Control of Ventilation [1]

Learning Objectives

- Describe the pathway and organization of the ‘automatic’ and ‘voluntary’ control of the respiratory system
- Delineate the receptors, and their stimulation, which affect the breathing
Organization of Respiratory Control System

Higher Centers in CNS (Cerebral Cortex, etc.)

Respiratory Rhythmic Generator (Medulla Oblongata)

Inspiratory Muscles

Expansion of Chest Wall & Inspiratory Airflow into Lungs

Gas Exchange

Receptor Reflexes (Pulmonary, Chest Wall, Airway)

Chemoreceptors

PO₂, PCO₂, H⁺
Uniqueness of Respiratory System

- Essential for life, under automatic and voluntary control
- A rhythmic, automatic breathing that an individual is normally unaware of
- The automatic breathing can be overridden by voluntary control (e.g. speaking, singing), and by involuntary non-rhythmic activities (e.g. coughing, sneezing)
Automatic Breathing:  
**Brainstem Respiratory Centers**

- **Medulla**
  - Dorsal respiratory group (DRG)
  - Ventral respiratory group (VRG)

- **Pons**
  - Pneumotaxic center or pontine respiratory group (PRG)
  - Apneustic center
Medullary Respiratory Centers (network)

- Respiratory rhythm can be generated within medulla without input from other structures
- Medullary neurons have intrinsic properties that provide the rhythmic activity
- DRG neurons are mainly inspiratory, increase the rate of firing during inspiration
- VRG is the more heterogeneous
Dorsal Respiratory Group (DRG)

- DRG neurons are contained within the nucleus of solitary tract or nucleus of tractus solitarius (NTS)
- DRG neurons primarily discharge during inspiration
- DRG neurons receive primary afferents from peripheral mechanical and chemoreceptors via vagus nerve (cranial nerve X, CNX) and glossopharyngeal nerve (CNIX)
Dorsal Respiratory Group (DRG)

- DRG neurons project primarily to the contralateral spinal cord and provide efferent connections to spinal motoneurons.
- DRG serves as the primary rhythmic respiratory drive to phrenic motoneurons in spinal cord at cervical level 3,4,5 (C3-5).
Nucleus of Tractus Solitarius (NTS)

- NTS contains secondary neurons and receives input from the peripheral chemoreceptors and baroreceptors.
- NTS constitutes the initial processing and integrative station for several respiratory and cardiovascular reflexes.
Ventral Respiratory Group (VRG)

- VRG is a bilaterally symmetrical column that extends from top of medulla (below facial nucleus) to C1 level of the cervical cord.
- Its location is ventral to the nucleus ambiguus.
- VRG can be divided into several subregions.
Ventral Respiratory Group (VRG)

- VRG contains both inspiratory and expiratory neurons
- **The pre- Bötzinger complex**, below the Bötzinger complex, **consists of neurons that play a critical role in respiratory rhythm generation**
  - PreBötC → DRG → phrenic motoneuron
  - PreBötC → other regions in VRG
  - PreBötC → Nucleus ambiguus
Nucleus Ambiguus (NA)

- It is a motor nucleus with fibers in the vagus (CNX) and glossopharyngeal (CNIX) nerves.
- It contains laryngeal/pharyngeal motoneurons innervating the intrinsic laryngeal and pharyngeal muscles with respiratory-related discharge pattern.
Nucleus Ambiguus (NA)

- When these neurons send signal to initiate a breath, the muscles of larynx are stimulated and the vocal cord abducts or move laterally outward, thereby decreasing the resistance of the upper airway and facilitating movement of air into the lungs
Muscles of the upper airway

- Nasal vestibules
- Tongue
- Soft palate & pharyngeal wall
- Hyoid arch
- Larynx

Generation of the Respiratory Rhythm

- Based on studies in isolated rat brainstem preparations and medullary slice preparation, supramedullary structures and DRG are not necessary for generation of the respiratory rhythm.

