Concentration of Precious Sleep: Piloting Survival or Attending Death?

To the Editor:
Tailoring depth of anesthesia to the needs of each individual patient, while mastering the inevitable cardiovascular side effects represents a core anesthesiologist’s skill. Novel inspiration to this daily challenge has recently been brought by Sessler et al., identifying the combination of low blood pressure, low bispectral index (BIS), and low minimum alveolar concentration of volatile anesthesia as a triaork of death. Looking at the cut-off parameters of this “triple low” may cause a wave of reflection, if not immediate malaise in each anesthesiologist, as values below the mortality threshold are routinely tolerated. The question arises: Are we harming all these patients, if not worse?

All three phenomena are inextricably entwined and intraoperative management is largely dictated by patient characteristics and intraoperative course. Low blood pressure was shown to determine adverse outcome in relation to age and duration of surgery, and the establishment of a causal relationship between low BIS values and intermediate-term outcome previously failed when malignancy and physical status were considered. Moreover, left ventricular dysfunction, systemic illness, or a complicated intraoperative course was shown to account for accumulated low BIS values, with no relation to end-tidal anesthetic gas concentrations. The abovementioned results emphasize that anesthetic management is influenced not only by anesthesia-related, but also a plethora of surgery-related, and patient-specific factors. It seems difficult to control all these interfering factors to achieve clear-cut scientific conclusions; however, discrimination of at least American Society of Anesthesiologists physical status and cause of death seems mandatory. It is hard to believe that a triple low in a 20-yr-old American Society of Anesthesiologists class I patient has the same prognostic value, if any at all, as that of a 70-yr-old American Society of Anesthesiologists class III patient. Although Sessler et al. certainly would agree with these considerations, their current study misses the opportunity to provide conclusive new insights in conjunction with clinically applicable concepts as the predictive role of important variables such as comorbidities, American Society of Anesthesiologists physical status, duration and difficulty of surgery (e.g., transfusion requirements), and cause of death were neglected. Moreover, no single low was associated with increased mortality, further impeding the identification of distinct manipulations of either mean arterial pressure, BIS, or minimum alveolar concentration as causal or pure epiphenomena. Hence, observation of a “double low,” and triple low should not be misinterpreted as differences in anesthetic sensitivity or outcome determinants per se. As before, attention is required not to injudiciously confound low BIS values as a pure reflection of anesthetic depth in the critically ill, just as the sufficient supply of minimal alveolar concentration values and provision of adequate perfusion pressures should be self-evident hallmarks of anesthesia.

However, despite its limitations, the study shines with its conceptual approach of desperately needed outcome research in anesthesiology. Many aspects of narcosis remain unexplored and things working as a matter of course on a daily basis are likely to impact patient morbidity and mortality. Prospective studies regarding the prognostic value of anesthetic characteristics are desirable, in particular, those targeting outcome improvement. Data supporting clinical decision making will help to manage the core anesthesiologist’s task of tailoring anesthetic depth to each individual needs and answer the question: How can we make a difference for the better?

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References
1. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S: Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology 2012; 116:1195–203
In Reply:

We reported that a “triple low” of mean arterial pressure, minimum alveolar concentration (MAC), and Bispectral Index (BIS) is associated with a fourfold increase in 30-day all-cause mortality compared with patients without low values.1 Yu and Liu point out that an association between triple lows and mortality may not be causal. We emphasized this obvious point in our article: “as in all registry analyses, it is impossible to make causal conclusions from these observations.” Nonetheless, our results indicate that two “double low” combinations and a triple low of mean arterial pressure, BIS, and MAC strongly predict postoperative mortality. We agree that triple low events are probably mostly markers for underlying disease. But perhaps some mortality can be prevented by anesthetic management—which remains an intriguing possibility.

Yu and Liu also comment that we did not present baseline risk factors for various combinations of “single,” double, and triple low combinations. We instead used a sophisticated multivariable model to adjust for baseline factors. This is a more useful approach than stratifying by risk because, to the extent that relevant potential confounders were included, results in each patient group can thus be directly compared. The more important question is whether all relevant confounders were included. Surely some are missing because even a dense registry such as ours does not include every potential predictor. Importantly, though, we included Risk Stratification Indexes; these powerful predictors of mortality and hospital length-of-stay are based on 240 and 1,096 International Classification of Disease version 9 codes and thus subsume considerable patient-level baseline and procedural detail.2 Yu and Liu state that we did not include intraoperative blood transfusion as a risk factor in our analysis. In fact, we did and our article specified that variables for each model were selected using forward conditional selection from a candidate pool containing “age, gender, race, body mass index, American Society of Anesthesiologists physical status, along with intraoperative factors including case-average estimates of blood concentration of propofol and fentanyl equivalents, estimated blood loss and administered erythrocyte volume, type of maintenance volatile anesthetic, whether nitrous oxide was used, and case duration.” Transfused blood volume remained in our final model for mortality and was reported in table 3.

Postoperative troponin values are available only for a small fraction of nonrandom patients and thus could not be included. But even if they were available, troponin elevations are consequences of damage already done. And besides, postoperative laboratory values cannot be the basis for intraoperative management enhancements that might improve outcome—which is our real interest.

We agree that only a clinical trial can determine whether intraoperative intervention to prevent or ameliorate triple low events actually improves outcomes. One (NCT00998894) is already in progress.

Lotz and Kehl assert that we did not include cause of death, transfusion requirement, or American Society of Anesthesiologists physical status score in our analysis. As mentioned above, we did include transfusion requirement and American Society of Anesthesiologists physical status in the pool of candidate risk factors; details that were specified in the Methods section of our article. Physical status was retained in both the length-of-stay and mortality models as reported in tables 2 and 3. Lotz and Kehl also assert that we neglected case duration and complexity. As specified above, duration was directly included in our statistical model; and complexity is subsumed into the Risk Stratification Indexes. Cause of death is of interest, but date of death was obtained from the Social Security Death Index, which does not include mortality cause.

Lotz and Kehl warn “not to injudiciously confound low BIS values as a pure reflection of anesthetic depth in the critically ill.” We fully agree and our article identified that there are “three potential causes of low BIS: (1) Low BIS is the normal response to generous doses of volatile anesthetics; (2) An alternative cause of low BIS is anesthetic sensitivity. This group is identified by the combination of low BIS and low MAC fraction. This is an atypical response because low MAC fraction should be associated with high BIS. That BIS was in fact low in some patients with low MAC fractions suggests an abnormal sensitivity to volatile anesthesia, potentially because of underlying illness; and (3) a third potential cause of low BIS is inadequate brain perfusion, resulting in ischemic suppression of brain metabolism. Brain hypoperfusion may especially occur in a fraction of patients who demonstrate low BIS combined with low mean arterial pressure.” This last group is potentially the most interesting because brain hypoperfusion should be preventable with adequate hemodynamic control.

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