Original Research

The Value of Left Ventricular Global Longitudinal Strain Assessed by Three-Dimensional Strain Imaging in the Early Detection of Anthracycline-Mediated Cardiotoxicity

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Introduction: Anthracyclines are important anticancer drugs, but their use is limited by acute and chronic cardiotoxicity. Current approaches to surveillance are often inadequate to detect myocardial disease. Strain imaging might detect earlier myocardial dysfunction. Speckle analysis of three-dimensional (3D) echocardiography improves information about left ventricular (LV) segmental and global deformation by avoiding the loss of speckles seen in monoplane bidimensional-strain analysis. We assessed whether early 3D-strain analysis could predict later anthracycline-induced cardiotoxicity.

Methods: Echocardiography, troponin T (TnT) and N-terminal pro-brain natriuretic peptide were used to evaluate 59 patients (age 51 ± 10 years) before, and at 12 and 36 weeks after anthracycline treatment. LV global longitudinal strain (3DGLS), global radial strain (3DGRS) and global circumferential strain (3DGCS) were determined using 3D-strain imaging before and after 12 weeks of chemotherapy. Percentage changes from baseline to 12 weeks after initiation of chemotherapy (Δ) were calculated for all parameters analysed.

Results: During the follow-up period, eight patients (13.5%) developed cardiotoxicity. At 12 weeks after the initiation of chemotherapy, isovolumic relaxation time, 3DGLS, 3DGCS and 3DGRS had deteriorated and troponin was elevated (all $p<0.05$), before any decrease in LV ejection fraction. Cumulative anthracycline dose at 12 weeks, ΔLVEF, Δ3DGLS and ΔTnT were predictors of the later development of cardiotoxicity on univariate logistic regression. By multiple logistic regression, Δ3DGLS emerged as the only independent predictor of later cardiotoxicity (Odds ratio 1.09, $p=0.04$).

Conclusions: Anthracycline therapy induced early deterioration of 3DGLS, 3DGCS and 3DGRS. Δ3DGLS seems to be a good predictor of the future development of anthracycline-induced cardiotoxicity.

Anthracyclines are among the most effective chemotherapeutic agents and have gained widespread use in the treatment of a number of haematological malignancies and solid tumors.[1] The efficacy of anthracycline agents is, however, limited by serious side effects and their inherent cardiotoxicity, with a consequent increased risk of morbidity and mortality in all patients undergoing chemotherapy with anthracyclines.[2,3] Current approaches to surveillance are often inadequate to detect myocardial disease, which can delay medical therapy and lead to symptomatic heart failure. Although easy to determine, left ventricular ejection fraction (LVEF) is not sufficiently sensitive to reveal subclinical or regional myocardial dysfunction.[2] Tissue Doppler imaging and strain im-

aging are sensitive, non-invasive echocardiographic techniques that allow the early detection of LV systolic dysfunction, before a decrease in conventional LVEF.[4] Although bidimensional (2D) global longitudinal strain (GLS) has been shown to be reproducible and accurate, 2D global circumferential strain (GCS) and 2D global radial strain (GRS) were less reliable, with measurement variability of >10% and 15%, respectively, which limits their use in the evaluation of LV systolic function in clinical practice.[5]

The use of three-dimensional (3D) echocardiography has been shown to improve accuracy and reproducibility and may be preferable to 2D techniques.[6] Three-dimensional strain imaging was developed as a new application that can be used for regional wall motion analysis of the entire LV and allows the determination of real 3D indices and the precise assessment of 3D wall motion.[7] Speckle analysis of 3D echocardiography improves information about LV segmental and global deformation by avoiding the loss of speckles seen in monoplane 2D-strain analysis.

It is now known that anthracyclines are more cardiotoxic than had been understood initially, and this holds true even at sub-maximal cumulative dosages.[8] The overall objective of this study was to assess whether 3D-strain imaging could be useful in the early prediction of the future development of anthracycline-induced cardiotoxicity.

Methods

Study population

Between May 2010 and July 2011, we analysed 92 consecutive patients who were in sinus rhythm and were referred to our clinic for evaluation of cardiac function before therapy with anthracyclines. Patients with LVEF<50%, inadequate echocardiographic images, prior treatment with cardiotoxic drugs or radiation therapy, known heart disease, renal failure, or allergy to ultrasound contrast agents, were not included in the study. Women who required treatment with trastuzumab after anthracycline during the follow-up period were also excluded. Thirty age-matched healthy subjects who came for a routine physical evaluation and had normal echocardiographic findings were included as a control group.

