

# Does left ventricular diastolic function deteriorate earlier than left ventricular systolic function in anthracycline cardiotoxicity?

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## Abstract

Cardiotoxicity is the most important complication in patients receiving anthracycline chemotherapy. We studied the left ventricular diastolic function (LVDF) and systolic function (LVSF) in these patients and assessed whether LVDF deteriorates earlier than LVSF. We prospectively studied 58 patients (mean age 48.02±13.87; 32 female, 26 male) on anthracycline treatment, before chemotherapy (S0) and after cumulative doses of 139±12 mg/m<sup>2</sup> (S1) and 308±14 mg/m<sup>2</sup> (S2). The LVSF was computed in terms of left ventricular ejection fraction (LVEF) from equilibrium radionuclide angiography (ERNA). The peak ejection rate (PER), peak filling rate (PFR), time to peak ejection rate (TPER), time to peak filling rate (TPFR), 1/3rd filling fraction and ratio of PFR and PER were calculated from ERNA and were also standardized using 150 baseline ERNA studies. Statistical analysis was done by repeated measures analysis of variance (ANOVA). We found significant decrease in LVEF (P<0.001) and PER (P<0.001) between the S1 and S2 studies and PFR (P<0.007) between the S0 and S1 studies. In conclusion in patients receiving anthracycline treatment, LVDF deteriorates earlier than left ventricular systolic function (LVSF).

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## Introduction

Anthracyclines are cytotoxic antibiotics and very effective anticancer agents for treatment of many solid tumors and hematological malignancies [1-5]. A clear dose-response relationship for anthracyclines in several curative chemotherapeutic regimens has been shown; decreased doses resulting in inferior survival and remission rates. However, higher doses can result in cardiotoxicity which limits their therapeutic potential and threatens cardiac function of many patients with cancer [6].

Echocardiography and equilibrium radionuclide angiography (ERNA) are routinely employed for the assessment of left ventricular function in these patients. Echocardiography has been used especially in pediatric patients [7], but in adults ERNA has been regarded as the best noninvasive method to identify subclinical anthracycline cardiotoxicity [8-10].

Assessment of left ventricular systolic function (LVSF) is commonly used to evaluate cardiac function during anthracycline treatment [8, 11-15]. There are conflicting reports for left ventricular diastolic function (LVDF) in these cases [16-23]. So, we formulated this study to evaluate both the LVSF and LVDF in these patients by serial ERNA in order to assess both these functions and whether LVDF deteriorates earlier than LVSF.

## Subjects and methods

A total of 58 patients (mean age 48.02±13.87; 32 female and 26 male) with no history of cardiac disease, diabetes mellitus or mediastinal radiotherapy were recruited. Twenty four patients (42%) were suffering from non Hodgkin's lymphoma and 34(58%) from ovarian carcinoma. In a prospective study, all patients were to undergo baseline ERNA study (S0) before the start of chemotherapy, followed by a first follow up study (S1) during chemotherapy and a second follow up study (S2) at the end of chemotherapy. The project was approved by our Institute Ethics Committee.

Equilibrium radionuclide angiography for determination of LVEF is a routinely performed procedure and required no standardization. The normal value of LVEF was taken as >50%. We, however standardized the peak ejection rate (PER), peak filling rate (PFR), time to peak ejection rate (TPER), time to peak filling rate (TPFR), first to third filling fraction (1/3rd FF) and the ratio of PFR to PER (PFR/PER) before starting the study. For standardization, 150 baseline ERNA studies of patients who were scheduled to receive anthracycline based chemotherapy and had previously referred to us for evaluation of their cardiac status were analyzed. These patients were selected to have a similar profile as compared to the patients recruited in our study. These patients had no history of cardiac disease and no previous administration of chemotherapeutic drugs or radiotherapy. These standardiza-

tion studies are not presented in this study but were used only in order to obtain normal ERNA values for comparison with the study population.

**Technique**

All patients had ERNA performed as follows: Stannous chloride, 15µg/kg body weight was first injected intravenously. Fifteen minutes later 740-925MBq of technetium-99m pertechnetate (<sup>99m</sup>TcO<sub>4</sub><sup>-</sup>) was administered and 20min later conventional ERNA study was acquired at 32 frames per cycle using low energy, all purpose collimator, on a dual head ECAM Siemens γ-camera, in anterior, left anterior oblique (for best septal view) and left lateral positions. Cardiac cycles with R-R intervals not within 10% of the average were rejected.

