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Cardiac biomarkers in a select cohort of Pediatric heart disease: Galectin-3, hsCRP and NT-proBNP

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Abstract

Patients with single ventricle physiology are the most vulnerable patients with congenital heart defects (CHD) requiring up to three cardiac surgical palliations to survive into adulthood. Long term survival of these patients is dependent upon excellent surgical intervention and outcomes, long term follow-up and prediction and anticipation of which patients in this cohort are most likely to have adverse outcomes. Biomarkers such as Galectin-3 (Gal-3), high sensitivity C-reactive protein (hsCRP) and N-Terminal-pro-B-type Natriuretic peptide (NT-proBNP) have proven useful in predicting outcomes in the vulnerable adult cardiac populations. However, there is a paucity of biomarker data in the pediatric population, particularly in patients with single ventricle physiology. To date, there are no pre-surgical values of hsCRP and Gal-3 and only some studies evaluating NT-proBNP levels in this population. Such pre-surgical data is needed to better understand the baseline activity of these biomarkers in this population and thus better understand the significance of changes after surgical interventions. We sought to establish baseline median and interquartile ranges for hsCRP, NT-proBNP and Gal-3 in patients with single ventricle physiology prior to any surgical or interventional palliation. Using a pre-existing pre-operative biorespository with samples collected between 2011 and 2018, 78 patients were included in the study. The median values for hsCRP, NT-proBNP and Gal-3 were 0.5 mg/L [0.5, 1.6], 13263 pg/ml [5804, 29767] and 6.4 ng/ml [4.5, 9.6] respectively. This study is novel in that there has been no previously published pre-surgical data for hsCRP and Gal-3 and only limited data for NT-proBNP in neonates with single ventricle physiology.

Keywords: Single ventricle, biomarkers, hsCRP, NT-proBNP, Gal-3.

Introduction

The incidence of congenital heart defects (CHD) in the United States is 8 per 1000. With advances in cardiovascular care and surgical techniques, there is an increasing prevalence of children living in the United States with CHD. Consequently, every year there are more than 11,000 hospitalizations related to heart failure in children that result in not only significant mortality and morbidity1, but also significant resource utilization with an estimated annual cost over $400 million2. Improvement in outcomes and reduction in resource utilization is dependent on timely prediction of complications and appropriate subsequent intervention. Complications arise in this population for a number of reasons including hemodynamic abnormalities that activate cytokines, neuro-hormones and vascular endothelial cells in patients with CHD. These factors can lead to pathological conditions such as cardiac fibrosis, hypertrophy and eventually heart failure and cell death. Such pathophysiology leads to changes in serum biomarkers. In adult heart failure patients, current guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure1. However, there is a significant gap in the pediatric cardiac population with regards to the understanding and use of biomarkers to predict adverse outcomes.

An important subset of pediatric patients at risk for heart failure is those with single ventricle physiology. In order to live into adulthood with the best cardiac function, these patients require up to three extensive palliative surgeries – typically before the age of five years. The first and most complex surgery occurs soon after birth with the second following three to six months thereafter. There is an average 12% mortality rate between the first and second surgery3 with a significant cost associated with these admissions. Utilizing biomarkers that predict which patients is highest risk of cardiac decompensation may allow for preemptive interventions that could potentially save lives and reduce resource utilization. Specific cardiac biomarkers have been used extensively in the adult cardiac population but much less so in the pediatric cardiac population.

Three biomarkers of particular interest, Galectin-3 (Gal-3), high sensitivity C-reactive protein (hsCRP) and N-Terminal-pro-B-type Natriuretic peptide (NT-proBNP) have shown great promise for their potential utility in predicting adverse outcomes in the adult cardiac population. However, these biomarkers have not been collectively studied in the pediatric cardiac population.

