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The Unbearableness of Being Light

Bradley A. Fritz, MD,

Thaddeus P. Budelier, MD, MSF,

Arbi Ben Abdallah, DES, PhD,

Michael S. Avidan, MBBCh

Department of Anesthesiology, Washington University School of Medicine, St Louis, Missouri.

> Sometimes you make up your mind about something without knowing why, and your decision persists by the power of inertia. Every year it gets harder to change.
>
> —Milan Kundera, *The Unbearable Lightness of Being*

A fundamental goal of general anesthesia is to ensure that patients who are subjected to the noxious trespass of invasive procedures are unconscious of their environment and are not experiencing the pain of surgery or the distress of drug-induced immobility. Thus, a core tenet for anesthesiologists has always been to ensure that our patients are sufficiently "deep." However, in recent years, this notion has been challenged. This is exemplified by a narrative review of anesthetic management and postoperative cognitive outcomes in older patients, in which Cottrell and Hartung[1] contend that "a substantial and growing body of evidence indicates that, *ceteris paribus* (with all else being equal), lighter is better than deeper." This conclusion is based on evidence linking markers of deep hypnotic components of general anesthesia, such as electroencephalogram (EEG) suppression or low bispectral index (BIS) readings, to postoperative delirium, death, and other undesirable outcomes. Although such associations have been reported multiple times in the literature,[2–5] making the decision to avoid deep anesthesia hypnosis based on these observational data requires

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Name: Thaddeus P. Budelier, MD, MSF.
Contribution: This author helped draft and edit this piece.
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Name: Arbi Ben Abdallah, DES, PhD.
Contribution: This author helped draft and edit this piece.
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Name: Michael S. Avidan, MBBCh.
Contribution: This author helped draft and edit this piece.
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This manuscript was handled by: Jean-Francois Pittet, MD.

Address correspondence to Bradley A. Fritz, MD, Department of Anesthesiology, Washington University School of Medicine, Campus Box 8054, 660 S Euclid Ave, St Louis, MO 63110. bafritz@wustl.edu.

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one to assume that the observed associations represent causal relationships. Nonetheless, the pendulum has swung decisively, and many anesthesia clinicians now believe dogmatically that deep hypnosis during anesthesia is injurious, and this belief has become entrenched in anesthesiology and critical care lore and literature, despite the lack of robust corroborative evidence and even some compelling contradictory evidence.[6–8]

The cleanest way to test for a causal relationship between EEG suppression and postoperative delirium would be to conduct a randomized trial in which patients receiving general anesthesia for surgery are randomized to experience EEG suppression or not. Unfortunately, randomizing patients to EEG suppression is much more complicated than randomizing patients to a pharmaceutical agent. Drug administration is under the anesthesia clinician's direct control, whereas the clinician can only attempt to prevent EEG suppression by modulating the doses of intravenous and volatile anesthetic agents. This process is imprecise because identical doses of medications may cause EEG suppression in some patients but not in others. Such dose–response variation between patients may in fact be informative (eg, patients who exhibit EEG suppression at lower concentrations of volatile anesthetic are more likely to experience outcomes such as postoperative delirium).[9] The same principle applies to patients who exhibit low BIS readings at low anesthetic concentrations. The "triple low" of low BIS, low anesthetic concentration, and low blood pressure has been associated with postoperative death,[10] but the failure of triple low alerts to improve outcomes suggests that this relationship may be noncausal.[11] Otherwise stated, low BIS readings and EEG suppression with anesthetic exposure reveal a vulnerable phenotype; anesthetic exposure is the stress test, and the EEG provides the readout. Having said this, 2 recent trials that have used mediation analysis do suggest that there might be a small causal contribution between EEG suppression and both delirium[12] and death.[13] Therefore, attempting to minimize EEG suppression in the operating room and in the intensive care unit is probably a reasonable goal.

Does the clinician's indirect control over duration of EEG suppression or low BIS readings mean anesthesiologists should not conduct randomized trials on this topic? No, it does not. Rather, it means that we must adequately report process measures (eg, actual duration of EEG suppression or low BIS in each group) when presenting trial results, and that we must incorporate these process measures into our interpretation of the overall trial findings. To date, 3 large trials have randomized patients to interventions impacting depth of anesthesia. The dual-center Cognitive Dysfunction After Anesthesia (CODA) trial randomized 450 patients to BIS-guided care (BIS goal, 40–60) and 452 patients to routine care, and BIS guidance was associated with reduced postoperative delirium incidence.[14] The single-center Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial randomized 614 patients to EEG-guided care (goal to avoid EEG suppression) and 618 patients to usual care.[8] No significant difference in postoperative delirium incidence was observed between the groups. The multicenter Balanced Anesthesia Study randomized 3316 patients to a target BIS of 50 and 3328 patients to a target BIS of 35.[7] Postoperative delirium was measured as an outcome, but these results have not yet been reported.

