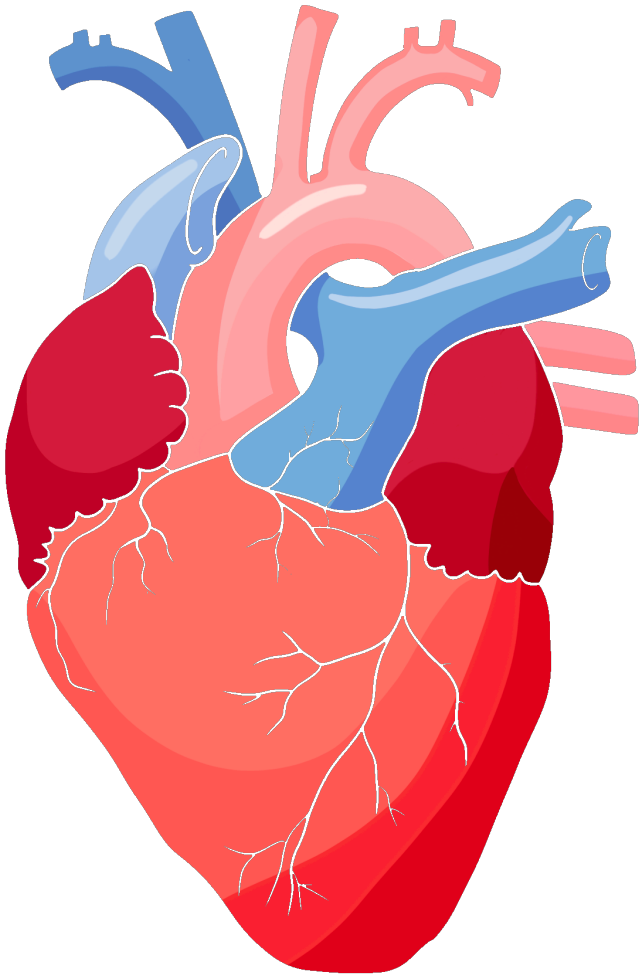

CARDIOVASCULAR PHYSIOLOGY

Ida Sletteng Karlsen • Trym Reiberg

Second Edition
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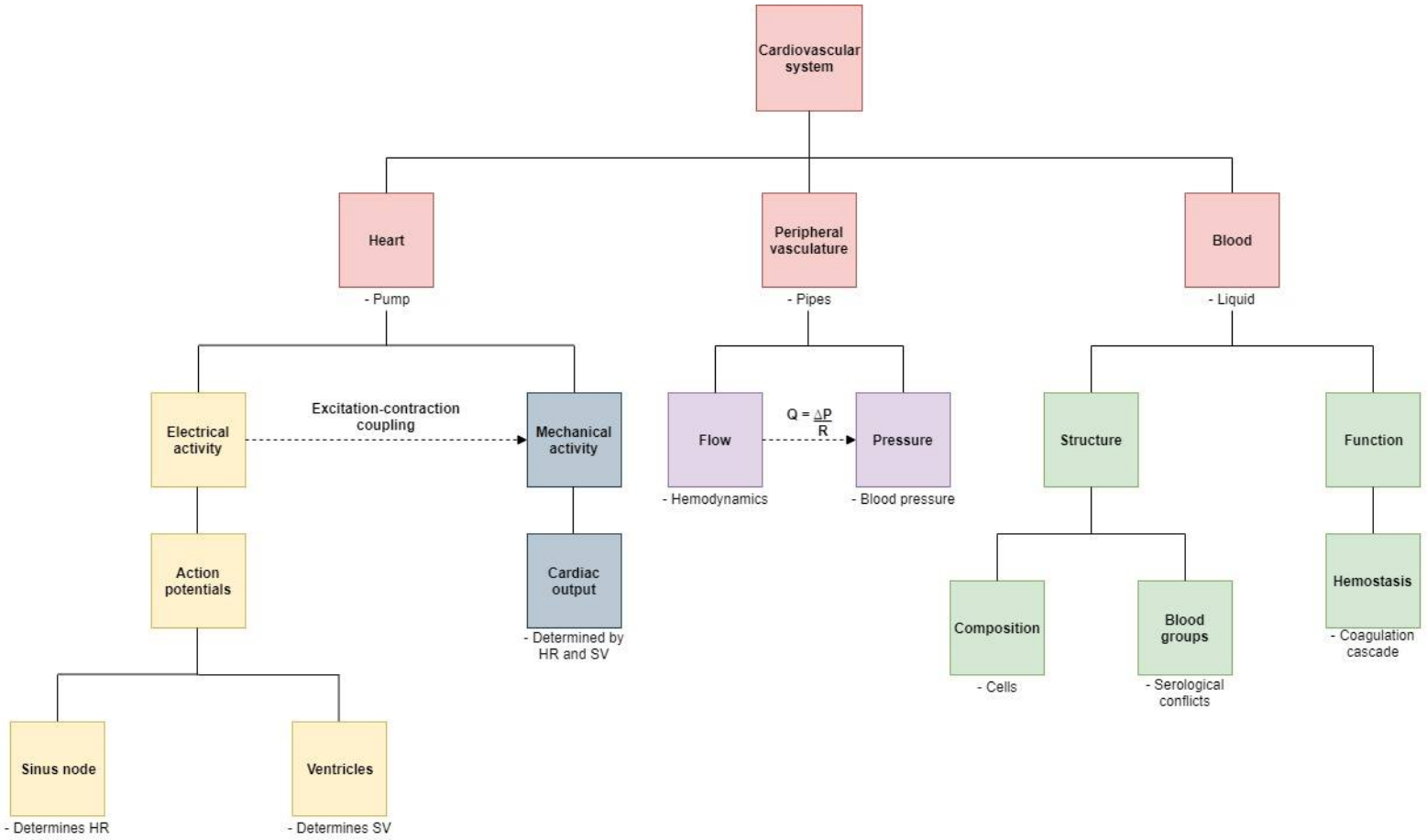
Section 1 – Overview of the Cardiovascular System

1.0 – Structure of the Cardiovascular System

- The cardiovascular system is a three-component system, consisting of the heart (*pump*), peripheral vasculature (*pipes*) and blood (*liquid*)
- In order to understand the system completely, it is important to acquire knowledge about all three components
- The flowchart below will function as the general structure of the booklet
- The topics will be presented from left to right



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2.1 – Connection Between Electrical – and Mechanical Activity
2.2 – Action Potentials
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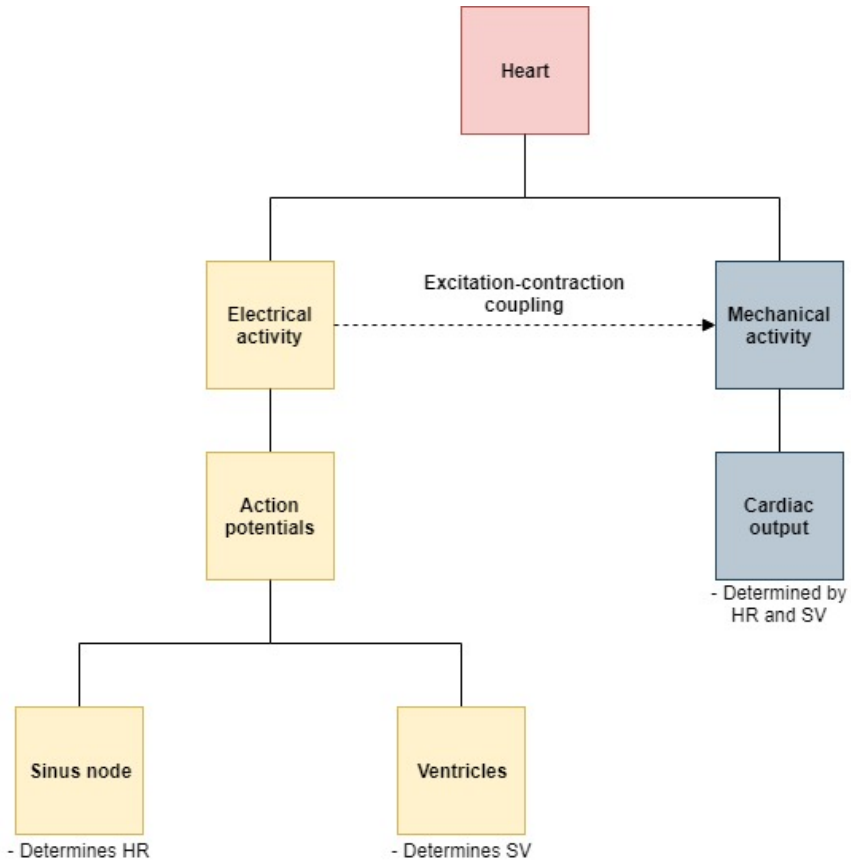
2.5 – Electrocardiography
2.6 – Test Yourself

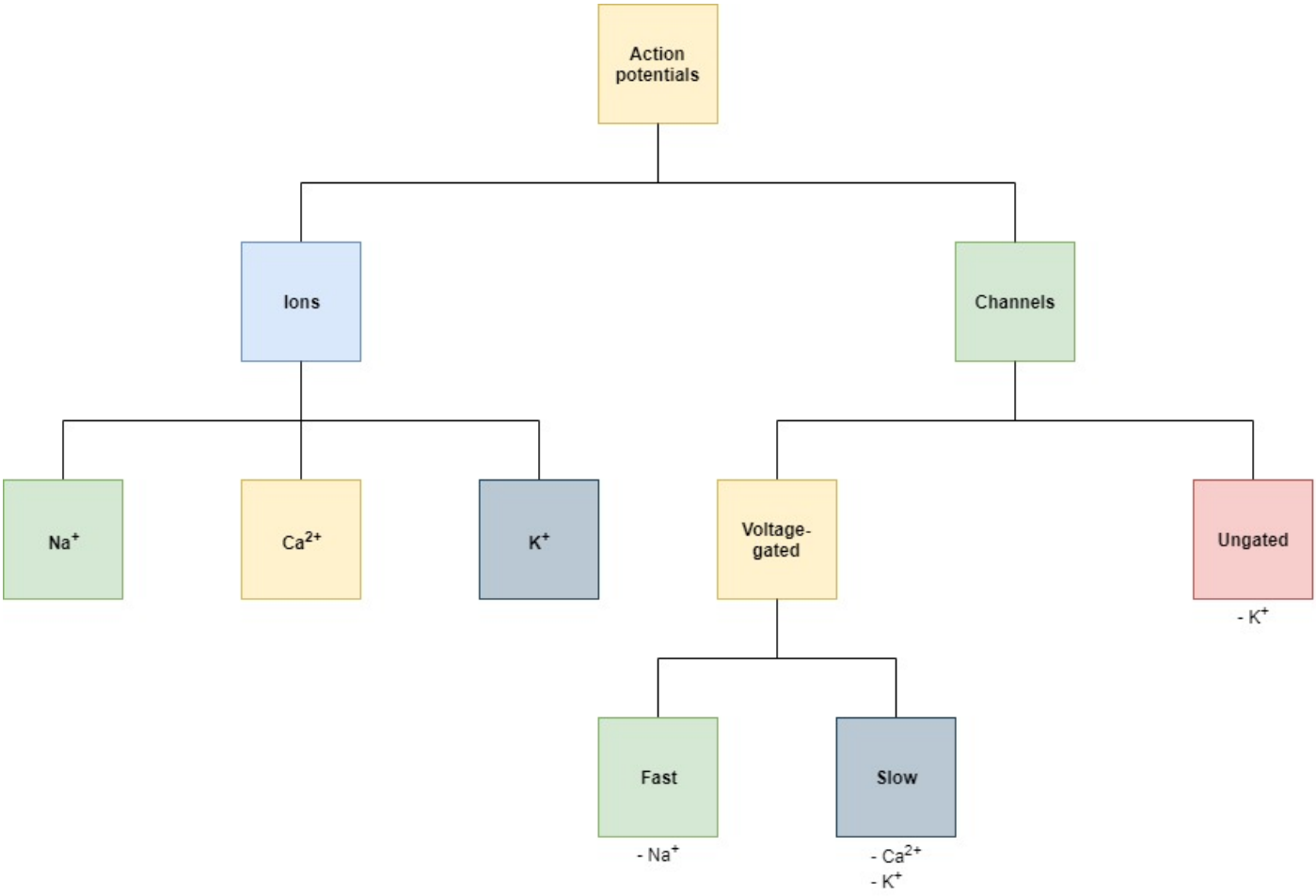
2.0 – Definition

- Cardiac electrophysiology is a term that covers everything associated with the electrical activity of the heart

2.1 – Connection Between Electrical – and Mechanical Activity of the Heart

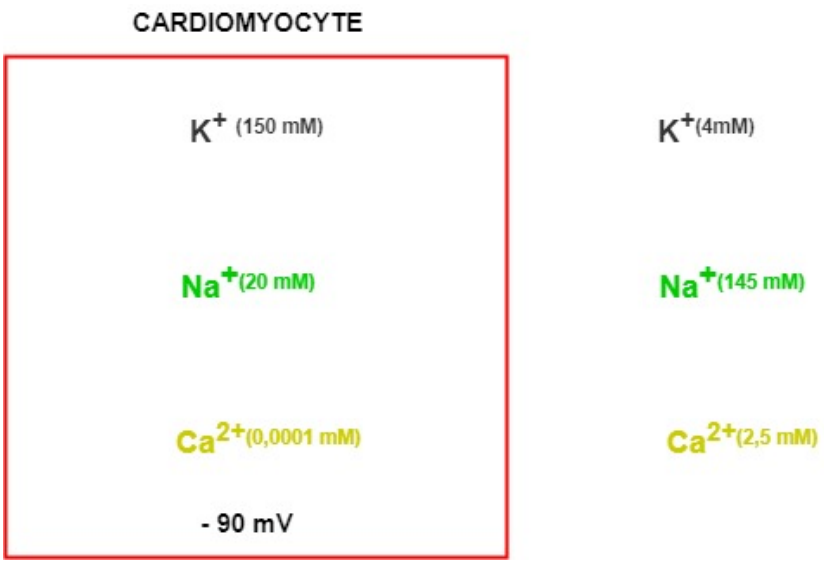


2.2 – Action Potentials



2.2.1 – Ions

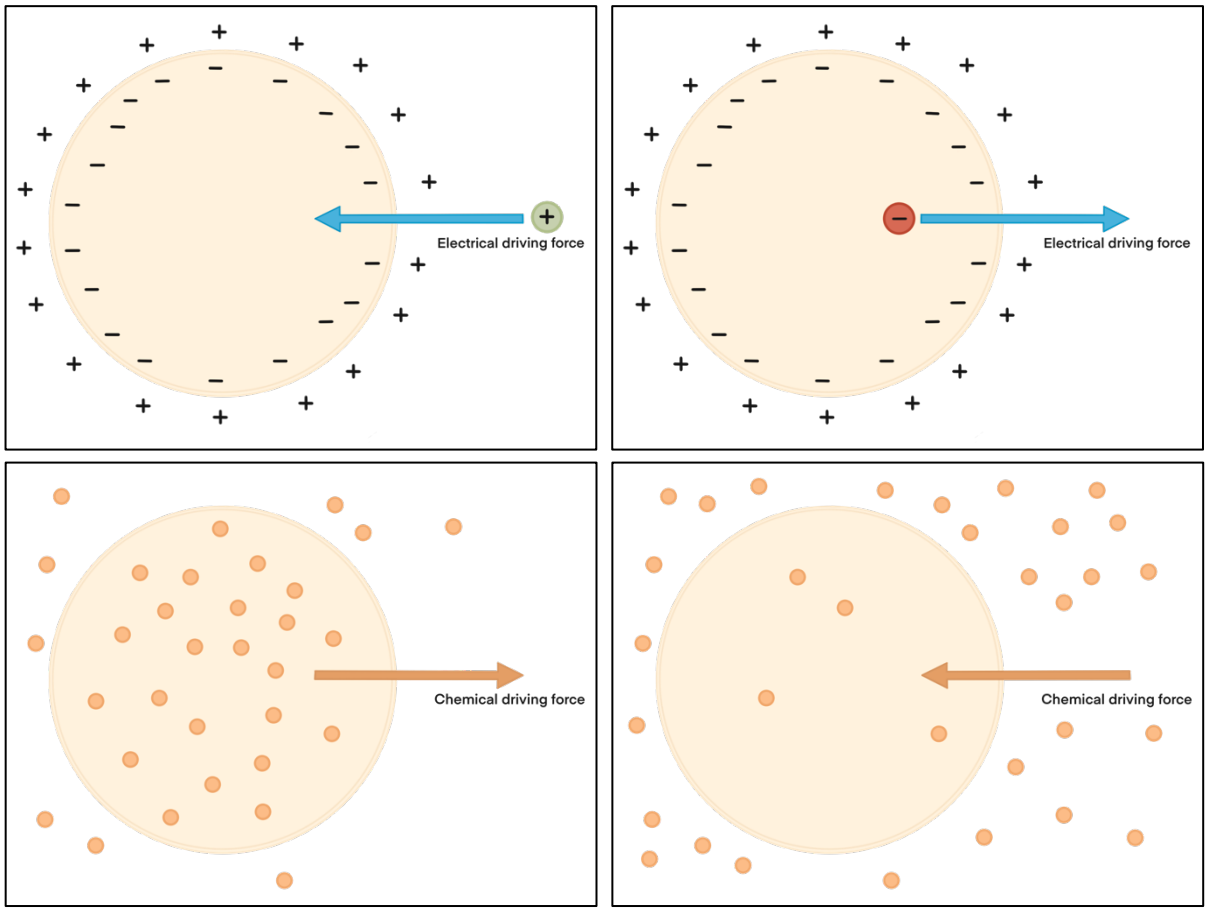
I. Distribution



II. Movement

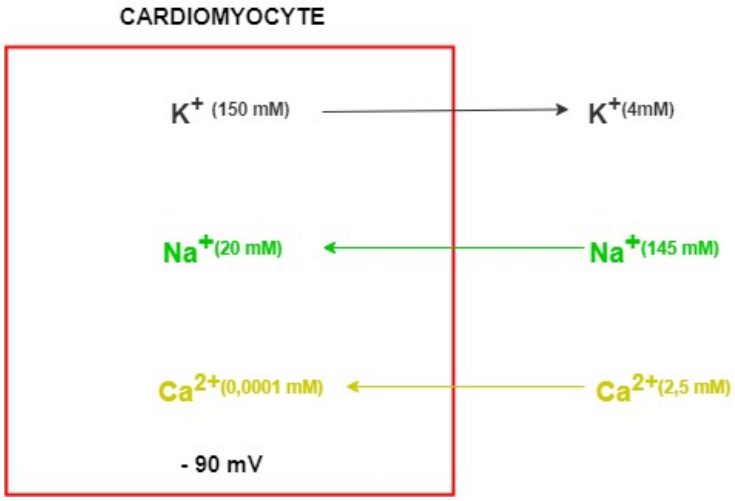
- There are two forces that drive the movement of ions across cellular membranes; electrical – and chemical forces

1. **<u>Electrical forces</u>:** Opposite charges attract each other
2. **<u>Chemical forces</u>:** An ion will diffuse from an area of higher concentration to an area of lower concentration



III. Examples

- **<u>Na^+</u>:** Goes *into* the cell, along the electrical – and chemical gradients
- **<u>Ca^{2+}</u>**: Goes *into* the cell, along the electrical – and chemical gradients
- **<u>K^+</u>:** Chemical gradient > electrical gradient → goes *out* of the cell



2.2.2 – Channels

	Mechanics	Ions	Rest	Depolarization
FAST voltage-gated channels	- Open fast - Close fast	Na^+	Closed	Open
SLOW voltage-gated channels	- Open slowly - Close slowly	- Ca^{2+} - K^+	Open	Closed
Ungated channels[1]	Always open	K^+	_____	_____

[1]The ungated channels are responsible for the resting membrane potential of the cardiomyocyte

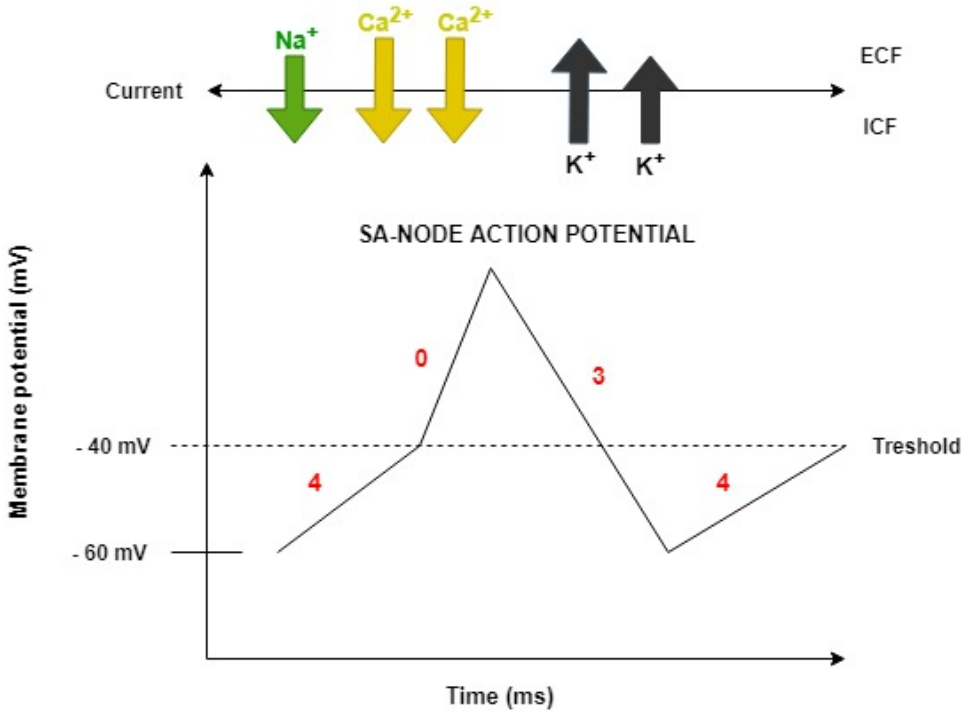
2.3 – Sinus Node Action Potential

2.3.1 – Phases

I. **Phase 4 (slow, spontaneous depolarization)**
- Na^+ influx through f-channels ("*funny current*")
- Ca^{2+} influx through slow voltage-gated Ca^{2+} channels (**T-type**)
- Absence of K^+ efflux

II. **Phase 0 (upstroke)**
- Ca^{2+} influx through slow voltage-gated Ca^{2+} channels (**L-type**)

III. **Phase 3 (repolarization)**
- K^+ efflux through slow voltage-gated – and ungated K^+ channels until the membrane potential is -60 mV



2.3.2 – Comparison of L – and T-type Ca^{2+} Channels

L-type Ca^{2+} channels	T-type Ca^{2+} channels
Long-lasting[1]	Transient[2]
Inhibited by calcium channel blockers	Not inhibited by calcium channel blockers
Mainly located in muscle tissue	Located in different tissues

[1] L for *long-lasting*

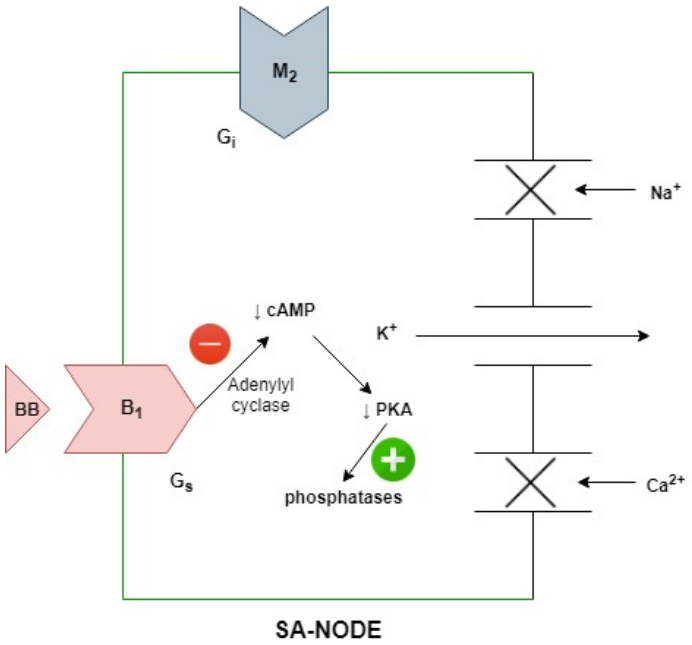
[2] T for *transient*

2.3.3 – Clinical Correlation

I. "What are the effects of BETA-BLOCKERS (BB) on the SA-node action potential and the heart rate?"

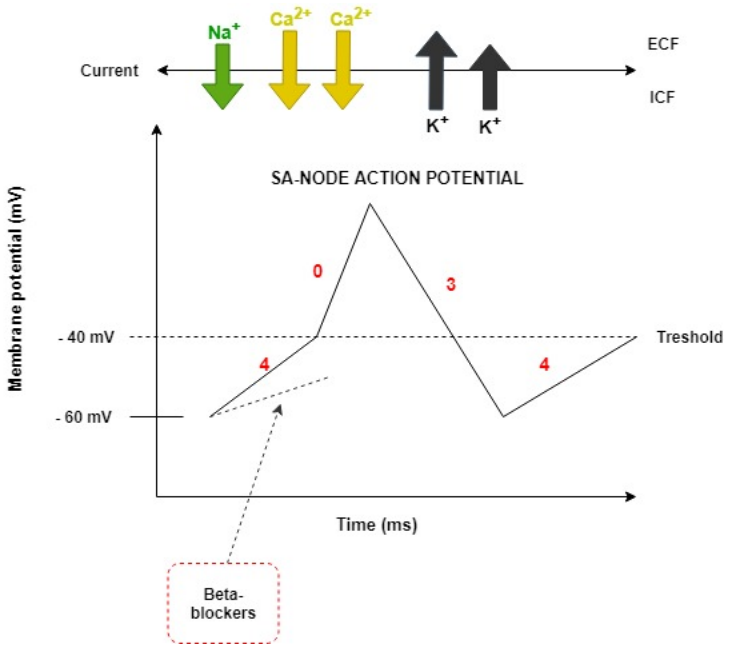
1. SA-node action potential

- Block B_1-receptors in the SA-node → inhibition of G_s-coupled receptor → inhibition of adenylyl cyclase → ↓cAMP → ↓PKA → activation of phosphatases → dephosphorylation of Na^+, Ca^{2+} - and K^+ channels → closure of Na^+ - and Ca^{2+} channels, opening of K^+ channels → K^+ efflux → ↓slope of phase 4



