Inhaled Nitric Oxide as a Preoperative Test (INOP Test I)

The INOP Test Study Group

David T. Balzer, MD; Henry W. Kort, MD; Ronald W. Day, MD; Howard M. Corneli, MD; John P. Kovalchin, MD; Bryan C. Cannon, MD; Stephen F. Kaine, MD; D. Dunbar Ivy, MD; Steven A. Webber, MD; Abraham Rothman, MD; Robert D. Ross, MD; Sanjeev Aggarwal, MD; Masato Takahashi, MD; J. Deane Waldman, MD, MBA

Background—This study was performed to determine whether a preoperative hemodynamic evaluation with oxygen and inhaled nitric oxide identifies patients with pulmonary hypertension who are appropriate candidates for corrective cardiac surgery or transplantation more accurately than an evaluation with oxygen alone.

Methods and Results—At 10 institutions, 124 patients with heart disease and severe pulmonary hypertension underwent cardiac catheterization to determine operability. The ratio of pulmonary and systemic vascular resistance (Rp:Rs) was determined at baseline while breathing ~21% to 30% oxygen, and in ~100% oxygen and ~100% oxygen with 10 to 80 parts per million nitric oxide to evaluate pulmonary vascular reactivity. Surgery was performed in 74 patients. Twelve patients died or developed right heart failure secondary to pulmonary hypertension following surgery. Rp:Rs<0.33 and a 20% decrease in Rp:Rs from baseline were chosen as 2 criteria for operability to determine, in retrospect, the efficacy of preoperative testing in patient selection. In comparison to an evaluation with oxygen alone, sensitivity (64% versus 97%) and accuracy (68% versus 90%) were increased by an evaluation with oxygen and nitric oxide when Rp:Rs<0.33 was used as the criterion for operability. Specificity was only 8% when a 20% decrease in Rp:Rs from baseline was used as the criterion for operability.

Conclusion—By using a combination of oxygen and inhaled nitric oxide, a greater number of appropriate candidates for corrective cardiac surgery or transplantation can be identified during preoperative testing when a specific value of Rp:Rs is used as a criterion for operability. **(*Circulation*. 2002;106[suppl I]:I-76-I-81.)**

Key Words: heart defects, congenital ■ hypertension, pulmonary ■ nitric oxide ■ oxygen ■ surgery

Patients with severe pulmonary hypertension have an increased risk of death or decreased exercise tolerance after corrective surgery or transplantation for congenital or acquired heart disease.[1–4] Preoperatively, a hemodynamic evaluation is usually performed in patients with clinical evidence of high pulmonary vascular resistance (Rp) to determine whether they are acceptable candidates for surgery. Supplemental oxygen may be used to decrease Rp and evaluate pulmonary vascular reactivity when Rp is excessively increased in room air alone.[5–7] Nitric oxide may also be used to evaluate pulmonary vascular reactivity. The combination of oxygen and inhaled nitric oxide frequently decreases Rp to a greater extent than oxygen or inhaled nitric oxide alone.[8–10] Thus, many institutions have empirically used inhaled nitric oxide during cardiac catheterization to determine whether patients are appropriate candidates for corrective cardiac surgery or transplantation.[11] This study was performed to determine whether a preoperative test with a combination of oxygen and inhaled nitric oxide identified patients who survived surgery without evidence of right heart failure more accurately than a preoperative test with oxygen alone.

Methods

Ten institutions provided results of preoperative hemodynamic testing with supplemental oxygen and inhaled nitric oxide. Each investigator obtained approval from the institution's review board for human research and the United States Food and Drug Administration to conduct individual studies. Informed consent was obtained from the patients or their parents. Investigators also obtained approval to collectively review, in retrospect, the results of preoperative testing and the outcome of patients who underwent surgery. Testing occurred from 1993 to 2001. Data collection occurred from January 2001 to May 2001.

From the St. Louis Children's Hospital, St. Louis, Mo. (D.T.B., H.W.K.); Primary Children's Medical Center, Salt Lake City, Utah (R.W.D., H.M.C.); Texas Children's Hospital, Houston, Tex. (J.P.K., B.C.C.); Children's Mercy Hospital, Kansas City, Mo. (S.F.K.); Children's Hospital of Denver, Denver, Colo. (D.D.I.); Children's Hospital of Pittsburgh, Pittsburgh, Pa. (S.A.W.); University of California, San Diego, San Diego, Calif. (A.R.); Children's Hospital of Michigan, Detroit, Mich. (R.D.R., S.A.); Children's Hospital of Los Angeles, Los Angeles, Calif. (M.T.); University of New Mexico, Albuquerque, NM (J.D.W.). Authors are listed according to the number of patients enrolled from their respective institutions.

