Differences in the Acute Pulmonary Vascular Effects of Oxygen with Nitric Oxide and Diltiazem: Implications for the Long-term Treatment of Pulmonary Arterial Hypertension

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ABSTRACT

Objective. Right heart catheterization is performed in patients with pulmonary arterial hypertension to determine the severity of disease and their pulmonary vascular reactivity. This study sought to determine whether the acute pulmonary vasodilatory effects of diltiazem and oxygen with nitric oxide are similar enough to support the practice of using nitric oxide as a surrogate agent to identify patients to treat with an oral calcium channel blocker alone.
Design. Retrospective descriptive study.
Setting. A tertiary medical center for children.
Patients. Twenty-four individuals (7 months to 17 years of age) with pulmonary arterial hypertension who met criteria for a favorable acute pulmonary vasodilatory response to oxygen with nitric oxide, and were also evaluated with intravenous diltiazem.
Interventions. Right heart catheterization and an evaluation of pulmonary vascular reactivity.
Outcome Measures. The pulmonary vasodilatory effects of oxygen, oxygen with nitric oxide, and intravenous diltiazem; and the need for medications other than amlodipine to decrease long-term pulmonary arterial pressure.
Results. Oxygen, oxygen with nitric oxide, and diltiazem acutely decreased pulmonary arterial pressure. Diltiazem also decreased systemic arterial pressure. A lower mean pulmonary arterial pressure was achieved with oxygen and nitric oxide than with diltiazem (30 ± 2 mm Hg vs. 39 ± 3 mm Hg, $P < .05$). Half of the patients who were treated long term with amlodipine alone failed to develop a long-term 20% decrease in pulmonary arterial pressure and were treated with additional medications.
Conclusions. The combination of oxygen and nitric oxide decreased pulmonary arterial pressure more than a dose of intravenous diltiazem that was large enough to decrease systemic arterial pressure. Oxygen and nitric oxide may identify patients who can be treated safely with a calcium channel blocker; however, they should not be used as surrogates to identify patients to treat with a calcium channel blocker alone.

Key Words. Calcium Channel Blocker; Nitric Oxide; Oxygen; Pulmonary Arterial Hypertension

Introduction

Pulmonary arterial hypertension is a potential long-term complication of congenital heart disease when shunt lesions are not repaired at an early age. Pulmonary vascular disease may persist or develop despite timely repair in patients with heritable pulmonary hypertension, lung disease, or other risk factors. Right heart catheterization and an evaluation of pulmonary vascular reactivity are performed in children with pulmonary arterial hypertension to determine whether they are acceptable candidates for treatment with an oral calcium channel blocker. Over time, pulmonary vascular reactivity has been defined by different criteria. A 20% decrease in mean pulmonary arterial pressure without a decrease in cardiac output has been used in many studies to identify patients who may respond favorably to treatment with an oral calcium channel blocker.[1–3] Ricciardi and associates showed a significant correlation between the pulmonary vasodilatory effects of inhaled nitric oxide and oral nifedipine.[4] Sitbon and associates observed that 33 of 38 patients with a favorable long-term response to a calcium channel blocker developed a mean pulmonary arterial pressure <40 mm Hg when acutely evaluated with inhaled

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nitric oxide, and 22 of 32 patients with an unfavorable long-term response to a calcium channel blocker developed a mean pulmonary arterial pressure >40 mm Hg when acutely evaluated with inhaled nitric oxide.[3] The American College of Chest Physicians subsequently recommended that responsive patients be identified by a decrease in mean pulmonary arterial pressure ≥10 mm Hg from baseline to a value of ≤40 mm Hg during an evaluation of pulmonary vascular reactivity with inhaled nitric oxide, intravenous epoprostenol, or intravenous adenosine (Level of Evidence: low; Benefit: substantial; Grade of Recommendation: B).[5] Responsive patients are treated with a calcium channel blocker alone.[6,7] Responsive patients may not receive financial coverage for additional medications. However, Yung and associates reported a 29% actuarial rate of treatment failure in responsive children with idiopathic pulmonary arterial hypertension within 3 years of initial treatment with a calcium channel blocker, using oxygen, digoxin, diuretics, and anticoagulation as needed.[1]

In this study, pulmonary vascular reactivity was evaluated with supplemental oxygen, oxygen with inhaled nitric oxide, and intravenous diltiazem during heart catheterization in a subset of patients at Primary Children's Medical Center. A retrospective review of the results of these procedures aimed to determine whether the pulmonary vasodilatory effects of oxygen with nitric oxide and diltiazem are similar enough to support recommendations that the response to oxygen with nitric oxide be used as a surrogate to identify patients to initially treat with an oral calcium channel blocker alone.

