Anesthetic Depth Is a Predictor of Mortality

It's Time to Take the Next Step

"The recognition of the existence of a problem is the first step in its solution."
—Martin H. Fischer

IN 2005, a study by Monk *et al.*[1] was the first to suggest that cumulative deep hypnotic time (cumulative duration of low bispectral index [BIS]) was an independent predictor of 1-yr mortality after major noncardiac surgery. Not surprisingly, the "validity of the mortality–hypnosis finding" was questioned, necessitating further investigation.[2] The report by Kertai *et al.*[3] in this issue of ANESTHESIOLOGY adds to the growing body of evidence confirming the association between cumulative duration of low BIS and postoperative mortality. In this investigation, 17.8% of patients died in the first 3 yr after cardiac surgery, with the risk of death increasing by 29% for every cumulative hour for which the BIS was less than 45 during surgery. Other perioperative factors associated with increased mortality included the EuroSCORE, erythrocyte transfusion, intraoperative infusion of norepinephrine, and prolonged intensive care unit stay.

As in the current study, previously published reports confirming the mortality–hypnosis association were all derived from secondary analyses of data collected prospectively for other purposes.[3–6] Lindholm *et al.*[4] examined the BIS data from a study originally designed to evaluate the effect of BIS monitoring on the incidence of intraoperative awareness and found that cumulative time at BIS less than 45 was associated with an increased risk of death for up to 2 yr after surgery. However, when preexisting malignancy was included in the analysis, the association between low BIS and mortality was found only in patients with malignancies associated with poorer life expectancies. The investigators in the B-Aware Trial recently reported their secondary analysis of long-term mortality and found that the absence of low BIS values (BIS < 40) was associated with improved survival and reduced morbidity (myocardial infarction and stroke).[5] Finally, a *post hoc* analysis of an observational study originally designed to investigate the use of BIS to monitor consciousness in mechanically ventilated, sedated adult intensive care unit patients confirmed this association in a nonsurgical population.[6] The authors compared two groups of patients with similar demographic and severity of illness characteristics and found that 39% experienced burst suppression. Patients who experienced burst suppression had a significantly higher 6-month mortality rate compared with patients who did not have burst suppression when sedated (59 *vs.* 33%). These three studies along with the current report by Kertai *et al.*[3] indicate that the mortality–hypnosis association is valid and deserves further rigorous investigation.

All the previous publications investigating the effect of low BIS on postoperative outcomes have identified preoperative comorbidity as an important independent risk factor for postoperative mortality,[1,4,5] leading to the hypothesis that these high-risk patients may have an increased susceptibility to anesthetic effects.[1] Kertai *et al.*[3] also found that increased preoperative comorbidity as defined by the EuroSCORE, a measure of cardiac operative risk, was associated with increased postoperative mortality. In this study, most patients (83%) with the longest duration of BIS less than 45 ($>$ 4 h) had abnormal left ventricular ejection fractions. Similarly, 67% of these patients were on β-receptor blockers before surgery, suggesting a history of chronic hypertension. Hypertension and a history of heart disease are two of the most important factors associated with the presence of cerebral white matter lesions and brain atrophy.[7,8] Therefore, we can hypothesize that high-risk patients have increased brain sensitivity to anesthetic agents, resulting in lower intraoperative BIS levels when given the same anesthetic dose as for healthier patients. The clinicians in the study by Kertai *et al.* administered similar amounts of inhalation anesthesia and adjuvant agents to patients during maintenance anesthesia (table 2),[3] suggesting that the BIS levels were not used for anesthetic management. The authors concluded that this finding indicates that the association of low BIS and mortality was independent of total anesthetic dose. However, another interpretation of these data can be posited. Expired anesthetic concentration is only an indirect

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measure of brain concentration and, by extension, cerebral anesthetic effect. There is evidence that brain impairment influences BIS readings. A study evaluating the performance of BIS in healthy and intellectually disabled children found that BIS levels were lower in the awake state, during anesthesia, and on the return of consciousness in intellectually disabled children.[9] If the patients with low BIS readings in the study by Kertai *et al.* had more central nervous system compromise related to white matter lesions and/or brain atrophy, the low intraoperative BIS readings may have been an indication of excessive anesthetic administration, possibly contributing to worsened outcomes. As an analogy, consider the drug adjustments that are required in patients with hepatic or renal impairment. Obviously, this question cannot be definitively answered until techniques to monitor the cerebral concentrations of anesthetic agents are developed.

