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Role of Speckle Tracking Echocardiography in the Evaluation of Breast Cancer Patients Undergoing Chemotherapy: Review and Meta-analysis of the Literature

Corinna Bergamini[1] · Giulia Dolci[1] · Stella Truong[1] · Luisa Zanolla[1] · Giovanni Benfari[1] · Elena Fiorio[2] · Andrea Rossi[1] · Flavio Luciano Ribichini[1]

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Abstract
Diagnosis and management of Cancer therapeutics-related cardiac dysfunction is of crucial importance in breast cancer (BC) patients. The role of advanced echocardiographic techniques, such as deformation imaging, in the diagnosis and characterization of patients receiving cancer therapy has so far involved relatively small studies in the research setting. Therefore, we conducted a meta-analysis and systematic review of observational studies evaluating myocardial changes during chemotherapy detected through conventional echocardiographic parameters, such as 2D left ventricular ejection fraction (2D LVEF), and 2D Speckle tracking echocardiography (STE). The literature search retrieved 487 research works, articles, of which 17 were found to be pertinent with this topic. After full article review, 16 studies were considered suitable for the present analysis. Two separate analyses, one for the anthracyclines-based therapeutic regimen and one for the trastuzumab based therapeutic regimen, were performed. A significant reduction in 2D LVEF and 2D STE parameters during cancer therapy was found in both the investigations. Peak systolic global longitudinal strain demonstrated to be the most consistent 2D STE parameter in detecting early myocardial changes among all the studies. Thus, we confirmed the role of 2D STE for the early detection of myocardial damage, suggesting its crucial role in monitoring BC patients and eventually driving the introduction of cardioprotective treatment.

Keywords Breast cancer · Cardiotoxicity · LVEF · Speckle tracking echocardiography

Introduction

Thanks to the new anticancer therapies, breast cancer (BC) is now considered a treatable disorder in a significant proportion of patients [1]. However, cardiotoxicity due to such treatments, also known as cancer therapeutics-related cardiac dysfunction (CTRCD) has become a relevant cause of morbidity and mortality not only during the treatment period but also life-long for the survivors [2]. The combination of potential cardiotoxic chemotherapy with molecular targeted therapy, such as trastuzumab, increases the magnitude of this problem [3]. In common practice, resting left ventricular ejection fraction (LVEF) determined by echocardiography is widely used to identify CTRCD; however, the reduction in LVEF mainly detects overt left ventricular (LV) dysfunction, when it might be too late to reverse the clinical course of the ongoing changes, suggesting the need for more sensitive parameters for the early detection of cardiac damage [4]. Of note, myocardial function can greatly vary without changing LVEF [5], therefore evidences in support of the use of 2D speckle tracking echocardiography (2D STE) as a promising tool in the early detection of LV function changes, are accumulating. Indeed, recent studies have shown that LV global longitudinal strain (GLS) by 2D STE is able to accurately

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✉ Corinna Bergamini
corinnabergamini@gmail.com

[1] Division of Cardiology, Department of Medicine, University of Verona, P.le Stefani 1, 37126 Verona, Italy

[2] Division of Oncology, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

predict a subsequent decrease in LVEF secondary to cancer therapy [6, 7]. Nonetheless, the use of this advanced echocardiographic measurement is still limited to laboratories with adequate expertise performing cardiac safety studies. Other 2D STE derived strain parameters, such as LV global radial strain (GRS) and LV global circumferential strain (GCS) still have a controversial and not fully established role because of the limited amount of data [7]. Thus the aim of this review and meta-analysis of the literature is two-fold: (1) to describe the prevalence of CTRCD in BC patients treated with chemotherapy; (2) to summarize the existing data about detection of early myocardial changes during cancer therapy through 2D STE parameters in the longitudinal, radial, and circumferential planes of the LV walls.

