# 9. Control of Ventilation

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Resp Control System

Elements
• Sensors - chemoreceptors
• Afferent limb - nerves
• Central – pons & medulla
• Effectors – resp mms

Central Controller
• Basal rate from brainstem
• Cortex can override

Brainstem
• Resp centres = Pons & medulla
• Receive input from
  o chemoreceptors
  o lungs
  o cortex
• major output to phrenic nerves
• pattern of insp & expiration:
  o complex interaction between spont pacemaker activity of medullary neurons
  o input/modulation of afferent inputs
  o can be very complex
• 3 main groups:
  Medulla resp centre
  o in reticular formation of medulla beneath floor of 4th vent
  o DIVE:
    ▪ Dorsal = inspiratory
    ▪ Ventral = expiratory
  o dorsal resp group – inspiration
    ▪ intrinsic periodic firing ⇒ insp
      ▪ latency
      ▪ building frequency of APs ⇒ crescendo over seconds
        ↑this builds insp mm activity in ramp fashion
      ▪ then fall to preinsp tone
    o within group have cells classified according to when active during inspiration:
      ▪ early insp
      ▪ insp ramp
      ▪ late onset insp neurons
    ▪ controls on group:
      ▪ insp ramp can be inhibiting (shortened) by impulses from pneumotaxic centre ⇒ ↑RR
      ▪ vagal & glossopharyngeal nerves
  o ventral resp group – expiration
    ▪ not active during quiet breathing as exp is passive
    ▪ cell classifications:
      ▪ early exp
      ▪ early peak whole expiratory
      ▪ exp ramp neurons
  ▪ activity in the medullary centre occurs in 3 phases:
    o insp phase:
      ▪ distinct start
      ▪ gradual incr in insp nerve & mm activity ie ramping
      ▪ activation of pharyngeal dilatory muscles
Control of Ventilation

- **exp phase 1:** ↓ in insp motor d/c ⇒ ↓ ing tone of insp mms
- **exp phase 2:**
  - insp nerves & mm inactive
  - ventral group & exp mms inactive during quiet breathing
  - progressively recruited with ↑ ing vent/forced expiration

**Apneustic Centre**
- in lower pons
- impulses from here have +ve effect on insp area of medulla ⇒ ↑ ramping of insp APs ⇒ ↓RR

**Pneumotaxic Centre**
- upper pons
- -ve input to medulla insp centre ⇒ ↓ ramping ⇒ ↑RR
- also regulates insp volume
- fine tunes medulla insp centre

**Cortex**
- can override function of brainstem within limits
- volunt hypervent ⇒ half ↓PCO2 ⇒ resp alkalosis ⇒ mm tetany ⇒ caropedal spasm
- volunt hypovent: limited by factors incl PO2 & PCO2

**Other Brain**
- limbic system & hypothalamus – rage & fear ⇒ breathing change

**Effectors**
- resp motor neurons (UMNs) in brainstem
- 2 separate areas which correspond to insp & exp mm activity
- complex central integration of resp control seen in medullary centre also seen in ant horn cell (UMN > LMN synapse)
- 3 groups of UMN synapse into ant horn cell:
  - 1st = from medullary centre (dorsal & ventral) – insp & exp control
  - 2nd = concerned with voluntary control of breathing eg need for speech
  - 3rd = concerned with involuntary non-rhythmic resp control eg swallow, cough, hiccup

**Sensors**
- central:
  - respond to PCO2
- peripheral:
  - respond mainly to PO2 but also slightly to other stimuli

**Central Chemoreceptors**
- ventral surface of medulla near exit of CN IX, X
- located in brain ECF (bathed in CSF)
- respond to changes in H+:
  - (↑H+ ⇒ ↑RR)
  - (↓H+ ⇒ ↓RR)
- composition of ECF around receptors is governed by:
  - CSF composition – most impt
  - Local blood flow
  - Local metabolism
- Bbb seperates blood flow & CSF:
  - Barrier impermeable to H+ & HCO3
  - changes in blood H+ have little effect
CO2 diffuses across easily

