Lecture 11
Control of Ventilation
(Regulation of Respiration)

Zuheir A Hasan
Professor of physiology
College of Medicine
HU
Lecture objectives

• Describe the general organization of the respiratory control system.
• Localize the centers that generate the spontaneous rhythm of breathing.
• Locate the pre-Bötzinger complex and describe its role in producing spontaneous respiration.
• Identify the location and probable functions of the dorsal and ventral groups of respiratory neurons, the pneumotaxic center, and the apneustic center in the brainstem.
• List the specific respiratory functions of the vagus nerves and the respiratory receptors in the carotid body, the aortic body, and the ventral surface of the medulla oblongata.
• State the ability of the brain cortex to override the normal pattern of inspiration and expiration temporarily.
• Describe the chemoreceptors (sensors) of the respiratory system for oxygen, carbon dioxide, and hydrogen ion concentration.
• Describe the effects of alterations in blood oxygen, carbon dioxide, and hydrogen ion levels on the control of breathing.
• Describe and explain the ventilatory responses to decreased O2 concentrations in the inspired air. Describe the effects of each of the main nonchemical factors that influence on respiration.
A cycle of inspiration and expiration is automatically established in the medullary respiratory center. Its output represents a final common pathway to the respiratory muscles, except for some voluntary pathways that may go directly from higher centers to the respiratory muscles (dashed line). Reflex responses from chemoreceptors and other sensors may modify the cycle of inspiration and expiration established by the medullary respiratory center.
Respiratory control centers in the brain stem

Pre Botzenger complex initiates basic rhythm of breathing ting
Dorsal respiratory group (causes inspiration)
Ventral respiratory group (VRG) (mainly causes expiration)
Pneumotaxic center (controls the rate and depth of breathing). Located dorsally in the superior portion of the pons
Apneustic center cause apneustic breathing
Respiratory Center

- Fourth ventricle
- Pneumotaxic center
- Inhibits
- ? Apneustic center
- Dorsal respiratory group (inspiration)
- Ventral respiratory group (expiration and inspiration)
- Vagus and glossopharyngeal
- Respiratory motor pathways
Brainstem respiratory control centers responsible for respiratory rhythm generation, activation of inspiratory and expiratory neuron and muscle activation, and monitoring lung inflation via pulmonary stretch receptors and alveolar ventilation via changes in arterial blood gas partial pressures.

Input from the central chemoreceptors was omitted for clarity. Hypothalamus and limbic system may modify respiratory center activity.
Dorsal respiratory group

- The dorsal respiratory groups are located bilaterally in the nucleus of the tractus solitarius (NTS).
- They consist mainly of inspiratory neurons that project primarily to the contralateral spinal cord.
- They serve as the principal initiators of the activity of the phrenic nerves and maintain the activity of the diaphragm.
- Dorsal respiratory group neurons send many collateral fibers to those in the ventral respiratory group, but the ventral respiratory group sends only a few collateral fibers to the dorsal respiratory group.
- The NTS receives visceral afferent fibers of the 9th cranial nerve (the glossopharyngeal) and the 10th cranial nerve (the vagus).
- These nerves carry information about the arterial Po2, Pco2, and pH from the carotid and aortic arterial chemoreceptors.
- In addition, the vagus nerve carries information from stretch receptors and other sensors in the lungs that may also exert profound influences on the control of breathing.
Inspiratory “Ramp” Signal

• it begins weakly and increases steadily in a ramp manner for about 2 seconds in normal respiration.

• It then ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and the chest wall to cause expiration.

• advantage of the ramp is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

• Two qualities of the inspiratory ramp are controlled
  • 1. *Rate of increase of the ramp signal* so that during heavy respiration, the ramp increases rapidly and therefore fills the lungs rapidly (no gasps)
  • 2. span (Limit): *limiting point at which the ramp suddenly ceases*, which is the usual method for controlling the rate of respiration; that is, the earlier the ramp ceases, the shorter the duration of inspiration and the higher the frequency of breathing.
Medullary Respiratory Center

Dorsal respiratory group
  • inspiration, intrinsic nerve activity

– Pneumotaxic center: limit inspiration, increase respiratory rate
Ventral respiratory group

• They consist of both inspiratory and expiratory neurons. These neurons are located in the nucleus ambiguus and nucleus retroambiguus.

• Some neurons from the ventral respiratory groups mainly project contralaterally to innervate inspiratory muscles and the expiratory muscles.

