# Inhaled Nitric Oxide in the Preoperative Evaluation of Pulmonary Hypertension in Heart Transplant Candidates

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***Objective:*** **The goal of this study was to evaluate the efficacy of 100% oxygen and inhaled nitric oxide (iNO) in decreasing pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG) in dilated cardiomyopathy patients being evaluated for orthotopic heart transplantation (OHT); who, despite maximal intravenous (IV) dilator therapy, had persistent moderate-to-severe pulmonary hypertension.**

***Design:*** **A prospective nonrandomized clinical study.**

***Setting:*** **University hospital, major transplant center.**

***Participants:*** **Twenty-one adult patients undergoing OHT evaluation.**

***Interventions:*** **One hundred percent oxygen and iNO at 20 and 40 ppm were sequentially administered to the patients once they were optimized with IV vasodilators and inotropes.**

***Measurements and Main Results:*** **Although no significant change was noted with oxygen, iNO 20 ppm reduced the mean pulmonary artery pressure (44.1 ± 1.7 to 38.6 ± 1.8 mmHg, $p < 0.05$), PVR index (823 ± 47 to 621 ± 55 dyne/s/m$^2$/cm$^5$, $p < 0.05$), TPG (22.4 ± 1.4 to 17.0 ± 1.5 mmHg, $p < 0.05$), and right ventricular stroke work index (14.7 ± 1.2 to 11.1 ± 1.2 g · m/m$^2$/beat, $p < 0.05$). In 13 of 21 patients, PVR decreased by greater than 25% after iNO therapy. Nine of these patients had PVR and TPG decrease to levels considered acceptable for OHT listing.**

***Conclusions:*** **iNO can further improve right ventricular hemodynamics even after presumed optimization with IV vasodilators and serves as a test of PVR reversibility during the preoperative assessment of OHT candidates.**



***KEY WORDS: inhaled nitric oxide, heart transplantation, pulmonary hypertension, preoperative, pulmonary vascular resistance***

AN IMPORTANT SOURCE of morbidity and mortality after orthotopic heart transplantation (OHT) is right ventricular (RV) failure because of the unaccustomed donor RV working against the recipient's high pulmonary vascular resistance (PVR).[1-3] In patients with dilated cardiomyopathy who have pulmonary hypertension secondary to chronic heart failure, both PVR >320 dyne/s/cm$^5$ or 4 Wood units (pulmonary vascular resistance index [PVRI] ≃500-650 dyne/s/m$^2$/cm$^5$) and a transpulmonary gradient (TPG) >15 mmHg adversely affect outcomes after OHT.[4-6] Irreversible pulmonary hypertension above these levels generally precludes such patients as candidates for OHT.

Dilated cardiomyopathy patients undergoing preoperative assessment for OHT candidacy are initially treated with intravenous (IV) vasodilators, which serve to optimize hemodynamics and test the degree of reversibility of PVR and TPG.[7-10] However, accompanying systemic hypotension limits maximal lowering of PVR and TPG in clinical settings. In contrast, inhaled nitric oxide (iNO) and oxygen act selectively on the pulmonary vasculature.[11-15] Although iNO and oxygen have been used as tests of PVR reversibility,[16-18] it is unclear if they can lead to further significant reductions in PVR and TPG after a maximally tolerated clinical response with IV therapy. Such a strategy can provide an additional test of true reversibility of pulmonary hypertension and, more importantly, identify additional patients who meet the above hemodynamic criteria for OHT.

The aim of the present study was to see if 100% oxygen and iNO (20 and 40 ppm) can serve as tests of reversibility of pulmonary hypertension in dilated cardiomyopathy patients who have persistent moderate-to-severe pulmonary hypertension despite clinical optimization with IV vasodilators. Additionally, the study sought to determine if iNO can lower PVR and TPG to levels considered acceptable for OHT.

## MATERIALS AND METHODS

After institutional review board approval, 21 consenting adult intensive care unit (ICU) patients with dilated cardiomyopathy and persistent moderate-to-severe pulmonary hypertension (mean pulmonary arterial pressure [MPAP] >35 mmHg and PVRI >500-650 dynes/s/m$^2$/cm$^5$ and TPG >15 mmHg) despite intravenous medical therapy were prospectively enrolled in the study. These patients were admitted to the ICU for optimization of heart failure and assessment of their candidacy for OHT.

