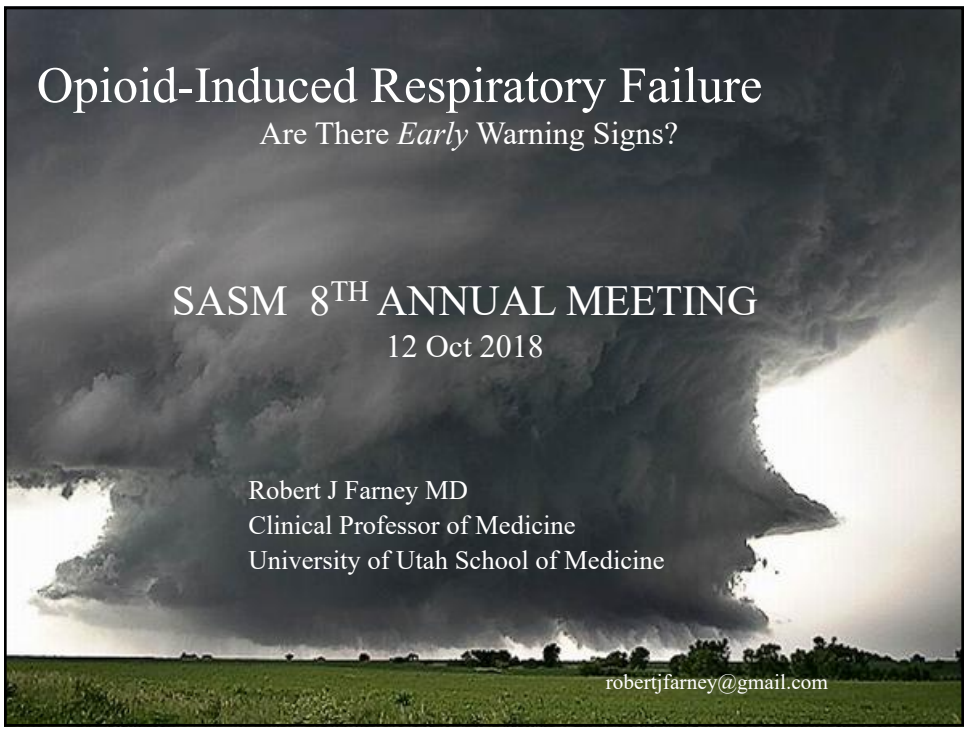
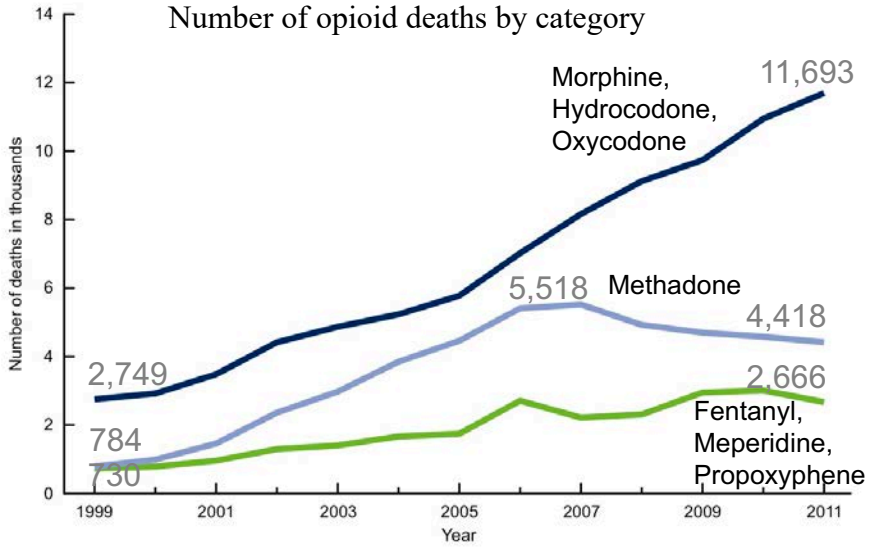

Opioid-Induced Respiratory Failure
Are There *Early* Warning Signs?
SASM 8TH ANNUAL MEETING
12 Oct 2018
Robert J Farney MD
Clinical Professor of Medicine
University of Utah School of Medicine
robertjfarney@gmail.com

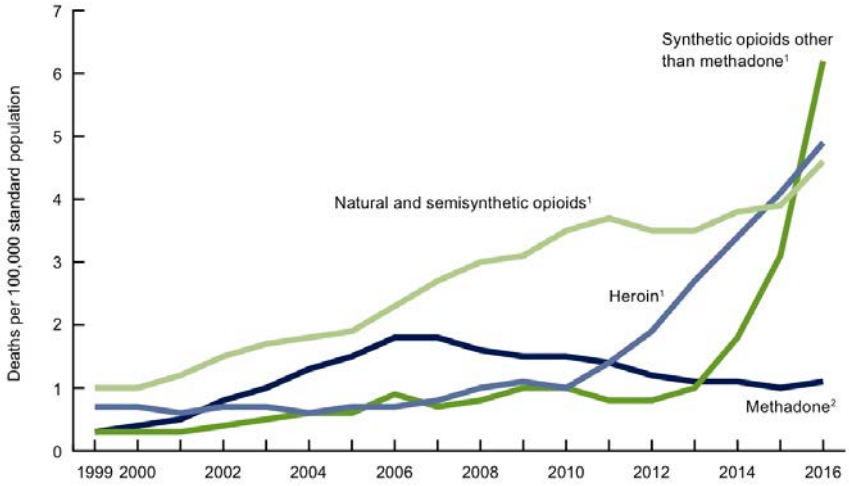
CASE REPORT

Drug-poisoning Deaths Involving Opioid Analgesics: United States, 1999-2011. Chen LH. NCHS Data Brief. Sep 2014



Drug Overdose Deaths in the United States, 1999-2016

H Hedegaard NCHS Data Brief. No. 294. December 2017



Anesthesia Patient Safety Foundation
Section Editor: Sorin J. Brull
REVIEW ARTICLE

CME **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*

Sleep Disordered Breathing	42-85% (mean 70%)
Central Sleep Apnea	14-60% (mean 24%)
Clinical risk factors	Non-predicting
Optimal therapy	Controversial

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. <u>How should respiratory depression be defined?</u>

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 — Respiratory Rate

Carbon Dioxide (End-Tidal CO_2)
Thermistor/Thermocouple
Acoustic device
Hygrometer

3. Arterial O_2 / CO_2 content

Photoplethysmography (Oximetry)
Carbon Dioxide (End-Tidal CO_2 or Transcutaneous CO_2)

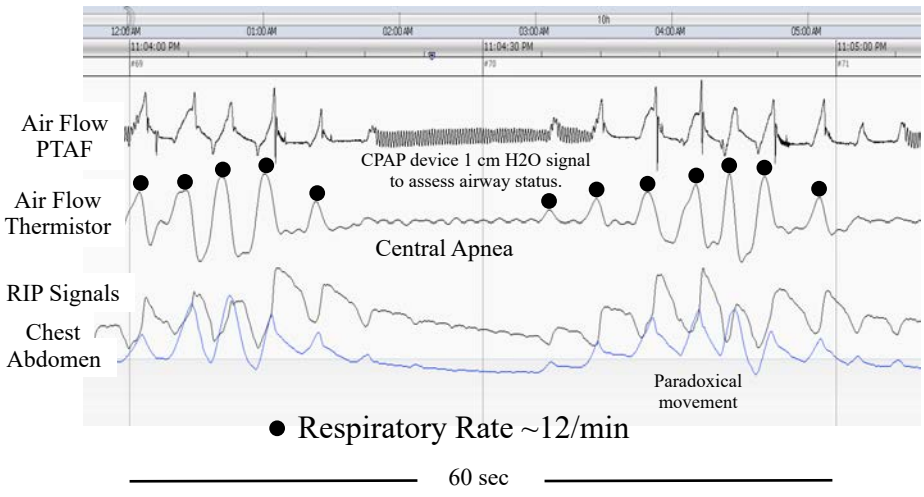
Definition of Opioid Induced Respiratory Depression Primary Clinical Measurements:

1. Respiratory Rate (< 8-10 bpm)
2. Oximetry (SpO_2 < 90-92%)
3. End-Tidal CO_2 ($ETCO_2$ > 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.

