Clin Res Cardiol 97:318–326 (2008)
DOI 10.1007/s00392-007-0633-6

ORIGINAL PAPER

Fotiní Dodos
Teresa Halbsguth
Erland Erdmann
Uta C. Hoppe

Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults

Received: 21 July 2007
Accepted: 20 November 2007
Published online: 14 January 2008

F. Dodos, MD · T. Halbsguth, MD
E. Erdmann, MD · U.C. Hoppe, MD (✉)
Department of Internal Medicine III
University of Cologne
Kerpener Str. 62
50937 Cologne, Germany
Tel.: +49-221/478-32397
Fax: +49-221/478-32396
E-Mail: uta.hoppe@uni-koeln.de

U.C. Hoppe, MD
Center for Molecular Medicine Cologne (CMMC)
University of Cologne
Cologne, Germany

Abstract *Background* Anthracycline therapy is limited by cardiotoxicity. Currently no diagnostic parameter is available allowing ubiquitous and reliable detection of preclinical anthracycline cardiomyopathy and prediction of prognosis. *Patients and methods* In 100 consecutive patients receiving anthracycline-based chemotherapy serial measurements of left ventricular systolic and diastolic function, Tei index (a Doppler echocardiographic parameter of global ventricular function), cardiac troponin T (cTnT) and NT-probrain natriuretic peptides (BNP) at baseline and during 1-year follow-up were performed. *Results* Mean ejection fraction (LVEF) significantly decreased immediately after completion of anthracycline therapy (mean dose 226.1 ± 8.3 mg/m^2) und further declined during follow-up (65.9 ± 0.6% Vs. 61.6 ± 0.7%; $P < 0.001$), while mean E/A ratio decreased after 6 months ($P = 0.05$). No patient presented with cardiac symptoms. The Tei index increased after therapy in the majority of patients (78.8%) compared with pre-therapy values indicating myocardial alteration in more patients than previously recognized. cTnT levels did not exceed the upper limit of the normal range in any patient. Seven patients had low-level elevations of cTnT. Only one of these patients developed a concomitant decrease in LVEF. Mean N-terminal-pro-BNP (NT-proBNP) levels did not significantly change after anthracycline administration. However, in 13 patients (15.3%) a marked, transient increase of NT-proBNP was obtained after the first anthracycline cycle without cardiac dysfunction presumably due to altered cardiac loading conditions during chemotherapy. *Conclusion* Low to moderate doses of anthracyclines resulted in subclinical myocardial alteration in more patients than so far noticed. Clinical implications of increased Tei index remain to be determined in long-term. Our results do not support that assessment of cTnT or BNP levels may safely replace serial echocardiographic evaluation of systolic and diastolic function for the monitoring of anthracycline cardiotoxicity.

Key words anthracycline – cardiotoxicity – cardiac troponin T – natriuretic peptides – Tei index – heart failure – BNP

Introduction

Anthracyclines are well established as highly efficacious antineoplastic agents for various hematological cancers and solid tumors. Despite measures taken to lessen or prevent cardiac injury, their use is limited by cardiotoxicity [8, 32]. Rarely, cardiotoxic effects may occur immediately after a single dose. More commonly anthracyclines induce progressive chronic cardiotoxicity resulting in cardiomyopathy which usually presents within 1 year of treatment [14]. Cardiotoxicity is related to the cumulative dosage. However, susceptibility to this severe side-effect is largely individual and a subset of patients shows signs of cardiomyopathy even at low anthracycline doses [26]. Thus, early detection and monitoring of cardiotoxic side-effects is a compelling need to omit further cardiac injury (i.e. by mediastinal radiotherapy) and ensure early initiation of heart failure therapy in affected patients.

Endomyocardial biopsy is considered a moderately sensitive indicator of chronic anthracycline-induced cardiotoxicity. However, its use for routine monitoring cannot be recommended because of its invasive nature [23]. Currently, the most common methods used to detect subclinical anthracycline-induced cardiomyopathic changes are radionuclide ventriculography and echocardiographic assessment of systolic and diastolic function with however limited sensitivity [43]. Recently, the Tei index, a Doppler echocardiographic parameter of global ventricular function has been introduced to study the impact of anthracyclines on ventricular function [2, 9, 13, 30]. Moreover, elevation of biochemical markers such as atrial and brain natriuretic peptides (BNP) and cardiac troponin-T (cTnT) have been suggested as surrogate for anthracycline-induced myocardial injury [11, 20, 21, 33]. cTnT, a component of the troponin complex of muscle cells, is used as a marker of myocardial damage in suspected myocardial infarction [28]. BNP is released chiefly by the cardiac ventricles in response to myocardial stresses and correlates well with impairment of systolic and diastolic cardiac function in heart failure [3, 17, 27, 31, 42]. However, the diagnostic value of these parameters in the early assessment of preclinical anthracycline cardiotoxicity remains largely undefined.

