Study On The Role Of NT-pro-BNP (Brain Natriuretic Peptide) And Troponin I In The Detection Of Anthracycline Induced Cardiotoxicity

Akshyaya Pradhan[1], Rohini Khurana[2], Abhishek Singh[3], Vijayant Devenraj[4], Jyoti Bajpai[5], M. L. B. Bhatt[6], Sanjay Mehrotra[7]

[1]-Assistant Professor, Department of Cardiology, K.G.M.U., Lucknow
[2]-Associate Professor, Department of Radiation Oncology, R.M.L.I.M.S., Lucknow
[3]-Assistant Professor, Department of Medicine, K.G.M.U., Lucknow
[4]- Associate Professor, Department of Cardiothoracic Surgery, K.G.M.U., Lucknow
[5]-Junior Resident, Department of Respiratory Medicine, K.G.M.U., Lucknow
[6]-Professor, Department of Radiotherapy, K.G.M.U., Lucknow
[7]-Professor, Department of Medicine, K.G.M.U., Lucknow

***Abstract*- Introduction**- Anthracyclines are commonly used anticancer drugs because of their proven potency but cardiotoxicity represents their most devastating effect .The present study was undertaken to explore the role of biomarkers (NT pro BNP & troponin I) for the detection of chemotherapy induced cardiotoxicity. **Methods**- Twenty two patients of malignancy who previously underwent anthracycline chemotherapy were enrolled after informed and written consent. Detailed two-dimensional echocardiography was done to detect left ventricular dysfunction. A single point estimation of either plasma NT pro BNP or troponin I was done. Fourteen age and sex matched healthy controls were taken for analysis too. **Results** - Although all patients were clinically asymptomatic, echocardiographic evidence of Left Ventricular Dysfunction (LVD) was present in 20 (91%) study subjects. LV diastolic dysfunction was prevalent (77%) from where as systolic dysfunction was present only in 14% subjects. There was a statistically significant decline in echocardiographic parameters (E/A ratio, IVRT and LVEF) following anthracycline chemotherapy vis-à-vis controls. In patients who developed LV dysfunction the mean dose of anthracycline was higher as compared to those who did not. The mean level of NT-pro BNP was higher in the study population as compared to controls , though not statistically significant (431 $\pm$ 597.13 pg/ml vs. 68.28 $\pm$ 28.39 pg/ml, p=0.11).However, the level of troponin I in study population was significantly higher as compared to controls (0.16 $\pm$ 0.27 ng/ml vs. 0.02 $\pm$ 0.01 ng/ml, p=0.02). There was a negative correlation of NT pro BNP levels with LVEF (r=-0.11) and peak E velocity (r=- 0.35). A similar positive correlation between NT pro BNP & IVRT (r= .006) was also seen. As regards to Troponin I, similar positive and negative correlation with IVRT (r= +0.08) and LVEF (r= -0.2) were seen respectively. The mean levels of NT pro BNP and troponin I were higher in patients who were co-administered additional chemotherapy. In the study, both plasma NT pro BNP and troponin I had a low Sensitivity of (40% & 10% respectively) but high Specificity (100%) in predicting LV dysfunction on echocardiography.

Conclusions- There is high prevalence of left ventricular dysfunction on echocardiography after anthracycline chemotherapy. LV diastolic dysfunction is more common than LV systolic dysfunction. Plasma NT pro BNP and Troponin-I levels are higher in patients who developed LV dysfunction following Chemotherapy. Both NT pro BNP and Troponin-I levels have low sensitivity and high specificity for detecting LV dysfunction following anthracycline chemotherapy. Biomarker levels showed a significant correlation with various echocardiographic parameters too.

