Serum B-Type Natriuretic Peptide as a Biomarker for Clinical Severity of Heart Failure in Pediatric Heart Disease

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A. Study Purpose and Rationale

Congestive heart failure is a chronic disease. One of the challenges in managing patients with heart failure is developing methods of assessing the severity of each patient's illness and tailoring treatment to match it. At present, there are numerous modalities used to describe patients in heart failure. The clinical history, examination, laboratory tests, radiographs, functional, and invasive testing all provide glimpses into the natural history of the disease, but only reveal unrelated facets of the disease. A great challenge is learning to connect this diverse stream of data. Several biochemical markers have been identified that are elevated in patients with heart failure and which react dynamically to changes in cardiac physiology. If they can reliably determine the progress of cardiac disease and guide therapy they would be a useful addition to the cardiologist's armamentarium. The purpose of this study is to determine if one of these markers, B-type natriuretic peptide (BNP) can reliably demonstrate the severity of illness in patients as determined by clinical history and other forms of testing.

BNP is a thirty-two amino acid peptide produced by ventricular myocytes, which has been shown to have vasodilatory, diuretic, and natriuretic properties. Additionally, there is evidence that suppresses both the sympathetic nervous system and renin-angiotensin axis, the neurohormonal axis linked to structural remodeling and ventricular dysfunction in chronic heart failure. Studies have demonstrated that levels of serum BNP are dramatically higher in patients with both acute and chronic heart failure. This was first demonstrated in patients presenting to emergency departments with a chief complaint of dyspnea. In these studies, a serum BNP, quantified by radioimmunoassay (RIA), over 100 pg/mol differentiated between cardiogenic and non-cardiogenic dyspnea with a sensitivity of 90% and specificity of 73-76%, rates superior to all other markers [1, 2] In other settings BNP has had mixed results as a screening test for cardiac disease. The use of BNP in a primary care setting as an initial screen for cardiac disease was not able to demonstrate improvements in screening for early heart failure [3].   However, in an ICU setting, BNP has been shown to be a sensitive screen for previously unidentified cardiac dysfunction [4]. This suggests that for populations with higher prevalence of cardiac failure, BNP can effectively screen for ventricular dysfunction.   Prospective trials comparing serum BNP to other diagnostic modalities, such as impedance cardiography and tissue Doppler, have confirmed BNP's efficacy as a screen for ventricular dysfunction, establishing serum BNP thresholds (98-150 pg/mol on RIA) for the detection of CHF with high sensitivity (65-92%) and specificity (85-88%) [4-6].

Several studies have demonstrated that serum BNP levels in children with ventricular stress are elevated, in a similar fashion to adults.   A retrospective study demonstrated that ventricular dysfunction can be correlated with elevated BNP (mean: 623 + 146 pg/mol) and that a cut-off of 40 pg/mol identified ventricular dysfunction with a sensitivity of 85% and specificity of 81% [7]. A prospective study in pediatric patients with ventricular septal defect corroborated this, noting that BNP could be used to identify increased ventricular pressure loads; BNP > 20 pg/mol screened for elevated pulmonary artery pressures (>20 mmHg) with a sensitivity of 82% and specificity of 89% [8]. This suggests that in both adult and pediatric populations BNP is grossly elevated in populations with increased ventricular stress. However, it is not clear whether adult normative data can be applied to children, as the hemodynamic profiles of children undergo radical changes through normal development. One small study in preterm infants demonstrated that BNP levels are transiently elevated in the first week of life, but that in patients with normal anatomy, BNP levels rapidly normalize to adult levels [9]. However, it is unclear 1) whether BNP levels remain at this level in normal children throughout their development and 2) whether serum BNP in a diseased state varies consistently in ill patients of different ages.