2. Heart rate

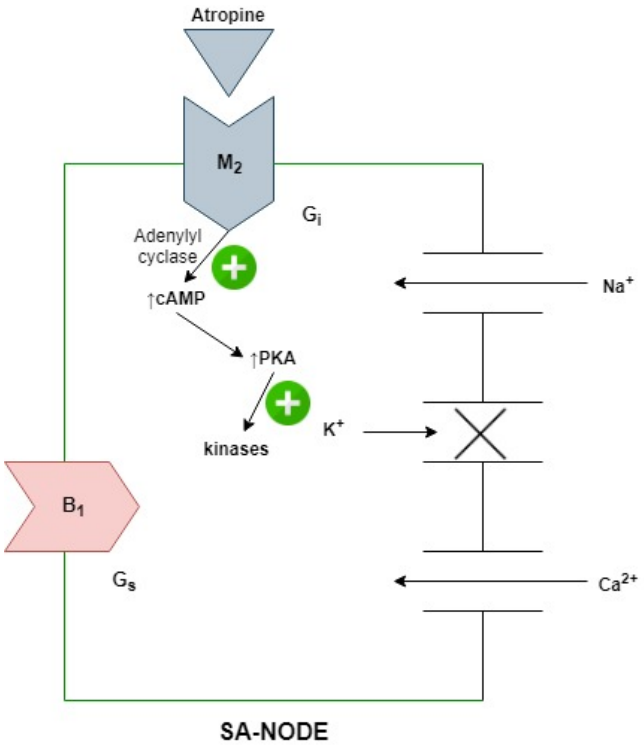
- ↓Slope of phase 4 → ↓HR



II. "What are effects of ATROPINE on the SA-node action potential and the heart rate?"

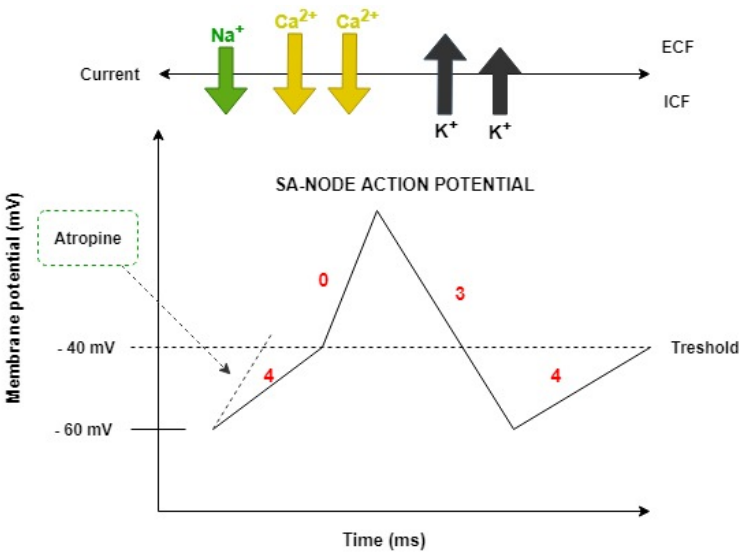
1. SA-node action potential

- Blocks M_2-receptors in the SA-node → inhibition of G_i-coupled receptor → disinhibition → stimulation of adenylyl cyclase → ↑cAMP → ↑PKA → activation of kinases → phosphorylation of Na^+, Ca^{2+} - and K^+ channels → opening of Na^+ - and Ca^{2+} channels, closure of K^+ channels → Na^+ - and Ca^{2+} influx → ↑slope of phase 4



2. Heart rate

- ↑Slope of phase 4 → ↑HR



2.4 – Ventricular Action Potential

2.4.1 – Phases

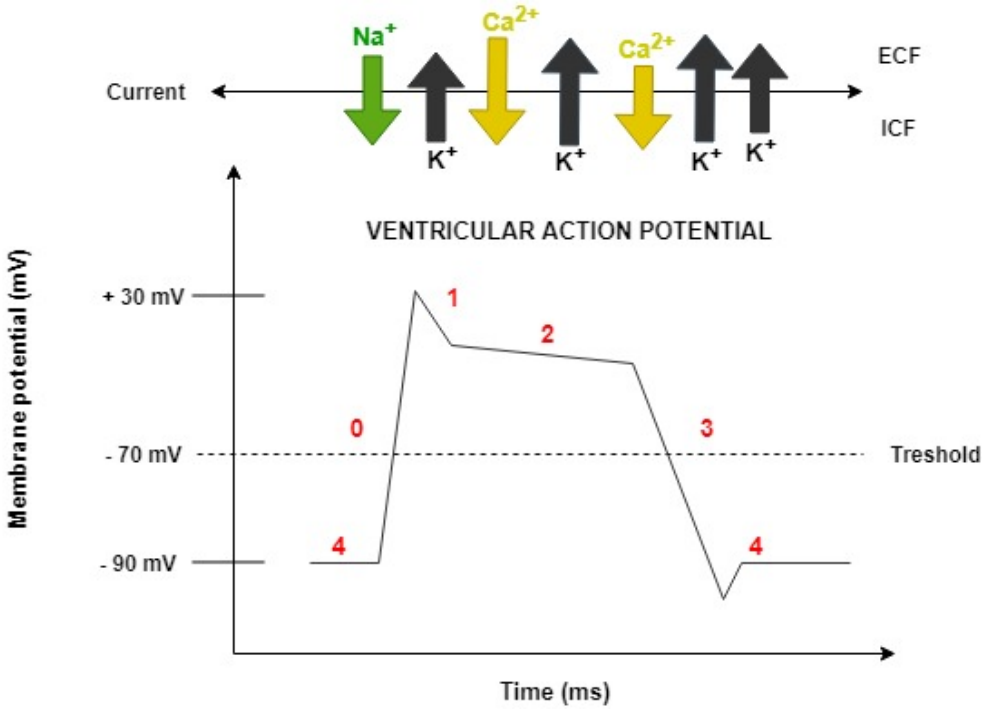
I. **Phase 0 (upstroke)**
- Rapid Na^+ influx through fast voltage-gated Na^+ channels

II. **Phase 1 (transient repolarization)**
- Closure of fast voltage-gated Na^+ channels
- Transient K^+ efflux

III. **Phase 2 (plateau)**
- Ca^{2+} influx through slow voltage-gated Ca^{2+} channels (**L-type**)
- K^+ efflux through slow voltage-gated – and ungated K^+ channels

IV. **Phase 3 (repolarization)**
- Closure of slow-voltage gated Ca^{2+} channels (**L-type**)
- K^+ efflux through slow voltage-gated – and ungated K^+ channels

V. **Phase 4 (resting phase)**
- Increased activity of the Na^+/K^+ ATP-ase → restoration of the resting membrane potential

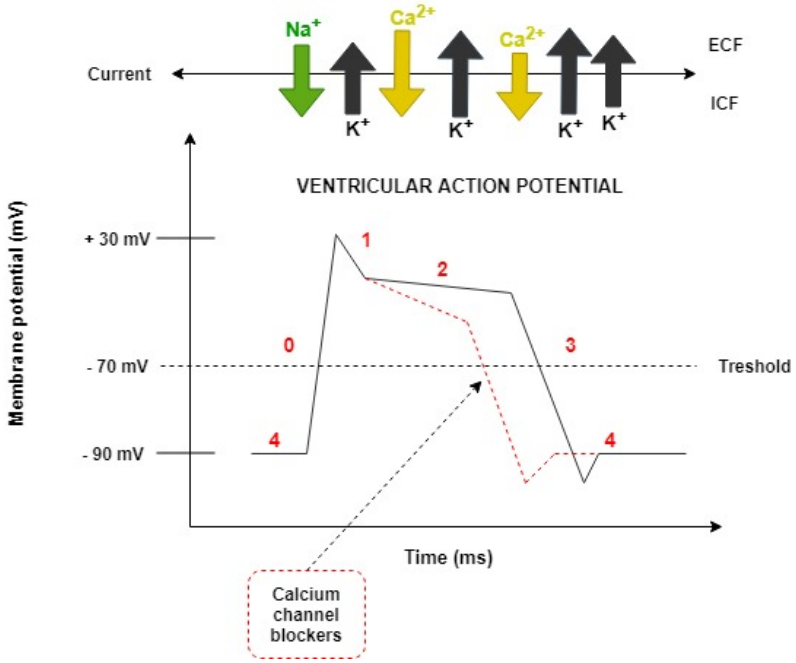


2.4.2 – Clinical Correlation

I. "What are the effects of CA^{2+} CHANNEL BLOCKERS (CCB) on the ventricular action potential and the stroke volume?"

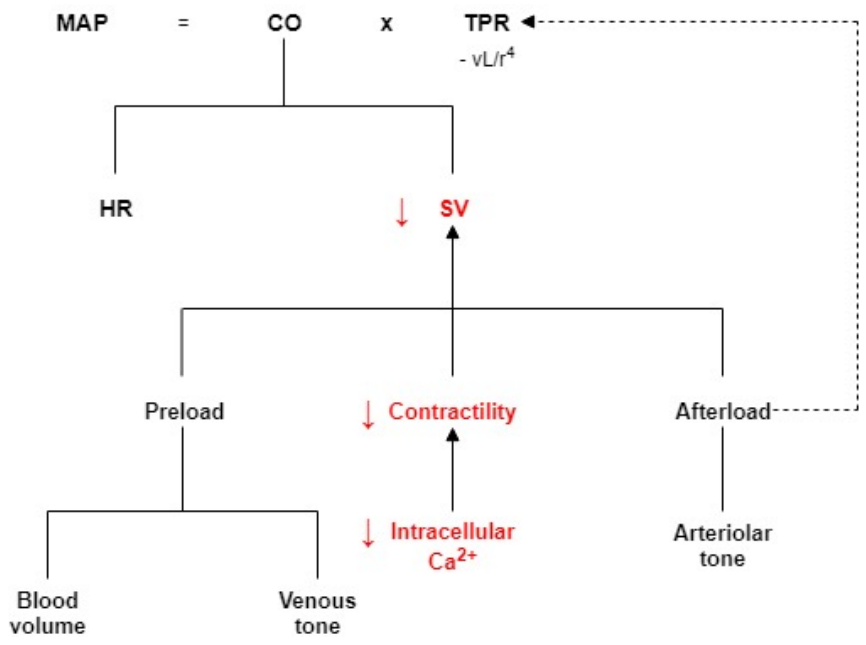
1. Ventricular action potential

- Block L-type Ca^{2+} channels → ↓Ca^{2+} influx → shortening of the plateau phase



2. Stroke volume

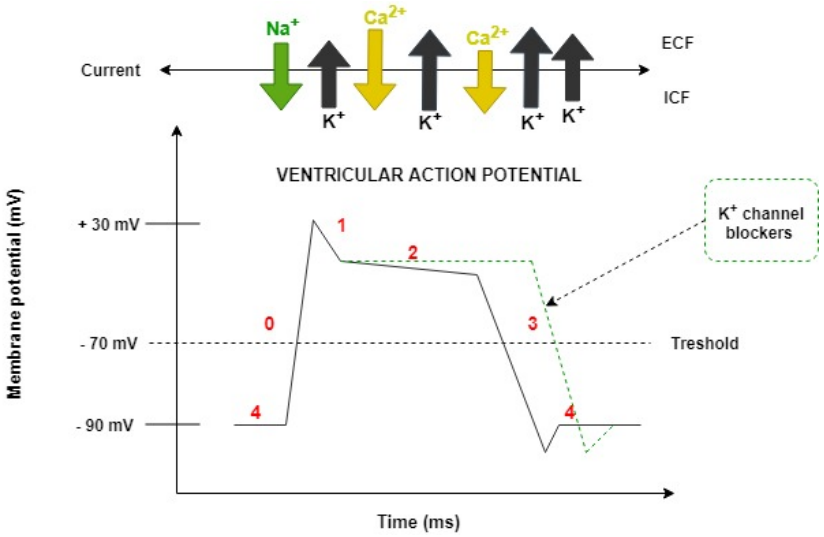
- Shortening of the plateau phase → ↓Ca^{2+} influx → ↓intracellular Ca^{2+} → ↓contractility → ↓SV



II. "What are the effects of K^+ CHANNEL BLOCKERS on the ventricular action potential and the stroke volume?"

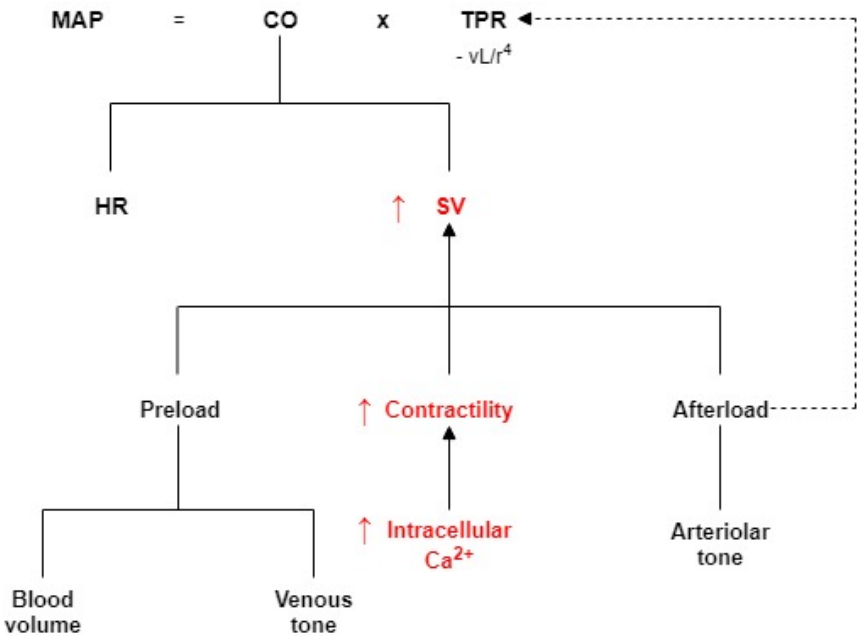
1. Ventricular action potential

- Block K^+ channels → ↓K^+ efflux → prolongation of the plateau phase



2. Stroke volume

- Prolongation of the plateau phase → ↑ Ca^{2+} influx → ↑intracellular Ca^{2+} → ↑contractility → ↑SV



2.4.3 – Comparison of the Sinus Node – and Ventricular Action Potential

	Depolarization	Plateau	Repolarization	APD	Event
SA-node	Ca^{2+} influx	- [1]	K^+ efflux	150 ms	HR
Ventricles	Na^+ influx	Ca^{2+} influx	K^+ efflux	250 ms[2]	SV

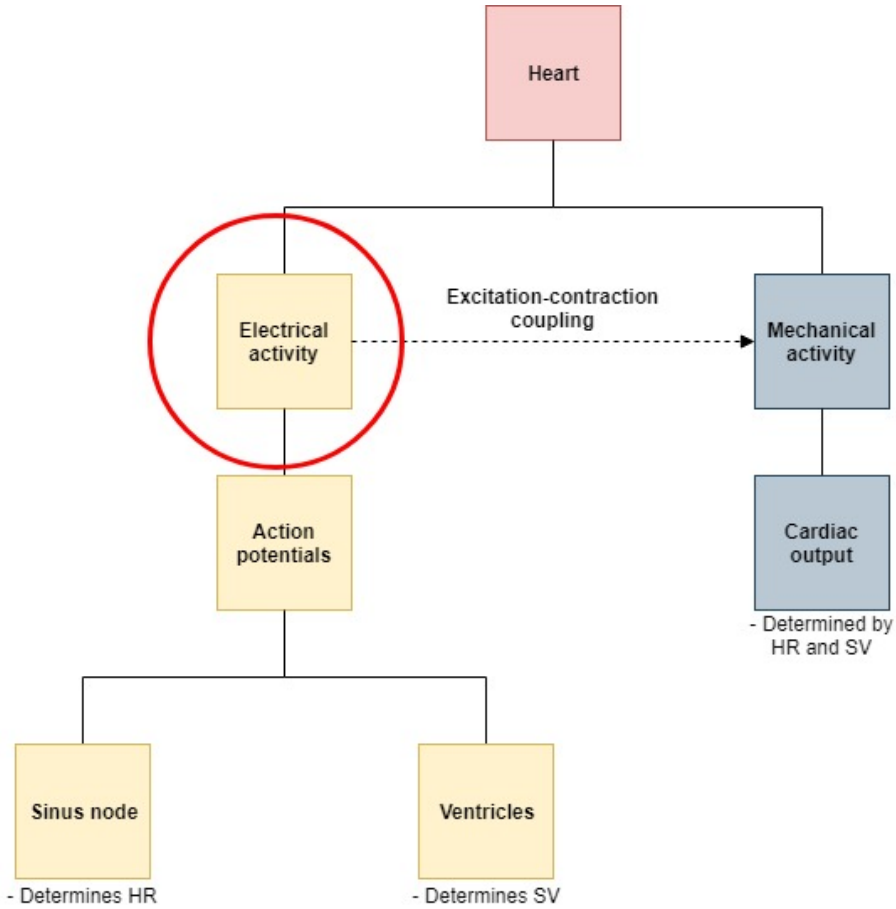
[1] Since there is no plateau phase in the SA-node action potential, there is no phase 1 or phase 2 (*as in the ventricular action potential*)

[2] Of all the action potentials in the human body, the action potential of the ventricles is the longest. This is because the ventricles need time to eject the blood.

2.5 – Electrocardiography

2.5.1 – Definition

- Electrocardiography (ECG) is a recording of the electrical activity of the heart
- The electrical activity of the heart is synonymous with action potentials
- Action potentials are composed of depolarization and repolarization
- Therefore, everything we can see on the ECG are manifestations of the two, fundamental electrical events in the heart; depolarization and repolarization



2.5.2 – Normal Pattern of Conduction in the Heart

I. SA-node

- The SA-node fires spontaneously and a wave of depolarization spreads into the atria through the internodal pathways and the Bachmann's bundle

II. AV-node

- The wave of depolarization enters the AV-node
- In the AV-node, the electrical impulse is slowed down in order to ensure that the ventricles have filled before they contract

III. Bundle of His

- From the AV-node, the wave of depolarization enters the bundle of His

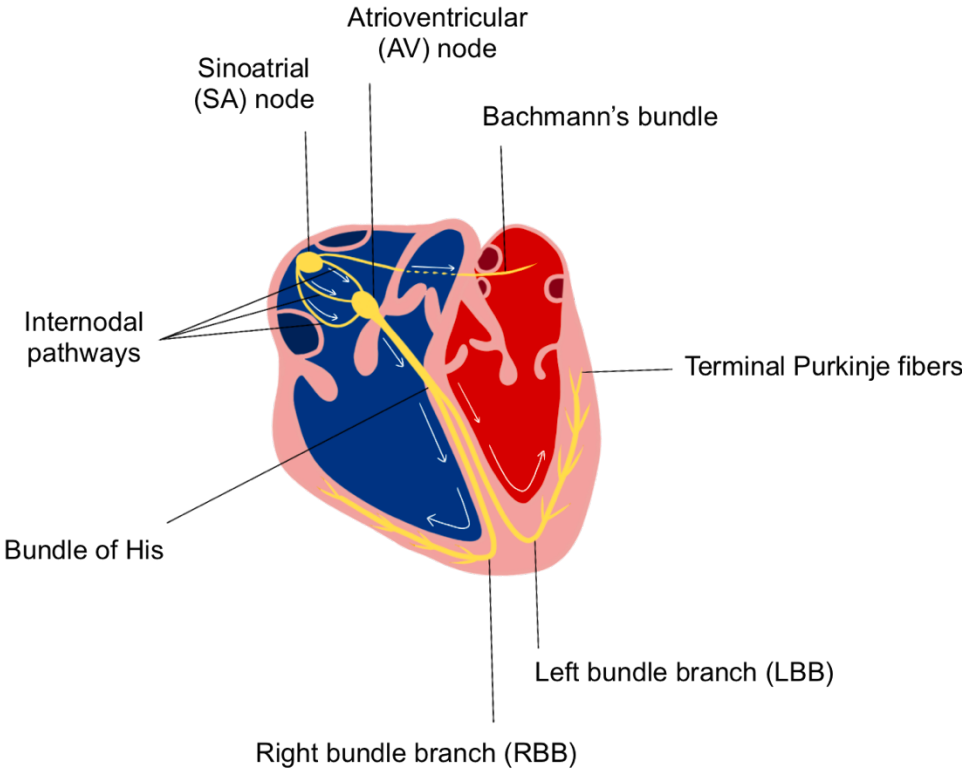
IV. Bundle branches

- The bundle of His divides into the right bundle branch (RBB) and the left bundle branch (LBB)
- The RBB is responsible for depolarization of the right side of the interventricular septum and the walls of the right ventricle, while the LBB is responsible for depolarization of the left side of the interventricular septum and the walls of the left ventricle

V. Purkinje system

- The bundle branches terminate into Purkinje fibers
- The Purkinje system delivers the current into the ventricular myocardium

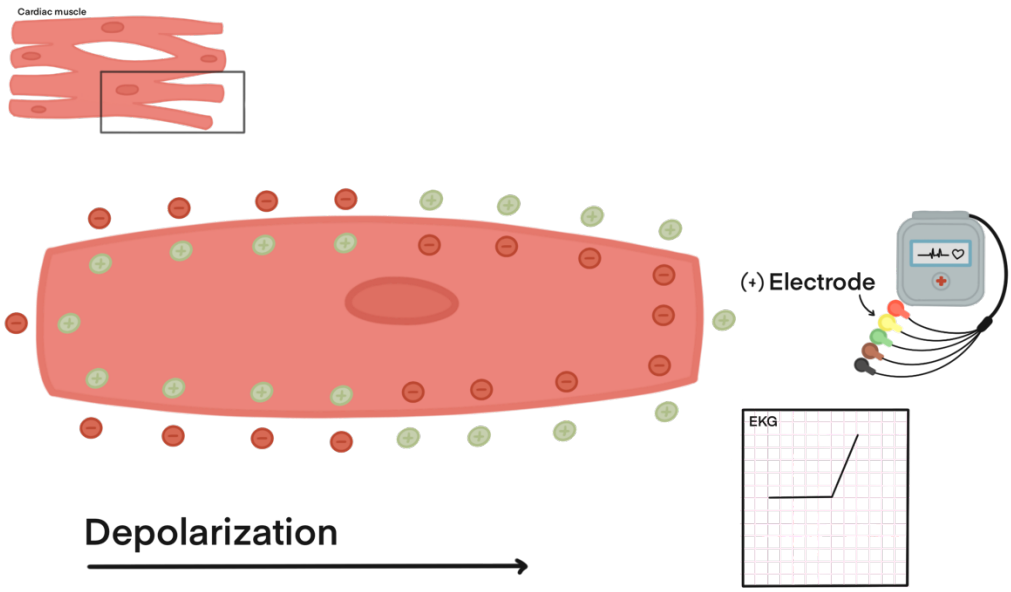
Note: Just as there is a wave of depolarization, there is a wave of repolarization – which travels in the opposite direction



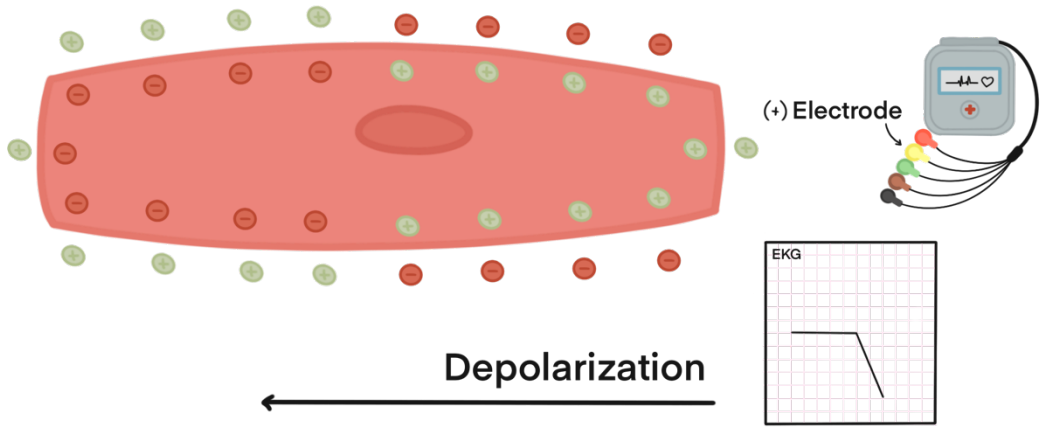
2.5.3 – Making Waves

I. Depolarization

- A wave of **depolarization** that moves **towards** an electrode gives a **positive** deflection

