Volatile Agents *versus* Propofol in Cardiac Surgery: Comment

To the Editor:

We read with great interest the systematic review and meta-analysis by Bonanni *et al.*,[1] recently published in Anesthesiology, in which the authors investigated how different anesthetic agents (volatile *vs.* propofol) affected outcomes in patients who had undergone cardiac surgery with cardiopulmonary bypass. The main finding—that volatile anesthetics were superior to propofol with regard to long-term mortality as well as cardioprotective effects—is clinically valuable information. Some methodologic issues should be further discussed and clarified, however, and there is a need for data validation, for three main reasons which we describe below.

First, we are skeptical about the authors' assertion that the majority of the studies were at low risk of bias (Supplemental Digital Content 2, http://links.lww.com/ALN/C280, in Bonanni *et al.*[1]). It is almost impossible for anesthesiologists to perform either total intravenous anesthesia or volatile induction and maintenance anesthesia blindly. Performance bias is therefore unavoidable in trials comparing these anesthesia methods,[2] and its potential influence will be stronger in some selected studies. A recent trial reported by Landoni *et al.*[3] that was included in the Bonanni *et al.*[1] meta-analysis was terminated early for the reason of futility, reducing the power of the study and leading to an underestimation of the treatment effect.[4] This may have induced bias. Because appraisal of risk of bias in included studies is an integral part of systematic review methodology, the authors should clarify why most of the trials they assessed were deemed to have low risk of bias.

Second, the positive results pertaining to improved long-term survival with volatile anesthetics are driven mainly by the study of Likhvantsev *et al.*,[5] but the long-term mortality rate in that study was considerably higher (18.8% in the propofol group) than it was in the other studies analyzed (4.2%), which Likhvantsev *et al.*[5] acknowledged in their study. In addition, we assume that their study entailed high risk of attrition bias, not low risk of bias. In the funnel plot of Figure 2,[1] there were 52 deaths in the volatile group (437 patients) and 81 in the propofol group (431 patients) in the study by Likhvantsev *et al.*[5] However, the original study of Likhvantsev *et al.*[5] reported that 1-yr mortality rates were 52 of 292 (17.8%) in the sevoflurane group and 81 of 326 (24.8%) in the total intravenous anesthesia group.[5] No explanation of the lost to follow-up rate at 1 yr was provided, but with more than a quarter of patients lost to follow-up—resulting in substantially incomplete outcome data—high risk of attrition bias is arguably inevitable. Accordingly, the authors should clearly state any assumptions or imputation methods to handle missing data, and the effects of imputation should be investigated *via* sensitivity analyses, which may change interpretations of the results.[6]

Last, we would like to see the overall quality of the evidence assessed *via* the grading of recommendations assessment, development, and evaluation (GRADE) framework for relevant outcomes.[7] The information thus derived would be valuable to the readers of Anesthesiology.

Competing Interests

The authors declare no competing interests.

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Volatile Agents *versus* Propofol in Cardiac Surgery: Reply

In Reply:

We thank Yonekura *et al.*[1] for raising the problem of the risk of bias in our meta-analysis.[2] First, we agree that it is almost impossible for anesthesiologists to perform fully blindly either volatile anesthetics or total intravenous anesthesia for anesthesia maintenance. Accordingly, some performance bias in trials comparing two anesthetics is unavoidable. However, such a bias can be markedly reduced if researchers other than anesthesiologists examine data and, more importantly, when outcomes are objective as in our meta-analysis. With regard to the recent article by Landoni *et al.*,[3] the early conclusion of the trial may have in fact underestimated the treatment effect, so the inclusion in our meta-analysis of the published data may in turn have theoretically reduced the treatment effect. Nevertheless, another recent meta-analysis reports low risk of bias with regard to the above-mentioned trial.[4] Moreover, by considering all recent meta-analyses that report in detail the risk of bias,[4–8] results are similar to ours (61% low risk, 31% unclear risk, 8% moderate/high risk).

Second, in our meta-analysis we considered data on 1-yr mortality reported by Likhvantsev *et al.*[9] in the result session (*i.e.*, 52 events in the volatile group and 81 in the total intravenous anesthesia group). However, we related these events to all studied patients (437 in the volatile group and 431 in the total intravenous anesthesia group) rather than to an unexplained number of 292 patients in the volatile group and 326 in the total intravenous anesthesia group. Accordingly, the mortality rate we reported is 11.9% *versus* 18.8% instead of 17.8% *versus* 24.8%. When combining data reported in tables 3 and 4, mortality is 17.8% in the volatile group (78 of 437 patients) and 25.3% in the total intravenous anesthesia group (109 of 431). The reason for these differences in results is unknown. According to the above-reported data, the Likhvantsev *et al.*[9] study has a high risk of attrition bias, even though this bias is considered low in the meta-analysis by Jiao *et al.*[4] or high in that by El Dib *et al.*[6]

Regarding the last point, we agree that the grading of recommendations assessment, development, and evaluation (GRADE) checklist[10] is probably more complete than Cochrane risk of bias, although the latter is predominant in recent meta-analyses including those on our topic. In conclusion, the careful reanalysis of methodologic issues seems to validate the results of our meta-analysis.

Competing Interests

The authors declare no competing interests.

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Correcting Acid Base Interpretation for High Altitudes

To the Editor:

Acid–base results normally report arterial values: overall acidity (pH), $Paco_2$, and Standard Base Excess (SBE). Although numerical values are customary, an interactive diagram (http://www.acid-base.com/interactive.php, accessed September 25, 2020) helps recognition by displaying results over zones radiating out from a normal center based on a meta-analysis of relevant papers (figs. 1 and 2).[1] The numerical values and the text are appropriate for managing patients at or near sea level.[2] However, as altitude increases, the ventilatory response to hypoxia induces chronic respiratory alkalosis, leading to a reduction in serum bicarbonate and thus progressively misleading results.

One author (I.S.) recognized the critical need for altitude-appropriate values, diagram, and text interpretations. He provided the equation relating altitude to acid–base diagrams, as well as the concept that in healthy altitude-adapted individuals, the metabolic component—Altitude Base Excess (ABE)—must be regarded as 0 mEq/l, *i.e.*, requiring no treatment.[3,4] AG created the resulting interactive acid–base diagram (https://www.acid-base.com/altitude.php, accessed September 25, 2020). The local high altitude from 4,920 feet up to 16,500 feet is inserted to obtain a diagram for adapted residents.

The scale values for the $Paco_2$ on the high-altitude diagram (fig. 2) vary with the altitude. Moving the mouse to the patient's pH and $Paco_2$ provides the ABE. The various zones all provide their customary interpretation just as they did at sea level but now altitude appropriate. This provides relevant text descriptions with a target for therapy, facilitates tracking a patient's progress, and makes abnormalities recognizable.

Illustrative Examples

These clinical examples are for patients living in Bogota, Colombia (altitude, 8,660 feet). They illustrate the critical value of the high-altitude diagram:

On the sea-level diagram (fig. 1), patient A appears to have normal acid base results (pH 7.4, $Paco_2$ level of 40 mmHg). However, he has chronic respiratory acidosis with metabolic alkalosis (compensation)—obvious on the high-altitude diagram (fig. 2).

On the sea-level diagram (fig. 1), patient B (pH 7.32, $Paco_2$ level of 40mmHg) apparently has pure metabolic acidosis, whereas he actually has pure respiratory acidosis due to drug overdose—obvious on the high-altitude diagram (fig. 2).