Speckle Tracking Analysis for Early Detection of Cardiotoxicity in Breast Cancer Patients

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Abstract

The aim of this retrospective study was to detect early cardiotoxicity by speckle tracking analysis. We analyzed 2D and 3D echocardiographic datasets (2DE and 3DE) in 65 patients treated for breast cancer with anthracycline and trastuzumab. We compared the temporal variations of the left ventricular ejection fraction (LVEF) obtained analyzing 2D and 3D datasets and of the strain values computed before, during and after chemotherapy administration. In addition, in a subgroup of 45 patients a complete echocardiographic examination was performed 6 months after completion of therapy. Cardiotoxicity onset definition varies depending on the method used to compute LVEF (16.9% by 2DE and 50.8% by 3DE). Thirty-three patients developed cardiotoxicity. Nine of them showed a reduction of longitudinal and radial strain values before LVEF reduction at the 16th week. Through 3D speckle tracking analysis early diagnosis of the cardio-toxicity onset seems achievable allowing the planning of cardio protective therapy without interrupting chemotherapy administration.

1. Introduction

Breast cancer and cardiovascular diseases are serious concerns for public health worldwide. A major advance in the treatment of breast cancer has been the introduction of trastuzumab, a monoclonal antibody against human epidermal growth factor receptor type 2 (HER2), in addition to adjuvant chemotherapy.

The efficacy of anthracycline agents is, however, limited by serious side effects including cardiotoxicity, resulting in an increased risk of morbidity and mortality in patients undergoing chemotherapy with anthracyclines.

Although in clinical practice left ventricular ejection fraction (LVEF) is considered the main parameter to evaluate cardiac function, it is not sufficiently sensitive to detect subclinical or regional myocardial dysfunction.[1] LVEF assessed by 2D echocardiography is routinely computed in patients treated with cardio-toxic drugs. Unfortunately, this index shows a decrease once cardiac damage has comprised ventricular function at a stage that could be irreversible.

Several parameters have been proposed for earlier detection of ventricular dysfunction; this would allow to act as soon as possible with preventive treatments for heart failure and/or to modify chemotherapeutic treatments.

The use of 3D echocardiography has been shown to improve the accuracy and reproducibility of LVEF and may be preferable to 2D techniques.[2-4]Dimensional strain imaging has been developed as a new application that could be used for regional wall motion analysis thus allowing the determination of volumetric indices for accurate assessment of wall motion in 3D.

Therefore, the aim of this retrospective study was to to detect early cardiotoxicity with speckle tracking analysis in selected patients with breast cancer treated with anthracyclines and trastuzumab.[5]

2. Methods

Sixty-five patients with histological or cytological diagnosis of breast cancer in early stage or locally advanced candidates for neoadjuvant therapy or treated with radical surgery, were enrolled in the study.

All patients had a complete echocardiographic examination after 15 days since the last anthracycline dose, before starting trastuzumab administration and at the following timings: at the first administration, after 16 weeks of treatment, after 32 weeks and finally at 48 weeks.

For every single patients we collected the following measurements: 2D LVEF applying the Simpson mono-planar method, 3D LVEF computed with EchoPAC software by GE Healthcare (3D-GE). In addition, longitudinal (GLS), circumferential (GCS), radial (GRS) and area (GAS) strain were computed from 3DE by EchoPAC, GE Healthcare.

Cardiotoxicity onset was defined as a reduction of LVEF greater than 10 percentage points, or an absolute value less than 53% [6], computed applying the Simpson mono-planar method to 2DE.

All data were acquired and analyzed by an experienced cardiologist who manually traced

endocardial contours.

All patients gave written informed consent in agreement with the local Ethics Committee.

2.1. Statistical analysis

Descriptive data was reported as absolute and relative frequencies for categorical variables and mean values and relative standard deviations (SD) were calculated for continuous variables.

Means values and 95% confidence intervals (95% CI) for each time point were presented for patients with cardiotoxicity and for patients without cardiotoxicity.