All patients were monitored by using a thermodilution pulmonary artery catheter. Cardiac output (CO) was measured using cold saline injections (average of 2-3 closely performed injections per dataset) that were made at end-expiration. Only values that were <15% of each other from within each dataset were averaged and used in the final analysis. Other hemodynamic parameters recorded include pulmonary artery pressures, pulmonary artery occlusion pressure (PAOP), central venous pressure (CVP), and systemic blood pressure. Derived hemodynamic variables were calculated as follows: cardiac index (CI) = CO/body surface area; PVRI = (MPAP − PAOP) × 80/CI; TPG = (MPAP − PAOP); and right ventricular stroke work index (RVSWI) = 0.0136 (MPAP − CVP) × CI/heart rate.

After admission to the ICU, all cardiomyopathy patients received between 1 to 3 days of IV cardiac drug therapy with vasodilators, inotropes, and diuretcs as part of their medical management of heart failure and assessment of PVR reversibility. The goal was to optimize hemodynamics using maximally tolerated doses of IV vasodilators and additional inotropes. The following steps were used toward optimizing hemodynamics and selecting patients for the study: all patients received IV diuretics and maximal titration of IV vasodilators in each patient was attempted, with the goal to reduce the systemic vascular resistance (SVR) <1,200 dynes/s/cm$^5$ while maintaining a systolic blood pressure >80 to 85 mmHg. All patients received IV vasodilator therapy consisting of 1 or more drugs (nitroglycerin, 0.5-3 μg/kg/min, nitroprusside, 0.5-3 μg/kg/min, and/or prostaglandin $E_1$, 0.01-0.1 μg/kg/min); if

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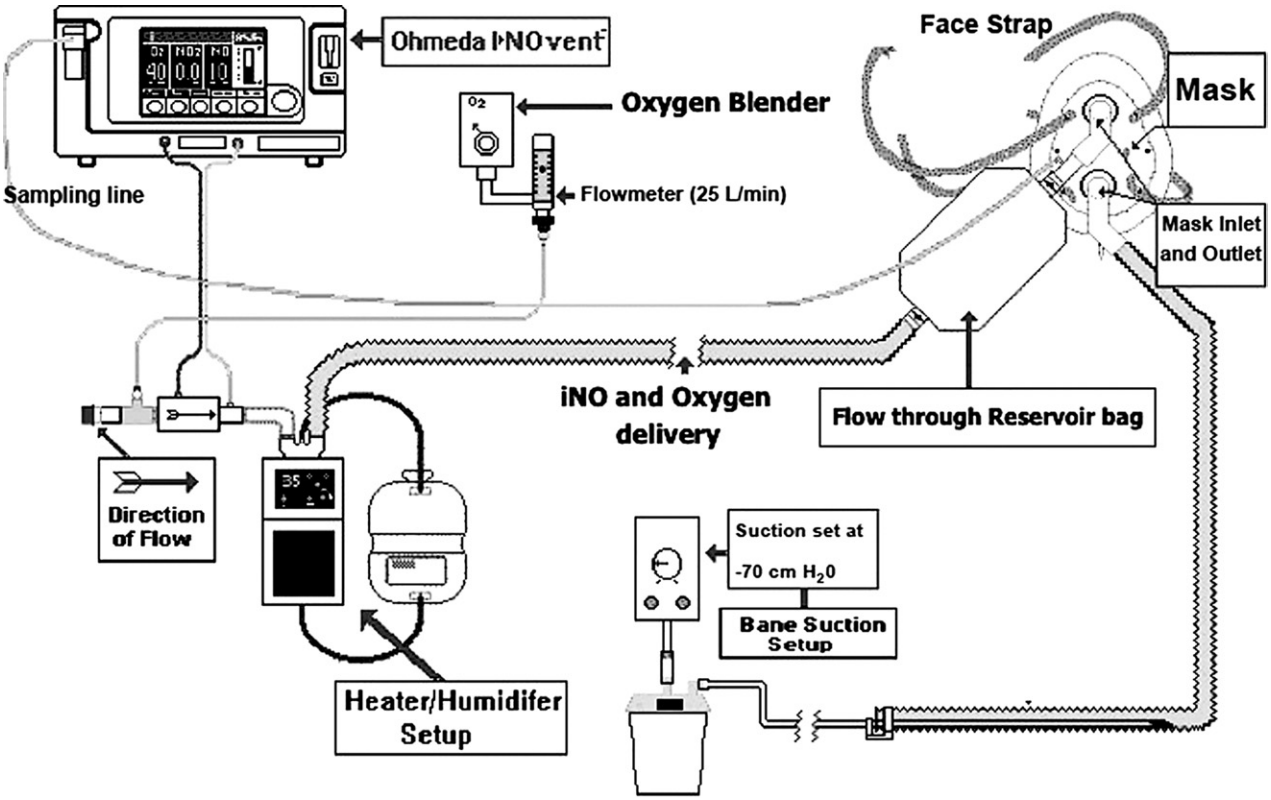