Furthermore, there are no studies that have evaluated the baseline hsCRP and Gal-3 values for neonates with single ventricle physiology prior to their first surgical palliation. As such, we sought to establish the median values and interquartile ranges for hsCRP, NT-proBNP and Gal-3 in neonates with single ventricle physiology prior to their first palliative surgery/intervention. Understanding the baseline activity of these key biomarkers in this population prior to surgical intervention is key to subsequently understanding how changes in these biomarkers may predict outcomes in these patients.

Materials and methods

All pediatric patients <30 days of age with single ventricle physiology with available serum samples who underwent a Stage 1 single ventricle palliation, hybrid procedure, or BT-shunt and were subsequently admitted to the Pediatric Cardiac ICU at Vanderbilt Monroe Carell Jr. Children's Hospital (VCH) between 2011 and 2018 were included in this study. EDTA anticoagulated blood specimens were collected from 78 patients before palliative surgical/interventional procedure and were entered into a Pediatric Congenital Heart Disease Biorepository (Vanderbilt IRB#101274). Plasma was separated and stored at -80˚C till used for this study. The Institutional Review Board approved this retrospective study (Vanderbilt IRB#191121).

Galectin-3 was measured using Quantikine® ELISA kit (R&D systems catalog# DGAL30) and high sensitivity C-reactive protein (hs-CRP) ELISA Kit (BioMatik EKC34032) according to the manufacturer's instructions. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration was measured using an electrochemiluminescence immunoassay on Roche Cobas e411 analyzer (Roche Elecsys ProBNP II, Roche Diagnostics, Indianapolis, IN). The intra-assay CV for NT-ProBNP is < 1.2%. All three biomarkers were measured at Cardiology Core Laboratory at Vanderbilt University Medical Center. Patient information such as demographics, age at time of surgery, clinical characteristics and surgical procedure were collected and managed using REDCap electronic data capture tools hosted at VCH. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources[4, 5]. Means and interquartile ranges were calculated.

Results

Serum samples from 78 neonates with single ventricle physiology admitted to VCH between 2011 and 2018 were included in this study. Forty-six of those patients were male and 32 were female. Sixty-seven patients had Hypoplastic Left Heart Syndrome (HLHS), two patients had Tricuspid Atresia (TA), and the remaining nine had Shone's Complex, Double Outlet Right Ventricle (DORV) or Double Inlet Left Ventricle (DILV). The median values for hsCRP, NT-proBNP and Gal-3 were 0.5 mg/L [0.5, 1.6], 13263 pg/ml [5804, 29,767] and 6.4 ng/mL [4.5, 9.6] respectively.

Discussion

We are the first to report the baseline values of hsCRP and Gal-3 in neonates with single ventricle physiology prior to their first palliative surgery. We report our findings related to the baseline level of NT-proBNP in this population for further comparison to other studies that have evaluated this biomarker in this population but also present it for concurrent consideration to its relationship to the other two unique biomarkers, hsCRP and Gal-3.

BNP is a protein that is released by the ventricles of the heart in response to either volume or pressure loading. The subsequent effect is diuresis and natriuresis, and the final result causes a decrease in intravascular volume thereby decreasing the preload and afterload on the ventricle. NT-proBNP is the inactive by-product of BNP as a result of the cleavage of the parent peptide Pro-BNP. BNP has a short half-life of 20 minutes while NT-proBNP has a longer half-life of 60-120 minutes6. Studies have evaluated BNP and NT-proBNP levels in the pediatric population7-9 but fewer studies have elucidated the baseline value of NT-proBNP values in infants10,11. Nir et al. looked at NT-proBNP values of 127 healthy individuals between 0 – 11 days. Between 0-2 days, the median value was 3,183 pg/ml while between 3-11 days, the median value was 2,210 pg/ml10. Mir et al. measured NT-proBNP values in control children (11 days -17 years) and those values ranged from 150 and 430 fmol/mL (10th and 90th percentile). In 21 children with congestive heart failure with associated diagnoses including HLHS, the levels ranged between 219 and 2008 fmol/ml12. In our sample size of 78, the median value was 13,263 pg/mL. NT-proBNP rapidly increases at birth and plateaus around days 3 to 4 followed by a steady decrease11. The average age when our samples were collected was on the 5th day of life, around the peak time of surge in value. This may explain the significantly elevated values seen in our study when compared to other studies12. Furthermore, the significant higher elevated levels in our study when compared to those in Nir et al. may be different due to the constant state of hemodynamic variability in neonates with single ventricle physiology prior to surgical or interventional palliation as compared to neonates with normal cardiac anatomy and physiology.

