Cardiac Output and venous return

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Definitions

Cardiac Output
- The quantity of blood pumped into the aorta each minute
- measured in milliliters (mL) per minute (min) or liters (L) per minute
- normally around 5,000 mL (5 L) per minute (5,000 mL/min or 5 L/min)

Venous Return
- The quantity of blood flowing from the veins into the right atrium each minute

Stoke Volume

End-Diastolic Volume – End-Systolic Volume = Stroke Volume

End-Diastolic Volume

End-Systolic Volume

Cardiac Output (CO)

Beat = stroke volume (SV)
= EDV – ESV
= 70 ml

Minute = Cardiac output (CO)
= SV x HR
= 5 liters / min

Minute / square meter of body surface area
= Cardiac index
= 3.2 liter / min / m²
Cardiac output (CO) is directly affected by...

- **heart rate** (HR), the number of times the heart beats each minute; and
- **stroke volume** (SV), the amount of blood ejected during each beat

\[
\text{CO} = \text{HR} \times \text{SV}
\]

- If HR increases, what will happen to cardiac output?
- If SV decreases, what will happen to cardiac output?

**Ejection Fraction**

**Definition:** It is the ratio of SV compared to EDV.

\[
\text{EF} = \frac{\text{SV}}{\text{EDV}} \times 100 = \frac{70}{135} \times 100
\]

**Value:** Normally it is about 50 – 60%.

**Importance:** It is used as an indicator for myocardial contractility.

**Cardiac Reserve**

- During exercise CO (Cardiac Output) may increase up to 10-25 liters/minute and up to 40 liters/minute during heavy exercise in athletes.
- Cardiac reserve is the difference between the cardiac output at rest and maximal cardiac output during heavy exercise.

**Determinants of Cardiac Output**

- **Contractility**
- **Preload**
- **Afterload**

**Important Relationships**

- **Preload:** the initial stretching of the cardiac myocytes prior to contraction.
- **End diastolic volume:** the volume of blood in a ventricle at the end of filling

- **Determining factor:**
  - Venous return
  - Preload Pumps up the heart
Some definitions

- **Afterload**: the force the sarcomere must overcome in order to shorten during systole.
- **Determining factor**: Aortic pressure

**Measurement of Cardiac Output**

- Electromagnetic flowmeter
- Indicator dilution (dye such as cardiogreen)
- Thermal dilution
- **Oxygen Fick Method**
  
  \[ CO = \frac{O_2 \text{ consumption}}{(A-V O_2 \text{ difference})} \]

**Fick Principle**

- Cardiac output = \( \frac{O_2 \text{ Consumption}}{[O_2] \text{ pulmonary vein} - [O_2] \text{ pulmonary artery}} \)

A man has a resting O2 consumption of 250 ml O2/min, a femoral arterial O2 content of 0.20 ml O2/ml blood, and a pulmonary arterial O2 content of 0.15 ml O2/ml blood.

\[ CO = \frac{250 \text{ ml O}_2/\text{min}}{0.20 \text{ ml O}_2/\text{ml} - 0.15 \text{ ml O}_2/\text{ml}} = 5000 \text{ ml/min} \]

**O2 Fick Problem**

- Pulmonary vein O2 content = 200 ml O2/L blood
- Pulmonary artery O2 content = 160 ml O2/L blood
- Lungs add 400 ml O2/min
- What is cardiac output?
- Answer: 400/(200-160) = 10 L/min

**Regulation of Cardiac output**

- **Extrinsic regulation**
  - Nervous supply of the heart.
  - Hormones or chemical
- **Intrinsic regulation**
  - It is the ability of the heart to change its stroke volume independent of nervous chemical or hormonal factors.

**Intrinsic autoregulation**

1. **Heterometric autoregulation**: Initial Length (Preload):
   - The major determinant of the force of contraction is the initial length of the muscle fiber.
   - The end diastolic volume (EDV) is used instead of length of muscle fiber.
   - The EDV is determined by the preload.
   - The term preload refers to the degree of passive stress exerted by the volume of blood in the ventricle just before its contraction.
Preload

• Preload can be defined as the initial stretching of the cardiac myocytes prior to contraction. It is related to the sarcomere length at the end of diastole.

