on myocardial function as Milrinone
No increased intracellular cAMP / Ca^{2+} concentrations

Opening of ATP-sensitive K^+ channels in vascular smooth muscle
→ vasodilation
Opening of ATP-sensitive K^+ channels (mitochondrial) in cardiomyocytes
→ cardioprotective effect

Dosage:
Loading 6-12 µg/kg/min for 10 minutes, maintenance 0.05-0.2 µg/kg/min for 24 hours. Hemodynamic improvement within 5-10 minutes. Long lasting effect for several days due to active metabolites.

Dosage activity:
0.05-0.2 µg/kg/min: usually moderate effect on BP, BP drop

LEVO-CTS Trial (03/2017)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

CONCLUSIONS

Prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass. (Funded by Tenax Therapeutics; LEVO-CTS ClinicalTrials.gov number, NCT02025621.)

CHEETAH Trial (03/2017)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

CONCLUSIONS

In patients who required perioperative hemodynamic support after cardiac surgery, low-dose levosimendan in addition to standard care did not result in lower 30-day mortality than placebo. (Funded by the Italian Ministry of Health; CHEETAH ClinicalTrials.gov number, NCT00994825.)

Omecamtiv Mecarbil

Cardiac myosin activator:

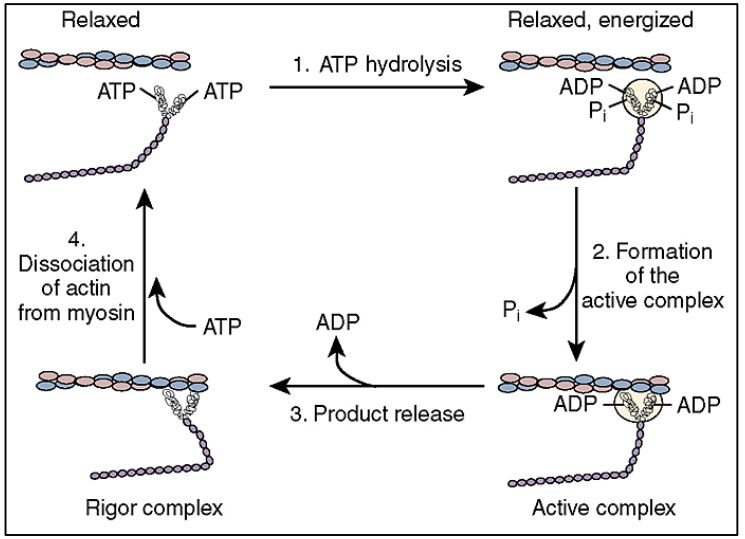
Augments the speed of ATP hydrolysis with consequent Pi release

Total number of myosin heads bound to actin filaments increases

“More hands pulling on the rope”

→ prolongs ejection time
→ increases stroke volume
→ no increase in intracellular cAMP
→ no increase in MVO_2

Galatic-HF: phase III trial, 8000 patients, 800 sites, 2017



Guidelines

Scandinavian SSAI clinical practice guideline on choice of inotropic agent for patients with acute circulatory failure

M. H. Møller[1], A. Granholm[1], E. Junttila[2], M. Haney[3], A. Oscarsson-Tibblin[4], A. Haavind[5], J. H. Laake[6], E. Wilkman[7], K. Ö. Sverrisson[8] and A. Perner[1]

[1]Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[2]Department of Anaesthesiology, Tampere University Hospital, Tampere, Finland
[3]Anaesthesiology and Intensive Care Medicine, Umeå University, Umeå, Sweden
[4]Department of Anaesthesiology and Intensive Care, Department of Medicine and Health, Linköping University, Linköping, Sweden
[5]Department of Anaesthesiology and Intensive Care, University Hospital Northern Norway, Tromsø, Norway
[6]Division of Critical Care, Oslo University Hospital, Oslo, Norway
[7]Division of Intensive Care Medicine, Department of Perioperative, Intensive Care and Pain Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[8]Department of Anesthesia & Critical Care, Landspitali University Hospital of Iceland, Reykjavik, Iceland

Guidelines

Correspondence
M. H. Møller, Department of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, DK - 2100 Copenhagen, Denmark
E-mail: mortenhylander@gmail.com

Conflict of interest
The authors declare no relevant conflicts of interest.

Funding
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Submitted 28 December 2017; accepted 3 January 2018; submission 24 November 2017.

