Int Cardiovasc Res J.2017;**11**(2):55-59.icrj.10514

International Cardiovascular Research Journal

www.ircrj.com

Speckle Tracking Echocardiography for Detection of Early Myocardial Changes in Patients Treated with Anthracyclines

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ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 06 Sep 2016
Revised: 14 Jan 2017
Accepted: 24 Jan 2017

Keywords:
Cardiotoxicity
Anthracycline
Adriamycin

ABSTRACT

Background: Anthracyclines, as cancer chemotherapeutic agents, play an undeniable role in treatment of several cancers. As cardiotoxicity is an important adverse reaction of anthracyclines, elucidation of asymptomatic and potentially symptomatic changes in Left Ventricular Ejection Fraction (LVEF) is of significant interest in patients receiving chemotherapy.

Objectives: This study aimed to examine the cardiac effects of Adriamycin therapy based on Speckle-Tracking Echocardiography (STE) and early diagnosis of patients at risk of cardiotoxicity.

Patients and Methods: This study was conducted on 30 breast cancer patients (> 18 years old) who were treated with Adriamycin-based chemotherapy. Conventional echocardiography, STE, Electrocardiogram (ECG), and biochemical markers measurements (troponin I and CK-MB) were performed prior to and after chemotherapy. In addition, longitudinal strain analysis was performed via STE using automated functional imaging.

Results: Echocardiographic findings showed significant decreases in Ejection Fraction (EF) after the therapy. However, no significant differences were found regarding pulse rate, systolic and diastolic blood pressure, ECG changes, troponin I, and CK-MB after the therapy. Based on the global longitudinal strain, the longitudinal strain was significantly decreased in the patients after the therapy (-22.1 ± 2.1 prior to and -19 ± 2.2 after the therapy, P = 0.001).

Conclusions: Cardiotoxicity during the early phase of anthracycline treatment can be detected via STE prior to observation of systolic function deterioration by conventional echocardiography. In fact, anthracycline-induced cardiotoxicity can be observed much earlier via STE compared to conventional echocardiography.

1. Background

Anthracycline, as a cancer chemotherapeutic agent, has made remarkable advances in treatment of malignancies, increasing patients' hope for treatment of their diseases. Doxorubicin (Adriamycin) is a potent, broad-spectrum, and frequently used anthracycline that plays an undeniable role in treatment of several cancers, such as solid tumors, leukemia, and lymphoma (1). Although it has been used for more than thirty years, it is considered to be the first choice of anti-neoplastic drugs. Unfortunately, efficacy of doxorubicin is often limited by development of cardiotoxicity, which leads to dilated cardiomyopathy that may evolve into heart failure (2-5). Doxorubicin cardiotoxicity manifests in several forms from acute arrhythmias and nonspecific Electrocardiogram (ECG) changes to decreased Left Ventricular Ejection Fraction

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(LVEF) known as acute or chronic complications (6). The incidence of acute cardiotoxicity is approximately 11% (7, 8) and it is caused by myocyte necrosis as a result of arachidonic acid metabolism alteration (9). Myopericarditis induces chest pain and sinus tachycardia, paroxysmal non-sustained supraventricular tachycardia, and premature atrial and ventricular beats lead to palpitation. Indeed, late cardiac effects due to anthracycline chemotherapy can manifest as cardiac failure months or even years after the completion of treatment, which is thought to be related to myocardial toxicity (10). In a trial on more than 3,000 patients with primary breast cancer, adjuvant anthracycline with or without paclitaxel was linked to a 1 - 2% incidence of Congestive Heart Failure (CHF) after treatment (11). Cardiac toxicity was also increased when doxorubicin was administered concurrently with other therapies, including paclitaxel and trastuzumab (12). Based on previous clinical events, the incidence of cardiotoxicity ranged from 0.4% to 41%, particularly when the cumulative dose of doxorubicin exceeded 300 mg/m2 (13). To detect cardiac damage, the adopted diagnostic modality depended mainly on estimation of LVEF using M-mode and two-dimensional echocardiography during doxorubicin therapy. However, it is not currently possible to accurately predict which patients receiving Adriamycin are at increased risk of cardiac toxicity. Surprisingly, there are few published data reporting the incidence of asymptomatic changes in LVEF in doxorubicin regimens (like other anthracyclines) in early-stage breast cancer (14-16). Cardiac biomarker molecules, such as troponin T (TnT), C-Reactive Protein (CRP), and Brain Natriuretic Peptide (BNP), have been shown to be sensitive markers of Left Ventricular (LV) dysfunction and powerful markers of morbidity and mortality in the heart failure setting (17, 18). However, their ability to predict early cardiac dysfunction remains unknown. Tissue Velocity Imaging (TVI) and strain imaging are sensitive, noninvasive echocardiographic techniques for early detection of LV systolic dysfunction before decrease in conventional LVEF (8). However, early detection of cardiac damage with cardiac biomarkers or TVI in the clinical setting has yet to be investigated. Additionally, cardiac Magnetic Resonance Imaging (MRI) might be used for noninvasive assessment of LV volumes and LVEF in the breast cancer setting (19). Although delayed enhancement imaging with cardiac MRI might identify patients with trastuzumab-mediated cardiotoxicity, its use for early prediction of LV dysfunction remains unexplored.