Correspondence to Ronald W. Day, MD, Pediatric Cardiology, Primary Children's Medical Center, 100 North Medical Drive, Salt Lake City, Utah 84113. E-mail ron.day@hsc.utah.edu

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Criteria for Patient Inclusion

Patients were required to fulfill all of the following criteria to be included in this study:

1. Presence of congenital or acquired heart disease under consideration for corrective surgery or cardiac transplantation.
2. A preoperative heart catheterization with sufficient measurements of blood pressure and oxygen saturation/content to calculate Rp, systemic vascular resistance (Rs), and Rp:Rs while breathing supplemental oxygen with, and without, inhaled nitric oxide.
3. An Rp:Rs≥0.33 during baseline measurements.

Criteria for Patient Exclusion

Patients with any of the following criteria were excluded from this study:

1. Heart defects that preclude an accurate calculation of Rp:Rs (branch pulmonary arterial stenosis, obstruction of isolated pulmonary veins, etc).
2. Residual heart defects after surgery, which may have had an impact on the severity of residual pulmonary hypertension (branch pulmonary arterial stenosis, pulmonary venous obstruction, significant atrioventricular valve regurgitation, etc).

Procedures

Rp, Rs, and Rp:Rs were determined by using the Fick principle with patients breathing <2 L/min nasal cannula oxygen or <30% oxygen with assisted ventilation (baseline), 5 to 15 L/min facemask oxygen or 100% oxygen with assisted ventilation (~100% oxygen), and ~100% oxygen with 10 to 80 parts per million nitric oxide for intervals of at least 7 minutes during cardiac catheterization. The methods of sedation and nitric oxide delivery were determined by the protocol of each institution. If more than 1 concentration of nitric oxide was tested, the amount that resulted in the lowest value of Rp:Rs was reported in this study. Operability was determined independently by the care providers of each institution. Poor outcome was defined as death or right heart failure secondary to pulmonary hypertension following surgery. The medical records of surviving patients were reviewed to determine whether care providers reported clinical evidence of right heart failure.

Statistical Analysis

The results of hemodynamic testing were compared by analysis of variance for repeated measures. Significant differences in arterial blood gases and hemodynamic measurements were determined by $P<0.05$ using the Scheffé test. An Rp:Rs<0.33 and a 20% decrease in Rp:Rs from baseline were selected as separate criteria for operability to determine, in retrospect, the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy (true positive plus true negative divided by total) with 95% confidence intervals (95% CI) for each test condition. Receiver operating characteristic curves were used to evaluate the corresponding balance between sensitivity and specificity over a range of Rp, or Rp:Rs, values.

Results

Patients

A total of 124 patients met the criteria for inclusion in the study. The mean age at the time of cardiac catheterization was 67 months with a median age of 28 months and a range of 1 to 569 months. Fifty-eight patients were male. Thirty-nine patients had a chromosomal abnormality. Thirty-five patients were on assisted ventilation during hemodynamic testing. Eighty-five patients had atrial or ventricular septal defects, 7 patients had only a patent ductus arteriosus, 12 patients had left heart obstructive disease, 8 patients had variations of transposition of the great arteries, and 12 patients had cardiomyopathy.