Therefore, in the present study for the first time we prospectively assessed and compared serum cTnT, BNP levels and Doppler echocardiographic Tei index for the detection and monitoring of anthracycline-induced cardiotoxicity over a period of 1 year in 100 adults undergoing cancer chemotherapy.

Patients and methods

Patient population

One hundred consecutive patients with the diagnosis of solid or haematological malignancy who had been scheduled to receive anthracycline-containing chemotherapy were enrolled in the study. Patients were excluded if they had a history of cardiovascular disease, prior use of anthracycline therapy, prior or additional mediastinal radiotherapy, chronic renal insufficiency (creatinine clearance <60 ml/min), liver disease (serum bilirubin >2.0 mg/dl, ALT and AST >100 U/l), uncontrolled systemic hypertension, left ventricular ejection fraction (LVEF) <55%, and were older than 70 years or younger than 18 years. All patients gave informed consent before participation in the study. The protocol was approved by the local ethics committee and all patients provided informed consent.

Cardiac evaluation

Pre-treatment and follow-up evaluation (24–72 h, 1, 6 and 12 months after the last course of the chemotherapy) consisted of a complete history, physical examination including symptoms and signs of heart failure, electrocardiogram, and echocardiography. Echocardiographic evaluations were performed with a GE Vingmed Ultrasound system (Vivid FiVe, Horten, Norway), digitized and analyzed using EchoPAC software version 6.3 (GE Medical Systems, Vivid FiVe, Milwaukee, USA). Systolic left ventricular function was assessed by left ventricular fractional shortening (FS) using the leading edge method and LVEF using the modified Simpson's method according to the American Society of Echocardiography criteria [29]. The following Doppler time intervals, mitral flow velocities and pulmonary vein flow velocities were calculated and analyzed for each patient: diastolic filling period, isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT), ejection time (ET), early peak flow velocity (peak E), deceleration time of peak E (DT), atrial peak flow velocity (peak A) and duration (A dur), E/A ratio, pulmonary systolic flow velocity (PVs), pulmonary diastolic flow velocity (PVd), pulmonary reversal flow velocity (PVa) and duration (PVa dur). The myocardial performance index or Tei index for combined evaluation of systolic and diastolic left ventricular function was computed with the equation: Tei index = (ICT + IRT)/ET [38]. All Doppler and echocardiographic measurements were the average of at least five consecutive cycles.

A cardiac event was defined as a decline in absolute value >20% in LVEF from baseline, a decline in

absolute value >10% in LVEF from baseline to below 55% or the occurrence of congestive heart failure [37].

Biochemical analysis

Routine blood chemistry and serial measurements of cTnT were performed in all patients, serial measurements of BNP in 60 patients (patient 41–100): before the anthracycline therapy, on the third to fifth day following the first dose of anthracycline administration, and 24–72 h, 1, 6 and 12 months after the last course of the chemotherapy. Serum cTnT levels were assessed by Elecsys Troponin T STAT Immunoassay on an Elecsys® 2010 immunoassay analyzer (Roche® Diagnostics GmbH, Mannheim, Germany) with a lower limit of 0.010 ng/ml. Any value below this limit was considered to be zero. The normal values of cTnT with this analyzer were 0.010–0.100 ng/ml. N-terminal-pro-BNP (NT-proBNP) was measured by Elecsys ECLIA on a Elecsys® 2010 immunoassay analyzer (Roche® Diagnostics GmbH, Mannheim, Germany). The detection limit was 5 pg/ml. Any value below this limit was considered to be zero. The normal values of NT-pro-BNP with this analyzer depend on gender and age (females <50 years: <153 pg/ml, females 50–70 years: <334 pg/ml; males <50 years: <88 pg/ml, males 50–70 years: <227 pg/ml).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 10.0. Data are presented as mean ± standard error of the mean (SEM). Statistical comparison within groups were performed using the paired *t* test and between groups by unpaired *t* test. Correlations between variables were tested by means of bivariate correlation testing.

Results

One hundred consecutive patients who received anthracycline containing chemotherapy were evaluated in the study. Forty-eight patients were male (48%) and 52 patients were female (52%). The mean age was 46.1 ± 1.3 years (range 20–70). Eighteen patients (18%) had a history of systemic hypertension which was well controlled under medication. Fifteen patients died of non-cardiac cause during follow-up, nine of them before the completion of the chemotherapy course, and three patients each within 1 and 6 months after chemotherapy, respectively.

Patient's histopathological diagnoses are presented in Table 1. Anthracyclines of the therapeutic regimens were doxorubicin (53%), epirubicin (29%), daunorubicin (15%), mitoxantrone (2%), and idarubicin (1%). The mean cumulative anthracycline dose estimated with the conversion factor for assessment of equivalent doses [14, 15] (Table 2) was 226.1 ± 8.3 mg/m^2 (range 90–400 mg/m^2).

