VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2012, Vol. 19, No. 4, pp. 363–368
10.5603/CJ.2012.0066

ISSN 1897–5593

The evaluation of doxorubicin-induced cardiotoxicity: Comparison of Doppler and tissue Doppler-derived myocardial performance index

S. Selim Ayhan[1], Kurtulus Özdemir[2], Mehmet Kayrak[2], Ahmet Bacaksiz[2], M. Akif Vatankulu[2], Önder Eren[3], Fatih Koc[2], Cetin Duman[2], Hakan Gülec[2], Kenan Demir[2], Hatem Ari[2], Osman Sönmez[2], Hasan Gök[2]

[1]Department of Cardiology, Abant Izzet Baysal University, Faculty of Medicine, Bolu, Turkey
[2]Department of Cardiology, Selcuk University Meram, Faculty of Medicine, Konya, Turkey
[3]Department of Oncology, Selcuk University Meram, Faculty of Medicine, Konya, Turkey

Abstract

Background: *Doxorubicin is a chemotherapeutic agent used in a wide spectrum of cancers. However, cardiotoxic effects have limited its clinical use. The early detection of doxorubicin-induced cardiotoxicity is crucial. The purpose of our study was to assess values of Doppler and tissue Doppler imaging (TDI)-derived myocardial performance index (MPI) in adult cancer patients receiving doxorubicin treatment.*

Methods: *A total of 45 patients underwent echocardiographic examinations before any doxorubicin had been administered and then after doxorubicin. Doppler and TDI-derived MPI of left ventricular (LV) were determined in the evaluation of cardiotoxicity. Additionally, TDI-derived MPI of right ventricular (RV) was determined.*

Results: *All patients underwent control echocardiographic examination after mean 5 ± 1.7 months. The LV MPI obtained by both Doppler and TDI were increased after doxorubicin treatment (0.56 ± 0.11, 0.61 ± 0.10, p = 0,005* vs *0.51 ± 0.09, 0.59 ± 0.09, p = 0.001, respectively). There was no correlation between Doppler-derived MPI and cumulative doxorubicin dose (coefficient of correlation 0.11, p = 0.6). TDI-derived MPI was correlated with cumulative doxorubicin dose (coefficient of correlation 0.35, p = 0.015), but this correlation is weak (r = 0.38). The study population was divided into two groups according to doxorubicin dose (below and above 300 mg level). There was a moderate correlation between TDI-derived MPI and less than 300 mg of doxorubicin dose (coefficient of correlation 0.51, p = 0.028). However, Doppler-derived MPI was not correlated with less than 300 mg of doxorubicin dose (coefficient of correlation 0.38, p = 0.123). Also, there was no significant change in the TDI-derived RV-MPI (0.49 ± 0.14, 0.50 ± 0.12, p = 0.56).*

Conclusions: *TDI-derived MPI is a useful parameter and an early indicator compared with Doppler-derived MPI in the detection of cardiotoxicity during the early stages. Also, doxorubicin administration does not affect RV function.* (Cardiol J 2012; 19, 4: 363–368)

Key words: doxorubicin, cardiotoxicity, myocardial performance index

Address for correspondence: S. Selim Ayhan, MD, Department of Cardiology, Abant Izzet Baysal University, School of Medicine, Gölköy yerleşkesi 14000 Bolu, Turkey, tel: (374) 2534656-3195, fax: (374) 2534615, e-mail: ssayhan@yahoo.com

Received: 11.11.2011 Accepted: 20.03.2012

Introduction

Anthracyclines are effective agents used in the treatment of hematological malignancies and solid tumors [1]. However, the cardiotoxic effects of anthracyclines have limited their clinical use. Increased free radical production and reduced myocardial antioxidants are believed to be the major mechanisms responsible for cardiotoxicity [2, 3]. More commonly, anthracyclines cause progressive chronic cardiotoxicity resulting in heart failure, which generally presents within 1 year of treatment [4]. Cardiotoxicity is related to cumulative dosage. However, sensitivity to this severe side-effect is usually individual and a subgroup of patients shows signs of cardiomyopathy even at low anthracycline doses [5].

