Kinesiology Faculty Publications and Presentations   Department of Kinesiology

3-1-2009

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Does Cardiac Morphology Predict Plasma Brain Natriuretic Peptide Levels in Adolescent Athletes?

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Abstract

Objective
The purpose of this study was to establish the relationship of plasma levels of brain natriuretic peptide (BNP) to physiological parameters and cardiac morphological characteristics in a population of young athletes. Our hypothesis is that physiological and cardiac morphological characteristics do not predict BNP levels in adolescent athletes.

Design
Observational study

Setting
Outpatient hospital

Patients
30 healthy male adolescent high school football players (16.0 +/- 1.1 yrs)

Intervention
Physical exam, electrocardiography, plasma BNP measurement by rapid fluorescent immunoassay, and limited echocardiography

Main Outcome Measure
Null hypothesis: physiologic parameters and cardiac morphology do not predict plasma BNP levels in healthy adolescent football players. Significance level set at $p < 0.05$.

Results
Plasma BNP for this population was 11.9 +/- 10.2 pg·ml⁻¹. There was no correlation between BNP and mean arterial pressure ($r = -0.09$, $p = 0.64$), BMI ($r = 0.11$, $p = 0.57$), interventricular septal thickness ($r = -0.15$, $p = 0.44$), left ventricular wall thickness ($r = 0.00$, $p = 0.99$), relative wall thickness ($r = -0.04$, $p = 0.84$), left ventricular mass ($r = 0.05$, $p = 0.79$), or left ventricular mass index ($r = 0.11$, $p = 0.55$).

Conclusion
Plasma BNP levels in healthy adolescent athletes have no correlation to BMI or LV mass, even when corrected for body surface area.

Keywords child; electrocardiography (EKG); cardiac physiology; echocardiography

Introduction.

Brain, or B-type, natriuretic peptide (BNP) is a 32 amino acid peptide synthesized and secreted from the human heart in response to left ventricular wall stress. It has been shown to cause natriuresis, inhibit the renin-angiotensin-aldosterone system, reduce plasma volume, and modulate vascular tone [1]. Plasma BNP

levels have been reliably demonstrated to be elevated in several cardiomyopathic states, including systolic and diastolic dysfunction, left ventricular hypertrophy, hypertrophic cardiomyopathy (HCM), and abnormal left ventricular filling patterns [1, 2]. BNP levels have been found to be transiently elevated in competitive athletes engaged in endurance events[3]. Although plasma levels of BNP have been studied in healthy adult athletes and found to correlate to LV mass [4], this is not without contradictory findings [5]. It has been suggested that BNP may be useful to screen for HCM in young athletes[6].

Bedside testing of plasma BNP levels is rapid, inexpensive, and shows linear measurements of BNP between 5 and 1300 pg·ml⁻¹. Normal values for plasma BNP have been established in healthy controls from neonates to adolescents [7]; however, there are no data currently available regarding correlation of BNP and physiologic characteristics of hearts in young athletes. The purpose of this study is to measure plasma levels of brain natriuretic peptide (BNP) and determine its correlation to physiological parameters and cardiac morphological characteristics in a population of young athletes.

Methods.

30 males between the ages of 14 and 18 from the local state champion high school football team were asked to voluntarily participate upon scheduling a state-required preparticipation physical exam. For purposes of detecting a meaningful difference in BNP levels from published reports, a cohort of 30 subjects should yield a statistical power >0.8, the number being capped at 30 due to availability of study resources. Participants would have been excluded from consideration if they had known cardiac disease or congenital malformation, kidney disease, or history of cardiac surgery; none met exclusion criteria.

Data collection occurred during the off-season (summer). Participants refrained from hard physical activity for 24 hours prior to the study. Study subjects filled out a standardized questionnaire for preparticipation physical exams, had blood pressure, heart rate, height, and weight determination, and underwent physical exam.

A single venous sample of blood was collected from each participant. Plasma BNP levels were then measured according to the manufacturer's instructions within two hours on the Triage® BNP testing meter (Biosite, Inc., San Diego, CA).

Each study participant had an electrocardiogram (EKG) performed which was interpreted by a board certified pediatric cardiologist. Each study participant underwent limited left ventricular echocardiography while the pediatric cardiologist was present to oversee the procedure and interpret the results. The pediatric cardiologist was blinded to the results of the BNP measurement.