R Farré Eur Respir J 1998;11:179-182

Pneumotach

Thermistor

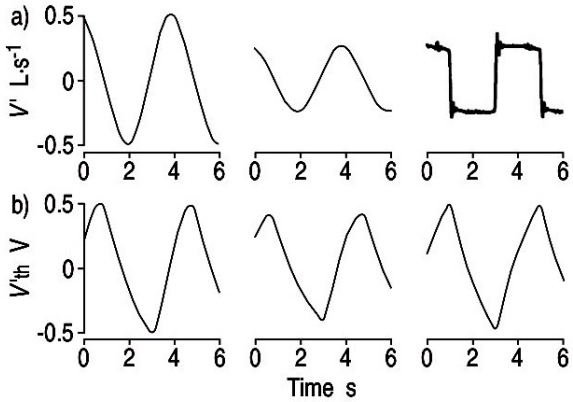
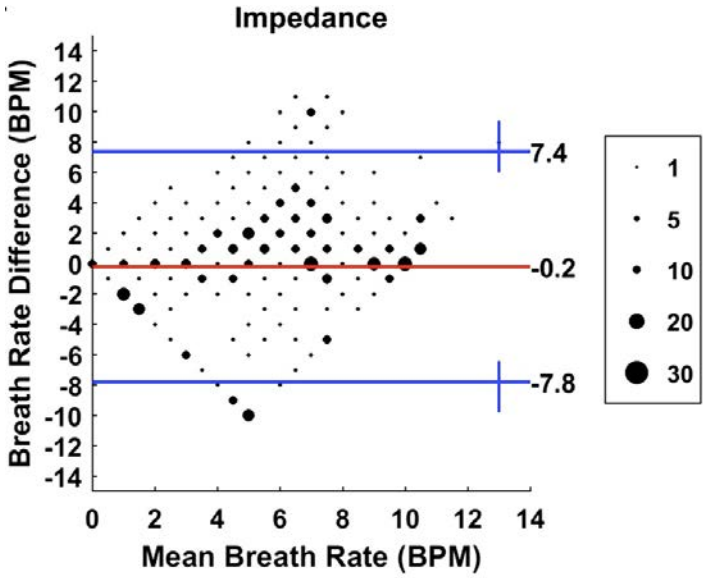


Fig. 2. – a) Actual flow measured by the pneumotachograph (V') for sinusoidal airflows of 1 $L \cdot s^{-1}$ and 0.5 $L \cdot s^{-1}$ and for a square-wave flow of 0.5 $L \cdot s^{-1}$ (peak-to-peak). b) Thermistor signal (V'th) recorded simultaneously.

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

S Ermer, L Brewer, J Orr et al. Anesth Analg 2018 in press



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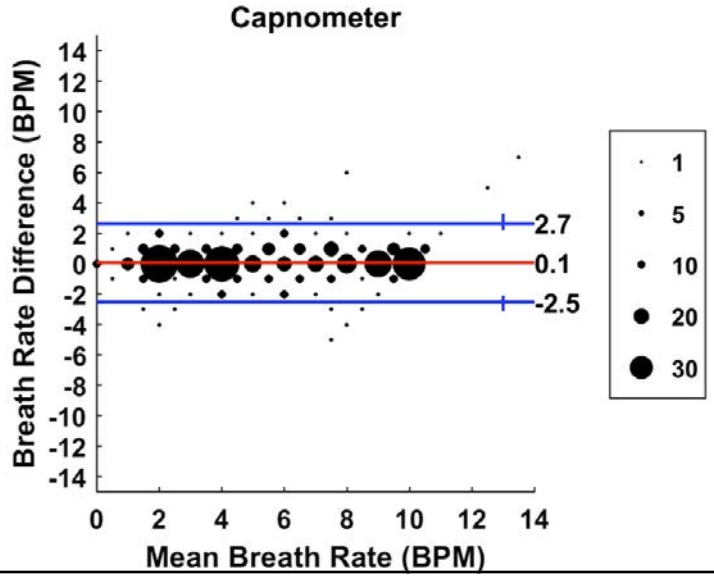


Patterns of unexpected in-hospital deaths: a root cause analysis.
Lawrence A Lynn, J Paul Curry. Patient Safety in Surgery 2011;5(3)1-24

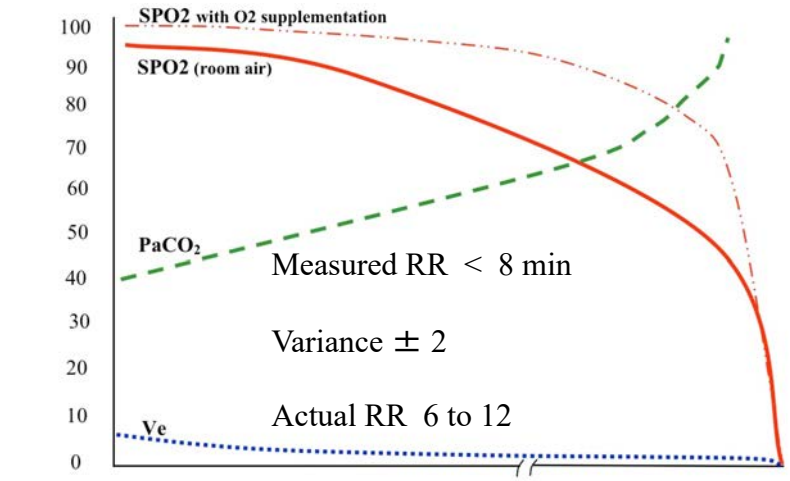


Figure 2 Type II Pattern of Unexpected Hospital Death (CO2 Narcosis)

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?

American Society for Pain Management Nursing Guidelines on Monitoring for Opioid-Induced Sedation and Respiratory Depression.

D Jarzyna Pain Management Nursing 2011;12(No 3):118-145

TABLE 2.
Risk Factors for Opioid-Induced Respiratory Depression

Patient may have one or more of the following to be considered high risk:
Age >55 years
Obesity (e.g., body mass index ≥30 kg/m^2)
Untreated obstructive sleep apnea
History of snoring or witnessed apneas
Excessive daytime sleepiness
Retrognathia
Neck circumference >17.5″
Preexisting pulmonary/cardiac disease or dysfunction, e.g., chronic obstructive pulmonary disease, congestive heart failure
Major organ failure (albumin level <30 g/L and/or blood urea nitrogen >30 mg/dL)
Dependent functional status (unable to walk 4 blocks or 2 sets of stairs or requiring assistance with ambulation)
Smoker (>20 pack-years)
American Society of Anesthesiologists patient status classification 3-5
Increased opioid dose requirement
- Opioid-naïve patients who require a high dose of opioid in short period of time, e.g., 10 mg IV morphine or equivalent in postanesthesia care unit (PACU)
- Opioid-tolerant patients who are given a significant amount of opioid in addition to their usual amount, such as the patient who takes an opioid analgesic before surgery for persistent pain and receives several IV opioid bolus doses in the PACU followed by high-dose IV patient-controlled analgesia (PCA) for ongoing acute postoperative pain

First 24 hours of opioid therapy (e.g., first 24 hours after surgery is a high-risk period for surgical patients)
Pain is controlled after a period of poor control
Prolonged surgery (>2 hours)
Thoracic and other large incisions that may interfere with adequate ventilation
Concomitant administration of sedating agents, such as benzodiazepines or antihistamines
Large single-bolus techniques, e.g., single-injection neuraxial morphine
Continuous opioid infusion in opioid-naïve patients, e.g., IV PCA with basal rate
Naloxone administration: Patients who are given naloxone for clinically significant respiratory depression are at risk for repeated 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:

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

* Compared to baseline prevalence for this institution

Respiratory depression associated with patient-controlled analgesia: a review of eight cases.

R Etches Can J Anaesth 1994;41(2):125-132

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"

Respiratory depression associated with patient-controlled analgesia: a review of eight cases.

R Etches Can J Anaesth 1994;41(2):125-132

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"

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

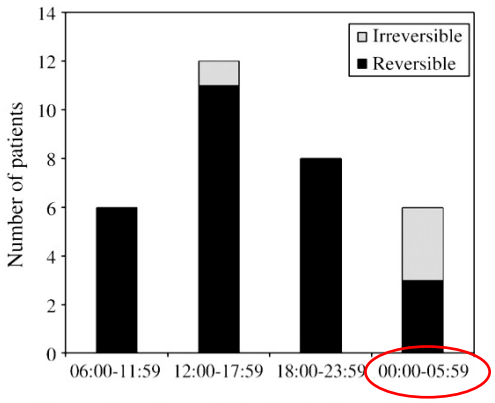
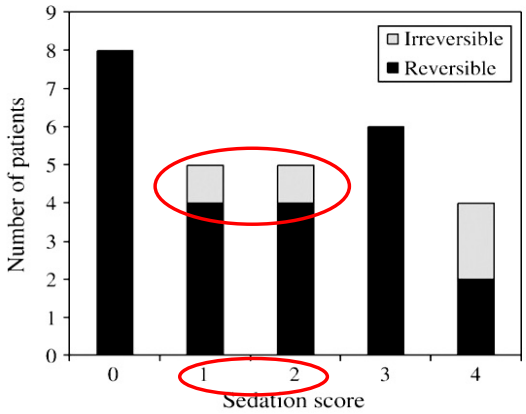


Fig. 2 Day-night pattern of life-threatening critical respiratory events.

