Can comprehensive echocardiographic evaluation provide an advantage to predict anthracycline-induced cardiomyopathy?

Kapsamlı ekokardiyografik inceleme antrasikline bağlı kardiyomiyopati gelişmesini öngörmede bir avantaj sağlar mı?

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ABSTRACT

Objectives: No definite markers have been established to identify patients in whom anthracycline-containing chemotherapy may represent a high risk for the development of cardiotoxicity. We aimed to evaluate the predictive value of comprehensive echocardiography in anthracycline-induced cardiomyopathy.

Study design: In a prospective design, the study included 39 patients (9 males, 30 females; mean age 53.7±11.5 years) who received antineoplastic therapy including anthracycline. Comprehensive echocardiographic examination including tissue Doppler imaging and coronary flow reserve was performed before treatment with anthracycline and at the end of a six-month follow-up.

Results: Eight patients (20.5%) developed cardiomyopathy during the follow-up period. Compared to patients with unaffected left ventricular ejection fraction at 6 months, patients with cardiomyopathy exhibited significant differences in baseline left ventricular systolic diameter, mitral E/A, E-wave deceleration time, Sm, Em, Em/Am ratio, Sm-Em duration, and the Tei index. In univariate logistic regression analysis, only Sm (OR 0.40, p=0.002) and the Tei index (OR 3.24, p=0.02) were significant variables for the development of cardiotoxicity. These two were also the only independent predictors of anthracycline cardiotoxicity in multivariate linear regression analysis. Receiver operating characteristic curve analysis yielded a cut-off value of 8 cm/sec for Sm and 0.38 for the Tei index to predict cardiomyopathy.

Conclusion: Our findings suggest that Sm and myocardial performance index (the Tei index) are significant independent markers to identify patients at high risk for the development of anthracycline-induced cardiomyopathy.

ÖZET

Amaç: Antrasiklin içeren kemoterapinin kardiyotoksisite gelişimi açısından yüksek risk oluşturduğu olguların belirlenmesi için henüz güçlü belirteçler ortaya konmamıştır. Bu çalışmada antrasikline bağlı kardiyomiyopati gelişmesinde kapsamlı ekokardiyografik incelemenin öngördürücü rolü değerlendirildi.

Çalışma planı: Çalışmaya, ileriye dönük bir tasarımla, antrasiklin içeren antineoplastik tedavi uygulanan 39 hasta (9 erkek, 30 kadın; ort. yaş 53.7±11.5) alındı. Hastalara, antrasiklinle kemoterapi öncesinde ve altı aylık takip sonunda, doku Doppler görüntüleme ve koroner akım rezervi de dahil kapsamlı ekokardiyografik inceleme yapıldı.

Bulgular: İzlem süresi içinde sekiz hastada (%20.5) kardiyomiyopati gelişti. Altıncı ayda sol ventrikül ejeksiyon fraksiyonu etkilenmemiş olan hastalarla karşılaştırıldığında, kardiyomiyopati gelişen grupta tedavi öncesi sol ventrikül sistolik çapı, mitral E/A, E dalgası yavaşlama zamanı, Sm, Em, Em/Am oranı, Sm-Em süresi ve Tei indeksi anlamlı farklılık gösterdi. Tekdeğişkenli lojistik regresyon analizinde sadece Sm (OR 0.40, p=0.002) ve Tei indeksi (OR 3.24, p=0.02) kardiyotoksisite gelişimi üzerine anlamlı etki gösterdi. Çokdeğişkenli lineer regresyon analizinde de sadece bu iki değişken antrasiklin kardiyotoksisitesinin bağımsız öngördürücüleri olarak bulundu. Alıcı işletim karakteristiği analizinde, kardiyomiyopati gelişimini öngörmede sınır değer Sm için 8 cm/sn, Tei indeksi için 0.38 bulundu.

Sonuç: Çalışmamızın bulguları, antrasikline bağlı kardiyomiyopati gelişmesi açısından yüksek riskli olguların belirlenmesinde Sm ve miyokart performans indeksinin (Tei indeksi) anlamlı bağımsız değişkenler olduğunu gösterdi.

