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ORIGINAL RESEARCH

Feasibility, Safety, and Short-Term Outcomes of Transcatheter Patent Ductus Arteriosus Closure in Premature Infants on High-Frequency Jet Ventilation

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BACKGROUND: Prolonged exposure to a hemodynamically significant patent ductus arteriosus (PDA) is associated with major morbidity, particularly in infants born at <27 weeks' gestation. High-frequency jet ventilation (HFJV) is a standard of care at our center. There are no data about transcatheter PDA closure while on HFJV. The aim of this study was to assess the feasibility, safety, and outcomes of HFJV during transcatheter PDA closure.

METHODS AND RESULTS: This is a retrospective cohort study of premature infants undergoing transcatheter device closure on HFJV. The primary outcome was successful device placement. Secondary outcomes included procedure time, fluoroscopy time and dose, time off unit, device complications, need for escalation in respiratory support, and 7-day survival. Subgroup comparative evaluation of patients managed with HFJV versus a small cohort of patients managed with conventional mechanical ventilation was performed. Thirty-eight patients were included in the study. Median age and median weight at PDA device closure for the HFJV cohort were 32 days (interquartile range, 25.25–42.0 days) and 1115 g (interquartile range, 885–1310 g), respectively. There was successful device placement in 100% of patients. There were no device complications noted. The time off unit and the procedure time were not significantly different between the HFJV group and the conventional ventilation group. Infants managed by HFJV had shorter median fluoroscopy times (4.5 versus 6.1 minutes; $P<0.05$) and no increased risk of adverse respiratory outcomes.

CONCLUSIONS: Transcatheter PDA closure in premature infants on HFJV is a safe and effective approach that does not compromise device placement success rate and does not lead to secondary complications.

Key Words: device closure ■ high-frequency jet ventilator ■ high-frequency ventilation ■ patent ductus arteriosus ■ transcatheter

The approach to patent ductus arteriosus (PDA) care in extremely preterm infants continues to be a subject of much controversy.[1–4] Until recently, the standard of care for definitive PDA closure was surgical intervention through a lateral thoracotomy technique. Several studies have demonstrated increased risk of postligation cardiac syndrome,[5] trauma-related complications (recurrent laryngeal nerve palsy, chylothorax), and adverse neurosensory impairment.[6] Contemporary opinion has moved away from viewing surgical PDA closure as being "more effective and less costly [and] superior to transcatheter placement of the occluder for closure of isolated PDA,"[7] with transcatheter closure now becoming widely adapted. Safety of

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CLINICAL PERSPECTIVE

What Is New?

- In premature infants, transcatheter patent ductus arteriosus closure can be done safely and effectively on high-frequency jet ventilation, without the need to transition patients to conventional mechanical ventilation.

What Are the Clinical Implications?

- This could limit unnecessary changes in ventilation strategy in a patient population that is exquisitely sensitive to changes in management.

Nonstandard Abbreviations and Acronyms

CMV	conventional mechanical ventilation
ELBW	extremely low birth weight
FiO_2	fraction of inspired oxygen
HFJV	high-frequency jet ventilation
PIP	peak inspiratory pressure

the Amplatzer Piccolo Occluder, which received FDA approval in 2019 for infants >700 g with a PDA, was recently confirmed in a cohort of 200 patients.[8]

Traditionally, transcatheter procedures have been performed on conventional mechanical ventilation, with PDA closure being no exception. Indeed, in a study of 100 such procedures done on infants <1000 g, only 12% of patients received the intervention while on high-frequency ventilation.[9] The use of high-frequency ventilation, both high-frequency oscillatory ventilation and high-frequency jet ventilation (HFJV), has been shown to decrease the incidence of bronchopulmonary dysplasia in infants with extremely low birth weight (ELBW).[10,11] The population of infants with ELBW, most likely to require definitive PDA closure, are also at greatest risk of lung injury and pulmonary vascular maldevelopment, and therefore may benefit most from minimizing volutrauma by maintaining high-frequency ventilation during transcatheter PDA closure. At our institution, first-intention HFJV from birth is the standard of care to minimize volutrauma when caring for infants with ELBW with respiratory distress syndrome that require invasive ventilation. It has been previously shown that the use of HFJV during surgical ligation did not impact surgical morbidity or mortality compared with conventional ventilation.[12] The use of first-intention HFJV at our institution has been associated with high survival rates at the limits of viability, which exceed national averages.[13] In developing a standardized approach during our transition to transcatheter PDA closure, guidelines for use of HFJV during the procedure were developed. The goal of this study was to assess the efficacy, feasibility, and safety of transcatheter PDA closure while on HFJV.

METHODS

This is a retrospective cohort study of preterm infants with a hemodynamically significant PDA undergoing transcatheter device closure while on HFJV. Patient selection for PDA closure was performed by the neonatal hemodynamics team in accordance with a standardized echocardiography approach. The eligible population included all premature infants with a hemodynamically significant PDA that underwent transcatheter PDA closure from the time of program inception in October 2019 until May 2021. The study was approved by the institutional review board at the University of Iowa (institutional review board ID No. 202103449). No informed consent was required. The data that support the findings of this study are available from the corresponding author upon reasonable request.

PDA Care

Comprehensive targeted neonatal echocardiography is performed by the neonatal hemodynamics team, according to a standardized protocol, which includes the assessment of intracardiac and aortic arch anatomy, characterization of PDA shunt volume, and assessment of pulmonary venous location/flow. A scoring system is used to determine the hemodynamic significance of a PDA (Table 1). The PDA score is used as a surrogate of shunt volume and a PDA with score of >6 is considered to be hemodynamically significant.[14] Premature infants with a hemodynamically significant PDA are referred for transcatheter closure after failed medical therapy (targeted acetaminophen or indomethacin [1–2] courses), or if medical therapy is contraindicated. The interventional cardiology and neonatal hemodynamics team triage individual cases to determine suitability for transcatheter PDA closure. Figure 1 provides an overview of our standardized workflow of PDA closure at our institution.

