# N-Terminal Pro Brain Natriuretic Peptide and Cardiac Function in Doxorubicin Administered Pediatric Patients

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***Objective:*** *Assess the use of N terminal pro brain natriuretic peptide (NT-pro BNP) to early diagnose ventricular dysfunction in doxorubicin-administered children.*
***Material and Method:*** *Fifty-five cancer patients who received accumulative dose of doxorubicin <300 mg/m$^2$ (group 1), 49 cases with accumulative dose $\geq$ 300 mg/m$^2$ (group 2) and 52 cases as a control group (group 3) were included in the study. Electrocardiogram, chest roentgenogram, echocardiogram, and serum NT-pro BNP were studied.*
***Results:*** *At age 1-10 years, there were significantly higher NT-pro BNP in group 2 than group1 (384 $\pm$ 291 vs. 92.2 $\pm$ 89 pg/ml; p = 0.001), and than group 3 (79 $\pm$ 92 pg/ml; p = 0.001). Patients with NT-pro BNP level >1 SD of the control group were more likely to have abnormal $\geq$ 2 echocardiographic parameters of left ventricular diastolic dysfunction than patients with NT-pro BNP $\leq$ 1 SD (OR = 3.8, 95% CI 1.18-12.5). Patients in group 2 were more likely to have abnormal $\geq$ 2 parameters of left ventricular diastolic dysfunction than patients in group 1 (OR = 2.8, 95% CI 1.07-7.7) and more likely to have NT-pro BNP >1 SD than group 1 (OR = 8, 95% CI 1.96-38.4). There were association of NT-pro BNP >1 SD, accumulative dose of doxorubicin $\geq$ 300 mg/m$^2$, and early left ventricular diastolic dysfunction by echocardiogram.*
***Conclusion:*** *Serum NT-pro BNP >1 SD has a high probability to diagnose early doxorubicin-induced cardiomyopathy in patient 1-10 years old.*

***Keywords:*** *Serum NT-pro BNP, Doxorubicin-induced cardiomyopathy, Diastolic dysfunction*

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Doxorubicin is an effective chemotherapy of cancer. However, the most serious side-effect is irreversible cardiomyopathy with grave prognosis[1,2]. At an accumulative dose of 450 mg/m$^2$, it was suggested to be the maximum dose in pediatric patients[3]. The exact mechanism of doxorubicin-induced cardiomyopathy remains unclear. However, most of the evidence indicated that the free radicals and oxidative stress might lead to a variety of subcellular damage in the myocardium[4,5]. Endomyocardial biopsy was reported to be the most sensitive and specific method to diagnose and monitor doxorubicin cardiotoxicity, however it had limitation in clinical use[6]. Guidelines had been developed for children who received doxorubicin[7]. The noninvasive methods to monitor and diagnose doxorubicin-induced cardiomyopathy were electrocardiography, serial echocardiography, and radionuclide ventriculography to assess left

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ventricular function. All had limited sensitivity to diagnose early cardiomyopathy[6]. Several studies have suggested that diastolic dysfunction was an early sign of doxorubicin-induced cardiomyopathy[8-11]. However, it required expertise to diagnose.

Brain natriuretic peptide (BNP) is mainly released from the ventricles. The releasing mechanism is induced by increasing wall stress in ventricles especially in congestive heart failure (CHF). The physiologic actions of BNP are prohibition of the sympathetic activity, vasodilatation, natriuresis, diuresis, and inhibition of the renin-angiotensin system[12]. BNP is released as a prohormone (pro BNP) and is cleaved into physiologically active BNP and the N-terminal fragment; NT-pro BNP. Both are in the circulation with different biological half lives: NT-pro BNP, 60-120 minutes and BNP, 20 minutes. NT-pro BNP is more stable in plasma and it accumulates at very high level in CHF, so it seems to be a more sensitive cardiac marker to diagnose CHF than BNP[13].

There was no difference in plasma BNP and NT-pro BNP in the assessment of ventricular function[14]. Many studies demonstrated that BNP could be used to follow-up left ventricular systolic and diastolic function during doxorubicin administration in adult patients[2,11,15-21]. Recently, there were a few studies in pediatric patients with doxorubicin administration showing that high levels of BNP correlated with impairment of left ventricular systolic function[22,23]. There was no study correlated NT-pro-BNP and cardiac function in children who received doxorubicin. Hence, our study attempts to correlate NT-pro BNP level and cardiac function in pediatric patients who have received doxorubicin for the earliest detection of ventricular dysfunction, which might alter the poor prognosis.

