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ORIGINAL RESEARCH

Anthracycline Therapy Is Associated With Cardiomyocyte Atrophy and Preclinical Manifestations of Heart Disease

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ABSTRACT

OBJECTIVES The goal of this study was to demonstrate that cardiac magnetic resonance could reveal anthracycline-induced early tissue remodeling and its relation to cardiac dysfunction and left ventricular (LV) atrophy.

BACKGROUND Serum biomarkers of cardiac dysfunction, although elevated after chemotherapy, lack specificity for the mechanism of myocardial tissue alterations.

METHODS A total of 27 women with breast cancer (mean age 51.8 ± 8.9 years, mean body mass index 26.9 ± 3.6 kg/m^2), underwent cardiac magnetic resonance before and up to 3 times after anthracycline therapy. Cardiac magnetic resonance variables were LV ejection fraction, normalized T2-weighted signal intensity for myocardial edema, extracellular volume (ECV), LV cardiomyocyte mass, intracellular water lifetime (τ_{ic}; a marker of cardiomyocyte size), and late gadolinium enhancement.

RESULTS At baseline, patients had a relatively low (10-year) Framingham cardiovascular event risk (median 5%), normal LV ejection fractions (mean 69.4 ± 3.6%), and normal LV mass index (51.4 ± 8.0 g/m^2), a mean ECV of 0.32 ± 0.038, mean τ_{ic} of 169 ± 69 ms, and no late gadolinium enhancement. At 351 to 700 days after anthracycline therapy (240 mg/m^2), mean LV ejection fraction had declined by 12% to 58 ± 6% ($p < 0.001$) and mean LV mass index by 19 g/m^2 to 36 ± 6 g/m^2 ($p < 0.001$), and mean ECV had increased by 0.037 to 0.36 ± 0.04 ($p = 0.004$), while mean τ_{ic} had decreased by 62 ms to 119 ± 54 ms ($p = 0.004$). Myocardial edema peaked at about 146 to 231 days ($p < 0.001$). LV mass index was associated with τ_{ic} ($\beta = 4.1 \pm 1.5$ g/m^2 per 100-ms increase in τ_{ic}, $p = 0.007$) but not with ECV. Cardiac troponin T (mean 4.6 ± 1.4 pg/ml at baseline) increased significantly after anthracycline treatment ($p < 0.001$). Total LV cardiomyocyte mass, estimated as: (1 − ECV) × LV mass, declined more rapidly after anthracycline therapy, with peak cardiac troponin T >10 pg/ml. There was no evidence for any significant interaction between 10-year cardiovascular event risk and the effect of anthracycline therapy.

CONCLUSIONS A decrease in LV mass after anthracycline therapy may result from cardiomyocyte atrophy, demonstrating that mechanisms other than interstitial fibrosis and edema can raise ECV. The loss of LV cardiomyocyte mass increased with the degree of cardiomyocyte injury, assessed by peak cardiac troponin T after anthracycline treatment. (Doxorubicin-Associated Cardiac Remodeling Followed by CMR in Breast Cancer Patients; NCT03000036)
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ABBREVIATIONS AND ACRONYMS

AIC = anthracycline-induced cardiotoxicity

BC = breast cancer

CM = cardiomyocyte mass

CMR = cardiac magnetic resonance

CRP = C-reactive protein

cTnT = cardiac troponin T

CVD = cardiovascular disease

ECV = extracellular volume

GAM = generalized additive model

HF = heart failure

LGE = late gadolinium-diethylenetriaminepentaacetic acid enhancement

LME = linear mixed-effects

LV = left ventricular

LVEF = left ventricular ejection fraction

τ_{ic} = intracellular lifetime of water

TR = repetition time

Anthracyclines are commonly implicated in adverse effects on the cardiovascular system (1), including potentially irreversible cardiomyopathy and incident heart failure (HF) (2). Mortality secondary to HF from anthracycline-induced cardiotoxicity (AIC) ranges from 30% to 70%, and a third of patients do not show improvement in left ventricular ejection fraction (LVEF) with HF therapy (3). Thus, there is a need to better understand the effects and mechanisms of AIC. Detecting early alterations in myocardial structure and function may facilitate earlier intervention and reduce HF.

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Recent experimental studies demonstrated that early and subclinical myocardial effects of AIC included increased levels of interstitial fibrosis, edema, and reduced cardiomyocyte size (4–6), which may all be potentially characterized by cardiac magnetic resonance (CMR).

In this study, we investigated AIC using novel CMR markers of myocardial tissue remodeling, including extracellular volume (ECV), a marker of interstitial fibrosis, and the intracellular lifetime of water (τ_{ic}), a marker of cardiomyocyte size. We hypothesized that these novel CMR indexes would further elucidate the mechanisms of myocardial injury in patients with breast cancer (BC) treated with anthracyclines (7) and their relation to biochemical indicators.

METHODS

STUDY DESIGN. Between 2012 and 2015, we enrolled 27 women with BC (NCT03000036). Patients were consecutively enrolled if they had received BC diagnoses and had planned adjuvant anthracycline-based therapy (doxorubicin in 4 cycles at 60 mg/m^2, total dose of 240 mg/m^2). Exclusion criteria were contraindications to CMR, kidney disease (glomerular filtration rate <40 ml/min), previous myocardial infarction, clinical diagnosis of HF, or moderate and severe valve disease. Serial CMR scans were obtained at baseline and consecutive time points (**Figure 1**). In addition, detailed medical history, standard anthropometric data, and laboratory evaluation were performed alongside CMR. Our local Institutional Review Board approved the study (Certificado de Apresentação para Apreciação Ética: 0675.0.146.000-11). All participants provided written informed consent prior to study enrollment.

FOLLOW-UP. Clinical assessment and CMR imaging were performed before and up to 3 times serially after cumulative anthracycline treatment (median times 140, 231, and 427 days from initiation of anthracycline therapy for visits 1, 2, and 3, respectively) (**Figure 1**). Because the CMR studies did not conform to an exact timetable (because of clinical exigencies and patient compliance), time ranges for study visits overlapped significantly (Online Table 1). For the longitudinal analysis, we therefore categorized the follow-up times into quartile ranges. Radiotherapy was performed in 25 patients (5,040 cGy; bilateral, n = 1; left side, n = 14; right side, n = 10) at a median time of 183 days (interquartile range: 160 to 266 days) after the baseline CMR examination. Trastuzumab, when clinically indicated, was initiated after the last CMR examination.

BIOCHEMICAL ANALYSIS. Blood samples were obtained at baseline and at each anthracycline cycle and before each CMR examination. Glucose, glycated hemoglobin, triglycerides, high- and low-density lipoprotein cholesterol (AU5800, Beckman Coulter, Brea, California) were obtained at baseline after 12 h of fasting. C-reactive protein (CRP) (CardioPhase, BN ProSpec System, Siemens Healthineers, Erlangen, Germany), creatine kinase, creatine kinase myocardial band (AU5800), and high-sensitivity cardiac troponin T (cTnT) (Cobas e601 immunoassay analyzers, Roche Diagnostics, Mannheim, Germany) were obtained at baseline, before each anthracycline cycle, and before each CMR visit.

CMR. Patients were imaged using a 3-T system (Achieva, Philips Medical Systems, Best, the Netherlands) with a 5-element phased-array surface coil. The CMR protocol comprised the following electrocardiographically gated imaging sequences: 1) breath-hold, black-blood T2-weighted imaging of edema in short axis using sensitivity encoding (factor = 1) for surface-coil intensity correction (5 to 10 slices with 10-mm thickness, repetition time [TR] 2[R-R], echo

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