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B-Type Natriuretic Peptide as a Marker for Cardiac Dysfunction in Anthracycline-Treated Children

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Background. Anthracyclines (AC) are useful antineoplastic agents, whose utility is limited by progressive cardiotoxicity. Our purpose was to evaluate plasma B-type natriuretic peptide (BNP), as a screening test for detecting late cardiac dysfunction in AC-treated children and to determine the prevalence of late cardiac dysfunction at low cumulative AC doses. ***Materials and Methods.*** This was a prospective study in which patients who had completed AC therapy at least 1 year earlier, underwent a detailed echocardiogram and a simultaneous BNP level. Cardiac dysfunction was defined as any one of the following: shortening fraction (FS) <29%, rate corrected velocity of circumferential fiber shortening (VCFc) $<0.9\ c\cdot sec^{-1}$, end systolic wall stress (ESWS) $>60\ g\cdot cm^{-2}$, abnormal VCFc: ESWS ratio or decreased mitral inflow velocity (E/A) ratios, compared to age-specific norms. ***Results.*** The cohort (n = 63) included 37 males with a median age of 13.1 years (range, 6.5–26.5 years). Cardiac dysfunction was found in 26 (41%) patients and in 40% of patients who received cumulative doses $<150\ mg\cdot m^{-2}$. ESWS was the most common abnormality. Mean BNP levels in the subset with abnormal function were significantly higher than the normal group (23.4 ± 25.3 vs. $14.2 \pm 8.9\ pg\cdot ml^{-1}$, $P = 0.02$). ***Conclusions.*** Plasma BNP was significantly elevated in AC-treated patients with late cardiac dysfunction, although there was considerable overlap of levels between groups with and without cardiac dysfunction. BNP may need further evaluation as a serial index of cardiac function in this population. Cardiac dysfunction was observed in a significant proportion of patients, even at low cumulative AC doses. Pediatr Blood Cancer 2007;49:812–816.

Key words: Anthracyclines-induced cardiotoxicity; BNP

INTRODUCTION

Anthracyclines (AC) are highly effective chemotherapeutic agents, whose full clinical potential is limited by cardiac toxicity (ACT) [1–4]. ACT is progressive, may become manifested many years after the completion of treatment and occurs at variable threshold doses [5–8]. The evolution of AC-induced subclinical cardiac dysfunction is not clearly understood and other than vigilant monitoring, there are no explicit guidelines for its management [6,9–11]. Therefore, each AC recipient requires monitoring for cardiotoxicity for a long period of time, the duration of which is not known.

Monitoring for ACT is most simply accomplished by echocardiographic measures, including fractional shortening (FS) and ejection fraction (EF) [12]. However, these measures are dependent on ventricular loading conditions and lack sensitivity for detecting ACT [13,14]. FS alone is reduced in 28% of AC-treated patients, whereas 57% have an abnormal left ventricular afterload, as measured by end systolic wall stress (ESWS) or contractility measured by the stress velocity index (SVI) [3]. These more sophisticated parameters are technically difficult to obtain in children. An objective, easily obtained biomarker of ventricular function would greatly add to the clinical care of AC-treated patients.

Plasma B-type natriuretic peptide (BNP) is a cardiac hormone secreted from the ventricles, in response to ventricular volume and pressure overload [15]. Levels increase in proportion to the severity of congestive heart failure (CHF) in adults and children [16–18]. In the pediatric age group, values of BNP of 7 ± 5.9 and $10.1 \pm 8.6\ pg\cdot ml^{-1}$ have been reported in healthy boys and girls, respectively [19]. Comparable BNP levels are noted in neonates after closure of patent ductus arteriosus and children with cardiomyopathy, without clinical signs of heart failure [20,21]. The role of BNP in screening for late onset ACT remains to be elucidated. One previous study found plasma BNP to be significantly elevated in patients with a reduction of FS or EF [22].

The rationale for our study was that plasma BNP may be elevated in AC-treated patients with late cardiac dysfunction. Our primary objective was to evaluate plasma BNP as a screening test for detecting late onset AC-induced cardiac dysfunction, in comparison to detailed sensitive indices, not ordinarily available from a clinical echo.

