

# Value of the New Doppler – Derived Myocardial Performance Index in Predicting Subclinical Cardiotoxicity in Children Treated with Anthracyclines

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## Abstract

**Background-** There are many limitations to the use of conventional echocardiography indices for the estimation of systolic and diastolic left ventricular (LV) function. Anthracycline chemotherapy causes myocardial damage, leading to acute or chronic congestive heart failure during or soon after treatment in a significant percentage of patients treated, depending on the total cumulative dose used. The aim of this study was to determine the usefulness of myocardial performance index (MPI) in evaluation of subclinical cardiotoxicity in patients undergoing chemotherapy with anthracyclines.

**Methods-** Seventy-five patients (41 male, 34 female, mean age  $9\pm 3$  years) with malignant solid tumors and hematologic malignancy were randomly selected and evaluated before, during and after therapy by 2-D, M-Mode and Doppler echocardiography; and the data were compared with 48 age- and sex-matched normal controls prospectively.

**Results-** Twenty-three patients were taking high doses of anthracyclines ( $>200\text{mg}/\text{m}^2$ ), whereas 52 patients were taking low doses of anthracyclines ( $<200\text{mg}/\text{m}^2$ ). Mean dose of anthracyclines in all the patients was  $140\pm 60\text{mg}/\text{m}^2$ . IVCT was prolonged ( $42\pm 11\text{msec}$  vs.  $28\pm 8\text{msec}$ , P-value=0.018) compared with normal control subjects. ET was shortened ( $220\pm 24\text{msec}$  vs.  $234\pm 14\text{msec}$ , P-value=0.025), and MPI was increased in the anthracycline-treated patients compared with normal control subjects ( $0.44\pm 0.06$  vs.  $0.34\pm 0.04$ , P-value =0.015). Also, we found no correlation between MPI and cumulative dose of anthracyclines in 52 patients taking lower doses ( $<200\text{mg}/\text{m}^2$ ) compared with 23 patients taking higher doses ( $>200\text{mg}/\text{m}^2$ ); MPI was  $0.42\pm 0.04$  vs.  $0.44\pm 0.08$ , with P-value =0.062 between the two groups. No significant difference was found in LVEF ( $0.58 \pm 0.12$  vs.  $0.64\pm 0.06$ , P-value=0.056) and LVFS ( $0.32\pm 0.08$  vs.  $0.36\pm 0.04$ , P-value=0.068) between the patients and normal controls.

**Conclusion-** The findings of this study suggest that anthracycline cardiotoxicity is subtle and subclinical and systolic functions are preserved. MPI is helpful in the discrimination of early cardiac involvement from anthracycline chemotherapy, especially in asymptomatic young patients with normal limited systolic function. Moreover, MPI can enhance the accuracy of echocardiographic diagnosis in early ventricular dysfunction. Cumulative dose of anthracyclines is not a suitable parameter in the determination of the risk of the severity of anthracycline cardiotoxicity. Recent advantages in diagnostic tests have allowed diagnosis at early stages of disease before massive cell injury and irreversible changes occur (*Iranian Heart Journal 2006; 7 (4): 43-48*).

**Key words:** myocardial performance index (MPI) ■ isovolumic relaxation time (IVRT) ■ isovolumic contraction time (IVCT) ■ ejection time (ET) ■ anthracycline.

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Early and late cardiotoxicity after treatment with anthracyclines is a potential life-threatening complication in pediatric and adolescent cancer survivors.<sup>1</sup>

Doxorubicin is an anthracycline agent that is effective in the treatment of various solid tumors and hematologic malignancies with wide usefulness.

Congestive heart failure due to anthracycline cardiotoxicity may occur unexpectedly after a variable period of several days to several years, associated with variable irreversible myocardial damage related to the cumulative dose of drug with marked individual variations in cardiotoxicity.<sup>7</sup> The need for a reliable and safe method for an early detection and monitoring of these patients is obvious.

