Nitrous oxide does not exacerbate pulmonary hypertension or ventricular dysfunction in patients with mitral valvular disease

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Using the rapid-response thermistor pulmonary artery catheter and transoesophageal echocardiography, this study examined the effects of 100 per cent oxygen, 70 per cent nitrous oxide/30 per cent oxygen, and 70 per cent nitrogen/30 per cent oxygen on the pulmonary circulation and ventricular function in ten patients with pulmonary hypertension. In comparison with baseline measurements, nitrous oxide administration resulted in small but statistically significant ($P < 0.05$) changes in mean arterial pressure (76 ± 14 to 67 ± 12), mean pulmonary arterial pressure (37 ± 14 to 33 ± 13 mm Hg), and cardiac output (3.7 ± 1.4 to 3.2 ± 1.1 L · min^{-1}). Seventy per cent nitrogen resulted in no significant changes from baseline. The repeat 100 per cent oxygen measurements were nearly identical to the nitrous oxide measurements. It is concluded that nitrous oxide does not exacerbate pulmonary hypertension or ventricular dysfunction during high-dose fentanyl anaesthesia in patients with mitral valvular disease.

Utilisant un cathéter d'artère pulmonaire thermistor à réponse rapide et l'échographie transoesophagienne, cette étude examine les effets de 100 pour cent d'oxygéne, 70 pour cent de protoxyde d'azote/30 pour cent d'oxygène, et 70 pour cent d'air/30 pour cent d'oxygène sur la circulation pulmonaire et la fonction ventriculaire chez des patients ayant une hypertension pulmonaire. Comparativement aux mesures de base, le protoxyde d'azote amena une petite différence statistiquement significative ($P < 0.05$) dans la pression artérielle moyenne (76 ± 14 à 67 ± 12), la pression moyenne de l'artère pulmonaire (37 ± 14 à 33 ± 13 mmHg), et le débit cardiaque (3,7 ± 1,4 à 3,2 ± 1,1 L · min^{-1}). L'administration de 70 pour cent d'air n'a pas amené de changement significatif comparativement au contrôle. L'administration de 100 pour cent d'oxygène a donné des valeurs approximativement identiques à celles lors de l'administration de protoxyde d'azote. On conclut que le protoxyde d'azote n'exacerbe pas l'hypertension pulmonaire ou la dysfonction ventriculaire lors d'une anesthésie à haute dose de fentanyl chez les patients ayant une maladie valvulaire mitrale.

Key Words
ANAESTHESIA: cardiac;
ANAESTHETIC GASES: nitrous oxide;
COMPLICATIONS: hypertension, pulmonary;
HEART: cardiac output, ventricles, function.

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Patients with severe cardiac disease are frequently anaesthetized with a high-dose opioid technique. In many cases, a supplemental anaesthetic is needed. Nitrous oxide's pharmacodynamic and pharmacokinetic properties make it a valuable adjunct to opioid anaesthesia. Despite the potential benefits, the use of nitrous oxide in patients with pulmonary hypertension remains controversial. Though Hickey *et al.* found no significant changes in pulmonary vascular resistance (PVR) in infants,[1] Schulte-Sasse *et al.* reported that nitrous oxide increased PVR in adults.[2] These investigators also measured right atrial pressure (RAP), and found no significant changes. However, because the right ventricle is compliant, large changes in volume and function may have occurred in the absence of significant changes in the RAP. Thus, the clinical implications of this measured increase in PVR is unclear. Using the rapid-response thermistor pulmonary arterial catheter and transoesophageal echocardiography, this study examined the effects of nitrous oxide on ventricular function and the pulmonary circulation during high-dose fentanyl anaesthesia.

Methods

The study protocol was approved by the institutional research administrative committee, and written informed

consent was obtained from each patient. Ten patients with pulmonary hypertension (PHT) scheduled for elective mitral valve repair or replacement were studied. Pulmonary hypertension was defined as a mean pulmonary artery pressure greater than 35 mmHG at diagnostic cardiac catheterization. No patient had co-existing coronary artery disease. The patients ranged in age from 42 to 66 yr, and were ASA physical status III and IV. To ensure valid measurements from the rapid response pulmonary arterial catheter (RRPAC), patients not in sinus rhythm were excluded from the study. Also patients with oesophageal disease were excluded.

