C22.4 Respiratory System

- Influence of CO2 on Blood pH
- Control of Respiration
- Homeostatic Imbalance
Influence of $\text{CO}_2$ on Blood pH

- **Carbonic acid–bicarbonate buffer system**
  - resists changes in blood pH
  
  - If $\text{H}^+$ concentration in blood rises
    - excess $\text{H}^+$ is removed by combining with $\text{HCO}_3^-$ → $\text{H}_2\text{CO}_3$
  
  - If $\text{H}^+$ concentration begins to drop
    - $\text{H}_2\text{CO}_3$ dissociates, releasing $\text{H}^+$

- $\text{HCO}_3^-$ is **alkaline reserve** of *carbonic acid-bicarbonate buffer system*
Influence of CO$_2$ on Blood pH

- Changes in respiratory rate and depth affect blood pH
  - Slow, shallow breathing $\rightarrow$ increased CO$_2$ in blood $\rightarrow$ drop in pH
  - Rapid, deep breathing $\rightarrow$ decreased CO$_2$ in blood $\rightarrow$ rise in pH

- *Changes in ventilation can adjust pH when disturbed by metabolic factors*
Control of Respiration

• Involves higher brain centers
  – Chemoreceptors
  – other reflexes

• Neural controls
  – Neurons in reticular formation of medulla and pons
  – Clustered neurons in medulla important
    • Ventral respiratory group
    • Dorsal respiratory group
Medullary Respiratory Centers

• Ventral respiratory group (VRG)
  – Rhythm-generating and integrative center
  – Sets eupnea (12 breaths/minute)
    • Normal respiratory rate and rhythm
  – Its inspiratory neurons excite inspiratory muscles via phrenic (diaphragm) and intercostal nerves (external intercostals)
  – Expiratory neurons inhibit inspiratory neurons
Medullary Respiratory Centers

• Dorsal respiratory group (DRG)
  – Near root of cranial nerve IX
  – Integrates input from peripheral stretch and chemoreceptors
    • sends information → VRG
Locations of respiratory centers and their postulated connections.

Pontine respiratory centers interact with medullary respiratory centers to smooth the respiratory pattern.

Ventral respiratory group (VRG) contains rhythm generators whose output drives respiration.

Dorsal respiratory group (DRG) integrates peripheral sensory input and modifies the rhythms generated by the VRG.

To inspiratory muscles

External intercostal muscles

Diaphragm
Pontine Respiratory Centers

- Influence and modify activity of VRG
- Smooth out transition between inspiration and expiration and vice versa
- Transmit impulses to VRG → modify and fine-tune breathing rhythms during
  - vocalization
  - Sleep
  - exercise
Generation of the Respiratory Rhythm

• Not well understood

• One hypothesis
  – Pacemaker neurons with intrinsic rhythmicity

• Most widely accepted hypothesis
  – Reciprocal inhibition of two sets of interconnected pacemaker neurons in medulla that generate rhythm
Factors influencing Breathing Rate and Depth

• Depth determined by how actively respiratory center stimulates respiratory muscles

• Rate determined by how long inspiratory center active

• Both modified in response to changing body demands
  – Most important are changing levels of CO₂, O₂, and H⁺
  – Sensed by central and peripheral chemoreceptors
Chemical Factors

- Influence of Pco₂
- Most potent - Most closely controlled
  
  - If blood Pco₂ levels rise (hypercapnia), CO₂ accumulates in brain →
  
  - CO₂ in brain hydrated // to form carbonic acid // which dissociates // to release // H⁺ to reduce pH
  
  - H⁺ stimulates central chemoreceptors of brain stem
  
  - Chemoreceptors synapse with respiratory regulatory centers
    - increased depth and rate of breathing
    - lower blood Pco₂ → pH rises
    - “blow off carbon dioxide!!!"
Changes in $P_cO_2$ and blood pH regulate ventilation by a negative feedback mechanism.
Depth and Rate of Breathing

- **Hyperventilation**
  - increased depth and rate of breathing that exceeds body's need to remove CO$_2$
  
  - Results in decreased blood CO$_2$ levels (**hypocapnia**)

  *Causes cerebral vasoconstriction and cerebral ischemia /** dizziness & fainting*

- **Apnea** – breathing cessation from abnormally low Pco$_2$
Chemical Factors

• Influence of $P_{O_2}$
  
  – Peripheral chemoreceptors in aortic and carotid bodies–arterial $O_2$ level sensors
    
    • When excited, cause respiratory centers to increase ventilation
  
  – Declining $P_{O_2}$ normally slight effect on ventilation
    
    • Huge $O_2$ reservoir bound to Hb
    • Requires substantial drop in arterial $P_{O_2}$ (to 60 mm Hg) to stimulate increased ventilation
Location and innervation of the peripheral chemoreceptors in the carotid and aortic bodies.