TABLE 1. Results of Hemodynamic Testing

	Patients Considered Operable (n=78)	Patients Considered Inoperable (n=46)
Age, months	46±8	102±15‡
pH 1	7.37±0.01	7.36±0.01
pH 2	7.37±0.01	7.36±0.01
pH 3	7.38±0.01	7.37±0.01
PO_2 1, kPa	8.4±0.4	8.3±0.4
(mm Hg)	(63±3)	(62±3)
PO_2 2, kPa	36.9±2.9*	26.9±2.7*‡
(mm Hg)	(277±22)*	(202±20)*‡
PO_2 3, kPa	38.5±1.6*	28.8±2.9*‡
(mm Hg)	(289±12)*	(216±22)*‡
Rp 1, dyne-s-cm^{-5}-m^2	1000±72	1896±200‡
(units-m^2)	(12.5±0.9)	(23.7±2.5)‡
Rp 2, dyne-s-cm^{-5}-m^2	560±48*	1584±168*‡
(units-m^2)	(7.0±0.6)*	(19.8±2.1)*‡
Rp 3, dyne-s-cm^{-5}-m^2	400±40*†	1400±160*‡
(units-m^2)	(5.0±0.5)*†	(17.5±2.0)*‡
Rs 1, dyne-s-cm^{-5}-m^2	1472±72	1640±112
(units-m^2)	(18.4±0.9)	(20.5±1.4)
Rs 2, dyne-s-cm^{-5}-m^2	1704±72*	1872±120*
(units-m^2)	(21.3±0.9)*	(23.4±1.5)*
Rs 3, dyne-s-cm^{-5}-m^2	1848±80*†	1872±120*
(units-m^2)	(23.1±1.0)*†	(23.4±1.5)*
Rp:Rs 1	0.87±0.15	1.21±0.12
Rp:Rs 2	0.38±0.07*	0.87±0.07*‡
Rp:Rs 3	0.22±0.02*	0.75±0.07*‡

(1) baseline; (2) ~100% oxygen; (3) ~100% oxygen and nitric oxide; (PO_2) arterial oxygen tension; (Rp) pulmonary vascular resistance index; (Rs) systemic vascular resistance index.

*$P<0.05$: in comparison to baseline.

†$P<0.05$: in comparison to ~100% oxygen.

‡$P<0.05$: in comparison to patients who were considered operable.

Seventy-eight patients were considered to be operable. Seventy-four patients had undergone surgery at the time of data collection. One patient died from an infection before surgery, and 3 patients were simply waiting for the procedure to be performed. Surviving patients were followed for a median duration of 26 months with a range of 3 to 87 months.

Hemodynamic Testing

The results of hemodynamic testing are listed in Table 1. Nitric oxide was delivered at a median concentration of 60 parts per million (range: 10 to 80 parts per million) for a median duration of 10 minutes. Blood gas measurements were performed during all test conditions in only 50 patients who were considered operable and only 42 patients who were considered inoperable. A greater increase in oxygen tension occurred with supplemental oxygen in patients who were considered operable. Rp was significantly greater during each test condition in patients who were considered inoperable

TABLE 2. Deaths Related to Pulmonary Hypertension

Deaths	Postoperative Interval	Comments
Early deaths (before postoperative discharge from hospital)		
1	37 days	Multi-system disease associated with prolonged right heart failure despite nitric oxide therapy
2	2 days	Pulmonary hypertensive crisis despite nitric oxide therapy
3	46 days	Prolonged right heart failure despite nitric oxide therapy and extracorporeal membrane oxygenation
4	42 days	Prolonged right heart failure and a terminal pulmonary hypertensive crisis associated with a febrile illness
5	3 days	Pulmonary hypertensive crisis despite nitric oxide therapy
6	42 days	Prolonged right heart failure and a terminal pulmonary hypertensive crisis when agitated during placement of an peripheral intravenous catheter
7	6 days	Pulmonary hypertensive crisis despite nitric oxide therapy
Late deaths (after postoperative discharge from hospital)		
Deaths	Postoperative Interval	Comments
8	5 months	Acute right heart failure associated with a febrile illness
9	44 months	Acute respiratory failure and pulmonary hypertension which did not resolve with nitric oxide therapy and extracorporeal membrane oxygenation
10	4 months	Sudden death: autopsy findings of interstitial pneumonitis and Grade III pulmonary vascular disease

than in patients who were considered operable. In both groups of patients, testing with oxygen resulted in a decrease in Rp and an increase in Rs. In patients who were considered operable, testing with oxygen and nitric oxide resulted in a greater decrease in Rp and a greater increase in Rs than testing with oxygen alone.

Outcome and the Results of Hemodynamic Testing

Of the 74 patients who underwent corrective surgery or transplantation, 3 patients were lost to follow-up after discharge from the hospital. Thus, outcome was determined for only 71 patients. Seven patients died during the postoperative period from complications of pulmonary hypertension. Four patients died 4 to 44 months after discharge from the hospital. One of these late deaths resulted from graft vasculopathy 24 months following transplantation. Pulmonary hypertension was felt to be a major contributing factor in each of the remaining 3 late deaths. The postoperative interval and circumstances of deaths related to pulmonary hypertension are provided in Table 2. Two surviving patients were reported by care providers to have right heart failure secondary to pulmonary hypertension.

