

Does Correcting the Numbers Improve Long-term Outcome?

ADVANCES in the understanding of anesthetic pharmacology and perioperative physiology, coupled with improved patient monitoring, have significantly contributed to improvements in quality of care and perioperative outcome.[1–3] In this issue of ANESTHESIOLOGY, Samarska *et al.* describe preclinical research that addresses the anesthetic modulatory effects on the physiologic adaptation to hemorrhagic shock; their data have led them to the conclusion that nitrous oxide promotes hemodynamic stability.[4] In their studies, mice were exposed to anesthesia, either isoflurane (1.4%) in oxygen (33%) or isoflurane (1.4%) plus nitrous oxide (66%) in oxygen (33%), and underwent a sham procedure, hemorrhagic shock, or shock plus fluid resuscitation, during which time hemodynamic measurements were obtained. Thereafter, vascular responsiveness was assessed *ex vivo* in aortic rings. Isoflurane treatment attenuated the maximal aortic contractile responses to phenylephrine, corroborating earlier reports with volatile anesthetics.[5] Shock, with or without resuscitation, mitigated the isoflurane-induced attenuation of phenylephrine responses, although the biphasic pattern of relaxation and then contraction with acetylcholine was altered. The *ex vivo* effects induced by *in vivo* isoflurane exposure were mitigated when supplemented with nitrous oxide. However, in the shock state the addition of nitrous oxide induced acidosis when compared with isoflurane, and further physiologic differences (such as oxygenation) confounds clear interpretation of the experimental findings. Even though animals were at different depths of anesthesia under these conditions, the authors attribute the pharmacologic properties of nitrous oxide for "normalizing" vasoreactivity, and speculate that nitrous oxide may induce increased perioperative hemodynamic stability.

Samarska *et al.* also observed that nitrous oxide exposure was associated with a higher mean arterial blood pressure in the sham-treated animals despite the increased depth of anesthesia[4]; this finding corroborates previous studies demonstrating the vasoconstrictive properties of nitrous oxide.[6] Yet recent clinical studies have reported minor difference in blood pressure when comparing nitrous oxide or air as the carrier gas.[6–9] Thus it is highly speculative that the modest increments (of the order of 10 mmHg) reported by Samarska *et al.* and others will exert a positive long-term clinical benefit.

This Editorial View accompanies the following article: Samarska IV, van Meurs M, Buikema H, Houwertjes MC, Wulfert FM, Molema I, Epema AH, Henning RH: Adjunct nitrous oxide normalizes vascular reactivity changes after hemorrhagic shock in mice under isoflurane anesthesia. ANESTHESIOLOGY 2009; 111:600–8.

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Placing Physiologic Normalization into Clinical Context

It is not possible to ascribe a benefit to the "normalization" achieved by the administration of nitrous oxide because there was no "nonanesthetized" control group, no correlation with postoperative hemodynamic changes, and no assessment of long-term outcome. Nonetheless, the authors' interest in improving hemodynamic stability in the postoperative period is commendable, especially as there is a tendency to view improvement as simply an intraoperative endpoint within anesthesiology. Rather our discipline needs to focus on endpoints of anesthetic management that are important by virtue of the fact that patient outcome is affected. In this manner, physiologic variables should not be used as surrogate markers for long-term outcomes unless their association is tightly correlated.

When Can Modifying Intraoperative Numbers Improve Long-term Outcome?

Identification of patient comorbidities is critical to understanding risk stratification of vulnerable patients and, therefore, their level of care. In addition, anesthesiologists need to determine the modifiable risk factors occurring in the perioperative period that may be manipulated to improve outcomes. A recent analysis started this process by evaluating the importance of intraoperative physiologic variables to determine long-term cardiovascular outcomes and death.[10] Data from this large cohort study identified higher-risk patients as having two or more comorbidities: Age, obesity, emergency surgery, previous cardiac intervention, congestive cardiac failure, cerebrovascular disease, and hypertension. Patients with two or more risk factors who had an adverse cardiac event were more likely to have had intraoperative hypotension (mean arterial pressure less than 50 mmHg or decreased by 40%, lasting at least 10 min) among other modifiable risks. Similar to previous data for vascular surgical patients,[11] those with three or more risk factors who sustained an adverse cardiac event were also more likely to have endured intraoperative tachycardia. Unfor-

tunately the study was underpowered to ascertain an independent effect of the hemodynamic variables on adverse cardiac events; adequately powered studies are required to further investigate these findings, and that of physiologic changes in the postoperative period,[11] to determine long-term patient outcomes.