Study protocol

All study participants underwent clinical examination, 12-lead electrocardiogram, transthoracic echocardiogram, troponin T (TnT) and N-terminal pro-brain natriuretic peptide (NTproBNP) measurements, within 3 ± 2 days before chemotherapy and at 12 weeks (84 ± 5 days) after the start of chemotherapy. Subsequently, LVEF, TnT and NTproBNP were determined at 36 weeks (252 ± 5 days) or in the case of any occurrence of heart failure symptoms. To avoid the influence of preload increase on the LV mechanics, the examination was not performed on the day of anthracycline administration. Cardiotoxicity was defined according to recent guidelines as a reduction of LVEF by ≥5% to <55% with symptoms of heart failure, or an asymptomatic reduction of LVEF by ≥10% to <55%.[9] According to a previously reported formula, we calculated the cumulative anthracycline dose using the following ratios: doxorubicin=1.0, daunorubicin=0.5, idarubicin=1.6, and epirubicin=0.6.[10,11] The study was approved by local institutional review boards and informed written consent was obtained from all patients.

Echocardiography

M-mode, 2D and Doppler echocardiographic examinations were performed with an ultrasonographic system (Vivid 9 General Electric, Milwaukee, WI), in accordance with guidelines,[12,13] by a single observer (CM). All images were digitally stored and analysed offline using EchoPac PC Dimension software (version 6.0, GE Healthcare, UK). LVEF was calculated from the apical two- and four-chamber views based on LV volumes, using the modified biplane Simpson rule.[12] An ultrasound contrast bolus of 0.5 mL of Sonovue® (Bracco Diagnostics, Inc.) was administered by a trained nurse through a 20-G vial in a proximal forearm vein, followed by flushing with at least 5 mL of 0.9% saline at a speed adjusted to optimise cavity opacification. The contrast-enhanced imaging was performed using predefined settings (low mechanical index <0.5, gain 60%, and compression 15%).

Peak early (E) and late (A) filling velocities were measured from the LV-inflow pattern at the tips of the mitral valve. Measurement of systolic pulmonary artery pressure was performed using the maximal regurgitant velocity at the tricuspid valve by continuous Doppler.[13] The myocardial performance index was determined using Doppler time intervals measured from mitral inflow and left ventricular outflow Doppler tracings.[13] All velocities were recorded for three consecutive cardiac cycles during end-expiratory apnoea, and the results were averaged.

Three-dimensional strain imaging was used for

LV myocardial deformation measurements.[14] The 3D-strain acquisitions were performed from the apical window with the patient in the left lateral decubitus position using a commercially available 3D matrix array transducer (Vivid E9 scanner, 3V-D probe, 2.5 MHz, GE Vingmed Ultrasound, Horten, Norway). To optimise the frame rate of acquisition, depth was minimised to include only the LV. In this study, a frame rate of 20 to 30 Hz was used. In each patient, 3D full-volume data sets were acquired in real time using four consecutive cardiac cycles during breath hold. The 3D-strain data sets were stored digitally for off-line analysis. Data analysis was performed using the original raw data from all 3D echocardiographic data sets on an EchoPAC software workstation (version BT11, 4D Auto LVQ; GE Healthcare, UK) for semi-automated endocardial surface detection. The method used to assess LV systolic function has been described previously.[14] Briefly, alignment with presentation of four-chamber, two-chamber, and three-chamber apical views, as well as the transverse plane, was performed. Orientation was performed automatically. The end-diastolic frame was automatically defined by R peak on the ECG and the end-systolic frame was estimated from the R-R interval. Both could be manually corrected. Automatic endocardial border delineation of the whole LV volume was processed at end diastole and end systole after positioning two landmarks on the mitral annulus and one on the LV apex on each apical view. Manual correction was performed at end diastole and end systole to ensure optimal LV delineation. The correct alignment of the contours with the endocardium during the cardiac cycle was controlled. A second semi-automated delineation was made in relation to the epicardium to delineate the region of interest for strain analysis. Lastly, the final 3D-strain analysis allowed the measurement of 3DGLS, 3DGCS and 3DGRS. The timing of aortic valve closure was obtained using pulsed-wave Doppler traces. Offline analysis was performed by two observers who were blinded to the clinical data.

Biological markers

TnT and NTproBNP were evaluated at three separate time points. Quantitative determinations of TnT levels were performed with a third-generation Roche Elecsys assay (Roche Diagnostics, Inc., Indianapolis, IN). The NTproBNP levels were measured with an electrochemiluminescence sandwich immunoassay (Elecsys ProBNP, Roche Diagnostics) with the Roche 2010 system.

