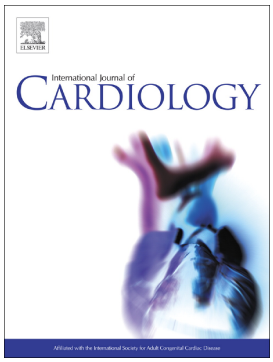

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Late Characterisation of Cardiac Effects Following Anthracycline and Trastuzumab Treatment in Breast Cancer Patients

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Keywords: chemotherapy, cardiotoxicity, breast cancer, cardiac magnetic resonance imaging, T1-mapping, left ventricular ejection fraction

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Abstract

Background: Anthracycline (A) and trastuzumab (T) chemotherapy have well recognized cardiac toxicity, potentially leading to significant morbidity and mortality. Our previous work in 46 prospectively enrolled breast cancer patients showed early left ventricular (LV) and right ventricular (RV) function decline at 1 and 3 months, but only persistent RV dysfunction at 12 months which correlated with myocardial oedema observed early (1 and 3 months) after administration of chemotherapy regimes.

Method: To investigate late cardiac effects, the same cohort were re-imaged with advanced Cardiovascular Magnetic Resonance (CMR) imaging including T1 mapping 5 +/- 1 year post chemotherapy.

Results: 26 out of 46 (50%) patients underwent follow up imaging. A statistical but non-clinically significant decrease was observed in LV ejection fraction (EF) from baseline to 5 years (72.2±6.6 to 65.4±9.3, $p<0.005$). Subjects with initial drop of LVEF by >10% at 3 months (n=5) or at 12 months (n=3) did not demonstrate any difference in LV or RVEF at 5 years. No correlation was observed between myocardial oedema and LV or RVEF at 5 years. At 5 years, T1 values were within normal limits overall (935± 48ms). One patients had significantly elevated (>1000ms) T1 values with no correlation to LV or RVEF. No subjects demonstrated replacement myocardial fibrosis at 5 years.

Conclusion: Using advanced CMR, contemporary chemotherapy regimes demonstrate minimal long term cardiac toxicity. There is minimal diffuse and no replacement fibrosis as demonstrated by LGE, following chemotherapy. This study suggests limiting serial imaging in these patients at 12 months post chemotherapy.

Post-chemotherapy cardiotoxic effects have been recognised as the main contributor to both acute and late non-cancer related mortality in breast cancer patients treated with adjuvant chemotherapy [1]. Early detection of this occurrence is essential to introduce alternative treatment strategies and/or commence cardioprotective therapy (such as renin-angiotensin aldosterone system inhibition) [1]. Cardiovascular magnetic resonance (CMR) is the gold standard for accurate and reproducible assessment of right ventricular (RV) and left ventricular (LV) volumes, function and mass [2]. Furthermore, modalities such as T1 mapping and late-gadolinium enhancement (LGE) enable myocardial tissue characterization including assessment of myocardial oedema, replacement fibrosis and diffuse fibrosis [3] [4]. Previously, we utilised these CMR parameters in chemotherapy naïve breast cancer participants receiving anthracycline and/or trastuzumab treatment to demonstrate early LV and RV functional decline at 1 and 4 months, but only persistent RV dysfunction at 12 months[5]. This decline was found to correlate to early myocardial oedema observed at 1 and 4 months. To investigate the late effects of these same treatments, the same patient cohort was reimaged with CMR 60±12 months post chemotherapy. Our primary aim was to assess, using multiparametic CMR, the long term structural and functional effects of anthracycline +/- trastuzumab (Herceptin) exposure in these patients, and compare the late findings with early post chemotherapy LV/RV changes.

Participants underwent cine, LGE and T1 mapping CMR imaging. T1 mapping was performed with the shMOLLI technique [6]. Normal T1 values were established in healthy volunteers as values between 950-980, with global T1 greater than 1000 being considered as abnormal, consistent with previous T1 mapping literature [7] [8]. LGE enhancement was assessed qualitatively and quantitatively as previously described [5]Echocardiography was performed for LV volumes and function, diastolic parameters (including mitral inflow for E:A ratio, tissue Doppler imaging for early diastolic mitral annular motion at both the septal and lateral annulus, E' and left atrial volumes) and strain analysis, providing a measure of global longitudinal strain (GLS).