Index Terms- Anthracycline, Cardiotoxicity, Left ventricular dysfunction, NT pro BNP, Troponin I

I. Introduction

In the era of chronic diseases cancer has become the commonest cause of death second only to coronary artery disease. Of the vast armamentarium available to fight cancer, chemotherapy remains the most potent and viable option. But because cancer chemotherapy is highly toxic, addressing complications of both disease and therapy have paramount importance. Due to their proven antineoplastic activity and efficacy, anthracyclines are widely used in oncological practice in systemic neoplasms (acute leukemia, malignant lymphoma) and various solid tumors, mainly the cancer of breast, lungs, thyroid gland and ovary as well as osteosarcoma, and soft tissue sarcomas. However, the clinical use of anthracyclines is limited by unique cumulative dose-limiting cardio-toxicity.[1-2]

The spectrum of Anthracycline-induced cardiac damage varies from arrhythmias, Left ventricular dysfunction (LVD) and pericarditis in acute stage to chronic heart failure in long term. The damage is dose related and incidence rises sharply when cumulative dose more than 450 mg/m^2 are administered. Although the causes of anthracycline -induced cardiotoxictiy are probably many, a large body of evidence points to free-radical-mediated myocyte damage.[3] Proven risk factors apart from dose include advanced age, preexisting cardiac disease, and mediastinal irradiation. Hence early detection of anthracycline induced cardiotoxictiy is vital before the complete syndrome of

cardiomyopathy or heart failure develops. Monitoring of drug induced myocardial damage becomes more significant in the wake of finding that dexrazoxane, an antioxidant that functions by chelating iron has significant cardio protection.[4] The role of routine cardiac biomarker in this scenario is unclear.[5-8] The present study was undertaken to evaluate the role of NT pro-BNP and Troponin I as markers of anthracycline induced cardiotoxictiy. We also to tried to evaluate the impact of total cumulative dose of anthracyclines. The effects of radiotherapy and other chemotherapeutic agents on development of anthracycline -induced cardiotoxicity were also studied.

II. METHODS

2.1 STUDY POPULATION:

Patients of malignancy who had received anthracycline chemotherapy in Department of Internal Medicine, Radiotherapy & Oncology were enrolled for study after obtaining written and informed consent. The following patients were excluded for the study:-

- Acute inflammatory states- sepsis, multi organ dysfunction
- Prior cardiac dysfunction- acute myocardial infarction, coronary artery disease, cardiomyopathy, rheumatic heart disease, severe hypertension.
- Renal dysfunction- Raised serum creatinine (>2.0gm%), decreased glomerular filtration rate (e-GFR < 60 ml/min).
- Diseases of lung
- Patients on other Cardiotoxic drugs
- Anemia (Hb <9.0 gm%)
- Metabolic disorders

1.2 METHODOLOGY

Our study group consisted of 22 patients of cancer on anthracycline chemotherapy, preferably at least three months elapsed after start of chemotherapy. In this study group a point study comprising of clinical evaluation and detailed 2D-echocardiographic examination evaluation of LV systolic and diastolic functions was done. Simultaneously patients were randomized for measurement of either plasma NT-pro BNP or Troponin I. We also enrolled 14 age and gender matched healthy controls (after proper clinical and 2D echocardiographic exam) and measured plasma NT-proBNP and Troponin I in them.

1.3 EVALUATION

A. Clinical evaluation:

1. History taking focusing mainly on:

- Cancer type and stage
- Time of starting chemotherapy
- History suggestive of cardiac failure in past or present
- Family history suggestive of cardiac disease
- Dose of chemotherapy- dose/cycle frequency.

2. Complete General Physical Examination.

B.**INVESTIGATIONS**

1. **Biochemical:**
   - Complete Hemogram
   - Urea, creatinine
   - Liver function test
   - Blood sugar
2. **Chest X-ray**
3. **ECG**
4. **Echocardiography**

Two-dimensional, M-mode, spectral, and color flow Doppler echocardiograms were obtained for evaluation of patients. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical four and two chamber views.

Left ventricular ejection fraction (LVEF) were derived from biplane apical (two and four chamber) views using a modified Simpson's rule algorithm.

The transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: E and A velocities as the peak values reached in the early diastole and following atrial contraction, respectively, and deceleration time as the interval from the E wave to the decline of the velocity to baseline.

