FISIOPATOLOGIA GENERALE

fisiopatologia cardiovascolare

1. regolazione della funzione cardiaca e introduzione
3. patologia ischemica e infarto miocardico
2. ipertrofia cardiaca e insufficienza cardiaca
4. disturbi dell'apparato valvolare
5. disturbi del ritmo

alterazioni idro-elettrolitiche

6. edemi
7. squilibrio elettrolitico: alterazione di sodio e potassio
8. squilibrio elettrolitico: alterazione di calcio e fosfato

fisiopatologia del rene

9. patologia renale: glomerulo e tubulopatie
10. patologia renale: insufficienza renale acuta
11. patologia renale: insufficienza renale cronica

fisiopatologia dell’apparato respiratorio

12. insufficienza respiratoria
13. patologia respiratoria: insufficienza respiratoria
14. patologie respiratorie ostruttive: asma, bpco

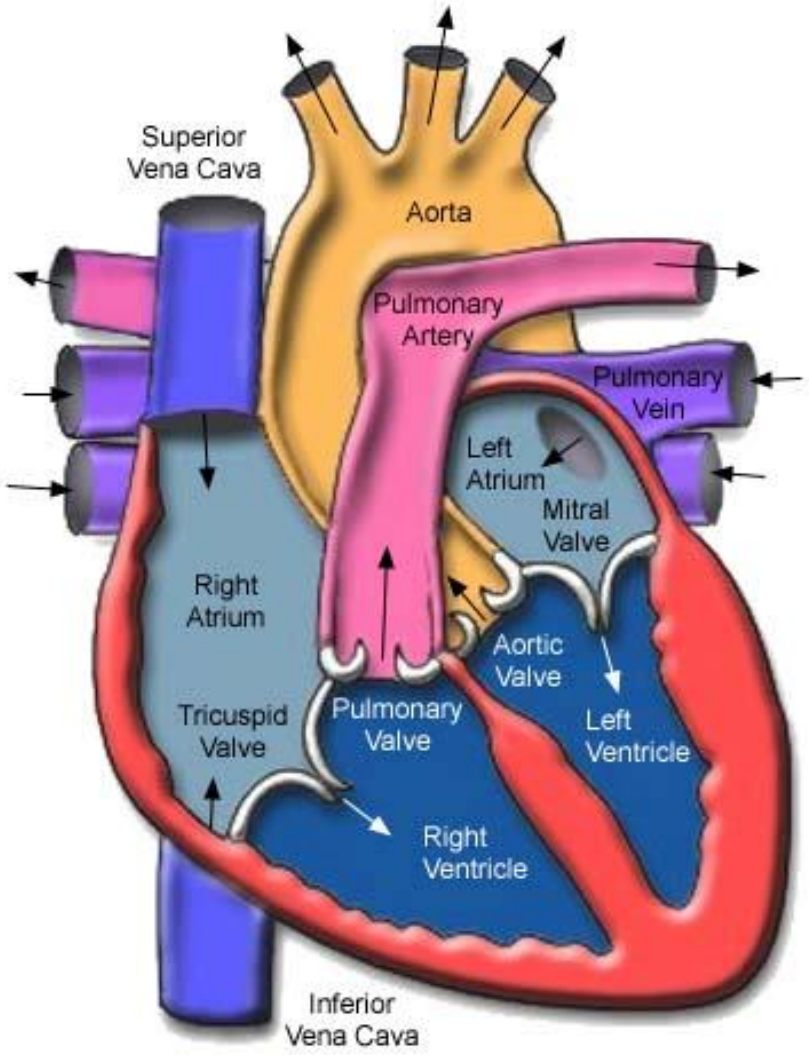
alterazioni dell’equilibrio acido-base

15. alcalosi e acidosi respiratoria
16. alcalosi e acidosi metabolica

fisiopatologia cardiovascolare

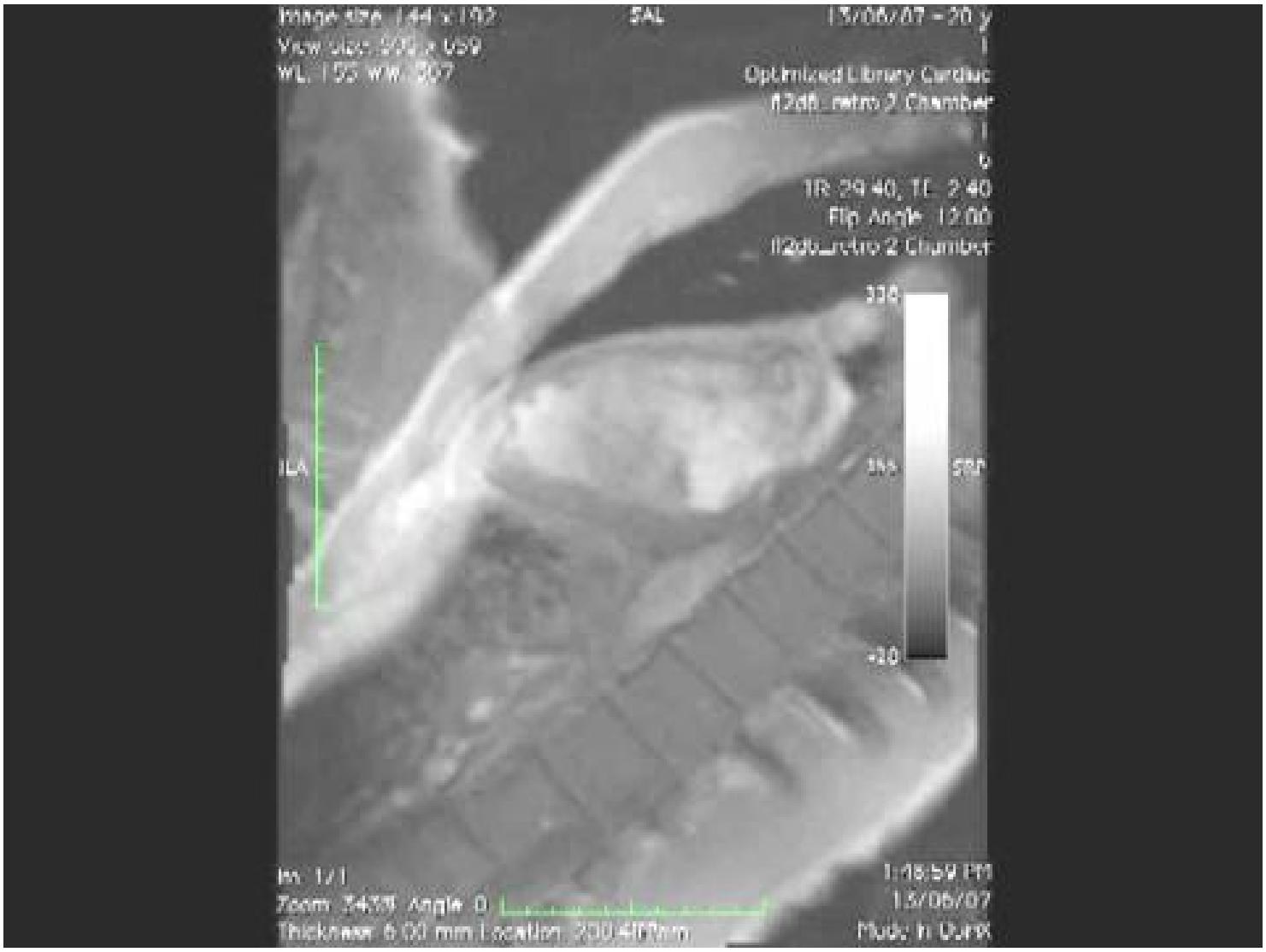
1. regolazione della funzione cardiaca e introduzione alla patologia cardiovascolare
2. insufficienza cardiaca
3. patologia ischemica e infarto miocardico
4. ipertrofia cardiaca e disturbi dell'apparato valvolare
5. disturbi del ritmo

The Cardiac Pump



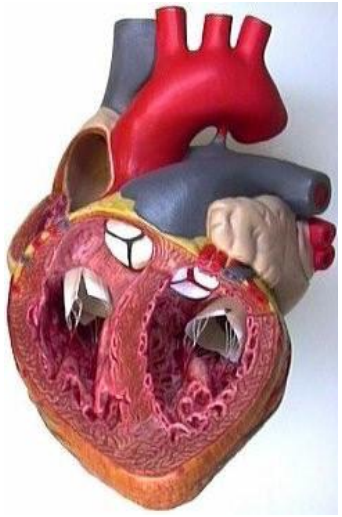
- 100,000 beats / day
- 7,500 L blood / day
- Cardiac output: 5 L at rest
- Left atrium: assist LV filling
- Left ventricle: systemic work
- Right atrium: assist RV filling
- Powers transport of nutrients, O_2, CO_2, waste and hormones, regulates metabolism.

anatomia funzionale della contrazione cardiaca

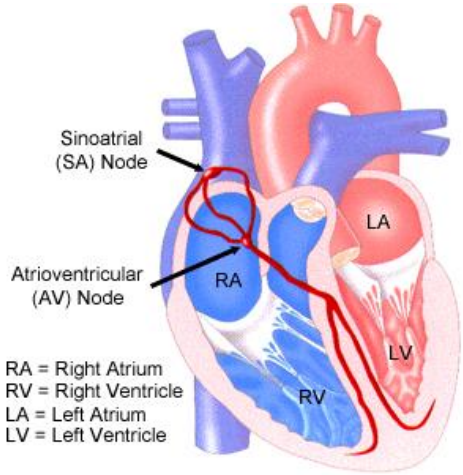


risonanza magnetica cardiovascolare

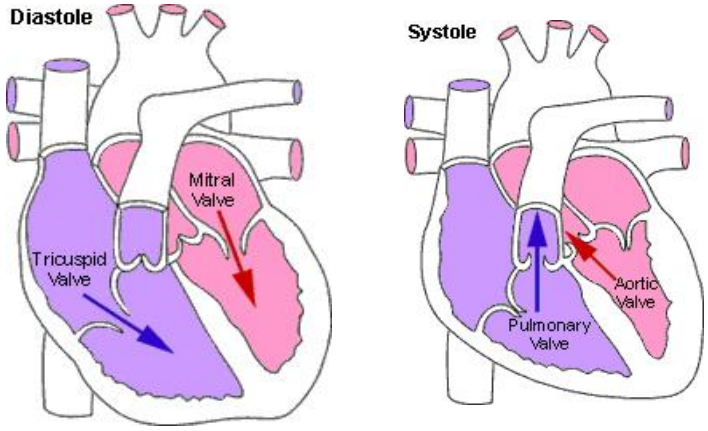
IL CUORE COME MOTORE MECCANICO



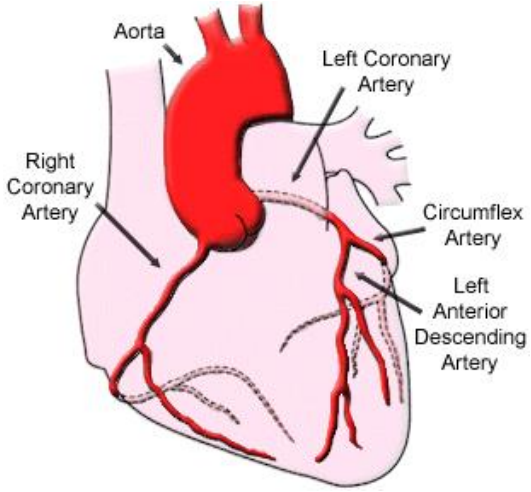
miocardio contrattile



sistema di conduzione

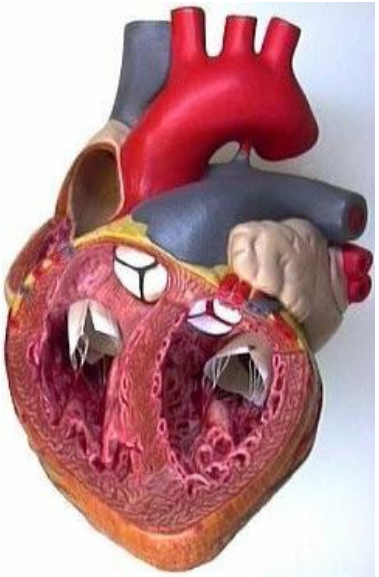


apparato valvolare



vasi coronarici

perché sia manenuta la funzione contrattile del miocardio di lavoro è necessaria l'integrità strutturale e funzionale del cardiomiocita:



apparato contrattile del cardiomiocita

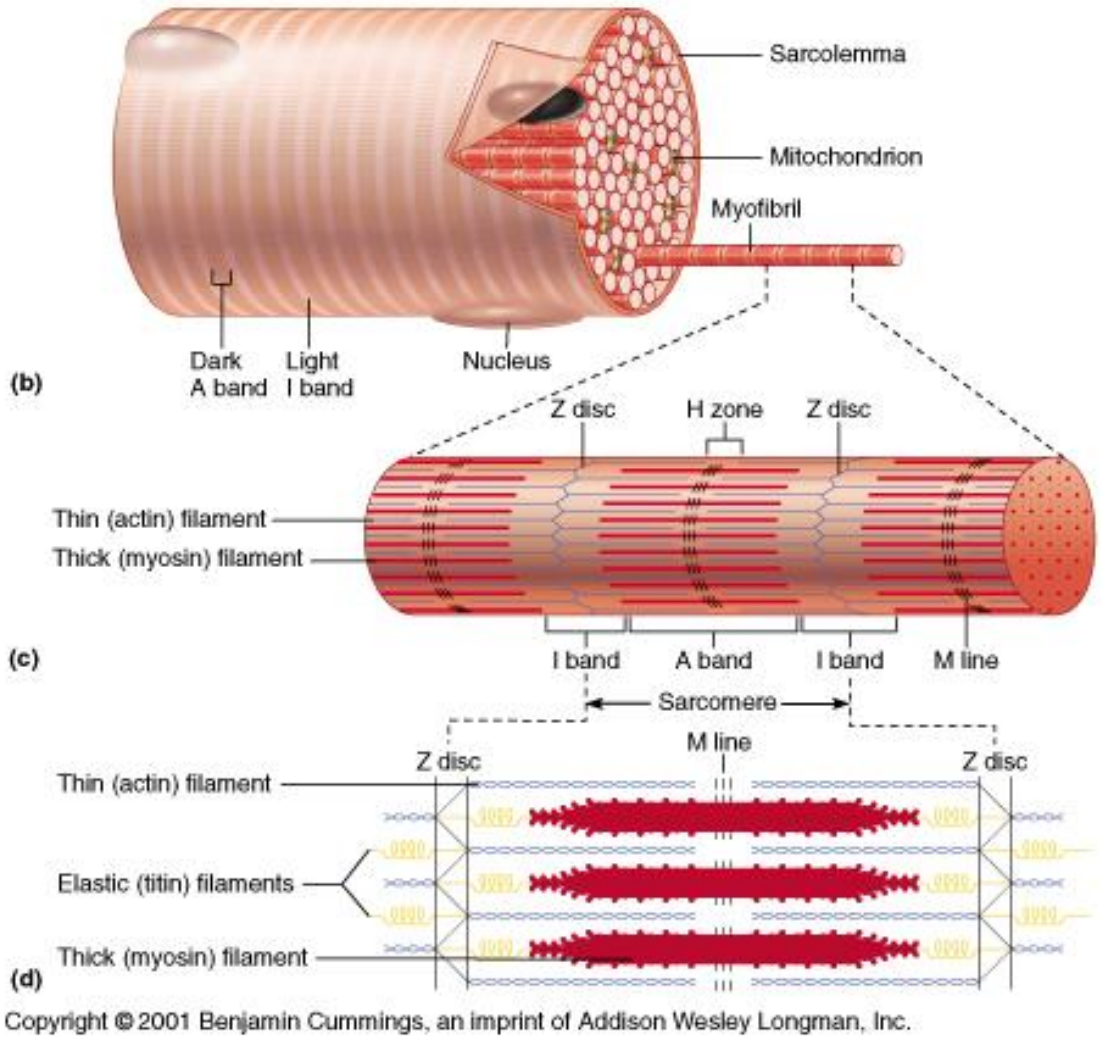
citoscheletro

segnali intracellulari che regolano l'attivazione della contrazione

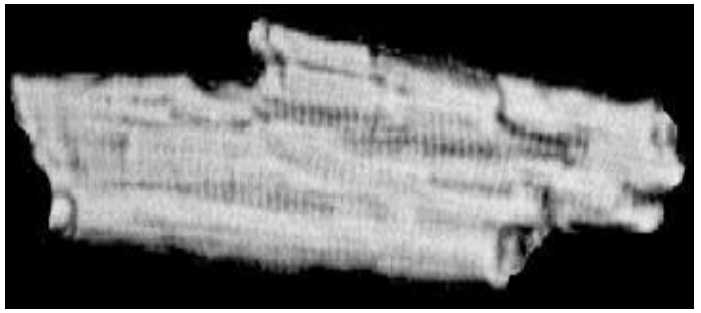
alterazioni congenite (primitive)

alterazioni acquisite (secondarie)

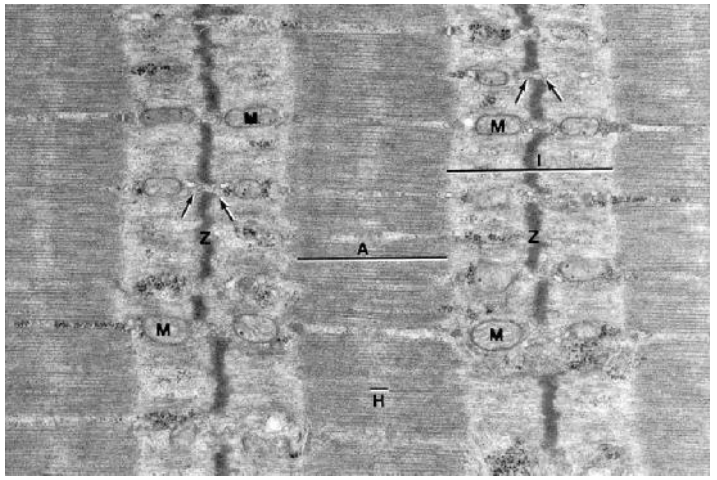
apparato contrattile del cuore: fibre muscolari e sarcomeri



singolo cardiomiocita isolato

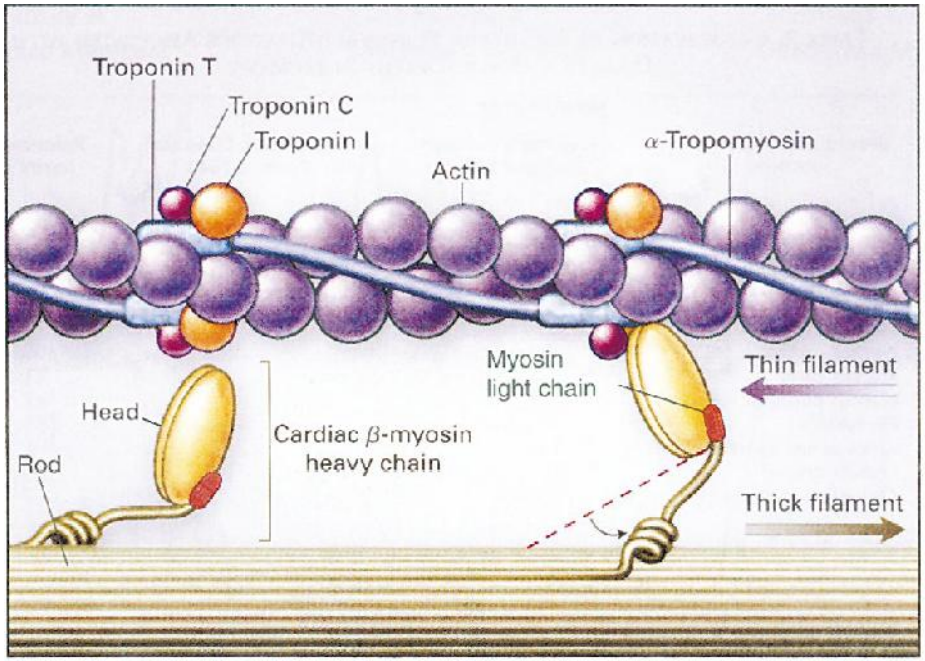


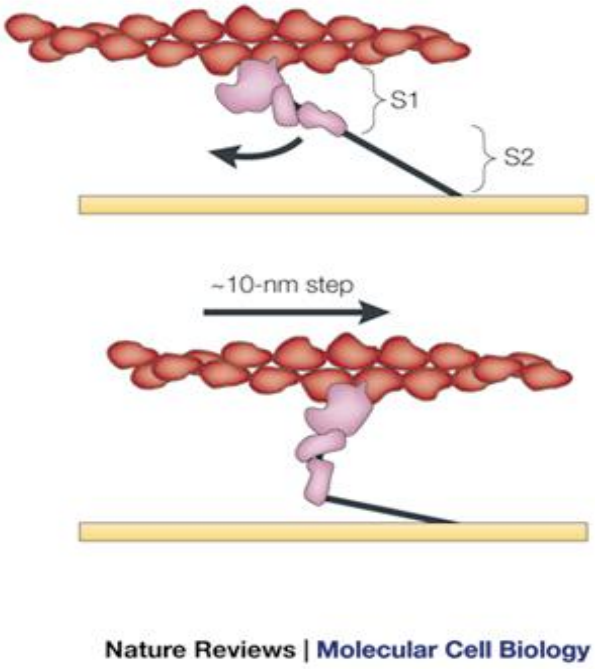
microfotografia al m. elettronico



la lunghezza dei filamenti sottili e dei filamenti spessi rimane costante durante l'accorciamento del sarcomero

lo scivolamento dei miofilamenti e' il motore molecolare della contrazione cardiaca



