

Nitrous Oxide-Induced Increased Homocysteine Concentrations Are Associated with Increased Postoperative Myocardial Ischemia in Patients Undergoing Carotid Endarterectomy

Neal H. Badner, MD, FRCP(C)*, W. Scott Beattie, MD, PhD, FRCP(C)‡, David Freeman, PhD†, and J. David Spence, MD, FRCP(C)†

Departments of *Anesthesiology and †Clinical Pharmacology, University of Western Ontario, London, Ontario; and ‡Department of Anesthesiology, McMaster University, Hamilton, Ontario, Canada

Nitrous oxide anesthesia causes increased postoperative plasma homocysteine levels. Acute increases in plasma homocysteine are associated with impaired endothelial function and procoagulant effects. This nitrous oxide-induced plasma homocysteine increase may therefore affect the risk of perioperative cardiovascular events. This prospective, randomized study was therefore designed to evaluate the effect of nitrous oxide anesthesia and postoperative plasma homocysteine levels on myocardial ischemia in patients undergoing carotid endarterectomy. After institutional review board approval and written informed consent, 90 ASA Class I–III patients presenting for elective carotid endarterectomy were randomized to receive general anesthesia with or without nitrous oxide. Prior to induction, on arrival in the postanesthesia care unit, and after 48 h, blood samples were obtained for homocysteine analysis. Three hours prior to induction and

for 48 h postoperatively patients were monitored by a three-channel, seven-lead Holter monitor. Postoperatively in the postanesthesia care unit and at 48 h the nitrous oxide group had increased mean plasma homocysteine concentrations of 15.5 ± 5.9 and 18.8 ± 14.7 when compared with the nonnitrous group of 11.4 ± 5.2 and 11.3 ± 4.0 $\mu\text{mol/L}$, $P < 0.001$. The nitrous oxide group had an increased incidence of ischemia (46% vs. 25%, $P < 0.05$), significantly more ischemia (63 ± 71 vs. 40 ± 68 min, $P < 0.05$), had more ischemic events (82 vs. 53, $P < 0.02$), and had more ischemic events lasting 30 min (23 vs. 14, $P < 0.05$) than the nonnitrous group. This study reconfirmed that intraoperative nitrous oxide is associated with postoperative increases in plasma homocysteine concentration. This was associated with an increase in postoperative myocardial ischemia.

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Chronic increases in plasma homocysteine concentrations are an independent risk factor for coronary artery and cerebrovascular disease (1,2). Plasma levels above 10 $\mu\text{mol/L}$ are associated with a doubling of vascular risk (1), whereas levels above 20 $\mu\text{mol/L}$ with a 10-fold increase in risk (2). Homocysteine levels above 12 $\mu\text{mol/L}$ occur in 20% of the general population, but in up to 60% of patients with vascular disease are not explained by the usual risk factors (1,2). Affected individuals have increased

homocysteine concentrations, as well as abnormal responses to methionine loading. Acute increases have also been shown both *in vivo* and *in vitro* to cause endothelial dysfunction, and to provide procoagulant effects (3–6), thus potentially mediating acute pathophysiologic states.

Nitrous oxide inhibits methionine synthase slowing the conversion of homocysteine to methionine and increasing homocysteine concentrations in lymphocyte cell cultures (7) and human liver biopsy samples (8). In a randomized, prospective study, we confirmed earlier studies (9,10) showing that nitrous oxide anesthesia leads to a marked increase in postoperative plasma homocysteine levels from ~ 12 – 24 $\mu\text{mol/L}$ (11). Any significance, however, of such changes in the perioperative period is unknown.

Previous studies investigating the ischemic potential of nitrous oxide have focused on intraoperative events and have largely ignored the postoperative

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Address correspondence and reprint requests to Dr. Neal H. Badner, Department of Anesthesiology, University Campus, London Health Sciences Center, 339 Windermere Road, London, Ontario, Canada N6A 5A5. Address e-mail to nbadner@julian.uwo.ca.

period (12). Because postoperative myocardial infarctions have been shown to occur with a peak incidence on the first postoperative night (13), this would temporally coincide with sequelae of nitrous oxide-induced homocysteine increases. The present study was therefore designed to evaluate the longer term effects of nitrous oxide anesthesia and postoperative plasma homocysteine levels on myocardial ischemia in patients undergoing carotid endarterectomy, a population at risk for coronary artery disease (14).

