Ventricular Performance is Associated with Need for Extracorporeal Membrane Oxygenation in Newborns with Congenital Diaphragmatic Hernia

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Objective To compare echocardiography (ECHO) findings of patients with congenital diaphragmatic hernia (CDH) who required extracorporeal membrane oxygenation (ECMO) to non-ECMO treated patients.

Study design We reviewed clinical and ECHO data of newborns with CDH born between 2009 and 2016. Exclusions included major anomalies, genetic syndromes, or no ECHO prior to ECMO. Pulmonary hypertension was assessed by ductal shunting and tricuspid regurgitant jet. Speckle tracking echocardiography (STE) assessed function by quantifying deformation.

Results Patients with CDH (15 ECMO and 29 with no ECMO) were analyzed. Most patients had a left CDH (88.6%). Age at ECHO was similar between groups. Outborn status ($P = .009$) and liver position ($P = .009$) were associated with need for ECMO. Compared with non-ECMO patients, patients who required ECMO had significantly decreased left and right ventricular function by both conventional and STE measures, as well as decreased right and left ventricular output. The right ventricular eccentricity index was higher in ECMO vs non-ECMO patients (2.2 vs 1.8, $P = .02$). There was no difference in pulmonary hypertension between CDH groups.

Conclusions Need for ECMO was associated with decreased left and right ventricular function, as assessed by standard and STE measures. There was no difference in pulmonary hypertension between non ECMO and ECMO patients. Abnormal cardiac function may explain nonresponse to pulmonary vasodilators in patients with CDH. Management strategies to improve cardiac function may reduce the need for ECMO in newborns with CDH. *(J Pediatr 2017;■■:■■-■■).*

Newborns with congenital diaphragmatic hernia (CDH) have pulmonary hypoplasia and pulmonary hypertension. CDH occurs in about 1 in 3000 live births[1] and is associated with decreased cross-sectional area of the pulmonary vascular bed, abnormal increase in vascular smooth muscle cells, altered vasoreactivity, and abnormal vascular response, all of which contribute to delayed transition and increased need for extracorporeal membrane oxygenation (ECMO).[2,3]

Inhaled nitric oxide (iNO) reduces the need for ECMO or death in term and near-term newborns with hypoxic respiratory failure associated with echocardiographic or clinical evidence of persistent pulmonary hypertension of the newborn.[4] However, multiple studies have failed to document a benefit of iNO in the population with CDH.[4]

For many years, the evaluation and management of patients with CDH has focused on the high pulmonary vascular resistance and pulmonary hypertension.[3] In addition to iNO, other pharmacologic management options include milrinone, sildenafil, prostacyclin analogs, vasopressin, and norepinephrine, although data regarding efficacy remain based on small case series.[3,5] Echocardiography is often used in infants with CDH to assess cardiac anatomy and performance and estimate pulmonary

AT/RVET	Acceleration time to right ventricular ejection time
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
EDSR	Early diastolic strain rate
EF	Ejection fraction
FAC	Fractional area change
iNO	Inhaled nitric oxide
LVOT	Left ventricular outflow tract
pGLS	Peak global longitudinal systolic
pGLSR	Peak global longitudinal strain rate
PW	Pulsed wave
RVOT	Right ventricular outflow tract
sBP	Systemic systolic blood pressure
sPAP	Systolic pulmonary arterial pressure
STE	Speckle tracking echocardiography
TAPSE	Tricuspid annular plane systolic excursion
VTI	Velocity time integral

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pressures. Conventionally employed assessments of systolic cardiac function of the left ventricle include shortening fraction (percent change of the inner diameter of the left ventricle during contraction) and ejection fraction (EF, percent change in the volume of the left ventricle during contraction). Speckle tracking echocardiography (STE) assesses ventricular function by looking at the myocardial deformation and measures the percent change in myocardial length (strain) and the speed at which it occurs (strain rate) during contraction.[6] STE tracks the grayscale speckles present on the echo image from frame to frame to derive information about the regional wall function of the myocardium.[7]

There are limited data on echocardiography measurements and their predictive value in the population with CDH in the first few days of life. Our objective was to compare echocardiography measures of right ventricular and left ventricular function including STE and pulmonary pressures in patients with CDH who required ECMO vs non-ECMO treated patients with CDH.

