Biological Cost of the Depression of Consciousness

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Speaker Disclosure

I have received research grants from Masimo Corp.
Postoperative cognitive impairment at extremes of life and with critical illness in response to depth of sedation and anesthesia


BACKGROUND: Anesthetics induce widespread cell death, permanent neuronal deletion, and neurocognitive impairment in immature animals, raising substantial concerns about similar effects occurring in young children. Epidemiologic studies have been unable to sufficiently address this concern, in part due to reliance on group-administered achievement tests, inability to assess brain structure, and limited control for confounders.

METHODS: We compared healthy participants of a language development study at age 5 to 18 years who had undergone surgery with anesthesia before 4 years of age ($n = 53$) with unexposed peers ($n = 53$) who were matched for age, gender, handedness, and socioeconomic status. Neurocognitive assessments included the Oral and Written Language Scales and the Wechsler Intelligence Scales (WAIS) or WISC, as appropriate for age. Brain structural comparisons were conducted by using T1-weighted MRI scans.

RESULTS: Average test scores were within population norms, regardless of surgical history. However, compared with control subjects, previously exposed children scored significantly lower in listening comprehension and performance IQ. Exposure did not lead to gross elimination of gray matter in regions previously identified as vulnerable in animals. Decreased performance IQ and language comprehension, however, were associated with lower gray matter density in the occipital cortex and cerebellum.

CONCLUSIONS: The present findings suggest that general anesthesia for a surgical procedure in early childhood may be associated with long-term diminution of language abilities and cognition, as well as regional volumetric alterations in brain structure. Although causation remains unresolved, these findings nonetheless warrant additional research into the phenomenon’s mechanism and mitigating strategies.
Fig 1: Windows of Plasticity in Brain Development

Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality

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Abstract
Burst Suppression on Processed Electroencephalography as a Predictor of Postcoma Delirium in Mechanically Ventilated ICU Patients

Jennifer M. Andersen, MD; Timothy D. Girard, MD, MSCI; Pratik P. Pandharipande, MD, MSCI; Mario A. Davidson, PhD; E. Wesley Ely, MD, MPH; Paula L. Watson, MD

**Objectives:** Many patients, due to a combination of illness and sedatives, spend a considerable amount of time in a comatose state that can include time in burst suppression. We sought to determine if burst suppression measured by processed electroencephalography during coma in sedative-exposed patients is a predictor of post-coma delirium during critical illness.

**Design:** Observational convenience sample cohort.

**Setting:** Medical and surgical ICUs in a tertiary care medical center.

**Patients:** Cohort of 124 mechanically ventilated ICU patients.

**Interventions:** None.

**Measurements and Main Results:** Depth of sedation was monitored twice daily using the Richmond Agitation-Sedation Scale and continuously monitored by processed electroencephalography. When noncomatose, patients were assessed for delirium twice daily using Confusion Assessment Method for the ICU. Multiple logistic regression and Cox proportional hazards regression were used to assess associations between time in burst suppression and both prevalence and time to resolution of delirium, respectively, adjusting for time in deep sedation and a principal component score consisting of Acute Physiology and Chronic Health Evaluation II score and cumulative doses of sedatives while comatose. Of the 124 patients enrolled and monitored, 55 patients either never had coma or never emerged from coma, yielding 69 patients for whom we performed these analyses; 42 of these 69 (61%) had post-coma delirium. Most patients had burst suppression during coma, although often short-lived (median [interquartile range] time in burst suppression, 6.4 [1–58] min). After adjusting for covariates, even this short time in burst suppression independently predicted a higher prevalence of post-coma delirium (odds ratio, 4.16; 95% CI, 1.27–13.62; \( p = 0.02 \)) and a lower likelihood (delayed) resolution of delirium (hazard ratio, 0.78; 95% CI, 0.53–0.98; \( p = 0.04 \)).