Table 1 Histopathologic diagnoses

Diagnosis	Number of patients
Non-Hodgkin lymphoma	37
Breast cancer	29
Hodgkins lymphoma	13
Acute myeloic leukemia	9
Multiple myeloma	3
Acute lymphatic leukemia	2
Lung cancer	2
Sarcoma	1
Chronic lymphatic leukemia	1
Malignant histiocytoma	1
Other malignancies	2

During the 1-year follow-up none of the surviving patients developed clinical signs or symptoms of heart failure, alterations of the electrocardiogram, renal or hepatic insufficiency.

Incidence of left ventricular systolic dysfunction

Echocardiograms obtained before anthracycline application showed normal LVEF (65.9 ± 0.6%, range 55–83) and FS (39.7 ± 0.5%, range 29–52) in all patients. While mean LVEF and mean FS remained within the normal range during follow-up, there was still a significant decrease immediately after completion of therapy compared to baseline (Fig. 1a, b). Moreover, mean LVEF and mean FS further declined significantly until the last evaluation 1 year after completion of chemotherapy (Fig. 1a, b).

A cardiac event defined as a reduction in absolute value >20% in LVEF from baseline or a decline in absolute value >10% in LVEF from baseline and below 55% [37] was obtained in 15 patients (17.7%). Seven of these patients presented with an additional reduction of the E/A ratio, three with an elevation of cTnT, while none exhibited an alteration of NT-proBNP levels. There was no correlation between

Table 2 Conversion factor for the anthracyclines [8]

Chemotherapeutic agents	Conversion factor	5% Incidence of cardiotoxicity (mg/m^2)
Doxorubicin	1	450
Epirubicin	0.5	935
Daunorubicin	0.5	900
Idarubicin	2	225
Mitoxantrone	2.2	200

