Opioid-Induced Respiratory Failure
Are There Early Warning Signs?

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Robert J Farney MD
Clinical Professor of Medicine
University of Utah School of Medicine

robertjfarney@gmail.com

CASE REPORT

Number of opioid deaths by category

Drug Overdose Deaths in the United States, 1999-2016
H Hedegaard  NCHS Data Brief. No. 294. December 2017
**Chronic Opioid Use and Central Sleep Apnea: A Review of the Prevalence, Mechanisms, and Perioperative Considerations**

Denis Correa, MBBS, MD; Robert J. Farney, MD; Frances Chung, MBBS, FRCPC; Arun Prasad, MBBS, FRCA, FRCPC; David Lam, BMSc; and Jean Wong, MD, FRCPC

<table>
<thead>
<tr>
<th>Sleep Disordered Breathing</th>
<th>42-85% (mean 70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Sleep Apnea</td>
<td>14-60% (mean 24%)</td>
</tr>
<tr>
<td>Clinical risk factors</td>
<td>Non-predicting</td>
</tr>
<tr>
<td>Optimal therapy</td>
<td>Controversial</td>
</tr>
</tbody>
</table>

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?

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**Definition of Opioid Induced Respiratory Depression**

1. Decreased central respiratory drive to thoracic bellows
   - Intercostal and diaphragmatic muscle activity
   - RR and $V_T$
   - Central Apneas
   - Hypoventilation

2. Decreased central respiratory drive to upper airway muscles
   - Genioglossus muscle activity
   - Upper airway resistance/obstruction
   - Obstructive Apneas

3. Depression of hypothalamic arousal system
   - Consciousness
Non-invasive Methods for Monitoring Respiration

1. Detection of Movement and Volume
   - Physical Examination
   - Transthoracic Impedance*
   - Inductive Plethysmography*
   - Strain-gauge transducers*
   - Accelerometer

   | Respiratory Rate | (*Tidal Volume) |

2. Detection of Airflow
   - Carbon Dioxide (End-Tidal CO₂)
   - Thermistor/Thermocouple
   - Acoustic device
   - Hygrometer

   | Respiratory Rate |

3. Arterial O₂ / CO₂ content
   - Photoplethysmography (Oximetry)
   - Carbon Dioxide (End-Tidal CO₂ or Transcutaneous CO₂)

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)
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.

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

4. RR does not assure adequate ventilation.

Respiratory Pattern versus Respiratory Rate
What is a breath?

Accuracy of thermistors and thermocouples as flow-measuring devices for detecting hypopneas.


Fig. 2. – a) Actual flow measured by the pneumotachograph (V) for sinusoidal airflows of 1 L·s⁻¹ and 0.5 L·s⁻¹ and for a square-wave flow of 0.5 L·s⁻¹ (peak-to-peak). b) Thermistor signal (V'in) recorded simultaneously.
Comparison of seven different sensors for detecting low respiratory rates using a single breath detection algorithm in non-intubated, sedated volunteers.

**Impedance**

Comparison of seven different sensors for detecting low respiratory rates using a single breath detection algorithm in non-intubated, sedated volunteers.

**Capnometer**
Patterns of unexpected in-hospital deaths: a root cause analysis.
Lawrence A Lynn, J Paul Curry. Patient Safety in Surgery 2011;5(3)1-24

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?
Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy.

S Ramachandran J Clin Anesthesia 2011;23:207-213

7 Significant* Co-morbid Risk Factors:

<table>
<thead>
<tr>
<th>Preoperative co-morbidity</th>
<th>N</th>
<th>Unadjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>5</td>
<td>34.9 (13.6 – 90.1)</td>
</tr>
<tr>
<td>Postoperative Acute Renal Failure</td>
<td>3</td>
<td>18.6 (5.8 – 59.5)</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>12</td>
<td>16.9 (8.3 – 34.5)</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>6</td>
<td>5.3 (2.2 – 12.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>4.7 (1.8 – 12.1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7</td>
<td>3.1 (1.3 – 7.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>1.9 (1.1 – 3.9)</td>
</tr>
</tbody>
</table>

* Compared to baseline prevalence for this institution
Respiratory depression associated with patient-controlled analgesia: a review of eight cases.