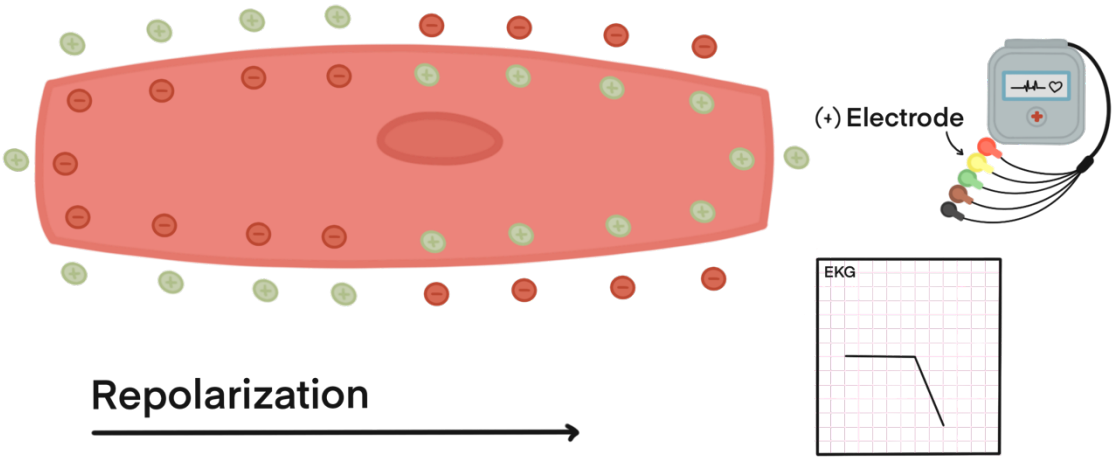


- A wave of **depolarization** that moves **away** from an electrode gives a **negative** deflection

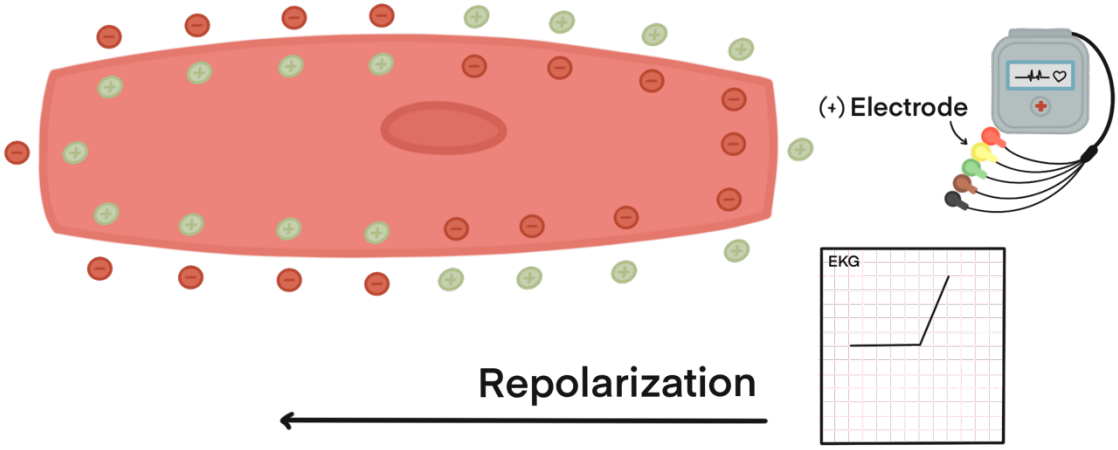


II. Repolarization

- A wave of **repolarization** that moves **towards** an electrode gives a **negative** deflection



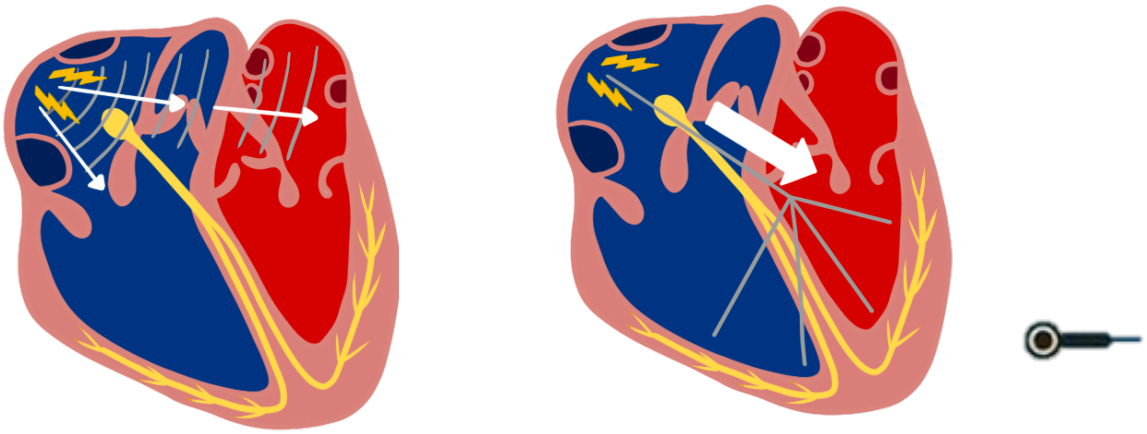
- A wave of **repolarization** that moves **away** from an electrode gives a **positive** deflection

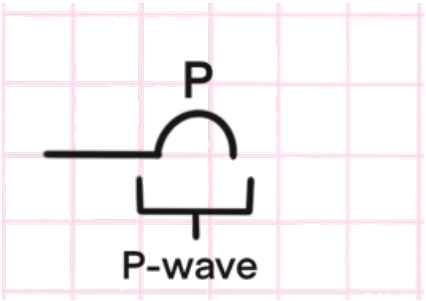


2.5.4 – Normal ECG

I. P-wave

- The sinus node fires spontaneously (*an event <u>not</u> visible on the ECG*)
- A wave of depolarization spreads from the SA-node and outward into the atria, resulting in atrial depolarization
- The mean vector of atrial depolarization is directed as shown in the figure
- The ECG will record a P-wave
- Depolarization of the atria results in atrial contraction

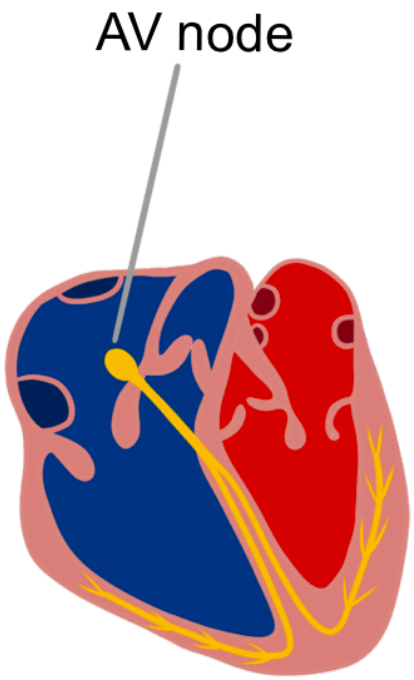


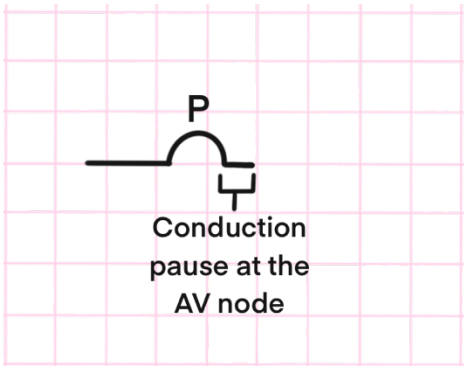


Electrical event	ECG	Mechanical event
Atrial depolarization	P-wave	Atrial contraction

II. PR-segment

- The wave of depolarization from the atria is prevented from communicating with the ventricles by the atrioventricular valves, which function as electrical gatekeepers
- Therefore, the wave of depolarization must pass through the AV-node, which slows conduction
- The ECG will record a flat line (*PR-segment*)
- This physiological delay in conduction is important, because it ensures that the ventricles have filled adequately before they contract



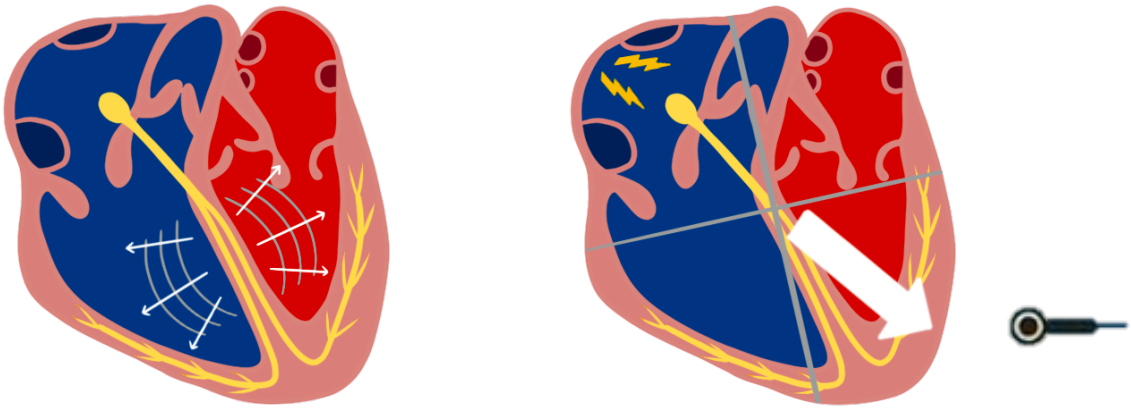


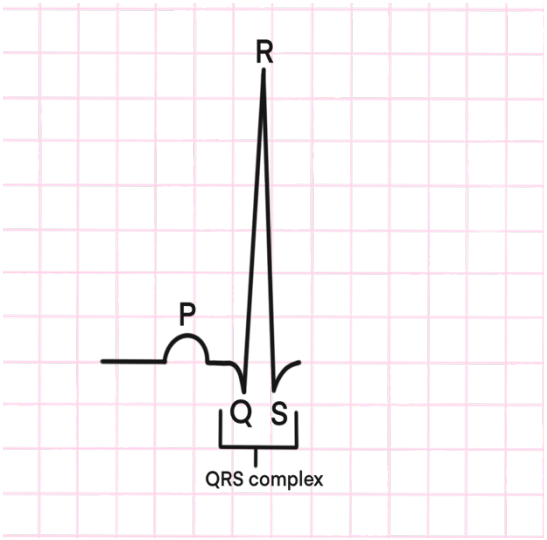
Electrical event	ECG	Mechanical event
Physiological delay in conduction	PR-segment	End of atrial contraction[1]

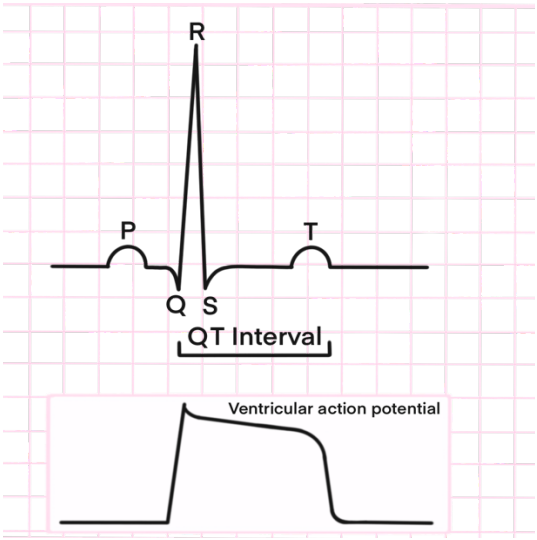
[1] The atria are no longer contracting, but blood is still flowing into the ventricles

III. QRS-complex

- After the physiological delay in conduction, the wave of depolarization escapes the AV-node and sweeps through the ventricles
- The mean vector of ventricular depolarization is directed as shown in the figure
- The ECG records a QRS-complex
- Ventricular depolarization results in ventricular contraction





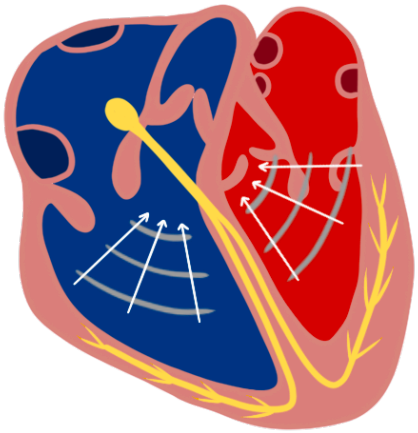


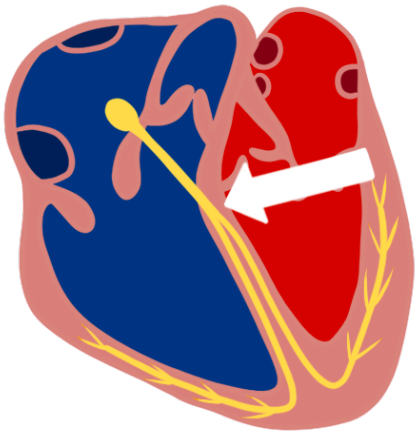
Electrical event	ECG	Mechanical event
- Ventricular depolarization - Atrial repolarization[1]	QRS complex	- Ventricular contraction - Atrial relaxation

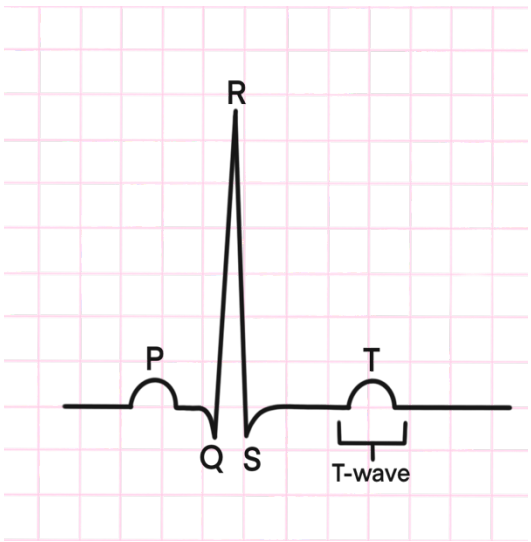
[1] Repolarization of the atria occurs simultaneously as the depolarization of the ventricles and is hidden by the more dominant QRS-complex

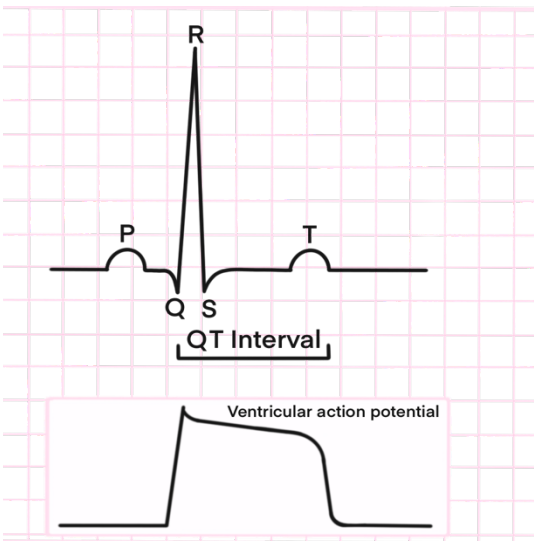
IV. T-wave

- After the ventricles have depolarized, they begin to repolarize
- Just as there is a wave of depolarization, there is a wave of repolarization
- The mean vector of ventricular repolarization is directed as shown in the figure
- The ECG records a T-wave
- Ventricular repolarization results in ventricular relaxation









Electrical event	ECG	Mechanical event
Ventricular repolarization	T-wave	Ventricular relaxation

2.6 – Test Yourself

1) Which ion(s) is/are responsible for connecting the electrical – and mechanical activity of the heart?

a) Na^+
b) K^+
c) Ca^{2+}
d) Cl^-
e) All of the above

2) Which ion(s) is/are responsible for the resting membrane potential of the cardiomyocyte?

a) Na^+
b) K^+
c) Ca^{2+}
d) None of the above
e) All of the above

3) Which phase of the action potential in the SA-node is responsible for the heart rate?

a) Phase 3
b) Phase 0
c) Phase 4
d) Phase 1
e) Phase 2

4) What is correct regarding contractility of the heart?

a) The contractility of the heart is directly proportional to the concentration of Ca^{2+}
b) The contractility of the heart is unaffected by Ca^{2+}
c) The contractility of the heart is inversely proportional to the concentration of Ca^{2+}
d) Contractility is the only factor affecting stroke volume
e) A and D are correct

5) What is the correct sequence of conduction of electrical activity in the heart?

a) SA-node → His bundle → internodal tracts → AV-node → bundle branches → Purkinje fibers
b) SA-node → internodal tracts → AV-node → His bundle → Purkinje fibers → bundle branches
c) SA-node → internodal tracts → AV-node → His bundle → bundle branches → Purkinje fibers
d) SA-node → bundle branches → AV-node → internodal tracts → His bundle → Purkinje fibers
e) None of the above

6) During normal conduction of electrical activity in the heart - how long is the physiological delay in the AV-node?

a) 50 ms
b) 70 ms
c) 100 ms
d) 110 ms
e) None of the above

7) Select the correct statement regarding making waves in ECG.

a) A wave of depolarization moving away from an electrode gives a positive deflection
b) A wave of repolarization moving towards an electrode gives a negative deflection
c) A wave of depolarization moving away from an electrode gives a negative deflection
d) A wave of repolarization moving towards an electrode gives a positive deflection
e) B and C are correct

8) Pair the correct electrical event and phase of the cardiac cycle.

a) Atrial depolarization – late diastole
b) Ventricular depolarization – early systole
c) Atrial repolarization – early diastole
d) A and B are correct
e) All of the above

9) ECG is an important tool in clinical medicine. What does the ECG record?

a) Cardiac output
b) Action potentials
c) Depolarization and repolarization
d) B and C are correct
e) All of the above

10) What is the correct sequence of electrical events in the heart?

a) Atrial depolarization → conduction through the AV-node → ventricular depolarization + atrial repolarization → ventricular repolarization
b) Conduction through the AV-node → atrial depolarization → ventricular depolarization → atrial repolarization → ventricular repolarization
c) Atrial depolarization → conduction through the AV-node → ventricular depolarization → ventricular repolarization → atrial repolarization
d) A and C are correct
e) None of the above

Section 3 – Cardiac Muscle Mechanics

3.0 – Systolic Performance of the Left Ventricle

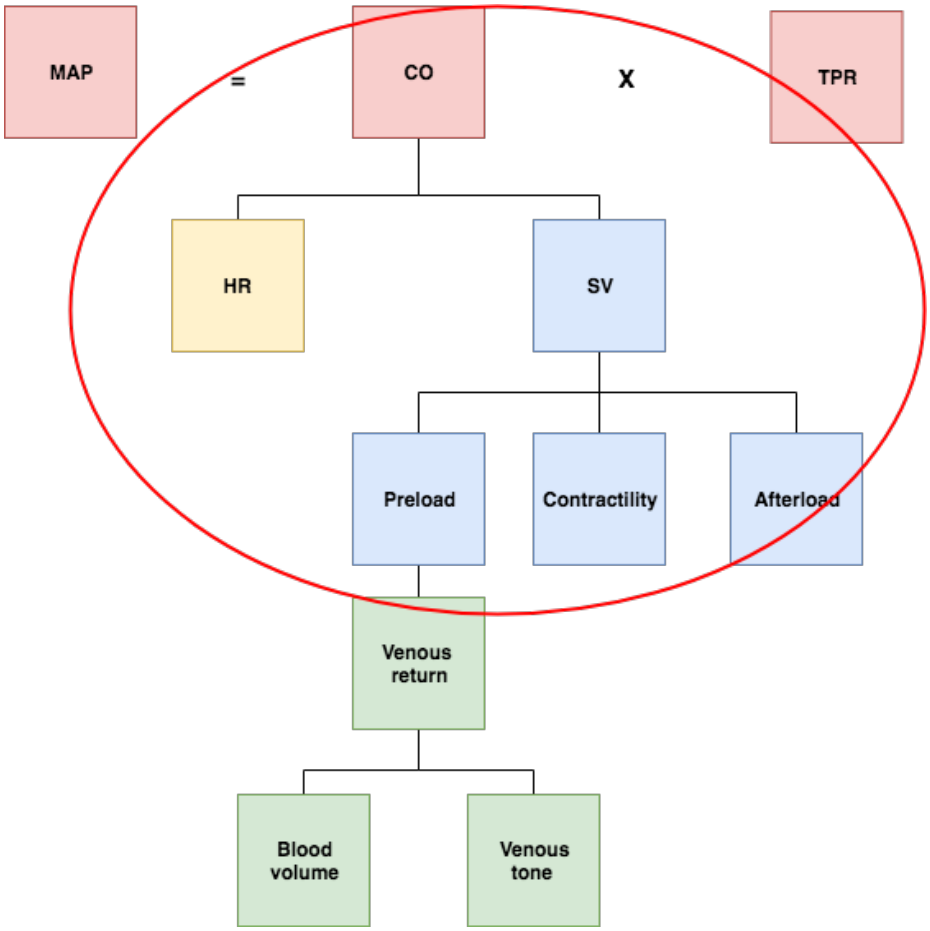
- The overall force generated by the left ventricle muscle during systole
- Synonymous with stroke volume (SV) and cardiac output (CO)

I. Cardiac output

- Amount of blood ejected by the left ventricle **per minute**
- Influenced by two variables
  1. Heart rate (HR)
  2. Stroke volume (SV)

II. Stroke volume

- Amount of blood ejected by the left ventricle **per beat**
- Influenced by three variables
  1. Contractility
  2. Preload
  3. Afterload



3.1 – Contractility

3.1.1 – Structure of the Cardiac Sarcomere

I. Sarcomeres

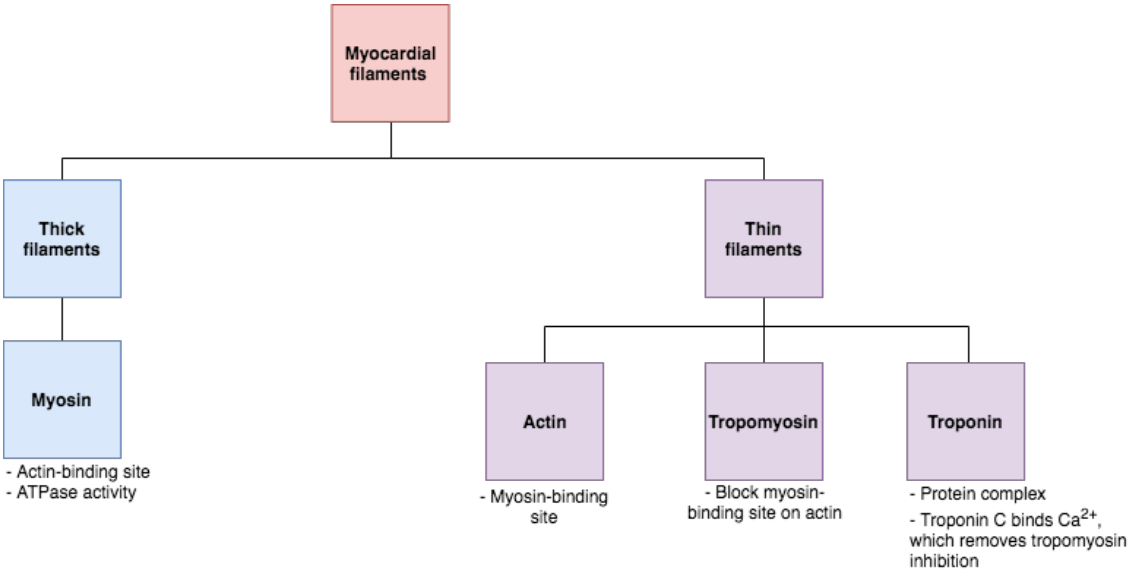
- Run from Z line to Z line
- Composed of thick filaments (*myosin*) and thin filaments (*actin, tropomyosin, troponin*)