Statistical analysis

Numerical variables are presented as mean value ± standard deviation (SD) and were compared using Student's t-tests or analysis of variance, as appropriate. Categorical variables are expressed as absolute values and frequency percentages and were compared using χ^2 tests. Pearson's correlation was used to investigate relations between variables. Receiver-operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity. Possible predictors of cardiotoxicity were tested using univariate nominal logistic regression. A multiple nominal logistic regression model was then applied to the univariate predictors. Intra- and inter-observer variability for 3D-strain parameters were measured by the intra-class correlation coefficient and by the coefficient of variation (CV) with the root-mean-square method. For the statistical analyses we used the software package SPSS version 11 (SPSS Inc, Chicago, IL). A statistical comparison of areas under independent ROC curves (AUC) was performed using Stata 10 software (College Station, TX). A p-value <0.05 was accepted as statistically significant.

Results

Patient characteristics

Of the initial 92 patients, 13 did not meet our inclusion criteria. Measurement of biplane LVEF was possible in 76 of the remaining 79 patients (96.2%). Seventeen patients (22%) were excluded because of poor acoustic windows that did not provide adequate echocardiographic image quality for 3D analysis. The remaining 59 patients formed our study group, with a mean age of 51 ± 10 years (35 women, 59.3%). Of these patients, 26 had breast cancer (44.1%), 12 had non-Hodgkin's lymphoma (20.3%) (Figure 1), 10 had Hodgkin's lymphoma (16.9%), 8 had acute lymphoblastic leukaemia (13.6%), 2 had acute myeloblastic leukaemia (3.4%), and 1 had osteosarcoma (1.7%). None of the patients were taking any other medication that could potentially influence cardiac function, including beta-blocker, calcium blocker, digitalis, trastuzumab, catecholamines and interferon. Follow up was completed in all patients. Characteristics of the study population are presented in Table 1.

