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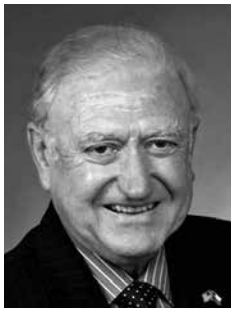
Biological cost of the depression of consciousness



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Abstract

The care of the brain and protection of cognitive function are critical aspects of our management of patients that are admitted to the intensive care unit or undergo general anesthesia and surgery. The depth of consciousness is frequently altered in an effort to make the patient comfortable during an unpleasant episode or procedure. This alteration in consciousness is often not controlled and patients maybe taken to very deep levels of unconsciousness or even coma and when returned to the conscious state are found to have acute brain dysfunction as exhibited by delirium and cognitive impairment. This may be compounded by the effects of sepsis and the inflammation of surgery and trauma causing endothelial dysfunction in the cerebral microcirculation. To prevent these deleterious effects on cognition, some of which maybe permanent, lighter controlled sedation with good analgesia is now being recommended in the intensive care unit. The concept of the "animated ICU" is being put forward, where the patient maintains cognitive function and is mobilized when feasible. When deeper levels of sedation or anesthesia are required brain function monitors that display the electroencephalogram pattern may control the depth of unconsciousness. Innovative new therapies are being investigated to protect the brain from inflammation and the developing brain from potentially neurotoxic anesthetic agents. The cognitive mind is the most vital asset that we have and must be closely protected from impairment. *Anestezjologia i Ratownictwo 2013; 7: 312-317.*

Keywords: sedation, intensive care unit, acute brain dysfunction, consciousness, brain monitoring

The body when asleep has no perception; but the soul when awake has cognizance of all things, sees what is visible, what is audible, walks, touches, feels pain, ponders. In a word, all the functions of the body and of soul are performed by the soul during sleep.
Hippocrates, "Dreams" [1]

The proper management of sedation in the critical care unit has always been challenging. Forty years ago most patients that required mechanical ventilation for life support during a critical illness were maintained in a paralyzed and comatose state. Frequently the physician would simply order the nurse to paralyze and ventilate and leave it to the nurse to manage sedation and analgesia. In most incidences this was managed by the administration of a long acting neuromuscular blocking agent together with large doses of morphine and diazepam. Occasionally too little sedation and analgesia were administered and this resulted in a terrified patient, who if recovered, experienced the development of posttraumatic shock disorder. When these patients recovered from their critical illness the return to functional consciousness and weaning from ventilator support was very long. These patients were followed up and many months later close family members would say, "Dad was not quite the same". Some

cognitive interaction problems were often recognized. Whether this was the result of the illness or the sedation was not known. As well as cognition problems many survivors of a critical illness also developed musculoskeletal issues from the prolonged time of immobility. Clearly we good to better! The late Tom Petty gave a vivid description of the current state of patients in critical care units.

> *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.*
> Petty TL. Suspended Life or Extending Death? [2]

The routine use of muscle relaxants was questioned and the focus moved to patient comfort and good analgesia. To try and address the sedation management in the nonparalyzed patient the first sedation scoring scale was developed [3] (table I). The aim was to tightly control the depth of sedation, let all the caregivers know where this level should be and titrate the drugs to achieve this level. The goal was to reduce the morbidity associated with chemical coma and to reduce the recovery time for the patient.

Table I. The Ramsay Sedation Scale

1	Anxious and agitated or restless or both
2	Cooperative, oriented, and tranquil
3	Responding to commands only
4	Asleep, brisk response to stimuli*
5	Asleep, sluggish response to stimuli*
6	Asleep, no response to stimuli*

* light glabellar tap
Ramsay, et al. *Brit Med J*. 1974; 2(920):656-659.

We found that survivors of acute respiratory distress syndrome continue to have functional limitations one year after their discharge from ICU [4]. The under-recognized consequence of immobility caused by critical illness includes major physical and neuropsychological sequelae. The physical effects include muscle wasting, entrapment neuropathy, peripheral nerve injury heterotopic ossification, contractures, alopecia, voice changes and chronic pain. The neuropsychological changes include delirium, cognitive dysfunction, anxiety, and depression, post-traumatic stress disorder, panic attack disorder and sleep problems [5].

The next major step in the measurement of sedation came when Riker recognized that agitation was associated with a poor outcome. He developed a scale that measured the degree of agitation as well as sedation: The Sedation Agitation Scale (table II).

Then The Richmond Agitation Sedation Scale was developed, a more reliable and validated tool (table III).

This was followed by the introduction of daily "sedation vacations", where appropriate, and this resulted with improved outcomes [6]. After this more aggressive interventions were developed. These were all based on having periods of time when the patient was allowed to be responsive and also given tasks to perform. This initially involved awakening the patient and performing spontaneously breathing trials [7]. Then trials with a team of medical personnel including occupational and respiratory therapy [8]. Patients on mechanical ventilation were given physical therapy and mobilized when possible. Again this appears to have improved outcomes and shortened stays in the intensive care ward and the hospital [9,10].