**Fig 1. Inhaled nitric oxide delivery setup.**

the cardiac index remained low or did not improve after the IV vasodilator therapy, inotropes (dopamine, 2-7 μg/kg/min, dobutamine, 2-7 μg/kg/min, and/or milrinone, 0.2-0.5 μg/kg/min) were added to the regimen to further improve hemodynamics so that PVR and TPG could be studied in the presence of a normal CI. Fifteen of 21 patients received inotropic therapy in addition to IV vasodilators. "Baseline" hemodynamic data were recorded after the initial "optimal" IV therapy achieved the target SVR (<1,200 dynes/s/m$^2$/cm$^5$) while keeping the blood pressure >80 to 85 mmHg and the CI ≥2.2 L/min/m$^2$. Only patients who had persistent moderate to severe pulmonary hypertension (MPAP >35 mmHg, PVRI >500-650 dynes/s/m$^2$/cm$^5$, and TPG >15 mmHg) despite initial IV therapy were included as test subjects for 100% oxygen and iNO study. ICU patients, in whom IV therapy improved MPAP and PVRI to lower levels, were not included in the study.

The administration of 100% oxygen and iNO was performed to test for further improvement in RV afterload indices; 4 of 21 patients were receiving oxygen therapy ($F_IO_2$ <30%) via nasal cannula before the start of the study to keep $SaO_2$ >95%. All hemodynamic parameters were recorded after IV therapy (baseline) and after 15 to 20 minutes of sequential administration of each of the following: first intervention, 100% oxygen; second intervention, iNO at 20 ppm in 100% oxygen; and third intervention, iNO at 40 ppm in 100% oxygen. Patients were considered responders if their PVRI decreased by 25% from baseline (hemodynamics after IV therapy). iNO was delivered by using an Ohmeda/iNOvent delivery system (INO Therapeutics, Clinton, NJ). The system was calibrated by the respiratory therapy team to deliver oxygen and iNO at concentrations very close to the programmed doses. The delivery setup used in the study is shown in Figure 1. With the patients breathing spontaneously, a nitric oxide and oxygen mixture (flow rate = 25 L/min) was injected into the inspiratory limb of the circuit and delivered to the patient via a tight-fitting nonrebreathing facemask. An electrochemical analyzer built into the system measured the concentration of delivered iNO. An oxygen analyzer was used to confirm the delivered oxygen concentration. Sampling of gases was performed from the facemask and close to the patient's mouth. Scavenging of all waste gases was performed. Other investigators have also previously described the use of comparable iNO delivery systems.[16,18]

All data were expressed as mean ± standard error of the mean. Statistical analysis of the data was performed by a repeated-measures analysis of variance test; $p < 0.05$ was accepted as significant.

## RESULTS

The mean age of the patients was 52 years (range 24-67 years). There were 13 men and 8 women in the study group. Body surface area ranged from 1.54 to 2.15 m$^2$ (mean 1.84, median 1.8). Twelve of twenty-one patients had ischemic dilated cardiomyopathy, whereas 9 of 21 had idiopathic dilated cardiomyopathy. Hemodynamics at the time of ICU admission and before the start of IV drug therapy (pre-IV therapy) are presented in Table 1. "Baseline" hemodynamic indices after IV therapy show overall improvement of the right- and left-sided function (Table 1). However, the study patients had persistent moderate-severe pulmonary hypertension after optimal IV therapy.