## Material and Method

### *Patients*

A cross-sectional study in oncologic pediatric patients was conducted at the Division of Hematology & Oncology and Outpatient Clinic, Department of Pediatrics, Siriraj Hospital between November 2004 and October 2005. Approval for the study was obtained from the Siriraj Hospital's Ethical Committee. Every consecutive hematologic malignancy patients who received the last dose of doxorubicin $\geq$ 1 month prior to the enrollment and whose parent consented for the study were recruited. The patients, age $\leq$ 18 years who had other health problems without cardiovascular disease and did not receive any kind of medications that affected the cardiovascular system were recruited as a control group.

### *Methods*

Demographic data, underlying diseases, and duration from the last dose of doxorubicin were recorded. Chest roentgenogram, electrocardiogram, echocardiography, and serum NT-pro BNP level were collected in patients who received doxorubicin. Echocardiography was performed with the Hewlett Packard Sonos 5500 (Hewlett-Packard Company, Andover, MA, USA) echocardiographic machine. All measurements were averaged from five cardiac cycles. Diastolic left ventricular function was assessed by Doppler flow in apical four-chamber and five-chamber views. The following parameters were measured:

Peak E: peak flow velocity of early left ventricular (LV) filling

Peak A: peak flow velocity of late LV filling

E/A ratio: ratio of peak early to peak late flow velocities

Deceleration time (DT): interval from peak E to baseline

Isovolumic relaxation time (IVRT): interval from aortic valve closure to mitral valve opening

Pulmonary vein systolic velocity (PVs)

Pulmonary vein diastolic velocity (PVd)

Pulmonary vein atrial reversal flow velocity (PVa) and duration (PVa dur)

PVs/PVd ratio: ratio of pulmonary vein systolic/diastolic velocity

Early diastolic dysfunction was defined by abnormal parameters of Doppler flow measurement at mitral valve inflow, left ventricular outflow, and pulmonary vein flow: < -1SD of peak flow velocity of early LV filling (E),< -1 SD ratio of peak early to peak late mitral inflow velocities (E/A ratio), >1 SD of deceleration time, >1 SD of isovolumic relaxation time, >1 SD of atrial reversal flow in pulmonary vein Doppler and >1 SD of atrial reversal flow duration in pulmonary vein Doppler. The normal diastolic function in children was based on the study of O'leary[24].

Left ventricular systolic function was assessed as fractional shortening; FS, and left ventricular ejection fraction; LVEF.

Three milliliters of blood was collected in glass tube containing EDTA for the measurement of NT-pro BNP level. Elecsys® 1010, 2010 or E170 (Roche Diagnostic Thailand Ltd, Bangkok, Thailand) with Electrochemiluminescence Immunoassay was used to measure the NT-pro BNP level in this study within

the range of 5-35,000 pg/ml. The accuracy of the measurement was 0.8-3% coefficient of variation.

***Statistical analysis***

All calculations were performed with SPSS program (version 10.0). Measured variables were described as mean ± SD, median (range) and Odds Ratio with 95% Confidence Interval. Statistical group comparisons were performed using the Kruskal-Wallis test and Mann-Whitney U-test for non-normal distribution variables. ANOVA and t-test were used for normal distribution variables. The Chi-Square test and Fisher's Exact test were used to test dichotomous variables. The significant level was set at p-value < 0.05.

**Results**

One hundred fifty six pediatric patients were included in the present study; 83 boys and 73 girls with mean age of 10.31 ± 3.7 years. One hundred and four cases had doxorubicin administration for cancer treatment and 52 cases with no doxorubicin administration and no cardiovascular problems. Fifty-five cases received doxorubicin at accumulative dose < 300 mg/m$^2$(group 1), 49 cases with accumulative dose ≥ 300 mg/m$^2$ (group 2), and 52 cases with normal cardiovascular system as a control group (group 3). Detail of mean NT-pro BNP levels of the three groups were demonstrated in Fig. 1. There were no statistical significant of age, gender, weight, height and duration from the last doxorubicin dosage among the three groups. However, there was a significant difference of serum level of NT- pro BNP among the three groups (p = 0.001) as shown in Table 1. There were also significant difference of underlying diseases in group 1 and 2. Chest x-ray, EKG, and echocardiographic data of group1 and 2 as shown in Table 2 were not different between the two groups.

