Nitrous Oxide Does Not Induce Myocardial Ischemia in Patients with Ischemic Heart Disease and Poor Ventricular Function


Despite evidence from animal experiments to the contrary, nitrous oxide (N₂O) reportedly does not induce myocardial ischemia when used as an adjunct to fentanyl anesthesia in patients with coronary artery disease who have well-preserved left ventricular (LV) function. However, the incidence of ischemia with N₂O administration in similar patients with poor LV function may be different. The effects of N₂O on segmental LV function, as determined by two-dimensional transesophageal echocardiography, changes in the ST-segment of the electrocardiogram were compared with the effects of an equal concentration of nitrogen (N₂) (crossover design) in 70 patients who required elective coronary artery bypass grafting. Of these patients, 24% had left ventricular ejection fraction (LVEF) ≤ 40%. Myocardial ischemia was diagnosed in 14 patients during the study. Four while awake, seven during induction of anesthesia and tracheal intubation, and four during the remainder of the study (one during N₂O and three during 100% oxygen; one patient had two distinct periods of ischemia). No value for LVEF could be found that would distinguish between patients who did or did not have ischemia during the study. Patients treated with beta-adrenergic blocking drugs preoperatively were less likely to develop ischemia (P < 0.05). Preoperative calcium channel blockers made no such difference. Onset of ischemia was not closely associated with hemodynamic changes. Thus, N₂O does not induce clinically detectable myocardial ischemia in patients who have coronary artery disease, and poor LV function in situations in which the effects of increasing anesthetic depth and mild depression of global myocardial function are deemed desirable or harmless. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous fentanyl. Sympathetic nervous system: beta-adrenergic antagonists.)

Recent reports from animal studies suggest that nitrous oxide (N₂O) may induce myocardial ischemia in patients who have ischemic heart disease.¹⁻³ Philbin et al. demonstrated that N₂O added to fentanyl anesthesia in dogs induced segmental contraction abnormalities in left ventricular (LV) segments served by a critically stenosed coronary artery.¹⁻³ Administration of halothane under similar circumstances produced profound global and regional ventricular dysfunction associated with decreases in coronary perfusion pressure.¶ Regional myocardial dysfunction seen with N₂O was worsened with the addition of halothane.³ Nathan demonstrated that substitution of 50% N₂O for an equipotent MAC equivalent increment of isoflurane in isoflurane-anesthetized dogs worsened myocardial ischemia and produced a maldistribution of myocardial blood flow in the region of myocardium supplied by a critically stenosed coronary artery.³ Wilkowski et al. showed that N₂O constricted the epicardial segment of the left anterior descending coronary artery in dogs without altering myocardial oxygen consumption.⁵ In contrast, Cahalan et al. found that N₂O did not induce myocardial ischemia when used as an adjunct to fentanyl anesthesia in 18 patients for elective coronary artery bypass surgery who had well-preserved LV function as evidenced by an LV ejection fraction (LVEF) of greater than 40%.⁶ Slavik et al. found similar results in a study of seven patients with good LV function.⁷ This result is additionally supported by Cason et al. who found no worsening of ischemia by addition of N₂O to fentanyl anesthesia in pigs when heart rate and perfusion pressure for the experimentally stenosed coronary artery were held constant.⁸

During the last decade, there has been a marked change in the clinical profile of patients undergoing coronary artery bypass surgery, including a threefold increase in those with ischemic heart disease and severe LV dysfunction.⁹ Can N₂O be safely used in these patients in clinical situations in which its anesthetic effects might otherwise be desirable, or does N₂O increase the risk of regional myocardial ischemia in these patients? The findings of Cahalan et al.⁹ and Slavik et al.⁷ may not be applicable to patients with poor LV function because the effects of N₂O on cardiovascular function are dependent on LV function.¹⁰⁻¹² N₂O has been reported to produce profound global myocardial depression, hypotension, and LV failure in patients with poor LV function because the direct myocardial depressant effects of N₂O are unopposed by the indirect sympathetic stimulant effects of N₂O usually seen in patients with preserved LV function.¹⁰⁻¹² To determine whether N₂O induces myocardial ischemia in patients with...
poor LV function, we have extended Cahalan’s study to include patients with LVEF less than 40%.