- Sensory nerve fiber in cranial nerve IX (pharyngeal branch of glossopharyngeal)
- External carotid artery
- Internal carotid artery
- Carotid body
- Common carotid artery
- Cranial nerve X (vagus nerve)
- Sensory nerve fiber in cranial nerve X
- Aortic bodies in aortic arch
- Aorta
- Heart
Chemical Factors

• Influence of arterial pH
  – Can modify respiratory rate and rhythm even if CO₂ and O₂ levels normal
  – Mediated by peripheral chemoreceptors
  – Decreased pH may reflect
    • CO₂ retention
    • accumulation of lactic acid
    • excess ketone bodies
  – Respiratory system controls attempt to raise pH by increasing respiratory rate and depth
Summary of Chemical Factors

• Rising CO$_2$ levels most powerful respiratory stimulant

• Normally blood Po$_2$ affects breathing only indirectly by influencing peripheral chemoreceptor sensitivity to changes in Pco$_2$
Summary of Chemical Factors

- When arterial Po$_2$ falls below 60 mm Hg
  - Po$_2$ becomes major stimulus for respiration (via peripheral chemoreceptors)

- Changes in arterial pH resulting from CO$_2$ retention or metabolic factors act indirectly through peripheral chemoreceptors
Influence of Higher Brain Centers

• Hypothalamic controls
  – act through limbic system to modify rate and depth of respiration
  – Example - breath holding that occurs in anger or gasping with pain
  – Rise in body temperature increases respiratory rate

• Cortical controls
  – direct signals from cerebral motor cortex that bypass medullary controls
  – Example - voluntary breath holding
    • Brain stem reinstates breathing when blood CO₂ critical
Pulmonary Irritant Reflexes

- Receptors in bronchioles respond to irritants
  - Communicate with respiratory centers via vagal nerve afferents

- Promote reflexive constriction of air passages

- Same irritant $\rightarrow$ cough in trachea or bronchi; sneeze in nasal cavity
Inflation Reflex

- Hering-Breuer Reflex (inflation reflex)
  - Stretch receptors in pleurae and airways stimulated by lung inflation
  - Inhibitory signals to medullary respiratory centers end inhalation and allow expiration
  - Acts as protective response more than normal regulatory mechanism
Neural and chemical influences on brain stem respiratory centers.

- Central chemoreceptors
- Peripheral chemoreceptors
- Stretch receptors
- Irritant receptors
- Receptors in muscles and joints
- Other receptors (e.g., pain) and emotional stimuli acting through the hypothalamus

Higher brain centers (cerebral cortex—voluntary control over breathing)
Respiratory Adjustments: Exercise

• Adjustments geared to both intensity and duration of exercise

• **Hyperpnea**
  – Increased ventilation (10 to 20 fold) in response to metabolic needs

• $\text{PcO}_2$, $\text{Po}_2$, and pH remain surprisingly constant during exercise
Respiratory Adjustments: Exercise

• Three neural factors cause increase in ventilation as exercise begins
  – Psychological stimuli — anticipation of exercise
  – Simultaneous cortical motor activation of skeletal muscles and respiratory centers
  – Excitatory impulses to respiratory centers from proprioceptors associated with
    • moving muscles
    • tendons, joints
Respiratory Adjustments: Exercise

• Ventilation declines suddenly as exercise ends because the three neural factors shut off

• Gradual decline to baseline because of decline in CO$_2$ flow after exercise ends

• Exercise $\rightarrow$ anaerobic respiration $\rightarrow$ lactic acid

  – Not from
    • poor respiratory function
    • insufficient cardiac output
    • skeletal muscle inability to increase oxygen uptake
Respiratory Adjustments: High Altitude

• Quick travel to altitudes above 2400 meters (8000 feet) may result in symptoms of acute mountain sickness (AMS)
  – Atmospheric pressure and Po$_2$ levels lower
  – Headaches, shortness of breath, nausea, and dizziness
  – In severe cases, lethal cerebral and pulmonary edema
Acclimatization to High Altitude

• **Acclimatization** – respiratory and hematopoietic adjustments to long-term move to high altitude
  
  – Chemoreceptors become more responsive to $\text{Pco}_2$ when $\text{Po}_2$ declines
  
  – **Substantial decline in $\text{Po}_2$ directly stimulates peripheral chemoreceptors**
  
  – Result - minute ventilation increases
  
  – Stabilizes in few days to 2–3 L/min higher than at sea level
Acclimatization to High Altitude

• Always lower-than-normal Hb saturation levels
  – Less $O_2$ available

• Decline in blood $O_2$ stimulates kidneys to accelerate production of EPO

• RBC numbers increase slowly to provide long-term compensation
Homeostatic Imbalances

• **Chronic obstructive pulmonary disease (COPD)**
  - Exemplified by chronic bronchitis and emphysema
  - Irreversible decrease in ability to force air out of lungs
  - Other common features
    • History of smoking in 80% of patients
    • **Dyspnea** - labored breathing ("air hunger")
    • Coughing and frequent pulmonary infections
    • Most develop respiratory failure (**hypoventilation**) accompanied by respiratory acidosis, hypoxemia
Homeostatic Imbalance

