Noninvasive Assessment of the Right and Left Ventricular Function in Neonates with Congenital Diaphragmatic Hernia with Persistent Pulmonary Hypertension Before and After Surgical Repair

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ABSTRACT

Objective: To measure right and left ventricular function in neonates with congenital diaphragmatic hernia (CDH) and persistent pulmonary hypertension of the newborn (PPHN) before and after surgical repair.

Methods: Ten newborns with CDH and PPHN before and after surgical repair and 24 normal newborns underwent Doppler echocardiographic measurements of the systolic time intervals (STI) and the index of myocardial performance (IMP) or Tei Index to assess pulmonary hypertension and ventricular function, respectively.

Results: In newborns with CDH and PPHN before surgical repair, STI pre-ejection time/ejection time ratio and pre-ejection time/acceleration time ratio (0.39 ± 0.19 and 1.22 ± 0.6) were significantly prolonged when compared to newborns with CDH and PPHN after surgical repair (0.21 ± 0.05 and 0.80 ± 0.2) and normal newborns (0.20 ± 0.04 and 0.59 ± 0.2), respectively (all $p < 0.001$). Left IMP and right IMP were also significantly prolonged in newborns with CDH and PPHN before surgery (0.38 ± 0.16 and 0.53 ± 0.25) when compared to newborns with CDH and PPHN after surgery (0.30 ± 0.07 and 0.28 ± 0.13) and normal newborns (0.26 ± 0.09 and 0.20 ± 0.10), respectively ($p < 0.05$, left IMP) and ($p < 0.001$, right IMP).

Conclusions: Significant pulmonary hypertension and abnormal left and right ventricular function were found in newborns with CDH and PPHN before surgical repair when compared to the newborns with CDH and PPHN after surgical repair and normal newborns. The STI and the IMP or Tei index can accurately estimate the consequences of pulmonary hypertension and left and right ventricular function in neonates with CDH and PPHN, which may affect management in these critically ill neonates.

Key Words: Congenital diaphragmatic hernia, persistent pulmonary hypertension, neonate, ventricular function, systolic time intervals, index of myocardial performance.

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INTRODUCTION

Cardiovascular complications are a major cause of morbidity and mortality in newborns with congenital diaphragmatic hernia (CDH) and persistent pulmonary hypertension of the newborn (PPHN). Therefore, accurate assessment of the degree of pulmonary hypertension and right and left ventricular function in newborns with CDH and PPHN is important in the initial evaluation of these patients, aiding in critical therapeutic decisions such as the need of inotropic support, nitric oxide therapy and/or Extracorporeal Membrane Oxygenation (ECMO) support, as well as determining surgical timing (1) and directing further follow-up. Echocardiography has been used to accurately estimate the degree of pulmonary hypertension and to assess left ventricular function in newborns with PPHN and predict outcome in newborns with PPHN secondary to CDH and other causes (1-5).

A relatively new index that combines systolic and diastolic indices (index of myocardial performance or IMP, "Tei index") has been used to assess both right and left ventricular function and to determine clinical status and predict prognosis in patients with primary pulmonary hypertension, atrial septal defects, Ebstein's anomaly, dilated cardiomyopathy, and hypertrophic cardiomyopathy (6-11). We have recently reported that it predicts episodes of rejection in heart transplant recipients (12). IMP is a Doppler echocardiographic method that is independent of geometric assumptions and has been used to evaluate the right and left ventricular function in patients with primary pulmonary hypertension or atrial septal defects where the right and left ventricular geometry are altered by right ventricular pressure or volume overload (13). These findings are also seen in patients with CDH and PPHN, due to right ventricular pressure overload where the interventricular septum is displaced towards the left ventricle. Depending on the side of CDH, changes in the left and right ventricular geometry can occur. Therefore, the IMP may be appropriate to evaluate patients with CDH and PPHN.

To our knowledge, however, noninvasive evaluation of right and left ventricular function has never been reported in newborns with CDH and PPHN. Therefore, the purpose of this study was to utilize the Tei index, a Doppler derived IMP combining systolic and diastolic ventricular function, before and after surgical repair, to determine right and left ventricular function in newborns with CDH and PPHN.