Methods

The Institutional Review Board of the University of Utah approved this study. The results of heart catheterization for patients who underwent an evaluation of pulmonary vascular reactivity using oxygen, oxygen with nitric oxide, and intravenous diltiazem were reviewed. Pulmonary vascular reactivity was evaluated with intravenous diltiazem to identify individuals who may respond poorly, or paradoxically, to a calcium channel blocker.

Inclusion Criteria

Twenty-four patients who responded favorably to oxygen with nitric oxide and were potential candidates for long-term treatment with an oral calcium channel blocker were included in this study. Patients with idiopathic disease, heritable disease, and pulmonary arterial hypertension associated with repaired congenital heart disease, portal hypertension, airway obstruction, and lung disease were included in the study. All patients had a baseline mean pulmonary arterial pressure greater than 25 mm Hg with a median of 50 mm Hg and a range of 28 mm Hg to 92 mm Hg.

Exclusion Criteria

Patients with congenital heart disease were not included in the study if their defects were not repaired. Patients with elevated left atrial pressure, areas of pulmonary venous obstruction, areas of branch pulmonary artery stenosis, pulmonary veno-occlusive disease, and pulmonary thromboembolic disease were not included in this study.

Protocol for the Evaluation of Pulmonary Vascular Reactivity

Initial hemodynamic measurements were performed with each patient breathing room air or a small amount of supplemental oxygen (baseline 1). Hemodynamic measurements were repeated after 10- to 15-minute intervals of approximately 100% oxygen, approximately 100% oxygen with inhaled nitric oxide, room air or a small amount of supplemental oxygen (baseline 2), and room air or a small amount of supplemental oxygen with intravenous diltiazem. A slightly greater amount of supplemental oxygen was usually used during baseline 2 and diltiazem than was used during baseline 1. An estimate of 100% oxygen was administered at a flow rate of 8–15 L/minute with a non-rebreathing face mask or an inspired fraction of approximately 1.0 through an endotracheal tube. The dose of nitric oxide was held constant at 20 parts per million (ppm) during each study because the pulmonary vasodilatory effects of 12 ppm and 60 ppm nitric oxide were similar in a previous study.[8] Nitric oxide was administered with oxygen because the vasodilatory effects of these agents may be additive.[8–10] The dose of diltiazem was started at 10–20 mcg/kg/minute and gradually increased until a stable decrease in mean systemic blood pressure of approximately 10% was observed. The median final dose of diltiazem was 40 mcg/kg/min with a range of 20–50 mcg/kg/min. Cardiac index was calculated by the Fick principle using estimated values of oxygen consumption. A consistent estimate of oxygen consumption was used for all stages of each evaluation of pulmonary vascular reactivity.

Acutely Responsive Patients

A favorable acute response to oxygen with nitric oxide was defined with either of the following criteria:

- a 20% decrease in mean pulmonary arterial pressure from baseline measurements (23 patients).[1]
- a decrease in mean pulmonary arterial pressure ≥10 mm Hg to a value of ≤35 mm Hg for patients with a baseline mean pulmonary arterial pressure >35 mm Hg, or a decrease in mean pulmonary arterial pressure to a value of ≤25 mm Hg for patients with a baseline mean pulmonary arterial pressure ≤35 mm Hg (18 patients).

Either criterion was used because it is unknown whether one is superior to the other.[11] The criterion of the American College of Chest Physicians was modified slightly such that a minimum decrease in mean pulmonary arterial pressure of 10 mm Hg was not required for patients with a baseline value ≤35 mm Hg because a value ≤25 mm Hg might be considered normal.