The early detection of anthracycline cardiotoxicity is very important because it may be useful in the prevention of heart failure. Therefore, evaluation of cardiac dysfunction is critical before changes become irreversible in the myocardium during treatment. Left ventricular ejection fraction (LVEF) is the most commonly used echocardiographic parameter. It has been the main indicator of cardiac dysfunction and a powerful predictor of mortality [6]. However, impairment in LVEF is often detected only after considerable myocyte loss has taken place.

The myocardial performance index (MPI) has been described as a noninvasive Doppler measurement of global (systolic and diastolic) ventricular function [7]. MPI may be calculated using the time intervals obtained by both Doppler and tissue Doppler imaging (TDI) [8]. MPI is defined as the ratio of the sum of isovolumic relaxation time (IRT) and isovolumic contraction time (ICT), over the ejection time (ET). In the evaluation of LV performance, TDI is more reliable than Doppler, given that it is less influenced by loading conditions and heart rate changes [7]. Although TDI-derived MPI is more reliable than Doppler-derived MPI, it has not been used to evaluate anthracycline cardiotoxicity in adult patients in the previous studies so far.

The aim of the current study was to assess values of MPI obtained by tissue Doppler imaging and MPI obtained by Doppler in adult cancer patients receiving doxorubicin therapy.

Methods

Study design

Forty-five patients requiring doxorubicin-containing chemotherapy for solid or hematological malignancy were enrolled in the study. All patients gave written informed consent prior to participation in the study. The local ethics committee approved the study and all patients provided informed consent.

Patients were excluded if they had a history of coronary artery disease, systemic hypertension, prior use of anthracycline therapy, prior or additional mediastinal radiotherapy, chronic renal failure, chronic obstructive lung disease, and any rhythm other than normal sinus rhythm. In addition, we excluded patients having the following echocardiographic criteria: (a) abnormal LV systolic function (EF $\leq$ 50% according to modified Simpson's method); (b) poor echo image quality; (c) moderate or severe valvular heart disease.

Blood pressure, heart rate, and demographic characteristics of the patients were recorded. The study was designed to assess each patient by echocardiography before they received doxorubicin and about 5 months after completion of their chemotherapy.

Echocardiography

The patients were evaluated before and after (mean of 5 months after the last cycle of the chemotherapy) doxorubicin therapy, using an Advanced Technology Laboratory 5000 echocardiography device with a 2–4 MHz transducer, according to recommendations of the American Society of Echocardiography. LVEF was estimated with Simpson's modified biplane methods. The mitral inflow velocity was recorded by placing the sample volume between the tips of the mitral leaflets from the apical 4-chamber view. The LV outflow pattern was recorded from the apical 5-chamber view by placing sample volume just below the aortic valve. Each Doppler measurement was calculated from an average of five consecutive cardiac cycles at a sweep speed of 100 mm/s. Doppler time intervals were measured from mitral inflow and LV outflow tract velocity.

The pulsed-wave TDI was performed by activating the tissue Doppler function in the same echocardiography machine. The filter settings were kept low, and gains were adjusted at the minimal optimal level to minimize noise and eliminate the signals produced by the transmitral flow. A 3.5-mm sample volume was used. In the apical 4-chamber view, the TDI cursor was placed at the septal and lateral sides of the mitral annulus, and right ventricular (RV) free wall side of the tricuspid annulus in such a way that the annulus moved along the sample volume line. In the apical 2-chamber view, the TDI cursor was placed at the anterior and inferior sides of the mitral annulus in the same manner. A Doppler velocity range of –15 to 15 cm/s was selected for this study. In the TDI, the systolic ve-