High-Frequency Jet Ventilation

All patients were sedated and muscle relaxed 1 to 2 hours before procedural departure using a low-dose morphine infusion (5–10 μg/kg per min) and a single dose of vecuronium (0.1 μg/kg) and lorazepam (0.1 mg/kg). A preprocedural chest x-ray and serial blood gases were performed until a blood gas in the patients' target range is achieved. Patients were then transported to the cardiac catheterization laboratory and positioned on the operating table by the NICU transport team

Table 1. Metrics Used to Determine the Iowa PDA Score

Marker	0 points	1 point	2 points
Mitral valve E-wave velocity, cm/s	<45	45–80	>80
IVRT, ms	>50	30–50	<30
PV D-wave velocity, cm/s	<30	30–50	>50
Left atrium/aorta ratio	<1.3	1.3–2.2	>2.2
LVO, mL/min per kg	<250	250–430	>430
Diastolic flow in descending aorta and/celiac/middle cerebral artery	Forward		Reversed

A PDA with a score of >6 is assumed to be hemodynamically significant. IVRT indicates isovolumic relaxation time; LVO, left ventricular outflow; PDA, patent ductus arteriosus; and PV, pulmonary vein.

and a member of the neonatal hemodynamics team (seniority equivalent to a neonatologist in years 1–3 of clinical practice) without breaking the patients' bedside respiratory circuit. Periprocedural decisions related to HFJV use are made by the neonatal team (present in the catheterization laboratory), according to standardized guidelines, in consultation with the anesthesiologist. HFJV was not paused at any point during the procedure except if required for patient care (ie, suctioning). Respiratory instability (increased need of oxygenation or ventilation) is managed according to the principles outlined in Table 2. Chest radiography and blood gas sampling is routinely performed upon return to the NICU to ensure optimal lung recruitment and ventilation. Capillary blood gas was used most frequently for pre- and postprocedure care. When an arterial line was present, arterial blood gas was preferentially used.

Device Placement

All devices were placed via femoral venous access. Ultrasound was used to place a 4-Fr Prelude IDeal sheath (Merit Medical, Jordan, UT) through the femoral vein. No arterial access was obtained. On certain occasions and based on NICU staff level of concern, an arterial line was placed in the radial artery before transportation to the catheterization lab in anticipation of the need for close blood pressure and blood gas monitoring in the postoperative period. A 4-Fr Angle Glidecath (Terumo, Somerset, NJ) with a 0.035" Tigerwire (Abbott Cardiovascular, Plymouth, MN) were advanced prograde across the PDA. Angiograms were taken within the PDA and used for identifying the PDA anatomy and to obtain measurements including the narrowest diameter and length, which was used to determine device size. Next,

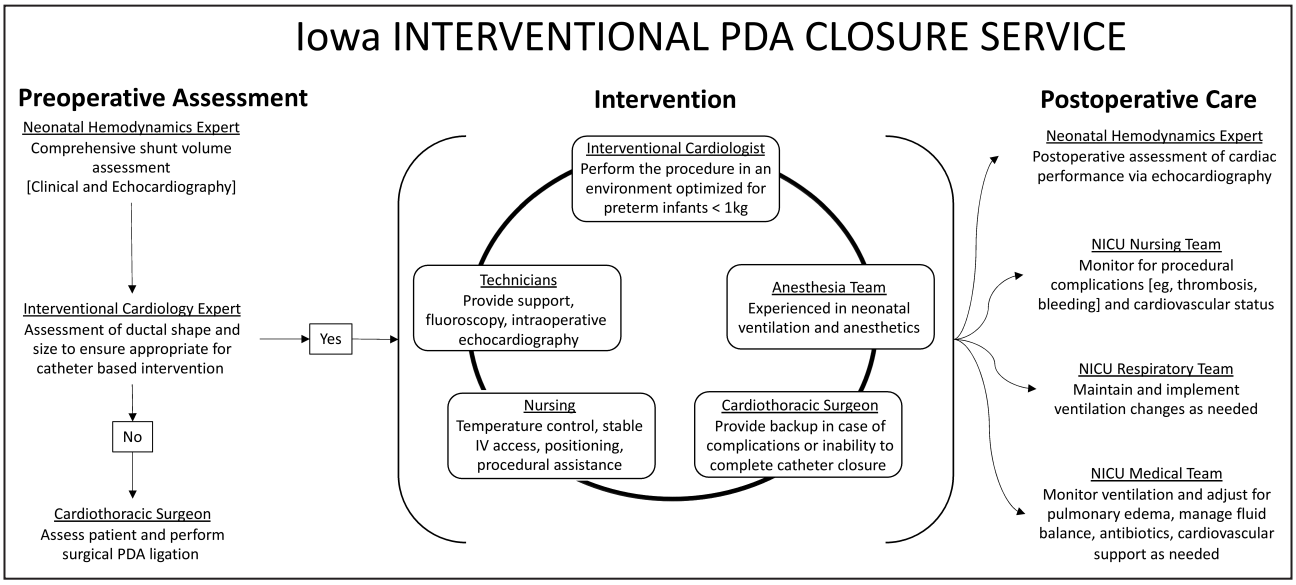

Figure 1. Patent ductus arteriosus (PDA) closure algorithm.
The algorithm that is used in PDA closure at our institution. All ducts being considered for PDA closure undergo an initial preoperative assessment by the interventional cardiology and neonatal hemodynamics teams. Transcatheter PDA closure is performed by a team consisting of pediatric interventional cardiologists, pediatric cardiac anesthesiologists, pediatric neonatal intensivists, pediatric cardiothoracic surgeons, nurses, and technicians. Postoperative care is assumed by the neonatal intensivists and the neonatal hemodynamics team. IV indicates intravenous; and NICU, neonatal intensive care unit. Reproduced from McNamara et al[15] with permission. Copyright ©2019 Elsevier.

Table 2. High-Frequency Jet Ventilator Adjustment Strategy

Event	Response
Hypercapnia (Pco_2>60 mm Hg)	Increase jet PIP by 1–2 to decrease Pco_2 by 2–4 mm Hg. Increase jet PIP by 2–4 to decrease Pco_2 by 5–8 mm Hg.
Hypocapnia (Pco_2<35 mm Hg)	Decrease jet PIP by 1–2 to increase Pco_2 by 2–4 mm Hg. Decrease jet PIP by 2–4 to increase Pco_2 by 5–8 mm Hg.
To improve oxygenation	Increase jet PIP and PEEP by 1–2 at the same time. Jet inspiratory time is fixed at 0.02 ms. Jet rate ranges from 240 to 600. Increase in jet rate can improve both oxygenation and ventilation.

Pco_2 indicates partial pressure of carbon dioxide; PEEP, peak end-expiratory pressure; and PIP, peak inspiratory pressure.

the glide catheter was removed over the wire and the piccolo delivery system (Amplatzer Torqvue LP catheter) advanced over the wire to the descending aorta. The Piccolo (Abbott Cardiovascular) device was prepared in the usual fashion and advanced through the introducer under fluoroscopic guidance to the end of the delivery system. The entire system was pulled back into the ductal ampulla before deploying the device. The device was deployed within the ductus. With the device still attached, pulmonary artery angiography was performed in left anterior oblique and caudal projection for the PA camera and straight lateral for the lateral camera. The angiogram explored the device position to confirm intraductal placement and patency of the left pulmonary artery. Periprocedural transthoracic echocardiography was performed to assess the aorta and pulmonary artery patency, residual shunt, and gradients across the branch pulmonary arteries and the descending aorta. After satisfactory positioning was confirmed, the device was released followed by another transthoracic echocardiography assessment for the aforementioned sites in addition to the tricuspid valve.

