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BNP levels in children with asymptomatic hypertrophic cardiomyopathy compared to healthy children: A possible screening test for sudden cardiac death in young athletes

1. Study Purpose and Rationale:

Sudden cardiac death (SCD) in young athletes in the United States is rare but devastating, causing considerable emotional and social impact on the general public and physician community. The precise frequency which sudden death occurs in young athletes is unknown, however the incidence of sudden death due to undiagnosed cardiovascular disease is reported to be about 1 in 220,000 (1). Approximately 90 competitive young athletes die suddenly and unexpectedly in the US each year. The average age is 17 to 23 years old, and up to 90% occurs during training or competition (1,2,3). A variety of cardiovascular diseases represent the most common causes of sudden death in athletes less than 35 years old, with the vast majority of them being congenital or acquired cardiac malformations. Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in these athletes, representing more than one third of the cases (4). HCM is a genetic disease of the cardiac sarcomere, caused by mutations in one of several genes, most of which encode components of the contractile apparatus. It has an autosomal dominant pattern of inheritance, and a gene mutation is identified in approximately 50-60% of the cases. It is characterized by asymmetrical hypertrophy of the left ventricle (without an identifiable hemodynamic cause), with variable clinical manifestations and morphologic and hemodynamic abnormalities. It occurs in about 1:500 in the general population (5)

In the United States, the current recommendation by the American Heart Association (AHA) is to screen all athletes for silent cardiovascular disease by taking a history and physical exam annually, focusing on 12-particular elements. Related to cardiovascular disease. Performing a 12-lead EKG is not recommended due the high false positive rate and the unfavorable cost-benefit analysis giving the relatively low prevalence of SCD in athletes. However, the quality of our current screening methods have come under scrutiny because of the inadequacies of questionnaires used for history taking and the level of training and expertise of individuals performing the examinations. One retrospective study, looked at 134 athletes who died suddenly and demonstrated that cardiovascular abnormalities were suspected by history and physical screening in only 3% (6). This finding is not surprising given that most patients with HCM have the non-obstructive form, with no or just a soft murmur, and only a few patients will have symptoms or report a definitive family history. There clearly needs to be improved screening methods in young athletes to help prevent the devastation of SCD during training or competition.

Brain, or B-type natriuretic peptide (BNP) is a 32 amino acid peptide synthesized and secreted from heart, primarily from the ventricle in response to left

ventricular wall stress. It has been shown to cause natriuresis, inhibit the plasma rennin-angiotensin-aldosterone system, reduce plasma volume, and modulate vascular tone (7). The primary stimulus for natriuretic peptide (NP) release is myocyte stretch, and they are synthesized as pre-prohormones, which are cleaved to prohormones, and at release from the cells, are cleaved to C-terminal biologically active peptide (BNP), and an N-terminal prohormone (NT-proBNP) that has no known biologic action (8). Plasma levels of NP's are elevated in many cardiac diseases, and therefore serve as a marker for heart disease in both pediatrics and adults. BNP and NT-proBNP can both be measured on a commercial laboratory platform and widely used in practice. In adult and pediatric population, BNP and NT-proBNP have shown good correlation, and neither has been shown to be superior. BNP and NT-proBNP plasma levels have been shown to be elevated in a wide range of heart disease, including ischemic heart disease, left ventricular and diastolic dysfunction, congenital heart defects, dilated cardiomyopathy, and hypertrophic cardiomyopathy. In addition, it has been shown to predict prognosis in adults and children with chronic heart failure (9).

Currently, the use of BNP or NT-proBNP levels as a screening tool for patients with asymptomatic hypertrophic cardiomyopathy is unclear. In adults with HCM, BNP levels correlate with heart failure symptoms, maximal wall thickness, systolic and diastolic dysfunction, and exercise capacity. One study in an adult population did show a statistically significant difference between patients with asymptomatic HCM and age-matched normal controls (10). However, there is limited data on HCM and BNP levels in the pediatric population. Kaski, J.P. et al. (9) looked at BNP levels and clinical features in pediatric patients with HCM. He found 71% of the patients had BNP levels exceeding the upper limit of normal defined as 32.7 pg/ml, and that BNP levels correlated with other markers of disease severity, including maximal LV wall thickness, LV outflow obstruction, left atrial size and echocardiographic measures of LV filling pressures. BNP levels did not correlate with subjectively assessed symptoms. A number of mechanisms may explain increase BNP levels in HCM patients, including local myocardial factors such as myocyte disarray and myocardial hypertrophy, and ventricular and hemodynamic alterations such as LV outflow tract obstruction, raised LV filling pressures, and myocardial ischemia. Pagourelias, E.D. et al. (11), in a pilot study showed in young adults (age 20-45yo), a BNP level <11.8 pg/ml had a specificity of 88% and a negative predictive value of 74% for excluding HCM in athletes. Other studies looking at BNP levels in athletes did not show a significant difference in BNP or NT-proBNP levels compared to publish normal values, and only weakly correlated with type or intensity of exercised performed (12). To my knowledge there has been no study comparing asymptomatic children with HCM compared to normal controls. I hypothesized that children with asymptomatic HCM will have higher BNP levels than healthy children, and a cutoff value that optimizes sensitivity and specificity can be determined to use as a adjunctive screening tool.