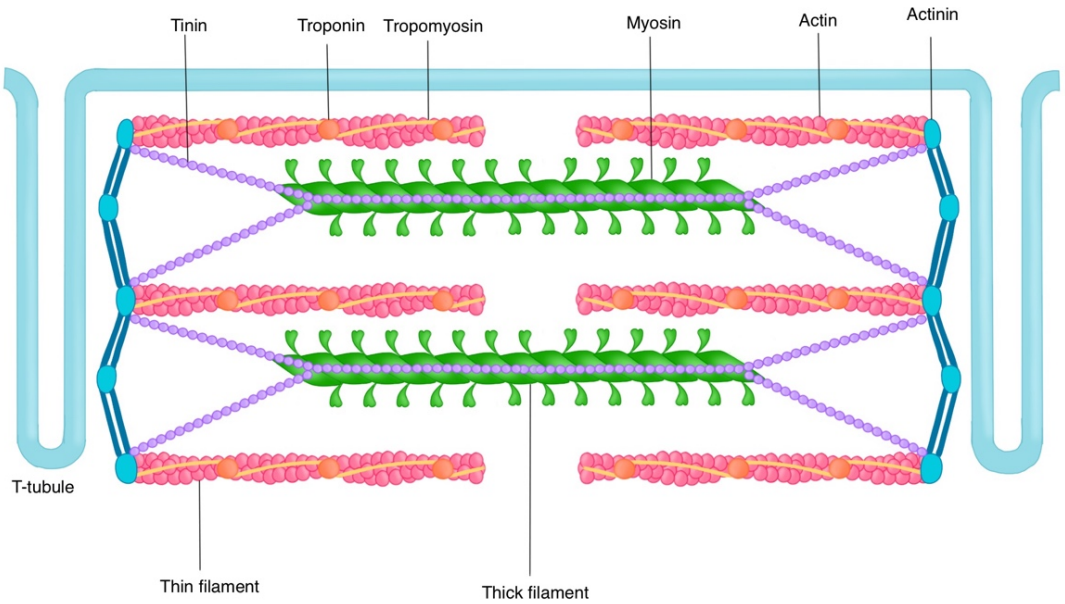
II. T-tubules

- Carry action potentials to the interior of the cell
- Form dyads (*connections*) with the sarcoplasmic reticulum (SR)

III. Sarcoplasmic reticulum

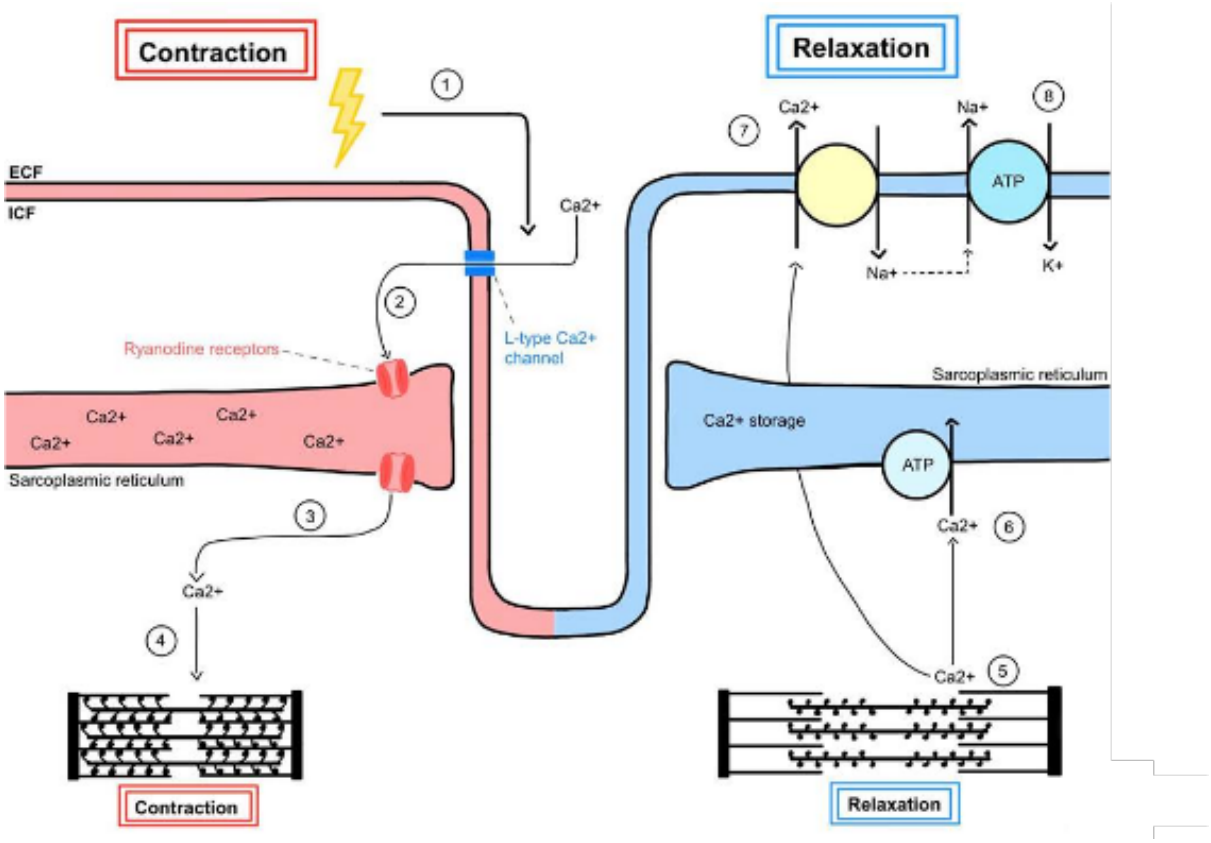
- Contains ryanodine receptors
- Site of storage and release of Ca^{2+}





3.1.2 – Excitation-Contraction Coupling

- Defined as the conversion of an electrical impulse (*action potential*) into a mechanical response (*contraction*)
- Ca^{2+} is the link between the electrical impulse and the mechanical response



Contraction	
Stage	**Event**
1	**Action Potential –** An action potential is initiated and the wave of depolarization is conducted to interior of the cell membrane through **t-tubules**
2	**Trigger Ca^{2+} -** During the plateau phase of the ventricular action potential, Ca^{2+} enters the cardiomyocyte through L-type Ca^{2+}channels (*dihydropyridine receptors*)
3	**Ca^{2+} induced Ca^{2+} release (CICR) -** Trigger Ca^{2+} activates ryanodine receptors on the SR and Ca^{2+} is subsequently released from the SR
4	**Cross-bridge formation -** Ca^{2+} binds Troponin C, leading to removal of the tropomyosin inhibition on myosin. Actin binds myosin, allowing cross-bridge formation and contraction

Relaxation	
Stage	**Event**
5	**Ca^{2+} detaches from troponin C**
6	**Ca^{2+} reuptake into SR by Ca^{2+}- ATP-ase –** Intracellular Ca^{2+} levels decrease
7	**Ca^{2+} - $3Na^{+}$ exchanger in sarcolemmal membrane** - Extrudes Ca^{2+} out of the cell, contributing to a further decrease in intracellular Ca^{2+}
8	**Na^{+}/K^{+} ATP-ase** – Restoration of the Na^{+} gradient

3.1.3 – Contractility

I. Definition

- The ability of the myocardial cells to develop force
- Synonymous with **inotropism**
  - i. Positive inotropism → ↑ contractility
  - ii. Negative inotropism → ↓ contractility

CALCULATION OF EJECTION FRACTION

- Q: "What is the estimated ejection fraction if end-diastolic volume is 120 mL and stroke volume is 75 mL?

- A:

EF = SV/EDV

EF = 75 mL / 120 mL

EF = 63%

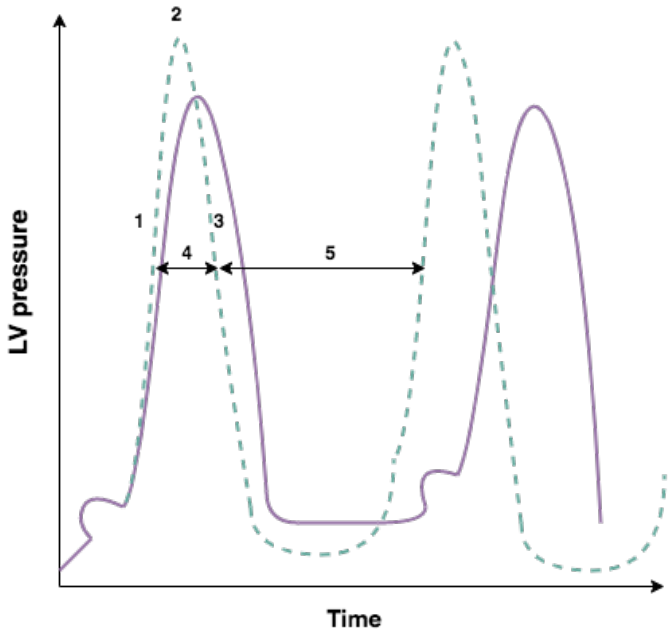
The left ventricle ejects 63% of the end-diastolic volume.

II. Strength of contractility

- Directly proportional to the intracellular Ca^{2+} concentration
  - i. ↑ Intracellular Ca^{2+} → ↑ contractility
  - ii. ↓ Intracellular Ca^{2+} → ↓ contractility

III. **Ejection fraction (EF)**

- Indicator of contractility
- It is defined as the fraction (%) of the end-diastolic volume (EDV) ejected **per beat**
- EF = Stroke volume/End-diastolic volume
  - i. ↑ Contractility → ↑ EF
  - ii. ↓ Contractility → ↓ EF



Phase	Description
1	Increased rate of left ventricular pressure development
2	- Increased peak left ventricular pressure - More forceful contraction
3	- Increased rate of left ventricular relaxation - Increased rate of calcium sequestration
4	- Decreased systolic interval due to effects of #1 and #3 - Less time in systole → decreased O_2 demand
5	- Increased diastolic interval (*if HR is constant*) - Increased time for filling → increased coronary flow → increased O_2 supply

IV. Mechanisms for Changing Contractility

	Inotropic effect	Mechanism
Autonomic nervous system		
Sympathetic stimulation	**Positive**	Catecholamine stimulation of β_1-receptors: **1. Phosphorylation of L-type Ca^{2+} channels** - ↑ Ca^{2+} entry → ↑ Ca^{2+}-induced Ca^{2+} release - ↑ Ca^{2+} released from the SR **2. Phospholamban phosphorylation** - Activation of Ca^{2+} ATP-ase → ↑ Ca^{2+} storage in the SR - Faster relaxation - More Ca^{2+} stored for subsequent release
Parasympathetic stimulation	**Negative**	**1. ACh[1] stimulaton of muscarinic receptors in the atria** - ↓ Ca^{2+} entry - ↓ Ca^{2+} release from SR
Heart rate		
Increased heart rate	**Positive**	**1. ↑ HR → ↑ AP[2]** - ↑ Amount of trigger Ca^{2+} - SR accumulates more Ca^{2+} for subsequent release **2. Positive staircase effect** (*Bowditch staircase*) - With each beat, more Ca^{2+} accumulates in SR until a maximum storage level is achieved - The **tension** developed on each beat increases **stepwise**
Decreased heart rate	**Negative**	**1. ↓ HR → ↓ AP** - ↓ Amount of trigger Ca^{2+} - SR accumulates less Ca^{2+} for subsequent release

[1]Acetylcholine

[2]Action potential

3.2 – Preload

I. Definition

- The workload on the ventricular muscle **prior** to contraction
- Determined by the volume of blood in the left ventricle at the end of diastole (*end-diastolic volume*)

II. Determinants of preload

- Preload is synonymous with venous return and end-diastolic volume

i. Venous return (VR)

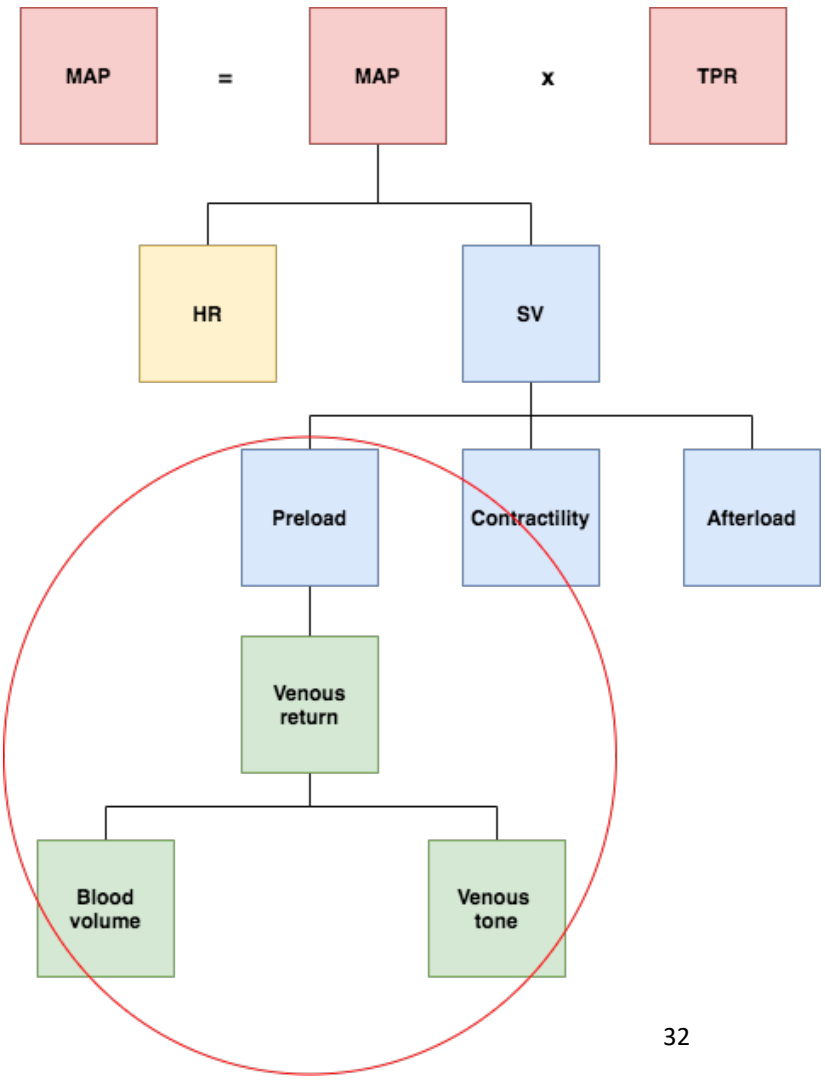
- **Definition:** return of blood to the heart from the venous system
- ↑ VR → ↑ EDV → ↑ preload → ↑ SV
- ↓ VR → ↓ EDV → ↓ preload → ↓ SV

a) Venous tone

- **Definition:** refers to the resistance of the veins
- ↑ Venous tone → ↑ VR → ↑ EDV → ↑ preload → ↑ SV
- ↓ Venous tone → ↓ VR → ↓ EDV → ↓ preload → ↓ SV

b) Blood volume

- ↑ Blood volume → ↑ VR → ↑ EDV → ↑ preload → ↑ SV
- ↓ Blood volume → ↓ VR → ↓ EDV → ↓ preload → ↓ SV



KEY POINT

- Q: "What is the difference between constriction of veins and constriction of arterioles?"

- A:

1) Arterioles

- Arterioles regulates peripheral resistance (TPR)
- Constriction of arterioles will increase the TPR

2) Veins

- Veins are the storage sites of blood volume
- Constriction of veins will increase blood flow to the heart
- The preload and stroke volume will increase

Note: Veins do not contribute to the TPR

3.2.1 – Frank-Starling Law

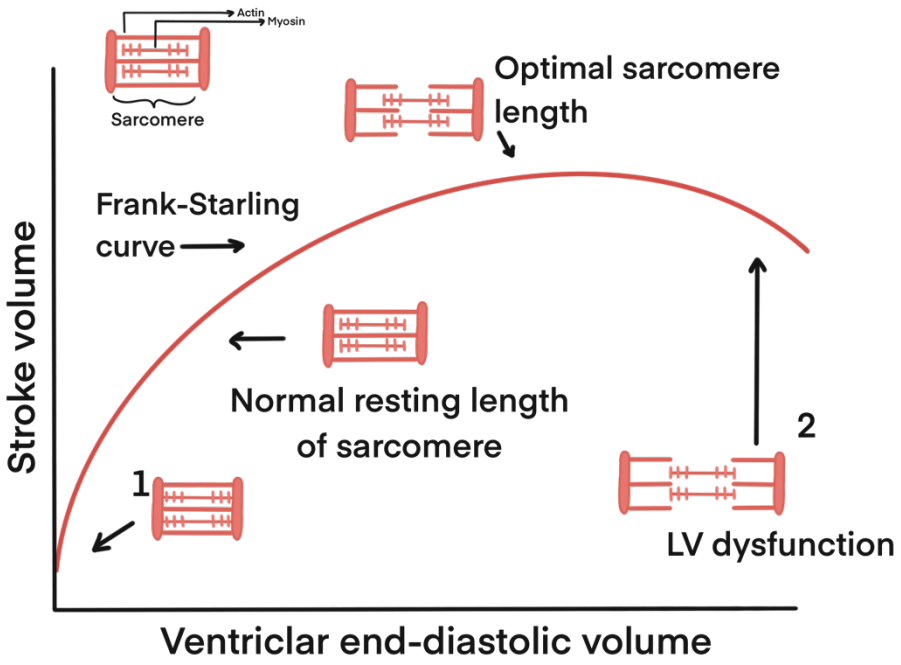
- Describes the relationship between EDV and SV
- Changes in EDV will alter the length of the myocardial sarcomeres

I. Increased end-diastolic volume

- Increased blood volume leads to increased stretch of sarcomeres
- The length of the sarcomeres moves towards optimal actin-myosin overlap
- ↑ Force of contraction → ↑ SV

II. Decreased end-diastolic volume

- Decreased blood volume leads to decreased stretch of sarcomeres
- The length of the sarcomeres moves away from optimal actin-myosin overlap
- ↓ Force of contraction → ↓ SV



[1] The sarcomere is already overly contracted at rest. Further contraction will be halted by the interaction of myosin against the Z-discs

[2] Very few myosin and actin filaments are overlapping. At this point, there will be less cross-bridge formation and decreased tension production

3.2.2 – Frank-Starling Law and Changes in Contractility

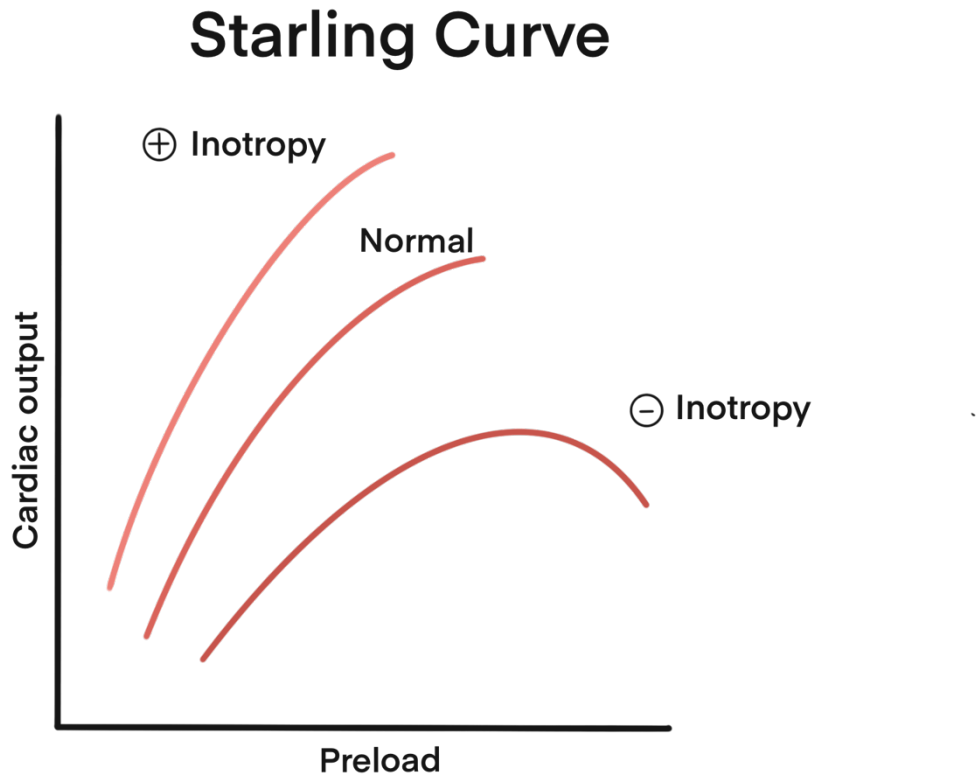
- The main factors influencing the systolic performance of the left ventricle is **contractility** and **preload**
- Changes in contractility will shift the Frank-Starling curve upward (*left*) or downward (*right*), depending on whether the **contractility** increases or decreases
- All points on the **same line** have the **same contractility**

I. Increased contractility

- **Curve:** Curve shifts to the **left**
- **Mechanism:** When compared to the normal curve, increased contractility causes an **increase in the cardiac output for any level of preload**
- **Example:** Sympathetic stimulation improves the contractility of the heart through stimulation of β_1-receptors. The cardiac output will always be greater than normal - independent of changes in preload

II. Decreased contractility

- **Curve:** Curve shifts to the **right**
- **Mechanism:** When compared to the normal curve, a decrease in contractility will cause a **decrease in the cardiac output for any level of preload**
- **Example:** Heart failure – the body tries to increase the cardiac output by increasing the amount of blood returning to the heart (*preload*). Since the contractility of a failing heart is poor, the cardiac output will never reach the same levels as in a normal heart



3.2.3 – Examples of Changes in Contractility

I. Example 1

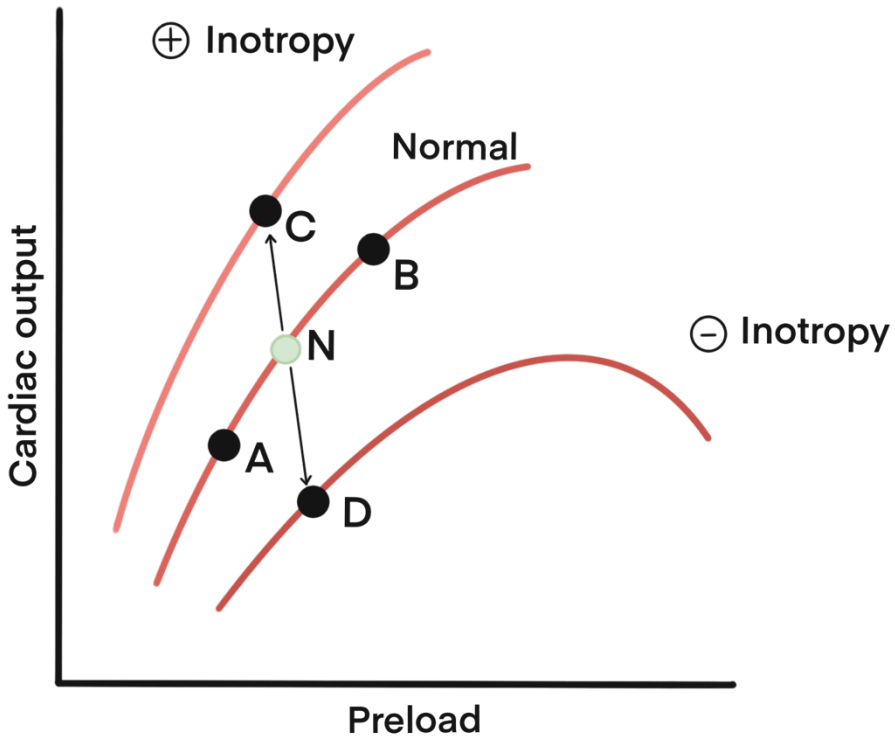
- Starting at N, which represents a normal resting individual:
  - **A.** Decreased cardiac output due to a reduction in preload
  - **B.** Increased cardiac output due to an increase in preload

II. Example 2

- **N → C**
- Point N and C have the same preload
- Preload is not the cause of increased cardiac output
- Increased cardiac output is therefore caused by increased contractility

III. Example 3

- **N → D**
- Point N and D have the same preload
- Preload is not the cause of decreased cardiac output
- Decreased cardiac output is therefore caused by decreased contractility



3.3 – Afterload

I. Definition

- The workload on the ventricular muscle **during** contraction
- Determined by the pressure the ventricles have to overcome to open the aortic valve and eject blood into the systemic circulation

II. Determinants of afterload

- Afterload is synonymous with total peripheral resistance and aortic pressure

i. Increased total peripheral resistance

- If total peripheral resistance increases, the left ventricle has to generate more force to overcome the pressure in the systemic circulation
- The left ventricle is unable to sustain the high pressure long enough to eject normal amounts of blood → ↓ SV

ii. Decreased total peripheral resistance

- If total peripheral resistance decreases, the left ventricle has to generate less force to overcome the pressure in the systemic circulation
- It will be easier for the ventricle to eject blood → ↑ SV

3.4 – Comparison of Preload and Afterload

	Preload	Afterload
Definition	Workload on the heart **prior** to contraction	Workload on the heart **during** contraction
Synonyms	- EDV - VR	- Aortic pressure - TPR
Phase of the cardiac cycle	Diastole	Systole
Effect on stroke volume when increased	↑ SV	↓ SV
Effect on stroke volume when decreased	↓ SV	↑ SV

3.5 – Test Yourself

1) What are the three most important variables affecting the stroke volume of the heart?
a) Contractility, preload and afterload
b) Contractility, heart rate and stroke volume
c) Contractility, preload and heart rate
d) Preload, venous return and cardiac output

2) Choose the correct statement regarding the definition of cardiac output.
a) It is the volume of blood ejected by the right ventricle per minute
b) It is the volume of blood ejected by the right ventricle per beat
c) It is the volume of blood ejected by the left ventricle per beat
d) It is the volume of blood ejected by the left ventricle per minute

3) The trigger Ca^{2+} enters the myocardial cell during which phase of the cardiac action potential?
a) The upstroke phase
b) The plateau phase
c) During the relative refractory period
d) During repolarization

4) During excitation-contraction coupling, a wave of depolarization spreads to the inferior of the cell membrane via _____. During the plateau phase of the cardiac action potential, _____Ca^{2+} enters the myocardial cell via L-type Ca2+ channels, also known as _____receptors. The calcium which enters the myocardial cell activates_____receptors on the sarcoplasmic reticulum. This process is also known as ____-induced _____-release. Tropomyosin inhibition on myosin will be removed when Ca^{2+} binds to _____. Myosin and actin can now bind and form cross-bridges, leading to contraction.