**Conclusions:** Time in burst suppression during coma, as measured by processed electroencephalography, was an independent predictor of prevalence and time to resolution of postcoma/post-deep sedation delirium. These findings of this single-center investigation support lighter sedation strategies. (Crit Care Med 2014; 42:2244–2251)
Patients in medical and surgical ICUs are at a high risk for long-term cognitive impairment. A longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at 3 months (40%)(P=0.001) and 12 months (34%)(P=0.004)

- 40% equivalent to TBI
- 26% equivalent to mild Alzheimer’s
Causes of Neurologic Failure

- Trauma/Increasing ICP
- Circulatory shock
- Hypoxemia/Hypoperfusion/Vasospasm
- Infection
- Systemic inflammation
- Metabolic and endocrine imbalances
- Pharmacologic agents; ?benzodiazepines
Acute Brain Dysfunction During Critical Illness – Result of Inflammation Causing Endothelial Dysfunction
Hughes et al
“But what I see these days are sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise..... By being awake and alert...they could interact with family....feel human...sustain the zest for living which is a requirement for survival”
One Year Outcomes in Survivors of ARDS

- Functional limitations 1 year later
- Most patients have muscle wasting and weakness.
- Depression and memory dysfunction increased in ARDS survivors. Chest 2009;135:678
Over Sedation in ICU

- Excessive sustained alteration in consciousness
- Prolonged time on mechanical ventilation
- Increased ventilator associated pneumonia
- Increased prolonged muscular weakness
  - Annals of Intensive Care 2013, 3:24
Consciousness

- No consciousness meter

Consciousness:
  - I can see, hear, smell and spatially perceive objects
  - Awareness of surroundings, time, orientation.

- How can you measure it?
<table>
<thead>
<tr>
<th>#</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious and agitated or restless or both</td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responding to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Asleep, brisk response to stimuli*</td>
</tr>
<tr>
<td>5</td>
<td>Asleep, sluggish response to stimuli*</td>
</tr>
<tr>
<td>6</td>
<td>Asleep, no response to stimuli*</td>
</tr>
</tbody>
</table>

* light glabellar tap

Controlled Sedation with Alphaxalone-Alphadolone

M. A. E. RAMSAY, T. M. SAVEGE, B. R. J. SIMPSON, R. GOODWIN

*British Medical Journal, 1974, 2, 656-659*

**Summary**

Alphaxalone-alphadolone (Althesin), diluted and administered as a controlled infusion, was used as a sedative for 30 patients in an intensive therapy unit. This technique allowed rapid and accurate control of the level of sedation. It had three particularly useful applications: it provided "light sleep," allowed rapid variation in the level of sedation, and enabled repeated assessment of the central nervous system.

Sedation was satisfactory for 86% of the total time, and no serious complications were attributed to the use of the drug. Furthermore, though alphaxalone-alphadolone was given for periods up to 20 days there was no evidence of tachyphylaxis or delay in recovery time.

**Method**

Thirty patients were selected on the sole ground that controlled sedation was required. They were all being treated in the intensive therapy unit, where continuous monitoring of vital signs could be undertaken by nurses at the bedside. The only patients excluded were those with gross hepatic failure. The following technique was used: a separate infusion was set up containing alphaxalone-alphadolone. A burette was included in the infusion set and 5 ml of the drug was added to 25 ml of 5% dextrose. The maximum dose of alphaxalone-alphadolone that could be given was thus 5 ml. The concentration of alphaxalone-alphadolone was increased if a restricted fluid intake required this. The infusion rate was controlled by an Ivac infusion pump. Occasionally it was necessary to give 2 ml undiluted alphaxalone-alphadolone to gain initial control in very restless patients. Six levels of sedation were formulated; three with the patient awake and three with the patient asleep.

 Awake levels were: 1, patient anxious and agitated or restless or both; 2, patient co-operative, orientated, and tranquil; 3,
Richmond Agitation Sedation Scale (RASS)

<table>
<thead>
<tr>
<th>Score</th>
<th>State</th>
<th>State Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 4</td>
<td>+ 3</td>
<td>+ 2</td>
</tr>
<tr>
<td></td>
<td>Combative</td>
<td>Very agitated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitated</td>
</tr>
<tr>
<td></td>
<td>+ 1</td>
<td>Restless</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>eye contact &gt; 10 sec</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>eye contact &lt; 10 sec</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>no eye contact</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>no response even with physical stimulation</td>
</tr>
</tbody>
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Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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Pain and Analgesia

• Pain is common in ICU patients

• Assessment should be routine (+1B)

• These are the most valid and reliable tools if patient unable to self-report:
  • The Behavioral Pain Scale (BPS) (B)
  • Critical Care Observation Tool (CPOT) (B)
Treatment of Pain