Finally, the left ventricular isovolumetric relaxation time (IVRT) was obtained from the apical five-chamber view with a continuous wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the left ventricular outflow tract and mitral orifice so as to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of trans-mitral flow. IVRT was taken as the time in the milliseconds (or seconds) from the end of ejection to the onset of left ventricular filling. Experienced cardiologists who were blinded to the BNP and troponin-I levels interpreted all echocardiograms.

ECHOCARDIOGRAPHIC CLASSIFICATIONS[9, 10]

Normal ventricular function was defined as LVEF ≥50%, absence of diastolic dysfunction. Systolic dysfunction was defined as ejection fraction <50%. Diastolic dysfunction was defined as impaired relaxation and restrictive and pseudo-normal pattern, based on the following definition.

Parameter	Normal	Delayed Relaxation	Pseudonormal	Restrictive
E/A	>1	<1	1-2	2
DT	<220	>220	150-200	<150
IVRT	<100	>100	60-100	<60
AR(cm/sec)	<35	<35	≥35	≥25
S/D	Young <1, adult ≥1	≥1	<1	<1

Systolic and diastolic dysfunction was defined as ejection fraction <50% with diastolic dysfunction as described above.

5. **NT-pro BNP Estimation**

Estimation of plasma NT-proBNP levels were done by Electrochemiluminescence sandwich immunoassay using two polyclonal antibodies directed against NT-proBNP amino acid 1-

21 and amino acid 39-50, respectively. Synthetic NT-proBNP (amino acid 1-76) was used as calibrator. The measuring ranges of the system was 5-35,000 pg/ml. normal values were as follows:

NT-proBNP (pg/ml)		Men	Women
Age	<50 yrs	<88	<153
	>50 yrs	<227	<334

6. Troponin-I Estimation

Troponin-I estimation was done by immunometric assay (IMMULITE analyzer) utilizing murine monoclonal Troponin-I antibody. Lyophilized troponin-I was used as Calibrator. The measuring range of the system was upto 180 ng/ml. Normal value 98% values were below 1ng/ml.

7. Statistical Analysis

Date were analyzed using statistical software package, STATA 9.2 (StataCorp, College station ,Texas, USA). A difference between the two values was considered to be significant only if 'p' value was found to be $<0.05.x^2$ statistics was used to test the association between two or more categorical variables. Two sample t-test was used to see the difference between the mean to two different groups, if data was normal distributed. If data was not found to be normally distributed, a non-parametric equivalent to two sample t-test, Mann Whitney test used to test the level of significance between two values. One way analysis of variance (Oneway ANOVA) was used to test the difference among >2 groups in case of normally distributed data otherwise its non-parametric equivalent Kruskall Wallis.

III. OBSERVATIONS AND RESULTS

3.1 Demographic Profile

A total of 22 patients of anthracycline chemotherapy and 14 age and sex matched healthy controls were enrolled in study. At the time of enrollment into study all of the patients were asymptomatic with respect to cardiovascular system.

As seen in table 1, the mean age in study population was 40.68 ± 15.5 years which was similar to that of control group (36.78 ± 13.85 years. Maximum patients in the study group (50%) belonged to 41-60 age group and a similar distribution was present in control group also. The sex distribution in control group is equal while males outnumbered females in study population, the male to female ratio being 3:2. The maximum number of patients enrolled in the study received anthracycline treatment for Non-Hodgkin's lymphoma (41%) followed by Carcinoma of breast. (Figure 1)

1.4 Anthracycline profile of study population

In the study 73% of the patients were given Doxorubicin (Adriamycin) as the chemotherapeutic agent whereas rest 27% received epirubicin for their disease. The median cumulative dose of anthracycline used in the study was 420mg and the drugs were administered at a median frequency of every 4 weeks. The median time between end of chemotherapy and enrollment in study was a median period of 3.5 months.

