Title

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Hemodynamic changes with umbilical cord milking in non-vigorous newborns: A randomized cluster crossover trial

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Abstract

Objective: To assess the hemodynamic safety and efficacy of umbilical cord milking (UCM) compared with early cord clamping (ECC) in non-vigorous newborn infants enrolled in a large multicenter randomized cluster-crossover trial.

Study Design: Two-hundred-twenty-seven non-vigorous term/near-term infants who were enrolled in the parent UCM vs. ECC trial consented for this sub-study. An echocardiogram was performed at 12±6 hours of age by sonographers blinded to randomization. The primary outcome was left ventricular output (LVO). Pre-specified secondary outcomes included measured superior vena cava (SVC) flow, right ventricular output (RVO), peak systolic strain, and peak systolic velocity by tissue doppler of the RV lateral wall and the interventricular septum.

Results: Non-vigorous infants receiving UCM had increased hemodynamic echocardiographic parameters as measured by higher LVO (225±64 vs. 187±52 ml/kg/min, $p<.001$), RVO (284±88 vs. 222±96 ml/kg/min, $p<.001$) and SVC flow (100±36 vs. 86±40 ml/kg/min, $p<.001$) compared with the ECC group. Peak systolic strain was lower (−17±3 vs. −22±3%, $p<.001$) but there was no difference in peak tissue doppler (.06 (.05, .07) vs. .06 (.05, .08) m/s).

Conclusion(s): Umbilical cord milking increased cardiac output (as measured by LVO) compared with ECC in non-vigorous newborns. Overall increases in measures of cerebral and pulmonary blood flow (as measured by SVC and RVO flow respectively) may explain improved outcomes associated with UCM (less cardiorespiratory support at birth and fewer cases of moderate-to-severe HIE) among non-vigorous newborn infants.

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Keywords

delayed cord clamping; early cord clamping; hypoxic ischemic encephalopathy

Facilitating a placental transfusion at birth allows the infant to obtain more of its fetal-placental blood volume and has been shown to improve iron stores and long-term neurodevelopmental outcomes in healthy term infants.[1, 2] Until recently there was only one pilot study evaluating cord management in non-vigorous term/near term newborns at birth.[3] This lack of evidence has prevented national and international resuscitation committees from making recommendations for providing a placental transfusion in this high-risk population.[4-8] Umbilical cord milking (UCM) can potentially provide some placental transfusion quickly by increasing neonatal blood volume and consequently pulmonary and cerebral flow.

We recently reported results from our large multicenter trial (N=1730, 10 centers) comparing UCM to early cord clamping (ECC) in non-vigorous infants at 35-41$^{6/7}$ weeks gestation (Milking In Non-Vigorous Infants (MINVI_ trial – NCT03631940). Outcomes demonstrated that patients with UCM had less need for cardiorespiratory support at delivery, improved 1 minute Apgar score, higher hemoglobin levels, lower incidence of moderate-to-severe hypoxic-ischemic encephalopathy (HIE) and less need for therapeutic hypothermia. [9] In other studies, UCM has demonstrated increased hemoglobin and blood pressure in term infants. [10, 11] However, hemodynamic changes that contribute to increased blood pressure and decreased incidence of HIE in term non-vigorous infants who receive UCM at birth are not known.

With ECC, approximately 30% of the feto-placental blood volume is discarded with the placenta. In addition, it is possible that non-vigorous infants may experience additional hypovolemia due to blood transferred from the fetus back towards the placenta during the labor process (i.e., from an occult, nuchal or prolapsed cord that can compress umbilical veins but not arteries). (28,29) Linderkamp reported that infants with Apgar scores ≤5 had lower blood volumes than infants with an Apgar scores of >5. [12] We hypothesized that infants with UCM would have improved cardiac output and measures of left and right heart function by echocardiography during the first postnatal day compared with those infants who received ECC at birth.

