Long term cardiovascular magnetic resonance phenotyping of anthracycline cardiomyopathy

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A B S T R A C T

Background: Anthracycline cardiomyopathy contributes to the morbidity and mortality of cancer survivors but long-term data are lacking. This study sought to describe the phenotype of long-term anthracycline cardiomyopathy, the prevalence of myocardial fibrosis and its association with cardiac remodeling, systolic function and clinical outcomes.

Methods and results: We undertook contrast-enhanced CMR in 81 cancer survivors at median 5 years after anthracycline (mean dose 279 SD 89 mg/m^2). Participants were aged 55 SD 14 years; 68% were female. Mean LVEF was impaired (49 SD 12%), driven by a pathological increase in iLVESV (47 SD 23 ml/m^2). 19% of participants exhibited LGE, which was associated with significant adverse left ventricular remodeling and reduced systolic function (iLVEDV: 102 SD 34 vs 83 SD 21 ml/m^2, p = 0.03; iLVESV 61 SD 32 vs 43 SD 20 ml/m^2, p = 0.03; LVEF: 43 SD 11 vs 50 SD 12%, p = 0.03). In subgroup analysis of 36 patients, 36% had elevated native T1 measurements, which was associated with significant adverse left ventricular remodeling (iLVEDV: 97 SD 22 vs 74 SD 19 ml/m^2, p = 0.002; iLVESV: 56 SD 22 vs 35 SD 15 ml/m^2, p = 0.005), reduced systolic function (LVEF 44 SD 13 vs 55 SD 9%, p = 0.01), and hospitalizations for heart failure (38% vs 9%, p = 0.03). Absolute native T1 measurements correlated significantly with iLVEDV (p ≤ 0.001, R^2 0.33), iLVESV (p < 0.001, R^2 0.36), LVEF (p < 0.001, R^2 0.35), LAVi (p = 0.04, R^2 0.12) and MAPSE (p = 0.02, R^2 0.14).

Conclusions: Long-term anthracycline cardiomyopathy is characterized by pathologically increased iLVESV. Both LGE and elevated native T1 measurements were associated with significant adverse cardiac remodeling and reduced systolic function, and the latter with heart failure hospitalizations.

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1. Introduction

Anthracycline cardiomyopathy is increasingly recognized as an important contributor to the morbidity and mortality of cancer survivors [1]. Consequently, international societies have published recommendations for the non-invasive monitoring of patients receiving potentially cardiotoxic agents [2–4]. Cardiovascular magnetic resonance (CMR) is the gold standard method for measuring ventricular volumes and function and has the unique capability to characterize myocardial tissue. CMR studies have focused on the early stages of anthracycline cardiomyopathy [5–8]. There are limited longitudinal studies examining cardiovascular structure and function over an extended period of time [9,10].

The early stages of anthracycline cardiomyopathy are characterized histologically by myocardial edema, inflammation and vacuolisation [11], whereas in the later stages, diffuse myocardial fibrosis predominates [12]. Discrete foci of myocardial fibrosis can be detected by late gadolinium enhancement (LGE) sequences with broad diagnostic and prognostic applications in cardiovascular medicine [13]. There are limited, somewhat conflicting data on the presence, extent and location of focal myocardial fibrosis detected by LGE in adult patients with anthracycline cardiomyopathy, [5,6,10,14] though it is generally reported to be an infrequent finding [11]. Furthermore, the qualitative nature of the analysis, which relies on the presence of normal myocardium for reference, means that the diffuse fibrosis typically associated

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with anthracycline cardiomyopathy may not be detectable. Novel quantitative techniques such as native myocardial T1 mapping and myocardial extracellular volume fraction (ECV) estimation using gadolinium-based contrast agents may be better able to detect diffuse fibrosis, with accumulating evidence of abnormal values following anthracycline treatment [15–17], and correlation with exercise capacity [16] and cardiac function [17] reported in paediatric and adult populations, respectively.

Therefore, the objectives of this study were to describe the long-term phenotype of anthracycline cardiomyopathy, determine the prevalence of focal (LGE) and diffuse (elevated native T1 measurements) myocardial fibrosis and their association with cardiac remodeling, function and clinical outcomes.