Methods

After IRB approval and written informed consent, 90 consecutive, eligible ASA Class I-III patients, age > 18, presenting for elective carotid endarterectomy, were randomized using a computer-generated random number table to receive general anesthesia with or without nitrous oxide. Patients were excluded if they had received an anesthetic within 30 days before their scheduled surgery, if they were currently taking medications known to affect plasma homocysteine (vitamins B₁₂ and B₆, folic acid, penicillamine, methotrexate, azarodine, isoniazid, cycloserine, phenelzine, or procarbazine); if they were vitamin B₁₂ or folate deficient, malnourished or cirrhotic; or if they had a pacemaker or left bundle branch block on electrocardiogram (ECG). Anesthesia was induced with propofol, an opioid (fentanyl or sufentanil), and nondepolarizing neuromuscular blocker. In the nitrous oxide group, anesthesia was maintained with opioid (fentanyl or sufentanil), isoflurane, and nitrous oxide/oxygen (inspired nitrous oxide > 50%). In the nonnitrous oxide group, anesthesia was maintained with opioid (fentanyl and sufentanil), isoflurane, and oxygen/air. All patients were monitored with standard clinical monitors, including radial artery invasive blood pressure. After emergence and tracheal extubation, patients were monitored in standard fashion in the postanesthesia care unit (PACU) and transferred to the ward. On the ward, patients were cared for by the neurosurgical team unaware of study group assignment. Pain was managed by intramuscular codeine 60 mg IM every 4 h as needed for 24 h followed by acetaminophen with codeine by mouth every 4 h as needed for 24 h. Preoperative cardiac medications were resumed postoperatively. Systolic blood pressure was maintained less than 180 mm Hg with hydralazine 10 mg IM every hour as needed for the first 24 h.

Intraoperative opioid—in fentanyl equivalents (where 1 μ g sufentanil = 7 μ g fentanyl) (15)—estimated average expired isoflurane concentrations, and amount of vasoconstrictors (phenylephrine and/or ephedrine) were recorded. Mean arterial blood pressure was noted prior to induction, after induction,

after carotid cross-clamping, and unclamping and after PACU arrival and discharge. Prior to induction on arrival in the PACU, and after 48 h, blood samples were obtained for homocysteine analysis. Levels were determined using high-performance liquid chromatography by individuals blinded to treatment group, as described elsewhere (16), but modified to include a short Novopack 5 cm C₁₈ (5 μ m) analytical column (Waters, Inc., Mississauga, Canada). At 5.0 μ mol/L (the low end of our population range), the coefficient of variation was 6.8%. Quality control was maintained with pooled patient plasma measuring 50 μ mol/L ($n = 10$, coefficient of variation = 7.0%).

Three hours prior to induction and for 48 h postoperatively patients were monitored by a three-channel (bipolar leads II, V2, and V5), Holter monitor (Rozin, Inc., Toronto, Canada). Myocardial ischemia was determined by a blinded technician using Mortara (Milwaukee, WI) MK5 software that averaged patients' heart rate for each hour. All episodes of ischemia were confirmed by an expert physician who was also blinded to patient randomization. ST segments were analyzed after all normal QRS complexes 60 ms after the J point. Ischemic episodes were defined as a 1-mm reversible planar or downward sloping shift from baseline lasting for more than 1 min. The ST segment had to return to baseline levels for more than 5 min for a second episode to be counted. For each ischemic episode, absolute ST depression in millimeters, change from baseline in millimeters, and duration of the episode in minutes were determined.

