Tropical Journal of Pharmaceutical Research October 2024; 23 (10): 1709-1715
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i10.16

Original Research Article

Cardiac magnetic resonance assessment of the effect of anthracycline-based chemotherapy on cardiac structure and function in breast cancer patients

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Sent for review: 23 June 2023 *Revised accepted: 16 September 2024*

Abstract

Purpose: *To use cardiac magnetic resonance (CMR) imaging to investigate the effect of anthracycline-based chemotherapy on cardiac structure and function in breast cancer patients.*

Methods: *A total of 20 breast cancer patients who received treatment at Shandong Cancer Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China between October 2021 and October 2022 were included in this study. The patients underwent surgical treatment and also received anthracycline-based chemotherapy after surgery. Before chemotherapy, and at 3 months and 6 months after chemotherapy, CMR examinations were performed on all the participants. Cardiac function parameters, viz, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF), were measured and compared at different time points.*

Results: *There were no significant differences in LVEF, LVEDV, and LVESV among different time points ($p > 0.05$). Similarly, there were no significant differences in RS, CS, LS, SRSR, SCSR, SLSR, DCSR, and DLSR among the different time points ($p > 0.05$). However, diastolic radial strain rate (DRSR) level at 6 months after treatment was significantly lower than the corresponding values before treatment and at 3 months post-treatment ($p > 0.05$), indicating a progressive decrease in DRSR over time.*

Conclusion: *Cardiac magnetic resonance imaging provides a valuable assessment of myocardial damage in breast cancer patients following anthracycline-based chemotherapy, while DRSR may serve as a sensitive parameter for early detection of myocardial injury using CMR. However, an improved study protocol should enhance the applicability of the approach.*

Keywords: *Cardiac magnetic resonance, Anthracycline-based chemotherapy, Breast cancer, Cardiac structure and function*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide. Anthracycline-based chemotherapy is frequently used in the treatment of breast cancer, and it produces significant therapeutic effectiveness [1]. However, studies have indicated that anthracycline-based drugs are associated with cardiac toxicity [2]. Cardiac toxicity primarily manifests as myocardial cell

necrosis, myocardial fibrosis, and left ventricular dysfunction [3]. Cardiac toxicity caused by anthracycline-based chemotherapy results in detrimental effects on their quality of life and long-term survival rates of breast cancer patients.

Cardiac magnetic resonance (CMR) [4] is one of the most commonly used non-invasive imaging techniques for evaluating cardiac structure and function. It provides information on cardiac structure at rest and allows for quantitative assessment of myocardial contractile function using strain imaging techniques [5]. Moreover, CMR provides detailed information on cardiac structure, function, and metabolic status, offering high resolution and sensitivity in the diagnosis of subtle myocardial damage [6]. Therefore, CMR has been widely employed in assessing cardiac toxicity and monitoring of the impact of chemotherapy on the heart. However, in practice, there are limited reports on the use of CMR for evaluation of the effects of anthracycline-based drugs on cardiac structure and function. Thus, the purpose of this study was to assess the impact of anthracycline-based chemotherapy on cardiac structure and function through CMR examinations of breast cancer patients, and to assess the potential utility of CMR in evaluating myocardial damage after anthracycline-based chemotherapy.

METHODS

Subjects

A total of twenty female breast cancer patients who received treatment at Shandong Cancer Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China from October 2021 to October 2022 were selected as the study participants. All the patients underwent surgical treatment and received anthracycline-based chemotherapy after surgery. This study was conducted in accordance with the principles of the Declaration of Helsinki [7]. The protocol was approved by the Institutional Review Board of Shandong Cancer Hospital Affiliated to Shandong First Medical University (approval no. 2021839). Twenty patients were enrolled in the study with an age range of 27 - 56 years (mean age: 47.65 ± 8.36 years). The mean height of the patients was 161.27 ± 3.89 cm, and the mean body mass index (BMI), 24.98 ± 4.03 kg/m^2, while the mean heart rate was 70.47 ± 7.82 beats per minute. The patients underwent partial or complete surgical resection for breast cancer. Fifteen (15) patients underwent modified radical mastectomy, while 5 patients underwent breast-conserving surgery. Following surgery, all the patients received systemic treatment primarily consisting of anthracycline-based chemotherapy. The drug used was Epirubicin, at a dose of 90 mg/m^2. Each treatment cycle was 21 days, with a 21-day interval between cycles. All patients completed a total of four treatment cycles. None of the patients received concurrent radiotherapy or targeted therapy with Trastuzumab. Before chemotherapy, and at 3- and 6-months post-chemotherapy, CMR examinations were conducted for all patients.