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



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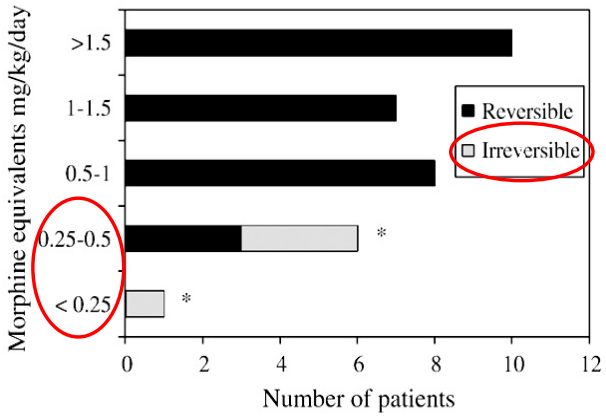


Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy.
S Ramachandran J Clin Anesthesia 2011;23:207-213

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.
1. 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/m^2) 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/m^2) 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

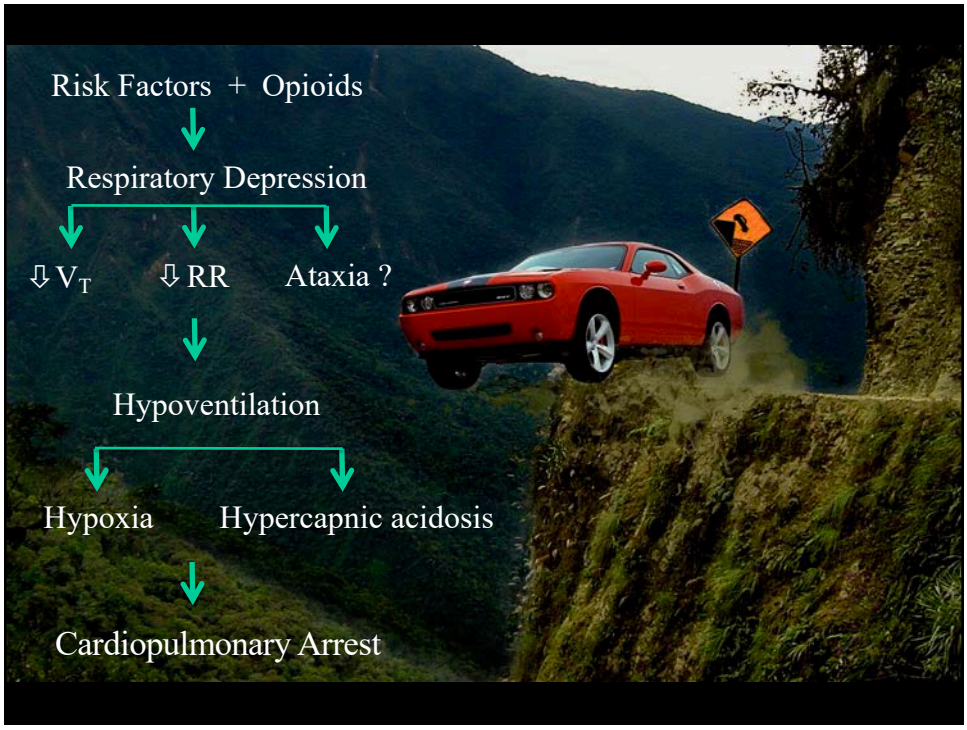
Post-Operative Day 2

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."



JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Chronic Opioid Use is a Risk Factor for the Development of Central Sleep Apnea and Ataxic Breathing

James M. Walker, Ph.D.; Robert J. Farney, M.D.; Steven M. Rhondeau, M.D.; Kathleen M Boyle, B.S.; Karen Valentine, B.S.; Tom V. Cloward, M.D.; Kevin C. Shilling, M.D.

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

Background: Chronic [illegible] pain management has increased dramatically without adequate study of potential deleterious effects on breathing during sleep. A retrospective study comparing 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 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 (SpO_2) 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 ($p < .001$), hypopnea ($p < .001$), and central apnea indexes ($p < .001$). Body mass index was inversely related to apnea-hypopnea index severity in the opioid group. Cheyne-Stokes or irregular breathing during NREM sleep was also more frequent 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 greater ($\chi^2 = 15.4$, $p = .017$).

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.

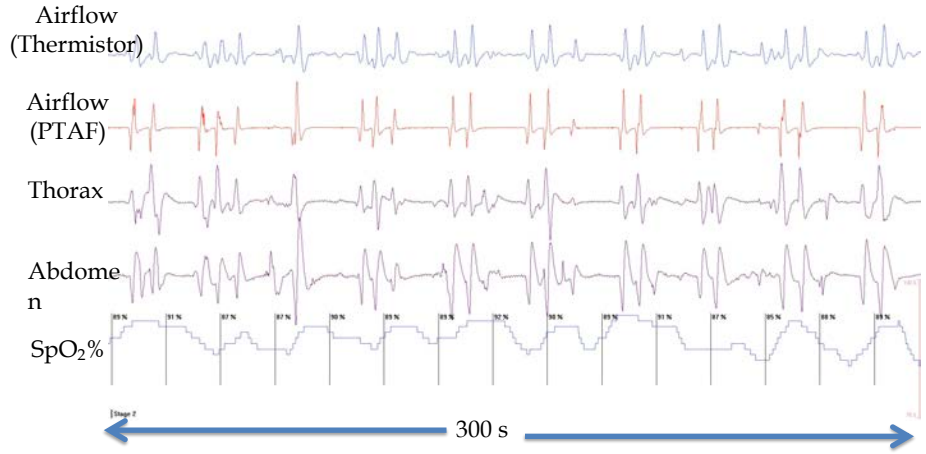
Keywords: Opioids, central apnea, ataxic breathing, irregular breathing

Citation: Walker JM; Farney RJ; Rhondeau 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.

	Opioid	Non-Opioid	p
AHI	43.5	30.2	<0.05
CAI	12.5	2.1	<0.001

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

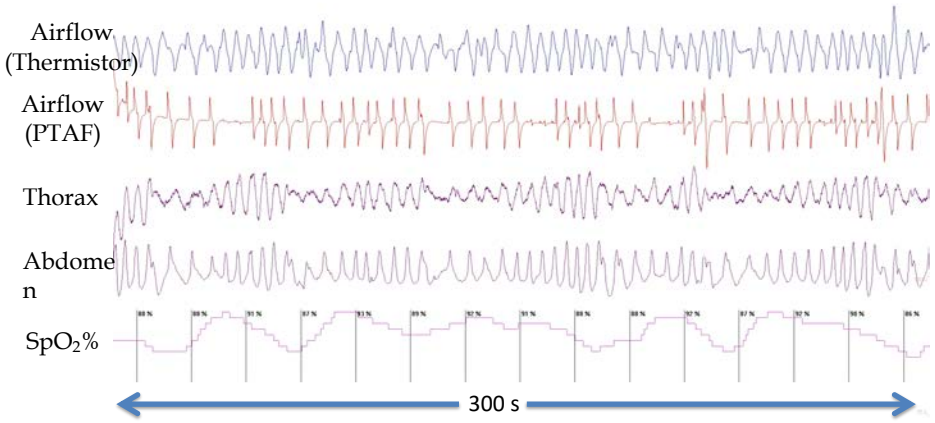
R.J. Farney. Eur Respir J 2013; 42:394-403



Severe Sleep Apnea/Hypopnea with ataxia (Biot's Respiration)

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

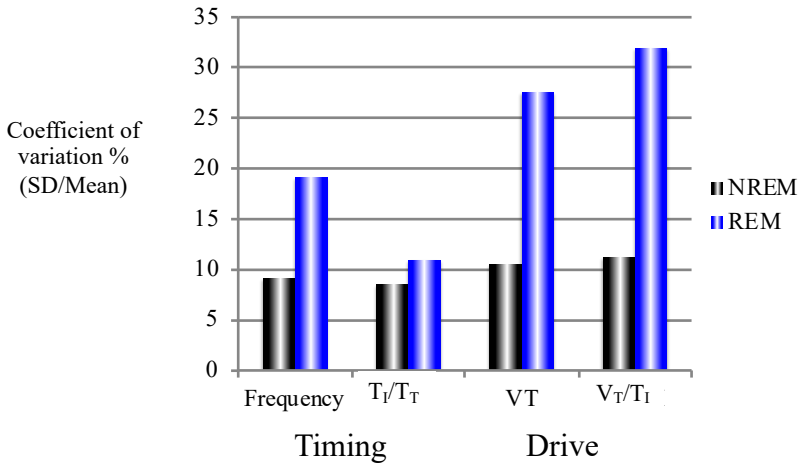
R.J. Farney. Eur Respir J 2013; 42:394-403



Mild Sleep Apnea/Hypopnea with ataxia (Biot's Respiration)

How do you measure variability ?

