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State-of-the-art CMR Mapping Techniques in the Detection of Subclinical Chemotherapy-induced Cardiotoxicity in Breast Cancer Patients

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Abstract: *Background:* The oncological treatments have improved survival rates but with an increased risk of cardiovascular disease (CVD). *Purpose:* To detect subclinical cardiotoxic changes using Cardiovascular Magnetic Resonance (CMR) and to define parameters for the prediction of late cardiac changes after 3 months follow-up. *Patients and methods:* We conducted a prospective study in 21 breast cancer patients who were scheduled to undergo treatment either with anthracyclines, trastuzumab, or docetaxel. CMR scans were performed before therapy onset as well as 3-6 days and 3 months thereafter. Native left ventricular (LV) T1 and T2 parameters were acquired in addition to standard parameters. *Results:* Compared to baseline, the mean left ventricular ejection fraction (LVEF) tended to mildly decrease during follow-up. A significant reduction in mean native T1 was found from 1246.6 ± 29.5 ms at baseline to 1231.4 ± 31.4 ms at 3-6 days, which was followed by significant increase after 3 months reaching 1265.8 ± 27.9 ms with p = 0.011 and 0.012, respectively. A significant increase in mean T2 was also found from 41.6 ± 3.4 ms at baseline to 43.8 ± 3.8 ms after 3 months with p = 0.045. From 21 patients, only 1 patient (4.8%) experienced cardiotoxicity. *Conclusion:* Treatment with potentially cardiotoxic drugs is associated with a change of CMR-derived native T1 which may enable an early identification of cardiotoxicity among breast cancer patients.

Keywords: Breast Cancer, Anthracyclines, Trastuzumab, Cardiotoxicity, T1 Mapping, Cardiac MRI

1. Introduction

Novel anti-cancer drugs have improved survival rates but at the cost of a significantly increased risk of CVD [1, 2].

Anthracyclines are known for relatively frequent cardiotoxic effects, which can be acute as myocarditis or chronic as ventricular dysfunction [3] or diffuse myocardial fibrosis [4]. Trastuzumab is one of the monoclonal antibody-based tyrosine kinase inhibitors [5, 3], with a demonstrated risk for ventricular dysfunction [6]. Docetaxel is a new anti-cancer drug that is suggested to induce LV diastolic dysfunction [7].

Until now, the proposed definitions rely on LVEF changes

which are often subtle during initial phase of therapy [1] and do not include the early subclinical changes [3].

CMR has many advantages which may allow early identification of cardiotoxicity [8]. It offers the opportunity of quantitative myocardial tissue assessment using novel methods such as T1 and T2 mapping [9]. Diffuse myocardial fibrosis was suggested by a study which reported increase of native T1 several years after anthracycline therapy [4]. However, CMR has not yet been established as the primary method for monitoring patients treated with cardiotoxic chemotherapy [8].

The aim of this study was to identify patients at risk based on early detection of cardiotoxic changes using state-of-the-art CMR techniques including T1 and T2 mapping and to identify parameters that could predict late cardiac changes after 3 months follow-up.

2. Patients and Methods

2.1. Study Population

This prospective observational longitudinal study was conducted during the period from April 2018 until June 2020. Twenty-one women diagnosed with breast cancer and scheduled to undergo treatment with anthracyclines, trastuzumab or docetaxel were enrolled. The inclusion criteria were: Age ≥18 years, no previous start of chemotherapy. The exclusion criteria included: Pre-existing symptomatic HF, recent myocardial infarction, renal failure (GFR ≤ 30 ml/min) and contraindications for magnetic resonance imaging.

2.2. Preliminary Assessment

All patients were subjected to medical history taking, clinical examination, 12-lead electrocardiography (ECG) and laboratory assessment including plasma N-terminal pro brain natriuretic peptide (NT-proBNP) and serum high-sensitivity troponin T (hs-TnT) alongside CMR.

