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Anthracyclines and regional myocardial damage in breast cancer patients. A multicentre study from the Working Group on Drug Cardiotoxicity and Cardioprotection, Italian Society of Cardiology (SIC)

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Abstract

Aims: In breast cancer (BC) patients treated with anthracyclines-based therapies, we aim at assessing whether adjuvant drugs impact cardiac function differently and whether their cardiotoxicity has a regional pattern.
Methods and results: In a multicentre study, 146 BC patients (56 ± 11 years) were prospectively enrolled and divided into three groups according to the received treatments: AC/EC-Group (doxorubicin or epirubicin + cyclophosphamide), AC/EC/Tax-Group (AC/EC + taxanes), FEC/Tax-Group (fluorouracil + EC + taxanes). Fifty-six patients of the total cohort also received trastuzumab. Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were calculated before starting chemotherapy (T0), at 3 months (T3), at 6 (T6), and 12 months (T12). A ≥10% drop of EF, while remaining within the normal range, was reached at T6 in 25.3% of patients from the whole cohort with an early decrease only in FEC/Tax-Group ($P = 0.04$). A ≥15% GLS reduction was observed in many more (61.6%) patients. GLS decreased early both in the whole population ($P < 0.001$) and in the subgroups. The FEC-Tax Group showed the worst GLS at T6. Trastuzumab further worsened GLS at T12 ($P = 0.031$). A significant reduction of GLS was observed in all LV segments and was more relevant in the anterior septum and apex.
Conclusions: The decrease of GLS is more precocious and pronounced in BC patients who received FEC + taxanes. Cardiac function further worsens after 6 months of adjuvant trastuzumab. All LV segments are damaged, with the anterior septum and the apex showing the greatest impairments.

Keywords
Cardiotoxicity, Breast cancer, Anthracyclines, Myocardial strain

Introduction
Cancer therapeutics-related cardiac dysfunction (CTR-CD) is the main manifestation of cardiotoxicity due to cancer therapy,[1] and it is defined as a left ventricular (LV) systolic dysfunction with a decrease in LV ejection fraction (EF) of ≥10 percentage points, to a value <50%.[2]
Although LVEF is still considered as the main parameter for assessing systolic function, its limits in the diagnosis of subclinical damage have been well known since several years. To overcome EF limitations, speckle-tracking echocardiography is extensively applied to date.[3–8] Global longitudinal strain (GLS) has been validated and included in the last consensus documents on cardiotoxicity[2,9] as a useful tool for detecting myocardial injury at an early stage. Currently, a relative GLS reduction ≥15% from baseline value is suggestive in this setting of cardiac damage even when LVEF is still preserved.[10] Therefore, GLS may help physicians to adopt tailored therapeutic strategies and start cardioprotective treatments whenever necessary.
While the incremental value of GLS in the detection of cardiotoxicity from chemotherapy has been recognized,[8] only a few studies tried to identify a typical pattern of regional impairment in LV mechanics.[4,11]
In the present multicentre prospective study involving a cohort of breast cancer (BC), patients we assessed subtle changes of LV function occurring with anthracyclines-based therapies and checked their persistence after anthracyclines discontinuation as well as the influence of adjuvant agents in determining an early onset and/or longer duration. We also explored whether some LV regions are more vulnerable than others to this kind of damage.

Methods
Study population
Enrolment criteria and design of the study (Figure 1) were previously shared and accepted among the participating centres.
Patients were consecutively recruited in a prospective way at eight participating centres (from the University Hospitals of Messina, Palermo, Naples, Pisa, Catania, Genoa, Turin, and Cagliari, Italy) with a minimum of 15 subjects that had to be enrolled per centre. At each of the recruitment centres, the following inclusion criteria had to be met: anthracyclines naïve BC patients >18 years old scheduled for receiving anthracyclines-based cancer therapy and afferent to the echocardiography laboratories before the treatment.
Patients exclusion criteria were the previous history of malignancies treated with cardiotoxic drugs and/or thoracic radiotherapy, history of cardiac disease (coronary artery disease, cardiomyopathies, more than mild valvular heart disease), non-sinus cardiac rhythm, left bundle branch block, previous cardiac surgery, inadequate transthoracic acoustic window.
Each patient underwent cardiologic consultation before starting chemotherapy (T_0) and at 3 (T_3), 6 (T_6), and 12 months (T_{12}) from the beginning of the treatment.
At the time of enrolment, cardiovascular risk factors and a detailed medical history were collected for all participants. Patients underwent complete cardiac examination, electrocardiogram, and echocardiogram at each visit (T_0, T_3, T_6, and T_{12}). Likewise, measurement of cardiac biomarkers, troponin I (Tn-I), and brain natriuretic peptide (BNP) was planned at baseline and at every scheduled check during follow-up (T_0, T_3, T_6, and T_{12}).
Written informed consents were obtained from all patients before their inclusion in the study. Every patient was free to drop the study anytime. The study was approved by the institutional review boards of all participating centres and complied with the Declaration of Helsinki.
The data underlying this article are available in the article and in its supplementary material.

Cancer therapy regimens and cardiotoxicity monitoring

The treatment program for recruited patients was the same for each participating centre. In particular, all patients underwent standard doses of anthracyclines (doxorubicin or epirubicin) and cardiotoxicity from anthracyclines was monitored at each planned step. Additional chemotherapeutic agents more frequently used were: cyclophosphamide, fluorouracil, and taxanes (docetaxel or paclitaxel) added to anthracyclines according to the following standard chemotherapy regimens: AC/EC (doxorubicin or epirubicin + cyclophosphamide), AC/EC-Tax (AC/EC + taxanes), FEC-Tax (Fluorouracil + EC + taxanes). In the adjuvant setting, anthracyclines infusion was repeated for 4–6 cycles, docetaxel every 3 weeks for up to 4 cycles, paclitaxel weekly for 12 weeks, according to standard systemic therapy for BC (more details regarding drugs doses, cycles, and other chemotherapeutic agents are included in the Supplementary data). Accordingly, patients were divided into three groups for evaluating cardiotoxicity related to each type of treatment: AC/EC-Group, AC/EC/Tax-Group, and FEC/Tax-Group. We focused on EF and GLS changes from T_0 to T_3 (early chemotherapy toxicity), T_6 (late chemotherapy toxicity), and T_{12} (late chemotherapy toxicity/recovery).