Methods

Search Strategy

An English-language literature review was performed through PubMed, Scopus, and Science Direct for any study evaluating the changes in 2D LVEF and 2D STE parameters in BC patients treated with anthracyclines and/or trastuzumab. Words employed in the search were: 'echocardiography', combined with 'breast cancer', 'cardiotoxicity', and 'cardiac toxicity'. Reference lists of obtained articles were checked to retrieve any relevant study on this issue. Unpublished data, data reported in abstract only and studies including < 10 patients were excluded from this analysis. Both prospective and retrospective studies published in English language as full-length articles reporting on 2D LVEF and 2D STE derived parameters changes during BC therapy with anthracyclines and/or trastuzumab were included.

Data Extraction

The authors retrieved data on the study design, study period, study size, prevalence of cardiac toxicity, cancer therapy schedule, patient demographics, and clinical and echocardiographic data. Changes in myocardial indexes observed respectively during anthracycline and trastuzumab treatment were reported separately, even in the case of subsequential treatment. The primary outcome of interest was a significant reduction in 2D LVEF, 2D GLS, 2D GRS, 2D GCS from baseline values. No attempt was made to get missing data from the authors. Any disagreement was solved by consensus of the coauthors. Study quality was assessed by the Newcastle–Ottawa criteria. This study was not financially supported.

Statistical Analysis

Continuous variables are presented as mean ± 1 standard deviation, while categorical variables are reported as proportion and 95% confidence interval (95% CI). Meta-analysis was performed using Stata/IC 14 for Windows (Stata Corp—4905 Lakeway Drive—College Station, Texas 77845 USA). Heterogeneity among trials was assessed by Cochran's Q test for heterogeneity, and by Higgins I^2. Due to the high heterogeneity of most of the variables, a random effects model was applied (DerSimonian–Laird). The effect size is reported as weighted mean difference (WMD) and 95% confidence interval. Pooled overall cardiotoxicity rates were estimated as a meta-analysis of binary data using a random-effect model. A $p < 0.05$ was considered statistically significant.

Results

The literature search yielded 487 research articles, of which 17 were found to be pertinent with this topic (Fig. 1) [6, 8–24]. After full article review, 16 studies were considered for the present analysis [8–19, 21–24]. Three of these articles were included in the anthracyclines as well as in the trastuzumab subgroups analysis [9, 16, 24]. Thirteen studies were focused on the evaluation of clinical and/or subclinical myocardial damage after anthracycline-based chemotherapy. Data extracted

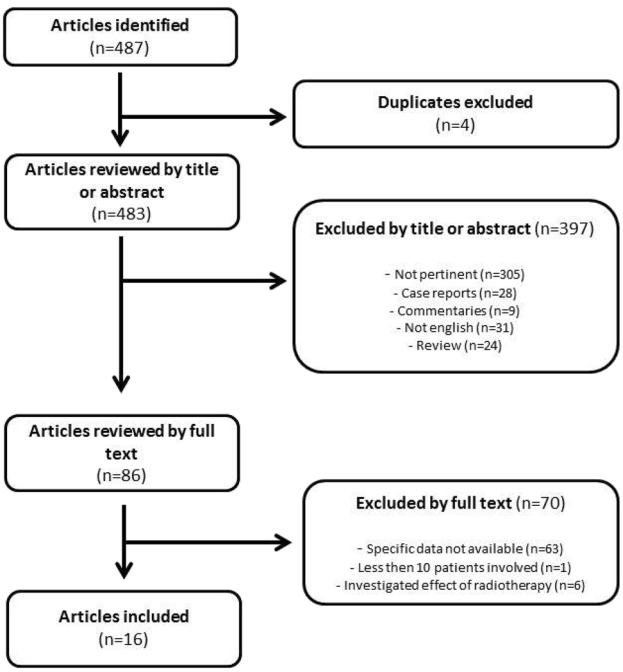

Fig. 1 Flow chart of the involved studies

by a comprehensive echocardiographic exam performed prior and after chemotherapy, with different time intervals between the two echo-evaluations among the studies, were analyzed [8–11, 13, 14, 16, 17, 19, 21–24]. Likewise, six studies investigating patients with serial echocardiographic exams performed every 3 months while on trastuzumab therapy, mainly for a 12 months follow-up or in some cases for a 6 months follow-up, were suitable for the analysis [9, 12, 15, 16, 18, 24].