Materials and Methods

With approval from our committee on Human Research and informed consent from each patient, we extended the study of Cahalan et al. to 52 more patients scheduled for elective coronary artery bypass surgery. We followed the same protocol in the same institution and used the same materials and methods, except that patients with a LVEF of less than 40% by preoperative angiography were not excluded. Patients with abnormal valvular function or preoperative bundle branch block were excluded.

Preparation

A preoperative electrocardiogram (ECG) was obtained 6–72 h before induction of anesthesia for each patient and interpreted by their cardiologists. On the morning of surgery, all patients received their customary morning dose of cardiac medications, including beta-adrenergic antagonists and calcium channel blockers, and, in addition, with oral lorazepam (1.0–2.5 mg). Pulmonary artery and subclavian artery (via radial artery) catheters were inserted percutaneously using local anesthesia. Electrodes for a standard 12-lead ECG were placed (Hewlett Packard, model 4750A). Patients rested for 10–15 min, and then before induction of anesthesia, hemodynamic and blood gas data, which included heart rate, systolic, mean, and diastolic, arterial, and pulmonary artery pressures, mean central venous and pulmonary capillary wedge pressures, cardiac output determined by thermal dilution, arterial and pulmonary artery (mixed venous) blood gases, and an ECG (standard diagnostic mode calibrated 1 mV/cm) were obtained.

During administration of 100% oxygen, anesthesia was induced with 15 μg/kg of iv fentanyl, and muscle relaxation was obtained with 0.1 mg/kg of iv pancuronium. Throughout the remainder of the study, a constant infusion of 0.2 μg·kg⁻¹·min⁻¹ of fentanyl was administered and ventilation was controlled to maintain normocarbia as determined by monitoring end-tidal carbon dioxide (CO₂). After tracheal intubation, a Hewlett Packard (Andover, Massachusetts) 5.0 MHz model 0950-1874 two-dimensional transesophageal echocardiographic transducer was inserted and positioned to obtain an LV short-axis cross section at the level of the papillary muscles. The transducer was connected to a Hewlett Packard ultrasonograph (model 77020AC).

Study Procedures

Following 20 min of ventilation with 100% oxygen, either 60% N₂ or 60% N₂O (balanced random assignment) was added to the inspired oxygen for 10 min. Then 100% oxygen was given for 10 min, and followed by 10 min of 60% N₂O or N₂, whichever had not been administered previously. Thus, all patients received both N₂O and N₂ in a standard crossover format. Immediately before each change in inspired gas mixture, the same variables that were determined before induction of anesthesia were measured again, and the echocardiogram was also recorded on videotape.

The responsible anesthesiologist confirmed that the anesthetic depth was appropriate for each patient by the absence of tearing, movement, perspiration, and the presence of stable hemodynamics. He was empowered to administer midazolam; and/or additional fentanyl, pancuronium, or other drugs if he considered this essential for the safe and proper conduct of the anesthesia. All such drug administrations were recorded. The responsible anesthesiologist could also terminate the study at any time if he thought that its continuation endangered the patient. Surgery did not begin until the study was concluded.

Data Analysis

The data were analyzed by period: 1) immediately before induction, “awake,” 2) 20 min after induction (on 100% oxygen), “baseline,” 3) after 10 min of exposure to the first test gas (N₂O or N₂), “first gas,” 4) after 10 min of 100% oxygen, “100% oxygen,” and 5) after 10 min of exposure to the remaining test gas (N₂ or N₂O), “second gas.” The awake ECG was compared with the preoperative ECG. For these and all subsequent ECG, onset of myocardial ischemia was diagnosed if two independent observers found ST-segment changes of more than 1 mm in any lead compared with the ECG of the previous period. For echocardiographic analysis, onset of myocardial ischemia was diagnosed if two independent observers found that segmental LV function deteriorated by more than one class when compared with segmental LV function in the previous period. Classes were rated as follows: 1 = normal contraction or hyperkinesis, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. This method of echocardiographic analysis has been previously described in detail. Guided by the papillary muscles, we divided the short-axis cross-sectional image into four segments. We considered segmental contraction normal when there was more than 30% radial shortening and considerable wall thickening, mildly hypokinetic when there was 10–30% radial shortening and slightly reduced wall thickening, severely hypokinetic when there was less than 10% radial shortening and minimal wall thickening, akinetic when there was no radial shortening or wall thickening, and dyskinetic when there was outward movement and thinning of the wall segment during systole. ECG and echocardiograms were
**TIME COURSE OF ISCHEMIA RELATIVE TO DATA COLLECTION**