Often conventional echocardiographic studies have focused on systolic parameters, but recently a new non-invasive Doppler-derived myocardial performance index combining systolic and diastolic functions was proposed in 1995 by Tei Chuwa et al., which incorporates both systolic and diastolic performance of the ventricles. The MPI or Tei index has proved to be a reliable method for the evaluation of LV systolic and diastolic functions with clear advantages over older established indices and prognostic value in many kinds of heart diseases.<sup>5</sup>

### Methods

The study group consisted of 75 patients: 41 male and 34 female at a mean age of  $9\pm 3$  years. The initial diagnosis had been made in the pediatric oncology department, and the patients had been referred to our pediatric cardiology department. They were examined before, during and after treatment, and they were randomly selected and studied prospectively. The data were compared with 48 age- and sex-matched normal subjects as the control group. None of the patients had received mediastinal irradiation.

Mean cumulative dose of anthracyclines was  $140\pm 60\text{mg/m}^2$ , with 23 patients taking high doses of anthracyclines ( $>200\text{mg/m}^2$ ) and 52 patients taking low doses of anthracyclines ( $<200\text{mg/m}^2$ ). The etiology of the primary neoplasm was leukemia in 48 patients, lymphoma in 18 patients, and Wilm's tumor and other solid tumors in 9 patients.

Each patient underwent several echocardiography examinations during treatment, and the results were compared with 48 age- and sex-matched controls.

For an assessment of the patients, transthoracic echocardiography was performed with Vivid 3 Vingmed system. All the measurements were obtained averaged from 3 cardiac cycles in patients with normal sinus rhythm, while ECG monitoring was carried out in the left lateral decubitus position.

Initially, routine diagnostic imaging including 2-D, M-mode, color flow mapping and continuous wave Doppler was performed. Subsequently, pulse Doppler flow across the mitral and aortic valve was assessed with simultaneous ECG recording. The sample volume was positioned between the tips of the mitral leaflets and just below the aortic valve for measurement of inflow and outflow time intervals and velocities.

LVEF, LVFS, LVESV and LVEDV were measured using a modified Simpson's method and M-mode echocardiography. Peak E, peak A, E/A ratio and E deceleration times was measured.

Time intervals between closure and reopening of the mitral valve are equal to the sum of IVRT, ET and IVRT, and LV outflow interval or ET was measured. The sum of IVCT + IVRT was obtained by subtracting these two intervals and IVCT, and IVRT was measured separately according to Figure 1.

The MPI measures the ratio of total isovolumic activity to the ET from this formula:  $\text{MPI} = \text{IVCT} + \text{IVRT} / \text{ET}$  (Fig.2).

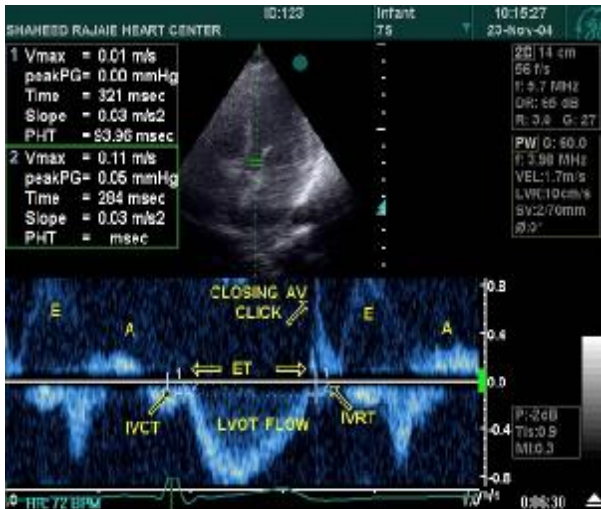


Fig 1. Pulse Doppler Flow across the aortic valve.

