

Pulmonary Vascular Responses to Nitrous Oxide in Patients with Normal and High Pulmonary Vascular Resistance

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The pulmonary vascular responses to 50 per cent nitrous oxide were studied in 32 anesthetized patients ventilated to maintain normal PaCO₂. One group consisted of sixteen patients with coronary artery disease (CAD) and normal pulmonary vascular resistance (PVR) about to undergo coronary artery bypass surgery. A second group consisted of 16 patients with markedly elevated PVR values due to chronic mitral valve stenosis (MVS). CAD patients showed a significant increase in PVR irrespective of whether halothane or fentanyl was used as background anesthetic. Individual changes, however, did not exceed the upper limit of normal and therefore are not considered to be of clinical importance in these patients. In patients with MVS subjected to fentanyl anesthesia, N₂O caused a marked increase in PVR from 357 to 530 dyn · s · cm⁻⁵. Halothane anesthesia did not significantly attenuate the effect of nitrous oxide on the pulmonary vasculature as mean PVR increased from 351 to 451 dyn · s · cm⁻⁵. These results suggest that the preexisting PVR value is of more importance for the pulmonary vascular response to N₂O than the influence of background anesthesia. We conclude that nitrous oxide should be used with caution in patients with elevated pulmonary vascular resistance, particularly in the presence of right ventricular dysfunction and/or right coronary artery disease. (Key words: Analgesics: fentanyl. Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Lung: pulmonary vascular resistance.)

SEVERAL AUTHORS HAVE STUDIED the systemic cardiovascular effects of nitrous oxide, demonstrating evidence of myocardial depression and peripheral vasoconstriction due to alpha-adrenergic stimulation.¹⁻⁸ The effect of nitrous oxide on the pulmonary circulation has not been investigated as extensively. Previous clinical studies have yielded conflicting results. Some of the variability of the reported data may be due to the different conditions present at the time the data were obtained. The addition of nitrous oxide to halothane-oxygen anesthesia in healthy subjects or in patients with aortic and/or mitral valve disease resulted in no significant change in pulmonary vascular resistance (PVR).^{9,10} The data of McCammon *et al.*¹¹ suggested that nitrous oxide has no effect on the pulmonary circulation when N₂O was added to diazepam in patients with coronary artery disease (CAD). In contrast, Lunn *et al.*⁸ reported a significant increase in PVR in patients with CAD during high-dose fentanyl anes-

thesia. PVR values, however, remained within normal limits throughout this study. Hilgenberg *et al.*¹² found an increase in PVR from 159 to 213 dyn · s · cm⁻⁵ during 50 per cent nitrous oxide inhalation in premedicated patients with mitral valve stenosis but concluded that the effect of nitrous oxide on pulmonary vascular resistance is not sufficient to recommend avoidance of nitrous oxide in patients with moderate pulmonary hypertension. Since measurements of the effect of nitrous oxide on the pulmonary circulation in patients with markedly elevated preexisting pulmonary vascular resistance are limited to the description of a single patient with mitral valve disease,⁶ data in a larger series of patients with high PVR (>200 dyn · s · cm⁻⁵) are necessary to resolve the question of the safety or hazard of nitrous oxide administration in such patients. Also, in order to assess the influence of background anesthesia on the response of the pulmonary circulation to the addition of nitrous oxide, two different anesthetic regimens (halothane and fentanyl) were compared.

Materials and Methods

A total of 32 cardiac surgical patients were studied. Written informed consent was obtained at the time of the preoperative visit. Consent procedures and study techniques conformed to appropriate ethical standards and were approved by the ethic committee of the Char-lottenburg Clinic, Free University of Berlin. One group consisted of sixteen patients with CAD and normal PVR about to undergo coronary artery bypass surgery. A second group of patients with mitral valve stenosis exhibited pulmonary hypertension associated with significantly elevated PVR (>200 dyn · s · cm⁻⁵). Each group was divided into two subgroups with different background anesthesia (diazepam/halothane or diazepam/fentanyl).