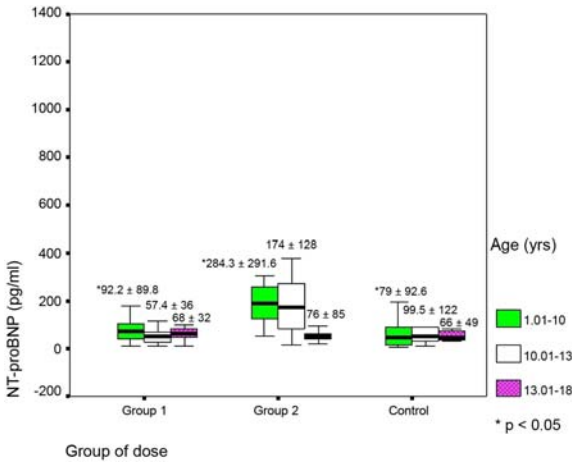


**Fig. 1** Serum NT-pro BNP level of the three groups in different ages

**Table 1.** Comparison of demographic data and serum NT-pro BNP level among the 3 groups

| | Group 1 < 300 mg/m$^2$ (55) | Group 2 ≥ 300 mg/m$^2$ (49) | Group 3 Control (52) | p-value |
|---|---|---|---|---|
| Age (years) | 10.3 ± 3.5 | 10.9 ± 3.6 | 9.6 ± 3.8 | 0.172 |
| Gender | | | | |
| | Male 33<br>Female 22 | Male 29<br>Female 20 | Male 21<br>Female 31 | 0.076 |
| Body weight (kg) | 36.6 ± 16.5 | 33.1 ± 14.9 | - | 0.286 |
| Height (cm) | 135.5 ± 21 | 134.4 ± 19.3 | - | 0.597 |
| Underlying diseases | | | | |
| | ALL 36<br>ANLL 12<br>Osteosarcoma 2<br>Lymphoma 1<br>Hepatoblastoma 4 | ALL 15<br>ANLL 7<br>Osteosarcoma 6<br>Lymphoma 5<br>Hepatoblastoma 3<br>Neuroblastoma 11<br>Sarcoma 2 | - | 0.001* |
| Duration from last dosage (months) | 40.9 ± 32.4 | 33.5 ± 32.8 | - | 0.238 |
| NT-pro BNP (pg/ml) | 75.0 ± 65.7 | 190.0 ± 228.9 | 101.2 ± 124.5 | 0.001* |

ALL, Acute lymphoblastic leukemia; ANLL, Acute non-lymphoblastic leukemia *p < 0.05

**Table 2.** Comparison of CXR, EKG and echocardiographic data between group 1 and 2

| | Group 1 $< 300$ mg/m$^2$ (55) | Group 2 $\geq 300$ mg/m$^2$ (49) | p-value |
|---|---|---|---|
| CXR | | | |
| CT ratio | 0.43 ± 0.04 | 0.43 ± 0.04 | 0.753 |
| EKG | | | |
| % of HR from normal | 96.50 ± 18.6 | 89.90 ± 13.1 | 0.163 |
| QRS duration (sec) | 0.056 ± 0.008 | 0.057 ± 0.008 | 0.659 |
| Echocardiography | | | |
| LA (mm) | 23.70 ± 3.0 | 23.00 ± 3.5 | 0.411 |
| LVEDD (mm) | 41.80 ± 6.7 | 41.60 ± 6.1 | 0.905 |
| SD of LVEDD | 1.60 ± 0.2 | 1.68 ± 0.02 | 0.186 |
| LVESD (mm) | 27.90 ± 4.6 | 27.90 ± 4.5 | 0.925 |
| LVPWD (mm) | 8.60 ± 2.5 | 7.90 ± 2 | 0.263 |
| FS (%) | 33.10 ± 4.4 | 32.80 ± 4.3 | 0.609 |
| EF (%) | 62.00 ± 5.8 | 61.50 ± 5.9 | 0.597 |
| E (mm) | 97.90 ± 19.7 | 93.90 ± 19.2 | 0.172 |
| A (mm) | 56.80 ± 12 | 57.30 ± 11.5 | 0.994 |
| SD of A | 1.70 ± 1.37 | 1.74 ± 1.19 | 0.717 |
| E/A | 1.70 ± 0.4 | 1.67 ± 0.3 | 0.659 |
| SD of E/A | -0.91 ± .64 | -0.99 ± .61 | 0.591 |
| DT (msec) | 135.50 ± 30.1 | 136.00 ± 26.9 | 0.912 |
| SD of DT | -1.20 ± 1.47 | -1.14 ± 1.23 | 0.701 |
| IVRT (msec) | 61.90 ± 11.3 | 63.20 ± 10.6 | 0.395 |
| SD of IVRT | -0.55 ± 0.91 | -0.39 ± 1.1 | 0.502 |
| PVs (cm/sec) | 60.60 ± 18.9 | 57.80 ± 14 | 0.685 |
| SD of PVs | 1.79 ± 2 | 1.48 ± 1.5 | 0.685 |
| PVd (cm/sec) | 56.10 ± 10.2 | 55.90 ± 9 | 0.859 |
| SD of PVd | -0.10 ± 1.1 | -0.20 ± 1 | 0.814 |
| PVs/PVd | 1.00 ± 0.27 | 1.00 ± 0.24 | 0.526 |
| PVA (cm/sec) | 27.40 ± 10.8 | 24.40 ± 5.4 | 0.201 |
| SD of PVA | 1.30 ± 2.3 | 1.74 ± 1.19 | 0.717 |
| PVA duration (msec) | 107.20 ± 32.8 | 97.10 ± 27.9 | 0.114 |
| SD of PVA duration | -1.00 ± 1.5 | -1.50 ± 1 | 0.112 |