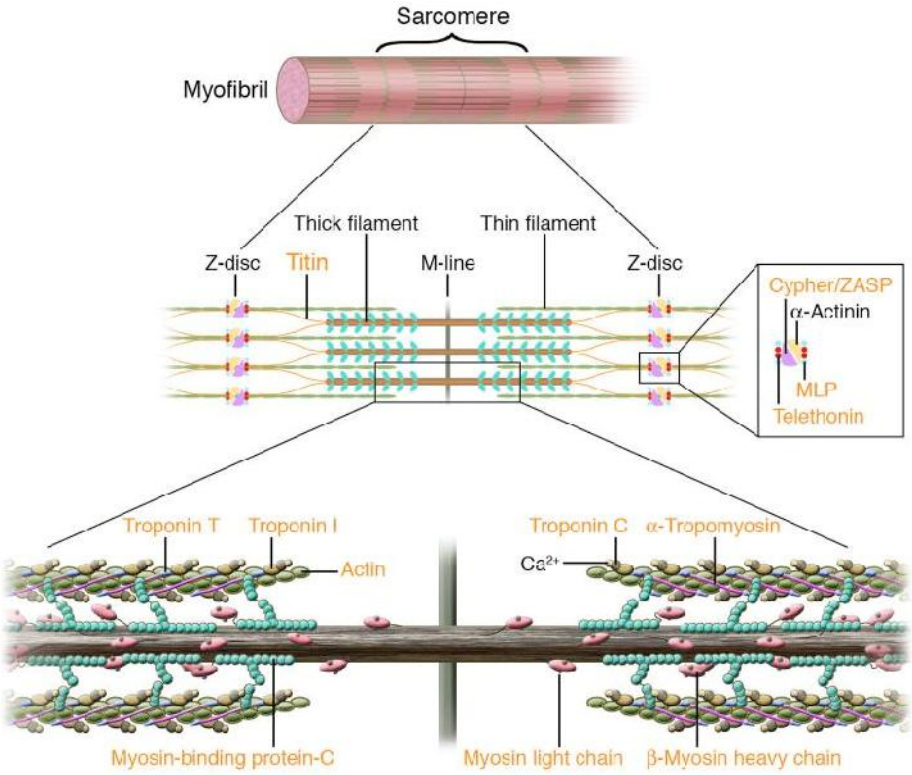


<u>miosina</u>: forma i filamenti spessi, ogni filamento contiene circa 300 molecole di miosina. le teste globulari hanno attivita' ATPasica ed interagiscono con l'actina. L'interazione induce il cambiamento conformazionale della testa della miosina, che fa compiere un 'passo' di 10 nm ai miofilamenti.
<u>actina:</u> forma lo scheletro dei filamenti sottili. non ha attivita' enzimatica.
<u>complesso troponina/tropomiosina</u>: in assenza di Ca2+, inibisce il legame di actina e miosina.

alterazioni dell'apparato contrattile sono causa di cardiomiopatie (congenite o acquisite)

ALTERAZIONI CONGENITE

-miosina
-M-bp C
-Actin
-Troponin I
-Tropomiosina



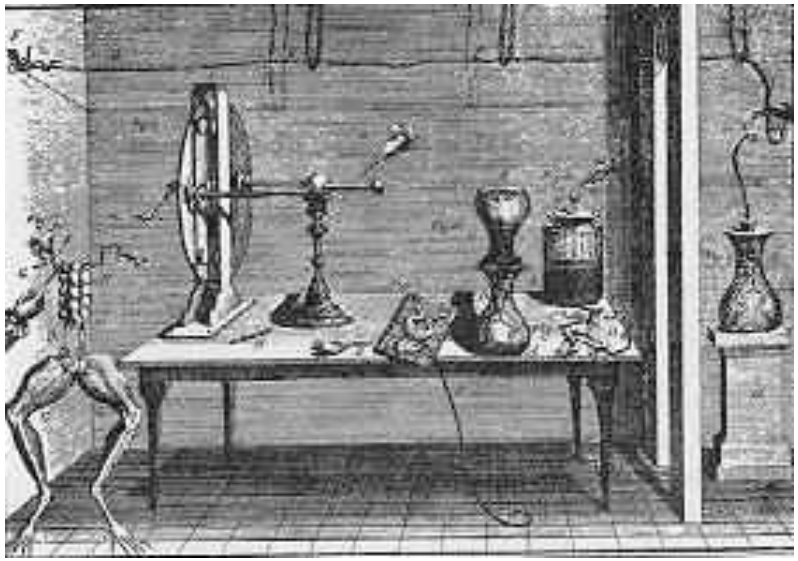
DISFUNZIONI ACQUISITE

-miosina
-troponina I
-troponina C

causa genetica di cardiomiopatie primitive (soprattutto cardiomiopatie ipertrofiche)

in ipertrofia cardiaca, insufficienza cardiaca

L’accoppiamento eccitazione-contrazione: una storia di furtunate intuizioni.



Luigi Galvani (1737-1798)

Dissecai una rana, la preparai e la collocai sopra una tavola sulla quale c'era una macchina elettrica … mentre uno dei miei assistenti toccava per caso leggermente con la punta di uno scalpello i nervi crurali di questa rana, a un tratto furono visti contrarsi tutti i muscoli degli arti come se fossero stati presi dalle più veementi convulsioni tossiche ... Ammirato dalle novità della cosa, subito avvertì me che ero completamente assorto e meco stesso d'altre cose ragionavo. Mi accese subito un incredibile desiderio di ripetere l'esperienza e di portare in luce ciò che di occulto c'era ancora nel fenomeno.

A FURTHER CONTRIBUTION REGARDING THE INFLUENCE OF THE DIFFERENT CONSTITUENTS OF THE BLOOD ON THE CONTRACTION OF THE HEART.

By SYDNEY RINGER, M.D., *Professor of Medicine at University College, London.* (Plate I.)

After the publication of a paper in the Journal of Physiology, Vol. III., No. 5, entitled "Concerning the influence exerted by each of the Constituents of the Blood on the Contraction of the Ventricle," I discovered, that the saline solution which I had used had not been prepared with distilled water, but with pipe water supplied by the New River Water Company. As this water contains minute traces of various inorganic substances, I at once tested the action of saline solution made with distilled water and I found that I did not get the effects described in the paper referred to. It is obvious therefore that the effects I had obtained are due to some of the inorganic constituents of the pipe water.

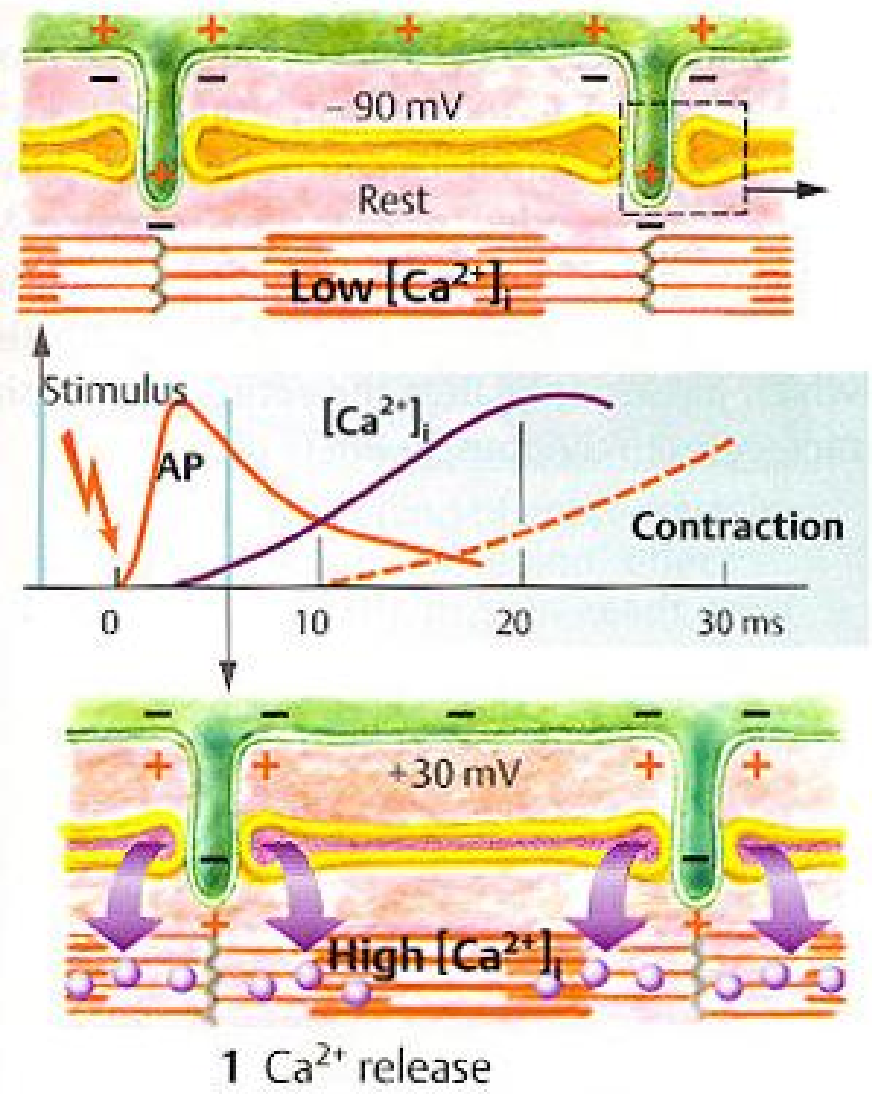
Water supplied by the New River Water Company contains 278·6 parts of solids per million.

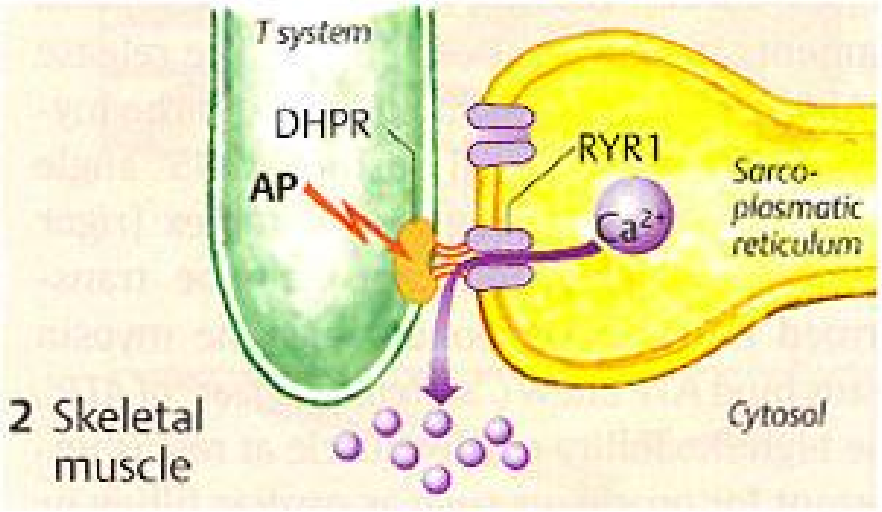
They consist of:

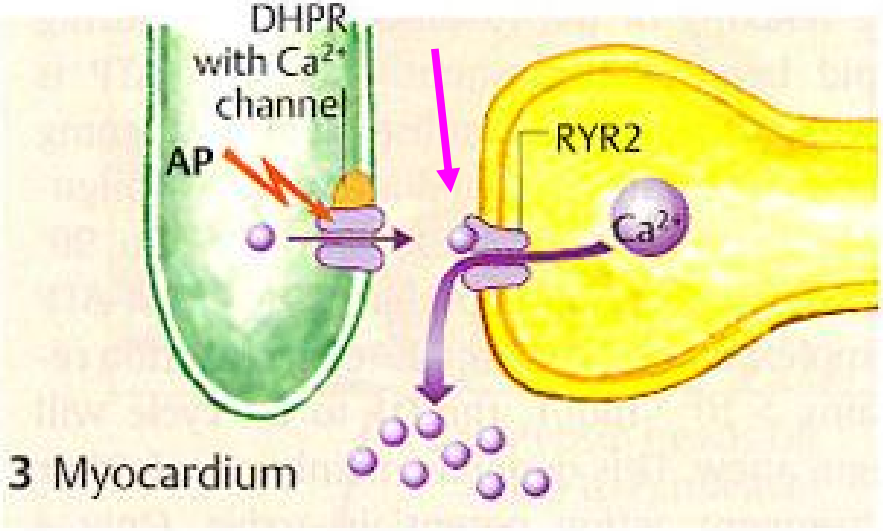
Calcium	38·3	per million.
Magnesium	4·5	,,
Sodium	23·3	,,
Potassium	7·1	,,
Combined Carbonic Acid	78·2	,,
Sulphuric Acid	55·8	,,
Chlorine	15	,,
Silicates	7·1	,,
Free Carbonic Acid	54·2	,,

This water is faintly alkaline to test-paper from bicarbonate of lime. Saline made with this water I found at first rounds the top of the trace of each contraction and later greatly prolongs diastolic dilatation, and that these effects are completely obviated by about 1 c. c. of 1 % solution

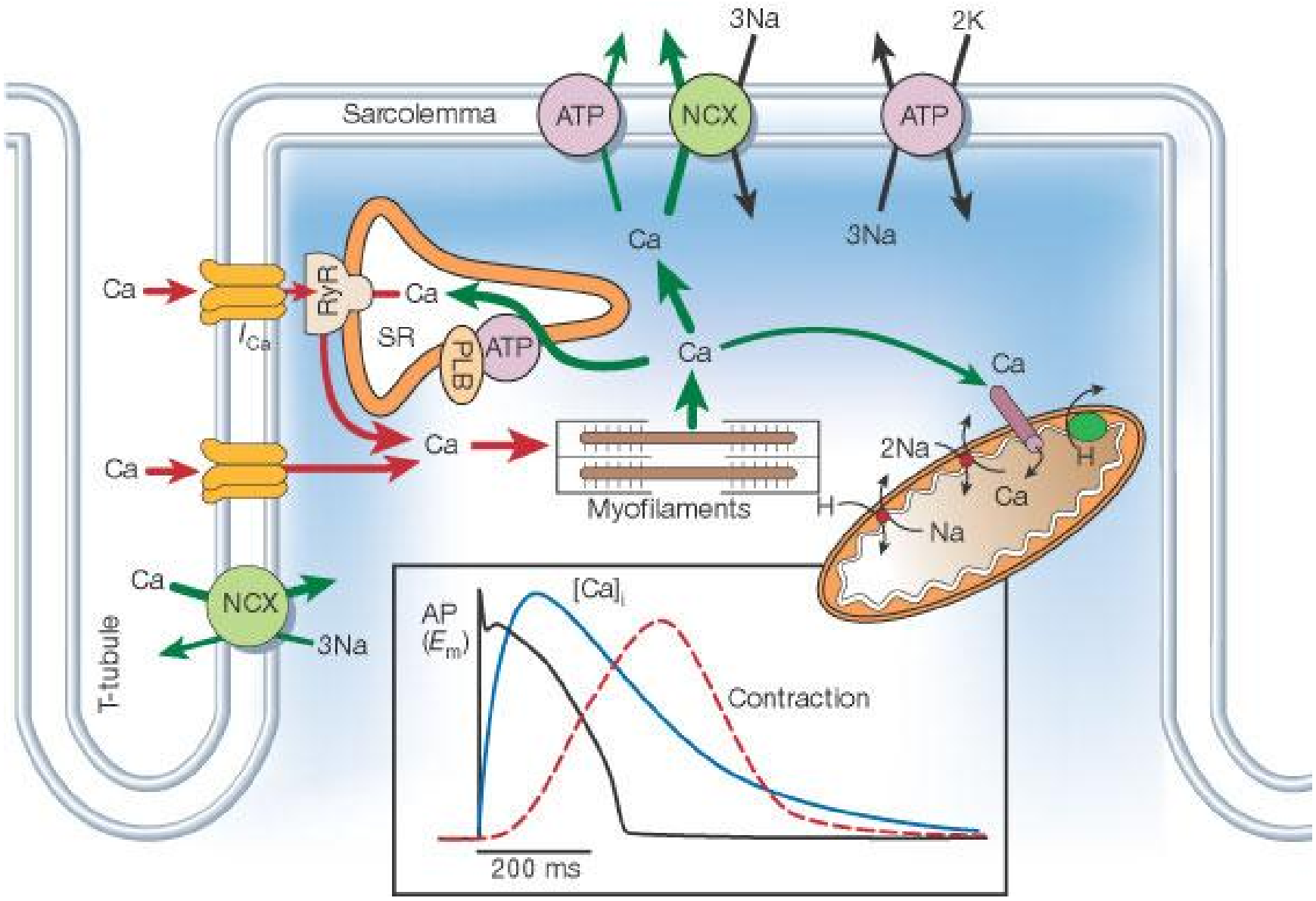
lo ione Ca^{2+} media l'attivazione del miocardio