<table>
<thead>
<tr>
<th>Awake Period 1</th>
<th>Baseline Period 2</th>
<th>1st Gas Period 3</th>
<th>Oxygen Period 4</th>
<th>2nd Gas Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>22X</td>
<td>•</td>
<td>0</td>
<td>22X</td>
<td>N2</td>
</tr>
<tr>
<td>69X</td>
<td>60X</td>
<td>61X</td>
<td>N20</td>
<td>66X</td>
</tr>
<tr>
<td>70X</td>
<td>69X</td>
<td>A</td>
<td>0</td>
<td>N20</td>
</tr>
<tr>
<td>40X</td>
<td>27X</td>
<td>34X</td>
<td>59X</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>48X</td>
<td>67X</td>
<td>5X</td>
<td>N20</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>20 min</th>
<th>10 min</th>
<th>10 min</th>
<th>10 min</th>
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</table>

Fig. 1. Ind = Induction of anesthesia; Int = tracheal intubation; nnX = onset of ischemia for patient number nn; O N2O = Resolution of ischemia during 60% N2O administration; O N2 = resolution of ischemia during 60% nitrogen administration; N = resolution of ischemia during 100% oxygen administration; = ischemia continued beyond the end of the study; A = study aborted due to persistent severe ischemia. *Same patient.

Evaluated independently and without knowledge of the patient’s clinical course.

Our additional 52 patients’ preoperative characteristics and hemodynamic responses were compared with those reported by Cahalan et al. (18 patients) by repeated measures analysis of variance (ANOVA) and multiple t tests, or by chi-square, or binomial methods, as appropriate. The a priori intention was to combine these two groups of data, which were obtained under identical conditions and by identical methods, if they were statistically indistinguishable. Validity of the crossover format was checked by the explicit method of Hills and Armitage (equivalent to ANOVA).

The combined data were examined for the effects of preoperative LVEF, beta-adrenergic antagonists, and calcium channel blockers on the incidence of onset of ischemia. It was also examined for the association between the incidence of 10% increases in heart rate, mean arterial pressure, or other observed hemodynamic changes and the incidence of onset of ischemia. A P value of <0.05 was considered statistically significant, except when adjusted by the Bonferroni correction.

**Results**

During the study the responsible anesthesiologists intervened in the interest of the patient’s safety and proper conduct of the anesthesics on five occasions. Atropine was administered to patient 30 during period 2 and patient 42 during period 4 to treat bradycardia (40 beats/min or less). Both patients were treated with beta-adrenergic antagonists preoperatively. Increases in heart rate were less than 10 beats/min, and neither patient developed any evidence of ischemia at any time during the study. Midazolam, 5 mg iv, was administered to patients 40 and 45 because they were judged by the responsible anesthesiologist to be too lightly anesthetized. This had no effect on the onset or resolution of ischemia. Patient 59 received fentanyl (two 100 μg iv boluses 4 min apart) and pancuronium (3 mg iv bolus) during period 4 when he began to “chew” on the tracheal tube and also had a 6% increase in heart rate to 96 beats/min, a 12% increase in arterial pressure to 151/77 mmHg, and ST-segment elevations in leads Vp–V4 with echocardiographic evidence of severe septal hypokinesis compared with the previous period. All evidence of ischemia resolved during the next and final period during which he received N2O. No patient experienced recall of the events of the study after induction of anesthesia. One patient who had no evidence of ischemia during the study was unable to weaned from cardiopulmonary bypass and died intraoperatively.