A, peak flow velocity of late LV filling; CT ratio, cardiothoracic ratio; DT, deceleration time; E, peak flow velocity of early LV filling; E/A, ratio of peak early to peak late flow velocities; EF, ejection fraction; FS, fractional shortening; HR, heart rate, IVRT, isovolumic relaxation time; LA, left atrium dimension; LVEDd, left ventricular end diastolic dimension; LVESd, left ventricular end systolic dimension; LVPWD, left ventricular posterior wall dimension; PVA, Pulmonary vein atrial reversal flow; PVd, pulmonary vein diastolic velocities; PVs, pulmonary vein systolic velocities; PVs/PVd, ratio of pulmonary vein systolic/diastolic velocity; * $p < 0.05$

No patient had clinical signs or symptoms of congestive heart failure in the present study. Echocardiography demonstrated normal left ventricular systolic function in every patient. NT-pro BNP levels of children with normal cardiovascular system at different ages was not significantly different from the previous study[12].

Patients with serum NT pro BNT level > 1 SD of control group were more likely to have abnormal left ventricular diastolic function ≥ 2 parameters than patients with serum NT pro-BNP level ≤ 1SD (OR = 3.8, 95% CI 1.18-12.52) (Table 3). There were more likely of patients in group 2 to have abnormal left ventricular diastolic function ≥ 2 parameters than patients in group 1 (OR = 2.8, 95% CI 1.07-7.7) (Table 4).

Ten patients with serum NT-pro BNP level > 1 SD had ≥ 2 abnormal parameters of left ventricular diastolic function and all were in group 2. Seven of ten patients (70%) had < -1 SD of E/A ratio and > 1 SD of PVa. Patients who exposed with higher dose of

**Table 3.** Correlation of NT pro-BNP and left ventricular diastolic function

| | Abnormal ≥ 2 parameters | Normal or abnormal ≤ 1 parameter | Odds ratio 95% CI |
|---|---|---|---|
| NT-pro BNP (> 1 SD) | 10 (56%) | 8 (44%) | 3.8 (1.18-12.52) |
| NT-pro BNP (≤ 1 SD) | 20 (25%) | 61 (75%) | p = 0.02 |

**Table 4.** Left ventricular diastolic function of patients in group1 and 2

| | Abnormal ≥ 2 parameters | Normal or abnormal ≤ 1 parameter | Odds ratio 95% CI |
|---|---|---|---|
| Group 2 ≥ 300 mg/m | 19 (39%) | 30 (61%) | 2.8 (1.07-7.7) |
| Group 1 < 300 mg/m | 10 (18%) | 45 (82%) | p = 0.03 |

**Table 5.** Possibility of group 1 and 2 to have serum NT-pro BNP level > 1 SD

| | NT-pro BNP (> 1 SD) | NT-pro BNP (≤ 1 SD) | Odds ratio 95% CI |
|---|---|---|---|
| Group 2 ≥ 300 mg/m | 15 (33%) | 31 (67%) | 8.0 (1.96-38.4) |
| Group 1 < 300 mg/m | 3 (6%) | 50 (94%) | p = 0.001 |

doxorubicin were more likely to have elevated serum NT-pro BNP level > 1 SD than group 1 (Table 5).