- Blood $\uparrow$PCO2 $\Rightarrow$ CO2 diffuse into CSF $\Rightarrow$ CO2 +HCO3 $\Rightarrow$ free H+ $\Rightarrow$ stim chemoreceptors $\Rightarrow$
  $\uparrow$afferent input into resp centre $\Rightarrow$ $\uparrow$alveolar ventilation
  $\downarrow$resultant $\uparrow$RR $\Rightarrow$ $\downarrow$PCO2 of blood & CSF
- Cerebral VD that accompanies $\uparrow$PCO2 enhances CO2 into CSF & to chemoreceptors

- Minute volume of vent $\uparrow$2-3L/min for each $\uparrow$mmHg PaCO2
- CSF
  - Normal pH = 7.32
  - Less proteins than blood $\therefore$ less buffering $\therefore$ change PCO2 in CSF $\Rightarrow$ bigger change in pH than
    in blood
- Prolonged CSF pH change eg PCO2 chronically raised in COPD:
  - Change over hours
  - $\uparrow$transport of HCO3- into CSF from blood
    $\downarrow$Cl- ions move out to maintain neutrality
  - $\therefore$ chemoreceptors are reset and lose sensitivity to high PCO2 level
  - CSF usually doesn’t return to 7.32
  - Move to hypoxic drive
  - Opposite is also true:
    - Chronic hyperventilation in ICU
    - Pt continue to hyperventilate when onto spont vent
  - Adjustment quicker than renal compensation
  - $\downarrow$CSF pH vital effect on RR and arterial PCO2
- Hypoxia:
  - no effect on central receptors
  - will directly depress the medullary resp centre in the absence of periph input

**Peripheral Chemoreceptors**

- 2 bodies:
  - Carotid bodies – bifurcation carotids
  - Aortic bodies – below aortic arch
- Contain glomus cells of 2 types:
  - Type I –
    - large dopamine content, connect to carotid sinus nerve
    $\downarrow$ site of chemoreception
  - Type II
- Carotid bodies:
  - most impt of 2 receptors
  - Afferent limb = glossopharyngeal nerve
- Aortic bodies:
  - Innervation from vagus
- Respond to:
  - Arterial PO2 (not venous) – [biggest effect]
    - Afferent firing begins around 500mmHg
    - Little firing until PO2 <100mmHg
    - Sensitive to low O2 tension NOT content
    $\downarrow$ $\therefore$ no response to anaemia/COHb
    - Response rate v fast
    - Only sensor for PO2
    - Hypoxic ventilatory drive
    - $\downarrow$MAP $\Rightarrow$ $\downarrow$perfusion of bodies $\Rightarrow$ $\uparrow$afferent firing $\Rightarrow$ hyperventilation
  - $\downarrow$pH
    - in carotid [not aortic bodies]
• **Blood flow to periph chemoreceptors:**
  - Per weight receive highest blood flow in body
  - Flow exceeds already high metabolic demand by x10
  - Met demand \( \therefore \) met by dissolved O2 fraction
• **Effects of activation of periph chemoreceptors:**
  - ↑Ventilation – obviously
  - also:
    - bradycardia
    - hypertension
    - ↑bronchiolar tone
    - ↑ed adrenal secretion
• **carotid vs aortic bodies:**
  - carotid:
    - ↑ed vent effects
  - aortic:
    - ↑ed circulatory effects
    - does not respond to pH changes
Lung Receptors

Pulmonary Stretch Receptors
- lie in airway smooth mm [not alveoli]
- impulses return via vagus nerve (myelinated)
- in general prevent hyperinflation of lungs
- 2 types
  - slowly adapts (SAR)
    - activity sustained with continued lung inflation
      - ie little adaptation
    - d/c in response to distension of lung
  - rapidly adapts (RAR)
    - superficial mucosal layers between epithelial cells
    - stim by changes in:
      - tidal volume
      - resp frequency
      - lung compliance
      - noxious gas/smoke
      - dusts
      - cold air
      - some mechanoreceptor functions
      - ± histamine release as in asthma attacks
    - d/c stretch BUT also nociceptive & chemosensitive [not SAR]
    - reflex \(\Rightarrow\) bronchoconstriction & \(\uparrow\) RR
- both d/c receptors via stretch \(\Rightarrow\) \(\uparrow\) exp time \(\Rightarrow\) \(\downarrow\) RR
  - Hering-Breuer inflation reflex
    - \(\downarrow\) only impt when tidal volume >1litre eg exercise
    - \(\downarrow\) also see deflation reflex \(\Rightarrow\) stim of inspiration activity