Overall, 1146 patients were included in the final analysis. Among these, 166 patients (15%) were eventually diagnosed with CTRCD and the diagnosis was established by transthoracic echocardiography. The estimated proportion prevalence of cardiotoxicity was 10% (95% CI 3–21%, $I^2 = 92.8\%$ 10 studies, 91 out of 913 patients) in subjects treated with anthracyclines and 25% (95% CI 1.8–32%, $I^2 = 50.3\%$ 5 studies, 75 out of 284 patients) in subjects included in the trastuzumab subgroup studies.

The included studies were predominantly prospective and single-center cohort studies focused on BC and hematological malignancies (Supplementary files 1 and 2). Demographic and clinical information regarding cardiovascular risk profile of each study population are presented in Table 1. Mean age ranged between 47 and 56 years old and mean 2D LVEF pre-chemotherapy was between 58.6 and 67%.

Anthracycline-Based Chemotherapy Studies

A total of 800 patients (range 27–140) were included in twelve studies investigating and reporting changes in 2D LVEF after anthracyclines-based therapy compared to baseline. Mean LVEF values ranged between 58.6 and 67.0% pre-anthracyclines and between 54.0 and 64.2% post-anthracyclines.

Overall, pooled analysis indicated that mean 2D LVEF decreased significantly after the conclusion of anthracyclines-based chemotherapy with −2.48% WMD (95% CI −3.76 to −1.20%; $p < 0.001$) using a random-effect model (Fig. 2, Panel a). There was a remarkable heterogeneity among studies ($I^2 = 89.5$; $\chi^2 = 104.7$—$p < 0.001$).

A total of 835 patients (range 27–140) were selected from 13 studies evaluating 2D STE variations during chemotherapy. Mean 2D GLS values ranged between −23.1 and −16.5% pre therapy and between −21.8 and −16.0% post therapy. Pooled analysis showed that after chemotherapy a significant reduction in 2D GLS occurred with 1.57% WMD (95% CI 1.07 to 2.07%; $p < 0.001$, Fig. 2, Panel b) and considerable heterogeneity among studies ($I^2 = 74.2\%$; $\chi^2 = 46.6$—$p < 0.001$). Concerning 2D GRS and 2D GCS a total of 444 patients (range 40–140) enrolled in 6 studies were evaluated. They were found to be both significantly altered after chemotherapy (2.33% WMD, 95% CI 4.21 to 0.44%; $p = 0.016$, Panel c Fig. 2; and 0.91% WMD; CI 95% 0.14 to 1.67%; $p = 0.020$, Panel d Fig. 2, respectively).

Table 1 Summary of the clinical data and 2D LVEF reported in the included studies