Left ventricular systolic and diastolic parameters were calculated from ERNA using a vendor provided protocol (Siemens processing protocol for multigated acquisition study). From the ERNA study, the first-degree derivative curve of the left ventricle was calculated. From this, PER and TPER were calculated and used for LVSF analysis and PFR, TPER and 1/3 FF were used for LVDF analysis.

**Statistical analysis**

Data were expressed as mean±standard deviation. The S0 population of the study was compared with the initial 150 studies analyzed for standardization. This was done to show that the patients in the study group composed of clinically relevant population. The demographics, sex and disease profile of both groups were compared by Pearson’s chi-square test and the age and study parameters were compared by independent-samples T-test. To look for the changes in the parameters over time and for the evaluation of cardiac function, the baseline and two follow-up studies were compared using repeated measures analysis of variance (repeated ANOVA). Post hoc analysis was then carried out to find out the significant differences between these groups. P value of <0.05 was taken as statistically significant.

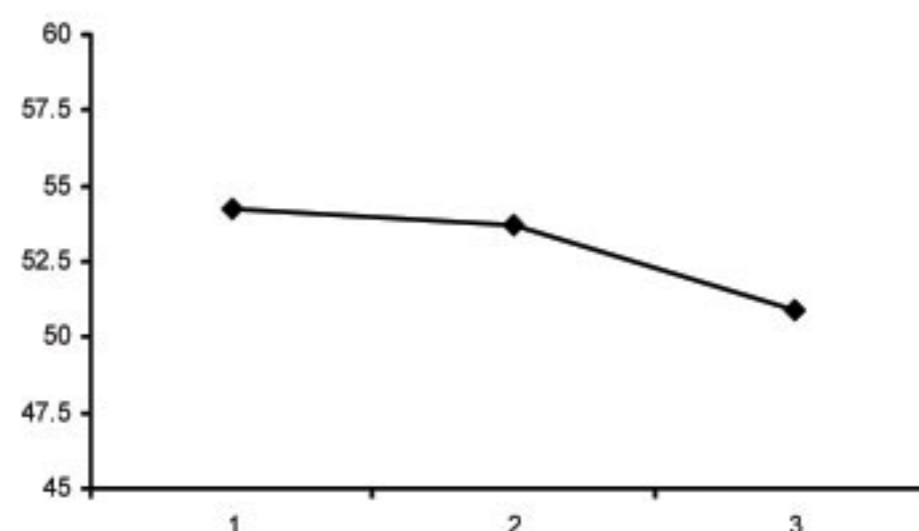
**Results**

Of the 58 patients recruited, 49 (84%) had one follow-up, and 47 (81%) completed two follow-ups in the 22 month study period (Three patients died of the primary disease, 6 patients were lost to follow-up after baseline study and 2 patients defaulted from treatment as anthracycline was stopped between follow-up studies). All patients had a baseline ERNA study (S0) before the start of chemotherapy. The first follow up study (S1) was performed after a cumulative anthracycline dose of 139 ± 12 mg/m<sup>2</sup> of body surface area and a second follow up study (S2) after 308 ± 14 mg/m<sup>2</sup> of body surface area. The total cumulative anthracycline doses ranged from 150 to 400 mg/m<sup>2</sup>. The anthracycline used in the chemotherapy regime of all the patients was Doxorubicin. No patient had any symptoms of congestive cardiac failure.

In comparing between the S0 population and the 150 studies used for ERNA standardization, no statistically significant difference was noted in age, sex, disease profile and the heart rate (HR) and also for all other parameters (Table 1).