Hemodynamics after administration of 100% oxygen and iNO at 20 and 40 ppm in 100% oxygen are given in Figure 2 and Table 1. No statistically significant change from baseline

**Table 1. Effect of iNO and High $F_IO_2$ on the Various Hemodynamic Parameters**

| | Right-Sided Hemodynamics | | | | | Left-Sided Hemodynamics | | |
|---|---|---|---|---|---|---|---|---|
| | MPAP | PVRI | TPG | RVSWI | CI | MAP | SVRI | PAOP |
| Pre-IV therapy | 47 ± 2.2 | 937 ± 75 | 22 ± 1.9 | 17 ± 1.4 | 1.7 ± 0.2 | 71 ± 31 | 2571 ± 64 | 26 ± 1.2 |
| Baseline (after IV therapy) | 44 ± 1.7 | 823 ± 47 | 22 ± 1.3 | 15 ± 1.2 | 2.2 ± 0.05 | 64 ± 1.3 | 1996 ± 51 | 22 ± 0.6 |
| 100% $O_2$ | 44 ± 1.8 | 809 ± 51 | 22 ± 1.4 | 14 ± 1.1 | 2.2 ± 0.03 | 65 ± 0.9 | 2003 ± 41 | 22 ± 0.5 |
| iNO 20 ppm | 39 ± 1.8 | 621 ± 55 | 16 ± 1.5 | 11 ± 1.2 | 2.2 ± 0.03 | 63 ± 1.2 | 2007 ± 39 | 22 ± 0.4 |
| iNO 40 ppm | 38 ± 1.5 | 605 ± 48 | 16 ± 1.6 | 11 ± 1.0 | 2.2 ± 0.04 | 66 ± 1.4 | 2026 ± 48 | 21 ± 0.3 |

NOTE. Numerical values in the table are mean ± SE.

Abbreviations: MPAP, mean pulmonary arterial pressure (mmHg); PVRI, pulmonary vascular resistance index (dynes/s/cm$^5$/m$^2$); TPG, transpulmonary gradient (mmHg); RVSWI, right ventricular stroke work index (g · m/m$^2$/beat); CI, cardiac index (L/min/m$^2$); MAP, mean arterial pressure (mmHg); SVRI, systemic vascular resistance index (dynes/s/cm$^5$); PAOP, pulmonary artery occlusion pressure (mmHg).

was noted in any of the measured hemodynamic parameters after administration of 100% oxygen. iNO, 20 ppm, therapy (in oxygen), however, improved all indices of RV hemodynamics from baseline ($p < 0.05$) (Fig 2 and Table 1). Individual responses to iNO, 20 ppm, are depicted in Figure 3 as changes from baseline in PVRI and TPG. In the entire group, increasing the dose of iNO from 20 to 40 ppm did not further improve any measure of RV hemodynamics ($p > 0.05$), although in 3 of 21 patients another ~10% decrease in PVRI was noted.

Twenty of twenty-one patients showed a >25% decrement in PVRI when compared with baseline (responders). In 9 of 13 of these iNO responders, PVR was reduced to <4 Woods units or PVRI <500 to 650 dyne/s/m$^2$/cm$^5$ and TPG decreased to less than 15 mmHg; levels considered acceptable for OHT. Of these, 7 patients underwent successful OHT; the remaining 2 patients died as a result of comorbid conditions while on the transplant list. Four of 13 patients who were responders but in whom PVR and TPG remained above the OHT criteria after