2.3. Image Acquisition

2.3.1. Transthoracic Echocardiography (TTE)

Was performed in all patients at baseline and 2nd follow-up. The size and function of both ventricles were evaluated.

2.3.2. CMR

All enrolled patients performed three CMR examinations using 3 T Philips Ingenia, Best, Netherlands or 3 T Siemens MAGNETOM Prisma Fit, Erlangen, Germany equipped with body or cardiac coil and retrospective ECG gating. Scans were performed at baseline as well as 3-6 days and 3 months after chemotherapy onset. All patients were scanned using the previously published techniques. A breath-hold steady-state free precession was used to perform cine acquisitions with the following typical parameters: field of view (FOV) = 350 × 350 mm^2, TR/TE =2.8/1.4 ms, slice thickness = 8 mm, voxel size = 2.2 × 2.2 × 8 mm^3, flip angle (FA) = 60°.

Native T1-mapping was performed using a breath-hold MOLLI sequence in three LV short axis (SAX) planes (basal, mid-ventricular and apical) with the following typical parameters: FOV = 300 × 300 mm^2, TR/TE =2.1/0.79 ms, slice thickness = 10 mm, voxel size = 2 × 2 × 10 mm^3 and FA = 20°.

T2-mapping in three SAX planes as in T1-mapping. A breath-hold turbo SE sequence was used with the following typical parameters: FOV = 350 × 350 mm^2, TR = 1000 ms, TE according to heart rate, slice thickness = 8-10 mm, voxel size = 2 × 2 × 8 mm^3, FA = 90°.

Late gadolinium enhancement (LGE) images were acquired 10 minutes after intravenous (IV) injection of contrast agent (Gadovist™, Bayer Healthcare Pharmaceuticals, Bergkamen, Germany) at a dose of (0.1 mmol/kg) only at baseline to exclude a pre-existing myocardial scar. A breath-hold T1-weighted inversion recovery sequence was used with the following typical parameters: FOV = 350 × 350 mm^2, TR/TE =4.1/1.97 ms, slice thickness = 8 mm, voxel size = 1.79 × 2.06 × 8 mm^3, FA = 15° and time of inversion = 250–425 ms.

2.4. CMR Analysis

All images were analyzed using certified post-processing (cvi42™ version 5.6.6, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The size and function of both ventricles as well as LV mass index were quantitatively evaluated through manually tracing the epi- and endocardial borders on successive SAX cine images at end-diastole and end-systole. Papillary muscles and trabeculations were excluded from the blood volume. Ventricular wall motion abnormality was also assessed on cine images. Epicardial and endocardial contours were manually traced for T1 and T2 mapping in three SAX slices (basal, mid-ventricular and apical) with the application of a 10% safety margin to avoid partial volume effects. Two independent readers evaluated the LGE images in two perpendicular slices.

2.5. Definition of Chemotherapy-related Cardiotoxicity

According to the previously published criteria [10], chemotherapy-related cardiotoxicity was defined in this study as LVEF reduction of ≥5% to a value of <55% when associated with HF symptoms or an asymptomatic LVEF reduction of ≥10% to a value of <55%.

2.6. Statistical Analysis

Data were analyzed using IBM® SPSS Statistics software version 26.0. All data are expressed either in mean ± standard deviation (SD), median & interquartile range (IQR) or frequency (number (n) - percentage (%)). Repeated measures analysis of variance (ANOVA) and Friedman's test were used to evaluate temporal changes of continuous parametric and non-parametric variables, respectively with Bonferroni correction for multiple pairwise comparisons with baseline. Relationships between different variables were assessed using Pearson's correlation coefficient. The effect of various factors such as presence of CV risk factor, type or dose of chemotherapy used was tested by calculating the interaction with the CMR changes. Statistical significance was defined as a p value < 0.05.

