Characterization of Inhaled Nitric Oxide Use for Cardiac Indications in Pediatric Patients*

OBJECTIVES: Characterize the use of inhaled nitric oxide (iNO) for pediatric cardiac patients and assess the relationship between patient characteristics before iNO initiation and outcomes following cardiac surgery.

DESIGN: Observational cohort study.

SETTING: PICU and cardiac ICUs in seven Collaborative Pediatric Critical Care Research Network hospitals.

PATIENTS: Consecutive patients, less than 18 years old, mechanically ventilated before or within 24 hours of iNO initiation. iNO was started for a cardiac indication and excluded newborns with congenital diaphragmatic hernia, meconium aspiration syndrome, and persistent pulmonary hypertension, or when iNO started at an outside institution.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Four-hundred seven patients with iNO initiation based on cardiac dysfunction. Cardiac dysfunction patients were administered iNO for a median of 4 days (2–7 d). There was significant morbidity with 51 of 407 (13%) requiring extracorporeal membrane oxygenation and 27 of 407 (7%) requiring renal replacement therapy after iNO initiation, and a 28-day mortality of 46 of 407 (11%). Of the 366 (90%) survivors, 64 of 366 patients (17%) had new morbidity as assessed by Functional Status Scale. Among the postoperative cardiac surgical group ($n = 301$), 37 of 301 (12%) had a superior cavopulmonary connection and nine of 301 (3%) had a Fontan procedure. Based on echocardiographic variables prior to iNO ($n = 160$) in the postoperative surgical group, right ventricle dysfunction was associated with 28-day and hospital mortalities (both, $p < 0.001$) and ventilator-free days ($p = 0.003$); tricuspid valve regurgitation was only associated with ventilator-free days ($p < 0.001$), whereas pulmonary hypertension was not associated with mortality or ventilator-free days.

CONCLUSIONS: Pediatric patients in whom iNO was initiated for a cardiac indication had a high mortality rate and significant morbidity. Right ventricular dysfunction, but not the presence of pulmonary hypertension on echocardiogram, was associated with ventilator-free days and mortality.

KEY WORDS: congenital heart disease; morbidity; nitric oxide; pediatrics; pulmonary hypertension; right ventricular failure

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There is significant variability in the utilization of inhaled nitric oxide (iNO) in PICUs. Although its use in pediatric acute respiratory distress syndrome has been controversial due to a lack of proven benefit (1, 2), consensus has developed recommending iNO use for treatment of pulmonary hypertension in the postoperative congenital heart disease patient and to reduce right ventricular afterload following heart transplantation or ventricular assist device implantation (3–5). The level of evidence supporting iNO in postoperative patients remains low, with the few small randomized studies published involving specific patient populations (6, 7). Nevertheless, there has been

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RESEARCH IN CONTEXT

- Utilization of inhaled nitric oxide (iNO) is highly variable in patients with heart disease with minimal evidence to guide clinicians.
- Most studies of iNO have excluded certain categories of congenital heart disease patients or did not have sufficient data to define the risks for the endpoints measured.
- Improved characterization of patient populations in which iNO is commonly used will help guide future studies in patients with congenital heart disease.

a documented trend of increased use of iNO in many cardiac populations with minimal prospective evidence to guide initiation, weaning, or transitioning to other less costly medical therapies for pulmonary hypertension (4, 8, 9).

The Collaborative Pediatric Critical Care Research Network (CPCCRN) developed this prospective observational study to characterize use of iNO in pediatric cardiac and respiratory failure patients across the seven clinical sites. The use of iNO in respiratory failure from this study has been previously published (2). The aim of this study was to characterize the use of iNO in the pediatric cardiac patient population and to assess the relationship between patient characteristics before iNO initiation and outcomes in patients following cardiac surgery.

MATERIALS AND METHODS

The project was approved with waiver of informed consent by the Central Institutional Review Board (IRB) at the University of Utah (IRB_00085265) for all clinical sites and the data coordinating center. iNO is labeled by the U.S. Food and Drug Administration for use in term and near-term neonates with hypoxic respiratory failure and pulmonary hypertension, and all other uses are considered off-label.

