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Pulmonary and Systemic Hemodynamic Effects of Nitrous Oxide in Infants with Normal and Elevated Pulmonary Vascular Resistance

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The hemodynamic response to 50% nitrous oxide was studied in 12 sedated but responsive infants in the intensive care unit following repair of their congenital heart disease. One-half of the infants studied had an elevated pulmonary vascular resistance index (PVRI > 3.5 Wood units). During mechanical ventilation with a fractional inspired O_2 concentration (FI_{O_2}) of 0.5, hemodynamic parameters were measured after equilibration with 50% nitrogen and then after 50% nitrous oxide. The sequence was repeated once to assure reproducibility of the responses. Average heart rate decreased by 9%, mean arterial blood pressure decreased by 12%, and cardiac index decreased by 13% in both the elevated and normal PVRI groups each time nitrous oxide was given. Although statistically significant, these changes would not generally be clinically important except in infants with severely compromised cardiovascular reserve. In contrast, pulmonary artery pressure and PVRI were not significantly changed by administration of 50% nitrous oxide in either the group with normal PVRI or the group with preexisting elevated PVRI. We conclude that while these mild depressant effects of nitrous oxide on *systemic* hemodynamics in infants are similar to those previously reported in adults, in infants nitrous oxide does not produce the elevations in pulmonary artery pressure and pulmonary vascular resistance seen in adults. (Key words: Anesthesia: pediatric. Anesthetic, gas: nitrous oxide. Lung: pulmonary artery; vascular resistance. Measurement techniques: arterial pressure; cardiac output.)

DESPITE USE OF nitrous oxide for anesthesia in infants for many decades, hemodynamic responses to nitrous oxide in human infants have not been documented. In anesthetized adult patients, most studies have shown that nitrous oxide decreases cardiac index (CI) and arterial pressure because of myocardial depression, particularly when narcotics have been given.[1–5] However, when given alone to adult volunteers or when given in combination with diazepam to adult patients, nitrous oxide produces no decrease in cardiac output or arterial pressure.[6,7] Effects of nitrous oxide on pulmonary vascular resistance (PVR) in adults vary, depending on preexisting levels of PVR. Small increases in PVR were observed in adults with normal PVR, but larger increases occurred in adults with elevated PVR.[1,8–10]

Many infants and small children with congenital heart disease have pulmonary hypertension due to intracardiac shunting, pulmonary vascular disease, or both. This situation may result in limited pulmonary blood flow, right-to-left intracardiac shunting, and subsequent hypoxemia. If nitrous oxide has the same effect on PVR in infants and small children that it has in adults, changes in the pulmonary circulation may be critical in small children with congenital heart disease, further increasing right heart afterload in pulmonary hypertension and potentially increasing right-to-left intracardiac shunting, thus intensifying hypoxemia. We therefore studied the hemodynamic effects of nitrous oxide in infants with normal PVR and in infants with elevated PVR.

Methods

The study protocol was approved by the institutional Committee on Clinical Investigation, and parental informed consent was obtained for the infants included in the study. We studied 12 infants in the intensive care unit 3–6 h following operative repair of congenital heart disease while they were fully ventilated but responsive. Table 1 describes the infants studied, together with the mean values of their blood gases during the study. As is conventional in discussions of pediatric hemodynamics, PVR data were indexed (PVRI) to facilitate comparison of different-size patients. Six infants were studied with normal pulmonary vascular resistance index (PVRI <2 Wood units) and six infants with elevated PVRI (>3.5 Wood units) measured at the time of the study.

PVRI measured at the time of the study determined classification of the infants into either group because calculation of PVR in the cardiac catheterization laboratory, often inaccurate in patients with intracardiac shunting, is not always carried out. Pulmonary blood flow cannot be directly measured in patients with shunting and must be estimated from oxygen saturation values in various chambers, some of which are often assumed rather than measured. All six infants with elevated PVRI at the time of the study had evidence of elevated PVRI prior to operation. Four infants had PVRI >3.5 Wood units calculated

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TABLE 1. Age, Weight, Diagnosis, and Mean Arterial Blood Gas Values of Study Infants (±SD)