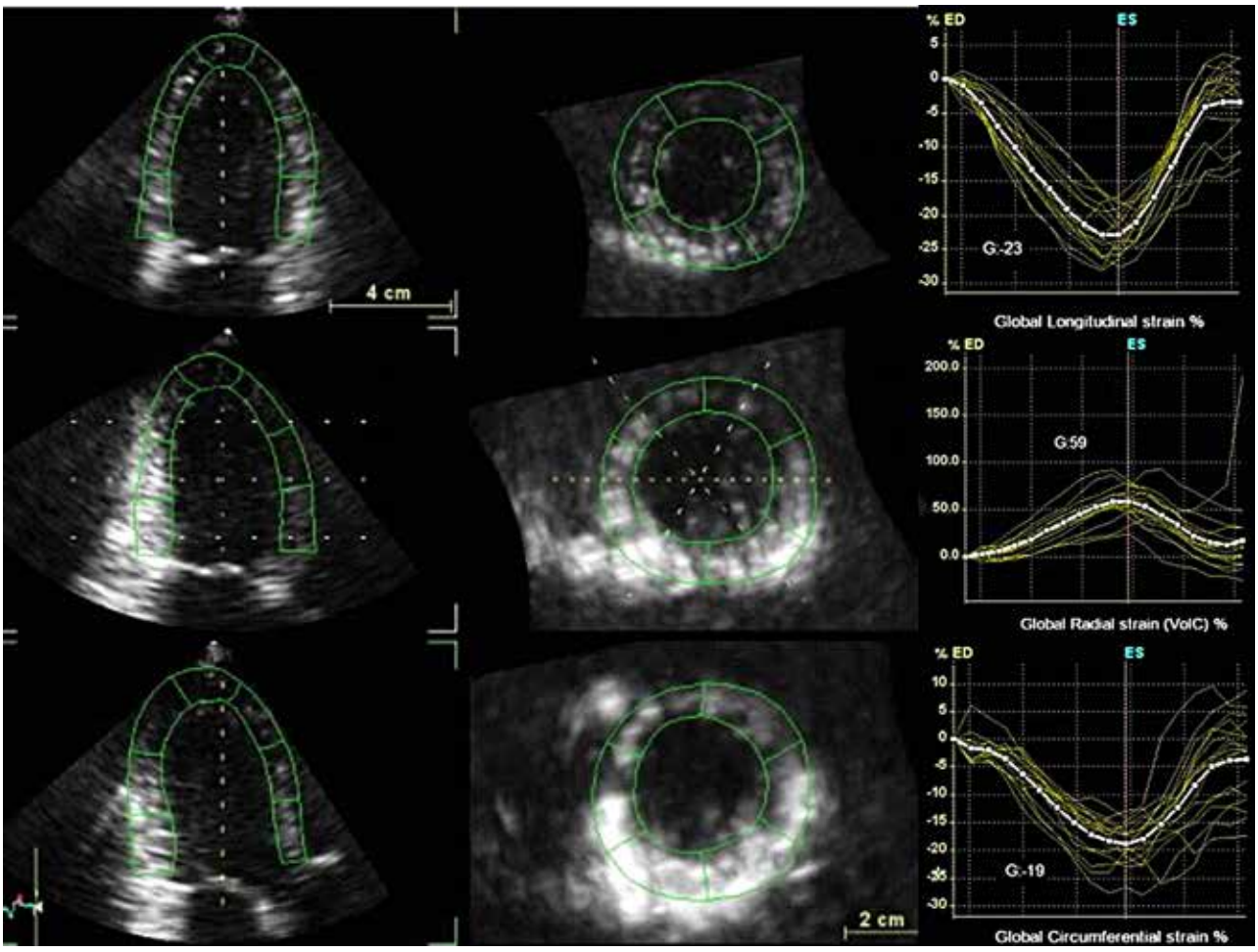

Figure 1. Analysis of left ventricular function using three-dimensional strain imaging in a patient with non-Hodgkin's lymphoma.

Table 1. Baseline characteristics.

Variable	Controls (n=30)	Study group (n=59)
Age (years)	50 ± 12	51 ± 10
Female/male sex, n (%)	19 (59.2%)/13 (40.8%)	35 (59.3%)/24 (40.7%)
Body surface area (m^2)	24.6 ± 4.7	25.1 ± 3.8
Heart rate (beats/min)	66 ± 7	73 ± 10*
Systolic blood pressure (mmHg)	119 ± 21	121 ± 17
Diastolic blood pressure (mmHg)	75 ± 12	76 ± 9
Cardiac risk factors:		
Blood pressure >140/>90 mmHg, n (%)	4 (13.3%)	7 (11.8%)
Total cholesterol >200 mg/dl, n (%)	2 (6.6%)	4 (6.7%)
Diabetes mellitus, n (%)	0 (0%)	1 (1.6%)
Smoker, n (%)	5 (16.6%)	10 (16.9%)
Family history of coronary artery disease, n (%)	4 (13.3)	8 (13.5%)
Type of cancer:		
Breast cancer, n (%)	-	26 (44.1%)
Non-Hodgkin's lymphoma, n (%)	-	12 (20.3%)
Hodgkin's lymphoma, n (%)	-	10 (16.9%)
Acute lymphoblastic leukaemia, n (%)	-	8 (13.6%)
Acute myeloblastic leukaemia, n (%)	-	2 (3.4%)
Osteosarcoma, n (%)	-	1 (1.7%)

*p<0.05 vs. controls.

Table 2. Clinical, echocardiographic and biomarker characteristics of patients before and after 12 weeks of treatment with anthracyclines.

Variable	Control	Study group		
		Baseline	12 weeks	Δ (%)
Cumulative anthracycline doses (mg/m^2)	0	0	175 ± 62*	-
Heart rate (beats/min)	66 ± 7*	73 ± 10	71 ± 13	2.8 ± 6.2
Systolic blood pressure (mmHg)	117 ± 19	119 ± 16	118 ± 18	2.1 ± 5.8
Diastolic blood pressure (mmHg)	72 ± 11	74 ± 9	72 ± 12	3.9 ± 4.0
Left atrial diameter (cm)	3.5 ± 0.5	3.6 ± 0.5	3.7 ± 0.6	2.4 ± 5.7
LV end-diastolic diameter (cm)	4.6 ± 0.4	4.6 ± 0.5	4.7 ± 0.4	1.8 ± 4.6
LV end-diastolic volume (mL)	79 ± 14	78 ± 16	80 ± 12	6.3 ± 9.1
LV end-systolic volume (mL)	32 ± 7.5	31 ± 7.1	33 ± 4.8	7.4 ± 6.5
LV ejection fraction (%)	60 ± 6.2	60 ± 5.6	59 ± 5.9	3.0 ± 7.3
Myocardial performance index	0.45 ± 0.09	0.46 ± 0.10	0.49 ± 0.17	6.5 ± 8.2
Pulmonary artery systolic pressure (mmHg)	25 ± 7	24 ± 9	27 ± 6	8.1 ± 3.2
Isovolumic relaxation time (ms)	74 ± 12	75 ± 8.3	95 ± 18*	26.9 ± 19.3
E wave (cm/s)	89 ± 20	95 ± 13	100 ± 20	4.5 ± 11.2
A wave (cm/s)	74 ± 21	81 ± 16	82 ± 19	1.9 ± 3.4
LV 3DGLS (%)	-20.1 ± 3.7	-19.4 ± 2.3	-17.5 ± 2.4*	10.1 ± 6.3
LV 3DGRS (%)	43.2 ± 7.8	42.4 ± 5.3	37.6 ± 5.4*	11.2 ± 6.1
LV 3DGCS (%)	21 ± 3.1	21.4 ± 1.7	20.9 ± 1.7*	2.2 ± 2.9
NTproBNP (pg/mL)	89 ± 65	96 ± 50	101 ± 47	14.6 ± 42.1
Troponin T (μg/L)	<0.01	<0.01	0.06 ± 0.08*	592 ± 857