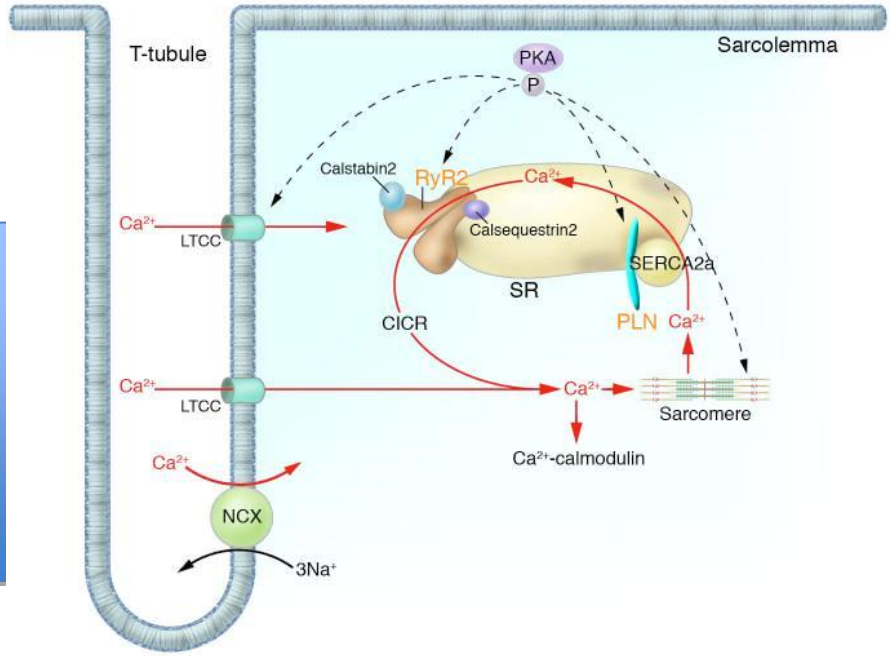
ruolo del Ca2+ nell'attivazione della contrazione



alterazioni delle proteine che regolano l'omeostasi del calcio sono causa di cardiomiopatie (congenite o acquisite)

ALTERAZIONI CONGENITE

-rec rianodinico
-fosfolambano
-canale Ca2+
-Ca2+ ATPasi



ALTERAZIONI ACQUISITE

-rec rianodinico
-fosfolambano
-canale Ca2+
-Ca2+ ATPasi
-proteine che legano Ca2+ nel SR

causa genetica di cardiomiopatie primitive

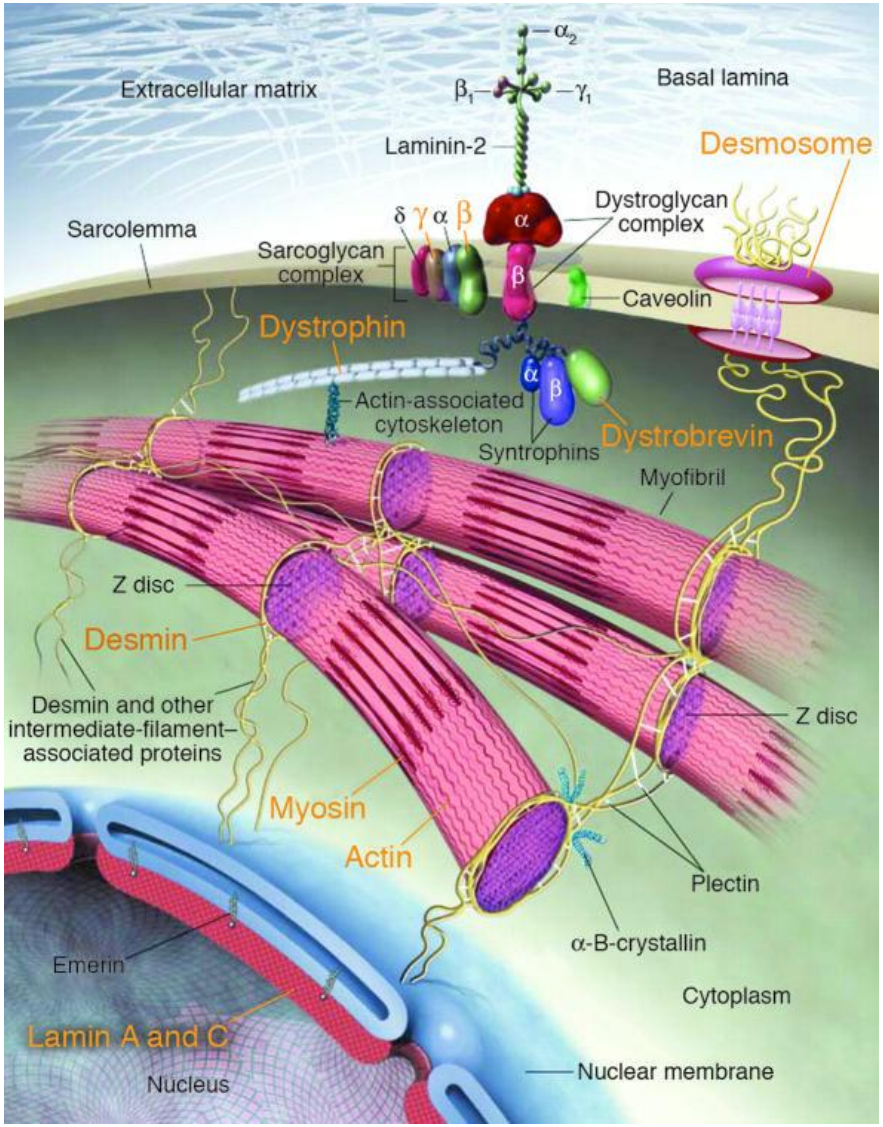
in ipertrofia cardiaca, insufficienza cardiaca

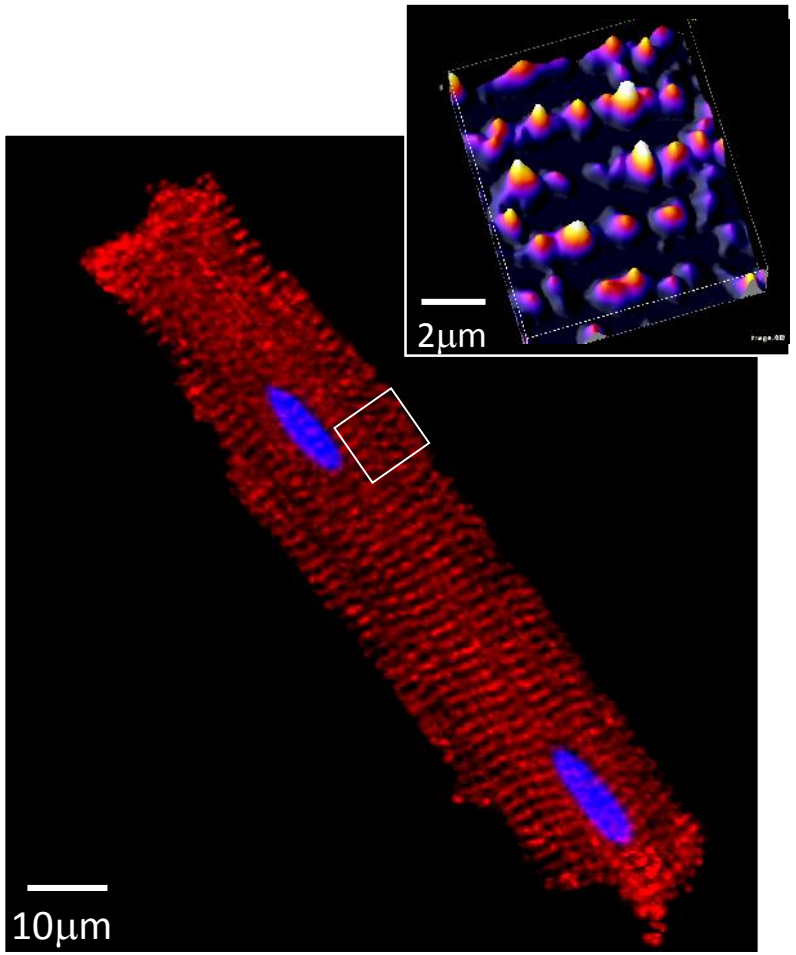
alterazioni congenite delle componenti del citoscheletro sono causa di cardiomiopatie primitive

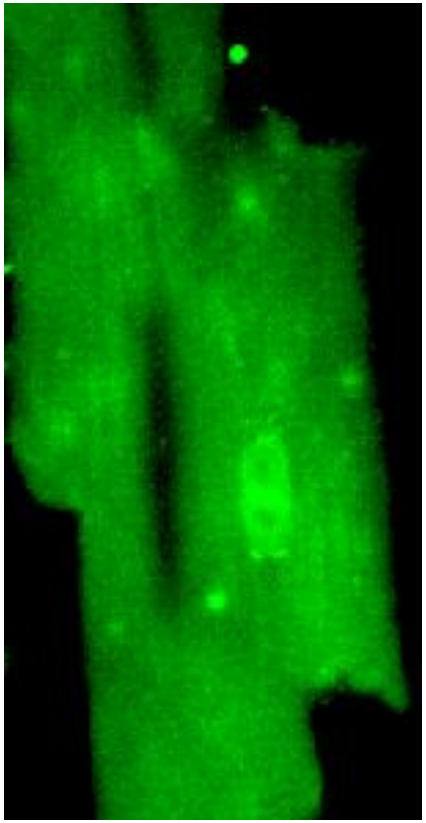
ALTERAZIONI CONGENITE

-distrofina
-distroglicano
-lamina A/C
-desmina

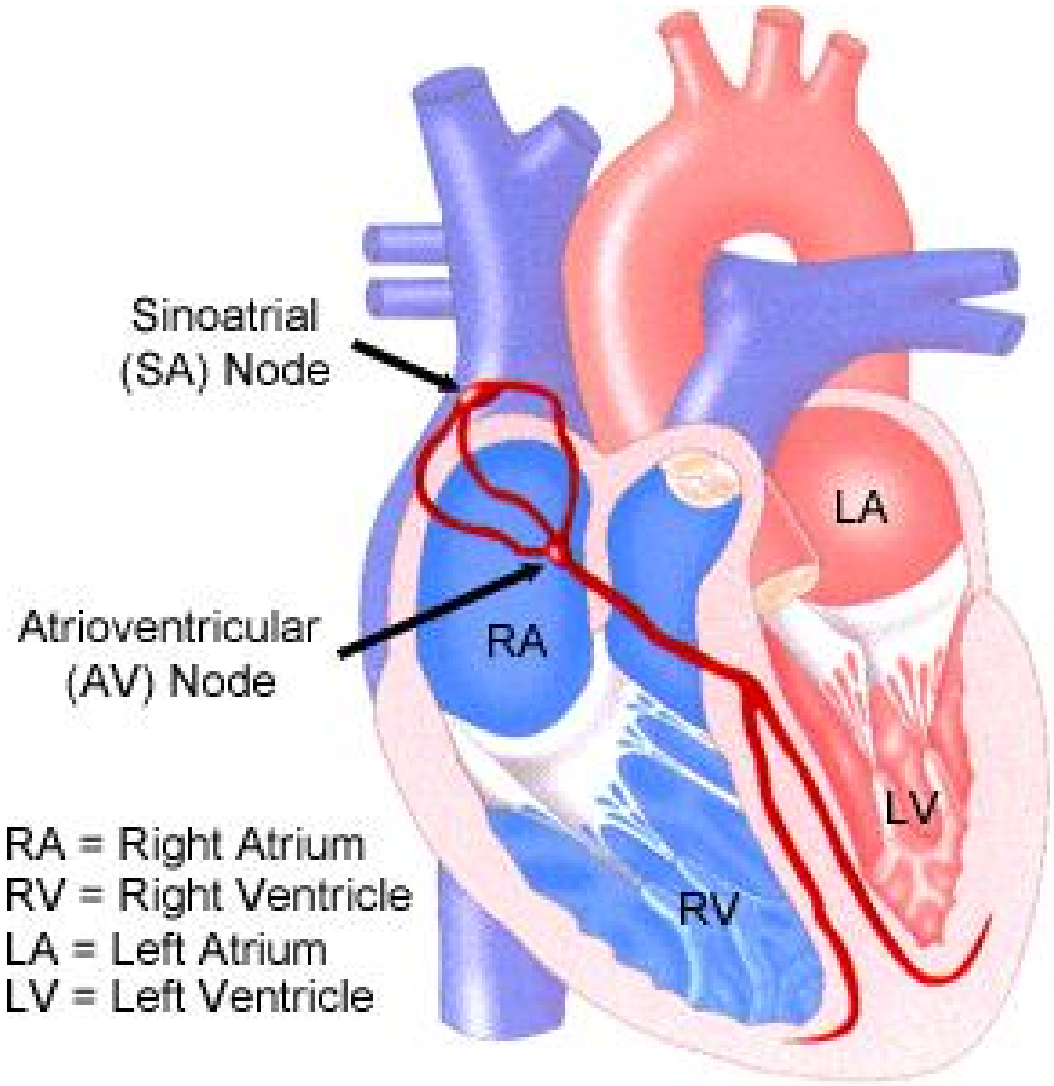
causa genetica di cardiomiopatie primitive (distrofie cardiache)




2μm
10μm

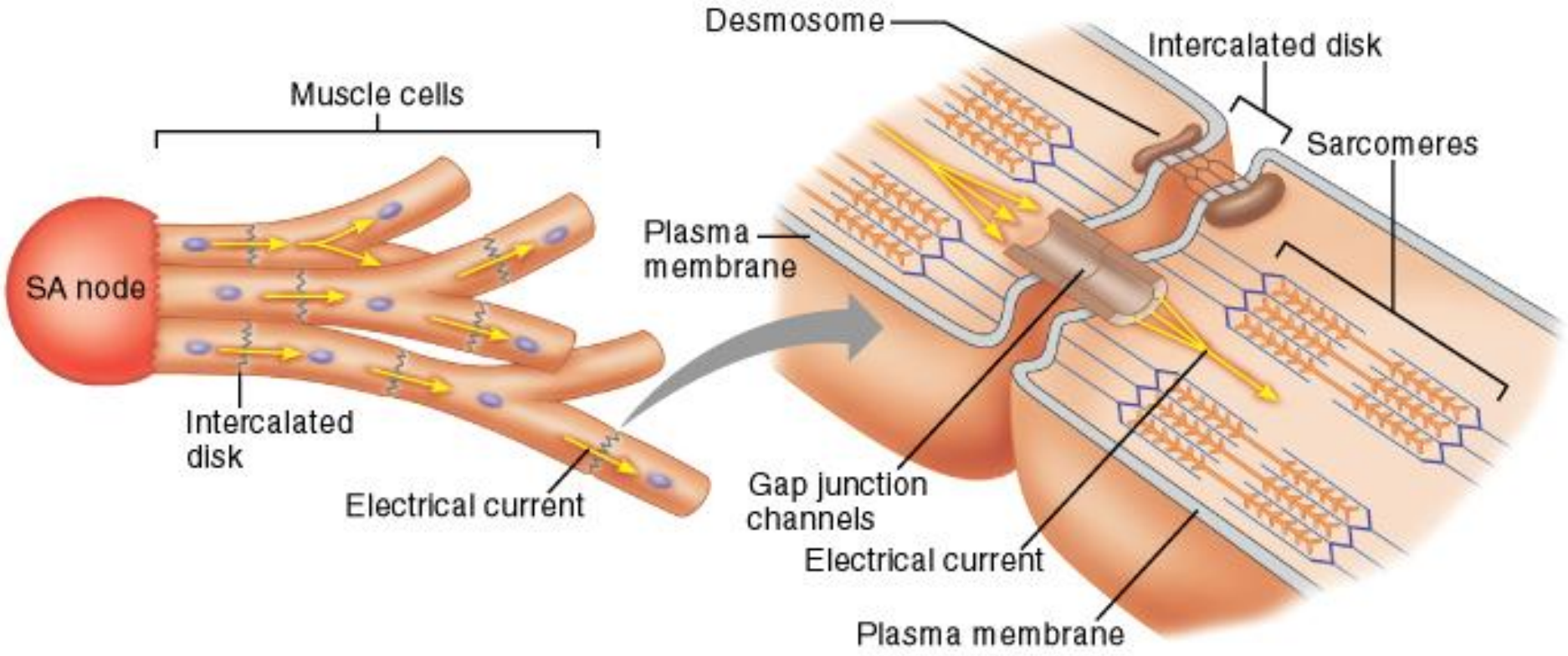


il sistema di conduzione cardiaco



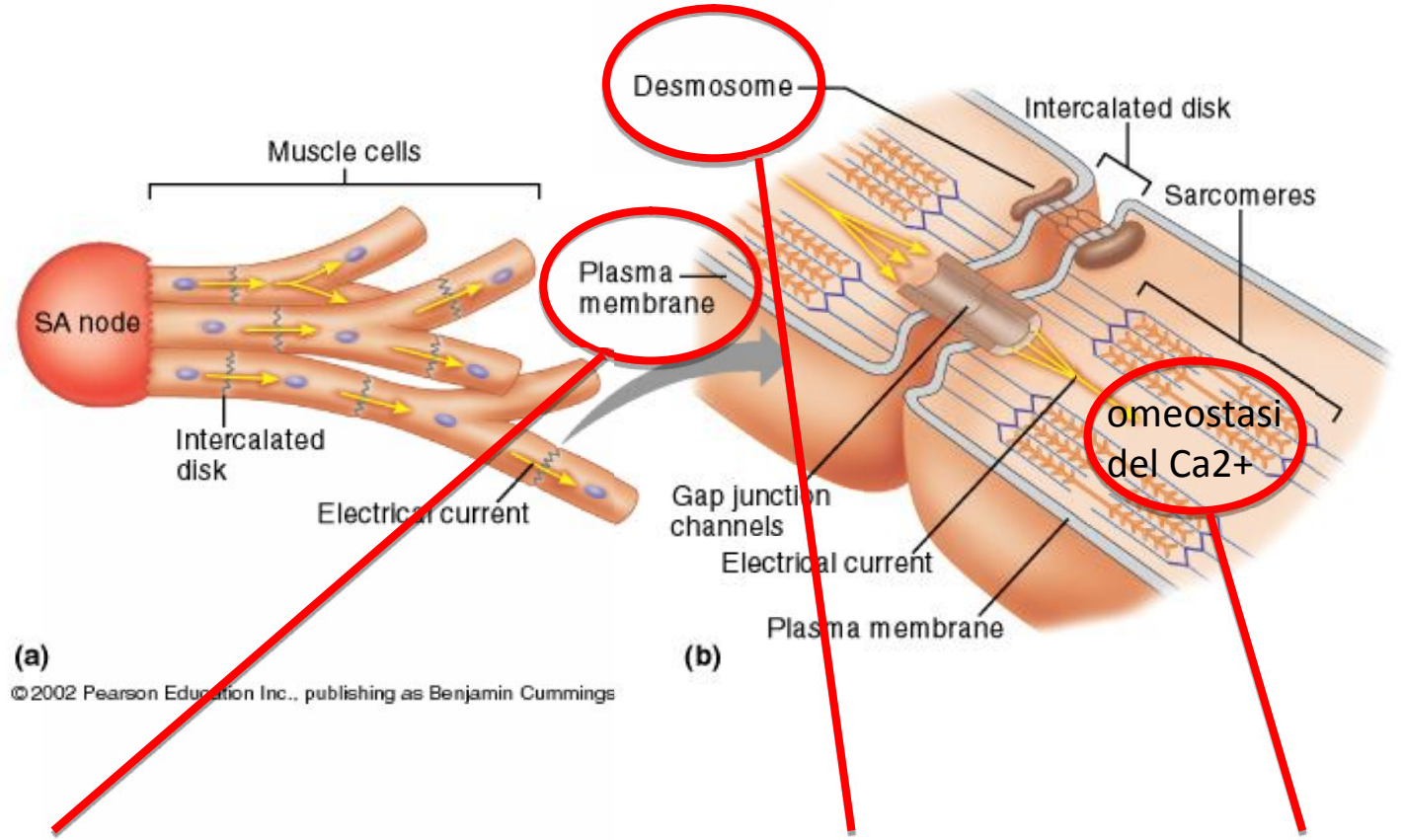
- **Intrinsic pacemaker**
- **Electrical impulses cause heart to beat (contract).**
- **Originates in the sinoatrial (SA) node, located at the top of the right atrium.**
- **SA node electrical impulse causes the atria to contract.**
- **The signal then passes through the atrioventricular (AV) node.**
- **The AV node delays the signal allowing for ventricular filling.**
- **Next the signals travels along the septal muscle fibers of the ventricles and into the walls, causing chamber contraction.**
- **The heart rate changes depending on physical demands, stress, or hormonal factors.**

il nodo SA e la conduzione intercellulare dell'impulso



An action potential (AP) is propagated as the result of current transmission through gap junctions. Since the cardiac AP is almost as long as cardiac contraction, its refractory period prevents propagation of another AP until the muscle relaxes: tetanization is not possible.

