Nitrous Oxide and Cardiovascular Outcome: Perspective from the POISE Trial

Rachel Eshima McKay, MD

Although numerous trials have been conducted over the past 2 decades assessing strategies to decrease the risk of postoperative myocardial infarction (MI), clinicians are still left with limited answers regarding which interventions will improve outcomes for their patients. Unfortunately, rates of cardiovascular complications after noncardiac surgery continue to be as high as 6% in patients with risk factors for coronary artery disease,[1–3] and these rates may increase over time. According to the US Census Bureau, between 2000 and 2010 the US population over age 65 years reached 40 million and the group aged 85 to 94 years experienced 30% increase in growth, a rate 3 times greater than that of the overall population. Recent observational studies have confirmed advanced age as a predictor of both postoperative myocardial damage and 30-day postoperative mortality.[1,4] Assuming that the age distribution of our surgical population will change in accordance with that of the population at large, we should expect that a growing number of patients will suffer costly postoperative cardiovascular complications in the future, unless we identify and implement effective risk reduction measures. Although numerous small studies have explored strategies to reduce risk of postoperative MI within the past 2 decades,[5–8] no large trial to date has offered conclusive evidence of a single, universally protective intervention.

Clinicians looking to the literature for evidence-based guidance in care of the high-risk surgical patient often encounter findings that appear to be inconsistent. For example, several studies have demonstrated that perioperative β-blockade can provide protection against postoperative ischemia, MI, and mortality,[5,6,9] whereas others failed to demonstrate this protective benefit.[10,11] More recently, results from the PeriOperative ISchemic Evaluation (POISE) trial,[12] the largest randomized controlled trial evaluating the impact of perioperative β-blockade on risk of nonfatal MI and 30-day all-cause mortality, challenged its unequivocal benefit. Devereaux et al.[12] showed that metoprolol, although effective in reducing ischemia and nonfatal MI, increased risk of stroke and death when administered in the manner prescribed by the trial investigators. Would modification of the POISE protocol (e.g., relating to specifics of the patient selection, chosen drug and dose) have mitigated the higher rate of stroke and death in the treatment group, or minimized or eliminated the findings showing protective effects on ischemia and nonfatal MI? These seemingly contradictory results remind us that (1) interventions whose benefits were once considered "intuitively reasonable" may be subsequently disproven by a large randomized controlled trial; and that (2) highly effective, beneficial drugs can, under certain circumstances, cause harm. The influence of genetic polymorphisms, affecting cytochrome P450 2D6 metabolic pathways or adrenergic receptor signaling mechanisms, on the risk versus benefit of perioperative β-blockade, is an area of ongoing investigation.[13]

The anesthesia provider faces the special challenge of identifying an anesthetic strategy that provides excellent operating conditions, predictable recovery of vital functions, and high patient satisfaction, without imposing liability on patient safety. Toward that end, the appropriate role of nitrous oxide, the world's oldest general anesthetic, has become the subject of recurring controversy. In one respect, it possesses numerous favorable properties (among others, low tissue solubility with minimal context sensitivity and relatively low acquisition cost). However, it does have indisputable disadvantages. It has the ability to expand gas-filled spaces, with the potential to cause direct patient injury in cases of pneumothorax, intestinal obstruction, or retinal detachment. Nitrous oxide administration at low fresh gas flow rates will lead to delivery of a hypoxic gas mixture, as the nitrous oxide becomes concentrated from profound decline in tissue uptake over time, unless the clinician adjusts gas partitioning with the guidance of a properly calibrated oxygen analyzer. Nitrous oxide exposure leads to inhibition of the transmethylation reaction necessary for maintenance of the myelin sheath, and in susceptible patients, cases of profound neurologic deterioration have been reported after a single exposure.[14] In addition to these obvious scenarios, nitrous oxide may also exert clinical impact not immediately recognized at the time of its administration. By irreversible oxidation of vitamin B12, nitrous oxide effectively impairs conversion of homocysteine to methionine, and consequently this impairment leads to dose-dependent plasma homocysteine

From the Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California.

Accepted for publication January 4, 2013.