Study	Age (years)	Female (%)	Hypertension (%)	Diabetes mellitus (%)	Hyperlipidemia (%)	Smokers (%)	2D LVEF (%)
Florescu et al. [14]	51 ± 8	40 (100)	0	0	5 (12.5)	11 (28)	60 ± 4
Stoodley et al. [21]	49 ± 9	52 (100)	13 (25)	2 (4)	11 (21)	13 (25)	58.6 ± 2.6
Tang et al. [22]	49 ± 8	86 (100)	11 (13)	5 (6)	16 (19)	8 (9)	64.99 ± 6.36
Cheng et al. [10]	50 ± 11	41 (100)	11 (27)	0	8 (20)	5 (12)	64 ± 6
Santoro et al. [19]	48.6 ± 11.1	100 (100)	/	/	/	/	62.6 ± 3.9
Toufan et al. [23]	46.6 ± 10.3	63 (100)	14 (22)	7 (11)	/	0	59.7 ± 6.5
Boyd et al. [8]	52 ± 9	140 (100)	31 (22)	8 (6)	26 (19)	36 (26)	60 ± 3
Sawaya et al. [6]	50 ± 10	81 (100)	26 (32)	1 (4)	18 (22)	6 (7)	64 ± 5
Lange et al. [16]	56	27 (100)	/	/	/	/	66.19 ± 7.79
Mele et al. [17]	53 ± 11	29 (97%)	9 (30)	2 (7)	9 (30)	6 (20)	63 ± 3
Cadeddu et al. [9]	51,4 ± 9.1	45 (100)	0	0	11 (24)	8 (18)	62.8 ± 2
Fei et al. [13]	46 ± 6	19 (100)	/	/	/	/	67 ± 4
Dogru et al. [11]	49 ± 10	35 (100)	14 (40)	1 (3)	5 (14)	0	/
Negishi et al. [18]	50 ± 11	81 (100)	17 (21)	6 (7)	13 (16)	12 (15)	62.3 ± 3.6
Fallah-Rad et al. [12]	47 ± 9	42 (100)	5 (12)	6 (14)	15 (36)	7 (17)	62.4 ± 4.7
Hare et al. [15]	51 ± 8	35 (100)	/	/	/	/	59.6 ± 7.3

Data are presented as mean ± SD or as number (percentages)