• The neurons in the nucleus ambiguus are primarily vagal motor neurons that innervate the ipsilateral laryngeal, pharyngeal, and tongue muscles involved in breathing and in maintaining the patency of the upper airway.

• VRG remains in active normal during inspiration.

• The ventral respiratory neurons do not appear to participate in the basic rhythmical oscillation that controls respiration.

• VRG has No pacemaker activity, but activated by the dorsal respiratory group to act and assist the dorsal group when greater pulmonary ventilation is needed (e.g. exercise).

• VRG supplies expiratory signals to the abdominal muscles during forced heavy expiration.
**Pneumotaxic center**

- known as the **pontine respiratory groups** (also called the **pneumotaxic center**),
- Probably function to “fine-tune” the breathing pattern and smooth the transitions between inspiration and expiration.
- Controls the "switch-off" point of the inspiratory ramp in DRG.
- Determines rate of ventilation and the tidal volume
- The pontine respiratory groups may also modulate the respiratory control system response to stimuli such as lung inflation, hypercapnia, and hypoxia.
apneustic center

• An area in the lower **pons** (the part of the brainstem just rostral to the medulla)

• In experimental animal it inhibits the switch-off of the inspiratory ramp signals

• Increases tidal volume and duration of inspiration (with occasional expiratory gasps).

• Its activity is inhibited by the pneumotaxic center and by vagal impulses.

• Its importance in human respiration ???
Chemical Control of Respiration
Chemosensors
Chemical Control of Respiration

Chemoreceptors

Central

Peripheral

Location: ventral medulla
Mediators: $\uparrow$ CO$_2$, H$^+$

Aortic arch (aortic bodies)
carotid sinus bifurcation (carotid bodies)

↓O$_2$
Chemical Control of Respiration

• Central chemoreceptors: Located in the ventral medulla

• Peripheral chemoreceptors: Located in aortic bodies and carotid bodies.

• Carbon Dioxide
  – central

• Hydrogen Ions
  – central

• Peripheral
  • Oxygen
Chemoreceptors

- The central chemoreceptors respond to local increases in hydrogen ion concentration or $P_{CO_2}$, or both. They do not respond to hypoxia.
- About 80–90% of the normal total steady-state response to increased carbon dioxide concentrations comes from the central chemoreceptors.
- The arterial chemoreceptors contribute only 10–20% of the steady-state response.
- Arterial chemoreceptors are more important in short-term transient responses to carbon dioxide.
Peripheral chemoreceptors

- The *carotid bodies* are located bilaterally in the bifurcations of the common carotid arteries.

- Their afferent nerve fibers pass through Hering’s nerves to the *glossopharyngeal nerves* and then to the dorsal respiratory area of the medulla.

- The *aortic bodies* are located along the arch of the aorta; their afferent nerve fibers pass through the *vagi*, also to the dorsal medullary respiratory area.

- Each of the chemoreceptor bodies receives its own special blood supply through a minute artery directly from the adjacent arterial trunk.

- Further, blood flow through these bodies is extreme, 20 times the weight of the bodies themselves each minute.

- Therefore, the receptors are not stimulated in conditions such as anemia or carbon monoxide poisoning, in which the amount of dissolved O2 in the blood reaching the receptors is generally normal, even though the combined O2 in the blood is markedly decreased,
THE RESPONSE TO HYPOXIA

• The ventilatory response to hypoxia arises solely from the peripheral chemoreceptors.

• Changes in O2 concentration have virtually no direct effect on the respiratory center itself to alter respiratory drive (although O2 changes do have an indirect effect).

• The carotid bodies are much more important in this response than are the aortic bodies.

• In the absence of the peripheral chemoreceptors, the effect of increasing degrees of hypoxia is a progressive direct depression of the central respiratory controller.

• Therefore, when the peripheral chemoreceptors are intact, their excitatory influence on the central respiratory controller must offset the direct depressant effect of hypoxia.

• Peripheral chemoreceptors detect PO2 level and increase ventilation when arterial PO2 is below 70 mm Hg.

• The activity of peripheral chemoreceptors increases usually leading to increase in ventilation does not occur until the arterial Po2 decreases below about 50–60 mm Hg.

