Cardiovascular regulation

Factors involved in the regulation of cardiovascular function include:
1. Autoregulation.
2. Neural regulation.
3. Hormonal regulation.

1-Local factors (autoregulation)
- Local factors change the pattern of blood flow within capillary beds in response to chemical changes in the interstitial fluids (humeral factors).
- This is an example of autoregulation at the tissue level.
- Autoregulation causes immediate, localized homeostatic adjustments.
- If autoregulation fails to normalize conditions at the tissue level, central and endocrine mechanisms are activated.

Control of Blood Flow
- Autoregulation (local control) - local automatic adjustment of blood flow to match specific local tissue metabolic needs
- Physical changes
  - Warming - ↑ vasodilatation
  - Cooling - ↑ vasoconstriction
- Chemical changes in local tissues generate metabolic byproducts
- vasodilators or vasoconstrictors
- Myogenic control
  - smooth muscle controls resistance
  - ↑ stretch ↑ contraction; ↓ stretch ↓ contraction

2-Central mechanisms (Neural regulation)
- Central mechanisms respond rapidly to changes in arterial pressure or blood gas levels at specific sites.
- When those changes occur, the cardiovascular centers (of the ANS) adjust cardiac output and peripheral resistance to maintain blood pressure and ensure adequate blood flow.

Nerve supply of CVS (ANS)
- A-The sympathetic nerves
- B-The parasympathetic nerves
Cardiovascular centers
- Centers responsible for neural regulation are complex cardiovascular centers (CVC) of the medulla oblongata (M.O.)
- Site: M.O.
- Function: Regulation of the functions of CVS by controlling the sympathetic and parasympathetic discharge to CVS and include 2 main centers which act in a reciprocal manner.
  1. The cardiac centers
  2. The vasomotor centers.

Cardiac centers
- Cardiac centers consist of:
  1. The Cardioacceleratory center (CAC): which increases cardiac output through noradrenergic sympathetic innervation of the heart:
     - Increase heart rate [+] chronotropic effect].
     - Increase force of cardiac contraction which increase the stroke volume (SV). [+ve inotropic effect].

Cardioinhibitory center
- Through parasympathetic (cholinergic system)
- No Vagal innervation to ventricles (Vagal escape)
- Vagal tone predominates the sympathetic tone for the heart during resting condition.

Summary of cardiac centers

<table>
<thead>
<tr>
<th>Cardioacceleratory center</th>
<th>Cardioinhibitory center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through sympathetic (noradrenergic system)</td>
<td>Through parasympathetic (cholinergic system)</td>
</tr>
<tr>
<td>+ve chronotropic effect</td>
<td>-ve chronotropic effect</td>
</tr>
<tr>
<td>+ve inotropic effect</td>
<td>=--------------------------</td>
</tr>
</tbody>
</table>

Vagal tone on SA node
The vasomotor centers

The vasomotor centers (VMC): This includes two components:

1. Vasomotor center (VMC or pressor area): A Very Large Group Responsible for Widespread vasoconstriction. (i.e. stimulation of VCC increases sympathetic discharge to the blood vessels, adrenal medullae and the heart (so it was also called The Cardioacceleratory center (CAC)).

2. Vasodilator center (VDC or depressor area): A Relatively small group responsible for vasodilatation (i.e. stimulation of VDC leads to generalized V.D. (through inhibiting the activity of VCC). Also VD Fibers of arterioles in skeletal muscles and the brain.

Effects of vasomotor centers

The vasomotor centers exert their effects by controlling the activity degree of sympathetic motor neurons:

1. Control of vasoconstriction.
   * The neurons innervating peripheral blood vessels in most tissues are noradrenergic neurons, releasing norepinephrine (NE).

2. Control of vasodilatation
   * Vasodilator neurons (sympathetic cholinergic vasodilator system) innervate blood vessels in skeletal muscles and in the brain.