LVEF left ventricular ejection fraction

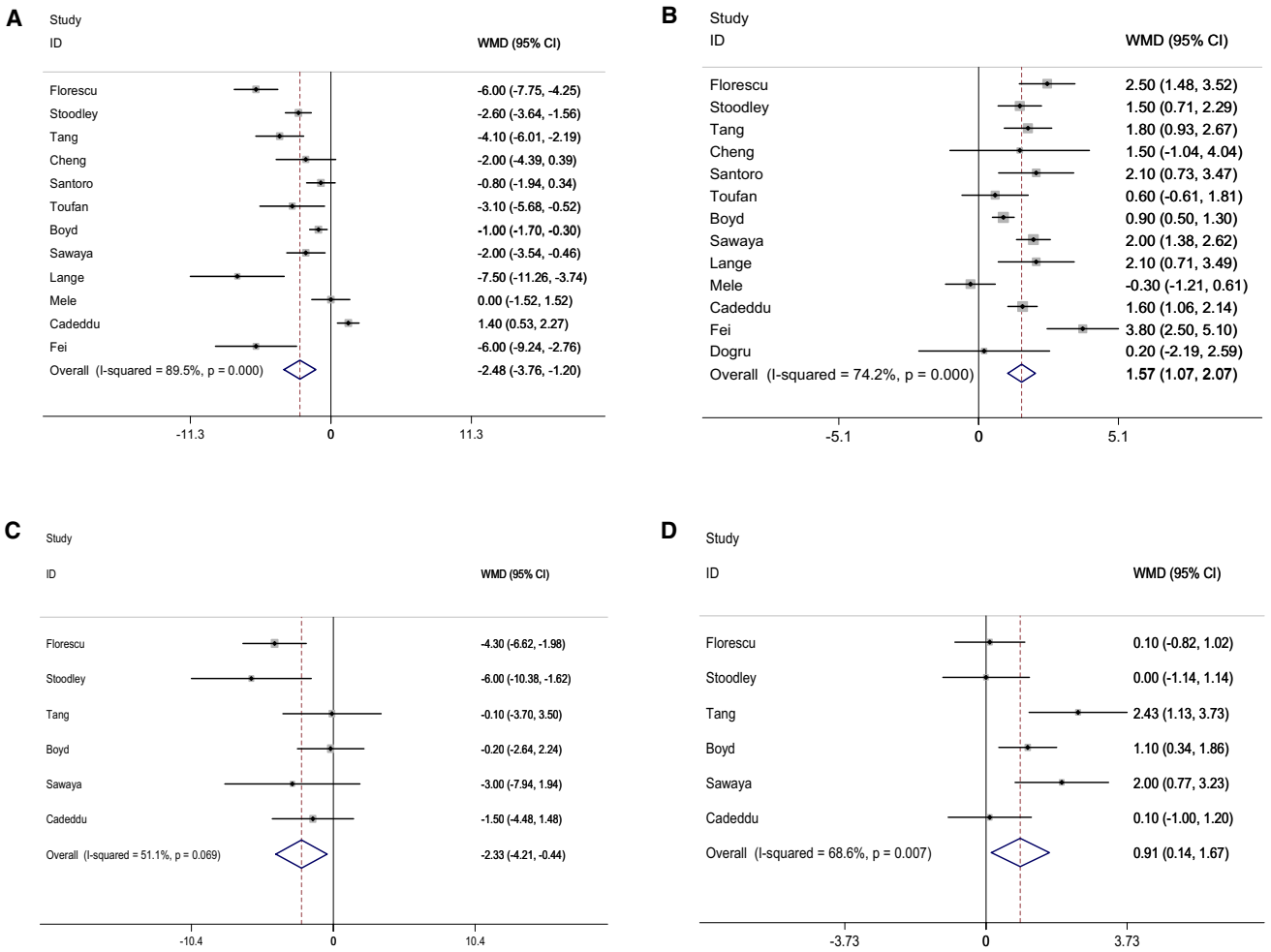

Fig. 2 Forest plot of weighted mean difference (WMD) of the association between LVEF reduction (Panel **a**), 2D GLS (Panel **b**), 2D GRS (Panel **c**), 2D GCS (Panel **d**) and anthracyclines therapy

Trastuzumab Therapy Studies

A total of 311 patients selected from 6 studies analyzing LVEF and 2D STE variations during Trastuzumab treatment were evaluated (range 27–81). Mean 2D LVEF values ranged between 58.7 and 64.2% before trastuzumab administration and ranged between 56.5 and 60.8% 6 months after trastuzumab starting. Pooled analysis indicated that 2D LVEF was significantly lower after 6 months from Trastuzumab therapy introduction than baseline with a 3.38% WMD (95% CI −4.77 to −2.00%, $p < 0.001$) and significant heterogeneity among studies ($I^2 = 90.6\%$; $\chi^2 = 52.98$, $p < 0.001$; Panel a Fig. 3). Five of these 6 studies involving 284 patients, also evaluated the 2D LVEF reduction after 12 months of trastuzumab therapy. A progressive 2D LVEF reduction was demonstrated (4.83 WMD, 95% CI −6.61 to −3.06, $p < 0.001$) with a significant heterogeneity among studies ($I^2 = 81.1\%$; $\chi^2 = 21.13$, $p < 0.001$; Panel b Fig. 3).

Mean 2D GLS values ranged between −20.2 and −16.0% before Trastuzumab administration and between −19.3 and −15.9% 6 months after the beginning of the treatment. A significant decrease in 2D GLS after 6 months of therapy occurred with 0.66 WMD (95% CI 0.33 to 0.99, $p < 0.001$), and some heterogeneity among studies ($I^2 = 51\%$; $\chi^2 = 10.2$, $p = 0.070$; Panel c Fig. 3). Five of the six studies involving 284 patients also considered 2D GLS at 12 months of follow-up; it ranged between −19.1 and −14 to 4%, with the evidence of a significant reduction (0.99 WMD, 95% CI 0.31 to 1.66, $p = 0.004$) and significant heterogeneity among studies ($I^2 = 74.9\%$; $\chi^2 = 15.93$, $p = 0.003$; Panel d Fig. 3). The same five studies assessed 2D GRS; its reduction during therapy was significant at 6 as well as 12 months follow-up (WMD of −5.27, 95% CI −9.13 to −1.42, $p = 0.007$; Panel e Fig. 3; −3.57 WMD, 95% CI −7.04 to −0.09, $p = 0.044$, Panel f Fig. 3; respectively).