Further studies have that BNP reacts dynamically to changes in ventricular stress. This is made most clear in a study performed on adult patients with pulmonary hypertension. The increased pressures in the pulmonary vasculature represent functional obstruction and pressure overload on the right ventricle, leading to hypertrophy and cardiac failure. Investigators have demonstrated that baseline serum BNP is elevated in this population (mean $828 + 217$ pg/mol) [10], as would predicted by previous studies. One treatment of pulmonary hypertension is epoprosterenol, an agent that reduces pulmonary vascular resistance and should reduce right ventricular stress. In various trials, recipients of epoprosterenol therapy can be stratified into responders and nonresponders, (both in terms of physiologic data and on clinical measures such as hospital admissions). This reflects the efficacy of therapy at reducing ventricular load. Interestingly, patients who responded to therapy demonstrated an early $70 + 7\%$ decrement in their serum BNP, predicting their clinical responsiveness, while nonresponders actually demonstrated a small but significant increase in their serum BNP ($11 + 19\%$) overall [10]. This establishes that BNP levels reflect changes in ventricular function and meaningful clinical improvement, and that these changes may antedate clinical changes. This would suggest a predictive value in serum BNP's, which would be useful to provide prognostic information about patients.

There are also studies that suggest that serum BNP levels can be used to estimate the severity of disease in CHF. The median level of BNP in adults (older than 40 years of age) presenting for physical exams in a primary care clinic was 29 pg/ml [3], and several studies have shown that patients with ventricular disease have significantly increased mean levels of BNP [4-6, 10]. One trial stratified adult patients that were diagnosed with CHF in the ED clinically and compared it to serum BNP. They found that BNP correlated with New York Hear Association (NYHA) grading (Class I: $244 + 286$ pg/mol, Class II: $389 + 374$ pg/mol, Class III: $640 + 447$ pg/mol, Class IV: 817 pg/mol) [1]. In pediatric populations, gross correlation between two classes of ventricular dysfunction (mild and severe) and serum BNP has been demonstrated in a retrospective study [7]. One prospective study has confirmed that serum BNP in adult and pediatric patients with congenital heart disease (ages 0-40) correlates with NYHA classification (control: $4 + 4$ pg/mol, Class I: $23 + 25$ pg/mol, Class II: $53 + 59$ pg/mol, Class III/IV: $150 + 144$ pg/mol) [11]. Grossly, surgical correction of the offending lesion also reduces serum BNP, again suggesting that BNP is a dynamic marker of ventricular load that can changes with clinical improvement in disease. Variance is high in all of these samples, suggesting that serum BNP does not distribute normally, but it is clear that as severity increases serum BNP also increases.

The goal of this study is to determine whether BNP increases with increasing clinical severity of heart failure. Further, we hope to determine whether BNP mirrors clinical severity of disease along with treatment. If it proves to have fidelity as a marker of severity, it may serve as a non-invasive marker to guide treatment and risk-stratify patients.

B. Study Design and Statistical Analysis

Design: This is a retrospective analysis. Patients meeting our inclusion criteria will be identified with the help of the Department of Biomedical Informatics Data Warehouse project. Study staff will review patient charts and divide them into four groups based on their NYHA/Ross Heart Failure Class at the time of their BNP. Upon review of their chart, study staff will produce a database describing their clinical information at the time of each BNP assay. We hypothesize that serum BNP will increase with increasing severity of disease. We will test this in the total population of patients who received BNP's at Columbia University Medical Center (CUMC) and the Morgan Stanley Children's Hospital of New York (MS-CHONY). A subgroup analysis of patients presenting without previous treatment to determine whether BNP levels reflect severity of heart disease independent of therapeutic regimen will also be performed.