Since the mid 1990s, cumulative AC doses have been empirically limited to below $550\ mg\cdot m^{-2}$ due to the high incidence of clinically important cardiotoxicity observed above this dose [23]. More recently, a further dose reduction to below $250\ mg\cdot m^{-2}$ has been suggested to reduce the incidence of ACT [9]. Limited information is available about the impact of progressive AC dose curtailment on the incidence of late cardiac dysfunction. Our secondary aim, therefore, was to define the prevalence of cardiac dysfunction using load-independent echocardiographic measures in a cohort of patients treated with low cumulative AC doses.

MATERIALS AND METHODS

This prospective non-interventional study was conducted at Children's Hospital of Michigan, after approval by the Human Investigation Committee. Patients were enrolled between October 2003 and June 2004 after obtaining written informed consent from parents or guardians.

Selection Criteria

Patients who had completed AC chemotherapy at least 1 year prior to enrollment were included. Patients with congenital heart

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disease, cardiomyopathy prior to initiation of chemotherapy, renal failure (serum creatinine more than twice the age-specific norms), patients who received mediastinal radiation, were pregnant or critically ill, were excluded. Each patient underwent an echocardiogram and simultaneous blood draw for BNP assay for research purposes.

Clinical Data

Clinical data obtained for each subject included demographics, clinical diagnosis, the cumulative dose of AC received, time elapsed since the completion of AC therapy, and cardiac symptoms.

Echocardiography

Echocardiograms were performed using a Phillips Sonos 5500 ultrasound machine. Each patient underwent M mode, 2D and Doppler echocardiogram with simultaneous recording of carotid pulse tracing, electrocardiogram, phonocardiogram, and blood pressure. Echo parameters were selected to measure (a) left ventricular systolic function (shortening fraction FS, ejection fraction EF and rate corrected mean velocity of circumferential fiber shortening VCFc), (b) afterload (end systolic wall stress ESWS), (c) contractility (Stress velocity index SVI), and (d) left ventricular diastolic function (peak E and A velocities and their ratio). FS and EF were calculated as described [24,25]. Shortening fraction below 29% and EF less than 64% were considered abnormal [12,25]. VCFc was obtained by the method described by Colan et al. [3,26] and considered abnormal below 0.90 $c \cdot sec^{-1}$. ESWS was calculated by the method described by Grossman et al. and considered abnormal above 60 $g \cdot cm^{-2}$ [3,27]. The SVI or the relationship between VCFc and ESWS were measured by the method described by Colan et al. [26]. A VCFc value two standard deviations below normal in relation to ESWS was considered to represent abnormal contractility [26,28]. E/A ratio was obtained by pulse Doppler at the mitral valve inflow and compared to established normal values [29]. All echocardiograms were read by a single cardiologist (MP) who was blinded to patient data and results of the BNP assay.

Abnormal cardiac function was defined by any one of the following criteria: FS <29%; VCFc <0.90 $c \cdot sec^{-1}$; ESWS >60 $g \cdot cm^{-2}$; abnormal VCFc: ESWS ratio; or decreased E/A ratio, based on age-specific normal values. EF was not included in our preset criteria of cardiac dysfunction due to inherent fallacies in its echocardiographic measurement in the pediatric age group [25].

Plasma BNP Assay

Blood samples (3 ml) were collected in K-EDTA tubes within 3 hours of the echocardiogram and were centrifuged immediately at 3,500 rpm for 10 min. Platelet-free plasma was stored at $-20^{\circ}C$. BNP assay was performed using the Triage BNP kit (Biosite Diagnostic, San Diego, California).

Statistical Analysis

Statistical analyses were performed using SPSS (version 12) software. Sample size was predetermined using a two-tailed test with a significance (alpha) set at 0.05 to achieve a power of 81%, based on the assumption that the BNP would be higher in patients with abnormal heart function on echocardiogram by 20 $pg \cdot dl^{-1}$ (corresponding to means $\pm$ SD of 9 ± 14.8 and 29 ± 31.2, respectively, based on a prior study) [22]. The number of patients required to achieve a power of 80% was 23 in each group. Since 50–60% of pediatric patients who receive AC have abnormal contractility and/or afterload, we enrolled 63 patients with an expectation of two nearly equal subsets—those with and without cardiac dysfunction [3]. Data were expressed as mean $\pm$ SD for continuous variables and as a number (percentage) for categorical variables. The two groups were compared for continuous variables using the Student *t*-test for independent samples [30]. Box and whisker plots of BNP levels were used to show the distribution in the subgroups based on cardiac function. Statistical significance was set as $P < 0.05$. All hypotheses were two tailed.