The patients received premedication 90 min before anaesthetic induction with morphine (0.08–0.15 mm·kg^{-1} IM) and scopolamine (0.003–0.006 mm·kg^{-1} IM) as individually determined for each patient. All cardiac medications were continued to the time of surgery. Peripheral venous, radial arterial, and rapid-response thermistor pulmonary arterial catheters (American Edwards Laboratories, Santa Ana, CA) were placed using local anaesthesia. Electrocardiographic leads II and modified V5, oxygen saturation, and respiratory gas concentrations were also monitored. Electrocardiographic and pressure tracings were recorded on a Hewlett-Packard Series 78000 Multichannel Pressure Recorder (Hewlett-Packard, Waltham, MA) from equisensitive Spectromed P2310 Pressure Transducers (Spectromed, Woodbridge, NJ) calibrated by aneroid manometry. Before each set of measurements, the zero reference point of the transducers was positioned at the level of the right atrium, 5 cm posterior to the angle of Louis. Intravenous fluid administration was limited to 500 ml crystalloid.

Haemodynamic measurements consisted of the following: heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and right atrial pressure (RAP). Standard formulae were used to calculate pulmonary vascular resistance (PVR) and right ventricular stroke work (RVSW). Thermodilution data were collected using the rapid response thermistor catheter and an REF-1® Cardiac Output Computer (American Edwards Laboratories, Santa Ana, CA). Ten ml, iced, five per cent dextrose were injected until three values within ten per cent of each other without an "alert" signal were obtained. The thermodilution signal was observed on the LCD screen of the cardiac output (CO) computer and artifactual signals were rejected. The multi-hole injectate port was positioned 2 cm cephalad to the tricuspid valve using pressure waveform monitoring. Cardiac output and right ventricular ejection fraction (RVEF) were determined from the thermodilution curve, and right ventricular end–diastolic volume (RVEDV), right ventricular end–systolic volume (RVESV), and stroke volume (SV) were computed.

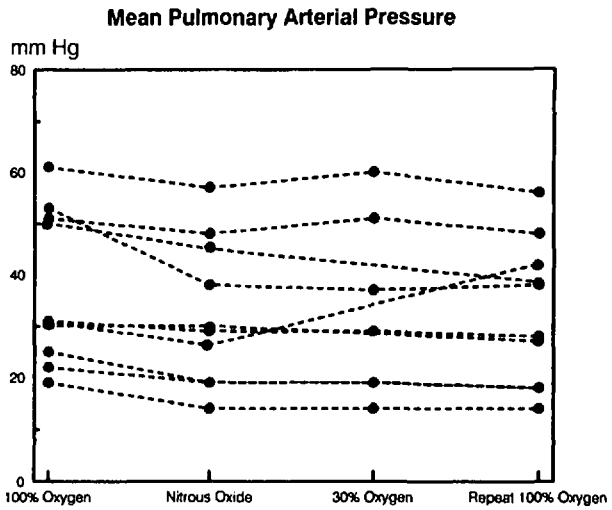

FIGURE 1 Individual patient responses in mean pulmonary arterial pressure (mmHg) to nitrous oxide administration.

Anaesthesia was induced with intravenous fentanyl (50–75 μg·kg^{-1}) and pancuronium (0.1 mg·kg^{-1}). After tracheal intubation, the lungs were ventilated with 100 per cent oxygen to maintain normocarbia. A 3.5 MHz transoesophageal echocardiographic probe (Diasonics® 6400 R, Milpitas, CA) was introduced and positioned to obtain a short axis view of the left ventricle at the mid-papillary muscle level. This position was held constant throughout the study period, and the echocardiographic images were recorded on videotape for off-line analysis. Ten minutes following tracheal intubation, in the absence of surgical stimulation, baseline measurements (PRE) were made. Both 70 per cent nitrous oxide/30 per cent oxygen (N_2O) and 70 per cent nitrogen/30 per cent oxygen (N_2) were administered in random sequence, and when stable end–tidal concentrations had been reached, measurements were performed. One hundred per cent oxygen was again administered, and when the washout of N_2O and N_2 was complete, the "return to baseline" measurement (RTB) was then obtained. Throughout the study period, ventilation was adjusted to maintain stable end–tidal carbon-dioxide concentrations, and peripheral oxygen saturation remained above 94 per cent in all patients.

