Opioid-Induced Respiratory Failure (OIRD)

Are There *Early* Warning Signs?

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Main Teaching Points

1. Opioids suppress all aspects of respiration including drive (RR and $V_T$) and pattern.

2. Respiratory effects occur mainly during sleep or non-awake states.

3. Sub-population with enhanced sensitivity and without known risk factors.

4. Quantified ataxic breathing patterns can aid early recognition of opioid induced respiratory depression (OIRD).
Sleep-disordered breathing in stable methadone programme patients: a pilot study
H Teichtahl Addiction 2001;96:395-403
Sleep-Disordered Breathing Associated with Long-term Opioid Therapy

RJ Farney, Walker JM, Cloward TV, Rhondeau S  Chest 2003;123:632-639

35 year old female: Chronic fatigue and poor sleep

Staging

- Movement Time
- Awake
- REM
- Stage 1
- Stage 2
- Stage 3
- Stage 4

Hydrocodone 2nd dose

SaO2

%
Recurrent extremely prolonged obstructive “hypopneas” only during NREM sleep.
Sleep-Disordered Breathing Associated with Long-term Opioid Therapy
RJ Farney, Walker JM, Cloward TV, Rhondeau S  Chest 2003;123:632-639

Reversal of prolonged obstructive “hypopnea” during NREM sleep
Sleep-Disordered Breathing Associated with Long-term Opioid Therapy
RJ Farney, Walker JM, Cloward TV, Rhondeau S  Chest 2003;123:632-639

CENTRAL APNEAS during NREM sleep. Unresponsive to nasal CPAP
CPAP = 16 cm H2O
Sleep-Disordered Breathing Associated with Long-term Opioid Therapy

RJ Farney, Walker JM, Cloward TV, Rhondeau S  Chest 2003;123:632-639

Tracheal sound
Airflow
Thorax
Abdomen
Oximetry

300 seconds

Ataxic breathing and severe hypoxia during NREM
Camille Biot (19 Dec 1850)
Contribution a l’étude de phénomène respiratoire de Cheyne-Stokes.
MC Biot. Lyon Mèd 1876; 23: 517-528, 561-567

“Biot’s” breathing in a 16 year old male with tuberculous meningitis.
Chronic Opioid Use is a Risk Factor for the Development of Central Sleep Apnea and Ataxic Breathing


Intermountain Sleep Disorders Center, Pulmonary Division, LDS Hospital, Salt Lake City, UT

Background: Chronic opioid therapy for pain results in a 70% increased dramatically without adequate study of potential deleterious effects. A retrospective cohort study of 60 patients taking chronic opioids matched for age, sex, and body mass index with 60 patients not taking opioids was conducted to determine the effect of morphine dose equivalent on breathing patterns during sleep.

Results: The apnea-hypopnea index was greater in the opioid group (43.5/h vs 30.2/h, \( p < .05 \)) due to increased central apneas (12.8/h vs 2.1/h, \( p < .001 \)). Arterial oxygen saturation (SpO2) in the opioid group was significantly lower during both wakefulness (difference 2.1%, \( p < .001 \)) and non-rapid eye movement (NREM) sleep (difference 2.2%, \( p < .001 \)) but not during rapid eye movement (REM) sleep (difference 1.2%) than in the nonopioid group. Within the opioid group, and after controlling for body mass index, age, and sex, there was a dose-response relationship between morphine dose equivalent and apnea-hypopnea (\( p < .001 \)), and central apnea indexes (\( p < .001 \)). Body mass index was inversely related to apnea-hypopnea index in the opioid group but not in the nonbreathing during NREM sleep was also more prevalent in patients who chronically used opioids (70% vs 5.0%, \( p < .001 \)) and more frequent (92%) at a morphine dose equivalent of 200 mg or higher (odds ratio = 15.4, \( p = .017 \)).

Conclusions: There is a dose-dependent relationship between chronic opioid use and the development of a peculiar pattern of respiration consisting of central sleep apneas and ataxic breathing. Although potentially significant, the clinical relevance of these observations remains to be established.