Inclusion criteria

Patients diagnosed with breast cancer who were aged 18 years or above; patients who underwent surgical treatment and required anthracycline-based chemotherapy, and those were able to undergo cardiac magnetic resonance (CMR) examination, were included in the study.

Exclusion criteria

The excluded patients were those with severe heart diseases such as heart failure or myocardial infarction; patients with concomitant systemic diseases such as diabetes and hypertension, and those with severe liver or renal dysfunction. Moreover, the excluded patients were those allergic to or intolerant of anthracycline drugs, and patients who were unable to undergo CMR examination or who had poor quality of image quality that might affect the study.

CMR examinations

The CMR examinations for all patients were conducted on a 3.0T MR system (USA). Cardiac-specific 8-channel phased-array receive coils were used for scanning under electrocardiogram and respiratory gating. Conventional cine scans of the left ventricle were performed. These comprised four-chamber cine images, left ventricular long-axis views, inflow-outflow views, and short-axis cine images of the entire left ventricle (from apex to base) using steady-state free precession (FIESTA) cine sequence imaging. The specific scanning parameters were as follows: FOV of 350 mm x 350 mm, TR of 3.6 ms, TE of 1.6 ms, bandwidth of 125 kHz, flip angle of 50^o, matrix size of 192 x 224, 0 slice gap, and slice thickness of 10 mm.

Acquisition and analysis of cardiac function indices

Data analysis was performed using GE post-processing workstation Report card 4.0 software. Based on the American Heart Association (AHA)

16-segment model, the endocardium and epicardium of the left ventricle at end-systole and end-diastole (including papillary muscles and trabeculae within the ventricular cavity) were manually traced on short-axis cine sequences of the left ventricle. Left ventricular end-diastolic volume (LVEDV), LVESV and LVEF were measured.

Strain analysis

The CVI 42 software (Canada) was used. The endocardium and epicardium of the left ventricle in the long-axis, short-axis, and four-chamber cine sequences were manually traced. The insertion point of the right ventricle was marked on the short-axis plane of the left ventricle. The software automatically calculated the strain parameters [radial strain (RS), systolic radial strain rate (SRSR), diastolic radial strain rate (DRSR), circumferential strain (CS), systolic circumferential strain rate (SCSR), diastolic circumferential strain rate (DCSR), longitudinal strain (LS), systolic longitudinal strain rate (SLSR), and diastolic longitudinal strain rate (DLSR)] for each segment (according to the AHA 16-segment model) and the overall left ventricle.

Statistical analysis

The GraphPad Prism 8 software was used for plotting, of graphs, while SPSS 22.0 software was used for data analysis. For continuous variables, the data are presented as mean ± standard deviation, and statistical analysis was performed using *t*-test or analysis of variance (ANOVA). Data for categorical variables are expressed as frequencies and percentages, and statistical analysis was performed using chi-square test or Fisher's exact test. The comparisons of cardiac function indices and strain parameters at baseline, 3 months, and 6 months of chemotherapy were done using analysis of variance (ANOVA, F-test), and correlation analysis was conducted using Spearman's test. Differences were considered significant at $p<0.05$.

RESULTS

Cardiac function indices

With relative prolongation of anthracycline-based chemotherapy, patients showed stage-based decreases in LVEF levels, while no significant changes were observed in LVEDV and LVESV levels. However, comparison of LVEF, LVEDV, and LVESV at different time points in patients showed no significant differences ($p > 0.05$). These results are shown in Table 1.