Neural Regulation

- **Sympathetic influence**
  - Epinephrine \( \uparrow \) HR (tachycardia) and \( \uparrow \) contractility
  - Norepinephrine \( \uparrow \) general vasoconstrictor
  - **Parasympathetic influence** acetylcholine \( \downarrow \) HR (bradycardia)

Extrinsic Innervation of the Heart

- **Heart is stimulated by the sympathetic cardioacceleratory center**
- **Heart is inhibited by the parasympathetic cardioinhibitory center**

Sympathetic input · HEART

- ACTIONS
  - Nerve fibers release NE
  - SA, atria, and ventricles
  - \( \uparrow \) HR and contractility
  - R side SA node
  - L side contractility

- MECHANISM
  - \( \beta_1 \) receptors – pacemaker activity
  - \( \beta_1 \) myocardium contraction

Parasympathetic input · HEART

- ACTIONS
  - Vagus nerve releases ACH
  - SA and myocardium
  - HR and conduction velocity
  - R side SA node (HR)
  - L side contractility (slight)

- MECHANISM
  - Muscarinic receptors (M2)
  - \( \beta_y \) subunit (HR)
  - Nitric oxide (weak inotropic effect)
11/13/13

**Sympathetic input – Blood vessels**

**ACTIONS**
- Activated: Vasoconstriction throughout body
- Skin/kidney BVs: most abundant
- De-activated: Vasodilation

**MECHANISM**
- Norepinephrine
  - $\alpha > \beta$
- Epinephrine
  - $\beta > \alpha$
- Vasoconstriction – $\alpha_1$
- Vasodilation – $\beta_2$

**Parasympathetic input – Blood vessels**

**ACTIONS**
- Vasoconstriction of BVs
- Less common than the sympathetic activity
- Salivary glands, i.g. glands, reproductive tissues

**MECHANISM**
- Ach increases vasodilation indirectly through other second messengers.

**3- Endocrine factors**

*(Hormonal regulation)*

- The endocrine system releases a hormone that enhances short-term adjustments and direct long-term changes in cardiovascular performance.

**1. Control of vasoconstriction**

*The neurons innervating peripheral blood vessels in most tissues are noradrenergic neurons, releasing norepinephrine (NE).*

*The response to NE release is the stimulation of smooth muscle in the walls of arterioles, producing vasoconstriction.*

**2. Control of vasodilatation**

*Vasodilator neurons (sympathetic cholinergic vasodilator system) innervate blood vessels in skeletal muscles and in the brain.*

*Stimulation of these neurons will relax smooth muscle cells in the walls of arterioles, producing vasodilatation.*

*Relaxation of smooth muscle cells is triggered by the appearance of Nitric Oxide (NO) in their surroundings.*

*The vasomotor centers may control NO release indirectly or directly.*

*The most common vasodilator synapses are cholinergic, and their synaptic knobs release Ach.*

*Ach. stimulates the release of NO by endothelial cells in the area; the NO then causes local vasodilatation.*

*Nitric oxide* has an immediate and direct relaxing effect on the vascular smooth muscle cells in the area.

*In most tissues, vasodilation is produced by decreasing the rate of tonic discharge in vasoconstrictor nerves.*
Sympathetic Vasomotor Tone

The sympathetic vasoconstrictor nerves are chronically active, producing a significant vasomotor tone.

Vasoconstrictor activity is normally sufficient to keep the arterioles partially constricted at rest.

Summary of vasomotor effects

<table>
<thead>
<tr>
<th>Dilation of arterioles</th>
<th>Constriction of arterioles</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>By decrease discharge of noradrenergic vasomotor nerves in most tissues (↓sympathetic tone).</em></td>
<td><em>By increase discharge of noradrenergic vasomotor nerves in most tissues. (↑sympathetic tone).</em></td>
</tr>
<tr>
<td><em>By activation of cholinergic dilator fibers to skeletal muscles and brain</em></td>
<td><em>By inhibition of cholinergic dilator fibers to skeletal muscles and brain</em></td>
</tr>
</tbody>
</table>