3. Results

3.1. Patients Characteristics

Table 1. *Baseline characteristics.*

	Total (n=21)
Age, (years)	51.4 ± 11.4
Body mass index (kg/m^2)	22.6 ± 2.9
Patients using co-existing cardiac medication, n (%)	3 (14)
Previous breast or mediastinal radiation, n (%)	2 (9.5)
History of another tumor, n (%)	1 (4.8)
Time from diagnosis until enrollment (months), Median (IQR)	1 (0-1)
Any cardiovascular risk factor, n (%)	16 (76)
Hypertension, n (%)	3 (14)
Dyslipidemia, n (%)	3 (14.3)
Overweight or obesity, n (%)	6 (28.6)
Smoking [a], n (%)	8 (38)
Family history of cardiovascular disease, n (%)	11 (52.4)
Heart rate (beat/minute)	72 ± 11.8

Data are expressed as mean ± SD and frequency (n - %) as well as median (IQR); [a], either active smoking or previous history of smoking.

The baseline characteristics of the enrolled patients are listed in *Table 1*. One patient (4.8%) had previous history of primary mediastinal B cell lymphoma. The median duration between start of chemotherapy and 1st follow-up was 4 days, while until 2nd follow-up was 97 days.

3.2. Cancer Treatments

Fourteen patients (28%) received epirubicin, 5 patients (10%) received trastuzumab and 2 patients (4%) received docetaxel with mean cumulative doses of 470 ± 80 mg/m^2, 2550 ± 750 mg and 477 ± 208 mg/m^2, respectively.

3.3. Changes During Follow-up

Changes in cardiac biomarkers and CMR parameters over 3 months were evaluated through multiple comparisons between baseline and 1st as well as 2nd follow-up.

3.3.1. Cardiac Biomarkers

Compared to baseline, significant elevation of plasma Nt-proBNP and serum hs-TnT was found at the 1st and 2nd follow-up with p value = 0.014 and 0.002, respectively, see *Table 2*. There was no significant interaction between treatment with epirubicin and change over time of hs-TnT (p = 0.67) or NT-proBNP (p = 0.79).

Table 2. *Changes in cardiac biomarkers.*

	Baseline (n=21)	1st Follow-up (n=21)	p value	2nd Follow-up (n=21)	p value
hs-TnT (pg/ml)	4 (4-5.5)	5 (4-6.7)	0.077	7 (4.5-12.5)	0.002*
Nt-proBNP (ng/l)	131 (82.5-174.5)	190 (111-242)	0.014*	118 (57.5-219)	0.958

Data are expressed as median (IQR); hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide; p, probability; *, significance <0.05. P values indicate significance of comparisons with baseline using Friedman's and Wilcoxon signed-rank tests.

3.3.2. CMR Parameters

The mean LVEF tended to mildly decrease during follow-up reaching (63.9% ± 4.7) at 2nd follow-up in comparison to baseline study (65.8% ± 4.7; p = 0.076). This change was accompanied by a mild increase of the mean left ventricular endsystolic volume index (LVESVi) from 23.3 ± 5 ml/m^2 at baseline reaching to 25.3 ± 6.7 ml/m^2 at 2nd follow-up with p = 0.059. A representative imaging example is shown in *Figure 1 a, b & c*. Moreover, a significant reduction in mean native T1 was found from 1246.6 ± 29.5 ms at baseline to 1231.4 ± 31.4 ms at 1st follow-up, *see Figure 2*, which was followed by significant elevation at 2nd follow-up reaching 1265.8 ± 27.9 ms with p = 0.011 and 0.012, respectively, *see Figure 1d & e*. There was also significant elevation in mean T2 from 41.6 ± 3.4 ms at baseline to 43.8 ± 3.8 ms at 2nd follow-up with p = 0.045, *see Figure 1f & g*. Out of 21 patients, only 1 patient (4.8%) experienced cardiotoxicity as defined by an LVEF reduction of >10% as compared with baseline. The mean individual changes in CMR functional and tissue characterization parameters as compared to baseline are listed in *Table 3*. There was no significant interaction between treatment with epirubicin and change over time of T1 or T2 with p = 0.134 and p = 0.328, respectively. Other parameters were within normal range at baseline and during follow-up. There was a significant correlation between changes at 3 months in LVEF and native myocardial T1 (Pearson's correlation coefficient = -0.473, p = 0.031), *see Figure 3*, as well as between morphological and functional parameters measured by TTE and CMR. No significant interaction was found between the changes in serum biomarkers or CMR parameters and the co-existing factors such as the different type and doses of chemotherapy as well as the presence of previous breast or mediastinal radiotherapy.