2. Study Design and Statistical Procedures:

This will be a prospective, case-control study to evaluate plasma BNP levels in asymptomatic children with HCM between the ages of 8-21 years old compared to

age matched healthy children. Children with HCM, who are seen for either a new patient or follow-up visit, and do not have any cardiac symptoms will be eligible for the study. The primary cardiologist will fill out a checklist containing yes or no questions to evaluate each patient for any cardiac symptoms, including chest pain, syncope, pre-syncope with exertion, dyspnea (at rest or with exertion), and/or palpitations. These selected patients will then be consented to get BNP levels drawn. Additional information will be collected as well, such as ethnicity, age, gender, BMI, EKG findings, Echo findings, heart rate and blood pressure measurements. Patients for the normal control group will be recruited at one of the 4 associated Columbia University pediatric ambulatory clinics. Children between the ages of 8 to 21 years old who are being seen for a well-child care visit, and have no chronic or acute medical conditions will be eligible for the study. Once they are consented, a trained phlebotomist from the clinic will obtain a BNP level from a venipuncture, which will be sent directly to the Columbia University Medical Center Laboratory. Other data such as ethnicity, age, gender, BMI, heart rate and blood pressure will collected as well. In addition, the pediatrician will fill out a form evaluating the patients for any cardiac symptoms as listed above, as well as family history of HCM, and/or sudden death in a young person (under 35 years old).

The primary outcome will look at BNP levels in asymptomatic children with HCM compared to age-matched healthy children. Based on the amount of patients with HCM that are seen annually at the Children's Hospital of New York's Cardiomyopathy Clinic, I expect to enroll 30 patients in case group. In order to increase the power of the study, I will enroll 120 controls matched for age and gender. For my power analysis, I will use published normal BNP levels, which slightly differed in boys and girls (age 2weeks old to 17years old) mean (SD) of 7 (5.9) and 10.1 (8.6), respectively (13). I will take an average standard deviation of the two groups, to be 7.3. I will use the unpaired t-test to compare the means of BNP levels amongst the two groups controlling for age and gender. In order to achieve 80% power with a p-value of 0.05,with a 4:1 control to study group ratio, I will need to see a difference of 4.2pg/ml between the two groups. Sensitivity, specificity and positive and negative predictive values will be calculated for a selected BNP cut-off point, to optimize the significance of the test as a screening tool for HCM in otherwise seeming healthy children.

3. Study Procedures:

Plasma BNP levels will be collected by venipuncture on all studied patients by a trained phlebotomist, and placed in tubes containing EDTA. BNP levels will be measured in the Columbia University Medical Center Laboratory using Triage BNP assay (Biosite Diagnostics, San Diego, California, USA), a two-site fluorescence immunoassay for BNP in whole-blood specimens (13). There are minimal risks to this procedure (please see below).

4. Study Drugs or Devices:

N/A

5. Study Questionnaires:

N/A

6. Study Subjects:
Inclusion Criteria:
Study Group:
- 8-21 years old with HCM (as diagnosed by cardiologist with EKG/ECHO findings)
–Seen at CHONY's Cardiomyopathy Clinic as either a new patient or follow-up visit

Control Group:
–8-21 years old
–Seen at annual well-child care visit at one of the four CHONY ambulatory clinics

Exclusion Criteria:
Study Group:
Any patient with prior or current cardiac symptoms, including syncope, presyncope with exertion, chest pain, dyspnea at rest or with exertion, and/or palpitations.
History of prior cardiac arrest
History of ICD placement
History of any cardiac surgery
History of any other cardiac abnormalities
Metabolic or syndromic HCM, including Noonan syndrome

Control Group:
Chronic or acute medical condition
Cardiac Symptoms (see above)
Family history of HCM and/or sudden death in person younger than 35 years old

7. Recruitment:

Patients in the study group will be recruited from the Children's Hospital of New York Cardiomyopathy Clinic, after their primary cardiologist gets their permission to be consented for the study. They will be recruited at either their first visit or a follow-up visit. Patients in the control group will be recruited at their well child visit, after getting permission for their primary medical doctor to speak with them regarding the study.

8. Confidentiality of Study Data:

All patients will be giving a unique study ID # and their name and MRN# will be removed from the database to ensure confidentiality. There will be a separate encrypted file correlating patient identifiers to this study number. There will be limited password protected access to this file. All study material will be kept in a locked office and password protected computers as well.

9. Potential Risks:

There are minimal risks associated with venipuncture, which include excessive bleeding, hematoma, fainting, and/or infection.

10. Potential Benefits:

Potential benefits to patients from this study are that if BNP is determined to be sensitive and specific marker for HCM, it may serve as a way to help screen a large amount of children for this potentially fatal disease. The current study does not offer any direct benefit for patients with HCM, but indirectly it may help better understand the disease process.

11. Alternatives:

Currently the only screening tool for HCM that is recommended by the American Heart Association (AHA) is from history and physical exam, including family history. AHA does not currently recommend screening children with an EKG (4).

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