Statistical Analysis

A paired *t*-test with a Bonferroni correction factor of 10 for all potential paired comparisons of the phases of heart catheterization was used to identify significant differences ($P < .05$) between inhaled nitric oxide with supplemental oxygen and intravenous diltiazem for arterial blood gases, heart rate, blood flow, vascular resistance, and blood pressure. A linear regression analysis was used to identify potential linear correlations between the pulmonary vasodilatory effects of oxygen, oxygen with nitric oxide, and diltiazem. Numerical data are expressed as mean ± standard error of the mean. The results of long-term treatment are reported descriptively without a statistical analysis because this was a retrospective study without predefined criteria for treatment failure. A Kaplan–Meier analysis of the interval between the onset of long-term treatment with an oral calcium channel blocker and the onset of treatment with additional medications was not performed. The timing of treatment with additional medications was influenced by factors other than treatment failure including: the personal preferences of referring physicians and families, the time that patients were referred to the author for treatment, and the time that additional medications became available for treatment.

Results

Demographic Information

There were 24 patients (10 female). The median age of patients was 5 years with a range of 7 months to 17 years. The diagnostic classification of patients is listed in Table 1. Patients with Down syndrome had multiple factors that were potentially associated with pulmonary hypertension including repaired congenital heart disease, airway obstruction, and lung disease. There were six patients with a patent foramen ovale and one patient with a very small residual ventricular septal defect following surgery. None of the patients had differences in oxygen saturation measurements from the superior vena cava and pulmonary arteries that were suggestive of a clinically significant shunt. Heart catheterization was performed when a diagnosis of pulmonary hypertension was initially confirmed in 13 patients, and for follow-up evaluations of pulmonary vascular reactivity in 11 patients. No patient had more than one evaluation of pulmonary vascular reactivity included in this study. Patients reside at altitudes of 1300 m to 2000 m. Heart catheterization was performed at an altitude of approximately 1500 m. An anesthesiologist provided sedation for nine patients. The remaining studies were performed with procedural sedation. Assisted ventilation was used to electively support eight patients during heart catheterization. There were no complications associated with the procedures.

Pulmonary Vascular Reactivity

The results of arterial blood gas, heart rate, blood flow, and vascular resistance measurements are shown in Table 2. Oxygen, oxygen with nitric oxide, and diltiazem all decreased pulmonary arterial pressure and pulmonary vascular resistance in comparison to the preceding baseline measurements. Diltiazem also decreased systemic arterial pressure and systemic vascular resistance. The combination of oxygen with nitric oxide decreased pulmonary arterial pressure and pulmonary vascular resistance more than oxygen alone. The use of supplemental oxygen was associated with a significant decrease in heart rate.

Table 1. Diagnostic Classification of Patients

	Number of Patients
Pulmonary arterial hypertension	
Idiopathic	5
Heritable	1
Associated with	
Congenital heart disease (repaired)	4
Portal hypertension	1
Lung disease	6
Multifactorial	
Down syndrome	7

Table 2. Arterial Blood Gases, Heart Rate, Blood Flow, and Vascular Resistance

Phase	pH	PO_2, mm Hg
Baseline 1	7.36 ± 0.01	67 ± 3
Oxygen	7.36 ± 0.01	393 ± 18
Oxygen with nitric oxide	7.36 ± 0.01	408 ± 13*
Baseline 2	7.36 ± 0.01	112 ± 24
Diltiazem	7.35 ± 0.01	112 ± 23
	HR, min^{-1}	CI, L/min-m^2
Baseline 1	97 ± 4	3.71 ± 0.12
Oxygen	84 ± 5	3.36 ± 0.13
Oxygen with nitric oxide	82 ± 5*	3.48 ± 0.11*
Baseline 2	90 ± 5	3.58 ± 0.14
Diltiazem	89 ± 5	3.85 ± 0.16
	Rp, Units-m^2	Rs, Units-m^2
Baseline 1	11.5 ± 1.0	16.4 ± 0.9
Oxygen	8.4 ± 0.9	18.6 ± 0.9
Oxygen with nitric oxide	6.2 ± 0.8*	18.3 ± 0.9*
Baseline 2	10.7 ± 1.0	18.0 ± 1.1
Diltiazem	7.3 ± 0.7	14.9 ± 1.0

*Significant difference between measurements for oxygen with nitric oxide and diltiazem, $P < .05$.
n = 24, mean ± standard error of the mean.
CI, cardiac index (pulmonary and systemic blood flow); HR, heart rate; PO_2, arterial oxygen tension; Rp, pulmonary vascular resistance index; Rs, systemic vascular resistance index.