*$p<0.05$ vs. baseline.
A – late diastolic transmitral flow velocity; E – early diastolic transmitral flow velocity; GCS – global circumferential strain; GLS – global longitudinal strain; GRS – global radial strain; LV – left ventricle; NTproBNP – N-terminal pro-brain natriuretic peptide; Δ – percentage changes between baseline and 12 weeks after initiation of chemotherapy versus baseline.

The averaged cumulative anthracycline dose was 175 ± 62 mg/m^2 at 12 weeks. Table 2 shows the changes in the parameters monitored in our study. The patient group was comparable with the healthy subjects in terms of clinical, biological and echocardiographic data, although the heart rate was greater in the patient group.

Early echocardiographic and biological changes

The left atrial and LV dimensions, LVEF, pulmonary artery systolic pressure, transmitral flow wave velocities and myocardial performance index did not show a significant change during the early period of treatment, although the cumulative dose of anthracyclines increased significantly at 12 weeks after the initiation of chemotherapy. In contrast, isovolumic relaxation time showed significant prolongation after the initiation of chemotherapy (Table 2).

In contrast with the most of the above parameters, 3D-strain analysis showed significant changes at 12 weeks after the initiation of chemotherapy. 3DGLS, 3DGCS and 3DGRS deteriorated during the early phase of the anthracyclines treatment. The intra-observer intra-class coefficients for 3DGLS, 3DGCS and 3DGRS were 0.94 (CV 2.7%), 0.92 (CV 3.0%), and 0.90 (CV 3.1%), respectively. The inter-observer intra-class coefficients for 3DGLS, 3DGCS and 3DGRS were 0.90 (CV 3.7%), 0.88 (CV 4.6%), and 0.83 (CV 4.9%), respectively.

No change in heart rate, blood pressure or NT-proBNP level was noted during the course of the study, but the TnT level increased significantly during the first 12 weeks of chemotherapy.

Cardiotoxicity

The average cumulative anthracycline dose was 256 ± 58 mg/m^2 at the end of the follow-up period. Eight patients (13.5%) met the criteria for cardiotoxicity. The percentage changes between baseline and 12 weeks after the initiation of chemotherapy (Δ) were calculated for the various parameters analysed. The characteristics of patients treated with anthracyclines who developed or did not develop cardiotoxicity are presented in Table 3. No patient developed symptomatic heart failure.

Table 4 shows the variables that predicted cardiotoxicity on univariate logistic regression. Cumulative anthracycline dose at 12 weeks, ΔLVEF, Δ3DGLS and ΔTnT were predictors of patients who developed cardiotoxicity. Age, sex, cardiac risk fac-

Table 3. Characteristics of patients treated with anthracyclines who developed or did not develop cardiotoxicity.