Factors affecting the activity of vasomotor area

<table>
<thead>
<tr>
<th>Excitatory inputs</th>
<th>Inhibitory inputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>From cortex then hypothalamus</td>
<td>From cortex then hypothalamus</td>
</tr>
<tr>
<td>From pain pathway and muscles</td>
<td>From lung</td>
</tr>
<tr>
<td>From chemoreceptors</td>
<td>From baroreceptors</td>
</tr>
</tbody>
</table>

Reflex Control of Cardiovascular Function

- Reflex Control of Cardiovascular Function
  - By regulation of cardiovascular centers which control sympathetic and parasympathetic discharge to heart and blood vessels.
  - These centers are activated by many impulses from:
    - Cardiovascular receptors and Extravascular receptors and under control from higher centers (cortex, hypothalamus, respiratory center).

Reflexes by CVS receptors

- 1- Arterial baroreceptors reflex (Mayer’s reflex)
- 2- Atrial stretch reflex (Bainbridge reflex)
- 3- Chemoreceptor reflex
- 4- Ventricular stretch reflex
- 5- Coronary chemoreflex

Afferent pathways for reflexes by CV receptors:
1- BUFFER NERVES.
2- VAGUS NERVE.

Efferent pathway for all reflexes
1- Sympathetic Or
2- Parasympathetic (VAGUS NERVE)
**Reflexes by extra-vascular receptors**

- 1- Pulmonary stretch reflex
- 2- From skeletal muscles receptors
- 3- From viscera and skin
- 4- From eye
- 5- From trigger areas (larynx, testes, epigastric area).

**Arterial baroreceptors**
(of sinoaortic reflex or Mayer’s reflex)

- **Location**: carotid sinus and aortic arch.
- **Stimulus**: increased B.P. (Its sensitivity start from mean arterial pressure 50-60 to 150-160 mmHg).
- **Afferent**: buffer nerves (carotid sinus and aortic nerves).
- **Center**: CVC.
- **Response**: 1- decreased heart rate
  2- decreased blood pressure.
  These receptors adapts with high blood pressure (resetting).

**Baroreceptors and Chemoreceptors Reflexes**

- **Cardio-inhibitory area**
- **Vasomotor area**
- **Cardioacceleratory area**
- **Sympathetic and Parasympathetic EFFERENTS**
- **TARGET ORGANS**
  - heart
  - blood vessels
  - adrenal medulla
  - glands (skin/sweat)

**Figure 1**: Location and innervation of arterial baroreceptors.
Atrial (Bainbridge) Reflex.

- A sympathetic reflex initiated by increased blood in the atria
- Causes stimulation of the SA node
- Stimulates baroreceptors in the atria, causing increased SNS stimulation
- Adjusts heart rate in response to venous return
- Stretch receptors in right atrium: trigger increase in heart rate through increased sympathetic activity.

Bainbridge reflex
(atrial stretch reflex)

- Receptors: baroreceptors type A, B.
- Location: in Atrial walls
- Stimulus for type A: increased atrial pressure during atrial systole
- Stimulus for type B: atrial distension during atrial diastole.
- Afferent: Vagus nerve
- Center: CVC in medulla oblongata
- Response: ↑ heart rate, ↓ B.P.
SIGNIFICANT: to equalize input with output of heart.

CORONARY STRETCH REFLEX
(Lt. vent. Stretch reflex)

- Receptors: baroreceptors
- Location: in Lt. ventricle near coronary vessels.
- Stimulus: Lt. vent. Distension.
- Afferent: Vagus nerve
- Center: CVC
- Response: ↓ heart rate, ↓ B.P.
SIGNIFICANT: to maintain Vagal tone that keeps low heart rate at rest.

Coronary chemoreflex
(Bezold-Jarisch reflex)

- Receptors: chemoreceptors (c-nerve fibers).
- Location: near coronary vessels of Lt. vent.
- Stimulus: chemical changes
- Center: CVC in medulla
- Response: ↓ heart rate, ↓ B.P.
SIGNIFICANT: In myocardial infarction, these receptors are stimulated by certain substances released from infarcted tissues and lead to hypotension (as index for severity of case).