3.3 Echocardiographic Observation

Echocardiographic evidence of Left Ventricular dysfunction (LVD) was present in 91% of cases.(Figure 2) LV diastolic dysfunction was prevalent (77%) from where as systolic dysfunction was present in only 14%.

The mitral inflow E/A ratio was found to be significantly decreased in study group after receiving chemotherapy (1.08±0.28 vs. 1.54± 0.31, p =0.0001)

Table:-1. Demographic Profile of Study Population

	Study (n=22)	Control (n=14)
Age (Mean ± SD, years)	40.68 ± 15.5	36.78 ± 13.85
Age Group		
0-20	1(4.5%)	1(7%)
21-40	8 (36.5%)	6(43%)
41-60	11(50%)	7(50%)
>61	2(9%)	0
Sex		
Male	13(59%)	9(41%)
Female	7(50%)	7(50%)
Disease		
Hodgkin's Lymphoma	4(18%)	N.A
Non-Hodgkin's Lymphoma	9(41%)	
Multiple Myeloma	2(10%)	
Carcinoma Breast	7(31%)	
Anthracycline		N.A
Doxorubicin	16(73%)	
Epirubicin	6(27%)	
Parameters of anthracycline administration		
Total Cumulative dose	420(mg)	
Frequency of drug administration	4(weeks)	
Time of enrollment following completion of chemotherapy	3.5(months)	

Table 2:- Echocardiographic & Biochemical parameters comparison between Patients & Control (N=22)

	Study	Control
Mitral pulse Doppler E/A ratio*	1.08 ± 0.28	1.54± 0.31
IVRT*(seconds)	0.11.± 0.06	0.07± 0.01
LVEF* (%)	53.7± 4.6	58.2± 2.1
NT pro BNP (pg/ml)	431 ± 597.13	68.28 ± 28.39
Troponin I*	0.16 ± 0.27	0.02 ± 0.01

(ng/ml)		
* Indicates a statistically significant difference		

The mean IVRT in significant he study group was significantly increased following anthracycline administration as compared to control (0.11± 0.06s vs. 0.07±0.01s, p=0.0044). There was also statistically significant decline in mean LVEF following anthracycline administration as compared to control and the decrease is statistically significant (53.7± 4.6 % vs. 58.2± 2.1 %,p= 0.0003, Table 2 & Figure 3).

The mean age patient with diastolic dysfunction was 38.6 ± 15.6 years while that of systolic dysfunction was 45.66 ± 4.04 years. While diastolic dysfunction was seen almost equally on both sexes, systolic dysfunction was exclusively seen in females.

Regarding factors affecting development LVD, incidence was higher with Epirubicin (99.9%) than with Adriamycin (87.5%) but the result was not statistically significant. In addition, systolic dysfunction was more common in Epirubin group. In the study group diastolic dysfunction was present among all irrespective of disease but systolic dysfunction more prevalent in patients of Non-hodgkin's lymphoma and carcinoma breast.In patients who developed LV dysfunction the mean dose was higher as compared to those who did not. LV systolic dysfunction developed as a mean dose of 480 mg, which is higher than the mean dose of 399.4 ± 120 mg at which patient developed diastolic dysfunction, as expected. But the result were not statistically significant (p=0.15).

The development of LV systolic dysfunction is more common when drug was given at longer intervals of 4 weeks but LV diastolic dysfunction developed at a frequency of 3.4 ± 0.9 weeks. In patients with LV systolic dysfunction median time of enrollment in study following chemotherapy completion was 5 months. In patients with LV diastolic dysfunction the duration was 4 months.

3.4 Effect of other Chemotherapeutic Agents and Radiotherapy on Echocardiography parameters

The administration of additional chemotherapeutic agents led a trend towards higher incidence LVD as compared to anthracycline alone, though not statistically significant (89% vs. 80%, p= 0.42). LV systolic dysfunction was seen only when additional anti neoplastic agents were given.LV systolic dysfunction was more common when cyclophosphamide was used as additional chemotherapeutic agent. Vincristine use as additional chemotherapeutic agent resulted in LV diastolic dysfunction only.