• The response to hypoxia is potentiated at higher arterial Pco2.
Organization of the carotid body. Type I (glomus) cells contain catecholamines. When exposed to hypoxia, they release ATP and Ach, which stimulate the cuplike endings of the carotid sinus nerve fibers in the glossopharyngeal nerve. The glia-like type II cells surround the type I cells and probably have a sustentacular function.
Mechanism of chemoreceptor stimulation during hypoxia

- Type I glomus cells have O2-sensitive K+ channels, whose conductance is reduced in proportion to the degree of hypoxia to which they are exposed.
- This reduces the K+ efflux, depolarizing the cell and causing Ca2+ influx, primarily via L-type voltage-gated Ca2+ channels.
- The Ca2+ influx triggers action potentials and transmitter release, with consequent excitation of the afferent
the effect of different levels of arterial PO2 on alveolar ventilation, showing a sixfold increase in ventilation as the PO2 decreases from the normal level of 100 mm Hg to 20 mm Hg.

The upper line shows that the arterial PCO2 was kept at a constant level during the measurements of this study; pH also was kept constant.
Peripheral Chemoreceptors

*Increased* Arterial Oxygen Stimulates the Chemoreceptors

- Carotid body-bifurcation of the carotids
  - responds to oxygen (greatest $\text{PO}_2 < 100 \text{ mmHg}$)
  - responds to carbon dioxide and hydrogen ion
The ventilatory responses to hypoxia at three different levels of arterial \( PCO_2 \) when \( Pco_2 \) is held constant

at a normal arterial \( Pco_2 \) of about 38–40 mm Hg, there is very little increase in ventilation until the arterial \( Po_2 \) decreases below about 50–60 mm Hg.

The response to hypoxia is potentiated at higher arterial \( Pco_2 \).

Note the dramatic effect on the ventilatory response to \( PAO_2 \) when \( PACO_2 \) is increased.
Central chemoreceptors response to PCO2
Control of Respiration Quantitative Effects of Blood PCO2 and Hydrogen Ion Concentration on Alveolar Ventilation

Changes in arterial PCO2 have greater effect than changes in arterial pH
Carbon dioxide response curve at different O$_2$ levels

![Graph showing the relationship between Alveolar Ventilation and PCO$_2$ at different PO$_2$ levels. The graph includes lines for PO$_2$ = 35, PO$_2$ = 50, and PO$_2$ = 100.]
Carbon dioxide response curve under different conditions

Metabolic acidosis
Relationship between PaCO₂ and alveolar ventilation in awake normal states, during sleep, after narcotic ingestion and deep anesthesia, and in the presence of metabolic acidosis.
The ventilatory response to P\textsubscript{CO\textsubscript{2}} is affected by the [H\textsuperscript{+}] of CSF and brainstem interstitial fluid.

During chronic metabolic acidosis (e.g., diabetic ketoacidosis), the [H\textsuperscript{+}] of CSF is increased and the ventilatory response to P\textsubscript{CO\textsubscript{2}} is increased. Conversely, during chronic metabolic alkalosis (a relatively uncommon condition), the [H\textsuperscript{+}] of CSF is decreased and the ventilatory response to inspired P\textsubscript{CO\textsubscript{2}} is decreased.
Composite effect showing the interrelated effects of PO2, CO2 and pH on alveolar ventilation.
Summary

• Carbon dioxide is major stimulus for increased respiration
• Acts on central chemosensitive area through changes pH
• Periphral Chemoreceptors are mainly affected by oxygen
NONCHEMICAL INFLUENCES ON RESPIRATION
RESPONSES MEDIATED BY RECEPTORS IN THE
AIRWAYS & LUNGS
Lung receptors

• Stretch Receptors
  – Located in smooth muscle of large and small airways
  – Minimize work of breathing by inhibiting large tidal volumes
  – Hering-Breuer reflex

• J receptors
  – Located capillary wall, interstitium
  – Lung disease and edema (pulmonary congestion)
  – Rapid shallow breathing (tachypnea)
  – Feeling of dyspnea in pulmonary congestion, edema due to heart failure
  – Pulmonary embolism Tachypnea or apnea
Other Reflexes

• Irritant receptors
  – Nasal mucosa, upper airways, possibly alveoli
  – Bronchoconstriction
  – Cough, sneeze

• Arterial Baroreceptors
  • Stimulation by elevated blood pressure results in brief apnea and bronchodilation

• Muscles and Tendons
  • Muscles of respiration as well as skeletal muscles, joints and tendons
  • Adjust ventilation to elevated workloads
  • Somatic pain increase ventilation and increase heart rate TVR
Hering–Breuer inflation reflex,