Keywords: Opioids, central apnea, ataxic breathing, irregular breathing

Citation: Walker JM; Farney RJ; Rhoneau SM; Boyle KM; Cloward TV; Shilling KC. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3(5):455-461.
A. 32 y/o female morphine dose equivalent 375 mg, BMI 22 kg/m²

B. 32 y/o female no opioids, BMI 23 kg/m²

Stage 2 NREM
Opioid Effects on Respiration
Pathophysiologic

Opioids can suppress all aspects of respiration:
Drive and Pattern

<table>
<thead>
<tr>
<th>Physiologic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing frequency, tidal volume</td>
</tr>
<tr>
<td>Obstructed pattern</td>
</tr>
<tr>
<td>Hypoventilation of CO$_2$ and O$_2$</td>
</tr>
<tr>
<td>Upper airway patency</td>
</tr>
<tr>
<td>Ataxic breathing</td>
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<tr>
<td>Brandywell &amp; abdominal compliance</td>
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<tr>
<td>Hyporeactivity</td>
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</tbody>
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Clinical:
Central apneas
Obstructive apneas
Hypopneas
Ataxic breathing
Bradypnea
Hypoxemia
Opioid Effects on Respiration
Physiologic

All commercially available narcotics are μ-opioid receptor agonists and reduce neuronal activity of both pain and respiratory neurons.

Mu-opioid receptors are widely distributed throughout the central and peripheral nervous systems: cortex, brain stem and carotid body.

Key targets: preBötzinger complex in ventral-lateral medulla & Kölliker-Fuse pontine neurons
Normal breathing requires preBötzinger complex neurokinin-1 receptor-expressing neurons.

PA Gray Nat Neurosci 2001;4(9):927-930
Normal breathing requires preBötzinger complex neurokinin-1 receptor-expressing neurons.

PA Gray   Nat Neurosci 2001;4(9):927-930

1. Rats with bilateral but not unilateral destruction of NK1R neurons developed severe ataxic breathing pattern 4-5 days after injection.

2. Ataxic patterns characterized by shortened respiratory periods and an irregular sequence of inspiratory efforts of near normal amplitude interspersed with prolonged apneas or very low amplitude inspiration.
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2. Ataxic patterns characterized by shortened respiratory periods and an irregular sequence of inspiratory efforts of near normal amplitude interspersed with prolonged apneas or very low amplitude inspiration.

3. Arterial blood gas profile showed respiratory depression:
   pH 7.26, PaCO2 56 mmHg and PaO2 77 mmHg.

4. Compared to control rats that showed increased respiratory rate and increased inspiratory amplitude for > 15 minutes to severe hypoxia (4.4% O₂/95.6% N₂), injected rats developed apneas of increasing and eventually fatal duration.
Opioids at the PreBötzinger complex depress breathing and cause persistent apnea.
PreBötzinger Complex Neurokinin-1 REceptor-Expressing Neurons Mediate Opioid-Induced Respiratory Depression

Opioids at the PreBötzinger complex depress breathing and cause persistent apnea.
Opioids suppress multiple components of respiration that can be measured and respiratory depression probably precedes acute cardiorespiratory arrest. So, what are the problems? What could possibly go wrong??

1. How should we monitor patients?
Opioids suppress multiple components of respiration that can be measured and respiratory depression probably precedes acute cardiorespiratory arrest.

So, what are the problems? What could possibly go wrong??

1. How should we monitor patients?
2. How should respiratory depression be defined?
Definition of Opioid Induced Respiratory Depression

Primary Clinical Measurements:

1. Respiratory Rate  (< 8-10 bpm)

2. Oximetry  (SpO₂ < 90-92%)

3. End-Tidal CO₂  (ETCO₂ > 50 mmHg)

4. Mental Status  (Sedated)

How do you assess these parameters in a sleeping patient on oxygen??
Why is the Respiratory Rate unreliable for detection opioid induced respiratory depression.

1. RR obtained by physical examination is notoriously inaccurate (e.g. poor technique, patient arousal).

2. Most technologies are not validated for detecting slow respiratory rates.
Why is the Respiratory Rate unreliable for detection opioid induced respiratory depression.

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2. Most technologies are not validated for detecting slow respiratory rates.

3. Automated methods are insensitive to respiratory patterns (e.g. apneas) resulting in inaccurate RR.
Severe Ataxic Breathing Pattern Secondary to Opioids

60 seconds

RR = 10/min

4 minutes
Severe Ataxic Breathing Pattern Secondary to Opioids

60 seconds
RR = 7/min

PTAF
Thermistor
Thorax
Abdomen
Oximetry

4 minutes
Why is the Respiratory Rate unreliable for detection of opioid induced respiratory depression.