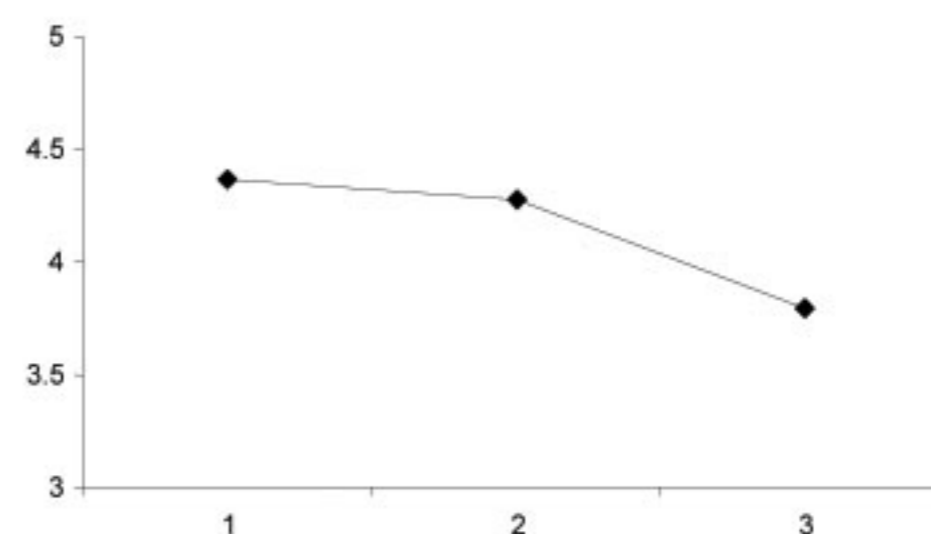
In the study group, two patients who initially had normal cardiac function (LVSF and LVDF) in S0 had a

significant fall in LVEF and PFR in the S1 study and so anthracycline treatment was stopped. Both patients were clinically asymptomatic. In the first of these patients, after 3 cycles of chemotherapy, LVEF fell from 60% to 42%. Three months later, LVEF recovered to 51%. In the second patient LVEF fell from 57% to 38% and after stopping anthracycline, LVEF partially recovered to 45%.

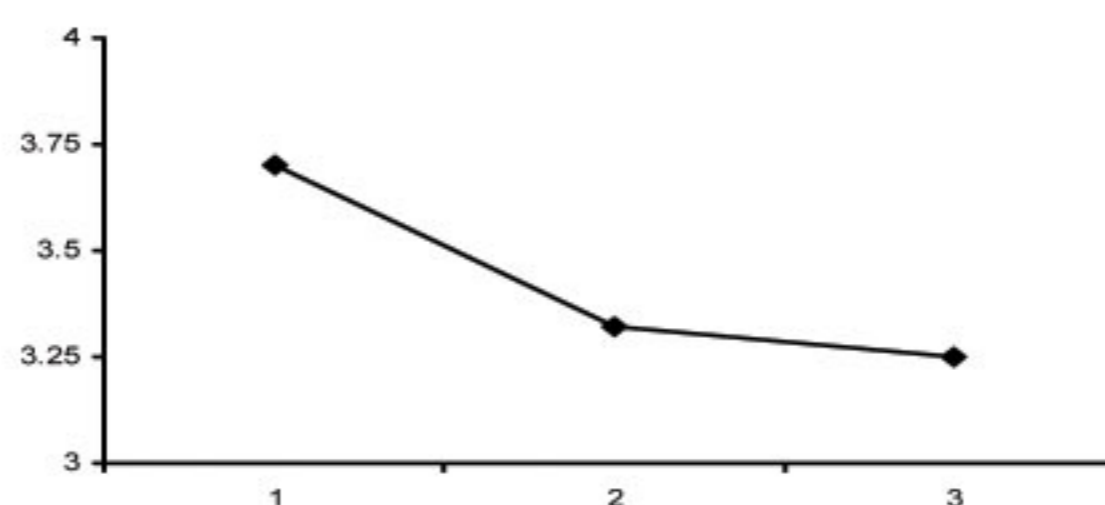


**Figure 1.** Trend of left ventricular ejection fraction showing significant fall between the first follow-up study (S1) and second follow-up study (S2).

By comparison of the baseline and the two follow-up studies in the study group (using repeated measurements ANOVA), statistically significant differences were seen for LVEF (P<0.001), PER (P<0.001) and PFR (P=0.007). No statistically significant changes were seen for HR, TPER, TPER, 1/3rd FF and PFR/PER. Moreover, for LVEF (S0 vs. S1: P=0.18, S0 vs. S2: P<0.001, S1 vs. S2: P=0.008) and PER (S0 vs. S1: P=0.122, S0 vs. S2: P<0.001, S1 vs. S2: P=0.004) statistically significant differences were seen only before the second follow-up study. While, for PFR (S0 vs. S1: P=0.009, S0 vs. S2: P<0.001, S1 vs. S2: P=0.123) statistically significant difference was seen before the first follow-up study itself. This difference of PFR deteriorating earlier than LVEF and PER is depicted in Figures 1, 2 and 3. The mean and standard deviation of all the parameters of the study group along with their statistical significance are shown in Table 2.