2. Methods

2.1. Study population

Consecutive patients referred for CMR at a tertiary referral center (Bristol Heart Institute, Bristol, United Kingdom) between January 2010 and January 2017 were screened for eligibility. Inclusion criteria were: age >18 years and evidence of cardiotoxicity after anthracycline chemotherapy, which was defined either as an LVEF of <57% or symptoms and/or signs of congestive heart failure. Exclusion criteria were: abnormal LV ejection fraction prior to therapy, concomitant cardiac disease that could cause heart failure including ischemic heart disease (infarct pattern on LGE or inducible myocardial ischemia during pharmacological stress), hypertrophic cardiomyopathy, moderate-severe valvular heart disease or valve replacement, history of excessive alcohol consumption (>28 standard units per week), active thyroid disease or family history of cardiomyopathy in a first degree relative. The local institutional research and innovation department (Bristol Royal Infirmary) approved the study and all patients provided written consent for use of anonymized data for research purposes at the time of CMR.

2.2. Clinical characteristics

The following data were collected: demographics, body surface area, body mass index, comorbidities, medications, cancer diagnosis, cancer therapy (including date, dose and type of therapy), New York Heart Association (NYHA) functional class at the time of CMR, hospitalizations for heart failure and all-cause mortality.

2.3. CMR - volumes and function

All patients underwent CMR at 1.5 Tesla (Avanto, Siemens, Erlangen, Germany). Short-axis steady state free precession (SSFP) whole left ventricular (LV) cines (typical scan parameters: 8 mm slice thickness, no slice gap, temporal resolution 38.1 ms, echo time 1.07 ms, in-plane pixel size 1.5×0.8 mm) were used to determine biventricular volumes, left atrial volumes, left ventricular ejection fraction (LVEF) and left ventricular mass, which were indexed to body surface area, according to previously described methods [18]. All measurements were performed by experienced CMR readers (IH/CBD) blinded to clinical details using previously validated [19] threshold-detection software (CMR42, Circle Cardiovascular Imaging, Calgary, Canada) by manually drawing the epicardial and endocardial borders at end systole and end diastole, taking particular care to track the mitral valve plane through the cardiac cycle.

2.4. CMR – LGE

LGE imaging was used to detect focal myocardial fibrosis according to previously described methods [18] after the administration of 0.1 mmol/kg Gadovist (Bayer, Reading, United Kingdom) with an inversion time progressively set to null normal myocardium. The presence, location and extent of LGE in each of the 16 American Heart Association (AHA) segments was adjudicated qualitatively by two experienced, independent CMR readers (IH/CBD) with consensus required in cases of discrepancy. Patients were divided into groups according to the presence of focal myocardial fibrosis.

2.5. CMR – native myocardial T1 mapping

Native myocardial T1 maps were obtained in short axis using the modified look-locker inversion recovery sequence i.e. 35° flip angle, 100 ms minimum TI, 80 ms TI increment, 150 ms time delay with 5-(3)-3 heartbeat acquisition scheme [20]. Regions of interest were drawn on motion-corrected T1 maps in the mid cavity interventricular septum to determine native myocardial T1 measurements using Argus software (Siemens, Germany) by an experienced CMR reader (IH), avoiding areas exhibiting LGE. Patients were divided into those with normal native myocardial T1 measurements (<1065 ms) and those with increased native myocardial T1 measurements (>1065 ms), according to the locally-established normal reference range of 1024 SD 41 ms (mean SD standard deviation) for a control population [21]. Secondary analysis, treating native myocardial T1 as a

continuous variable was undertaken to explore correlations with cardiac morphology and function. ECV was calculated using the established formula [22]:

$$ECV = \frac{\Delta R1_{myocardium}}{\Delta R1_{blood}} \times (1 - Hematocrit)$$

where

$$\Delta R1 = \left(\frac{1}{T1_{postcontrast}} - \frac{1}{T1_{native}} \right).$$

2.6. Statistical analysis

Descriptive statistics were reported for all study data, including means and standard deviations for continuous variables, and counts and percentages for categorical variables. Differences between groups were assessed with student *t*-test and Mann-Whitney *U* test for normally and non-normally distributed variables, respectively. Univariate and multivariate linear regression models were built to assess the association between outcomes of interest and one or more predictors, including controlling for age and gender in some of the associations. A *p* value <0.05 was taken to indicate statistical significance. The analysis was carried out in Stata (Stata v. 13, StatCorp LLC, Texas United States).