Consecutive eligible patients treated with iNO in the pediatric or cardiac ICU of the seven CPCCRN institutions between October 15, 2015, and October 31, 2016, were included. Eligible patients were less than 18 years old and mechanically ventilated either before or within 24 hours of iNO initiation. Patients with iNO started at an outside institution; newborns with congenital diaphragmatic hernia, meconium aspiration syndrome, or persistent pulmonary hypertension of the newborn; or who were previously enrolled in the study were excluded. Patients were categorized as receiving iNO for primary respiratory dysfunction or cardiac dysfunction. Subjects within the primary cardiac dysfunction group were subclassified in mutually exclusive groups of cardiomyopathy, extracorporeal membrane oxygenation (ECMO) or VAD placement for cardiomyopathy, congenital heart disease, postoperative heart transplantation, or preexisting diagnosis of pulmonary hypertension.

As this was an observational study, iNO administration and ventilator management were at the discretion of the treating physicians. All data were abstracted from the medical record. Data were abstracted from the medical record just prior to the time of iNO initiation and continued daily until 28 days, discharge from the ICU, or death, whichever occurred first. Admission data included demographics, acute and chronic diagnoses, and prehospitalization technology dependence. The only surgical procedures captured were whether the patient underwent a superior cavopulmonary connection (SCPC) (including a bidirectional Glenn or hemi-Fontan), Fontan procedure, heart transplant, or ventricular assist device implantation prior to iNO initiation. Daily data collection included the use of ICU technologies (e.g., ECMO and renal replacement therapy), cardiac arrest, echocardiogram use, pulmonary hypertension medications, and mechanical ventilation. Ventilator-free days (VFDs) in the first 28 days were calculated from the intubation/extubation logs starting on day 0. Patients who died or required ventilation for more than 28 days were assigned zero VFDs. In chronically ventilated patients, VFDs were calculated from ICU admission time to returning to prehospital ventilator settings. Patients discharged from the hospital were assumed to be alive and not mechanically ventilated for the purpose of calculating 28-day mortality and VFDs (10). Functional Status Scale (FSS) score was determined prior to ICU admission and at ICU discharge or 28 days (11). New ICU morbidity was defined as an increase in the FSS score of ≥3.

ICU and hospital lengths of stay were truncated at 8 months for the five patients remaining in the ICU

or hospital at study end. Echocardiographic reports were abstracted by a single reviewer (J.T.B.) to assess the presence of pulmonary hypertension, right ventricle dysfunction, tricuspid valve regurgitation, an atrial shunt, and congenital heart disease including the fundamental cardiac diagnosis. The presence of pulmonary hypertension was defined as a tricuspid valve velocity greater than 3 m/s, septal flattening during systole, or a stated diagnosis in the report, rather than the recently published hemodynamic criteria from 2019 (12). Echocardiograms were obtained at the discretion of the treating physicians.

All summaries reported counts and percentages for categorical variables; medians and interquartile ranges (IQRs) were reported for continuous variables. Severity of tricuspid valve regurgitation and right ventricle dysfunction were treated as ordinal variables. Fisher exact, Wilcoxon rank-sum, Cochrane-Armitage, Jonckheere-Terpstra, and Kruskal-Wallis tests were used to appropriately account for the several measurement scales in the outcomes as well as the predictors. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). *p* values were based on two-sided alternatives and considered significant when less than 0.05. No adjustment was made for multiple comparisons, and all results should be considered exploratory.

RESULTS

Demographic variables for the 407 patients with iNO initiation for cardiac dysfunction are summarized in **Table 1**. Importantly, only 58 of 407 of cardiac patients (14%) had preexisting pulmonary hypertension, of which 36 of 58 (62%) were on medical therapy for pulmonary hypertension prior to hospitalization. Mechanical ventilation was initiated a median of 7 hours (IQR, 4–27 hr) prior to iNO start and at a median of 20 parts per million (IQR, 20–20); median duration of iNO therapy was 4 days (IQR, 2–7 d).

Outcomes for the cohort are summarized in **Table 2** with center-specific outcome data presented in **Supplemental Table 1** (http://links.lww.com/PCC/B973). There was substantial overall morbidity and mortality after iNO initiation with 51 of 407 (13%) requiring ECMO, 27 of 407 (7%) requiring renal replacement therapy, and 42 of 407 (10%) with a cardiac arrest, and a 28-day mortality of 46/407 (11%). Sixty-four of 366 patients (17%) had new morbidity at 28 days or date of ICU discharge based on FSS score. Clinical variables of

TABLE 1.
Demographics of Patients With Inhaled Nitric Oxide Started for Cardiac Dysfunction