The author declares no conflicts of interest.

Reprints will not be available from the author.

Address correspondence to Rachel Eshima McKay, MD, Department of Anesthesia and Perioperative Care, University of California San Francisco, 521 Parnassus Avenue, C450 San Francisco, CA 94143-0648. Address e-mail to eshimar@anesthesia.ucsf.edu.

DOI: 10.1213/ANE.0b013e3182870e46

elevation.[15] Elevated plasma homocysteine, among the general population, is associated with increased risk of ischemic heart disease, stroke, and thrombosis.[16,17] Surgical patients receiving nitrous oxide not only develop higher plasma homocysteine levels after surgery, compared with patients not receiving nitrous oxide,[18,19] but these values often remain elevated for several days thereafter.[20] Many investigators have hypothesized that this nitrous oxide–mediated homocysteine elevation may contribute to increased incidence of adverse postoperative cardiovascular events. Addressing this potential cardiovascular risk to those receiving nitrous oxide, compared with controls, one study has shown a subsequently greater incidence of myocardial ischemia, detected by Holter monitoring, during the 48-hour period after surgery.[21] On the basis of these findings, an hypothesis associating nitrous oxide with adverse cardiovascular sequelae would seem plausible. Interestingly, in the past several years, possibly coincident with publications suggesting a higher incidence of both cardiac[21] and other[22] adverse outcomes, nitrous oxide administration has declined in the United States, utilized in 33% of all general anesthetics given in 2009 but only 21% of those in 2011 (http://www.hraresearch.com/expertise/hospital-data-audits, Healthcare Research and Analytics Operating Room Audit, accessed August 13, 2012).

In this issue of *Anesthesia & Analgesia*, Leslie et al.[23] examined the impact of nitrous oxide administration on the composite outcomes of nonfatal MI and 30-day all-cause mortality among the subjects in the POISE trial. Contrary to what we might have expected based on previous investigations, Leslie et al.[23] found no evidence supporting the hypothesis linking nitrous oxide to adverse cardiovascular events. How might this be explained? First, the previously described hypothesis, perhaps even the conclusions, may be flawed. The POISE trial, unlike the trials investigating homocysteine levels, measured objective, clinically relevant end points. Although homocysteine elevation in the perioperative milieu appears to be associated with postoperative morbidity, there are several sources of uncertainty. First, regarding the chosen experimental outcome, Badner et al.[21] used myocardial ischemia, a surrogate measure, based on Holter evidence of ST depression within 48 hours of surgery as the measured end point, finding a significantly greater incidence after nitrous oxide exposure compared with controls. Although ST segment depression detected by continuous electrocardiogram monitoring has clear predictive association with subsequent major adverse cardiac events,[24,25] it does not, by itself, constitute a clinically significant outcome. Another issue involves the possible confounding issue of F_{IO_2}– in the ENIGMA trial, the control group received approximately >70% inspired oxygen, compared with 33% F_{IO_2} in the nitrous oxide group. The relationship between F_{IO_2} and outcome has itself been the subject of intense scrutiny and speculation over the past decade. Finally, Myles et al.[18] concluded that although nitrous oxide did increase risk of overall morbidity, this association could not be explained by homocysteine elevation alone. At most, elevated plasma homocysteine might provide partial influence, among many others, for the clinically relevant end points measured in the trial. Might nitrous oxide exert other physiologic influence that could, in contrast to the possible harm exerted by metabolic inhibition, offer other benefits, such as greater circulatory stability? Nitrous oxide is known to exert heterogeneous circulatory effects, depending on the presence of concomitant anesthetics, but overall increases α-adrenergic tone under most circumstances.[26] Thus, the use of nitrous oxide, combined with lesser amounts of volatile agents, propofol or opioids, might allow the clinician to economize use of the more depressant anesthetic or drug. Previous experiments have shown that administration of potent inhaled anesthetic in nitrous oxide–oxygen versus oxygen alone, at equivalent minimum alveolar concentration multiples, results in less pronounced decrease in mean arterial pressure, likely due to both the sparing of the potent anesthetic and nitrous's direct effect on peripheral vascular resistance.[27–29] One small study of patients undergoing coronary artery bypass surgery indicated that although episodic exposure to 70% nitrous oxide did not result in segmental wall motion abnormality or electrocardiogram change indicative of ischemia, the cause and significance of persistent left ventricular hypokinesis in 1 of 7 subjects after initial nitrous oxide exposure remains unclear.[29] Findings suggesting that nitrous oxide affords better circulatory stability, compared with an equivalent minimum alveolar concentration fraction of a more depressant anesthetic, speak to the need for further clinical outcome studies weighing this potentially beneficial characteristic against the clinical cost of perioperative plasma homocysteine elevation.