Left ventricular myocardial strain parameters

The comparisons of RS, CS, LS, SRSR, SCSR, SLSR, DCSR, and DLSR at different time points in patients showed no significant differences. However, the DRSR level at 6 months after treatment was significantly lower than those before treatment and at 3 months after treatment ($p > 0.05$), indicating a stage-wise decrease in DRSR level. These results are presented in Table 2.

Table 1: Comparison of levels of cardiac function indices at different time points in patients

Stage of treatment	LVEF (%)	LVEDV (ml)	LVESV (ml)
Before treatment	66.83±3.94	122.36±21.38	40.21±6.43
3 months after treatment	65.37±3.89	127.85±19.94	43.72±8.51
6 months after treatment	63.91±4.24	124.16±20.32	43.65±6.62
F	2.643	0.370	1.533
P-value	0.079	0.691	0.224

*$P < 0.05$ vs before chemotherapy; #$p < 0.05$ vs 3 months after treatment

Table 2: Comparison of left ventricular myocardial strain parameters at different time points in patients

Strain parameter	Before treatment	3 months after treatment	6 months after treatment	*F*	*P*-value
RS	33.82±7.05	31.67±7.68	29.96±9.45	1.133	0.329
CS	-19.94±2.23	-20.05±2.12	-19.32±1.85	0.721	0.490
LS	-10.93±4.36	-10.11±2.07	-9.26±1.96	1.541	0.222
SRSR	1.85±0.58	1.73±0.53	1.41±0.62	3.098	0.052
SCSR	-0.96±0.14	-0.95±0.13	-0.91±0.12	0.825	0.443
SLSR	-0.54±0.31	-0.57±0.15	-0.44±0.23	1.621	0.206
DRSR	-2.08±0.57	-1.83±0.51	-1.45±0.48*#	7.405	0.001
DCSR	1.07±0.15	1.08±0.16	0.98±0.18	2.260	0.113
DLSR	0.62±0.24	0.58±0.18	0.51±0.11	1.821	0.171

*$P < 0.05$ vs before chemotherapy; #$p < 0.05$ vs 3 months after treatment

Correlation between cardiac function indices, left ventricular myocardial strain parameters, and duration of anthracycline-based chemotherapy

There was a negative correlation between LVEF value and the relative duration of anthracycline-based chemotherapy (r = -0.394, *p* = 0.033). Moreover, the left ventricular myocardial strain parameters, i.e., RS, SRSR, DRSR, CS, and DCSR were negatively correlated with the relative duration of anthracycline-based chemotherapy (r = -0.423, *p* = 0.021; r = -0.395, *p* = 0.034; r = -0.357, *p* = 0.049; r = -0.437, *p* = 0.014, and r = -0.372, *p* = 0.042, respectively). These results are presented in Table 3 and Figure 1.

Table 3: Correlation between cardiac function indices, left ventricular myocardial strain parameters, and duration of anthracycline-based chemotherapy in patients

Index	*r*	*P*-value
Cardiac Function Index		
LVEF	-0.394	0.033
LVEDV	-0.159	0.514
LVESV	-0.272	0.123
Left ventricular myocardial strain parameters		
RS	-0.423	0.021
CS	-0.395	0.034
LS	-0.289	0.120
SRSR	-0.357	0.049
SCSR	-0.132	0.483
SLSR	-0.285	0.122
DRSR	-0.437	0.014
DCSR	-0.372	0.042
DLSR	-0.283	0.123

DISCUSSION

Anthracycline-based drugs which are frequently used in breast cancer chemotherapy, exert their effects by interfering with DNA replication and repair processes in tumor cells, thereby inhibiting their growth and division. Anthracycline-based drugs are crucial in breast cancer treatment, as they are frequently included in chemotherapy regimens either as neoadjuvant treatment, adjuvant treatment, or main treatment of metastatic breast cancer [8]. These drugs have been proven effective in reducing tumor size, lowering risk of metastasis, and improving patient survival rates.

However, their use also carries the risk of cardiac toxicity [9]. The cardiac toxicity primarily manifests as myocardial damage and fibrosis of myocardial cells, leading to impaired myocardial contractile function and development of heart failure. Studies have revealed that the occurrence of cardiac toxicity in patients is associated with factors such as dosage, cumulative dose, and method of administration of anthracycline-based drugs, as well as sensitivity levels of individual patients [10].