Nonrandom Variability of Respiration During Sleep in Healthy Humans. S Rostig Sleep 2005;28(4):411-417.



Respiratory Variability during Sleep in Methadone Maintenance Treatment Patients.

C.D. Nguyen J Clin Sleep Med 2016;12(4):607-616.

Variables	MMT Patients (50)	Controls (19)
AGE years	35 (9)	35 (9)
BMI kg/m^2	27 (6)	27 (5)
AHI	17.7 (17)	9.9 (10) p < .05
CAI	6.7 (14)	0.3 (0.3) p < .001
Smoker	92 %	21%

Measurements: Inter-breath intervals extracted from PTAF 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.

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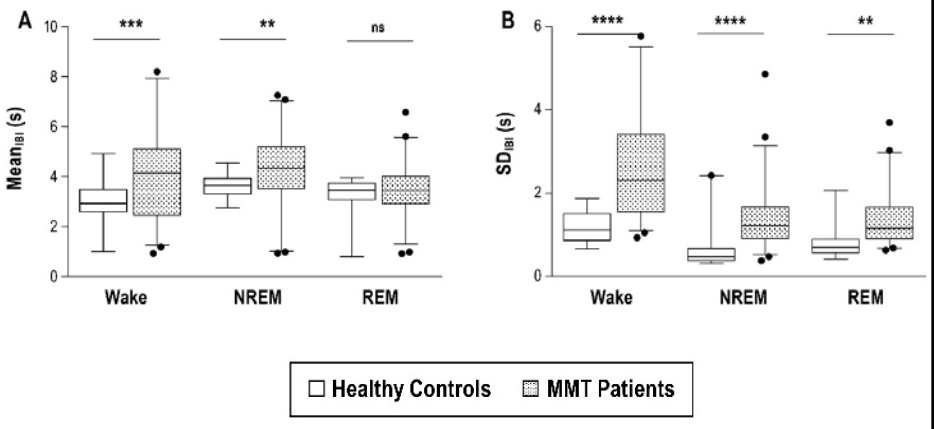

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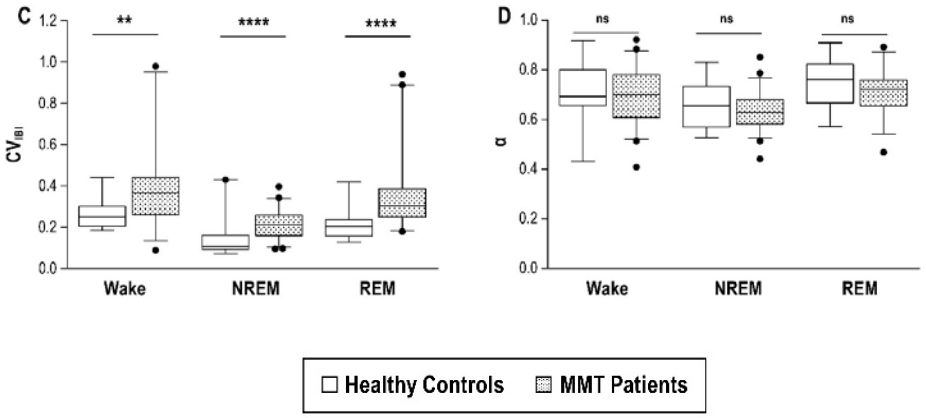


Breath interval as a measure of dynamic opioid effect.

J.A. Smart Brit J Anaesth 2000;84(6):735-738

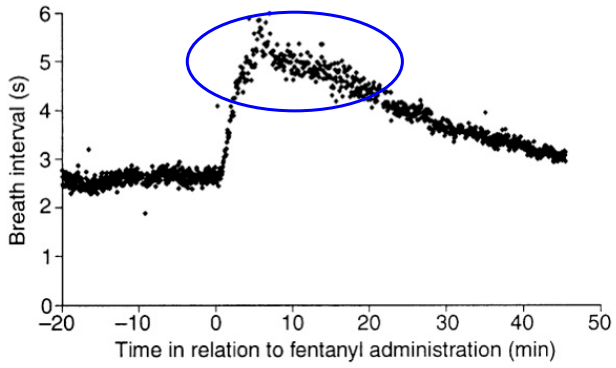


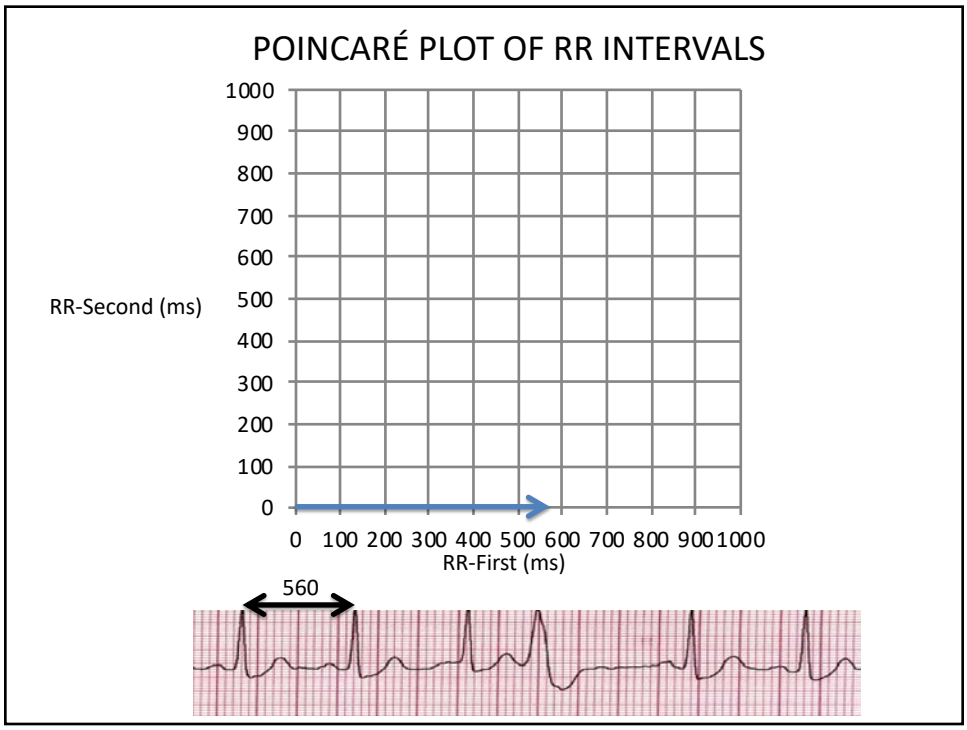
Fig 1 Serial measurements of breath interval before and after fentanyl 40 μg i.v. at time 0. Values before time 0 provide baseline. Breath interval did not return completely to baseline before surgery finished.