- Stretch receptors within smooth muscle of large and small airways
- **Afferent Pathway Vagus nerve inhibits DRG**
- Hering–Breuer inflation reflex was originally believed to be an important determinant of the rate and depth of ventilation
- Recent studies have cast doubt on this conclusion because the threshold of the reflex is much higher than the normal tidal volume during eupneic breathing.
- Tidal volumes of 800–1,500 mL are generally required to elicit this reflex in conscious eupneic adults
- The reflex may help minimize the work of breathing by inhibiting large tidal volumes as well as prevent overdistention of the alveoli.
- Neonates have Hering–Breuer inflation reflex thresholds within their normal tidal volume ranges, and the reflex may be an important influence on their tidal volumes and respiratory rates.
Reflexes elicited by lung by deflation

- Deflation of the lungs increases the ventilatory rate.
- Could be a result of decreased stretch receptor activity or of stimulation of other pulmonary receptors, or rapidly adapting receptors such as the irritant receptors and J receptors.
- The afferent pathway is the vagus, and the effect is increased minute ventilation (hyperpnea).
- This reflex may be responsible for the increased ventilation elicited when the lungs are deflated abnormally, as in pneumothorax.
- It may play a role in the periodic spontaneous deep breaths (sighs) to take or let out a long loud breath often as an expression of sadness or relief.
- Sighs They consist of a slow deep inspiration (larger than a normal tidal volume) followed by a slow deep expiration.
Reflexes elicited by lung by deflation

The Hering–Breuer deflation reflex

- May be important in helping to actively maintain functional residual capacities (FRCs) in infants.
- Infants’ FRC is not determined passively like those of adults because the inward recoil of their lungs is considerably greater than the outward recoil of their very compliant chest walls.
Effects of higher brain centers on  The spontaneous rhythmicity generated in the medullary respiratory center

• The rhythmicity generated in the medullary respiratory center can be completely overridden (at least temporarily) by influences from higher brain centers.

• **maximum voluntary ventilation** (MVV) greatest minute ventilations obtainable from healthy conscious human subjects can be attained voluntarily, exceeding those obtained with the stimuli of severe exercise, hypercapnia, or hypoxia.

• **maximum voluntary ventilation** (MVV) **test** often used to assess respiratory function.

• Conversely, the respiratory rhythm can be completely suppressed for several minutes by voluntary breath holding, until the chemical drive to breath (high $P_{\text{co2}}$ and low $P_{\text{po2}}$ and pH) overrides the voluntary suppression of breathing at the breakpoint.

• Example  During speech, singing, or playing a wind instrument, the normal cycle of inspiration and expiration is automatically modified by higher brain centers.

• In certain emotional states, chronic hyperventilation severe enough to cause respiratory alkalosis may occur.
Cheyne-Stokes breathing, showing changing PCO2 in the pulmonary blood (red line) and delayed changes in the PCO2 of the CSF of the respiratory center

Cheyne-Stokes respiration is a type of breathing disorder characterized by cyclical episodes of apnea and hyperventilation.

Thus tidal volume and consequently arterial blood gases wax and wanes.

Caused by low cardiac output, heart failure uremia, and brain tumors.
Kussmaul breathing

- is characterized by a deep, rapid breathing pattern. It is typically an indication that the body or organs have become too acidic.
- In an attempt to expel carbon dioxide, which is an acidic compound in blood, the body starts to breathe faster and deeper.
- This abnormal breathing pattern is often caused by diabetic ketoacidosis, which is a serious complication of type 1 and, less often, type 2 diabetes.
The two main types of sleep apnea: obstructive and central sleep apnea.

**A**, In obstructive sleep apnea, the pleural pressure oscillations increase as CO$_2$ rises. This indicates that resistance to airflow is very high as a result of upper airway obstruction. **B**, Central sleep apnea is characterized by no attempt to breathe, as demonstrated by no oscillations in pleural pressure.
Chronic respiratory failure

- Chronic respiratory failure is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination.
- It is classified as either hypoxemic or hypercapnic respiratory failure.
- Hypoxemic respiratory failure is characterized by an arterial oxygen tension (PaO$_2$) lower than 60 mmHg with a normal or low arterial carbon dioxide tension (PaCO$_2$). This is the most common form of respiratory failure.
- Hypercapnic respiratory failure is characterized by a PaCO$_2$ higher than 50 mmHg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air.