METHODS

Study Population

The study population consisted of 10 newborns diagnosed with CDH and PPHN and 24 normal newborns. There were 8 patients with left CDH and 2 with right CDH. Six of these patients with CDH and PPHN required ECMO. All of the neonates with CDH received mechanical ventilation, inotropic support and nitric oxide therapy. Neonates were included if they met the following criteria: absence of congenital heart disease, major congenital malformations and/or chromosomal abnormalities. The Institutional Review Board approved the study protocol.

As per study protocol, no extra sedation was given solely for the purpose of conducting this study. Standard transthoracic echocardiography was performed in normal newborns and newborns with CDH and PPHN within the first 48 hours of life. Subsequently the newborns with CDH and PPHN underwent a repeat transthoracic echocardiogram after surgical repair. None of the echocardiographic studies were done during ECMO support.

Doppler Echocardiographic Examination

Complete two-dimensional echocardiography, pulsed-wave (PW) Doppler, continuous wave (CW) and color Doppler echocardiographic studies were performed with a Hewlett Packard Sonos 2000 and 5500 and Acuson 128XP with simultaneous electrocardiographic recording. Standard two-dimensional views were performed to assess intracardiac anatomy and the great vessels. The presence and size of a patent ductus arteriosus and patent foramen ovale were evaluated by two-dimensional echocardiography and color Doppler echocardiography. Doppler tracing was done at a paper speed of 50 or 100mm/sec and recorded on a 3/4 inch videotape.

PPHN was diagnosed echocardiographically by increased right sided pressures estimated by measuring the tricuspid regurgitation (TR) jet with CW Doppler from either the parasternal short axis view and/or the apical 4-chamber view, and right ventricular systolic pressure (RVSP) was calculated by the Bernoulli equation. In addition, evidence of right to left shunting by color Doppler across the patent ductus arteriosus and/or patent foramen ovale and right systolic time intervals (STI) were obtained utilizing PW Doppler at the level of the pulmonary valve.

The right STI were obtained. Pre-ejection time (PEP) was measured from the onset of the QRS tracing to the onset of the right ventricular ejection time. Ejection time (ET) was measured as the duration of the right ventricular ejection Doppler from the opening to the closure of the pulmonary valve. Acceleration time (AT) was determined from the onset of the Doppler right ventricular ET to the peak velocity of flow and deceleration time (DT) from the peak velocity of flow to the cessation of the right ventricular ET, then ratios were obtained dividing PEP by ET and PEP by AT.

The left ventricular IMP or Tei index was obtained by positioning at the apex to obtain apical 4- and 5-chamber views, then PW Doppler of the mitral valve inflow at the tips of the leaflets and PW Doppler of the aortic outflow at the level of aortic valve were performed. The right ventricular IMP or Tei index was obtained by positioning the transducer in the parasternal short axis view and obtaining PW Doppler of the tricuspid valve inflow at the tips of the leaflets and PW Doppler of the pulmonary outflow at the level of the pulmonary valve. The left ventricular cardiac output (Qs) was obtained from the continuity equation by measuring the left ventricular outflow tract from the parasternal long axis view and obtaining the Doppler mean velocity of the aorta from the apical 5-chamber view. The heart rate was taken from the cardiac monitor or from the patient's echocardiogram. The right ventricular cardiac output (Qp) was obtained by measuring the pulmonary valve diameter from the parasternal long axis or short axis view; the Doppler mean velocity was obtained from the parasternal short axis view, along with the heart rate determination. The ratio between Qp and Qs was also obtained in each group.

Measurements of right STI, as well as right and left ventricular IMP and Qp and Qs, were calculated using an off-line commercial digitizing system (TomTec Imaging Systems, Munich, Germany), and the average of three measurements was obtained. Simultaneous systemic arterial blood pressure was measured from the umbilical arterial catheter. To determine the left and right IMP, Doppler time intervals were obtained as follows: interval a was between the cessation of the A wave and the onset of the next E wave of the mitral and tricuspid valve inflow. The interval b or ventricular ET was the duration of the outflow Doppler velocity from the opening to the closure of the aortic and pulmonary

valves. The interval c was measured from the tallest part of the R wave in the electrocardiogram tracing to the onset of the next E wave of the mitral and tricuspid valve inflow. The interval d was measured from the tallest part of the R wave in the electrocardiogram tracing to the end of the ventricular ejection time of the aortic and pulmonary valves. The isovolumic relaxation time (IRT) was the difference between the interval c and interval d (IRT = c-d), and the isovolumic contraction time (ICT) was obtained by subtracting the interval b and the IRT from the interval a (ICT= [a-b]- IRT). The IMP or Tei index was determined by the following formula: (ICT+IRT)/ET or (a-b)/b (Figure) (14).

