

# Early Detection of Cardiotoxicity in Chemotherapy-Treated Patients from Real-time 3D Echocardiography

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## Abstract

*Cardiotoxicity is a well-known adverse effect of various chemotherapeutic agents that can be monitored by echocardiography. A decrease of left ventricular ejection fraction (LVEF) during the therapy might indicate dangerous effects of the drug on the myocardium and triggers consideration of therapy modification or interruption. We hypothesized myocardial deformation could identify preclinical myocardial dysfunction earlier than conventional LVEF allowing the administration of treatments to avoid cardiac side-effects. Sixty-five patients who were newly diagnosed with breast cancer, were enrolled to be evaluated by echocardiography before cancer therapy, during the therapy at 16 weeks (16w) and at follow up after 32 weeks (32w). Following the recommendation, 24 patients (36.9%) showed cardiotoxicity; 11 (16.9%) interrupted the therapy due to a severe cardiac dysfunction and at 32w only 4 patients recovered. In this group at 16w, strain analysis showed a significant reduction for all strain values that were all predictive of cardiotoxicity independently from LVEF and radial strain resulted an independent prognostic index of cardiotoxicity. The assessment of myocardial deformation indexes might provide additional echocardiographic tools to assess cardio-toxic effects beyond LVEF.*

## 1. Introduction

Ultrasound imaging is worldwide recognized as the standard diagnostic and screening technique of choice for cardiac assessment. New emerging areas of application include early detection of the adverse effects of various chemotherapeutic agents in cancer patients [1,2]. Nowadays, since cancer patients survive longer, the impact of cardiotoxicity associated with the use of cancer treatment on cardiac morbidity and mortality is increasing and should be investigated.

Cardiotoxicity is defined as a reduction of the left ventricular ejection fraction (LVEF) of  $>5\%$  to  $<55\%$  with symptoms of heart failure or asymptomatic reduction of the LVEF of  $>10\%$  to  $\leq 55\%$  [2]. Following the recommendation, in cardiotoxicity conditions, chemotherapy modification or interruption should be taken into consideration [3]. Therefore, LVEF measurements should be not only accurate but also have the lowest temporal variability such that changes in LVEF truly represent cardiotoxicity.

Both 2D and 3D echocardiographic techniques can be used to assess LVEF. Increased accuracy and reproducibility of volumetric approach compared to 2D techniques has been previously reported [4]. Consequently, 3D echocardiography may be preferable to 2D echo also for the cardiotoxicity assessment. Recent studies aimed to identify the best echocardiographic method for quantification of LV volumes and LVEF in patients undergoing cancer chemotherapy and non-contrast 3D echocardiography was the most reproducible technique for LVEF and LV volume measurements over 1 year follow-up [5].

Considering LVEF assessment has major limitations including its limited accuracy due to image quality and geometric modeling and its dependence on loading conditions, recently, myocardial deformation indexes have been proposed to identify pre-clinical cardiac dysfunction earlier than conventional LVEF. Several studies investigated new measures of LV function, such as strain and strain rate that could possibly identify at risk patients with more accuracy and at an earlier stage [6,7]. Unfortunately this finding was reported on small cohort of patients and needs confirmation in other studies. A comprehensive review of the use of echocardiography to evaluate cardiac effects of chemotherapy is presented in [8].

Having available the echo technique with the lowest temporal variability and these indexes able to predict late-onset LV systolic dysfunction secondary to cancer therapy, would allow the administration of treatments to avoid these toxic side-effects.

The aim of this prospective study was to investigate whether changes in tissue deformation are able to identify LV dysfunction earlier than LVEF in selected patients treated with anthracyclines and trastuzumab, using 2D and 3D echocardiographic data.

## 2. Methods

Sixty-five patients newly diagnosed with breast cancer (age:  $53.2 \pm 11.3$  yrs, 54 ductal carcinoma and 11 lobular carcinoma), were prospectively enrolled in the database approved by the Ethical Review Board at the Romagnolo Scientific Institute for the Study and Treatment of Cancer (IRST).

Inclusion criteria consisted of having had (1) all echocardiographic studies performed with Vivid E9 (GE Healthcare, Milwaukee, Wisconsin) ultrasound system; (2) a complete 2D and 3D echo examination before cancer therapy administration, during the therapy at 16 weeks (16w) and at follow up after 32 weeks (32w); (3) LVEF > 50% before the chemotherapy administration; (4) the exclusive assumption of anthracyclines and trastuzumab as chemotherapy.

As part of the chemotherapy protocol, all patients received a complete echocardiographic examination and myocardial strain assessment. In each patient this examination included: apical 2- and 4-chamber and triplane acquisitions, short axis views at basal, mid and apical levels and M-mode. Echo Doppler was also acquired. In addition a 3D full volume dataset of the LV was obtained with ecg-gated acquisition optimized to acquire at the highest possible volume rates.