**DATA EXCLUSIONS**

The study was aborted in two cases (fig. 1, patients 69 and 70). In both cases the patients developed gross ST-segment changes while awake during insertion of arterial and pulmonary artery catheters and complained of severe angoral chest pain. Ischemia did not resolve with induction of anesthesia. Both patients became hemodynamically unstable and one required brief external cardiac compression and counter shock for ventricular fibrillation. The two studies were aborted before insertion of the esophageal echocardiographic transducer and the patients went directly to surgery. Both patients did well.

A total of 5,040 ST-segments (70 patients, 12 leads, at the five study periods and the preoperative ECG) were expected for analysis. The preoperative ECG of three pa-
Nitrous Oxide and Myocardial Ischemia

Patients were not obtainable, but none of these patients had ST-segment changes on their period 1 ECG, nor did they have any evidence of ischemia during the study. ECG during period 2 through 5 were not obtained for the two patients whose studies were aborted before period 2 data collection. One or both observers could not interpret 40 other ST-segments because of variability in the isoelectric baseline or interference. This was most often due to skeletal muscle artifact on awake ECG. Another 52 ST-segments were not analyzed because of right bundle branch block or interventricular conduction delay. Thus, 96% (4,816 of 5,040) of the ST-segments was analyzed.

Echocardiograms of 1,120 LV segments (70 patients, four LV segments, at four intervals) were expected for analysis. Echocardiograms were not obtained from the two aborted studies, and adequate images were not obtained for 38 other LV segments. Thus, 93% of the LV segments were analyzed for wall motion abnormalities. Eighteen of the 38 excluded LV segments (47%) were inferior wall segments. This was because the inferior portion of the LV short-axis echocardiogram was not adequately seen at any time during the study in three patients with otherwise adequate images. None of these three patients had myocardial ischemia based on ECG or interpretable echocardiographic segments. No other single ECG lead or echocardiographic segment was excluded with greater frequency than any other lead or segment.

Preoperative Characteristics

There was no significant difference between the preoperative characteristics of the patients of Cahalan et al.6 and ours, except that there were more patients (P = 0.03, binomial) on preoperative beta-adrenergic antagonists in the patients of Cahalan et al.6 (17 of 18, 94.5%) than our patients (17 of 52, 67%), and, as intended, our group included patients with LVEF of less than 40% (17 patients). There was also no difference in hemodynamic status during period 1 (awake, pre-induction) between their patients and ours (ANOVA). Preoperative patient data for the combined 70 patients are listed in table 1.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Parameters: Preoperative Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>No. of vessels</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Beta-adrenergic antagonists (%)</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
</tr>
<tr>
<td>Gender (%)</td>
</tr>
</tbody>
</table>

Values are mean ± SD; ranges are in parentheses.
No. of vessels = the number (1, 2, or 3) of coronary arteries found to have one or more regions of stenosis of >50% by preoperative coronary angiography.

Table 2. Awake and Baseline Hemodynamics (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Period 1 (awake)</th>
<th>Period 2 (baseline)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>68.0 ± 12.8</td>
<td>71.7 ± 14.5</td>
<td>0.005</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>94.2 ± 12.1</td>
<td>86.2 ± 15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAP (mmHg)</td>
<td>15.2 ± 5.2</td>
<td>15.1 ± 5.0</td>
<td>0.016</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5.7 ± 2.4</td>
<td>6.0 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9.6 ± 4.1</td>
<td>8.5 ± 4.0</td>
<td>0.009</td>
</tr>
<tr>
<td>CI (/min·m²)</td>
<td>2.7 ± 0.5</td>
<td>2.4 ± 0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>SVR (dyne·s/cm²)</td>
<td>1,481 ± 410</td>
<td>1,515 ± 443</td>
<td></td>
</tr>
<tr>
<td>PVR (dyne·s/cm²)</td>
<td>118 ± 59</td>
<td>120 ± 49</td>
<td></td>
</tr>
<tr>
<td>SVI (ml/M²)</td>
<td>40.0 ± 8.5</td>
<td>33.7 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVSWI (g/M)</td>
<td>46.0 ± 11.4</td>
<td>36.0 ± 11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVSWI (g/M)</td>
<td>6.1 ± 2.6</td>
<td>4.3 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CVP = mean central venous pressure; PVR = pulmonary vascular resistance.
* P values < 0.05 by Student's t test are listed.