Methods:

Non-vigorous infants enrolled in the parent MINVI trial at 2 of 10 MINVI centers (Sharp Mary Birch Hospital for Women & Newborns and Sharp Grossmont Hospital) were eligible for this optional ancillary echocardiogram study. Briefly, the MINVI trial was a pragmatic cluster-randomized crossover trial of infants between 35$^{0/7}$-41 $^{6/7}$ weeks.[9] Centers were randomized to UCM (milking the intact cord 4 times) or ECC (clamping <60 seconds after birth) for one year and then crossed over to the other arm for an additional year. Sharp Mary Birch (SMB) and Sharp Grossmont Hospital (SGH) were assigned to the UCM group in the first arm of the trial. In the first arm of the study the SMB site enrolled in the UCM group from January 2019 to July 2019 and the SGH site enrolled form January 2019 to December

2019. In the second arm of the study SMB enrolled from February 2020 to October 2020 and the SGH site enrolled from February 2020 to May 2021. Umbilical milking was performed by grasping the umbilical cord with the finger and thumb and milking it towards the infant allowing for placental refill without occlusion on the placental end and the maneuver was repeated. Computer generated randomization of sites was performed once IRB approval was obtained. This sub-study was approved at both Sharp Institutional Review Boards.

Inclusion criteria were that the infant was enrolled in the parent trial which included only infants who were non-vigorous at birth and born between 35-41$^{6/7}$ weeks gestation. Exclusion criteria were known major congenital or chromosomal anomalies of newborn, known cardiac defects other than small atrial septal defect, ventricular septal defect and patent ductus arteriosus, complete placental abruption/cutting through the placenta at time of delivery, monochorionic multiples, cord avulsion, presence of non-reducible nuchal cord, and perinatal providers unaware of the protocol. If the infant met the inclusion criteria and a parent consented, echocardiographic measurements were performed at 12 ± 6 hours of age by research sonographers blinded to infant randomization group.

The primary outcome was cardiac output as measured by left ventricular output (LVO, ml/kg/min) [13] Secondary outcomes included superior vena cava (SVC) flow (ml/kg/min), right ventricular output (RVO – ml/kg/min), left ventricular systolic strain using Speckle Tracking deformation technique on echocardiography, and peak systolic velocity by tissue doppler imaging in the interventricular septum and RV free wall.[14] Other exploratory outcomes included diastolic velocity, isovolemic contraction time, tricuspid annulus plane systolic excursion (TAPSE), and patent ductus arteriosus shunt (when present with diameter and direction of flow), and an estimation of pulmonary arterial pressure when a tricuspid regurgitant jet was present. Measurements were performed as previously reported.[34]

All images were acquired by two trained experienced cardiac research sonographers (NT, OK) using a 6S phased array transducer (GE E95 ultrasound machine, Madison, Wisconsin). They received prior training by the primary investigator as well as an assessment of inter and intra-observer variability, and they were blinded to the study.

All measurements were performed offline by a blinded second investigator (YS) at a later time using GE EchoPAC software and were entered into REDCap. The second investigator (YS) was not involved in the primary study and was not aware of the assignment of each hospital or dates of birth. The echocardiograms were all reviewed at the completion of both arms in random order to avoid any ascertainment bias.[15]

Statistical Analysis:

The sample size was based on LVO measurements in term and near term infants of 240 ml/kg/min with an SD of 33 ml/kg/min. [16, 17] A conservative sample size calculation to detect a 15% absolute increase in LVO showed that at least 140 subjects were required (70 subjects in each arm) for an 80% power and a p-value <0.05. We estimated at least 100 subjects in each arm would be eligible at the two sites for sufficient power and could account for patients with poor data quality or drop out (up to 30 percent). Data were collected and

managed using REDCap electronic data capture tool hosted at the University of California San Diego, ACTRI Biomedical Informatics Division and managed by the lead site.

We performed statistical analysis using SPSS Version 24 (Armonk, NY: IBM Corp). Data were verified for accurate data entry, formats, coding and missing observations. The largest and smallest values for each variable were examined for accuracy and plausibility. Variables were examined for variability, normality, frequency distribution, skewness and kurtosis. Data were subsequently evaluated using descriptive, univariable, and adjusted analyses. All significance tests were two-sided with a critical alpha level of 0.05. Comparison of demographic and neonatal data were made using logistic regression, chi square test or Fisher's Exact tests for dichotomous or categorical variables, Student's t tests for comparison of means for normally distributed continuous variables, and Mann-Whitney tests were used as a non-parametric test for variables failing to meet normal distribution requirements.