3. Results

3.1. Patient characteristics

81 patients were eligible for inclusion (62 with LVEF <57% and 19 with symptoms and/or signs of heart failure). Their baseline characteristics are summarized in Table 1. Mean age was 55 SD 14 years; 68% were women. The majority of patients were treated for breast cancer (58%) or hematological malignancy (38%). 56 of the patients (69%) had a baseline LVEF >55% on echocardiography. Baseline data was not available for 23 patients (28%), commonly because their treatment was administered in excess of 10 years prior to CMR. Baseline echo was not undertaken in 2 patients (2%) due to perceived low clinical risk of cardiomyopathy. As a component of a variety of chemotherapeutic regimens, the mean cumulative equivalent doxorubicin dose was 279 SD 89 mg/m^2 (range 50–450 mg/m^2). Anthracycline dose did not correlate significantly with ventricular volumes or systolic function; neither did the administration of radiotherapy (p > 0.05 in all cases). Median time from therapy to CMR was 60 months (interquartile range 17–152 months). Follow-up commenced at the time of referral for CMR and medical records were reviewed a median of 21 months (interquartile range 12–33 months) after CMR. During the study, 28% of the study population were hospitalized with a diagnosis of heart failure recorded in their medical records and 6% died. Overall LVEF was impaired (49 SD 12%), driven by a pathologically increased iLVESV (47 SD 23 ml/m^2) when compared to established normal reference ranges [23]. iLVEDV (87 SD 25 ml/m^2) remained within established normal reference ranges, albeit toward the upper limit [23], as did indexed left ventricular mass (iLVM) (58 SD 15 g/m^2).

The predominant left ventricular phenotypes were (Fig. 1, Panel A): normal iLVM and normal iLVEDV (33%; normal phenotype), normal iLVM and high iLVEDV (22%; eccentric dilatation) and small iLVM and normal iLVEDV (21%; myocardial atrophy).

3.2. LGE imaging for focal myocardial fibrosis

LGE was observed in 19% of patients and was located exclusively in the mid-myocardium (non-ischaemic pattern) affecting a mean of 2.6 SD 1.4 segments in each patient. The commonest affected myocardial segment was the basal inferoseptal segment (53% of patients with LGE exhibited it here; Fig. 1. Panel C).

Patients with LGE were more likely to be male (67 vs 36%, p = 0.01), have diabetes (13% vs 2%, p = 0.03) and were scanned at a greater time interval after cancer therapy (153 SD 110 vs 96 SD 116 months, p = 0.02). No other differences in baseline characteristics of patients with and without LGE were identified, including cumulative

anthracycline dose (310 SD 101 vs 272 SD 85 mg/m², p = 0.23; Table 1).

Patients with LGE had significantly reduced LVEF (43 SD 11 vs 50 SD 12%, p = 0.03) and significantly increased iLVEDV (102 SD 34 vs 83 SD 21 ml/m², p = 0.03), iLVESV (61 SD 32 vs 43 SD 20 ml/m², p = 0.03) and iLVM (65 SD 14 vs 56 SD 14 g/m², p = 0.04), compared to those without (Table 2). No significant differences in right ventricular volumes or systolic function, MAPSE or LAVi were observed. Hospitalizations with heart failure were similar between groups. 2 patients (13%) with LGE died during follow-up in comparison to three (5%) patients without (Table 2).

Multivariable regression analysis adjusting for age, sex, and diabetic status showed that the presence of LGE had a significant positive association with iLVEDV (p = 0.03, CI 2.15–31.0), and iLVESV (p = 0.03, CI 1.29–28.2) but not with LVEF (p = 0.17, CI 11.7–2.08) or other parameters.