Finally, the survey of 2D GCS was performed in 3 studies involving 207 patients; mean 2D GCS 6 months after

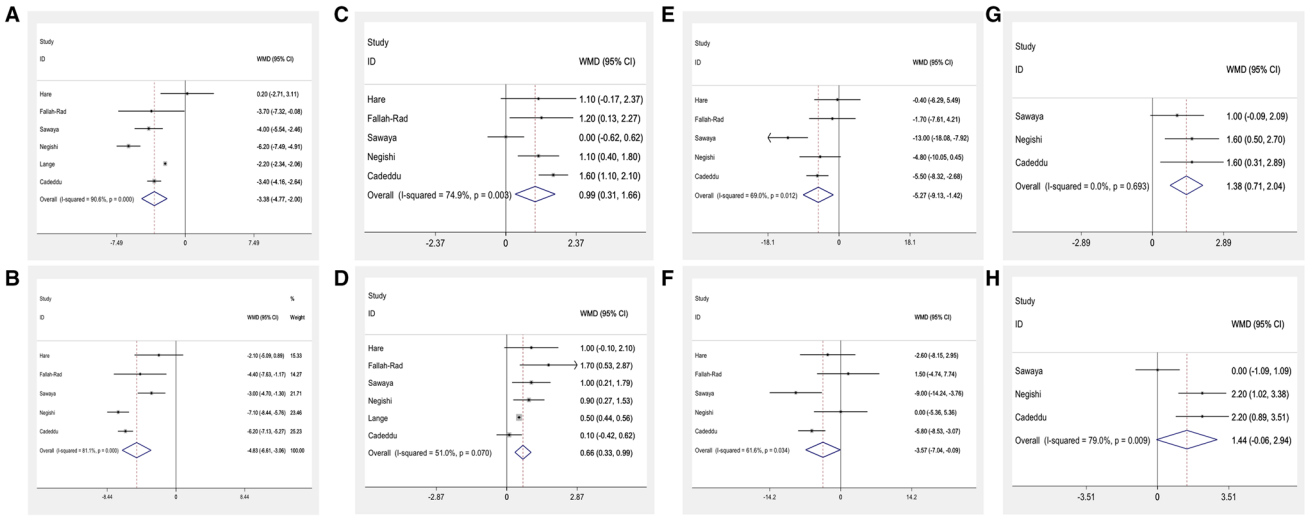

Fig. 3 Forest plot of weighted mean difference (WMD) of the association between 2DLVEF reduction and trastuzumab therapy after a 6 months (Panel **a**) and a 12 months (Panel **b**) follow-up. Forest plot of weighted mean difference (WMD) of the association between 2DGLS reduction and trastuzumab therapy after a 6 months (Panel **c**) and a 12 months (Panel **d**) follow-up. Forest plot of weighted mean difference (WMD) of the association between 2DGRS reduction and trastuzumab therapy after a 6 months (Panel **e**) and a 12 months (Panel **f**) follow-up. Forest plot of weighted mean difference (WMD) of the association between 2DGCS reduction and trastuzumab therapy after a 6 months (Panel **g**) and a 12 months (Panel **h**) follow-up

trastuzumab starting significantly decreased (1.36 WMD, 95% CI 0.71 to 2.04, $p < 0.001$; Panel g Fig. 3) with no significant heterogeneity among studies. At 12 months follow-up a reduction in mean 2D GCS was shown but lacking in statistical significance (1.44 WMD, 95% CI − 0.06 to 2.94, $p = 0.06$), and with significant heterogeneity among studies ($I^2 = 79\%$; $\chi^2 = 9.52$, $p = 0.009$; Panel h Fig. 3).