Study Context: University of Alberta
Jan 1992 to Mar 1993
Adult Orthopedic and Surgical Pts on PCA
Retrospective review of 1600 subjects

Search Criteria: “Respiratory depression associated with anaesthesia”

8 Patients found with respiratory depression/failure
0 Deaths (All treated with Naloxone and oxygen)
6 “Early” (≤ 24 hours)  5 “Immediate” (< 6 hours)
7 “Unrousable, Difficult to arouse, Very drowsy, GCS 3”
4 RR 4-7/min  3 RR not reported  1 RR 32 & shallow
4 Cyanotic or Hypoxic  4 No information of oxygen
Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy.
S Ramachandran J Clin Anesthesia 2011;23:207-213

Study Context: University of Michigan
6 year period (Aug 2000 to Jul 2007)
Retrospective review of 87,650 subjects

LT-CRE definitions: Unresponsive and hypoxic or apneic patient needing rescue therapy during concurrent opioid therapy.
Reversible or irreversible
Early or Late (≤ or > 24 hours after end of anesthesia)

Results: 32 LT-CREs (5 in PACU and 27 on General Floor)
28 Reversible 4 Deaths
26 “early” (< 24 hours) with 11 “immediate” (< 6 hours)
3 of 4 deaths were “early”

Fig. 2 Day-night pattern of life-threatening critical respiratory events.
Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy.
S Ramachandran J Clin Anesthesia 2011;23:207-213
Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy.
S Ramachandran J Clin Anesthesia 2011;23:207-213

1. The majority of deaths (75%) and reversible LT-CREs (81.3%) occurred within the first 24 hours of opioid therapy.

2. Increased opioid sensitivity unrelated to dose may play a role in irreversible events.

3. Sedation scores did not appear to predict LT-CRE except that no irreversible events occurred with alert patients.

4. SpO2 and Respiratory rates were recorded in only 50% of records and therefore were not included in the analysis.

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: “Kussmall 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/m²) 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.”

Risk Factors + Opioids
Respiratory Depression
↓ VT  ↓ RR  Ataxia ?
Hypoventilation
Hypoxia  Hypercapnic acidosis
Cardiopulmonary Arrest
<table>
<thead>
<tr>
<th></th>
<th>Opioid</th>
<th>Non-Opioid</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH1</td>
<td>43.5</td>
<td>30.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CAI</td>
<td>12.5</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
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</table>

Opioid use was associated with a significantly higher arochar mass index and oxygen sporadisch in the opioid group (43.5 vs 30.2, p < 0.05) due to increased arochar indexes (12.8 vs 2.1, p < 0.001) and increased oxygen sporadisch (SpO₂) in the opioid group (30.2 vs 2.1, p < 0.001). Airflow sporadisch in patients receiving therapy with buprenorphine/naloxone. R.J. Farney. Eur Respir J 2013; 42:394-403.

Severe 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)

How do you measure variability?
Respiratory Variability during Sleep in Methadone Maintenance Treatment Patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MMT Patients (50)</th>
<th>Controls (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE years</td>
<td>35 (9)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>27 (6)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>AHI</td>
<td>17.7 (17)</td>
<td>9.9 (10)</td>
</tr>
<tr>
<td>CAI</td>
<td>6.7 (14)</td>
<td>0.3 (0.3)</td>
</tr>
<tr>
<td>Smoker</td>
<td>92 %</td>
<td>21%</td>
</tr>
</tbody>
</table>

**Measurements:** Inter-breath intervals extracted from PTA signals.
Blood methadone levels.

**Analysis:**
- Standard Deviation (SD)
- Coefficient of variation (SD/Mean)
- Detrended Fluctuation analysis exponent (α)
Respiratory Variability during Sleep in Methadone Maintenance Treatment Patients.

Breath interval as a measure of dynamic opioid effect.
J.A. Smart Brit J Anaesth 2000;84(6):735-738

**Fig 1** Serial measurements of breath interval before and after fentanyl 40 μg i.v. at time 0. Values before time 0 provide baseline. Breath interval did not return completely to baseline before surgery finished.
Jules Henri Poincaré
29 Apr 1854 – 17 Jul 1912
Father of Chaos Theory

“Mathematics is the art of giving the same name to different things.”

POINCARE PLOT OF RR INTERVALS

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

RR-Second (ms)

RR-First (ms)

560
360

POINCARÉ PLOT OF RR INTERVALS

RR-Second (ms)

RR-First (ms)

360
760
POINCARE PLOT OF RR INTERVALS

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

Poincare Plot of RR Intervals showing the relationship between consecutive heart rate intervals. The plot displays the distribution of RR intervals, with the x-axis representing RR-First (ms) and the y-axis representing RR-Second (ms). The plot includes a linear relationship indicated by the diagonal line, and points above and below this line represent the deviation from the expected linear relationship.

An example of a Poincare Plot is shown, indicating the variability in heart rate intervals. The plot highlights the clustering of data points and the deviation from the linear trend, which can provide insights into the timing and regularity of heartbeats.
Do Existing Measures of Poincarè Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?

A computer based expert system to identify and quantify opioid induced ataxic breathing.
S. Ermer, RJ Farney, L Brewer
Comparison of seven different sensors for detecting low respiratory rates using a single breath detection algorithm in non-intubated, sedated volunteers. 

Adaptive Servoventilation (ASV) in Patients with Sleep Disordered Breathing Associated with Chronic Opioid Medications for Non-Malignant Pain. 
Do Existing Measures of Poincaré Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?

![Poincaré Plot Diagram]

Ataxia Score 0

![Ataxia Score Diagram]
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 evidence for impending life threatening critical respiratory events.

Thank you