Table 3. *Changes in CMR functional and tissue characterization parameters.*

CMR parameters	1st Follow-up (n=21)	p value	2nd Follow-up (n=21)	p value
LVEF (%)	-0.81 ± 3.91	0.354	-1.86 ± 4.55	0.076
LVESVi (ml/m^2)	0.43 ± 3.59	0.523	2.05 ± 4.69	0.059
Native myocardial T1 (ms)	-15.19 ± 25	0.011*	19.24 ± 32	0.012*
Myocardial T2 (ms)	0.86 ± 1.93	0.166	2.24 ± 2.74	0.045*

Data are expressed as mean of individual change in comparison to the baseline ± SD; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index, p, probability; *, significance <0.05. P values indicate significance through adjusted (Bonferroni) pairwise comparisons with baseline.

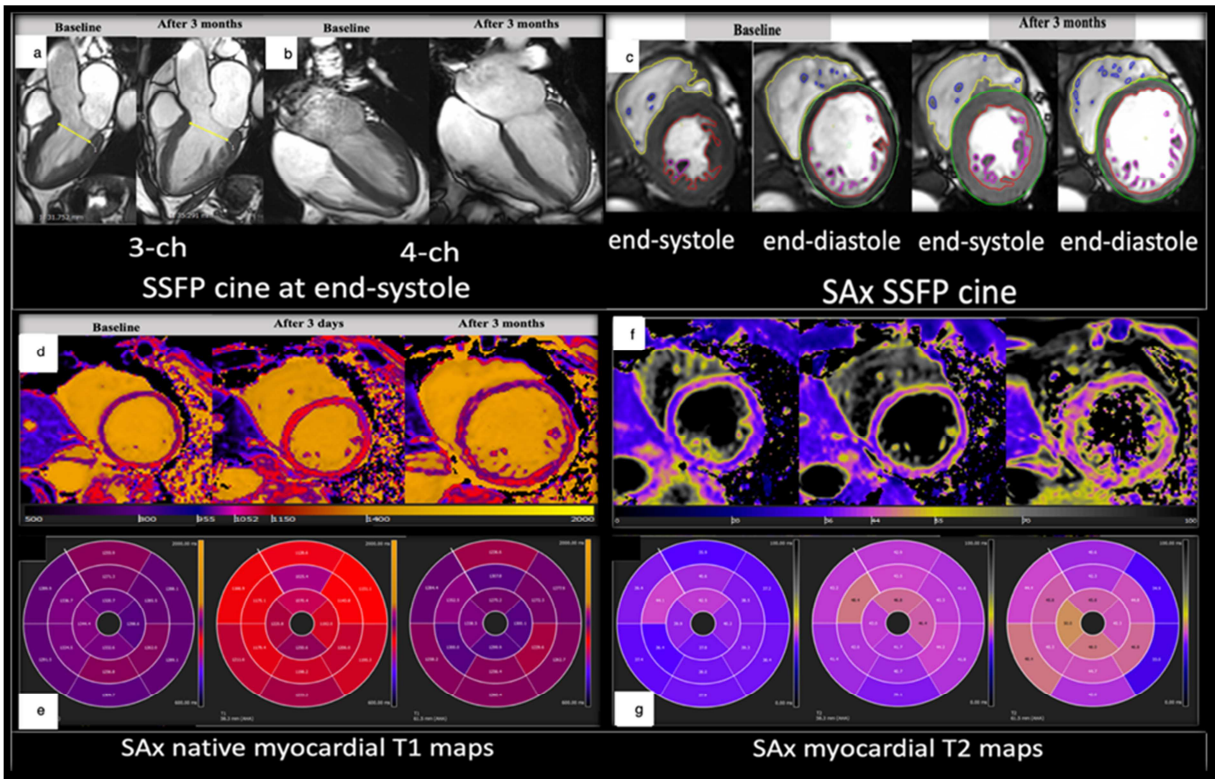

Figure 1. *Representative images of trastuzumab-induced cardiotoxicity. Cine 3-chamber (a) and 4-chamber views (b) as well as short axis view (c) during baseline study (LVEF = 66%) and 3 months thereafter (LVEF = 54%). Native T1 (d) showed reduction of global left ventricular value after 3 days (baseline = 1196 ms, 1st follow-up = 1172 ms and 2nd follow-up = 1277 ms). Myocardial T2 (f) showed subtle elevation of global value after 3 months (baseline = 40 ms, 1st follow-up = 43 ms and 2nd follow-up = 44 ms). The average segmental T1 and T2 times are displayed as 'bull's eye' images (e) & (g), respectively. The color maps represent continuous T1 and T2 values. LVEF, left ventricular ejection fraction.*