Baseline characteristics of patients who developed or did not developed cardiotoxicity were compared using the Chi-square test.

The normality of distributions was assessed by Shapiro-Wilk test and, as distributions are normal, the comparison of echocardiographic measurements between two groups was done using the *t* test.

Paired *t* test was used to compare the mean values of LVEF, 3D-GLS, 3D-GCS, 3D-GAS and 3D-GRS.

A repeated measures analysis of variance (ANOVA) was used to determine whether there were significant differences in the way mean echocardiographic parameters values changed over time. Changes in the parameters were compared with baseline using contrast analysis.

All analyses were performed using SAS Statistical software (version 9.3, SAS Institute, Cary, NC, USA) and $p < 0.05$ was considered to be statistically significant.

3. Results

The number of patients showing a cardiotoxicity onset was different depending on the echo data analyzed: 11 patients with 2DE; 33 patients with 3DE-GE corresponding to 16,9% and 50.8% respectively.

By comparing 3D-GE LVEF in the two groups of patients, a statistically significant variation was found only for patients with cardiotoxicity at 16, 32 and 48 weeks, compared to baseline.

Mean baseline LVEF was 60.5% (± 5.9) in the study population and was similar in the two groups of patients with or without cardiotoxicity. LVEF and strain value decreases were statistically significant at 48 weeks only in the group of patients with cardiotoxicity ($p<0.0001$) (Table 1).

The intergroup differences in LVEF and strain trend over time showed the deepest drop at 16 weeks ($p<0.0001$).

The 33 patients with cardio-toxicity were treated with ACE inhibitors + beta-blockers from the 16th week .

3D-GLS peaks were calculated in all patients without observing a statistically significant trend between baseline and 16 weeks, 32 weeks and 48 weeks.

In the group of patients with cardiotoxicity (n=33), 3D–GLS, 3D-GRS and 3D-GAS evaluated through the analysis of the variance for repeated measurements (ANOVA), showed a significant reduction of the values with respect to the baseline values at the 16th week ($p < 0,0001$), and then a rise after cardio-protective treatment at the 32th week compared to the basal values even when LVFE was recovered. No significant changes were observed for circumferential strain. Considering a variation of 10%, in 1 patient in 9 cardiotoxic patients (11%) LVEF was reduced; 8 patients (89%) showed a decrease in 3D-GLS and 6 patients (67%) showed a reduction in 3D-GRS.

Figure 1 reports the mean percentage differences at 8 weeks compared to pre-therapy value in 9 patients: all parameters are reduced but a significant reduction was detected only for longitudinal strain ($p = 0.006$) and radial strain ($p = 0.046$)

In 45 patients, echocardiographic examination at 6 months after completion of therapy was available (Table 2). Significant differences were detected for the strain values, while no significant changes were found for LVEF. In particular, patients with cardiotoxicity showed greater differences compared to patients without cardiotoxicity; in patients without cardiac toxicity, LVEF showed no substantial differences while strains maintained important differences. This data suggest strain could be indicators of late cardiotoxicity not detectable through the determination of LVEF. In particular, considering the two groups of patients with and without cardiotoxicity, the strain values remained low in patients with cardiotoxicity who were treated with cardio-protective drugs. Importantly, patients without cardiotoxicity, at the end of therapy, showed a statistically significant decrease in strain values from baseline, while preserving a normal ejection fraction.

4. Discussion and conclusion

Many studies have shown the cardio-toxicity effect of taxanes, anthracyclines and Herceptin through a reduction of baseline LVEF.[6] According to this criteria, we have pursued our research in order to find early cardio-toxicity with speckle tracking analysis.

Despite some limitations, this study has shown that through the echocardiographic monitoring of oncologic patients treated with cardio-toxic drugs, we can obtain an early detection of cardiac dysfunction. This would allow to act therapeutically with ACE inhibitors and beta-blockers as soon as a strain alterations arise.