Table 3 shows the results of hemodynamic testing for patients who had a good outcome following surgery in comparison to the results of patients who died or had clinical evidence of right heart failure secondary to pulmonary hypertension. The patients who experienced a poor outcome were not significantly older or younger. Rp was greater in patients with a poor outcome in comparison to patients with a good outcome. In both groups of patients however, Rp or Rp:Rs decreased significantly with oxygen alone or oxygen in combination with nitric oxide.

Potential Value of Preoperative Testing With a Combination of Supplemental Oxygen and Inhaled Nitric Oxide

An Rp:Rs<0.33 and a 20% decrease in Rp:Rs from baseline were chosen as separate criteria for operability to determine, in retrospect, the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy for each test condition. The results for each criterion are shown in Table 4 and Table 5, respectively. When Rp:Rs<0.33 was used as the criterion for operability, sensitivity and accuracy were increased by using nitric oxide in combination with oxygen. Only 9 patients with an Rp:Rs≥0.33 during oxygen and nitric oxide inhalation underwent surgery. When a 20% decrease in Rp:Rs from baseline was used as the criterion for operability, specificity was only 8% while breathing oxygen alone or oxygen in combination with nitric oxide. Only 1 patient with

TABLE 3. Outcome and the Results of Hemodynamic Testing

	Good Outcome n=59	Poor Outcome n=12
Age, months	52±9	26±19
Rp 1, dyne-s-cm^{-5}-m^2	872±64	1712±272‡
(units-m^2)	(10.9±0.8)	(21.4±3.4)‡
Rp 2, dyne-s-cm^{-5}-m^2	472±40*	1016±200*‡
(units-m^2)	(5.9±0.5)*	(12.7±2.5)*‡
Rp 3, dyne-s-cm^{-5}-m^2	328±24*†	744±176*‡
(units-m^2)	(4.1±0.3)*†	(9.3±2.2)*‡
Rs 1, dyne-s-cm^{-5}-m^2	1488±80	1400±248
(units-m^2)	(18.6±1.0)	(17.5±3.1)
Rs 2, dyne-s-cm^{-5}-m^2	1736±80*	1520±248
(units-m^2)	(21.7±1.0)*	(19.0±3.1)
Rs 3, dyne-s-cm^{-5}-m^2	1848±88*	1784±296
(units-m^2)	(23.1±1.1)*	(22.3±3.7)
Rp:Rs 1	0.68±0.11	1.98±0.72
Rp:Rs 2	0.28±0.02*	0.94±0.38‡
Rp:Rs 3	0.18±0.01*	0.43±0.07*‡

(1) baseline; (2) ~100% oxygen; (3) ~100% oxygen and nitric oxide; (Rp) pulmonary vascular resistance index; (Rs) systemic vascular resistance index.
*$P<0.05$: in comparison to baseline.
†$P<0.05$: in comparison to ~100% oxygen.
‡$P<0.05$: in comparison to patients who had a good outcome.

TABLE 4. Rp : Rs<0.33 as a Criterion for Operability

	Survival Without Right Heart Failure	Death or Right Heart Failure
∼100% O_2		
Rp : Rs<0.33	38	2
Rp : Rs≥0.33	21	10
∼100% O_2 and NO		
Rp : Rs<0.33	57	5
Rp : Rs≥0.33	2	7
	∼100% O_2	∼100% O_2 and NO
Sensitivity, %	64 (53, 76)	97 (91, 100)*
Specificity, %	83 (62, 98)	58 (35, 85)
Accuracy, %	68 (57, 78)	90 (83, 96)*
Positive Predictive Value, %	95 (87, 99)	92 (84, 97)
Negative Predictive Value, %	32 (19, 51)	78 (52, 97)*

(95% CI).
*No overlap of 95% CI.
CI, confidence interval; O_2, oxygen; NO, nitric oxide; Rp : Rs, ratio of pulmonary and systemic vascular resistance.

