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Norihiko Senju · Satoshi Ikeda · Seiji Koga
Yoshiyuki Miyahara · Kunihiro Tsukasaki
Masao Tomonaga · Shigeru Kohno

The echocardiographic Tei-index reflects early myocardial damage induced by anthracyclines in patients with hematological malignancies

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Abstract Anthracyclines are antineoplastic agents that are effective against solid tumors and hematological malignancies. However, drug-induced cardiotoxicity imposes dose limitations. Myocardial damage due to anthracyclines has been assessed by measuring left ventricular ejection fraction (LVEF) or fraction shortening (FS) by echocardiography and criteria for discontinuing treatment have been established based on these indexes. However, cardiotoxicity is already irreversible when either LVEF or FS fulfills these criteria. The Tei-index has recently been established to assess combined systolic and diastolic myocardial function during echocardiography. It can also detect small changes in cardiac function. We therefore surmised that the Tei-index would reflect early myocardial damage induced by anthracyclines. We treated 23 patients with the anthracycline, doxorubicin (DXR), and examined them at least twice during the treatment. An additional dose of DXR significantly correlated with a change in the Tei-index (ΔTei-index). In contrast, a change in LVEF did not correlate with increased doses of DXR. The ΔTei-index did not correlate with either LVEF or the Tei-index before treatment. These results suggested that the ΔTei-index is a more sensitive indicator of early cardiotoxicity induced by anthracyclines than LVEF regardless of its value before treatment.

Key words Echocardiography · Tei-index · Left ventricular ejection fraction · Anthracycline · Cardiotoxicity

N. Senju[1] · S. Ikeda (✉) · S. Koga[1] · Y. Miyahara · K. Tsukasaki · M. Tomonaga · S. Kohno
Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
Tel. +81-95-849-7280; Fax +81-95-849-7285
e-mail: sikeda@nagasaki-u.ac.jp

K. Tsukasaki · M. Tomonaga
Department of Hematology, Nagasaki University School of Medicine, Nagasaki, Japan

[1]Both authors contributed equally to this study.

Introduction

Anthracyclines are antineoplastic drugs that are widely applied to treat a variety of solid tumors and hematological malignancies.[1] Regimens that include anthracyclines can induce remission in 60%–70% of previously untreated patients with adult acute myeloid leukemia (AML).[2,3] The antitumor effects of these agents are associated with topoisomerase II inhibition, which occurs as a result of anthracycline intercalation between adjacent DNA base pairs and hydroxyl free radical production.[4] Despite their effectiveness against neoplasms, clinical use is limited by cumulative dose-limiting cardiotoxicity. Overt heart failure arises in 4.5%–7% of patients treated with anthracyclines and the incidence of abnormalities in cardiac function increases with time.[5] Anthracycline-induced congestive heart failure is usually due to permanent changes in the myocardium, that are most consistent with the contractile failure of cardiomyopathy.[5] Therefore, evaluation of cardiac dysfunction before changes become irreversible in the myocardium during treatment is critical. Left ventricular ejection fraction (LVEF) measured by echocardiography has been the main indicator of cardiac dysfunction and a powerful predictor of mortality.[6,7] However, this indicator is less sensitive in detecting cardiac dysfunction in that changes have already become irreversible in the myocardium by the time LVEF is determined.

The Tei-index has recently been established to assess combined systolic and diastolic myocardial function using Doppler echocardiography.[8] The index accurately predicts morbidity and mortality in patients with idiopathic dilated cardiomyopathy, cardiac amyloidosis, primary pulmonary hypertension. and acute myocardial infarction.[9–18] Furthermore, the Tei-index is a sensitive indicator of overall cardiac dysfunction in patients with mild to moderate congestive heart failure.[12] We also reported the significance of the Tei-index before and after hemodialysis in patients with chronic renal failure.[19]

Here, we show that a change in the Tei-index correlates with additional doses of anthracyclines, whereas that in

LVEF does not. Thus, a change in the Tei-index (ΔTei-index) might reflect early myocardial damage induced by anthracyclines in patients with AML, adult T-cell lymphoma, and malignant lymphoma.

Patients and methods

We treated 23 patients (12 men and 11 women; age 17–72 years, mean ± SD 47.2 ± 18.1 years) with the anthracycline, doxorubicin (DXR), at the Department of Hematology, Nagasaki University Hospital between 1998 and 2000 (Table 1). The patients comprised 12 with AML, 5 with adult T-cell leukemia, and 6 with malignant lymphoma, who had all undergone echocardiography more than twice during treatment. The total amount of administered DXR was below 420 mg/m^2, and the averaged interval of each echocardiography examination was 88.8 ± 83.6 days. The inclusion criteria were a normal sinus rhythm and no evidence of bundle branch block and atrioventricular block, and the absence of asynergy or significant valvular disease on echocardiography. We obtained informed consent from all patients to participate in this study.