Data Collection

Basic demographic information collected included birth weight, sex, and gestational age at birth. Information about PDA closure included age (age in days and gestational age) and weight at the time of procedure. Echocardiography information from the immediate precatheterization echocardiogram were collected and included ejection fraction, presence and severity of tricuspid regurgitation, presence or absence of atrial- and ventricular-level shunts, size of PDA, directionality of shunting across the PDA, maximum velocity of flow across the PDA, and presence or absence of descending aorta flow reversal. Similar metrics were collected from the echocardiogram obtained immediately after device placement with the addition of presence/absence of residual PDA flow, aortic stenosis, and branch pulmonary artery stenosis. Stenosis across the branch pulmonary arteries and the descending aorta was defined as a flow velocity of ≥2 m/s. In addition, we collected information about the type of ventilation. For patients on HFJV, ventilator settings just before transport to the catheterization laboratory were compared with those 24 hours after return from the catheterization laboratory. Settings within 1 hour before transport were designated as "precatheterization" settings, while settings 24 hours after return from the catheterization laboratory were designated as "postcatheterization" settings. Fraction of inspired oxygen (FiO_2), jet peak inspiratory pressure (PIP), mean airway pressure, jet peak end-expiratory pressure, jet rate, intermittent mechanical ventilation, intermittent mechanical ventilation PIP, and intermittent mechanical ventilation inspiratory time were recorded. Respiratory severity score was calculated from these data and defined as mean airway pressure×FiO_2. Data regarding success of the procedure, the size of the device used, procedure time (difference of time in minutes between sheath placement and sheath removal), time off unit (time between departure from NICU and return to NICU), and access site were all collected. Finally, the total time spent on an HFJV ventilator, the time spent on HFJV following the procedure, the need to initiate milrinone following the procedure, and the length of time on milrinone were also collected.

Outcomes

The primary outcome was successful device placement. Secondary outcomes included procedure time, fluoroscopy time and dose, time off unit, device complications (embolization, aorta, or left pulmonary artery obstruction, tricuspid valve injury, and residual shunt/hemolysis), the need for escalation in respiratory support, the rate of pneumothorax or need for resuscitation, and 7-day survival.

Statistical Analysis

A convenience sample size was chosen to provide preliminary hypothesis-generating data. Descriptive analyses were performed on the total population. Normality of the data was assessed using the Shapiro-Wilk test. Comparison between the HFJV cohort and a small cohort of patients managed with conventional

mechanical ventilation (CMV) was done via the Mann-Whitney test. The Wilcoxon signed-rank test was used to compare within-patient data, namely, the FiO_2, mean airway pressure, and the respiratory support immediately before and 24 hours after catheterization for the HFJV cohort.

RESULTS

Demographics

In total, 38 patients underwent PDA device closure, of whom 29 (76.3%) were managed using HFJV and 9 (23.7%) managed on CMV (Table 3). The cohort included 26 male and 12 female patients. The median weight and gestational age at birth for neonates undergoing PDA closure on HFJV were 650 g (interquartile range [IQR], 570–825) and 24 weeks (IQR, 23–26 weeks), respectively. The median age and weight at intervention for the HFJV cohort were 32 days (IQR, 25–35 days) and 1115 g (IQR, 885–1310 g). The smallest patient that underwent device closure was 705 grams (Figure 2). All patients had evidence of moderate-high-volume exclusive left-to-right PDA shunts with a median PDA score of 8 across the entire cohort (IQR, 7–9). There was descending aortic flow reversal seen in 27 patients (71%). The median number of medical therapies attempted before transcatheter PDA occlusion was 3 attempts (IQR, 2–3.75 attempts).

Primary Outcome

The success rate for device placement was 100% for the entire cohort.

Secondary Outcomes

Survival and Complications

Seven-day survival was 100%. Only 1 patient died, 2 months after the procedure, from an unrelated sepsis episode. There were no device-related adverse events.

Cardiac Catheterization Metrics

For the HFJV cohort, median procedure time was 32 minutes (IQR, 29–42 minutes), median fluoroscopy time was 4.5 minutes (IQR, 3.55–6.3 minutes), and median fluoroscopy dose indexed by body surface area was 29.40 mGy.cm^2 (IQR, 19.70–38.50 mGy.cm^2). Femoral access was successfully obtained in all patients. Median time off unit was 109 minutes (IQR, 100–125 minutes) for the HFJV cohort. The PDA was successfully closed in all 38 patients (100%). There was complete resolution of flow across the PDA within 24 hours in 36 patients (95%). There was evidence of a residual trans-device flow in 2 patients on the immediate postprocedural echocardiogram, which had completely resolved within 1 month in both instances and was not associated evidence of hemolysis seen during this time period. Device size varied between 3–2 (16 patients, 42%), 4–2 (20 patients, 52.5%), and 4–4 (2 patients, 5.5%). There was neither left pulmonary artery nor descending aortic stenosis or tricuspid valve injury noted.

Critical Care Metrics

There were no episodes of pneumothorax, need for resuscitation, or use of inhaled nitric oxide in the entire cohort. All patients on HFJV were exclusively managed on this mode of ventilation for the entire procedure, and none required rescue conventional ventilation. In

Table 3. Demographics

	All	HFJV	CMV	*P* value
Total number of patients, n (%)	38 (100)	29 (76.3)	9 (23.7)	
Male, n (%)	26 (68)	18 (62)	8 (89)	>0.05
Median PDA score (IQR)	8 (7–9)	8 (6.5–9)	7 (5.5–9.5)	>0.05
Median number of medical therapies	3	3	3	
Median gestational age at birth in weeks (IQR)	24.5 (23–26)	24 (23–26)	25 (24–26)	>0.05
Median weight at birth in grams (IQR)	679 (580–882)	650 (570–825)	810 (750–900)	>0.05
Median age at catheterization in days (IQR)	32 (25.25–42)	32 (25–35)	42 (31–43)	>0.05
Median weight at catheterization in grams (IQR)	1125 (909–1350)	1115 (885–1310)	1313 (1025–1755)	>0.05
Device size, n (%)				
3–2	16 (42)	15 (52)	1 (11)	
4–2	20 (53)	12 (41)	8 (89)	
4–4	2 (5)	2 (7)	0	

Table highlighting the demographic data of the entire population and showing the differences between the HFJV group and the CMV group. CMV indicates conventional mechanical ventilation; HFJV, high-frequency jet ventilation; IQR, interquartile range (25th, 75th percentile); and PDA, patent ductus arteriosus.