Two-dimensional transthoracic echocardiography before and during treatment

Echocardiographic examinations were performed at each centre by using the same ultrasound system (GE-E95 Vingmed Ultrasound AS, Horten, Norway) equipped with a cardiac M4S transducer. The data collection mode and the image acquisition technique were shared between the centres so that the same dataset was obtained for each patient. A comprehensive evaluation of cardiac dimensions and function as well as a careful assessment of valves and pericardium was done both at baseline and at each step during the follow-up.

Analysis of two-dimensional (2D) strain was performed offline through the automated function imaging, using semiautomatic tracking on high frame rate (>50 frames/s) apical views (four, two, and three chambers), previously transferred to an Echo-Pac workstation (V.202, GE). The LV GLS bull's eye map was derived and GLS mean values were calculated at each step (T0, T3, T6, T12). A relative reduction of ≥15% in GLS values between pre- and post-chemotherapy was considered clinically significant for defining cardiac damage, according to current recommendations.[10]

Further methodological details on conventional and speckle-tracking echocardiography that were applied in the study, are present in the Supplementary data.

In patients who met the criteria of subclinical cardiotoxicity (GLS drop of ≥15% from the baseline), the GLS bull's eye before treatment and the one corresponding to the peak of GLS reduction during treatment were analysed for each patient to compare the segmental values from baseline to the time of GLS drop. The difference of segmental longitudinal strain (from baseline to the time of GLS drop), named delta longitudinal strain (Δ-LS), was calculated to detect the myocardial region with the most relevant drop in myocardial deformation. We used a cut-off of Δ-LS ≥4% to identify segments with the greatest damage; conversely, segments with a Δ-LS <2% were considered as spared from the injury and those with Δ-LS in an intermediate range (≥2 but< 4), as only slightly impaired. These cut-off values were derived from, respectively, the 25th (Δ-LS = 2%) and 75th (Δ-LS = 4%) percentiles of the variation, before and after chemotherapy, of the myocardial strain of the overall segments.

Statistical analysis

Data were analysed using SPSS (V.20 for Windows; SPSS Inc., Chicago, IL, USA). The data are expressed as mean ± standard deviation. Chi-square test was employed to compare categorical variables. Repeated measures one-way analysis of variance (ANOVA), implemented with post hoc Bonferroni test, was used to compare continuous variables at different stages of follow-up. ANOVA was adjusted for covariates including main cardiovascular risk factors and anti-hypertensive drugs. Paired Student's T-test was used to compare segmental strain values between baseline and follow-up. Intra-observer and inter-observer variability in the measurement of the segmental strain were assessed by performing Bland–Altman analysis and calculating the intra-class correlation coefficient (the results are reported in the Supplementary data, Tables S1 and S2).

A P-value ≤0.05 was considered significant.

Results

Baseline patients' characteristics

One-hundred and forty-six patients (mean age 56 ± 11 years, 98.6% female) with BC (62% invasive ductal carcinoma; 8% invasive lobular carcinoma; 30% other rarer histological types) were included in the study. Baseline demographic and clinical characteristics of the overall population as well as cancer treatment received are detailed in Tables 1 and 2 respectively, and more extensively described in Supplementary data.

Clinical evaluation, biomarkers, and echocardiography in the whole population during follow-up

All patients were regularly followed by a cardio-oncologists team at each referring centre from baseline until 12 months after initiation of chemotherapy. Calculated mean duration of the overall follow-up was 309 ± 109 days. No patient developed symptoms of heart failure (HF) and the ECGs remained unremarkable throughout the follow-up.

Data from standard transthoracic echocardiography and biomarkers of the overall population at each step are summarized in Table 3.

With regard to biomarkers, Tn-I showed a slight increase at T_3 vs. T0 (0.03 ± 0.03 ng/mL vs. 0.01 ± 0.008 ng/mL, P = 0.004); similarly, a significant increase of BNP was found at T_3 vs. T_0 (55 ± 32.3 pg/mL vs. 36.9 ± 25 pg/mL, P = 0.01). Although increased, both Tn-I and BNP values remained in the normal range and returned to baseline values at the last follow-up after 1-year (T_{12}) from the onset of chemotherapy.

In the whole population, LVEF showed a mild and stable reduction at every stage compared to the baseline (Table 3). A ≥ 10% drop in EF compared to the baseline was reached in 34 patients (23.3%) at 3 months and in 37 (25.3%) at 6 months; however, EF absolute values remained >50% (with no patient developing cardiotoxicity according to the EF criterion[2]).

Alterations of myocardial function identified by using 2D strain off-line analysis were more relevant. A relative reduction of GLS ≥15% (subclinical damage) compared to the baseline was observed in 61.6% (90/146) of patients after chemotherapy, a much higher number than that identified by EF. In addition, GLS decreased in the whole population from T_0 (−20.8 ± 2.7 %) to T_3 (−18.7 ± 2.9%, P < 0.001), keeping this stable trend at T_6 (−18.1 ± 2.7%, P < 0.001) and T12 (−18.2 ± 3%, P < 0.001), meaning early onset of myocardial injury (Table 3).

Analysis of LVEF and GLS changes according to chemotherapy protocols

Table 4 shows LVEF and GLS data in groups divided according to the type of chemotherapy.

In the whole population, EF did not decrease below the normal range (>50%) regardless of the type of chemotherapy. However, significant differences about EF trend can be observed according to the different drug protocols. In patients treated with AC/EC protocol, a non-significant reduction of LVEF has been observed during the 12-month follow-up. However, when taxanes were added to the protocol, a significant impairment of LVEF occurred after 6 months (P = 0.003). When the protocol included taxanes, anthracyclines, and florouracil a significant decrease of LVEF already occurred early, after three months, (T_3 vs. T_0, P = 0.04), and it was more evident at T_6 (T_6 vs. T_0, P = 0.001).

More relevant and earlier were the alterations of myocardial function which were identified by 2D strain. Indeed, GLS decreased in the overall population since T_3. Moreover, while in the other groups no significant differences were observed between T_3 and T_6, in FEC-Tax Group a further GLS reduction was observed at T_6 (-17.8 ± 2.7%) compared to T_3 (−19± 2.2%; P=0.02 T_6 vs.T_3) (Table 4, Figure 2).

