

“Triple Low”

Murderer, Mediator, or Mirror

EVERY anesthesiologist has encountered the difficult case of a patient that simply does not “tolerate” a typical general anesthetic; even low concentrations of a potent volatile agent may result in significant hypotension that requires aggressive treatment. In this issue of ANESTHESIOLOGY, Sessler *et al.*, from the Cleveland Clinic (Cleveland, Ohio) and Covidien (Mansfield, Massachusetts), demonstrate that this intraoperative observation may hold clinical significance for the patient’s postoperative outcome.¹

By integrating physiologic monitoring, electronic health record, administrative, and national death data, they evaluated the mortality and hospital length of stay for patients having inpatient surgery. Some patients concurrently demonstrated intraoperative retrospectively defined “low” volatile minimum alveolar concentration (MAC) equivalents, “low” blood pressure, and “low” bispectral index values, a phenomenon the investigators have dubbed “triple low.” They observed that, although the study adjusted for patient age, sex, comorbidities, and surgical complexity, patients demonstrating “triple low” still had four times the hazard of death within 30 days compared to patients who did not have a triple low. Reinforcing the plausibility of their findings, Sessler *et al.* showed that a combination of any “double low” was associated with increased postoperative mortality. In addition, patients who had triple low episodes were more likely to have a prolonged hospital stay. The analysis is sophisticated and has many strengths. Notably, short-term 30-day mortality was the primary outcome, which increases the possibility of a causal contribution of intraoperative events. The inclusion of age, comorbidities, and surgical complexity in the multivariate analyses improves the likelihood of quantifying the independent association of intraoperative parameters and postoperative outcomes.

Photo: J. P. Rathmell.

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“Although patients with triple low had increased mortality, ... whether preventing a triple low would change outcomes or even be feasible [is uncertain].”

period of time with a mean arterial blood pressure less than 75 mmHg was just as predictive as was the duration of triple low.⁶

Overall, the data presented by Sessler *et al.* are thought-provoking. As the authors state, it is unclear whether triple low causes increased mortality or is simply detecting patients with underlying risk of increased mortality. Triple low may simply be an intraoperative stress test. It is also conceivable that a hybrid of the two concepts is at play: for a given patient, triple low may serve as a marker of disease, but allowing the patient to remain hypotensive may cause end organ hypoperfusion. Future studies involving controlled, protocol-driven management to prevent triple low will be needed to elucidate the causal *versus* epiphenomenon conundrum. It will also be important to determine whether intraoperative alerts based on triple low confer any advantage over alerts based on hypotension alone.

Sessler *et al.* appropriately caution that it would be premature to alter intraoperative care based solely on their ob-

These data add to the existing body of literature evaluating associations among intraoperative parameters and postoperative outcomes. Although early single-center literature intimated that relatively excessive anesthetic depth, suggested by low bispectral index values, might be associated with mortality,² other investigators were unable to reproduce this finding after adjusting for cancer-related deaths.^{3,4} The data of Sessler *et al.* appear to confirm that patients with low bispectral index values without concomitant low blood pressure or low volatile anesthetic concentration do not have increased 30-day mortality. Thus, the accumulating evidence suggests that the interaction between intraoperative parameters and postoperative outcomes is more complicated than the notion that “deep hypnotic time” is dangerous. More recently, two different centers have observed intraoperative hypotension to be a predictor of mortality.^{5,6} In fact, the

◆ This Editorial View accompanies the following article: 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.

servational, hypothesis-generating study. Several important limitations to the data, many highlighted by the authors, limit their ability to warrant intraoperative anesthetic management changes. As a single-center data set, the applicability of the findings to other patient care settings is debatable. Because low blood pressure, low MAC equivalents, and low bispectral index values were defined as one standard deviation from the single-center population means rather than clinical thresholds, center-specific patterns of care are intertwined inextricably with the authors' observations. Although patients with triple low had increased mortality, the observational nature of the analysis leaves uncertain whether preventing a triple low would change outcomes or even be feasible. A triple low may simply reflect the patient's underlying disease. The authors attempted to control for patient comorbidities and procedural risk using their recently published Risk Stratification Index.⁷ However, the index is based upon billing data using International Classification of Diseases discharge diagnoses and procedural codes. Triple low may be detecting the important clinical differences between two patients both defined as having "congestive heart failure" according to billing data. It may be an objective proxy for the "eyeball test" performed by clinicians to assess a patient's frailty. Recent surgical literature has established quantitative measures of patient frailty by examining the cross-sectional area of the psoas muscle. Researchers have observed a risk-adjusted relationship between decreasing psoas muscle size and postoperative mortality for patients undergoing a variety of procedures.^{8–10} Triple low may be a similar phenomenon: an objective measure of the historically subjective concept of patient frailty.