- **Multimodal**
  - **Pharmacological & non-pharmacological** (music, massage, sleep)
  - **Opioids** – 1\textsuperscript{st} line for non-neuropathic pain
    - All available IV opioids titrated to similar pain intensity endpoints equally effective
    - Use non-opioids to limit side effects of opioids
    - NSAIDs acetaminophen, ibuprofen – renal/liver function, risk bleed???
    - **Dexmedetomidine** reduce need for opioids

- **Neuropathic Pain:** Enteral gabapentin or carbamazepine in addition to IV opioids

- **Consider regional** – LA +/- opioids
  - Check coagulation
  - Clear neuraxial spine
  - Monitor volume status carefully
Agitation & Sedation

- Monitor for depth of sedation
  - Use protocols for monitoring, reassess regularly

- Richmond agitation sedation scale (RASS) & Sedation-Agitation Scale (SAS) most valid & reliable scales for assessing quality & Depth of Sedation:
  Recommend objective measures of brain function (BIS, Sedline (PSI), SE, AEP, & NI) as 1st method to monitor Depth of Sedation in comatose and/or paralyzed patients. Monitor EEG for non-convulsive seizure activity
Sedation

• Controlled **lighter sedation** better than deeper sedation unless clinically contraindicated

• Maintain **cognitive function**
  • Shorter length mechanical ventilation, LOS in ICU and hospital
Delirium

• Routinely monitor for delirium

• Confusion Assessment Method in the ICU (CAM-ICU)

• Intensive Care Delirium Screening Checklist (ICDSC)
  • most valid & reliable delirium monitoring tools
  • Quick & reliable
DELIRIUM – Prevention & Treatment

- Early mobilization as able

- No clear cut pharmacological agent or protocol appears to prevent delirium
  - Haloperidol, atypical antipsychotics, **DO NOT** appear to prevent delirium
  - Dexmedetomidine and atypical antipsychotics may shorten the duration of delirium
  - No evidence of efficacy for haloperidol

- BZ use may be a risk factor for delirium

- Conflicting data on risk of various opioids
Strategy

- Whole-body rehabilitation “Animation” with a highly coordinated, multidisciplinary team implementing:
  - Co-operative sedation
  - Spontaneous breathing trials
  - Good Analgesia
  - Physical and occupational therapy

- RESULTS IN: Superior functional and cognitive patient outcomes

WD Schweickert, MC Pohlman, AS Pohlman et al
LANCET 2009;373:1874-82
## Daily Wake-up Study: Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Wake-up Group</th>
<th>Standard of Care Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical ventilation duration (days)</strong></td>
<td>4.9 (2.5-8.6)</td>
<td>7.3 (3.4-16.1)</td>
</tr>
<tr>
<td><strong>ICU LOS (days)</strong></td>
<td>6.4 (3.9-12.0)</td>
<td>9.9 (4.7-17.9)</td>
</tr>
</tbody>
</table>

*P=.004. †P=.02

Girard TD, et al. ABC Trial
The Lancet 2008; 371 126-134

- Daily Awakening Sedation combined with Spontaneous Breathing Trial

- Adding Respiratory Therapy to Sedation Team

- ↓ duration of MV; ↓ ICU & Hosp LOS; Improved 1 year mortality
ICU SEDATION TEAM

RN

Patient

MD
ICU SEDATION TEAM

Patient

RN

MD

RPh
ICU SEDATION TEAM

Patient

- RN
- PT/OT
- RPh
- RT
- MD
The Animated ICU

- Minimize neuromuscular blockade
- Sedation strategies to avoid accumulation and prolonged effects
- Early physical therapy
- Reduce/avoid opiate therapies
- Dexmedetomidine allows interactive safe comfortable care in many patients
Analgesia with cognitive sedation

- Patients should be in the COMFORT ZONE
- Protect the brain and the mind
- Aim for early extubation, mobilization and conversation
- ANALGOSEDATION without coma or delirium
Cognitive ICU
Religiosity Associated with Prolonged Survival in Liver Transplant Recipients

Franco Bonaguidi, Claudio Michelassi, Franco Filipponi, and Daniele Rovai

1Institute of Clinical Physiology, National Research Council, Pisa, Italy; and 2Liver Transplant Unit, University of Pisa, Cisanello Hospital, Pisa, Italy
Figure 1. Kaplan-Meier survival curves for patients undergoing liver transplantation.
The Effect of a Positive Affect

- In severe illness a positive affect is related to survival in a dose-response pattern.