Cardiotoxicity onset varies depending on the method used to diagnose it. The timing of patient monitoring is

also important and the preliminary results of this study shows it is necessary to monitor the patient from the eighth week and no longer than the sixteenth week.

In our study, at the sixteenth week, the decline of strain values is in correspondence of the decrease of LVEF and this may mislead the examiner. The administration of ACE inhibitors and beta blockers starting at the 8th week when strain values decrease and LVEF is still normal, yielded excellent results for the recovery of LVEF and allowed not to interrupt the therapy with.

The recovery of normal values for LVEF following cardio-protective therapy administration corresponded to a persistent decrease in strain also at 48 weeks.

At 6 months after the cessation of therapy, there was a failure to recover strain values in cardiotoxic patients and a slight decrease in strain values even in the non cardiotoxic group. This could be attributed to a late cardiotoxic effect of anthracyclines. Therefore, some cardio passive protection and a long-term monitoring could be suggested also in patients without cardiotoxicity.

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Table 1: Mean value (standard deviation) of echocardiographic parameters in patients with or without cardiotoxicity at different time point/over time (n=65) [1]ANOVA contrast; [2]unpaired t-test; [3]ANOVA repeated measures within each group.

		Pts without cardiotoxicity (n=32)		**Pts with cardiotoxicity (n=33)**		**Intergroup difference (95% CI)**	**p-value[2]**
		Mean value (SD)	**p-value[1]**	**Mean value (SD)**	**p-value[1]**		
EF3D-GE	Pre-therapy	58.5 (4.3)	-	63.0 (6.7)	-	4.52 (-1.73 to 7.32)	0.204
	16 wks	59.2 (6.1)	0.476	**49.9 (5.5)**	<0.0001	-9.32 (-12.32 to -6.32)	<0.0001
	32 wks	59.3 (6.3)	0.429	60.5 (5.7)	0.013	1.20 (-1.90 to 4.30)	0.443
	48 wks	59.1 (5.0)	0.488	57.6 (7.2)	0.004	-1.52 (-4.61 to 1.56)	0.328
	p-value[3]		0.856		<0.0001		-
3D-GLS	Pre-therapy	-19.7 (3.2)	-	-19.6 (3.9)	-	0.09 (-1.70 to 1.89)	0.918
	16 wks	-19.0 (3.6)	0.337	-14.6 (2.9)	<0.0001	4.44 (2.75 to 6.13)	<0.0001

	32 wks	-19.0 (3.6)	0.366	-17.7 (2.8)	0.010	1.36 (-0.32 to 3.05)	0.111
	48 wks	-18.5 (2.8)	0.078	-17.1 (2.5)	0.001	1.37 (-0.01 to 2.76)	0.051
	p-value[3]		0.323		<0.0001		-
3D-GCS	Pre-therapy	-16.3 (3.3)	-	-17.3 (3.6)	-	-1.08 (-2.83 to 0.68)	0.224
	16 wks	-16.7 (5.1)	0.526	-13.4 (3.3)	<0.0001	3.37 (1.11 to 5.63)	0.004
	32 wks	-16.3 (3.2)	1.000	-16.0 (3.1)	0.109	0.26 (-1.34 to 1.85)	0.748
	48 wks	-15.8 (2.6)	0.334	-15.7 (2.8)	0.022	0.10 (-1.28 to 1.49)	0.880
	p-value[3]		0.557		<0.0001		-
3D-GAS	Pre-therapy	-31.3 (4.7)	-	-32.1 (5.3)	-	-0.83 (-3.35 to 1.70)	0.516
	16 wks	-30.3 (5.1)	0.300	-24.0 (4.7)	<0.0001	6.22 (3.69 to 8.75)	<0.0001
	32 wks	-30.8 (4.8)	0.568	-29.2 (4.1)	0.009	1.59 (-0.71 to 3.88)	0.172
	48 wks	-29.9 (4.4)	0.129	-28.7 (3.7)	0.0006	1.21 (-0.90 to 3.32)	0.255
	p-value[3]		0.439		<0.0001		-
3D-GRS	Pre-therapy	51.9 (11.0)	-	54.0 (11.6)	-	2.08 (-3.70 to 7.85)	0.475
	16 wks	50.9 (11.4)	0.600	37.1 (9.2)	<0.0001	-13.74 (-19.10 to -8.37)	<0.0001
	32 wks	50.3 (11.0)	0.418	47.1 (8.5)	0.004	-3.18 (-8.31 to 1.94)	0.219
	48 wks	48.4 (8.9)	0.079	45.9 (8.0)	0.0008	-2.47 (-6.83 to 1.88)	0.261
	p-value[3]		0.307		<0.0001		-