RESULTS

Subject Characteristics

Eighty patients were identified from the echo database in the cardiology clinic. Two could not be traced and 15 patients refused consent. Sixty-three patients were enrolled in the study including 37 (59%) males and 26 (41%) females. The median age at enrollment was 13.1 years (range, 6.5–26.5) and the median interval since completion of AC treatment was 3.8 years (range, 1.1–17.5). The clinical diagnoses included acute lymphocytic leukemia in 29 (46%), Wilms tumor in 12 (19%), osteosarcoma in 12 (19%), and lymphoma in 10 patients (16%). Five patients were on cardiac medications (ACE inhibitors and digoxin) for ventricular dysfunction, of whom three were symptomatic with CHF, while two had asymptomatic abnormal LV function. None of our patients had a history of acute cardiac failure immediately following an AC dose. The median cumulative dose of AC received was 165 $mg \cdot m^{-2}$ (range, 45–520; mean 160 $mg \cdot m^{-2}$). The cumulative AC dose received was less than 150 $mg \cdot m^{-2}$ in 29 (46%) patients, between 150 and 300 $mg \cdot m^{-2}$ in 20 (31.7%), between 300 and 450 mg/m^2 in 13 (20.6%) patients, and 520 $mg \cdot m^{-2}$ in 1 (1.5%). No patient received more than 550 $mg \cdot m^{-2}$.

Echocardiographic Data

Twenty-six (41%) patients had at least one cardiac abnormality on echocardiogram. The most frequently detected abnormality was ESWS (range, 61–86 $g \cdot cm^{-2}$; median 66 $g \cdot cm^{-2}$; mean 68.7 $g \cdot cm^{-2}$) in 20 patients (31.7%). The nine (14%) patients who had abnormal shortening fractions (range, 23–28; median 26%; mean 26%) also had low EF (range 54–63, mean 60). Seven out of 63 (11.1%) had abnormal VCFc (range 0.76–0.9; median 0.84 $c \cdot sec^{-1}$; mean 0.84 $c \cdot sec^{-1}$) and 6 patients (9.5%) had an abnormal stress velocity index. All three patients with clinical CHF had low FS; two had four abnormal parameters (FS, ESWS, VCFc, and SVI). Diastolic function (peak E/A velocities and their ratio) was normal in all patients, with the E/A ratios ranging from 1.33 to 3.05, with a mean (SD) of 2.06 ± 0.43 (median 2.03). Baseline characteristics of the groups with normal and abnormal cardiac function are shown (Table I). The two groups were similar in the mean cumulative dose of AC received (204.7 ± 100.6 $mg \cdot m^{-2}$ abnormal cardiac function vs. 223.1 ± 127.7 $mg \cdot m^{-2}$ normal cardiac function, $P = 0.54$) and interval post-AC treatment

TABLE I. Clinical and Demographic Characteristics

	Normal cardiac function	Abnormal cardiac function	*P*-value
Male gender	26/37 (70%)	11/26 (42%)	0.12
Median age at time of diagnosis of cancer (years)	7.1	5.7	0.74
Median age at time of enrollment (years)	12.1	14.3	0.96
Median interval Post-AC-treatment (years)	3.8	3.6	0.64
Median cumulative anthracycline dose ($mg \cdot m^{-2}$)	165	180	0.54

(5.6 ± 4.4 years abnormal cardiac function and 5.1 ± 3.7 years normal cardiac function, $P = 0.64$).

Table II shows the number of patients with each cardiac abnormality as a function of the cumulative dose received. Age at treatment, interval of follow-up, and cumulative dose were not risk factors for cardiac dysfunction on multivariate analysis. At all doses, ESWS was the most frequently detected abnormality, present in 9 of 12 (75%) at cumulative AC doses below 150 $mg \cdot m^{-2}$, 7 of 10 (70%) between 150 and 300 $mg \cdot m^{-2}$, and all 4 (100%) patients receiving 300–450 $mg \cdot m^{-2}$. Twelve out of 29 patients (40%) who had received cumulative doses below 150 $mg \cdot m^{-2}$ had evidence of cardiac dysfunction, including 4 patients who had received doses as low as 90 $mg \cdot m^{-2}$. The patient who received a cumulative dose of 520 $mg \cdot m^{-2}$ had normal cardiac function after 12.4 years of follow-up.