Linear regression was used to model the primary and secondary continuous outcomes by randomization group with UCM as the referent group as compared with ECC. Study site was included as an independent variable in the multivariable models to ascertain the relationship between study site and randomization assignment.

Results:

Of 448 eligible infants enrolled at the two participating centers, 227 had an echocardiogram performed from January 2019 through May 2021. Sixty-one infants from the SMB site and 45 babies from the SGH site had echocardiograms in the first arm of the study. Seventy-four infants from SMB and 47 infants from SGH had echocardiograms in the second arm of the study. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome are shown in Figure 1. All prespecified primary and secondary outcomes were adjusted by site. One infant in each group received the wrong treatment but was analyzed as intent to treat. Demographics and baseline characteristics are shown in Table 1. There were no significant differences in maternal characteristics between the two groups. Umbilical arterial cord pH was lower in the early cord clamping group. Infant sex distribution and birth weight were similar between the two groups. Echocardiography was performed at a mean of 15 hours after birth in both groups. The primary outcome of cardiac output (as measured by LVO) was increased in infants randomized to UCM (225 ± 64 vs 187 ± 52 ml/kg/min, $p<.001$). Components of LVO including left velocity time integral (15 ± 4.2 vs. 13.2 ±1.7 cm, $p=.016$) and aortic diameter (.72 ± .07 vs .76 ± .06) $p=0.003$) were higher in the UCM compared with the ECC group, whereas heart rate (118± 14 vs 116±12. p=0.64) was similar. Prespecified secondary outcomes (Table 2) for RVO and SVC flow were also higher in infants randomized to UCM vs ECC. A lower peak systolic strain was seen among infants assigned to UCM at birth compared with ECC, but peak systolic velocity by tissue doppler imaging in interventricular septum was similar.

In exploratory analyses (Table 3, available online), Tricuspid annular plane systolic excursion (TAPSE) was lower in the infants who had UCM, but within normal range.

The number of infants with low (<6 mm) TAPSE was not different (7 (7%) vs 8 (7%), p=0.99). Hemoglobin was also higher in infants receiving UCM compared with ECC. Other measures of diastolic cardiac function assessed by tissue doppler imaging were not different. Components of the tissue doppler and systolic strain measurements are in Appendix 1.

Discussion

We performed hemodynamic assessments in a large sample of infants who were non-vigorous at birth and randomized to two different cord management strategies, UCM vs. ECC. Although the parent trial of 1730 infants demonstrated short term benefits and safety for the cord milking strategy, it did not report hemodynamic measurements which could help explain differences in the reported outcomes. This hemodynamic sub-study demonstrates that UCM was associated with increased left and right ventricular outputs, increased systemic blood flow (as shown by SVC flow) and decreased strain (by peak longitudinal and circumferential strain).

There have been several trials evaluating the hemodynamics of cord management, but most have involved infants born preterm. The largest trial compared ECC to delayed cord clamping (DCC, 60 seconds) in 266 infants born preterm on the first postnatal day.[18] Measures of systemic blood flow (measured by SVC flow) were not different between the two groups despite an increase in hemoglobin (by 0.9 g/dL). However, these infants were not depressed or non-vigorous at birth. It is possible that hematologic benefit (increased hemoglobin likely due to higher blood volume) from DCC may not be associated with hemodynamic changes. In contrast, smaller studies of cord milking in infants born preterm have had mixed results with some demonstrating increases in systemic blood flow [19, 20] with others showing no significant differences. [21]

A randomized controlled trial of healthy term infants comparing UCM to ECC did not demonstrate a difference in SVC flow but found higher left atrial diameters and left atrium to aorta diastolic diameters. [22] Their data suggested that term infants may receive additional blood volume with UCM and the lack of changes in systemic blood flow may have been due to better neonatal adaptation seen in vigorous term infants. These results suggest that in healthy infants born at term and preterm, UCM is associated with increased blood volume but does not necessarily result in increased systemic blood flow.

