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Brain-type natriuretic peptide levels correlate with pulmonary hypertension and requirement for extracorporeal membrane oxygenation in congenital diaphragmatic hernia

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ABSTRACT

Purpose: B-type natriuretic peptide (BNP), an established biomarker of ventricular pressure overload, is used in the assessment of children with pulmonary hypertension (PH). PH is commonly observed in congenital diaphragmatic hernia (CDH). However, the use of BNP levels to guide treatment in this patient population has not been well defined. In this study, we investigate BNP levels in a large cohort of CDH patients treated at a single institution.

Methods: We retrospectively reviewed charts of all CDH patients enrolled in our pulmonary hypoplasia program from 2004–2013. PH was assessed by echocardiography using defined criteria, and patients were further stratified into the following cohorts: no PH, short-term PH (requiring nitric oxide but no additional vasodilatory therapy), long-term PH (requiring continued vasodilatory therapy post-discharge), and ECMO (requiring ECMO therapy).

Results: A total of 132 patients were studied. BNP levels were significantly increased in patients with PH compared to patients with normal pulmonary pressures ($P < 0.01$). BNP levels were not significantly different between the ST-PH, LT-PH, and ECMO cohorts, but all levels in all three cohorts were significantly increased compared to patients who did not develop PH.

Conclusion: Our findings indicate that plasma BNP levels correlate with pulmonary hypertension as well as the requirement for ECMO in CDH patients. Monitoring of serial BNP levels may provide a useful prognostic tool in the management of CDH.

B-type natriuretic peptide (BNP) is a 32-amino acid peptide hormone secreted by the ventricles in response to ventricular pressure and volume overload [1]. BNP causes vasodilation, has a diuretic as well as natriuretic effect and has been shown to correlate with echocardiographic findings of ventricular strain [2]. An established clinical biomarker of ventricular strain in congestive heart failure, BNP is commonly utilized in the assessment of disease severity and treatment response in adult cardiac patients. While initially studied in the adult cardiac disease population, there is increasing interest in determining the utility of BNP levels in the assessment of congenital heart disease and pulmonary hypertension. BNP levels have been shown to be elevated in children with complex congenital heart disease and correlate with New York Heart Association functional class [3]. BNP levels have also been studied in persistent pulmonary hypertension of the newborn, a condition with no underlying congenital heart defect [4]. In this patient population, levels correlated with echocardiographic measures of PH including gradient of tricuspid regurgitation.

Congenital diaphragmatic hernia (CDH) represents one of the most challenging patient populations encountered in pediatric surgery and neonatology. Despite advances in neonatal intensive care, CDH patients continue to face a high burden of morbidity and mortality, with pulmonary hypoplasia and pulmonary hypertension (PH) representing the most important factors determining patient survival [5]. Pulmonary vascular changes in CDH are well described and include reduced pulmonary arteries per unit lung volume as well as peripheral muscularization of small arteries with medial and adventitial thickening [6]. Severe PH impacts survival and long-term functional outcomes, and also represents the most frequent indication for the initiation of extracorporeal membrane oxygenation (ECMO) therapy in this patient population. However, the use of BNP levels to assess disease severity and guide treatment in CDH patients has not been described in the literature. In this study, we investigate BNP levels in a large cohort of CDH patients treated at a single institution with specific attention to the correlation of levels with the degree of PH, the need for ECMO support and the changes in BNP levels over the course of surgical correction of the CDH.

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1. Materials and methods

This is a retrospective review of all CDH patients treated at the Children's Hospital of Philadelphia and enrolled in the Pulmonary Hypoplasia Program between January 2004 and December 2012. This study was approved by the CHOP Institutional Review Board, Committee for the Protection of Human Subjects (IRB 06-003779). Recorded data on patient demographics, prenatal course and imaging, surgical repair, laboratory investigations including BNP levels, and postoperative course were analyzed. Prenatal CDH severity was assessed by liver position and lung to head ratio (LHR) on ultrafast fetal MRI and detailed sonographic evaluation as previously described [7]. Exclusion criteria included patients managed by palliative management or withdrawal of care shortly after birth, patients referred to our center following initial management at another institution, CDH repair at another institution and patients with no recorded BNP levels. Echocardiography was performed as clinically indicated to assess right ventricular pressures, with PH defined according to standard criteria (right ventricular systolic pressure estimate [RVSPE] >27 mmHg, right ventricular dilation/enlargement/hypertrophy, septal flattening). Patients were further stratified into the following cohorts: no PH, short-term PH (requiring nitric oxide but no additional vasodilatory therapy), long-term PH (requiring continued vasodilatory therapy post-discharge), and ECMO (requiring ECMO therapy). BNP levels were measured once weekly throughout the course of the neonatal intensive care unit (NICU) stay, as well as at regular follow-up appointments through the Pulmonary Hypoplasia Program, with serum samples sent to our central laboratory for processing. BNP levels are expressed in pmol/L. Pharmacologic vasodilatory therpy included inhaled nitric oxide as well as the cGMP-specific phosphodiesterase type 5 inhibitor sildenafil.

