

## Is the “Triple Low” Association with Death Statistically Valid or Reflective of Clinical Practice?

To the Editor:

We are intrigued to read Willingham *et al.*'s<sup>1</sup> strongly worded retrospective, observational conclusion from three previously reported trials that the concurrence of intraoperative hypotension, low minimum alveolar concentration, and low bispectral index (BIS), the so-called “triple low,” was independently associated with postoperative death. We have several observations noting that several of the current authors were original contributors to the referenced studies.

1. None of the three clinical trials used to collect data for this study were designed to evaluate the current hypothesis, and all were powered to evaluate awareness with use of the BIS monitor. Neither of Avidan *et al.*'s<sup>2,3</sup> studies were able to show superiority of a BIS-guided protocol in preventing awareness, and Mashour *et al.*'s<sup>4</sup> study was terminated early for futility. There is no power analysis presented of the aggregate data used in this study to support a potential “triple low” hypothesis.
2. Each medical comorbidity listed in table 1 of the current study has a clinically and statistically significantly greater incidence in the triple low group, along with decreased doses of listed analgesics and sedatives, longer case lengths, and greater incidence of cardiopulmonary bypass. Thus, no reader would disagree that the triple low cohort was significantly sicker and not surprisingly at higher risk for mortality. However, no amount of statistical tap-dancing with propensity analysis can then safely remove 73% of this unmatched cohort to come up with a conveniently matched cohort of only one quarter of the subjects. This matched group is coincidentally not matched for size, being only 63% of the size of the original triple low group.
3. Hazard ratios presented in table 2 accentuate the clinical anesthesiologist's expectation that American Society of Anesthesiologists physical status more than or equal to 4 and the presence of cancer, chronic obstructive pulmonary disease, peripheral vascular disease, or dysrhythmia significantly dwarf the effect of “triple low” at 1.08, all with a hazard ratio of 2 or greater. Is this an instance of statistical significance overwhelming clinical relevance?
4. In daily practice, appropriate variation of the depth of anesthesia and management of hypotension is a clinical art so that the periods of “triple low” are assiduously guarded against by adjustment of at least two, if not all three, of the “triple low” variables if BIS is being used. Having multiple

15-min epochs of “triple low” runs counter to the intent of current clinical practice as prompt treatment of hypotension and decreased depth of anesthesia are initial responses for any reasonable clinician faced with this dilemma.

For all of these reasons, the alarming title and inferences need to be followed with clear caveats, including use of research-based protocols in the previous studies, which may not accurately reflect immediate corrections in current clinical practice, incorporation of only a quarter of the original cohort for matching, and the retrospective propensity analysis. These suggest that conclusions be tempered with caution until these statistical and clinical concerns can be addressed in future prospective investigations.

### Competing Interests

The authors declare no competing interests.

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### References

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## Not Really Triple Low?

To the Editor:

We read with great interest the article “Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death” by Willingham *et al.*<sup>1</sup> This study is based on data from three previous publications by the same group where they determined the incidence of awareness