Group	n	Age (month)	Weight (kg)	Diagnosis	pH_a	$Paco_2$ mmHg	Pao_2 (mmHg)
Elevated PVR	6	12.5 (±6.2)	7.4 (±2.5)	CAVC × 4, VSD × 2	7.47 (±.04)	35 (±5)	113 (±31)
Normal PVR	6	8.5 (±5)	7.3 ± 2.2	TOF × 3, CAVC, VSD, MR	7.49 (±.04)	34 (±6)	155 (±46)

PVR = pulmonary vascular resistance; VSD = ventricular septal defect; CAVC = complete atrioventricular canal; TOF = tetralogy of Fallot; MR = mitral regurgitation.

at cardiac catheterization preoperatively; one had PVRI >2.0 but <3.5 Wood units: and one did not have PVRI calculated at catheterization, but lung biopsy at the time of operation showed a moderate degree of pulmonary vascular obstructive disease consistent with a PVRI of >3.5 Wood units. None of the six infants with normal PVRI at the time of the study had elevated PVRI as calculated at the time of preoperative catheterization.

Only hemodynamically stable infants not requiring inotropic support were studied. Indwelling right and left atrial, pulmonary artery, and radial artery catheters were inserted during the operation, as is routine in our institution, along with a separate pulmonary artery thermistor. Postoperative chest x-rays and pressure tracings confirmed the position of the intrathoracic catheters. Pulmonary arterial oxygen saturations of less than 80% in the intensive care unit confirmed the absence of residual left-to-right intracardiac shunts.

All infants had received approximately 50 μg/kg of fentanyl together with pancuronium for anesthesia prior to cardiopulmonary bypass and subsequent deep hypothermic circulatory arrest; no additional fentanyl was given after bypass. No other anesthetic agents were used in any infant. In the intensive care unit five of six infants in each group received, for sedation, one or more doses of morphine (0.1 mg/kg every 2 h) up to 1 h prior to the study.

Hemodynamic measurements included left atrial pressure (LAP) and right atrial pressure (RAP); mean pulmonary arterial pressure (MPAP) and systemic arterial pressure; and a thermodilution cardiac output determined by injecting either 1 or 3 ml of 5% dextrose solution (0° C) through the right atrial catheter. The volume of injectate depended on the infant's weight. Thermodilution curves were examined and three determinations of cardiac output were obtained for each measurement period. Successive cardiac output determinations were generally within 5% of each other and always within 10%.

Using 12-min equilibration periods, four sets of hemodynamic measurements were made as follows: 1) after periods of ventilation with 50% nitrogen; 2) then 50% nitrous oxide; and 3) again after 50% nitrogen; 4) followed by 50% nitrous oxide. The order of measurement was not varied, but the second set of measurements was done to check reproducibility of the responses obtained. To avoid the effects of varying fractional inspired O_2 concentration (FI_{O_2}) on PVR, FI_{O_2} was maintained at 0.5 at all times and verified with an inline oxygen analyzer. Ventilator settings were unchanged throughout the study. Arterial blood gases were measured during the study when the FI_{O_2} was 0.5. All hemodynamic indices were calculated using body surface areas derived from a computer program based on the height and weight of each infant. The mean pressure gradient across the pulmonary or systemic vascular bed divided by the CI was used to calculate PVRI and systemic vascular resistance index (SVRI) in Wood units ($mmHg \cdot^{-1} \cdot min \cdot m^2$) for each infant. The same calculations were used to determine PVRI in the catheterization laboratory.

Separate mean values and standard deviations for each variable were calculated for the group with normal PVRI and for the group with elevated PVRI. One-way analyses of variance (ANOVA) for repeated measures were used for each group to determine whether significant differences occurred among the four measurement periods (50% nitrogen; 50% nitrous oxide; 50% nitrogen; and 50% nitrous oxide). When significant differences were noted with ANOVA, the Bonferroni modification of the t test for multiple comparisons (two) was used to test the significance of changes between the two sequential periods of nitrogen and nitrous oxide administration. A P value of <0.05 was considered statistically significant.

Results

There were no statistically significant differences between the mean arterial blood gas values of the two groups shown in table 1, although the Pa_{O_2} tended to be lower in the group with elevated PVRI. The lower Pa_{O_2} in the infants with elevated PVRI was not surprising because they had at least a moderate degree of pulmonary vascular obstructive disease.