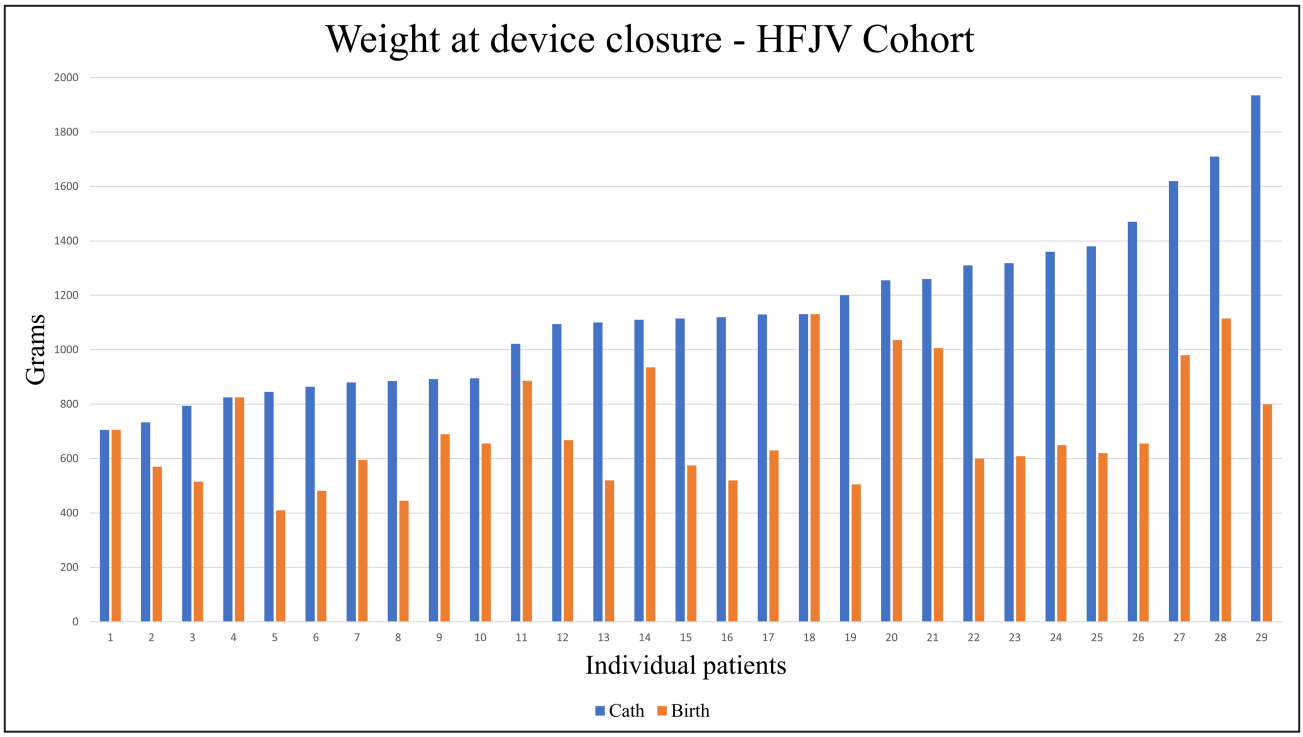

Figure 2. Weight distribution of high-frequency jet ventilation (HFJV) cohort.
Weight distribution (weight at cardiac catheterization and weight at birth) of all patients undergoing patent ductus arteriosus (PDA) closure while on (HFJV). Weight at device closure ranged from 705 g to 1935 g. Weight at birth ranged from 410 g to 1131 g.

addition, all these patients were maintained on HFJV after the procedure. When comparing HFJV before and after catheterization respiratory support, we found that patients on the HFJV had lower mean airway pressure 24 hours after catheterization (12.5±2.2 mm Hg versus 11.7±2.2 mm Hg; $P<0.05$) but higher mean FiO_2 24 hours after catheterization (44.2±16.6% versus 48.8±15.4%; $P<0.05$). Subsequently, there was no significant difference in mean respiratory severity score (mean airway pressure ×FiO_2 5.7±2.6 versus 5.9±2.6; $P>0.05$). Seventy-three percent of our HFJV cohort required milrinone within 4 days of cardiac catheterization, though in most cases treatment was started within 24 hours after catheterization. Median length of time on milrinone was 21 hours (IQR, 0–39 hours) for the HFJV cohort. Indications to start milrinone outside of the immediate perioperative period (n=23) included sustained systemic hypertension with worsening oxygenation. In total, patients spent a median of 49 days (IQR, 44.5–57 days) on an HFJV, most of that spent before catheterization. Indeed, the median time required to deescalate patients from HFJV after catheterization was 13 days (IQR, 7.5–24 days).

Comparison of HFJV Group to CMV Group

A small portion of our cohort (9 patients; 23.7%) underwent transcatheter PDA closure on CMV. Median gestational age at birth (24 weeks [IQR, 23–26 weeks] versus 25 weeks [IQR, 24–26 weeks]; U=81; $P>0.05$), weight at birth (650 g [IQR, 570–825 g] versus 810 g [IQR, 750–900 g]; U=84; $P>0.05$), age in days at time of catheterization (32 days [IQR, 25–35 days] versus 42 days [IQR, 31–43 days]; U=91; $P>0.05$), and weight at the time of catheterization (1115 g [IQR, 885–1310 g] versus 1313 g [IQR, 1025–1755 g]; U=76; $P>0.05$) were not different between the 2 groups (Table 3). From a procedural standpoint, median time off unit (109 minutes [IQR, 100–125 minutes] versus 121 minutes [IQR, 92–163 minutes]; U=103; $P>0.05$) and median procedure time (32 minutes [IQR, 29–42 minutes] versus 38 minutes [IQR, 33–47 minutes]; U=95; $P>0.05$) were comparable between groups. Interestingly, median fluoroscopy time was shorter for the HFJV cohort (4.5 minutes [IQR, 3.6–6.3 minutes] versus 6.1 minutes [IQR, 5.3–8.3 minutes]; U=64; $P<0.05$) and median fluoroscopy dose, though not statistically significant, favored a smaller dose of fluoroscopy for the HFJV cohort (29.4 mGy.cm^2 [IQR, 19.7–38.5 mGy.cm^2] versus 56.0 mGy.cm^2 [IQR, 32.9–58.9 mGy.cm^2], U=78, $0.1>P>0.05$). Both cohorts had rates of milrinone requirement after catheterization that where not statistically significant at 63% for the HFJV cohort and 71% for the CMV cohort (Table 4). Finally, the median length of time on milrinone was not statistically significant between the

Table 4. Metrics of Cardiac Catheterization for HFJV vs CMV

	HFJV (IQR)	CMV (IQR)	*P* value
Median time off unit, min	109 (100–125)	121 (92–163)	>0.05
Median procedure time, min	32 (29–42)	38 (33–47)	>0.05
Median fluoroscopy time, min	4.5 (3.6–6.3)	6.1 (5.3–8.3)	<0.05
Median fluoroscopy dose, mGy.cm^2	29.4 (19.7–38.5)	56 (32.9–58.9)	>0.05
Patients requiring milrinone after PDA closure, %	63	71	>0.05
Median time on milrinone after PDA closure, h	24 (21–48)	51.5 (27.5–68)	>0.05

Comparison of cardiac catheterization metrics between the HFJV group and the CMV group. Only the fluoroscopy time was significantly different between the times, with the HFJV group have shorter fluoroscopy times. CMV indicates conventional mechanical ventilation; HFJV, high-frequency jet ventilation; IQR, interquartile range (25th, 75th percentile); and PDA, patent ductus arteriosus.