Citation
Møller MH, Granholm A, Junttila E, Haney M, Oscarsson-Tibblin A, Haavind A, Laake JH, Wilkman E, Örn Sverrisson K, Perner A. Scandinavian SSAI clinical practice guideline on choice of inotropic agent for patients with acute circulatory failure. Acta Anaesthesiologica Scandinavica 2018

doi: 10.1111/aas.13089

Background: Adult critically ill patients often suffer from acute circulatory failure and those with low cardiac output may be treated with inotropic agents. The aim of this Scandinavian Society of Anaesthesiology and Intensive Care Medicine guideline was to present patient-important treatment recommendations on this topic.
Methods: This guideline was developed according to GRADE. We assessed the following subpopulations of patients with shock: (1) shock in general, (2) septic shock, (3) cardiogenic shock, (4) hypovolemic shock, (5) shock after cardiac surgery, and (6) other types of shock, including vasodilatory shock. We assessed patient-important outcome measures, including mortality and serious adverse reactions.
Results: For all patients, we suggest against the routine use of any inotropic agent, including dobutamine, as compared to placebo/no treatment (very low quality of evidence). For patients with shock in general, and in those with septic and other types of shock, we suggest using dobutamine rather than levosimendan or epinephrine (very low quality of evidence). For patients with cardiogenic shock and in those with shock after cardiac surgery, we suggest using dobutamine rather than milrinone (very low quality of evidence). For the other clinical questions, we refrained from giving any recommendations or suggestions.
Conclusions: We suggest against the routine use of any inotropic agent in adult patients with shock. If used, we suggest using dobutamine rather than other inotropic agents for the majority of patients, however, the quality of evidence was very low, implying high uncertainty on the balance between the benefits and harms of inotropic agents.

LeoPARDS Trial (10/2016)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

A.C. Gordon, G.D. Perkins, M. Singer, D.F. McAuley, R.M.L. Orme, S. Santhakumaran, A.J. Mason, M. Cross, F. Al-Beidh, J. Best-Lane, D. Brealey, C.L. Nutt, J.J. McNamee, H. Reschreiter, A. Breen, K.D. Liu, and D. Ashby

CONCLUSIONS

The addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality. Levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrhythmia. (Funded by the NIHR Efficacy and Mechanism Evaluation Programme and others; LeoPARDS Current Controlled Trials number, ISRCTN12776039.)

LeoPARDS Trial (10/2016)

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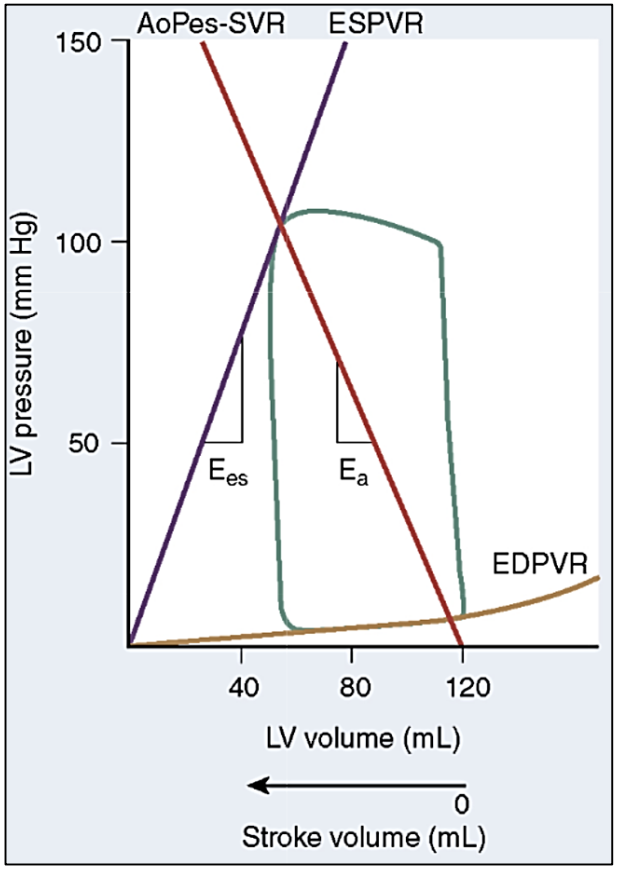
Treatment group:

→ higher HR but same CI

→ higher percentage of patients on norepinephrine on higher doses

→ increased effective arterial elastance due to increased SVR

→ increased ESV → decreased SV



Key messages part I:

Sarcomere
Laplace‘s law
Definitions preload, afterload, contractility
Myocardial oxygen supply and demand
Ohm‘s law
Hypoxia

Key messages part II:

Inotropes:
→Different mechanisms of action
→Afterload reduction as a major component in inodilators
→Conflicting results in studies