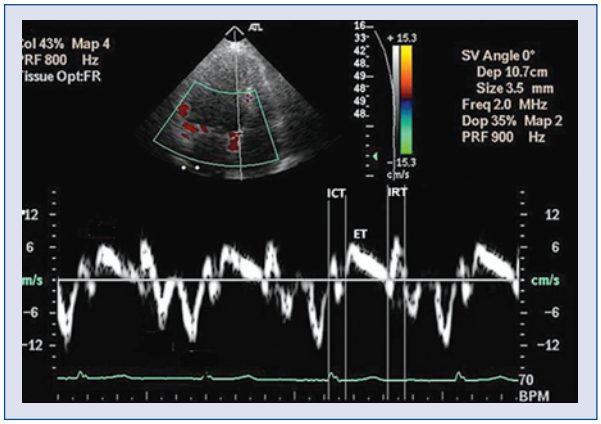

Figure 1. The measurement of the TDI-derived time intervals. The MPI is calculated by the formula [(ICT + IRT)/ET].

Table 1. Study group baseline demographics.

Variable	Value
Gender (female/male)	37:8
Age [years]	50.1 ± 13.6
Type of anthracycline	Doxorubicine
Dose of anthracycline [mg/m^2]	268.3 ± 49.9
Number of cyclus	4.8 ± 0.9
Time of control echocardiography [m]	5 ± 1.7
Body surface area	1.71 ± 0.11
Type of cancer:	
Breast	33
Non-Hodgkins Lymphoma	5
Hodgkins Lymphoma	4
Leiomyosarcoma	3

locity duration was measured as ET, whereas the time between the end of the systolic velocity and the beginning of early diastolic velocity was recorded as IRT, and the time between the end of the late diastolic velocity and the beginning of systolic velocity was recorded as ICT (Fig. 1). The MPI was also calculated using the same parameters obtained by Doppler method or TDI [MPI = (IRT + ICT)/ET]. The mean values of these parameters were calculated with values obtained from 4 different LV sites.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 15.0. All data were expressed as mean values ± SD. All parameters before and after chemotherapy were compared by paired t tests. Correlations between variables were tested by means of bivariate correlation testing. Analysis of the differences of the measurements by Doppler and by TDI methods was performed according to the Bland-Altman technique. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study group are listed in Table 1. The mean cumulative doxorubicin dose was 268.3 ± 49.9 mg/m^2 (range: 150–360 mg). All patients underwent control echocardiographic examination after mean 5 ± 1.7 months. All patients completed the planned treatment. Symptomatic diastolic heart failure developed in one patient. The rest of the patients tolerated the treatment well.

No significant changes in LVEF were observed. The LV-MPI and LV Sm obtained by both Doppler and TDI were impaired after chemotherapy (Table 2). There was no correlation between Doppler-derived MPI and cumulative doxorubicin dose (coefficient of correlation 0.11, $p = 0.6$). On the other hand, TDI-derived MPI was correlated with cumulative doxorubicin dose (coefficient of correlation 0.35, $p = 0.015$) but this correlation is weak. The study population was divided into two groups according to doxorubicin dose (below and above 300 mg level). In correlation analysis, there was a moderate correlation between TDI-derived MPI and less than 300 mg of doxorubicin dose (coefficient of correlation 0.51, $p = 0.028$). However, Doppler-derived MPI was not correlated with less than 300 mg of doxorubicin dose (coefficient of correlation 0.38, $p = 0.123$).

Besides, there was no significant change in the RV-MPI and RV Sm obtained by TDI after therapy (Table 2). The comparison of MPI obtained by Doppler and TDI was tested by the Bland-Altman method. Plots figures obtained by Bland-Altman were shown to be in compliance with one another pretreatment and post-treatment (Figs. 2A, B, respectively). However, a larger limit agreement was found. For this reason, small changes in MPI could not be correctly detected by conventional MPI.