2 groups (24 hours for HFJV [IQR, 21–48 hours] versus 51.5 hours for CMV [IQR, 27.5–68 hours]; U=35; *P*>0.05).

DISCUSSION

The presence of a PDA has been associated with various morbidities as well as an increase in mortality in preterm infants.[2,16,17] Infants who require interventional closure represent the subgroup of infants with ELBW with greatest ventilator requirements, most likely because of the consequences of prolonged shunt exposure.[18] In some centers, premature infants born as early as 22 weeks are routinely placed on HFJV[19] to minimize volutrauma. There are limited data regarding the feasibility, safety, and outcomes of HFJV as the primary strategy during transcatheter PDA closure in premature infants. In this pilot observational study, we demonstrated that transcatheter PDA closure is both safe and feasible in infants with ELBW managed using HFJV.

Rates of successful transcatheter PDA closure in premature infants has been reported between 81% and 100%.[20–23] Our data are consistent with prior literature. Specifically, our universal success rates in device placement suggests that HFJV does not compromise rates of successful device placement. Our data further suggests that this is a safe ventilation strategy with no recorded episodes of pneumothorax and a 100% 7-day survival rate. There was no need for escalation in respiratory care after PDA closure with a comparable pre- and post-PDA ligation respiratory severity score. Prior data about the use of HFJV during cardiac catheterization procedures are limited. Studies that have appraised the safety and efficacy of this ventilation strategy in the catheterization laboratory have focused on adults undergoing electrophysiology procedures and have found it to be advantageous.[24–27] The proposed characteristics that lend themselves to making HFJV a successful ventilation strategy for electrophysiology procedures, namely, the low-volume breaths that minimize respirophasic cardiac excursion[27] and potentially stabilize the heart,[24,28] could theoretically assist in transcatheter PDA closure and could, in part, explain the high success rate in our cohort. One would expect that such a stabilizing effect would be particularly important in infants with ELBW where PDA size can be exceptionally small.

The concern that HFJV could compromise angiographic and echocardiographic guidance of transcatheter PDA closure could explain some of the hesitation around performing transcatheter PDA closure on patients maintained on HFJV. Our experience has been quite contrary to that with no limitation noted on the utility of transthoracic echocardiography guidance during PDA closure (Figure 3). Similarly, we found HFJV did not compromise the quality of angiograms obtained during PDA closure (Figure 4).

Interestingly, we noted lower mean airway pressure 24 hours after PDA closure, likely related to the cumulative effects of elimination of PDA-related pulmonary overcirculation with subsequent decrease in pulmonary edema and our standardized approach to post-procedural hemodynamic care. The strict institutional protocols implemented by the NICU and anesthesia teams at our institution are likely the primary driver of the near-absent morbidity/mortality of transcatheter PDA closure in this population. While these data are promising, they should not be interpreted as superiority in either form of ventilation strategy.

In our cohort, patients on HFJV received a median radiation dose of 1.75 mGy (IQR, 1.23–2.7 mGy) and a median dose area product of 29.40 mGy.cm^2 (IQR, 19.70–38.50 mGy.cm^2). These values are less than prior studies of transcatheter PDA closure in infants with ELBW,[9] where reported mean radiation was 1278.9 mGy.cm,[2,29] and studies of a similar procedure in children ranging in age from 0 to 17.6 years of age, where reported mean radiation dose area product in that population was 1010 mGy.cm.[2,30] This reduction in radiation exposure is likely the result of several