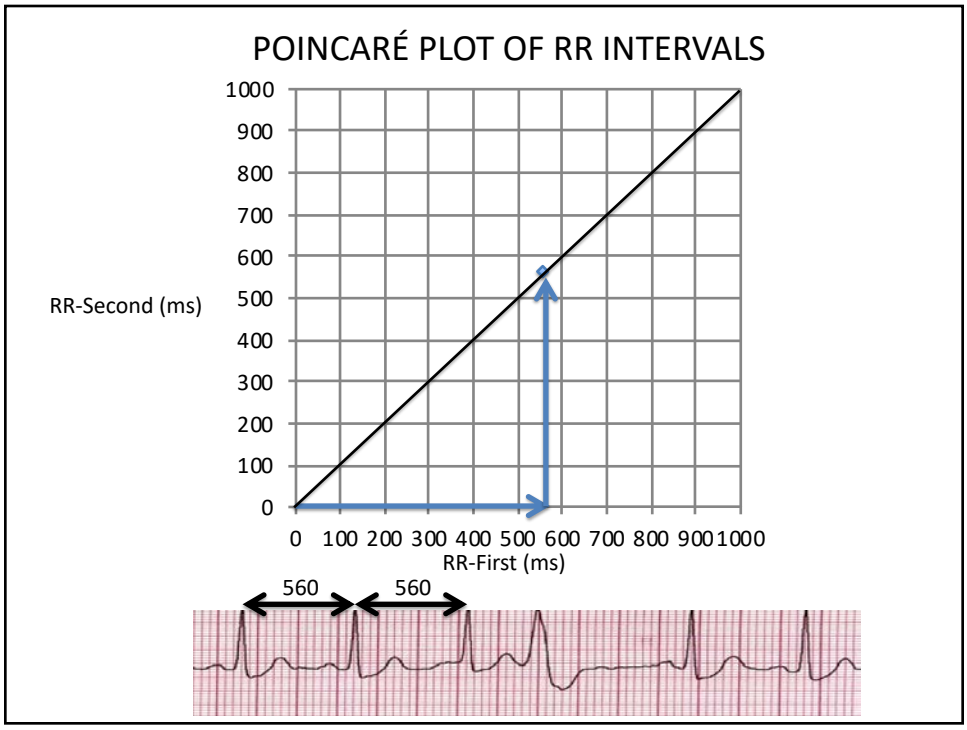
Jules Henri Poincaré

29 Apr 1854 – 17 Jul 1912

Father of Chaos Theory

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

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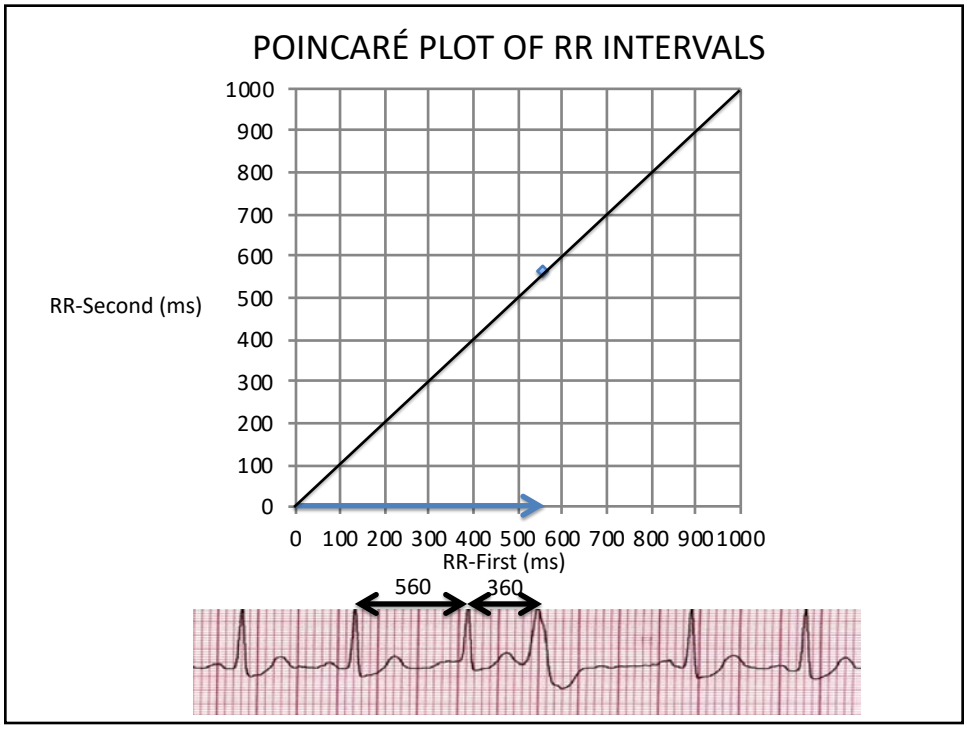
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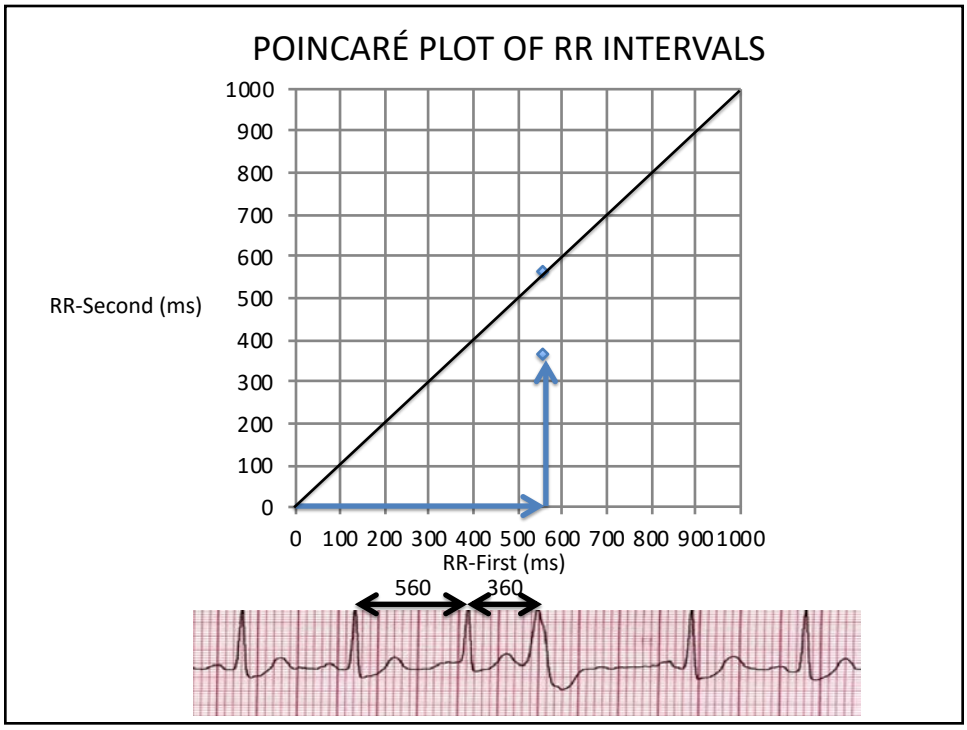
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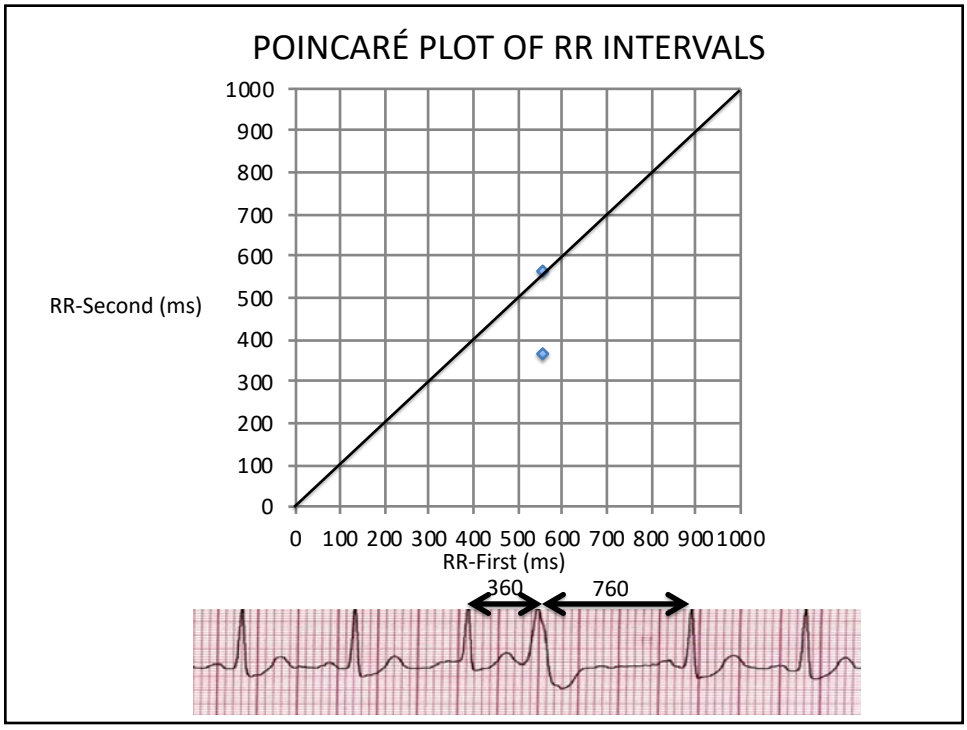
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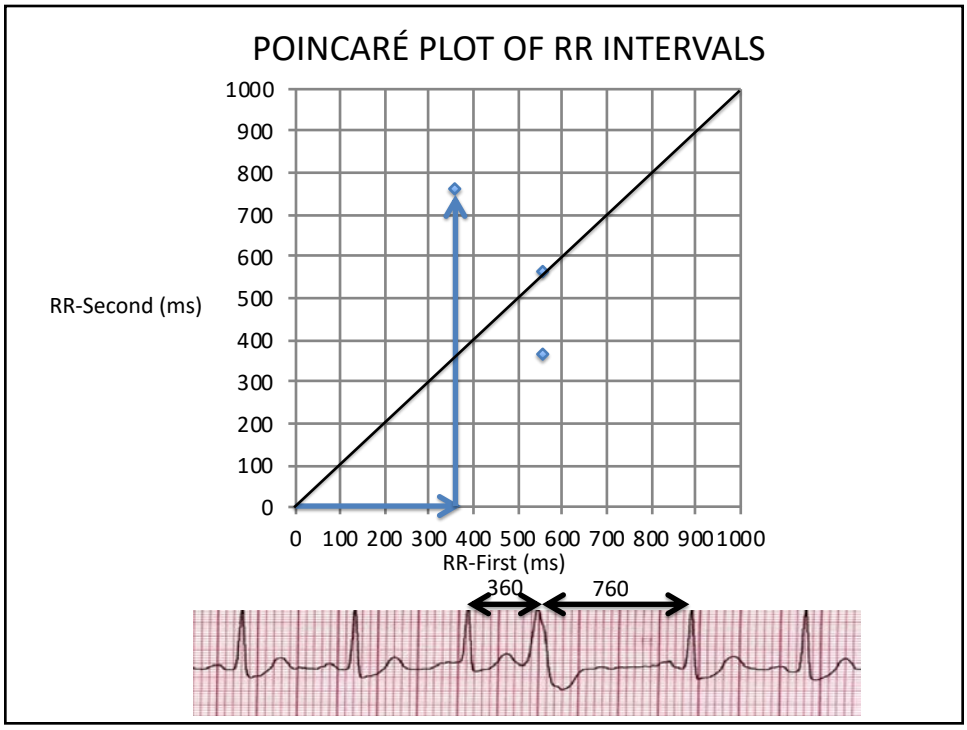
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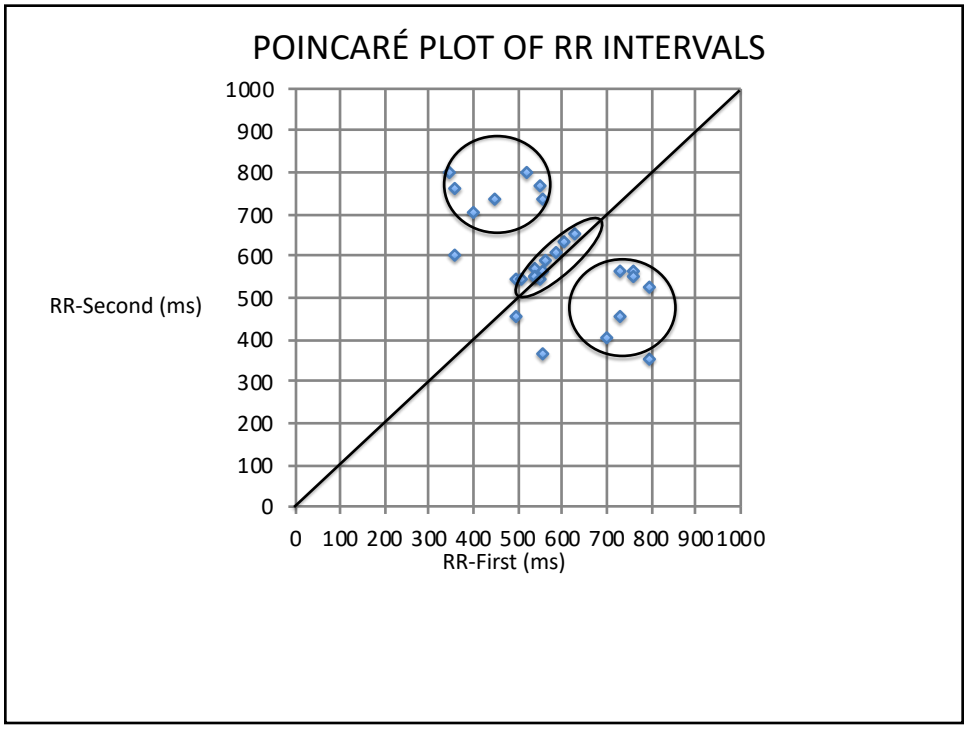
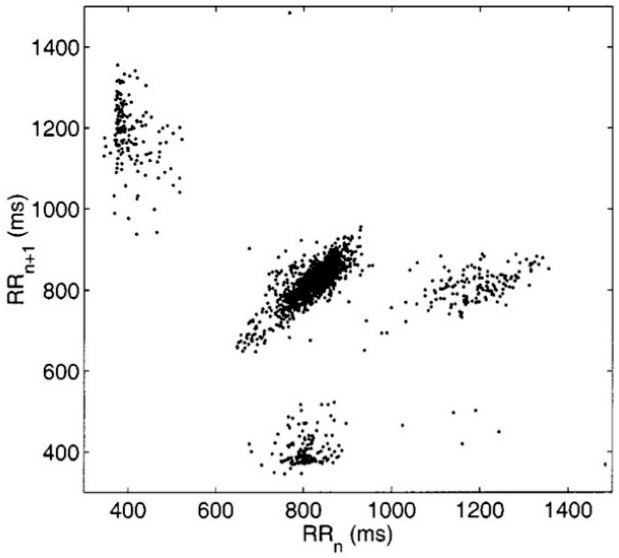
360
760