The following echocardiographic parameters were then computed offline:

- end diastolic and end systolic diameters (EDD and ESD) from the M-mode acquisition;
- LV volumes at ED and ES and EF applying the 2D biplane method by manual contouring of the 4- and 2ch views of the LV (Figure 1a);
- LV volumes at ED and ES and EF using both EchoPAC (GE Healthcare) and 4D LV-Function (Tomtec, Unterschleissheim, Germany) analysis package (Figure 1b and 1c);
- deceleration time, E/A, E/E' from Doppler acquisition;
- an index of LV torsion (from short axis views), longitudinal, circumferential and radial strain (from 4D acquisition) using the strain analysis available in the EchoPAC software.

For each patient clinical risk factors were also collected (hypertension, smoking, cholesterol level, etc.)

The statistical analysis of these data included:

- median values and corresponding range or mean value standard deviation for continuous variables;
- absolute values and percentages for continuous

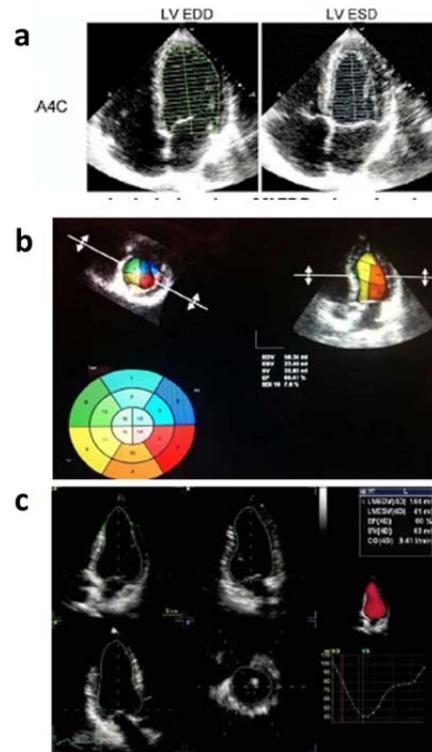


Figure 1. End diastolic and end systolic volumes computed analyzing (a) the 2D biplane method by manual contouring of the 4- and 2-ch views of the LV and the 3D full volume datasets using 4D LV-Function (b) and EchoPAC (c) software.

variables;

- chi-square or Fisher's exact test to evaluate the association of clinical parameters and cardiotoxicity level;
- analysis of variance for repeated measures to evaluate the mean values of the variations of all the parameters at 3 timings (pre-chemotherapy, 16w and 32w);
- logistic regression analysis to compute the odds ratios (OR) and the 95% confidence intervals (95% CIs) to determine which echocardiographic parameters could be predictive of cardiotoxicity earlier than LVEF;
- backward logistic regression analysis applied to determine which predictive echocardiographic parameters were independent.

In addition patients were divided into two groups defined depending on the onset of cardiotoxicity as defined by the recommendations. In these two groups of patients t-test was applied to compare the parameters' average values at the same timings and to assess the percentage changes in EF values and the 4 strain values at 16w compared with the same computed pre-chemotherapy and at 32w.

All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC, USA).

### 3. Results

Following the recommendation, 24 patients (36.9%) showed cardiotoxicity (LVEF mean reduction of 22% at 16w ( $p < 0.0001$ ) and of 4.9% at 32w); eleven (16.9%) patients interrupted the therapy due to a severe cardiac dysfunction for at least 1 month and at 32w only 4 patients recovered.

The 24 patients with cardiotoxicity were treated with ACE inhibitors and beta-blockers after the 16w. The 41 patients who did not undergo cardiac toxicity had no decay in time of the LVFE (pre-chemotherapy: 58.0 (4.8)%; at 16w: 57.8(6.4)% and at 32w: 58.6 (6.2)).

In the cardiotoxicity group at 16w, strain analysis showed a significant reduction for all strain values. In the other group, strain analysis did not show any statistically significant changes during chemotherapy administration (Table 1).

Strain values were all predictive of cardiotoxicity independently from LVEF. Applying a logistic backward stepwise regression model, the radial strain resulted an independent prognostic index of cardiotoxicity with a decrease of 10% in the risk of cardiotoxicity at the increase of the radial strain value (Table 2).

In addition, further considering the average percentage change of longitudinal, circumferential and radial strain in the two groups over time, we found a difference statistically significant for all of them with the exception of the longitudinal strain change between pre-chemotherapy and 32w (Table 3).

The parameters deceleration time, E/A and E/E' did not change significantly over time.

Finally, no significant statistical difference was found between the clinical variables characterizing the two groups of patients.

### 4. Discussion and conclusion

The occurrence of cardiac electrophysiology dysfunction or/and myocardial damage caused by chemotherapy is a relatively new area of investigation in which echocardiography could have a strategic role. In this prospective study we investigated whether changes in tissue deformation are able to identify LV dysfunction earlier than LVEF in selected patients treated with anthracyclines and trastuzumab, using echocardiography.

Previous studies show myocardial deformation indexes could detect cardiac dysfunction before LVEF in patients with breast cancer. The predictive value of

Table 1. Values expressed as mean (SD); Group 1: Patients with cardiotoxicity (n=24); Group 2: Patients without cardiotoxicity (n=41); \* $p < 0.0001$  group 1 before therapy vs 16w.