- Positive affect can be considered a resource for medium-term survival

Baylor Sedation Strategies

- **Comfort, Calm and Co-operative:**
  - Dexmedetomidine 0.2 – 1.4 mcgs/kg.h plus low dose fentanyl. Titrate to RSS 2-3

- **Moderate Sedation:** Propofol up to 50 mcgs/kg/min. Titrate to RSS 3-4. Plus fentanyl

- **Deep Sedation:** Fentanyl and midazolam infusion and SedLine Root monitoring and titrate to RSS 5-6
Pitfall of Pulse Oximetry

The pulse oximeter is a LATE detector of respiratory depression if supplemental oxygen is being administered.
Patient 8 hours postop in ICU, sitting in chair with nasal cannula O₂ at 3l/min. RN in room documenting on computer Rounded on patient and RN says “she is doing well O₂ sat 98%”
I found her unresponsive and RR 4.

- pH 6.86
- pCO2 148
- pO2 202
- HCO3 25
- O2 Sat 98%
Respiratory rate: the neglected vital sign

Michelle A Cretikos, Rinaldo Bellomo, Ken Hillman, Jack Chen, Simon Finfer and Arthas Flabouris

Recording a full set of vital signs (pulse rate, blood pressure, respiratory rate and temperature) at least daily is considered standard for monitoring patients on acute hospital wards. However, two recent multicentre studies found that the level of documentation of vital signs in many hospitals is poor.1,2 Of the four vital signs, respiratory rate, in particular, is often not recorded, even when the patient's primary problem is a respiratory condition.2-6 This is in spite of the fact that an abnormal respiratory rate has been shown to be an important predictor of serious events such as cardiac arrest and admission to an intensive care unit (ICU).3,7-10

**Respiratory rate as an indicator of serious illness**

In 1993, Fieselmann and colleagues reported that a respiratory

**ABSTRACT**

- The level of documentation of vital signs in many hospitals is extremely poor, and respiratory rate, in particular, is often not recorded.
- There is substantial evidence that an abnormal respiratory rate is a predictor of potentially serious clinical events.
- Nurses and doctors need to be more aware of the importance of an abnormal respiratory rate as a marker of serious illness.
- Hospital systems that encourage appropriate responses to an elevated respiratory rate and other abnormal vital signs can be rapidly implemented. Such systems help to raise and sustain awareness of the importance of vital signs.

MJA 2008; 188: 657–659
Current Respiration Rate Methods

- Physical assessment (intermittent)
- Transthoracic impedance (continuous)
  - Requires monitor and ECG electrodes
  - As chest expands impedance changes
  - Respiration rate measured from cyclical changes in impedance
  - Cannot differentiate PARADOXICAL breathing with no air movement
- Capnography (continuous)
  - Direct monitoring of the inhaled and exhaled concentration or partial pressure of CO2 using sensor mask or nasal cannula
  - Respiration rate measured by CO2 waveform analysis
  - Shape of waveform can provide additional information
  - Hypoventilation may result in LOW EtCO2 because of poor alveolar exchange
Human Observation

- Intermittent
- Cannot be audited
- Should assess: Respiratory Rate; Pattern; Depth; Quality
- Difficult to distinguish CO2 narcosis from natural sleep
Transthoracic Impedance Plethysmography

- The changing air volumes in the lungs alter thoracic impedance.
- Continuous monitor of respiratory rate
- Historically has been limited in detecting obstructed breathing
- Newer technology is more sensitive and more accurate and measures TV, MV and RR. Voscopoulos et al. Anesth Analg 2013;117:91–100)
Airflow Sensors

- **Sensors**: can detect airflow as expired air is warmer more humid and contains carbon dioxide.

- **Temperature**: Real-time infrared thermography. In the neonate respiration was monitored based on a 0.3 degree C to 0.5 degree C temperature difference between inspiration and expiration. Abbas et al. Biomed Eng Online 2011:10:93.