## Discussion

Incidence of CHF in cancer patients after treatment with doxorubicin were 3-5% and 7-26% at accumulative dose of 400 mg/m$^2$ and 550 mg/m$^2$ respectively[1,2]. There was a report of 2.5 years survival rate in patients with doxorubicin-induced cardiomyopathy at 40% and poor response to treatment[4]. Early detection and management could alter the dismal prognosis.

In the present study, there was a significant difference of underlying diseases in group 1 and 2. Underlying malignancy in group 2 required accumulative dose of doxorubicin ≥ 300 mg/m$^2$ to complete the treatment protocols and some patients had relapse of the diseases. There were no patients who developed clinical signs and symptoms of CHF in this study. This is because our oncologists prescribed the standard regimen of doxorubicin and were aware of the complications. However, in our experience, there were cases of doxorubicin-induced cardiomyopathy with intractable heart failure. Chest x-ray, EKG had been demonstrated to have low sensitivity and specificity in the diagnosis of doxorubicin-induced cardiomyopathy[15,25]. Acute EKG changes and arrhythmias following doxorubicin therapy had been reported about 10% of patients with accumulative doxorubicin dose of > 400 mg/m$^2$[26] but did not adequately predict CHF[6,25]. Echocardiography demonstrated normal left ventricle systolic function in all patients and there was no significant difference in terms of diastolic function parameters between group 1 and 2. This could be explained by the low incidence of cardiotoxicity at the accumulative doxorubicin dose of less than 450 mg/m$^2$, which was given in our patients.

Plasma BNP has been proven to be the best single marker for left ventricular systolic dysfunction, diastolic dysfunction, hypertrophy and increased end diastolic pressure (LVEDP) in adult[27]. The present study showed the association between the increased accumulative dose of doxorubicin and the increased secretion of natriuretic peptide, which is consistent with the findings from previous report in adult patients[11]. Suzuki et al. found a significant increase in BNP level during anthracycline-based chemotherapy,

however, in most of these patients, the elevations were transient. Two thirds of the patients with persistently elevated BNP level subsequently died from circulatory failure. Moreover, the increase in BNP level correlated with diastolic LV dysfunction[19]. There were reports of significantly elevated BNP and NT-pro BNP levels in children with doxorubicin administration in comparison with healthy control, which are consistent with this study[22,28]. There was no significant difference of serum NT-pro BNP level in the control group when compared to the previous study[12]. Recent study demonstrated association between higher accumulative dose of doxorubicin with reduced left ventricular mass and higher serum NT-pro BNP level[29].

During the evolution of sub-clinical LV dysfunction, the increased secretion of NT-pro BNP is more closely associated with the impairment of LV diastolic function. O'leary reported Doppler parameters of the normal diastolic function in childhood and abnormal relaxation was the earliest sign to diagnose left ventricular dysfunction. This resulted in prolongation of isovolumic relaxation time, mitral inflow deceleration time, and variable pulmonary venous atrial reversal flow[24]. Several studies suggested that left ventricular diastolic dysfunction was an early sign of anthracycline-induced cardiac dysfunction[10,30-32]. Decreased E/A ratio by 20% of baseline and prolongation of the IVRT by 32% (from 65 ms to 86 ms) were found before the detection of decreased left ventricular shortening fraction[10]. There were reports showing impaired left ventricular diastolic function: prolonged IVRT and decreased E/A ratio 23-27% at doxorubicin dose of > 250 mg/m$^2$[30] and 450 mg/m$^2$[32] respectively.

At serum NT-pro BNP > 1 SD, there was 3.8 times of patients to have abnormal diastolic function ($\geq$ 2 Doppler parameters) when compared to patients with normal or > 1 SD of serum NT-pro BNP level. In 10 patients with NT-pro BNP > 1 SD and $\geq$ 2 abnormal diastolic function parameters, we found 7 in 10 patients (70%) that had E/A ratio < -1 SD (decreased E/A ratio > 34%) and PVa > 1 SD (increased PVa > 34%). Our results were consistent with the previous reports that showed the development of doxorubicin-induced LV diastolic dysfunction after increased BNP and inverse correlation between E/A ratio and plasma BNP[11,33]. There was also a report which demonstrated abnormal diastolic filling pattern (decreased E velocity, prolonged IVRT) associated with higher plasma BNP levels in children who received anthracycline when compared to healthy control[34]. Another study showed that children who received doxorubicin 300-600 mg/m$^2$, 12.9% developed cardiac dysfunction with significantly elevated plasma NT-pro BNP level[28]. In addition to close monitoring cardiovascular parameters, prevention of doxorubicin-induced cardiomyopathy includes limitation of cumulative dose, usage of anthracycline analogues, adding cardioprotectant agents, and usage of liposomal anthracyclines[35], which may not be practical and are unavailable in most institutes. The earliest detection by sensitive method is essential in this group of patients.