In patients who received radiotherapy in addition to anthracycline, all developed LVD on echocardiography.

3.5 Biomarkers Profile

The mean level of NT-pro BNP is 431 ± 597.13 pg/ml in the study population as compared to 68.28 ± 28.39 pg/ml in the controls. But the increase is not statistically significant (p=0.11), when Mann Whitney test was applied.

The levels of plasma NT pro BNP were abnormal in 40% of patients with LVD dysfunction. NT pro BNP was abnormal in 60% cases of LV diastolic dysfunction. The mean and median values were overall higher in diastolic dysfunction but the result are not statistically significant (p=0.3)

The mean level of troponin I in study population was 0.16 ± 0.27 ng/ml while that of control was 0.02 ± 0.01 ng/ml.(p=0.02)

Abnormal levels of troponin I were found only in 10% cases of LVD although the mean levels and medium levels of patients with LVD were significantly higher than patients without LVD.

The correlation analysis revealed a negative correlation between NT pro BNP and LVEF (r=-0.11). Also, there is also a negative correlation between NT pro BNP and peak E velocity (r=-0.35). A similar positive correlation between NT pro BNP & IVRT of (+ .006) is also seen (Table 3).

As regards to Troponin I similar positive and negative correlation with IVRT (r= +0.08) and LVEF (r= -0.2) are seen respective. A negative correlation between E/A ratio and Troponin-I is also seen (r= -0.11). None of the values were statistically significant.

The mean levels of NT pro BNP were higher in patients who were co-administered additional chemotherapy.

The mean Troponin-I levels were higher in patients who were co-administered additional chemotherapy.(Table 4)

Median plasma NT pro BNP level did not rise with co-administration of radiotherapy.

Median values of troponin-I were higher in patients given additional radiotherapy.

In the study plasma NT pro BNP had a Sensitivity of 40% and Specificity of 100% in predicting LV dysfunction on echocardiography. The positive predictive value was 100% and Negative predictive value was 54%.

In the study plasma Troponin-I had a Sensitivity of 10% and Specifictiy of 100% in predicting LV dysfunction on echocardiography. The positive predictive value was 100% and Negative predictive value was 50%.

Table: 3. Correlation analysis of NT pro BNP and Troponin I with Various Echocardiographic parameters

	BNP	LVEF	Mitral Valve flow E/A ratio	LV IVRT	Mitral valve flow peak E Velocity	Troponin I
BNP	1.000					
LVEF	-0.1114 0.7592	1.0000				

Mitral Valve flow E/A ratio	0.5038 0.1376	0.3018 0.1723	1.0000			
LVIVRT	0.0067 0.9854	- 0.3328 0.1302	- 0.2038 0.3523	1.0000		
Mitral valve flow peak E velocity	- 0.3503 0.3211	0.0825 0.7151	- 0.0586 0.7955	- 0.2878 0.1940	1.0000	
Troponin I	0.0000	- .02045 0.5238	- 0.1151 0.7218	0.0800 0.8049	0.2527 0.4280	1.0000

IV. DISCUSSION

Cardiotoxicity is the most devastating side effect of anthracycline administration. In this study we tried to evaluate the cardiotoxic effects of anthracyclines in twenty-two patients by clinical examination and echocardiography. We also probed into the role of two plasma markers NT pro BNP and Troponin I in the scenario of anthracycline cardiotoxicity. Many studies have focused on case of symptomatic LV dysfunction following anthracycline chemotherapy but only a few of the have concentrated on asymptomatic LV dysfunction.

The majority (50%) of our patients belonged to age group 41-60 years. Most (41%) of the patients enrolled in the study were given anthracycline chemotherapy for Non-Hodgkin's lymphoma. All of our patients were clinically asymptomatic, but left ventricular dysfunction was alarmingly detected in majority of the patients on echocardiography. LV Diastolic dysfunction was present in 77% of patients and LV systolic dysfunction in 14% patients after anthracycline administration. Various studies by Murat et al[11], Bonneterre et al[13] & Hequet et al[14] have shown that the incidence of asymptomatic LV dysfunction following chemotherapy is between 13%-50%. Higher incidence of LV dysfunction in our study could be explained on the basis of larger mean total cumulative dose of anthracycline (420mg) used in our study.