J Receptors
- endings of nonmyelinated C fibers
- found in alveolar walls close to capillaries
- afferent vagus in nonmyelinated fibres
- cause rapid shallow breathing (although intense stim \(\Rightarrow\) apnoea)
- activated by:
  - engorgement of pulmon capillaries
  - \(\uparrow\) interstitial fluid volume of alveolar wall
  - \(\downarrow\) cause rapid shallow breathing in LVF & pulmon oedema

Bronchial C fibers
- supplied by bronchial circ (not pulmon circ as in J receptor)
- cause:
  - rapid shallow breathing
  - bronchoconstriction
  - mucous secretion

Other Receptors
- joint & mm receptors:
  - impulse from moving mm part of stim for ventilation in early exercise
- gamma system:
  - resp mms contain mm spindles which sens elongation \(\Rightarrow\) reflex control of strength of contraction
  - involved when large efforts required to move lung in obstruction \(\Rightarrow\) dyspnoea
- phrenic nerve afferents:
  - phrenic stim \(\Rightarrow\) \(\downarrow\) phrenic efferent activity
  - but stimulation of some smaller ones has opposite effect
By Adam Hollingworth

9. Control of Ventilation

- role? = perception & compensation for incr inspiratory loads
- impt in ‘breaking point’ during breath holding

**arterial baroreceptors:**
- primary role in circulatory control but has some effect on resp system
- ↑bp ⇒ reflex hypoventilation or apnoea via sinus baroreceptors
- converse true: ↓bp⇒ hyperventilation
- process unknown

**pain & temp:**
- pain: period of apnoea followed by hyperventilation

**Lung Reflexes**

**inflation reflex:**
- inhibition of inspiration in response to ↑ed pulmon transmural pressure eg sustained lung inflation
- significance in man uncertain
- present in neonates & infants

**deflation reflex** = augmentation of inspiration in response to deflation

**head’s paradoxical reflex:**
- =reversal of inflation reflex
- sudden inflation ⇒ transient insp effort before onset of apnoea (due to inflation reflex)
- might be ‘gasp reflex’ in neonates
- could be norm feature of breathing in adults

**Reflexes in URT**

**nose:**
- respond to mechanical & chemical stim
- can cause apnoea as part of diving reflex
- irritant receptors
- ⇒ sneeze, cough, bronchoconstriction

**pharynx:**
- mechanoreceptors respond to pressure
- activate pharyngeal dilator mms
- irritants cause:
  - bronchodilation
  - HTN
  - Tachycardia
  - ↑secretions in LRT

**larynx:**
- dense innervation:
  - supraglottic = SLN (internal branch)
  - infraglottic = RLN
- irritant receptors – stim ⇒
  - cough
  - laryngospasm
  - bronchoconstriction

**cough reflex:**
- elicited by chemical or mechanical stimuli arising in larynx,trachea,carina, main bronchi
- can be voluntarily or involuntarily
- reflex has 3 stages:
  - inspiration – enough input for expiratory part
  - build up of pressure in lungs by contraction of exp mms against closed glottis
  - forceful expiration through narrowed airway
  - high velocity airflow sweeps irritant material up towards pharynx
  - ↑pressure of 300mmHg in throax, arterial blood & CSF can be seen
o heating of skin ⇒ ↑RR

Other Inputs
• higher centres:
  o cerebral cortex –
    ▪ start of exercise
    ▪ coordination with speak/cough
  o pons – pontine breathing
  o hypothalamus
    ▪ pain/fear/anxiety/temp
• hormonal influences: Adrenaline & NA

Integrated Response
Response to CO2
• = most impt control of vent under norm circumstances
• ↑ventilation by
  o central chemoreceptors - ↑H+ in brain ECF from ↑PCO2 in blood
  o periph chemoreceptors –
    ▪ only play a role if significant ↓ventilation or hypoxia
    ▪ primarily respond to ↓PO2 but also respond to (↑PaCO2 & ↓pH)
  o anaerobic metabolism ⇒ ↑lactic acidosis ⇒ carotid chemoreceptor ↑ventilation
• vent response is magnified if PO2 is lowered:

![Diagram](image)