alterazioni nella proteine che regolano la conduzione dell'impulso causano aritmie cardiache



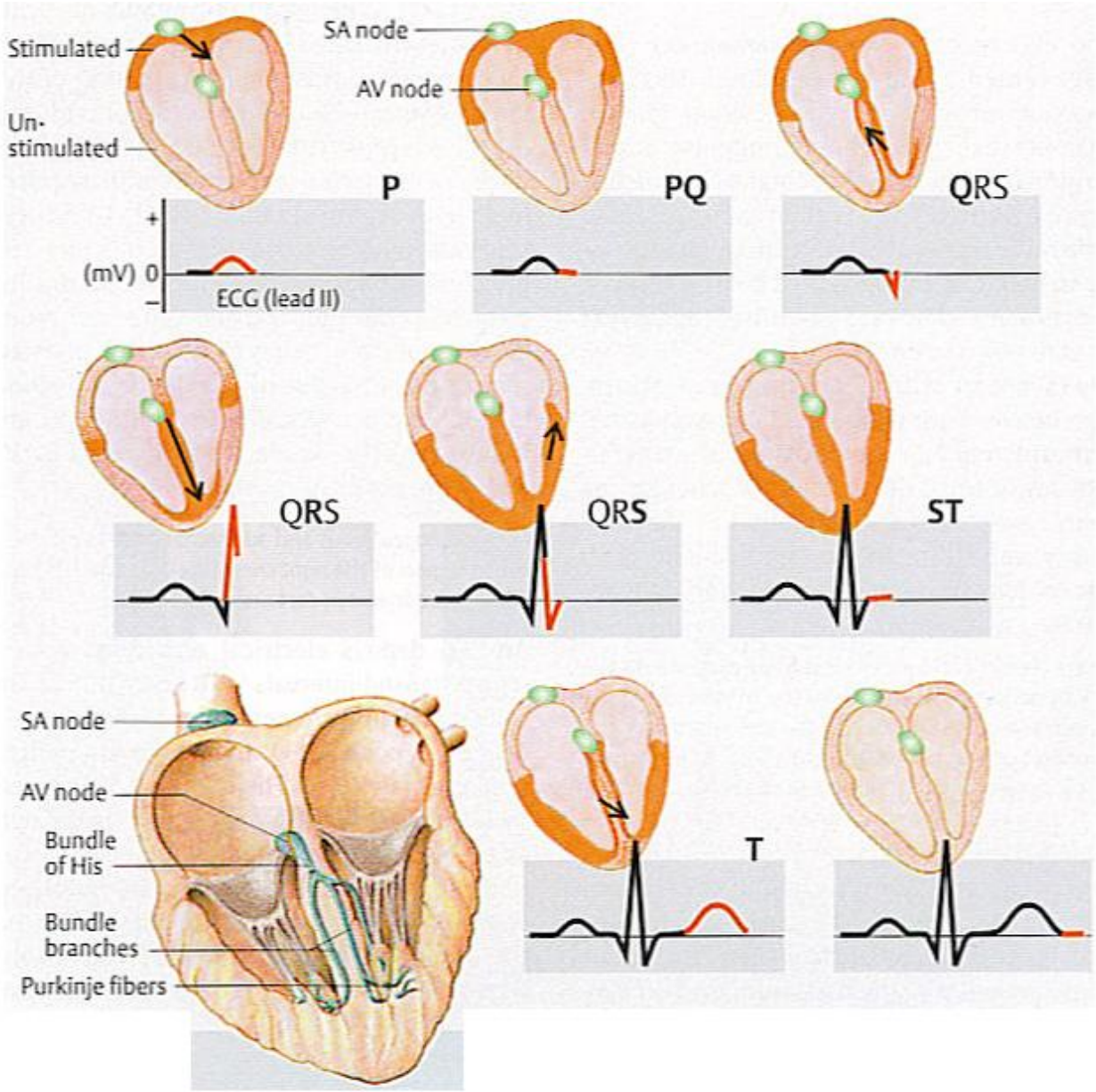
canale Na+
canale K+
scambiatore Na/Ca

proteine desmosomiali
desmogleina, desmocollina

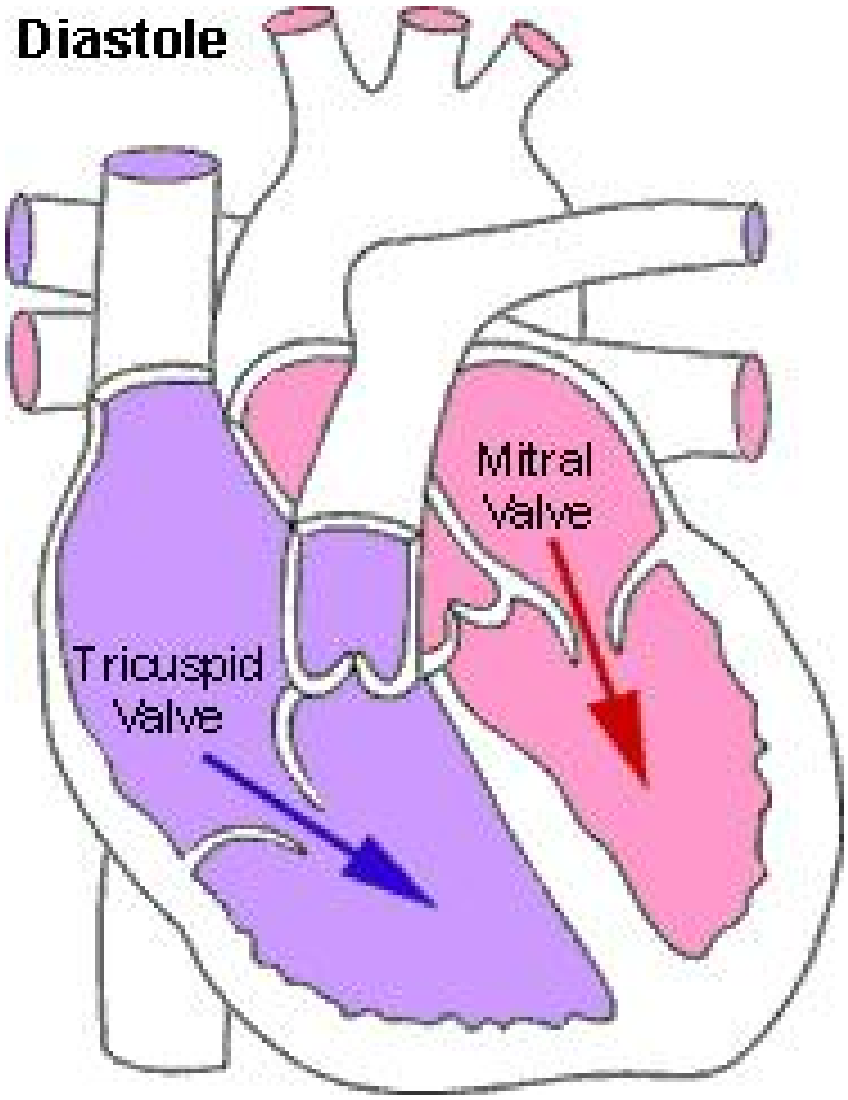
recettore rianodinico
fosfolambano

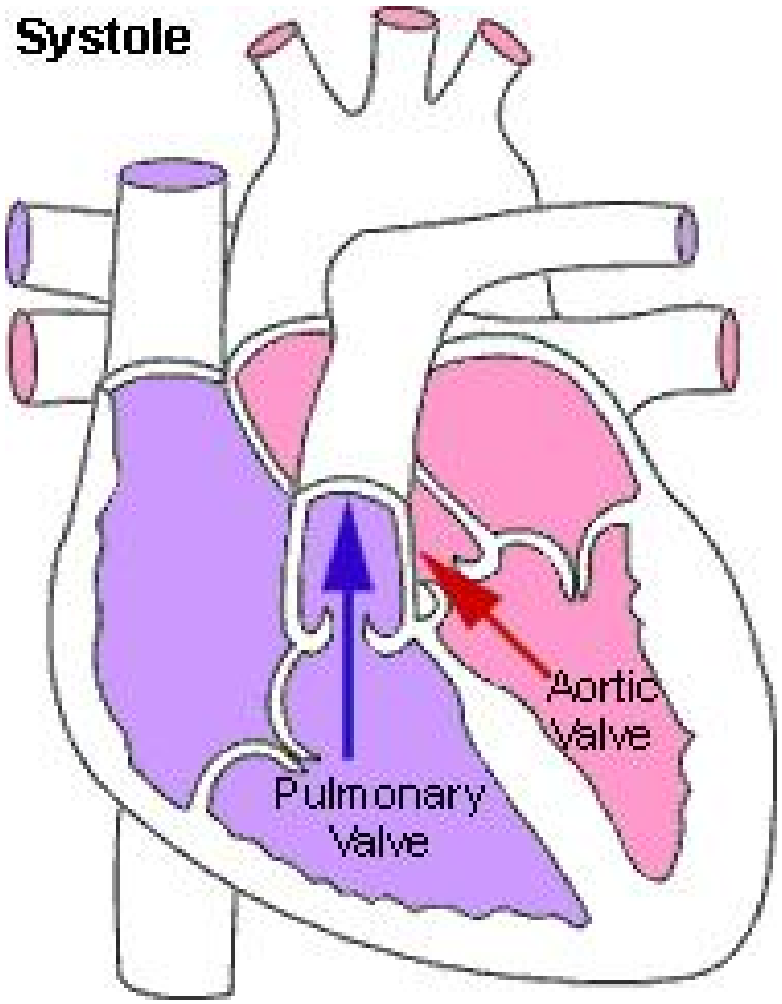
le stesse molecole sono bersaglio di alterazioni secondarie ad ipertrofia o ischemia cardiaca (acquisiti)

Excitation Vectors and ECG

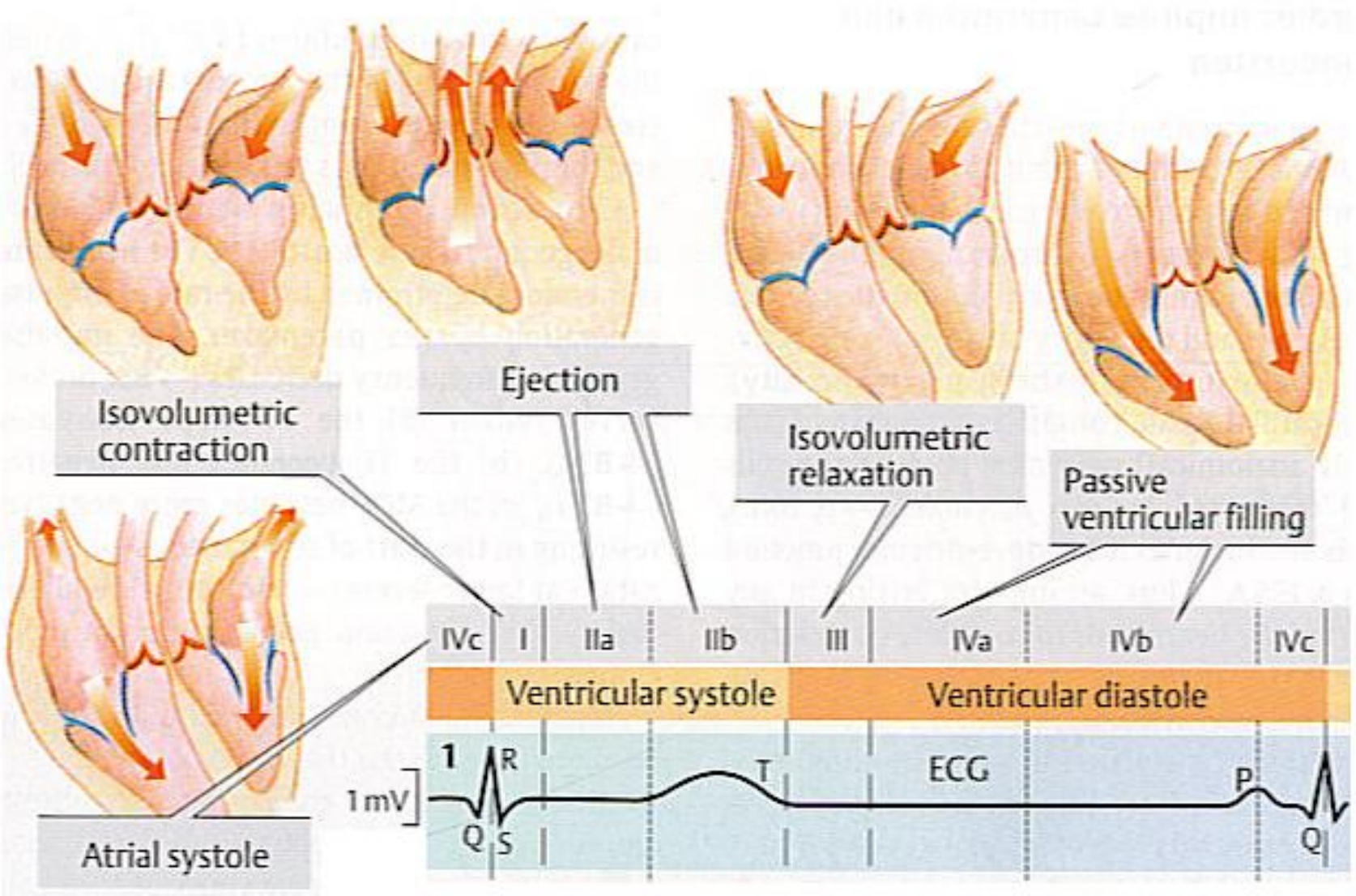


The Heart Valves

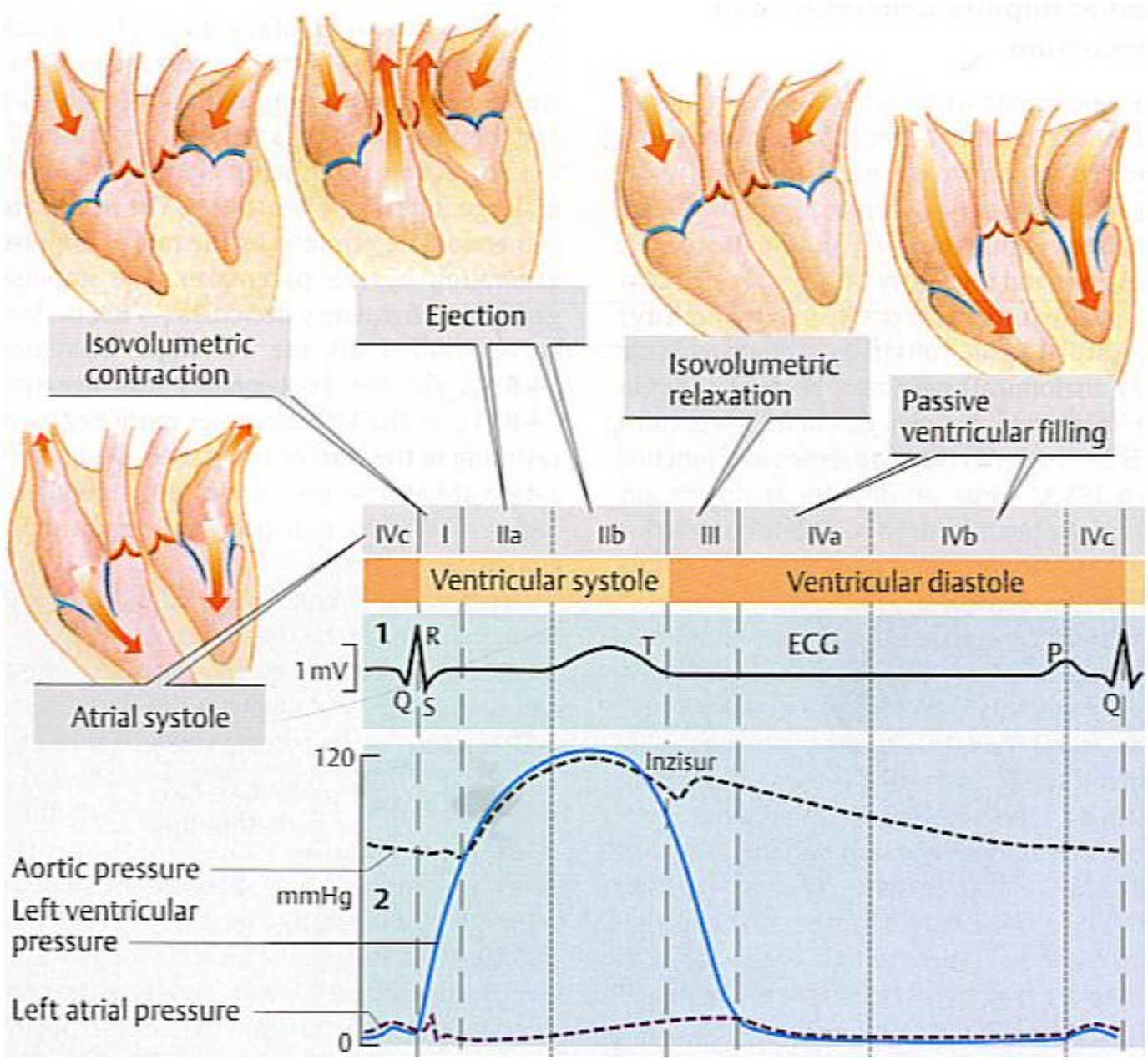




Blood Flow and ECG



Aortic-LV-LA Pressures



ESP = 120 mmHg

MAP = 90 mmHg

EDP < 10 mmHg

L’APPARATO VALVOLARE cardiaco può andare incontro a disfunzioni che causano principalmente due tipi di alterazione:

1- la valvola non si apre completamente = STENOSI valvolare

una valvola che non apre completamente oppone una resistenza maggiore al flusso di sangue che passa attraverso l’ostio valvolare.