Anthracycline chemotherapy patients developed statistically significant altercations in Echocardiographic parameters. In patients with LV diastolic dysfunction an increase in mean left Ventricular IVRT and decrease in mitral valve flow E/A ratio was observed on echocardiography. The mean LVEF of the anthracycline group was significantly lower than their healthy counterparts. Nousianen et al [14] observed a similar decrease in LVEF and mitral E/A ratio following anthracycline chemotherapy. Maria et al [15] also observed similar alteration in LV diastolic parameter (E/A ratio & IVRT) and LV systolic parameters (LVEF) following chemotherapy.

LV diastolic dysfunction occurred at a mean dose of 399 $\pm$ 120 mg and LV systolic dysfunction occurred at a dose of 480 mg. In patients with LV Diastolic dysfunction median time of enrollment in study after chemotherapy was 4 months. LV systolic dysfunction patients entered the study after a median period of 5 months following chemotherapy.

Epirubicin cause a higher incidence (of LVD vis-à-vis Doxorubicin. Incidence of systolic dysfunction was also higher in patients of Epirubicin group. This can be explained on the difference in pharmacokinetic properties.[16].Corollary to this observation, high incidence of systolic dysfunction was seen in Carcinoma Breast where Epirubicin was used.

Mean Plasma NT pro BNP levels were higher in anthracycline chemotherapy patients than in control, though values did not attain statistical significance. **Patrick et al.** found elevated mean BNP levels about 3 times and abnormal values in 26% of their patients after a mean follow up of 6.5 years.[8]

In patients with LV dysfunction on echocardiography, plasma NT pro BNP had sensitivity of 40% and specificity of 100% in detection of LV dysfunction.This low sensitivity in the study can be explained on the basis of low sample size (N=10) in which test was performed.In patients with LV diastolic dysfunction, the levels of plasma NT pro BNP had a negative correlation with mitral valve flow Peak E velocity and positive correlation with IVRT on echocardiography. In patients with LV diastolic dysfunction levels of this marker had a negative correlation with LVEF. These results indicate a trend between rising NT pro BNP level and deteriorating LV function indices on echocardiograph. Median levels of NT pro BNP were high when additional anticancer drugs were given.

Troponin I, other serum marker used in the study showed a similar trend. The mean levels were significantly higher in the anthracycline chemotherapy population (0.15 $\pm$ 0.24 vs 002 $\pm$ 0.01). In patients with LVD, abnormal valve were found only in 1 out of 10 patients. In the study Troponin I had a sensitivity of 10% and specificity of 100% in detection of LV dysfunction. There was also a negative correlation between rising Troponin I levels and LVEF in patients with LV systolic dysfunction. In patients with LV diastolic dysfunction negative correlation between mitral valve flow E/A ratio (r= - 0.11) and positive correlation with IVRT (r=0.08) was present. These observations indicate toward a correlation between rising troponin I early echocardiography changes in LV diastolic and systolic function. With additional echocardiography and radiotherapy the mean levels were higher than the cohort which received anthracycline alone.

V. LIMITATIONS

Total sample size was small and the study involved a single point estimation of plasma NT pro BNP and Troponin I following anthracycline chemotherapy.

VI. CONCLUSIONS

There is high prevalence of asymptomatic left ventricular dysfunction on echocardiography after anthracylcine chemotherapy. LV diastolic dysfunction was more common than LV systolic dysfunction.Left ventricular dysfunction was related to total cumulative dose of anthracycline.

Co-administration of Additional chemotherapeutic agents (cyclophosphamide and vincristine) & radiotherapy was associated with increased incidence of LV dysfunction.

Plasma NT pro BNP and Troponin-I levels were higher in patients who developed LV dysfunction following Chemotherapy.