Hemodynamics

Hemodynamic values before and after induction of anesthesia are listed in table 2. Mean arterial pressure (MAP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume index (SVI), and left (LVSWI) and right ventricular stroke work indices (RVSWI) decreased after induction of anesthesia. These results are not statistically distinguishable from those reported by Cahalan et al.6 except that for Cahalan's patients the PCWP decreased an average of 5.0 mmHg with induction of anesthesia, whereas it rose an average of 0.2 mmHg for our additional patients (t tests with Bonferroni correction, P < 0.001). If the seven patients who developed ischemia during induction of anesthesia, all of whom were in our additional group and 4 of whom (patients 27, 34, 67, and 68) had rises in PCWP and increasing heart rate (HR), are excluded, then this difference disappears.

Analysis by the explicit method of Hills and Armitage showed that the order of administration of N₂O or N₂ had no effect on the change in hemodynamics induced by these agents relative to the preceding 100% oxygen control periods (P < 0.05) and that there were no significant carryover effects. The crossover format was found to be valid.18

The mean percent changes between 100% oxygen administration and subsequent N₂O or N₂ are shown in figure 2. They were analyzed by multiple t tests with application of the Bonferroni correction. Administration of N₂O but not N₂ decreased HR (10%, P < 0.0001), CI (16.5%, P < 0.0001), SVI (6.4%, P < 0.0004), LVSWI (15.8%, P < 0.0001), and RVSWI (15.1%, P < 0.0001), and increased systemic vascular resistance (SVR) (6.9%, P < 0.0002). Both N₂O and N₂ decreased MAP (8.9%, P < 0.0001 and 3.6%, P < 0.006), and PAP (5.8%, P < 0.003 and 5.2%, P < 0.03). The response to N₂O was...
significantly different from the response to N2 for HR (P < 0.0001), MAP (P < 0.005), CI (P < 0.0001), SVI (P < 0.002), SVR (P < 0.0001), LVSWI (P < 0.0001), and RVSWI (P < 0.02).

The decreases in MAP and mean PAP and lack of significant change in CI observed with N2 administration suggest an underlying gradual and progressive vasodilation persisting from the baseline period throughout the study period. This trend is detectable in this analysis because the challenge periods follow their respective 100% O2 control periods. Existence of this trend in no way detracts from the validity of the crossover design.16

The mean paired difference by patient (MPD) in hemodynamic response for N2O compared with N2 was significant (P < 0.0001) for HR (MPD = -8.7%), MAP (MPD = -5.6%), CI (MPD = -16%), SVI (MPD = -7%), and LVSWI (MPD = -13%). This is an even stronger statistical evaluation of the differences in hemodynamic responses between N2O and N2 than that found with the unpaired statistics and indicates a consistent pattern of response among our subjects.16

There was no statistically significant difference in the percent change hemodynamic responses between N2O and N2 for those patients with LVEF ≤0.40 compared with those with LVEF >0.40. Similarly, there was no statistically significant difference in the percent change hemodynamic responses between N2O and N2 for those patients who had myocardial ischemia diagnosed during the study compared with those who did not.

No significant change in arterial pH or base excess occurred during the study, and neither N2O nor N2 administration ever produced an arterial oxygen tension of <100 mmHg or a mixed venous oxygen tension of <30 mmHg.

**Myocardial Ischemia**

Nine patients (13%) had ischemia diagnosed on the preoperative ECG by their cardiologists. Only one of these (patient 40) also had ischemia by ECG while awake in the operating room before induction of anesthesia. His ischemia resolved during induction of anesthesia, before period 2 data collection. Three other patients (patients 22, 69, and 70) had ECG evidence of ischemia while awake in the operating room before induction of anesthesia, but only two of them complained of angina. Both of these patients (69 and 70) became unstable with induction of anesthesia and the study was aborted. Patient 22 had ischemia while awake, which resolved after induction of anesthesia (before collection of the period 2 data) but then recurred during period 4.