Variable	Cardiotoxicity		p
	Yes (n=8)	No (n=51)	
Age (years)	52.6 ± 10.3	50.6 ± 10.1	0.59
Female/male gender, n (%)	5(62.5%)/3(37.5%)	30(58.8%)/21(41.2%)	0.84
Cardiac risk factors:			
Blood pressure >140/>90 mmHg, n (%)	1 (12.5%)	6 (11.7%)	0.95
Total cholesterol >200 mg/dL, n (%)	1 (12.5%)	3 (5.8%)	0.48
Diabetes mellitus, n (%)	0 (0%)	1 (1.9%)	0.69
Smoker, n (%)	1 (12.5%)	9 (17.6%)	0.71
Family history of CAD, n (%)	1 (12.5%)	7 (13.7%)	0.92
Baseline:			
LV ejection fraction (%)	60 ± 3.2	61 ± 5.9	0.72
Isovolumic relaxation time (ms)	79 ± 9.3	74 ± 8.1	0.13
E wave (cm/s)	97 ± 15	94 ± 13	0.25
A (cm/s)	84 ± 18	80 ± 15	0.21
Myocardial performance index	0.46 ± 0.12	0.45 ± 0.09	0.79
Pulmonary artery systolic pressure (mmHg)	26 ± 10	23 ± 8.8	0.11
3DGLS (%)	-20.8 ± 1.1	-19.3 ± 2.4	0.08
3DGRS (%)	45.6 ± 2.8	41.8 ± 5.4	0.07
3DGCS (%)	22.5 ± 1.3	21.4 ± 1.8	0.07
NTproBNP (pg/mL)	99 ± 60	95 ± 49	0.34
Troponin T (μg/L)	<0.01	<0.01	1
At 12 weeks:			
Cumulative anthracycline doses (mg/m^2)	251 ± 21	163 ± 58	<0.001
LV ejection fraction (%)	54 ± 3.0	59 ± 5.5	0.01
Isovolumic relaxation time (ms)	100 ± 18.1	94 ± 18.4	0.44
E wave (cm/s)	108 ± 24	103 ± 19	0.54
A wave (cm/s)	75 ± 17	83 ± 19	0.09
Myocardial performance index	0.54 ± 0.12	0.48 ± 0.17	0.03
Pulmonary artery systolic pressure (mmHg)	29 ± 6	27 ± 6.3	0.13
3DGLS (%)	-17.3 ± 1.1	-17.6 ± 2.5	0.78
3DGRS (%)	40.7 ± 5.9	37.1 ± 5.2	0.06
3DGCS (%)	21.8 ± 1.5	20.8 ± 1.6	0.11
NTproBNP (pg/mL)	174 ± 13	88 ± 39	<0.001
Troponin T (μg/L)	0.15 ± 0.16	0.05 ± 0.06	0.001
End of the follow-up period:			
Cumulative anthracycline doses (mg/m^2)	327 ± 21	245 ± 51	<0.001
LV ejection fraction (%)	42 ± 3.7	55 ± 5.6	<0.001

A – late diastolic transmitral flow velocity; CAD – coronary artery disease; E – early diastolic transmitral flow velocity; 3DGCS – three-dimensional global circumferential strain; 3DGLS – three-dimensional global longitudinal strain; 3DGRS – three-dimensional global radial strain; LV – left ventricle; NTproBNP – N-terminal pro-brain natriuretic peptide.

tors, Δ blood pressure, Δ heart rate, ΔLV and Δ left atrial dimensions, Δ pulmonary artery systolic pressure, Δ myocardial performance index, Δ isovolumic relaxation time, ΔE, ΔA, Δ3DGRS, Δ3DGCS, and ΔNTproBNP, were not associated with future cardiotoxicity. On multiple logistic regression analysis (Table 4), including all the univariate predictors, Δ3DGLS emerged as the only independent predictor of later cardiotoxicity (Odds ratio 1.09, p=0.04).

To identify the optimal cut-off for Δ3DGLS, ROC curves were constructed. (Figure 2) The ROC curves found Δ3DGLS to be the best echocardiographic predictor of patients who developed cardiotoxicity during the follow up (AUC=0.90, 95% confidence interval, CI=0.81–0.99, p<0.001), followed by the cumulative anthracycline dose at 12 weeks (AUC=0.82, 95% CI=0.69–0.94, p<0.001) and ΔLVEF (AUC=0.81, 95% CI=0.70–0.92, p<0.001). For the other variables analysed the value of AUC was lower. A statistical comparison of the ROC curves demonstrated significant differences between Δ3DGLS and cumulative anthracycline dose at 12 weeks (p=0.04), and between Δ3DGLS and ΔLVEF (p=0.03). The optimal cut-off for Δ3DGLS was 13.7%, with a sensitivity of 88% and specificity of 71%. LV 3DGLS deteriorated by >13.7% from base-

Table 4. Variables associated with anthracycline-induced cardiotoxicity in univariate and multiple nominal logistic regression models.

Variable	Univariate logistic regression analysis			Multiple logistic regression analysis		
	Odds ratio	p	95% CI	Odds ratio	p	95% CI
Cumulative anthracycline doses at 12 weeks	1.06	0.006	1.01-1.11	0.08	0.061	0.001–0.17
ΔLV 3DGLS	1.65	0.008	1.13-2.4	1.09	0.041	0.06-2.25
ΔLVEF	1.21	0.011	1.04-1.41	0.45	0.133	0.13-1.05
ΔTroponin T	0.99	0.029	0.997-0.999	0.01	0.948	0.002-0.02

Δ – percentage changes between baseline and 12 weeks after initiation of chemotherapy versus baseline; EF – ejection fraction; 3DGLS – three-dimensional global longitudinal strain; LV – left ventricle; 95%CI – 95% confidence interval.