Two-dimensional (2D), M-mode, and pulsed Doppler echocardiography were performed on each patient using an SSD-5500 echocardiograph (Aloka, Tokyo, Japan). The patients were examined using a 2.5-MHz probe while in the left lateral recumbent position for parasternal long-axis views and in the dorsal supine position for apical long-axis views. Left ventricular end-diastolic and end-systolic dimensions were measured from M-mode echocardiograms of the left ventricle using the leading edge method, and left ventricular ejection fraction (LVEF) was calculated using the Teichholz method.[20] The mitral inflow velocity was recorded from the apical long axis view with the pulsed Doppler sample volume (size 2 mm) positioned at the tips of the mitral leaflets during diastole. In addition, the LV outflow velocity was recorded from the same view with the pulsed Doppler sample volume (2 mm) positioned just below the aortic annulus. The Tei-index was calculated from the Doppler time interval (Fig. 1).[8] The Doppler time intervals were recorded at 100 mm/s during the end-expiratory phase. All measurements were obtained during 5 consecutive cardiac cycles and the average values were computed. Changes (Δ) in parameter values were calculated by subtracting values before from those after two echocardiography examinations. In patients who had undergone more than three sessions of echocardiography in a clinically stable state, we calculated changes in these parameters in the interval between two examinations. The intraobserver and interobserver coefficients of variation were 4.1% ± 4.0% and 5.3% ± 5.1%, respectively, in our manner.[21]

Statistically, all results are expressed as mean ±SD. Correlations between two parameters are described using Pearson's correlation. All data were statistically analyzed using SPSS II version 11 software (Chicago, IL, USA). A P value of less than 0.05 was considered significant.

Table 1. Characteristics of patients

	Value
Sex (male:female)	12:11
Age (years)	47.2 ± 18.1
LVEF (%)	73.4 ± 9.7
Tei-index	0.39 ± 0.17
Additional dose of anthracyclines (mg)	149.4 ± 133.8

LVEF, left ventricular ejection fraction

Results

None of our patients developed arrhythmia, acute heart failure, or death due to DXR. The LVEF was slightly, but not significantly exacerbated (from 73.4% ± 9.7% to 72.4% ± 12.1%) as was the Tei-index (from 0.39 ± 0.17 to 0.43 ± 0.18) before and after DXR treatment.

Since cardiotoxicity is induced by anthracyclines dependently on the administered dose, we examined the relationship between an additional dose of DXR between two examinations (Δdose), 149.4 ± 133.8 mg, and ΔLVEF or the

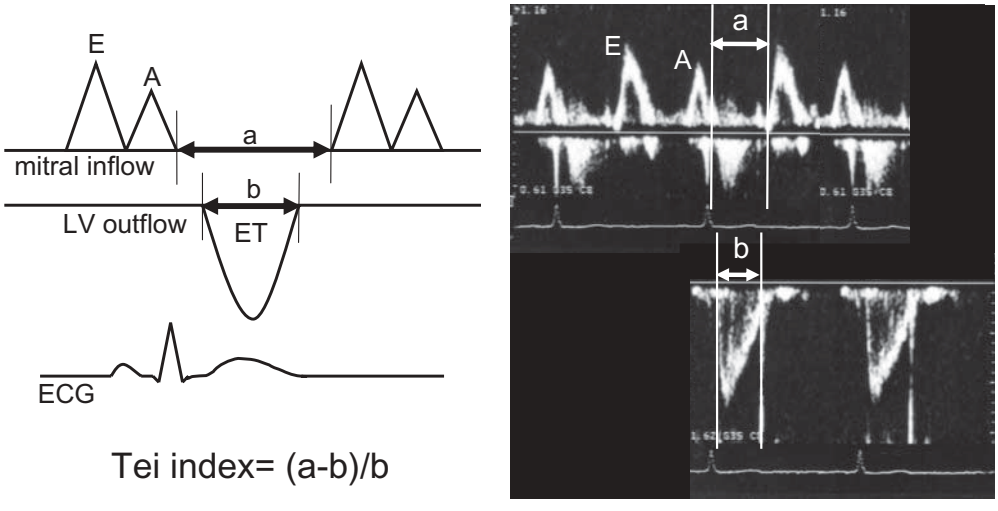

Fig. 1. Schema for measuring Tei-index. Tei-index is derived as (a – b/b), where a is the interval between cessation and onset of mitral inflow, and b is ejection time (ET) of left ventricular (LV) outflow. *ECG*, electrocardiogram; *E*, peak velocity of mitral inflow in early diastole; *A*, peak velocity of mitral inflow in late diastole