Both NT pro BNP and Troponin-I levels had low sensitivity and high specificity for detecting LV dysfunction following anthracycline chemotherapy.

Both NT pro BNP and Troponin-I levels showed a negative correlation with LVEF and mitral valve flow peak E velocity on echocardiography. There was also a positive correlation with IVRT on echocardiography.

REFERENCES

[1] Wojtacki J, Nowak EL. et al Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention- review of the literature. Med Sci Monit 2000;6(2):411-420.

[2] Ng R, Better N, Green MD. Anticancer agents and cardiotoxicity. Semin Oncol 33:2, 2006.

[3] Peng X, Chen B, Lim CC, Sawyer DB. The cardiotoxicity of anthracycline chemotherapeutics. Mol Interv 5:163, 2005.

[4] Swain SM, Whaley FS, Gerber MC, et al: Cardioprotection with dexrazoxane for doxorubicin- containing therapy in advanced breast cancer. J Clin Oncol 15:1318, 1997.

[5] Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 109:2749, 2004.

[6] Cardinale D, Sandri MT, Martenoni A et al. Myocardial injury revealed by plasma troponin I in breast cancer patients treated high dose chemotherapy. Ann Oncol 2002;13:710-715

[7] Okamura h, Yoshida T, et al. Brain Natriuretic peptide is predictor of anthracycline induced cardiotoxicity. Acta hematol 2000; 14:158-163.

[8] Perik PJ, De Vries EGE, Boomsma F.et al. Use of natriuretic peptide for detecting Cardiac Dysfunction in Long-term Disease-free Breast Cancer Survivors. Anticancer research 2005; 25: 3651-3657

[9] Little WC, Applegate RJ. Congestive heart failure: Systolic and diastolic Function.J Cardiothor Vasc Anesthesia 1993;7(4):2-5

[10] Garcia MJ, Thomas JD, Klein AL. Doppler echocardiographic application for study of diastolic dysfunction. J Am Coll Cardiol 1998 ;32: 865-75

[11] Soker M, Kervancioglu M. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. Saudi Med J 2005;26;1197-1202

[12] Bonneterre J, Roché H, Kerbrat P, Fumoleau P, Goudier MJ, Fargeot P et al. Long-Term Cardiac Follow-Up in Relapse-Free Patients After Six Courses of Fluorouracil, Epirubicin, and Cyclophosphamide, With Either 50 or 100 mg of Epirubicin, As Adjuvant Therapy for Node-Positive Breast Cancer: French Adjuvant Study Group. J Clinical Oncol 2004; 22: 3070-3079.

[13] Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D.Subclinical Late Cardiomyopathy After Doxorubicin Therapy for Lymphoma in Adults. J Clinical Oncol 2004; 22: 1864-1871

[14] Nousiainen T, Vanninen E, Jantunen E, Puustinen J, Remes J, Rantala A et al.Natriuretic peptides during the development of doxorubicin-induced left ventricular diastolic dysfunction. J Intern Med. 2002 Mar;251(3):228-34.

[15] Sandri MT, Salvatici M, Cardinale D et al. N-terminal Pro BNP after high dose chemotherapy. A marker of cardiac dysfunction ? Clinical Chemistry 2005;51: 1405-1410.

[16] Pouna P, Adèle SB, Gouverneur G, Tariosse L, Robert J.Evaluation of anthracycline cardiotoxicity with the model of isolated, perfused rat heart: comparison of new analogues versus doxorubicin. Cancer Chemotherapy and Pharmacology 1995;35:257-261

AUTHORS

First Author- Akshyaya Pradhan MD,DM, Assistant Professor, Department of Cardiology, KGMU, Lucknow, India. **E**mail- akshyaya33@gmail.com

Second Author- Rohini Khurana MD, Associate Professor, Department of Radiation Oncology, R.M.L.I.M.S., Lucknow.**E**mail-drrohinisethi@gmail.com