In the patients with CAD maintenance antianginal therapy consisted of sublingual nitroglycerin, long-acting nitrates (isosorbide dinitrate, 60-120 mg/day per os) and propranolol (40-240 mg/day per os). The daily oral maintenance dose of glycosides was 0.2-0.4 mg of β-acetyl-digoxin. The patients with mitral valve disease only received digitalis. The last single dose of these drugs was given 12 to 16 h before operation. Premedication consisted of oral diazepam (0.15 mg/kg) 90 min prior to induction of anesthesia.

Upon arrival in the operating room, electrocardiogram leads were attached and peripheral intravenous cannulas

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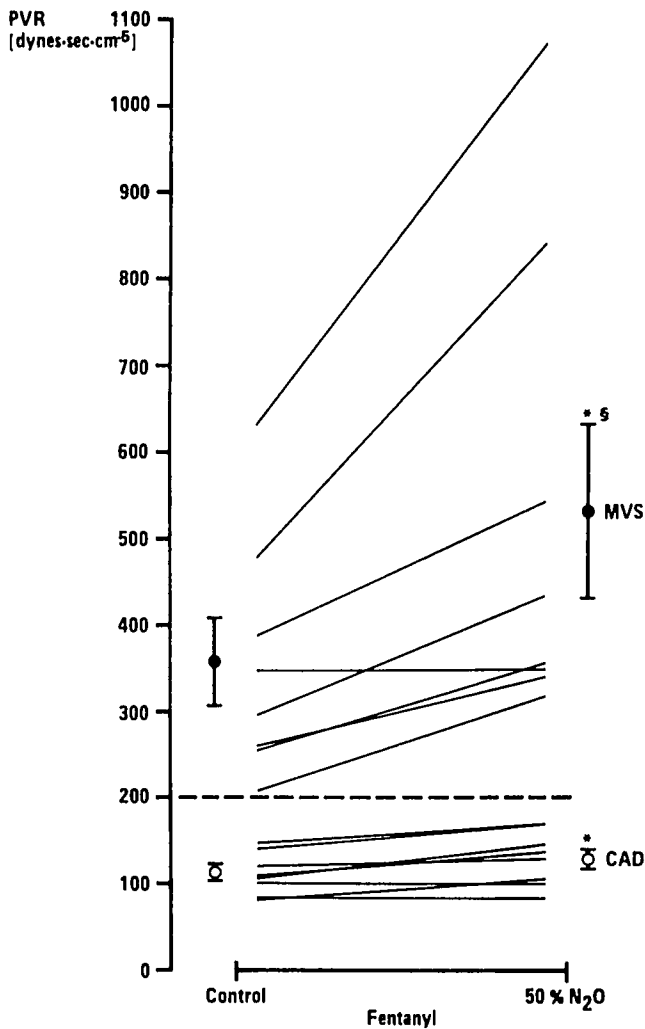


FIG. 1. Individual and mean changes (\pm SEM) of pulmonary vascular resistance (PVR) after addition of 50 per cent N_2O to fentanyl in eight patients with coronary artery disease (CAD, open symbols) and normal control pulmonary vascular resistance compared to the effects of N_2O in eight patients with mitral valve stenosis (MVS, closed symbols) and high preexisting PVR values. * $2\alpha \leq 0.05$ (effects of 50 per cent N_2O compared to controls, Wilcoxon test for paired data) § $2\alpha \leq 0.05$ (effects of 50 per cent N_2O in MVS patients compared to changes in CAD patients, Wilcoxon test for unpaired data).

and a 20-gauge radial artery catheter were placed. A 7-F Swan-Ganz thermodilution flow-directed catheter was introduced into the pulmonary circulation via the right internal jugular vein. This catheter was used for measuring right atrial pressure (RAP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). All pressures were measured using Statham P 23[®] db transducers and were recorded together with a lead V₅ of the electrocardiogram on a Hellige EK 21[®] eight-channel recorder and display oscilloscope. Cardiac output (CO) was measured in triplicate by thermodilution (Edwards 9520[®] cardiac output computer).

Systemic and pulmonary vascular resistance (SVR, PVR), cardiac index (CI), and stroke index (SI) were calculated.

