Cardiac magnetic relaxometry versus ejection fraction in anthracycline-related cardiac changes: a systematic review and meta-analysis

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ABSTRACT

Purpose The purpose of this meta-analysis is to compare the magnitude of the changes in left ventricular ejection fraction (LVEF) and cardiac magnetic resonance (CMR) relaxometry techniques soon after the completion of anthracycline therapy. Anthracyclines are associated with myocardial functional and morphological changes. LVEF is currently used to identify the functional changes. Anthracyclines can also cause myocardial inflammation and oedema. This can be assessed using CMR relaxometry techniques; T1 and T2 mapping and extracellular volume (ECV) fraction.

Methods Three databases were systematically searched for studies evaluating CMR relaxometry parameter at baseline and ±1 months after anthracycline completion (the last search date 17 March 2023). CMR parameters pre and post anthracycline-based chemotherapy were abstracted. A random effects model was used to pool mean difference (MD) in LVEF and ECV. Standardised mean difference (SMD) was also calculated for T1 and T2 mapping due to the variations in techniques, normal ranges and for the comparison among the parameters.

Results A total of 296 patients were included from 10 studies. 84% were female with a mean age of 54.9 years. Statistically significant alterations were observed in LVEF (MD −3.38% (95% CI −5.13%, −1.62%)) and ECV (1.92% (1.30%, 2.53%)). The pooled SMDs were also significant in LVEF, T1, T2 and ECV with −0.61 (−0.91, −0.30), 0.53 (0.16, 0.90), 0.59 (0.22, 0.96) and 0.74 (0.41, 1.06), respectively.

Conclusions Our meta-analysis demonstrated small but significant alterations in CMR relaxometry parameters soon after anthracycline therapy, where ECV was superior to LVEF and T1 or T2 mapping. However, these short-term MDs were below the minimal detectable differences.

INTRODUCTION

Advances in cancer treatment have led to a substantial increase in cancer survivors over the last decade.1 This has been largely driven by the development of new cancer therapies and improved treatment regimes. These treatments can have cardiotoxic effects, and combined with the shared risk factors of an ageing population, patients with cancer are at risk of cancer therapeutics-related cardiac dysfunction (CTRCD).

Anthracyclines are the backbone of many cancer therapy regimes such as breast, sarcoma and haematological malignancies. They are associated with CTRCD, even after a single dose, which in turn can cause myocardial inflammation and oedema.2,3 The identification of anthracycline CTRCD currently uses a change in left ventricular ejection fraction (LVEF) and/or clinical symptoms.4 Identification of anthracycline-related CTRCD is important, as early identification and prompt treatment are crucial for recovery of cardiac function.5

Cardiac magnetic resonance (CMR) is the non-invasive gold standard method for the diagnosis of myocardial inflammation and has a key role in cardio-oncology.6,7 CMR relaxometry techniques such as T1 and T2 mapping and extracellular volume (ECV)
fraction have been proposed as potential imaging techniques superior to LVEF in identifying anthracycline-related myocardial alterations. Despite this, there is conflicting evidence on which parameter is better at identifying these changes, if any at all. As a result, there is no clear consensus on whether any one CMR relaxometry parameter is best at identifying anthracycline-related myocardial changes.

Therefore, we performed a systematic review and meta-analysis of studies that assessed the magnitude of the changes in LVEF and CMR relaxometry techniques soon after the completion of anthracycline therapy to consolidate available literature using a standard approach.

METHODS

Search strategy

We performed a systematic review of literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify all cardio-oncology studies involving baseline and serial CMR relaxometry scans in those undergoing anthracycline chemotherapy. The search strategy was designed to address our aim, and we followed a structured patient, intervention, control and outcome (PICO) format to define our inclusion criteria. The population included patients with any malignancy who required anthracycline-based chemotherapy and underwent pre-anthracycline and post-anthracycline CMRs with CMR relaxometry performed. If clinical trials were identified, we focused on the placebo arms of these eligible trials, so that only patients who did not receive any cardioprotective intervention were included. We searched MEDLINE, EMBASE and SCOPUS, from database inception until the search date 17 March 2023, to identify eligible studies. Key search terms that were used included ‘antineoplastic agents’, ‘anthracycline’, ‘cardiotoxicity’ and ‘magnetic resonance imaging’. Our search strategies for all included databases are provided in online supplemental table S1. We also performed manual searches of reference lists from relevant systematic reviews and guidelines and incorporated additional relevant studies into our overall search. The study was prospectively registered in the PROSPERO database of systematic reviews (registration number: CRD42020196296). Our primary outcome was the change in LVEF, T1 and T2 mapping times, and ECV fraction from baseline to post anthracycline-based chemotherapy with CMR imaging.