5) Select the correct statement(s) regarding contractility.
a) It is also known as inotropism
b) It is inversely proportional to the intracellular calcium concentration
c) Changes in contractility does not necessarily affect the ejection fraction
d) Increased contractility leads to increased rate of pressure development, increased peak left ventricular pressure and decreased rate of relaxation
e) All of the above
f) A, C and D are correct

6) Select the correct statement(s) regarding preload.
a) It is affected by the tone of capacitance vessels
b) It is determined by the amount of blood in the left ventricle after diastole
c) Dilation of veins will decrease preload
d) Blood volume and venous tone are variables which may affect the level of preload
e) All of the above

7) Select the correct statement(s) regarding the Frank-Starling law.

a) Describes the relationship between the end-diastolic volume and stroke volume

b) Increased EDV will lead to stretch of the sarcomere towards optimum actin-myosin overlap and therefore increased stroke volume

c) Increased EDV will lead to increased sympathetic stimulation and therefore increased stroke volume

d) A and B

8) Compare the systolic performance of heart A and heart B. What is the explanation for the decreased cardiac output in heart B, when the preload of both hearts is the same?

Heart A:

Cardiac output: 5 L/min

Preload: 120mL

Heart B:

Cardiac output: 3L/min

Preload: 120mL

a) This is a normal variation between the heart of a woman and the heart of a man

b) The contractility of heart A is better than the contractility of heart B

c) The contractility of heart B is poor and the Frank-Starling curve of heart B will be shifted to the right

d) The contractility of heart B is poor and the Frank-Starling curve of heart B will be shifted to the left

e) A,B and C is correct

f) B and C is correct

9) The workload on the heart during contraction will increase with which of the following?

a) Afterload

b) Aortic pressure

c) The total peripheral resistance

d) A and B

d) All of the above

Section 4 – The Cardiac Cycle

4.0 – Overview

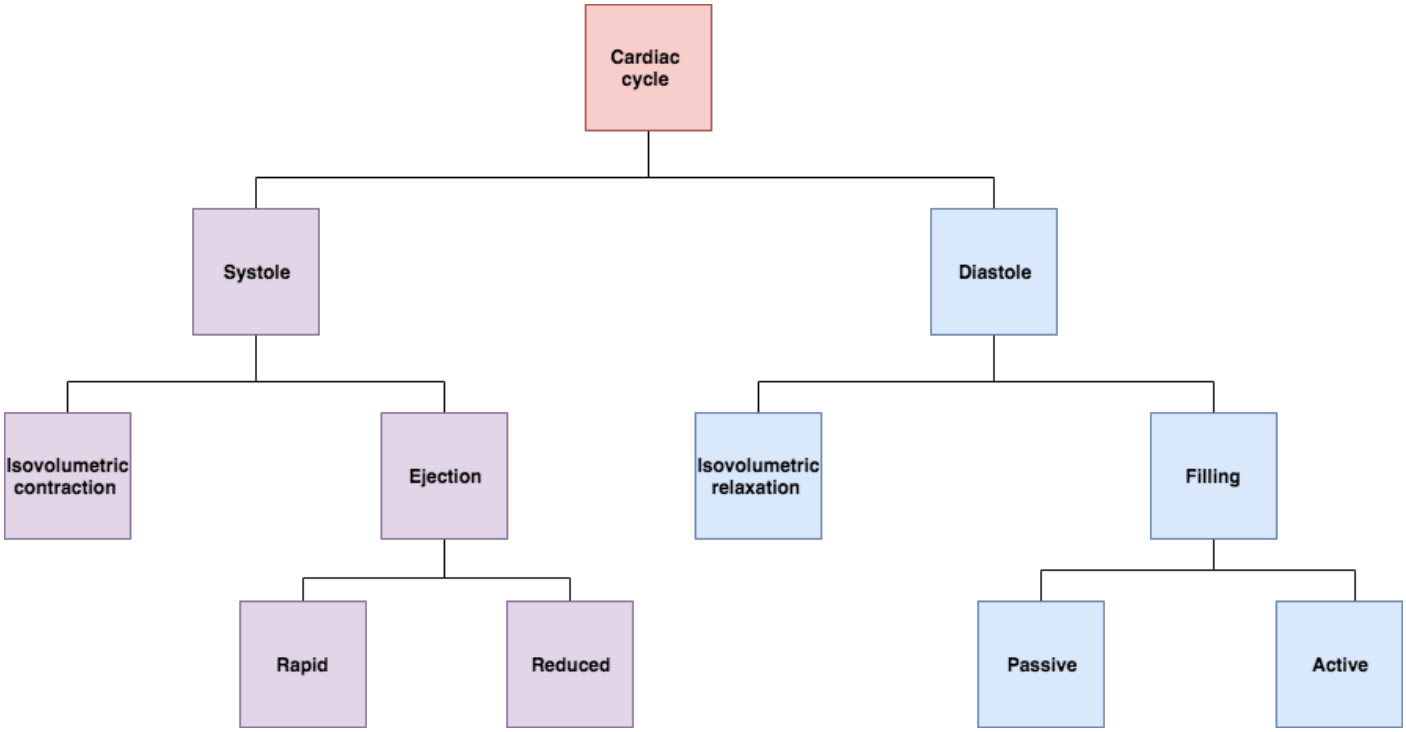
- The cardiac cycle refers to the electrical and mechanical events of a single cardiac cycle
- Consists of **systole** and **diastole**

I. Systolic Events – Contraction

1. Isovolumetric contraction
2. Ventricular ejection

II. Diastolic Events – Filling

1. Isovolumetric relaxation
2. Ventricular filling
    - Passive filling
    - Active filling (*atrial contraction*)

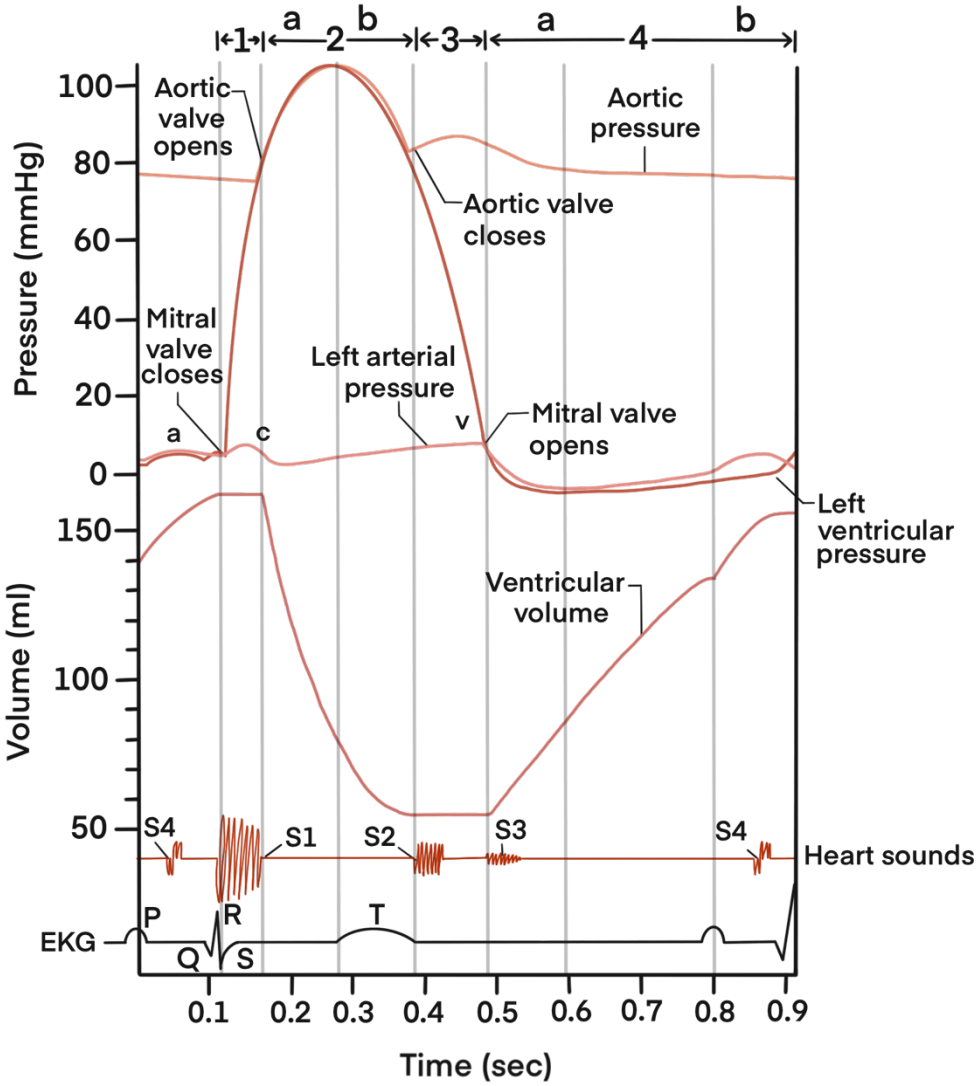


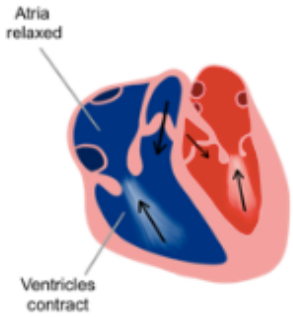
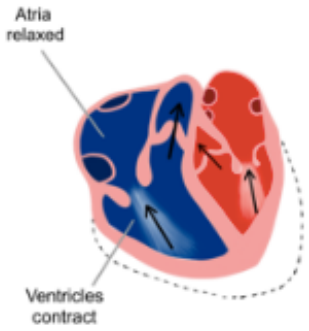
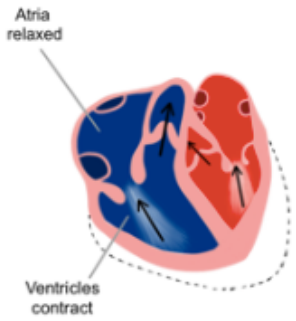
4.1 – Phases of the Cardiac Cycle

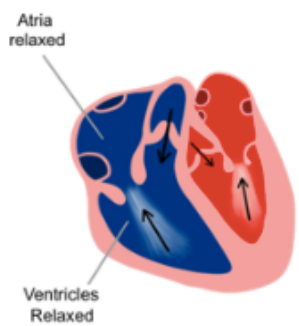
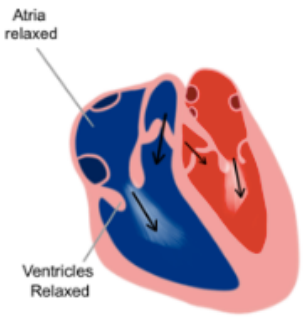
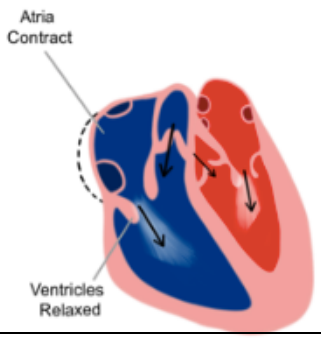
I. General principles

- **Effects of pressure on the valves:** there is always a pressure difference between the chambers of the heart, which causes the valves to open or close
- **Heart sounds:** closure of the heart valves produces physiological heart sounds
- **Isovolumetric phases:** all valves are closed and there is no change in ventricular volume
- **End-systolic volume:** the volume remaining in the left ventricle after systole
- **End-diastolic volume:** the volume remaining in the left ventricle after diastole

II. Pressure-volume curve and cycles



Systole	1) Isovolumetric ventricular contraction	2) Ventricular ejection	
		a) Rapid	b) Reduced
ECG	QRS complex	ST segment	T-wave
Left ventricular pressure	Increasing pressure	Maximal	Decreasing
Left ventricular volume	- No change	Decrease rapidly	Decrease to a minimal value (ESV≈ 50 ml)
Valves	Mitral valve closes	Aortic valve opens	_____
Heart sounds	S_1	_____	_____
Illustration			

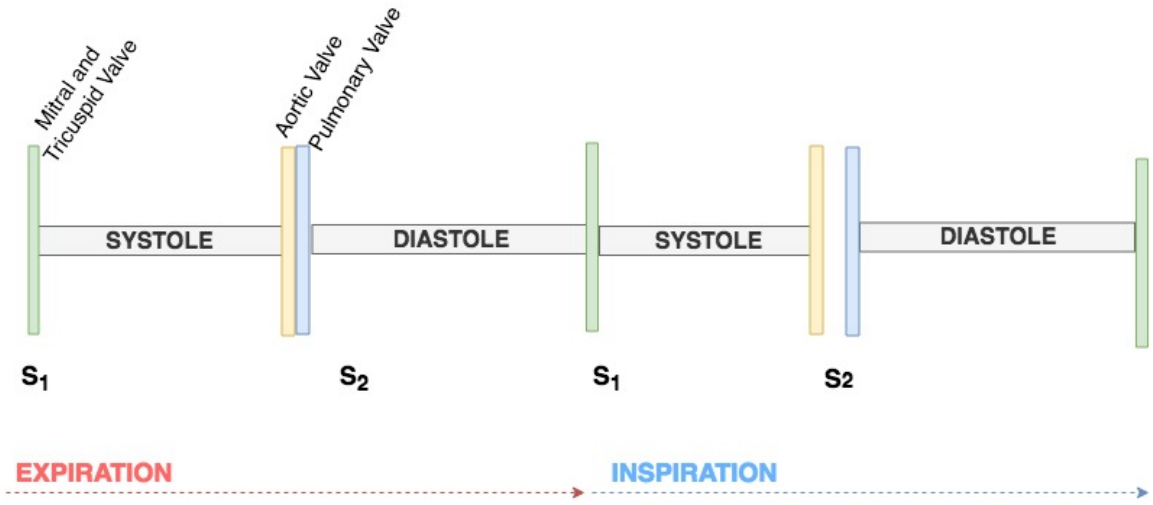
Diastole	3) Isovolumetric ventricular relaxation	4) Ventricular filling	
		a) Passive	b) Active
ECG	_____	_____	- P-wave - Atrial contraction
Left ventricular pressure	Decreasing	Remains low	Remains low
Left ventricular volume	No change	Increasing	Increase to a maximal value (EDV ≈ 120ml)
Valves	Aortic valve close	Mitral valve opens	_____
Heart Sounds	S_2	S_3	S_4
Illustration			

4.2 – Heart Sounds

I. Physiological heart sounds

	S_1	S_2
Caused by	Closure of the atrioventricular valves (*mitral and tricuspid*)	Closure of the semilunar valves (*aortic and pulmonary*)
Phase of the cardiac cycle	Systole	Diastole
Mechanical event	Isovolumetric ventricular contraction	Isovolumetric ventricular relaxation
Splitting	No	Yes [1]

[1] Inspiration increases venous return to the right ventricle, resulting in increased blood volume. The right ventricle has to eject more blood, which will delay the closure of the pulmonary valve relative to the aortic valve (*see the figure below*)



II. Pathological heart sounds

	S_3	S_4
Phase of the cardiac cycle	Early diastole	Late diastole
Mechanical event	Passive filling of the left ventricle	Active filling of the left ventricle
Caused by	Rapid, turbulent blood flow entering the left ventricle during early diastole	Vibration of the stiff wall of the left ventricle during atrial contraction
Comments	- Normal finding in children and athletes - Indicates volume overload in adults	Implies hypertrophy of the left ventricle

4.3 – Pressure-Volume Loop

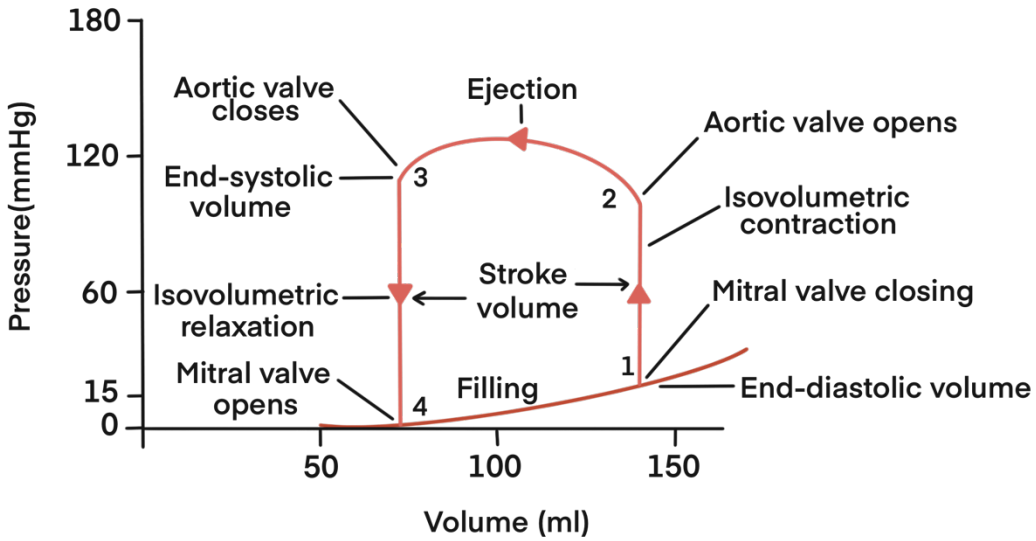
- Illustrates the relationship between the intraventricular pressure and intraventricular volume of **a single cardiac cycle**

I. Systole

1. Isovolumetric contraction
2. Ventricular ejection

II. Diastole

3. Isovolumetric relaxation
4. Ventricular filling

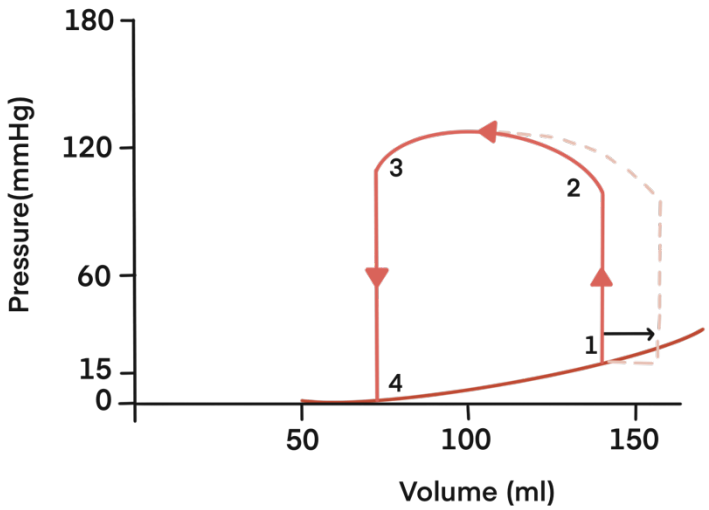


	Phase	Valves	Left ventricular pressure	Left ventricular volume
Systole				
1 → 2	Isovolumetric contraction	**- MV[1]: Closes (S_1)** - AV[2]: Closed	Increasing	No change
2→ 3	Ventricular ejection	- MV: Closed - AV: Opens	- LV[3] pressure > aortic pressure - AV opens → ejection	- Decreases - LV volume = ESV
Diastole				
3 → 4	Isovolumetric relaxation	- MV: Closed **- AV: Closes (S_2)**	- LV pressure < aortic pressure - AV close	No change
4 → 1	Ventricular filling	- MV: Opens - AV: Closed	- LA pressure > LV pressure - MV opens	- Increases - LV volume =EDV

[1]Mitral valve
[2]Aortic valve
[3]Left ventricle

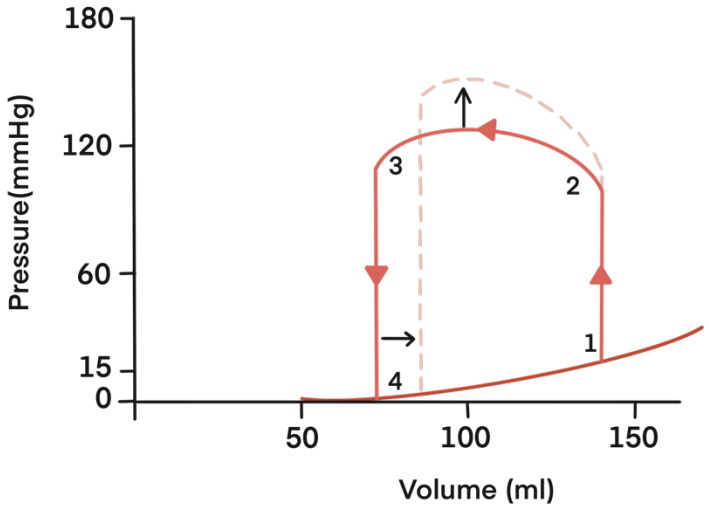
4.3.1 – Changes in the Pressure-Volume Loops

I. Increased preload



- Increased preload implies an increase in end-diastolic volume and the curve will be shifted to the right
- According to the Frank-Starling law, an increase in preload will lead to increased stroke volume
- An increase in stroke volume increases the width of the loop (SV= EDV-ESV)

II. Increased afterload



- Increased afterload implies an increase in the aortic pressure or total peripheral resistance
- The left ventricle generates more pressure to open the aortic valve and the loop is shifted upward
- The left ventricle is unable to keep the high pressure long enough and less blood is ejected
- The end-systolic volume increases and the curve is shifted to the right

III. Summary

	Increasing preload	Increasing afterload
Stroke volume	↑	↓
End-diastolic volume	↑	N
End-systolic volume	N	↑

4.4 – Test Yourself

1) Starting from systole, place the different phases of the cardiac cycle into the correct order.
1. Isovolumetric ventricular relaxation, 2. Isovolumetric ventricular contraction, 3. Ventricular filling (*passive phase*), 4. Ventricular Ejection, 5. Ventricular filling (*active phase*):
a) 2 – 4 – 1 – 5 – 3
b) 1 – 3 – 5 – 2 – 4
c) 2 – 4 – 1 – 3 – 5
d) 1 – 2 – 3 – 4 – 5

2) The mitral valve closes:
a) During ventricular ejection
b) During isovolumetric ventricular relaxation
c) Immediately after the passive phase of ventricular filling
d) During isovolumetric ventricular contraction

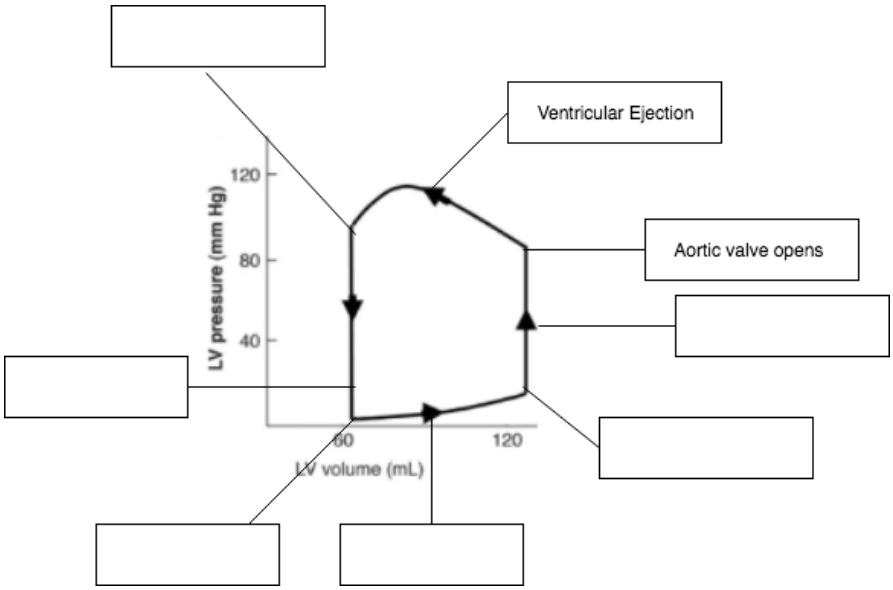
3) Choose the correct statement regarding the opening of the aortic valve.
a) The aortic valve opens because the aortic pressure is higher than the left ventricular pressure
b) The aortic valve opens during isovolumetric ventricular relaxation
c) The aortic valve opens during the ejection phase of the cardiac cycle, because the pressure generated by the left ventricle exceeds the pressure in the aorta
d) The aortic valve opens during isovolumetric contraction at the point where the pressure generated by the left ventricle exceeds the pressure in the aorta

4) Choose the correct statement(s) regarding the closure of the mitral valve.
a) The mitral valve closes because the pressure in the left ventricle is higher than the pressure in the left atrium
b) It produces the first heart sound
c) In order for the mitral valve to close, the pressure in the left atrium has to be higher than the pressure in the left ventricle
d) A and B are correct

5) Physiologic splitting of the 2nd heart sound can be explained by which of the following?
a) Delayed closure of the tricuspid valve
b) During inspiration, there is an increase in cardiac output which causes a more forceful contraction of the left ventricle and the aortic valve will close before the pulmonary valve
c) During inspiration, there is an increase in blood volume returning to the right ventricle. The resulting increase in blood volume will prolong the ejection time of the right ventricle and the closure of the pulmonary valve will be delayed
D) It occurs as a result of expiration

6) Place the missing events of the cardiac cycle on the pressure-volume loop.

a) Mitral valve opens
b) Mitral valve closes
c) Isovolumetric ventricular contraction
d) Isovolumetric ventricular relaxation
e) Aortic valve closes
f) Ventricular filling