Statistical analysis consisted of unpaired *t*-tests for demographic and intraoperative data and analysis of variance for repeated measures for hemodynamic measurements and homocysteine levels, and χ^2 analysis for nonparametric demographic and ischemia data. Analyses were performed with StatView software (Abacus Concepts, Berkeley, CA), and *P* value < 0.05 was considered significant. Univariate risk ratios for postoperative ischemia were calculated to test for prognostic variables. Step-wise logistic regression was then performed on variables with a *P* value less than 0.1. Variables that improved the regression to a *P* value less than 0.05 were then entered into the model. The sample size was sufficient to detect a 50% difference in the duration of myocardial ischemia in minutes/24 h assuming 50% of patients would have ischemia lasting 75 min/24 h, with a standard deviation of 65 min, at the 0.05 significance level with 80% power.

Results

Ninety patients were randomly assigned to receive nitrous oxide or nonnitrous oxide general anesthetics. One patient assigned to the nonnitrous oxide group

inappropriately received >50% nitrous oxide and was analyzed with the nitrous oxide patients. Four patients did not complete the 48-h study period, two required reoperation for hematoma formation (both nonnitrous oxide), and two patients had Holter monitoring inappropriately discontinued (one from each group). Data obtained prior to these events were recorded and analyzed. There were no significant differences between the nitrous oxide and nonnitrous oxide groups in terms of demographic variables (age, weight, gender, risk factors, or preoperative medications) as shown in Table 1. Their intraoperative and postoperative management (duration, opioid, vasoconstrictors, mean arterial pressure, heart rate, and analgesics) was also not different between the two groups other than inspired isoflurane concentration being lower in the nitrous oxide group, as shown in Table 2. The heart rate and blood pressure did differ as a function of time throughout the study, $P < .0001$ for both variables.

Four 48-h blood samples (1 nitrous oxide patient and 3 nonnitrous oxide patients) were not obtained as previously described. Although there was no difference in mean baseline plasma homocysteine concentrations (12.7 ± 5.0 vs. 11.9 ± 5.3 $\mu\text{mol/L}$, $P = 0.46$, nitrous vs. nonnitrous), there was a significant increase during the operation such that, in the PACU and by 48 h, the nitrous group had increased mean homocysteine concentrations of 15.5 ± 5.9 and 18.8 ± 14.7 , compared with the nonnitrous group of 11.4 ± 5.2 and 11.3 ± 4.0 ($P < 0.001$), as shown in Fig. 1. Forty (89%) nitrous oxide patients vs. 13 (30%) nonnitrous oxide patients had increased homocysteine concentrations postoperatively, a difference that was statistically significant ($P < 0.0001$).

Six patients' Holter recording (4 nitrous oxide group, 2 nonnitrous oxide group) were not analyzable at all due to Holter malfunction, whereas one patient with a left bundle branch block was enrolled and assigned to the nitrous oxide group leaving 42 patients in the nitrous oxide group and 41 patients in the nonnitrous oxide group. There were no differences in the preoperative and intraoperative incidence of ischemia between the two groups. Postoperatively, however, the nitrous oxide group had a higher incidence of ischemia, significantly longer ischemic events during the first 24 and 48 h, more episodes of ischemia, and more events lasting 30 min or longer than the nonnitrous oxide group, as shown in Table 3. There was, however, no difference between the two groups in the number of individuals with 2 h or more of cumulative ischemia.

The univariate predictors for postoperative myocardial ischemia are shown in Table 4. The relative risk of developing postoperative myocardial ischemia increased twofold with the use of nitrous oxide and postoperative plasma levels of homocysteine greater

than 17 $\mu\text{mol/L}$. The presence of pre- and/or intraoperative ischemia increased the risk of postoperative ischemia almost fourfold. The use of isoflurane greater than 0.7% was not significantly associated with a change in risk. The use of β -adrenergic blockers was found to decrease the risk of postoperative ischemia by 50%, with a P value of 0.051, whereas other variables (including gender, age >70, and diabetes) were not significant predictors. In the stepwise model pre- and/or intraoperative ischemia and nitrous oxide were the only significant predictors of postoperative ischemia.