**Figure 2.** Trend of peak ejection rate showing significant fall between S1 and S2.



**Figure 3.** Trend of peak filling rate showing significant fall between baseline study (S0) and S1.

## Discussion

Anthracyclines are a group of antitumour antibiotics, which rank among the most effective anticancer drugs ever developed [1]. Anthracyclines are well established as highly efficacious antineoplastic agents for various hemopoietic [2] and solid tumors [3-5].

The first anthracyclines were isolated from the pigment-producing *Streptomyces peucetius* early in the 1960s and were named doxorubicin (DOX) and daunorubicin (DNR). As with any other anticancer agent, however, the clinical

**Table 1.** Parameters of the 150 studies used for standardization and S0 of the study group in statistical analysis done by independent-samples 't' test

Parameters	Standardization (n = 150)	Group S0 of study group (n=58)	P value
HR(b/min)	90.45±15.83	86.12±14.62	0.107
LVEF(%)	55.17±3.88	54.21±2.51	0.125
PER(ESV/sec)	4.613±1.26	4.36±0.53	0.196
PFR(EDV/sec)	3.535±0.83	3.701±0.61	0.225
TPER(msecs)	34.95±24.51	32.42±15.32	0.584
TPFR(msecs)	172.67±65.71	169.02±38.52	0.674
1/3rd FF	0.703±0.14	0.734±0.16	0.268
PFR/PER	0.785±0.27	0.855±0.15	0.102

HR- heart rate, LVEF- left ventricular ejection fraction; PER- peak ejection rate, PFR- peak filling rate, TPER- Time to peak ejection rate, TPFR- Time to peak filling rate, 1/3<sup>rd</sup> FF - First third filling fraction, S0 - Baseline study before start of chemotherapy

use of both DOX and DNR soon proved to be hampered by development of resistance in tumor cells and toxicity in the form of chronic cardiomyopathy and congestive heart failure (CHF). The search for a "better anthracycline" has resulted in some 2000 analogs by chemical modifications or substitutions and/or conjugations that were introduced in the tetracyclic ring, the side chain, or the aminosaccharide [1]. Yet only few analogs reached the stage of clinical development and approval; among them, epirubicin and idarubicin enjoy popularity as useful alternatives to DOX or DNR, respectively. A few more anthracyclines have attained clinical approval; these include pirarubicin, aclarubicin, and mitoxantrone. Both pirarubicin and aclarubicin demonstrate only modest improvements over DOX and DNR in terms of drug resistance but both have cardiotoxic effects [24, 25].

The cardiotoxicity of anthracyclines limits their therapeutic potential and the incidence of congestive heart failure (CHF) induced correlates with the total dose administered. Doxorubicin is the most commonly used anthracycline and the most studied for its cardiotoxic effects. Cardiotoxicity is uncommon at a cumulative total dose  $\leq 450$  mg/m<sup>2</sup> and this incidence sharply increases at a dose of  $\geq 550$  mg/m<sup>2</sup>, but cardiac failure has been noted in patients receiving a lower dose and absent at larger doses such as 5000 mg/m<sup>2</sup> [5-6, 11, 26, 27]. Although the factors influencing the development of anthracycline cardiotoxicity are still unclear, there is an absolute need for continuous monitoring of cardiac function in these patients. Reversibility of anthracycline-induced heart failure has been seen after cessation of treatment [28]. There is definitely a need to reliably monitor cardiac function of patients on anthracycline treatment. Electrocardiography systolic time intervals and

**Table 2.** Parameters of the baseline and the two follow-up studies of the study group in statistical analysis done by repeated measures ANOVA and post hoc test

Parameters	Study group			P value	Post hoc analysis		
	S0	S1	S2		S0 vs S	S0 vs S	S1 vs S
HR (b/min)	86.12±14.62	83.10±14.44	82.23±11.26	0.092	0.158	0.039	0.579
LVEF(%)	54.21±2.51	53.70±3.58	50.9±2.37	0.001	0.188	0.001	0.008
PER (ESV/sec)	4.36±0.53	4.27±0.66	3.79±0.56	0.001	0.122	0.001	0.004
PFR (EDV/sec)	3.70±0.61	3.32±0.64	3.25±0.61	0.007	0.009	0.001	0.123
TPER (msec)	32.42±15.32	41.57±20.72	48.63±18.03	0.07	0.084	0.065	0.092
TPFR (msec)	169.02±38.52	174.93±43	185.74±47.49	0.100	0.452	0.055	0.134
1/3 <sup>rd</sup> FF	0.73±0.16	0.76±0.17	0.79±0.10	0.079	0.305	0.058	0.253
PFR/PER	0.85±0.15	0.78±0.12	0.86±0.16	0.064	0.125	0.617	0.086