7) The QRS complex represents:

a) Atrial contraction
b) Ventricular repolarization
c) Ventricular ejection
d) Isovolumetric ventricular contraction

8) The first heart sound is produced by?

a) Opening of the mitral valve
b) Closure of the aortic valve
c) Closure of the mitral valve
d) Closure of the tricuspid valve
e) C and D are correct

Section 5 – Hemodynamics

5.0 – Definition

- Hemodynamics refers to everything affecting blood flow in the cardiovascular system

5.1 – Pattern of Normal Blood Flow

I. Step 1

- Oxygenated blood from the lungs goes into the left atrium through the pulmonary veins
- Contraction of the left atrium results in filling of the left ventricle through the mitral valve

II. Step 2

- Blood is ejected from the left ventricle and into the aorta through the aortic valve
- When the left ventricle contracts, the pressure in the ventricle increases – forcing the aortic valve to open
- Blood is driven through the arterial system by the pressure gradient created by the left ventricle

III. Step 3

- The total cardiac output (CO) is distributed among the different organs in the body
- The distribution of blood flow is not a fixed process, but can be altered by redistribution of blood flow, alteration of CO or a combination of these mechanisms

IV. Step 4

- Blood leaving the organs is called venous blood and is collected by veins of increasing size
- Venous blood contains less O_2 and more CO_2

V. Step 5

- Superior vena cava (SVC) returns the venous blood from the head, neck and upper extremities, while the inferior vena cava (IVC) returns the venous blood from the rest of the body
- The mixed venous blood collects in the right atrium
- In a steady state, the venous return to the right atrium equals the CO from the left ventricle

VI. **Step 6**

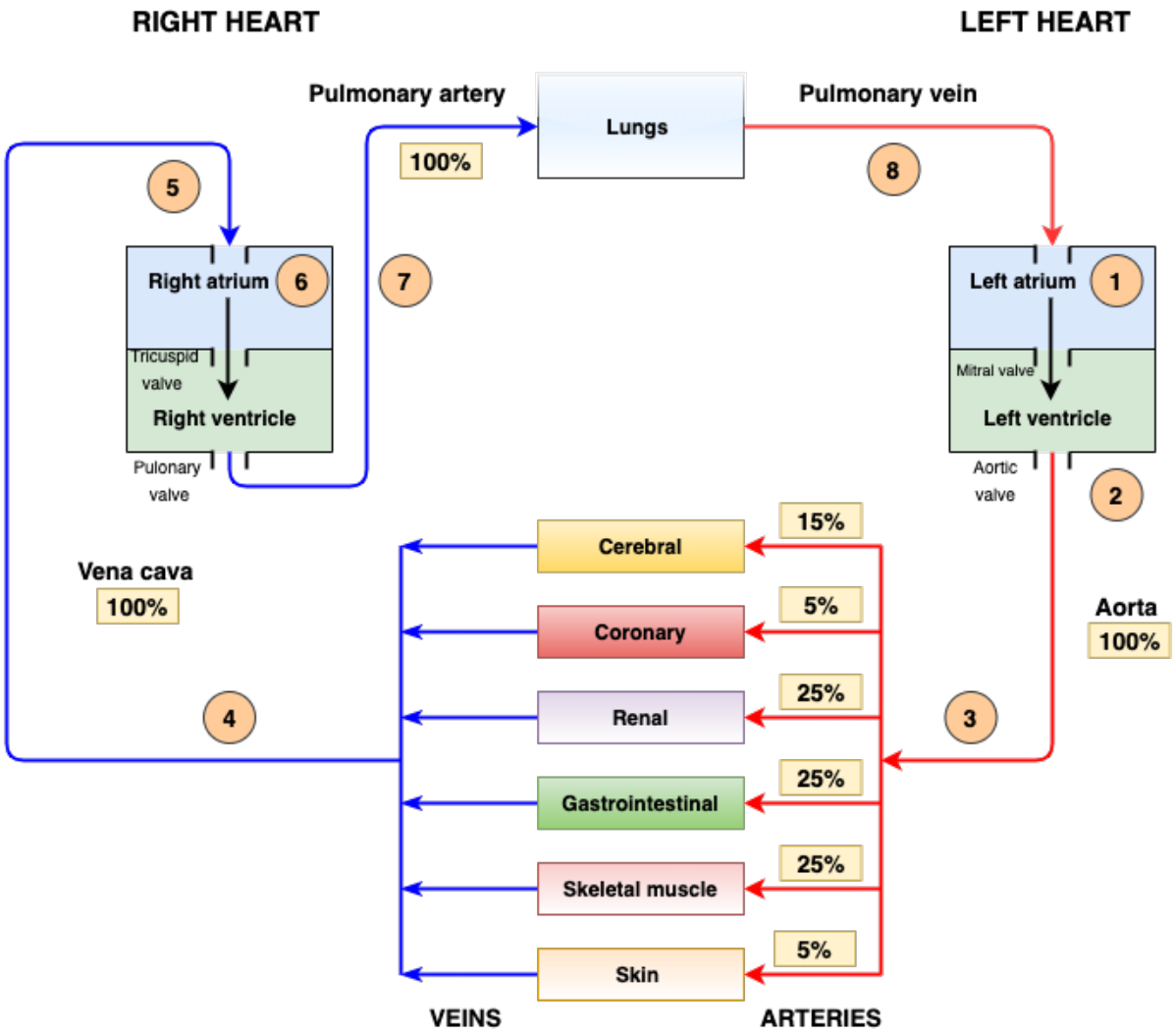
- Contraction of the right atrium results in filling of the right ventricle through the tricuspid valve

VII. **Step 7**

- Blood is ejected from the right ventricle into the pulmonary circulation through the pulmonary valve
- The amount of blood ejected from the right ventricle is equal to the amount of blood ejected from the left ventricle
- In the pulmonary capillaries, gas exchange occurs

VIII. **Step 8**

- Oxygenated blood is returned to the left atrium through the pulmonary veins and the cycle repeats itself

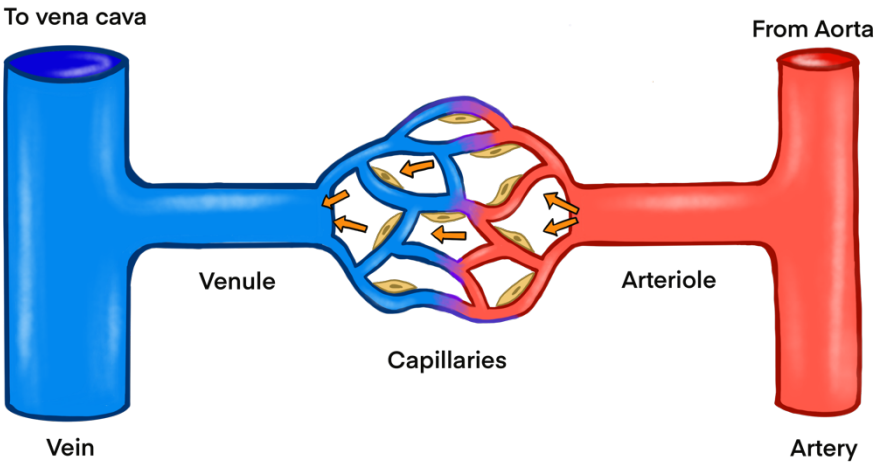


5.2 – Systemic Circulation

5.2.1 – Vessels

I. Overview

- The illustration shows the direction of blood flow in the systemic circulation
- Aorta → arteries of decreasing size → arterioles → capillaries → venules → veins of increasing size → vena cava



II. Arteries, capillaries and veins

	Arteries	Capillaries	Veins
Definition	- Go away from the heart	- Between arteries and veins	- Go to the heart
Function	- Carry **oxygenated** blood[1] and nutrients from the heart to the peripheral tissues	- Exchange of O_2 and nutrients - Removal of waste products	- Carry **deoxygenated** blood[2] and waste products from the peripheral tissues to the heart
Pressure	- High	- Low	- Lowest[3]
Valves	- No	- No	- Yes[4]
Speed of blood flow	- High	- Lowest[4]	- Low
Diameter of the lumen	- Small[5]	- Smallest	- Large
Thickness of the wall	- Thick	- Extremely thin	- Thin

[1] An exception is the pulmonary arteries, which carry deoxygenated blood
[2] An exception is the pulmonary veins, which carry oxygenated blood
[3] Highest compliance
[4] Prevent backflow (*or ensure forward flow*) due to the low pressure gradient in the venous system
[5] Velocity of blood flow is inversely proportional to the cross-sectional area (*which is proportional to the number of vessels*)
[6] Thick wall

5.2.2 – Series – and Parallel Circulations

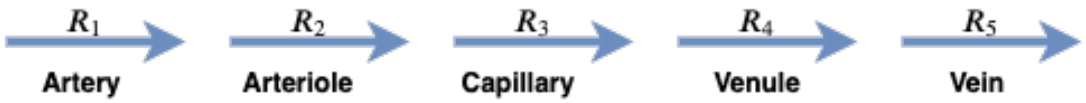
I. Overview

	Series	Parallel
Organization	Within organs	Between organs
Flow	Equal at all points[1]	Not equal at all points[2]
Total resistance	Always greater than the sum of the individual resistances	Always lower than the sum of the individual resistances
Adding resistance	Increase the total resistance	Decrease the total resistance
Removing resistance[3]	Decrease the total resistance	Increase the total resistance

[1] Dependent flow
[2] Independent flow
[3] A clinical example of removing resistance is the donation of an organ

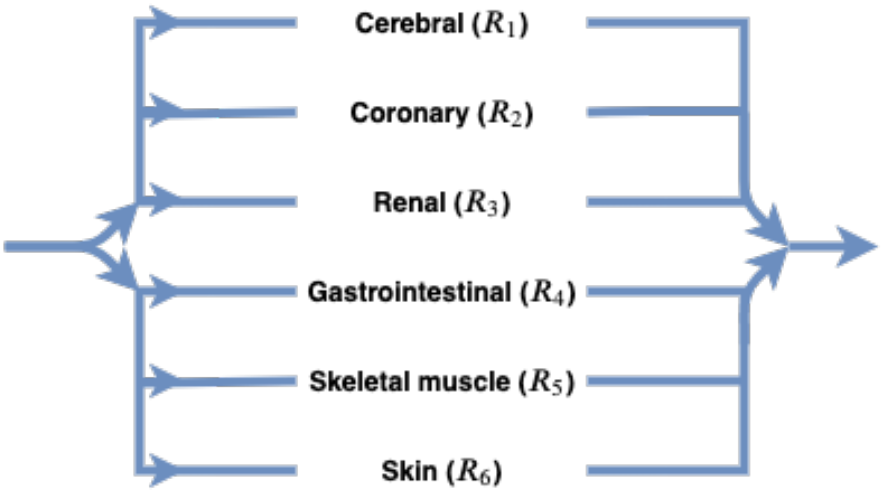
SERIES RESISTANCE

$$R_{total} = R_1 + R_2 + R_3 + R_4 + R_5$$



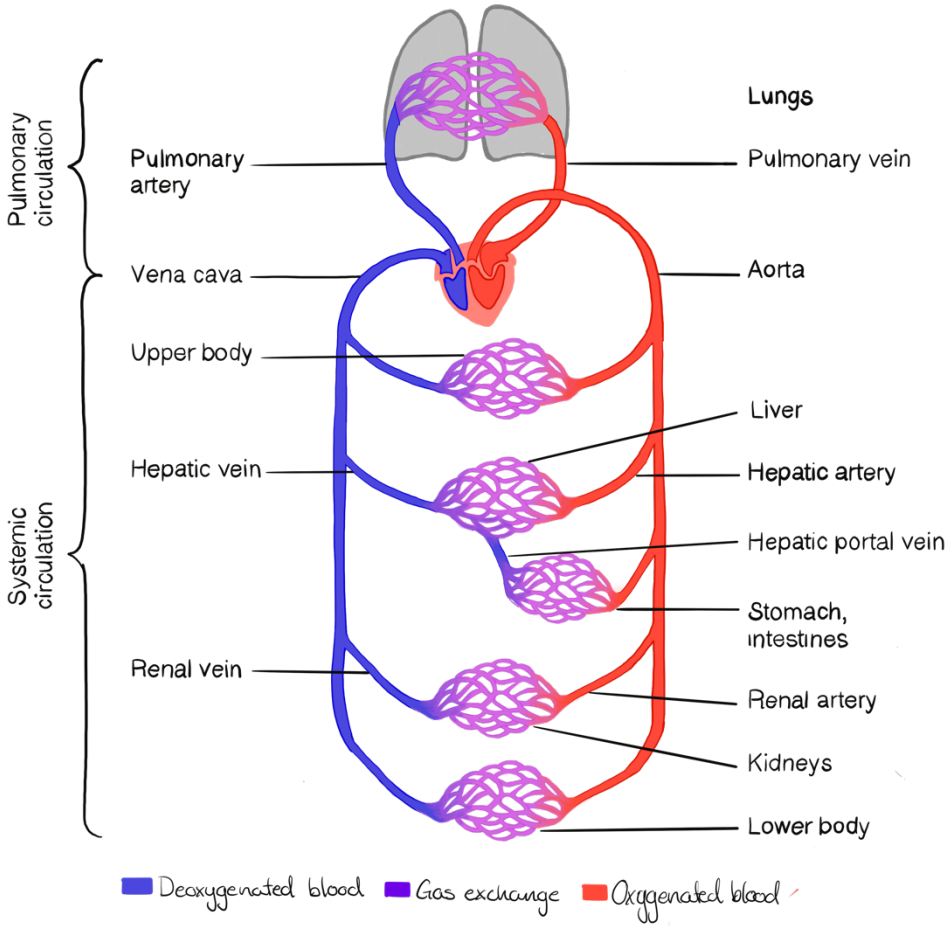
PARALLELL RESISTANCE

$$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} + \frac{1}{R_5} + \frac{1}{R_6}$$



II. Examples

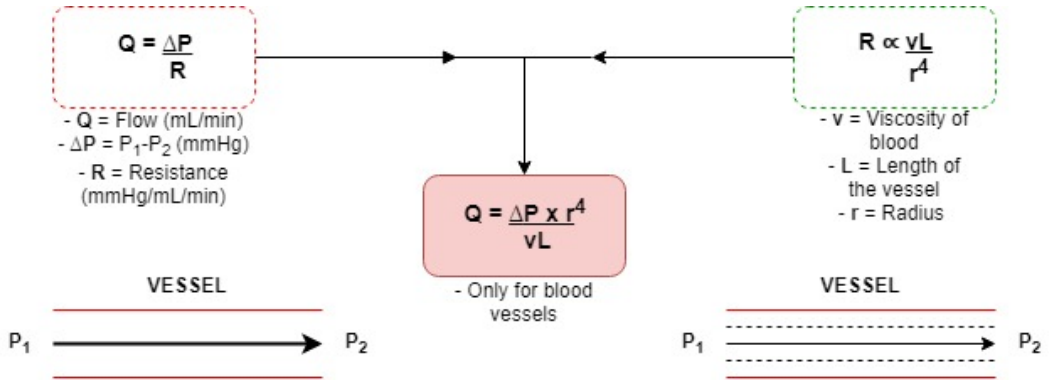
- The organs of the systemic circulation are arranged in parallel
- The systemic – and pulmonary circulations are coupled in series



5.3 – Flow

5.3.1 – Overview

- The pressure gradient is the driving force of blood flow ("*gas pedal*")
- Resistance is the impediment of blood flow ("*brakes*")



5.3.2 – Pressure Gradients

- The concept of pressure gradients in the cardiovascular system is best understood by comparing the pulmonary – and systemic circulations

	Pulmonary circulation		Systemic circulation
Right ventricle	25/0 mmHg	**Left ventricle**	120/0 mmHg
Pulmonary artery	25/8 mmHg	**Aorta**	120/80 mmHg
Mean pulmonary artery pressure	15 mmHg	**Mean aortic pressure**	93 mmHg
Pulmonary capillaries	7-9 mmHg	**Systemic capillaries**	30-50 mmHg
Pulmonary veins	5 mmHg	**Systemic veins**	15 mmHg
Left atrium	5-10 mmHg	**Right atrium**	0 mmHg

$$\Delta P_{pulm} = p(PA) - p(PV)$$
$$= 15\ mmHg - 5\ mmHg$$
$$= 10\ mmHg$$

$$\Delta P_{sys} = p(Aorta) - p(RA)$$
$$= 93\ mmHg - 0\ mmHg$$
$$= 93\ mmHg$$

- The pressure gradients determine blood flow
- **But how can the blood flow be equal in the pulmonary – and systemic circulations if the pressure gradient is larger in the systemic circulation?**

CLINICAL CORRELATION

- Q: «Why does right ventricular failure lead to peripheral edema?"

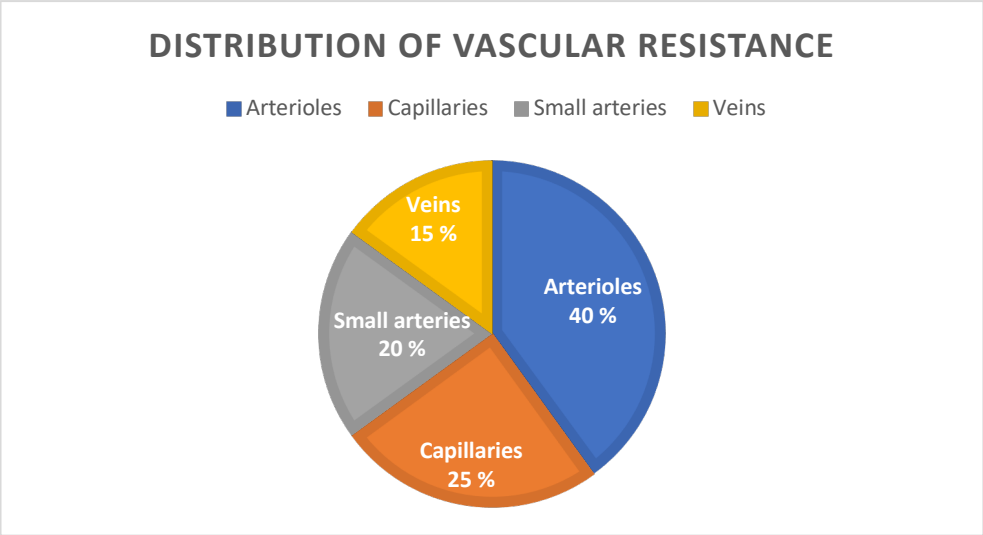
- **A:** Right ventricular failure → ↑pressure in the right atrium → ↓ ΔP_{sys} → ↓venous return → pooling of the blood in the veins → ↑hydrostatic pressure in the capillaries → ↑filtration → peripheral edema

5.3.3 – Resistance

- Resistance is determined by *Pouiselle equation*
- r^4 is the most important factor affecting resistance

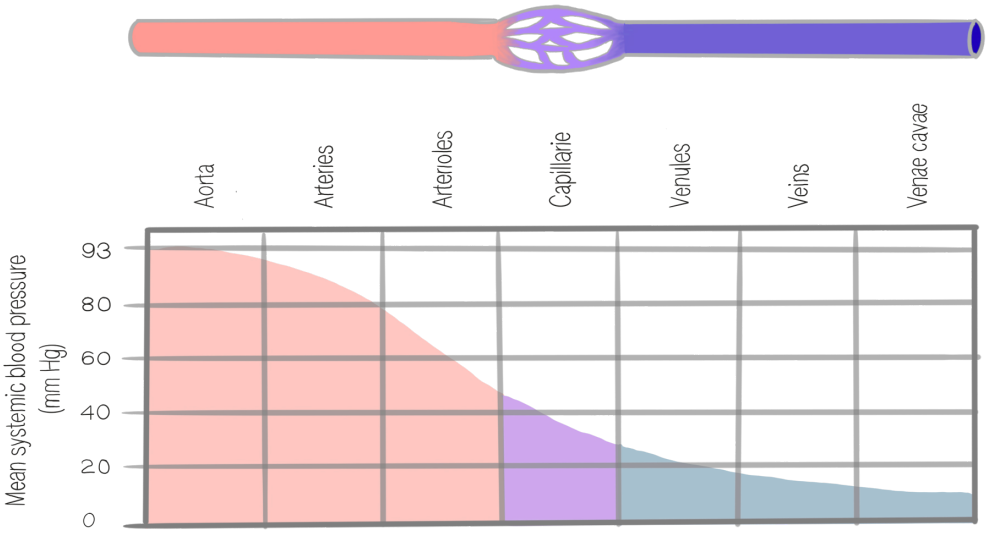
$$R \propto \frac{vL}{r^4}$$

- R = Resistance
- v = Viscosity of blood
- L = Length of the vessel
- r = Radius



- **<u>Highest resistance</u>:** Arterioles
- The smooth muscle in the walls of the arterioles is tonically active
- Vasoconstriction leads to a decrease in the radius, which increases resistance

- **<u>Greatest pressure drop</u>**: Arterioles



5.3.4 – Comparison of the Pulmonary – and Systemic Circulations

- **How can the blood flow be equal in the pulmonary – and systemic circulations if the pressure gradient is larger in the systemic circulation?**

	Pulmonary circulation	Systemic circulation
Pressure	Low	High
Pressure gradient	Small[1]	Large[2]
Resistance	Low	High
Flow[3]	5 L/min	5 L/min

[1] 10 mmHg
[2] 93 mmHg
[3] 70 kg male

5.3.5 – Hemodynamic Concepts

I. Viscosity

- Viscosity describes the internal resistance of a moving liquid
- It correlates closely with the concept of thickness

$$Q = \frac{\Delta P \times r^4}{vL}$$

- Only for blood vessels

$$R \propto \frac{vL}{r^4}$$

- R = Resistance
- v = Viscosity of blood
- L = Length of the vessel
- r = Radius

- The concept of viscosity is best understood with clinical examples

	Polycythemia	Anemia
Definition	Increased hematocrit[1]	Decreased hematocrit[1]
Viscosity	High	Low
Resistance	High	Low
Flow	Decreased	Increased
Consequence	Thrombosis[2]	Murmur[3]

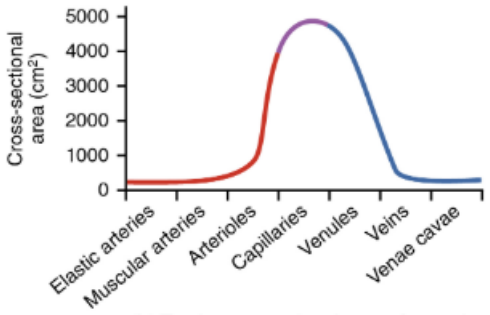
[1] Hematocrit is the ratio of the volume of red blood cells to the total volume of blood (*volume percentage of red blood cells*)
[2] Stasis is a part of Virchow's triad of thrombosis
[3] "*Whooshing*" or "*swishing*" sounds over the heart, caused by turbulent blood flow

II. Cross-sectional area (CSA)

- Refers to the sum of the radii of all vessels of a given type
- CSA is directly proportional the number of vessels

$$A = \Sigma r$$

- A= Cross-sectional area (cm^2)
- r = Radii (cm)



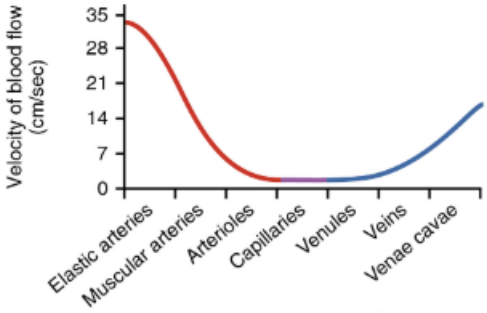
- **Highest CSA:** Capillaries
- **Lowest CSA**: Aorta

III. Velocity

- Refers to the linear rate of displacement of blood per unit time
- Velocity is inversely proportional to the CSA

$$V = \frac{Q}{A}$$

- V= Velocity (cm/s)
- Q= Flow (mL/s)
- A= Cross-sectional area (cm^2)



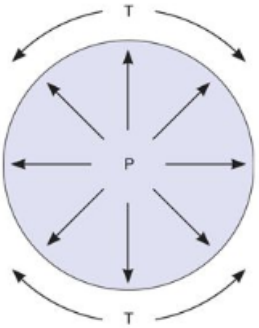
- **Highest velocity:** Aorta
- **Lowest velocity:** Capillaries

IV. Wall tension

- Refers to the tension within the wall of a given vessel
- Determined by La Place law

$$T \propto Pr$$

- T = Wall tension
- P = Internal pressure
- r = radius



- **Highest wall tension:** Aorta

CLINICAL CORRELATION

- **Q: "Why is the aorta the vessel in the body which is most prone to the formation of aneurysms?"**
- **A:** The aorta is the vessel in the body with the highest radius and pressure → highest wall tension

V. Compliance

- Refers to the ability of a structure to expand
- It is inversely proportional to elasticity (*which is the ability to recoil*)

$$C = \frac{\Delta V}{\Delta P}$$

- C = Compliance (mL/mmHg)
- ΔV = Change in volume (mL)
- ΔP = Change in pressure (mmHg)

	Arteries	Veins
Structure of the wall	- Three layers (*adventitia*, *media*, *intima*) - Abundance of elastic tissue and smooth muscle	- Three layers (*adventitia*, *media*, *intima*) - Small amounts of elastic tissue and smooth muscle
Elasticity	High	Low
Compliance	Low	High
Flow	Directly proportional to r^4	Inversely proportional to r
Vasoconstriction	Decrease flow	Increase flow
Vasodilation	Increase flow	Decrease flow