Despite the uncertainties raised by Leslie et al.[23] in the case against nitrous oxide, there are legitimate reasons to maintain skepticism for findings that would seemingly support a case for its continued use. First, because randomization of subjects was to β-blockade versus placebo, rather than to nitrous oxide versus oxygen (or versus other anesthetic technique), it is not reasonable to assume that similar characteristics existed between patients who either did or did not receive nitrous oxide and some of these characteristics may have been influential of the primary outcome. Second, Propensity Scoring can certainly improve matching of characteristics between those subjects exposed versus unexposed in an observational trial, thereby decreasing selection bias. Unfortunately, it cannot eliminate such bias entirely.[30] Propensity Scoring makes adjustments for identifiable characteristics, but cannot adjust for factors that nobody measured or knew about. Furthermore, the Propensity Score matching process may underestimate disparity between characteristics when substantial overlap does not exist between groups; examination of the Leslie et al.'s[23] data suggests that nitrous use was at least somewhat influenced by the country and hospital in which the subject underwent surgery. In considering this possibility of allocation bias, factors that might be difficult to identify in a post hoc analysis include issues related to the planned surgery, as well as the clinician's judgment of the patient's clinical condition at the time, including his anticipated tolerance for lower F_{IO_2}. And, because nitrous oxide administration was a conscious choice on the part of the clinician, cointervention may have served to further confound, e.g., by proportional adjustment of other anesthetics. Last, nitrous oxide was treated as a binary (yes/no) predictor—no distinction was made between administration of high inspired concentration over several

hours versus brief administration, e.g., during the final 15 to 20 minutes of a case after anesthetics with higher tissue solubility have been discontinued. As we have learned from the primary findings of many trials, including POISE, the clinical impact of a drug may vary depending on numerous circumstances under which it is given.

Overall, the findings of Leslie et al.,[23] for now, are reassuring. Despite the described methodological limitations, there are strong arguments to be made in favor of these post hoc findings. Large clinical trials are time consuming and expensive, and our anticipated greater resource constraints may make such trials even more difficult to conduct in the future. Although observational studies will not provide the same certainty about cause and effect as will randomized trials, more sophisticated analytical techniques and selection of appropriate, clinically relevant outcomes may enable us to minimize bias, and ask multiple research questions using the data derived from a single large trial. The most reliable method toward understanding the impact of nitrous oxide on outcome would come from an adequately powered, well-designed randomized controlled trial. In fact, the ongoing ENIGMA-2 trial, a large, mulicenter study of high-risk patients assigned to nitrous oxide–oxygen versus nitrogen–oxygen (F_{IO_2} = 0.3 in all cases), with primary end points of cardiovascular events and all-cause mortality at 30 days after surgery, promises to shed light on the question more definitively. Nevertheless, as the authors have justly stated in their discussion, the findings of this POISE post hoc analysis will undoubtedly generate further hypotheses and avenues of investigation.

DISCLOSURES

Name: Rachel Eshima McKay, MD.
Contribution: This author wrote the manuscript.
Attestation: Rachel Eshima McKay approved the final manuscript. Rachel Eshima McKay is the archival author.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI.