Plasma BNP

The median BNP level for the cohort was 12.2 $pg \cdot dl^{-1}$ (range, 5–117 $pg \cdot dl^{-1}$). Mean (±SD) plasma BNP levels were significantly higher in the presence of abnormal cardiac function (23.4 ± 25.3 $pg \cdot dl^{-1}$, $n = 26$ vs. 14.2 ± 8.9 $pg \cdot dl^{-1}$, $n = 37$, $P = 0.02$; Fig. 1). Plasma BNP levels were higher when FS was low (32.4 ± 34.9 ($n = 9$) vs. 15.6 ± 12.4 ($n = 54$), $P < 0.008$). When all four systolic parameters were abnormal, plasma BNP was significantly higher than when one to three parameters were abnormal (69.2 ± 67.1 ($n = 2$) vs. 19.6 ± 17.3 ($n = 24$), $P < 0.005$). Plasma BNP levels in the five subjects on cardiac medications were significantly higher than the rest of the cohort (49.8 ± 40.2 vs. 15.2 ± 11.9 $pg \cdot ml^{-1}$, $P < 0.001$). When the five patients on medications were excluded, BNP levels remained significantly higher when cardiac function was abnormal than when function was normal (19.4 ± 17.6 vs. 14.1 ± 8.9, $P = 0.02$). Table III depicts the mean plasma BNP levels in the subgroups with normal and abnormal function for each echocardiographic parameter. Plasma BNP was significantly higher in patients with abnormal FS, VCFc, and SVI, but not ESWS.

DISCUSSION

Among AC-treated patients, 41% had an abnormality of cardiac function at a mean follow-up interval of 5.2 years, the majority of whom were asymptomatic. Nine (14%) patients had abnormal FS and EF, the commonly used clinical parameters. The most sensitive echo parameter for diagnosis of subclinical ACT was ESWS, representing 80% of cardiac abnormalities, while contractility by SVI was abnormal in only 24% of patients. Patients receiving doses as low as 90 $mg \cdot m^{-2}$ had cardiac dysfunction. Plasma BNP was significantly higher in patients with cardiac dysfunction and when multiple echo parameters were abnormal. Plasma BNP was significantly elevated in the presence of abnormal contractility, although the elevation of BNP with increased ESWS did not reach statistical significance. These findings assume importance, given the growing numbers of AC treated patients and that AC use is mainly limited by cardiotoxicity [5–7,31].

Our finding of the association of an elevated BNP with late AC-induced cardiac dysfunction is similar to studies in adults, where a significant increase in plasma BNP has been noted in AC-treated patients with clinical or subclinical heart failure [32–34]. Previous data in children are limited. While one previous study reported elevation of plasma BNP (29 ± 31.2 vs. 9 ± 14.8 $pg \cdot ml^{-1}$) in patients with left ventricular dysfunction, compared to patients with normal function, another reported higher BNP levels in the AC-treated group as a whole, compared to untreated controls (10.5 ± 10.2 vs. 4.09 ± 2.2 $pg \cdot ml^{-1}$) [22,35]. Both studies enrolled patients soon after completion of AC therapy when LV dysfunction could represent acute toxicity, which is not predictive of late ACT. Neither study excluded patients who had received chest radiation, which can worsen ACT. Moreover, VCFc, ESWS, and SVI were not utilized.