Our study evaluated a population with potentially adverse adaptation at birth due to poor tone, color or breathing. Our hypothesis that UCM would improve transition in this population was substantiated by a higher 1-minute Apgar score, less need for cardiopulmonary interventions at birth, fewer cases of moderate to severe HIE, and less requirement for therapeutic hypothermia in the UCM group. We speculate that these benefits are multifactorial. Potential factors playing a role include increased blood volume[23] leading to increased cardiac output which was evidenced by our primary and several secondary outcomes. Other factors such as increased transfer of stem cells[24], pro-angiogenic and anti-apoptotic messengers, hormones and growth factors in the fetal-placenta blood received, along with correction of hypovolemia caused by selective obstruction of the umbilical vein,

and higher oxygen delivery to the tissues due to higher hemoglobin and blood flow may contribute to improvement in outcomes with UCM.[25]

In our study, although the flow measures (LVO, SVC, and RVO) were higher among infants randomized to UCM, other measures of cardiac systolic and diastolic function were conflicting. All average measurements (LVO, SVC, RVO, strain, and TAPSE) were within the normal range. Measures of LV systolic strain were slightly lower but measures of diastolic function using tissue doppler imaging in the interventricular septum were not different. In our exploratory analysis, there was a difference in the absolute TAPSE values between the two groups, but the incidence of abnormal values (<6 mm) was not different. Similarly, there was no difference in the peak systolic velocities in the RV free wall. These data suggest there was no difference in the systolic cardiac functions between the two groups. The differences in results may be due to the variable effects of volume loading the ventricles.

A limitation of our study is the ability to conduct a proper cluster analysis of a two-center trial which was conducted in the parent study. Both centers were randomized to the same sequence of the crossover design and our results were adjusted by site to compensate for this limitation. Although an individual patient randomization would have avoided this, it would have been difficult to do in the context of our research question. The groups at baseline were similar however there was a trend for increased need for therapeutic hypothermia and a lower arterial cord pH which may have contributed to lower cardiac function in infants randomized to early cord clamping.

There are potentially adverse effects associated with UCM. We have previously demonstrated that UCM in infants born at <28 weeks of gestation is associated with an increase in severe intraventricular hemorrhage likely due to the fragility of the germinal matrix in this age group.[26] Rapid changes in blood volume could potentially lead to fluctuations in blood pressure and cerebral blood flow leading to intraventricular hemorrhage and potentially worse neurological outcomes although prior studies on UCM in term infants do not report any harm.

In the setting of a mature term circulatory system with cerebral autoregulation, the risk of intraventricular hemorrhage or other harm is low. [26] In the setting of poor function and hypovolemia there should be an increase in systolic and diastolic function, however it is also possible that there may have been a degree of volume overload potentially decreasing measures of systolic function. Some neonates with perinatal depression and non-vigorous states may have associated hypovolemia and poor perfusion as ECC leaves about 30% of the term fetal-neonatal blood volume in the placenta. [27, 28] Severe hypovolemia could be due to a redistribution of placental blood during labor from a nuchal, occult or prolapsed cord followed by ECC. [29, 30] Milking the intact cord may restore some blood volume (nearly 15 to 18 mL/kg for term infants) [31] and reduce hypovolemia in these situations. [32] The restoration of some of the fetal-neonatal blood volume could have contributed to increased LVO, RVO and SVC flow in infants randomized to UCM. Alternatively, the increase RVO and LVO may be compensatory for lower RV (measured by TAPSE) and LV (measured by strain) function.

Concerns about cord milking from an animal model demonstrating fluctuations in blood flow with cord milking have been reported. [33] Although the basic laws of physiology apply to all mammals; the structure of the umbilical cord and placenta are very different. Lambs have two umbilical veins and two arteries. In addition, the lack of Wharton's jelly and having multiple placental cotyledons in an atonic uterus under general anesthesia differentiates a lamb model from human making it difficult to apply findings from animal models to clinical findings. Blank et al have elegantly shown that fluctuations with cord milking can alter carotid blood flow. [33] It has been shown that cord milking in infants born extremely preterm is associated with intraventricular hemorrhage probably due to a similar hemodynamic effect. [26] The lack of placental transfusion (net blood flow towards the neonate) with milking in lambs is controversial. Chandrasekharan et al[34] have shown that UCM with simultaneous ventilation results in neonatal blood volume to be 85.5±10% of fetoplacental volume. In contrast early cord clamping results in a neonatal blood volume of 65±14%. Umbilical cord milking without ventilation was associated with 72±10% neonatal blood volume. These results suggest that cord milking in lambs results in minimal "blood volume transfer" in the absence of respiration and that respirations (as in some babies in the MINVI trial) can facilitate placental transfusion. McAdams et al have shown that milking the umbilical cord four times can result in 48.5±19 ml of blood transfused from placenta with intact umbilical cords in humans. [23] Whereas animal studies provide mechanistic basis for many aspects of cord management, inherent physiological and anatomic differences and study design can lead to differences when comparing animal to clinical studies as outlined in a recent editorial. [35]