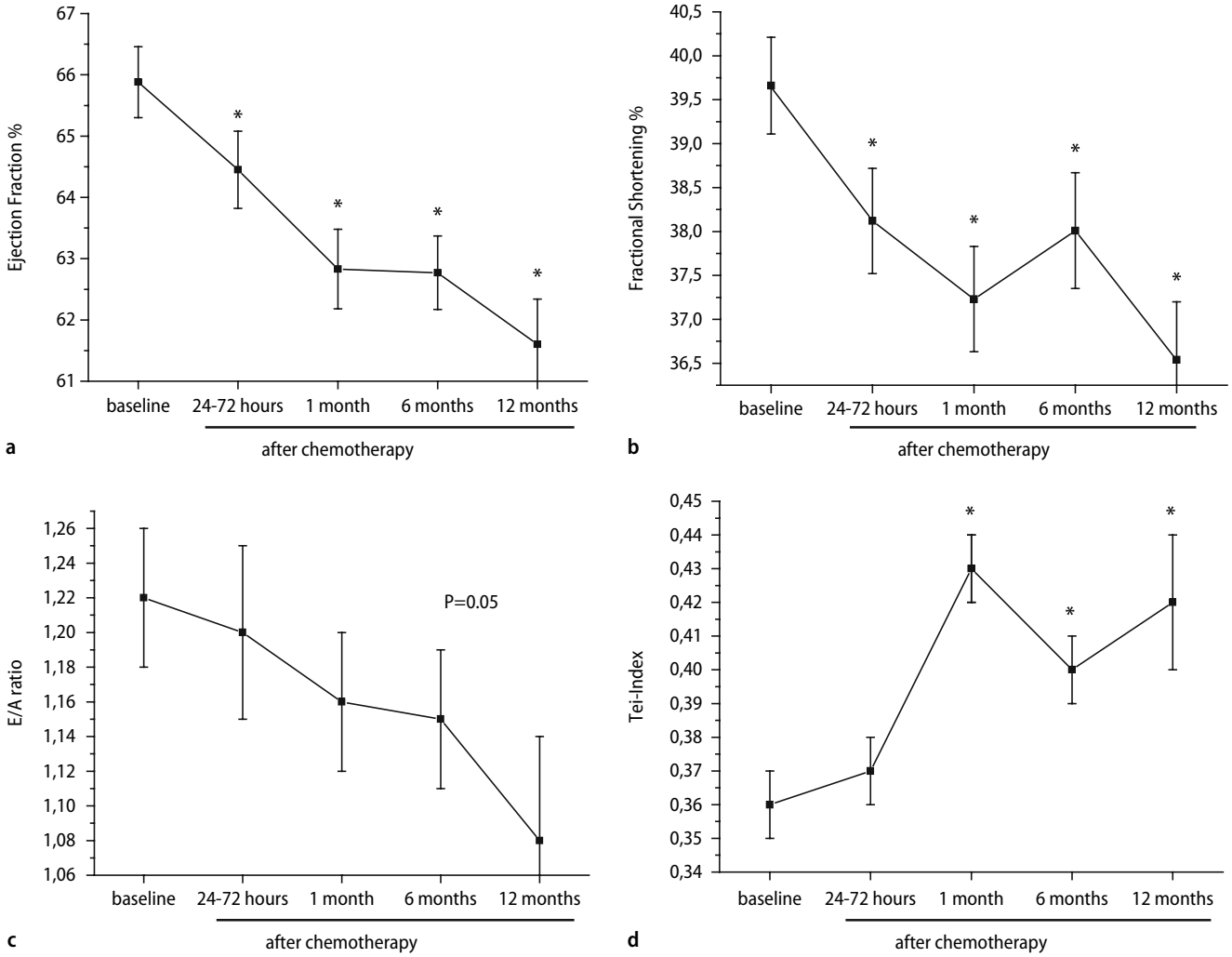

Fig. 1 Echocardiographic parameters levels at baseline and during follow-up after anthracycline therapy. **a** Mean ejection fraction and **b** fractional shortening significant decreased immediately after completion of therapy (64.5 ± 0.6% Vs. 65.9 ± 0.6%, $P = 0.0004$, and 38.1 ± 0.6% Vs. 39.7 ± 0.5%, $P = 0.005$; respectively), and further declined significantly until the last evaluation one year after completion of chemotherapy (61.6 ± 0.7%, $P = 0.008$ Vs. 24–72 h; and 36.5 ± 0.6%, $P = 0.012$ Vs. 24–72 h; respectively). **c** Mean E/A ratio decreased 6 months after anthracycline treatment ($P = 0.05$ Vs. control). **d** Tei index combining systolic and diastolic parameters detected cardiac functional changes 1 month after anthracycline chemotherapy

depression of systolic cardiac function and the cumulative anthracycline dose (coefficient of correlation 0.123, $P = 0.26$).

Diastolic dysfunction presents later than systolic dysfunction

The average values of diastolic filling parameters are summarized in Table 3. Compared to baseline mean E/A ratio decreased during follow-up, which almost reached statistical significance ($P = 0.05$) after 6 months (Fig. 1c). Forty-seven patients (55.3%) presented with a decrease ≥0.2 of the E/A ratio during follow-up visits. The decline of the E/A ratio did not correlate with the cumulative anthracycline dose (coefficient of correlation 0.157, $P = 0.15$), with systolic dysfunction (coefficient of correlation 0.106, $P = 0.34$) or a history of systemic hypertension (coefficient of correlation 0.087, $P = 0.42$). Mean values of heart rate and deceleration time did not significantly change over time (Table 3).

Tei Index altered in the majority of patients

The Tei index increased after therapy in 67 patients (78.8%) compared with pre-therapy values. Mean Tei index remained unchanged immediately after completion of anthracycline therapy (0.36 ± 0.01, range

Table 3 Average Doppler parameters for assessment of diastolic function before, during and after anthracycline therapy

Variables	Before chemotherapy	After chemotherapy				*P* value*
		Immediately	1 month	6 months	1 year	
Heart rate (bpm)	76.64 ± 1.38	73.59 ± 1.21	76.73 ± 1.25	72.78 ± 1.23	73.67 ± 1.17	0.198
Peak E velocity (cm/s)	0.79 ± 0.02	0.80 ± 0.02	0.73 ± 0.02	0.73 ± 0.02	0.71 ± 0.02	0.05
Peak A velocity (cm/s)	0.67 ± 0.02	0.68 ± 0.02	0.66 ± 0.02	0.66 ± 0.02	0.67 ± 0.02	0.25
A dur	128 ± 2.1	123 ± 1.7	128 ± 1.7	138 ± 2.7	131 ± 1.8	0.85
E/A ratio	1.22 ± 0.04	1.20 ± 0.04	1.16 ± 0.04	1.15 ± 0.04	1.08 ± 0.05	0.05
DT	205 ± 4.3	200 ± 4.3	198 ± 3.8	203 ± 3.9	205 ± 3.6	0.58
PVs	0.64 ± 0.01	0.67 ± 0.01	0.61 ± 0.01	0.59 ± 0.01	0.59 ± 0.01	0.20
PVd	0.50 ± 0.01	0.52 ± 0.01	0.48 ± 0.01	0.47 ± 0.01	0.46 ± 0.01	0.55
PVa	0.28 ± 0.004	0.29 ± 0.004	0.28 ± 0.004	0.30 ± 0.006	0.28 ± 0.005	0.84
PVa dur	113 ± 2.1	107 ± 1.6	111 ± 1.7	116 ± 2.0	121 ± 1.6	1.00
PVs/PVd	1.33 ± 0.03	1.34 ± 0.03	1.32 ± 0.03	1.31 ± 0.03	1.35 ± 0.03	0.93
PVa dur/A dur	0.90 ± 0.01	0.88 ± 0.01	0.88 ± 0.01	0.86 ± 0.01	0.93 ± 0.01	0.89

*1 year versus baseline

0.12–0.74 Vs. 0.37 ± 0.01, range 0.15–0.91; $P = 0.24$), however, 1 month after anthracycline application mean values significantly increased (0.43 ± 0.01, range 0.15–0.91, $P < 0.00001$) and remained elevated during further follow-up (Fig. 1d). No patient showed a decrease of the Tei index. Changes in Tei index did not correlate significantly with the cumulative anthracycline dose (coefficient of correlation 0.052, $P = 0.64$) nor with deterioration of the ejection fraction (coefficient of correlation 0.121, $P = 0.28$). However, we obtained a moderate relation between the increase of the Tei index and alteration of diastolic function, i.e. decline of the E/A ratio (coefficient of correlation 0.266, $P = 0.02$).