Clearly it is important to "correct the numbers" intraoperatively, but how? Perhaps if tachycardia predisposes patients with three or more cardiovascular risk factors to adverse cardiac events, then these are the subjects who are most likely to benefit from perioperative β-blockade.[11,12] Exposing patients with fewer risk factors may merely increase their chance of hypotension and thus increase their cardiac and stroke risk.[13] These findings also question the clinical significance of nitrous oxide-induced improvement in intraoperative mean arterial blood pressure, suggesting that this effect will be too modest alone (approximately 10 mmHg) to alter cardiac risk. Whether postoperative hemodynamic parameters are improved after nitrous oxide exposure remains unknown.

Long-term Anesthetic Effects: Nitrous Oxide Case Study

The use of nitrous oxide for the maintenance of anesthesia exemplifies the need to focus on long-term outcomes. While the purported increased hemodynamic stability ("correcting the numbers") with nitrous oxide has been regarded as good for cardiac risk, other factors may mitigate this benefit; for example, halogenated volatile anesthetics consistently demonstrate superior organ-protective effects as compared with nitrous oxide or intravenous agents in experimental studies.[14–16] This may translate into improved tolerance to lower perfusion pressure or reduced oxygen supply with an anesthetic technique that is based solely on halogenated volatile anesthesia. Thus the addition of nitrous oxide, while "sparing" the volatile, may reduce this potential benefit accrued from the volatile anesthetic gas. Similarly, individual anesthetic effects on cellular metabolism could also be important.[17] Nitrous oxide may also influence cardiac risk by increasing homocysteine levels.[18,19] Raised homocysteine levels predispose to higher cardiac risk in the community[20] and in cardiac surgical patients[21] *via* endothelial dysfunction and possible effects on coagulation.[19] Putatively related to this increased perioperative myocardial ischemia, increased homocysteine levels have been noted with nitrous oxide-based anesthesia (however, long-term follow-up of these patients has not been conducted).[18] To further ignite debate, nitrous oxide administration was recently associated with an increased number of delayed ischemic neurologic events in a *post hoc* subgroup analysis of the intraoperative hypothermia for aneurysm surgery trial.[8] Again this may be secondary to raised homocysteine levels in the nitrous oxide group (although these were not measured). Critically though, the long-term outcomes between the nitrous oxide and no nitrous oxide groups were not different.

Therefore, the use of nitrous oxide to improve hemodynamic stability based on the assumption that it will alter long-term patient outcomes may be flawed. It is therefore timely that the ENIGMA-II trial protocol has recently been published.[22] ENIGMA-II is designed to ask whether nitrous oxide predisposes to adverse cardiac events based on its ability to modify homocysteine levels. The trial has a solid scientific foundation,[19,22,23] with proof of principal demonstrated in smaller clinical trials.[18,23] ENIGMA-II will be a 7,000-patient study designed to evaluate whether avoidance of nitrous oxide administration is associated with a 25% decrease risk of cardiac events or death ($\alpha = 0.05$; $\beta = 0.1$). Of course it is possible that the study may find that the higher intraoperative mean arterial blood pressure induced by nitrous oxide may improve outcomes. Whatever the results of ENIGMA II, the critical approach here is to focus on long-term patient outcomes; outcomes that matter to the patient.

Impact of Long-term Outcome Studies

Long-term outcomes studies are needed to define the optimal anesthetic management for the more than 234 million patients who undergo surgery each year.[24] Going beyond the results that are based on cohorts of "average" patients, anesthesiologists will need to further personalize care for the individual patients, using careful clinical phenotyping that will be guided in the future by biomarkers that evolve from postgenomic research endeavors. Both our specialty and the welfare of our patients will benefit from rigorous translation of the evidence from well-conducted clinical research into practice. Our discipline's research program has to focus on long-term outcomes to improve endpoints that both matter to the patient and improve the efficiency of healthcare resource use. Defining how to "correct the numbers" is a critical part of this approach; we need studies to define how these values should be modified. It is more than likely that anesthesiologists can continue to improve long-term patient outcomes, but we need the studies to demonstrate how.

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