The hemodynamic results are shown in tables 2 and 3, respectively, for the infants with normal PVRI and with elevated PVRI. In both groups, heart rate (HR), mean arterial pressure (MAP), and CI all decreased significantly with 50% nitrous oxide compared with the preceding control period (50% nitrogen) on both administrations. MPAP, LAP, RAP, stroke volume index (SVI), SVRI,

TABLE 2. Hemodynamic Responses to 50% N_2O in Infants with Normal PVR (mean ± SD)

Variable	(1) 50% N_2	(2) 50% N_2O	(3) 50% N_2	(4) 50% N_2O
Heart rate (beats/min)	125 ± 20	114 ± 18†	117 ± 17	109 ± 14*
MAP (mmHg)	76 ± 10	66 ± 11†	77 ± 10	68 ± 10†
RAP (mmHg)	9 ± 2	9 ± 2	10 ± 2	9 ± 3
MPAP (mmHg)	16 ± 2	15 ± 3	16 ± 2	16 ± 4
LAP (mmHg)	12 ± 4	12 ± 4	12 ± 4	13 ± 5
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.2 ± 0.7	2.7 ± 0.5†	3.1 ± 0.5	2.8 ± 0.6*
SVI ($ml \cdot beat^{-1} \cdot m^{-2}$)	27 ± 10	25 ± 9	27 ± 7	27 ± 10
SVRI (Wood units)	22 ± 5	22 ± 4	23 ± 4	22 ± 5
PVRI (Wood units)	1.4 ± 0.5	1.4 ± 0.2	1.4 ± 0.4	1.3 ± 0.4

See text for abbreviations.
Wood units = $mmHg \cdot l^{-1} \cdot min \cdot m^2$.

* $P < 0.05$ compared with preceding 50% N_2 measurement.
† $P < 0.01$ compared with preceding 50% N_2 measurement.

and PVRI did not change significantly with nitrous oxide on either administration.

Figure 1 shows the individual PVRI data for all infants. In only one infant did the PVRI increase appreciably with both administrations of nitrous oxide. Other infants showed little change in PVRI with nitrous oxide, and two infants decreased their PVRI with both administrations of nitrous oxide.

Discussion

To our knowledge, no complete studies of the hemodynamic response to nitrous oxide in infants and young children have previously been published, although abstracts and one report of animal studies have appeared. Eisele *et al.*[11] found a significant increase in pulmonary artery pressure and PVRI in newborn lambs given nitrous oxide, whereas Weng *et al.*§ found that nitrous oxide in newborn piglets did not affect either pulmonary or systemic vascular resistance, suggesting considerable species differences in the pulmonary vascular response to nitrous oxide. A study in children reported that nitrous oxide increased PVR in older children.¶ However, results of this study are less easily interpreted because a gas mixture of 75% nitrous oxide/25% oxygen was compared with 100% oxygen, a known pulmonary vasodilator.

Indirect support for our results comes from a study of infants and small children with cyanotic congenital heart disease and right-to-left shunting breathing 70% nitrous oxide–halothane during induction of anesthesia.[12] There was no decrease in arterial oxygen saturation on induction with 70% nitrous oxide and halothane, suggesting no substantial increase in PVR with 70% nitrous oxide. Despite use of 70% nitrous oxide, substantial increases in saturation occurred in several children, which would not be expected to result from the small changes in FI_{O_2} (0.21 to 0.30) in the setting of cyanotic congenital heart disease. Alternatively, a decrease in oxygen consumption with halothane or inhibition of increases in PVR by the halothane used in this study may have obscured decreases in arterial oxygen saturation resulting from increased PVR and increased right-to-left shunting.

Our results in these infants with serious congenital heart disease and residual circulating levels of narcotics were not too different from those obtained in adults with heart disease receiving narcotics, except for the response of the pulmonary vasculature. Similar to findings in adult patients, HR, cardiac output, and systemic arterial pressure all were decreased by 50% nitrous oxide in our infants.[1–4,13,14] Although statistically significant, the changes in arterial pressure and cardiac output averaged only 12–13% in both groups, and these changes would not be clinically important in most infants undergoing cardiothoracic operations. Systemic vascular resistance did not change in either group of infants in the present study, whereas increases, no change, and decreases have been reported in adults.[1,5,8–10]

