Risk Assessment and Monitoring of Right Ventricular Function in Congenital Diaphragmatic Hernia

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Congenital diaphragmatic hernia (CDH) is a developmental defect with discontinuity of the diaphragm resulting in protrusion of abdominal viscera into the thoracic cavity. The diaphragm arises through controlled signaling pathways linked to the lungs, pulmonary vasculature, and cardiac development (1). The initial insult in CDH occurs during embryogenesis, resulting in aberrant bilateral pulmonary parenchymal and cardiovascular development, followed by ongoing inhibition of growth secondary to compression by abdominal contents. These developmental abnormalities contribute to the clinical phenotypes in CDH, with evidence of pulmonary hypoplasia, pulmonary hypertension, and ventricular dysfunction all contributing to morbidity and mortality (2).

In addition to the degree of pulmonary hypoplasia and subsequent pulmonary hypertension, early right ventricular (RV) dysfunction has been shown to be an independent determinant of survival and extracorporeal membrane oxygenation (ECMO) use in infants with CDH (3). The hemodynamic consequences of abnormal pulmonary parenchymal and vascular development result in persistent exposure of the right ventricle to increased afterload. Right heart function is further compromised by an inefficient neonatal myocardium that is sensitive to changes in loading conditions. Accordingly, the critical challenge for the right ventricle in infants with CDH is to remain hemodynamically coupled to the pulmonary circulation.

With increased recognition that RV function is a key mediator of disease severity and clinical outcomes, and not simply a side effect of increased pulmonary vascular resistance, it is imperative to consider diagnostic strategies that characterize the major determinants of RV function in infants with CDH. The functional assessment of the right ventricle has historically been difficult because of its thin-walled tripartite structure. Recently, myocardial deformation assessed by using two-dimensional speckle tracking echocardiography has been validated in neonates (4) and has been used to quantitatively characterize RV function in infants with CDH, in whom a lower magnitude of RV strain was associated with need for ECMO (5). In addition, there has been a renewed interest in developing biomarkers to assess the longitudinal response of the right ventricle to changes in loading conditions. B-type natriuretic peptide (BNP), a polypeptide secreted from both ventricles in response to elevated wall stress, has been associated with RV and left ventricular (LV) dysfunction and outcomes in infants with CDH (6). Despite these associations, there remains a need to correlate these cardiac biomarkers with more sophisticated echocardiographic techniques, including speckle tracking–derived strain, to assess ventricular function in CDH newborns.

In this issue of *AnnalsATS*, Avitabile and colleagues (pp. 1431–1439) leveraged a large cohort of infants with CDH to demonstrate that ongoing RV systolic dysfunction after hernia repair can be detected by using a combination of elevated BNP and a lower magnitude of myocardial deformation (7). This single-center retrospective study builds on previous reports that investigated associations of ventricular dysfunction with abnormal BNP after therapeutic interventions in infants with CDH (8, 9). In the current study of 460 BNP–echocardiogram pairs obtained preoperatively, in the immediate postoperative period and during recovery, the majority of infants had abnormal RV strain and BNP concentrations before surgical repair but demonstrated improvement afterward. Higher concentrations of BNP were associated with lower-magnitude RV strain during the recovery period, but this association was not present during the preoperative or immediate postoperative period. A history of ECMO was linked to abnormal BNP concentrations and a lower magnitude of RV strain after CDH repair, but only elevated BNP after repair was associated with mortality. Although RV strain demonstrated high sensitivity with poor specificity for mortality, the magnitude of RV strain was lower in patients with pulmonary hypertension at 6 months of age. There was no correlation between BNP concentrations and pulmonary hypertension.

This study is timely because of the increased recognition of the impact of ventricular performance before and after CDH repair on clinical outcomes. Much of the current evidence has centered on ventricular dysfunction within the initial 48 hours (10–12). A multicenter registry cohort study reported early qualitative cardiac dysfunction in 39% of patients (3). Avitabile and colleagues (7) observed that abnormal RV strain was present in 86% of infants before surgery and was associated with pulmonary hypertension at 6 months of age, suggesting that myocardial-deformation imaging may be a more sensitive marker of RV dysfunction in this population. Implementation of cardiac-strain imaging in neonates has been limited by variations in image acquisition, echocardiographic equipment, and postacquisition image analysis, but by linking

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RV strain to clinical outcomes, including ECMO use and persistence of pulmonary hypertension, the current study supports strain analysis as a complementary modality for longitudinal assessment of ventricular function in CDH infants.

Although previous studies have demonstrated that BNP correlated with pulmonary hypertension severity, cardiac dysfunction, and the need for ECMO in patients with CDH (13, 14), this is one of the first studies to focus on the correlation of these cardiac biomarkers with assessment of ventricular function by myocardial deformation. Avitabile and colleagues (7) demonstrate an association of higher BNP concentrations with lower-magnitude RV strain after CDH repair, supporting the combined use of quantitative echocardiographic measures and biomarkers to comprehensively assess the determinants of RV performance along the life course of infants with CDH.

The clinical significance of these results should be interpreted within the framework of the intrinsic limitations in this study. The focus of the current study was only on RV systolic function in the perioperative period and did not evaluate LV function. In infants with CDH, LV dysfunction, often diastolic, results from a combination of LV hypoplasia and impaired filling due to septal bowing associated with increased RV afterload. In the multicenter registry study, 55% of patients with RV dysfunction also had LV dysfunction (3). As LV dysfunction commonly occurs in the setting of RV dysfunction and is associated with outcomes in infants with CDH (11), the findings by Avitabile and colleagues (7) that *1*) lower magnitudes of RV strain were not associated with mortality and *2*) BNP concentrations were not correlated with RV strain or pulmonary hypertension as identified by using late echocardiograms is potentially confounded by the impact of LV dysfunction in this population. Because LV diastolic dysfunction in CDH has been reported to be transient (15), it is likely that the LV dysfunction may have contributed to early alterations in BNP concentrations, but with improvement of LV function, there was a blunted response for BNP.

The intrinsic characteristics of the developing myocardium further contribute to the pathophysiology of RV dysfunction in CDH. The neonatal myocardium is composed of an underdeveloped contractile system that predisposes the myocardium to diastolic dysfunction. Although this current study is one of the first to report RV systolic dysfunction using novel strain imaging, it did not assess diastolic function with strain-rate analysis (5). Although strain is influenced by loading conditions (16), strain rate is a more accurate reflection of intrinsic myocardial contractility and diastolic function, which may be impaired in the less mature myocardium (16).

Early evidence of RV systolic dysfunction in newborns with CDH adds to the growing list of complications after CDH that increase the risk of adverse outcomes. Avitabile and colleagues (7) have now shown that echocardiographic evidence of RV systolic dysfunction together with assessment of strain imaging and BNP are noninvasive quantitative measures of illness severity and early predictors of outcomes in infants with CDH. The current study also supports RV strain and BNP as potential markers of RV recovery in CDH infants after repair. Recognizing that RV dysfunction may persist beyond the neonatal period and be further exacerbated with hypoxemia, infection, sedation, and timing of surgery, future studies should use these early risk factors as predictive biomarkers toward enrolling these infants with CDH into clinical intervention trials. ■

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