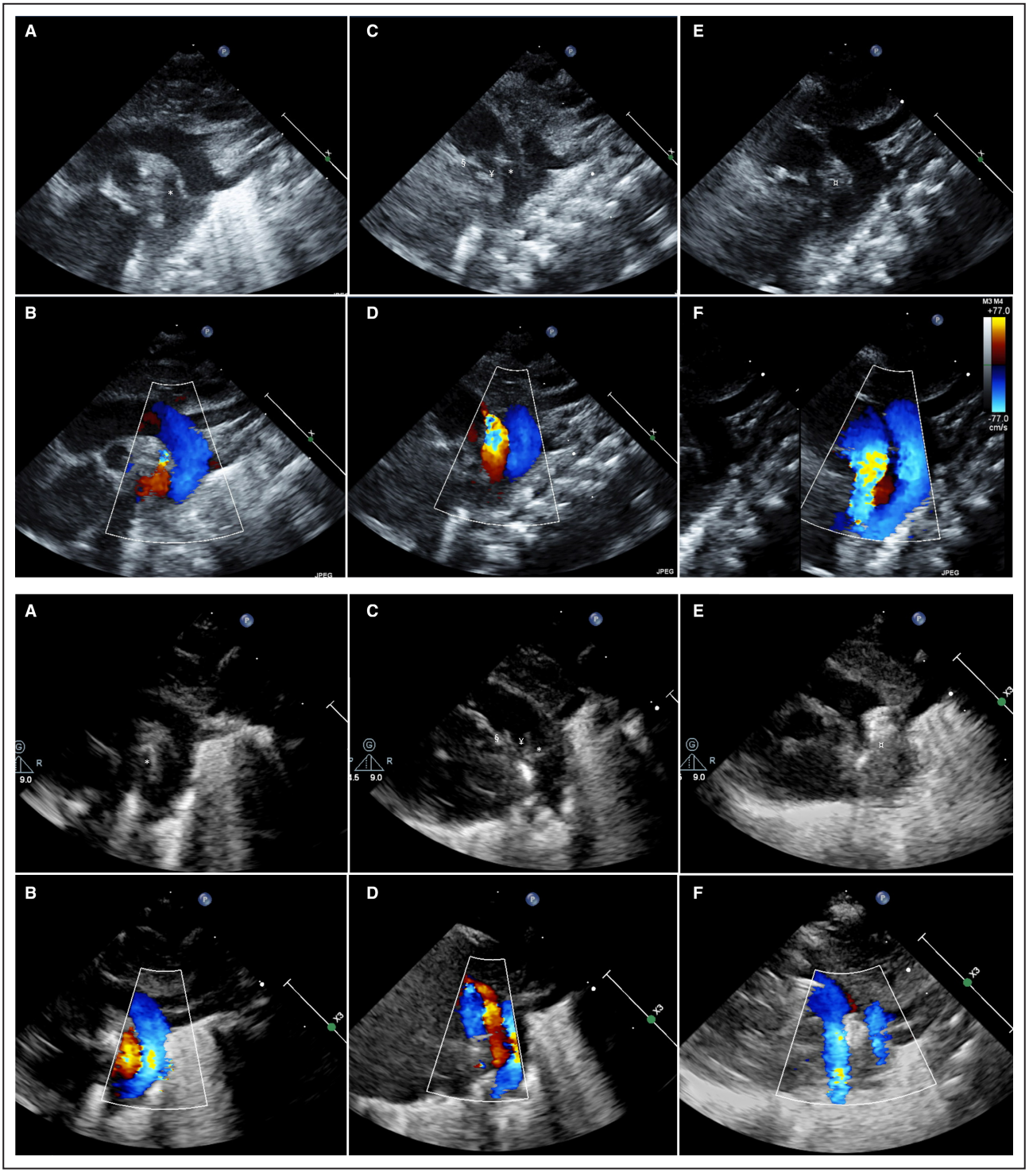

Figure 3. Comparison of echocardiographic images obtained during transcatheter patent ductus arteriosus (PDA) closure on conventional mechanical ventilation (CMV) and high-frequency jet ventilation (HFJV).
Top – Echocardiographic images obtained from a patient onCMV. (**A**) Two-dimensional arch view, PDA (*) takeoff seen from descending aorta. (**B**) With color, left (L) to right (R) shunting across the PDA is noted. (**C**) Two-dimensional 3-finger view showing PDA (*), descending aorta, left pulmonary artery (¥), and right pulmonary artery (§). (**D**) Three-finger view in color showing L to R shunting across the PDA with aliasing of flow toward the pulmonary end. (**E**) Two-dimensional arch view showing the device (¤) in good position. (**F**) Arch view in color showing no flow across the device. **Bottom** – Echocardiographic images obtained from a patient on HFJV. (**A**) Two-dimensional arch view, PDA (*) takeoff seen from descending aorta. (**B**) With color, left (L) to right (R) shunting across the PDA is noted. (**C**) Two-dimensional 3-finger view showing PDA (*), descending aorta, left pulmonary artery (¥) and right pulmonary artery (§). (**D**) Three-finger view in color showing L to R shunting across the PDA. (**E**) Two-dimensional arch view showing the device (¤) in good position. (**F**) Arch view in color showing no flow across the device.

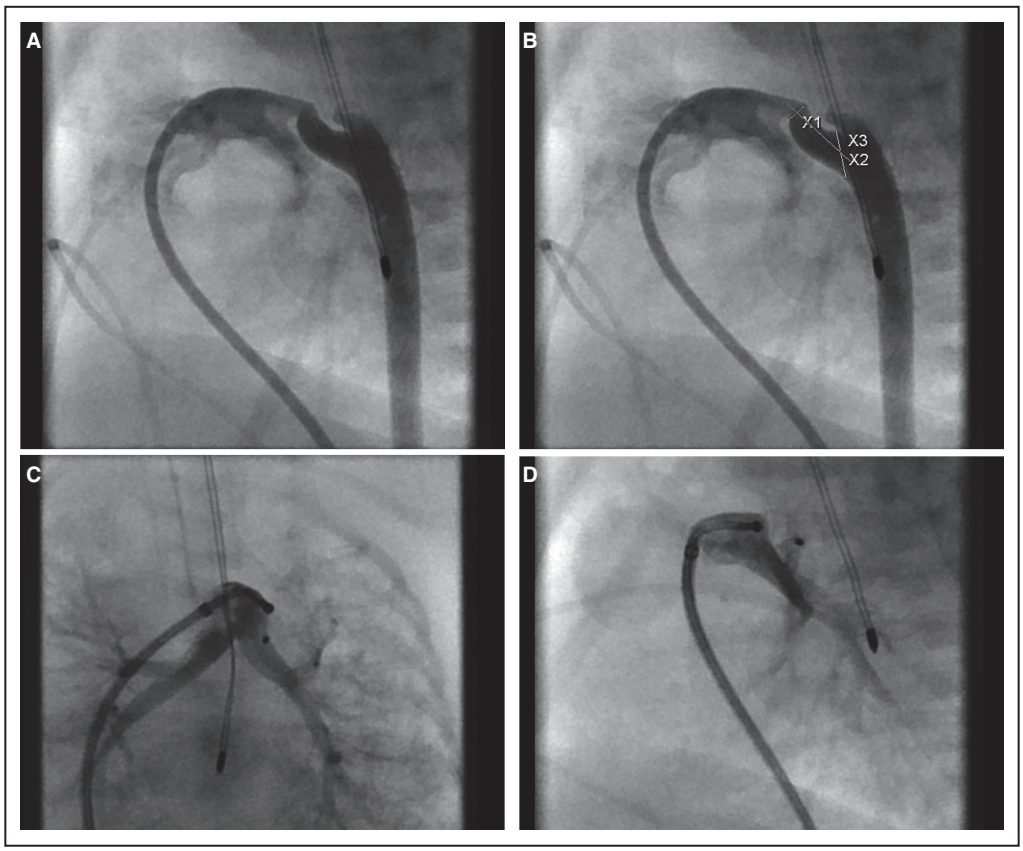

Figure 4. Angiograms obtained for a patient on high-frequency jet ventilation during transcatheter patent ductus arteriosus (PDA) closure.
Angiograms are from the same patient whose transthoracic echocardiography images are shown in Figure 3 Panel 2. (**A**) A catheter is positioned in the PDA, which is engaged from the pulmonary side. A lateral angiogram shows contrast filling a type E PDA and the descending aorta. (**B**) Measurements of the aortic ampulla, the narrowest portion of the PDA, and the length of the PDA are obtained. (**C**) After intraductal deployment of a 3–2 Piccolo device (Abbott Cardiovascular, Plymouth, MN), an anterior angiogram shows wide-open pulmonary arteries. (**D**) A lateral angiogram with contrast injected into the main pulmonary artery showing a closed PDA with no contrast into the descending aorta.

mitigation strategies used in our catheterization laboratory including the use of lower frame rates (7.5 frames/s) and collimation. In addition, our median fluoroscopy time of 4.5 minutes is shorter than comparable studies where reported mean fluoroscopy exposure duration was ranged from 4.99 to 12.9 minutes.[9] This could also be contributing to the lower radiation dose in our cohort.