Discussion

The main results of the present meta-analysis on BC patients undergoing chemotherapy are:

(1) despite heterogeneity across studies the estimated proportion prevalence of cardiotoxicity is significant;
(2) 2D LVEF, the widely used method to define systolic myocardial function and CTRCD, shows a significant decrease during both chemotherapy and trastuzumab, although the magnitude of the variations is of little entity;
(3) the most advanced echocardiographic technique, such as 2D STE, presents significant modifications as well, in particular GLS significantly decreases after both anthracyclines and trastuzumab therapy. The relative greater entity of such variations as respect to 2D LVEF may enhance its usefulness in the detection of subclinical LV dysfunction.

The estimated proportion prevalence of LVEF reduction meeting the definition of CTRCD is in line with the large published registries, where a percentage up to 9% of cardiac dysfunction after anthracycline-based chemotherapy was reported and rates of asymptomatic LVEF decline up to 19% with combined anthracycline and trastuzumab treatment were observed [25, 26].

2D LVEF changes detected after anthracycline-based chemotherapy and during the course of trastuzumab treatment were subtle, as the observed 3–5% variations were of little entity and could be often misdiagnosed during routine clinical practice.

As shown in our analysis, myocardial deformation indexes impairment was detected both after anthracyclines and trastuzumab treatment. Overall, a significant reduction in all the 2D strain derived parameters (GLS, GRS, GCS) after ahthracyclines therapy was found. The studies included in the analysis mostly showed concordant results, with two exceptions: Mele and colleagues who showed an stable 2D GLS after anthracyclines therapy and Dogru et al. who demonstrated a decrease in this parameter in the BC subgroup of patients, although not significant [11, 17]. A consistent reduction of 2D GCS during therapy was found, with the only exception for the work of Stoodley and colleagues [21]. Furthermore, among the trastuzumab subgroup studies, all the tree 2D derived strain parameters were significantly reduced after 6 months of therapy. 2D GLS was the only parameter significantly modified across the studies after 12 months, while, overall, 2D GCS was not significantly reduced. Concerning 2D GRS, the analysis demonstrated

a significant reduction of this parameter, but not all the involved studies showed a coherent result after the same follow-up time.

As cardiac toxicity is more likely to be a slow, progressive, and continuous phenomenon leading to symptomatic heart failure even after several years, early diagnosis and risk stratification of patients is mandatory [25]. 3D echocardiographic volumetric assessment has a demonstrated higher accuracy than 2D LVEF in detecting subclinical changes [27] and also 3D echocardiography derived strain analysis has been shown to be significantly altered after chemotherapy but, the feasibility of these parameters is poor, and significantly limits their routine applicability [19]. As 2D strain analysis has a demonstrated lower or at least comparable intra and inter-observer variability than 2D LVEF [28], a higher sensitivity in detecting LV function subclinical changes [29], and moreover a higher feasibility than 3D echocardiography analysis [19], 2D strain parameters may represent the cornerstone method in cardiac evaluation during cancer therapy.

The present analysis shows early ongoing alterations in myocardial deformations indexes in all the tree planes of the LV wall (longitudinal, circumferential, regional) suggesting that all myocardial layers can be involved in cardiotoxic injury and that, as previously reported [19], the myocardial layers deformations are not independent [30]. Of note, 2D GCS and 2D GRS show a higher variability between studies and are less consistently altered than 2D GLS. This may be explained by the lower reproducibility of these measurements [7], by a lack of uniformity between vendor and by a more complex software analysis. Moreover, the interpretation of radial and circumferential strain is known to be complicated by substantial transmural non-uniformity in the normal LV [31]. Such geometrical effects are of less magnitude for longitudinal strain although a layer-specific strain analysis might increase the diagnostic accuracy. Furthermore the echo-timing may play a role, being the different layers of the myocardial fibers presumably involved with different time-frame in the cardiotoxic process. Indeed, GLS is known to be the first one affected in many physiopathological processes as the majority of longitudinally-oriented fibers lay in the subendocardium, more prone to be damaged as a layer [5]. It has been described that when a reduction in GLS occurs, GCS, which reflects the circumferentially oriented fibers, may compensate in order to preserve the LV pump function [32, 33]. Precisely, this mechanism is still not fully understood, since in several cases a decrease in both GLS and GCS with preserved LVEF was reported [32, 34].