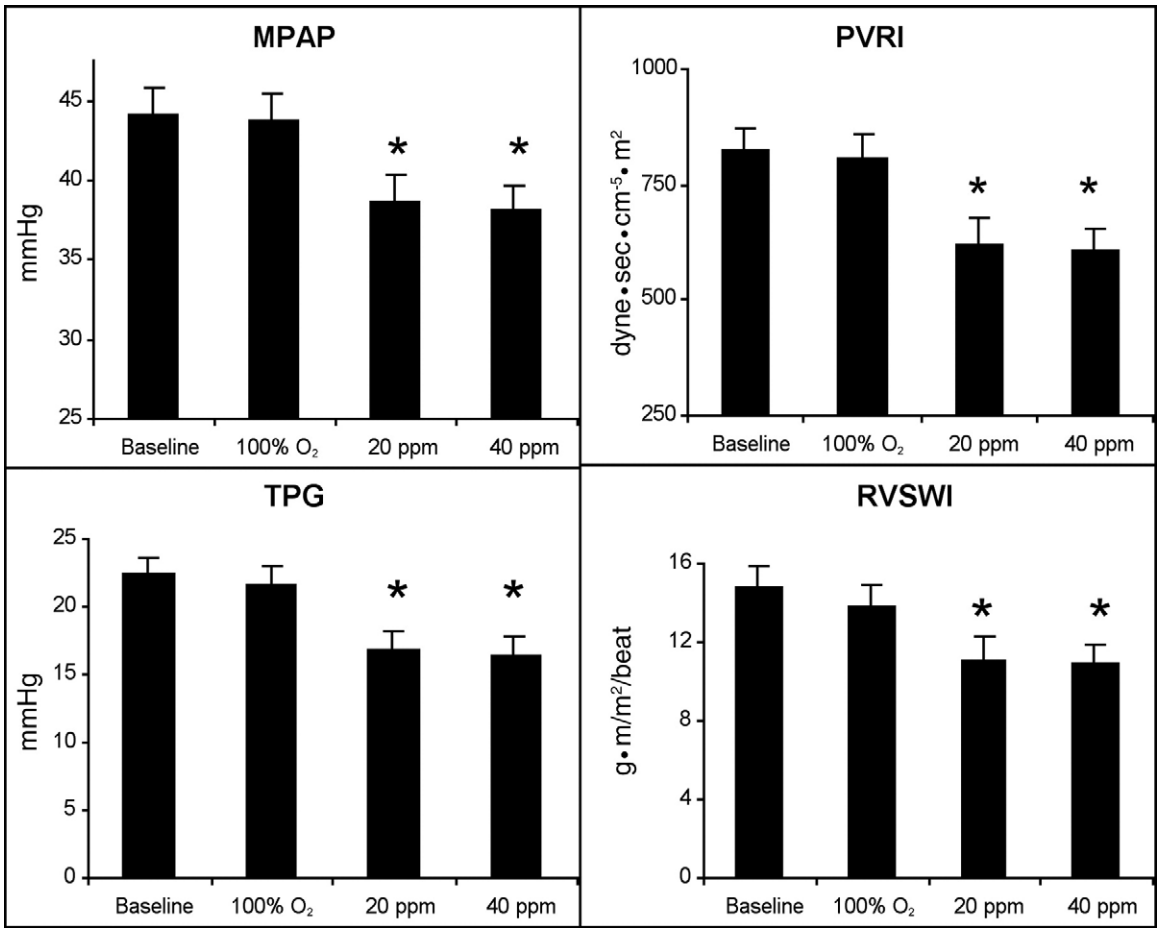


**Fig 2. Effect of iNO (20 and 40 ppm) and high $F_IO_2$ on RV hemodynamics; *$p < 0.05$.**

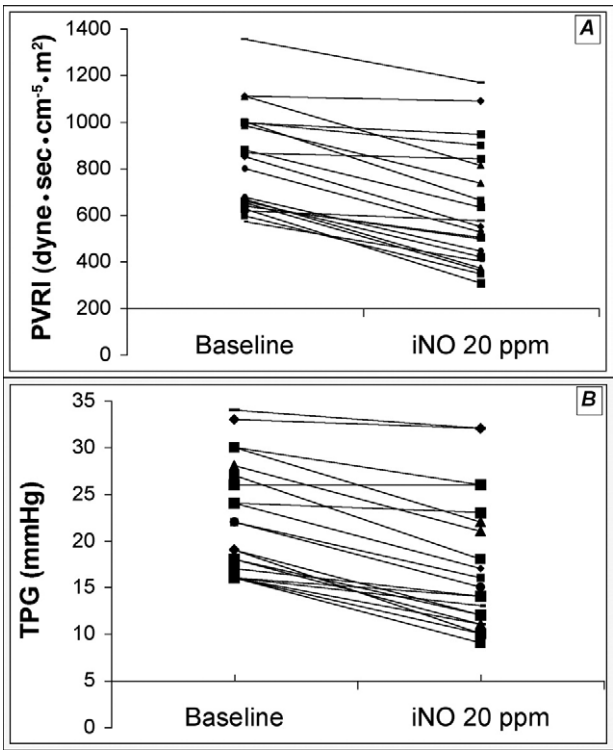


**Fig 3. Individual responses to iNO, 20 ppm, are depicted as changes in (A) PVRI and (B) TPG (compared with baseline).**