REFERENCES

1. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307: 2295–304
2. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9
3. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011;154:523–8
4. Alcock RF, Kouzios D, Naoum C, Hillis GS, Brieger DB. Perioperative myocardial necrosis in patients at high cardiovascular risk undergoing elective non-cardiac surgery. Heart 2012;98:792–8
5. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20
6. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789–94
7. Wallace AW, Galindez D, Salahieh A, Layug EL, Lazo EA, Haratonik KA, Boisvert DM, Kardatzke D. Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology 2004;101:284–93
8. O'Neil-Callahan K, Katsimaglis G, Tepper MR, Ryan J, Mosby C, Ioannidis JP, Danias PG. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (StaRRS) study. J Am Coll Cardiol 2005;45:336–42
9. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. Anesthesiology 1998;88:7–17
10. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Nørgaard P, Fruergaard K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jørgensen L, Jørgensen J, Rovsing ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Mølgaard Y, Foss NB, Elkjaer J, Dehlie B, Boysen K, Zaric D, Munksgaard A, Madsen JB, Øberg B, Khanykin B, Blemmer T, Yndgaard S, Perko G, Wang LP, Winkel P, Hilden J, Jensen P, Salas N; DIPOM Trial Group. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482
11. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am Heart J 2006;152:983–90
12. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–47
13. Nagele P, Liggett SB. Genetic variation, β-blockers, and perioperative myocardial infarction. Anesthesiology 2011;115:1316–27
14. Flippo TS, Holder WD Jr. Neurologic degeneration associated with nitrous oxide anesthesia in patients with vitamin B12 deficiency. Arch Surg 1993;128:1391–5
15. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesth 1987;59:3–13
16. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202
17. Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. J Am Coll Cardiol 1996;27:517–27
18. Myles PS, Chan MT, Leslie K, Peyton P, Paech M, Forbes A. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br J Anaesth 2008;100:780–6
19. Badner NH, Drader K, Freeman D, Spence JD. The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine. Anesth Analg 1998;87:711–3
20. Ermens AA, Refsum H, Rupreht J, Spijkers LJ, Guttormsen AB, Lindemans J, Ueland PM, Abels J. Monitoring cobalamin inactivation during nitrous oxide anesthesia by determination of homocysteine and folate in plasma and urine. Clin Pharmacol Ther 1991;49:385–93
21. Badner NH, Beattie WS, Freeman D, Spence JD. Nitrous oxide-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in

patients undergoing carotid endarterectomy. Anesth Analg 2000;91:1073–9
22. Myles PS, Leslie K, Peyton P, Paech M, Forbes A, Chan MT, Sessler D, Devereaux PJ, Silbert BS, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S; ANZCA Trials Group. Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial: rationale and design. Am Heart J 2009;157:488–494.e1
23. Leslie K, Myles P, Devereaux PJ, Forbes A, RaoMelancini P, Williamosn E, Xu S, Foex P, Pogue J, Arrieta M, Bryson G, Paul J, Paech M, Merchat R, Choi P, Sear J, Yang H. Nitrous oxide and serious morbidity and mortality in the POISE trial. Anesth Analg 2013;116:1034–40
24. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990;323:1781–8
25. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547–54
26. Eisele JH, Smith NT. Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 1972;51:956–63
27. Cahalan MK, Prakash O, Rulf EN, Cahalan MT, Mayala AP, Lurz FC, Rosseel P, Lachitjaran E, Siphanto K, Gussenhoven EJ. Addition of nitrous oxide to fentanyl anesthesia does not induce myocardial ischemia in patients with ischemic heart disease. Anesthesiology 1987;67:925–9
28. Cahalan MK, Weiskopf RB, Eger EI 2nd, Yasuda N, Ionescu P, Rampil IJ, Lockhart SH, Freire B, Peterson NA. Hemodynamic effects of desflurane/nitrous oxide anesthesia in volunteers. Anesth Analg 1991;73:157–64
29. Slavik JR, LaMantia KR, Kopriva CJ, Prokop E, Ezekowitz MD, Barash PG. Does nitrous oxide cause regional wall motion abnormalities in patients with coronary artery disease? An evaluation by two-dimensional transesophageal echocardiography. Anesth Analg 1988;67:695–700
30. Cook T, Shadish W, Campbell D. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston: Houghton-Mifflin, 2002