Cardiac troponin T unrelated to echocardiographic parameters

Cardiac troponin T levels did not exceed the upper limit of the normal range (>0.1 ng/ml; i.e. used for the detection of myocardial infarction) in any patient. We only observed "low-level" elevations of cTnT previously described in children after anthracycline treatment [20]. One patient had an elevated cTnT of 0.05 ng/ml before the initiation of anthracycline therapy, indicating the possible presence of myocardial injury unrelated to chemotherapy. This patient presented with a reversible increase of cTnT to a maximal value of 0.09 ng/ml which dropped to baseline 1 month after the end of chemotherapy. In this particular patient exhibiting the most pronounced changes of cTnT, no alteration of systolic or diastolic function could, however, be detected (EF 74% and 71%; E/A ratio 0.70 and 0.74 at baseline and at end of study, respectively).

In the remaining population seven patients had any elevations of cTnT, two of which presented with multiple elevations during follow-up. As compared with patients who did not have increased cTnT levels, those who did had a similar baseline LVEF (67.3 ± 1.8% Vs. 65.8 ± 0.6%; $P = 0.59$) but had a lower E/A ratio (0.95 ± 0.07 Vs. 1.24 ± 0.04; $P = 0.04$), and were older (55.5 ± 2.4 Vs. 44.9 ± 1.1; $P = 0.02$). Elevated cTnT levels were not predictive of the development of systolic or diastolic dysfunction after anthracycline administration, i.e. six of seven patients had a normal LVEF and E/A ratio 1 year after chemotherapy. Only one patient who showed an increase of cTnT levels developed a concomitant decrease in LVEF from 65% to 50% without any change of diastolic function (E/A ratio 0.7).

Only five values (three patients) of a total of 137 cTnT measurements (3.6%) additionally performed during chemotherapy within 72 h after anthracycline application were >0.01 ng/ml. cTnT did not further increase in these patients during follow-up and were not predictive of the development of LV dysfunction.

Early changes in NT-proBNP do not predict cardiac dysfunction

In the total population mean NT-proBNP levels did not significantly change after anthracycline administration compared with pre-therapy values (Fig. 2). However, in 13 patients (15.3%, six male, seven female) a marked, transient increase of NT-proBNP above the age- and gender-related upper limit was obtained after the first anthracycline cycle with a mean increase of 157.7 ± 50.4 pg/ml, range 8–711. Five of these patients had a history of systemic hypertension. Patients with and without an early elevation of NT-proBNP had a similar LVEF (64.9 ± 1.1% Vs. 67.4 ± 0.5%; $P = 0.10$) and E/A ratio (1.23 ± 0.09 Vs. 1.16 ± 0.03; $P = 0.50$) at baseline. There was no correlation between delta NT-proBNP and delta Tei index from baseline to 12 months follow-up (coefficient of correlation 0.138, $P = 0.3$). No individual with early NT-proBNP increase developed

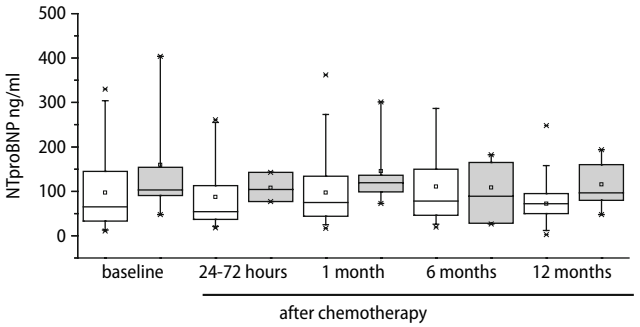

Fig. 2 NT-proBNP levels at baseline and during follow-up after anthracycline therapy stratified according to the development of a cardiac event/LV dysfunction (*white* no cardiac event, *gray* cardiac event). Mean NT-proBNP levels did not significantly change during follow-up in either group. There was no significant difference between groups

systolic dysfunction, and only four patients presented with a reduction of the E/A ratio during follow-up. All of these patients had normal NT-proBNP levels during further follow-up.

In two additional patients NT-proBNP increased above the age- and gender-related upper limit 6 months after completion of anthracycline treatment. Late elevation of NT-proBNP was not associated with a change in LVEF, E/A ratio or Tei index.