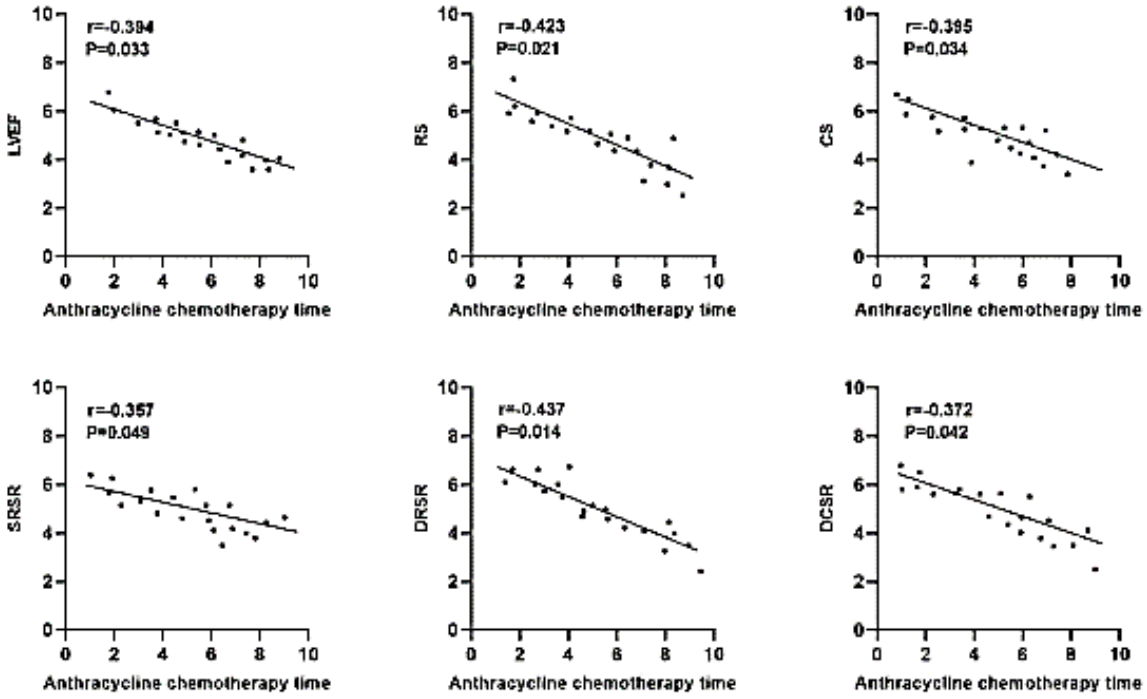

Figure 1: Analyses of correlation between cardiac function indices, left ventricular myocardial strain parameters, and duration of anthracycline-based chemotherapy among patients

The specific mechanisms underlying the cardiac toxicity of anthracycline-based drugs have not yet been fully elucidated in practice. However, several important hypotheses have been proposed. It has been hypothesized that anthracycline-based drugs generate free radicals which trigger oxidative stress reactions that cause oxidative damage and injury to myocardial cells [11]. Secondly, these drugs may disrupt mitochondrial function in myocardial cells, resulting in mitochondrial damage and disturbances in energy metabolism [12]. Furthermore, anthracycline-based drugs may damage the myocardium by interfering with calcium ion homeostasis, cellular apoptosis, and inflammatory responses in myocardial cells [13]. For breast cancer patients, cardiac toxicity poses a significant limitation to anthracycline-based drug therapy. Therefore, early detection of myocardial damage caused by anthracycline-based chemotherapy has attracted significant interest.