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Myocardial contractile dysfunction is the most serious cardiotoxic effect of anthracycline therapy, causing a major limitation for the usage of this effective antineoplastic treatment. The estimated cumulative percentages of doxorubicin-induced cardiac dysfunction were reported as 5%, 26%, and 48% at cumulative doses of 400 mg/m^2, 500 mg/m^2, and 700 mg/m^2, respectively.[1] However, there is a non-linear correlation between the incidence of contractile dysfunction and the cumulative dose of anthracyclines, with toxicity varying significantly among different agents.[2] Accordingly, numerous reports have demonstrated evidence for cardiac dysfunction with cumulative anthracycline dosages less than 250 mg/m^2.[3] In addition to the total cumulative dose of anthracycline, several patient-related features including ageing, prior irradiation therapy, hypertension, diabetes, and obesity have been reported as risk factors associated with anthracycline cardiotoxicity.[4] However, there has not been any recommended technique to asses the pre-existing risk before starting therapy with anthracycline.

Echocardiography is a widely used noninvasive method of monitoring the cardiotoxicity of cancer therapy. It does not involve the use of ionizing radiation and provides a wider spectrum of information on cardiac morphology and function. Parameters of systolic (left ventricular ejection fraction, left ventricular fractional shortening, and systolic wall thickening] and diastolic function [mitral in flow pattern early/atrial (E/A) ratio, mitral E-wave deceleration time, isovolumetric relaxation time and pulmonary venous flow pattern], and valvular function can be assessed. With modern echocardiography equipment and techniques such as tissue Doppler imaging, it is possible to obtain images in the vast majority of patients. However, there is no prospective study concerning usage of echocardiography in predicting anthracycline-induced cardiomyopathy. We designed this prospective study to determine the predictive role of comprehensive echocardiographic examination.

PATIENTS AND METHODS

Study population

On a prospective basis, we documented the patients who were planned to receive antineoplastic therapy, including anthracycline, for malignancies between January 2009 and December 2009. After applying our inclusion and exclusion criteria, the overall study population consisted of 54 subjects. Of these, a total of 15 patients (27.8%) were further excluded due to subsequent mortality (n=12), development of paraplegia during follow-up (n=1), and inadequate record keeping (n=2). Thus, data on 39 patients (72.2%) were available for final analysis. Inclusion criteria were age of 18-75 years and administration of antineoplastic therapy including anthracycline. Before enrollment, all subjects were asymptomatic and free from cardiovascular diseases. Exclusion criteria were the presence of the following: any systemic disease such as diabetes, hypo/hyperthyroidism, hypertension, hemolytic, hepatic, and renal diseases; present or past history of coronary artery disease, congestive heart failure symptoms, LVEF <50%, established structural heart disease such as cardiomyopathy, and moderate or severe mitral or aortic valve disease; and history of chemotherapy or radiotherapy, and planned radiotherapy. In addition, subjects who had ST-segment or T-wave changes specific for myocardial ischemia, Q waves, and incidental left bundle branch block on electrocardiography were excluded from the study. The study was carried out in compliance with the Declaration of Helsinki. Written informed consent was obtained from each subject, and the study protocol was approved by the institutional ethics committee.

Abbreviations:

CFR *Coronary flow reserve*
LAD *Left anterior descending*
LV *Left ventricular*
LVEF *Left ventricular ejection fraction*
TDI *Tissue Doppler imaging*

Study design

In each subject, physical examination included measurement of height (centimeters) and weight (kilograms), a resting 12-lead electrocardiogram was obtained, and total cumulative dose of anthracycline and laboratory findings were recorded. A comprehensive echocardiographic examination was performed at baseline and at the end of a six-month follow-up.

Echocardiographic examination

Each subject was examined using a Vingmed System Five GE Echocardiography System (Norway) equipped with 2.5V2C and 5V2C broadband transducers with second harmonic imaging capability. Echocardiographic examination included two-dimensional, M-mode, and subsequent transthoracic Doppler harmonic imaging. Echocardiography was performed by the same investigator blinded to clinical data, and the echocardiogram recordings were assessed by two cardiologists blinded to the patient's data. Left ventricular ejection fraction was calculated by the modified Simpson's rule using two-dimensional end-systolic and end-diastolic volume measurements in the apical four-chamber view.