Statistical Analysis

Continuous data are expressed as mean ± SD. Analysis of variance and the Student-Newman-Keuls multiple range test were used to compare the differences among the three groups. Linear regression analysis was used to correlate the right and left ventricular IMP with the heart rate. Values were considered significantly different at $p< 0.05$.

RESULTS

Significant differences in the Apgar scores and heart rate were noted. Statistically significant differences were also found in gestational age and length between newborns with CDH and PPHN and normal newborns (although not clinically significant), and birth weight was similar in both groups (Table 1).

Tricuspid insufficiency was not seen in most of the normal newborns; therefore the RVSP was not calculated in this group of patients (Table 2). In the group of newborns with CDH and PPHN before surgical repair, the mean RVSP was elevated and the mean RVSP/systolic arterial blood pressure ratio was found to be close to 1, indicating systemic levels of pulmonary hypertension. The RVSP fell by 30% after surgical repair but the change was not statistically significant. AT, ET ($p<0.001$) and DT ($p<0.05$) were found to be significantly shortened in newborns with CDH and PPHN before and after surgical repair when compared to the normal newborns. Prior to surgical repair, PEP and the ratios PEP/AT and PEP/ET were significantly prolonged ($p<0.05$) and ($p<0.001$) respectively, in the newborns with CDH and PPHN. These values fell significantly following surgical repair and were then statistically similar to values in normal newborns, suggesting marked improvement in the severity of pulmonary hypertension.

A summary of the Doppler measurements of ventricular function are demonstrated in Table 3. The LV IRT and LV ICT were statistically similar among the three groups, but the LV Tei index was significantly greater in newborns with CDH and PPHN before surgical repair compared with that in normal newborns ($p<0.05$). Although, the left ventricular ET was not analyzed, the increased LV Tei index suggested that shortening of the ejection time might have been the factor affecting the LV Tei index in newborns with CDH and PPHN before surgical repair.

The RV IRT was prolonged in newborns with CDH and PPHN before surgical repair compared with that in normal newborns ($p<0.05$). The RV ICT was significantly prolonged in newborns with CDH and PPHN before surgical repair ($p<0.05$), but the values fell

Table 1. Clinical characteristics of the study population

	CDH and PPHN (n=10)	Normal (n=24)
Gestational age (weeks)	37.2 ± 1.7	38.6 ± 1.5*
Apgar 1'	4 ± 2	8 ± 1**
Apgar 5'	6 ± 2	9 ± 1**
Weight (grams)	3045 ± 418	3428 ± 638
Length (centimeters)	47 ± 2	50 ± 2*
Heart rate (beats per minute)	145 ± 24	123 ± 9**

*p<0.05; **p<0.001
CDH, congenital diaphragmatic hernia
PPHN, persistent pulmonary hypertension of the newborn

Table 2. Assessment of pulmonary hypertension

	Preoperative CDH and PPHN (n=10)	Postoperative CDH and PPHN (n=10)	Normal NB (n=24)
RVSP (mmHg)	54 ± 16	38 ± 27	---
AT (msec)	57 ± 19	54 ± 13	83 ± 16**
DT (msec)	117 ± 28	131 ± 33	160 ± 30*
ET (msec)	167 ± 32	185 ± 15	223 ± 17**
PEP (msec)	62 ± 24 †	40 ± 7	47 ± 9
PEP/AT	1.22 ± 0.6*†	0.80 ± 0.2	0.59 ± 0.2
PEP/ET	0.39 ± 0.19*†	0.21 ± 0.05	0.20 ± 0.04

*p<0.05 compared with preoperative and postoperative CDH
**p<0.001 compared with preoperative and postoperative CDH
†p<0.05 compared with postoperative CDH and Normal NB
*†p<0.001 compared with postoperative CDH and Normal NB
CDH, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn; NB, newborn; RSVP, right ventricular systolic pressure; AT, acceleration time; DT, deceleration time; ET, ejection time; PEP, pre-ejection time