Outcomes and Definitions: Quantifying the severity of illness in congestive heart failure is primarily accomplished through symptom scales such as the New York Heart Association (NYHA) Heart Failure Class. This system assigns a patient to one of four classes depending on the degree of effort needed to elicit symptoms, including symptoms at rest (class IV), on less-than-ordinary exertion (class

III), ordinary exertion (class II), and levels of exertion that limit patients without disease (class I) [12]. The NYHA's reliance on verbal reportage of symptoms is developmentally inappropriate in children under the age of five. The Ross Heart Failure Class is a scale that has been used as an analogue of the NYHA class for children under 5 years of age. It has been correlated with higher plasma norepinephrine levels and down-regulation of beta-receptor density on cells in infants and children with heart failure secondary to large left-to-right shunt [13, 14] and is commonly used in parallel with the NYHA class. Both the NYHA and Ross classes are used in both research and clinical work to quantify severity of CHF in patients. In this study, heart failure class will be derived from review of the chart.

The primary outcome is the serum BNP. Serum BNP is a continuous variable measured by a radioimmunoassay test kit produced by the Shionogi and Co. and distributed by Bayer Corporation. The standard curve range of this test is between 4 and 2000 pg/ml. Studies have demonstrated that it can detect a minimum concentration of 6.9 pg/ml, with a CV<10% across a range of 43 and 1830 pg/ml [15]. The total CV were between 3.4, 2.9, and 2.4% at BNP concentrations of 48, 461, and 1768 respectively [16].

Additional data that will be collected from the chart includes age, height, weight, echocardiographic fractional shortening, pulmonary capillary wedge pressures, cardiac index, ejection fraction by angiogram or MUGA, exercise testing (anaerobic threshold and heart rate), medication regimen, and clinical outcomes (hospitalization, interventions, and death). These will be used as secondary outcomes of severity of heart failure in these patients.

Analysis: Analysis of the primary outcome will be performed initially with analysis of variance (ANOVA) testing. If this test demonstrates a significant difference in BNP in the different groups of interest, we will use pair-wise, two-sided student's t-tests to determine if differences are significant or not. Analysis of secondary outcomes will be analyzed similarly. We are not powered for these multiple comparisons. They are included to demonstrate the internal validity of the study: that the symptom scales are physiologically relevant representations of the patient's clinical state.

Sample Size: Two studies (one in adults and one in children) have attempted to correlate the severity of heart failure symptoms with levels of BNP [1, 11]. Both groups noted significant increases in BNP as severity of heart failure symptoms increased. Because the mean BNP's in the two studies were qualitatively different, we will use the data derived from a pediatric population. In a retrospective analysis of patients with heart failure secondary to congenital heart disease (CHD), the patients with more severe heart failure (based on NYHA/Ross class criteria) were shown to have increased serum levels of BNP (control: 4 ± 4, class I: 23 ± 25, class II: 53 ± 59, class III/IV: 150 ± 144) [11]. Utilizing this data to calculate appropriate sample sizes for this study is hampered by several factors. The study was not powered to provide comparisons between all groups (only between each class of severity and the control population). The study population featured a small number of severely ill children, and as a result they pooled the two most severe classes of illness (NYHA/Ross class III and class IV). Finally, the sample's means and standard deviations suggest that serum BNP was not normally distributed in this population. These factors all complicate sample size calculations.

Our assumptions for powering this study are: alpha = 0.05, power = 0.8, with the intent to perform pair-wise student's t-tests between all groups. Given that in previous studies BNP failed to distribute normally, we plan to use a natural logarithm (ln) transformation to normalize the data. Without the raw data from either of the previous studies, we also are forced to estimate the standard deviation at 0.4. Previous studies suggest that differences between subsequent classes of heart failure are between 200 and 300% changes between subsequent classes. Approaching the problem more conservatively, we propose to power the study to detect a 33% increase in serum BNP between adjacent groups at 80%. The result of this is a sample size of 37 patients in each class of heart failure.

C. Study Procedure

N/A

D. Study Drugs

N/A

E. Medical Devices

N/A

F. Study Questionaires

N/A

G. Study Subjects

Subject population is all patients between the ages of 0 and 21 years from whom a serum B-type natriuretic peptide (BNP) was drawn between the years 2000 and 2005 at the Morgan-Stanley Children's Hospital of New York. Exclusion criteria include 1) BNP level drawn within 30 days of cardiopulmonary surgery, 2) current hemodialysis, 3) the presence of primary pulmonary hypertension, and 4) renal failure (Cr >1). The sample will be stratified by etiology of heart failure.