- PCO2 held to within 3mmHg during normal day
- Rises slightly during sleep
- ↓PCO2 very effective in ↓stim to vent
- vent response to CO2 is ↓ed by:
  o sleep
  o ↑age
  o trained athletes
  o drugs – eg opiates & barbituates
  ▪ eg opioids act:
    ▪ direct inhibition on medullary centre via mu receptors
• indirectly on pons via delta receptors
  o (↑ed WOB) – neural output not reduced but not as effective in producing vent
• trained athletes have low CO2 sensitivity

**Response to Oxygen**
• only periph chemoreceptors involved
• virtually no control at normal PCO2 levels
  ➜ if PCO2 35.8: PO2 needs to <50mmHg before ↑vent
• ↑ing PCO2 levels ⇒ ↑O2 sensitivity & vent response
• control becomes impt
  o high altitude
  o long term hypoxaemia by chronic lung disease
    ▪ chronic CO2 retention ⇒ pH brain ECF compensated by inc intake of HCO3-
    ▪ lost most of incr stim to ventilation from CO2
    ▪ also no pH stim of periph chemoreceptors due to renal compensation
  ➜ ↓: ↓PaO2 becomes chief stim to ventilate

**Response to pH**
• ↓art pH ⇒ ↑RR
• difficult to separate response to ↑CO2 to ↓pH
• met acidosis – partially compensated have ↑pH & ↓PCO2
  ➜ compensation driven by pH receptors
• sensed in
  o periph chemoreceptors – main
  o central chemoreceptors – only if large pH change where bbb becomes permeable to H+ ions

**Response to Exercise**
• normal ventilation 4L/min
• exercise ⇒ ↑total ventilation 120Litre/min x15 resting level
• cause of ↑ventilation largely unknown
• changes in exercise:
  o PaCO2 ↓ slightly during severe ex
  o PaO2 slightly ↑
    ➜ although may ↓ in strenuous ex
  o pH – constant mod ex, ↓during strenuous due to lactic acid
• stimuli suggested:
  o passive movement of limb – muscle receptors
  o oscillations in PaO2 & PaCO2 not the mean
  o central chemoreceptors regulate PCO2 by a servomechanism
  o ↑CO2 load presented to lungs in venous blood ⇒ ↑vent
  o ↑temp
  o impulses from the motor cortex

**Abnormal Patterns of Breathing**
• severe hypoxaemia ⇒ Cheyne Stokes resp:
  o pattern:
    ▪ apnoea 10-20 secs
    ▪ period hyperventilation with fluctuating Vt
  o seen at
    ▪ high altitude when asleep
    ▪ heart disease
    ▪ brain damage
  o caused by delay in chemoreceptors sensing change in PCO2 ∴ resp centre hunts for equilibrium but overshoots
Physiology of Breath Holding

**Influence of PCO2 & PO2**
- with breathholding after breathing RA:
  - PACO2 (\& PaCO2) remain constant @ breaking point
  - \~50mmHg
  - concominant hypoxia is more important
- preoxygenation:
  - delays onset of hypoxia
  - breath holding times much more prolonged
  - \( \uparrow \)PCO3 at breaking point
- if resect carotid body:
  - breaking point cure displaced up & left
    \( \leftarrow \) ie tolerate higher PaCO2 and lower PaO2
- experienced breath holders have blunted response to PaCO2 but not to hypoxia
- extreme duration of breath holding can be achieved:
  - post hyperventilation & preoxygenation
  - can see up to 14mins
  - limited by decreasing lung volume towards RV due to O2 uptake

**Effect of Lung Volume**
- time before break point directly proportional to lung volume at onset of breath hold
- due to:
  - uptake of O2 from alveoli
  - \( \uparrow \)ing afferent activity form diaphragm/chest wall/lung as lung volume \( \downarrow \)
    \( \leftarrow \) if block all glossopharyngeal & vagal afferents & NMB then \( \Rightarrow \) prolonged breath hold
- \( \therefore \) much of distress towards end breath hold due to frustration \& involuntaryresp mm contraction
Summary

- Central chemoreceptors respond to changes in the concentration of CO2, which alters the pH of CSF.
- Alterations in HCO3- of CSF modulate pH.
- Peripheral chemoreceptors:
  - Chiefly carotid body
  - Respond to ↓PO2 & ↑PCO2 & ↑H+
  - Response to O2 small above 50mmHg
  - Response to CO2 less than central receptors but more rapid
- PCO2 is the most important factor controlling ventilation in normal conditions.
- PO2 is only important at high altitude and lung disease.
- Exercise causes a significant increase in ventilation but why?