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All 3 trials reported statistically significant differences in process measures between the 2 groups. As shown in the Table, the CODA trial included healthier patients undergoing shorter surgeries compared to the other 2 trials. The difference in minimum alveolar concentration (MAC) was smaller in ENGAGES than in the other 2 trials, although the median MAC in the ENGAGES usual care group was similar to the mean MAC in the CODA routine care group and lower than the median MAC in the Balanced low BIS group. Despite similar MAC, the ENGAGES usual care group spent more time with a BIS <40 than the CODA routine care group. This finding may be explained by longer duration of surgery in ENGAGES, by higher severity of illness in ENGAGES (potentially placing patients at a higher risk for low BIS readings despite similar MACs), or by more frequent periods of transient high MAC in ENGAGES (not captured by the summary measure), leading to episodes of low BIS.

Based on existing evidence, it is unclear whether the increased risk associated with EEG suppression or periods of low BIS follows a dose–response pattern (in which risk increases linearly with increased duration of exposure) or a threshold pattern (in which any exposure above the threshold results in an equal increase in risk). Multiple groups of investigators, including the CODA group, have entered duration of EEG suppression or low BIS readings into prediction models as a continuous variable, suggesting that they feel that a dose–response relationship is likely.[2,3,14] Furthermore, each of these groups found a significant association between the continuous exposure and an outcome. However, these results cannot rule out a threshold effect. As demonstrated in figures found in a recently published secondary analysis of the ENGAGES trial, the number of patients who experienced any EEG suppression or any period of a BIS <40 was similar in the EEG-guided and usual care groups, but the time spent in EEG suppression was lower in the EEG-guided group.[12] Thus, the ENGAGES intervention would have been expected to mitigate a dose–response effect, but not necessarily impact a threshold effect.

Cottrell and Hartung[1] state that “even if the only benefit of using processed EEG measurement of anesthetic depth was to train anesthesiologists to avoid hypotension by keeping anesthetic depth on the light side, that would be sufficient justification to encourage its use.” We fear that such a philosophy may have unintended consequences. In expressing our concern, we wish to stress that there is an important difference between advocating the avoidance of unnecessarily deep hypnotic component of anesthesia, potentially suggested by EEG suppression, and the active pursuit of light anesthesia. The BIS is an unreliable indicator of unconsciousness, especially when neuromuscular-blocking agents are administered. This was vividly demonstrated in a study of awake healthy volunteers, in which administration of either succinylcholine or rocuronium caused the BIS readings to drop into the 50s, or sometimes 40s, in the absence of any sedative or hypnotic medications.[15] Had these volunteers been undergoing surgery, they could theoretically have experienced (distressing) intraoperative awareness despite BIS readings that were indicative of adequate hypnotic depth of general anesthesia. In a real-world pragmatic setting using the isolated forearm technique, Sanders et al[16] showed that after induction of anesthesia, approximately 5% of patients revealed by communicating with their isolated forearms that they were conscious, and about half of them indicated that they were in pain. Of particular concern, during these conscious episodes, some patients had a frontal EEG waveform that

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has previously been thought to be reliably indicative of unconsciousness; there were alpha spindles phase amplitude coupled with slow delta waves.[17] Thus, even those who have expertise in EEG waveform interpretation might not be able to know with certainty that their patients are unconscious during intended general anesthesia based on established EEG criteria.

Studies on intraoperative awareness have focused almost exclusively on awareness with recall, detected postoperatively by patient interview. Patients who experience intraoperative awareness frequently manifest long-term psychological sequelae, such as post-traumatic stress disorder. Patients can experience awareness, even if they do not subsequently retain memories of that awareness. It may be tempting to think such an event is not clinically important if the patient does not remember it after surgery. However, the analogous goals of end-of-life care illustrate the flaw in this logic. A terminally ill woman in the intensive care unit whose family has decided to withdraw life-sustaining therapies may be considered. No clinician would imagine withholding analgesic or anxiolytic medication from this patient, even though she will have no recall of her antemortem suffering after she has died. As medical practitioners, and especially as anesthesiologists, our goal is to prevent current suffering, not merely to prevent future recall of current suffering. The same principle applies when we provide anesthetic care in the operating room.