Arterial chemoreceptors

- Location: carotid and aortic bodies.
- Stimulus: decreased B.P
- Afferent: buffer nerves (carotid sinus and aortic nerves).
- Center: CVC.
- Response: 1- increased heart rate
  2- increased blood pressure.

Baroreceptor and Chemoreceptor Reflexes

1. Carotid sinus baroreceptors
2. Aortic arch baroreceptors
3. Chemoreceptors in the carotid body
4. Chemoreceptors in the aorta
5. Chemoreceptors in the medulla oblongata
6. Circulation
7. Adrenal medulla
8. Epinephrine and norepinephrine
Cortical and Peripheral Influences

- Cerebral cortex impulses pass through medulla oblongata.
- Peripheral input
  - Mechanoreceptors
  - Baroreceptors
  - Chemoreceptors

REFLEXES FROM EXTRAVASCULAR RECEPTORS

1. Pulmonary stretch reflex
   - Receptors: baroreceptors
   - Location: in bronchial wall
   - Stimulus: lung inflation (inspiration)
   - Afferent: Vagus nerve
   - Response: ↑ heart rate; ↓ B.P
   SIGNIFICANCE: With inspiration, venous return is increased and the input for heart is also increased. So that, by this reflex increased heart rate to equalize input with output without increase in B.P (Like Bainbridge reflex).

Pulmonary chemoreflex

- Receptors: chemoreceptors (C-nerve fiber)
- Location: near lung capillaries
- Stimulus: chemical changes
- Afferent: Vagus nerve
- Center: CVC
- Response: ↓ heart rate; ↓ B.P
SIGNIFICANT: unknown

From skeletal muscles

- Receptors: certain receptors
- Location: in muscle and joint
- Stimulus: contraction
- Afferent: somatic afferent nerve
- Center: CAC, VCC
- Response: ↑ heart rate; ↑ B.P
SIGNIFICANCE: To increase blood flow to active muscles

From skin, viscera

- Stimulation of pain and cold receptors lead to ————↑ heart rate
- But severe pain lead to ——↓ heart rate

From eyes

Pressure on eyeball lead to bradycardia by ↑ vagal discharge to heart.
SIGNIFICANCE: Used in treatment of paroxysmal atrial tachycardia attack.
**From trigger areas**

- Pressure on these areas lead to bradycardia
- If the pressure is more increased, it can lead to cardiac arrest.
- **Trigger areas** (larynx, epigastric area & testes).

**Notes**

- Stimuli that increased heart rate also ↑ BP
- Stimuli that ↓ heart rate also ↓ BP
- However, there are exceptions:
  *Production of tachycardia + hypotension by stimulation of:
  1. Atrial stretch reflex (Bainbridge reflex)
  2. Pulmonary stretch reflex
  *Production of bradycardia + hypertension by ↑ intracranial pressure.

**Mechanism:** ↑ intracranial pressure → local hypoxia by ↓ blood flow to medulla →↑ discharge from VCC → Hypertension → Stimulate arterial baroreceptors → lead to bradycardia.

- End result: hypertension + bradycardia.

**Hormonal regulation of CVS**

**1. Vasoconstrictor System:**
- **Antidiuretic Hormone**
- Angiotensin II
- Erythropoietin
- Norepinephrine
- Serotonin

**2. Vasodilator System:**
- ANP
- Kinins = Bradykinin + Lysyl Bradykinin (Kalidin)
- Adrenomedullin
- VIP = Vasoactive Inhibitory Peptide
- Epinephrine = Vasoactive in SK, muscles and liver
- Histamine

**Antidiuretic hormone**

- Site of release: posterior pituitary gland
- Stimulus for its release:
  1. ↓ blood volume
  2. ↑ plasma osmolarity
  3. Angiotensin II
- **Its effect**
  1. Immediate: vasoconstriction
  2. Delay: water retention
**Angiotensin II**