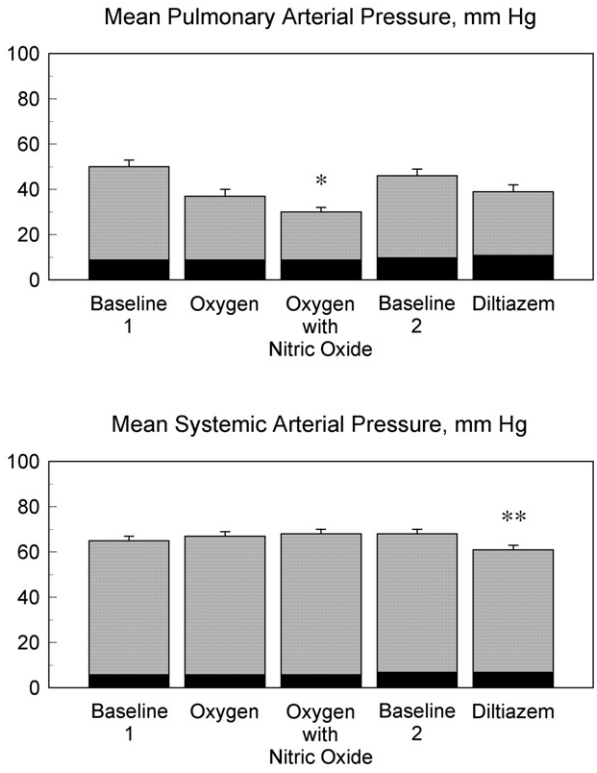

Figure 1. Influence of vasodilatory agents on pulmonary and systemic arterial pressures. The mean pulmonary arterial pressures and the mean systemic arterial pressures for 24 patients who were responsive to approximately 100% oxygen with 20 parts per million nitric oxide during heart catheterization are shown. The mean pulmonary arterial pressure during treatment with a combination of oxygen with nitric oxide was lower than the mean pulmonary arterial pressure during baseline 1, oxygen, baseline 2, and an intravenous infusion of a median dose of 40 mcg/kg/min diltiazem (*$P < .05$). The mean systemic arterial pressure during treatment with an intravenous infusion of diltiazem was lower than the mean systemic arterial pressure during oxygen with nitric oxide and baseline 2 (**$P < .05$). The corresponding mean pulmonary arterial wedge pressures are shown in black with the mean pulmonary arterial pressures shown in gray. The corresponding right atrial pressures are shown in black with the mean systemic arterial pressures shown in gray.

There was a significant correlation between the values of pulmonary vascular resistance ($r^2 = 0.744$, $P < .001$) and mean pulmonary arterial pressure ($r^2 = 0.705$, $P < .001$) during baseline 1 and baseline 2. There was a significant correlation between the values of pulmonary vascular resistance ($r^2 = 0.624$, $P < .001$) and mean pulmonary arterial pressure ($r^2 = 0.512$, $P < .001$) during oxygen and diltiazem. There was a significant correlation between the values of pulmonary vascular resistance ($r^2 = 0.873$, $P < .001$) and mean pulmonary arterial pressure ($r^2 = 0.752$, $P < .001$) during oxygen with nitric oxide and diltiazem. Despite significant correlations, the pulmonary vascular resistance and the mean pulmonary arterial pressure was lower with oxygen and nitric oxide than with diltiazem (30 ± 2 mm Hg vs. 39 ± 3 mm Hg, $P < .05$). The mean pulmonary arterial blood pressures, mean pulmonary arterial wedge pressures, mean systemic arterial blood pressures, and mean right atrial pressures during each stage of the hemodynamic evaluations are shown in Figure 1.