Table 1: Baseline clinical and chemotherapy characteristics

Variable (n=26)			
Age (years)	53.1±9.6		
Chemotherapy regime	Anthracycline (%)	Trastuzumab (%)	Combined (%)
	62	30	8
Systolic blood pressure (mmHg)	115.3±16.1		
Diastolic blood pressure (mmHg)	66.5±10.2		
Height (m)	1.63±0.1		
Weight (kg)	70.4±16.6		

Baseline and clinical characteristics of the study population are described in Table 1. 26 of the original 46 (57%) participants returned for follow-up CMR and echocardiograms after 60 months. This reduced rate of follow-up was attributed to a number of factors; 5 of the original 46 (11%) participants were deceased, however none were due to cardiovascular complications, 5 (11%) had moved interstate or overseas, 8 (17%) were unwilling to participate for varying reasons, and 1 (approx. 2%) was unable to complete the scan due to claustrophobia. In the initial study, one participant was found to demonstrate cardiotoxicity at 12 months and was therefore not included in this current study.

Global T1 values were within normal limits for all participants, (935+/-48ms), except one who demonstrated elevated T1 (>1000ms). There was no correlation between T1 values and RVEF or LVEF at 60 months. LGE findings did not demonstrate replacement myocardial fibrosis in any participants at 5 years. All echo parameters remained stable from baseline to 60 months (table 2).

Table 2: CMR characteristics from baseline to 60 months

Time point	LVEDV (mL)	LVESV (mL)	LVEF (%)	GLS (echo, %)	RVEDV (mL)	RVESV (mL)	RVEF (%)
Baseline	115.9±23.2	33.9±12.6	72.2±6.6	-21.8±3.2	116.1±26.4	45.3±11.6	60.9±6.0
1 month	116.9±21.3	36.7±13.0*	69.0±7.0*	-21.3±2.7	121.6±28.7*	52.4±14.3*	56.9±5.9
3 month	115.8±21	42.3±14.2*	65.0±6.7*	-19.5±2.0*	117.8±23.4*	52.1±13.0*	56.5±6.4
12 months	125.1±24.8	44.7±17.0*	65.1±6.9*	-19.7±2.2	122.6±19.0*	57.5±12.8*	53.3±6.8
60 months	109.1±27.1~	38.51±17.4*~	65.4±9.3*	-21.2±2.8	103.5±20.8*~	37.8±12.2*~	63.8±7.9~

*statistically significant from baseline

~60 month data different from 12 month data

Despite our previous findings depicting significant functional changes in RV and LV at 12 months, our long term follow up data did not show continuation of this effect at 60 months. A statistically significant drop in left ventricular ejection fraction (LVEF) was observed from baseline to 12 months (72.2% to 65.1%, p=0.004, table 2); however this was unchanged from 12 months to 60 months, and still within normal range of LVEF. Hence, there was no clinically significant change in systolic function based on our data. Of importance, there was not any difference in LVEF or RVEF at 60 months in those participants that originally demonstrated a decrease of >10% in either of these parameters. There was not any correlation of myocardial oedema with either LVEF or RVEF at 60 months, as we previously observed at 12 months.

To the best of our knowledge, our study is the first to assess long-term cardiotoxicity in post chemotherapy patients utilising T1 mapping in CMR. Our principal findings demonstrate three main points. (1) Global T1 mapping values was normal in all but 1 participant, indicating no significant

underlying myocardial damage due to chemotherapy. (2) Significant functional changes in both the LV and RV, as detected by CMR, indicate injury starting 3 months and persisting to 12 months, but these are reversed at 60 months. (3) This phenomenon is consistent with no minimal diffuse fibrosis, no replacement fibrosis and no myocardial oedema at 60 months.