Frank-Starling Relationship

• Because we cannot measure sarcomere length directly, we must use indirect indices of preload.
  - LVEDV (left ventricular end-diastolic volume)
  - LVEDP (left ventricular end-diastolic pressure)
  - PCWP (pulmonary capillary wedge pressure)
  - CVP (central venous pressure)
Frank-Starling Mechanism

- When venous return to the heart is increased, ventricular filling increases, as does preload. This stretching of the myocytes causes an increase in force generation, which enables the heart to eject the additional venous return and thereby increase stroke volume.
- Simply stated: The heart pumps the blood that is returned to it.

Frank-Starling Mechanism

- Allows the heart to readily adapt to changes in venous return.
- The Frank-Starling Mechanism plays an important role in balancing the output of the 2 ventricles.
- In summary: Increasing venous return and ventricular preload leads to an increase in stroke volume.

Frank-Starling Mechanism

- There is no single Frank-Starling Curve for the ventricle. Instead, there is a family of curves with each curve defined by the existing conditions of afterload and inotropy.

Length-tension curve

(Frank-Starling)

Optimal length

End-diastolic volume (EDV) (ml)

Stroke volume (SV) (ml)

Normal resting length

B1

A1

Increase in EDV

Increase in SV

Starling’s Law of the Heart

The muscle developed tension is increased upon increasing the initial length (preload) up to a certain limit. Further increase in muscle length beyond this limit depresses the muscle developed tension and this is not seen in the normal heart but only in heart failure.
**Frank-Starling Curves**

![Image](image_url)

*Figure 3. Family of Frank-Starling curves. Changes in afterload and inotropy shift the Frank-Starling curve up or down.*

- **Frank Starling**
- Intrinsic regulation of heart pumping
- Increased venous return leads to increased stroke volume
- \( CO = SV \times HR \)

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**Homeometric autoregulation**

- It follows the heterometric regulation.
- It can occur for long time.
- It is an afterload phenomenon.
- It is initiated by the increase in aortic pressure.
- The increase in myocardial contraction increases SV by the decrease in ESV.
- EDV returns to the normal value (not changed).

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**Afterload**

- More precisely defined in terms of ventricular wall stress:
  - LaPlace’s Law: \( \sigma = \frac{Pr}{h} \)
  - \( P \) = ventricular pressure
  - \( R \) = ventricular radius
  - \( h \) = wall thickness

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**Afterload**

- Afterload can be viewed as the "load" that the heart must eject blood against.
- In simple terms, the afterload is closely related to the aortic pressure.

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**Afterload is better defined in relation to ventricular wall stress**

- \( \sigma \propto \frac{Pr}{h} \)
Afterload

- Afterload is increased by:
  - Increased aortic pressure
  - Increased systemic vascular resistance
  - Aortic valve stenosis
  - Ventricular dilation

Effects of Afterload

- What effect will hypertension have on afterload?
  - **Heterometric**
    - Occurs at first (followed by homeometric regulation).
    - Rapid (Immediate after increase in VR)
    - Short (few minutes)
    - Increase
    - Following the heterometric regulation.
    - Slow (after few min)
    - Long (Maintain the elevated stroke volume for long time).
  - **Homeometric**
    - Constant (or slightly increased)
    - Increase
    - Stretch of ventricular muscle fibers.
    - Shortening
    - Starling law
    - Pre load

- What effect will hypertension have on stroke volume?

<table>
<thead>
<tr>
<th>Heterometric</th>
<th>Homeometric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>EDV</td>
<td></td>
</tr>
<tr>
<td>JESV</td>
<td>Constant</td>
</tr>
<tr>
<td>JSV</td>
<td>Increase</td>
</tr>
<tr>
<td>ESV</td>
<td>Present</td>
</tr>
<tr>
<td>Starling law</td>
<td>Increase of the aortic pressure</td>
</tr>
<tr>
<td>Pre load</td>
<td>After load.</td>
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</tbody>
</table>
Anrep Effect

• An abrupt increase in afterload can cause a modest increase in inotropy.