Discussion

Significant increase has been determined in LV-MPI obtained by Doppler and TDI. Moreover, the current study demonstrated an obvious correlation between doxorubicin dose and TDI-derived

Table 2. Standard and tissue Doppler echocardiographic measurements before and after doxorubicine treatment.

	Before treatment	After treatment	P
Standard echo			
Left ventricular ejection fraction	61,50 ± 2,85	60,94 ± 2,45	NS
E velocity	69.44 ± 14.83	63.02 ± 13.85	0.001
E/A ratio	0.99 ± 0.39	0.91 ± 0.27	0.03
Isovolumetric relaxation time	95.15 ± 21.11	103.51 ± 18.56	0.004
LV-MPI	0.56 ± 0.11	0.61 ± 0.10	0.005
Tissue Doppler			
LV-MPI	0.51 ± 0.09	0.59 ± 0.09	0.001
LV Sm [cm/sn]	9.85 ± 1.45	8.74 ± 1.29	0.001
RV-MPI	0.49 ± 0.14	0.50 ± 0.12	NS
RV Sm [cm/sn]	14.07 ± 2.72	13.56 ± 2.60	NS

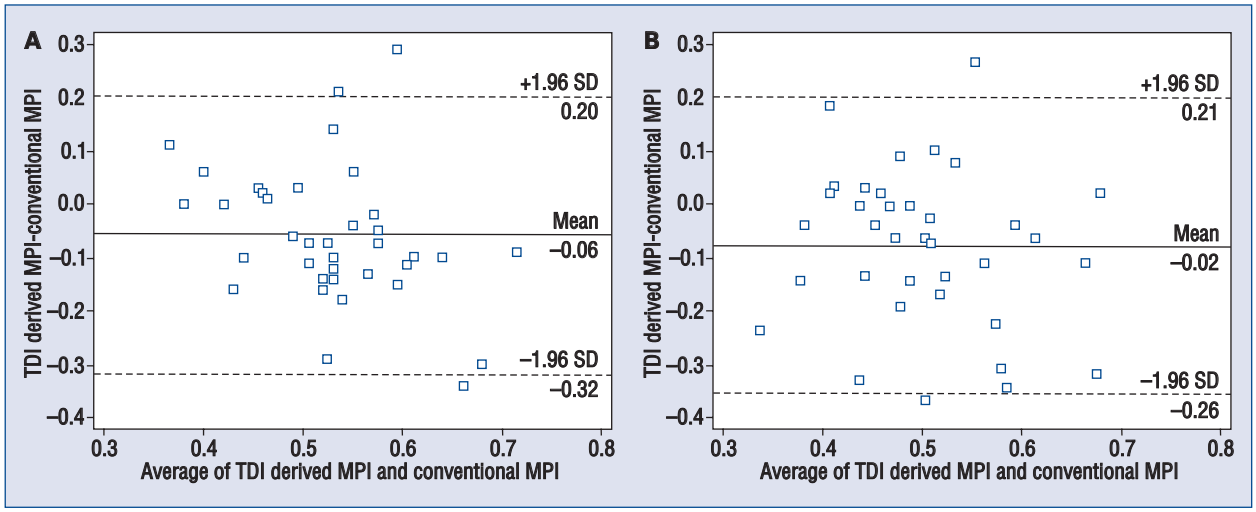

Figure 2. Bland-Altman plot of the difference between the Doppler-derived MPI and tissue Doppler-derived MPI. Solid and dashed lines, the mean (average) ± 1.96 SD, respectively. **A.** Pre-treatment period; **B.** Post-treatment period.

MPI. However, there was no significant correlation between doxorubicin dose and Doppler-derived MPI.

Although doxorubicin is a highly effective antineoplastic agent, its early and late stage cardiotoxic effects limit its use. Because of the high mortality and insufficiency of treatment options for patients who develop cardiomyopathy, early diagnosis of cardio toxicity is very important. In a series of more than 3,900 patients treated with anthracycline, Von Hoff et al. [4] noted that congestive heart failure secondary to anthracycline-induced chronic cardiomyopathy occurred 0 to 231 days after the completion of doxorubicin therapy. Already, it is known that the incidence of congestive heart failure secondary to doxorubicin-induced cardiomyopathy depends on the cumulative dose of the drug.