The papillary muscles were excluded from the cavity in the tracing.[5] At 6-month follow-up, patients whose resting LVEF decreased by ≥20 units from the baseline to a final value of ≥50%, or by ≥10 units from the baseline to <50%, and/or who exhibited clinical evidence for congestive heart failure were considered to have developed cardiomyopathy.[6-8]

The pulsed Doppler sample volume was positioned at the mitral leaflet tips. Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E/A ratio, and mitral E-wave deceleration time were measured by transmitral Doppler imaging.

The TDI program was set to the pulsed-wave Doppler mode. Filters were set to exclude high-frequency signals, and the Nyquist limit was adjusted to a velocity range of -15 to 20 cm/sec. Gains were minimized to allow for a clear tissue signal with minimal background noise. All TDI recordings were obtained during normal respiration. Using the apical four-chamber view, a 5-mm sample volume was placed at the lateral corner of the mitral annulus and subsequently at the medial (or septal) corner.[9] The resulting velocities were recorded for 5-10 cardiac cycles at a sweep speed of 100 mm/sec. The following parameters were measured in each region and averaged: peak velocities (cm/sec) of the myocardial systolic (Sm), myocardial early (Em), and atrial (Am) waves, Em/Am ratio, and Sm-Em duration. On tissue Doppler images, the time interval from the end to the onset of the mitral annular velocity pattern during diastole (am) and the duration of the S wave (bm) were measured and used to calculate the Tei index as (am – bm)/bm.[10] All diastolic and time interval parameters were measured in three consecutive cardiac cycles and averaged.

Measurement of left ventricular mass

Left ventricular mass was calculated from M-mode recordings on parasternal long-axis images according to the corrected American Society of Echocardiography cube method.[5] Left ventricular mass index was calculated as LV mass divided by height.

Evaluation of coronary microvascular function

Visualization of the distal left anterior descending coronary artery was performed using a modified, foreshortened, 2-chamber view obtained by sliding the transducer superiorly and medially from an apical 2-chamber view. Coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity set in the range of 8.9 to 24.0 cm/sec.[11] The left ventricle was imaged on the long-axis cross-section, and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was searched by color Doppler flow mapping. Doppler recordings of the LAD were obtained during dipyridamole infusion at a rate of 0.56 mg/kg over 4 minutes. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components. Coronary diastolic peak velocities were measured at baseline and after dipyridamole by averaging the highest three Doppler signals for each measurement. Coronary flow reserve was defined as the ratio of hyperemic to baseline diastolic peak velocities.[11]

To test reproducibility of major data points, the measurements were repeated two or three days later in six subjects. Intraobserver agreement was assessed by calculating the intraclass correlation coefficient, which yielded 0.865 for LVEF, 0.973 for Sm, 0.962 for the Tei index, and 0.884 for CFR measurements.

Statistical analysis

Statistical data were processed using the SPSS 9.0 (for Windows) software package. Data were expressed as mean ± standard deviation. To test the incidence of cardiomyopathy after six months, the two-tailed Fisher's exact test was used; then, the patients were divided into two groups based on LVEF and were compared using the Mann-Whitney U-test. Logistic-regression analysis was adjusted for significant baseline predictors of anthracycline-induced cardiomyopathy. The relationships of baseline variables with the changes in LVEF from the baseline were assessed by univariate linear regression analysis, and multivariate linear regression analysis to assess the independency of the relationship. In addition, a logistic regression analysis was performed to assess the relationship between baseline variables and the development to cardiomyopathy at the end of six-month follow-up. Receiver operating characteristic (ROC) curves were constructed for Sm and the Tei index for prediction of cardiotoxicity. A *P* value of less than 0.05 was considered significant.

RESULTS

During the six-month follow-up period of 39 patients, eight patients (20.5%) developed cardiomyopathy. Of these, two patients complained of heart failure symp-

Table 1. Baseline demographic, clinical, and echocardiographic characteristics of the patients