TABLE 6. Rp : Rs<0.33 as a Criterion for Operability: 30 Patients With Rp : Rs≥0.33 in Oxygen

	Survival Without Right Heart Failure	Death or Right Heart Failure
∼100% O_2		
Rp : Rs<0.33	0	0
Rp : Rs≥0.33	20	10
∼100% O_2 and NO		
Rp : Rs<0.33	18	3
Rp : Rs≥0.33	2	7
	∼100% O_2	∼100% O_2 and NO
Sensitivity, %	0 (0, 17)	90 (75, 99)*
Specificity, %	100 (69, 100)	70 (44, 93)
Accuracy, %	33 (20, 53)	83 (69, 94)*
Positive Predictive Value, %	—	86 (70, 97)
Negative Predictive Value, %	33 (20, 53)	78 (52, 97)

(95% CI).
*No overlap of 95% CI.
CI, confidence interval; O_2, oxygen; NO, nitric oxide; Rp : Rs, ratio of pulmonary and systemic vascular resistance.

a decrease in Rp:Rs<20% during oxygen and nitric oxide inhalation underwent surgery.

There were 30 patients with Rp:Rs≥0.33 in oxygen alone. All of these patients might have been considered inoperable if an Rp:Rs<0.33 was used to select patients for corrective surgery or transplantation and nitric oxide was not available. As shown in Table 6, sensitivity and accuracy increased by using a combination of oxygen and nitric oxide with Rp:Rs<0.33 as the criterion for operability.

Figure 1 shows the receiver operating characteristic curves which were developed by plotting sensitivity against (1 – specificity) for values of Rp and Rp:Rs for oxygen alone and oxygen in combination with inhaled nitric oxide in this study. In each case, the curves for Rp and Rp:Rs are similar and neither variable is associated with a point of inflection with exceptionally high sensitivity and high specificity. In oxygen alone, an optimal balance in sensitivity and specificity would be achieved if Rp<8.2 U-m^2 and Rp:Rs<0.42 were used as potential criteria for operability. In a combination of oxygen and inhaled nitric oxide, an optimal balance in sensitivity and specificity would be achieved if Rp<5.3 U-m^2 and Rp:Rs<0.27 were used as potential criteria for operability.

Figure 2 shows the individual values of Rp of patients during preoperative testing with oxygen alone, and oxygen in

TABLE 5. A 20% Decrease in Rp : Rs from Baseline as a Criterion for Operability

	Survival Without Right Heart Failure	Death or Right Heart Failure
∼100% O_2		
>20% decrease in Rp : Rs	49	11
≤20% decrease in Rp : Rs	10	1
∼100% O_2 and NO		
>20% decrease in Rp : Rs	59	11
≤20% decrease in Rp : Rs	0	1
	∼100% O_2	∼100% O_2 and NO
Sensitivity, %	83 (73, 92)	100 (94, 100)*
Specificity, %	8 (2, 38)	8 (2, 38)
Accuracy, %	70 (60, 81)	85 (76, 92)
Positive Predictive Value, %	82 (72, 91)	84 (75, 92)
Negative Predictive Value, %	9 (2, 42)	100 (2, 100)

(95% CI)
*No overlap of 95% CI.
CI, confidence interval; O_2, oxygen; NO, nitric oxide; Rp : Rs, ratio of pulmonary and systemic vascular resistance.

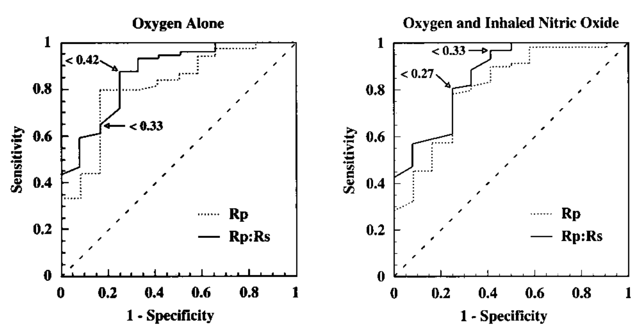

Figure 1. Receiver operating characteristic curves for Rp and Rp:Rs during inhalation of oxygen alone and oxygen with nitric oxide. The curves are similar for Rp and Rp:Rs during inhalation of oxygen alone and oxygen in combination with nitric oxide. Area under the curve (95% CI) in oxygen alone: Rp=0.82 (0.69, 0.95), Rp:Rs=0.87 (0.77, 0.98). Area under the curve (95% CI) in a combination of oxygen and inhaled nitric oxide: Rp=0.81 (0.67, 0.95), Rp:Rs=0.86 (0.74, 0.98). Optimal balance in sensitivity and specificity in oxygen alone: Rp<8.2 U-m^2, Rp:Rs<0.42. Optimal balance in sensitivity and specificity in a combination of oxygen and inhaled nitric oxide: Rp<5.3 U-m^2, Rp:Rs<0.27. Rp: pulmonary vascular resistance index, Rs: systemic vascular resistance index.

