

# Untangling the Triple Low

## Causal Inference in Anesthesia Research

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**I**N 1965, Sir Austin Bradford Hill<sup>1</sup> published a landmark article in which he considered under what circumstances could a clinician convert an observed association into a verdict of causation. In other words, if there is a link between a risk factor and an adverse outcome, does it hold true that removing or reducing this risk factor will reduce the risk of that adverse outcome occurring? He outlined nine criteria to support causal inference (table 1). Bradford Hill emphasized that clinicians should not solely rely upon these as hard and fast rules for evidence—he reminded readers that, “None of my nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis .... What they can do, with greater or less strength, is to help answer the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”<sup>1</sup> He went on to remind readers that statistical tests of significance can not (and do not) answer this question.

It is with this background that readers should consider the evidence addressing the “triple low” hypothesis first outlined by Sessler *et al.* in *ANESTHESIOLOGY* in 2012.<sup>2</sup> In brief, the triple low refers to an intraoperative state in which there is hypotension during the delivery of low alveolar concentration of volatile anesthesia, combined with a low bispectral index (BIS), a state presumed to reflect anesthetic hypersensitivity. Sessler *et al.*<sup>2</sup> found that the triple low state was associated with a higher risk of 30-day mortality. This line of research first began with Monk *et al.*,<sup>3</sup> who in 2005 reported an intriguing relation between



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cumulative deep hypnotic time as indicated by a low BIS and 1-yr mortality. Many other studies have since found similar associations.<sup>4</sup>

In this issue of *ANESTHESIOLOGY*, Kertai *et al.*<sup>5</sup> attempted to reproduce Sessler *et al.*'s original findings in an observational study of an electronic perioperative database that included 16,263 patients undergoing noncardiac surgery. They did identify an association between the cumulative duration of the triple low state and 30-day mortality, but this association disappeared *after* adjusting for specific patient- and procedure-related characteristics. In other words, the triple low state was not independently associated with 30-day mortality.

There are several reasons why this study may have missed a true association—similar to many large-scale observational studies, the data were derived from an electronic perioperative medical record linked to administrative databases whose prime purposes are not research; the latter is more likely to have inaccurate and incomplete data and a greater risk of residual confounding compared with prospectively collected data in a clinical trial.<sup>6</sup> On the contrary, such datasets are large and so provide statistical power, are readily available, and offer greater generalizability because they reflect routine practice.

With multivariable testing, Kertai *et al.*<sup>5</sup> found a possible relation between low blood pressure alone ( $P = 0.0197$ ), and intriguingly, a low BIS seemed to be associated with a lower risk of mortality (but  $P = 0.0683$ ). These findings could indicate true associations or they could be false because of residual confounding or collinearity.<sup>7,8</sup> Great caution is needed when interpreting multivariable

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**Table 1.** An Outline of the Bradford Hill Criteria<sup>1</sup>

Criteria	Explanation
1. Strength of association	The stronger the relation between a risk factor and the effect (outcome), the less likely it is that the relation is due to a third or extraneous factor.
2. Consistency	Multiple studies in a range of settings report similar results.
3. Specificity	Ideally, the effect has only one cause.
4. Temporality	The purported cause should be present before the effect occurs.
5. Biological gradient	A dose–response relation between the risk factor and the effect.
6. Biological plausibility	There should be a rational and theoretical basis explaining how or why the risk factor led to the effect.
7. Coherence	The association should not conflict with known facts.
8. Experimental evidence	Is there any supportive research based on experiment; if preventive action is taken, does the effect dissipate?
9. Analogy	A previously accepted phenomenon in one area can be applied to another.

analysis of nonrandomized data. Spurious associations can appear because one variable is associated with a third, perhaps unmeasured, variable that is truly linked in a causal pathway. Reliable multivariable analysis should also consider interaction terms and avoid overfitting of data and model instability.<sup>8</sup> Most of these concerns were admirably addressed by Kertai *et al.* in their analyses. Their findings are robust and believable.

A most obvious explanation for the original triple low-mortality association is that frail and/or elderly patients are both more likely to enter a triple low state during anesthesia and are more likely to die after surgery—that is, some aspect(s) of a patient’s health status is likely to be the true causal factor. In their analysis, Kertai *et al.* found that older age, poorer physical status, emergency surgery, and a surgical risk index score remained significant predictors of 30-day mortality. Once these confounding factors were accounted for in the multivariable model, the triple low state was found to be unrelated to mortality.

If we apply the Bradford Hill criteria (table 1), the association between the triple low state and mortality is weak, inconsistent, could be explained by other factors that are supported by stronger evidence (*e.g.*, patient frailty), and is only based on nonrandomized data from one study. On the contrary, the hypothesis has some plausibility in that the larger doses of some anesthetic drugs might be immunosuppressive or neurotoxic, the triple low state incorporates hypotension which we know can impair vital organ perfusion, it is temporally related, and there is a demonstrable biological gradient. So, if we take up Bradford Hill’s challenge and ask ourselves, *is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?* The answer is clearly yes, it is most likely an epiphenomenon. The weight of evidence supporting a causal relation between triple low, or a low BIS, and excess mortality is unconvincing, but the concept is not yet ready to be dismissed because the triple low state, unlike the other factors identified by Kertai *et al.*,<sup>5</sup> is potentially modifiable such that it could change how we practice anesthesia around the world.

How should anesthesiologists respond to the disparate results from the “triple low” and “low BIS” observational studies? The underlying hypotheses deserve our ongoing attention and need testing with definitive randomized trials. At least two such related trials are underway—see [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00998894) and [www.anzctr.org.au](http://www.anzctr.org.au) (ACTRN12612000632897). But at this point in time, there is no justification in avoiding the triple low state or a low BIS on the basis of current evidence. As stated by Bradford Hill,<sup>1</sup> “*All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore knowledge we already have, or to postpone the action that it appears to demand at a given time.*” We have a moral and ethical duty to our patients and society to pursue knowledge that informs our practice to make anesthesia safer and more cost-effective.

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### Competing Interests

Dr. Myles is a coauthor on postoperative nausea and vomiting guidelines led by Tong J. Gan, M.D., M.H.S., F.R.C.A., the senior author of the accompanying article, and is a chief investigator on the BALANCED trial ([www.anzctr.org.au](http://www.anzctr.org.au), ACTRN12612000632897), a large clinical trial comparing two levels of anesthetic depth on 1-yr mortality after major surgery.

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