> LV mass index was calculated by dividing the LV mass by body surface area (BSA).
> Left ventricular wall thickness = IVSTd + LVPWd
> Relative wall thickness = IVSTd+LVPWd / LVEDD

Descriptive statistics were employed to define the cohort, and EKG findings were described. BNP levels were compared with univariate linear regression analysis to BMI, mean arterial pressure, and echocardiographic parameters. Significance level defined as $p < 0.05$. All statistics were completed on SPSS v.10.0 (SPSS, Inc., Chicago, IL).

Ethical considerations.

Institutional Review Board approval was obtained from Boise State University prior to study initiation. Written informed consent was obtained from all participants and their legal guardians.

Results.

Characteristics of study subjects are presented in **Table 1.** There were no abnormal cardiovascular findings on any physical exam.

Electrocardiographic characteristics of study subjects are presented in **Table 2**. No echocardiographic abnormalities were found.

Plasma BNP measurements (mean +/- SD) were 11.9 +/- 10.2 pg·ml⁻¹ and ranged from undetectable (<5 pg·ml⁻¹) to 41.7 pg·ml⁻¹.

Echocardiographic characteristics of study subjects are presented in **Table 3**.

There was no significant correlation between BNP values and mean arterial pressure (r = -0.09, p = 0.64), BMI (r = 0.11, p = 0.57), interventricular septal thickness (r = -0.15, p = 0.44), LV wall thickness (r = 0.00, p = 0.99), relative wall thickness (r = -0.04 p = 0.84), LV mass (r = 0.05, p = 0.79), or LV mass index (r = 0.11, p = 0.55). Scatter diagram is shown in **Figure 1.**

Discussion.

Our results document levels of plasma BNP as well as the electrocardiographic and echocardiographic characteristics of a healthy young male group of athletes, and find no significant correlation between the plasma BNP levels measured in these athletes and BMI, MAP, or observed cardiac parameters.

Morphologic evaluation of the heart has been reliably conducted since the early 1970's with echocardiography, the noninvasive use of ultrasound-generated images of the heart to quantify cardiac dimensions and dynamic function [8]. Since that time, ranges of cardiac dimensions have been studied and described in virtually all populations, including children[9, 10], athletes [4, 11-17], and patients with HCM [18, 19]. Echocardiography has also allowed the morphologic characterization of athlete's heart syndrome, a constellation of physiologic adaptations to exercise that maintains or enhances cardiac function in response to stress.[20] The development of biventricular enlargement in athlete's heart syndrome presents a challenge in differentiating young athletes with HCM from those with cardiac adaptation to exercise.[21] Reference echocardiographic measurements in children and adolescents have been historically based on normalizing values to body surface area[9, 10]. Studies describing norms and upper limits of cardiac measurements in young athletes are given for comparison in **Table 4**. Echocardiography in our study population (**Table 3**) did not reveal any pathologic cardiac lesions, and measurements obtained were mostly below the upper limits of normal in young athletes.

The EKG findings in our population of athletes were in keeping with prior descriptions of athletic subjects [20] and of normal adolescents. All of the features noted by electrocardiography have been found in populations of athletes without pathologic cardiac changes, and have been attributed to physiologic adaptation to enhance cardiac function, including increased parasympathetic tone and biventricular enlargement [20]. This underscores an important point about electrocardiography in athletes and adolescents: benign aberrances in EKG's are common, and may demonstrate an electrophysiologic adaptation to exercise that has not grossly manifested as a morphologic adaptation. In this regard, these EKG findings should be viewed as normal.

The Breathing Not Properly study established BNP levels > 100 pg/ml to be sensitive at differentiating CHF from lung disease in the emergency department[22]; this has been further stratified to differentiate "gray zone" BNP levels from 100-500 pg/ml in the REDHOT study[23]. In practice, utilizing BNP for heart failure diagnosis and monitoring must take into consideration factors such as age and gender, but there are generally no situations where BNP levels are routinely and persistently elevated >100 pg/ml without underlying cardiac pathology[24]. We were able to identify three studies published specifically to describe normal levels of BNP in neonates to adolescents[7, 25, 26]. Several studies have reported the value of using plasma BNP levels in children to assess status of various cardiac disorders, including VSD[27], heart

transplant[28], CHF vs. lung disease[29], chemotherapy[30], Duchenne's muscular dystrophy[31], Kawasaki[32], and congenital heart disease[33, 34]. These studies have reported BNP levels from 20 – 100 pg/ml as sufficiently sensitive and specific to discern a clinical difference. While the utility of BNP measurement in HCM has yet to be fully elucidated[35, 36], it has been suggested that increased expression of BNP may be a characteristic feature of HCM[2]. BNP values from our study population of 11.9 +/- 10.2 pg·ml⁻¹ are comparable to prior studies of BNP levels in normal adolescents [7, 26] (Table 5). To our knowledge, this is the first study on BNP levels in a population of adolescent athletes.