Table 3. Doppler measurements of ventricular function

	Preoperative CDH and PPHN (n=10)	Postoperative CDH and PPHN (n=10)	Normal NB (n=24)
LV IRT (msec)	38 ± 17	33 ± 11	40 ± 12
LV ICT (msec)	22 ± 12	20 ± 14	14 ± 11
LV Tei index	0.38 ± 0.16*	0.30 ± 0.07	0.26 ± 0.09
RV IRT (msec)	51 ± 18*	43 ± 18	33 ± 17
RV ICT (msec)	34 ± 21†	12 ± 11	14 ± 10
RV Tei index	0.53 ± 0.25*†	0.28 ± 0.13	0.20 ± 0.10
Qp (l/min)	2.7 ± 1.0	5.0 ± 1.5‡	3.0 ± 0.7
Qs (l/min)	2.0 ± 1.2	4.0 ± 1.9‡	2.4 ± 0.5
Qp/Qs	1.4 ± 0.5	1.3 ± 0.4	1.2 ± 0.2

*p<0.05 compared with normal newborns
†p<0.05 compared with postoperative CDH and normal newborns
*†p<0.001 compared with postoperative CDH and normal newborns
‡p<0.01 compared with preoperative CDH and normal newborns
CDH, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn; NB, newborn; LV, left ventricle; RV, right ventricle; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; Qp, right ventricular cardiac output; Qs, left ventricular cardiac output.

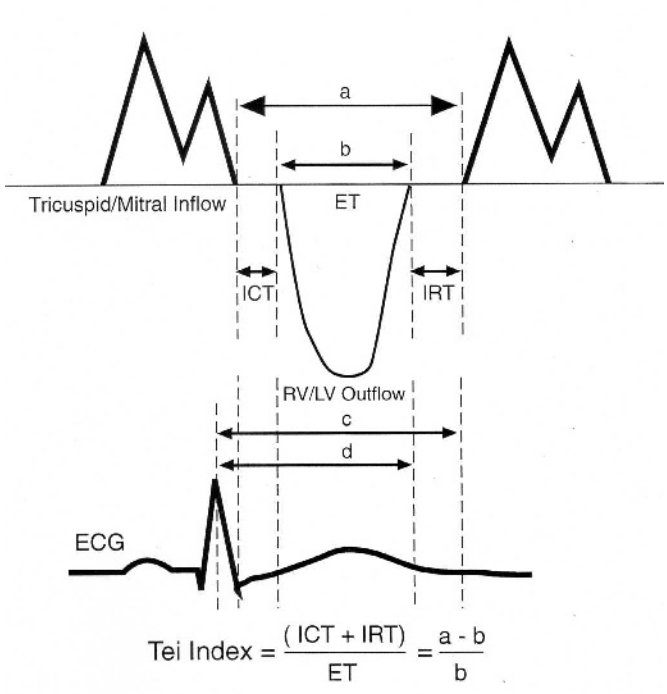

Figure. The right and left Tei index or IMP were obtained as follows: Interval a was between the cessation of the A wave and the onset of the next E wave of the tricuspid or mitral valve inflow. The interval b or ventricular ET was the duration of the RV or LV outflow. The interval c was measured from the tallest part of the R wave in the electrocardiogram tracing to the onset of the next E wave of the tricuspid or mitral valve inflow. The interval d was measured from the tallest part of the R wave in the electrocardiogram tracing to the end of the ventricular ejection time of the RV or LV outflow. The isovolumic relaxation time (IRT) was the difference between the interval c and interval d (IRT =c-d), and the isovolumic contraction time (ICT) was obtained by subtracting the interval b and the IRT from the interval a (ICT= [a-b]- IRT). The IMP or Tei index was determined by the following formula: (ICT+IRT)/ET or (a-b)/b.

significantly following surgical repair and were then statistically similar to values in normal newborns. The RV Tei index was also significantly higher in newborns with CDH and PPHN before surgical repair, and these values also fell significantly after surgical repair to levels that were statistically similar to normal newborns.

Right and left ventricular cardiac outputs and Qp/Qs ratio were statistically similar between the newborns with CDH and PPHN before surgical repair and the normal newborns. After surgical repair, the Qp and Qs increased significantly compared to the other two groups (p<0.001), but the Qp/Qs ratio remained unchanged. There was no significant correlation between the heart rate and either the RV Tei index (p= 0.91) or the LV Tei index (p=0.44).