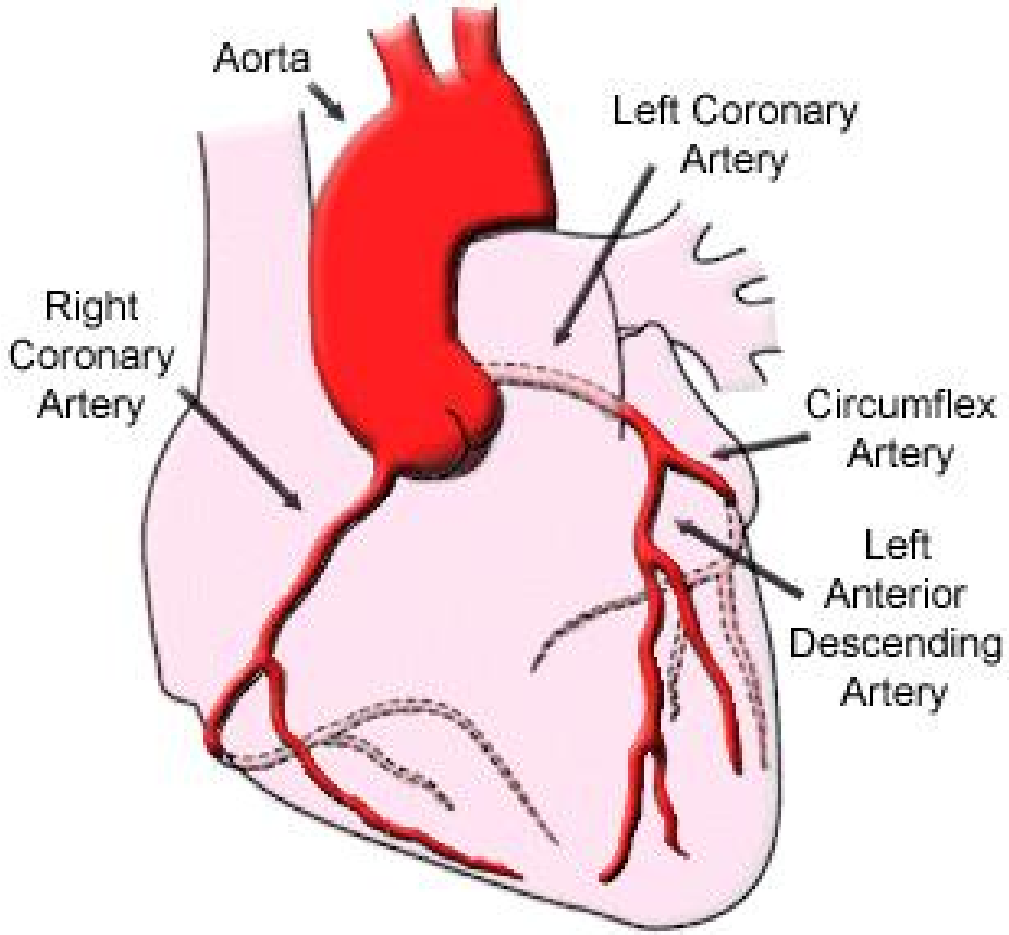
2- la valvola non si chiude completamente = INSUFFICIENZA valvolare

una valvola che non chiude completamente non contiene il sangue nella camera a valle della stessa.

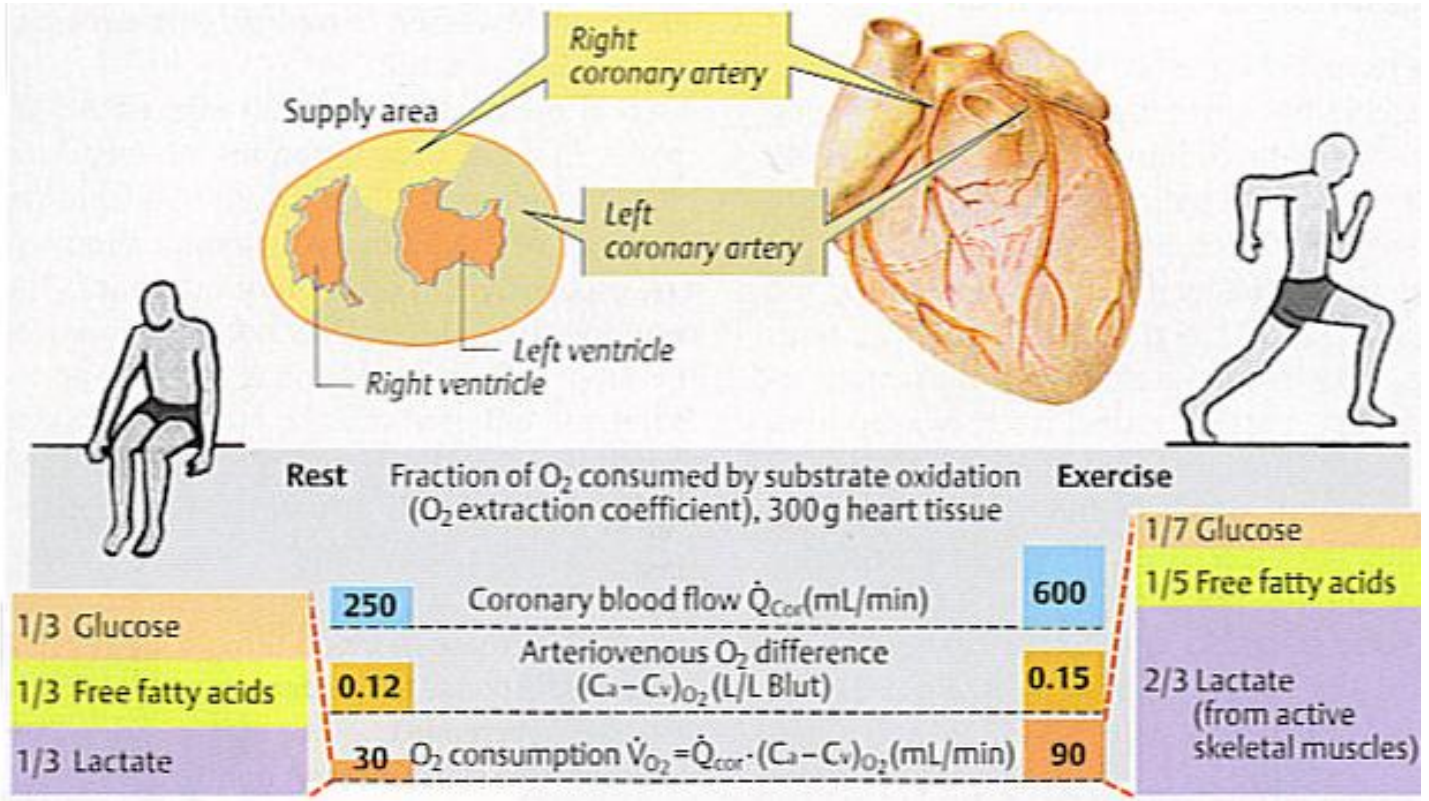
Le CAUSE delle malattie valvolari sono (raro) congenite o acquisite, quasi sempre primitive.

Le MANIFESTAZIONI fisiopatologiche delle malattie valvolari dipendono dal tipo e dall’entità del difetto, e dalla valvola colpita.

la vascolarizzazione del miocardio: vasi coronarici



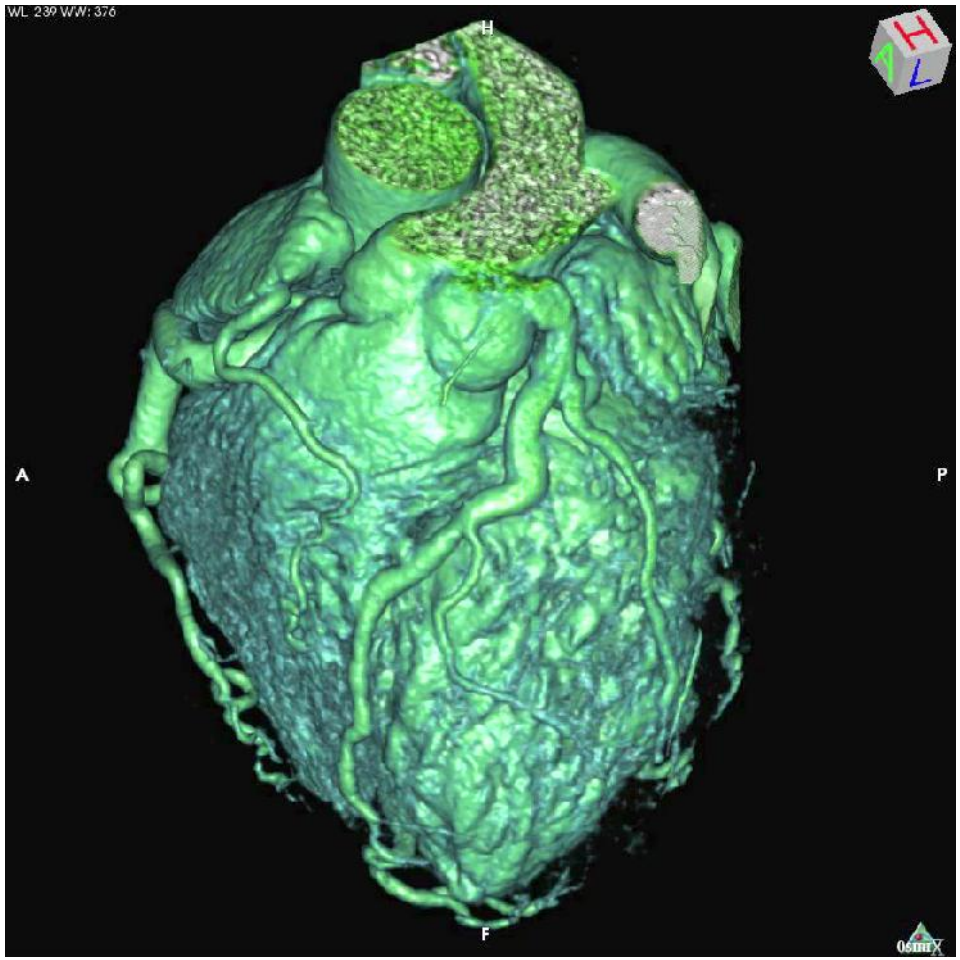
- **First vessels branching off the aorta**
- Left = LCA
- Right = RCA
- LCA = CX + LAD
- LCA perfuses about 2/3 of the heart muscle including the left ventricle
- RCA mainly perfuses smaller right heart

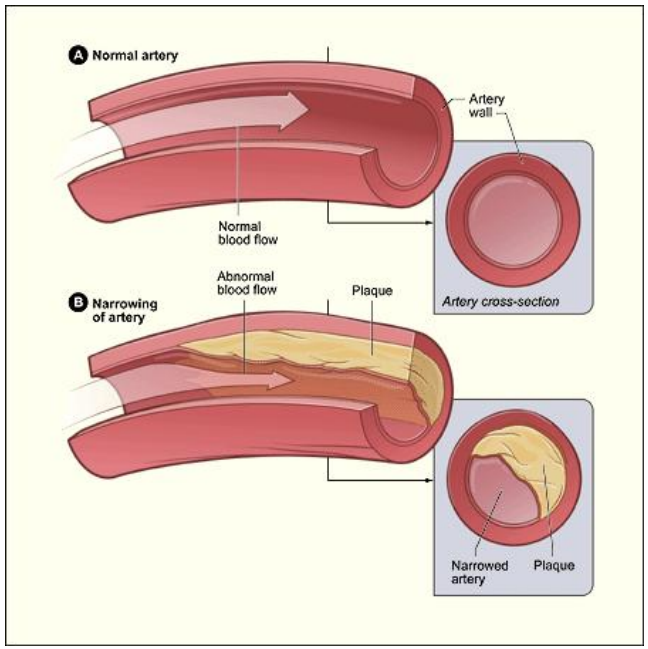


Coronary blood flow: LCA = 6/7 x Q_{cor}; phasic; depends on LV pressure.
Myocardial O_2 consumption = is high with 60% oxygen extraction at rest.
Aerobic metabolism → Increase in Q_{cor} only way to adapt to exercise.
Coronary reserve: regulation of vessel resistance → 4-5fold increase of Q_{cor} and O_2

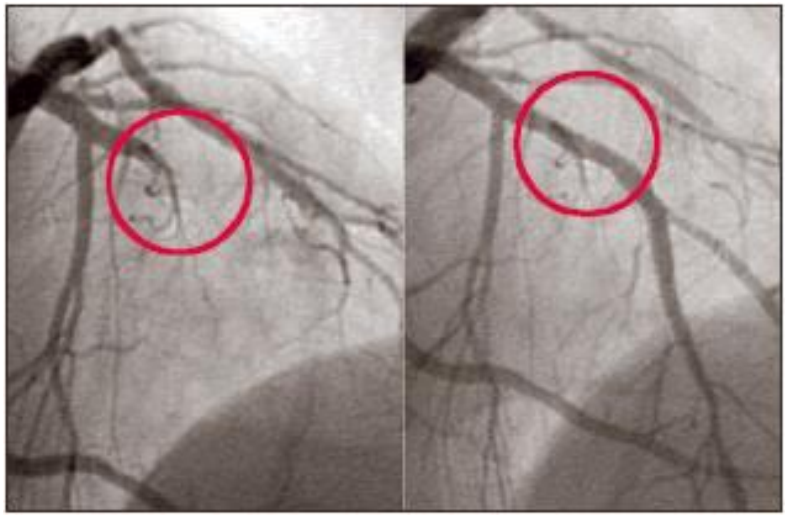
Metabolic: O_2, adenosine, lactate, H^+; **Endothelial:** NO; **Neurohumoral:** NE→ β2AR
Rest: Fueled by FFA, glucose, lactate, → +O_2 → AcCoA → Krebs cycle → ATP
Exercise: Increase of lactate (SM) → inhibit FA uptake → 70% lactate consumption

la vascolarizzazione del miocardio: vasi coronarici





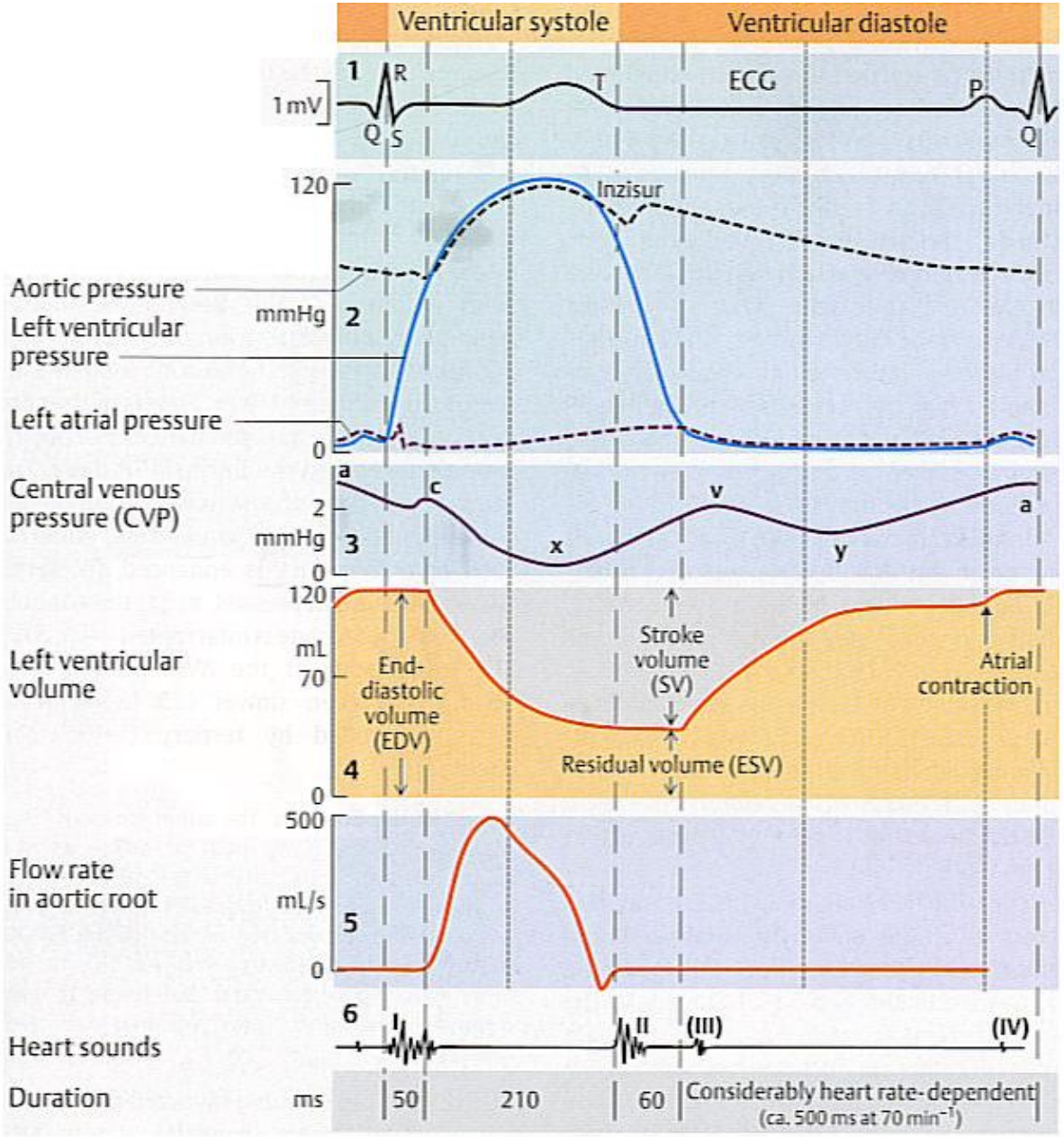
cardiopatia ischemica: aterosclerosi coronarica



cardiopatia ischemica acuta: occlusione ACUTA della coronaria = INFARTO MIOCARDICO

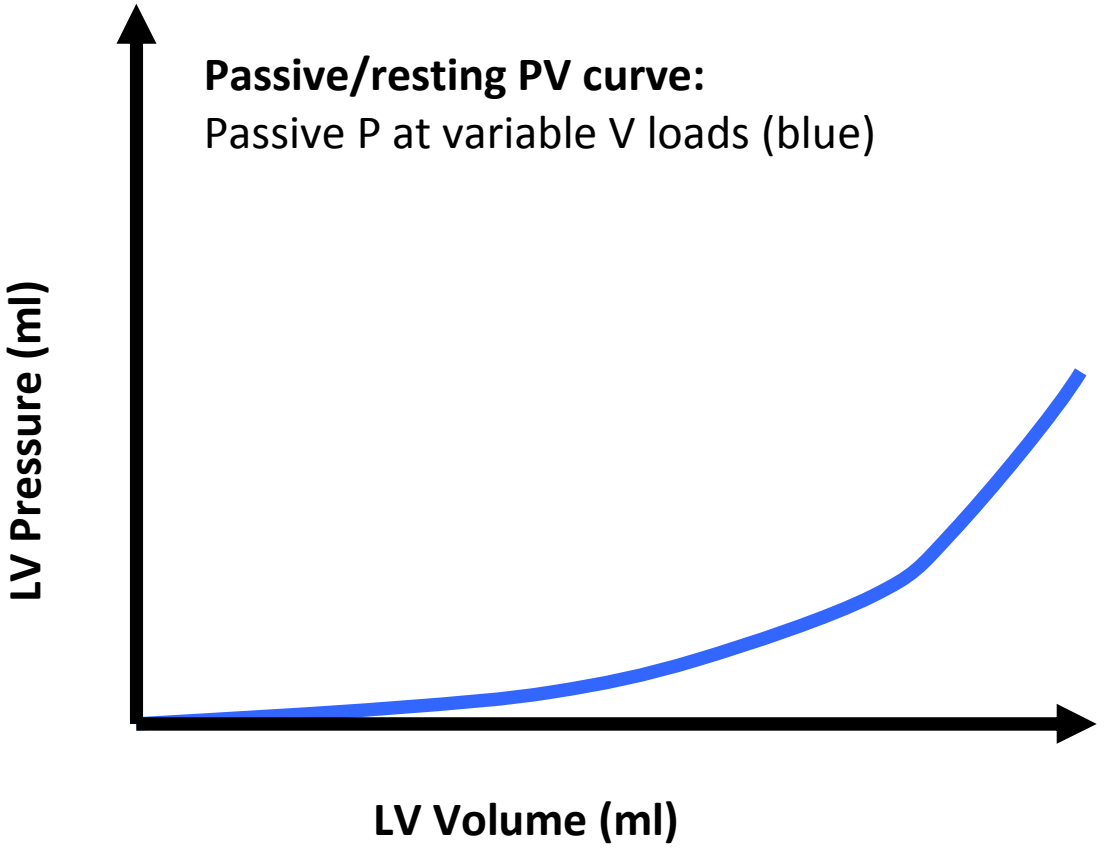
cardiopatia ischemica acuta: occlusione CRONICA della coronaria limitante il flusso coronarico massimo = CARDIOPATIA ISCHEMICA CRONICA