Study selection

Databases were searched by two independent reviewers (CY and SP), and pertinent articles were screened by title, abstract and full text. Disputes between the two reviewers were adjudicated by a third, senior author (KN). Studies were included according to the following criteria: (1) written in English, (2) sample size 10 or more, (3) pre and post (1±1 months after anthracycline completion, which is 4±1 months post baseline) anthracycline CMR performed with LVEF and relaxometry techniques, and (4) full-text published articles. Articles were excluded for the following reasons: (1) only animal or paediatric data were reported, or (2) participants had previously received anthracycline-based therapy prior to baseline CMR assessment to avoid measuring pre-existing cardiotoxicity.

Data extraction

Patient characteristics such as sample size, age, sex and cancer type were extracted into an electronic data-entry form. Cancer therapy protocols including anthracycline type and dose were also obtained. We used conversion factors described in the 2016 European Society of Cardiology (ESC) position paper to standardise anthracycline types into a single measure termed doxorubicin equivalent anthracycline dose (EAD). For example, this allowed epirubicin doses to be scaled to doxorubicin dose with scaling factors of 0.7. LVEF and CMR relaxometry values pre and post anthracycline therapy, along with corresponding SD, were also included to ascertain the mean difference (MD) in unadjusted LVEF and CMR relaxometry values after anthracycline administration. If SD were not available in the main or supplementary text, corresponding authors were contacted to obtain the raw data, other statistical information and scanning protocols. If data remained outstanding, it was derived using published methods from statistical significance tests or CIs.

Statistical analysis

Data were meta-analysed with R statistical software V.3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) with the ‘metafor’ package. A random effects model was used as primary analytical method to pool the MD between LVEF and ECV fraction pre and post anthracycline therapy. We chose the random effects model because we assumed that the effects being estimated in the different studies are not identical but follow some distribution. More precisely, we assumed that LVEF and CMR relaxometry changes due to anthracycline cardiotoxicity varies from study to study and the true change for these studies would be distributed around a mean. A fixed effects model was also used as sensitivity analysis. We calculated standardised mean difference (SMD, also known as Cohen’s D) in particularly for T1 and T2 acquisition times pre and post anthracycline therapy because of the variation in T1 and T2 acquisition technique and variation between scanners. SMD has been used in a previous review to assess pooled effect size of CMR relaxometry. Findings were considered statistically significant if p<0.05. Heterogeneity between studies was assessed using I². We used the Cochrane Risk of Bias (ROB) Tool V.2 for randomised controlled trials and plotted outcomes as either ‘low’, ‘some concern’ or ‘high’ across the five primary domains. Other studies were assessed by the Newcastle–Ottawa (NO) quality assessment scale (QAS).
RESULTS

We identified 10 studies relevant to our analysis after performing a literature search in accordance with the PRISMA guidelines, as shown in figure 1. Baseline characteristics for each included study are summarised in table 1. A total of 296 patients were included, 84% were female with a mean age of 54.9 years. Among the 10 studies, 6 studies focused on breast cancer, 3 on a combination of breast, lymphoma and sarcoma, and 1 on sarcoma. Five of the studies used doxorubicin exclusively, two used doxorubicin and epirubicin, two used epirubicin, and the anthracycline agent was not specified in one study. Regarding anthracycline dosing, the mean doxorubicin EAD was 266 mg/m². Patients were followed up for an average of 9.2 months across the 10 included studies; however, we only used follow-up data on completion of anthracycline therapy (3–5 months post baseline). All the studies used CMR to measure LVEF.

Six studies used 1.5 Tesla (T) CMR, three with 3T CMR and one study unspecified. There is variation in CMR relaxometry parameters due to variation in imaging acquisition techniques. The T1 mapping studies we analysed used modified Look-Locker technique (MOLLI) (six studies) and shortened modified Look-Locker technique (shMOLLI) (one study). We did not use saturation recovery single shot acquisition (SASHA) T1 values as the only study that provided these values also provided shMOLLI values, which were used instead. T2 technique commonly use steady-state free precession (SSFP) or gradient-spin-echo (GraSE). Our analysis involved predominantly the T2-SSFP technique.

LVEF and CMR relaxometry measures pre and post chemotherapy for each included trial are shown in table 2. The pooled MDs in LVEF and ECV pre and post anthracycline-based chemotherapy are shown in figure 2. Using a random effects model, the overall change in pooled MD of LVEF and ECV were −3.38% (95% CI −5.13%, −1.62%) (ie, 3.38 percentage point reduction in EF) and 1.92% (1.30%, 2.53%) (ie, 1.92 percentage increase in ECV), respectively. There was substantial heterogeneity for MD in LVEF among included studies, with an I² statistic of 69%; whereas studies included for ECV analysis were homogeneous with an I² statistic of 0%. Subsequent subgroup analysis showed significantly reduced heterogeneity of LVEF to 51% when limited to the articles with 1.5T magnet.