Speckle-Tracking Echocardiography (STE) is a new noninvasive quantitative ultrasound technique for accurate evaluation of global and regional myocardial function based on analysis of motion of tissues in the heart on routine two-dimensional sonograms (20).

2. Objectives

Elucidation of asymptomatic and potentially symptomatic changes in LVEF is currently of significant interest in patients receiving chemotherapy. Therefore, the present study aims to investigate the role of STE in detection of cardiomyopathy in patients treated with Adriamycin.

3. Patients and Methods

3.1. Study Design

This prospective study was conducted on 30 cancerous patients treated with chemotherapy who were referred to Imam Reza clinic of radiation oncology and Namazi and Shahid Faghihi wards of oncology and gynecology between January 2013 and January 2014. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences and written informed consents were obtained from all participants.

3.2. Participants

Patients over 18 years of age diagnosed with HER-2-overexpressing breast cancer who were planned to be treated with anthracycline-containing chemotherapy protocols (Adriamycin) and herceptin were eligible. The participants with a history of cardiotoxic drug use, CHF or LVEF < 50%, myocardial infarct during the past year, prosthetic heart valves, moderate to severe valve disease, arrhythmia disorder, and history of severe chronic diseases were excluded from the study.

3.3. Cardiac Assessment

In order to obtain the values of cardiotoxicity, LVEF, strain rate, longitudinal strain, ECG, and biochemical markers (troponin I and CK-MB) of all participants were measured at two time points (baseline and after completion of the therapy). In addition, baseline characteristics of the participants, including age, side of breast cancer, dose of chemotherapy, systolic blood pressure, diastolic blood pressure, heart rate, and cardiac risk factors, were obtained by a data gathering form.

3.4. Measurements

3.4.1. Electrocardiogram

Twelve-lead ECG was performed for detection of any abnormal findings compatible with cardiomyopathy either before or after therapy.

3.4.2. Conventional Echocardiography

All patients were imaged in the left lateral decubitus position using the general electric E9 conventional echocardiography machine. All echocardiograms were analyzed by a specified reader. LVEF was calculated from the apical 4- and 2-chamber views using the modified Simpson biplane method.

3.4.3. Speckle-Tracking Echocardiography

STE was performed using the same machine; displacement of myocardial speckles in each spot was analyzed and tracked frame to frame. Besides, longitudinal strain was assessed using Automated Functional Imaging (AFI). Global longitudinal peak strain was also automatically calculated as an averaged value of the peak longitudinal strain in all 3 image planes (apical 2- and 4-chamber and long-axis views).

3.4.4. Chemistry

Immunochemiluminescence method (Architect i2000sr, Abbot Diagnostics, USA) was used to determine plasma

troponin I level quantitatively (upper normal limit: 0.5ng/ml). Additionally, plasma CK–MB activity was measured using chemical IFCC-DGK C Photometry.

3.5. Statistical Analysis

All statistical analyses were performed using the SPSS statistical software, v. 17 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous data were expressed as mean ± Standard Deviation (SD). Independent t-test and ANOVA were used to compare the groups regarding the study variables. Chi-square test and Fisher's exact test were also used for categorical variables. P values ≤ 0.05 were considered to be statistically significant.