1. RR obtained by physical examination is notoriously inaccurate (e.g. poor technique, patient arousal).

2. Most technologies are not validated for detecting slow respiratory rates.

3. Automated methods are insensitive to respiratory patterns (e.g. apneas) resulting in inaccurate RR.

4. RR does not equate to adequate ventilation.
Opioids suppress multiple components of respiration that can be measured and respiratory depression probably precedes acute cardiorespiratory arrest.

So, what are the problems? What could possibly go wrong??

1. How should we monitor patients?
2. How should respiratory depression be defined?
3. Does any measurement or set of observations predict the onset of respiratory depression?
Opioids suppress multiple components of respiration that can be measured and respiratory depression probably precedes acute cardiorespiratory arrest.

So, what are the problems? What could possibly go wrong??

1. How should we monitor patients?

2. How should respiratory depression be defined?

3. Does any measurement or set of observations predict the onset of respiratory depression?

4. Are there warning signs that actually predict cardiorespiratory arrest?
Three Sudden Postoperative Respiratory Arrests Associated with Epidural Opioids in Patients with Sleep Apnea

A.M. Ostermeier  Anesth Analg 1997;85:452-460

41 year old female (BMI 36.7 kg/m²) underwent right hip arthroplasty

Post-Operative Day 3
08:00 Alert  0/10 pain

11:00 Asleep but easily arousable  0/10 pain

Epidural bupivacaine and fentanyl continued

12:00 Found unresponsive:  “Kussmaul respiration”
RR 18/min
Rapid breathing (RR 20-30 breaths)
Apnea (20-40 seconds)

Resuscitation efforts unsuccessful
Three Sudden Postoperative Respiratory Arrests Associated with Epidural Opioids in Patients with Sleep Apnea
A.M. Ostermeier  Anesth Analg 1997;85:452-460

66 year old male (BMI 36.3 kg/m²) underwent right hip arthroplasty

Post-Operative Day 2
09:00 Alert/Oriented RR 20/min
Oxygen discontinued

13:45 Oximetry on room air: SpO2 86%
Nasal oxygen resumed: SpO2 98%

Post-Operative Day 3
06:30 “Checked by Orthopedic service”

07:00 Seen by nurses and orthopedic physicians
“He was sleeping” and not disturbed
RR 14/min HR 120/min BP 105/50 mmHg

07:25 Found unresponsive: Resuscitation efforts unsuccessful
Three Sudden Postoperative Respiratory Arrests Associated with Epidural Opioids in Patients with Sleep Apnea

A.M. Ostermeier Anesth Analg 1997;85:452-460

47 year old male (BMI 27.5 kg/m$^2$) underwent ventral hernia repair

**Post-Operative Day 2**

06:00 “Slight unimportant changes in vital signs” since 12:00 (MN)
   “No pain”
   RR 14/min   BP 110/50   HR 78 bpm

   Continuous epidural bupivacaine and fentanyl without dose activation by the patient

07:00 Found “breathless, with cool skin and cyanotic. He was asystolic and advanced cardiac life support was given.”

   “Died later.”
Cardiopulmonary Arrest
Risk Factors + Opioids
Risk Factors + Opioids

Respiratory Depression

- $V_T$ decreases
- $RR$ decreases
- Ataxia?

Cardiopulmonary Arrest
Risk Factors + Opioids

Respiratory Depression

↓ VT  ↓ RR  Ataxia ?

Hypoventilation

Hypoxia  Hypercapnic acidosis

Cardiopulmonary Arrest
Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone.

Severe Sleep Apnea/Hypopnea with ataxia (Biot’s Respiration)
Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone.

Moderate Sleep Apnea/Hypopnea with ataxia (Biot’s Respiration)
Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone.

Mild Sleep Apnea/Hypopnea with ataxia (Biot’s Respiration)
An automated algorithm incorporating Poincaré analysis can quantify the severity of opioid-induced ataxic breathing.

An automated algorithm incorporating Poincaré analysis can quantify the severity of opioid-induced ataxic breathing.