Variable	Overall, *n* = 407, *n* (%)
Age	
Neonate < 1 mo	141 (35)
Infant < 1 yr	169 (42)
Child < 12 yr	76 (19)
Adolescent 12–18 yr	21 (5)
Male	233 (57)
Race	
White	201 (49)
Black or African American	69 (17)
Other and unknown	137 (34)
Ethnicity	
Hispanic or Latino	67 (16)
Not Hispanic or Latino	285 (70)
Unknown or not reported	55 (14)
Prematurity	87 (21)
Prehospital chronic pulmonary hypertension	58 (14)
Prehospital chronic pulmonary hypertension treatment[a]	36 (62)
Prehospital technology dependence	74 (18)
Home/chronic ventilator[b]	18 (24)
Any chronic diagnosis	367 (90)
Lung disease of infancy (bronchopulmonary dysplasia)	13 (3)
Chromosomal defects	77 (19)
Hospital admit to iNO initiation (hr), median (Q1–Q3)	*n* = 400, 113 (29–299)
Mechanical ventilation start to iNO initiation, hr,[c] median (Q1–Q3)	*n* = 380, 7 (4–27)
Location of iNO initiation	
PICU	36 (9)
Cardiac ICU	209 (51)
Cardiac operating room	145 (36)
Other	13 (3)
Unknown	4 (1)
Initial dose of iNO, parts per million, median (Q1–Q3)	20 (20–20)
Days on continuous iNO, median (Q1–Q3)	4 (2–7)

iNO = inhaled nitric oxide.
[a]Percentage calculated from patients with prehospitalization pulmonary hypertension.
[b]Percentage based on patients with a prehospital technology dependence (i.e., need for oxygen, tracheostomy, home/chronic ventilator, and chronic vascular access).
[c]Subjects who started iNO prior to mechanical ventilation were excluded.

TABLE 2.
Outcomes of Patients With Inhaled Nitric Oxide Started for Cardiac Dysfunction

Outcome	Overall, *n* = 407, *n* (%)
Extracorporeal membrane oxygenation use after iNO initiation	51 (13)
Cardiac arrest after iNO initiation	42 (10)
Renal replacement after iNO initiation	27 (7)
Ventilator-free days,[a] median (Q1–Q3)	*n* = 396, 19 (5–24)
ICU length of stay, d, median (Q1–Q3)	18 (9–36)
Hospital length of stay, d, median (Q1–Q3)	33 (17–67)
Day 28 mortality	46 (11)
Hospital mortality	66 (16)
New morbidity[b]	*n* = 366, 64 (17)

iNO = inhaled nitric oxide.
[a]Ventilator-free days (VFDs) in the first 28 d were calculated from the intubation/extubation logs starting on day 0. Patients who died or required ventilation for more than 28 d were assigned zero VFDs. In chronically ventilated patients, VFDs were calculated from the time of ICU admission to returning to baseline (prehospital) ventilator settings. Patients discharged from the hospital were assumed to be alive and not mechanically ventilated for the purpose of calculating 28-day mortality and VFDs.
[b]Based on greater than or equal to 3 Functional Status Scale increase from baseline at time of ICU discharge or day 28.

prematurity and chromosomal defects were not associated with any of the outcomes (**Supplemental Table 2**, http://links.lww.com/PCC/B973).

Comparison of Cardiac Subgroups

Patients were stratified into groups with cardiomyopathy (*n* = 5), cardiomyopathy post-ECMO or VAD placement (*n* = 17), congenital heart disease (*n* = 328), postoperative heart transplantation (*n* = 25), and pulmonary hypertension without congenital heart disease (*n* = 32) (**Supplemental Table 3**, http://links.lww.com/PCC/B973). Of the 328 patients with congenital heart disease confirmed by echocardiogram reports, the most common fundamental cardiac diagnoses were hypoplastic left heart (58, 17%), other single ventricle lesion (34, 10%), ventricular septal defect (27, 8%), transposition of the great arteries (22, 7%), complete atrioventricular septal defect (21, 6%), total anomalous pulmonary venous connection (18, 5%), and truncus arteriosus (with or without interrupted aortic arch) (17, 5%). Outcomes of the cardiac subgroups are presented in **Table 3**. In patients with congenital heart disease, most were weaned off iNO with only 19 of 328 of patients (6%) receiving sildenafil or tadalafil. ICU and hospital mortality ranged from 4% to 60% among the different cardiac subgroups.