Infants with single ventricle physiology, particularly, HLHS, are at risk of significant activation of the inflammatory cascade, related to the hemodynamic instability present due to constant imbalances in systemic and pulmonary vascular resistance prior to stabilization with the first surgical or interventional palliation. Biomarkers of inflammation like hsCRP and IL-6 have been individually evaluated in pediatric patients with cardiovascular disease13,14. Unlike regular CRP, hsCRP can detect low levels of inflammation in what appears to be otherwise well controlled systemic inflammatory or immunologic disorders. These lower, yet still elevated levels, can predict adverse outcomes. In adults with coronary artery disease, low level elevations of hsCRP have been found to be an independent risk factor for future adverse coronary events15. In our study, the median preoperative value

of hsCRP was 0.5mg/L which was lower than expected in patients with single ventricle physiology. Existing data has revealed that levels of other inflammatory markers such as IL-6 are elevated in preoperative neonates with single ventricle physiology13. This elevation may be due to low levels of inflammation due to the ongoing imbalance between pulmonary and systemic circulation. Our data does not reveal that hsCRP levels coincide with elevations seen with other inflammatory markers in this patient population. However, without other studies to which to compare, our data provide initial information and insight into the baseline levels of hsCRP in patients with single ventricle physiology, but more studies are needed.

Extrapolating data from the adult biomarker literature, we examined the baseline activity of another novel and very promising biomarker, Galectin-3. The Galectins are proteins that are involved in regulation of inflammation, immunity and cancer. Studies have demonstrated up-regulation of Galectin-3 in hypertrophied hearts, its effects on macrophages and fibroblasts along with the development of fibrosis16. This pathophysiology is relevant due to the effect of cardiac re-modelling and its downstream adverse clinical effects related to heart failure. One review article noted that an elevation in plasma Galectin-3 levels was the best independent predictor of 60-day mortality or combination of death/recurrent decompensated heart failure within 60 days17. Another study evaluated normal Gal-3 values in 240 children aged 2-17 years of age without heart failure. They found that the median Gal-3 value was 12 with a range of 6 – 10018. In our study, the median value was 6.4ng/mL with a range of 4.5 to 9.6. Because no other studies exist evaluating the baseline activity of Gal-3 in this patient population, these data will need further evaluation to see if there is any association of the pre-operative Gal-3 level with subsequent outcomes.

Conclusion

As our understanding of heart disease continues to evolve and grow, it is important to identify and evaluate biomarkers that may provide further prediction and understanding of outcomes in these patients. Such biomarkers may prove to have the greatest utility in the most vulnerable cohort of patients with cardiac disease that are at highest risk of morbidity and mortality. In the pediatric population, patients with single ventricle physiology are the highest risk cohort. Studying, understanding, and utilizing biomarkers that have association with adverse health outcomes will allow identification of patients with single ventricle physiology that may be at greatest risk for future clinical decompensation. In the adult cardiac population, the American Heart Association emphasizes the role of cardiac biomarkers in diagnosis, management and prognostication. There is an obvious paucity in the understanding and utilization of cardiac biomarkers in pediatric heart disease, specifically in patients with single ventricle physiology. The first step in increasing utilization is understanding the activity of relevant biomarkers in this vulnerable population. Our novel findings make that first step demonstrating the baseline pre-surgical values of three biomarkers, hsCRP, NT-proBNP and Galectin-3, in neonates with single ventricle physiology. These data provide the preliminary steps in further evaluating how the baseline values of these biomarkers may be associated with future outcomes in this patient population.

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