To evaluate the effect of trastuzumab when added to the other chemotherapy protocol, we compared patients who underwent chemotherapy with (n = 56) and without trastuzumab (n = 90). In the whole population we found that the reduction of LVEF was still significant after 12 months, only in patients who received trastuzumab (Table 5, Figure 3). Moreover, the addition of trastuzumab to chemotherapy determined a

progressive worsening of GLS throughout the follow-up with persistent lower values than those observed at the same step in the group treated with conventional chemotherapy without trastuzumab (Table 5, Figure 3). The same trend was observed and was more evident when analysing each single chemotherapy protocol according to the addition of trastuzumab (Table 6, Figure 2). In particular, FEC-Tax and AC/EC-Tax patients who received trastuzumab showed a significant GLS reduction at T_{12} ($p < 0.001$ for both), which did not occur in patients receiving only chemotherapy (Table 6). No patient of the AC/EC Group received adjuvant trastuzumab at the end of anthracyclines.

Bull's eye regional analysis

The results of the regional analysis of bull's eye from basal deformation to that of the peak of reduction analysed in patients (n = 90/146, 61.6%) reaching subclinical damage (GLS drop ≥15%) are described in Table 7. A significant decrease of LS was observed in all segments, but a greater impairment was found in all (basal-mid-apical) segments of the anterior septum (mean value after chemotherapy = −14.8 ± 2.3%; mean Δ-LS ≥ 4%) and in the apex (mean value after chemotherapy= -16.5 ± 2.6%; mean Δ-LS ≥ 4%) (Figure 4). A less evident reduction was present in basal and mid-segments of the inferior wall; indeed, although their mean values after chemotherapy were close to normal (-17.7 ± 3.1%), the change from baseline (Δ-LS) was > 2%. Conversely, basal and mid-segments of the inferior septum (mean value after chemotherapy = −17 ± 2.1%; mean Δ-LS < 2%) and basal and mid-segments of the inferior-lateral wall (mean value after chemotherapy = −17.9 ± 3.1%; mean Δ-LS < 2%) appeared relatively spared by chemotherapy-related myocardial injury.

Discussion

The main findings of our study are the following: (i) Impaired LV function occurs in most patients with BC treated with anthracyclines; importantly, GLS, but not LVEF is able to recognize early myocardial damage; (ii) chemotherapy regimens including fluorouracil and taxanes beyond anthracyclines are associated with the earliest and more pronounced GLS decrease; (iii) trastuzumab also leads to a further and persisting GLS reduction after 6 months of treatment ; (iv) the most relevant chemotherapy-mediated decrease of regional strain seems to involve the anterior septum and the apex.

Our study showed that, although the mean EF value of the study population decreased during chemotherapy, it remained in the normal ranges. Indeed, a late (T_6) drop ≥10% compared to baseline value was reached in 25.3% of patients, with an EF absolute value remaining >50% so that no patient developed cardiotoxicity according to the EF criterion. Therefore, this mild and stable reduction of EF may not actually have a real clinical impact, because it would not change in any way the management of these patients. Nonetheless, we agree that EF values around 50% could be a sort of 'red-flag' suggestive of initial myocardial damage.

On the contrary, GLS was more sensitive and identified subclinical alterations of the LV systolic function, as pointed out in recent recommendations.[12]

Moreover, we confirm the results of previous studies, identifying an early reduction of GLS in most of our patients, with a significant fall of GLS already at 3-months after starting therapy.[13–15] No patients developed HF symptoms during the follow-up and only a subclinical LV dysfunction was identified. However, the early identification of myocardial damage secondary to anticancer treatment could allow to prevent the development of an overt HF, guaranteeing at the same time the best anticancer treatment to the patients. The SUCCOUR trial[16] in this regard has just proven that patients diagnosed with CTRCD in the EF-guided arm had a larger reduction in LVEF at follow-up than in the GLS-guided arm (9.1 ± 10.9% versus 2.9 ± 7.4%, p = 0.03).

Beyond anthracyclines, docetaxel and paclitaxel are frequently used in breast cancer, in combination with or after anthracyclines and cyclophosphamide, fluorouracil, and followed or not by trastuzumab.[17,18] All these agents appear to increase the incidence of HF; however, the contribution of individual agents in multidrug therapies is frequently difficult to assess.[19]

There is currently no consensus on the optimal treatment and/or prophylaxis of these cardiotoxicities, beside early detection and therapy discontinuation.[20] In the trastuzumab setting, quarterly imaging has demonstrated a cumulative percentage of reduced LVEF (LVEF drop by >10–15% or to <50%) of 10% at 3 months, 19% at 6 months, and 25% at 12 months of therapy, respectively, in patients with prior anthracyclines exposure.[21] The serial assessment of GLS in patients undergoing trastuzumab has demonstrated superior predictive value for future cardiotoxicity compared with changes in LVEF.[6,14,21] Abnormal GLS has been consistently shown to precede diagnostic LVEF reductions by about 3 months in adjuvant trastuzumab treatment, which may provide a window of opportunity to initiate cardioprotective therapy and prevent discontinuation of potentially life-saving anticancer treatment.[3]

Accordingly, we found a significant decrease of systolic function in every group of chemotherapy, as per the well-known effects of anthracyclines-based chemotherapy. Interestingly, the FEC-Tax Group showed an earlier reduction of EF already at T_3, not observed in other types of treatment, and the worst GLS value compared to the other groups at T_6. Altogether these data seem to identify FEC-Tax treatment as likely the more cardiotoxic. On the other hand, as previously shown, fluorouracil itself may induce direct myocardial injury and impair oxygen delivery, probably leading to more serious cardiotoxicity in treated patients. However, we are not able to determine whether the early GLS reduction in this chemotherapy regimen is dependent on the action of fluorouracil alone or, more likely, it is the effect of its combination with epirubicin and cyclophosphamide. Anyway, this group of patients may need to be closely monitoring to prevent HF.

Of note, the addition of trastuzumab to conventional chemotherapy did not impact on EF at follow-up, while it induced a further and persistent worsening of GLS until T_{12}, confirming the cardiotoxic role of trastuzumab beyond anthracyclines[22] and the incremental value of GLS beyond EF.