In 27 patients the initial echocardiograms after placement of the echocardiography probe revealed at least one LV segment with severe hypokinesis (class 3) or worse. Eighteen of these 27 patients (67%) had no ischemia during the study, and in all cases there were Q-waves or re-polarization abnormalities in an ECG lead distribution consistent with the echocardiographic location of the abnormal LV wall motion. The other nine of these 27 patients had ischemia diagnosed during the study. Three had only acute ST-segment changes, suggesting acute ischemia as the etiology for the wall motion abnormalities.
that were seen echocardiographically. The other six had both Q-waves on their preoperative ECG and acute ST-segment changes during the study in lead distributions, suggesting a combination of acute ischemia and prior myocardial infarction as the etiology for the wall motion abnormalities.

Ischemia was diagnosed in a total of 14 patients during the study. The time course of the ischemia for these patients is shown in figure 1. The diagnosis was made on the basis of echocardiographic changes alone with no evidence of ischemia by ECG in two patients (5 and 68) and on ECG changes alone in two patients (69 and 70) in whom the study was aborted before placement of the echo probe. In all other cases there were both echocardiographic and ECG changes.

In seven patients (50, 68, 27, 34, 48, 67, and 61) ischemia developed during induction of anesthesia or after tracheal intubation but before baseline data collection. It persisted throughout the study period in three of these patients and was unchanged in patient 50, but it progressively resolved in patients 68 and 61.

Patients were much more likely to develop ischemia during induction of anesthesia and intubation, period 2, than during any other study period ($P < 0.002$, binomial). Only four patients developed myocardial ischemia during periods 3 through 5: one during N₂O and three during 100% oxygen.

A change of more than one grade in LV segmental contraction was found in the inferior segment in eight cases, the septal segment in five cases, and the anterior segment in one case.

**LEFT VENTRICULAR EJECTION FRACTION**

The mean LVEF for all 70 patients was 0.52 (SD, 0.15; range, 0.23–0.77), and 17 of them (24%) had an LVEF of $\leq 0.40$. For patients who had ischemia diagnosed during the study, mean LVEF was $0.51 \pm 0.13$ (SD) and for those who did not it was $0.53 \pm 0.15$ (SD). The incidence of ischemia in patients with LVEF $\leq 0.40$ was four of 17 (24%), and in patients with LVEF $>0.40$ was ten of 53 (19%), which is not statistically significant ($P > 0.45$). No value for LVEF could be found that would distinguish between patients who did or did not have ischemia diagnosed during the study (chi-square at the $P < 0.05$ level of significance) (fig. 3).

**BETA-ADRENERGIC ANTAGONIST AND CALCIUM CHANNEL BLOCKER USAGE**

Of the 70 patients, 52 were treated with beta-adrenergic antagonists preoperatively, and seven of these developed ischemia during the study. Of the 18 patients who were not treated with beta-adrenergic antagonists, seven also developed ischemia. As expected, ischemia was significantly more likely to occur in patients who were not treated with beta-adrenergic antagonists preoperatively ($P = 0.05$, binomial). The incidence of ischemia in patients being treated with preoperative beta-adrenergic antagonists was not related to LVEF (binomial, $P = 0.16$). Based on these data, it is expected that patients not treated with beta-adrenergic antagonists are almost 3 times as likely (2.9:1) to develop ischemia as patients who are treated with beta-adrenergic antagonists (95% confidence limits, 0.67:1 to 11.5:1).

Calcium channel blockers were taken preoperatively by 52 patients (not necessarily the same patients who were taking beta-adrenergic antagonists), ten of whom developed ischemia. Four of the 18 patients who were not treated with calcium channel blockers developed ischemia. The incidence of patients being treated with preoperative calcium channel blockers was not related to LVEF (binomial, $P = 0.49$). As expected, preoperative therapy with calcium channel blockers was unrelated to the likelihood of ischemia during the study ($P = 0.95$, chi-square).