Synopsis of Cardiac Cycle

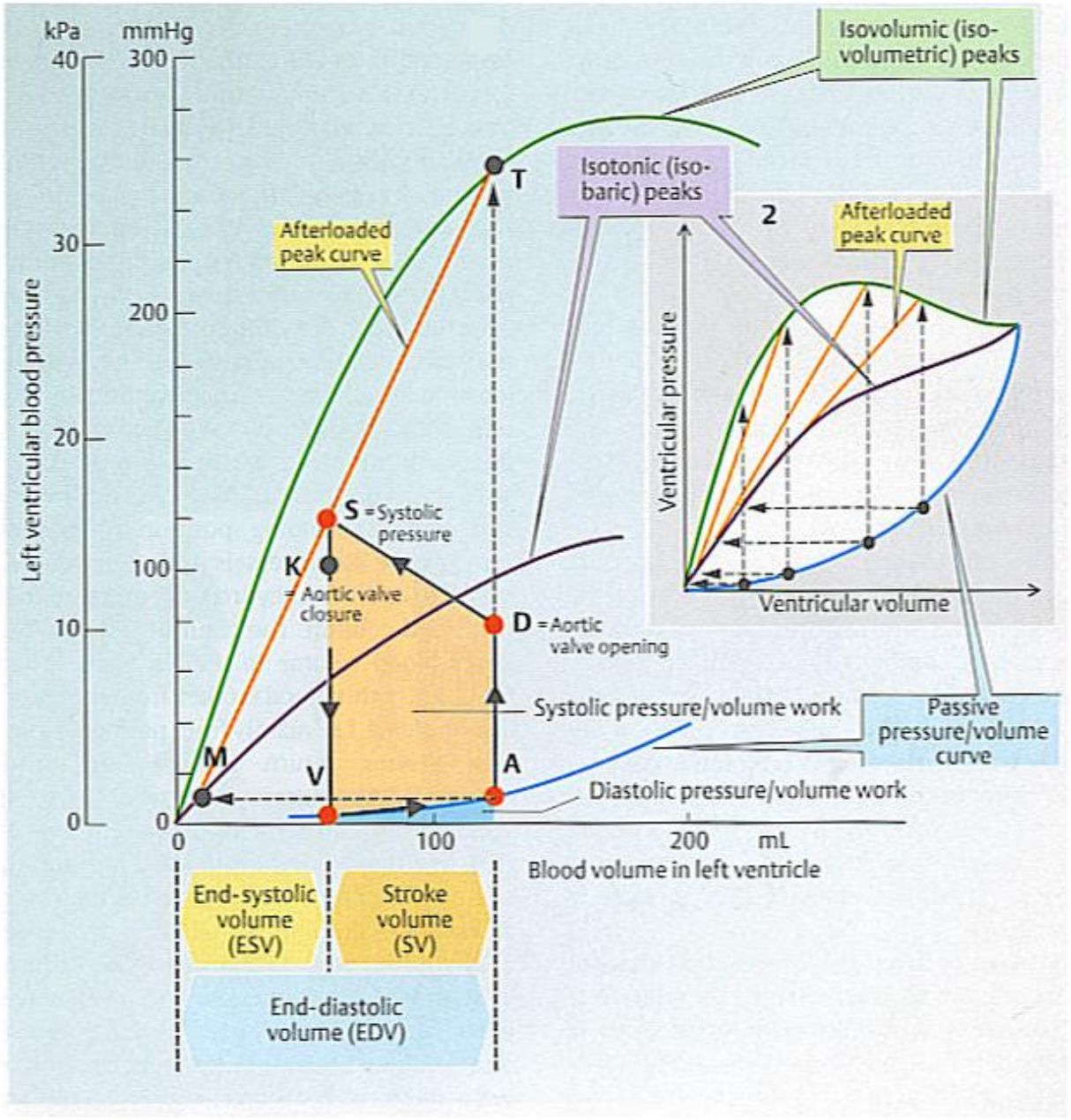


Mean blood pressure =
80 + 1/3 (110-80)
Systole begins with excitation and opening of the valves
Atrial systole
Ventricular systole
Diastole is the period between systoles
The **stroke volume** is 70 mL at rest
The **end-diastolic volume** is 120-140 mL at rest
Phases of contraction and relaxation

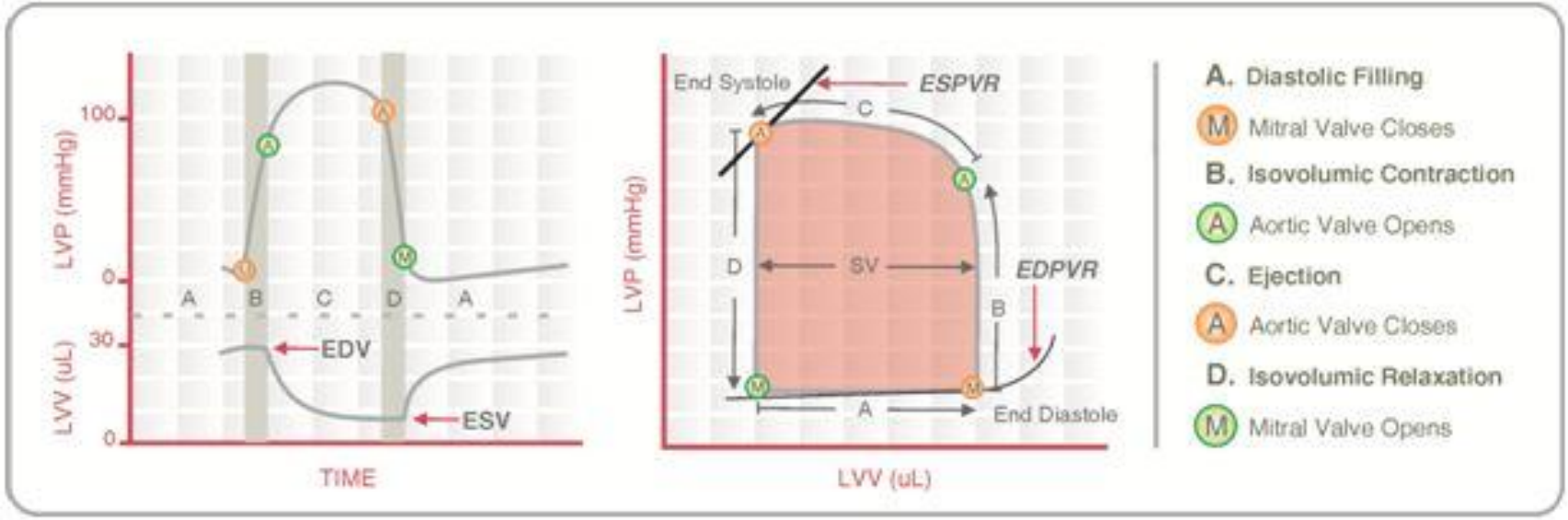
VI. LV Pressure-Volume Loop (Force-Length Relationship)



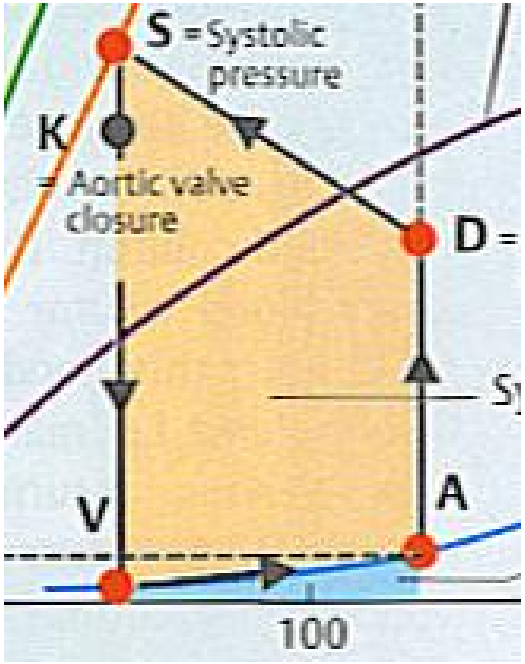
PV Loop Construction



Changes in P over V
A-D-S-V-A cycle
Blue: passive P at var. V
Green: peak P at var. V
Violet: P fixed V ejected
Orange: After-loaded:
A-D → D-S
P at S lies on line defined by isovolumic and isotonic values at A
Connects points T, M


LVP (mmHg)
100
0
LVV (uL)
30
0
A
B
C
D
A
EDV
ESV
TIME
End Systole
ESPVR
C
D
SV
EDPVR
B
A
End Diastole
LVP (mmHg)
LVV (uL)
A. Diastolic Filling
M Mitral Valve Closes
B. Isovolumic Contraction
A Aortic Valve Opens
C. Ejection
A Aortic Valve Closes
D. Isovolumic Relaxation
M Mitral Valve Opens

Ventricular Work Diagram Phases



- PV loop during cardiac cycle =
  area represents LV work during cardiac cycle
- End-diastolic V (EDV) = 125 mL (A)
- **Isovolumic contraction A-D**:
  P rises - aortic valve opens (D)
- **Ejection D-S**: Ventricular volume minus SV - P rises
- When systolic P max → V remains constant (S)
- P drops slightly caused by relaxation and reversal of **aortic flow and aortic valve closure** (K)
- **Iso-volumetric relaxation** K-V:
  rapid P decrease → close to 0 mmHg
- End-systolic V (EDV) = 60 mL
- **Diastolic filling V-A**:
  P rises slightly during filling

Integrated area (orange) = cardiac work

REGOLAZIONE DELL'ATTIVITA' CARDIACA

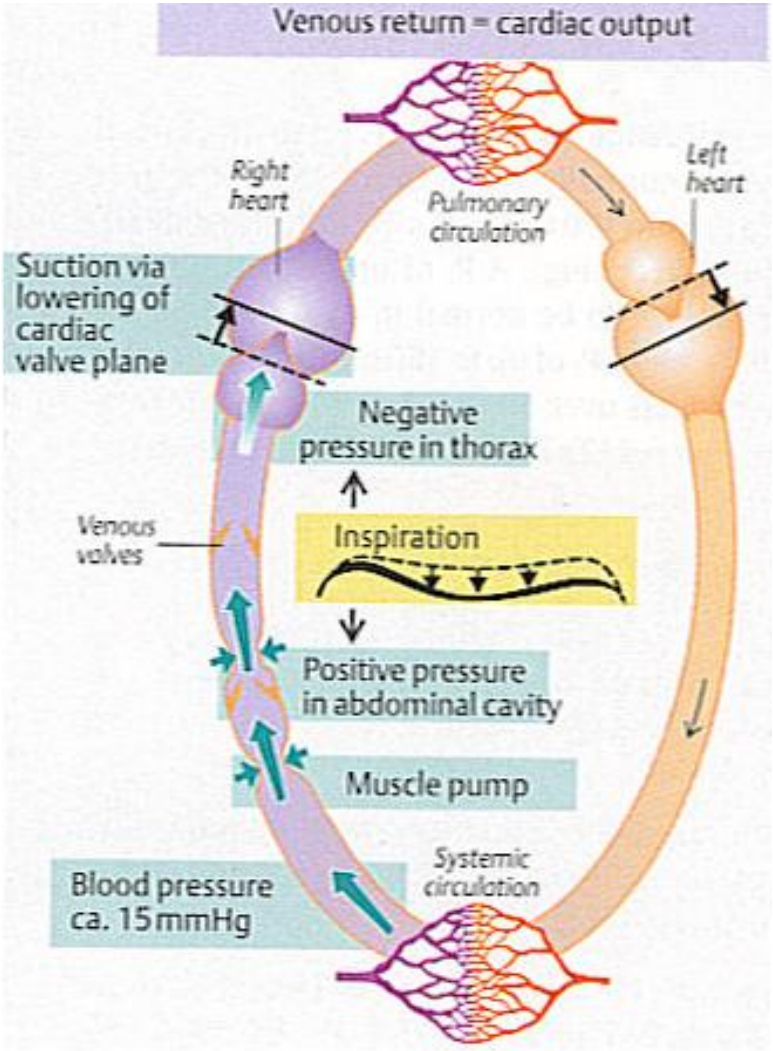
durante l'esercizio fisico, la gittata cardiaca deve aumentare dai 5 L/min a valori 5-7 volte superiori (circa 30 L/min).

come viene regolata l'attivita' cardiaca in risposta alla domanda metabolica dell'organismo.

1- meccanismo di autoregolazione (regolazione intrinseca): legge del cuore di Frank-Starling

2- controllo neuroumorale dell'attivita' cardiaca: sistema nervoso autonomo

Venous Return



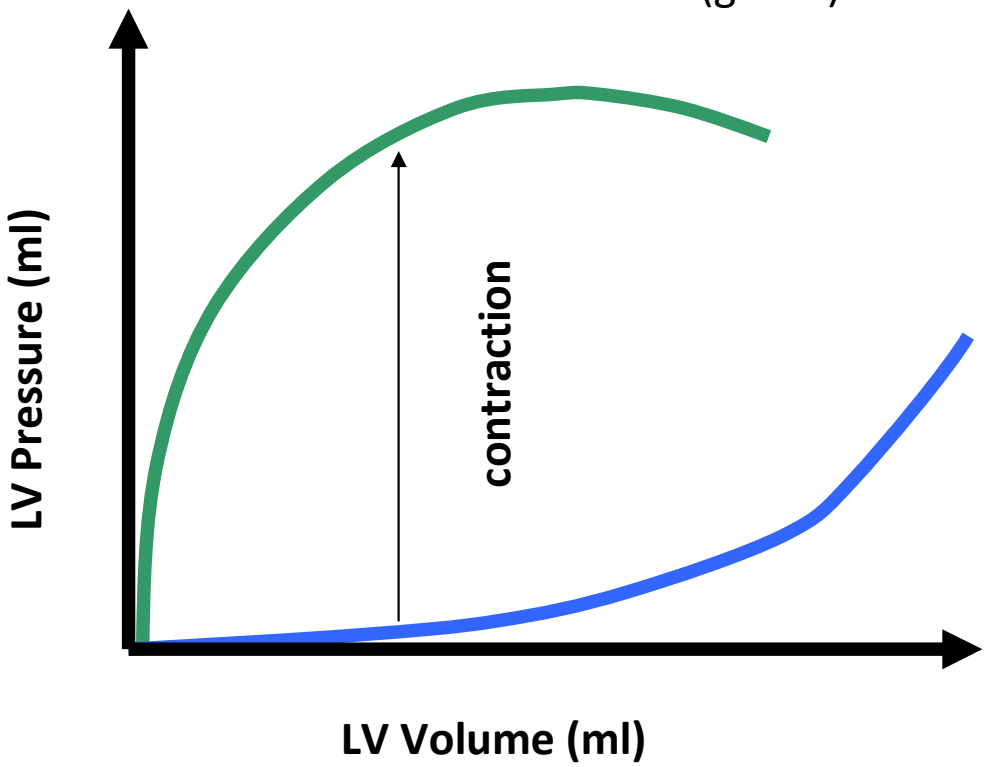
Driving forces for venous return

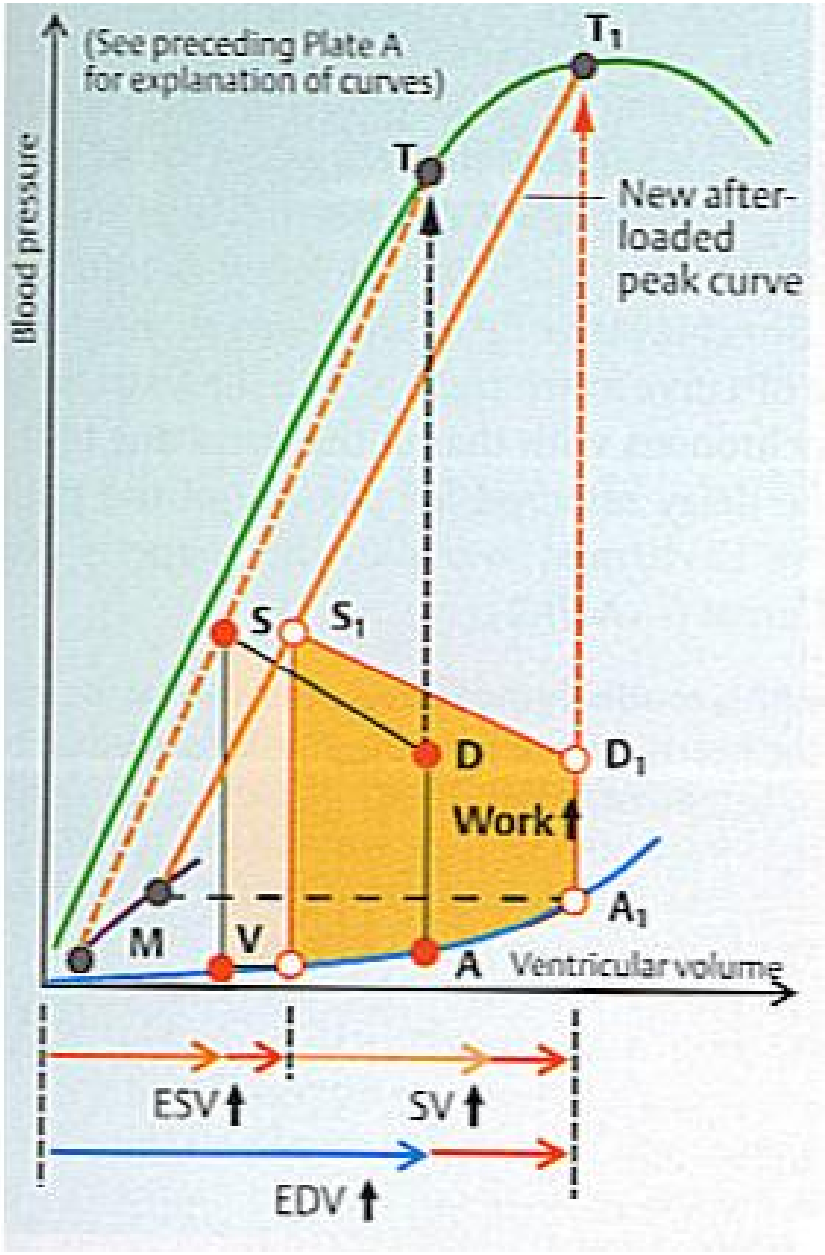
- Postcapillary BP 15 mmHg
- Muscle pump
- Venous Valves
- Negative inspiratory pressure and positive abdominal pressure
- Suction due to movement of cardiac valve plane

Orthostatic Reflex

Standing up raises leg blood +0.4L
Venous return to LA decreased
Increase HR + TPR
Prevents orthostatic collapse!