Long-term Outcome

Only 12 patients met criteria for a favorable acute response to diltiazem using the same criteria that were used to define a favorable response to oxygen with nitric oxide. Thirteen patients were treated with amlodipine long term. Patients were followed for a median of 53 months with a range of 3 to 94 months following heart catheterization. Three patients moved and were no longer followed 4 to 23 months following heart catheterization. One patient who did not respond to diltiazem, and was not treated with amlodipine, died early after surgery for portal hypertension. There were no other deaths. The medications that were used to treat patients long-term are shown in Table 3. All of the patients who were not acutely responsive to diltiazem were treated with other medications based upon the discretion of the author or referring

Table 3. Long-term Medical Therapy

	Total	O_2	CCB	PDE5I	ERA	PGI_2
Acute response to diltiazem, n	12	9	11	7	4	2
No acute response to diltiazem, n	12	10	2	11	4	3

CCB, calcium channel blocker (amlodipine); ERA, endothelin receptor antagonist; O_2, supplemental oxygen; PDE5I, phosphodiesterase V inhibitor; PGI_2, prostacyclin analog.

Table 4. Patients with and without a 20% Decrease in Pulmonary Arterial Pressure with Amlodipine Alone

Decrease in Pulmonary Arterial Pressure	≥20%	<20%
Number of patients	4	4
Age, y	11 ± 3	6 ± 3
Mean pulmonary arterial pressure, mm Hg		
Baseline 1	54 ± 2	52 ± 10
Oxygen with nitric oxide	25 ± 3	29 ± 3
Diltiazem	35 ± 3	36 ± 5
Dose of amlodipine, mg/kg/day	0.17 ± 0.02	0.23 ± 0.03

cardiologist, including two patients who had been treated with amlodipine alone based upon their response to oxygen with nitric oxide in a previous procedure. Eleven of the 12 patients who were acutely responsive to diltiazem were treated with amlodipine based upon the discretion of the author or referring cardiologist. Four of these 11 patients required no additional medications approved for the treatment of pulmonary hypertension other than oxygen long term, three patients were treated from the onset with oxygen and additional medications in combination with amlodipine, and four patients were treated with additional medications after failure to achieve a 20% decrease in systolic pulmonary arterial pressure by echocardiography (n = 3) or a 20% decrease in mean pulmonary arterial pressure by catheterization (n = 1). Three of these four patients developed a 20% improvement in pulmonary arterial pressure following treatment with additional medications. The mean age, mean pulmonary arterial pressures, and mean dose of amlodipine for the patients who responded to diltiazem during heart catheterization and did or did not develop a 20% decrease in pulmonary arterial pressure are listed in Table 4. There were no significant differences between the listed values for these patients.

Discussion

This study describes the acute pulmonary vascular effects of supplemental oxygen, oxygen with inhaled nitric oxide, and intravenous diltiazem for a subset of patients who underwent heart catheterization for pulmonary arterial hypertension at a children's hospital. An adequate dose of diltiazem was used to significantly decrease mean systemic arterial blood pressure. However, diltiazem did not decrease the mean pulmonary arterial pressure as much as the combination of oxygen and nitric oxide. Half of the patients who were acutely responsive to diltiazem, and treated with amlodipine alone, failed to develop a long-term 20% decrease in pulmonary arterial pressure and were treated with additional medications.

This study is consistent with previous studies that have identified significant correlations between the pulmonary vasodilatory effects of nitric oxide and calcium channel blockers. However, a significant correlation does not imply that the values of mean pulmonary arterial pressure are the same for both drugs. Half of the patients who met criteria for an acute response to oxygen and nitric oxide did not meet criteria for an acute response to diltiazem. The combination of oxygen and nitric oxide was a superior acute pulmonary vasodilator in this subset of patients. For this reason, oxygen and nitric oxide should not be used to identify patients to treat with a calcium channel blocker alone. Oxygen and nitric oxide may define a level of pulmonary vascular reactivity that cannot be achieved by long-term treatment with an oral calcium channel blocker alone. This study suggests that the acute response to diltiazem may also fail to identify patients who can be treated long-term with amlodipine alone. We may need to develop better methods to identify the most appropriate patients to treat with calcium channel blockers, and other agents.