• The mechanism of the Anrep Effect is not fully understood.

Extrinsic regulation

- It is the adjustment of CO via change of heart rate (HR) and/or stroke volume (SV).
- It acts through either autonomic nerve supply of the heart and/or hormones (chemicals) in the blood.

Extrinsic regulation

- Nervous regulation
- Hormonal (chemical) regulation

Heart Rate is directly affected by factors called chronotropic agents (or factors). These factors may be positive or negative.

Positive chronotropic agents...
- increase heart rate and
- include epinephrine, norepinephrine and beta agonists (e.g., isoproterenol).

• What effect will sympathetic nerve impulses have on heart rate?

Negative chronotropic agents...
- decrease heart rate and
- include acetylcholine (ACh) and beta antagonists (e.g., propranolol).

• What effect will parasympathetic nerve impulses have on heart rate?
Heart Rate

- Changes in heart rate are generally more important quantitatively in producing changes in cardiac output than are changes in stroke volume.
- Changes in heart rate alone inversely affect stroke volume.

Heart Rate

- At high HR
  - The decrease in SV is greater than the increase in HR (decreased filling time).
- At low HR
  - Decrease in HR is greater than decrement in SV.

Bowditch (Treppe) Effect

- An increase in heart rate will also cause positive inotropy (Bowditch effect, Treppe or "staircase" phenomenon).
- This is due to an increase in intracellular Ca++ with a higher heart rate:
  - More depolarizations per minute
  - Inability of Na+/K+-ATPase to keep up with influx of Na+; thus, the Na+-Ca++ exchange pump doesn’t function as well.

Heart rate regulation:

<table>
<thead>
<tr>
<th>Area affected</th>
<th>Parasympathetic stimulation</th>
<th>Sympathetic stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-SA Node</td>
<td>Decrease heart rate</td>
<td>Increase heart rate</td>
</tr>
<tr>
<td>2-Atrial muscle</td>
<td>Decrease contractility</td>
<td>Increase contractility</td>
</tr>
<tr>
<td>3-AV Node</td>
<td>Decrease excitability (increase AV node delay)</td>
<td>Increase excitability (decrease AV node delay)</td>
</tr>
<tr>
<td>4-Ventricles conductive system</td>
<td>No effect</td>
<td>Increase conduction through His bundle and Purkinje cells</td>
</tr>
<tr>
<td>5-Ventricle muscle</td>
<td>No effect</td>
<td>Increase contractility</td>
</tr>
<tr>
<td>6-Adrenal medulla</td>
<td>No effect</td>
<td>Increase sympathetic secretion which enhances sympathetic stimulation on heart</td>
</tr>
<tr>
<td>7-Veins</td>
<td>No effect</td>
<td>Increase venous return (by vasoconstriction of veins) which increase cardiac contraction (Frank-Starling mechanism)</td>
</tr>
</tbody>
</table>
Effect Of ANS on HR:

The parasympathetic and sympathetic nervous systems act together on heart rate in antagonistic (opposing) way, during rest the parasympathetic nervous system dominate more than the sympathetic nervous system.

What happen if all autonomic nerves to the heart are cut?
The heart rate will be 100/min, which is the inherent rhythm of the SA (which is the SA Node discharge when it is free from the normal inhibitory dominant parasympathetic effect at rest).

A Cardiovascular control center in the brain stem coordinates the autonomic activity to the heart. If heart rate is to be increased this center control the increase in sympathetic activity and at same time decrease the parasympathetic activity and vice versa.

Sympathetic stimulation can increase stroke volume and cardiac output by:

A-Increase force of contraction:
- Under sympathetic stimulation with the EDV=135 ml, the Stroke volume will be 100 ml and End Systolic Volume (ESV)=35 ml only.
- Sympathetic stimulation shift the Frank-Starling curve up and to the left and according to the degree of sympathetic stimulation it is the degree of the shift up to a maximal increase in strength of contraction 100% greater than resting strength.