Isovolumic peak curve:
Peak P at variable V loads (green)

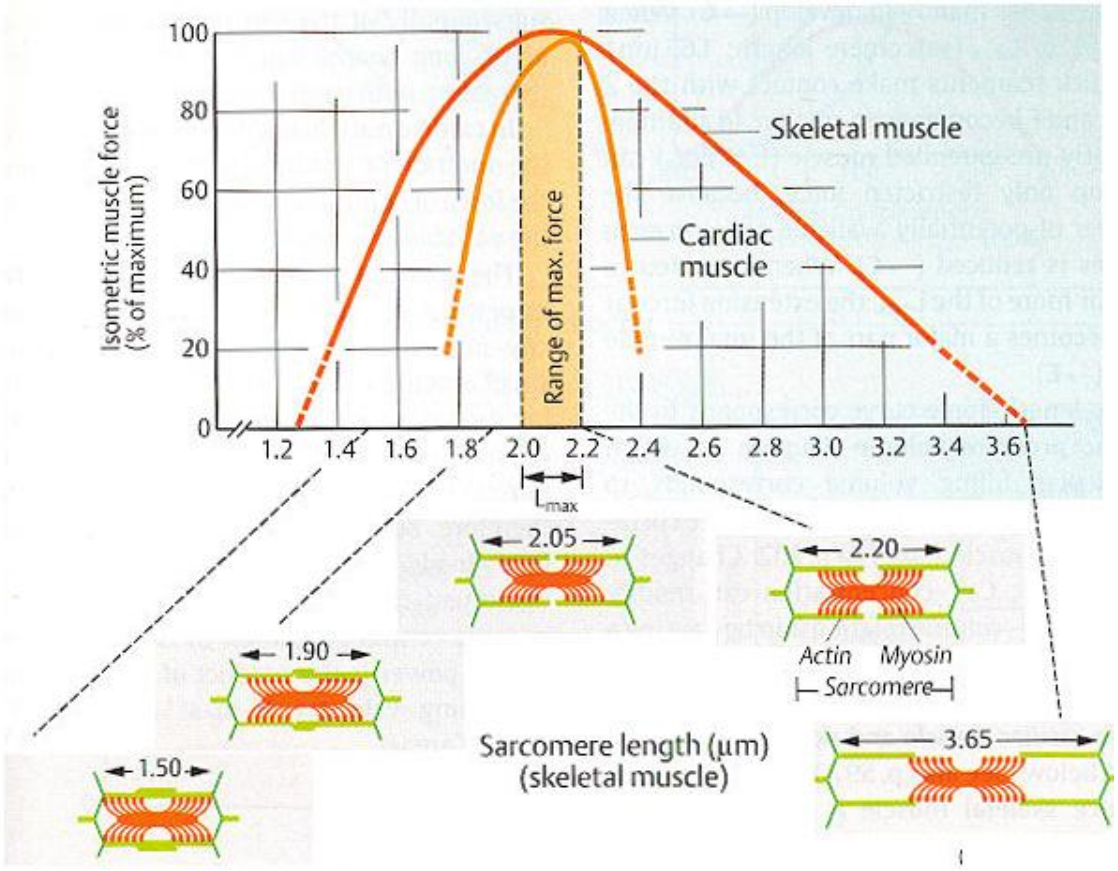




meccanismo di Frank-Starling
il cuore risponde ad un aumento del precarico (volume telediastolico, EDV)
con un aumento della contrattilita'

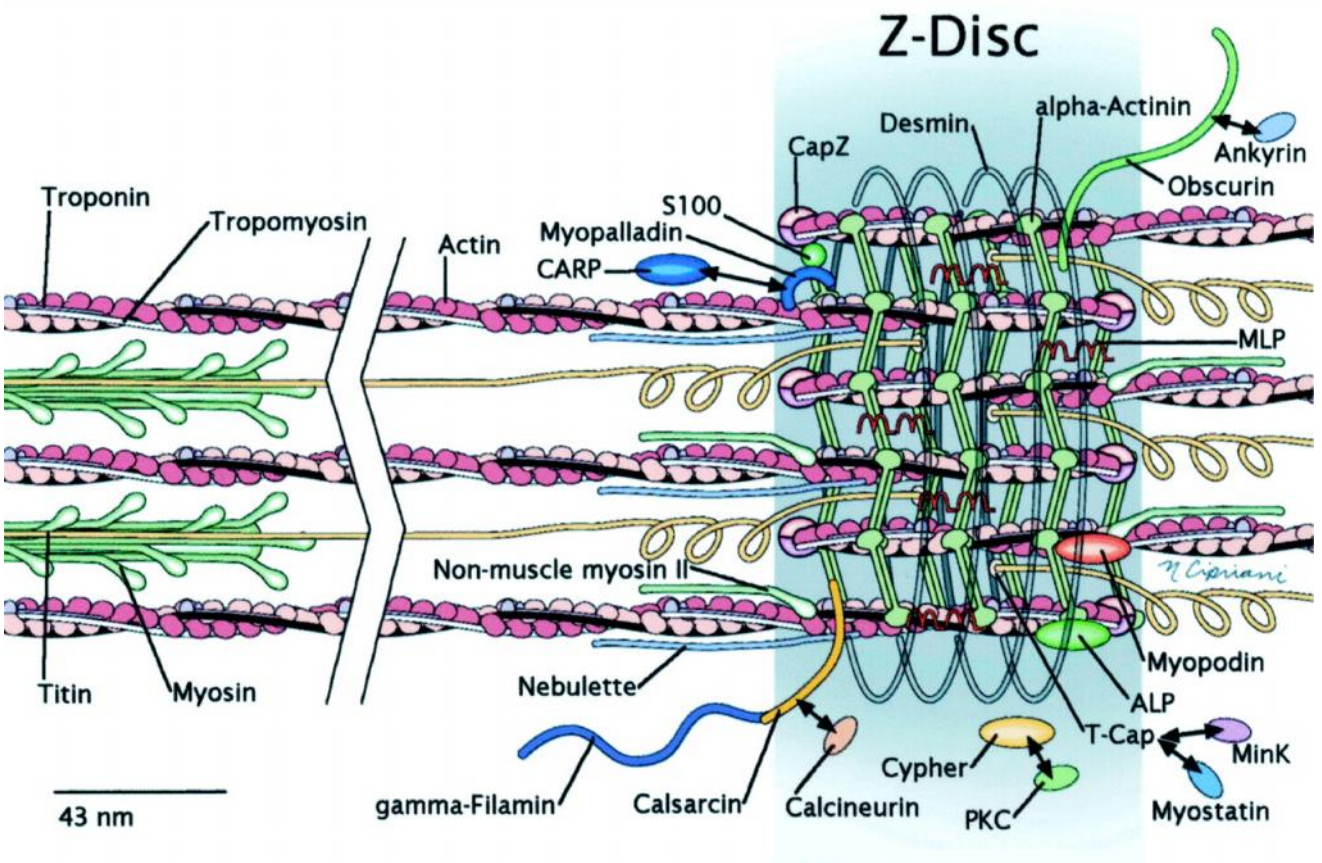
Un aumento del precarico induce uno spostamento a destra della curva P/V.

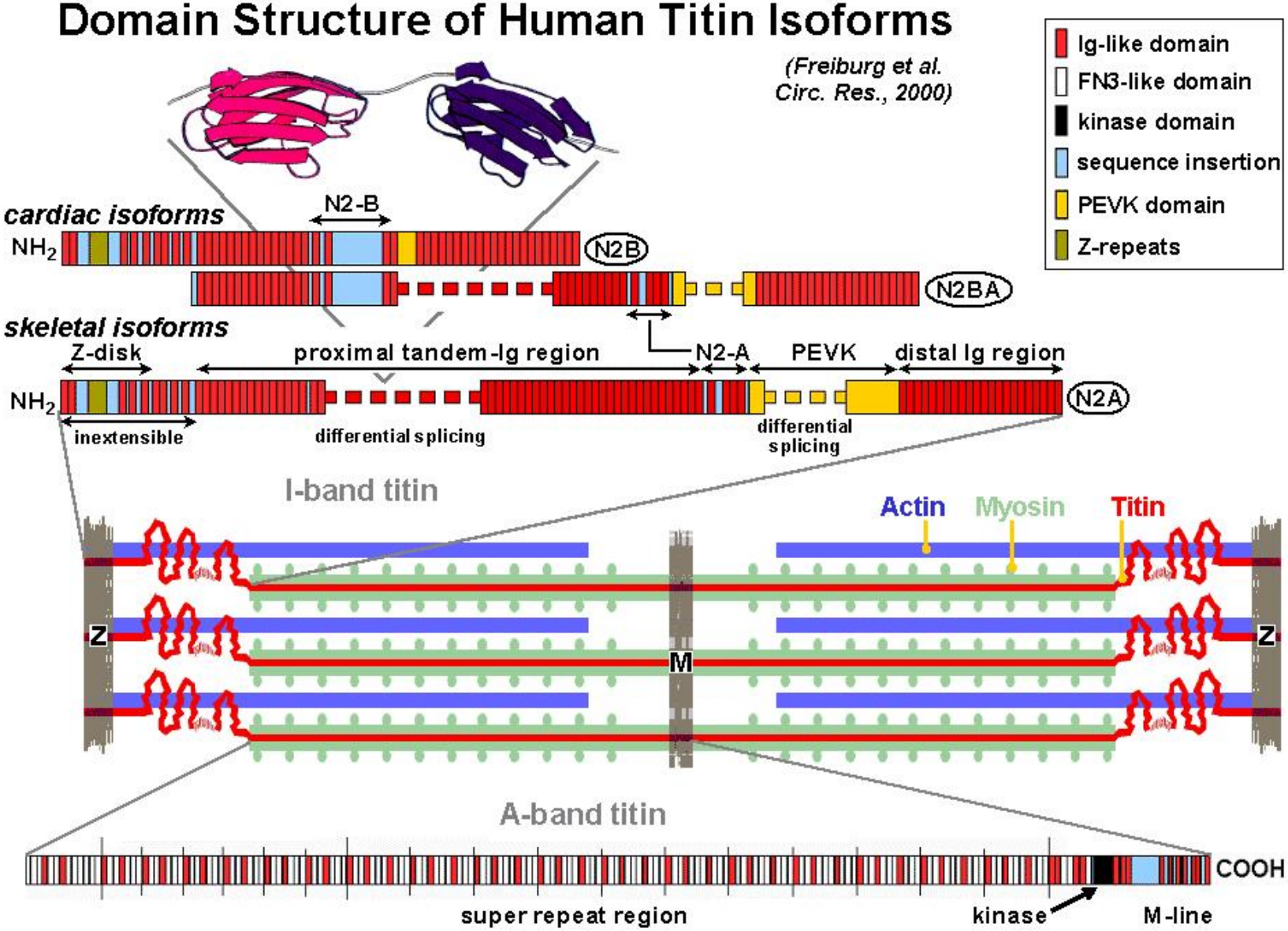
Stretch → Sarcomere length



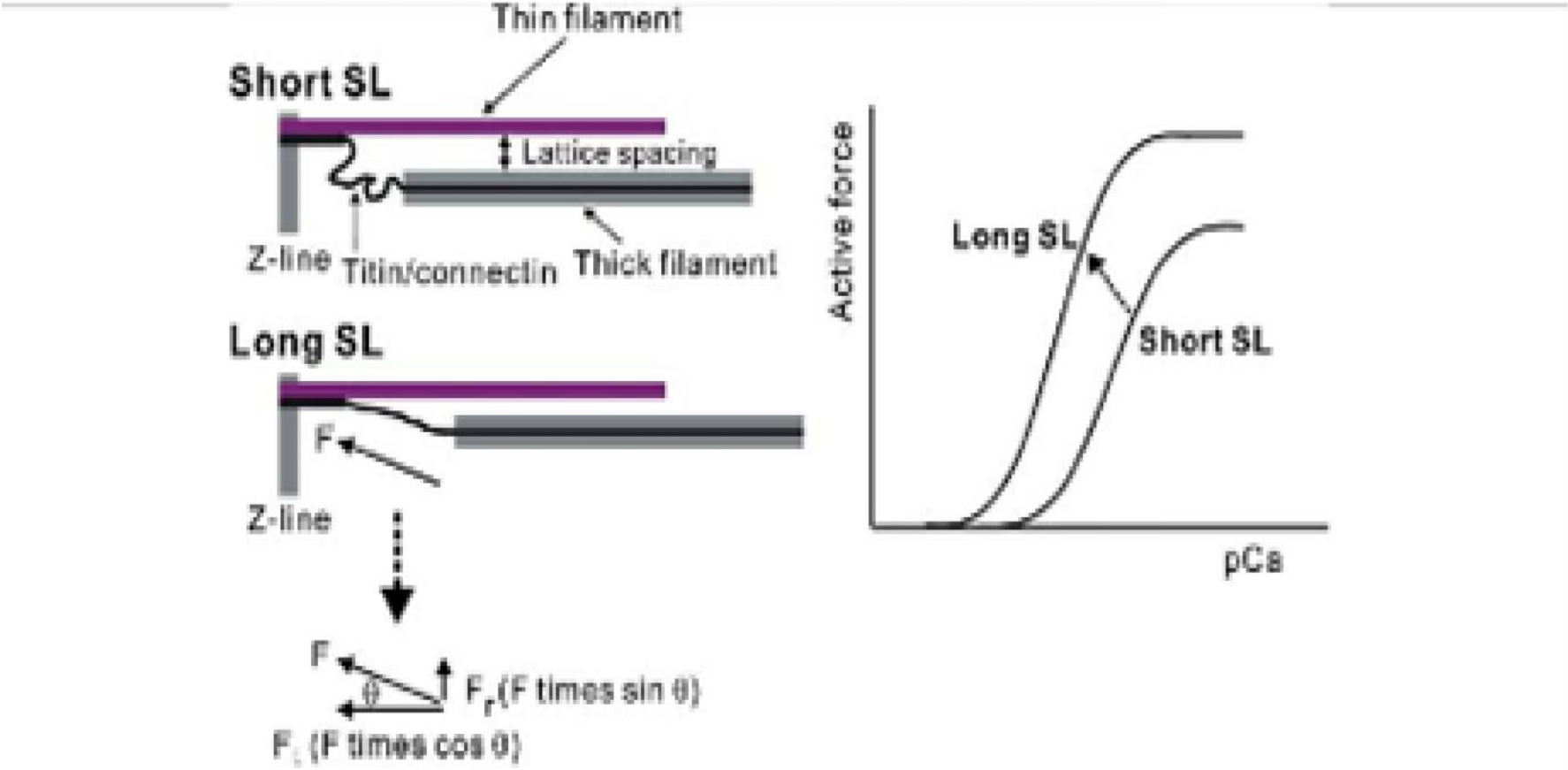
- Resting muscle containing ATP can be stretched easily
- Stretching force increases exponentially
- Resistance to stretch by elastic molecule **titin** (6/myosin fil.)
- **Stretch or sarcomere length determine maximal force**

Stretch → Sarcomere length: complex protein machinery




Domain Structure of Human Titin Isoforms
(Freiburg et al. Circ. Res., 2000)
Ig-like domain
FN3-like domain
kinase domain
sequence insertion
PEVK domain
Z-repeats
cardiac isoforms
N2-B
NH2
N2B
N2BA
skeletal isoforms
Z-disk
proximal tandem-Ig region
N2-A
PEVK
distal Ig region
NH2
N2A
inextensible
differential splicing
differential splicing
I-band titin
Actin
Myosin
Titin
Z
M
Z
A-band titin
COOH
super repeat region
kinase
M-line

Mechanisms of sarcomere sensitization upon increased stretch

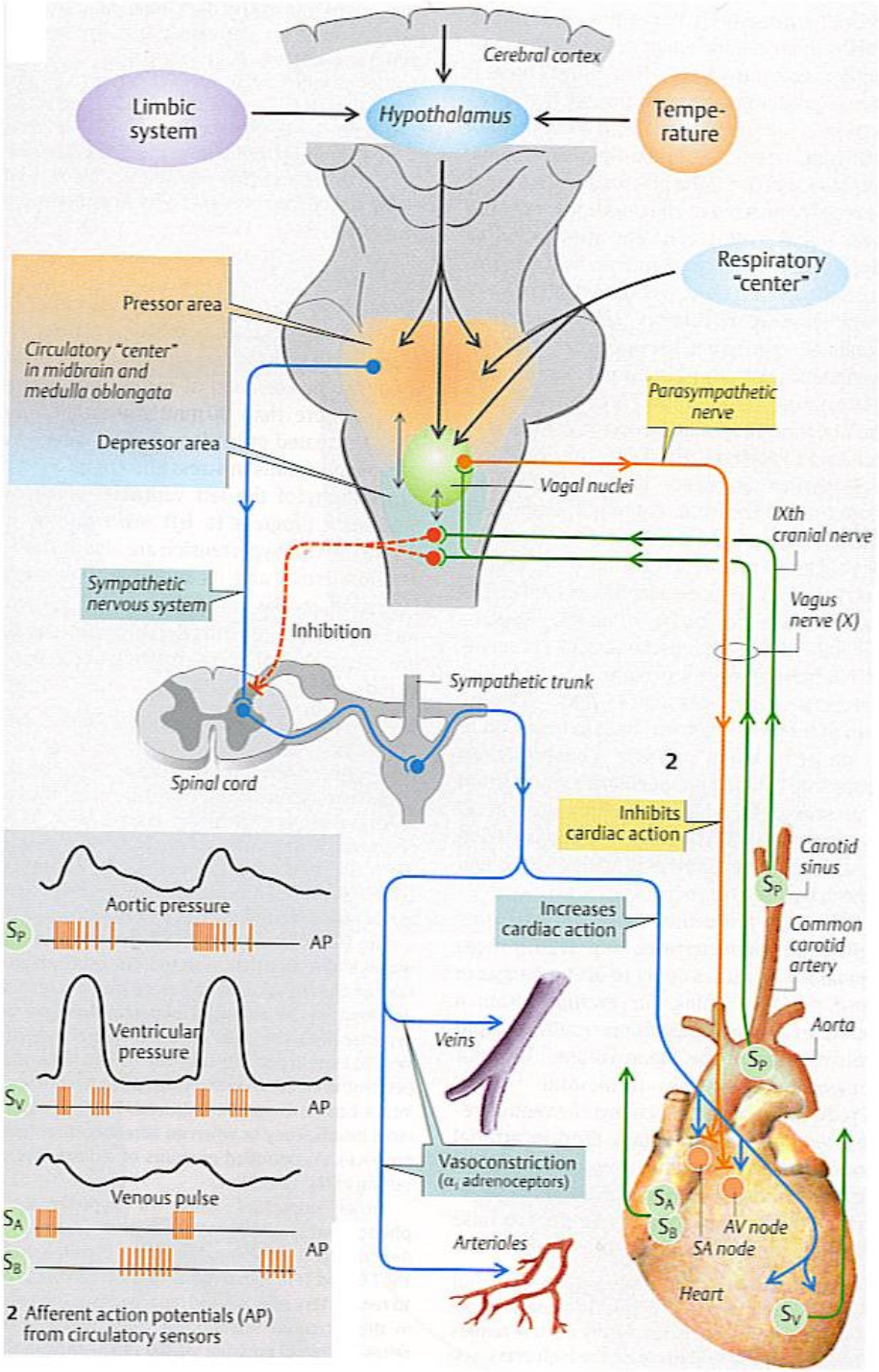


2- controllo neuroumorale dell'attivita' cardiaca: sistema nervoso autonomo

L'attivazione del sistema nervoso simpatico è il principale meccanismo neuroumorale che controlla continuamente l'attività cardiaca.

