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Echocardiographic correlates of persistent pulmonary hypertension of the newborn☆,☆☆

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ABSTRACT

Aims: To compare echocardiographic (ECHO) measures of ventricular function and hemodynamics of infants with persistent pulmonary hypertension of the newborn (PPHN) and normal controls; and to examine their association with clinical outcomes in PPHN.
Design/subjects: We performed a retrospective review of ECHOs of mechanically ventilated infants (≥34 weeks gestational age) with PPHN. Infants with congenital heart disease were excluded. Controls had normal ECHOs within 1 week of age.
Outcomes: ECHOs measures included a) right (RVO) and left ventricular output (LVO) b) RV and LV myocardial performance index (MPI) c) right ventricular systolic to diastolic duration (S/D) ratio and d) eccentricity index in systole (EIs) and diastole (EId).
Results: Infants with PPHN (n = 117), 63% of whom were males, had mean (SD) GA and birth weights of 38.6 (1.9) weeks and 3.3 (0.65) kg respectively. LVO, RVO and EIs were significantly lower and heart rate, MPI and RV S/D ratio were significantly higher in infants with PPHN, compared to controls (n = 35). The mean RV S/D ratios were significantly higher in infants with PPHN who died or required ECMO (n = 61), compared to survivors without ECMO (n = 56). Increasing RV S/D ratio was independently associated with a reduction in survival without ECMO [0.21; 95% C.I. 0.06–0.74, p = 0.015]. RV S/D ratio > 1.3 had a sensitivity of 93 (95% C.I. 85–99) % for death or ECMO.
Conclusions: Elevated RV S/D ratio, a marker of global RV dysfunction, was associated with adverse outcomes in PPHN. Its routine measurement in this population may aid risk-identification and targeted interventions.

1. Introduction

The reported incidence of persistent pulmonary hypertension of the newborn (PPHN) is 1–2/1000 live births [1,2]. PPHN is associated with a 10% mortality rate, despite the use of inhaled nitric oxide (iNO) and extra-corporeal membrane oxygenation (ECMO) [2,3]. Reduced ventricular outputs have been reported in two-thirds of infants with PPHN and may be related to increased right ventricular (RV) afterload, altered left ventricular (LV) geometry or myocardial ischemia [4]. A comprehensive echocardiographic (ECHO) assessment is an integral element of the management of infants with PPHN. The purpose of ECHO is to exclude structural congenital heart disease and to objectively measure ventricular function and severity of pulmonary hypertension. A conventional ECHO, however, has limited ability to detect RV dysfunction and pulmonary hypertension in the absence of a tricuspid regurgitant jet. Newer Doppler ECHO parameters such as myocardial performance index (MPI) have been shown to correlate with clinical status in adults with idiopathic pulmonary artery hypertension [5]. Dyer and colleagues found a strong correlation (r = 0.94) between MPI and mean pulmonary artery pressures on cardiac catheterization and response to treatment among 12 children with pulmonary hypertension [6]. Others have demonstrated the utility of MPI among infants with congenital heart disease as a quantitative relatively load-independent measure of RV function [7]. Small studies in infants with pulmonary hypertension have found elevations in RV MPI and reductions in peak systolic isovolumic contraction velocity and systolic ejection velocity, compared to controls [8,9]. Alkon and colleagues found that the RV systolic to diastolic duration (S/D) ratio was significantly higher in 47 older children with pulmonary arterial hypertension, compared to controls [10]. We have previously shown that both MPI and RV S/D ratios are useful markers of pulmonary hypertension in neonates with congenital diaphragmatic hernia [11,12].

Abbreviations: ECHO, Echocardiogram; ECMO, extracorporeal membrane oxygenator; EIs, eccentricity index in systole; EId, eccentricity index in diastole; LVO, left ventricular output; MPI, myocardial performance index; PPHN, Persistent pulmonary hypertension of the newborn; RVO, right ventricular output; S/D, Ratio of systolic to diastolic durations.

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The objectives of the current study were to assess ECHO parameters of RV and LV function and hemodynamics of infants with PPHN, in comparison to normal controls, and to examine their association, if any, with clinical outcomes in PPHN.

2. Material and methods

This was a retrospective review of medical records and ECHOs performed for clinical indications. We included a convenience sample of late preterm and term (≥34 weeks gestational age) infants a) with PPHN, b) who were admitted to Children's Hospital of Michigan level IV Neonatal Intensive Care Unit (NICU) between January 1st, 2002 and September 30th, 2010, c) who underwent an ECHO within the first week of life and d) received mechanical ventilation. Infants with a congenital structural heart lesion, except patent foramen ovale and patent ductus arteriosus (PDA) and congenital diaphragmatic hernia were excluded. Eligible infants were identified using the electronic discharge database. All infants were outborn and referred to our level IV NICU for iNO or ECMO. The control group of infants was identified using the ECHO database and included neonates on whom an ECHO performed for a murmur within 1 week of age confirmed normal anatomy. Medical records were reviewed to obtain demographic data, clinical characteristics such as ventilator duration, need for iNO and ECMO and survival until discharge for infants with PPHN. The first ECHO of each patient was reviewed by a single reader (SA) to obtain indices of systolic, diastolic and global cardiac function. The following ECHO measurements were performed offline, using previously validated measurement techniques:

A) Systolic function:

1. *Cardiac output*: LV output (LVO) was calculated using the aortic diameter and velocity time integral (VTI) measured by pulse wave Doppler at the aortic valve annulus from parasternal long-axis at the end of systole and apical 5-chamber views, respectively and standard formula [13]. Similarly, RVO was calculated using the pulmonary valve annulus diameter and VTI at the pulmonary valve annulus from parasternal short-axis and subcostal views, respectively. VTI was measured using at least five consecutive cardiac cycles. The heart rate was measured from the beginning of one ejection cycle to the beginning of the next.
2. *Shortening fraction (SF)* was obtained on M-mode imaging as the ratio of the difference between the LV end-diastolic and end-systolic diameters to the LV end-diastolic diameter.