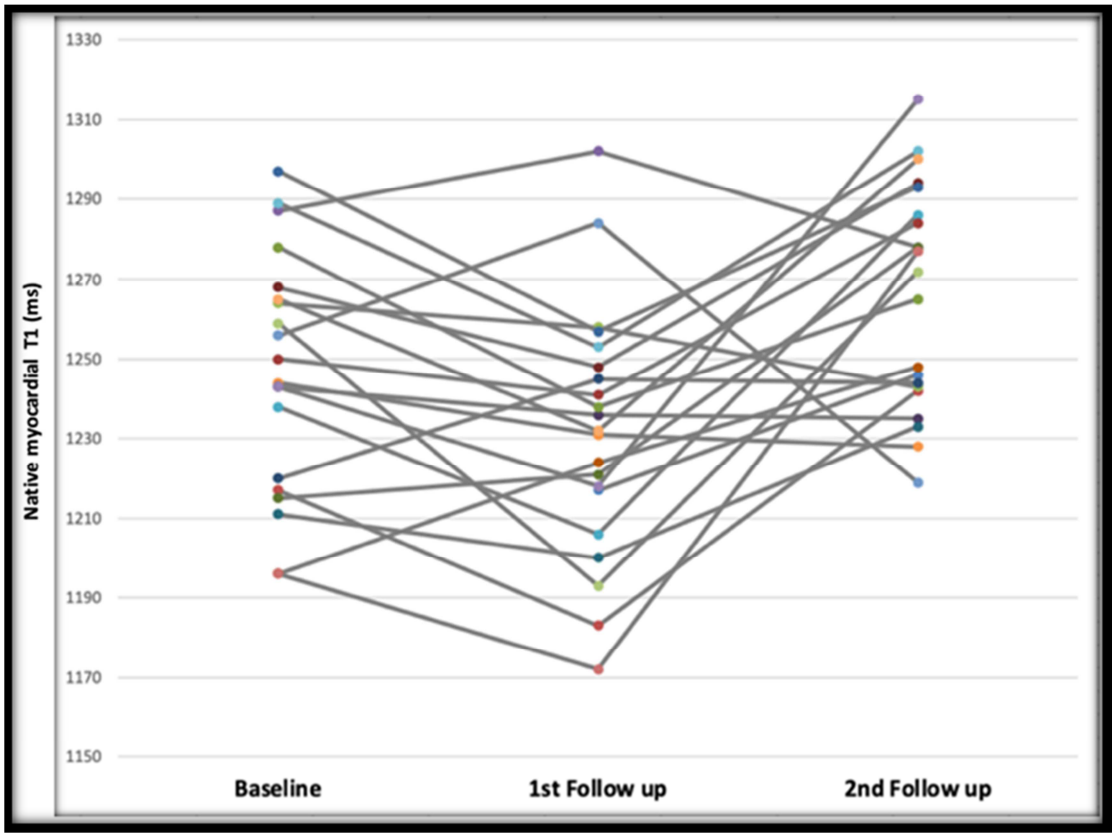

Figure 2. *Individual changes of native T1 over the follow-up period.*

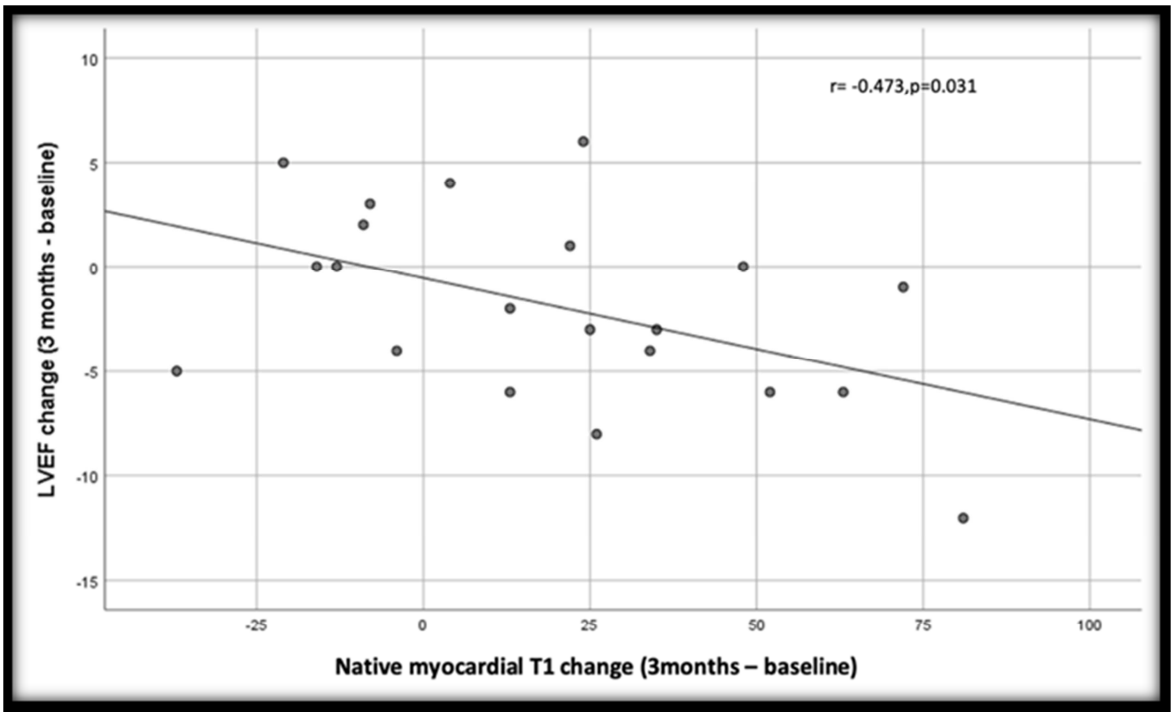

Figure 3. *Relationship between changes in LVEF (%) and native T1 (ms) over 3 months.*

4. Discussion

Our study shows that treatment with potentially cardiotoxic drugs are associated with changes of myocardial T1 as a CMR-derived biomarker. These occur even in the absence of an overt cardiotoxic reaction in a short time follow-up of 3 month.

Over the follow-up period, we found a mild yet significant increase of cardiac biomarkers including plasma NT-proBNP and serum hs-TnT. Other studies also reported that serum hs-TnT reaches its peak during anthracycline therapy. Early elevation of serum hs-TnT with trastuzumab therapy may indicate a worse prognosis [11]. In contrast, no significant change was previously reported in plasma NT-proBNP during trastuzumab [8] or anthracycline therapy [12].