	All patients (n=39)			With cardiomyopathy at 6 month (n=8)			Without cardiomyopathy at 6 month (n=31)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Age (years)			53.7±11.5			50.1±6.1			54.6±12.4
Gender									
Male	9	23.1		2	25.0		7	22.6	
Female	30	76.9		6	75.0		24	77.4	
Height (cm)			159.3±8.1			157.2±7.0			160.0±8.3
Weight (cm)			69.1±13.1			69.5±14.1			69.0±13.0
Body mass index (kg/m^2)			27.3±4.9			28.1±5.8			27.0±4.8
Body mass index <30 kg/m^2	13	33.3		3	37.5		10	32.3	
Hypertension	11	28.2		1	12.5		10	32.3	
Systolic blood pressure (mmHg)			126.1±20.3			126.9±16.7			126.0±21.5
Diastolic blood pressure (mmHg)			76.1±11.9			75.6±12.9			76.2±11.8
Heart rate (bpm)			78.3±10.6			82.1±12.3			77.3±10.1
Hemoglobin (g/dl)			11.7±2.2			13.1±1.7			11.4±2.2
Type of cancer									
Breast	23	59.0		6	75.0		17	54.8	
Lymphoma	11	28.2		2	25.0		9	29.0	
Other	5	12.8		–			5	16.1	
Total anthracycline dose (mg/m^2)			448.3±131.2			466.9±105.4			443.5±138.2
Echocardiographic findings									
Left ventricle									
Diastolic diameter (cm)			4.5±0.4			4.7±0.5			4.5±0.4
Systolic diameter (cm)			2.9±0.3			3.1±0.4*			2.8±0.3
End-diastolic volume (ml)			114.8±30.9			111.5±38.0			115.8±29.0
End-systolic volume (ml)			44.6±13.4			43.8±18.7			44.9±11.9
Ejection fraction (%)			61.5±5.1			61.0±7.2			61.7±4.6
Mass index (g/m^2)			58.8±12.4			66.0±12.4			57.0±11.9
Left atrial diameter (cm)			3.3±0.5			3.5±0.6			3.3±0.5
Mitral E max (cm/sec)			83.8±17.4			79.3±18.2			85.1±17.4
Mitral A max (cm/sec)			83.9±18.7			88.5±21.1			82.8±12.4
E/A			1.04±0.28			0.91±0.15*			1.08±0.31
Mitral E wave deceleration time (msec)			209.0±38.1			230.8±36.3*			203.0±36.9
Isovolumetric relaxation time (msec)			105.4±19.9			110.5±22.0			104.0±19.5
Sm (cm/sec)			9.33±1.51			8.25±1.04**			9.61±1.50
Em (cm/sec)			8.95±2.38			7.62±1.41*			9.29±2.48
Am (cm/sec)			10.46±1.68			10.63±1.92			10.42±1.65
Em/Am			0.89±0.30			0.74±0.21*			0.92±0.31
Sm-Em duration (msec)			87.6±16.9			97.3±17.1*			85.2±16.2
E/Em (or E/E')			9.84±2.70			10.79±3.51			9.60±2.46
Tei index			0.43±0.08			0.47±0.07*			0.41±0.08
Diastolic peak flow of the LAD									
Baseline (cm/sec)			28.9±6.3			29.4±8.5			28.8±5.4
Hyperemic (cm/sec)			59.9±18.0			63.1±22.2			59.0±17.2
Coronary flow reserve			2.10±0.57			2.11±0.36			2.10±0.62

LAD: Left anterior descending coronary artery; *p<0.05 and **p<0.01 for cardiomyopathy *vs.* normal ejection fraction at 6-month visit.

Table 2. Univariate logistic regression analysis of the baseline variables to predict the development of cardiomyopathy at six-month follow-up

	Odds ratio	95% confidence interval	*p*
Age	0.92	0.86 – 1.00	0.39
Gender	0.29	0.09 – 0.94	0.61
Body mass index	1.11	0.96 – 1.29	0.17
Hypertension	1.09	0.94 – 1.27	0.27
Total anthracycline dose	1.19	1.03 – 1.47	0.79
Left ventricle			
Diastolic diameter	0.99	0.97 – 1.00	0.18
Systolic diameter	1.14	0.97 – 1.25	0.07
End-diastolic volume	0.90	0.83 – 0.97	0.61
End-systolic volume	0.99	0.98 – 1.00	0.73
Ejection fraction	1.00	0.99 – 1.01	0.79
Mass index	1.14	0.93 – 1.27	0.08
Left atrial diameter	0.58	0.16 – 2.07	0.42
Mitral E max	1.01	0.97 – 1.05	0.30
Mitral A max	1.33	0.83 – 2.13	0.35
E/A	0.89	0.76 – 1.17	0.08
Mitral E wave deceleration time	1.45	1.33 – 1.57	0.06
Isovolumetric relaxation time	1.02	0.99 – 1.05	0.18
Sm	0.40	0.17 – 0.5	**0.002**
Em	0.81	0.68 – 1.35	0.06
Am	0.60	0.09 – 4.14	0.61
Em/Am	0.77	0.57 – 1.03	0.07
Sm-Em duration	1.14	0.84 – 1.55	0.07
E/Em (or E/E')	1.28	0.98 – 1.68	0.08
Tei index	3.24	1.40 – 4.4	**0.02**
Coronary flow reserve	0.58	0.16 – 2.07	0.40