In order to investigate for a possible regional pattern of anthracyclines-mediated myocardial damage, we analysed the bull's eyes at basal and at the peak of GLS reduction, comparing the values of each LV 17 segments. Even if all myocardial segments showed a significant reduction of longitudinal strain, we observed that the anterior septum and the apex showed the greatest impairment (mean 'delta' strain ≥4%). In patients receiving anthracyclines, regional wall motion abnormalities involving in particular the apical segments, have long been recognized.[23] Poterucha et al.[4] found that changes of LV longitudinal strain in mid and apical segments were moderately predictive of decreased LVEF and that changes in LV segmental longitudinal strain in the apical cap were correlated with cumulative anthracyclines doses. Similarly, previous studies also observed a significant reduction of longitudinal strain involving the interventricular septum.[24] The explanation for this regional pattern is currently unclear, but shear stress forces acting differently in relation to LV geometry, as well as increased exposure to anthracyclines of regions of terminal circulation, or the differential local activation of signal transduction pathways of fibrosis or apoptosis, can be hypothesized as underlying mechanisms. However, the pattern of myocardial damage that we have shown could not reflect what usually occurs after anthracyclines exposure and could be affected by loading conditions (anaemia, hypovolaemia, etc.) as well as multidrug treatments. Nonetheless, while these findings need confirmation in further studies, our data highlight that it is crucial not only to consider global function (GLS) but also to look carefully at the polar map of deformation which is a faithful representation of the site as well as the extent of the heart damage.

Limitations and Conclusions

Our multicentre prospective study is limited by the relatively small sample size that could have partially affected our results. As all patients enrolled in our study underwent anthracyclines, we cannot evaluate the independent cardiotoxic effect of each additional drug (i.e. fluorouracil, cyclophosphamide, taxanes, trastuzumab, etc.) included in the different treatments beyond anthracyclines. Moreover, at the moment we are unable to demonstrate whether regional and global reductions of LS are predictive of late cardiac dysfunction because a long-term data are not available. However, a long-term follow-up is ongoing.

Lastly, the cardiotoxic effect of radiotherapy was not investigated due to the differences existing in timing and total cumulative dosage among patients. On the other hand, radiation-induced cardiac damage may occur several years (>5 years) after irradiation.[25] A long-term follow-up to investigate both the prevalence of radiotherapy-related cardiac damage is ongoing too.
In conclusion, we confirm that GLS is more sensitive than conventional echocardiography in early detection of anthracyclines-cardiotoxicity, and is able to discriminate different degrees of cardiotoxicity among several anthracycline-based regimens, as shown in patients treated with FEC-Tax or trastuzumab. Finally, segmental changes involving the anterior septum and the apex could represent a regional model of cardiotoxicity that might be typically induced by anthracyclines, thus supporting the need for implementing a more detailed echocardiographic analysis focused not only on EF and GLS but also on the regional strain.[26]

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Table 1.

Demographic and clinical baseline data of the study population

Variables	**Patients (n = 146)**
Age (years)	56 ± 11
Female, n (%)	144 (98.6)
Invasive ductal carcinoma, n (%)	90 (62)
Invasive lobular carcinoma, n (%)	12 (8)
Others histological types, n (%)	44 (30)
Heart rate, bpm	74 ± 13
BSA (m2)	1.7 ± 13
SBP (mmHg)	124 ± 17
DBP (mmHg)	77 ± 11
Arterial hypertension, n (%)	51 (35)
Dyslipidaemia, n (%)	37 (25)
Diabetes mellitus, n (%)	24 (16)
Smoker, n (%)	29 (20)
ACEi/ARB, n (%)	29 (20)
Beta-blockers, n (%)	22 (15)
Diuretics, n (%)	10 (6.8)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2.

Distribution of all patients receiving anthracyclines

Chemotherapy, n (%)	**146 (100%)**
Chemotherapy without trastuzumab	90 (61.6)
Chemotherapy + trastuzumab	56 (38.3)
Chemotherapy groups	
AC/EC, n (%)	30 (20.5)
AC/EC- Tax, n (%)	69 (47.3)
FEC- Tax, n (%)	47 (32.2)
Other agents[a], n (%)	5 (3.4)

AC, doxorubicin + cyclophosphamide; EC, epirubicin + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; Tax, taxanes (docetaxel/paclitaxel).

[a] Capecitabine, Gemcitabine, Carboplatin, Cisplatin, Bevacizumab, Vinorelbine.

Table 3.

Changes of the principal variables during follow-up in overall population

Patients, *n* = 146	**T_0**	**T_3**	**T_6**	**T_{12}**	***P*-value**
SBP (mmHg)	124 ± 17	126 ± 15	127 ± 16	130 ± 18*	*0.03 vs. T_0
DBP (mmHg)	77 ± 11	75 ± 10	76 ± 10	78 ± 11	0.4
HR (b/m′)	74 ± 13	75 ± 10	74 ± 10	*71 ± 12	*0.04 vs. all
Troponin I (ng/mL)	0.01 ± 0.008	0.03 ± 0.03*	0.02 ± 0.01	0.01 ± 0.01	* 0.004 vs. T_0
BNP (pg/mL)	36.9 ± 25	55 ± 32.3*	39.1 ± 22.6	33.5 ± 18.3°	* 0.01 vs. T_0 , °0.04 vs. T_3
LVEF (%)	62 ± 5	60 ± 5*	59 ± 5°	59 ± 4#	*,°,# <0.001 vs. T_0
EDVi (mL/m^2)	43.1 ± 13.4	44 ± 13.2	43.1 ± 12.4	41.1 ± 13.6*	* 0.03 vs. T_3
ESVi (mL/m^2)	17.9 ± 5.2	19.7 ± 5.2*	20.3 ± 5.3°	19.4 ± 5.2	* 0.005 vs. T_0,°<0.001 vs. T_0
WMSI	1 ± 0	1 ± 0	1 ± 0	1 ± 0	
S′ mean (cm/s)	7.7 ± 1.5	7.4 ± 1.8	7.2 ± 1.5*	7.3 ± 1.5°	* <0.001 vs. T_0,°0.002 vs. T_0
LV GLS (%)	−20.8 ± 2.7	−18.7 ± 2.9*	−18.1 ± 2.7°	−18.2 ± 3#	*,°,# <0.001 vs. T_0
LAVi (mL/m^2)	29.5 ± 9.4	28.9 ± 7.8	28.4 ± 8.3	28.2 ± 8.3	0.3
E/*A*	1.04 ± 0.42	1.05 ± 0.42	1.03 ± 0.39	1 ± 0.38	0.06
E/*E*′	8 ± 2.8	8 ± 2.3	8.3 ± 2.3	8.3 ± 2.7	0.1
TAPSE (mm)	23 ± 4	23 ± 4	22 ± 4	24 ± 4*	* 0.001 vs. T_3
s-PAP (mmHg)	27 ± 7	28 ± 8	27 ± 7	28 ± 5	0.9

BNP, brain natriuretic peptide; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; GLS, global longitudinal strain; HR, heart rate; LAVi, left atrial volume indexed; LV, left ventricle; LVEF, left ventricle ejection fraction; s-PAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score.