Discussion

Cardiovascular toxicity of anthracycline therapy can lead to severe complications. Early detection and treatment of cardiotoxic side-effects could markedly reduce the development of clinical manifestations. However, currently no diagnostic parameter is available allowing ubiquitous, sensitive, and specific detection of preclinical anthracycline cardiomyopathy and prediction of prognosis. In the present study for the first time we prospectively evaluated and compared the diagnostic value of echocardiography, including the Tei myocardial performance index, and biochemical markers in a large adult population treated with anthracyclines. Alterations of systolic function emerged earliest after anthracycline administration. Changes of the Tei index occurred in the majority of patients indicating a thus far underestimated incidence of anthracycline-induced myocardial alteration. Elevation of the surrogate markers NT-proBNP and cTnT was not related to cardiac dysfunction.

A decrease of systolic function within the first year after chemotherapy is associated with an increased incidence of dilated cardiomyopathy during further follow-up [12, 25, 34]. Although we did not observe any overt heart failure in our patients, significant reduction of mean LVEF was evident immediately after anthracycline chemotherapy, with 18% of patients developing a predefined cardiac event [37]. To detect anthracycline-induced cardiotoxicity, assessment of the diastolic function is being recommended in addition to systolic parameters though diastolic dysfunction has been detected inconsistently following anthracycline administration [43]. In small patient populations a reduction of the E/A ratio and/or an IVRT increase was observed in the absence of any systolic alteration [19, 22, 35, 41], while others reported a deterioration of systolic function without diastolic dysfunction [10]. In the present 100 consecutive patients we obtained a reduction of the E/A ratio 6 months after anthracycline chemotherapy, which however did not reach statistical significance and was not related to a decrease in LVEF. Although long-term follow-up of patients with diastolic impairment is required, currently available data thus indicate, that changes of diastolic parameters are less sensitive than systolic dysfunction for early detection of subclinical anthracycline cardiotoxicity.

Since the Tei index combines systolic and diastolic echocardiographic parameters, it might prove more sensitive to identify preclinical cardiotoxic side-effects than either analysis alone. The Tei index has been shown to correlate well with other invasive and non-invasive measures of LV function [39]. Moreover, the Tei index demonstrated to be a powerful predictor of outcome in dilated cardiomyopathy and primary pulmonary hypertension [7, 44]. In our adult population mean Tei index significantly increased 1 month after anthracycline chemotherapy. Thus, changes of Tei index were obtained earlier than alterations of the E/A ratio, but later than the reduction of LVEF. An elevation of the Tei index occurred in the majority of patients treated, i.e. in almost 80%. This indicates that even at the low to moderate anthracycline doses used, alterations of myocardial performance are more frequent than previously recognized. In fact, this is in agreement with a report of pediatric patients. While most authors only provided mean Tei indices which consistently increased after anthracycline administration, Ishii et al. [13] also observed a rise of Tei index in 83–100% of children treated with anthracyclines [9, 30]. To date, the management of asymptomatic patients with preserved systolic function but abnormal Tei index is not clear because the prognostic importance of subclinical changes of myocardial function detected by Tei index is still uncertain. While these myocardial abnormalities might get long-term clinical relevance in individuals, the Tei index does seem to provide sufficient specificity since during long-term survival of patients with malignancies it can be expected that not more than 20–40% will eventually develop anthracycline-induced heart failure.

In addition or as alternative to echocardiographic evaluation reliable biochemical markers is a compelling need for the early detection of anthracycline-induced cardiotoxicity. Serum levels of cTnT are increasingly becoming recognized as potential markers of even subclinical myocardial damage. In spontaneously hypertensive rats, an animal model developing cardiomyopathy, additional administration of anthracyclines increased cTnT levels which correlated with histopathological changes [11], suggesting potential clinical usefulness. Indeed, marked elevation of cTnI measured within 72 h after high-dose chemotherapy was associated with an increased risk for subsequent systolic dysfunction and clinical heart failure [4, 5]. However, the predictive value of both early and delayed low-level elevation of cTnT, that remains within the reference range, is controversial especially in adults [1, 16, 20, 21]. While cTnT significantly increased in children treated with doxorubicin compared to the dexrazoxane + doxorubicin group, both groups presented with a similar reduction in echocardiographic systolic function parameters [20]. No diastolic cardiac evaluation and to date no long-term clinical follow-up of these patients are available. In 28 adults echocardiographic evaluation revealed LVEF decrease >10% in three of seven patients with delayed cTnT positivity [1]. Conversely, others reported no change of systolic function, but a more pronounced reduction in the E/A ratio in those with raised cTnT levels [15] Our results in 100 consecutive patients do not support a reliable clinical implication of low-level cTnT elevation during or after anthracycline treatment in adults, as we did not obtain any relation to the development of systolic or diastolic dysfunction. Therefore, a potential value of cTnT levels in monitoring of anthracycline side-effects might be limited to marked elevations after high-dose chemotherapy. While in our patients and previous studies third generation cTnT assays were used, recently precommercial new-generation highly sensitive Troponin T (hsTnT) assay demonstrated a prognostic value in a stable heart failure population [18]. It remains to be determined in future studies whether hsTnT might also prove useful for early detection of anthracycline-induced cardiotoxicity in adults.