Effect-site target controlled infusions of low dose Propofol and escalating doses of Remifentanil administered to 26 normal volunteers.
Protocol at each target effect site concentration pair

1. Stabilization
   - Time: 0 - 10 up to 20
   - Aim 1: Steady state drug reached
   - Aim 2: Subject not talking or perturbed

2. Monitoring
   - Time: 10 up to 30
   - Possible repeated computer prompts
   - Classify Airway Events

3. OAA/S, BP NIBP
   - Time: 30
   - If no airway events, proceed to next drug step

4. Ventilation Prompting Protocol
   - Time: 30 - 35
   - Possible repeated computer prompts

5. Quiet
   - Time: 35

6. OAA/S
   - Time: 36

7. RB
   - Time: 36

Change Drug

- Observer Assessment of Alertness Score (1-5):
  1. Subject is awake
  2. Subject is talking or makes eye contact
  3. No involuntary eye movement
  4. At least 30 breaths

If no airway events, proceed to next drug step.
Adaptive Servoventilation (ASV) in Patients with Sleep Disordered Breathing Associated with Chronic Opioid Medications for Non-Malignant Pain.

Jules Henri Poincaré
29 Apr 1854 – 17 Jul 1912
Father of Chaos Theory
POINCARE PLOT OF RR INTERVALS

RR-First (ms) vs RR-Second (ms)
POINCARÉ PLOT OF RR INTERVALS

RR-Second (ms)

RR-First (ms)

0 100 200 300 400 500 600 700 800 900 1000

0 100 200 300 400 500 600 700 800 900 1000

560 360
POINCARÉ PLOT OF RR INTERVALS

Acceleration

RR-First (ms)

RR-Second (ms)

560

360
POINCARÉ PLOT OF RR INTERVALS

RR-First (ms) vs. RR-Second (ms)

Deceleration

Heart rate variability analysis with Poincaré plot.
Do Existing Measures of Poincarè Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?
Do Existing Measures of Poincaré Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?

An automated algorithm incorporating Poincaré analysis can quantify the severity of opioid-induced ataxic breathing.

Ataxia Score 0

Air Flow Waveform

RIP Flow

PTAF

Poincaré Plot

Interbreath Interval at \( t = i + 1 \) (sec)

Factor change in Tidal Volume

Interbreath Interval at \( t = i \) (sec)

Chest: Blue
Abdomen: Red
Ataxia Score 1

Air Flow Waveform

RIP Flow

PTAF

Interbreath Interval at $t = i + 1$ (sec)

Poincaré Plot

Factor change in Tidal Volume

Chest: Blue
Abdomen: Red

(minutes)
Ataxia Score 2

Air Flow Waveform

RIP Flow

PTAF

Interbreath Interval at $t = i + 1$ (sec)

Poincaré Plot

Factor change in Tidal Volume

Chest: Blue
Abdomen: Red

(minutes)
Ataxia Score 3

Air Flow Waveform

RIP Flow

PTAF

Poincaré Plot

Factor change in Tidal Volume

Interbreath Interval at t = i (sec)

Interbreath Interval at t = i + 1 (sec)

Chest: Blue
Abdomen: Red

(minutes)
Ataxia Score 4

Air Flow Waveform

RIP Flow

PTAF

Interbreath Interval at $t = i + 1$ (sec)

Poincaré Plot

Factor change in Tidal Volume

Chest: Blue
Abdomen: Red

(minutes)
Subject 23 gradually going off the cliff
Subject 4 suddenly going off the cliff
Animated Poincaré Plot of Progressively Severe Ataxic Breathing
Respiratory Rate 8-10/min

(N = 21)

- OAAS 0: 4.8%
- OAAS 1: 23.9%
- OAAS 2: 71.4%
Respiratory Rate 8-10/min
(N = 21)

71.4%
OAAS 0

4.8%
OAAS 1

23.9%
OAAS 2

14.3%
OAAS 3

14.3%
OAAS 4

9.5%
OAAS 5

Respiratory Rate 8-10/min

ATAXIA SCORE

0 1 2 3 4
Respiratory Rate 5-7/min

(N = 36)

ATAXIA SCORE

0 1 2 3 4
Respiratory Rate 0-4/min

(N = 50)

%
Respiratory Rate > 10/min

(N = 14)

% of participants in each OAAS category:

- OAAS 0: 2.1%
- OAAS 1: 14.3%
- OAAS 2: 7.1%
- OAAS 3: 35.7%

ATAXIA SCORE:

- 0
- 1
- 2
- 3
- 4
CONCLUSIONS:

1. Threshold values (i.e. RR, SpO2, ETCO2) may be useful in defining the state of respiratory depression but evidence is lacking that any reliably predict cardiorespiratory arrest.

2. Erratic breathing is an important physiologic consequence of opioid induced respiratory depression and can be quantified for clinical applications and further research.

3. Patterns of erratic breathing could provide early evidence for impending life threatening critical respiratory events.