

To clarify how cultured neurons may be relevant to memory processes, I wish to point out that at both the cellular and the molecular level, most fundamental mechanisms underlying synaptic plasticity are preserved in a vast majority of *in vitro* (slices or cultured neurons) preparations. These plastic changes in synaptic activity, in turn, are thought to form the basis for learning and memory in most animals—ranging from worms, snails, and flies to humans. Therefore, it is highly appropriate and useful to take advantage of *in vitro* preparations for understanding complex processes such as learning and memory. Regarding the usefulness of the model system for studies on synaptic plasticity and learning and memory, I wish to point out that mine was the first laboratory to have reconstructed the entire respiratory network in cell culture.<sup>2</sup> I demonstrated that the *in vivo* reconstructed circuit, comprising behaviorally and functionally well-defined neurons, was sufficient to generate patterned respiratory rhythm in a manner similar to that seen *in vivo*. Both the Lukowiak (University of Calgary, Calgary, Alberta, Canada) and my laboratory have since demonstrated that the respiratory behavior in *Lymnaea* can be operantly conditioned<sup>2-7</sup> to exhibit short-, intermediate-, and long-term memory and have identified the locus for these memory related changes<sup>7</sup> at the level of a single neuron. By selectively removing a single cell in the intact animals, I have subsequently provided direct evidence regarding the storage site for learning and memory-related changes in individual neurons.<sup>8-15</sup> Moreover, using the cell culture model, I have not only defined the mechanisms that regulate synaptic efficacy<sup>16,17</sup> but also identified novel proteins<sup>18</sup> that can modulate synaptic strength *via* interactions with the glial cells. Therefore, I believe that the *Lymnaea* model is equally well suited for studies in synaptic plasticity and learning and memory—as has been the case in *Aplysia*.

Notwithstanding these strengths of my model and a clear demonstration in my article<sup>1</sup> that anesthetics do not affect short-term potentiation, I have still been very careful in drawing a generalized conclusion about the actions of sevoflurane on learning and memory. Specifically, I have explicitly stated in my article that “these data should be treated with caution as learning and memory involve a larger population of neurons, often requiring interplay between complex cognitive information processing mechanisms in the brain” (Discussion, first paragraph, page 924).

In the context of unresolved issues of whether anesthetics affect memory, the bottom line is that we still do not have the answer—nonwithstanding Dr. Ghoneim's claim that anesthetics have been shown to block learning and memory. I believe that unequivocal evidence in this regard would still require a multidisciplinary approach and concerted efforts by both clinical investigators and basic scientists.

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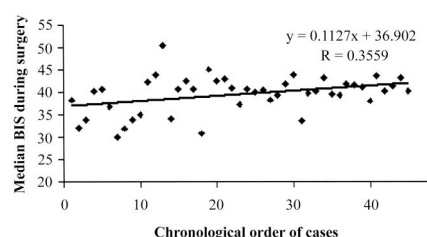
## Regular Clinical Use Bispectral Index Monitoring May Result in Lighter Depth of Anesthesia as Reflected in Average Higher Bispectral Index Values

**To the Editor:**—A recent study demonstrated that cumulative deep hypnotic time (Bispectral Index of the electroencephalogram [BIS] below 45) is a significant variable in postoperative outcomes.<sup>1</sup> The importance of anesthetic duration and depth is interesting and somewhat surprising, and emphasizes the need to more carefully evaluate the impact of intraoperative management strategies on outcome.<sup>2</sup> Anesthesiologists are now more concerned with assuring adequate

depth of anesthesia for both clinical and professional liability reasons. We investigated whether the regular use of BIS monitoring could lead anesthesiologists to work with lighter levels of depth of anesthesia.

Data collected during consecutive neurosurgical interventions (research committee approved and informed consent) with the same anesthesiologist were used in this study. Data were systematically collect on the same weekday in the same operating room during a whole year. Patients were submitted to general anesthesia using propofol (1% Fresenius; Fresenius Kabi Pharma Portugal Lda., Carnaxide, Portugal) and remifentanyl (20 µg/ml Ultiva®; GlaxoSmithKline-Produtos Farmacêuticos Lda., Algés, Portugal). Patients with pathologies that

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**Fig. 1.** Linear regression between the median Bispectral Index (BIS) during surgery and the chronological order of the case. Statistical significant correlation ( $P = 0.0148$ ) and positive slope ( $P < 0.05$ ).