Table 4.

LVEF and GLS changes up to 6 months in overall population according to the type of chemotherapy

Chemotherapy	T_0	T_3	T_6	
LVEF (%)				
AC/EC	63 ± 3	63 ± 6	61 ± 1	NS
AC/EC-Tax	62 ± 6	60 ± 6	59 ± 7*	*0.003 vs. T_0
FEC-Tax	63 ± 5	60 ± 5*	58 ± 5§	*0.04 vs. T_0, §0.001 vs. T_0
LV GLS (%)				
AC/EC	−22.5 ± 0.1	−19.2 ± 0.4*	−18.5 ± 0.9§	* 0.002 vs. T_0, § <0.001 vs. T_0
AC/EC-Tax	−20.7 ± 3.2	−18.5 ± 3.5*	−18.2 ± 2.9§	*0.001 vs. T_0, §<0.001 vs. T_0
FEC-Tax	−20.7 ± 2.2	−19 ± 2.2*	−17.8 ± 2.7§°	*0.01 vs. T_0, §<0.001 vs. T_0, °0.02 vs. T_3

Table 5.

LVEF and GLS changes during follow-up in patients underwent chemotherapy with (n = 56) and without (n = 90) trastuzumab

	T_0	T_3	T_6	T_{12}	*P*-value
LVEF (%)					
CT without TRZ, *n* = 90	62 ± 5	60.5 ± 5.3	59.3 ± 5.3*	60.2 ± 4.7	*0.005 vs. T_0
CT +TRZ, *n* = 56	63 ± 5.3	60.5 ± 6.2	59 ± 5.2*	60 ± 4.4°	*0.027 vs. T_0, °<0.001 vs. T_0
LV GLS (%)					
CT without TRZ, *n* = 90	−21.3 ± 3.2	−18.9 ± 3.8*	−18 ± 2.9°	−18.5 ± 3.6§	*0.03 vs. T_0; °<0.001 vs. T_0; §0.003 vs. T_0
CT + TRZ, *n* = 56	−20.8 ± 2.5	−18.3 ± 1.7*	−18.5 ± 2.3§	−17.7 ± 2.1°	*0.001 vs. T_0, §0.001; vs. T_0, °0.031 vs. T_0

CT, chemotherapy; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction; TRZ, trastuzumab.
Infusion of TRZ started on average at 6 months after anthracyclines infusion and continued for 1 year. For further explanation see the text.

Table 6.

LVEF and GLS changes in each group of chemotherapy according to the addition of trastuzumab at T_6

	Start anthracyclines		*Start trastuzumab*				
	T_0		**T_6**		**T_{12}**		
	TRZ YES	**TRZ NO**	**TRZ YES**	**TRZ NO**	**TRZ YES**	**TRZ NO**	
LVEF (%)							
AC/EC		63 ± 3		61 ± 1		61 ± 2	ns
AC/EC-Tax	61 ± 5	63 ± 7	59 ± 5	58.5 ± 6	59 ± 4	60.4 ± 5	ns
FEC-Tax	66 ± 3	63 ± 5	58 ± 7	60 ± 6	60 ± 5	61 ± 3	ns
GLS (%)							
AC/EC		−22.5 ± 0.1		−18.5 ± 0.9§		−18.2 ± 3*	§*<0.001 vs. T_0
AC/EC-Tax	−20.5 ± 3.5	−21.4 ± 2.4	−18 ± 3.7§	−18.3 ± 3°	−17.9 ± 3*	−19.1 ± 3	* < 0.001 vs T_0 , § 0.02 vs. T_0, ° 0.002 vs T_0
FEC-Tax	−20.2 ± 0.9	20.8 ± 2.3	−16 ± 1	−18 ± 2.8	−14.7 ± 1*	−17.7 ± 2.9	*<0.001 vs. T_0

For abbreviations see Tables 2-3.

Table 7.

Mean values of segmental longitudinal strain and delta (Δ) strain between steps in pts with a GLS drop ≥15% during follow-up

	Before chemotherapy	**Follow-up**	***P*-value**	**Difference between steps**

				(Δ-strain)
Basal segments				
Inferoseptal	−16.5 ± 2.5	−15.8 ± 2.4	<0.001	0.9 ± 0.3
Anteroseptal	−19.2 ± 2.9	−14.5 ± 2.6	<0.001	4.8 ± 1.7
Anterior	−19.8 ± 3.5	−16.6 ± 3.1	<0.001	3 ± 1.2
Anterolateral	−19.3 ± 3.1	−17.3 ± 3.4	0.001	2.1 ± 1.3
Inferolateral	−19.6 ± 3.3	−17.8 ± 3.9	0.015	1.7 ± 0.7
Inferior	−20.6 ± 3.5	−18.3 ± 2.9	0.015	2.5 ± 1.3
Mid-segments				
Inferoseptal	−19.5 ± 2.7	−18.6 ± 1.9	0.005	0.8 ± 0.3
Anteroseptal	−18.1 ± 3.6	−14.2 ± 2.6	0.004	5.1 ± 1.4
Anterior	−17.9 ± 3.1	−15.3 ± 2.5	0.017	2.5 ± 1.4
Anterolateral	−18.5 ± 3.7	−15 ± 3.5	<0.001	3.7 ± 1.4
Inferolateral	−18.6 ± 2.7	−18 ± 2.3	0.009	0.6 ± 0.4
Inferior	−21.4 ± 3.7	−17.1 ± 3.6	<0.001	3.5 ± 1.3
Apical segments				
Septal	−20 ± 2.1	−15.9 ± 1.8	0.026	4.1 ± 1
Anterior	−19 ± 3.3	−14.3 ± 2.5	0.005	5.6 ± 1.2
Lateral	−20.7 ± 2.3	−17.3 ± 2.5	<0.001	3.3 ± 1.2
Inferior	−22.5 ± 3.8	−17.7 ± 3.6	<0.001	4.9 ± 1.5
Apical cap	−22.5 ± 2.2	−17.7 ± 2.6	0.001	4.9 ± 1.3

Figure 1.

Design of the study.