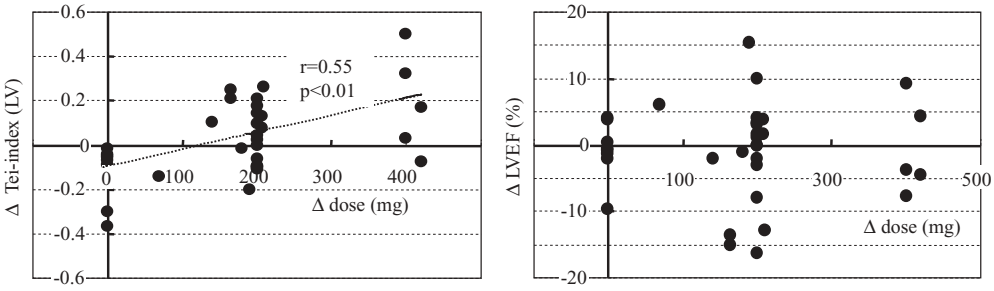

Fig. 2. Relationship between additional doses of doxorubicin (Δ*dose*), and changes in Tei-index (Δ*Tei-index*) or left ventricular ejection fraction (Δ*LVEF*) between two examinations

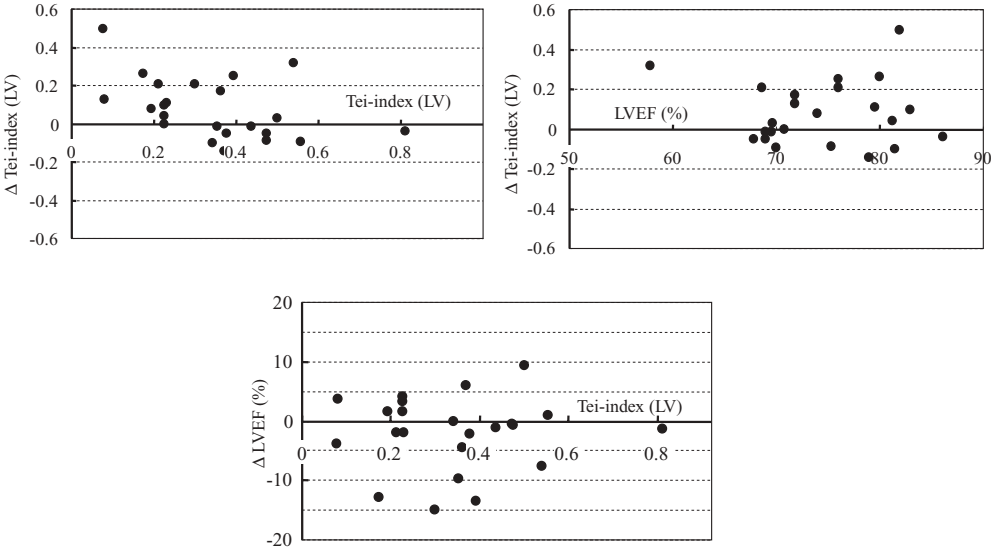

Fig. 3. Upper Relationship between changes in Tei-index (Δ*Tei-index*) and Tei-index or left ventricular ejection fraction (*LVEF*) before doses of doxorubicin were increased. **Lower** Relationship between change in LVEF (ΔLVEF) and in Tei-index before doxorubicin dose was increased

ΔTei-index. Figure 2 shows that the Δdose significantly correlated with the ΔTei-index ($r = 0.55$, $P < 0.05$). In contrast, the Δdose did not correlate with ΔLVEF.

Based on these results, we examined whether the LVEF value and Tei-index before adding the extra dose of DXR can estimate the ΔTei-index. Figure 3 shows that neither of these values correlated with the ΔTei-index, and that ΔLVEF did not correlate with the Tei-index before adding the extra DXR dose.

