Progress in Pediatric Cardiology 48 (2018) 107–110

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Echocardiography derived pulmonary artery capacitance and right ventricular outflow velocity time integral on first day of life can predict survival in congenital diaphragmatic hernia

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ARTICLE INFO

Keywords:
Pulmonary artery capacitance
Pulmonary vascular resistance
Congenital diaphragmatic hernia
Extra corporeal membrane oxygenation
Right ventricular outflow tract velocity time integral

ABSTRACT

Correlation between right ventricle systolic pressure (derived from moderate/severe tricuspid regurgitation) and survival of congenital diaphragmatic hernia (CDH) infants was established. We hypothesize that other non-tricuspid valve regurgitation (TR) dependent Echo parameters can predict CDH mortality. Our retrospective study included 20 CDH infants from January 2008 to September 2015. Inclusion criteria included: all CDH patients admitted to our neonatal intensive care unit. Exclusion criteria were: hereditary malformation of air ways, congenital heart disease other than patent ductus arteriosus (PDA) and/or PFO (patent foramen ovale) or atrial septal defect (ASD), sepsis, genetic syndromes and high frequency ventilation usage. Relevant non-Echo data was collected. The following Echo parameters were evaluated: severity of TR, ratio between systolic and diastolic duration of right ventricle (RV), pulmonary artery capacitance (PAC), RV outflow tract velocity time integral (RVOT VTI), and others.

CDH survivors showed higher RVOT VTI (12.3 ± 3 ml vs 9 ± 3.1 ml), and higher PAC (0.3 ± 0,2 $ml^3 \times mm\ Hg^{-1}$ versus 0.18 ± 0.07 $m^3 \times mm\ Hg^{-1}$). Cronbach's alpha for intra-rater reliability was 0.82 for PAC and 0.98 for RVOT VTI and for inter-rater reliability was 0.74 and 0.89 consecutively. RVOT VTI of value > 10.5 ml and PAC of value > 0.24 $ml^3 \times mm\ Hg^{-1}$ differentiated CDH survivors with area under curve (AUC) 0.78($p = 0.02$) and AUC 0.89($p = 0.002$) consecutively with sensitivity and specificity for both > 70%. Proportional Hazard analysis showed PAC < 0.24 has a mortality risk ratio of 25.8 versus 4.36 for RVOT VTI < 10.5. First 24 h echo derived (PAC) and (RVOT VTI) can predict survivors in congenital diaphragmatic hernia patients.

Abbreviations used

CDH	congenital diaphragmatic hernia
PAC	pulmonary artery capacitance
PVR	pulmonary vascular resistance
RVOT VTI	right ventricular outflow velocity time integral
AT	acceleration time
RVET	right ventricular ejection time

1. Introduction

Congenital diaphragmatic hernia (CDH) occurs in around 2.7 per 100, 000 live born infants [1] and remains an often-lethal condition despite many advances in prenatal and neonatal care [2].

The congenital diaphragmatic hernia study group recently reported factors associated with survival in infants with CDH but this analysis did not include any echocardiographic features that predict their survival [2]. Despite this, echocardiography is the standard of care for the bedside non-invasive assessment of pulmonary vascular abnormalities and the functional status of the right heart.

Previous studies have shown that the ratio between systolic duration obtained from tricuspid regurgitation time (SD) to diastolic tricuspid inflow time (DD) of > 1.3 had a sensitivity of 92.8% and specificity of 61.5% to predict mortality in CDH [3–5]. The pulmonary to systemic pressure ratio (PSR) by echocardiography using quantifiable TR jet (moderate or severe) of 0.9 can predict surgical mortality in CDH infants with a sensitivity of 100% and specificity of 84% [6,7]. Unfortunately, reliable SD/DD ratio and reliable PSR depend upon the presence of easily quantifiable tricuspid regurgitation (moderate to

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https://doi.org/10.1016/j.ppedcard.2018.01.001
Received 28 February 2017; Received in revised form 23 August 2017; Accepted 3 January 2018
Available online 05 January 2018
1058-9813/

severe) to estimate pulmonary artery pressure.

Since moderate to severe tricuspid regurgitation is present only in 61% of neonatal patients with pulmonary hypertension secondary to bronchopulmonary dysplasia [8] with no similar study for CDH infants, a more robust battery of echocardiographic tools to estimate not only pulmonary pressure, but also the cardiopulmonary interaction are needed.

Based on this background information, we hypothesize that there may be other echo parameters that better reflect the total right ventricle–pulmonary vascular interaction in CDH patients and are not dependent solely on the TR jet. Perhaps, these echo parameters could prospectively predict survival in CDH patients.

2. Methods

After institutional review board approval, we reviewed the records of 28 consecutive congenital diaphragmatic hernia patients treated at our institution from January 2008 through December 2015. Inclusion criteria included: all congenital diaphragmatic hernia patients admitted to Virginia Commonwealth University neonatal intensive care unit. Exclusion criteria were: genetic syndrome (e.g. Down syndrome), hereditary malformation of upper or lower air way disease, pulmonary vein stenosis, aorto pulmonary collaterals and congenital heart disease other than PDA and/or PFO (ASD) or inadequate echo data. Also, we excluded neonates with meconium aspiration, perinatal hypoxia, hypothermia, hypercarbia, sepsis or high frequency ventilated neonates due to its known effect on pulmonary vascular resistance (PVR) and PAC [9].