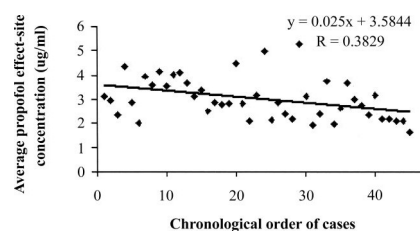
could influence the results or showed obvious alteration of mental status were excluded. Patients were monitored with an A-2000XP BIS® monitor (Aspect Medical Systems, Newton, MA) using a BIS-Sensor® (Aspect Medical Systems) placed according to the instructions of the manufacturer and an AS3 Datex monitor (Datex-Engstrom, Helsinki, Finland) connected by an RS-232 interface to a personal computer using Rugloop II® software for data capture every 5 s. Rugloop II® was used to control *via* the RS-232 interface the remifentanyl infusion pump (Asena Alaris TIVA; Alaris Medical Systems, San Diego, CA) and the propofol infusion pump (Asena Alaris GH, Alaris Medical Systems) using the pharmacokinetic-pharmacodynamic models of Minto *et al.*<sup>3</sup> and Schnider *et al.*<sup>4</sup> for remifentanyl and propofol, respectively. Induction of anesthesia was performed with a propofol infusion (target-controlled infusion) with an initial effect site target of 5  $\mu\text{g}/\text{ml}$  and a remifentanyl infusion (target-controlled infusion) with an initial plasma target of 2.5  $\text{ng}/\text{ml}$ . Loss of consciousness was defined as loss of eye opening in response to a tap on the forehead and calling the patient's name. Rocuronium (10  $\text{mg}/\text{ml}$  Esmeron®; Organon Portuguesa Lda., Lisboa, Portugal) was used for muscle relaxation. The drugs' target concentrations were manually controlled by the anesthesiologist during the entire surgery.

Data distribution is expressed as mean  $\pm$  SD. Statistical correlation analysis, linear regression, and the Student *t* test were performed using MATLAB 6.5.1 (The Mathworks Inc., Natick, MA).  $P < 0.05$  was considered significant. Average BIS and median BIS during the maintenance phase were calculated retrospectively from the anesthetic record and related to the chronological order of the case. The anesthesiologist was blind to the objective of this study.

Forty-five patients met the selection criteria. Patients were aged  $49.8 \pm 16.5$  yr, weighed  $67.8 \pm 13.4$  kg, and were  $160.5 \pm 8.8$  cm tall. Thirty-three were female. The case duration was  $287.3 \pm 161.6$  min.

During surgery, the average BIS value was  $39.89 \pm 4.04$ , and the median BIS value was  $39.49 \pm 4.1$ . The propofol average effect site and plasma concentrations were  $3.01 \pm 0.86$  and  $2.98 \pm 0.84$   $\mu\text{g}/\text{ml}$ , respectively. The average propofol dose was  $0.10 \pm 0.03$   $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The total amount of propofol was  $1,940 \pm 1,289$  mg. The remifentanyl average effect site and plasma concentrations were  $3.13 \pm 0.89$  and  $3.15 \pm 0.9$   $\text{ng}/\text{ml}$ , respectively. The average remifentanyl dose was  $0.11 \pm 0.04$   $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The total amount of remifentanyl was  $2,093 \pm 1,355$   $\mu\text{g}$ .

There were significant positive correlations between the chronological order of the case and average BIS ( $P = 0.0164$ ) and the chronological order of the case and median BIS ( $P = 0.0148$ ; fig. 1). The average effect site propofol concentration decreased significantly over time ( $P = 0.0094$ ), as did the plasma propofol concentration ( $P = 0.0112$ ). Figure 2 shows the relation between the average propofol dose during surgery and the chronological order of the case ( $P = 0.006$ ). There was no significant correlation between the remifentanyl dose or concentration and time.



**Fig. 2.** Linear regression between the average propofol dose ( $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during surgery and the chronological order of the case. Statistical significant correlation ( $P = 0.006$ ) and negative slope ( $P < 0.01$ ).

The possibility of observing the central nervous system response through BIS increased the anesthesiologist's confidence in the level of depth of anesthesia (learning trend) and improved the clinical management. The increasing trend in BIS values with clinical practice was accompanied by a decreasing trend in propofol consumption.

Anesthetic depth is often used as a tool to provide better control of hemodynamic variables.<sup>2</sup> However, hemodynamic depression is one of the major factors associated with perioperative coma and death.<sup>5</sup> A long duration of intraoperative systolic hypotension is also associated with increased risk of postoperative mortality.<sup>1</sup> By controlling depth of anesthesia using BIS, one can more easily control the associated hemodynamic variability (*e.g.*, using nonanesthetic drugs).

In our study, we observed that the regular use of BIS monitoring led to higher BIS values and, therefore, lower propofol consumption. This is in accord with the results of Guignard *et al.*,<sup>6</sup> who reported a reduced consumption of isoflurane when its titration was guided by BIS monitoring without higher incidence of light anesthesia.

In conclusion, the regular use of BIS monitoring by the anesthesiologist resulted in average higher BIS values. The increasing BIS trend with clinical practice also represented a trend toward safer BIS values (BIS between 45 and 60). This BIS trend was associated with a decrease over time of propofol average concentrations and consumption. Between the first and the last patients, there was an average decrease of 1,077 mg propofol per patient. The decrease in propofol consumption with time was a consequence of the experience with BIS monitoring acquired by the anesthesiologist (*i.e.*, trying to avoid excessive anesthesia), with potential benefits to the patients.

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