**HEMODYNAMIC CHANGES AND ONSET OF ISCHEMIA**

There were 56 instances of at least a 10% increase in HR over the previous period, irrespective of inspired gas mixture (280 possibilities), (range of HR, 49–110 beats/min). Only seven of these were associated with the onset of ischemia (range of maximum HR, 68–110 beats/min), but in six of these the HR increased to $>90$ beats/min concurrent with onset of ischemia. Four of the seven patients were not taking preoperative beta-adrenergic antagonists, but this was not significant (binomial $P = 0.077$). Because there were a total of 15 instances of onset of...
ischemia (one patient twice), the likelihood of onset of ischemia being associated with a $>$10% increase in HR was 47% (binomial $P = 0.015$).

There were 17 instances of at least a 10% increase in MAP over the previous period regardless of the inspired gas mixture (range, 70–142 mmHg). Only three of these were associated with the onset of ischemia. These were increases to 101, 102, and 142 mmHg, which were considerably above the MAP average of 83.6 mmHg. The likelihood of onset of ischemia being associated with such an increase in MAP was 18% (binomial $P = 0.03$).

There was no association between changes in CI and onset of ischemia ($P > 0.2$, binomial).

**Discussion**

Using 12-lead electrocardiography and transesophageal two-dimensional echocardiography (2D-TEE) in 70 patients scheduled for coronary artery bypass surgery, we detected the onset of myocardial ischemia in only one patient during administration of 60% $N_2O$ and none during 60% $N_2$. In contrast, three patients developed ischemia during anesthesia with 100% oxygen, four patients during the preoperative preparations prior to induction of anesthesia, and six patients during the induction of anesthesia and tracheal intubation (also during 100% oxygen). These results include the 18 patients reported by Cahalan et al. and support their conclusion that $N_2O$ administered during fentanyl anesthesia does not induce myocardial ischemia in patients with ischemic heart disease. However, the current study extends this conclusion to an additional patient population, those with depressed LV function.

The overall incidence of myocardial ischemia in our study is comparable to the 15–48% incidence of ischemia found in similar human patient populations. However, our results are not consistent with those obtained by Philbin et al. and Nathan in dogs. This may be due to one or more of the following reasons.

First, there may be interspecies differences in the response to administration of $N_2O$. All the studies done in dogs, except Nathan’s most recent study, confirm induction of ischemia by $N_2O$, but the study done in pigs and all the clinical studies done in humans do not. This is still a possibility because no species-independent physiologic or biochemical mechanism for the reported effects of $N_2O$ on segmental wall motion has been yet proposed or confirmed, but it seems unlikely in view of Nathan’s most recent findings.

Second, Philbin et al. and Nathan used sonomicrometry with epicardially implanted microcrystals to measure wall motion, whereas all studies in humans have used 2D-TEE. Sonomicrometry has a resolution of $<$0.1 mm, whereas the resolution of 2D-TEE is approximately 1–2 mm. In our study the sensitivity of 2D-TEE is further degraded because qualitative rather than quantitative analysis techniques were employed. However, Slavik et al. utilized an automated quantitative measurement technique in their series of seven patients and still did not detect induction of ischemia by $N_2O$. The possibility that $N_2O$ induces changes in myocardial function too subtle for detection by 2D-TEE remains unresolved.

Third, changes in hemodynamics related to, coincident with, or even incidental to administration of $N_2O$ may contribute to the incidence of ischemia. In the study by Cahalan et al. administration of $N_2O$ was associated with an 8 beat/min decrease in HR ($P < 0.01$). With our larger patient population sample size, we were able to detect not only an 8.7% (6 beats/min, $P < 0.0001$) decrease in HR, but also an approximately 5% (4.6 mmHg, $P < 0.0001$) decrease in MAP and a 16% (380 ml·min$^{-1}$·m$^{-2}$, $P < 0.0001$) decrease in CI with administration of $N_2O$ compared with $N_2$ (fig. 2). Slavik et al. also found decreases in HR, blood pressure, and cardiac output as we did, but they were not statistically significantly due to their smaller sample size. Philbin et al. similarly found significantly lower HR (12%) and cardiac output (17%) in dogs but a maintained coronary blood flow with $N_2O$ compared with $N_2$. Leone et al. found that addition of 0.7% halothane to 60% $N_2O$ markedly worsened regional myocardial dysfunction. This was accompanied by a 9% increase in HR, 28% decrease in MAP, and a 30% decrease in coronary perfusion pressure. In all of these studies, administration of $N_2O$ led to a deepening of anesthetic depth and mild but detectable global depression of myocardial function.