Although the mortality–hypnosis association remains poorly understood, the use of BIS-derived data to predict outcome after hypoxic-ischemic encephalopathy is logical and well established. Electroencephalographic testing has long been a part of the evaluation of patients in coma, and recent studies have shown that BIS can be helpful in predicting mortality and neurologic outcome in comatose patients with hypoxic-ischemic encephalopathy with normal body temperature[10] and those undergoing therapeutic hypothermia.[11,12] A study involving comatose patients with hypoxic-ischemic encephalopathy undergoing emergency surgery demonstrated that BIS data collected during surgery were a better predictor than physicians' clinical judgment or patients' pupillary light responses in identifying patients with a good chance of recovery.[13] Perhaps, low BIS during anesthesia will prove to be helpful in predicting other outcomes as well.

A central question remains unanswered regarding the mortality–hypnosis association: can anesthetic management influence long-term outcomes or is the BIS® monitor (Aspect Medical Systems, Newton, MA) simply identifying patients whose brains are especially sensitive to anesthesia? Stated another way, by avoiding deep anesthesia, as documented with BIS, can we improve outcomes or are low BIS levels just another marker of comorbidity associated with a greater risk of postoperative death? The secondary analysis of the B-Aware trial provides a glimpse into a possible solution to this question.[5] In the original study, patients at high risk for awareness were randomized to receive an anesthetic directed by routine clinical parameters (routine care) or by BIS values.[14] The target range of BIS in the BIS-directed group was 40–60. For the purposes of the secondary analysis, the investigators compared three BIS groups for postoperative morbidity (myocardial infarction and stroke) and mortality outcomes. The three groups were as follows: (1) patients randomly assigned to the routine care group (no BIS); (2) patients randomly assigned to the BIS-directed group who experienced BIS values less than 40 for more than 5 min (low BIS); and (3) patients who were randomly assigned to the BIS-directed group who did not experience a BIS less than 40 for more than 5 min (optimal BIS). The initial analysis found no difference in outcomes between the patients who had routine care and those who received BIS-directed care. However, on further investigation, the researchers found that the optimal BIS group had significantly lower mortality and morbidity rates compared with both the no BIS and the low BIS groups. These results suggest that although BIS monitoring *per se* did not affect important outcomes, the maintenance of BIS values between 40 and 60 reduced the risk of morbidity and mortality.

The recognition of this problem raises multiple questions. Is low BIS just a marker of comorbidity and imminent death or will intraoperative BIS optimization improve outcomes in high-risk patients? Do high-risk patients have greater susceptibility to anesthetic agents than heathier patients? Is it even possible to maintain BIS at optimal levels in high-risk patients undergoing surgery? Will low intraoperative BIS values identify patients whose outcomes can be improved by intensive postoperative strategies? We now recognize that the hypnosis-mortality association exists; it is time to take the next step toward a better understanding of this phenomenon.

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ANESTHESIOLOGY REFLECTIONS

Edward Barber's "Anesthetic Nausea" Protocol

By 1914 a Chicagoland dentist–anesthetist named Edward S. Barber, D.D.S., was promoting his protocol for use on dental patients under "nitrous-oxid [*sic*] and oxygen" whose complexion had turned "a greenish color which is a forerunner of nausea." Barber recommended halting the anesthetic and, once the patient opened his or her eyes, leaning the patient forward in the dental chair. Barber would then have his lady assistant hold a kidney basin in her left hand and a sponge in her right. After the patient's face was sponged with cold water and the patient's neck draped with a cold, wet towel, Barber would use his own torso to force the patient "downwards so that the stomach comes in contact with the knees and the head is lowered as far as possible." Note in Barber's staged photograph (*above,* courtesy of the Wood Library-Museum) how the dentist uses his left hand to cradle the patient's forehead and his right to hold a broken ammonia ampoule under the patient's nose. To ensure that this "anesthetic nausea" protocol could be observed, Barber refused to anesthetize corseted ladies, because "the body cannot be pinched up enough to compress the stomach sufficiently and expel the gas." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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