Now a group in Denmark has just reported on a pilot study where critically ill patients were given no sedation at all but were given good analgesia. Again in this trial outcomes as measured by length of stay in the ICU and the hospital were improved. No Sedation: *No sedation of critically ill patients receiving mechanical ventilation is associated with an increase in days without ventilation, a shorter stay in ICU and shorter stay in hospital* [11].

However the no sedation group had a 20% incidence of agitated delirium compared to 7% in the control group. Also this study group required the presence of an extra person at their bedside to comfort and reassure them.

Good *analgesia first* as opposed to *sedation first,* may provide the optimal comfort zone for the critically ill patient requiring mechanical ventilation [12].

Analgosedation techniques were indeed the first techniques described by Hippocrates and may improve outcomes today.

Perhaps what we are really learning is the value of the cognitive mind in overcoming life-threatening illness [13]. Another group were able to demonstrate the power of 'religiosity', the belief in a god, with improved survival in liver transplant recipients [14].

Delirium has been demonstrated in several studies to be an indicator of increased morbidity and mortality for the ICU patient.

Table II. The Riker Sedation Agitation Scale

Score	Description	Example
7	Dangerous agitation	Pulling at tubes and catheters; striking staff
6	Very agitated	Does not calm to voice; needs physical restraints
5	Agitated	Anxious; calms to voice
4	Calm and cooperative	Relaxed; follows commands
3	Sedated	Awakens to verbal stimuli
2	Very sedated	Arouses with physical stimuli
1	Unarousable	No response to noxious stimuli

Table III. The Richmond Agitation Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to Staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening
-2	Light sedation	Briefly awakens with eye contact to voice
-3	Moderate sedation	Response to voice but no eye contact
-4	Deep sedation	No response to voice; response to physical stimulation
-5	Unrousable	No response to verbal or physical stimulation

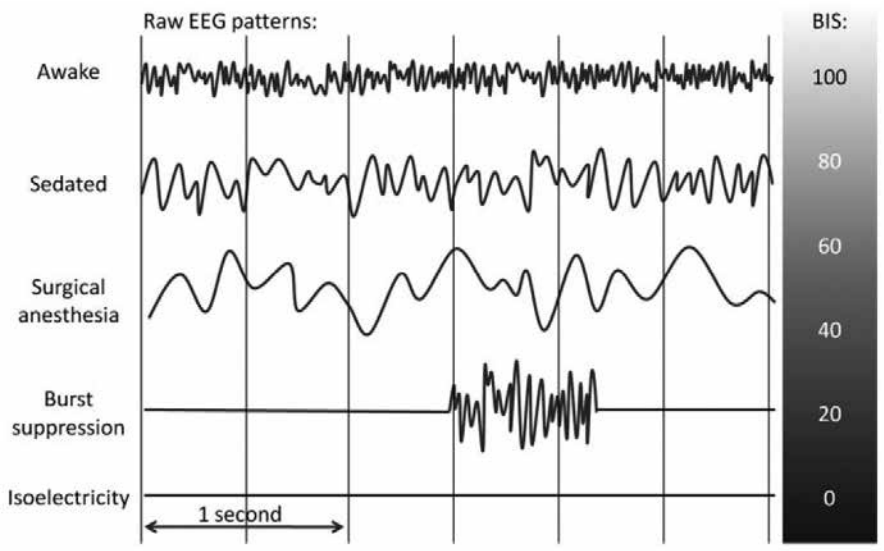

Figure 1. Representative electroencephalogram (EEG) patterns at different stages of anaesthesia as described in the text

Certainly the advantages of the "animated" critical care protocol would appear to be faster and improved recovery of critically ill patients. We now need to do the psychological tests to look for untoward sequelae such as posttraumatic stress disorder.

The Society of Critical Care Medicine developed new guidelines in 2013 for the management of pain, agitation and delirium [15]. The conclusions recommended lighter sedation with good analgesia and maintain cognitive function when possible. The rec-