Lee et al. [9] demonstrated that abnormalities of diastolic function in adult patients resulted when patients received lower doses of anthracycline than doses producing significant changes in systolic function. Marchandise et al. [10] found a prolongation of the IRT (from 65 ms to 86 ms) and a reduction in E velocity (from 60 ms to 49 ms) in anthracycline-treated adults. In agreement with previous studies, we also found a significant decrease in E velocity and E\A ratio, as well as significant prolongation in IRT.

The MPI has been shown to correlate well with other invasive and noninvasive measures of LV

function in adults [11]. The MPI correctly estimates morbidity and mortality in patients with cardiac amyloidosis, primary pulmonary hypertension, idiopathic dilated cardiomyopathy, and acute myocardial infarction [12–16]. In previous studies, it has been shown that Doppler-derived MPI is a useful method and parameter for the detection of anthracycline cardiotoxicity [17, 18]. Eidem et al. [17] have detected an increase of Doppler-derived MPI in children treated with anthracyclines. The authors indicated that Doppler-derived MPI is a more sensitive parameter detecting for subclinical cardiotoxicity than conventional echocardiographic measures such as E/A ratio, and IRT. In another study, Senju et al. [19] examined 23 patients during anthracycline treatment. They found that change in the Doppler--derived MPI is a more sensitive indicator of early cardiotoxicity than LVEF and that there was a correlation between doxorubicin dose and Doppler--derived MPI. In our study, although Doppler--derived MPI has significantly increased, it did not correlate with doxorubicin dose. There may be two possible reasons of this: first, post-treatment echocardiographic evaluation was performed during earlier stages than in the other studies; second, the doxorubicin dose was lower in our study than in previous studies.

To our knowledge, this study is the first time that TDI-derived MPI has been used for detection of cardiotoxicity after doxorubicin therapy in adult patients. In our study, we found a rise of TDI-derived MPI after therapy and this rise correlated doxorubicin dose, contrary to Doppler-derived MPI. This result shows that TDI-derived MPI is more sensitive and a more useful parameter than Doppler-derived MPI in detecting subclinical cardiotoxicity, especially during the early period.

In the literature, there have been few data about RV functions after doxorubicin therapy. Eidem et al. reported that the Doppler-derived MPI of RV is not significantly changed in association with the use of anthracyclines in children [17]. Belham et al. [20] examined 23 patients during anthracycline treatment. They found that anthracycline administration was significantly associated with an increase in the Doppler-derived MPI of LV and that there was no significant change in the Doppler-derived MPI of RV. The authors concluded that this difference may have resulted from ventricular functional reserve and afterload differences between LV and RV. In our study, RV functions were evaluated by the TDI-derived MPI. We showed that TDI-derived MPI of RV did not significantly change with the use of doxorubicin. To our knowledge, this finding obtained by TDI-derived MPI is the first to demonstrate different effects on RV functions associated with the use of the doxorubicin.

Results of this study have indicated that both systolic and diastolic dysfunctions of LV may develop during the early stages after even low-dose doxorubicin therapy. Our study showed that TDI--derived MPI is a useful parameter and an early indicator compared with Doppler-derived MPI in the detection of ventricular dysfunction caused by doxorubicin in adult patients. On the other hand, to the best of our knowledge, this study is the first to show via TDI method that doxorubicin therapy has negatively affected LV functions but does not affect RV functions. Further prospective, randomized and placebo-controlled clinical studies are needed to investigate the value of TDI-derived MPI in echocardiographic evaluations and the follow-up of the ventricular function in patients with subclinical cardiac damage.