On the other hand, the response of the pulmonary vasculature differed markedly from the responses reported in adults.[1,8–10] Whereas no significant increase in either pulmonary artery pressure or PVRI occurred either in infants with normal PVRI or elevated PVRI, Schulte-Sasse *et al.*[9] have suggested that the level of preexisting PVR is the decisive factor in the magnitude of the pulmonary vascular response to nitrous oxide. They found a 16% increase in baseline PVRI (2.5 Wood units) with 50% nitrous oxide in patients with coronary artery disease and a 48% increase in baseline PVRI (7.4) of patients with severe pulmonary hypertension secondary to mitral stenosis. Similarly, Hilgenberg *et al.*[10] found a 33% increase

§ Weng JT, Smith RA, Smith DE, Kirby RR: Pulmonary and systemic vascular response to nitrous oxide in newborn piglets (abstract). Society of Cardiovascular Anesthesiologists 4th Annual Meeting, p 59, 1982.

¶ Landry LD, Emerson CW, Philbin DM, Palacios I, Goldblatt A, Block P: The effect of nitrous oxide on pulmonary vascular resistance in children (abstract). Anesth Analg 59:548–549, 1980.

TABLE 3. Hemodynamic Responses to 50% N_2O in Infants with Elevated PVR (mean ± SD)

Variable	(1) 50% N_2	(2) 50% N_2O	(3) 50% N_2	(4) 50% N_2O
Heart rate (beats/min)	111 ± 13	104 ± 15†	113 ± 12	100 ± 17†
MAP (mmHg)	79 ± 5	70 ± 8†	81 ± 7	72 ± 10†
RAP (mmHg)	9 ± 3	9 ± 4	10 ± 3	9 ± 3
MPAP (mmHg)	25 ± 2	24 ± 2	26 ± 2	24 ± 2
LAP (mmHg)	9 ± 2	8 ± 3	10 ± 4	9 ± 2
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.6 ± 1.2	3.2 ± 1.0*	3.6 ± 1.1	3.1 ± 0.9†
SVI ($ml \cdot beat^{-1} \cdot m^{-2}$)	33 ± 12	31 ± 11	32 ± 11	32 ± 10
SVRI (Wood units)	21 ± 4	21 ± 5	22 ± 7	21 ± 4
PVRI (Wood units)	4.8 ± 1.2	5.3 ± 1.5	4.9 ± 1.5	5.0 ± 1.2

See text for abbreviations.
Wood units = $mmHg \cdot l^{-1} \cdot min \cdot m^2$.

* $P < 0.05$ compared with preceding 50% N_2 measurement.
† $P < 0.01$ compared with preceding 50% N_2 measurement.

in baseline PVRI (3.3 Wood units) with 50% nitrous oxide in adults with moderate pulmonary hypertension secondary to mitral stenosis.

It is not surprising, therefore, that we found no significant increase in PVRI in the group of infants with normal baseline PVRI (1.4 Wood units). However, in the infants with elevated baseline PVRI (4.8 Wood units), a greater increase in PVRI with nitrous oxide might have been expected. This should have been apparent, even in the relatively small number of infants studied. In fact, only one of six infants with elevated PVRI had an appreciable, consistent increase in PVRI with nitrous oxide. Whether a higher concentration of nitrous oxide(70–75%) would have consistently produced increased PVRI in these infants is unclear from our study.

Age may explain the different responses of the infant pulmonary vasculature to nitrous oxide. The pulmonary vasculature and also, presumably, its sympathetic innervation are immature and still undergoing development in normal infants. In infants with congenital heart disease, maturation of the pulmonary vasculature is often markedly delayed and PVR may remain elevated.[15] This immaturity of the pulmonary vasculature might explain the lack of response of the pulmonary vasculature, because nitrous oxide produces an activation of the sympathetic nervous system. In one study the vasoconstrictive effects of nitrous oxide in the pulmonary bed of adults was blocked by phentolamine, an alpha-adrenergic blocker.[1] Recent studies have suggested that nitrous oxide causes peripheral release of norepinephrine from the pulmonary artery itself.[16] If alpha-adrenergic stimulation with peripheral release of catecholamines is the mechanism of the increase in PVR with nitrous oxide, immaturity of the sympathetic innervation of the pulmonary vasculature might explain the lack of response that was found.