Statistical analysis was performed using Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. $P \leq 0.05$ was considered significant. All data analysis was conducted using GraphPad Prism 6.0 (La Jolla, CA).

2. Results

2.1. Patient population and presence of PH

From January 2004 through December 2012, 225 neonates with CDH were enrolled in the Pulmonary Hypoplasia Program. A total of 58 patients were excluded from further study due to lack of serum BNP measurement, 19 were excluded due to palliative management or withdrawal of care shortly after birth, and 16 were excluded due to CDH repair at another institution. Of the remaining 132 patients, 53 (40%) had no evidence of PH while 79 (60%) had echocardiographic and clinical findings of PH including echocardiographic demonstrated elevation of right-sided pressures as well as pre-ductal versus post-ductal oxygen saturations demonstrating significant shunting. This cohort was further divided based upon PH severity, with 38 patients requiring short-term treatment with nitric oxide alone (ST-PH), 18 patients requiring nitric oxide in addition to chronic pulmonary vasodilatory therapy with sildenafil (LT-PH), and 32 patients requiring ECMO therapy (all of whom required nitric oxide therapy and 9 of whom also required sildenafil therapy) (Fig. 1).

Patient demographics, prenatal assessment of CDH severity and perinatal clinical course as they relate to the severity of PH are summarized in Table 1. There were no significant differences in gender, side of defect, gestational age at delivery, or birth weight with respect to the presence or severity of PH. Median LHR was significantly decreased in all PH patients compared to patients with no PH (1.0 versus 1.4, $P < 0.01$), and was also significantly reduced in each subset of PH patients compared to patients with normal pulmonary pressures (Table 1, $P < 0.01$ for all subsets). Similarly, the percentage of patients with herniation of liver into the thoracic cavity was also significantly increased in PH patients compared to patients with no PH (62% versus 19%, $P = <0.01$), and was also significantly increased across all subsets of PH patients (Table 1, $P < 0.01$ for all subsets).

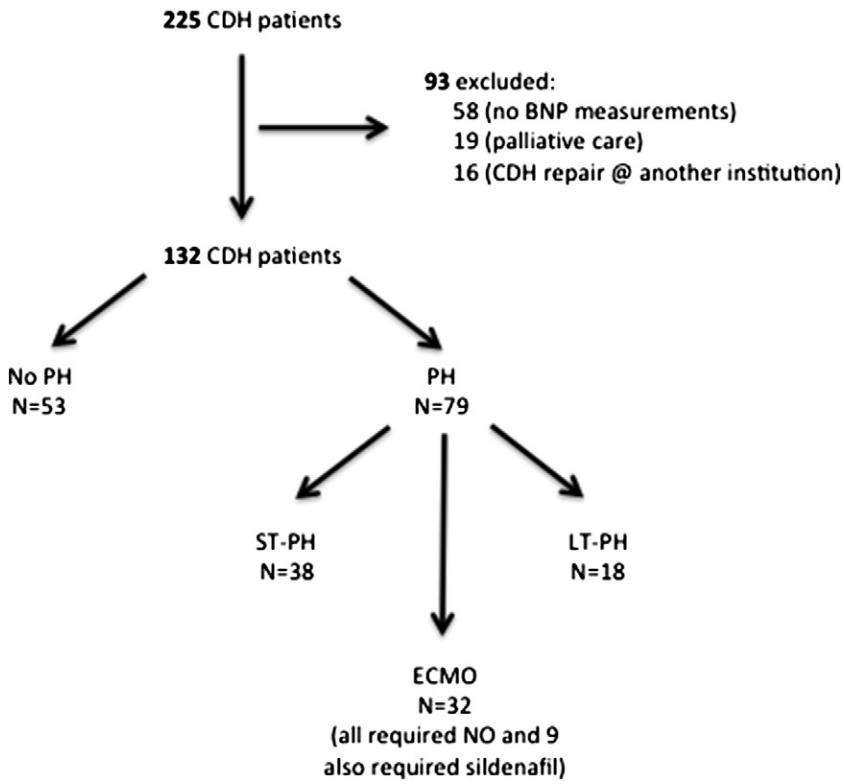

Fig. 1. CDH patient population.