To compare the effect sizes of alterations in CMR relaxometry parameters, we calculated pooled SMD pre and post anthracycline-based chemotherapy (figure 3). The overall change in pooled SMD value for LVEF, T1, T2 and ECV were −0.61 (−0.91, −0.30), 0.53 (0.16, 0.90), 0.59 (0.22, 0.96) and 0.74 (0.41, 1.06), respectively. Significant heterogeneity was noted for the SMDs in LVEF, T1 and T2 time with an I² statistic of 65%, 70% and 75%; while studies included for ECV or T1 analysis were homogeneous with an I² statistic of 35%. The pooled MD and SMD for each CMR parameter are summarised in table 3.

DISCUSSION

This is the first systematic review and meta-analysis to determine the pooled magnitude of the alterations in LVEF and CMR relaxometry techniques soon after the completion of anthracycline therapy. Our key findings are (1) ECV performed early post completion of anthracycline therapy identifies myocardial changes slightly better than LVEF, T1 and T2 mapping. (2) The pooled SMDs in LVEF, T1 and T2 were similar, suggesting that the incremental role of T1 and T2 mapping in CTRCD assessment over LVEF maybe limited. (3) Our pooled risk of bias assessment by individual study is included in online supplemental supplementary tables S2 and S3.

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.
Table 1  Baseline characteristics of included studies

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<th>Author</th>
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<th>T1</th>
<th>T2</th>
<th>ECV</th>
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<th>Mean age (years)</th>
<th>Cancer type</th>
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Mixed—both breast cancer and haematological malignancies.
CMR, cardiac magnetic resonance; EAD, equivalent anthracycline dose standardised to doxorubicin.
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CMR, cardiac magnetic resonance; ECV, extracellular volume; LVEF, left ventricular ejection fraction.
MD for these CMR parameters were below the reported minimal detectable differences of healthy controls in recent studies.14

T1 mapping provides a surrogate measure of intracellular and extracellular alterations, whereas T2 mapping is a surrogate measure of myocardial water content.26 ECV is a surrogate measure of interstitial fibrosis. These measures allow one to identify changes in myocardial tissue characteristics such as fibrosis, oedema, inflammation and fat infiltration. As a result, CMR relaxometry has been proposed as a potential imaging biomarker in detecting anthracycline-related cardiac alterations and CTRCD.8 11 13 15 17

Accommodating for differences among CMR scanners and acquisition techniques, we compared parameters using SMD to perform a pooled analysis as used before.22 Our T1, T2, ECV and LVEF pooled findings of a SMD change of 0.53 (0.16, 0.90), 0.59 (0.22, 0.96), 0.74 (0.41, 1.06) and −0.61 (−0.91, −0.30), respectively, are in keeping with numerous studies.8 9 12 13 15 27–29 However, no study has compared the changes among each CMR relaxometry parameters with LVEF. The pooled ECV SMD values indicate these parameters maybe a better imaging parameter at identifying early cardiac changes post anthracycline therapy than T1 and T2 mapping (0.74 vs 0.53 and 0.59, respectively). The increase in ECV we observed in this study is similar to another study’s effect size (SMD 0.8) in patients with anthracycline mediated cardiomyopathy.32 30 The superiority of ECV over T1 or T2 mapping would be due to its method of calculation. In MR relaxometry, several key factors affect the T1 and T2 values, including magnet strength (1.5T or 3T), sequence (MOLLI, ShMOLLI, etc) and vendor. When calculation the ECV, these factors are cancelled out. Our results suggest that ECV changes can begin early post anthracycline therapy.22 In this study, the ECV had the largest pooled SMDs. This indicates the incremental role of ECV over LVEF in CTRCD assessment. However, this requires further investigation with larger studies as the incremental benefit was small.