Anesthesia was induced with either diazepam (0.5 mg/kg)/fentanyl (7.5–10 μ g/kg) or diazepam (0.5 mg/kg)/halothane (initial inspiratory concentration 1.5–2.0 per cent). Endotracheal intubation was facilitated with pancuronium bromide (0.1 mg/kg). Ventilation was controlled with an Engstroem-ventilator (ER 300) using a non-rebreathing system. Oxygen was added to air or halothane-air to achieve an inspired concentration of 50 per cent as indicated by an oxygen analyzer (Tekmar T 25[®]). The inspired halothane concentration was reduced to 0.6–1.0 per cent after intubation and then kept constant. Normoventilation was controlled by measuring end-tidal CO_2 -concentration (Datex CD 101[®]) and arterial blood P_{CO_2} (AVL 938 blood-gas analyzer). To achieve stable hemodynamic conditions, we waited for at least 30 min after intubation, before control measurements were performed. During the period of data collection no fluid was infused, all measurements were made at end-expiration with zero end-expiratory pressure. The nitrogen in the inspired gas mixture was discontinued and nitrous oxide (50 per cent) was substituted. After 10 min all measurements were repeated.

Statistical significance of the results was assessed using the Wilcoxon test for correlated and uncorrelated data, respectively. Statistical significance was defined as $2\alpha \leq 0.05$. Data are presented as means \pm SEM.

Results

Patients with CAD receiving diazepam/fentanyl anesthesia (fig. 1 and table 1) showed a small but significant increase in the average pulmonary vascular resistance by 16 per cent; PVR values, however, remained within normal limits (PVR increased from 112 to 130 $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$). HR, CI, and MAP slightly decreased ($2\alpha \leq 0.05$) and mean pulmonary artery pressure and systemic vascular resistance did not change.

In the patients with mitral valve stenosis (MVS) and markedly elevated PVR (control value during diazepam/fentanyl anesthesia: $357 \pm 49 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$) the addition of 50 per cent N_2O caused a significantly greater elevation of pulmonary vascular resistance (48 per cent) compared to CAD-patients with normal PVR. Individual data (fig. 1) show that two of the patients with MVS developed striking increases of PVR from 630 to 1,068 $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ and from 478 to 838 $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$, respectively. PA pressures increased from 36 to 43 mmHg, and CI fell from 1.9 to 1.6 $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($2\alpha \leq 0.05$). Systemic vascular resistance did not change significantly.

Patients with coronary artery disease subjected to diazepam/halothane anesthesia (fig. 2 and table 2) showed a small increase in PVR from 106 to 116 $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$

TABLE 1. Hemodynamics and Arterial Blood-gas Data (Mean \pm SEM) before and after N₂O Administration

	Coronary Artery Disease		Mitral Valve Stenosis	
	Fentanyl		Fentanyl	
	Control	N ₂ O	Control	N ₂ O
Heart rate (beats/min)	68 \pm 4	64 \pm 4*	84 \pm 7	80 \pm 6
Cardiac index (l \cdot min ⁻¹ \cdot m ⁻²)	2.4 \pm 0.1	2.3 \pm 0.1*	1.9 \pm 0.1	1.6 \pm 0.1*
Stroke index (ml \cdot beat ⁻¹ \cdot m ⁻²)	37 \pm 2	37 \pm 2	24 \pm 3	22 \pm 3
Mean arterial pressure (mmHg)	80 \pm 4	72 \pm 4*	68 \pm 4	65 \pm 4
Mean right atrial pressure (mmHg)	5 \pm 1	6 \pm 1	6 \pm 1	7 \pm 1
Mean pulmonary artery pressure (mmHg)	15 \pm 1	15 \pm 1	36 \pm 1	43 \pm 2*
Mean pulmonary capillary wedge pressure (mmHg)	9 \pm 1	8 \pm 1	22 \pm 1	25 \pm 2
Systemic vascular resistance (dyn \cdot s \cdot cm ⁻⁵)	1,309 \pm 75	1,245 \pm 72	1,637 \pm 226	1,729 \pm 241
Pulmonary vascular resistance (dyn \cdot s \cdot cm ⁻⁵)	112 \pm 8	130 \pm 11*	357 \pm 49	530 \pm 98*
PaO ₂ (mmHg)	164 \pm 5	171 \pm 10	148 \pm 26	150 \pm 26
P _a CO ₂ (mmHg)	39 \pm 2	42 \pm 2	40 \pm 1	40 \pm 1

* $2\alpha \leq 0.05$ (control vs. N₂O).