To our knowledge, ours is the largest study to evaluate plasma BNP for the detection of late ACT using sensitive echocardiographic indices. We believe our finding of a mild but significant elevation in plasma BNP with cardiac dysfunction is of clinical interest. Although largely asymptomatic, an increase in plasma BNP may

TABLE II. Effect of Cumulative AC Dose on Echocardiographic Parameters of Cardiac Function

Dose/(n)	Any abnormality	Abnormal FS	Abnormal EF	Abnormal ESWS	Abnormal VCFc	Abnormal SVI
<150 $mg \cdot m^{-2}$ (29)	12	3	3	9	3	2
150–300 $mg \cdot m^{-2}$ (20)	10	5	5	7	3	3
300–450 $mg \cdot m^{-2}$ (13)	4	1	1	4	1	1
>450 $mg \cdot m^{-2}$ (1)	0	0	0	0	0	0
	26	9	9	20	7	6

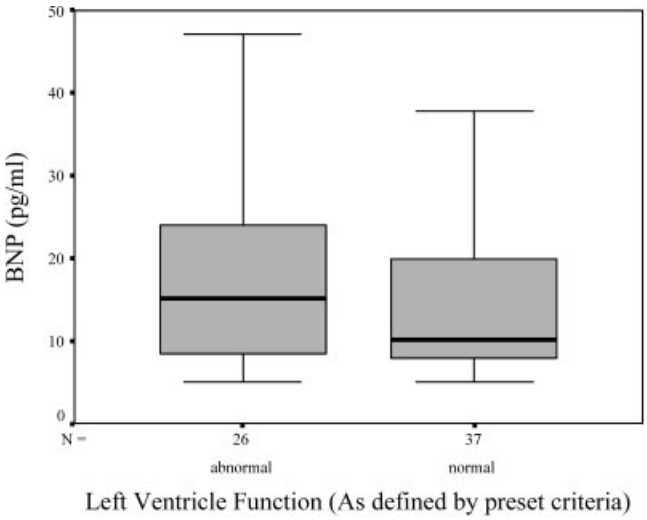

Fig. 1. Plasma BNP values in the groups with and without abnormal cardiac function as defined by specified criteria. The lower and upper bounds of the boxes indicate the 25th and 75th percentile values, respectively. The horizontal line indicates the median and the whisker bars represent the 10th and 90th percentiles.

be a biochemical surrogate for subtle but potentially progressive cardiac dysfunction. Indeed, the value of plasma BNP may lie in serial monitoring, where a change in plasma BNP may predict a decline in cardiac function for an individual patient. Further studies are needed to evaluate plasma BNP in this manner. We are currently conducting such a study.

A limitation of our study is that although plasma BNP was significantly higher from a statistical standpoint in patients with cardiac dysfunction, there was wide variation in the levels, precluding determination of a cut-off level with high sensitivity and specificity to discriminate between patients with normal cardiac function from those without. The overlap of BNP levels makes it unwise to use BNP as a sole screening method for ACT. BNP could not differentiate abnormal from normal ESWS in our study (mean BNP 23.5 abnormal vs. 15.4 normal ESWS). We suspect that our small sample size was not powered to detect differences in BNP in the subgroups for each individual echocardiographic parameter, which larger studies may uncover.

We also report the prevalence and characteristics of late cardiac dysfunction at curtailed AC doses, using sensitive echocardiographic parameters. Our observed prevalence of late cardiac abnormalities is similar to recent reports in which the mean cumulative AC doses were approximately 300 mg·m^{-2} [9,36–39].

TABLE III. Plasma BNP in Groups With Normal and Abnormal Function for Each Echocardiographic Parameter

	BNP (mean ± SD) pg·ml^{-1}		
	Abnormal function	Normal function	*P*-value
FS	32.4 ± 34.9	15.6 ± 12.4	0.009
VCFS	36.4 ± 39.1	15.6 ± 12.4	0.004
ESWS	23.5 ± 27.5	15.4 ± 10.7	0.09
SVI	32.3 ± 41.7	16.5 ± 13.4	0.04

Our finding that even in the children who received cumulative doses below 150 mg·m^{-2}, 40% had late cardiac dysfunction is novel and disturbing. We did not detect diastolic dysfunction in any of our patients, conflicting with some previous studies but consistent with others [40–42]. The established correlation between cumulative AC dose and cardiac dysfunction was not noted in our dataset, probably due to the small sample size.

Plasma BNP was significantly elevated in patients with late AC-induced cardiac dysfunction, although there was considerable overlap of levels in patients with normal and abnormal function. Serial measures of plasma BNP merit further evaluation for monitoring of AC-related cardiotoxicity. Even when treated with low cumulative AC doses, about 40% of AC-treated children had abnormal ventricular function.

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