B-Increase venous return:
Sympathetic stimulation also cause vasoconstriction of the veins which squeezes more blood from the veins to the heart (more filling) which in turn increase EDV and stroke volume.

Resting heart without sympathetic:
End-diastolic volume
135 ml
Stroke volume
70 ml
End-systolic volume
65 ml
**Sympathetic stimulation:**

- **End-diastolic volume**: 135 ml
- **Stroke volume**: 100 ml
- **End-systolic volume**: 35 ml

Shifting of Frank-Starling curve up and to the left by sympathetic stimulation:

- **Frank-Starling curve on sympathetic stimulation**
- **Normal Frank-Starling curve**

**Effects of increased sympathetic stimulation on Cardiac output**

- Increased slope of Pacemaker potential
- Increased force of ventricular contraction
- Increased heart rate
- Increased stroke volume
- Increased cardiac output

**Effects of increased parasympathetic stimulation on Cardiac output**

- Decreased slope of Pacemaker potential
- Decreased force of atrial contraction
- Decreased heart rate
- Decreased ventricular filling
- Decreased cardiac output

**Cardiac output**

- **Heart rate**
- **Stroke volume**

Extrinsic control

- Sympathetic activity
- Parasympathetic activity

Intrinsic control

- End-diastolic volume

Venous return

**What effect will increased heart rate have on stroke volume (if other factors stay the same)?**

- **Filling time** is inversely related to heart rate; as heart rate increases, filling time decreases.
- Chronotropic agents affect filling time, thus they affect EDV. However, these agents may also affect contractility such that the effects on stroke volume are less straightforward.
2. Hormonal (chemical) regulation

- **Catecholamine**: Causes increase CO (Its actions similar to sympathetic stimulation).

- **Thyroxin hormone**: Causes increase CO by increasing the number and sensitivity of B1 receptors to catecholamine.

- **Insulin hormone**: Causes increase of CO. It has +ve inotropic action (increases SV and CO).

- **Glucagon hormone**: Causes increase of CO. It has +ve inotropic action (increases SV and CO).

- **Digitalis drug**: Causes increase of CO (It has +ve inotropic action).

- **Acetyl choline**: Causes decrease CO (Action similar to parasympathetic stimulation).

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Extrinsic factors Affecting Myocardial Contraction Force (Inotropic Factors)

**Contractility**

- The inherent capacity of the myocardium to contract independently of changes in afterload or preload.

- Changes in contractility are caused by intrinsic cellular mechanisms that regulate the interaction between actin and myosin independent of sarcomere length.

- Increased rate and/or quantity of Calcium delivered to myofilaments during contraction

- Alternate name is inotropy.

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Positive inotropic agents...

- increase contractility and
- epinephrine, norepinephrine and cardiac glycosides (e.g., digitalis)

- What effect will epinephrine have on stroke volume?
Negative inotropic agents...
- decrease contractility and
- include calcium channel blockers (e.g., verapamil).

What effect will blocking calcium channels have on stroke volume?

Extrinsic factors Affecting Myocardial Contraction Force (Inotropic Factors)

1) Nervous Factors:
   a) Sympathetic stimulation increases strength of contraction (positive inotropic factor) through its Ca ++ raising effect.
   b) Parasympathetic stimulation has a negative inotropic effect due to its intracellular Ca ++ lowering action (opposite to sympathetic).

2) Neurohormones:
   a. Epinephrine & norepinephrine : are positive inotropic factors (similar to sympathetic).
   b. Acetylcholine : is negative inotropic factor (similar to parasympathetic).

3) ECF ions:
   Effects of variations in Ca++ and K + ions:
   a. Ca++ infusion (intravenous) may stop the heart during systole (Ca++ rigor).
   b. Effects of hyperkalaemia: Depresses cardiac contractility and may stop the heart during diastole so increased K + ions have a negative inotropic effect.

4) Drugs:
   Digitalis used in the treatment of heart failure is the most important of all; it acts through inhibition of Na+ K+ ATPase & thus Na+ ions accumulate inside the cells & stimulate Na+ Ca++ exchanger (between intracellular Na+ & extracellular Ca++) which increases the intracellular Ca++ concentration.