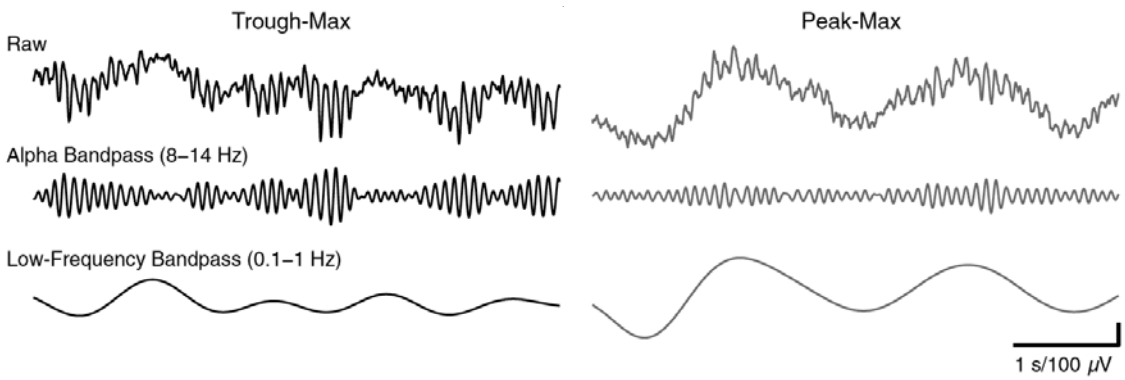

Figure 2. The trough-max pattern observed in the time-domain EEG trace of an individual subject and the peak-max pattern observed in the time-domain EEG trace of an individual subject

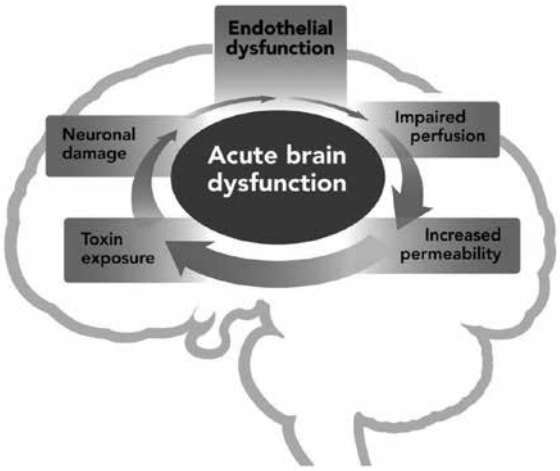

Figure 3. Acute brain dysfunction during critical illness – result of inflammation causing endothelial dysfunction

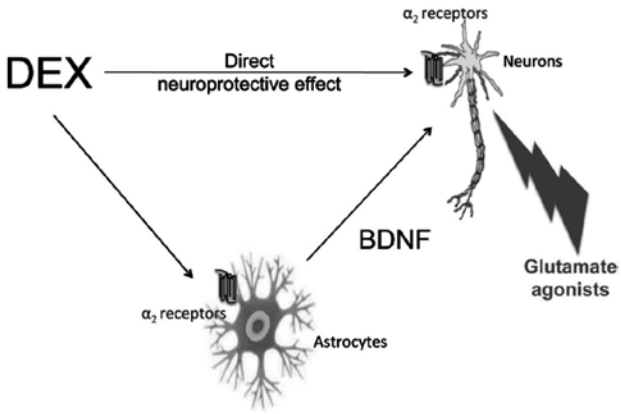

Figure 4. Schematic representation of the direct and indirect neuroprotective effect of dexmedetomidine
BDNF = Brain-derived Neurotrophic Factor
DEX = Dexmedetomidine

ommendations also included the use of brain function monitors when sedation scores could not be used or when non-convulsive seizure activity was suspected. The electroencephalographic (EEG) pattern is more valuable than the calculated index that many commercial companies have developed. The basic patterns of awake, asleep and coma are very easily identified [16]. More recently it has been demonstrated that if the EEG pattern is converted to sound – electroencephalophone - it can facilitate identifying depth of anaesthesia [17].

On close examination of the EEG signal the transition from awake to asleep and asleep can clearly be differentiated from that of a patient deeply asleep [18]. The position of the waves in the trough or on the peak of a large wave creates the signature (figure 2).

Postoperative cognitive disorders are a growing concern especially in the elderly. The elderly patient is frequently taken to burst suppression levels of anaesthesia by the same amount of drug that would keep a younger patient to a much lighter level [19]. Reducing anaesthesia exposure by titrating drug dosing based on real-time EEG monitoring may help reduce the incidence of postoperative cognitive disorders [20].

Acute brain dysfunction during critical illness is prevalent and may be the result of sepsis induced endothelial dysfunction [21] (figure 3). Therefore the use of brain dysfunction monitoring such as the Confusion Assessment Method for ICU are essential. Postoperative cognitive impairment had also been shown in the animal model to be related to the inflammation of surgery and can be prevented by the use of powerful inflammatory cytokine blockers [22-24].

There has been some evidence that patients receiving dexmedetomidine for ICU sedation experience less delirium than other patients [25,26]. Recently the anti-inflammatory action and brain protection effects of dexmedetomidine have been demonstrated [27,28] (figure 4).

The biological cost of the depression of consciousness maybe very significant. At a young age when the brain is developing anaesthetic drugs may inhibit development of neurons and even cause neuroapoptosis [29]. At all ages the brain is vulnerable during the perioperative period and may exhibit emergence delirium, postoperative delirium or postoperative cognitive decline [30]. At older age groups this maybe more severe and result in a permanent cognitive impairment. Therefore it is imperative that we monitor the brain and develop protective measures to prevent these catastrophic events.

Conflict of interest
None

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