Careful examination of the CODA, ENGAGES, and Balanced trials reveals real concern regarding insufficient anesthesia in the “light anesthesia” groups of all 3 trials, with a strong possibility that patients in these groups might have experienced unintended intraoperative awareness, albeit without explicit recall. In the CODA trial, the mean age and nitrous oxide–adjusted MAC in the BIS-guided group was 0.57, with a standard deviation of 0.29.[14] Assuming a normal distribution, we can infer that approximately 16% of these patients would have received an average inhaled anesthetic concentration of <0.28 MAC (1 standard deviation below the mean) for their surgery.[18,19] Of great concern, this volatile anesthetic concentration is below MAC awake. Furthermore, the majority of patients in the CODA trial received nitrous oxide at a mean fractional concentration of 63%, which, in a 60-year-old patient, is approximately 0.7 MAC. Given that the mean age–adjusted and nitrous oxide–adjusted MAC in the BIS-guided group was 0.57 (ie, <0.7), it follows that many patients likely received nitrous oxide as the sole hypnotic anesthetic agent.[18,19] Such a technique carries an unacceptably high risk of intraoperative awareness. Finally, 25% of patients in the BIS-guided group had mean BIS readings >57 during their surgeries. Thus, by both MAC and BIS criteria, the administration of hypnotic agents to many patients in the CODA trial in the BIS-guided group would be regarded as unacceptably low by many clinicians.[18,19] Other concerns regarding the methodology and interpretation of the CODA trial have been elaborated elsewhere.[18,19] In the Balanced trial, there were no significant benefits reported in the “light anesthesia” (high BIS) group. But of concern, intraoperative awareness with recall was reported by one patient in this group.[7] We are unable to know how many patients in the Balanced trial might have experienced distressing awareness while unable to move, despite not retaining explicit memories thereof. Results from ENGAGES, in which undesirable intraoperative movement was scrupulously recorded, are also troubling. In the “light anesthesia group” (EEG guided), 22.3% (137 of 614) of patients had ≥1 episode of undesirable intraoperative movement, compared with 15.4% (95 of 618) in the usual care

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group ($P = .002$).[8] Many patients move during surgery without being awake, but one of the signs of awareness during intended general anesthesia is undesirable patient movement, which cannot occur with profound neuromuscular blockade.

With the tools currently available to guide anesthetic administration, it is difficult for clinicians to know whether they are providing too much, too little, or just enough hypnotic agent. The consequences of administering insufficient hypnotic agent are clear: patients are at risk for intraoperative awareness, particularly if they have received neuromuscular-blocking agents. The consequences of excessive hypnotic agent administration are more ambiguous. There are associations between markers of deep hypnotic time with general anesthesia and adverse outcomes, but we do not know whether these associations are causal or epiphenomenal. Unless it is clearly shown that deep hypnosis is injurious and absent a reliable indicator of unconsciousness during intended general anesthesia in the presence of neuromuscular-blocking agents, we confidently contend that to err deep is better than to err unbearably light.

GLOSSARY

ASA PS	American Society of Anesthesiologists physical status
BIS	bispectral index
CODA	Cognitive Dysfunction After Anesthesia
EEG	electroencephalogram
ENGAGES	Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes
MAC	minimum alveolar concentration

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Table.

Patient Characteristics and Process Measures in the CODA, ENGAGES, and Balanced Randomized Trials

	CODA		ENGAGES		Balanced	
	BIS Group	**Routine Care**	**EEG Guided**	**Usual Care**	**BIS 50**	**BIS 35**
N	450	452	614	618	3316	3328
Age (y)	68 ± 8	68 ± 8	70 [65–75]	69 [65–76]	72 ± 7	72 ± 7
ASA PS >II	76 (17%)	70 (16%)	525 (86%)	520 (84%)	3316 (100%)	3328 (100%)
Duration of surgery (min)	126 ± 60	120 ± 66	265 [192–344]	264 [186–349]	200 [145–272]	195 [144–274]
Age-unadjusted MAC	0.48[a]	0.78[a]	0.69 [0.62–0.77]	0.80 [0.71–0.86]	0.62 [0.52–0.73]	0.88 [0.74–1.04]
Age-adjusted MAC	0.57 ± 0.29	0.93 ± 0.34	0.83 [0.75–0.93][b]	0.96 [0.85–1.03][b]	0.78 [0.65–0.91][b]	1.10 [0.93–1.30][b]
BIS	53.2 ± 8.9	38.6 ± 6.5	Not reported	Not reported	47.2 [43.7–50.5]	38.8 [36.3–42.4]
Minutes with BIS <40	7.2 ± 7.8	22.8 ± 7.3	32 [9–81]	60 [19–132]	Not reported	Not reported
Minutes of EEG suppression	Not reported	Not reported	7 [1–23]	13 [2–58]	Not reported	Not reported

Values are mean ± standard deviation, number (%), or median [interquartile range].

Abbreviations: ASA PS, American Society of Anesthesiologists physical status; BIS, bispectral index; CODA, Cognitive Dysfunction after Anesthesia; EEG, electroencephalogram; ENGAGES, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; MAC, minimum alveolar concentration.

[a]The CODA trial reported age-adjusted MAC in the article. Unadjusted MAC (ie, where 1 is the MAC value for an average 40-year-old human) was calculated by applying the formula from Nickalls and Mapleson[20] to the mean age-adjusted MAC and mean age reported in the article.

[b]The ENGAGES trial and the Balanced Anesthesia Study reported unadjusted MAC in the articles. Age-adjusted MAC was calculated by applying the formula from Nickalls and Mapleson[20] to the median unadjusted MAC and the mean (or median) age reported in the article.

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