iNO test were continued on long-term vasodilator therapy to further improve right-sided hemodynamics to levels where OHT would be possible. The nonresponders were not considered suitable candidates for OHT and remained on standard medical management with persistent moderate-severe pulmonary hypertension.

Baseline CVP and PAOP in the patient group were 11 ± 0.4 and 22 ± 1.4 mmHg. Neither $O_2$ nor iNO altered right ventricular (RV) and left ventricular (LV) preload because CVP and PAOP remained unchanged after these maneuvers ($p > 0.05$). Heart rates after the 100% $O_2$ and iNO tests were not significantly different when compared with baseline (iNO 20 ppm, 84 ± 7 beats/min; baseline, 86 ± 5 beats/min) ($p > 0.05$). Measures of LV afterload, including systemic vascular resistance index, mean arterial pressure (MAP), and CI, remained unchanged between baseline and after 100% $O_2$, or iNO at 20 or 40 ppm ($p > 0.05$) (Table 1).

No adverse effects of oxygen or iNO therapy were noted with the short-term administration of these drugs in any of the patients in this study. After the iNO test, all patients were continued on their standard IV vasodilator and inotropic therapy to maintain optimal hemodynamics.

## DISCUSSION

Recipients' pulmonary hypertension adversely affects outcome after OHT. Therefore, careful preoperative evaluation and patient selection are important for the success of this surgery.[1-5,19,20] In this study, it was shown that iNO administration is a good preoperative test for determining the reversibility of PVR and TPG in OHT candidates.

The criteria for acceptable PVR and TPG limits that apply to patient selection for OHT vary in different centers. Patients with irreversibly high PVR or TPG (>4 Wood units and >15 mmHg, respectively) are excluded as candidates for this operation.[4,5] A major constraint in testing reversibility of PVR using the conventional intravenous vasodilators is the accompanying systemic hypotension. A few studies that report the use of iNO in reducing PVR describe its effect when it was administered by itself or in comparison with other vasodilators administered separately.[16,18,21] However, it is unclear from these studies if iNO can further reduce PVR in OHT candidates who have been clinically "optimized" by IV vasodilators and inotropes. Study of this response is extremely relevant because it may identify more patients with reversible PVR who meet the hemodynamic criteria for OHT. Any further reduction in PVR would also be a direct measure of the benefit of iNO. Adatia et al[21] administered iNO to 11 OHT candidates, of whom 6 had dilated cardiomyopathy, and showed that iNO (80 ppm) effectively decreased the PVR by about 40% and MPAP by 15%. iNO responses were not compared with any other conventional vasodilator. Kieler-Jensen et al[16] in their study of 12 cardiomyopathy patients compared the lowering of the PVR/SVR ratio as an index of pulmonary vascular selectivity between iNO and the IV vasodilators. PVR/SVR ratio was reduced by iNO but remained unchanged with the IV vasodilators. However, the response to iNO was not studied in the presence of vasodilators such as nitroglycerin, nitroprusside, or prostaglandins, drugs that are still the first line of treatment in these patients. Baseline optimization of hemodynamics (CO, MPAP, SVR, and PAOP) also allows for a more accurate assessment of the RV afterload indices because both PVR and TPG are affected by several of these hemodynamic parameters.