3.3. Native myocardial T1 mapping techniques

Native myocardial T1 mapping sequences were available for analysis in a subgroup of 36 patients. 23 patients (64%) had normal native myocardial T1 measurements (1023 SD 28 ms), and 13 (36%) had increased native myocardial T1 measurements (1092 SD 20 ms) using the mean native myocardial T1 + 1 SD (1065 ms) of a locally-derived healthy control population as a cut point (Table 2) [21]. Baseline characteristics were matched (Table 1).

Patients with increased native myocardial T1 measurements had significantly reduced LVEF (44 SD 13 vs 55 SD 9%, p = 0.01) and significantly increased iLVEDV (97 SD 22 vs 74 SD 19 ml/m², p = 0.002) and iLVESV (56 SD 22 vs 35 SD 15 ml/m², p = 0.005), compared to those with normal measurements, differences which persisted in regression analysis controlling for age and sex (LVEF [p = 0.003, CI −20.4 to −4.7], iLVEDV [p = 0.004, CI 8.8–40.9], iLVESV [p = 0.001, CI 9.9–37.6]). Regression analysis controlling for age and sex also revealed that LAVi was significantly increased in patients with increased native myocardial T1 measurements (p = 0.02, CI 2.3–24.3). Furthermore, hospitalizations for heart failure were higher (38% vs 9%, p = 0.03) in patients with increased native myocardial T1 measurements. The only death occurred in the group with normal native myocardial T1 measurements. Among patients with increased native myocardial T1 measurements, 1 (8%) also had evidence of focal fibrosis by LGE.

Secondary analysis treating native myocardial T1 as a continuous variable demonstrated significant positive correlations with iLVEDV (p ≤ 0.001, CI 0.15–0.48, R² 0.33), iLVESV (p < 0.001, CI 0.15–0.44, R² 0.36), LAVi (p = 0.04, CI 0.01–0.28, R²0.12) and LV mass indexed (p = 0.01, CI 0.04–0.27, 0.18); and significant negative correlations with LVEF (p < 0.001, CI −0.24 to −0.08, R² 0.35) and MAPSE (p = 0.02, CI −0.05 to −0.004, R² 0.14) (Fig. 2. Panels A–F). In 31 patients with post-contrast mapping sequences available for analysis, ECV correlated significantly with iLVEDV (p = 0.003, CI 111–476, R² 0.27) and iLVESV (p = 0.02, CI 42–378, R² 0.18) but not with LVEF (p = 0.1, CI −187−18, R² 0.09) or other parameters.

4. Discussion

This study provides several insights into the characteristics of late anthracycline cardiomyopathy. First, we observed that the primary driver of reduced LVEF in late phase anthracycline cardiomyopathy appeared to be a pathological increase in iLVESV and the predominant left ventricular phenotypes were: normal mass and normal volume, eccentric dilatation or myocardial atrophy with normal volume. Second, the prevalence of focal myocardial fibrosis at median 5 years post-therapy was relatively low (19%) and distributed exclusively in the mid-myocardium with a predilection for the basal and mid interventricular septum. Third, patients with LGE had significantly reduced LVEF compared to those without. Fourth, in subgroup analysis, the prevalence

of elevated native myocardial T1 measurements was relatively high (36%) and these patients had significantly reduced systolic function (LVEF), adverse left ventricular remodeling and a higher rate of hospitalization for heart failure compared to those with normal native myocardial T1 measurements. Fifth, native myocardial T1 measurements and ECV correlated with left ventricular volumes, and native T1 correlated with LVEF but ECV did not.

4.1. Cardiac morphology and function

In keeping with previous reports, the predominant mechanism of cardiotoxicity in our cohort was a pathological increase in iLVESV [5,7]. Both iLVM and iLVEDV, as well as all measures of RV volume and systolic function remained within established reference ranges [23]. Interestingly, iLVEDV was toward the upper limits of normal in the cohort as a whole but pathologically elevated in the subgroup of patients with focal fibrosis by LGE, suggesting that patients who exhibit focal fibrosis have a more severe or advanced cardiomyopathy than those who do not, though this was not associated with adverse clinical outcomes. In addition, a higher iLVM was observed in patients with focal fibrosis compared to those without. This elevation in mass is likely to be due to eccentric dilatation, rather than true hypertrophy, given that only 1% of the population had true LV hypertrophy (defined by a normal iLVEDV and high indexed left ventricular mass). Whilst the comparison is not direct, this finding is at odds to a previous report correlating lower iLVM with adverse clinical outcomes [9], and may relate to the differing timing, methodology and populations of the studies. A recently published longitudinal echocardiography study of breast cancer patients described a relative increase in indexed left ventricular mass, which was sustained at 3 years of follow-up [24]. Interestingly, cumulative anthracycline dose was not significantly associated with ventricular volumes or systolic function, which may relate to the relatively small sample size and absence of very high doses of anthracycline in our cohort.