Discussion

We showed that the ΔTei-index closely correlates with Δdose, although the value of Tei-index or LVEF before adding extra DXR did not correlate with the ΔTei-index. The value of anthracyclines in the treatment of a wide spectrum of hematological malignancies has been established.[1,4–6,22] However, the cumulative dose of these agents should be carefully considered because of their cardiotoxicity. Anthracyclines cause a dose-dependent, autonomic nerve disturbance of the heart and myocardial damage in rats.[23–25] Although the mechanism of anthracycline-induced cardiotoxicity has not been clarified, endogenous histamine, arachidonic acid metabolites, platelet-derived activating factors, and calcium as well as superoxide induced by anthracyclines might contribute to myocardial damage.[26] The cardiotoxicity of anthracyclines is evident within a few days (acute phase) of administration, and for about 2 weeks to several months (chronic phase) thereafter. During the acute phase, transient arrhythmia and pericarditis appear that are independent of the cumulative dose of the agents. In contrast, dose-dependent myocardial damage occurs during the chronic phase. Von Hoff et al.[27] reported that the chronic cardiotoxicity of DXR is related to cumulative dose, age, and period between administrations, and that the incidence of heart failure increases over a cumulative dose of 550 mg/m^2. Bistow et al.[28] suggested that the total dose of anthracyclines should be below 300 mg/m^2 in patients who are over 70 years of age or have a cardiac dysfunction. The maximum dose in Japan is considered to be about 500 mg/m^2.

Chronic myocardial damage induced by DXR has been examined in myocardial biopsies as well as in myocardial scintigrams and echocardiograms. Among these, echocardiography is the most useful assessment tool because it is easy to manipulate, reproducible, and noninvasive.[29–32] As a criterion for discontinuing anthracyclines, the suggested values of fraction shortening (FS) and LVEF measured by echocardiography are below 29%[32] and 55%,[33] respectively, despite the cumulative amount of DXR. However, myocardial damage has already progressed and is close to becoming irreversible at the point of FS and LVEF reduction.

Therefore, new indicators for assessing early asymptomatic cardiotoxicity under the maximal dose of DXR are required. The Tei-index is considered to detect early myocardial dysfunction, which the LVEF and FS indexes cannot identify.[8,9] Moreover, several reports suggest that the Tei-index is useful for evaluating the severity and prognosis of various cardiopulmonary diseases, such as DCM, chronic heart failure, ischemic heart diseases, congenital heart diseases, valvular diseases, cardiac amyloidosis, and pulmonary hypertension.[9–18] Therefore, we considered that the Tei-index could be a good indicator of cardiotoxicity induced by anthracyclines.

The maximum cumulative dose of DXR in the present study was 420 mg/m^2 at which none of the patients developed heart failure and arrhythmia or died. Therefore, this cumulative dose could not be responsible for obvious cardiotoxicity. Under these conditions, our data showed that the Δdose significantly correlated with the ΔTei-index, but not with ΔLVEF. Therefore, the ΔTei-index might reflect early myocardial damage induced by a lower dose of DXR than that required to cause obvious cardiotoxicity and a significant decrease in LVEF. The ΔTei-index did not correlate with the Tei-index or LVEF before adding the extra DXR dose. Previous studies of the Tei-index have demonstrated that the value of anthracycline-induced cardiotoxicity increases with increasing cumulative dosage of anthracyclines in children with malignant neoplasms.[34–36] We showed here in adults with hematological malignancies that the ΔTei-index, but not the Tei-index itself, increased and correlated with increasing dosage of an anthracycline relatively sooner than described in previous studies.[35,36] Our results imply that the ΔTei-index is a good indicator of early subclinical myocardial damage induced by DXR, which is independent of basal values and LVEF.

Limitations

The present study has several limitations. We examined whether the Tei-index is a more sensitive and useful indicator of cardiotoxicity compared with LVEF because the latter is still considered a "standard indicator" of left ventricular (LV) function.[36] To define the criteria for discontinuing anthracycline, we did not examine relationships between the Tei-index and other indicators for assessing myocardial damage, such as plasma natriuretic peptides levels, LV diastolic functions using Doppler echocardiography, and parameters determined by radionuclide imaging. The numbers of patients might be also insufficient. The Tei-index is thought to be influenced by loading conditions but not by heart rate and blood pressure.[8] Although we performed echocardiography upon our patients while clinically stable, we could not deny that overloading might have affected the index after treatment. We described above that the recommended cumulative dosage of anthracyclines for Japanese patients is below 500 mg/m^2. Consistent with this, we applied a maximum dose of 420 mg/m^2. Thus, no obvious symptoms were clinically related to cardiac function in our patients, who had normal heart functions before treatment. Furthermore, whether the ΔTei-index and Δdose closely correlate at DXR doses above 420 mg/m^2 remains unclear. Eidem et al.[35] reported that the Tei-index tended to improve, but remained high compared with the baseline after discontinuing anthracyclines. We did not evaluate changes in the Tei-index after discontinuing treatment nor did we perform a long follow-up study. Further study is required to overcome these limitations.

Conclusion

Under a cumulative dose of DXR that causes obvious myocardial damage, the ΔTei-index might be a sensitive indicator of early cardiotoxicity induced by anthracyclines.

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