In a subset of non-vigorous infants, persistent poor perfusion may lead to decreased organ perfusion and ischemia resulting in HIE, [36] myocardial dysfunction, decreased contractility associated with myocardial and pulmonary hypoperfusion. [37, 38] Reduced left ventricular preload from low pulmonary venous return and low neonatal blood volume further exacerbates systemic hypoperfusion and may result in organ ischemia likely leading to multi-organ dysfunction and adverse outcomes commonly seen. [39] Additional blood volume from the placenta secondary to UCM increases hemoglobin, systemic and pulmonary blood flow as shown in our study and enhances oxygen delivery to the tissues. Considering the alternative of ECC, an intervention with no physiologic rationale, these hemodynamic data support the use of intact cord milking in near-term/term non-vigorous newborns.

In our study, intact umbilical cord milking increased cardiac output as measured by ventricular output compared with early cord clamping in non-vigorous newborns. The hemodynamic changes of UCM, at least partially, provide a mechanistic explanation for the positive outcomes seen in the parent MINVI trial demonstrating less cardiorespiratory interventions and less moderate to severe HIE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statements:

Data will be available after the primary follow-up paper is published. Individual participant data (including data dictionaries) will be available upon review by the study PI.

Abbreviations and Acronyms:

ECC	Early cord clamping
HIE	Hypoxic ischemic encephalopathy
LVO	Left ventricular output
RVO	Right ventricular output
SVC	Superior vena cava
TAPSE	Tricuspid annular plane systolic excursion
UCM	Umbilical cord milking
SMB	Sharp Mary Birch
SGH	Sharp Grossmont Hospital

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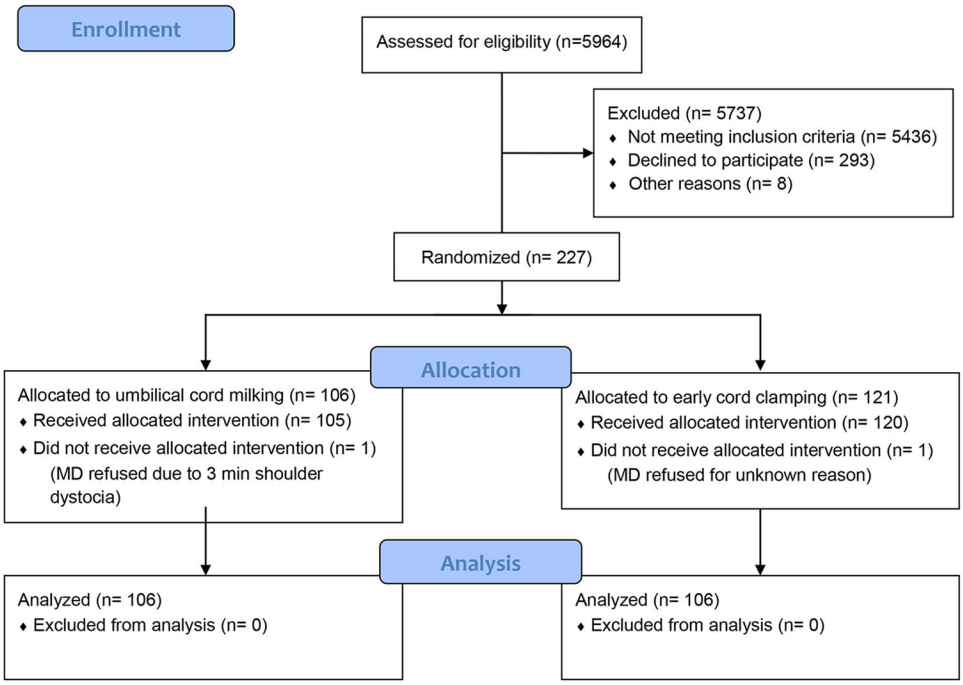

Figure 1.
CONSORT Diagram

Table 1.