• Emphysema
  – Permanent enlargement of alveoli
  – Destruction of alveolar walls
  – Decreased lung elasticity results in
    • Accessory muscles necessary for breathing
      – → exhaustion from energy usage
    • Hyperinflation → flattened diaphragm → reduced ventilation efficiency
    • Damaged pulmonary capillaries → enlarged right ventricle
    • Hypoxia / EPO increase / erythocytosis / increase blood viscosity / heart failure
Homeostatic Imbalance

• Chronic bronchitis
  – Inhaled irritants $\rightarrow$ chronic excessive mucus $\rightarrow$
  – Inflamed and fibroed lower respiratory passageways $\rightarrow$
  – Obstructed airways $\rightarrow$
  – Impaired lung ventilation and gas exchange $\rightarrow$
  – Frequent pulmonary infections
Homeostatic Imbalance

• COPD symptoms and treatment
  – Strength of innate respiratory drive → different symptoms in patients
    • "Pink puffers“ – thin; near-normal blood gases
    • "Blue bloaters“ – stocky, hypoxic
  – Treated with bronchodilators, corticosteroids, oxygen, sometimes surgery
The pathogenesis of COPD.

- Tobacco smoke
- Air pollution
- α-1 antitrypsin deficiency

Continual bronchial irritation and inflammation

Chronic bronchitis
- Excess mucus production
- Chronic productive cough

Breakdown of elastin in connective tissue of lungs

Emphysema
- Destruction of alveolar walls
- Loss of lung elasticity

- Airway obstruction or air trapping
- Dyspnea
- Frequent infections

- Hypoventilation
- Hypoxemia
- Respiratory acidosis
Homeostatic Imbalances

- Asthma – called reversible COPD
  - Characterized by coughing, dyspnea, wheezing, and chest tightness
  - Active inflammation of airways precedes bronchospasms
  - Airway inflammation is immune response caused by release of interleukins, production of IgE, and recruitment of inflammatory cells
  - Airways thickened with inflammatory exudate magnify effect of bronchospasms
Homeostatic Imbalances

• Tuberculosis (TB)
  – Infectious disease caused by bacterium *Mycobacterium tuberculosis*
  – Symptoms = fever, night sweats, weight loss, racking cough, coughing up blood
  – Treatment = 12-month course of antibiotics
    • Growing global problem with antibiotic resistant strains
Homeostatic Imbalances

• Lung cancer
  – Leading cause of cancer deaths in North America
  – 90% of all cases result of smoking
  – Three most common types

• Adenocarcinoma (~40% of cases) originates in peripheral lung areas - bronchial glands, alveolar cells

• Squamous cell carcinoma (20–40% of cases) in bronchial epithelium

• Small cell carcinoma (~20% of cases) contains lymphocyte-like cells that originate in primary bronchi and subsequently metastasize
Homeostatic Imbalance

- Lung cancer
  - Early detection key to survival
  - Helical CT scan better than chest X ray
  - Developing breath test of gold nanoparticles
  - If no metastasis → surgery to remove diseased lung tissue
  - If metastasis → radiation and chemotherapy
Homeostatic Imbalance

• Potential new therapies for lung cancer
  – Antibodies targeting growth factors required by tumor; or deliver toxic agents to tumor
  – Cancer vaccines to stimulate immune system
  – Gene therapy to replace defective genes
Developmental Aspects

• Upper respiratory structures develop first

• **Olfactory placodes** invaginate into **olfactory pits** (→ nasal cavities) by fourth week

• **Laryngotracheal bud** present by fifth week

• Mucosae of bronchi and lung alveoli present by eighth week
Figure 22.28  Embryonic development of the respiratory system.

- Frontonasal elevation
- Olfactory placode
- Stomodeum (future mouth)

4 weeks: anterior superficial view of the embryo’s head

5 weeks: left lateral view of the developing lower respiratory passageway mucosae

- Future mouth
- Pharynx
- Eye
- Foregut
- Olfactory placode
- Esophagus
- Liver
- Trachea
- Bronchial buds
- Laryngotracheal bud
Developmental Aspects

- By 28th week, premature baby can breathe on its own
- During fetal life, lungs filled with fluid and blood bypasses lungs
- Gas exchange takes place via placenta
Homeostatic Imbalance

• Cystic fibrosis
  – Most common lethal genetic disease in North America
  – Abnormal, viscous mucus clogs passageways → bacterial infections
    • Affects lungs, pancreatic ducts, reproductive ducts
  – Cause—abnormal gene for Cl⁻ membrane channel
Homeostatic Imbalance

• Treatments for cystic fibrosis
  – Mucus-dissolving drugs; manipulation to loosen mucus; antibiotics
  – Research into
    • Introducing normal genes
    • Prodding different protein $\rightarrow$ Cl⁻ channel
    • Freeing patient's abnormal protein from ER to $\rightarrow$ Cl⁻ channels
    • Inhaling hypertonic saline to thin mucus
Developmental Aspects

• At birth, respiratory centers activated, alveoli inflate, and lungs begin to function
• Two weeks after birth before lungs fully inflated
• Respiratory rate highest in newborns and slows until adulthood
• Lungs continue to mature and more alveoli formed until young adulthood
• Respiratory efficiency decreases in old age