POINCARÉ PLOT OF RR INTERVALS
RR-Second (ms)
1000
900
800
700
600
500
400
300
200
100
0
0 100 200 300 400 500 600 700 800 900 1000
RR-First (ms)

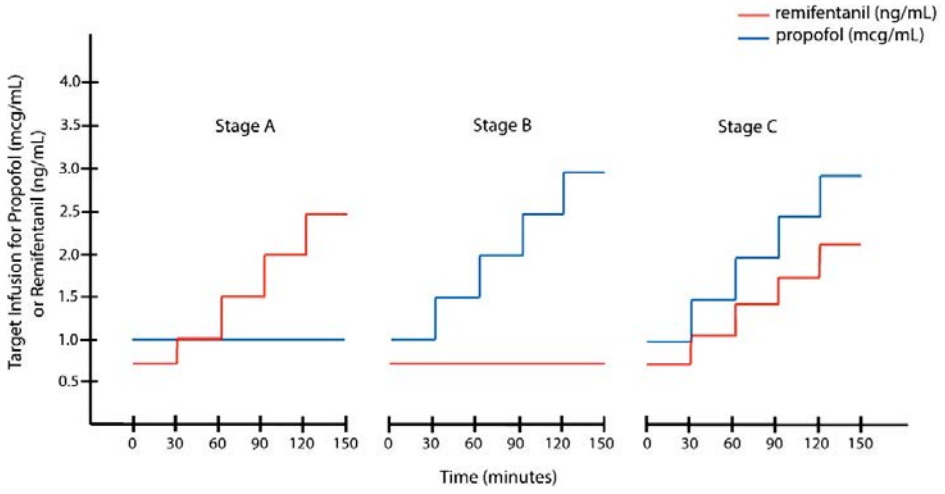
Do Existing Measures of Poincarè Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?

M. Brennan. IEEE Transactions on Biomedical Engineering. 2001;48:1342-1347.



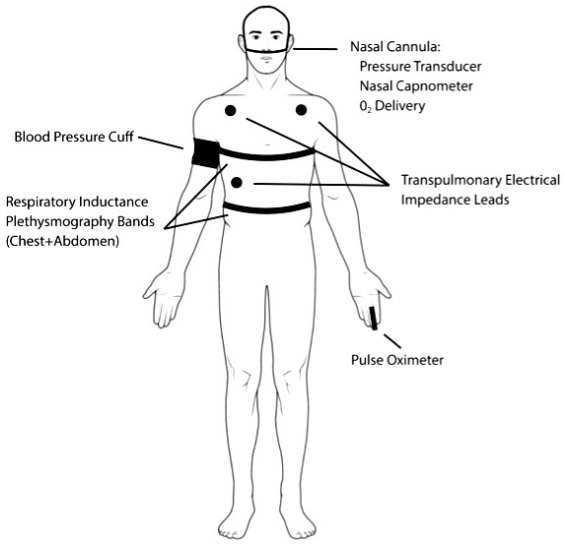
A computer based expert system to identify and quantify opioid induced ataxic breathing.

S. Ermer, RJ Farney, L Brewer



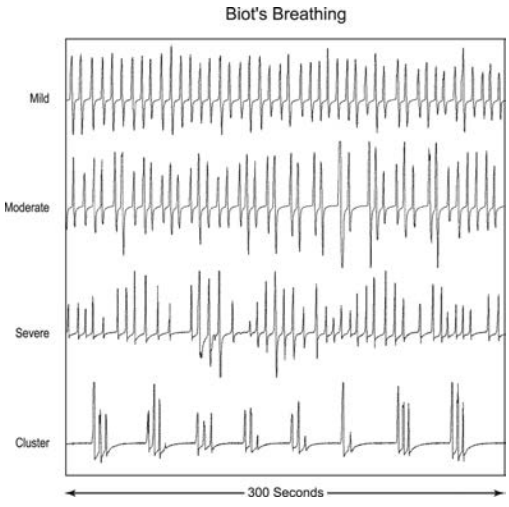
Comparison of seven different sensors for detecting low respiratory rates using a single breath detection algorithm in non-intubated, sedated volunteers.