The pathophysiology of increased PVRI in these infants also might explain the difference in findings. The infants with elevated PVRI in our study were older and had large left-to-right shunts preoperatively, with high pulmonary blood flow and pulmonary artery hypertension, compared with the infants with normal PVRI. High pressure and flow in the pulmonary tree for a prolonged period lead to development of pulmonary vascular obstructive disease with increased muscular thickness of pulmonary arteries and arterioles, narrowing of the lumen, and decreased arborization of the pulmonary arteries, as demonstrated in the lung biopsy from one of the infants with elevated PVRI. In contrast, the adults with elevated PVRI studied had pulmonary hypertension with normal or low-normal flows secondary to mitral stenosis. In mitral stenosis, pulmonary venous hypertension is thought to lead to a re-

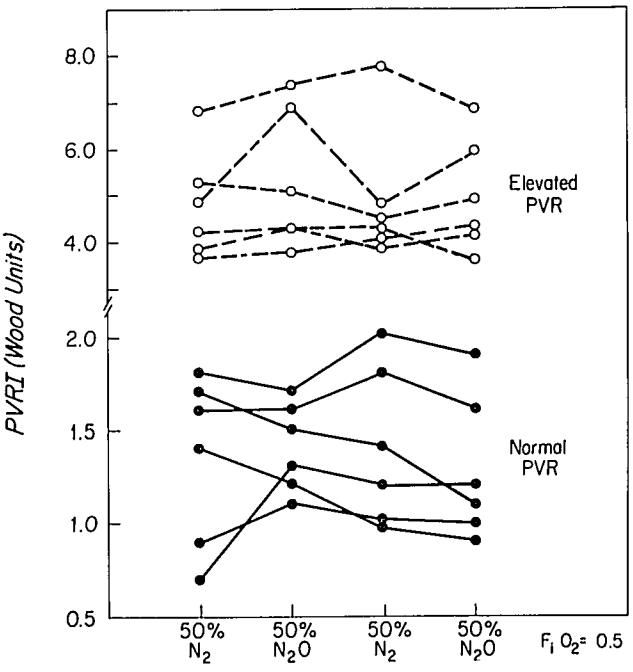

FIG. 1. Individual pulmonary vascular resistance index (PVRI) response to 50% nitrous oxide or nitrogen in six infants with elevated PVRI and six infants with normal baseline PVRI. Note that FI_{O_2} remains fixed at 0.5 for all measurements.

active increase in PVR. Whether these two distinctly different pathophysiologic mechanisms, structural alterations in the pulmonary arterial tree *versus* a reactive response in a more normal pulmonary vascular bed, lead to different responses in the pulmonary vasculature is unknown.

Whether our findings would also apply to infants and children with more severe pulmonary vascular disease (PVRI > 8–10 Wood units) is unclear, but these infants rarely have repair of congenital cardiac lesions. Likewise, these findings may not apply to other forms of pulmonary hypertension in infants and small children.

Because of previous findings in adults, it has been suggested that nitrous oxide might be undesirable in patients with pulmonary hypertension and cardiac shunting. Our study demonstrates that in infants with heart disease and a moderate degree of pulmonary vascular disease, 50% nitrous oxide does not significantly increase PVRI. It does, however, mildly decrease cardiac output and arterial pressure in these infants. Although these mild decreases are unlikely to be clinically important in infants with only mild to moderate decreases in cardiac reserve such as we studied, the depression of arterial pressure and cardiac output by nitrous oxide may be more marked in infants with severely compromised cardiovascular reserves requiring pressor support.

Use of nitrous oxide for induction and maintenance of anesthesia in infants with intracardiac shunting or pulmonary hypertension should, thus, result in only minimal and unimportant clinical changes in shunting, pulmonary artery pressures, or systemic hemodynamics so long as cardiovascular function is not severely compromised. However, in severely compromised infants requiring pressor support, we would avoid use of nitrous oxide altogether because of our findings and because depression of cardiac output by nitrous oxide has been reported to be greater in the more severely compromised myocardium.[4] In other infants with depressed circulation in the immediate postbypass period, we would also avoid nitrous oxide because of potentially greater deleterious effects on systemic hemodynamics in a depressed myocardium during this time.

Decisions about the use of nitrous oxide in infants and small children with cardiac disease and variable amounts of pulmonary vascular disease should be based on the considerations outlined in this article, rather than on previous findings in adults.

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