- **Humidity**: A miniature optical humidity sensor is placed on a face mask and measures water vapor of exhaled air. Mathew et al. Biomed Opt Express 2012;3:3325
Photoplethysmography Derived Respiratory Rate $\text{RR}_\text{oxi}$

- Continuous monitoring of respiratory rate, SpO2 and pulse rate.
- Derives respiratory rate from the variability in baseline of the plethysmogram
- The pleth variability index can predict fluid responsiveness in the mechanically ventilated patient
- Sensitive to movement artifacts and vasoconstriction
- Obstructed airflow affects pleth signal does this affect rate calculation?
Capnography measures ventilation and provides a graphical waveform available for interpretation.
Small pin holes deliver pillow of oxygen around both nose and mouth.

Uni-Junction™ of sampling ports prevents dilution from non-breathing source.

Increased surface area provides greater sampling accuracy in the presence of low tidal volume.

Figure 3. CO₂ sampling/O₂ delivery for non-intubated patients. Source: Oridion Capnography, Inc., Needham, MA. Used with permission.
Acoustic Respiration Rate (RRa)
Accurate > Easy-to-Use > Patient-Tolerant

When used with other clinical variables, first-ever continuous and noninvasive monitoring of acoustic respiration rate (RRa) may help clinicians assess respiratory status and help determine treatment options.
The Accuracy, Precision and Reliability of Measuring Ventilatory Rate and Detecting Ventilatory Pause by Rainbow Acoustic Monitoring and Capnometry

Michael A. E. Ramsay, MD,* Mohammad Usman, PhD,† Elaine Lagow, RN,† Minerva Mendoza, RN,§ Emylene Untalan, RN,§ and Edward De Vol, PhD‖

BACKGROUND: Current methods for monitoring ventilatory rate have limitations including poor accuracy and precision and low patient tolerance. In this study, we evaluated a new acoustic ventilatory rate monitoring technology for accuracy, precision, reliability, and the ability to detect pauses in ventilation, relative to capnometry and a reference method in postsurgical patients.

METHODS: Adult patients presenting to the postanesthesia care unit were connected to a Pulse CO-Oximeter with acoustic monitoring technology (Rad-87, version 7804, Masimo, Irvine, CA) through an adhesive bioacoustic sensor (RAS-125, rev C) applied to the neck. Each subject also wore a nasal cannula connected to a bedside capnometer (Capnostream20, version 4.5, Oridion, Needham, MA). The acoustic monitor and capnometer were connected to a computer for continuous acoustic and inspiratory carbon dioxide waveform recordings. Recordings were retrospectively analyzed by a trained technician in a setting that allowed for the simultaneous viewing of both waveforms while listening to the breathing sounds from the acoustic signal to determine inspiration and expiration reference markers within the ventilatory cycle without using the acoustic monitor- or capnometer-calculated ventilatory rate. This allowed the automatic calculation of a reference ventilatory rate for each device through a software program (TagEditor, Masimo). Accuracy (relative to the respective reference) and precision of each device were estimated and compared with each other. Sensitivity for detection of pauses in ventilation, defined as no inspiration or expiration activity in the reference ventilatory cycle for ≥30 seconds, was also determined. The devices were also evaluated for their reliability, i.e., the percentage of the time when each displayed a value and did not drop a measurement.

RESULTS: Thirty-three adults (73% female) with age of 45 ± 14 years and weight 117 ± 42 kg were enrolled. A total of 3712 minutes of monitoring time (average 112 minutes per subject) were analyzed across the 2 devices, reference ventilatory rates ranged from 1.9 to 49.1 bpm. Acoustic monitoring showed significantly greater accuracy ($P = 0.0056$) and precision ($P = 0.0024$) for respiratory rate as compared with capnometry. On average, both devices displayed data over 97% of the monitored time. The (0.95, 0.95) lower tolerance limits for the acoustic monitor and capnometer were 94% and 84%, respectively. Acoustic monitoring was marginally more sensitive ($P = 0.0481$) to pauses in ventilation (81% vs 62%) in 21 apneic events.

CONCLUSIONS: In this study of a population of postsurgical patients, the acoustic monitor and capnometer both reliably monitored ventilatory rate. The acoustic monitor was statistically more accurate and more precise than the capnometer, but differences in performance were modest. It is not known whether the observed differences are clinically significant. The acoustic monitor was more sensitive to detecting pauses in ventilation. Acoustic monitoring may provide an effective and convenient means of monitoring ventilatory rate in postsurgical patients. (Anesth Analg 2013;117:69–75)
Snore Out

Inspiration
Expiration
SnoreOut

Capno CO2 Waveform

SnoreOut

Capno
Breathing is Good!
Thanks for your attention