Among patients with congenital heart disease, 301 (92%) had iNO initiated after surgical repair, which included 37 patients (12%) who had an SCPC and nine patients (3%) who had a Fontan procedure. Only three of 37 (8%) SCPC and two of nine (22%) Fontan patients had a preoperative concern for pulmonary hypertension. Characteristics of iNO utilization and outcomes for these unique single-ventricle palliations are presented in **Table 4**.

Comparison of Echocardiogram Findings

Echocardiography was used per institutional practice. Only 68% (275/407) of patients had an echocardiogram performed within 12 hours prior to initiation of iNO, preexisting pulmonary hypertension patients having the lowest percentage (14/32, 44%) compared with 60–88% of patients in other cardiac subgroups (**Supplemental Table 4**, http://links.lww.com/PCC/B973). When echocardiogram results were reviewed from day 0 to day 28 or ICU discharge, only 32% of patients (98/306) with congenital heart disease, the largest subgroup of patients, had findings of pulmonary hypertension. In patients without echocardiographic findings of pulmonary hypertension, 87/194 (45%) had some degree of right ventricular dysfunction. Echocardiographic findings are outlined in **Supplemental Tables 4** and **5** (http://links.lww.com/PCC/B973) for type of cardiac dysfunction and postoperative SCPC and Fontan patients, respectively. Among postoperative SCPC patients, nine of 35 (26%) demonstrated moderate or severe tricuspid valve regurgitation, and 14 of 35 (40%) had moderate or severe single ventricle dysfunction. In patients who underwent Fontan and received iNO, none had moderate or severe tricuspid valve regurgitation and two of seven (29%) had severe single-ventricle dysfunction.

The association of echocardiographic variables prior to the start of iNO with outcomes in postoperative congenital cardiac surgery patients (*n* = 160) is

TABLE 3.
Outcomes by Type of Primary Cardiac Dysfunction (*n* = 407)

Outcome	Primary Cardiac Dysfunction, *n* (%)				
	Cardiomyopathy (*n* = 5)	ECMO or Ventricular Assist Device Placement for Cardiomyopathy (*n* = 17)	Congenital Heart Disease (*n* = 328)	Heart Transplant–Postoperative (*n* = 25)	Pulmonary Hypertension Without Congenital Heart Disease (*n* = 32)
ICU events					
ECMO use after iNO initiation	0 (0)	3 (18)	42 (13)	2 (8)	4 (13)
Cardiac arrest after iNO initiation	1 (20)	3 (18)	30 (9)	1 (4)	7 (22)
Renal replacement use after iNO initiation	0 (0)	2 (12)	18 (5)	2 (8)	5 (16)
Initial dose of iNO (parts per million), median (Q1–Q3)	20 (20–40)	20 (20–40)	20 (20–20)	20 (20–30)	20 (20–40)
Days on continuous iNO, median (Q1–Q3)	5 (4–10)	5 (4–9)	4 (2–7)	6 (4–7)	7 (3–17)
Sildenafil or tadalafil use, median (Q1–Q3)	0 (0)	0 (0)	19 (6)	0 (0)	14 (44)
ICU					
Mortality	3 (60)	2 (12)	47 (14)	1 (4)	10 (31)
New morbidity among survivors	1 (50)	3 (20)	35 (13)	5 (21)	5 (23)
Length of stay, d, median (Q1–Q3)					
Overall	16 (13–26)	27 (15–68)	17 (9–33)	25 (11–57)	18 (11–37)
Survivors[a]	40 (26–54)	27 (15–68)	15 (8–28)	26 (10–63)	18 (11–28)
Nonsurvivors[a]	13 (1–16)	40 (5–75)	36 (21–99)	25 (25–25)	21 (14–45)
Day 28					
Mortality[b]	3 (60)	1 (6)	34 (10)	1 (4)	7 (22)
Ventilator-free days, median (Q1–Q3)	0 (0–11)	15 (4–25)	20 (6–24)	21 (16–25)	16 (0–20)
Hospital					
Mortality	3 (60)	2 (12)	49 (15)	1 (4)	11 (34)
Length of stay, d, median (Q1–Q3)					
Overall	16 (13–28)	83 (40–110)	31 (16–61]	55 (26–128)	30 (17–102)
Survivors[c]	51 (28–73)	85 (40–123)	30 (16–58)	55 (32–136)	31 (18–101)
Nonsurvivors[c]	13 (1–16)	40 (5–75)	42 (22–99)	25 (25–25)	25 (15–103)

iNO = inhaled nitric oxide, ECMO = extracorporeal membrane oxygenation.