toms which were treated with diuretics and angiotensin-converting enzyme inhibitors. Table 1 shows baseline general characteristics, risk factors, and echocardiographic findings of the patients including those who developed cardiomyopathy and who had normal LVEF at the end of the six-month follow-up. There were no significant differences with regard to baseline characteristics between patients with and without cardiomyopathy at the end of the follow-up; however, these two groups exhibited significant differences in LV systolic diameter, mitral E/A, E-wave deceleration time, Sm, Em, Em/Am, Sm-Em duration, and the Tei index.

Table 2 shows the results of univariate logistic regression analysis with crude odds ratios and 95% confidence intervals of the baseline variables to predict the development of cardiomyopathy. Age, gender, body-mass index, hypertension, and total cumulative anthracycline dose had no significant effect on the development of anthracycline-induced cardiotoxicity. Among echocardiographic parameters, LV systolic diameter, LV mass index, mitral E/A, E-wave deceleration time, Em, Em/Am, Sm-Em duration, and mitral E/E' showed only a trend towards a significant role for cardiotoxicity. Only the Tei index and Sm were significant predictors in univariate regression analysis. Similarly, in multivariate linear regression analysis, Sm (OR 0.40, 95% CI 0.17-0.95, p=0.002) and the Tei index (OR 3.24, 95% CI 1.40-4.94, p=0.02) were the only independent predictors of anthracycline cardiotoxicity.

Receiver operating characteristic curve analysis yielded a cut-off value of 8 cm/sec for Sm and 0.38

for the Tei index. These cut-off values differentiated the patients with and without cardiomyopathy with sensitivity rates of 75% and 88% and specificity rates of 96% and 65% for Sm and the Tei index, respectively.

DISCUSSION

In this 6-month prospective study, we found that Sm and myocardial performance index, but not CFR reflecting coronary microvascular function, were significant independent markers to identify patients at high risk for anthracycline-induced cardiomyopathy. The best cut-off values to estimate anthracycline-induced cardiomyopathy were 8 cm/sec for Sm and 0.38 for the Tei index.

Cardiotoxicity associated with anthracycline is a cumulative and dose-related progressive myocardial damage leading to clinical events ranging from an asymptomatic reduction in LVEF to irreversible life-threatening congestive heart failure.[12] Although several risk factors have been reported, no consensus exists on optimal monitoring for associated adverse cardiac effects of anthracycline therapy in patients with malignancy. Accordingly, the present study aimed to evaluate whether comprehensive echocardiography can help predict anthracycline-induced LV systolic dysfunction before starting therapy.

In several studies, the total cumulative dose of anthracycline was found as the best predictor of cardiotoxicity.[13,14] In addition, many other factors including intercurrent cardiotoxic therapies, prior irradiation therapy, advanced age, female sex, preexisting cardiac dysfunction, hypertension, and obesity increase the risk for cardiotoxicity, particularly when high cumulative doses of anthracycline are given following bolus administration.[14-17] However, in our study, these risk factors were not found to have a relationship with cardiomyopathy.

Serial noninvasive surveillance for anthracycline cardiotoxicity has centered on the echocardiographic assessment of LV systolic function using ejection-phase indices, namely, fractional shortening and LVEF. However, changes in these indices are most commonly late clinical findings and thus are often not helpful for the early identification of subclinical myocardial dysfunction. Moreover, these methods cannot be used to predict cardiotoxicity before administration of anthracycline therapy.