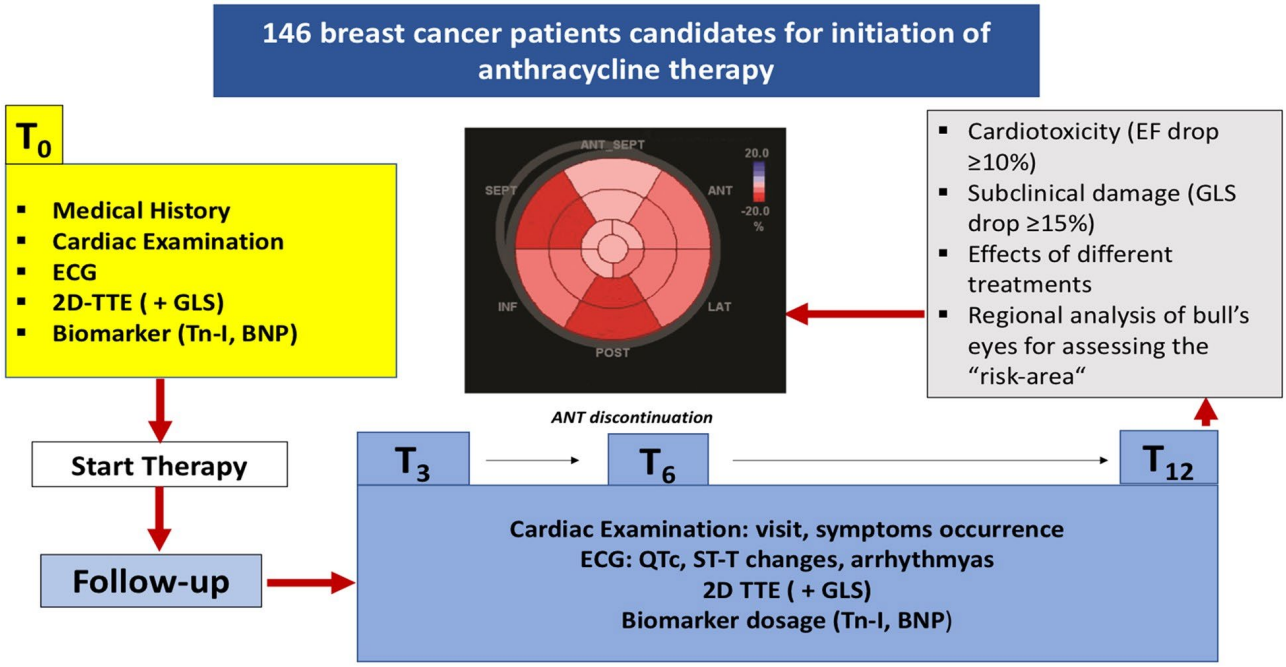


Figure 2.

Changes of LVEF (A) and GLS (B) from baseline until 1 year according to the type of chemotherapy and the addition of trastuzumab at T_6. At 12 months, there was a no significant decrease of LVEF in each protocol, whether or not trastuzumab was administered. (B). In all groups, GLS decreased over time, with a greater extent at 12 months ($P < 0.001$ vs. baseline), with the only exception of the patients who underwent AC/EC – Tax without trastuzumab showing the worst GLS value at 6 months ($P = 0.002$ vs. baseline). See Tables 2-3 for abbreviations.

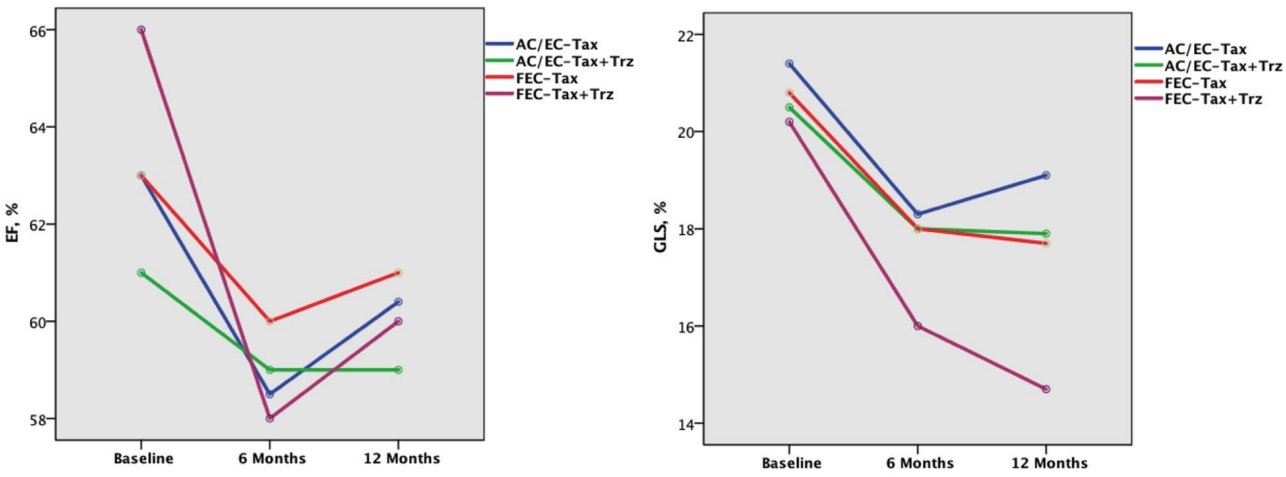


Figure 3.

Changes of LVEF (A) and GLS (B) from baseline until 1 year in patients treated only with chemotherapy (blue line) and in those receiving also trastuzumab (green line). The significant drop of both LVEF (A) and GLS (B) from baseline (before starting chemotherapy) to 6 months is due to cardiotoxicity from anthracyclines. At 6 months 56 patients start trastuzumab, however, LVEF (A) is unable to identify the reduction of systolic function 6 months later in these patients. Conversely, GLS (B) reveals that at 12 months patients receiving only chemotherapy moved towards a recovery from myocardial injury (blue line), while those receiving also trastuzumab (green line) had a further decrease of systolic function. See Table 5 for P-values. Trast, trastuzumab.