[a]Survivors for ICU length of stay (LOS) include all subjects discharged from the ICU alive.

[b]Day-28 mortality is assessed at day 28 or hospital discharge, whichever comes first.

[c]Survivors for hospital LOS included all subjects discharged from the hospital alive.

presented in **Table 5** and **Supplemental Table 6** (http://links.lww.com/PCC/B973). The degree of right-ventricle dysfunction was associated with 28-day mortality ($p < 0.001$), hospital mortality ($p < 0.001$), and reduced VFD ($p = 0.003$). The degree of tricuspid valve regurgitation was associated with reduced VFD ($p < 0.001$) but not 28-day or hospital mortality. Moderate or severe right ventricular dysfunction was

AT THE BEDSIDE

- In patients with inhaled nitric oxide (iNO) started for a cardiac indication, right ventricular dysfunction is associated with mortality.
- Evidence of pulmonary hypertension on echocardiography is not associated with mortality in patients with iNO started for a cardiac indication.
- Future prospective trials should consider this group of high risk patients to help guide study design and power analysis.

associated with hospital mortality after controlling for tricuspid valve regurgitation (odds ratio 3.45 [1.48–8.26]; $p = 0.004$). There continued to be no association between the degree of tricuspid valve regurgitation and vital status at hospital discharge after controlling for right ventricular dysfunction (**Supplemental Table 7**, http://links.lww.com/PCC/B973). The presence of pulmonary hypertension on echocardiography was not associated with 28-day mortality, hospital mortality, or VFDs. Of the 378 of 407 patients with an echocardiogram on study, only 193 (51%) had an echocardiogram both before and after iNO initiation. The follow-up echocardiograms were performed a median of 6.6 days (2.5–12.9 d) after iNO initiation, approximately 65% longer than the median duration of iNO use in the cardiac indication population.

DISCUSSION

Our data represent a robust description of the contemporary clinical practice for usage of iNO in patients with cardiac dysfunction across multiple large academic children's hospitals. Unexpectedly, iNO was used in a large number of patients with single-ventricle anatomy. iNO was started without prior echocardiographic evidence of elevated pulmonary pressure in nearly one-third of cases. Furthermore, the majority of patients did not demonstrate findings of elevated pulmonary pressures by echocardiography at any time point. Finally, in those patients in whom iNO was started, the degree of right ventricular dysfunction was strongly associated with mortality, whereas echocardiographic evidence of pulmonary hypertension was not related to mortality.

Utilization of iNO in certain patient groups such as postoperative cardiac surgery and postheart transplantation, and in those with chronic pulmonary hypertension was not unexpected. The most common congenital heart lesions in our series were similar to previous studies of iNO, but uniquely included a very large population of single-ventricle patients (6–8). Previous prospective studies of iNO in pediatric cardiac surgical patients provide limited data on single ventricles or exclude single-ventricle patients (6, 7, 13). Fundamentally, the use of iNO in the single-ventricle patient population is interesting in that staged surgical palliation requires low pulmonary vascular resistance to be successful. Despite iNO improving saturations and reducing the transpulmonary gradient in fenestrated Fontan and SCPC patients, more recent small case series have not demonstrated an improvement in outcomes related to length of stay or pleural effusions in the postoperative Fontan patient with pulmonary vasodilator therapy (14–16). It is unknown whether iNO was started in Fontan and SCPC patients in our study due to hypoxia or hemodynamic alterations as no hemodynamic data were collected as part of the study protocol. There were only a few patients who underwent cavopulmonary connections who were presumed to have preexisting concerns for elevated pulmonary artery pressures. However, the mortality in patients with use of iNO following SCPC (11%) or Fontan (11%) completion in our cohort far exceeded expected mortality based on the reported outcomes from the Society of Thoracic Surgeons with a reported mortality for SCPC of 1.8% (IQR, 0.0–2.7%) and 1.0% (IQR, 0.0–0.4%) for Fontan operation (17).