It is interesting to note that there was considerable heterogeneity in the left ventricular phenotypes, though the majority of the study population displayed either a normal left ventricular phenotype (normal iLVEDV and normal LVMi), eccentric dilatation (normal LVMi and elevated iLVEDV), or a phenotype of myocardial atrophy (low LVMi and normal iLVEDV), with only a minority (11%) exhibiting the so-called Grinch syndrome phenotype (low iLVEDV with or without a normal LVMi) previously described by a paediatric study utilizing echocardiography [25]. Aside from methodological differences, this may also point to differing remodeling between children and adults.

4.2. LGE imaging - focal fibrosis

Commensurate with previous reports of both early [5,10], and late [9] anthracycline cardiomyopathy, the prevalence of LGE at a median interval of 5 years post-therapy was low. Interestingly, the minority of patients with LGE exhibited significantly higher indexed LV volumes and significantly lower LVEF than those without, though no association with adverse clinical outcomes was demonstrated. This is in keeping with the published anthracycline cardiomyopathy literature to date but inconsistent with meta-analysis of non-ischemic cardiomyopathies as a whole, where the presence of LGE predicts adverse cardiovascular outcomes [26]. The absence of this association could in part be due to the low prevalence of LGE and small sample size in studies of anthracycline cardiomyopathy to date but may also represent the limitation of this technique to detect the diffuse myocardial fibrosis typically associated with anthracycline cardiomyopathy [12]. It is noteworthy that patients with LGE were assessed after a significantly greater period than those without, which raises the question as to whether fibrosis develops over time and may explain why early studies of anthracycline cardiomyopathy have reported such a low prevalence of LGE. However, in univariate regression modeling of LGE, time interval between

chemotherapy and CMR was not significantly associated with left ventricular volumes or any parameters of systolic function, therefore it was excluded from the multivariable model.

4.3. Native myocardial T1 mapping – diffuse fibrosis

Historically, diffuse myocardial fibrosis has been difficult to detect without the inherent risks attached to invasive cardiac biopsy. However, the advent of native myocardial T1 mapping and ECV techniques by CMR now permit the quantification of diffuse fibrosis non-invasively [27] with excellent reproducibility and robust validation against biopsy-proven collagen volume fraction and extracellular space reported in explanted hearts [28] and biopsied patients with dilated cardiomyopathy [29]. Two previous studies of anthracycline cardiomyopathy in adults have described abnormal elevation of ECV in cancer survivors 3 years [15] and 7 years [17] after anthracycline treatment. The former established that this elevation occurs independently of other risk factors and the latter correlated this elevation directly with left atrial volume and negatively with diastolic function, and also described higher ECV in patients with reduced LVEF, compared to those with preserved LVEF. A further paediatric study provided complementary data correlating native myocardial T1 and ECV with exercise capacity, anthracycline dose and subtle ventricular remodeling [16]. Our study complements this work by demonstrating significant correlations between absolute native myocardial T1 measurements, ECV and measures of left ventricular volumes and systolic function in anthracycline cardiomyopathy and in this regard, provides novel insight. Patients with increased native myocardial T1 measurements displayed significant adverse left ventricular remodeling and reduced systolic function (as measured by LVEF), compared to those with normal native myocardial T1 measurements. A greater number of hospitalizations occurred in the sub-group with increased native myocardial T1 measurements. In addition, absolute values of native myocardial T1 and ECV correlated significantly with left ventricular volumes and native myocardial T1 also correlated with LVEF, MAPSE and LAVi. All of which would pathophysiologically suggest a greater burden of diffuse fibrosis in patients with larger ventricular volumes and worse systolic function. Finally, it is noteworthy that 13 (36%) of our subgroup had diffuse fibrosis judged by an abnormal native myocardial T1 measurement, but only 1 (8%) of these had coexisting evidence of focal fibrosis when assessed qualitatively by LGE. Therefore, relying solely on LGE would have misclassified 92% of these patients as not having fibrosis. This finding is again in keeping with the histopathological report of focal fibrosis in only 10% of explanted hearts with anthracycline cardiomyopathy [12]. CMR T1 techniques appear to offer additional insight in anthracycline cardiomyopathy, yet the precise role of these sequences as a diagnostic tool, method of monitoring and means of guiding therapy is yet to be defined and large scale, collaborative effort from multiple stakeholders is warranted.