Discussion

This prospective, randomized, evaluator-blinded study reconfirmed that intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine concentration. Ninety-one percent of our patients who received nitrous oxide experienced an increase in plasma homocysteine, with an average increase of ~ 7 $\mu\text{mol/L}$ (56% over baseline) in plasma homocysteine levels during the first 48 hours postoperatively when compared with the nonnitrous oxide group. This increase is somewhat less than that of our previous study (11); however, the exposure to nitrous oxide in the present study was ~ 1.67 , as opposed to 2.6 minimum alveolar concentration (MAC)-hour (% of N_2O minimum alveolar concentration [which is 100%] * time in hours) in our previous work. The known *in vitro* inverse linear rate of depression of methionine synthetase as a function of exposure to nitrous oxide explains the difference in the amount of change of plasma homocysteine between our two studies (8).

Our study also identified an increase in the incidence and duration of myocardial ischemia, and the number of episodes lasting longer than 30 minutes as measured by the Holter monitor. The use of nitrous oxide was also found to be a significant predictor of postoperative ischemia when regression analysis is used. This is in contrast to previous work in which nitrous oxide was not shown to produce an increase in myocardial ischemia (12,17,18). The fundamental difference between our study and these others was that the other studies only looked for ischemia in the intraoperative period. The study by Kozmary et al. (12), was almost identical to ours, except that the Holter monitoring only occurred intraoperatively. Postoperatively, Kozmary et al. looked for differences in rates of myocardial infarction using once daily ECGs and enzymes; however, the study was underpowered to show a difference in this outcome. Our study also used a three-channel Holter system as opposed to a two-lead system, thereby increasing the sensitivity of detecting myocardial ischemia. Interestingly, another

Table 1. Demographic Data

	Nitrous oxide	Nonnitrous oxide	P value
Male	35 (76)	33 (75)	0.90
Age (yr)	68.6 ± 7.4	67.3 ± 8.8	0.46
Weight (kg)	80 ± 13	77 ± 12	0.27
Risk factors			
Hypertension	30 (65)	29 (65)	0.94
Diabetes	7 (15)	6 (14)	0.56
Hypercholesterolemia	27 (60)	27 (63)	0.79
Smoking	13 (28)	13 (30)	0.36
Preoperative medications			
β-blockers	16 (35)	15 (34)	0.95
Acetylsalicylic acid	42 (91)	38 (86)	0.46
Calcium channel blockers	11 (24)	7 (16)	0.34

Values are means ± SD, or n (%).

Table 2. Perioperative Data

	Nitrous oxide	Nonnitrous oxide	p value
OR time (min)	204 ± 32	203 ± 29	0.93
OR fentanyl (μg)	289 ± 86	320 ± 150	0.23
Fet isoflurane (%)	0.48 ± 0.16	0.67 ± 0.22	<0.0001
MAP (mm Hg)			
Preinduction	112 ± 16	110 ± 14	
Postinduction	89 ± 25	82 ± 23	
Post clamp	94 ± 12	92 ± 14	0.38
Clamp removal	87 ± 13	88 ± 12	
PACU arrival	101 ± 18	96 ± 21	
PACU discharge	87 ± 18	91 ± 18	
Vasoconstrictor usage			
Phenylephrine (μg)	88 ± 154	110 ± 350	0.75
Ephedrine (mg)	7.7 ± 10.8	6.4 ± 9.9	0.53
HR (bpm)			
Preoperative	67.9 ± 3.9	72.3 ± 5.0	
Induction	73.2 ± 5.3	72.5 ± 4.6	
Emergence	81.5 ± 6.9	80.4 ± 6.1	
PACU	70.5 ± 5.3	71.8 ± 4.6	0.44
12 h postop	72.1 ± 4.8	75.6 ± 5.7	
24 h postop	74.1 ± 4.3	77.9 ± 5.7	
48 h postop	79.0 ± 6.8	80.8 ± 6.0	
Postoperative			
IM codeine (mg)	88 ± 93	114 ± 113	0.22
Acetaminophen 300 mg and 30 mg codeine (no.)	2.4 ± 3.2	3.6 ± 4.5	0.14
Hydralazine (mg)	5.5 ± 8.1	4.9 ± 10.2	0.73

Values are means ± SD, or n (%).