	Before therapy		16 w		32 w	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
<b>Strain (%)</b>						
Longitudinal	-20.2 (4.0)*	-19.3 (3.6)	-14.0 (3.2)	-18.3 (4.1)	-17.8 (2.8)	-18.9 (3.5)
Circumferential	-18.0 (3.3)*	-16.4 (3.4)	-13.3 (3.3)	-16.4 (4.9)	-15.9 (3.1)	-16.2 (3.1)
Radial	56.2 (11.6)*	51.3 (11.6)	36.7 (9.4)	48.9 (12.2)	47.3 (8.6)	49.9 (10.6)

Table 2. Results of the univariate logistic regression analysis

Strain	OR (95% CI)	p	risk
Longitudinal	1.33 (1.13-1.57)	0.0007	33%
Circumferential	1.26 (1.05-1.51)	0.009	26%
Radial	0.90 (10.85-0.96)	0.0006	-10%

Table 3. Values expressed as mean; Group 1: Patients with cardiotoxicity (n=24); Group 2: Patients without cardiotoxicity (n=41); prechemo: before cancer therapy administration; 16w: during the therapy at 16 weeks; 32w: at follow up after 32 weeks; p value  $< 0.05$ .

	Group 1	Group 2	p
<b>Longitudinal Strain</b>			
prechemo-16w	-29.2%	+2.1%	0.0003
prechemo-32w	-8.9%	+1.8%	0.153
16w-32w	+31.3%	+7.6%	0.0003
<b>Circumferential Strain</b>			
prechemo-16w	-24.9%	+2.2%	0.0004
prechemo-32w	-9.3%	+1.9%	0.047
16w-32w	+26.4%	+3.9%	0.005
<b>Radial Strain</b>			
prechemo-16w	-33.9%	-1.2%	$< 0.0001$
prechemo-32w	-13.1%	+1.4%	0.0035
16w-32w	+34.6%	+6.5%	0.0009

longitudinal and radial strain was reported in [9] from magnetic resonance imaging. Longitudinal strain assessed by speckle tracking echocardiography has been proved to be useful in the prediction of cardiotoxicity [6]. A reduction in radial strain was also identified from 2D speckle tracking echocardiography before reduction in LVEF and associated with histologic changes [10]. Overall, there is no consensus about which parameters should be computed to predict LV dysfunction earlier than LVEF, and additional studies are required.

The present study confirms the findings regarding myocardial deformation indexes in a relatively large cohort of patients and emphasize the role of radial strain as the most sensitive in predicting cardiotoxicity. Importantly, in the group of 11 patients who interrupted the chemotherapy due to a severe cardiac dysfunction, only 4 patients totally recovered the LVEF value they had before the therapy showing that trastuzumab, administered after a standard dose of anthracycline, is not harmless and its effects are not reversible. In these patients the prediction of the cardiotoxicity onset would allow the modulation of cancer therapy and/or the administration of therapies such as angiotensin-converting enzyme inhibitors.

Future investigations include the noninvasive acquisition of blood biomarkers to have a “real” gold standard to measure myocardial damage and further follow-up.

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## References

- [1] Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, Gorissen W, Houle H. Two- and three-dimensional speckle tracking echocardiography: Clinical Applications and Future Directions. *Echocardiography* 2013;30(1):88-105.
- [2] Mor-avi V, Lang RM. Is echocardiography reliable for monitoring the adverse cardiac effects of chemotherapy? *JACC* 2013;61(1):85-86.
- [3] Martin M, Esteva FJ, Alba E, Khandheria B, Perez-Isla L, Garcia-Saenz JA, Marquez A, Sengupta P, Zamorano J. Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: Review and expert recommendations. *Oncologist* 2009;14:1–11.
- [4] Lang RM, Mor-Avi V, Dent JM, Kramer CM. Three-dimensional echocardiography: is it ready for everyday clinical use? *J Am Coll Cardiol Img* 2009; 2:114-117.
- [5] Thanvendiranatan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes. *JACC* 2013; 61(1):77-84.
- [6] Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, Cohen V, Banchs J, Carver JR, Wiegers SE, Martin P, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging* 2012;5:596-603.
- [7] Hare J, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. *Am Heart J* 2009;158(2):294-301.
- [8] Oreto L, Todaro MC, Umland MM, Kramer C, Qamar R, Carerj S, Khandheria BK, Paterick TE. Use of echocardiography to evaluate the cardiac effects of therapies used in cancer treatment: what do we know? *JASE* 2012; 25(11):1141-1152.
- [9] Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick ID, Singal PK, Krahn M, Grenier D, Jassal DS. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol*. 2011;57(22):2263-70.
- [10] Migrino RQ, Aggarwal D, Konorev E, Brahmabhatt T, Bright M, Kalyanaraman B. Early detection of doxorubicin cardiomyopathy using two-dimensional strain echocardiography. *Ultrasound Med Biol* 2008;34(2):208-14.

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