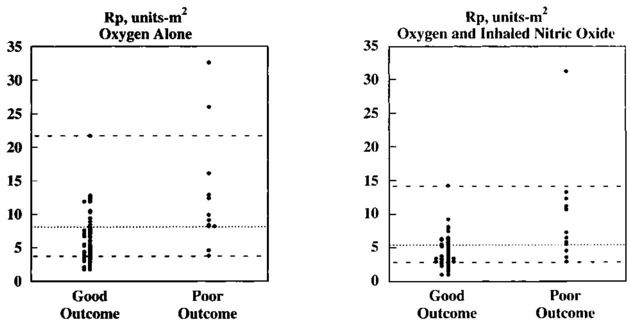

Figure 2. Rp during preoperative testing according to outcome following surgery. In oxygen alone, the lowest value of Rp, which was associated with a poor outcome secondary to pulmonary hypertension was 4.6 U-m^2. The highest value of Rp, which was associated with a good outcome was 21.7 U-m^2. In a combination of oxygen and nitric oxide, the lowest value of Rp, which was associated with a poor outcome secondary to pulmonary hypertension was 2.7 U-m^2. The highest value of Rp, which was associated with a good outcome was 14.1 U-m^2. Testing with inhaled nitric oxide decreased the range of overlapping values of Rp that were associated with good outcomes and poor outcomes. An optimal balance in sensitivity and specificity correlated with an Rp<8.2 U-m^2 in oxygen alone and an Rp<5.3 U-m^2 in a combination of oxygen and nitric oxide as criteria for operability. Rp: pulmonary vascular resistance index.

combination with inhaled nitric oxide. The range of overlapping values of Rp which were associated with good outcomes and poor outcomes was decreased by a combination of oxygen and inhaled nitric oxide.

Figure 3 shows the individual values of Rp:Rs of patients during preoperative testing with oxygen alone, and oxygen in combination with inhaled nitric oxide. The range of overlapping values of Rp:Rs that were associated with good outcomes and poor outcomes was also decreased by a combination of oxygen and inhaled nitric oxide.

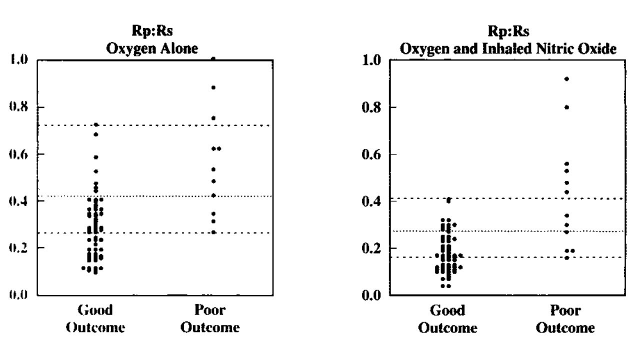

Figure 3. Rp:Rs during preoperative testing according to outcome following surgery. In oxygen alone, the lowest value of Rp:Rs that was associated with a poor outcome secondary to pulmonary hypertension was 0.26. The highest value of Rp:Rs that was associated with a good outcome was 0.72. In a combination of oxygen and nitric oxide, the lowest value of Rp:Rs that was associated with a poor outcome secondary to pulmonary hypertension was 0.16. The highest value of Rp:Rs that was associated with a good outcome was 0.41. Testing with inhaled nitric oxide decreased the range of overlapping values of Rp:Rs that were associated with good outcomes and poor outcomes. An optimal balance in sensitivity and specificity correlated with an Rp:Rs<0.42 in oxygen alone and an Rp:Rs<0.27 in a combination of oxygen and nitric oxide as criteria for operability. Rp: pulmonary vascular resistance index, Rs: systemic vascular resistance index.