OR = operating room; Fet = fraction of end-tidal gas; MAP = mean arterial pressure, HR = heart rate, IM = intramuscular; PACU = postanesthesia care unit.

study, that by Hohner et al. (19), did note increased intraoperative myocardial ischemia in patients undergoing abdominal aortic surgery with nitrous oxide, but no difference postoperatively. However, the postoperative measurements were ECGs done only once daily and these could easily have missed events that our continuous monitoring would have discovered. Our study is the first one whereby nitrous oxide-induced homocysteine increases were associated with postoperative changes in myocardial ischemia.

Although we have shown no causality, it is the first time that plasma homocysteine concentrations have been associated with an increased likelihood of developing postoperative myocardial ischemia. We noted a twofold increase in the risk of developing postoperative myocardial ischemia with plasma homocysteine levels greater than 17 μmol/L. The escalating risk of myocardial ischemia at these levels is consistent with the known long-term increase in risk of vascular events at these same levels (1,2). The magnitude of the

Homocysteine Concentrations

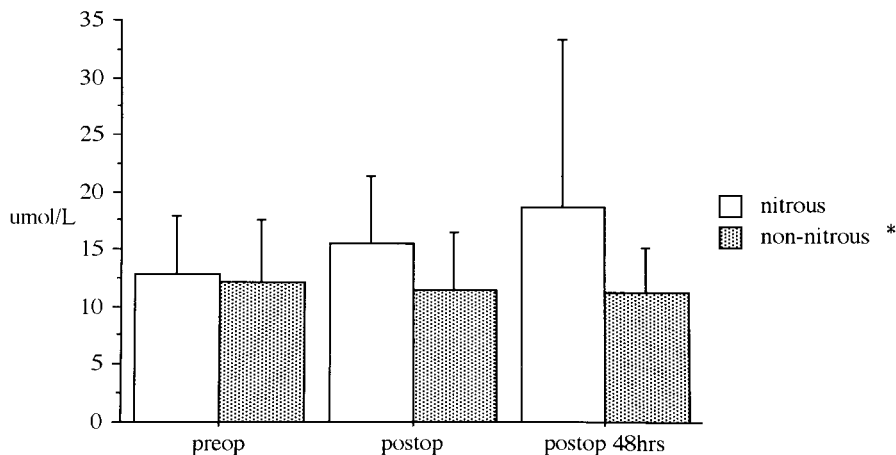


Figure 1. Comparison of mean plasma homocysteine concentrations as a function of time. Values are means \pm SD. * $P < 0.001$, nitrous oxide vs. nonnitrous oxide. postop = postoperative.

Table 3. Postoperative Ischemic Data

	Nitrous oxide	Nonnitrous oxide	<i>p</i> value
No. of Holter analyzable pts.	42	41	
Preoperative			
No. of pts. with ischemia	2	4	0.414
No. of episodes of ischemia	3	6	0.291
HR with ischemia	71 \pm 5	70 \pm 4	0.986
Intraoperative			
No. of pts. with ischemia	8	9	0.748
No. of episodes of ischemia	11	12	0.801
HR with ischemia	98 \pm 13	96 \pm 11	0.869
Postoperative			
No. of pts. with ischemia	19 (46)	11 (26)	0.045
Ischemia/24 h (min)	56 \pm 69	17 \pm 29	0.007
Ischemia/48 h (min)	63 \pm 70	40 \pm 68	0.047
No. of episodes of ischemia	82	53	0.018
HR with ischemia	88 \pm 26	89 \pm 25	0.675
No. of episodes >30 min	23	14	0.049
No. of pts. with total ischemia > 2 h	10 (24)	6 (14)	0.310

Values are means \pm SD, or *n* (%).
HR = heart rate, pts. = patients.

increasing risk for myocardial ischemia from plasma homocysteine in our study was, however, less than that for vascular disease, and may reflect the short-term nature of our study. We also noted, as others have, the beneficial effects of β -adrenergic blockers in reducing postoperative myocardial ischemia, as well as the increased risk of the presence of pre- and/or intraoperative ischemia.