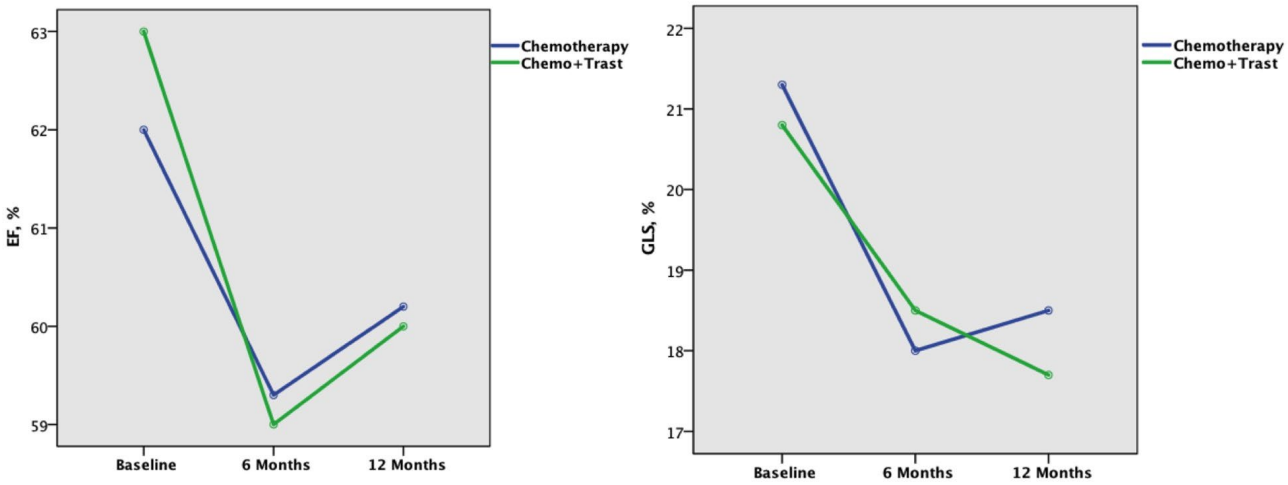
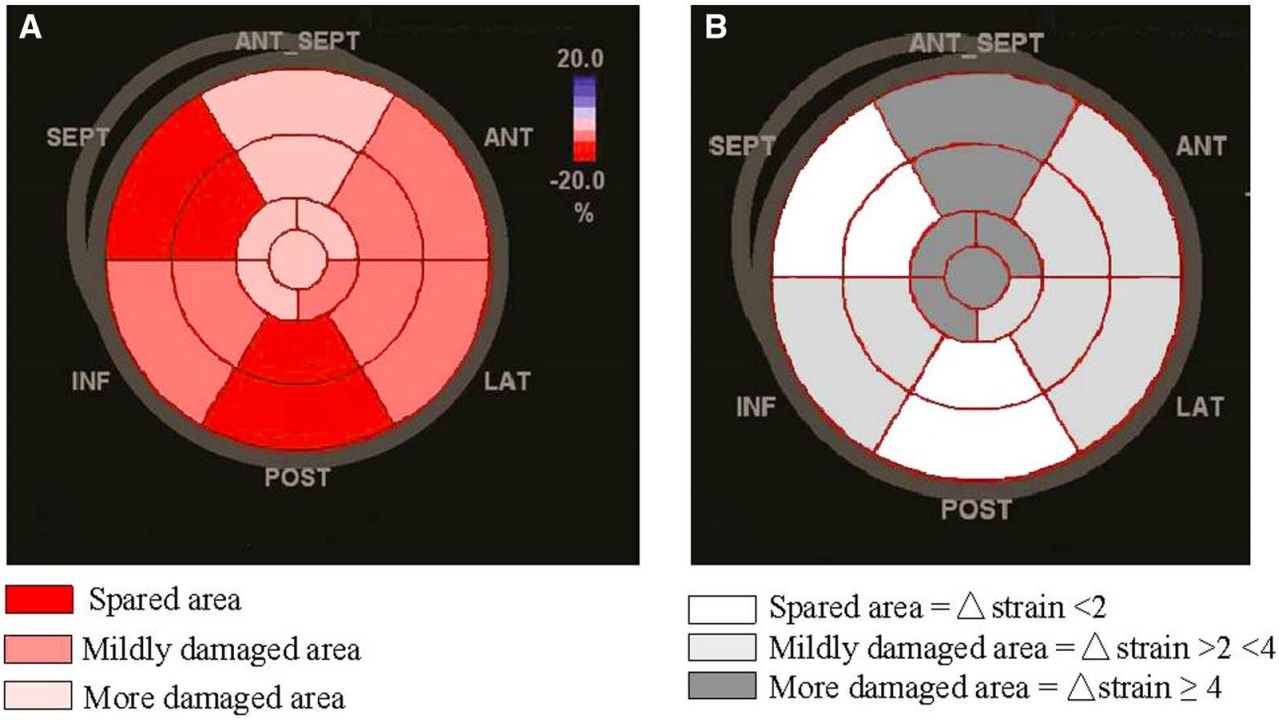


Figure 4.

Pattern of anthracyclines mediated regional myocardial damage by speckle-tracking echocardiography shown in A by mean values of longitudinal strain (%) and in B by delta strain (%). Apex and anterior septum (pink segments in A; dark-grey segments in B) show the greater impairment.



SUPPLEMENTARY METHODS

Cancer therapy regimens and cardiotoxicity monitoring

Patients were divided in 3 groups for evaluating cardiotoxicity related to each type of treatment (Table 2):

1. *AC/EC Group* including patients underwent 4 to 6 cycles doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2, per cycle;
2. *AC/EC-Tax Group* including patients underwent 4 or 6 cycles of doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2, per cycle followed by docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly for 12 weeks
3. *FEC-Tax Group* including patients underwent 3 to 6 cycles of fluorouracil 500 mg/m^2 + epirubicin 75 mg/m^2 + cyclophosphamide 500 mg/m^2, per cycle followed in the most of patients by docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly for 12 weeks

Trastuzumab (8 mg/m^2 as starting dose followed by 6mg/m^2 every 3 weeks for the following 12 months) was used only in Human Epidermal Growth Factor-2 (HER-2) positive patients with an inter-cycle interval of 21 days after anthracyclines infusion, as current standard of care. To assess cardiotoxicity from trastuzumab we compared EF and GLS values at T_6 (before starting trastuzumab) with those at T_{12} (ongoing trastuzumab), respectively for both parameters.

In the few advanced settings, beyond anthracyclines and taxanes, other antineoplastic agents were used in monotherapy or in combination regimens, including carboplatin, cisplatin, methotrexate, bevacizumab, vinorelbine and capecitabine. Pertuzumab (initial loading dose of 840 mg, followed by a maintenance dose of 420 mg) was used as first-line treatment in combination with trastuzumab and docetaxel, in HER-2 positive metastatic or unresectable breast cancer.