echocardiography are of limited value as predictors of early impending left ventricular failure [28-30]. Endocardial biopsy though is highly specific for early toxic effect on heart, is invasive, costly and requires highly skilled personnel, which in most centers precludes its routine use [31-33].

Studies in the literature regarding the monitoring of patients receiving anthracycline treatment vary widely in the evaluation techniques, study design and the parameters used. Equilibrium radionuclide angiography has been a reliable and reproducible test for monitoring and evaluation of left ventricular function in patients undergoing anthracycline chemotherapy. Serial

monitoring using ERNA allows the detection of a predetermined decrease in LVEF that predicts subsequent cardiac dysfunction [34-36]. This strategy allows for a reduction in the cumulative dose of the drug administered to the patients, which reduces the incidence of cardiac dysfunction. Guidelines for monitoring anthracycline cardiotoxicity with doxorubicin resulted in a greater than 4-fold reduction in incidence of overt heart failure [35]. The strategy of these guidelines was to allow the maximum dose of doxorubicin to be administered on an individually determined threshold for subclinical cardiotoxicity.

Systolic function evaluation by ERNA is conventionally used for monitoring patients on anthracycline treatment [11-15], but few studies suggest that impairment of LVDF is a more sensitive indicator while others report contrasting results [16-23]. Sobic et al evaluated thirty-two patients on anthracycline using ERNA for systolic and diastolic left ventricular parameters before and after chemotherapy. They found that diastolic left ventricular parameters significantly differed before and after completion of chemotherapy whereas LVEF did not differ significantly. These authors indicated that left ventricular diastolic dysfunction may be an early sign of cardiotoxicity [16].

In the current study, 150 baseline RNVs were analyzed for standardization of PER, PFR, TPER, TPER, and 1/3rd FF. Otherwise published the values for these parameters to be expected in ERNA in a normal population and these values closely correlated with the values obtained in our study [37]. Moreover, no statistically significant difference was found between these parameters in our baseline (S0) study group and the parameters used for standardization. This indicates that the patients in our study consisted of a clinically relevant population. A baseline evaluation of cardiac function ensured that patients with impaired cardiac function were not recruited. The two follow-up studies after anthracycline in these patients helped to monitor the cardiac function over time.

In our study, LVEF, PER and PFR showed statistically significant differences in the whole study period. LVEF and PER showed statistically significant differences between the S1 and the S2 study whereas for PFR, statistically significant difference was seen between S0 and S1. This suggests that the ventricular diastolic parameter PFR deteriorated earlier than the LVEF and the systolic parameter, PER. The other parameters like, TPER, TPER and 1/3rd FF did not show significant change which may be due to the timing of cardiac evaluation. It is possible that the parameters which do not show statistically significant differences were yet to change later or have already recovered or will not change perhaps for a long time.

In another study, three patients developed clinical CHF after cumulative doxorubicin doses of 264, 440, and 450 mg/m<sup>2</sup>, respectively, despite serial monitoring of systolic cardiac function by ERNA. All three patients had depressed LVDF, as shown by a decreased PFR preceding a change in LVSF, which was assessed by left ventricular injection fraction (LVEF) prior to the development of clinical CHF. They suggested serial monitoring of the PFR, in addition to LVEF in all patients on anthracyclines [17]. In our study, no patient had symptoms of CHF, which could be attributed to low cumulative dose of administered anthracycline (308±14mg/m<sup>2</sup>) in our patient population. However our results strongly suggest that deterioration of LVDF in terms of PFR precedes decrease in LVSF. Although in our study group, no patient had overt clinical symptoms in a larger patient population receiving higher cumulative dose of anthracycline a deterioration of LVDF preceding the LVSF may be useful indicator of impending clinical CHF.

*In conclusion*, in our study the diastolic parameter PFR deteriorated in patients receiving low cumulative anthracycline dose of 139 ± 12 mg/m<sup>2</sup> and deteriorated earlier than systolic function.

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