CMR is playing an increasingly important role in the assessment of cardiotoxicity [13]. It has many advantages such as the lack of ionizing radiation and the ability of non-invasive tissue characterization. CMR is considered the standard reference for cardiac function evaluation [14]. In our study, the LVEF tended to mildly decrease during follow-up which was associated with mild increase of the mean LVESVi. This finding is consistent with another study that followed 53 cancer patients treated with anthracycline and showed that LVEF and LVESV start deteriorating as early as one month and remain abnormal 6 months after therapy initiation [12]. Another study, conducted on breast cancer patients treated with trastuzumab, also found that LVEF started to decrease after 3 months, followed by a significant reduction after 6 months [15]. In our study, the follow-up started as early as 3-6 days after chemotherapy onset and thus we could confirm an early decrease in LVEF.

Relatively recently, CMR myocardial mapping has been increasingly used for myocardial tissue characterization. This approach allows for quantitatively assessing diffuse myocardial tissue alteration [9]. Moreover, the presence of LGE reflects the presence of irreversible myocardial damage [1]. In this study, no LGE was found at baseline which suggests the lack of pre-existing myocardial scar.

In our study, the tissue characterization parameters (native T1 and T2) showed significant changes during follow-up. There was a significant reduction in native T1 3-6 days after chemotherapy onset, which was followed by significant increase after 3 months. This early decrease in native T1 was previously reported as a decrease of native T1 48 hours after the 1st dose of anthracyclines. In contrast to our study this pehnomenon was only observed in patients with acute cardiotoxicity [9]. The relatively late increase in native T1 was also reported by Haslbauer et al. who reported a significant increase in native T1 within 3 months after chemotherapy initiation and remained elevated until >12 months. They concluded that native T1 is the most effective predictor of chemotherapy-induced cardiotoxicity. The same group also found a significant elevation in T2 within 3 months after chemotherapy start which was followed by later recovery [16]. This observation is similar to our findings, as we found significant increase in T2 3 months after chemotherapy initiation. Significant elevation in T2 was also reported by Galán-Arriola and colleagues 6 weeks after intracoronary doxorubicin injection in twenty pigs and considered it as the earliest marker of anthracycline-induced cardiotoxicity [17]. The mechanism of the initial native T1 reduction is still unclear. A reduced native T1 is observed with intracellular accumulation of iron or lipids [18]. An increased native T1 indicates presence of myocardial edema or diffuse fibrosis. An increased T2 is useful for the

diagnosis of acute inflammatory processes such as myocarditis or acute infarction [19]. One recognized hypothesis of anthracyclines-related cardiotoxicity includes the formation of anthracycline-iron complexes. Moreover, it was also proposed that anthracyclines may allow an increase in cellular levels of iron which potentiate iron-mediated oxidative stress [20]. This may explain the initial decrease in native T1 among our cohort.

In this study, there was no significant difference in changes of CMR parameters between the different doses of chemotherapy. This finding was previously highlighted in other study showing that anthracycline-related cardiotoxicity can occur with any given dose. Moreover, the higher risk of trastuzumab-induced cardiotoxicity was not related to the cumulative dose but was mainly observed with concomitant use of anthracyclines [3]. In our study, there was no concomitant use of both treatments.

5. Study Limitations

Include the small sample size and short follow-up period. Therefore, studies with larger cohorts and longer follow-up are recommended for validation of our findings. The heterogeneity of cancer treatments is also considered limitation of this study. However, the longitudinal follow-up has improved the accuracy of our results together with the absence of significant difference in CMR temporal changes regarding the different chemotherapy types and doses.

6. Conclusion

Our study shows that breast cancer treatment may cause early cardiac tissue alteration in the absence of significant reduction of ventricular systolic performance. CMR derived myocardial mapping, specifically the early decrease of native T1 times may enable early identification of cardiotoxicity among breast cancer patients treated with anthracyclines or trastuzumab and thus may allow identification of patients at risk. However, further studies with larger cohorts and longer follow-up are recommended for validation of our findings.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Standards

This study was approved by the local ethics committee of University of Heidelberg, Germany. All enrolled patients gave written informed consent before participation.

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