Each treatment was administered until disease progression or unacceptable toxicity, taking into consideration the maximum cumulative dose for anthracyclines. For hormone-receptors positive

patients, endocrine therapy, mainly including tamoxifen and aromatase inhibitors, was administered according to menopausal status.

Radiotherapy on breast, or chest wall, and regional nodes, was also administered in candidate patients after chemotherapy based on current guidelines indications

Two-dimensional transthoracic echocardiography before and during treatment

The LV end-diastolic and end-systolic volumes were measured and indexed to body surface area, and LVEF was calculated using biplane Simpson method (1): a ≥10% drop in LVEF between pre and post chemotherapy was considered as cut-off to define cardiotoxicity. LV segmental kinesis was also evaluated and wall motion score index (WMSI) calculated at each step. Indexed left atrium (LA) biplane volumes were measured and mitral flow peak early (E), late (A) diastolic filling velocities and E/A ratio were obtained as markers of diastolic function. In addition, spectral tissue Doppler imaging was used to obtain peak systolic and peak early diastolic mitral annulus velocity (S' and E', respectively) and E/E' ratio was derived. The systolic pulmonary artery pressure (s-PAP) was obtained through tricuspid regurgitation, and right atrial pressure was added when appropriate.

Analysis of 2D strain was performed offline through the automated function imaging, using semiautomatic tracking on high frame rate (>50 frames/s) apical views (four, two, and three chambers), previously transferred to an Echo-Pac workstation (V.202, GE). Adequate tracking was verified and was manually corrected if necessary. Segmental LV myocardial strain was assessed in 17 segments (six basal, six mid, and five apical segments, including the apical cap) according to the American Society of Echocardiography's 17- segment standardized myocardial echocardiographic nomenclature.(1) The LV GLS bull's eye map was derived and GLS mean values were calculated at each step (T_0, T_3, T_6, T_{12}). A relative reduction of ≥15% in GLS values between pre- and post-

chemotherapy was considered clinically significant for defining cardiac damage, according to current recommendations.(2)

As previously described, we particularly focused on LVEF and GLS changes that were analysed at each step both in overall population and in the three groups divided per received treatment, in order to identify the most cardiotoxic chemotherapy.

Furthermore, an additional analysis of LVEF and GLS changes from T_6 to T_{12} was performed in patients treated compared to those untreated with trastuzumab to evaluate the additive role of this monoclonal antibody in myocardial function impairment.

SUPPLEMENTARY RESULTS

Baseline characteristics

Recruited patients showed different stages of cancer disease with no BC recurrence.

Cardiovascular risk profile was on average low to moderate(3). Indeed, mean blood pressure (BP) and heart rate (HR) were normal, only 20% were smokers and arterial hypertension was the most prevalent risk factor (35%). A few patients were affected by diabetes (16%) and dyslipidaemia (25%). In addition, they were all asymptomatic for dyspnoea, angina or syncope and no one showed arrythmias or signs heart failure at baseline clinical examination. The ECGs were unremarkable in all patients with a normal QTc mean value. Further, 20% were already treated with angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE_i/ARBs) and 15% with beta-blockers.

All 146 (100%) patients received anthracyclines combined with further agents with the following distribution, as listed in Table 2: 30 patients (20.5%) received AC or EC (*AC/EC Group*), 69 patients (47.3%) received AC or EC followed by taxanes (*AC/EC-Tax Group)* and 47 patients (32.2%) received FEC followed by taxanes (*FEC-Tax Group).* In the majority of patients treated with taxanes

(102/116, 88%) this therapy was started at the end of anthracyclines (from 4 to 6 months according to the duration of anthracyclines treatment).

Furthermore, of the total population, 38.3% (56/146) HER-2 receptors positive patients were treated with trastuzumab immediately after chemotherapy, whereas 61.6% (90/146) were not candidates for such adjuvant therapy (Table 1). Only 5/146 (3.4%) patients received pertuzumab. Moreover, in 5/146 patients (3.4%) other chemotherapeutic agents (carboplatin, cisplatin, bevacizumab, vinorelbine, gemcitabine, capecitabine) were further added in combination therapy because of a more advanced stage of the disease.

The majority of patients (80%) were also scheduled to go on with endocrine therapy for an average of five years. Finally, 70.5% of patients (103/146) were scheduled for receiving radiotherapy on breast or chest wall and regional nodes according to standard indication and protocols after chemotherapy.(4)

SUPPLEMENTARY TABLES

Supplementary Table. 1

Intra-observer variability		
	Mean±SD (Bland Altman)	**Intraclass Correlation (ICC)**
Basal segments		
Inferoseptal	-1.1±0.2	0.901
Anteroseptal	-0.9±0.1	0.904
Anterior	-1.3±0.2	0.889
Anterolateral	-1.3±0.3	0.884
Inferolateral	-0.7±0.1	0.908
Inferior	-0.9±0.2	0.903
Mid segments		
Inferoseptal	-1.1±0.2	0.897
Anteroseptal	-0.8±0.1	0.911
Anterior	-1.2±0.3	0.898
Anterolateral	-1.1±0.3	0.902
Inferolateral	-0.9±0.2	0.903
Inferior	-0.8±0.2	0.912
Apical segments		
Septal	-1.2±0.3	0.890
Anterior	-1.3±0.4	0.881
Lateral	-1.1±0.3	0.900
Inferior	-1.1±0.2	0.903
Apical cap	-1.2±0.3	0.896

Supplementary Table. 2

Inter-observer variability		
	Mean±SD (Bland Altman)	**Intraclass Correlation (ICC)**
Basal segments		
Inferoseptal	-1.5±0.4	0.857
Anteroseptal	-1.2±0.3	0.883
Anterior	-1.6±0.4	0.846
Anterolateral	-1.5±0.4	0.860
Inferolateral	-1.0±0.3	0.905
Inferior	-1.1±0.5	0.902
Mid segments		
Inferoseptal	-1.4±0.4	0.869
Anteroseptal	-1.1±0.2	0.908
Anterior	-1.5±0.5	0.859
Anterolateral	-1.4±0.5	0.867
Inferolateral	-1.3±0.4	0.882
Inferior	-1.1±0.4	0.904
Apical segments		
Septal	-1.6±0.3	0.848
Anterior	-1.6±0.4	0.845
Lateral	-1.4±0.4	0.864
Inferior	-1.5±0.3	0.861
Apical cap	-1.7±0.2	0.840

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