We plan to survey the entire eligible population without regard to sex or ethnic background. The MS-CHONY Division of Pediatric Cardiology has a wide catchment area, and we do not expect that our study population will not deviate significantly from the national demographics of pediatric heart disease. We aim to sample a complete range of disease severities, establishing how BNP varies across that spectrum.

Minors are a vulnerable population. The focus of this study is on a number of diseases that are congenital or are predominantly manifest in children. Thus, pediatric heart failure must be considered a separate entity from its adult counterpart. As a result, participation of minors is vital to the study's external validity.

H. Recruitment

This is a retrospective study. Patients meeting our inclusion criteria will be identified using a search of the Columbia University Department of Bioinformatics Data Warehouse Program. The results of this search will be compared to reviewing the MS-CHONY Division of Pediatric Cardiology Echocardiography, Catheterization Lab, Exercise Testing, and Patient Care Databases, as well as a search on the WEBCIS system for ICD-9 codes for cardiomyopathy, congenital heart disease, congestive heart failure, and decreased ventricular function in patients between birth and twenty-one years of age. This is to insure the external validity of the study: to insure that we are taking a representative sample of patients who are being treated for congenital heart disease, cardiomyopathy, and other causes of diminished ventricular function.

I. Confidentiality

We will maintain appropriate security measures for the subject identifiers, including a) storing physical files in a locked cabinet to which only study staff have access with a key and b) maintaining a secure database to which the PI and key study staff have access via a password.

We will formulate a coding system for patients, which is independent of identifying information. Identifiers will be listed on a sheet that matches each patient and their personal health information with their unique identifier. This sheet will remain separate from the database in a locked cabinet in the Division of Pediatric Cardiology. It will be destroyed at the conclusion of research. Only study staff will

have access to the PHI. Because the study is retrospective we do not anticipate any scenarios that would obligate us to contact other bodies and pass on PHI.

We are requesting a waiver from consent. This study poses no risk of harm to participants and the study would be unfeasible if consents were required. This a retrospective study, no further information will be gathered from patients and no contact with patients will be required, and there is no risk to participants. Additionally, this retrospective study requires a large number of patients who were treated at this institution. Many of them were severely ill at the time that their information was gathered, and, sadly, many may be deceased. These two factors would make collecting consents difficult or impossible.

This retrospective study however is also intended as a pilot study for a prospective trial in the same population. We would like to maintain access to PHI as a means of contacting the patients in the event that information affecting their care emerges from the results of the study and to recruit them for potential prospective studies.

J. Conflict of Interest

N/A

K. Location

This is a retrospective study utilizing data collected from patients who were seen and cared for at both Columbia University Medical Center and Morgan Stanley Children's Hospital of New York in New York City, New York. There are no additional institutions participating.

L. Potential Risks

This is a retrospective trial and thus there are no direct risks to speak of. We will protect patient confidentiality in as strict a manner as possible (see below).

M. Potential Benefits

As a retrospective study there is little chance that the individual participant will directly benefit from having their information as part of this study. However, this study aims to begin developing evidence-based strategies and algorithms for optimally managing heart disease, and participation in this study will benefit future generations of children with these conditions.

N. Alternative Therapies

N/A

O. Compensation to Subjects

N/A

P. Costs to Subjects

N/A

Q. Minors as Research Subjects

This is a study of pediatric heart disease. Our particular interest is in disease entities that are congenital (congenital heart disease) or have overwhelmingly higher incidence in a pediatric population (idiopathic dilated cardiomyopathy). Our interest is centered on how these diseases affect children, and therefore the research can only be performed with participation of children.

R. Radiation or Radioactive Substances

N/A

S. References

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