Surgery was delayed until the completion of the study protocol. Following this, patients received IV benzodiazepine and additional fentanyl as needed prior to surgical incision.

The echocardiographic data were analyzed by tracing the end–diastolic area (EDA) and end–systolic area

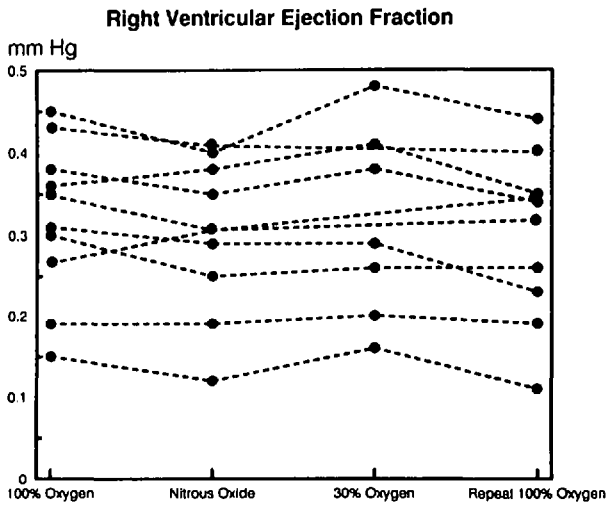

FIGURE 2 Individual patient responses in right ventricular ejection fraction to nitrous oxide administration.

(ESA) from four consecutive cardiac cycles using an electric pen and activated grid system on a Diasonics® CardioRevue centre that was calibrated for each recording. A single blinded observer traced all of the images. Ejection fraction area (EFA) was calculated by the formula:

$$EFA = \frac{EDA\text{-}ESA}{EDA}$$

Student's paired t test with Bonferroni's correction was used to compare changes among measurement periods (N_2O vs N_2, N_2O vs PRE, N_2 vs PRE, RTB vs PRE). Due to the small sample size employed, power analysis was performed to estimate the likelihood of a Type II error. Power analysis was conducted to determine the sample size necessary to detect a 20 per cent change from baseline with a 90 per cent power ($\beta = 0.1$).[3] Significance was defined as $P < 0.05$. All data are reported as means ± SD.

Results

All ten patients received N_2O. However, only seven patients received both N_2 and N_2O, because N_2 was not available on one machine used in the study. No patient demonstrated haemodynamic instability, and there were no complications attributable to the study. The individual patient responses to nitrous oxide administration for MPAP and RVEF are depicted in Figures 1 and 2. As seen in the graphs, the patients did not experience a statistically significant increase in MPAP, or a decrease in right ventricular function.

Results are summarized in the Table. In comparison with the baseline measurements (PRE), N_2O was associated with statistically significant decreases in MAP (12 per cent), MPAP (11 per cent), CO (13 per cent). No statistically significant changes were associated with N_2. The 100 per cent oxygen "return to baseline" was associated with statistically significant decreases in HR

TABLE Haemodynamic, thermodilution, and echocardiographic values

	100% O_2 (PRE)	*70% N_2O/30% O_2*	*70% N_2/30% O_2*	*100% O_2 (RTB)*
HR (bpm)	77 ± 20	72 ± 18	80 ± 22	69 ± 19*
MAP (mmHg)	76 ± 14	67 ± 12*	71 ± 13	71 ± 13*
MPAP (mmHg)	37 ± 15	33 ± 14*	33 ± 17	31 ± 14*
PCWP (mmHg)	27 ± 10	25 ± 10†	25 ± 13†	24 ± 10†
RAP (mmHg)	13 ± 4	12 ± 4†	11 ± 5†	11 ± 4†
CO ($L \cdot min^{-1}$)	3.72 ± 1.37	3.24 ± 1.11*	3.79 ± 1.70	3.16 ± 1.12*
SV (ml)	48 ± 14	46 ± 14	48 ± 18	47 ± 13
RVEF	0.32 ± 0.10	0.30 ± 0.09	0.31 ± 0.12	0.30 ± 0.10
RVESV (ml)	110 ± 36	112 ± 34	112 ± 38	120 ± 45
RVEDV (ml)	159 ± 38	158 ± 34	159 ± 43	167 ± 45
EDA (cm^2)	18.7 ± 4.6	19.0 ± 4.3	18.9 ± 5.2	18.7 ± 4.1
ESA (cm^2)	8.9 ± 5.0	9.1 ± 5.1	10.1 ± 5.1	8.8 ± 4.2†
EFA	0.55 ± 15	0.54 ± 0.18	0.49 ± 0.18	0.54 ± 0.16

*$P < 0.05$ compared with baseline.