Methods

Clinical and echocardiographic data of newborns with CDH hospitalized at Lucile Packard Children's Hospital were collected retrospectively between 2009 and 2016. All patients with CDH were identified from the CDH Study Group and the Stanford Center for Clinic Informatics databases. Study data were collected and managed using REDCap electronic data capture tools hosted at the Stanford Center for Clinical Informatics (hosted at Stanford University, Palo Alto, CA; developed at Vanderbilt University, Nashville, TN). REDCap is a secure, web-based application designed to support data capture for research.[8]

Only patients with a diagnosis of CDH made during neonatal period were included. Patients were excluded if they had major anomalies, genetic syndromes, or no echocardiography was performed at our institution. Pulmonary pressure was assessed by ductus flow velocity-derived gradient during systole or, if no ductus was present, tricuspid regurgitation jet velocity plus estimated right atrial pressure (5 mm Hg), when a full Doppler envelop was available. Pulmonary hypertension has traditionally been defined as a mean pulmonary arterial pressure above 25 mm Hg or a systolic pulmonary arterial pressure above 40 mm Hg.[9] However, this definition does not take into account the transitional physiology of the newborn. Hence, in our population of newborns with CDH, pulmonary hypertension was assessed by comparing the estimated systolic main pulmonary artery pressure to the systolic systemic blood pressure at the time of the echocardiography.

Our institutional ECMO criteria include 1 or more of the following: inability to maintain preductal O_2 saturations greater than 85% despite optimization of ventilation (with limitation of peak inspiratory pressure of 24 cm H_2O on conventional ventilation or, mean airway pressure of 15 cm H_2O on high frequency oscillatory ventilation) and initiation of iNO, oxygenation index (mean airway pressure × FiO_2/PaO_2) of more than 40 for at least 3 hours, metabolic acidosis, and/or hypotension resistant to fluid boluses and appropriate inotropic support. Duration of ventilation was measured from the date of the first intubation to the date of the final extubation during the first hospitalization. Duration of hospitalization was calculated for patients who survived.

The first echocardiogram was analyzed for each patient. Stored images on the LPCH image server were reviewed. Images had been acquired using Philips iE33, Philips EPIQ 7 (Philips Medical Systems, Bothell, Washington), Siemens Sequoia C512, or Siemens SC2000 (Siemens Medical Solutions USA, Mountain View, California). The echocardiogram measures were performed by 1 investigator, blinded to the ECMO status of the patient at the time of image analysis.

EF was calculated using 2 methods for each patient. The 5/6 area length method calculates left ventricular EF using the left ventricular chamber area from the parasternal short axis and the longitudinal dimension of the left ventricle in the 4-chamber view.[10-12] The modified Simpson's method calculates left ventricular EF using the summation of disks to estimate the end-diastolic and end-systolic volume from the apical 4-chamber endocardial area tracing.

Fractional area change (FAC) of the right ventricle was calculated from the endocardial area tracing of the right ventricle in the apical 4-chamber view.[13] Tricuspid annular plane systolic excursion (TAPSE) was measured from the lateral tricuspid valve annulus.[14] Measurements of the right ventricle size (tricuspid valve, basal diameter, midcavity diameter, and longitudinal dimension) were performed at end diastole.[15]

Eccentricity index is the ratio of largest left ventricle dimension (parallel to the septum at the midpapillary muscle view in the parasternal short axis), to the dimension perpendicular to the septum at end systole.[14] It is a quantification of septal configuration and the transmural pressure gradient. Right ventricular outflow tract (RVOT) acceleration time to right ventricular ejection time (AT/RVET) ratio was measured from the pulsed wave (PW) Doppler envelope of the RVOT. This ratio, a surrogate of pulmonary vascular resistance, compares the time to reach peak stroke distance in the pulmonary artery with the overall right ventricular ejection time but is influenced by cardiac output.[14,16,17] Velocity time integral (VTI) of the RVOT was measured by tracing the PW Doppler envelope of the RVOT in the parasternal short axis view. VTI of the left ventricular outflow tract (LVOT) was measured in the apical 3-chamber view. VTI is a surrogate measure for output in the corresponding vessel.[18]

Images of the apical 4-chamber view were stored as Digital Imaging and Communications in Medicine format and were transferred on the VVI platform for strain analysis (VVI 3.01.45; Siemens Medical Solutions USA). Myocardial deformation assessment by speckle-tracking echocardiography (STE) measures myocardial function by regional and global myocardial strain and strain rate quantification.[19,20] The measure of strain refers to the change in distance separating 2 areas of the myocardium during 1 cardiac cycle compared with its initial distance, whereas strain rate is the strain divided by the systolic time interval.[20] Peak global longitudinal strain (pGLS) and peak global longitudinal strain rate (pGLSR) of the left ventricle are thought to be more sensitive to changes in left ventricular

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