Basics of Ventilatory Control and Central Sleep Apnea

April 15, 2015
Loutfi S. Aboussouan, M.D.

Outline of Presentation

- Pathophysiology
  - Closed Loop Feedback Mechanism
  - Controller gain: Ve response to pCO₂ change
  - Plant gain: pCO₂ response to change in Ve
  - Interaction of controller and plant gain to determine steady state ventilation and pCO₂
  - Hypocapnic apneic threshold
  - Loop gain
  - Circulatory delay
Outline of Presentation

- Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia
Controller Gain in the control of Respiration

Central Controller
Voluntary
Involuntary
Pons, Medulla

Sensors
Chemoreceptors
Lung and other receptors

Effectors
Respiratory muscles

Signal
pCO₂, pO₂, pH …

Controller Gain: The ventilatory response to CO₂

Ventilatory responses to changes in PCO₂
Controller Gain

Plant Gain in the control of Respiration

Central Controller
- Voluntary
- Involuntary
- Pons, Medulla

Sensors
- Chemoreceptors
- Lung and other receptors

Effectors
- Respiratory muscles

Signal
- pCO2, pO2, pH …
Plant Gain: The CO₂ change with ventilation
Resting Metabolic Hyperbola

\[ pCO2 = \frac{0.862VCO2}{VE(1 - VD / VT)} \]

Closed Loop Control of Respiration

Central Controller
- Voluntary
- Involuntary
- Pons, Medulla

Sensors
- Chemoreceptors
- Lung and other receptors

Signal
- pCO₂, pO₂, pH ...

Effectors
- Respiratory muscles
Closed Loop Arterial pCO2 regulation

Controller Gain
\[ \text{Ve} = k_1 \text{pCO2} + b \]

Plant Gain
\[ \text{pCO2} = \frac{k_2 \text{VCO2}}{\text{Ve}(1-Vd/Vt)} \]

pCO2 response to change in ventilation

Ve = k1pCO2 + b

pCO2

Plant Gain
pCO2 = k2VCO2/[Ve(1-Vd/Vt)]

pCO2 response to change in ventilation

Ve = k1pCO2 + b

pCO2

Ventilatory responses to changes in PCO₂ and PO₂

End tidal Pco₂ mmHg

End tidal Po₂ mmHg

normal resting equilibrium point

Chemoresponsiveness (Controller Gain)

Resting Ventilation

Resting Pco₂

basal ventilation or “wakefulness” drive

resting metabolic hyperbola (Plant Gain)

Chemoresponsiveness (Controller Gain)

Resting Ventilation
Ventilatory responses to changes in PCO₂ and PO₂

Ventilation L/min

End tidal Po₂ mmHg

End tidal PCO₂ mmHg

Resting Ventilation

normal resting equilibrium point

Recruitment Threshold (breakpoint)

resting metabolic hyperbola

basal ventilation or "wakefulness" drive

Resting PO₂

Resting PCO₂

Chemoresponsiveness (slope)

Ventilation responses to changes in PCO₂ and PO₂
Ventilatory responses to changes in PCO$_2$ and PO$_2$
Ventilatory responses to changes in PCO$_2$ and PO$_2$
Ventilatory responses to changes in PCO$_2$ and PO$_2$
Ventilatory responses to changes in PCO₂ and PO₂

Loop Gain = response to disturbance/disturbance itself

Fig 5. LC is the ventilatory responses to disturbance ratio. (A) Example of LC = 0.73. The respiratory control system is damped with a transient reduction in ventilation (a) producing a smaller response (b) in the opposite direction (c) to (a) (d) as large as the disturbance. The next response (e) will also be (f) as large as (b), etc. Thus, a LC of 0.73 produces transient fluctuations in ventilation, but ventilation eventually returns to a steady state (c). LC > 1.0 (g) amplifies the disturbance, ventilation, therefore, oscillates without returning to baseline. The system is unstable (h). LC < 1.0 (i) is less stable. The closer LC is to zero, the smaller the fluctuations in ventilation, and the more stable the system.