- **Neurons responsible for rhythm generation are located in the pre-Bötzinger complex (preBötC), within VRG.**
Pontine Respiratory Center

- There are at least 2 respiratory centers in pons
  - Pneumotaxic center or pontine respiratory group (PRG) occupies a region of rostral pons
  - Apneustic center represents throughout the caudal pontine reticular formation

- **Pons is not essential for respiratory rhythm generation**

- They influence and modulate the activity of medullary respiratory neurons
Pontine Respiratory Group (PRG)

- PRG assists in making a smooth transition from inspiration to expiration during respiratory cycle
- PRG receives afferent input from vagal reflexes related to lung volume
- PRG prevents lung overinflation by inhibiting DRG activity
Injury to PRG, can lead to apneustic breathing, a respiratory pattern characterized by breaths with an increase in inspiratory time, a decrease in respiratory frequency, and an increase in the tidal volume.
Generation of the Respiratory Rhythm
Automatic Ventilatory Activity after Various Levels of Transection

Diagram showing PRG, DRG, VRG, and Apneustic center.
Automatic Ventilatory Activity after Pons Transection

**Breathing Pattern**

- **Vagi Intact**
  - Level I
  - Section above the pons causes no significant alteration of normal respiratory rhythm (eupnea).

- **Vagi Cut**
  - Inspiration is enhanced because the Hering-Breuer response is abolished.

- Vagotomy removes afferent input from stretch receptors.

Apneustic center

- PRG
- DRG
- VRG
Automatic Ventilatory Activity after Midpontine Transection

- **Level I**
  - **Breathing Pattern**
    - **Vagi Intact**
    - **Vagi Cut**

- **Level II**
  - **Breathing Pattern**
    - **Vagi Intact**
    - **Vagi Cut**

- **Section at midpontine level**
  - Increases the depth of breathing because signals from the pneumotaxic center (PRG) in upper pons normally terminate inspiration.

- When vagotomy is added, apneusis (sustained inspiratory effort) results.

- Both central and peripheral inhibition of inspiration have been eliminated.
Transection between medulla and spinal cord

- **Section between spinal cord and medulla.**
- Basic respiratory rhythm disappears suggesting that the respiratory rhythm generator is at medullary levels.
Voluntary (Volitional) Breathing:

It is mediated by the descending corticospinal tract from the motor cortex in cerebrum to the spinal motoneurons supplying the diaphragm and intercostal muscles
Interaction between Voluntary and Involuntary Control of Breathing

- Certain pathological lesion can disrupt anatomical/physiological pathway for automatic and voluntary breathing separately.

- In speaking, singing, vocalization, laughing, crying, anxiety, automatic breathing is suppressed while voluntary breathing takes over.

- There are connections among extrapyramidal system, cerebellum, limbic system and corticospinal tract to allow the coordination of respiratory muscle during voluntary acts.

- Disorders of breathing and speaking that occur in diseases of the cerebellum and extrapyramidal system must be explained by disruption of these connections.

- The precise location of these various connections is still unknown.

- Extrapyramidal system = motor pathway other than corticospinal tract.
Descending Motor Pathways Concerned with Breathing:

- The fiber tracts responsible for involuntary rhythmic breathing and volitional breathing descend along different pathways in the spinal cord.
- They converge on the anterior horn cells supplying the respiratory muscles.
- The input from medullary DRG, VRG descends in the reticulospinal tract, in the anterolateral funiculus of the spinal cord.
- Voluntary control of breathing is mediated by the corticospinal tract in the dorsolateral column.
Respiratory Reflexes

- Airway sensory receptors
- Reflexes from Upper Airway
- Reflexes from tracheobronchial tree and lung
- Baroreceptor reflex
- Reflexes from chest wall and somatosensory reflex
- Chemoreceptor reflex
Respiratory Reflexes from the Lungs and Airways

- Input from airway afferent nerves to CNS is integrated in the brainstem and leads to sensations and various reflex outputs.
- The autonomic and respiratory reflexes:
  - Help maintain airway wall homeostasis
  - Serve to aid the gas exchange
  - Serve host defense functions
- Dysfunction of respiratory reflexes may contribute to excessive coughing, bronchospasm, mucus overproduction, inappropriate sensations of air hunger.
Airway Sensory Receptors

- **Mechanoreceptors or Stretch Receptors**
  - Respond to mechanical forces caused by the inflation and deflation of respiration
  - Afferent nerve: myelinated A-type nerve fibers

- **Nociceptors**
  - Respond to the threat of tissue damage (trauma, inflammation, excessive stretch, etc.)
  - Afferent nerve: nonmyelinated capsicin-sensitive C fibers
Stretch Receptors

Increase in lung volume
- Slowly adapting receptor firings
- Changing volume over time

Decrease in lung volume
- Rapidly adapting receptor firings
- Changing volume over time
- Slowly adapting receptor firings
Slowly Adapting Stretch Receptors