As above mentioned, when a combined therapy of anthracyclines and trastuzumab is administered the incidence of 2D LVEF drop is higher compared to a single drug regimen [26]. According to this statement we found a significant reduction in all the strain parameters when a combined therapy was performed, therefore a synergic effect of the two drugs may be hypothesized. Interestingly, after a few months of just trastuzumab treatment, i.e., at 12 months follow-up, we found a less consistent drop of the 2D STE, especially 2D GCS and 2D GRS.

2D GLS seems to be the crucial parameter for a comprehensive evaluation of the entire LV systolic function [29], even if a segmental pattern of cardiac damage has been shown [16]. Hence, Lange et al. [16]., demonstrated a significant reduction in regional longitudinal strain for the septal, anterior and antero-lateral LV walls, in line with other reports described in the literature [35]. The explanation of this phenomenon could lie in the different share stress forces acting at different LV level related to geometrical reasons and local activation of signal transduction pathways of pathological processes such as fibrosis or apoptosis [36]. Impressively, this regional pathological pattern was also reported in patients diagnosed with anthracycline cardiotoxicity through cardiac magnetic resonance analysis showing late gadolinium enhancement in well localized areas of the LV wall [37].

The long-term implications of the detected changes in 2D derived strain parameters during therapy is another important issue that still needs to be clarified [7]. Also the absolute value of detected 2D GLS per se may have a role. Indeed, Fei et al. were able to demonstrate that the 2D GLS value at the cardiotoxicity time point itself was independently associated to the reversibility of CTRCD after correcting for 2D LVEF and left ventricular end-diastolic volume [13].

Cardiovascular imaging has an important role in the early identification of cardiac injury: the detected LV function subclinical alterations, even if they do not meet the diagnostic criteria of cardiotoxicity [38], may represent the target for cardio-oncological multi-disciplinary management of BC patients [19].

Several limitations have to be acknowledged for the present study. First, this meta-analysis was yielded by papers showing significant heterogeneity in the study design and cardiotoxicity definition. In particular, the timing of echocardiographic evaluation during and after cancer therapy across the studies is not uniform and this may present some implications in the detection of the myocardial changes. Second, the studies involved patients treated with different chemotherapeutic agents and combinations. Furthermore, no complete data were available to analyze the association between type or cumulative dose of anthracyclines and subsequent development of 2D LVEF and 2D derived strain analysis parameters reduction. Third, different software were used to analyze 2D STE in the analyzed works. Fourth, the changes in 2D STE parameters were more pronounced in patients who developed CTRCD, but we didn't perform a separate analysis for these subjects. Therefore, this could have influenced the trend of 2D STE parameters in the overall population analysis. Finally, a long-term follow-up after

the conclusion of chemotherapy is needed to better typify the encountered myocardial changes and their prognostic impact.

In conclusion, the present study confirms the relative frequent prevalence of cardiotoxicity in BC patients during chemotherapy. The greater modifications of 2D strain parameters after cancer therapy compared to the little entity LVEF reduction highlights the importance of such advanced echocardiographic technique. Including 2D derived strain parameters in the echocardiographic evaluation during cancer therapy may allow an early identification of cardiac damage and therefore provide a way to minimize cardiac related mortality and morbidity while undergoing chemotherapy and afterwards.

Compliance with Ethical Standards

Conflict of interest Drs. Corinna Bergamini, Giulia Dolci, Stella Truong, Luisa Zanolla, Giovanni Benfari, Elena Fiorio, Andrea Rossi and Flavio Luciano Ribichini have no conflicts of interest or financial ties to disclose.

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