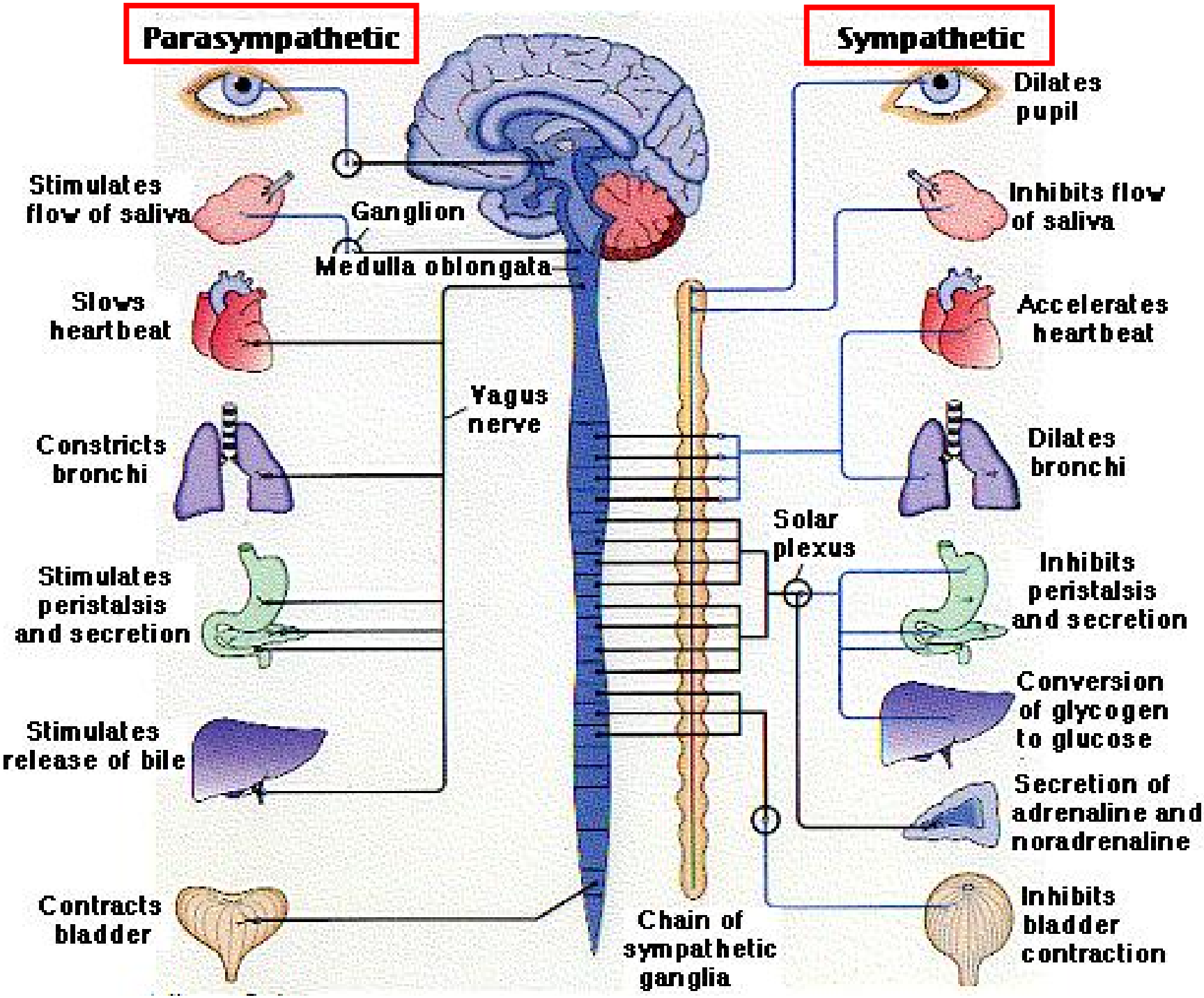
Variazioni posturali, aumentata domanda metabolica dell'organismo (p.es esercizio fisico), stress emozionale, calo del riempimento di sangue dell'albero vascolare, sono stimoli che inducono il rilascio di agonisti dei recettori adrenergici da parte dei nervi cardiaci e del surrene.

Il meccanismo sensore della domanda di sangue del circolo è principalmente attivato dalla ridotta pressione di perfusione in particolari distretti (es. arco aortico, carotide)



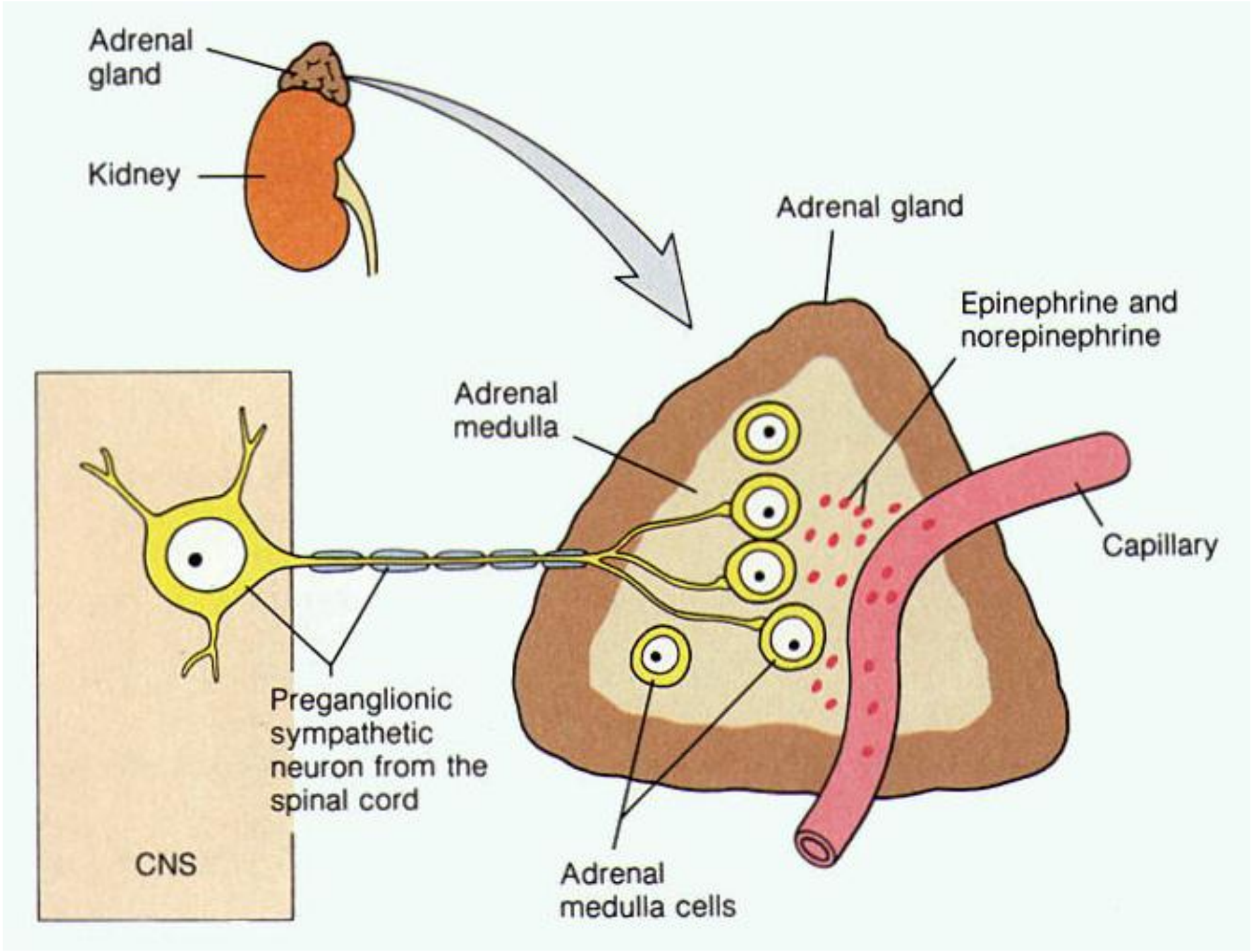
SNS Regulation

Medulla oblongata and pons CNS circulatory control centers
Circulatory sensors (S)
Baroceptors in high pressure system in aorta and carotid artery
Stretch-sensors in low pressure system atria and vena cava, and in the left ventricle
Sensors measure arterial blood pressure, pulse rate, and filling pressure (blood volume).
A sensors mainly react to atrial contraction.
B sensors react to passive filling stretch.
P sensors react to blood pressure stretch.
Pressor area which transmits sympathetic nerve impulses to the heart and vessels.
Depressor area transmits parasympathetic impulses to the heart.
Connected through dorsal nuclei of the vagus nerve for circulatory reflexes.
Also connected to respiratory center


Parasympathetic
Sympathetic
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Vagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction

Adrenergic nerves in rabbit heart

Schiaffino, unpublished

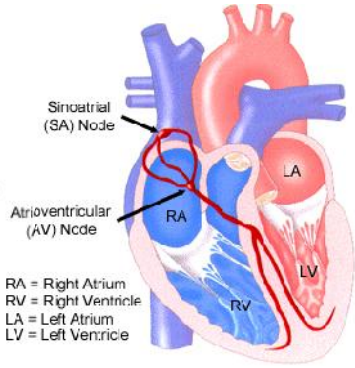

Adrenal gland
Kidney
Adrenal gland
Epinephrine and norepinephrine
Adrenal medulla
Capillary
Preganglionic sympathetic neuron from the spinal cord
CNS
Adrenal medulla cells

bersagli dell'attivazione del SNS

Catecolamine
(adrenalina,noradrenalina)

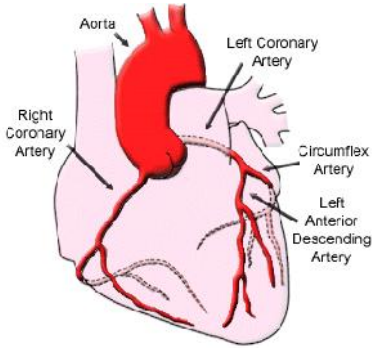
<u>miocardio contrattile:</u>

- Aumento della forza di contrazione (effetto inotropo)
- Aumento della capacità di rilasciamento (eff. Lusitropo)



<u>sistema di conduzione</u>

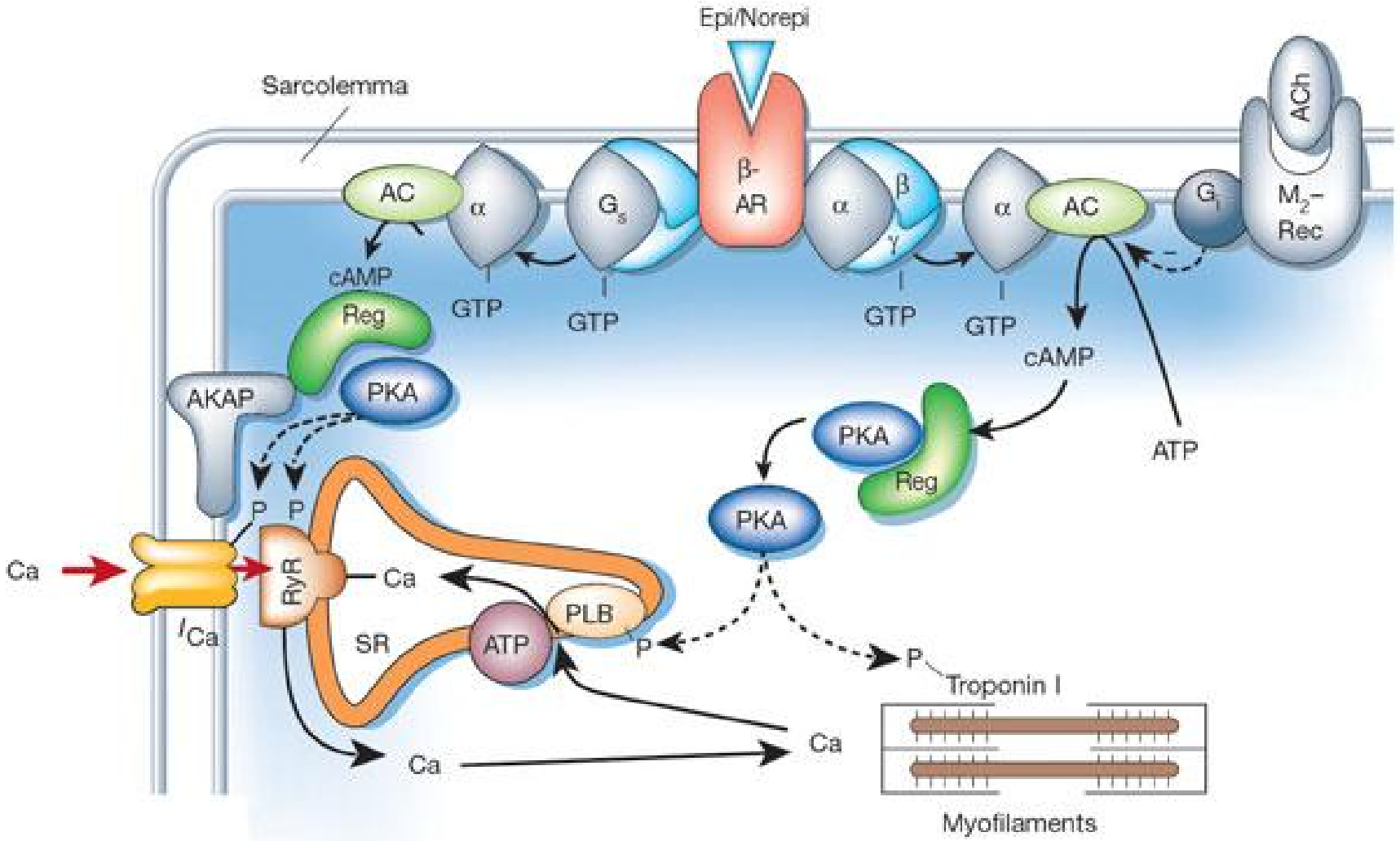
- Aumento della frequenza cardiaca (eff. cronotropo)



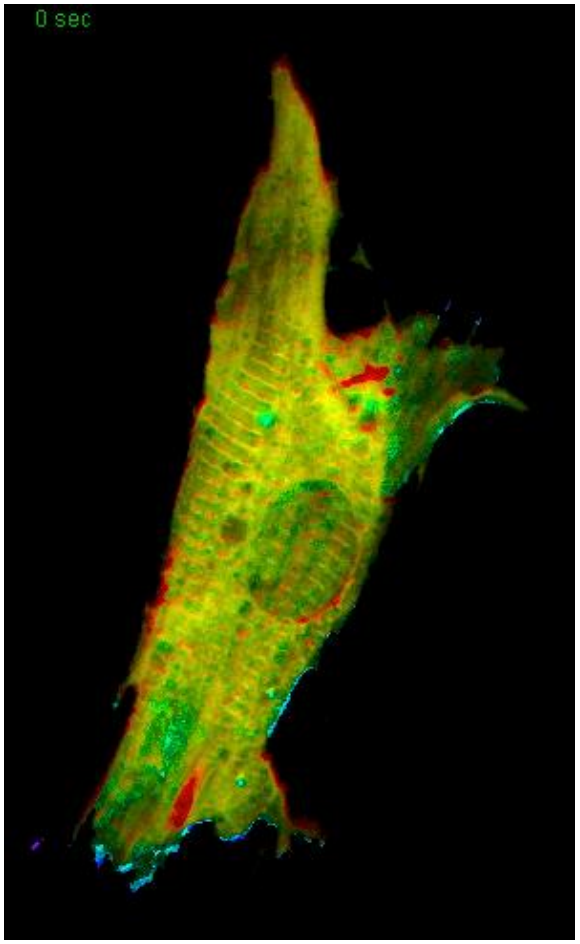
<u>vasi coronarici</u>

Vasodilatazione coronarica

Signal transduction of β-adrenergic receptor activation

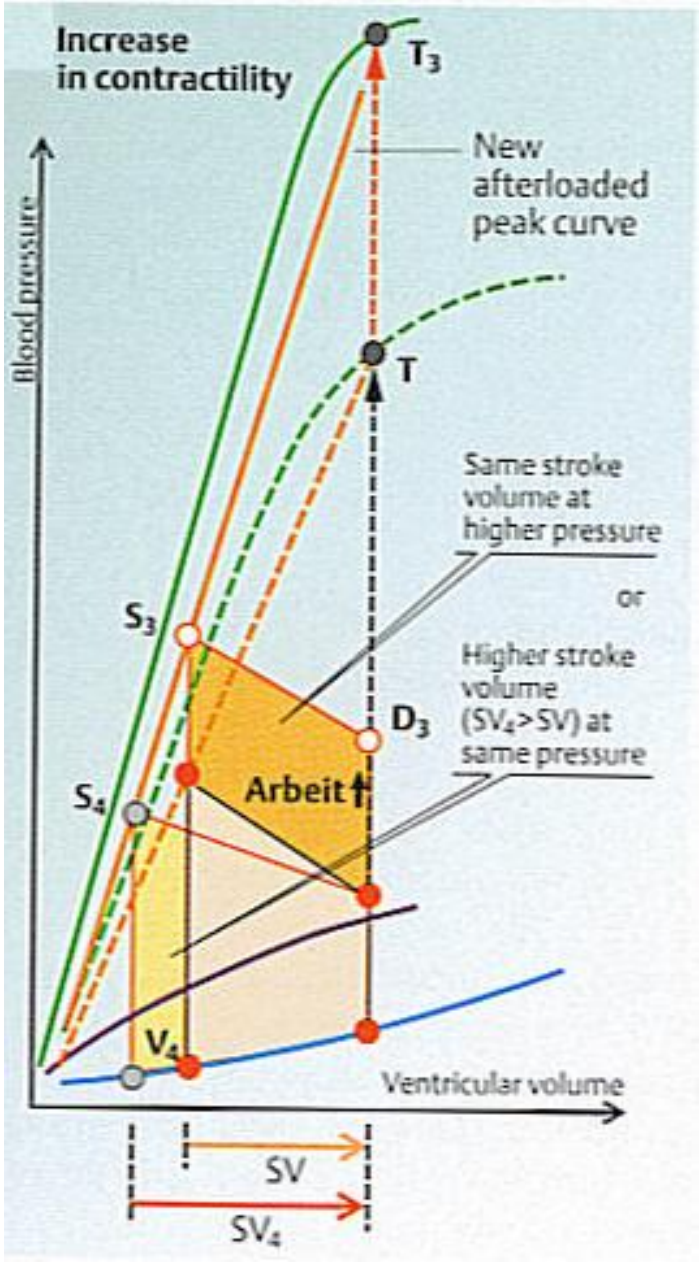


Stimulation of β-adrenergic receptors increases intracellular cAMP



Cardiomyocyte stimulated with
Noradrenaline (10nM)

Contractility/Inotropism Changes



β1-adrenoreptor stimulation

Increase isovolumic pressure peaks:
Increased pressure levels D3
Eject larger SV

Acceleration of relaxation:
Enable more rapid diastolic filling
Decreased end-diastolic pressure
SV_4 > SV, ESV decreased

Increased work and energy consumption