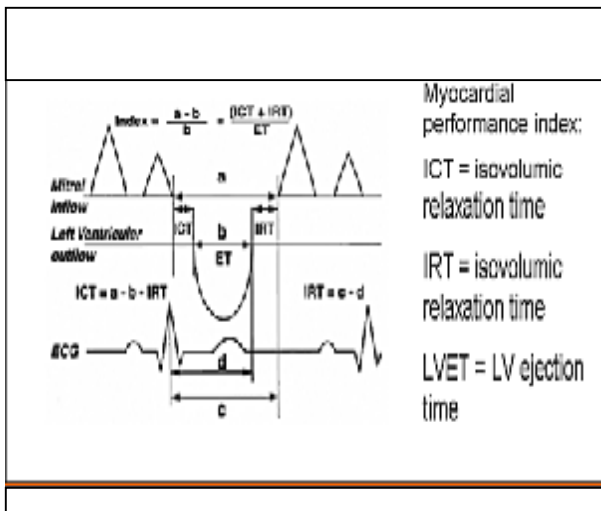


Fig 2. Calculation of the Myocardial performance index.

**Statistical Analysis:**

Data are expressed as mean value ± SD. Differences between continuous variables were determined by using unpaired student's t- test between the study groups of patients and matched healthy control subjects. A value of P<0.05 was considered statistically significant.

**Results**

No significant difference was found in LVEF (0.58 ± 0.12 vs. 0.64±0.06, P value=0.074) and LVFS (0.32±0.08 vs. 0.36±0.04, P

value=0.082) between patients treated with anthracyclines and normal control group.

In 2 patients with NYHA functional class III whose heart failure started early after the initiation of anthracyclines, LVEF and LVFS were significantly decreased.

There was no significant differences in time intervals measured between the onset of R wave in the ECG and mitral valve opening between the two groups (320±22 msec vs. 335±16 msec, P value =0.069).

IVCT was significantly prolonged in patients compared with control subjects (42 ±11 msec vs. 28±8 msec, P value =0.018).

ET was shortened in patients compared with normal subjects (220±24 msec vs. 245±18msec, P value =0.025).

MPI was significantly increased in patients compared with the control group (0.44±0.06 vs. 0.34±0.04, P value =0.015).

There was no correlation between MPI and cumulative doses of anthracyclines between 52 patients taking lower doses (<200mg/m<sup>2</sup>) compared with 23 patients taking higher doses (>200mg/m<sup>2</sup>) (0.42±0.04 vs. 0.44±0.08, P value=0.088).

**Table I. 2-D and M-mode measurement in patients treated with anthracycline and control subjects (Mean ± SD).**

	<b>Patients No :75</b>	<b>Control Subjects No:48</b>	<b>P Value*</b>
LVEDD	3.6±0.6	3.4±0.3	0/093
LVESD	2.4±0.4	2.1±0.3	0/085
LVPWD	0.6±0.2	0.8±0.2	0/072
LVEDV	44±11	38±8	0/064
LVESV	18±8	16±4	0/078
LVFS%	32±8	36±4	0/082
LVEF%	58±12	64±6	0/074

\* Significant at the 0.05 level

**Table II. Doppler LV diastolic parameters and time intervals in patients treated with anthracyclines and control subjects (Mean ± SD).**

	Patients No. 75	Control Subjects No. 48	P Value*
Peak E (cm/sec)	95±11	86±6	0.170
Peak A (cm/sec)	48±8	38±4	0.194
E Decel. time (msec)	128±24	140±26	0.144
IVCT+ET+IVRT (msec)	320±22	335±16	0.069
ET (msec)	220±24	245±18	0.025
IVCT (msec)	42±11	28±8	0.018
MPI or Tei Index	0.44±0.06	0.34±0.04	0.015

\*Significant at the 0.05 level

**Table III. Doppler time intervals according to cumulative dose of anthracyclines (mean ±SD).**

	Low dose <200 mg/m <sup>2</sup> No. 52	High dose >200mg/m <sup>2</sup> No. 23	P Value*
IVCT+ ET+IVRT	330±18	318±24	0.125
ET	228±20	218±24	0.098
IVRT	58±12	52±14	0.224
IVCT	40±8	46±12	0.180
MPI	0.42±0.04	0.44±0.08	0.088

\*Significant at the 0.05 level

### Discussion

Anthracycline chemotherapy causes myocardial damage, leading to acute or chronic congestive heart failure with marked individual variation in cardiotoxicity.