4. Results

This study was performed on 30 patients with the mean age of 51 ± 11.8 (range: 32 - 77) years. The patients' baseline characteristics have been presented in Table 1. The patients received a mean dose of 346 mg/m2 Adriamycin during an average of 6.8 ± 1.6 months of therapy. The majority of patients (n = 15) had left side involvement of breast cancer and 13 (42.3%) had right side involvement.

Table 1. Baseline Characteristics of the Study Patients

Variables	Breast Cancer Patients, (n = 30)
Age, years	51 ± 11.8
Adriamycin dosage, mg/m2	346
Side of breast cancer (%)	
Left	15 (50%)
Right	13 (43.3%)
Bilateral	2 (6.7%)

The results indicated no significant differences in pulse rate, systolic and diastolic blood pressure, ECG changes, troponin I, and CK-MB after therapy. However, echocardiographic findings showed a significant decrease in EF after the course of treatment. EF values decreased to below the normal level in 5 patients after therapy. The mean EF was 65.6 ± 6.1% before anthracycline therapy versus 60.1 ± 6.2% post therapy (P = 0.005). However, no significant changes were observed in the stage of diastolic function after the treatment course (Table 2).

Based on the global longitudinal strain, the participants' longitudinal strain significantly decreased after therapy (P = 0.001). Accordingly, it decreased from -22.1 ± 2.1 prior to the treatment course to -19 ± 2.2 after that. There were 18 patients (60%) with the global longitudinal strain less than -20. Among the patients with post-therapy EFs < 55%, the decrease in the longitudinal strain was significant based on the global longitudinal strain (P = 0.001). The global longitudinal strain also significantly decreased in 19 out of the 25 patients (76%) with normal EFs following therapy (P = 0.01) (Table 3).

5. Discussion

Cardiotoxicity during the early phase of anthracycline treatment can be detected via STE prior to observation of systolic function deterioration by conventional echocardiography. Anthracyclines have been commonly and effectively used to treat hematological and solid-organ cancers since the 1960s (7). The incidence of acute cardiotoxicity is approximately 11%. The mechanisms of these acute changes are not clearly known, but they are thought to be associated with myocardial edema (21). Chronic cardiotoxicity occurs less frequently with an approximate incidence of 1.7%, and can begin 30 days to 10 years after the last dose of anthracycline. Indeed, it is usually nonreversible (22).

Echocardiography is a commonly used, simple, and cost-effective technique for determining structural abnormalities and measuring cardiac functions. LV Fractional Shortening (FS) and EF are the most commonly used parameters to evaluate LV systolic function. However, EF alone is inadequate for assessing cardiac functions (23-27).

Yu Kang et al. evaluated subclinical myocardial injury shortly after epirubicin exposure in asymptomatic patients with large B-cell non-Hodgkin lymphoma using two-dimensional STE. They concluded that subtle abnormalities in myocardial systolic function in asymptomatic patients would be detected shortly after anthracycline exposure by two-dimensional STE (28). These findings are compatible with ours among patients with breast cancer after doxorubicin chemotherapy.

Cardiotoxicity related to anthracycline treatment has a strong positive correlation with the cumulative dose. In a study on 3,941 patients treated with anthracycline, 88

Table 2. Cardiovascular Evaluation of Cardiactoxicity in the Study Patients

	Pre-therapy	Post-therapy	P value
Pulse rate	78.9 ± 11.1	81.6 ± 11.7	0.17
Systolic BP	123 ± 10.7	122.9 ± 10.1	0.97
Diastolic BP	76.2 ± 7.9	75.8 ± 6.8	0.76
Troponin I	0.1	0.1	Ns
CK-MB	28.3 ± 14.1	34.4 ± 15.1	0.08
Ejection fraction	65.6 ± 6.1	60.1 ± 6.2	0.005

Abbreviations: BP, blood pressure; CK-MB, creatine kinase-MB

Table 3. Speckle-Tracking Echocardiography Outcomes According to Ejection Fraction Values

Longitudinal	Patients with EF < 55% before Chemotherapy, (n = 5)			Patients with normal EF before Chemotherapy, (n = 25)		
	Pre-therapy	Post-therapy	P value	Pre-therapy	Post-therapy	P value
Global longitudinal strain	-21.1 ± 2.7	-17 ± 4.1	0.001	-22.3 ± 1.9	-19.5 ± 1.7	0.01