- **Site of its formation:** in circulation
- **Stimulus for its formation:** renin from kidneys
- **Its effects:**
  1. **Short term effects**
     - a. Potent vasoconstrictor → ↑ B.P
     - b. +ve inotropic effect on heart → ↑ C.O.
  2. **Long term effects**
     - a. Stimulates ADH secretion
     - b. Stimulates aldosterone secretion
     - c. Stimulates thirst center

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**Angiotonin II (All)**

- angiotensinogen (α2-globulin)
- renin (kidney)
- angiotensin I (decapeptide)
- converting enzyme (pneumoangiogram)
- angiotensin II (octapeptide) + AT1 receptor
- angiotensinase A
- angiotensin III (heptapeptide)

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**Renin-angiotensin-aldosterone system (RAAS)**

- **Site of release:** kidney
- **Stimulus for its release:** hypoxia
- **Its effects:** stimulates red cells production (erythropoiesis), elevating blood volume and improve oxygen carrying capacity.

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**Erythropoietin**

- **Site of release:** kidney
- **Stimulus for its release:** hypoxia
- **Its effects:** stimulates red cells production (erythropoiesis), elevating blood volume and improve oxygen carrying capacity.

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**Noradrenaline**

- Elevates B.P and decreases heart rate indirectly (by Marey's reflex)

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**Contractility and Norepinephrine**

- **Sympathetic stimulation releases norepinephrine and initiates a cyclic AMP second-messenger system**
**Adrenaline**

- **Small doses**: increase heart rate by a direct action on B1 receptors in SA node.
- **Large doses**: increase B.P which leads to a decrease of the heart rate by Marey's reflex.

**Atrial natriuretic peptide (ANP)**

- **Site of release**: cardiac muscle cells in wall of Rt. Atrium
- **Stimulus for its release**: stretch of Rt. Atrium during diastole by hypervolemia
- **Its effects**:
  1. ↑ Na+ and water excretion
  2. Vasodilatation
  3. Inhibits thirst center
  4. ↓ ADH release
  5. ↓ aldosterone release
  6. ↓ epinephrine and norepinephrine

End result = ↓ B.P and blood volume

**ATRIAL NATRIURETIC PEPTIDE**

**kinins**

- Are hormones of tissues (local hormone).
  But small amount present in circulation.
- Are activated by plasma or tissues kallikrin which activated by factor XII.
- Are vasodilator indirectly through Nitric Oxide (NO).

**ENDOTHELIN**

**ADRENOMEDULLIN**

- Is a polypeptide found in plasma and in many tissues.
- **FUNCTIONS**:
  1. Depressor = vasodilator via NO
  2. Inhibits aldosterone secretion
  3. Inhibits peripheral sympathetic nerve activity
Factors affecting heart rate

Heart rate accelerated by:
- ↓ baroreceptors activity in arteries, Lt. vent., pulmonary circulation
- ↑ atrial stretch receptors activity
- Inspiration
- Anger, most pain stimuli, excitement
- Epinephrine, thyroid hormones
- Bainbridge reflex
- Hypoxia, exercise, fever

Heart rate slowed by:
- ↑ baroreceptors activity in arteries, Lt. vent., pulmonary circulation
- Expiration
- Fear, pain from trigeminal nerve and grief
- Norepinephrine
- ↑ intracranial pressure

INTRINSIC REGULATION

FRANK STARLING
- HEART RATE AND FORCE

INTRINSIC REGULATION
OF THE HEART

FRANK STARLING LAW OF THE HEART
AND BACK TO THE VENTRICULAR FUNCTION CURVE

REGULATION OVERVIEW

Blood Distribution at Rest

Blood Distribution at Rest

CO = 5 L/min
Blood Distribution -- Exercise

Heavy Exercise

Rest

CO = 25 L/min

20 L/min

0.75 L/min