In isoflurane-anesthetized dogs, Nathan maintained a constant depth of anesthesia by comparing $N_2O$ with a MAC equivalent end-tidal concentration of isoflurane in $N_2$. He found a greater depression of LV function with the MAC equivalent of isoflurane than with $N_2O$, including a 5% slower HR and an 8% lower systolic aortic pressure but maintained coronary perfusion pressure distal to the experimental obstruction. Despite this reversal of relative hemodynamic depression with administration of $N_2O$ compared with the control period, Nathan’s results agreed with the results of Philbin et al. that there was induction of ischemia with administration of $N_2O$. However, in his subsequent work, he found that if the HR, systolic arterial pressure, and left atrial pressure were held

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constant, there was no change in systolic shortening or subendocardial/subepicardial blood flow ratio. He concluded that the worsening of ischemia that he previously observed was due to increased myocardial oxygen demand. Similarly, in pigs, Cason et al. controlled HR and maintained coronary perfusion pressure and found no induction of ischemia with administration of N₂O compared with N₂. They further stated that, in their preparation, decreasing coronary perfusion pressure by as little as 5 mmHg typically produced a 15–20% decrease in systolic shortening.

We found no difference in the hemodynamic response of patients with LVEF ≤0.40 compared with the response of patients with well-preserved LV function, most likely because of the effects of the narcotic (fentanyl) anesthetic regimen. However, we did find a loose association between the incidence of ischemia and changes of 10% in HR (47% of ischemic incidents, P = 0.015) or MAP (18% of ischemic incidents, P = 0.03). The reports of Deanfield et al. and Slogoff and Keats also suggest that ischemic episodes are related to changes in HR or MAP of this magnitude only 20–30% of the time. The small changes in hemodynamics seen in this study and by other investigators during the administration of N₂O to humans should not be expected to significantly contribute to the incidence of clinical ischemia, even for patients with poor LV function.

In contrast, we confirm the findings of Slogoff and Keats that there is a strong temporal relationship between ischemia and anesthetic events, such as induction of anesthesia and tracheal intubation, which are known to produce intense sympathetic stimulation. Additionally, we found that patients who had an indication of ischemia by ST-segment abnormalities on either the routine 12-lead diagnostic preoperative ECG or a 12-lead diagnostic ECG obtained on arrival in the operating suite, or on both, were more likely to have ischemia during our study. Slogoff and Keats similarly reported that a large proportion (almost half) of their patients with perioperative ischemic episodes arrived in the operating room with an ST-segment depression difference of 0.1 mm or more compared with their preoperative ECG, and 48% (87 of 182 patients) of these had distinct episodes of ischemia following induction of anesthesia and before the beginning of cardiopulmonary bypass.

The results of this study suggest that N₂O is safe to use in clinical situations where its effects of deepening anesthetic depth and mild depression of global myocardial function are deemed desirable or harmless, even in patients with severe ischemic heart disease and poor LV function. This study also confirms that the preoperative use of beta-adrenergic antagonists, but not calcium channel blocking agents, decreases the incidence of myocardial ischemia, at least within the time from pre-induction of anesthesia until surgical incision. The authors gratefully acknowledge the assistance of staff anesthesiologists Eddy Cruz, M.D., Yvon L., J. M. Deryck, M.D., Ronald Scheppe M.D., Wahjudi Siphanto, M.D., and A. Van der Woerd, M.D., and nurse anesthetists P. Van der Schelde, J. Koopmans, R. Kleijweg, D. Thompson, E. Ramou, and R. Hoogewaard who assisted in the care and preparation of the patients during the study. They also gratefully acknowledge the advice and cooperation of Egbert Bos, Professor of Cardiac Surgery and the Thorax Center staff surgeons, including J. M. Quegebeur, B. P. Moctar, and L. A. van Herwerden. The authors also thank Ron van Domberg, J. Van Es, and John H. Smiley, M.D., for aid in interpreting and processing the data, and to W. Vletter and J. McGhie for assistance with echocardiographic equipment.

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