Echocardiography LVEF remains the primary imaging modality for cardiac function assessment due to its higher availability and lower cost despite CMR being the gold standard with superior reproducibility.4 31–34 Our recent meta-analysis involving echocardiographic LVEF demonstrated a pooled mean decline in those undergoing anthracycline therapy of −5.6% (−3.3%, −7.95).29 Our study identified the pooled CMR LVEF MD decline was even smaller at −3.38% (−5.13%, −1.62%). This value is below the smallest detectable change in CMR of 5.8% in a healthy CMR cohort, suggesting CMR LVEF alone be inadequate to detect CTRCD early post anthracycline cessation.35 When CMR LVEF is compared with CMR relaxometry techniques, only ECV appears to be slightly better at detecting cardiac changes early post anthracycline therapy. Thus, the role of CMR relaxometry in the assessment of cardiac changes early post anthracycline therapy is limited in current literature. Besides, our T1, T2 and ECV MD values were below the minimal detectable differences in a recent CMR study; T1: 29 ms, T2: 3.0 ms and ECV: 2.2%.14 Therefore, like LVEF, serial CMR relaxometry may not be sensitive enough to identify...
Meta-analysis

The use of MD in our study may be limited due to pooling of values from different scanner field strengths and imaging techniques. Thus, further prospective studies are needed to determine the extent of this limitation. Lastly, it is important to note we were not able to obtain complete data of those who did and did not develop CTRCD, thus we cannot comment on the ability of these parameters to predict CTRCD. Nevertheless, we are the first study to describe the natural history of changes in CMR relaxometry pre and post anthracycline therapy, which will be useful in planning future studies in this field. The

Figure 3  Forest plots for standardised mean difference (SMD) in MRI relaxometry parameters. Using a random effects model, the overall change in pooled SMD value for left ventricular ejection fraction (LVEF) (A), extracellular volume (ECV) (B), T1 (C), and T2 (D) were −0.61 (−0.78, −0.43), 0.74 (0.41, 1.06), 0.53 (0.16, 0.90) and 0.59 (0.22, 0.96), respectively.

Table 3  Pooled mean difference and standardised by CMR parameters

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<td>−3.38</td>
<td>−5.13, −1.62</td>
<td>−0.61</td>
<td>−0.91, −0.30</td>
</tr>
<tr>
<td>T1 (ms)</td>
<td>20.84</td>
<td>8.02, 33.66</td>
<td>0.53</td>
<td>0.16, 0.90</td>
</tr>
<tr>
<td>T2 (ms)</td>
<td>2.16</td>
<td>0.72, 3.61</td>
<td>0.59</td>
<td>0.22, 0.96</td>
</tr>
<tr>
<td>ECV (%)</td>
<td>1.92</td>
<td>1.30, 2.53</td>
<td>0.74</td>
<td>0.41, 1.06</td>
</tr>
</tbody>
</table>

ECV, extracellular volume; LVEF, left ventricular ejection fraction; ms, milliseconds.

anthracycline-related changes at an individual patient level. Furthermore, the use of MD in our study may be limited due to pooling of values from different scanner field strengths and imaging techniques. Thus, further prospective studies are needed to determine the extent of this limitation. Lastly, it is important to note we were not able to obtain complete data of those who did and did not develop CTRCD, thus we cannot comment on the ability of these parameters to predict CTRCD. Nevertheless, we are the first study to describe the natural history of changes in CMR relaxometry pre and post anthracycline therapy, which will be useful in planning future studies in this field. The

next step, maybe to assess the role of a combination approach of CMR relaxometry with other biomarkers to optimise anthracycline-related changes as well as longer term studies.

Limitations
Several points merit consideration in the interpretation of our results. First, like all meta-analyses, this work is limited by variations in the original studies and publication bias, although we followed standard approaches to detect this. Likewise, the constituent observational studies may be limited by biases in the recruitment process. We could not perform individual patient data meta-analysis although we contacted the corresponding authors multiple times. This did not allow us to extensively explore the underlying reasons for such marked heterogeneity among the T1 and T2 mapping studies. Second, CMR relaxometry is a relatively novel technique with differences between CMR field strengths, acquisition technique, analysis software and measurement techniques, which may have caused heterogeneity between studies. Third, our sample size was small, partly due to only early CMR scans post anthracycline being analysed. We were unable to assess longer term changes (>12 months), as only four studies were identified (three for T2 and one for ECV) (online supplemental tables S4). Fourth, the studied population was predominantly female undergoing anthracycline therapy for breast cancer. This limits the external validity of our review to male patients and to patients with non-breast cancer malignancies receiving anthracyclines.

CONCLUSIONS
Although current literature on the role of CMR relaxometry in the short-term post anthracycline therapy is limited, our meta-analysis demonstrated small but significant alterations in CMR relaxometry parameters soon after anthracycline therapy, where ECV was slightly superior to LVEF and T1 or T2 mapping. There is not sufficient data to support the role of CMR relaxometry in the short-term post anthracycline therapy as the changes are below the minimal detectable difference and thus future studies at longer time points post anthracyline chemotherapy must be considered.

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Contributors KN and CY conceptualised the study design. CY and SP collected data. PJ performed the statistical analysis. CY drafted the manuscript. All authors edited and approved the final manuscript. KN, as the guarantor, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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