Non echocardiographic data collection included the following demographic data: gestational age, sex, birth weight, and 5 min Apgar score, prenatal versus postnatal diagnosis, hernia sidedness, liver position, ECMO duration, Score of Neonatal Acute Physiology (SNAPII) score at 24 h [10], repair (direct versus patch) and mortality.

We evaluated the following echocardiographic parameters that were collected in the first 24 h of life (Table 1 for methodological details). This data included the following standardized echocardiographic measurements: right ventricular systolic pressure (RVSP) calculated application of Bernoulli's equation to the tricuspid regurgitation peak velocity without using agitated saline, pulmonary diastolic pressure (PDP) estimate [11], PAC [12], TR jet derived PVR [13]. Also, we collected: PVR estimation using pre ejection time [14], (SD/DD) [5], pulmonary artery acceleration time (AT), deceleration index (DI), and the ratio between AT and right ventricular ejection time RVET(AT/RVET) [11]. Finally, pulsed wave derived Tei index, right ventricle outflow tract velocity tissue integral, and eccentricity index of RV [11] were also included. Measurements included for each patient was the average from three cycles. MN only collected all already measured data (severity of tricuspid regurgitation and pulmonary systolic pressure). Both MN and ZG calculated other nine parameters as shown in Table 1 blinded from each other. Also, MN and ZG were blinded for CDH patients' outcome. Of note, none of the CDH infants received inhaled Nitric Oxide before our first echo.

SPSS 22.0 was used to calculate mean/SD or percentages and statistical significance for collected data between survival and non-survival using Mann Whitney *U* test (nonparametric data).

Significant values were analyzed using receiver-operating curve (ROC) to calculate potential cut off values for statistically significant parameters followed by calculation of sensitivity, and specificity. Cronbach's alpha was used to calculate intra-rater and inter-rater reliability for pulmonary artery capacitance. Also, Kaplan Meier survival factors analysis was done for significant echo parameters.

3. Results

We reviewed all 28 CDH infants presenting over the 7-year period. Eight infants were excluded due to meconium aspiration ($n = 2$), perinatal hypoxia (n = 2), positive for group B streptococci ($n = 20$, hypothermia ($n = 1$) and inadequate echo data (n = 1). The remaining 20 patients represent the study group.

Frequency of liver herniation ($p = 0.02$), ECMO duration ($p = 0.003$) and type of repair ($p = 0.0001$) differentiated survivors from non-survivors in CDH patients. While, gestational age ($p = 0.05$), gender ($p = 0.6$), birth weight ($p = 0.07$), five minute Apgar ($p = 0.1$), timing of diagnosis ($p = 0.2$), SNAPII score (p = 0.1) were unable to make this differentiation in CDH infants. All non-echocardiographic parameters were summarized in Table 2.

CDH survivors showed higher RVOT VTI (12.3 ± 3 ml vs 9 ± 3.1 ml, $p = 0.02$)), and higher PAC (0.3 ± 0,2 $ml^3 \times mm\ Hg^{-1}$ versus 0.18 ± 0.07 $ml^3 \times mm\ Hg^{-1}$, $p = 0.002$). Other echocardiographic parameters were unable to differentiate survivors from non survivors; severity of tricuspid regurgitation ($p = 0.7$), systolic duration (p = 0.7) diastolic durations ($p = 0.2$), SD/DD ratio ($p = 0.4$), PSP

Table 1
Summary of echocardiographic techniques and windows.

Parameters	Technique	Echocardiographic window
Pulmonary systolic pressure (PSP)	Bernoulli equation of tricuspid regurgitation peak velocity plus right atrial "V" wave.	Apical 4 chamber [11]
Systolic duration to diastolic duration (SD: DD)	Ratio between systolic duration of tricuspid regurgitation to diastolic tricuspid inflow	Apical 4 chamber [5]
Pulmonary diastolic pressure (PDP)	PDP = 0.49 X systolic pulmonary pressure Or pulmonary incompetence end diastolic pressure(if there is PI)	Short axis parasternal [11]
Pulmonary arterial capacitance (PAC)	PAC = RV stroke volume/PSP-PADP RV stroke volume = (PA annulus diameter in cm/2)^2 × RVOT VTI	Short axis parasternal view [12]
Right ventricular outflow velocity time integral (RVOT VTI)	Tracing pulsed Doppler of right ventricular outflow tract	Subcostal right anterior oblique view or short axis basal view [11]
Pulmonary vascular resistance using TR (PVR-TR derived)	Algorithm derived from result of ratio between tricuspid regurgitation velocities to RVOT VTI.	Short axis parasternal view [13]
Pulmonary vascular resistance without TR (PVR-non TR)	PVR equals $-0.156 + 1.154 * [(PEP/ACT)/TT]$ PEP: pre ejection period ACT: acceleration time TT: total systolic time	Pulsed Doppler of pulmonary flow at short axis parasternal view [14]
Pulmonary artery flow intervals	AT: acceleration time DI: deceleration index ET: ejection time	Pulsed Doppler of pulmonary flow at short axis parasternal view [11]
Eccentricity index	Ratio of the length of two axes; one axis is parallel to interventricular septum and one was perpendicular to the ventricular septum	Parasternal short-axis (papillary muscle level) [11]
Tei index	(Systolic duration -pulmonary blood flow)/systolic duration	Combined apical 4 chambers and short axis parasternal [11]