- SARs adapt slowly to the new lung volume.
- SARs continue to fire at a constant rate after they have reached a new constant length.
- They are located among smooth muscle cells within the intra- and extrathoracic airways.
- SARs are more responsive to inflation and conduct an action potential at greater velocity than RARs.
Rapidly Adapting Stretch Receptors

- RARs change their firing rate quickly after the stimulus is released
- RARs are ‘rapidly adapting’ to the new state
- Their location is in association with airway mucosal layer
- RARs can be stimulated by chemical stimuli (e.g. cigarette smoke, prostaglandins, histamine) and mechanical stimuli (e.g. dust)
  - perceived as irritating to the lungs
  - as known as *Irritant Receptors*
Nociceptors

- The unmyelinated C fibers endings innervate the lung parenchyma and airway walls
- They respond to many noxious causes of tissue damage and to the mediators, also respond to mechanical irritant stimuli
Reflexes from the Upper Airway

- The upper airway is identified with the extrathoracic portion of the respiratory tract.
- It comprises the nasal passages, nasopharynx, oropharynx, larynx, and the cranial half of the trachea.
- It plays essential roles in olfaction, swallowing, conditioning of inspired air, phonation, defense against pollutants, preservation of airway patency and regulation of breathing pattern.
Sneeze

- It can be evoked by mechanical and chemical irritations of the nose.
- It is characterized as following:
  - A deep inspiration ~ TLC, serves to lengthen the expiratory muscle, optimising the length-tension relationship.
  - Followed by a forced expiration due to isometric contraction of expiratory muscle against a closed glottis and a constricted pharynx → ↑ intrathoracic pressure > 100 mmHg → narrowing of the airways.
  - A blast of air is expelled through the mouth and nose as the glottis and pharynx are suddenly reopened.
  - The large pressure difference between the airways and the atmosphere coupled with airway narrowing produces rapid turbulent flow rates through trachea.
  - Such high airflow rates through narrowed airways can carry the irritant, mucus out of the respiratory tract.
- Sneeze cannot be performed voluntarily.
Sneeze

Medulla

Afferent Nerves:
- Trigeminal (CN V)

RARs, C-fiber nerve endings in nose etc.

Irritants [mechanical, chemical]

Efferent Nerves:
- Recurrent laryngeal nerve of vagus, phrenic, spinal nerves

SNEEZE
1. Deep inspiration
2. Closure of glottis
3. Expiratory muscle contraction
4. Opening of glottis
5. Explosive rush of air out of tracheaobronchial tree
Swallowing

- It can be elicited from the pharynx
- During swallowing
  - Respiratory activity ceases as the epiglottis covers the larynx
  - Diaphragm and abductor laryngeal muscles are inhibited
  - The thyroarytenoid, the main adductor muscle of the larynx, is activated
- Afferent pathway: glossopharyngeal nerve (CN IX)
Reflexes from tracheobronchial tree and lungs

- Cough reflex
- Pulmonary Stretch Reflexes
  - Inflation reflex
  - Deflation reflex
- J receptor reflex
Cough

- It is protective against food or foreign material entering the airway
- It is responsible for aiding in clearance of secretions produced within the tracheobronchial tree, in addition to mucociliary clearance
- Yellow/green sputum reflects the presence of numerous leukocytes
- Cough may be initiated either voluntarily or reflexively
- Induced and natural cough can be suppressed voluntarily
- Sensory receptors: RARs (Irritant receptor) and C-fiber nerve ending in larynx, trachea, major bronchi, pharynx, lung parenchyma, pleura, diaphragm, pericardium, external ear
Cough

Afferent Nerves: **Vagus**, trigeminal, glossopharyngeal, phrenic nerves

RARs, C-fiber nerve endings in airway, larynx, etc.

**Irritants [mechanical, chemical]** (cigarette smoke, noxious fumes, dusts, chemicals, secretions)

**Medulla**

| NTS | Bötzinger complex/VRG |

**Efferent Nerves:**
- Recurrent laryngeal nerve of vagus, phrenic, spinal nerves

**COUGH**
1. Deep inspiration
2. Closure of glottis
3. Expiratory muscle contraction
4. Opening of glottis
5. Explosive rush of air out of tracheaobronchial tree
Pulmonary Stretch Reflex: -
Hering-Breuer Reflex

**Inflation Reflex**

Sustained lung inflation or ↑ tidal volume

↑ Transmural pressure in airway wall

Inhibition of inspiration

Prolonged expiration
Pulmonary Stretch Reflex: - Hering-Breuer Reflex

Deflation Reflex
Sustained lung deflation or ↓ tidal volume
↓ Transmural pressure in airway wall
Excitation of inspiration
↓ Hyperpnea
J Receptor Reflex