B) Global myocardial function:

1. *Myocardial Performance Index (MPI)*: RV and LV MPI were calculated by dividing the sum of isovolumic contraction and relaxation times by the ejection time, using the formula (A–B)/B, where A was the time span between the end of one mitral flow Doppler envelop to the beginning of the next envelop and B was the ejection time. An increase in MPI indicates impaired global myocardial function. MPI is independent of heart rate and blood pressure and is unaffected by angle insonation or the PDA [7,12].
2. *Ratio of systolic to diastolic duration (S/D)*: S/D was measured offline in triplicate from the best Doppler signal of tricuspid regurgitation (TR) from either apical 4-chamber view or parasternal short axis view. The systolic duration was calculated from the onset to the termination of TR and diastolic duration as the time between two jets of TR. Heart rate was calculated from R–R interval from beginning of one to the next TR jet. The measures were taken as an average of 3 consecutive cardiac cycles [11].

C) Pulmonary hypertension:

1. *RV systolic pressure (RVSP)* was estimated using continuous-wave Doppler from the apical four-chamber view, incorporating modified Bernoulli equation.
2. The *direction of shunt across the PDA* was recorded on a high parasternal ductal view and labeled as left to right, bidirectional or entirely right to left.
3. *Eccentricity index in systole (EIs) and diastole (EId)*: LV eccentricity index, a measure of the displacement of inter-ventricular septum, was derived from the para-sternal mid-papillary short-axis view at both end-systole and end-diastole, using Ryan's method [12,14].
4. *Ratio of tricuspid and mitral valve diameters*, measured in apical four chamber views in end diastole, was taken as a surrogate of RV size in relation to LV size.

At our center, mechanical ventilation is designed to maintain normal pH, normoxemia and normocarbia. iNO is initiated at an oxygenation index of 20 and ECMO is considered for refractory hypoxemia and/or hypotension. High frequency oscillator, surfactant, fluid resuscitation and inotropic (e.g. dopamine, dobutamine, epinephrine and milrinone in that order) support are used, as appropriate. The Human Investigation Committee of Wayne State University approved the study and waived parental consent.

2.1. Statistical analysis

Statistical analyses were conducted using SPSS software (version 20). Data were described as mean ± SD, median (range) and n (%) as appropriate. Bivariate comparisons of clinical and ECHO characteristics between groups (PPHN and controls; subgroups of PPHN) included chi square test and t tests. Binary regression was used to examine the association between ECHO variables and outcomes in infants with PPHN. The diagnostic accuracy of ECHO measures found to be significantly different on bivariate comparisons was further analyzed by calculating the area under the receiver operating characteristics (ROC) curve. Optimal cut-offs were derived and sensitivity, specificity and negative and positive predictive values with 95% confidence intervals (C.I.s) obtained. Significance was taken as a p value of <0.05.

3. Results

We identified 117 infants with PPHN who met eligibility criteria. The mean ± SD gestational age and birth weight were 38.6 ± 1.9 weeks and 3.3 ± 0.65 kg respectively and 74 (63%) of the infants were males. The mean ± SD birth weight of the term normal controls (N = 35), 17 (49%) of whom were males, was 3.1 ± 0.64 kg. Table 1 is a comparison of ECHO parameters of infants with PPHN (n = 117) and normal controls (n = 35). A Doppler interrogation of tricuspid regurgitant jet

Table 1
Comparison of characteristics between infants with PPHN and normal controls.

	PPHN group (n = 117)	Control group (n = 35)	P value
Age at ECHO (days)	1.1 ± 1	1.4 ± 1	0.087
Weight (kg)	3.3 ± 0.65	3.1 ± 0.64	0.075
Gender (male)	73 (63%)	17 (49%)	0.09
Heart rate (bpm)	156 ± 26	137 ± 17	0.0001
LVO (l/m^2/min)	2.5 ± 0.98	6.0 ± 1.6	0.0001
RVO (l/m^2/min)	4.0 ± 1.6	5.3 ± 1.8	0.0001
SF	38.5 ± 8.9	38.2 ± 6.5	0.80
LV MPI	0.48 ± 0.17	0.29 ± 0.06	0.0001
RV MPI	0.49 ± 0.41	0.25 ± 0.08	0.001
Right S	23.5 ± 4.5	23.8 ± 3.3	0.71
Right D	15.8 ± 3.8	21.9 ± 2.8	0.0001
RV S/D	1.5 ± 0.38 (n = 97)	1.09 ± 0.14	0.0001
RVSP (mm Hg)	49.5 ± 19.8 (n = 71)	25.8 ± 10.7 (n = 16)	0.0001
PDA	84 (72%)	12 (34%)	0.0001
EIs	0.7 ± 0.13	0.87 ± 0.16	0.0001
EId	0.9 ± 0.68	0.9 ± 0.08	0.83
Tricuspid:mitral diameter ratio	1.17 ± 0.15	1.10 ± 0.10	0.009