Discussion

This study confirms that a combination of oxygen and inhaled nitric oxide frequently decreases Rp more than oxygen alone. Specificity is too low to use pulmonary vascular reactivity, defined a decrease in Rp:Rs≥20%, as the only criterion for operability. However, a greater number of acceptable candidates for surgery can be identified with a combination of oxygen and inhaled nitric oxide when an Rp:Rs<0.33 is used as a criterion for operability. Nitric oxide may also improve the precision of preoperative testing by decreasing the range of overlapping values of Rp, or Rp:Rs, which are associated with good outcomes and poor outcomes.

Patients

This study focused on patients who would traditionally be considered to have an increased risk for complications from pulmonary hypertension following corrective surgery or transplantation. Patients with relatively low baseline values of Rp:Rs were excluded because an assessment of pulmonary vascular reactivity would normally not be needed to determine whether they were acceptable candidates for surgery. Patients were also excluded if they had anatomical abnormalities, which precluded an accurate assessment of Rp and Rs, or that may have resulted in right heart failure following surgery without an actual increase in Rp. By combining the results of several institutions, we were able to evaluate the pulmonary vascular response to inhaled nitric oxide and its significance in a relatively large number of patients. Less than 5% of the patients were lost to follow-up after corrective surgery or transplantation.

This study was limited by the small number of patients with an Rp:Rs≥0.33, or a decrease in Rp:Rs<20% from baseline, during a combination of oxygen and nitric oxide inhalation who underwent surgery. A less substantial change in sensitivity and specificity would be expected to result from preoperative testing with inhaled nitric oxide if our estimates of positive predictive value and negative predictive value were accurate, and if more of the patients who were considered inoperable had undergone surgery. However, this may be an appropriate ethical limitation. A greater number of patients would have experienced a poor outcome if the clinical judgment of care providers had been ignored and surgery was performed in more patients with relatively high, or fixed, values of Rp and Rp:Rs.

This study did not include an evaluation of the outcome of patients who were considered inoperable. Some patients with pulmonary hypertension may survive longer and experience a better quality of life if they are not subjected to surgery. For this reason, future studies should prospectively evaluate of the outcome of patients who are considered inoperable, as well as the outcome of patients who are considered operable.

Hemodynamic Testing

A combination of supplemental oxygen and inhaled nitric oxide decreased Rp more than supplemental oxygen alone. This study did not evaluate the ideal concentration of nitric oxide to use in preoperative testing. Atz and associates have proposed that a subgroup of responsive patients may be overlooked unless a nitric oxide concentration of 80 parts per million is used during preoperative testing.[10] However, other studies have identified no significant difference in the pulmonary vascular response to nitric oxide over the same range of concentrations that were used in this study.[8–9] A relatively high median concentration of 60 parts per million was used in this study. The ideal duration of nitric oxide inhalation during a preoperative test remains unknown. Hyperventilation and other pharmacological agents are alternative methods to test pulmonary vascular reactivity. In this study, the values of pH were normal and reasonably constant. The influence of assisted ventilation and other pulmonary vasodilators was not evaluated.

Outcome and the Results of Hemodynamic Testing

Patients with a good postoperative outcome had significantly lower baseline values of Rp than patients who died or developed right heart failure following surgery. In a combination of oxygen and inhaled nitric oxide, intermediate mean values of Rp and Rp:Rs were achieved by patients who had a poor outcome in comparison to patients who had a good outcome and patients who were considered inoperable. Pulmonary vascular reactivity alone is probably an inadequate criterion to determine whether a patient is operable because oxygen, and a combination of oxygen and inhaled nitric oxide, significantly decreased Rp and Rp:Rs in each group of patients.

This study is limited by a lack of objective measures in the clinical diagnosis of right heart failure. However, death accounted for the majority of patients with a poor outcome in this study. Well-defined measures of morbidity during the early, intermediate, and long-term stages of follow-up are needed in future studies to avoid underestimating the incidence of complications from pulmonary hypertension after corrective surgery and transplantation.

Potential Value of Preoperative Testing With a Combination of Supplemental Oxygen and Inhaled Nitric Oxide

This study demonstrates that a preoperative hemodynamic evaluation with a combination of supplemental oxygen and inhaled nitric oxide identifies a greater number of appropriate candidates for corrective surgery or transplantation than a preoperative evaluation with oxygen alone. Unfortunately, death is a genuine risk for patients who may be selected inappropriately for surgery based on a false-positive response to oxygen and nitric oxide inhalation.