## Conclusion

There was an association between serum NT-pro BNP level > 1 SD, accumulative doses of doxorubicin $\geq$ 300 mg/m$^2$ and early left ventricular diastolic dysfunction especially E/A < -1 SD and PVa > 1 SD. Serum NT-pro BNP level >1 SD have a high probability to be used as an early sign of doxorubicin-induced cardiomyopathy in children age 1-10 years.

## Limitations of the current study

Prospective longitudinal study with larger sample size and higher accumulative doxorubicin dosage might give more precise information regarding the NT pro BNP and left ventricular diastolic dysfunction. Tissue Doppler imaging study will add more accurate data in the assessment of left ventricular diastolic function.

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## *N-terminal pro brain natriuretic peptide* และการทำงานของหัวใจในเด็กที่ได้รับยา *doxorubicin*

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*การศึกษานี้ทำขึ้นเพื่อประเมินการใช้ N-terminal pro brain natriuretic peptide (NT-pro BNP) ในการวินิจฉัยการทำงานบกพร่องของเวนตริเคิลระยะต้นในผู้ป่วยเด็กที่ได้รับการรักษาด้วย doxorubicin มีผู้ป่วยเด็กที่เป็นมะเร็งจำนวน 55 ราย ที่ได้รับยา doxorubicin ขนาดสะสม < 300 มก./ม.$^2$ (กลุ่ม 1) จำนวน 49 ราย ได้รับยาขนาดสะสม ≥ 300 มก./ม.$^2$ (กลุ่ม 2) และ 52 ราย ไม่มีปัญหาทางหัวใจและหลอดเลือด อีกทั้งไม่ได้รับยา doxorubicin เป็นกลุ่มควบคุม (กลุ่ม 3) โดยได้ศึกษาคลื่นไฟฟ้าหัวใจ ภาพถ่ายรังสีทรวงอก การตรวจหัวใจด้วยคลื่นเสียงสะท้อนความถี่สูง และระดับ NT-pro BNP ในซีรัมของผู้ป่วยเหล่านี้พบว่า ในผู้ป่วยที่มีช่วงอายุ 1-10 ปี มีระดับ NT-pro BNP ในกลุ่ม 2 สูงกว่ากลุ่ม 1 (384 ± 291 vs 92.2 ± 89 พิโคกรัม/มล.) และสูงกว่ากลุ่ม 3 (79 ± 92 พิโคกรัม/มล.) อย่างมีนัยสำคัญทางสถิติ ผู้ป่วยที่มีระดับ NT-pro BNP > 1 SD มีโอกาสที่จะพบการทำงานของเวนตริเคิลซ้ายแบบ diastolic ผิดปกติ ≥ 2 parameters ของการตรวจด้วยคลื่นเสียงสะท้อนความถี่สูงมากกว่ากลุ่มที่ NT-pro BNP ≤ 1 SD (OR = 3.8, 95% CI 1.18-12.52) และพบว่า ผู้ป่วยในกลุ่ม 2 มีโอกาสที่จะมีการทำงานของเวนตริเคิลซ้ายแบบ diastolic ผิดปกติ ≥ 2 parameters และ NT-pro BNP > 1 SD มากกว่ากลุ่ม 1; OR = 2.8, 95% CI 1.07-7.7 และ OR = 8, 95% CI 1.96-38.4 ตามลำดับ พบว่ามีความสัมพันธ์ของระดับ NT-pro BNP > 1 SD, การได้รับ doxorubicin ขนาดสะสม ≥ 300 มก./ม.$^2$ และการทำงานของเวนตริเคิลซ้ายผิดปกติแบบ diastolic ระยะต้น การศึกษานี้สนับสนุนว่าผู้ป่วยเด็กอายุ 1-10 ปี ที่มีระดับ NT-pro BNP ในซีรัม > 1 SD มีโอกาสสูงที่จะมีปัญหาการทำงานของหัวใจผิดปกติในระยะต้นจาก doxorubicin*