The incidence of symptomatic cardiac failure in children treated only with doxorubicin was reported at 3%; and when additional cardiotoxic agents were employed, the incidence of cardiac failure increased.<sup>1</sup>

There has been considerable discussion about both the value and the timing of monitoring for anthracycline cardiotoxicity. LVEF and LVFS at rest are used by many oncologists to

guide anthracycline therapy and progressive loss of cardiac myocytes known to occur with increasing cumulative anthracycline dose that is associated with a progressive reduction in LVEF and LVFS.

In this study, the MPI combining systolic and diastolic time intervals was compared with conventional echocardiographic variables.

Although in previous studies<sup>1,3</sup> the incidence of cardiac abnormalities in doxorubicin-treated patients appeared to increase with duration of disease and cumulative dose of drug, the present study demonstrated progressive asymptomatic cardiac abnormalities without correlation to cumulative dose and duration of disease.

We observed significant changes in global combined systolic and diastolic function, while no change in conventional echocardiographic variable was seen in patients treated with anthracyclines with NYHA functional class I-II.

Lipshultz et al.,<sup>7,8</sup> studying a cohort of anthracycline-treated children including patients with previous echocardiographic abnormalities with early and late CHF, showed an overall decrease of LV systolic function.

Bullock et al.<sup>3,4</sup> concluded that regular monitoring of LVFS during anthracycline treatment can identify patients at higher risk of subsequent cardiotoxicity, patients with LVFS <30% at any stage, patients with LVFS <32% with doxorubicin dose >200mg/m<sup>2</sup> and all patients with a decrease in LVFS >2-3% per 100mg/m<sup>2</sup> appear to be at increased risk of significant cardiotoxicity.

Postma et al.<sup>1</sup> reported females to be at higher risk for reduced contractility, which is in accordance with the results of others. It has been suggested that this is because females are exposed to higher anthracycline concentration than males, due to lower clearance ratio and higher percentage of body fat.

Stoddard et al.<sup>6</sup> also showed that in patients treated with doxorubicin, redistribution of the LV filling pattern is present with an increased

atrial contribution to LV diastolic filling with a depressed early peak velocity and a reduced E/A ratio.

However, in our patients we observed no significant correlation between MPI and diastolic disorder and cumulative dose of anthracyclines.

We found that IVCT was prolonged and ET was shortened with significantly increased MPI in anthracycline-treated patients compared with normal controls, while LVEF and LVFS which are generally used for the assessment of systolic function were not accurate indices for the evaluation of anthracycline-treated patients.

### Conclusion

This study suggests that MPI and IVCT are useful parameters in monitoring early ventricular dysfunction in asymptomatic young patients treated with anthracyclines, while conventional systolic indices are preserved and not changed.

Diagnosis should ideally be made at an early stage of cardiac dysfunction before substantial massive myocardial cell injury and impaired function with irreversible changes ensue.

Cumulative dose of anthracyclines is not an accurate and suitable index for determining the severity of anthracycline toxicity because of marked individual variations in cardiotoxicity and multiple factors involved in cardiac dysfunction. We, therefore, need a reliable and accurate method for an early detection of these patients.

We believe that prospective studies in patients with different doses of anthracyclines are required to determine the prognostic importance of MPI when we decide to adjust or stop anthracyclines.

Dose adjustment of anthracyclines and treatment of asymptomatic patients with subclinical LV dysfunction are still controversial issues. ACE inhibitors have been reported to improve echocardiographic abnormalities in young patients with asymptomatic LV dysfunction and may be

beneficial in asymptomatic patients with subtle progressive abnormalities.<sup>16</sup>

### Limitations

Risk factors for late cardiotoxicity including cumulative dose, young age, female sex and length of treatment are known to be particular risks for anthracycline-induced cardiotoxicity. Consequently, many prospective studies involving serial measurements at different ages, sex, doses and length of treatment are required to evaluate the true role of MPI and its prognostic importance and determine the time of drug adjustment or discontinuity, especially in young patients with asymptomatic cardiac dysfunction.

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