The possible acute pathophysiologic mechanisms of this increased myocardial ischemia could be due to endothelial dysfunction or procoagulant effects (3). Endothelial dysfunction has been demonstrated in volunteers as inhibition of flow-mediated vasodilation resulting from exposures to homocysteine as short as 2-4 hours (4,5), as well as *in vitro* studies showing acute endothelial cytotoxic effects (3). The known acute procoagulant effects include increased platelet

adhesiveness, factor V activation, protein C inhibition, and antithrombin and plasminogen activator binding (3). These actions are probably mediated by the consumption of nitric oxide and/or production of hydrogen peroxide (20). To avoid this homocysteine-induced increase in myocardial ischemia, a potential option, other than not using nitrous oxide, would be to treat patients with known ischemic heart disease or those with risk factors with B vitamins (folic acid, pyridoxine, and B₁₂) in the preoperative period. The use of these vitamins over a six-week period lowers basal plasma homocysteine levels (21,22) and, more importantly, slows the progression of carotid atherosclerosis (23). The appropriate dosage and timing of this vitamin therapy to prevent perioperative nitrous oxide-induced homocysteine increases is, however, unknown.

Table 4. Myocardial Ischemia Predictors

Univariate predictors	Relative risk	<i>p</i> value	
Study variables			
Nitrous oxide	1.9	0.049	
Homocysteine > 17 μmol/L	2.0	0.045	
Pre- and intraoperative ischemia	3.7	0.020	
Isoflurane end-tidal > 0.7%	1.4	0.456	
Demographic variables			
Sex	1.0	0.996	
Age > 70 yr	1.2	0.597	
Diabetes	1.9	0.080	
β-blocker use	0.5	0.051	
Step-wise logistic regression analysis			
	F	Odds ratio	<i>p</i> value
Intraoperative ischemia	13.3	4.2	0.001
Nitrous oxide	4.1	2.7	0.047

This study was designed as a preliminary investigation and therefore measured only postoperative ischemia, a surrogate measure, and not myocardial infarction, death, or other outcomes. Many studies have, however, shown a correlation between postoperative myocardial ischemia and adverse cardiac outcomes (24–27). Ouyang et al. (24), and Raby et al. (25) noted that the presence of myocardial ischemia was a risk factor for adverse cardiac events, whereas Landesberg et al. (26) and Fleisher et al. (27) determined that “long-duration” ischemia, defined as episodes greater than 30 minutes (Fleisher) or a cumulative total of 2 hours (Landesberg), was required for adverse outcomes. We were able to show a significantly higher incidence and longer duration of ischemia, as well as more episodes lasting 30 minutes or longer in the nitrous oxide homocysteine increased group. There was, however, not a significant difference in the number of individuals with two or more hours of total ischemia. Based on our findings, we believe a larger outcome study is now warranted.

A limitation of our study was that the anesthetics were not blinded. However, we feel that this did not affect the outcome of the study, since the routine postoperative care of the patients as well as the determination of homocysteine concentrations and Holter analysis were all performed by individuals blinded to the treatment group. We also did not specify guidelines for hemodynamic and pain management. However, as shown in Table 2, there were no differences in hemodynamic variables nor in the use of vasoactive or analgesic medication at any time point between patients in either study group.

The only obvious difference in patient management between the two groups was the small increase in end-tidal isoflurane concentration of ~0.2%, which was necessary to supply the additional anesthesia that nitrous oxide would have contributed. This could be considered significant in view of the evidence that isoflurane has cardioprotective properties. These findings have occurred in animal studies with group differences of 1 MAC isoflurane (28). However, several large clinical studies have shown no difference in the incidence of myocardial ischemia with isoflurane when compared with an opioid-based anesthetic (29,30). Conversely, in two smaller studies, isoflurane, when given to similar groups of patients as our study undergoing carotid endarterectomy, either in comparison with propofol (31) or when used in larger concentration with phenylephrine (32), actually led to significantly more intra- and postoperative myocardial ischemia. Lastly, since there was no difference in intraoperative ischemia incidence and the use of isoflurane was not significant in the *post-hoc* regression analysis, it is unlikely that the 0.2 MAC isoflurane difference significantly affected our findings.

In summary, we have shown in a prospective, randomized, controlled study that nitrous oxide leads to significant increases in plasma homocysteine concentrations that are associated with an increase in myocardial ischemia. Further studies are required to confirm this finding and to investigate differences in cardiovascular outcome.

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