

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.*'s¹ 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^{2,3} studies were able to show superiority of a BIS-guided protocol in preventing awareness, and Mashour *et al.*'s⁴ 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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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.*¹ This study is based on data from three previous publications by the same group where they determined the incidence of awareness

with the use of end-expired gas monitoring and bispectral index.²⁻⁴ In the first study, non-age-adjusted minimal alveolar concentration (MAC) was used (n = 2,000),² while in the last two studies, age-adjusted MAC was used (n = 6,041 and 21,601).^{3,4} In this study, Willingham *et al.* converted age-adjusted MAC to non-age-adjusted MAC, and they defined low MAC as less than 0.8. The authors do not give a rationale for doing so, and we think that using non-age-adjusted MAC values may have influenced their conclusions.

Indeed, it is generally accepted that MAC is age dependent: MAC is lower in elderly patients.⁵⁻⁷ Therefore, using non-age-adjusted MAC values underestimates the depth of anesthesia in their elderly patients; thus, these patients may have been overdosed; this is not uncommon even today.⁸ For example, in an 80-yr-old patient, an end-tidal sevoflurane concentration of 1.6% would be 0.8 non-age-adjusted MAC, but this would be about 1.23 age-adjusted MAC,⁷ which is simply not a “low MAC.” We are curious whether the conclusions of this study would be the same if age-adjusted MAC values were used. Is it possible that many patients in this study have “a double low (mean arterial pressure and bispectral index) and one high (MAC)” instead of a “triple low”?

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Pivalizza *et al.* and Dr. Carette *et al.* for their letters in response to our research on increased postoperative mortality associated with intraoperative “triple low”: concurrent low mean arterial pressure (less than 75 mmHg), low volatile anesthetic minimum alveolar concentration (MAC; less than 0.8), and low bispectral index (less than 45).¹

We are surprised that Pivalizza *et al.* found our conclusion to be strongly worded when the adjective “weak” is the chief qualifier in our abstract’s conclusion: “There is a *weak* [emphasis added] independent association between the triple low state and postoperative mortality...”¹ Pivalizza *et al.* raise four specific points. (1) We did not conduct a power analysis since we used a convenience sample from previously conducted studies. The concern cannot be that our study was underpowered that—contrary to our hypothesis—we found a positive result (*i.e.*, a significant association between “triple low” and postoperative death). The concern could be that our study was “overpowered” in that a very large study can find statistically significant, but clinically irrelevant, results. However, death is an important outcome, and even a small impact on mortality could be clinically important. (2) We are more sanguine than the letter writers about the potential for propensity score matching to balance risk factors between groups in nonrandomized studies. Nonetheless, we agree that prospective clinical trials are better able, in general, to reveal causal links than observational studies, where confounders are more likely. (3) We agree that “triple low” was less potently associated with death than preexisting risk factors (*e.g.*, American Society of Anesthesiologists physical status and chronic obstructive pulmonary disease). But the salient point is that “triple low” is potentially modifiable or even avoidable (during general anesthesia), whereas patient comorbidities are largely immutable. (4) We are baffled by the contention in point 4 that sensible anesthesiologists currently assiduously guard against epochs of “triple low,” since the arguments put forward in the rest of the letter seem to suggest that “triple low” is not likely to be injurious and that our results reflect statistical “tap-dancing” or clinical irrelevance. Moreover, despite peer-reviewed data demonstrating that intraoperative hypotension is common² and likely harmful,^{3,4} there are no peer-reviewed data demonstrating that clinicians routinely avoid hypotension by administering medications or decreasing depth of anesthesia. Nor have any standard protocols for the treatment of hypotension (*e.g.*, decrease depth of anesthesia, administer fluids, infuse vasopressors, institute inotropes) been established in any surgical setting or in any patient