The present study results show that iNO, 20 ppm, in oxygen can further reduce PVR and TPG. Increasing the dose of iNO to 40 ppm had only a limited benefit in a few patients (3/21). Of the 13 patients who responded to iNO (PVR decrease >25%), 9 patients achieved PVR and TPG criteria considered acceptable for OHT listing. Seven of them have successfully undergone OHT. This implies that OHT can be considered in a subgroup of patients who are responsive to iNO but have only a limited response to IV vasodilators. iNO therapy not only decreased RV afterload but also improved RVSWI (a measure of RV work and function). The pharmacokinetics of iNO makes it an ideal drug for selective pulmonary vasodilation. Its ultrashort half-life in the circulation because of rapid inactivation by binding to heme (3,000 times higher affinity for nitric oxide than for oxygen)[22] prevents iNO from having any systemic hemodynamic effects. These data support this theory because there were no changes in MAP, systemic vascular resistance index, and CI. Methemoglobinemia and nitrogen dioxide toxicity, 2 side effects that can be seen with long-term therapy or with use of much higher doses of the drug, were not seen in the study.

It was also observed that in the cardiomyopathy group, 100% oxygen therapy alone was ineffective in improving RV hemodynamics. This result is in contrast to the previously reported use of 100% oxygen therapy in determining reversibility of

PVR in patients with congenital heart and primary pulmonary diseases.[13,14] In these studies, high inspired oxygen therapy accounted for a 6% to 13% reduction in MPAP and a 20% to 30% lowering of PVR. Presumably, a different etiology of pulmonary hypertension in these patients may have accounted for the beneficial effect of oxygen observed in these studies.

Ideally, OHT candidates should have a reduction in PVR that is sustained until the time of their surgery. This study design did not allow for assessment of this long-term decrease but showed the potential for reversibility of PVR with iNO use in the preoperative period. Reversibility of PVR in response to iNO has been suggested to be a good predictor of postoperative outcomes after cardiac surgery in patients with pulmonary hypertension.[23] The results of the trial (INOP Test I) show that a preoperative reduction in PVR/SVR ratio by 20% from the baseline after iNO therapy along with a PVR/SVR ratio that was $<0.33$ was associated with less morbidity and mortality in these patients.[23]

A concern regarding iNO therapy in OHT candidates is the possibility of further elevation in left-sided filling pressures resulting from enhanced pulmonary venous return. This phenomenon has been reported in cardiomyopathy patients who had inadequate hemodynamic optimization before iNO therapy.[16,24] Kieler-Jensen et al[16] in their series of 12 patients (baseline CO 3.1 L/min, SVR 2,000 dynes/s/cm$^5$, and MAP 81 mmHg) reported increasing of the PAOP from 28 to 33 mmHg after iNO (20 ppm). In contrast to these findings, other investigators (Sablotzki et al[25]) have reported a lowering of PAOP with iNO in patients with cardiomyopathy. Patients in their group, however, had better baseline hemodynamics (C.I 2.5 L/min/m$^2$ and PAOP 18 mmHg).[25] The present study group did not manifest any worsening of PAOP. In these dilated cardiomyopathy patients, IV vasodilator and inotropic therapy might have contributed to better ventricular compliance. Additionally, decreases in the RV afterload and RV systolic pressures with iNO in these patients with moderate-severe pulmonary hypertension might have also improved LV compliance as a result of diminished LV compression effect imposed by the RV. These interesting results from this study have important clinical implications in suggesting that iNO might be safe to use in hemodynamically optimized heart-failure patients.

This study has a few limitations. The authors did not randomize the initial IV therapy but instead chose the attainment of hemodynamic endpoints as indicators of maximal optimization with the combination intravenous therapy used as part of the clinical care of these patients. The goal was to study the efficacy of iNO therapy in a clinical setting. Additionally, it was chosen not to randomize the order of iNO (20 and 40 ppm) or oxygen therapy among these patients but allowed each patient to receive all 3 inhaled therapies sequentially in a predetermined order. Although previous investigators have suggested other doses (2-80 ppm) of iNO to be efficacious in treating pulmonary hypertension, only 2 of the more commonly used iNO concentrations were studied. Despite these limitations, the results of this study highlight the role of iNO in preoperative OHT evaluation.

In conclusion, the preoperative administration of iNO by a facemask is a simple procedure that is well tolerated by patients. The iNO trial provides important clinical information regarding the degree of reversibility of PVR. In these patients, administration of 100% oxygen alone did not result in a significant reduction in RV afterload. The addition of iNO (20 ppm) was sufficient to show a substantial reduction in RV afterload and should be considered as a preoperative test during evaluation of OHT candidacy.

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