It has been reported that anthracycline therapy can also affect LV diastolic function and diastolic filling patterns, which are assessed by conventional Doppler imaging.[8] Tissue Doppler imaging is a relatively new echocardiographic technique that uses Doppler principles to measure the velocities of myocardial motion. It has been shown that systolic and diastolic myocardial velocities correlate well with systolic and diastolic ventricular function.[18,19] Parameters of TDI are less affected by load conditions, and it is nearly always possible to obtain recordings of mitral annular velocities of sufficient quality.[19,20] Therefore, TDI is a simple method by which both systolic and diastolic function can be evaluated at the same time. Mitral annular or basal LV velocities reflect the long-axis motion of the ventricle, which is an important component of LV systolic and diastolic function.[21,22] Several parameters of TDI velocity analysis have been shown to be useful to predict long-term prognosis, in particular, Sm, Em, and E/E'. The use of threshold values of Em and E/E' provides independent and incremental prognostic information in a number of major cardiac diseases, such as heart failure, acute myocardial infarction, and hypertension.[22] It has been shown that peak Sm correlates well with LVEF, and a cut-off value of >7.5 cm/sec predicts normal global LV function with a sensitivity of 79% and specificity of 88%.[23] Furthermore, Sm is also a sensitive marker of mildly impaired LV systolic function,[24] and lower Sm values are associated with increased mortality.[25] In the present study, we found that Sm, but not Em and E/E', was an independent predictor of anthracycline-induced cardiomyopathy.

The Tei index is a Doppler echocardiographic parameter that reflects global LV function. It has been demonstrated that increases in the TDI-derived Tei index correlate with increasing degrees of LV diastolic dysfunction,[10] while it correlates fairly with echocardiographic parameters of LV diastolic and systolic function and filling pressures. Moreover, it offers the advantage of simultaneous recording of both tissue Doppler components from the myocardium during the same cardiac cycle. This makes the TDI-derived Tei index a simple and feasible tool to assess global LV function.[10] Recently, the Tei index has been proposed to study the impact of anthracyclines on ventricular function. In a prospective study of 100 adults who received anthracycline-based chemotherapy, the Tei index increased in 78.8% of the patients after anthracycline therapy compared with baseline values, indicating alterations in myocardial function.[26] However, there is no study designed to determine whether the Tei index can predict overall cardiac risk in patients receiving anthracycline-containing chemotherapy

regimens. Belham et al.[27] reported that the Tei index detected worsening LV function earlier in the course of treatment with anthracyclines with a greater significance than any other standard echocardiographic measurement, but did not predict functional cardiotoxicity. The results of our prospective study suggest that the Tei index may predict the risk for anthracycline-induced cardiomyopathy in patients receiving anthracycline-containing chemotherapy.

Coronary flow reserve determined noninvasively by transthoracic Doppler echocardiography is a reliable marker of coronary microvascular function and its feasibility has been validated.[28] Furthermore, CFR measured by transthoracic Doppler echocardiography has been shown to have an excellent correlation with CFR measured by positron emission tomography.[29] Reduced CFR was reported to be a poor prognostic indicator and an independent predictor of subsequent cardiac events in patients with idiopathic LV dysfunction.[30] However, CFR was not found as a predictor of anthracycline-induced cardiomyopathy in our study.

Study limitations

Several important limitations of our study should be noted. First, the present study does not provide insight into the pathophysiology of anthracycline-induced cardiomyopathy. From our results, a causal relationship cannot be demonstrated. Second, the existence of coronary artery disease was ruled out only by resting electrocardiogram and echocardiography, without the use of stress tests including imaging tests. Therefore, we cannot be fully confident about exclusion of patients with epicardial coronary artery disease. Third, the study did not have a control group. Fourth, although TDI parameters appear to be less load dependent than those of conventional blood flow Doppler, assessment of subclinical LV dysfunction based on tissue velocities may have some limitations. Therefore, strain imaging would provide a more sensitive and accurate evaluation of myocardial contractility. Fourth, the sample size together with only eight consequent events was relatively small to draw meaningful results; thus, the present study can only serve to provide a trend and our results should be verified by larger trials with higher numbers of events.

In conclusion, this 6-month prospective study suggests that Sm and myocardial performance index, in other words the Tei index, but not CFR reflecting coronary microvascular function, are significant independent markers to identify high-risk patients for anthracycline-induced cardiomyopathy.

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Key words: Anthracyclines/adverse effects; cardiomyopathies; drug interactions; echocardiography, Doppler; myocardial contraction; neoplasms/drug therapy; ventricular function, left.

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