†Power < 90 per cent of detecting a 20 per cent change from baseline.

HR = heart rate, MAP = mean arterial pressure, MPAP = mean pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure, RAP = right atrial pressure, CO = cardiac output, SV = stroke volume, RVEF = right ventricular ejection fraction, RVESV = right ventricular end-systolic volume, RVEDV = right ventricular end-diastolic volume, EDA = left ventricular end-diastolic area, ESA = left ventricular end-systolic area, EFA = left ventricular ejection fraction area

(10 per cent), MAP (−6 per cent), MPAP (16 per cent), and CO (15 per cent). There were no statistically significant differences between N_2 and N_2O for any variable examined.

Due to the small sample size, a power analysis was performed on the comparisons that did not achieve statistical significance. A clinically important difference was assumed to be a 20 per cent change from the baseline value. The sample size required to detect a 20 per cent change from the baseline with 90 per cent power ($\beta = 0.1$) was calculated. The results of the power analysis indicated that the sample size was large enough to achieve greater than 90 per cent power in all comparisons except those involving PCWP, RAP, and ESA.

Discussion

Pulmonary hypertension secondary to mitral valvular disease is not an uncommon finding in patients presenting for cardiac and noncardiac surgery. In the current study, anaesthetized patients with this form of pulmonary hypertension were given 70 per cent nitrous oxide/30 per cent oxygen, and 70 per cent nitrogen/30 per cent oxygen (in random sequence), and then returned to 100 per cent oxygen. The response of the pulmonary circulation and ventricular function to the nitrous oxide was evaluated with the rapid-response thermistor pulmonary artery catheter, and transoesophageal echocardiography. There were slight but statistically significant decreases in MAP, PCWP, MPAP, and CO, in response to nitrous oxide. There were no changes in response to 70 per cent nitrogen. Several of these variables (HR, MAP, MPAP, CO) did not return to baseline values when 100 per cent oxygen was reinstituted. None of these statistically significant changes was clinically important. Furthermore, the changes seen in PCWP and thermodilution data were within the limits of error of the measurement techniques.

Patients anaesthetized with a high-dose narcotic technique may require an additional anaesthetic agent to lessen the possibility of intraoperative awareness[4] and to blunt the haemodynamic response to surgical stimulation.[5] Ideally, this agent should have a rapid onset of action, and, in the event of deleterious consequences, a rapid elimination. Nitrous oxide, because of its low blood/gas partition coefficient, has these desirable pharmacokinetic qualities. Pharmacodynamically, nitrous oxide is an effective analgesic and amnesic that is capable of suppressing the response to surgical stimuli in paediatric patients undergoing cardiac surgery,[6] and sedating and controlling blood pressure in adult post-cardiac surgery patients.[7]

Despite these desirable properties, the use of nitrous oxide in patients with pulmonary hypertension has been restricted by concerns that nitrous oxide may increase PVR and cause right ventricular dysfunction. In patients anaesthetized with 1–2 $mg \cdot kg^{-1}$ morphine sulfate, Wong *et al.* noted a significant rise in CVP after nitrous oxide administration.[8] Lappas *et al.* studied the effects of nitrous oxide on the pulmonary circulation in patients also anaesthetized with 2 $mg \cdot kg^{-1}$ morphine.[9] They reported that nitrous oxide increased PVR and MPAP, and postulated that nitrous oxide may produce alpha-adrenergic stimulation. Subsequent research has shown that nitrous oxide may release norepinephrine from nerve terminals in the pulmonary artery of the dog.[10] In patients with pre-existing pulmonary hypertension anaesthetized with either halothane (0.6–1.0 per cent) and fentanyl (7.5–10 $\mu g \cdot kg^{-1}$), and diazepam (0.5 $mg \cdot kg^{-1}$), Schulte-Sasse *et al.* found that nitrous oxide increased PVR and MPAP, but did not effect CVP.[2] In contrast to these results, Hickey *et al.* found nitrous oxide did not increase CVP, PAP or PVR in paediatric patients with pulmonary hypertension after a high-dose fentanyl (50 $\mu g \cdot kg^{-1}$) anaesthetic.[1]