DISCUSSION

Using Doppler echocardiography and a relatively new index of myocardial function (Tei index or IMP), we found abnormalities of both left and right ventricular function along with severe pulmonary hypertension in newborns with CDH and PPHN which dramatically improved, and for the most part normalized, following successful surgical repair of these newborns.

Infants with CDH are challenging to manage and often have other associated anomalies. In a series of 48 patients with CDH, cardiac anomalies were present in 11 of 48 (23%) and mortality of these patients with cardiovascular abnormalities was 73% versus 27% in those without cardiac abnormalities (15). In another series of 166 high risk patients with CDH (symptomatic in the first 6 hours of life), 63% had cardiac anomalies, excluding patent ductus arteriosus and patent foramen ovale, and none survived (16). Left ventricular hypoplasia had been documented by Siebert et al. (17) by weighing hearts of infants with left CDH at autopsy and by Schwartz et al. (18) using echocardiographic estimates of left ventricular mass. Patients with left CDH had a significantly lower indexed left ventricular mass than control patients. Children with left CDH who required ECMO before repair of CDH had a significantly

lower indexed left ventricular mass than those who did not require ECMO before repair (p=0.07) The difference in the mean left ventricular mass index in survivors with left CDH versus nonsurvivors was close to being significant (p=0.07). Both studies suggested that decreased left ventricular mass may be associated with an increase in hemodynamic complications in infants with left CDH (17, 18). A study by Baumgart et al. demonstrated that cardiac angle (persistence of cardiac angle deviation from normal after repair), redistribution of fetal cardiac output (shown by increased Qp/Qs ratios) and left heart hypoplasia (shown by decreased indexed left ventricular mass) reduced survival in neonates with CDH requiring ECMO (19). This study showed similar Qp/Qs ratios in patients with CDH before and after surgical repair and normal newborns.

In our present study, we demonstrated abnormal global right and left ventricular function in neonates with CDH and PPHN before surgery measured by the IMP or Tei index. After improvement of pulmonary hypertension and surgical repair of the diaphragmatic hernia, these indices decreased significantly with normalization of right and left ventricular function, when compared with the normal newborn group. The IMP is potentially a valuable method to document ventricular abnormalities in patients with CDH and PPHN because these patients frequently require aggressive medical management and about 50% require veno-venous vs veno-arterial ECMO support.

The IMP or Tei index has been described to assess myocardial function and to determine clinical status and outcome in patients with primary pulmonary hypertension, hypertrophic cardiomyopathy, and Ebstein's anomaly, as well as other diseases (6-11,13). Routinely used methods to determine the degree of pulmonary hypoplasia, severity of PPHN and outcome are based on arterial blood gas determinations and/or conventional ventilatory setting measurements, such as alveolar arterial gradients (A-aDo_2), oxygenation index and ventilatory indices (20-22). Echocardiography measurements of the hilar pulmonary artery dimensions and the modified McGoon index [(right pulmonary artery diameter + left pulmonary artery diameter) ÷ the descending aorta diameter] have been reported as useful methods to predict pulmonary hypoplasia, risk of developing PPHN, and predicting outcome in patients with CDH. A modified McGoon index of <1.3 clearly differentiated survivors from nonsurvivors (sensitivity of 85% and specificity of 100%) (3). Our data also confirm the results reported by Kim et al. where right ventricular pressure overload can compromise the left ventricular function (13). Since the degree of airway and vascular development and reactivity ultimately will manifest clinically in the severity of the pulmonary hypertension (23) and indirectly will affect the ventricular function, we speculate that the IMP may help accurately assess the degree of severity of the disease and/or outcome of these patients. Further studies are needed, obtaining these noninvasive assessments of pulmonary pressures and right and left ventricular function to determine if these indices can help stratify patients into different areas of the spectrum of preoperative and postoperative management in newborns with various congenital heart abnormalities.

CONCLUSIONS

This study demonstrates that the IMP or Tei index can be applied to neonates with CDH and PPHN in order to obtain a noninvasive quantitative assessment of right and left ventricular function. This is an important tool in the management of these critically ill neonates that may have an effect on the overall outcome.

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