Juxtacapillary receptor in alveoli innervated by unmyelinated C fiber

Stimuli: Pulmonary vascular congestion, pulmonary embolism

Afferent Nerves: Vagus

Efferent Nerves: vagus, phrenic, spinal nerves

tachypnea, apnea, dyspnea

Medulla
Baroreceptor Reflex

Stimuli: $\uparrow$ systemic arterial blood pressure

Afferent Nerves:
- Glossopharyngeal
- Vagus

Efferent Nerves:
- Vagus, phrenic, spinal nerves

Carotid sinus

Aortic arch

Apnea

Location and innervation of arterial baroreceptors.
Baroreceptor Reflex

Stimuli: ↓ systemic arterial blood pressure

Afferent Nerves:
- Glossopharyngeal
- Vagus

Medulla

Efferent Nerves:
- vagus, phrenic, spinal nerves
- Carotid Sinus Nerve to Nerve IX

Locations and innervation of arterial baroreceptors.

Tachypnea

→ ↑ Venous return
→ ↑ Cardiac output
Reflexes from chest wall and somatosensory reflex

- Stretch of chest wall muscles
- Proprioception from joints, tendons
- Ergoreflex
- Somatic pain
Muscle Spindle

- Muscle spindle fiber (intrafusal fiber)
- Contractile fiber (extrafusal fiber)
Muscle Spindle and Golgi Tendon
Muscle Spindles

- They are located in the skeletal muscles
- They are found in intercostal muscles
- Muscle spindle contains intrafusal fibers that are attached to the sensory apparatus within the spindle [spindle receptor]
- The spindle receptor is centrally localized and attached to muscle spindle fiber [intrafusal fiber]
- Muscle spindle fibers are located at the end of muscle spindles and are innervated by gamma fibers
- Muscle spindles are arranged in parallel with the main contracting fibers [extrafusal fiber] of the muscles
Muscle Spindle Reflex

Muscle spindle fiber (intrafusal fiber) attach to each end of capsule

muscle contracts and shortens normally

CNS

no change in feedback

no change in spindle receptor firing

spindle receptor in capsule

spindle receptor firing
Muscle Spindle and Receptor

- Stretch of spindle receptor → to reduce spindle receptor tension

- Brain and spinal cord send a signal to the ventilatory muscle to contract, a signal is simultaneously sent over $\alpha$ motoneurons and over the $\gamma$ fibers to the muscle spindle fibers
  → muscle spindle fibers and contractile fibers contract and shorten
  → spindle receptor is not stretched
  → no change in output from spindle receptor
Muscle Spindle and Receptor

- The command signal from motor cortex is sent as a corollary discharge to sensory cortex to generate a sense of effort.
- A copy of the signal to fusimotor neurons (g motoneurons) is sent to sensory areas where this is subtracted from the total signal sent back by muscle spindle receptors.
Muscle Spindle and Load Compensation

Muscle contracts but shortening of main (extrafusal) fibers is impaired.

Increased spindle receptor firing.

Muscle spindle fibers shorten and stretch spindle receptor.
With high airway resistance and/or low compliance, the ventilatory muscles will shorten minimally.

→ muscle spindle shortens due to $\gamma$ fiber activation BUT no shortening in contractile fiber

→ spindle receptor will be stretched and activated

→ receptor send afferent signal to CNS to further increase the contraction of the ventilatory muscle
Proprioception Reflex

- Afferent from musculoskeletal system (muscle, tendon, joint) at extremities can produce a reflex increase in ventilation
- It has an important role in the hyperventilation of exercise
- Passive movement of animals’ limbs that simulates exercise was shown to lead to an increase in ventilation
Ergoreflex

- A signal from exercising muscle can stimulates ventilation, and is enhanced by circulatory occlusion
- An increase in circulating \([K^+]\) may be a natural stimulant of the muscle ergoreceptor or metaboreceptor or chemoreceptor
- Ergoreflex has a role in the control of hemodynamics and autonomic response (sympathetic)
- There is an abnormal ventilatory response in conditions with muscle wasting and peripheral metabolic abnormalities despite normal lung function and ventilatory control
Reflex Respiratory Responses to Pain

- Somatic pain $\rightarrow$ hyperpnea
- Visceral pain $\rightarrow$ apnea or decreased ventilation