In the early stages after administration of anthracycline-based drugs to breast cancer patients, the left ventricular ejection fraction (LVEF) often remains within the normal range, with cardiac toxicity occurring in the subclinical stage, which makes it difficult to diagnose using conventional methods [14]. Endomyocardial biopsy (EMB) is currently the most accurate method for assessing anthracycline-induced cardiac toxicity [15]. However, due to its invasive nature and technical requirements, its application is severely limited. The most widely used method for assessing the risk of cardiac toxicity in breast cancer patients before and after chemotherapy is LVEF, while cardiac magnetic resonance (CMR) is used to detect subtle changes in left ventricular ejection fraction [16]. A study on patients undergoing anthracycline-based drug therapy found that during chemotherapy, CMR provided more accurate information on LVEF changes, when compared to echocardiography [17].

The CMR myocardial strain imaging is a novel post-processing technique that quantitatively analyzes abnormal myocardial wall motion [18]. To date, this technique has been widely used in the diagnosis of various cardiac diseases such as hypertrophic cardiomyopathy and ischemic cardiomyopathy [19-21]. However, there is still relatively limited studies on CMR and myocardial strain imaging in the context of heart tumor. Therefore, the present study used CMR to evaluate the impact of anthracycline-based drug therapy on cardiac structure and function in breast cancer patients.

A total of 20 breast cancer patients who received anthracycline-based drug therapy were included in this study. The results showed a negative correlation between LVEF and the relative duration of anthracycline-based chemotherapy, indicating that as the duration and cumulative dose of anthracycline-based drugs increased, cardiac toxicity gradually became apparent and worsened. However, no significant differences were observed in the comparison of LVEF data obtained at different time points, indicating that although LVEF showed a decreasing trend, it is not accurate for assessing left ventricular dysfunction. Furthermore, the results of this study showed negative correlations between the left ventricular myocardial strain parameters RS, CS, SRSR, DRSR, DCSR, and the relative duration of anthracycline-based chemotherapy. This suggests that myocardial strain, like EF, may be an indicator of the presence of cardiac toxicity, and that as cardiac toxicity accumulates, myocardial strain gradually decreases. Among these parameters, DRSR showed the strongest correlation with the relative duration of anthracycline-based chemotherapy. Additionally, comparison between groups revealed that only DRSR exhibited a significant decrease, while the differences in other myocardial strain parameters were not of statistical significance. Therefore, this study has demonstrated that DRSR may be a sensitive parameter for early detection of myocardial damage.

Limitations of this study

Although this study has produced some important data regarding the impact of anthracycline-based drugs on the cardiac structure and function of breast cancer patients, it has several limitations. The sample size was small. Only 20 breast cancer patients were used as subjects. This relatively small sample size may limit the accuracy and generalizability of the results. A study with larger sample size may provide a more comprehensive understanding of the effects of anthracycline-based drugs on the heart. Moreover, the observation time points were limited. In this study, cardiac magnetic resonance imaging was conducted before chemotherapy, at 3 months of chemotherapy, and at 6 months of chemotherapy, thereby restricting observations to these three time points. However, anthracycline-based drugs may cause cardiac toxicity after long-term use. Therefore, for patients undergoing long-term chemotherapy, longer observation periods may be more meaningful. In addition, there was no control group. This study only observed changes in cardiac structure and function in breast cancer patients receiving anthracycline-based

chemotherapy, without a control group for comparison. The inclusion of a control group of breast cancer patients administered alternative treatment or no chemotherapy would provide a better evaluation of the specific effects of anthracycline-based drugs on the heart. Another limitation concerns lack of long-term outcomes. The study was primarily focused on the impact of anthracycline-based drugs on cardiac structure and function, without including evaluation of long-term outcomes such as survival rates and the incidence of heart failure. Subsequent studies will incorporate longer-term follow-ups to assess the long-term cardiovascular safety of anthracycline-based drugs in breast cancer patients.

CONCLUSION

This study has demonstrated that CMR is useful, to some extent, for diagnosing myocardial damage caused by anthracycline-based chemotherapy in breast cancer patients. Moreover, DRSR may be a sensitive parameter for early detection of myocardial damage using CMR. It will be necessary to improve the study protocol in the future in order to enhance the applicability of the study outcome.

DECLARATIONS

Acknowledgements

None.

Funding

None provided.

Ethical approval

The protocol was approved by the Institutional Review Board of Shandong Cancer Hospital Affiliated to Shandong First Medical University (approval no. 2021839).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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