(9 per cent, $2\alpha \leq 0.05$) when nitrogen was replaced by N₂O. PA pressure remained unaffected. In the presence of unchanged CI and a fall in MAP, systemic vascular resistance decreased slightly.

In the patients with elevated PVR (MVS group) subjected to halothane background anesthesia, nitrous oxide produced an average increase in pulmonary vascular resistance from 351 to 451 dyn \cdot s \cdot cm⁻⁵ (28 per cent, $2\alpha \leq 0.05$). Mean pulmonary artery pressure increased from 40 to 45 mmHg ($2\alpha \leq 0.05$) and SVR was not affected. The change in PVR due to N₂O was not significantly different from that observed in the CAD group with normal PVR and halothane anesthesia; however, individual increases of more than 100 dyn \cdot s \cdot cm⁻⁵ were observed in three patients.

The control PVR values in both MVS groups were almost identical (351 vs. 357 dyn \cdot s \cdot cm⁻⁵). In comparison to fentanyl, halothane did not significantly attenuate the pulmonary vasoconstrictive effects of N₂O (451 vs. 530 dyn \cdot s \cdot cm⁻⁵).

Arterial blood-gas tensions did not differ significantly between groups (table 1 and 2).

Discussion

The pulmonary vascular effects of nitrous oxide have been supposed to depend on whether N₂O is administered alone or in combination with other anesthetics.^{6,8-12} The data of Lappas *et al.*⁶ suggested that the preexisting pulmonary vascular resistance probably is of more importance for the pulmonary vascular response to N₂O than the influence of background anesthesia. These authors described a dramatic increase of the PVR in a single patient with markedly elevated PVR due to mitral valve stenosis. The vasoconstrictive effect of nitrous oxide was reversed by the administration of the α -receptor blocker phentolamine.

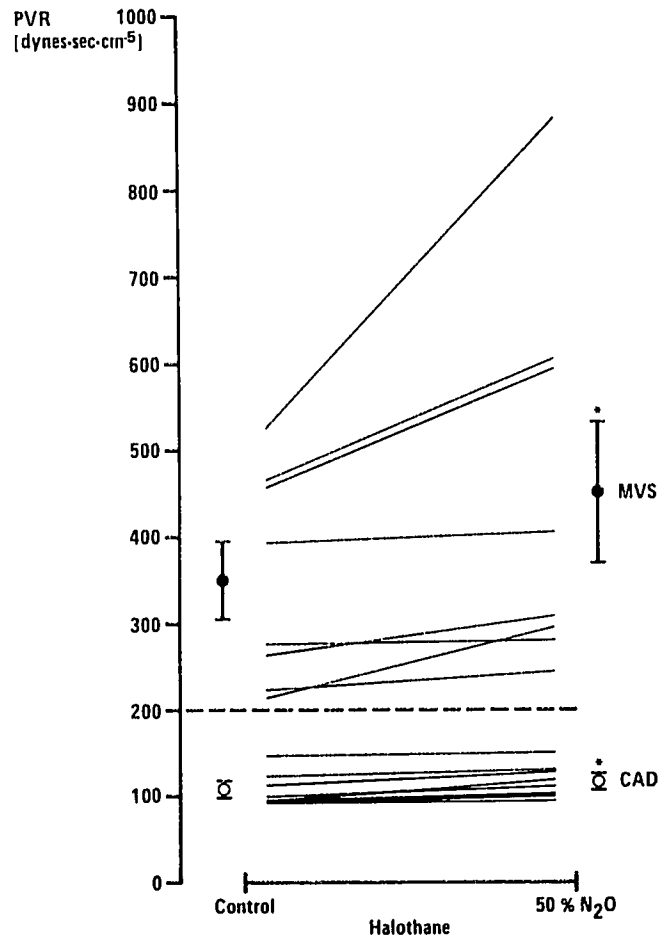
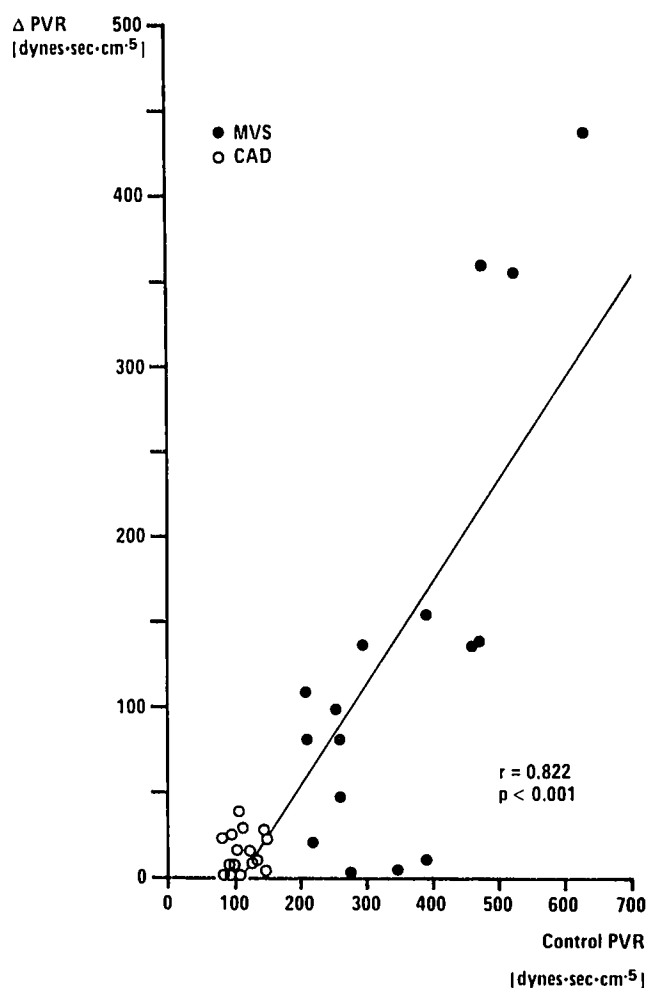