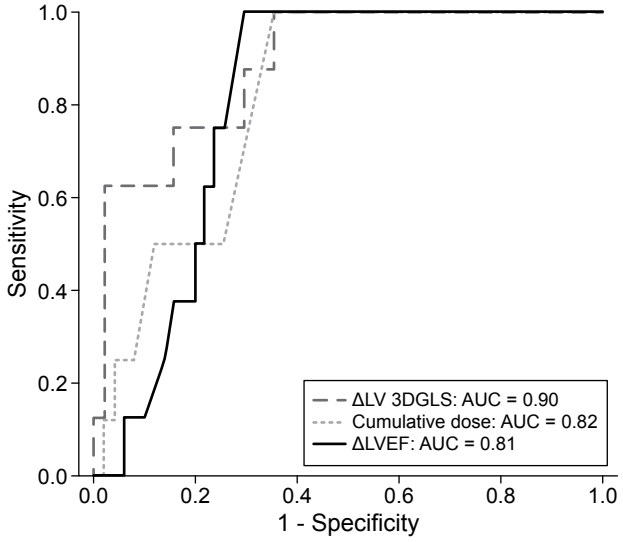

Figure 2. Receiver operating characteristic (ROC) curves for Δ3DGLS of the left ventricle, cumulative dose of anthracycline at 12 weeks and ΔLVEF to predict future development of anthracycline-mediated cardiotoxicity. Δ – percentage changes between baseline and 12 weeks after initiation of chemotherapy versus baseline; AUC – area under ROC curve; LVEF – left ventricular ejection fraction; 3DGLS – three-dimensional global longitudinal strain.

line in 22 patients (37%) during the first 12 weeks of chemotherapy.

Simple linear regression analysis showed that Δ3DGLS (r=0.57, p<0.001), Δ3DGCS (r=0.32, p=0.02), and Δ3DGRS (r=-0.27, p=0.04) exhibited significant correlations with the anthracycline dose administered during the first 12 weeks.

Discussion

Main findings

The results of the present study demonstrate that, in patients treated with anthracyclines, an early deterioration of 3DGLS predicts the later occurrence of cardiotoxicity. At 12 weeks after the initiation of chemotherapy, on multiple logistic regression analysis, Δ3DGLS was the only independent predictor of the future development of anthracycline-induced cardiac toxicity. Deterioration of 3DGLS, 3DGRS and 3DGCS was inversely correlated with the cumulative dose of anthracycline. These parameters, which are markers of myocardial deformation, deteriorated before any LVEF decrease.

Anthracycline induced-cardiotoxicity

Anthracyclines are an important class of agents for the treatment of a wide spectrum of haematological malignancies and solid tumours, but their use is limited by cardiotoxicity, which can manifest as acute or sub-acute injury immediately after treatment, but also as late-onset cardiomyopathy years later.[8] Data from the oncology literature, however, indicate that more than one half of all patients exposed to anthracycline will show some degree of cardiac dysfunction 10 to 20 years after chemotherapy.[15] Anthracycline toxicity is thought to be mediated largely by intracellular oxidative stress and is characterised by myocardial cell necrosis, apoptosis, and mitochondrial dysfunction.[16] A number of findings point to autophagy as playing a central role in doxorubicin-induced cardiomyopathy. This toxicity is cumulative and dose-dependent, with an incidence of clinically detected heart failure of 1.6% to 2.1% of patients within the first year after treatment.[17] Prospective studies have observed doxorubicin-related decreased LVEF in 16%, 38%, and 65% of patients receiving doxorubicin cumulative doses of 300 mg/m^2, 450 mg/m^2, and 550 mg/m^2, respectively.[18] For this reason, the maximum lifetime cumulative dose for doxorubicin is 400 to 550 mg/m^2, as recently recommended.[1] In our study group, the average cumulative anthracycline dose was 256 ± 58 mg/m^2 and represented a predictor of chemotherapy-induced cardiotoxicity. Of our patients, 13.5% met

the criteria for cardiotoxicity. Compared with other more frequent forms of cardiomyopathy, anthracycline-induced cardiomyopathy has been associated with an especially poor prognosis, with a 2-year mortality rate of up to 60%, and is also believed to be refractory to conventional therapy.[15] These data highlight the importance of an early diagnosis and start of treatment for achieving a reversion of LV dysfunction.

Assessment of anthracycline cardiotoxicity

LVEF, assessed by 2D echocardiography, has traditionally been used to assess the cardiac impact of chemotherapy, but its limitations require the development of better measurement techniques.[4,19-24] Deterioration in LVEF represents a relatively late stage of systolic impairment, after the myocardium has exhausted its considerable functional reserve.[24] In accordance with previous studies, our results confirm that LVEF is not sufficiently accurate for the early detection of impaired myocardial function.