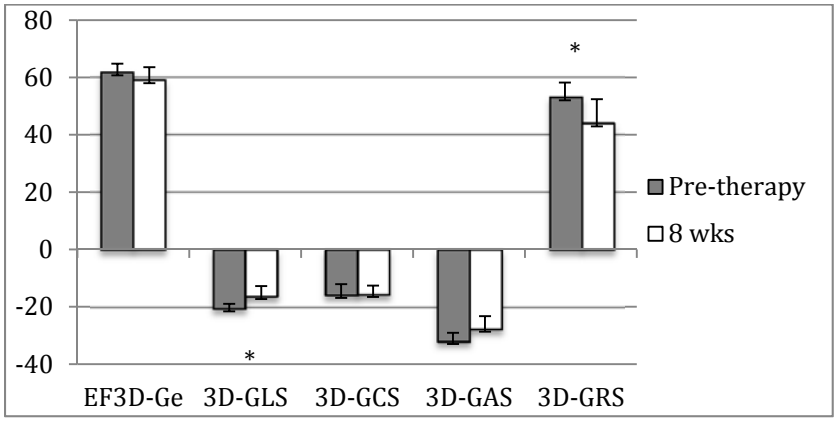

Figure 1 Mean percentage differences at 8 weeks vs pre-therapy (n=9) *statistical difference p< 0.05

Table 2: Mean value (±standard deviation) pre-therapy and after 6 months from the end of therapy (n=45). *paired t-test

	Pre-therapy	After 6 months from the end of therapy	Difference (95% CI)	p*
EF3D-GE	60.2±5.6	58.8±4.3	-1.42 (-3.16 to 0.33)	0.109
3D-GLS	-19.5±3.4	-17.1±3.0	-2.44 (-3.38 to -1.50)	<0.0001
3D-GCS	-16.4±3.6	-15.2±2.8	-1.26 (-2.38 to -0.13)	0.029
3D-GAS	-31.3±4.9	-28.3±4.4	-2.98 (-4.45 to -1.51)	0.0002
3D-GRS	51.6±10.7	44.4±8.9	-7.29 (-10.28 to -4.29)	<0.0001
Pts without cardiotoxicity				
EF3D-GE	58.0±4.3	58.7±4.0	0.64 (-1.51 to 2.79)	0.545
3D-GLS	-19.5±3.2	-17.5±2.7	-2.04 (-3.09 to -0.99)	0.0005
3D-GCS	-15.9±3.3	-14.8±2.8	-1.12 (-2.32 to 0.08)	0.066
3D-GAS	-30.8±4.8	-28.4±4.0	-2.40 (-4.12 to -0.82)	0.008
3D-GRS	50.1±10.2	44.2±7.9	-5.88 (-9.32 to -2.43)	0.002
Pts with cardiotoxicity				
EF3D-GE	63.2±5.9	58.9±4.9	-4.28 (-6.83 to -1.73)	0.002
3D-GLS	-19.5±3.9	-16.5±3.3	-3.00 (-4.81 to -1.19)	0.003
3D-GCS	-17.2±3.9	-15.8±2.8	-1.44 (-0.83 to 3.72)	0.197
3D-GAS	-32.1±5.0	-28.3±4.9	-3.78 (-6.55 to -1.00)	0.011
3D-GRS	53.7±11.4	44.5±10.3	-9.17 (-14.76 to -3.57)	0.003