In receiver operating characteristic analysis, an ideal test is portrayed by a curve with a high gain in sensitivity and little loss in specificity. This study suggests that the reliability of preoperative testing is limited, even when a combination of oxygen and inhaled nitric oxide is used. However, the significance of the receiver operating characteristic curves must be interpreted cautiously in this clinical setting because sensitivity and specificity are influenced by the number of patients with high, or fixed, values of Rp:Rs who are allowed to undergo surgery.

In this study, an optimal balance in sensitivity and specificity would have been achieved by using an Rp:Rs$<$0.42 in oxygen alone, and an Rp:Rs$<$0.27 in oxygen and inhaled nitric oxide, as criteria for operability. These values differ from previously proposed criteria of Rp:Rs$<$0.30 to 0.33.[1,12] Nitric oxide may only change the value of Rp:Rs that best defines a patient's operative risk. It is unlikely that patients with an Rp:Rs$>$0.41 during oxygen and nitric oxide inhalation are operable. It is also unlikely that patients with an Rp:Rs$<$0.16 are inoperable. This still leaves a relatively broad range of Rp:Rs values for which the outcome of corrective surgery or transplantation is less certain. However, the range of uncertainty is less than the range of uncertainty for values of Rp:Rs if oxygen alone were used as the only preoperative test. This may be the primary benefit of using a combination of pulmonary vasodilatory agents during a preoperative evaluation.

Our results suggest that inhaled nitric oxide may be a valuable tool in the preoperative evaluation of patients with heart disease and pulmonary hypertension. However, additional studies are needed to determine (a) the most appropriate values of Rp and Rp:Rs to use for patient selection, and (b) the optimal combination of assisted ventilation, supplemental oxygen, inhaled nitric oxide and other pulmonary vasodilators that will narrow the range of Rp:Rs values for which the outcome of corrective surgery and transplantation remains uncertain.

References

1. Friedli B, Kidd BSL, Mustard WT, et al. Ventricular septal defect with increased pulmonary vascular resistance: late results of surgical closure. *Am J Cardiol.* 1974;33:403–409.
2. Hallidie-Smith KA, Wilson RSE, Hart A, et al. Functional status of patients with large ventricular septal defect and pulmonary vascular disease 6 to 16 years after surgical closure of their defect in childhood. *Brit Heart J.* 1977;39:1093–1101.
3. Hopkins RA, Bull C, Haworth SG, et al. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. *Eur J Cardiothorac Surg.* 1991;5:628–634.
4. Murali S, Kormos RL, Uretsky BF, et al. Preoperative pulmonary hemodynamics and early mortality after orthotopic cardiac transplantation: the Pittsburgh experience. *Am Heart J.* 1993;126:896–904.
5. Marshall HW, Swan HJC, Burchell HB, et al. Effect of breathing oxygen on pulmonary vascular resistance in patients with ventricular septal defect. *Circulation.* 1961;23:241–252.
6. Lock JE, Einzig S, Bass JL, et al. The pulmonary vascular response to supplemental oxygen and its influence on operative results in children with ventricular septal defect. *Pediatr Cardiol.* 1982;3:41–46.
7. Davies NJH, Shinebourne EA, Scallan MJ, et al. Pulmonary vascular resistance in children with congenital heart disease. *Thorax.* 1984;39:895–900.
8. Roberts JD, Lang P, Bigatello LM, et al. Inhaled nitric oxide in congenital heart disease. *Circulation.* 1993;87:447–453.
9. Day RW, Lynch JM, Shaddy RE, et al. Pulmonary vasodilatory effects of 12 and 60 parts per million inhaled nitric oxide in children with ventricular septal defect. *Am J Cardiol.* 1995;75:196–198.
10. Atz AM, Adatia I, Lock JE, et al. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol.* 1999;33:813–819.
11. Waldman JD. From PediHeart: inhaled nitric oxide - in clinical trial or in clinical practice? *Pediatr Cardiol.* 2000;21:274.
12. Berner M, Beghetti M, Spahr-Schopfer I, et al. Inhaled nitric oxide to test the vasodilatory capacity of the pulmonary vascular bed in children with long-standing pulmonary hypertension and congenital heart disease. *Am J Cardiol.* 1996;77:532–535.