If the association between triple low and death is causal, the pathophysiologic mechanisms by which triple low could increase all-cause mortality are unclear. Certainly, untreated hypotension could contribute to damage of major organs, such as the brain, heart, and kidneys. Low bispectral index values (less than 40 to 30) typically occur when there is electroencephalographic burst suppression.^{11,12} Unlike many other electroencephalographic features seen during general anesthesia, such as spindles and slow delta waves, burst suppression is not a physiologically normal rhythm. Burst suppression appears more frequently during general anesthesia in patients who have coronary artery disease¹¹ and has been implicated as a harbinger of 6-month mortality in medical intensive care unit patients.¹³ It is hypothesized that prolonged burst suppression might precipitate neurologic injury.^{11,13} Thus, it is conceivable that the triple low combination could be causally implicated in some deaths. However, it is hard to imagine how hypotension, burst suppression, or low volatile anesthetic concentration could promote cancer-related deaths. The current study by Sessler *et al.* does not identify the causes of death, but based on previous studies, a substantial proportion of deaths are likely to have been related to advanced cancer.^{2–4,14}

The analysis presented in this issue of ANESTHESIOLOGY lacks several important data elements needed to establish a

convincing relationship between intraoperative parameters and postoperative outcomes. For example, the calculated MAC equivalents did not include nitrous oxide, which may explain why the average MAC across 24,120 patients was a surprisingly low 0.56. Next, maintenance doses of MAC-sparing agents, such as propofol, dexmedetomidine, and opiates, apparently were not incorporated into the analysis. Because the primary outcome of mortality has a low baseline rate of 0.5% in the studied population, the authors were forced to amalgamate a diverse group of patient and procedural risks into a single population by the need to achieve statistical power. Intuitively, specific groups of patients may be more likely to exhibit or be affected by triple low and warrant focused analyses.

Despite its limitations, this impressive study demonstrates that the era of anesthesiology insularism is coming to a close. What we observe, and possibly what we do, during our brief intraoperative relationship with the patient probably is relevant to long-term patient outcomes. Future research efforts must be dedicated to reproducing or refuting the current findings and exploring how perioperative management could contribute to improved patient trajectories. In doing so, the field of anesthesiology will demonstrate its value to patients long after they have left the operating room.

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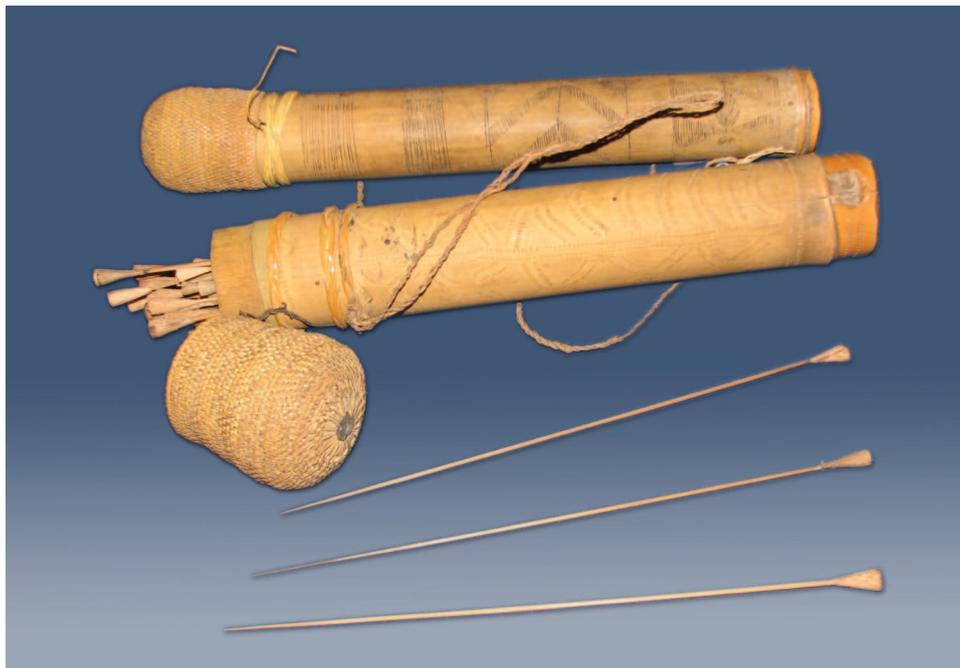
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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Quivers of Curare-tipped Blow Gun Darts



Today's anesthesiologists use curare-like agents as adjuvants for decreasing patients' total anesthetic drug load, particularly of the ether-like organic solvents employed for general inhalational anesthesia. Few physicians realize the debt that we owe to Ecuador and surrounding countries, whose indigenous hunters wore blow gun quivers (above) full of curare-tipped missiles to dart overhead prey, such as monkeys and birds. Sadly, hunters who failed to dart away quickly enough were occasionally themselves darted by their own missile's return to earth. When a hunter would spot the telltale signs of his companion's eyelids growing heavy from the curare poison, the pair would rest against a tree and reminisce about their adventures together as the companion's respirations faltered and finally failed. (Copyright © the American Society of Anesthesiologists, Inc.)

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