The results of this study contrast markedly with those of Wong *et al.*, Lappas *et al.*, and Schulte-Sasse *et al.* This might be explained by differences in anaesthetic technique. The only other study conducted during high-dose fentanyl anaesthesia[1] found that nitrous oxide had negligible haemodynamic effects. However, Schulte-Sasse *et al.* employed a lower dose of fentanyl (10 $\mu g \cdot kg^{-1}$) and waited a longer time (30 min) after intubation to collect the data. Lower blood levels of the fentanyl would have resulted. It is possible that the interaction of nitrous oxide and fentanyl is related to the dose of fentanyl. At lower doses, nitrous oxide may release norepinephrine (as it does in dogs), but high-dose narcotic anaesthesia may have blunted a catecholamine response to nitrous oxide

Differences in experimental methodology might also help to explain the results of the current study. None of the other studies cited had a "return to baseline" phase of the experiment. The increases in MPAP and CVP may have also resulted from some form of noxious stimulation, and not from the nitrous oxide per se. If the responses to nitrous oxide were shown to resolve upon withdrawal of the agent, this would provide stronger evidence that the observed changes were due to nitrous oxide, and not due to confounding factors.

In order to study adequately the effects of nitrous oxide on the right ventricle and pulmonary vasculature, it is important to document more information than just RAP, MAP and PVR. The right ventricle is highly compliant, so that large volume changes may occur before a measureable change in RAP occurs. In addition, right ventricular afterload varies during the cardiac cycle and is poorly represented by PVR. In this study, the rapid-response

thermistor pulmonary artery catheter (RRPAC) was utilized to assess right ventricular volumes and ejection fractions. The RRPAC is a 7.5 French four-lumen pulmonary artery catheter with a multi-hole injectate port located 21 cm from the distal tip, electrodes (to detect R waves), and a rapid-response thermistor. The rapid-response thermistor (50 msec) is ten times faster than thermistors found on standard catheters. The catheter connects to an interactive computer that uses an algorithm based on the system response of a pulsatile chamber to a bolus injection. First-pass radionuclide measurements of RVEF correlate closely with this thermodilution technique ($r = 0.92$).[11]

This investigation was limited by the accuracy and reproducibility of the thermodilution technique. Thermodilution ejection fraction determinations may correlate well with radionuclide determinations, but there is a certain amount of error inherent in the method. Furthermore, when thermodilution SV is divided by thermodilution RVEF to generate a value for RVEDV, the error is magnified. The reproducibility of these experimental variables was less of a problem when respiratory variation was eliminated by making the thermodilution injections during apnoea at end-expiration.

Many patients with pulmonary hypertension secondary to mitral valve disease are not in sinus rhythm. Thus the sample size is limited in number. Since these patients were still in sinus rhythm, the study participants may represent a select group, with better right ventricular function than the "average" patient with mitral valvular disease.

The effects of 70 per cent nitrogen/30 per cent oxygen were similar to those of nitrous oxide when compared with baseline. In addition, there were no statistically significant differences between the N_2O and N_2. Thus, the influence of the change in FiO_2 on the pulmonary vasculature and right ventricular function was not clinically important in this study.

The patients did not return to their baseline values after the withdrawal of nitrous oxide. A possible explanation for this observation is that, after the induction of anaesthesia in the absence of surgical stimulation, there is a progressive loss of sympathetic tone before surgical stimulation. In a study using an identical anaesthetic technique by Girard *et al.*, HR, MAP, and CO tended to decrease following placebo infusion during an unstimulated period.[12] A control group in the current study would strengthen this argument, but was not practical due to the very selective nature of the inclusion criteria.

In conclusion, patients with pulmonary hypertension secondary to mitral valvular disease who were anaesthetized with a high-dose fentanyl technique, had statistically significant, but clinically minor changes in MAP, CO, MPAP, RVESV, and PCWP. The results of the study suggest that nitrous oxide does not have adverse effects on the pulmonary circulation or either ventricle, and may be used with appropriate monitoring in patients with pulmonary hypertension.

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