S Ermer, L Brewer, J Orr et al. Anesth Analg 2018 in press



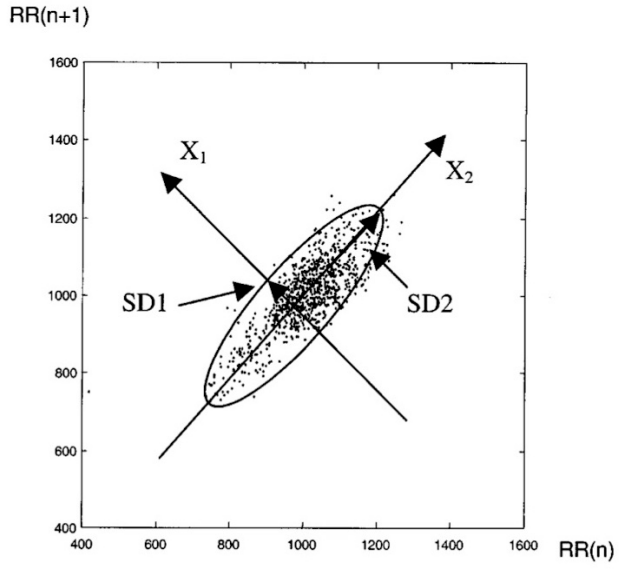
Adaptive Servoventilation (ASV) in Patients with Sleep Disordered Breathing Associated with Chronic Opioid Medications for Non-Malignant Pain.

RJ Farney J Clin Sleep Med 2008;4(4):311-319

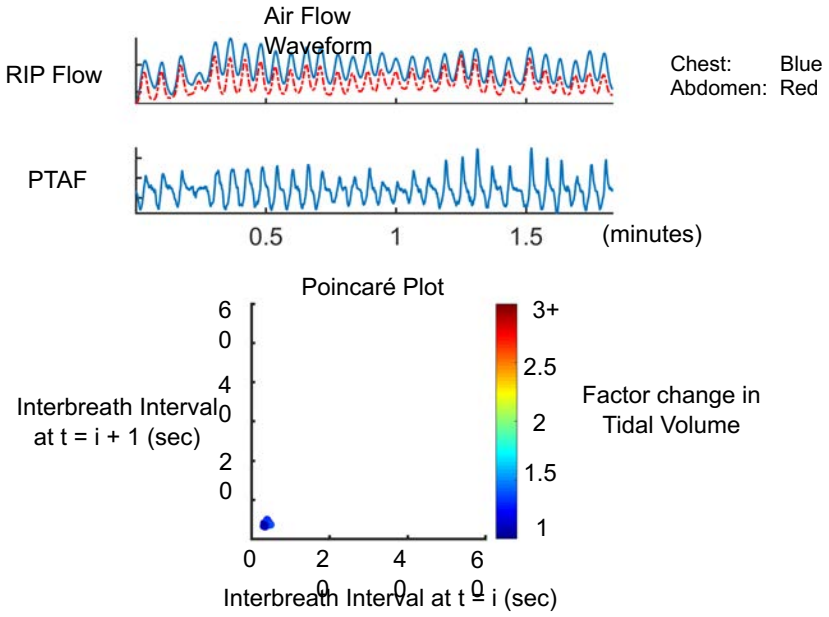


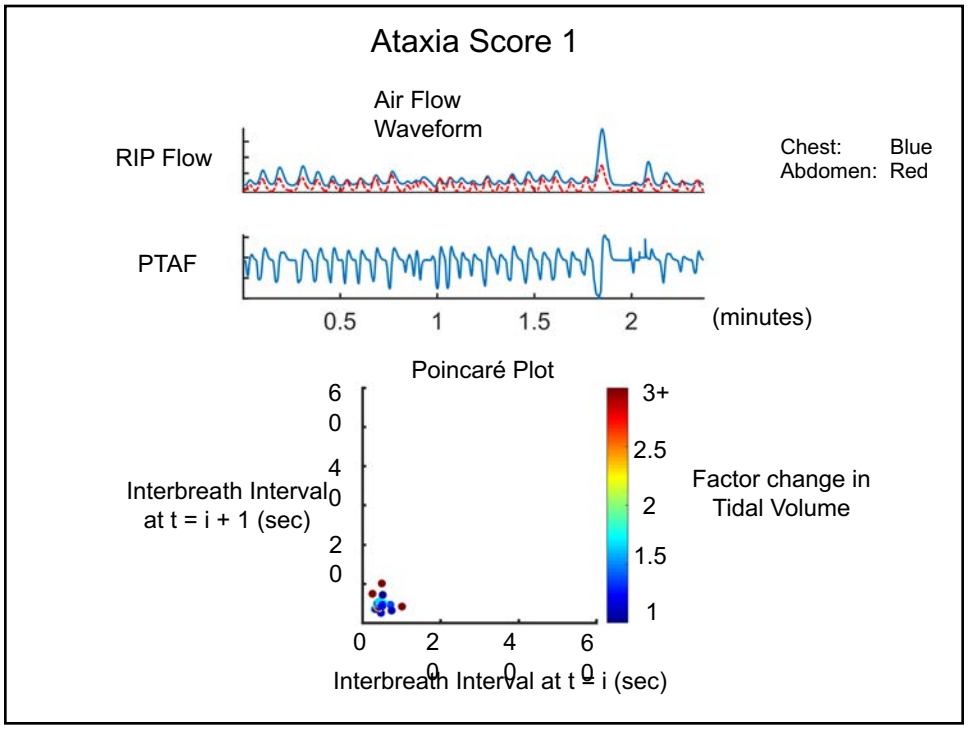
Do Existing Measures of Poincaré Plot Geometry Reflect Nonlinear Features of Heart Rate Variability?

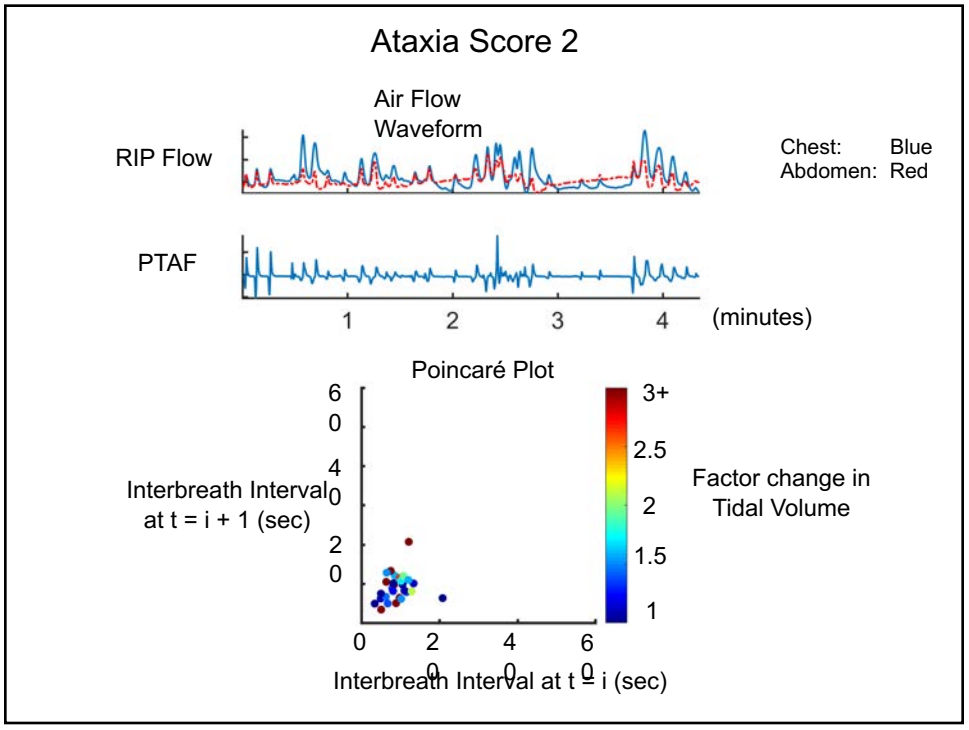
M. Brennan. IEEE Transactions on Biomedical Engineering. 2001;48:1342-1347.