An evaluation of pulmonary vascular reactivity with a calcium channel blocker has fallen out of favor due to concerns of a potential adverse response. In previous adult studies, a dose of an oral calcium channel blocker was usually started and increased over an extended period of time while monitoring hemodynamic measurements in the setting of an intensive care unit. Sublingual nifedipine has previously been used in children and young adults during heart catheterization.[12] The current study suggests that intravenous diltiazem can be titrated and given safely during heart catheterization in young patients with moderately severe pulmonary hypertension who respond reasonably well to oxygen and nitric oxide. Thereby, patients with a limited response to a calcium channel blocker can readily be

identified and avoid a potentially ineffective trial of outpatient therapy.

A failure in long-term treatment was arbitrarily defined by the use of additional medications in patients who failed to experience a 20% decrease in pulmonary arterial pressure. A 20% improvement may be adequate to identify a modest favorable response. However, it is possible that a greater degree of improvement can be achieved, particularly in acutely responsive patients. Three of the four patients in this study who failed to improve with amlodipine subsequently improved when treated with additional medications. It is unknown whether the fourth patient would have improved if treated earlier in the course of his disease, or simply needed a different additional medication.

Limitations

This is a retrospective descriptive study with the following limitations:

- A relatively small number of patients were included in the study.
- It is unknown whether a maximal pulmonary vasodilatory response occurred with the amounts of oxygen, nitric oxide, and diltiazem that were used during acute vasodilator testing in this study. However, a sufficient amount of diltiazem was used to significantly decrease mean systemic arterial pressure. It is unknown whether an adequate dose of amlodipine was used for long-term therapy. However, the patients who failed to develop a 20% decrease in pulmonary arterial pressure were not treated with significantly lower doses than other patients.
- Responsive patients are usually treated with an oral calcium channel blocker in the dihydropyridine class. It may be more appropriate to evaluate acute pulmonary vascular reactivity with intravenous nicardipine than diltiazem.
- A 20% decrease in pulmonary vascular resistance was used as one definition for acutely responsive patients.[1] A 20% decrease in pulmonary vascular resistance is not an acceptable criterion to evaluate pulmonary vascular reactivity prior to repair of congenital heart disease.[13] However, most of the patients in this study also satisfied a definition for an adequate acute response that is consistent with guidelines proposed by the American College of Chest Physicians.[5]
- There were potential errors in the calculations of blood flow and vascular resistance using assumed and consistent values of oxygen consumption. For this reason, the effects of each agent on direct measurements of mean pulmonary arterial pressure and mean systemic pressure were reported. There were no patients with residual shunts that would have influenced the pulmonary arterial pressure. Thermodilution may be an alternative method to estimate cardiac output in patients without a significant shunt. However, thermodilution may also have limitations, particularly in small children.
- It is possible that a combination of 100% oxygen and diltiazem would have decreased the mean pulmonary arterial pressure as much as oxygen and nitric oxide. However, the amount of supplemental oxygen that was used with diltiazem in this study is similar to the amount of oxygen that patients might use at home long term.
- No conclusions concerning the long-term efficacy of treatment with a calcium channel blocker were made by this study because objective measures for the long-term outcome of patients were not evaluated, other than the use of additional medications. However, a decrease in pulmonary arterial pressure is a reasonable goal for medical therapy in responsive patients.
- This study did not evaluate the effects of altitude on treatment failure.

In conclusion, a combination of supplemental oxygen and inhaled nitric oxide decreases mean pulmonary arterial pressure more than an intravenous dose of diltiazem that significantly decreases mean pulmonary arterial pressure and mean systemic arterial pressure. This discrepancy is sufficiently large that the results of acute vasodilator testing with nitric oxide and other surrogate agents should probably not be used to propose treatment with agents that have different mechanisms of smooth muscle relaxation. Surrogate agents may identify patients who can safely be treated with a calcium channel blocker; however, treatment failure may commonly occur if long-term therapy is initiated with a single agent that fails to optimally decrease pulmonary arterial pressure. Prospective studies are needed to determine whether additional medications can be used in combination with a calcium channel blocker long-term to further decrease pulmonary arterial pressure and prevent treatment failure for acutely responsive patients.

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