Wellman et al. Respir Physiol Neurobiol 2008;162:144–151
Loop Gain

- Same delay and disturbance (hypoveritailation) in each case
- B: Damping
- C: Increase controller gain results in sustained oscillations
- D: Increase plant gain results in sustained oscillations
- Stability of the system depends on the “loop gain” a composite measure of plant and controller gains as well as total lag

Khoo. Sleep and Breathing. Marcel Dekker (2000)

Controller Gain: The ventilatory response to CO2
Hypocapnic-Apneic Threshold in NREM Sleep

- End tidal Pco2 mmHg
- End tidal Po2 mmHg

Controller Gain: Ventilation as function of pCO2

Plant Gain: pCO2 as function of ventilation (metabolic hyperbola)


Increase in ventilation required to reach the AT is much less with increased controller gain.
Increase in ventilation required to reach the AT is much less with increased controller gain

Controller Gain: Ventilation as function of $pCO_2$

Plant Gain: $pCO_2$ as function of ventilation (metabolic hyperbola)

End tidal $pCO_2$ mmHg

hypoapneic apneic threshold in NREM


Increase in ventilation required to reach the AT is much less with increased controller gain

Controller Gain: Ventilation as function of $pCO_2$

$CO_2$ Reserve

Plant Gain: $pCO_2$ as function of ventilation (metabolic hyperbola)

End tidal $pCO_2$ mmHg

hypoapneic apneic threshold in NREM

Ventilatory responses to changes in PCO$_2$ and PO$_2$ with increase loop and/or plant gain

Outline of Presentation

- Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia
Central apneas when PCO$_2$ drops below the hypocapneic threshold

Controller Gain: Ventilation as function of pCO$_2$

Plant Gain: pCO$_2$ as function of ventilation (metabolic hyperbola)

End tidal Pco$_2$ mmHg
Central Apnea in a Normal Individual

Post-hyperventilation apnea: Nasal mechanical ventilation for three minutes was used to induce hypocapnia, which causes a 6 mmHg decrease in inhaled CO2 (PetCO2) during stable NREM sleep. Central apnea occurs upon cessation of mechanical hyperventilation.

Central Apnea after Coughing
Central apnea after Sleep Talking

![Graph showing central apnea after sleep talking](image1)

Central Apnea Following an Obstructive Event and Arousal

![Graph showing central apnea following an obstructive event and arousal](image2)
Outline of Presentation

- Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia

Pharyngeal narrowing/occlusion during central apnea

Obstructive Apnea Following a Central Apnea

Outline of Presentation

• Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia
Central Apnea in Cheynes Stokes Breathing

Naughton and Filho. Progress in Cardiovascular Diseases 2009; 51:339-349

Pathophysiology of Cheyne-Stokes Breathing

- Hypocapnia
- Increased chemoreceptor responsiveness
- Hypoxia
- State changes and arousals
- Upper airway instability
- Prolonged circulation time
Cheyne-Stokes Respiration
Pathophysiology: Hypocapnia

Hanly et al. Chest 104:1079, 1993

Cheyne-Stokes Respiration
Pathophysiology: Ventilatory Response to Carbon Dioxide

Cheyne Stokes

- Hypocapnia to below the apneic threshold initiates an apnea. PaCO2 begins to rise.
- The respiratory control center detects the increasing PaCO2 with a delay due to the increased circulatory time. Hypercapnia exists by the time the respiratory control center terminates the apnea.
- The hypercapnia then stimulates robust hyperpnea, which yields marked hypocapnia and allows the cycle of events to repeat.
Pathophysiology of Cheyne-Stokes Breathing

- Onset of CSA (A): due to reduction in pCO2
- CSA length (AB): proportional to reduction in pCO2
- Hyperpnea (BC) and period breathing cycle length (AC) are proportional to lung to carotid body circulation time and inversely to CO


How to differentiate periodic breathing from Cheyne Stokes breathing

- An important differentiating factor in Cheyne Stokes breathing due to heart failure from periodic breathing due to instability in the control of breathing may be a significantly longer cycle length (> 40 seconds) in heart failure corresponding to the prolonged circulation time

Hall et al. Am J Respir Crit Care Med 1996;154:376-81
Persistence of periodic breathing and central apneas in OSA after tracheostomy (Events with Trach Open)

Naughton and Filho. Progress in Cardiovascular Diseases 2009; 51:339-349

Central Apnea in Cheynes Stokes Breathing

Naughton and Filho. Progress in Cardiovascular Diseases 2009; 51:339-349
Outline of Presentation

- Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia

Ideal split-night study showing profound saw tooth desaturations resolving after CPAP.
Complex Sleep Apnea
Note increase in central events with bilevel PAP

Complex Sleep Apnea
Conversion to central apnea on CPAP
Plenty of Events Except in Supine REM Sleep
Outline of Presentation

- Applications in sleep disease states
  - Central Sleep Apnea in normal individuals and after arousals
  - Obstructive Sleep Apnea
  - Cheyne Stokes Breathing
  - Complex Sleep Apnea
  - Conditions of hypoxemia

Conditions of Hypoxemia

Berssenbrugge et al. J Physiol 1983;343:507-524