4.4. Study limitations

This was a retrospective single-center study of a small and relatively heterogeneous cohort of patients referred for CMR on clinical grounds and, as such, the findings should be interpreted in this context and viewed as hypothesis-generating. The small sample size and low number of events mean that firm conclusions, particularly regarding clinical outcomes, cannot be drawn and large, prospectively conducted, multicenter studies are warranted to address this area of important clinical uncertainty. Native myocardial T1 mapping sequences and ECV estimation were not available for the entire study population due to the introduction of this sequence to our department in 2015, though we feel that this subgroup provides insight into the utility of this sequence in anthracycline cardiomyopathy. Finally, complementary echocardiographic, electrocardiographic, blood biomarker (including Troponin and BNP) and histopathological data were not

consistently available and the cross-sectional design of the study meant that temporal changes could not be assessed. A prospective study incorporating these measures prior to, during and after cancer therapy could address these limitations.

5. Conclusions

Late stage anthracycline cardiomyopathy is characterized by pathological increase in iLVESV, normal or dilated iLVEDV, low (19%) prevalence of focal septal fibrosis identified by LGE, and higher (36%) prevalence of diffuse fibrosis identified by elevated native T1 measurements. Both forms of fibrosis were associated with adverse left ventricular remodeling and reduced LVEF. A higher rate of hospitalization for heart failure was observed in patients with elevated native myocardial T1 mapping measurements.

Abbreviations

CMR	cardiovascular magnetic resonance
LGE	late gadolinium enhancement
LV	left ventricle
iLVEDV	left ventricular end-diastolic volume indexed
iLVESV	indexed left ventricular end-systolic volume indexed
LVEF	left ventricular ejection fraction
ECV	extracellular volume
MAPSE	mitral annular plane systolic excursion
TAPSE	tricuspid annular plane systolic excursion
LAVi	left atrial volume indexed

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Appendix A. Supplementary data

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References

[1] M.S. Ewer, S.M. Ewer, Cardiotoxicity of anticancer treatments: what the cardiologist needs to know, Nat. Rev. Cardiol. 7 (10) (2010) 564–575.

[2] J.C. Plana, M. Galderisi, A. Barac, et al., Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 27 (9) (2014) 911–939.

[3] J. Zamorano, An ESC position paper on cardio-oncology, Eur. Heart J. 37 (36) (2016) 2739–2740.

[4] S.H. Armenian, C. Lacchetti, A. Barac, et al., Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline, J. Clin. Oncol. 35 (8) (2017) 893–911.

[5] B.C. Drafts, K.M. Twomley, R. D'Agostino, et al., Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease, JACC Cardiovasc. Imaging 6 (8) (2013) 877–885.

[6] M.A. Lunning, S. Kutty, E.T. Rome, et al., Cardiac magnetic resonance imaging for the assessment of the myocardium after doxorubicin-based chemotherapy, Am. J. Clin. Oncol. 38 (4) (2015) 377–381.

[7] N. Chaosuwannakit, R. D'Agostino, C.A. Hamilton, et al., Aortic stiffness increases upon receipt of anthracycline chemotherapy, J. Clin. Oncol. 28 (1) (2010) 166–172.

[8] R. Wassmuth, S. Lentzsch, U. Erdbruegger, et al., Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging-a pilot study, Am. Heart J. 141 (6) (2001) 1007–1013.

[9] T.G. Neilan, O.R. Coelho-Filho, D. Pena-Herrera, et al., Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines, Am. J. Cardiol. 110 (11) (2012) 1679–1686.