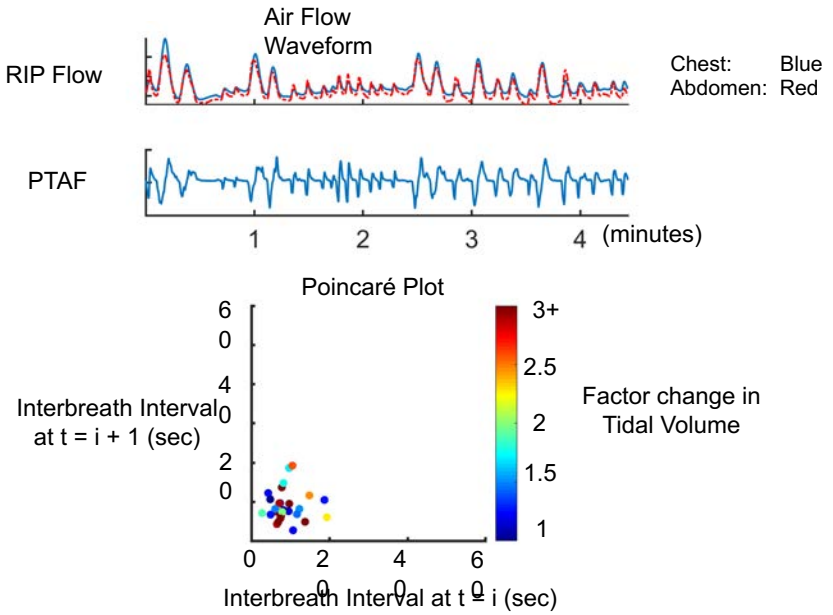
Ataxia Score 0



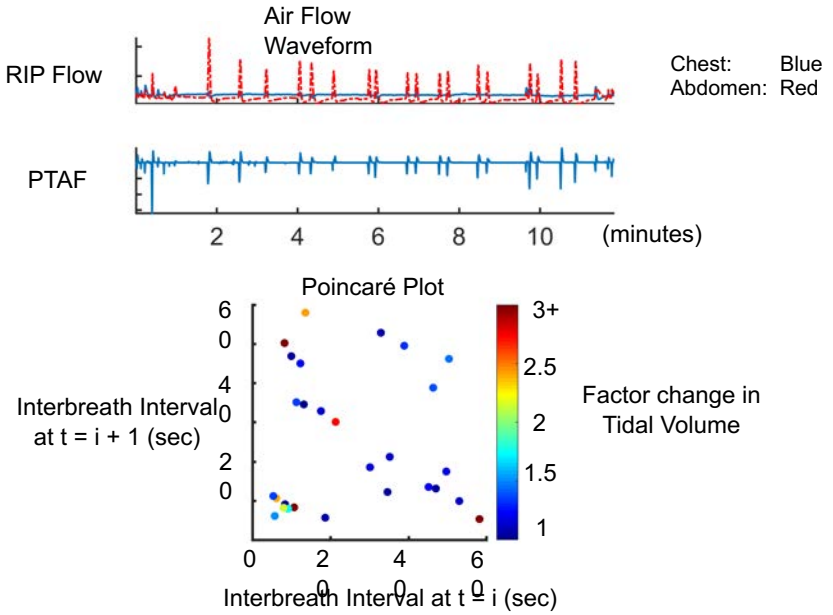

Ataxia Score 1
Air Flow Waveform
RIP Flow
Chest: Blue
Abdomen: Red
PTAF
0.5
1
1.5
2
(minutes)
Poincaré Plot
Interbreath Interval at t = i + 1 (sec)
Factor change in Tidal Volume
3+
2.5
2
1.5
1
Interbreath Interval at t = i (sec)

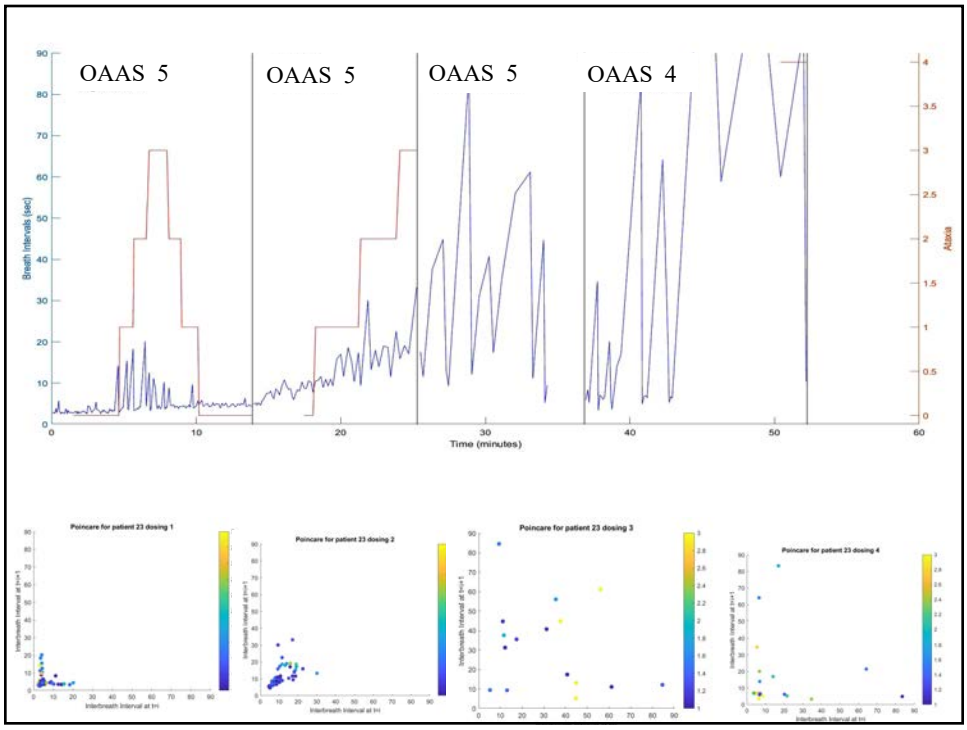

Ataxia Score 2
Air Flow Waveform
RIP Flow
Chest: Blue
Abdomen: Red
PTAF
1
2
3
4
(minutes)
Poincaré Plot
Interbreath Interval at t = i + 1 (sec)
Factor change in Tidal Volume
3+
2.5
2
1.5
1
Interbreath Interval at t = i (sec)

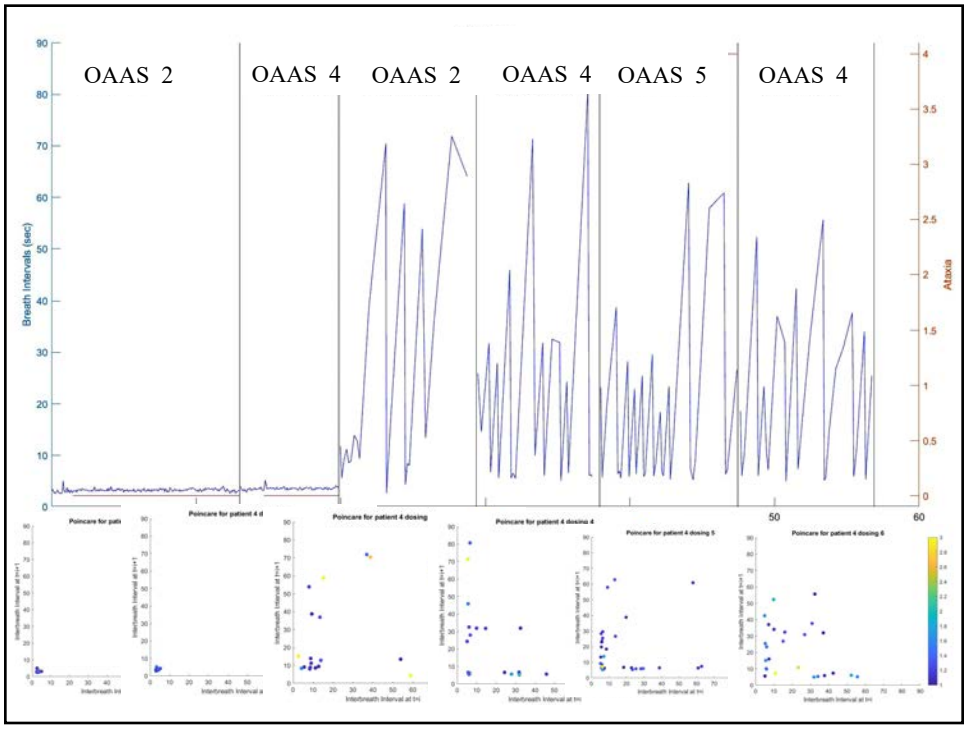
Ataxia Score 3



Ataxia Score 4




OAAS 5
OAAS 5
OAAS 5
OAAS 4
Breath Intervals (sec)
Ataxia
Time (minutes)
Poincare for patient 23 dosing 1
Poincare for patient 23 dosing 2
Poincare for patient 23 dosing 3
Poincare for patient 23 dosing 4


OAAS 2
OAAS 4
OAAS 2
OAAS 4
OAAS 5
OAAS 4
Breath Intervals (sec)
Ataxia
Poincare for patient 4 dosing
Poincare for patient 4 dosing 5
Poincare for patient 4 dosing 6

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