Abbreviation: EF, ejection fraction

patients developed symptomatic heart failure during the follow-up period depending on the cumulative dose they were given. The incidence of cardiotoxicity was 0.14% in the patients receiving less than 400 mg/m2, 7.7% among those who received 550 mg/m2, and 18% in those treated with 551 - 700 mg/m2 (29). In another study, about one-fourths of 630 patients receiving cumulative anthracycline doses of 550 mg/m2 developed heart failure (22). Considering these findings, the cumulative anthracycline dose should not exceed 550 mg/m2. However, sensitivity to anthracycline varies widely among individuals due to different polymorphisms in the carbonyl reductase gene; a group of patients can tolerate the dose of 1,000 mg/m2, whereas others exhibit toxic effects at doses ≤ 300 mg/m2 (30). Alternative methods other than limiting the total anthracycline dose that can minimize the risk of cardiotoxicity include intravenous infusion instead of bolus therapy, use of structural analogs, liposomal encapsulation of the anthracycline molecule, and use of cardioprotective agents (31).

STE is a new method used to evaluate myocardial functions. In the present study, regional decreases in the longitudinal strain levels were observed in the patients based on STE before decreases in systolic function were noted via conventional echocardiography. EF and FS (indicators of systolic function) evaluated via conventional echocardiography are usually indicative of global functions of the heart, whereas STE facilitates assessment of the myocardium segment by segment and region by region. STE was reported to be a sensitive imaging method for detecting early cardiotoxicity and for taking precautions in advanced stages (9). Dogru et al. reported that cardiotoxicity during the early phase of anthracycline treatment could be detected via STE prior to observation of systolic function deterioration (31). Based on our findings, there was a significant deterioration in systolic function in the breast cancer patients post anthracycline therapy. Decrease in systolic function of five patients was detected via conventional echocardiography. Moreover, STE showed significant decreases in the global longitudinal strain values of these five patients. These findings show that the data of conventional echocardiography were in accordance with those of STE.

Al-Biltagi et al. compared 25 children with newly diagnosed Acute Lymphocytic Leukemia (ALL) who received doxorubicin therapy before and after the treatment. Their results showed that two-dimensional longitudinal strain echocardiography (STE) was more sensitive compared to conventional and Pulsed Tissue Doppler (PTD) in detecting early LV doxorubicin-induced cardiotoxicity in children with ALL (9).

STE measurements are strongly affected by such parameters as image quality, frame speed, and heart rate. In the present study, measurements were deliberately performed when the patients had normal heart rates and were not in a hyperkinetic state due to such factors as infection or anemia. This setting shows that the present findings were not affected by any hyperkinetic states, but were related to cardiotoxicity.

In the research performed by Piegari et al., doxorubicin was administered to 14 rats. Standard echocardiography, STE, and histological samplings were performed prior to the treatment and 2 and 4 weeks after that. They showed histological cardiac damage beside STE abnormal results two weeks post therapy. Nonetheless, the standard echocardiography showed normal findings at the same time (32).

The current study had some limitations. Firstly, radial and circumferential strains were not measured for evaluating other aspects of myocardial function. Additionally, longer follow-up periods together with larger sample sizes will help clarify whether STE abnormalities can help predict the occurrence of clinical heart failure or not.

5.1. Conclusion

In conclusion, STE may help detect anthracycline-induced cardiotoxicity earlier than conventional echocardiography.

Acknowledgements

The present article was extracted from the thesis written by Dr. Farid Mirzaee.

Authors' Contribution

Study concept and design: Moaref, Attar. Acquisition of data: Mirzaee, Amirmoezi, Mohammadianpanah. Analysis and interpretation of data: Mirzaee, Attar, Mohammadianpanah. Drafting of the manuscript: Amirmoezi. Critical revision of the manuscript for important intellectual content: Moaref, Attar, Amirmoezi. Statistical analysis: Moaref, Attar.

Funding/Support

This investigation was extracted from a thesis financially supported by the Research Vice-chancellor of Shiraz University of Medical Sciences (grant No. 5266).

Financial Disclosure

The authors have no financial interests related to the material in this manuscript.

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