[10] C. Lawley, C. Wainwright, E. Segelov, J. Lynch, J. Beith, J. McCrohon, Pilot study evaluating the role of cardiac magnetic resonance imaging in monitoring adjuvant trastuzumab therapy for breast cancer, Asia Pac. J. Clin. Oncol. 8 (1) (2012) 95–100.

[11] P. Thavendiranathan, B.J. Wintersperger, S.D. Flamm, T.H. Marwick, Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review, Circ. Cardiovasc. Imaging 6 (6) (2013) 1080–1091.

[12] B.N. Bernaba, J.B. Chan, C.K. Lai, M.C. Fishbein, Pathology of late-onset anthracycline cardiomyopathy, Cardiovasc. Pathol. 19 (5) (2010) 308–311.

[13] J. Stirrat, J.A. White, The prognostic role of late gadolinium enhancement magnetic resonance imaging in patients with cardiomyopathy, Can. J. Cardiol. 29 (3) (2013) 329–336.

[14] N. Fallah-Rad, J.R. Walker, A. Wassef, et al., The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy, J. Am. Coll. Cardiol. 57 (22) (2011) 2263–2270.

[15] J.H. Jordan, S. Vasu, T.M. Morgan, et al., Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors, Circ. Cardiovasc. Imaging 9 (8) (2016).

[16] E.B. Tham, M.J. Haykowsky, K. Chow, et al., Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling, J. Cardiovasc. Magn. Reson. 15 (2013) 48.

[17] T.G. Neilan, O.R. Coelho-Filho, R.V. Shah, et al., Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy, Am. J. Cardiol. 111 (5) (2013) 717–722.

[18] A.M. Maceira, S.K. Prasad, M. Khan, D.J. Pennell, Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 8 (3) (2006) 417–426.

[19] H. Childs, L. Ma, M. Ma, et al., Comparison of long and short axis quantification of left ventricular volume parameters by cardiovascular magnetic resonance, with ex-vivo validation, J. Cardiovasc. Magn. Reson. 13 (2011) 40.

[20] D.R. Messroghli, A. Radjenovic, S. Kozerke, D.M. Higgins, M.U. Sivananthan, J.P. Ridgway, Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart, Magn. Reson. Med. 52 (1) (2004) 141–146.

[21] J.C. Rodrigues, A.M. Amadu, A.G. Dastidar, et al., Comprehensive characterisation of hypertensive heart disease left ventricular phenotypes, Heart 102 (20) (2016) 1671–1679.

[22] A.S. Flett, M.P. Hayward, M.T. Ashworth, et al., Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans, Circulation. 122 (2) (2010) 138–144.

[23] N. Kawel-Boehm, A. Maceira, E.R. Valsangiacomo-Buechel, et al., Normal values for cardiovascular magnetic resonance in adults and children, J. Cardiovasc. Magn. Reson. 17 (2015) 29.

[24] H.K. Narayan, B. Finkelman, B. French, et al., Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up, Circulation 135 (15) (2017) 1397–1412.

[25] S.E. Lipshultz, Hearts too small for body size after doxorubicin for childhood ALL: the Grinch syndrome, J. Clin. Oncol. 32 (5) (2014) (Abstr).

[26] S. Kuruvilla, N. Adenaw, A.B. Katwal, M.J. Lipinski, C.M. Kramer, M. Salerno, Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis, Circ. Cardiovasc. Imaging 7 (2) (2014) 250–258.

[27] K.Y. Diao, Z.G. Yang, H.Y. Xu, et al., Histologic validation of myocardial fibrosis measured by T1 mapping: a systematic review and meta-analysis, J. Cardiovasc. Magn. Reson. 18 (1) (2016) 92.

[28] C.A. Miller, J.H. Naish, P. Bishop, et al., Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume, Circ. Cardiovasc. Imaging 6 (3) (2013) 373–383.

[29] S. Nakamori, K. Dohi, M. Ishida, et al., Native T1 mapping and extracellular volume mapping for the assessment of diffuse myocardial fibrosis in dilated cardiomyopathy, JACC Cardiovasc. Imaging 11 (1) (2018) 48–59.