FIG. 2. Individual and mean changes (\pm SEM) of pulmonary vascular resistance (PVR) after addition of 50 per cent N₂O to halothane in eight patients with coronary artery disease (CAD, open symbols) and normal control pulmonary vascular resistance compared to the effects of N₂O in eight patients with mitral valve stenosis (MVS, closed symbols) and high preexisting PVR values. * $2\alpha \leq 0.05$ (effects of 50 per cent N₂O compared to controls, Wilcoxon test for paired data).

TABLE 2. Hemodynamics and Arterial Blood-gas Data (Mean \pm SEM) before and after N₂O Administration

	Coronary Artery Disease		Mitral Valve Stenosis	
	Halothane		Halothane	
	Control	N ₂ O	Control	N ₂ O
Heart rate (beats/min)	76 \pm 4	74 \pm 4	87 \pm 4	90 \pm 4
Cardiac index (l \cdot min ⁻¹ \cdot m ⁻²)	2.8 \pm 0.2	2.8 \pm 0.2	2.0 \pm 0.2	1.8 \pm 0.1
Stroke index (ml \cdot beat ⁻¹ \cdot m ⁻²)	37 \pm 2	38 \pm 2	23 \pm 1	20 \pm 2
Mean arterial pressure (mmHg)	79 \pm 2	72 \pm 2*	72 \pm 2	68 \pm 3
Mean right atrial pressure (mmHg)	6 \pm 1	6 \pm 1	8 \pm 1	10 \pm 1
Mean pulmonary artery pressure (mmHg)	16 \pm 2	17 \pm 1	40 \pm 5	45 \pm 5*
Mean pulmonary capillary wedge pressure (mmHg)	9 \pm 1	9 \pm 1	27 \pm 3	30 \pm 4
Systemic vascular resistance (dyn \cdot s \cdot cm ⁻⁵)	1,162 \pm 90	1,038 \pm 72*	1,702 \pm 172	1,743 \pm 191
Pulmonary vascular resistance (dyn \cdot s \cdot cm ⁻⁵)	106 \pm 7	116 \pm 7*	351 \pm 44	451 \pm 79*
PaO ₂ (mmHg)	167 \pm 10	180 \pm 10	144 \pm 17	143 \pm 19
PaCO ₂ (mmHg)	39 \pm 1	41 \pm 1	37 \pm 2	38 \pm 1

* $2\alpha \leq 0.05$ (control *vs.* N₂O).FIG. 3. The relationship between control pulmonary vascular resistances and changes in PVR after the addition of 50 per cent nitrous oxide in cardiac surgical patients. ($n = 32$, $y = -64.1 + 0.6x$).