Subgroup analysis, comparing the HFJV group to the CMV group, showed comparable demographic characteristics. Interestingly, fluoroscopy time was shorter in the HFJV group. The difference in fluoroscopy dose did not reach statistical significance, although the specific dose received by patients in the HFJV group was close to 50% lower. These observations could be explained, in part, by the stability of the patients on HFJV that is achieved through adhering to a standardized preprocedural protocol that is followed in our NICU as part of the medical optimization of these premature infants before transcatheter PDA closure (refer to Data S1 for said protocol). Another possible explanation for this observation is that use of HFJV allows for quicker procedures similar to the effect noted in adult studies assessing HFJV for ablation studies. There was no intergroup difference in average time off unit. Interestingly, the longest time off unit was a patient who was converted from HFJV to CMV a few days before the procedure and subsequently required adjustment of his ventilator in the catheterization laboratory because of suboptimal gases. The results of this study highlight the ability to perform transcatheter PDA closure on HFJV safely, obviating the need to transition patients to conventional ventilation before the PDA device closure and potentially avoiding such delays. These data are particularly reassuring considering the learning curve for transporting patients on HFJV, successful device placement, and using HFJV in the cardiac catheterization laboratory.

Limitations

Our study has several important limitations. First, the groups were not randomized, and the study was not designed to assess differences between the 2 modes of ventilation. As such, clinical effectiveness data between the HFJV and CMV groups should be cautiously interpreted. Nevertheless, side-by-side comparison provides some insight into the performance of transcatheter-based PDA closure on HFJV as compared with a more conventional method of ventilation and at least demonstrates noninferiority. Second, our sample size is small. Third, we were unable to extract any documentation of access attempts and or time needed to obtain access. Both metrics are of interest and are now part of our documentation for premature infants undergoing transcatheter PDA closure. Fourth, the translatability of our success to other centers with less experience in use of HFJV and without a targeted neonatal echocardiography–guided approach to left ventricular support, is unknown. Finally, the long-term impact of a periprocedural ventilation strategy on adverse respiratory outcomes such as bronchopulmonary dysplasia or chronic pulmonary hypertension was not evaluated. The comparable respiratory course after intervention would suggest no increased risk for infants managed with HFJV.

CONCLUSIONS

HFJV is the standard of care at our center. We sought to assess the feasibility, safety, and outcomes of transcatheter PDA closure for premature infants on HFJV. Our study provided novel insight and demonstrated safe and effective transcatheter PDA closure in infants on HFJV. Although preliminary, these data suggest that a first-intention HFJV approach is associated with excellent short-term outcomes, does not lead to secondary complications, and in some respects may be superior to conventional ventilation. Confirmatory evidence is best obtained through a well-designed randomized controlled trial on HFJV versus CMV.

ARTICLE INFORMATION

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Supplemental Material

Data S1

REFERENCES

1. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed*. 2007;92:F498–F502. doi: 10.1136/adc.2005.092734
2. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics*. 2020;146. doi: 10.1542/peds.2020-1209
3. Backes CH, Cheatham SL, Deyo GM, Leopold S, Ball MK, Smith CV, Garg V, Holzer RJ, Cheatham JP, Berman DP. Percutaneous patent ductus arteriosus (PDA) closure in very preterm infants: feasibility and complications. *J Am Heart Assoc*. 2016;5. doi: 10.1161/jaha.115.002923
4. Mitchell CC, Rivera BK, Cooper JN, Smith CV, Berman DP, Slaughter JL, Backes CH. Percutaneous closure of the patent ductus arteriosus: opportunities moving forward. *Congenit Heart Dis*. 2019;14:95–99. doi: 10.1111/chd.12704
5. Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention. *J Perinatol*. 2008;28:803–810. doi: 10.1038/jp.2008.101
6. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr*. 2007;150:229–234. 234.e221. doi: 10.1016/j.jpeds.2006.11.039
7. Gray DT, Fyler DC, Walker AM, Weinstein MC, Chalmers TC. Clinical outcomes and costs of transcatheter as compared with surgical closure of patent ductus arteriosus. The patient ductus arteriosus closure comparative study group. *N Engl J Med*. 1993;329:1517–1523. doi: 10.1056/nejm199311183292101
8. Sathanandam SK, Gutfinger D, O'Brien L, Forbes TJ, Gillespie MJ, Berman DP, Armstrong AK, Shahanavaz S, Jones TK, Morray BH, et al. Amplatzer Piccolo Occluder clinical trial for percutaneous closure of the patent ductus arteriosus in patients ≥700 grams. *Catheter Cardiovasc Interv*. 2020;96:1266–1276. doi: 10.1002/ccd.28973
9. Philip R, Tailor N, Johnson JN, Apalodimas L, Cunningham J, Hoy J, Waller Iii BR, Sathanandam S. Single-center experience of 100 consecutive percutaneous patent ductus arteriosus closures in infants ≤1000 grams. *Circ Cardiovasc Interv*. 2021;14:e010600. doi: 10.1161/circinterventions.121.010600
10. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med*. 2002;347:643–652. doi: 10.1056/NEJMoa012750
11. Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM, Kaneta MK, Davis JM. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics*. 1997;100:593–599. doi: 10.1542/peds.100.4.593
12. Noonan M, Turek JW, Dagle JM, McElroy SJ. Intraoperative high-frequency jet ventilation is equivalent to conventional ventilation during patent ductus arteriosus ligation. *World J Pediatr Congenit Heart Surg*. 2017;8:570–574. doi: 10.1177/2150135117717974
13. Watkins PL, Dagle JM, Bell EF, Colaizy TT. Outcomes at 18 to 22 months of corrected age for infants born at 22 to 25 weeks of gestation in a center practicing active management. *J Pediatr*. 2020;217:52–58. e51. doi: 10.1016/j.jpeds.2019.08.028
14. Rios DR, Martins FF, El-Khuffash A, Weisz DE, Giesinger RE, McNamara PJ. Early role of the atrial-level communication in premature infants with patent ductus arteriosus. *J Am Soc Echocardiogr*. 2021;34:423–432. e421. doi: 10.1016/j.echo.2020.11.008
15. McNamara PJ, Giesinger RE, Backes CH. Cardiac catheterisation for closure of patent ductus arteriosus. *Lancet Child Adolesc Health*. 2019;3:290–292. doi: 10.1016/s2352-4642(19)30088-4
16. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, Sekar K. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. *Pediatrics*. 2009;123:e138–e144. doi: 10.1542/peds.2008-2418

17. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. *J Pediatr Gastroenterol Nutr*. 2005;40:184–188. doi: 10.1097/00005176-200502000-00019
18. Weisz DE, Mirea L, Rosenberg E, Jang M, Ly L, Church PT, Kelly E, Kim SJ, Jain A, McNamara PJ, et al. Association of patent ductus arteriosus ligation with death or neurodevelopmental impairment among extremely preterm infants. *JAMA Pediatr*. 2017;171:443–449. doi: 10.1001/jamapediatrics.2016.5143
19. Sindelar R, Nakanishi H, Stanford AH, Colaizy TT, Klein JM. Respiratory management for extremely premature infants born at 22 to 23 weeks of gestation in proactive centers in Sweden, Japan, and USA. *Semin Perinatol*. 2021;151540: doi: 10.1016/j.semperi.2021.151540
20. Baspinar O, Sahin DA, Sulu A, Irdem A, Gokaslan G, Sivasli E, Kilinc M. Transcatheter closure of patent ductus arteriosus in under 6 kg and premature infants. *J Interv Cardiol*. 2015;28:180–189. doi: 10.1111/joic.12196
21. Morville P, Akhavi A. Transcatheter closure of hemodynamic significant patent ductus arteriosus in 32 premature infants by amplatzer ductal occluder additional size-ADOIIAS. *Catheter Cardiovasc Interv*. 2017;90:612–617. doi: 10.1002/ccd.27091
22. Zahn EM, Peck D, Phillips A, Nevin P, Basaker K, Simmons C, McRae ME, Early T, Garg R. Transcatheter closure of patent ductus arteriosus in extremely premature newborns: early results and midterm follow-up. *JACC Cardiovasc Interv*. 2016;9:2429–2437. doi: 10.1016/j.jcin.2016.09.019
23. Zahn EM, Nevin P, Simmons C, Garg R. A novel technique for transcatheter patent ductus arteriosus closure in extremely preterm infants using commercially available technology. *Catheter Cardiovasc Interv*. 2015;85:240–248. doi: 10.1002/ccd.25534
24. Babapoor-Farrokhran S, Alzubi J, Port Z, Khraisha O, Mainigi SK. Utility of high-frequency jet ventilation in atrial fibrillation ablation. *J Innov Card Rhythm Manag*. 2021;12:4590–4593. doi: 10.19102/icrm.2021.120708
25. Williams JL, Valencia V, Lugg D, Gray R, Hollis D, Toth JW, Benson R, Defrancesco-Loukas MA, Stevenson RT, Teiken PJ. High frequency jet ventilation during ablation of supraventricular and ventricular arrhythmias: efficacy, patient tolerance and safety. *J Innov Card Rhythm Manag*. 2011;2:7.
26. Aizer A, Qiu JK, Cheng AV, Wu PB, Barbhaiya CR, Jankelson L, Linton P, Bernstein SA, Park DS, Holmes DS, et al. Rapid pacing and high-frequency jet ventilation additively improve catheter stability during atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2020;31:1678–1686. doi: 10.1111/jce.14507
27. Sivasambu B, Hakim JB, Barodka V, Chrispin J, Berger RD, Ashikaga H, Ciuffo L, Tao S, Calkins H, Marine JE, et al. Initiation of a high-frequency jet ventilation strategy for catheter ablation for atrial fibrillation: safety and outcomes data. *JACC Clin Electrophysiol*. 2018;4:1519–1525. doi: 10.1016/j.jacep.2018.08.016
28. Goode JS Jr, Taylor RL, Buffington CW, Klain MM, Schwartzman D. High-frequency jet ventilation: utility in posterior left atrial catheter ablation. *Heart Rhythm*. 2006;3:13–19. doi: 10.1016/j.hrthm.2005.09.013
29. Wang JN, Lin YC, Hsieh ML, Wei YJ, Ju YT, Wu JM. Transcatheter closure of patent ductus arteriosus in premature infants with very low birth weight. *Front Pediatr*. 2020;8. doi: 10.3389/fped.2020.615919
30. Villemain O, Malekzadeh-Milani S, Sitefane F, Mostefa-Kara M, Boudjemline Y. Radiation exposure in transcatheter patent ductus arteriosus closure: time to tune? *Cardiol Young*. 2018;28:653–660. doi: 10.1017/s1047951117002839

SUPPLEMENTAL MATERIAL

Data S1.

Pre-procedural medical optimization: Pre-procedural care is standardized in the NICU. A chest radiograph is performed on the morning of the procedure to verify endotracheal tube placement as well as lung recruitment and central lines. Prior to transportation to the catheterization laboratory, the infant is started on a morphine infusion and given a dose of lorazepam (0.1 mcg/kg) for sedation and vecuronium (0.1 mcg/kg) for muscle relaxation. A blood gas (arterial or capillary) is obtained 15-30 minutes after such that ventilator adjustments can be made prior to mobilization. Once HFJV settings are optimized, the infant is transported to the catheterization lab accompanied by a multidisciplinary team including bedside nurse, respiratory therapist and an advanced neonatal-perinatal fellow. The infant is transported in an overbed, connected to the ventilator at all times. A member of the NICU medical team and the respiratory therapist remain for the duration of the PDA catheter procedure and interact closely with the anesthesia team to optimize ventilator settings, if necessary, throughout the case.

Periprocedural Stabilization: For patients identified as needing transcatheter PDA closure, a stress dose of hydrocortisone is given on the morning of the procedure (1-2 mg/kg intravenous load followed by 0.5 mg/kg every 6 hours for 24-72 hours). In addition, TnECHO is routinely performed within 24 hours prior to the procedure to confirm ductal status. Repeat TnECHO evaluation is performed 1 hour after PDA closure to evaluate risk for post-interventional left ventricular (LV) dysfunction due to altered loading conditions. Patients with LV output of less

than 180 ml/kg/min and/or features of abnormal LV systolic or diastolic performance are started on prophylactic milrinone infusion (0.33 mcg/kg/min for infants >1kg or 0.2 mcg/kg/min for infants <1kg). Dose is augmented in patients with progressive systemic hypertension and/or impaired oxygenation/ventilation. Infants with persistence evidence of low cardiac output or systemic hypotension despite milrinone infusion are started on either a dobutamine infusion (5-10 mcg/kg/min) or a low dose epinephrine infusion (0.01-0.03 mcg/kg/min). Infants that show evidence of diastolic hypotension are first given a fluid bolus, and then started on vasopressors if there is no improvement.

TnECHO evaluation: A Vivid E90 cardiovascular ultrasound system (GE Medical Systems, Milwaukee, Wisconsin, USA) is used to perform the TnECHO. The 12-MHz high-frequency phased-array transducer probe is used throughout the study. Standard two-dimensional, M-mode, color Doppler, pulse-wave Doppler, and continuous-wave Doppler images were obtained. All echocardiography analyses were performed using a dedicated workstation (EchoPAC version BT10; GE Medical Systems) by a single trained investigator, who was blinded to the clinical information, to minimize bias. Three consecutive cardiac cycles were evaluated and averaged for each measurement to be used in the study.