Anthracylines and trastuzumab are well known for their cardiotoxic effects, however previous studies looking at cardiotoxicity have tended to be retrospective and short-term. Although previous studies have conducted T1 mapping on post- chemotherapy patients up to three months, to our knowledge we are the first study evaluating this modality at 5 years, detecting no significant elevation of T1 values [9]. Cardiotoxicity tends to be demonstrated through damage to the myocardium, generally shown as fibrosis through tissue characterisation methods such as T1 mapping and LGE. High T1 values (>1000ms) are indicative of an increase in interstitial space as seen in diffuse myocardial fibrosis or oedema and it is reassuring that this prospective serially followed chemotherapy cohort did not demonstrate this. Similarly, the initial increase in oedema in a third of our patients at 1 month and in almost half our participants at either 1 or 4 months was resolved by 60 months, demonstrating no long term injury.

Anthracycline-induced cardiotoxicity tends to be detected using echocardiographic studies and is clinically followed up to evaluate LV function. However, due to significant interstudy and interobserver variability, it is possible that underlying early damage may be missed by this technique, and hence echocardiography is not as effective in detecting early prognostic markers [10]. Biopsy remains the gold standard of myocardial damage assessment post chemotherapy, however it is an invasive process and the ability to predict clinical outcome is questionable [10]. Hence, CMR remains the optimal tool for non-invasive detection of subclinical cardiotoxicity which may otherwise go unidentified. In particular, CMR modalities such as T1, T2 relaxation times and late-gadolinium enhancement provide further tissue characterisation giving new insight disease progression to be determined.

Interestingly, we observed a marked, but non-clinically significant drop in LVEF at 3 months, which, based on previous studies, may be considered a sign of acute cardiotoxicity, however this was not sustained at 60 months, indicating chronic cardiotoxicity was not an issue for these patients. Previous studies have indicated that subacute and chronic forms of anthracycline-induced cardiotoxicity tend not to be reversible, but the prospectively collected CMR data from this study is not consistent with this. Despite the initial decrease in both LVEF at 3 months, and RVEF at 12 months, there was an improvement in the 60 month data, tending back to baseline [11]. This may be indicative of RV function being restored, a feature which is not completely understood, or alternatively, related to serial imaging assessment being done by CMR (a more reproducible technique) than 2D echocardiography.

Previously papers have indicated that changes in GLS tend to occur prior to LVEF dysfunction, however our study demonstrates synonymous changes, with both LVEF and GLS tending to decrease around 3 months [12]. However, this may be due to previous studies utilising echocardiography to determine LVEF, whereas we determined this value through CMR techniques, a more precise marker of global LV function.

The European Society of Medical Oncology guidelines recommend left ventricular dysfunction assessment at three month intervals for a 12 month duration, after which annual echos should be undertaken [13, 14]. However, the guidelines do not specify how this dysfunction be assessed and a decrease in LVEF, as determined through 2D echocardiography, is the current marker to confirm post-chemotherapy cardiotoxicity. In our study, the LVEF remained within a clinically normal range throughout the 60 months, and was assessed with advanced CMR imaging, as opposed to echocardiography. Furthermore; as no new long-term cardiotoxicity occured in those patients without 12 month cardioxicity, we propose that long-term (60 months) follow-up advanced imaging may be unnecessary.

A limitation of this study is the small sample size in the original cohort (n=46) which further decreased (n=26) by the 60 months follow up. Hence, a larger sample of patients needs to be investigated. The dose-dependency of the cardiotoxicity was also not identified, which may also be correlated with cardiotoxicity [15]. Hence, based on our results, we can conclude that as no long term cardiotoxicity occurred in our cohort, thesepatients may only need echocardiographic or CMR follow up for the first 12 months post commencement of anthracycline and or trastuzumab chemotherapy. However, this cannot be generalised across all breast cancer therapy patients, as different chemotherapy regimes, and particularly different doses, may require more strict monitoring over a long period of time [16].

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Highlights

- Advanced CMR demonstrated no long-term cardiotoxicity in post-chemotherapy breast cancer patients
- T1 Mapping and Late Gadolinium Enhancement indicated no significant replacement or diffuse fibrosis in long-term post- chemotherapy patients
- Limiting long-term serial imaging in post-chemotherapy patients is proposed, depending on the dose and drug type.