Characteristics at Baseline

	*UCM	*ECC	*P*-value
Maternal Data	**N=106**	**N=121**	
Any diabetes	14 (13)	16 (13)	.99
Any hypertension	14 (13)	17 (14)	.85
Intrauterine inflammation/infection	19 (18)	27 (22)	.41
Group B Streptococcus positive	19 (18)	18 (15)	.17
Cesarean delivery	49 (46)	53 (44)	.71
General anesthesia	2 (2)	7 (6)	.13
†Multiple gestation	1 (1)	3 (2)	.38
§Rupture of membranes (hr.)	7 [2, 14]	6 [0, 14]	.18
Infant Data			
Female	45 (42)	50 (41)	.86
Weight at birth	3443 ± 543	3386 ± 584	.46
Gestational age	39.3 ± 1.4	39.2 ± 1.5	.11
‡Poor color	105 (99)	118 (98)	.38
‡Poor tone	104 (98)	117 (97)	.28
‡Poor respiratory effort	103 (97)	120 (99)	.25
Therapeutic hypothermia	5 (4.7)	17 (14)	.06
Volume expanders	20 (19)	30 (25)	.99
§Time of echo	13 [10, 17]	15 [11, 17]	.19
Cardiac inotropes	3 (3)	5 (4)	.99
Venous Cord gas pH	7.266 ± .095	7.234 ± .122	.06
Venous Cord gas BE	−6.60 ± 3.12	−7.31 ± 4.22	.20
Arterial Cord gas pH	7.173 ± .104	7.125 ± .140	.02
Arterial Cord gas BE	−8.74 ± 3.96	−9.77 ± 5.11	.18

Data are n (%), mean ± SD, or median [interquartile range].

*UCM – umbilical cord milking; ECC – early cord clamping

†Only data from one infant from each sets of multiples is represented in this data set

‡Evaluated in the first 15 seconds of life

§Mann-Whitney U test

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Table 2.

Pre-defined Primary and Secondary Outcomes

	UCM	ECC		Model with Site included		Standardized Co-efficient			
	N=106	N=121	*Unadjusted P*-value	F test	Adjusted P-value	Beta	t	P-value	95% CI for B
Primary Outcome									
Left ventricular output* (ml/Kg/min)	225 ± 64	187 ± 52	<.001	12.933	<.001	−.112	−1.756	.080	(−29.321, 1.689)
Secondary Outcomes									
Right ventricular output† (ml/Kg/min)	284 ± 88	222 ± 95	<.001	−9.102	<.001	−.046	−.724	.470	(−33.876, 15.671)
Superior vena cava flow‡ (ml/Kg/min)	100 ± 36	86 ± 40	.01	−18.389	<.001	−.231	−3.392	.001	(−29.081, −7.698)
Peak systolic strain§ (%)	−17 ± 3	−22 ± 3	<.001	−.004	<.001	.000	−.009	.993	(−.873, .866)
Peak systolic velocity‖ (meters/sec)	.06 ± .02	.07 ± .02	.31	−.003	.495	−.077	−1.069	.287	(−.007, .002)

Data are mean ± SD

UCM – umbilical cord milking

ECC – early cord clamping

Table 3

Exploratory Outcomes

	UCM	ECC	
	N=106	**N=121**	
Mean Blood Pressure at time of echocardiography (mmHg)	45 ± 7	46 ± 7	0.61
Hemoglobin (g/dL)	17.6 ± 2.1	16.5 ± 2.4	<.001
Tricuspid annular plane systolic excursion (mm)	9.04 ± 2.2	9.65 ± 1.7	0.023
Patent ductus arteriosus present (%)	88 (83)	110 (91)	0.08
Diameter of ductus arteriosus (cm)	0.19 ± .10	0.20 ± .10	0.57
Peak pulmonary artery pressure (mmHg)	27 ± 15	27 ± 14	0.77
Direction of ductal shunt	**N=87**	**N=108**	
All Left to Right	59 (68)	80 (74)	0.36
All Right to Left	0 (0)	1 (.9)	0.37
Bidirectional	28 (32)	27 (25)	0.29

Data are n (%), mean ±SD.