It should be acknowledged that this study was limited by a small sample size and the fact that no subjects showed abnormal cardiac structural changes. Results should be interpreted in this light and used as a basis for further studies on the subject.

Conclusions.

Our findings demonstrate that adolescent athletes have similar levels of BNP when compared to normal healthy children, and imply there is no correlation between LV morphology and BNP levels in a young healthy athletic population. Future research should evaluate BNP levels in other athletic groups and in athletes with echocardiographic changes of increased LV mass, to better define the role of BNP levels in detecting cardiac pathology.

Acknowledgments.

Conflicts of interest.

All authors report no conflicting interest

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Table 1 Characteristics of study subjects. Values are mean +/- SD.

Age (yrs)	16.0 +/- 1.1
BMI	23.8 +/- 3.1
BSA (m²)	1.9 +/- 0.2
HR	62.6 +/- 8.7
Systolic blood pressure	118.9 +/- 12.3
Diastolic blood pressure	69.6 +/- 7.9
MAP	86 +/- 7.8

Table 2 Frequency of electrocardiographic findings in study subjects

Sinus arrhythmia	13
Bradycardia (HR < 60 bpm)	12
Normal	7
Left ventricular hypertrophy (R wave in aVL > 11 mm)	2
Early repolarization (benign ST segment elevation)	2
Intraventricular conduction delay (QRS > 0.10 s)	2
Rightward axis (90-120 degrees)	1
Short PR (PR < 0.12 s)	1
Fusion complexes with ventricular escape	1

Table 3 Echocardiographic measurements. IVSTd = interventricular septal thickness in diastole; LVPWd = LV posterior wall thickness in diastole; LVEDD = left ventricular end diastolic dimension. Values given as mean +/- SD.

N	30
Median Age (yrs)	16.0 +/- 1.1
IVSTd (mm)	8.4 +/- 1.6
LVPWd (mm)	9.2 +/- 1.6
LVEDD (mm)	51.9 +/- 4.1
LV wall thickness (mm)	17.6 +/- 2.8
LV mass (g)	190.2 +/- 38.7
LV mass index (g/m²)	98.3 +/- 17.6

*Table 4. Echocardiographic measurements from other studies for comparison, presented as mean +/- SD. See Table 3 for abbreviation key. *Normative data presented by body surface area (BSA); these data are presented for a BSA of 2.0 m². †A review of 25 prior studies.*

Study	n	Median Age (yrs)	IVSTd (mm)	LVPWd (mm)	LVEDD (mm)	LV mass (g)	LV mass index (g•m⁻²)
Kampmann*[10]	2036		9.3 +/- 1.25	8.1 +/- 1.5	53.4 +/- 4		
Maron†[15]	381-701	23	10.4	10.7	53.9	265	
Somauroo, et al[14]	171	16.7	10.3 +/- 1.4	10.0 +/- 1.5	51.4 +/- 3.9	229.8 +/- 44	
Sharma, et al[17]	720	15.7	9.4 +/- 1.3	9.3 +/- 1.3	50.8 +/- 3.7		113 +/- 33.3
Date - Dynamic[4]	20	26.8 +/- 8.5				318.3 +/- 48	
Date - Static[4]	15	24.7 +/- 2.6				496.2 +/- 114.8	
Almeida, et al[5]	8	29.9 +/- 0.8					180.7 +/- 10.3
Yamazaki, et al[16]	7	20 +/- 1					152.3 +/- 16.2

Table 5. Plasma BNP measurements from previous studies of children and adolescents. BNP values given as mean +/- SD.

Study	n	Age (yrs.)	BNP (pg•ml⁻¹) +/- SD
Ationu & Carter[25]	20	10.0-15.0	31 +/- 4
Koch & Singer[7]	31	10-17.6	5.1 +/- 3.5
Yoshibayashi, et al.[26]	40	0-16	9.3 +/- 4.8
Kunii, et al.[37]	253	0-16	5.3 +/- 3.8
Ohuchi, et al.[38]	54	1.0-40	4 +/- 4
Law, et al.[34]	17	0.3-18.5	22 +/- 5

Figure 1 Scatter diagram of physiologic paramaeters vs. BNP levels