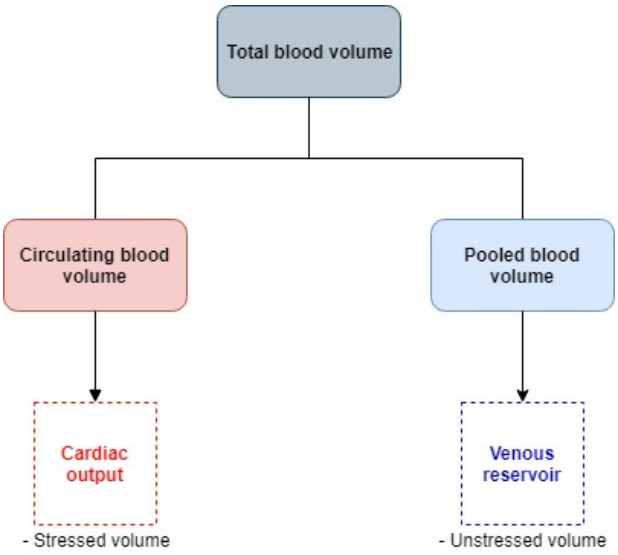
- **Q: "A patient in your hospital has signs of dehydration. You decide to give fluids intravenously. Why is the rate of the intravenous infusion so important?"**
- **A:** This concept is best understood by comparing what happens in dehydration and what happens when a patient is given intravenous infusion of fluids

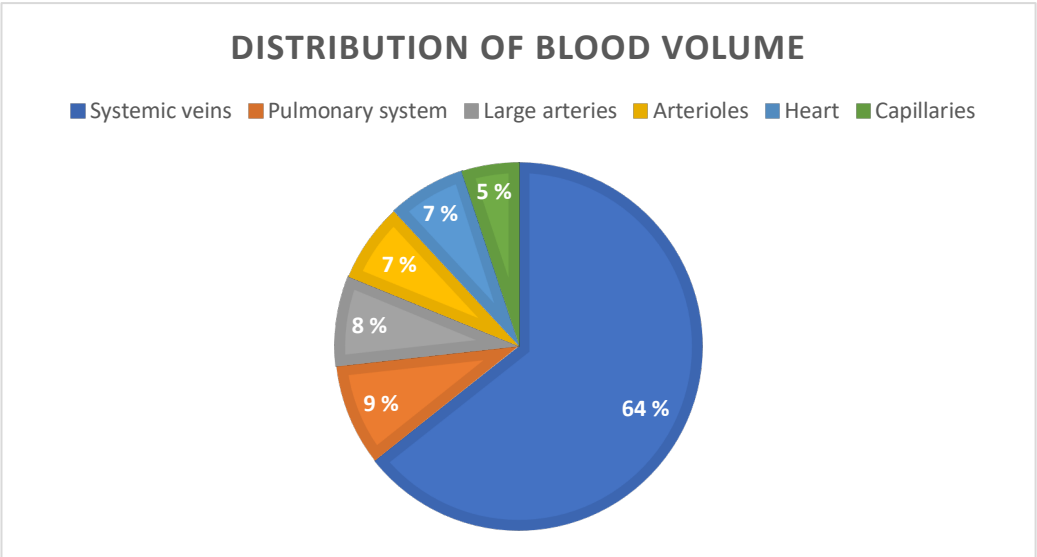
1. Dehydration

- Loss of fluids → ↓ venous pressure → passive and active constriction of systemic veins → ↑blood flow → ↑ preload → maintenance of CO

2. Intravenous infusion of fluids

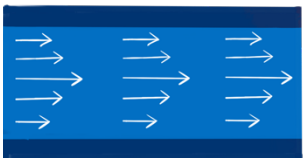
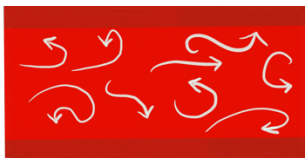
- Infusion of fluids → ↑venous pressure → passive distension of systemic veins → ↓ blood flow → ↓preload → ↓CO





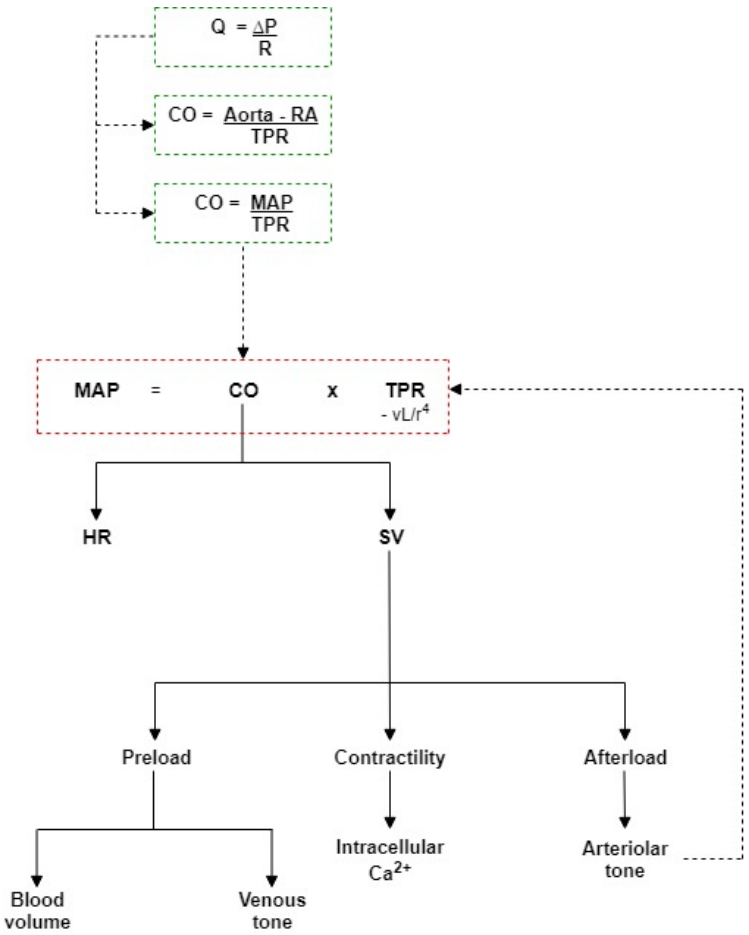
- **<u>Highest blood volume</u>:** Systemic veins and the pulmonary system
- The degree of pooling of blood is determined by compliance

5.3.6 – Types of Flow

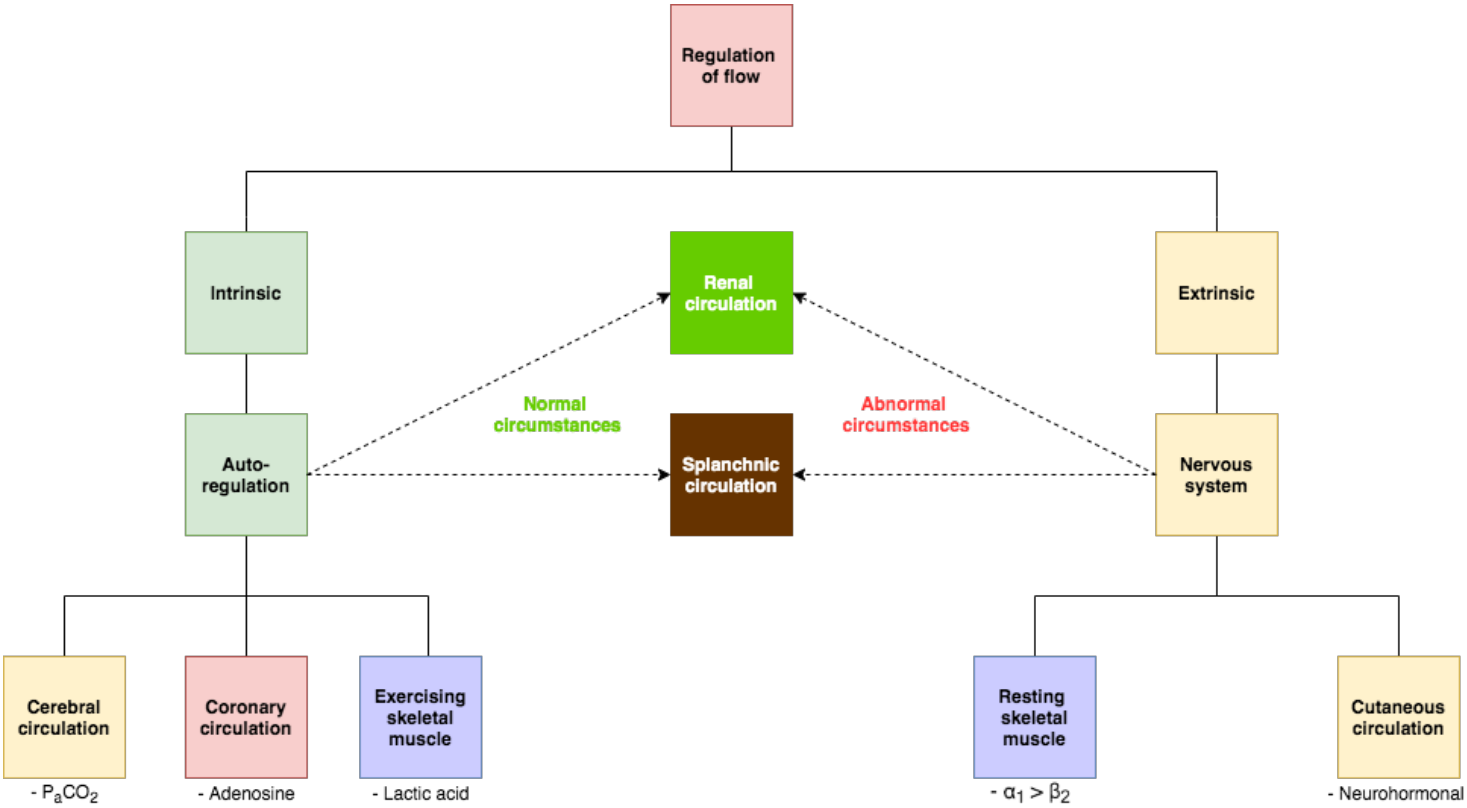
	Laminar flow	Turbulent flow
Characteristics	- Occurs in layers - Present in the cardiovascular system, except in the heart - Highest velocity in the center	- Does not occur in layers - Produces murmurs in the heart and bruits in vessels - Produces more resistance
Reynolds number[1]	< 2,000	> 3,000[2]
Risk of thrombosis[3]	Decreased	Increased
Appearance		

[1] Reynolds number is not the same for all vessels (e.g., *atherosclerosis decreases the Reynolds number of a given vessel*)
[2] In the range of 2000-3000, there is an increased likelihood of turbulent flow – while values > 3000 always predict turbulent flow
[3] Turbulence is a part of Virchow's triad of thrombosis

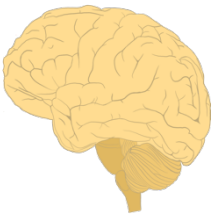
5.3.7 – Connection Between Blood Flow and Mean Arterial Pressure



5.4 – Regulation of Flow



5.4.1 - Cerebral Circulation



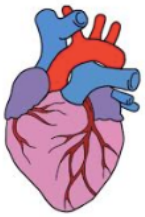
I. Regulation

- Extrinsic → autoregulation
- Controlled by the levels of P_aCO_2 ($\propto P_ACO_2$)
- Increased levels of CO_2 → vasodilation
- Decreased levels of CO_2 → vasoconstriction

$$P_ACO_2 = \frac{\text{Metabolism}}{V_A}$$

- P_ACO_2 = Partial pressure of CO_2 in alveoli
- V_A = Alveolar ventilation

5.4.2 – Coronary Circulation



I. Regulation

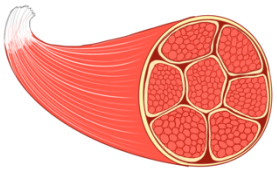
- Extrinsic → autoregulation
- Controlled by the levels of adenosine
- Increased levels of adenosine → vasodilation
- Decreased levels of adenosine → vasoconstriction

Flow in the left coronary artery	Flow in the right coronary artery
Minimal flow during systole[1]	Significant flow during systole
Greatest flow during diastole	Greatest flow during diastole

[1] The left ventricle is three times larger than the right ventricle. During systole, contraction of the left ventricle will result in compression of the left coronary artery – leading to decreased flow

5.4.3 – Skeletal Muscle

I. Exercise



- Extrinsic → autoregulation
- Controlled by the levels of lactic acid
- Increased levels of lactic acid → vasodilation
- Decreased levels of lactic acid → vasoconstriction

II. Rest

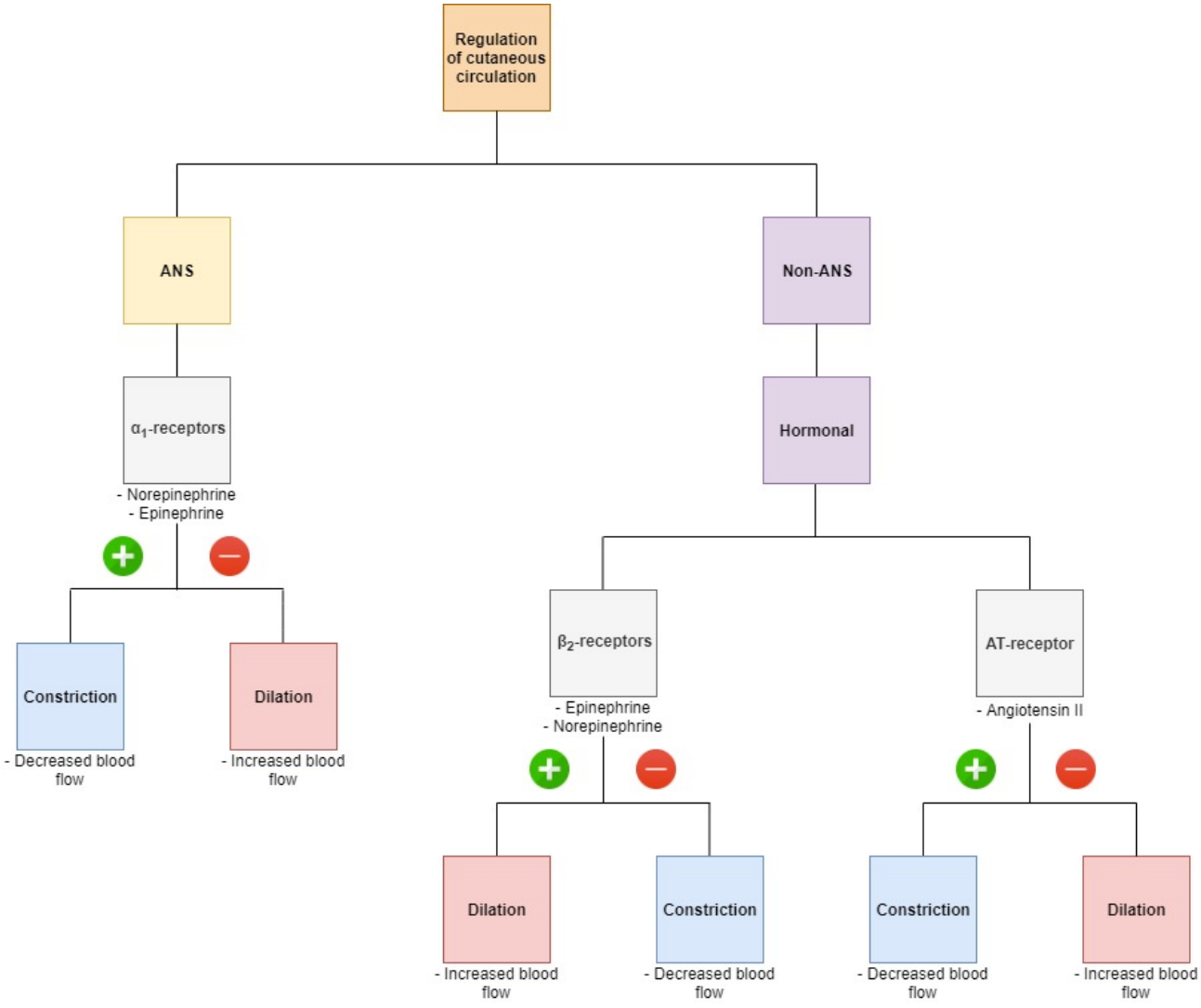
- Intrinsic → nervous system
- Controlled by α_1 – and β_2-receptors
- Activation of α_1-recepetors →vasoconstriction
- Activation of β_2-receptors → vasodilation

Note: In a resting individual, the α_1-receptors are more activated than the β_2-receptors in the arteries of the skeletal muscle

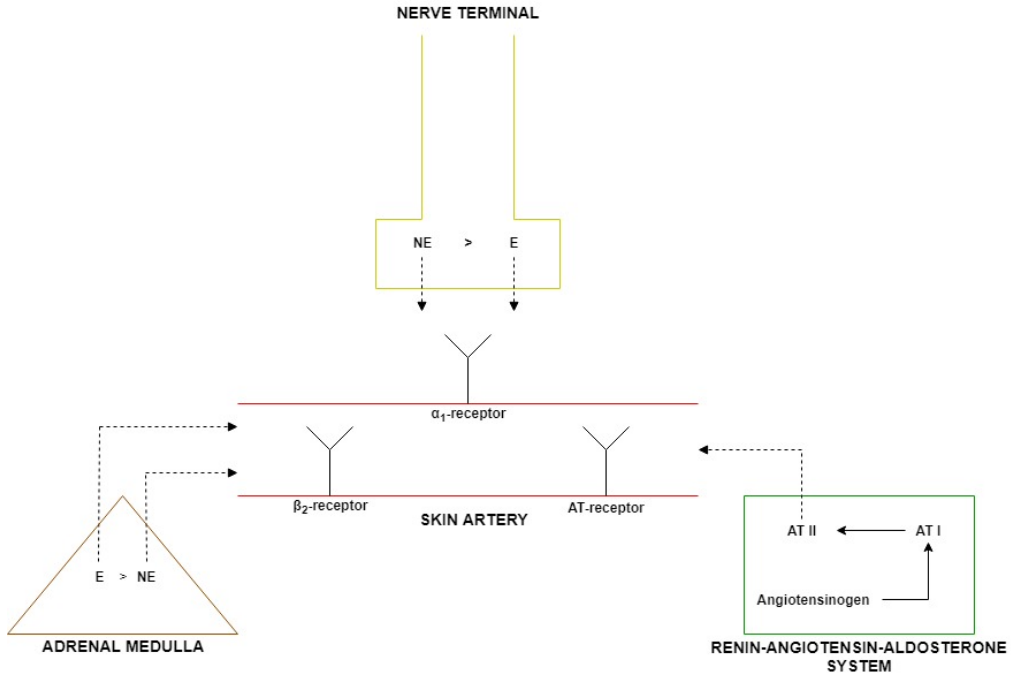
5.4.4 – Cutaneous Circulation

I. Regulation

- Intrinsic → neurohormonal
- Controlled by α_1-receptors >> β_2-receptors > AT-receptors
- Activation of α_1-receptors → vasoconstriction
- Activation of β_2-receptors → vasodilation
- Activation of AT-receptors → vasoconstriction

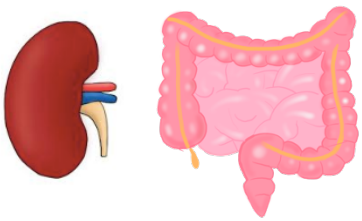


II. Differences between α_1 – and β_2-receptors



α_1-receptor	β_2-receptor
Activated by the release of norepinephrine and epinephrine from nerve terminals (*neurotransmitters*)	Activated by circulating epinephrine and norepinephrine produced in the adrenal medulla (*hormones*)
Innervated	Non-innervated
Vasoconstriction	Vasodilation

5.4.5 – Renal – and Splanchnic Circulations



I. Regulation

- Exist in both worlds
- Normal circumstances → intrinsic →autoregulation
- Abnormal circumstances → extrinsic → nervous system

5.5 – Test Yourself

1) Select the correct statement(s) regarding normal blood flow.
a) Arteries always contain more O_2 than veins
b) Superior vena cava returns the blood from the head, neck, upper extremities and abdomen
c) Mixed venous blood is a collection of blood from the superior vena cava and the inferior vena cava
d) A and C are correct
e) All of the above

2) Select the correct sequence(s) of blood flow in the systemic – and pulmonary circulations.
a) Pulmonary capillaries → pulmonary arteries → left atrium → left ventricle → aorta
b) Arterioles → systemic capillaries → venules → veins → vena cava
c) Right atrium → right ventricle → pulmonary veins → pulmonary capillaries → pulmonary arteries
d) All of the above
e) None of the above

3) Why is the blood flow equal in the pulmonary – and systemic circulation?
a) The pulmonary – and systemic circulation are coupled in series
b) The resistance is higher in the pulmonary circulation, compared with the systemic circulation
c) The pulmonary – and systemic circulation are coupled in parallel
d) A and B are correct
e) None of the above

4) Why does right ventricular failure lead to peripheral edema?
a) Increased pressure in the right atrium
b) Pooling of blood in the veins
c) Increased hydrostatic pressure in the arteries
d) A and B are correct
e) All of the above

5) Select the correct statement(s) regarding vessels.
a) The speed of blood flow in the veins is the lowest, because they contain the smallest pressure
b) Vasoconstriction of veins leads to increased blood flow
c) The degree of elastic tissue and smooth muscle affects the compliance of arteries and veins
d) B and C are correct
e) All of the above

6) Select the correct statement(s) regarding hemodynamic concepts.
a) Cross-sectional area depends indirectly on the size of the vessels
b) Increased viscosity leads to decreased risk of thrombosis
c) Arterioles are the vessels with the highest resistance
d) A and C are correct
e) None of the above

7) Select the false statement(s) regarding hemodynamic concepts.
a) The major factor determining resistance is the radius
b) Laminar flow does not occur in the heart
c) Turbulent flow may create bruits in the heart and murmurs in the vessels
d) Atherosclerosis increases the Reynolds number of a given vessel
e) C and D are false

8) A man presents with symptoms and signs of myocardial infarction. Imaging reveals 50 % obstruction of the left coronary artery. Based on the degree of obstruction – what would be the increase in resistance of the same artery?
a) 6-fold increase
b) 8-fold increase
c) 16-fold increase
d) Impossible to calculate
e) None of the above

9) Select the correct statement(s) regarding series – and parallel circulations.
a) Since the heart and the lungs are two separate organs, the systemic – and pulmonary circulations are coupled in parallel
b) Flow is independent in a series circulation
c) If a woman donated a kidney to her brother, the total peripheral resistance would decrease accordingly
d) All of the above
e) None of the above

10) Select the correct statement(s) regarding compliance and elasticity.
a) Elasticity is determined by the amount of smooth muscle
b) The fundamental characteristic of a compliant vessel is to expand with a large increase in pressure
c) Elasticity decreases with age
d) Compliance decreases with age
e) B and C are correct

11) Select the correct statement(s) regarding distribution of blood volume.
a) Systemic veins contain the largest amount of blood, because they have the highest elasticity
b) Around 40 % of the blood volume, at any given moment, is present in the systemic veins
c) The systemic veins, along with the pulmonary system, constitute the biggest reservoir of blood
d) All of the above
e) None of the above

12) Select the correct statement(s) regarding distribution of vascular resistance.
a) The arterioles have the highest pressure drop in the systemic circulation, because they have the highest resistance
b) Abundance of smooth muscle is characteristic of resistance vessels
c) Besides the arterioles, the capillaries are the most important factor contributing to vascular resistance
d) A and C are correct
e) All of the above

13) Select the correct statement(s) regarding regulation of flow.
a) Extrinsic regulation involves the nervous system
b) During exercise, there is no change in the cerebral circulation
c) In a resting individual, the α_1-receptors are more activated than the β_2-receptors in the arteries of skeletal muscle
d) B and C are correct
e) None of the above

14) Select the false statement regarding regulation of flow.
a) Hyperventilation leads to decreased levels of CO_2, which causes vasoconstriction
b) Adenosine is a vasodilatory metabolite
c) The partial pressure of CO_2 in the alveoli is proportional to the partial pressure of CO_2 in the pulmonary veins
d) The left ventricle compress the left coronary artery during the systolic phase of the cardiac cycle
e) The greatest flow in the right coronary artery is during the diastolic phase of the cardiac cycle

15) Select the correct statement(s) regarding cutaneous circulation.
a) β_2-receptors respond to epinephrine and norepinephrine released from nerve terminals
b) α_1-receptors are of greater physiological importance than the β_2-receptors
c) Vasodilation is a result of relaxation of smooth muscle in the vessels
d) B and C are correct
e) All of the above