Echocardiography serves as one of the most important tools for evaluating pulmonary hypertension in the ICU setting and is frequently used in the cardiac patient population (5). Nevertheless, we discovered that many patients did not have echocardiographic imaging prior to iNO initiation, suggesting that presumed postoperative right-ventricle dysfunction, clinical concerns for pulmonary hypertensive crisis, or intraoperative concerns were the triggers for initiation. We found an association between right-ventricle dysfunction and increased ICU mortality in the pediatric cardiac patient population similar to findings in adults with acute respiratory distress syndrome and

TABLE 4.
Inhaled Nitric Oxide Characteristics and Patient Outcomes for Single-Ventricle Patients (Among Subjects With Cardiac Surgery)

Characteristic or Outcome	Overall (*n* = 301)	Superior Cavopulmonary Connection (*n* = 37)	Fontan (*n* = 9)
iNO characteristics			
Hospital admit to iNO initiation, hr, median (Q1–Q3)	*n* = 296, 126 (39–312)	*n* = 36, 70 (11–362)	*n* = 9, 17 (10–68)
Mechanical ventilation start to iNO initiation, hr,[a] median (Q1–Q3)	*n* = 293, 7 (4–19)	*n* = 36, 8 (5–14)	*n* = 8, 9 (8–14)
Location of iNO initiation, *n* (%)			
PICU	12 (4)	0 (0)	0 (0)
Cardiac ICU	148 (49)	21 (57)	7 (78)
Cardiac operating room	137 (46)	15 (41)	2 (22)
Other	4 (1)	1 (3)	0 (0)
Initial dose of iNO, parts per million, median (Q1–Q3)	20 (20–40)	20 (20–20)	20 (20–20)
Days on continuous iNO, median (Q1–Q3)	4 (2–6)	5 (3–9)	8 (4–20)
Outcomes			
Extracorporeal membrane oxygenation use after iNO initiation	33 (11)	4 (11)	2 (22)
Renal replacement after iNO initiation	9 (3)	1 (3)	0 (0)
ICU length of stay, d, median (Q1–Q3)	17 (9–34)	21 (8–37)	23 (6–40)
Hospital length of stay, d, median (Q1–Q3)	33 (18–62)	32 (16–61)	48 (16–78)
Day 28			
Mortality	25 (8)	4 (11)	1 (11)
Ventilator-free days, median (Q1–Q3)	*n* = 298, 21 (7–24)	*n* = 37, 21 (3–24)	*n* = 9, 20 (11–26)
Total survivors, *n* (%)	279 (93)	33 (89)	8 (89)
New morbidity among survivors, *n* (%)	39 (14)	5 (15)	2 (25)

iNO = inhaled nitric oxide.[a]Subjects were excluded from this summary because they started iNO before starting mechanical ventilation.

in patients with pulmonary hypertension (18, 19). Elevation of pulmonary artery pressure alone may not have a significant impact on cardiac output until right-ventricular function decreases, which rationally would impact organ perfusion and ultimately survival. The presence of significant right-ventricle dysfunction in our patients was associated with worse survival and fewer VFDs, suggesting that additional therapies beyond iNO may need to be more aggressively instituted to impact outcomes. It is important to realize that the findings of right-ventricle dysfunction by echocardiography were based on standard-of-care echocardiogram reports, rather than more advanced imaging techniques such as tissue Doppler imaging, strain and strain rate, or tricuspid annular plane systolic excursion, which could potentially further characterize and identify patients at risk (20).

Postoperative cardiac surgery, posttransplant, and chronic pulmonary hypertension patients have treatment guidelines available in the United States and Europe aimed at identifying patients at risk (5, 21). Notably, iNO has become an accepted standard of care to treat postoperative pulmonary hypertension in the dosing ranges we report (3, 5, 22). Previous randomized studies of iNO in pediatric postoperative congenital heart disease patients have not demonstrated a mortality benefit; however, those studies were underpowered with small numbers of patients and only looked at specific conditions (6, 7). It is also likely that these previous studies did not sufficiently risk stratify patients prior to administration of iNO. Our data suggest that a significant driver for morbidity and mortality associated with pediatric cardiac patients is right-ventricle dysfunction more than the presence of

TABLE 5.