The measurement of serum BNP is a potent biochemical marker with diagnostic and prognostic implications in heart failure patients. It has been supposed that natriuretic peptides might identify those patients with cardiotoxic cancer therapy at risk of serious cardiac complications [24, 33, 36]. However, consistent with previous reports [6, 40] in the present analysis 15% of patients receiving anthracyclines exhibited transient NT-proBNP elevation during treatment which was not associated with the development of cardiac dysfunction or symptoms during follow-up. Thus, when there is ongoing chemotherapy BNP levels seem to be influenced by a variety of factors, particularly altered cardiac loading conditions that invalidate its use as a guide for anthracycline interruption. The value of delayed increase of natriuretic peptides is controversial. Elevation of mean levels that remained in the normal range was not predictive of cardiac impairment or symptoms [24, 36]. Similar to our results, in previous studies few patients exhibited natriuretic peptide values exciding the reference range, with only a subset of these developing cardiac dysfunction or overt heart failure [24, 36], which limits usefulness of BNP for routine screening in patients receiving anthracycline-based therapy.

In conclusion, low to moderate doses of anthracyclines resulted in subclinical myocardial changes in more patients than previously noticed. Follow-up over several years will be required to determine the clinical implication of altered myocardial function detected by the Tei index. Our observations do not support that to date measurements of cTnT or BNP levels may safely replace serial echocardiographic evaluation of systolic and diastolic function for the monitoring of anthracycline cardiotoxicity.

References

1. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, Sill H (2003) Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. Ann Hematol 82:218–222
2. Belham M, Kruger A, Pritchard C (2006) The Tei index identifies a differential effect on left and right ventricular function with low-dose anthracycline chemotherapy. J Am Soc Echocardiogr 19:206–210
3. Brenner JS, Dolmetsch RE (2007) TrpC3 regulates hypertrophy-associated gene expression without affecting myocyte beating or cell size. PLoS ONE 2:e802
4. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, Cinieri S, Martinelli G, Fiorentini C, Cipolla CM (2002) Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 13:710–715

5. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinelli G, Cipolla CM, Fiorentini C (2000) Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 36:517–522
6. Daugaard G, Lassen U, Bie P, Pedersen EB, Jensen KT, Abildgaard U, Hesse B, Kjaer A (2005) Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. Eur J Heart Fail 7:87–93
7. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB (1998) Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. Am J Cardiol 82:1071–1076
8. Efferth T, Giaisi M, Merling A, Krammer PH, Li-Weber M (2007) Artesunate induces ROS-mediated apoptosis in doxorubicin-resistant T leukemia cells. PLoS ONE 2:e693
9. Eidem BW, Sapp BG, Suarez CR, Cetta F (2001) Usefulness of the myocardial performance index for early detection of anthracycline-induced cardiotoxicity in children. Am J Cardiol 87:1120–1122, A1129
10. Ewer MS, Ali MK, Gibbs HR, Swafford J, Graff KL, Cangir A, Jaffe N, Thapar MK (1994) Cardiac diastolic function in pediatric patients receiving doxorubicin. Acta Oncol 33:645–649
11. Herman EH, Zhang J, Lipshultz SE, Rifai N, Chadwick D, Takeda K, Yu ZX, Ferrans VJ (1999) Correlation between serum levels of cardiac troponin-T and the severity of the chronic cardiomyopathy induced by doxorubicin. J Clin Oncol 17:2237–2243
12. Hullin R, Matthes J, von Vietinghoff S, Bodi I, Rubio M, D'Souza K, Friedrich Khan I, Rottlander D, Hoppe UC, Mohacsi P, Schmitteckert E, Gilsbach R, Bunemann M, Hein L, Schwartz A, Herzig S (2007) Increased expression of the auxiliary beta2-subunit of ventricular L-type Ca^{2+} channels leads to single-channel activity characteristic of heart failure. PLoS ONE 2:e292
13. Ishii M, Tsutsumi T, Himeno W, Eto G, Furui J, Hashino K, Sugahara Y, Muta H, Akagi T, Ando A, Eguchi H, Kato H (2000) Sequential evaluation of left ventricular myocardial performance in children after anthracycline therapy. Am J Cardiol 86:1279–1281, A1279
14. Keefe DL (2001) Anthracycline-induced cardiomyopathy. Semin Oncol 28(Suppl 12):2–7
15. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoyek S, Aksoy S, Celik I, Kes S, Tekuzman G (2005) cTnT can be a useful marker for early detection of anthracycline cardiotoxicity. Ann Oncol 16:798–804
16. Kremer LC, Bastiaansen BA, Offringa M, Lam J, van Straalen JP, de Winter RJ, Voute PA (2002) Troponin T in the first 24 hours after the administration of chemotherapy and the detection of myocardial damage in children. Eur J Cancer 38:686–689
17. Kurz K, Voelker R, Zdunek D, Wergeland R, Hess G, Ivandic B, Katus H, Giannitsis E (2007) Effect of stress-induced reversible ischemia on serum concentrations of ischemia-modified albumin, natriuretic peptides and placental growth factor. Clin Res Cardiol 96:152–159
18. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 116:1242–1249
19. Lee BH, Goodenday LS, Muswick GJ, Yasnoff WA, Leighton RF, Skeel RT (1987) Alterations in left ventricular diastolic function with doxorubicin therapy. J Am Coll Cardiol 9:184–188
20. Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, Colan SD, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, Samson Y, Schorin MA, Gelber RD, Sallan SE (2004) The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 351:145–153
21. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, Ottlinger ME (1997) Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 96:2641–2648
22. Marchandise B, Schroeder E, Bosly A, Doyen C, Weynants P, Kremer R, Pouleur H (1989) Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J 118:92–98
23. Mason JW, Bristow MR, Billingham ME, Daniels JR (1978) Invasive and noninvasive methods of assessing adriamycin cardiotoxic effects in man: superiority of histopathologic assessment using endomyocardial biopsy. Cancer Treat Rep 62:857–864
24. Meinardi MT, van Veldhuisen DJ, Gietema JA, Dolsma WV, Boomsma F, van den Berg MP, Volkers C, Haaksma J, de Vries EG, Sleijfer DT, van der Graaf WT (2001) Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol 19:2746–2753
25. Nousiainen T, Jantunen E, Vanninen E, Hartikainen J (2002) Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. Br J Cancer 86:1697–1700
26. Pai VB, Nahata MC (2000) Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug Saf 22:263–302
27. Ribeiro I, Kawakami Y, Buscher D, Raya A, Rodriguez-Leon J, Morita M, Rodriguez Esteban C, Izpisua Belmonte JC (2007) Tbx2 and Tbx3 regulate the dynamics of cell proliferation during heart remodeling. PLoS ONE 2:e398
28. Roth HJ, Leithauser RM, Doppelmayr H, Doppelmayr M, Finkernagel H, von Duvillard SP, Korff S, Katus HA, Giannitsis E, Beneke R (2007) Cardiospecificity of the 3rd generation cardiac troponin T assay during and after a 216 km ultra-endurance marathon run in death valley. Clin Res Cardiol 96:359–364
29. Sahn DJ, DeMaria A, Kisslo J, Weyman A (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58:1072–1083
30. Sato T, Harada K, Tamura M, Watanabe A, Ishii M, Takada G (2001) Cardiorespiratory exercise capacity and its relation to a new Doppler index in children previously treated with anthracycline. J Am Soc Echocardiogr 14:256–263
31. Scharhag J, Herrmann M, Weissinger M, Herrmann W, Kindermann W (2007) N-terminal B-type natriuretic peptide concentrations are similarly increased by 30 minutes of moderate and brisk walking in patients with coronary artery disease. Clin Res Cardiol 96:218–226
32. Shan K, Lincoff AM, Young JB (1996) Anthracycline-induced cardiotoxicity. Ann Intern Med 125:47–58
33. Snowden JA, Hill GR, Hunt P, Carnoutsos S, Spearing RL, Espiner E, Hart DN (2000) Assessment of cardiotoxicity during haemopoietic stem cell transplantation with plasma brain natriuretic peptide. Bone Marrow Transplant 26:309–313

34. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML (1991) Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 266:1672–1677
35. Stoddard MF, Seeger J, Liddell NE, Hadley TJ, Sullivan DM, Kupersmith J (1992) Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-induced systolic dysfunction in humans. J Am Coll Cardiol 20:62–69
36. Suzuki T, Hayashi D, Yamazaki T, Mizuno T, Kanda Y, Komuro I, Kurabayashi M, Yamaoki K, Mitani K, Hirai H, Nagai R, Yazaki Y (1998) Elevated B-type natriuretic peptide levels after anthracycline administration. Am Heart J 136:362–363
37. Swain SM, Whaley FS, Ewer MS (2003) Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 97:2869–2879
38. Tei C (1995) New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 26:135–136
39. Tei C, Nishimura RA, Seward JB, Tajik AJ (1997) Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. Am J Soc Echocardiogr 10:169–178
40. Tikanoja T, Riikonen P, Perkkio M, Helenius T (1998) Serum N-terminal atrial natriuretic peptide (NT-ANP) in the cardiac follow-up in children with cancer. Med Pediatr Oncol 31:73–78
41. Tjeerdsma G, Meinardi MT, van Der Graaf WT, van Den Berg MP, Mulder NH, Crijns HJ, de Vries EG, van Veldhuisen DJ (1999) Early detection of anthracycline induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function: autonomic versus echocardiographic variables. Heart 81:419–423
42. Weber M, Kleine C, Keil E, Rau M, Berkowitsch A, Elsaesser A, Mitrovic V, Hamm C (2006) Release pattern of N-terminal pro B-type natriuretic peptide (NT-proBNP) in acute coronary syndromes. Clin Res Cardiol 95:270–280
43. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, Durand JB, Gibbs H, Zafarmand AA, Ewer MS (2004) Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 109:3122–3131
44. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB (1998) Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 81:1157–1161