Our data demonstrate that patients with coronary artery disease, all of which had a control PVR value of less than 150 dyn \cdot s \cdot cm⁻⁵, showed a statistically significant increase in PVR during nitrous oxide administration, irrespective of whether halothane or fentanyl were used as background anesthetics. However, the observed increase in PVR and the alterations in other measured or calculated hemodynamic variables are probably not of clinical significance. This conclusion is consistent with the findings of others^{6,11} who also reported only small changes in PVR when nitrous oxide was administered in CAD patients with normal preexisting PVR values. The study of Lunn *et al.*,⁸ which also was performed in CAD patients, however, suggests that the vasoconstrictive and myocardial depressant effects of nitrous oxide are exaggerated in the presence of high-dose fentanyl anesthesia (75 μ g/kg). These authors reported a significant increase in PVR (90 to 164 dyn \cdot s \cdot cm⁻⁵) and in SVR (1,385 to 2,270 dyn \cdot s \cdot cm⁻⁵), a marked fall in cardiac output (4.6 to 3.1 l/min), and a reduction in stroke volume from 73 to 42 ml, an effect not observed in our study when nitrous oxide was added to low doses of fentanyl or during halothane anesthesia combined with diazepam.

Our results obtained in the two groups of patients with severely elevated PVR secondary to chronic mitral valve stenosis show that the level of preexisting pulmonary vascular resistance is the decisive factor in the magnitude of the pulmonary vascular response to the addition of nitrous oxide. Figure 3 supports this conclusion. There was a significant correlation between the initial pulmonary vascular resistance and the changes in PVR after N₂O. In addition, the greatest increases in PVR were observed in the three patients with the highest initial values.

We cannot exclude the possibility that the maintenance of preoperative antianginal therapy (long-acting nitrates and propranolol) in our CAD patients interfered with the hemodynamic effects of N₂O and may have contributed to the observed differences between the CAD and MVS groups. The data of Lappas *et al.*,⁶ however, suggest that a drug interaction was unlikely to play a major role in our investigation, since these authors reported a comparable small increase of the PVR in their CAD patients, who were not pretreated with long-acting nitrates and in whom propranolol was discontinued 48 h prior to operation.

Our results failed to demonstrate a significant attenuation of the N₂O effects by halothane anesthesia. Stoelting *et al.*¹⁰ investigated the pulmonary vascular effects of nitrous oxide added to halothane in patients with moderate pulmonary hypertension due to aortic and/or mitral valve disease, but with normal PVR. These authors found no change in pulmonary vascular resistance. This result may be due to the existence of normal PVR control values rather than to the use of halothane. The present study documented a disparate action of nitrous oxide on the vascular beds of the systemic and the pulmonary circulation. The lack of systemic vasoconstriction in both of our patient groups is in agreement with the results of others who studied the effects of N₂O alone,^{12,13} in the presence of morphine or fentanyl,^{6,14} and in combination with diazepam,¹¹ halothane,¹⁰ or enflurane.¹⁵ In contrast, several investigators reported an increase in systemic vascular resistance, when nitrous oxide was given alone² or added to fentanyl or morphine anesthesia.^{3-5,8} Systemic vascular constriction was also found when N₂O was administered during halothane anesthesia.¹ Some of the differences of the reported data may be due to variable conditions present at the times the data were collected, among which background anesthesia is not likely to be an important factor.

In conclusion, the present study suggests that the pulmonary vasoconstrictive effects of nitrous oxide in patients with normal preexisting pulmonary vascular resistance probably are of no clinical significance. However, in patients with pulmonary hypertension and already elevated PVR values due to chronic mitral valve stenosis,

nitrous oxide can produce striking additional increases in pulmonary vascular tone. This effect might be particularly undesirable in patients with right ventricular dysfunction or in the presence of right coronary artery disease.

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