Limitations of study

First, subclinical or silent coronary artery disease cannot be excluded in patients without performing coronary angiography. Already, because most of our patients were young and female, it was very likely that our patient population had a low incidence of coronary artery disease. Secondly, previously presented myocardial disease cannot be excluded, as myocardial histology was not investigated. Thirdly, in our study, increased baseline value of MPI may be associated with malignancy and this may have influenced our results. Finally, the small number of patients and absence of a control group may also act as another limitation of our study.

Conflict of interest: none declared

References

1. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin chemotherapy: Efficacy, safety and pharmacological basis of an intermittent single high dose schedule. Cancer, 1974; 33: 19–27.
2. Barry E, Alvarez JA, Scully RE, Miller TL, Lipshultz SE. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Exp Opin Pharmacother, 2007; 8: 1039–1058.
3. Singal PK, Li T, Kumar D, Danelisen I, Iliskovic N. Adriamycin--induced heart failure: mechanism and modulation. Mol Cell Biochem, 2000; 207: 77–85.
4. Von Hoff DD, Layard MW, Basa P et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med, 1979; 91: 710–717.
5. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: A prospective, blinded, long-term

observational study of outcome in 120 patients. Ann Oncol, 2002; 13: 699–709.
6. Borow KM, Henderson IC, Neuman A et al. Assessment of left ventricular contractility in patients receiving doxorubicin. Ann Intern Med, 1983; 99: 750–756.
7. Tei C, Ling LH, Hodge DO et al. New index of combined systolic and diastolic myocardial performance: A simple and reproducible measure of cardiac function: A study in normals and dilated cardiomyopathy. J Cardiol, 1995; 26: 357–366.
8. Ozdemir K, Altunkeser BB, Icli A, Ozdil H, Gok H. New parameters in identification of right ventricular myocardial infarction and proximal right coronary artery lesion. Chest, 2003; 124: 219–226.
9. Lee BH, Goodenday LS, Muswick GJ et al. Alternations in left ventricular diastolic function with doxorubicin therapy. J Am Coll Cardiol, 1987; 9: 184–188.
10. Marchandise B, Schroeder E, Bosly A et al. Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J, 1989; 118: 92–98.
11. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr, 1997; 10: 169–178.
12. Tei C, Dujardin KS, Hodge DO et al. Doppler index combining systolic and diastolic myocardial performance: Clinical value in cardiac amyloidosis. J Am Coll Cardiol, 1996; 28: 658–664.
13. Yeo TC, Dujardin KS, Tei C et al. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol, 1998; 81: 1157–1161.
14. Dujardin KS, Tei C, Yeo TC et al. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. Am J Cardiol, 1998; 82: 1071––1076.
15. Sasao H, Noda R, Hasegawa T et al. Prognostic value of the Tei index combining systolic and diastolic myocardial performance in patients with acute myocardial infarction treated by successful primary angioplasty. Heart Vessels, 2004; 19: 68–74.
16. Bruch C, Schmermund A, Marin D et al. Tei-index in patients with mild-to-moderate congestive heart failure. Eur Heart J, 2000; 21: 1888–1895.
17. Eidem BW, Sapp BG, Suarez CR et al. Usefulness of the myocardial performance index for detection of anthracycline induced cardiotoxicity in children. Am J Cardiol, 2001; 87: 1120–1122.
18. Ocal B, Oguz D, Karademir S et al. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin-treated patients and its correlation to conventional echo/Doppler indices. Pediatr Cardiol, 2002; 23: 522––527.
19. Senju N, Ikeda S, Koga S et al. The echocardiographic Tei-index reflects early myocardial damage induced by anthracycline in patients with hematological malignancies. Heart Vessels, 2007; 22: 393–397.
20. Belham M, Kruger A, Pritchard C. The Tei index identifies a differential effect on left and right ventricular function with low-dose anthracycline chemotherapy. J Am Soc Echocardiogr, 2006; 19: 206–210.