Associations of Echocardiographic Parameters Prior to Inhaled Nitric Oxide With Outcomes in Postoperative Cardiac Surgery Patients ($n = 160$)[a]

	Hospital Mortality, *n* (%)			Ventilator-Free Days[b]	
Echo Abstraction Results	Dead ($n = 16$)	Alive ($n = 144$)	*p*	Ventilator-Free Day, median (Q1–Q3)	*p*
Pulmonary hypertension present[c]					
No	7 (7)	87 (93)	0.284[d]	22.0 (18.0–24.0)	0.086[e]
Yes	9 (14)	57 (86)		19.5 (3.0–24.0)	
Tricuspid valve regurgitation[f]					
Severe	1 (20)	4 (80)	0.063[g]	24.0 (3.0–25.0)	< 0.001[h]
Moderate	6 (20)	24 (80)		14.0 (6.0–23.0)	
Mild	6 (9)	58 (91)		20.0 (16.0–24.0)	
Trivial	1 (2)	41 (98)		23.0 (18.0–25.0)	
None	2 (11)	17 (89)		24.0 (22.0–25.0)	
Right ventricular dysfunction[f]					
Severe	9 (38)	15 (63)	< 0.001[g]	17.5 (0.0–23.0)	0.003[h]
Moderate	1 (4)	25 (96)		18.5 (12.0–22.0)	
Mild	2 (7)	26 (93)		23.0 (17.0–25.0)	
Normal	4 (5)	78 (95)		22.5 (18.0–24.0)	
Atrial shunt present					
Right to left	1 (4)	22 (96)	0.773[d]	19.0 (7.0–23.0)	0.336[i]
Bidirectional	1 (6)	17 (94)		20.0 (18.0–24.0)	
Left to right	5 (12)	38 (88)		21.0 (14.0–24.0)	
None	9 (12)	67 (88)		23.0 (14.0–25.0)	

[a]Percentages reported in this table are rowwise and include all postoperative cardiac surgical subjects (excluding Fontan and superior cavopulmonary connections) with an echocardiogram abstraction prior to inhaled nitric oxide.

[b]Ventilator-free days (VFDs) in the first 28 d were calculated from the intubation/extubation logs starting on day 0. Patients who died or required ventilation for more than 28 d were assigned zero VFDs. In chronically ventilated patients, VFDs were calculated from the time of ICU admission to returning to baseline (prehospital) ventilator settings. Patients discharged from the hospital were assumed to be alive and not mechanically ventilated for the purpose of calculating 28-d mortality and VFDs.

[c]The presence of pulmonary hypertension was defined as a tricuspid valve velocity greater than 3 meters/s, septal flattening during systole, or as a stated diagnosis in the report.

[d]Fisher exact test.

[e]Wilcoxon rank-sum test.

[f]Categorization of tricuspid valve regurgitation and degree of right ventricular dysfunction were based on clinical echocardiogram reports per each institution's standard.

[g]Cochran-Armitage test for trend.

[h]Jonckheere-Terpstra test.

[i]Kruskal-Wallis test.

pulmonary hypertension (as assessed by echocardiography). Importantly, we did not examine the impact of iNO on pulmonary hypertension, right ventricle function, mortality, or morbidity, and future work is needed to better categorize those patients who would most benefit from iNO.

There are several limitations to our study findings. Although all patients requiring iNO at each participating clinical site were enrolled and all available study data were captured, the decision to institute the therapy was up to local policies and individual practitioner preferences. Additionally, this study did not collect

invasive hemodynamic data or preoperative cardiac catheterization data, which may have influenced decisions to initiate iNO. Echocardiograms were obtained based on clinical practice, and as a result, the number of studies available prior to initiation of iNO was limited. Although respiratory data were captured with the study protocol, no data on other routine treatments for pulmonary hypertension (e.g., sedation, paralysis, and alkalization) were collected, which limited our ability to account for potential confounders that could have influenced the significance of our results. Thus, the associations between echocardiographic findings (right ventricular dysfunction and tricuspid regurgitation) and outcomes are based on univariate analysis. Finally, because outcomes for all surgical patients were not captured, it is not possible to compare outcomes of patients in whom iNO was initiated to outcomes of similarly ill patients who did not receive iNO; thus, it does not allow us to infer equipoise for iNO use to inform future studies.

CONCLUSIONS

This study represents the largest prospectively collected cohort of pediatric cardiac patients examining the clinical utilization of iNO. The data highlight the common utilization of iNO in postoperative single-ventricle patients at all stages of palliation, a patient population with minimal available prospective data to guide care, and in whom successful surgical outcomes are predicated on maintaining low pulmonary vascular resistance. Importantly, we demonstrated by univariate analysis that there remains a high mortality rate in pediatric cardiac patients with right-ventricle dysfunction in whom iNO is initiated. This highlights a potential shortcoming of previous prospective studies of iNO where risk stratification occurred based on presence of pulmonary hypertension, rather than right-ventricle dysfunction.

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