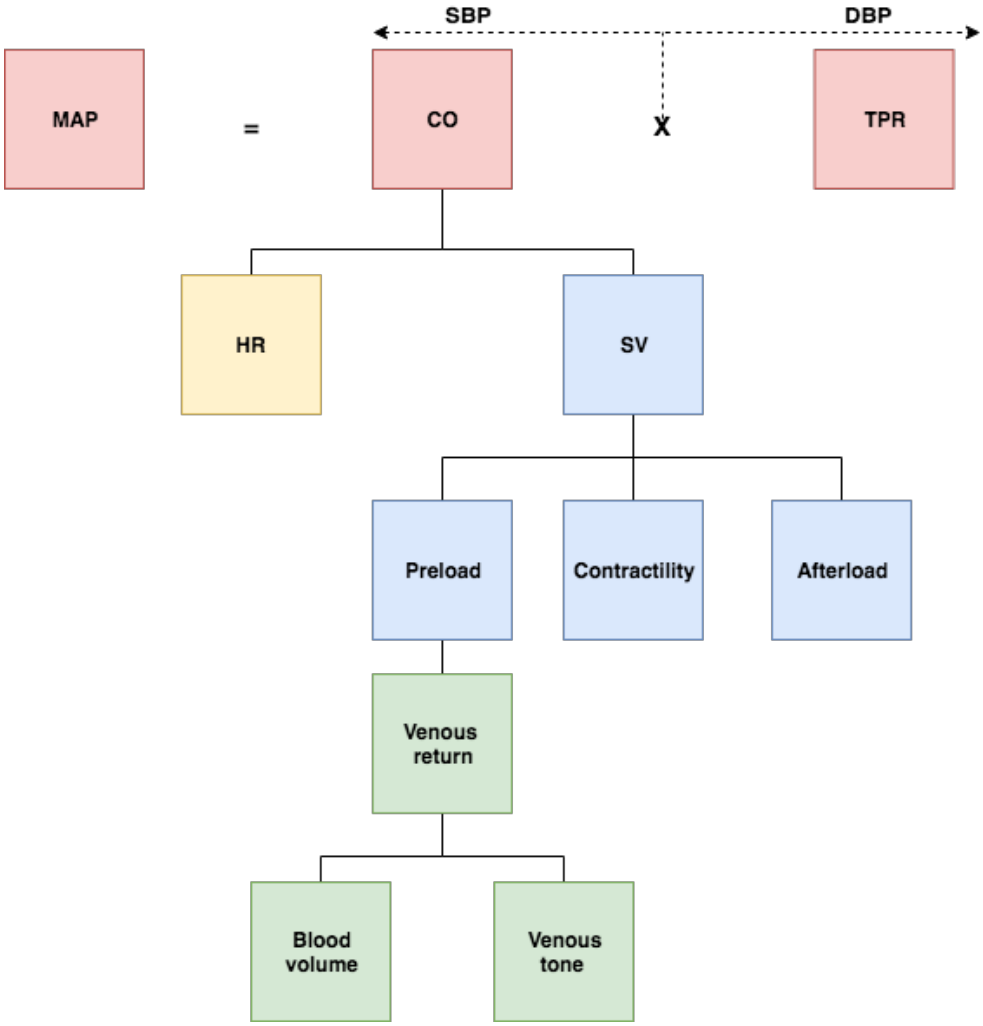
Section 6 – Regulation of Blood Pressure

6.0 – Central Terms

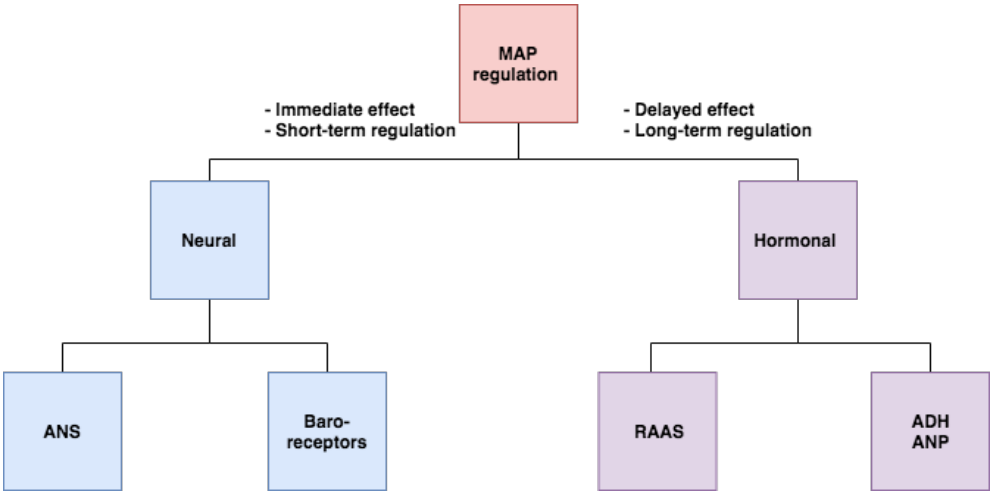
	Definition	Increase with	Decrease with	Comments
Mean arterial pressure	- Average blood pressure of a single cardiac cycle - 1/3 SBP[1]+ 2/3 DBP[2]	- ↑ CO - ↑ TPR	- ↓ CO - ↓ TPR	
Total peripheral resistance	Resistance of systemic arterioles	- ↑ Arteriolar tone - Vasoconstriction	- ↓ Arteriolar tone - Vasodilation	$TPR = vL/r^4$
Cardiac output	Amount of blood ejected by the left ventricle per minute (mL/min)	- ↑ Contractility - ↑ Preload - ↑ Venous tone - ↑ Blood volume	↑ Afterload	
Stroke volume	Amount of blood ejected by the left ventricle per beat (mL/beat)	- ↑ Contractility - ↑ Preload	↑ Afterload	**S**troke **V**olume affected by **C**ontractility, **A**fterload and **P**reload **SV CAP**
Preload	Workload on the heart **prior** to contraction	- ↑ Venous tone - ↑ Blood volume	- ↓ Venous tone - ↓ Blood volume	
Afterload	Workload on the heart **during** contraction	- ↑ TPR - ↑ Aortic pressure	- ↓ TPR - ↓ Aortic pressure	
Contractility	The ability of the heart muscle to generate force	B_1 stimulation	B_1 blockade	

[1]Systolic blood pressure
[2]Diastolic blood pressure

6.1 – Mean Arterial Pressure



6.2 – Regulation of Blood Pressure



6.3 – Neural Regulation

6.3.1 – Nervous System

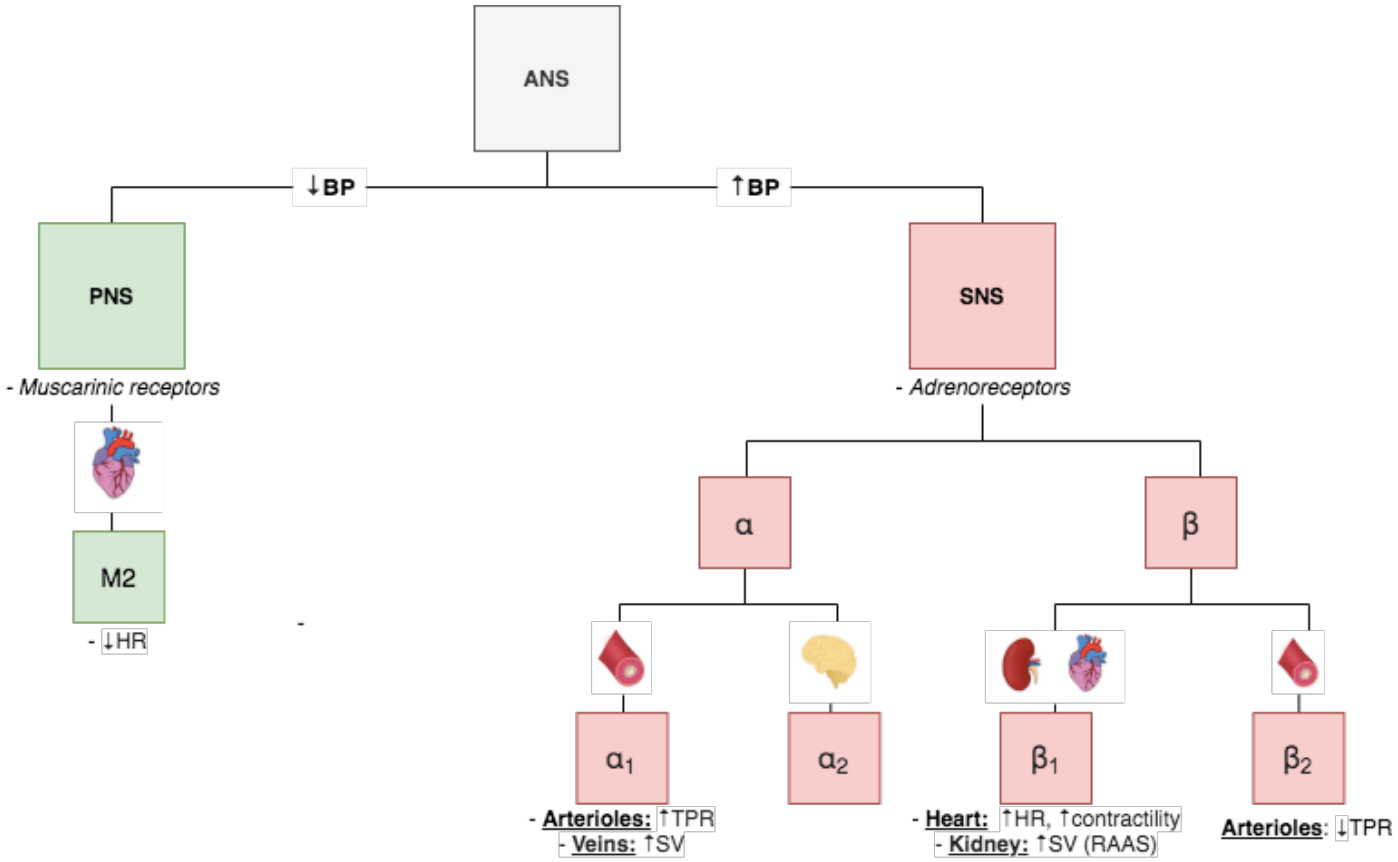
- Mediated by the **autonomic nervous system** (ANS)

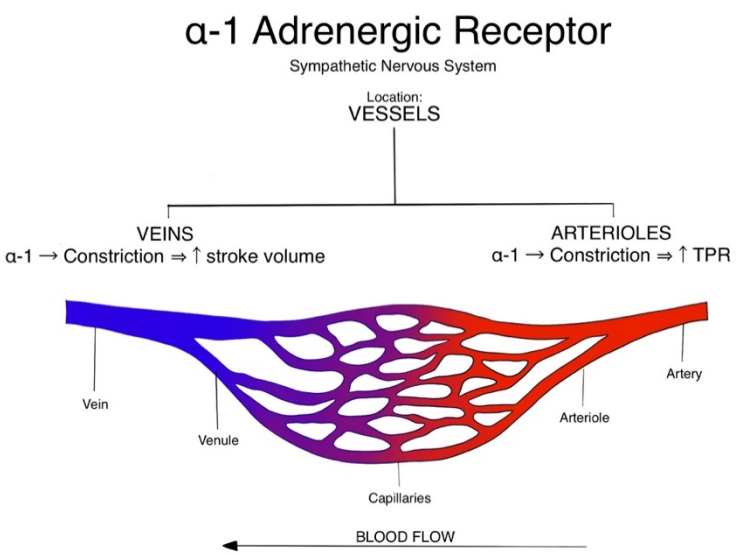
I. ANS division

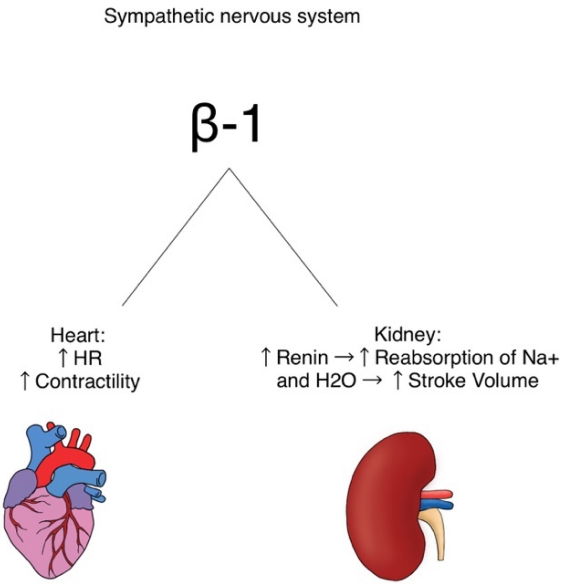
- Parasympathetic nervous system (PNS) aims to **decrease** blood pressure
- Sympathetic nervous system (SNS) aims to **increase** blood pressure

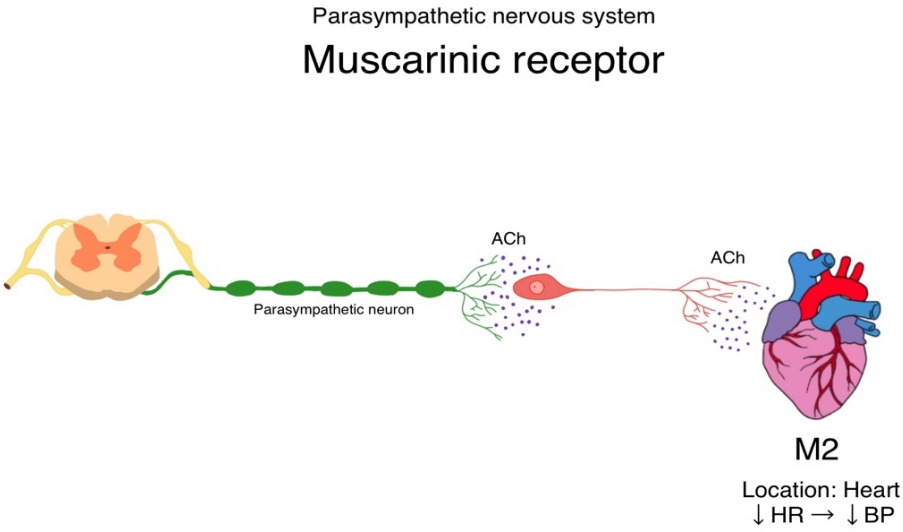
II. Effects

- Mediated by neurotransmitters which bind:
  1. Muscarinic receptors (PNS)
  2. Adrenoreceptors (SNS)




α-1 Adrenergic Receptor
Sympathetic Nervous System
Location:
VESSELS
VEINS
α-1 → Constriction ⇒ ↑ stroke volume
ARTERIOLES
α-1 → Constriction ⇒ ↑ TPR
Vein
Venule
Capillaries
Arteriole
Artery
BLOOD FLOW


Sympathetic nervous system
β-1
Heart:
↑ HR
↑ Contractility
Kidney:
↑ Renin → ↑ Reabsorption of Na+
and H2O → ↑ Stroke Volume

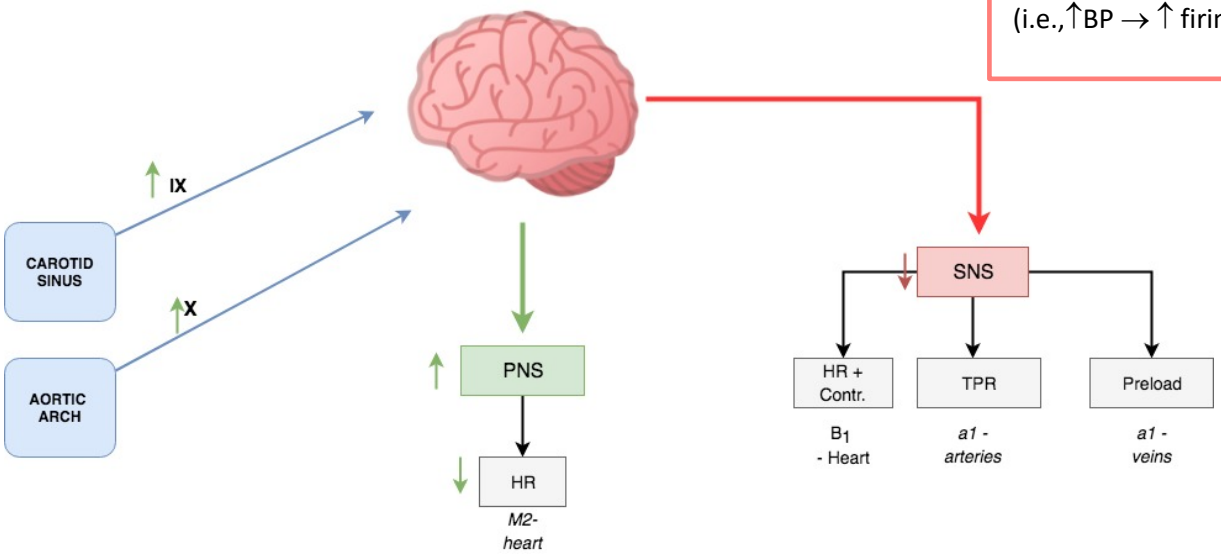

Parasympathetic nervous system
Muscarinic receptor
ACh
ACh
Parasympathetic neuron
M2
Location: Heart
↓ HR → ↓ BP

6.3.1 – Baroreceptors

- Receptors which are sensitive to **pressure** and **stretch**
- Activated by **rapid** changes in blood pressure
- Located in the **carotid sinus** and **aortic arch**
- Information from **carotid sinus** is carried via **CN IX** (*glossopharyngeal nerve*)
- Information from **aortic arch** is carried via **CN X** (*vagus nerve*)

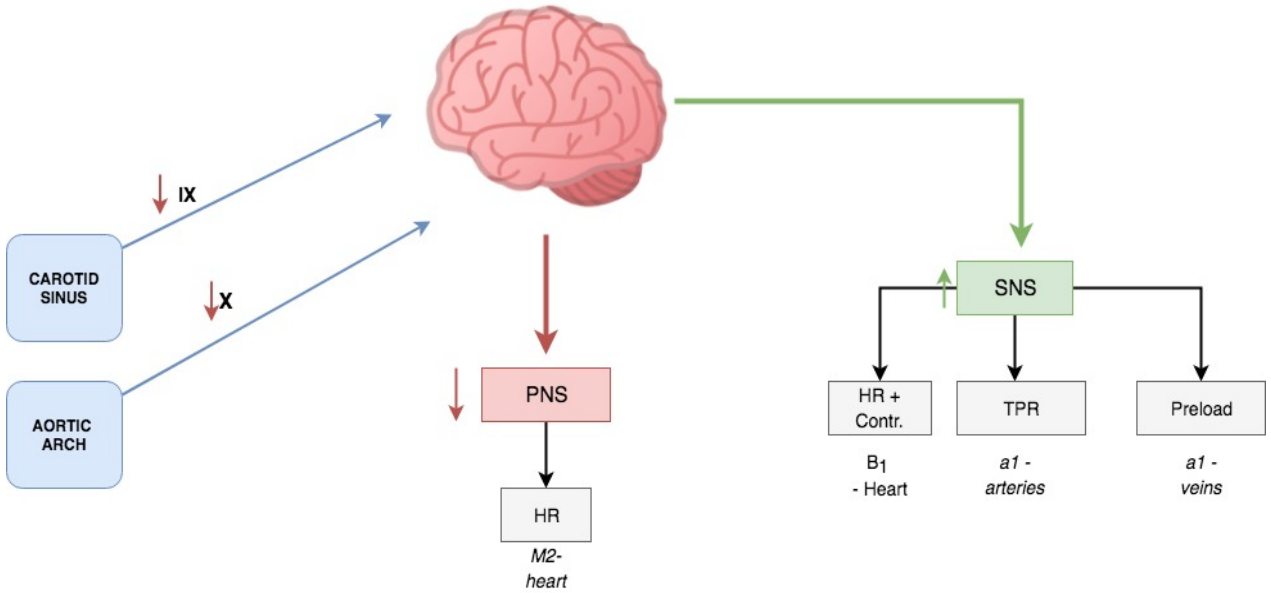
RULE
- BP ∝ Firing rate
(i.e.,↑BP → ↑ firing rate)

I. Increased blood pressure



↑BP —↑ arterial pressure → ↑ stretch → ↑ baroreceptor firing → ↓ sympathetic firing and ↑ parasympathetic stimulation → ↓ HR, ↓ contractility and vasodilation

II. Decreased blood pressure

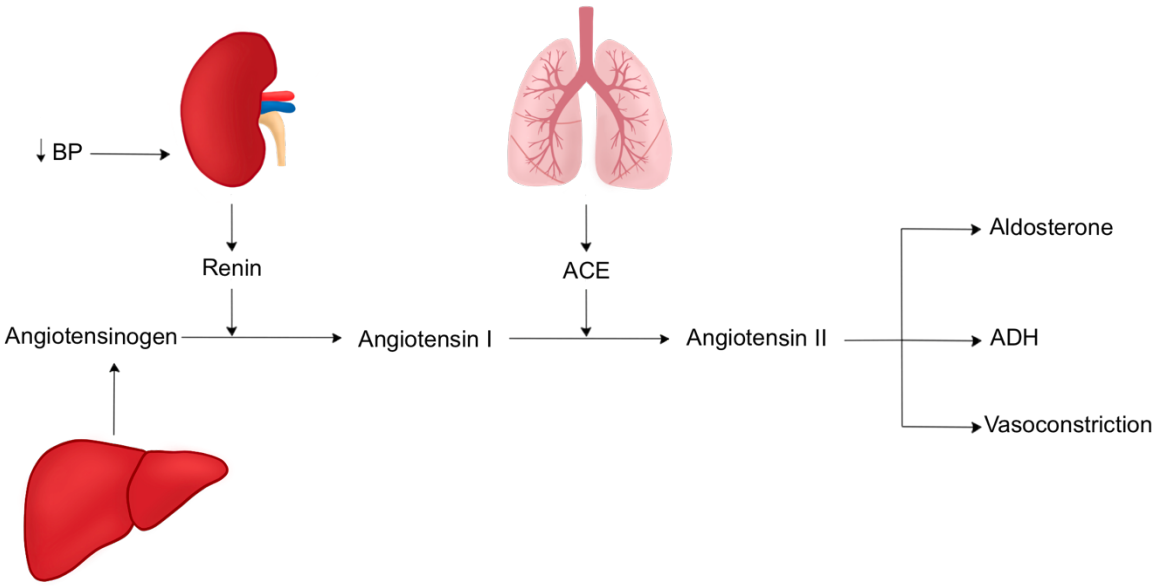


↓ BP—↓ arterial pressure → ↓ stretch → ↓ baroreceptor firing → ↑ sympathetic firing and ↓ parasympathetic stimulation → ↑ HR, ↑contractility and vasoconstriction

	Blood pressure	PNS activity	SNS activity	Notes
Increased discharge rate	↑	↑	↓	
Decreased discharge rate	↓	↓	↑	
Carotid massage	↑	↑	↓	

6.4 – Hormonal Regulation

6.4.1 – Renin-Angiotensin-Aldosterone System



6.4.2 – Atrial natriuretic peptide (ANP) and anti-diuretic hormone (ADH)

I. Atrial natriuretic peptide

- Aims to decrease blood pressure during periods of volume overload

II. Anti-diuretcic hormone

- Aims to increase blood pressure during periods of volume depletion

	ANP	ADH
Properties	Hormone	Hormone
Released by	Stretched atria	Posterior pituitary gland
Effects on blood pressure	- **Natriuresis:** ↓Na^+ → ↓H_20 → ↓ blood volume - **Arteriolar vasodilation:** ↓TPR	- **Reabsorption of water:** ↑ Blood volume → ↑BP

6.5 – Test Yourself

1) Which of the following will increase the amount of blood pumped by the left ventricle per beat?
a) Increased HR
b) Increased afterload
c) Increased TPR
d) Increased venous tone

2) β_1-stimulation results in?
a) Increased sodium and water retention by the kidney
b) Increased stroke volume
c) Increased cardiac output
d) All of the above

3) The autonomic nervous system elicits an _____ (immediate/delayed) **effect on blood pressure and is responsible for** _____(short-term/long-term) **regulation of blood pressure. Hormones, especially the Renin-Angiotensin-Aldosterone system, elicits a** _____(delayed/immediate) **effect on blood pressure and is responsible for** _____(short-term/long-term) **regulation of blood pressure.**

4) The parasympathetic nervous system aims to _____(decrease/increase) **the blood pressure via the stimulation of** _____**receptors** (muscarinic/adrenergic). **The sympathetic nervous system aims to** _____(decrease/increase) **the blood pressure via the stimulation of** _____**receptors** (muscarinic/adrenergic).

5) Concerning the baroreceptors, which cranial nerve is responsible for carrying information from the carotid sinus to the brain?
a) Glossopharyngeal
b) Vagus
c) Hypoglossal
d) Trigeminal

6) What are the effect(s) of increased baroreceptor discharge rate?
a) Inhibition of the parasympathetic nervous system and stimulation of the sympathetic nervous system
b) Inhibition of the sympathetic nervous system and stimulation of the parasympathetic nervous system
c) Increased contractility, increased total peripheral resistance and increased venous return
d) Increased contractility, increased preload and increased total peripheral resistance
e) A, D, C
f) A and D

7) Select the correct statement(s) regarding carotid massage

a) It can slow the rate of conduction through the AV node and subsequently decrease the heart rate

b) Pressure is applied on the carotid sinus for 10 seconds. The firing rate from the glossopharyngeal nerve will increase, and the sympathetic nervous system will be stimulated in order to increase blood pressure

c) Pressure is applied on the carotid sinus for 10 seconds. The firing rate from the glossopharyngeal nerve will increase, and the parasympathetic nervous system will be stimulated in order to decrease blood pressure

d) A and B

e) A and C

8) α_1 stimulation results in:

a) Increased TPR

b) Increased cardiac output

c) Increased preload

d) A and C

e) All of the above