Among the Doppler echocardiographic parameters, only isovolumic relaxation time showed significant prolongation after the initiation of chemotherapy. Pulmonary artery systolic pressure, transmitral flow wave velocities and the myocardial performance index did not show significant change during the study period. Stoddard et al prospectively evaluated 26 patients before the start of chemotherapy and 3 weeks after cumulative doses.[25] He observed prolongation of the isovolumic relaxation time preceding a significant decrease in LVEF. Similarly, Motoki et al suggested in a recent study that isovolumic relaxation time might be useful in cases where strain analysis is not available.[19] In our group, no conventional Doppler parameter was an independent predictor for early detection of cardiotoxicity.

Myocardial strain imaging has revealed interesting capabilities for identifying chemotherapy-induced LV dysfunction.[4,18,20,22,24] Recent reports using 2D-strain imaging showed that a decrease in LV GLS,[4,22,23] radial strain,[4,20-22,26] and torsion[19] might be useful in detecting subclinical myocardial damage due to chemotherapy. As suggested by Sawaya et al, the superiority of 2D-strain analysis over LVEF could be explained by the regional pattern of chemotherapy-induced cardiotoxicity (in the early stages the function of some myocardial segments may compensate for others, leading to a preserved LVEF) and by the lower variability (especially in the longitudinal dimension).[23] In a recent study by Reant et al, although LV 2DGLS was shown to be reproducible and accurate, 2DGCS and 2DGRS were less reliable, which limits their use for LV systolic function evaluation in clinical practice.[5] Cardiac motion involves 3D rotation, contraction, and shortening, which might cause the "disappearance" of some of the speckles from the 2D view by through-plane motion. Three-dimensional echocardiography improves information on LV segmental and global deformation by avoiding the loss of speckles seen in monoplane 2D-strain analysis.[7] The reproducibility of 3D-strain markers appears to be sufficient for clinical use, being superior to that of 2D-strain imaging for circumferential and radial strain analyses.[5,6] Three-dimensional echocardiography reduced the time of analysis for LV strains by 25% compared with 2D-strain imaging.[5] In our study, 3D-strain imaging was a sensitive tool for the early detection of subclinical myocardial damage. The parameters 3DGLS, 3DGCS and 3DGRS deteriorated early after anthracycline administration, before any decrease in LVEF. We also found that at 12 weeks' cumulative anthracycline dose, ΔLVEF, Δ3DGLS and ΔTnT were predictors of the later development of anthracycline-induced cardiac toxicity. On multiple logistic regression analysis, Δ3DGLS emerged as the only independent predictor of later cardiotoxicity. Δ3DGRS and Δ3DGCS did not reach statistical significance, probably because the reduction in longitudinal function could precede the reduction in radial and circumferential function, as reported in previous studies.[2,27,28]

Our data showed that ΔTnT was associated with the late occurrence of cardiotoxicity on univariate analysis. Today, solid data indicate that troponin gives us the ability to detect chemotherapy-induced cardiotoxicity.[15,23,29,30] In our group, Δ3DGLS was a stronger predictor of later anthracycline-induced LV dysfunction. The early change in NTproBNP level was not predictive of a later decrease in the LVEF. In the setting of chemotherapy, however, data regarding the use of NTproBNP for monitoring are inconclusive.[4,17,31]

Clinical implications

This study highlights the potential application of 3D-strain imaging in the early detection of subclinical LV myocardial dysfunction during treatment with anthracycline. To our knowledge, this study demonstrates for the first time that 3D-strain is an accurate and

practical method of screening for potential cardiotoxicity among patients with cancer who are receiving anthracycline therapy. Δ3DGLS could be useful to identify the early alteration of cardiac function in patients who require further treatment with an adjuvant (such as trastuzumab), in order to prevent the progression to an irreversible stage of cardiac dysfunction. It may help target patients who could benefit from closer cardiac monitoring, earlier initiation of cardioprotective medical therapy, or fewer anticancer drugs.

Limitations

The study was limited to a population with good image quality, which explains the high proportion of patients excluded from analysis. Variability of strain measurements is an inherent limitation of the technique; however, our measurements are similar to other published data.[5-7] Our study was a single-centre study and its reproduction in other centres or by multi-centre studies would argue for its validity. It was performed in a relatively small group of patients and did not provide longer-term follow up of the clinical implications of early anthracycline-induced changes in 3D-strain parameters. Future studies are necessary to compare the value of 3D-strain with that of the 2D-strain and tissue Doppler parameters.

Conclusions

Three-dimensional strain imaging appears to be a useful non-invasive method for the early detection of anthracycline-induced myocardial damage. Early deterioration of 3DGLS, 3DGRS and 3DGCS was inversely correlated with the cumulative dose of anthracycline and was identified before any LVEF decrease. Δ3DGLS can predict the later occurrence of cardiotoxicity with good accuracy.

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