Third Author- Abhishek Singh MD, Associate Professor, Department of Internal Medicine, K.G.M.U., Lucknow, India. **E**mail- docabhishek23@ rediffmail.com

Fourth Author- Vijayant Devenraj Mch , Associate Professor, Department of Cardiothoracic Surgery, K.G.M.U., Lucknow, India **E**mail -vijayantdevenraj@ gmail.com

Fifth Author- Jyoti Bajpai MBBS, Junior Resident, Department of Respiratory Medicine, K.G.M.U., Lucknow. **E**mail- jyotibajpai33@gmail.com

Sixth Author- M.L.B.Bhatt MD, Professor, Department of Radiotherapy, K.G.M.U., Lucknow, India **E**mail- drmlbhatt@gmail.com

Seventh Author- Sanjay Mehrotra MD, Professor, Department of Medicine, K.G.M.U., Lucknow, India. **E**mail- rmllabs@hotmail.com

Corresponding Author- Rohini Khurana MD , Associate Professor, Department of Radiotherapy, R.M.L. Institute of Medical Sciences, Lucknow, India **E**mail- drrohinisethi@gmail.com

Acknowledgement-
Sandip Barik, Senior Resident**,** Department of Radiotherapy, R.M.L.I.M.S., Lucknow

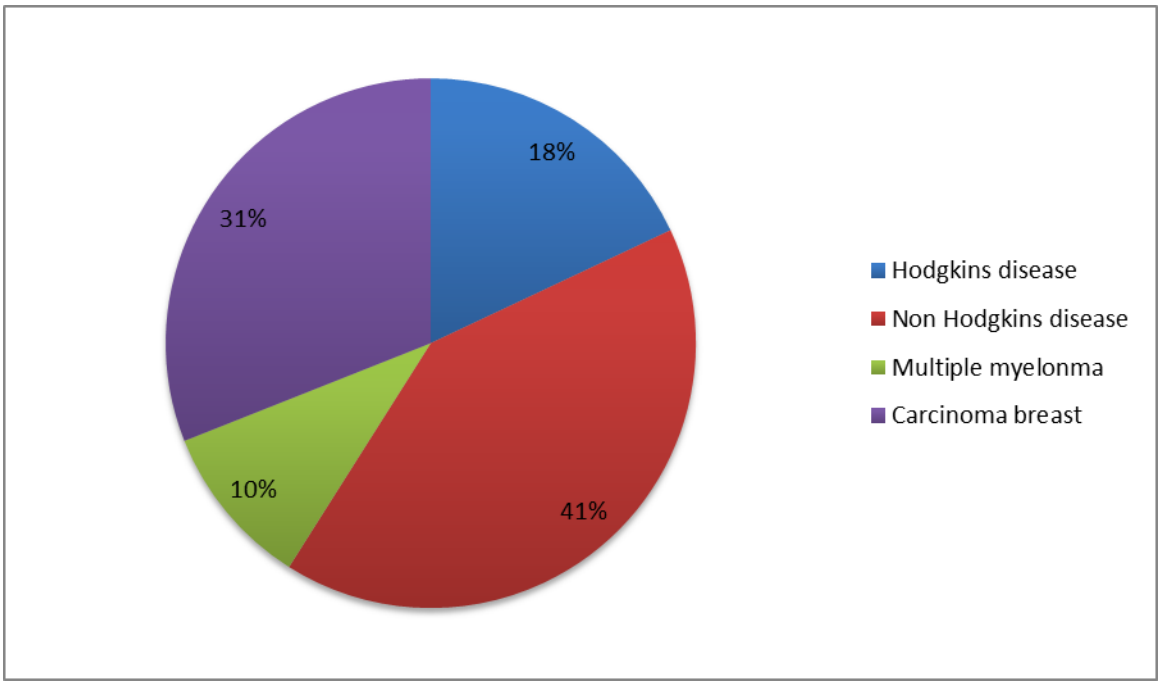

Figure 1. Distribution of Primary Neoplastic diagnoses for which chemotherapy was given in Study

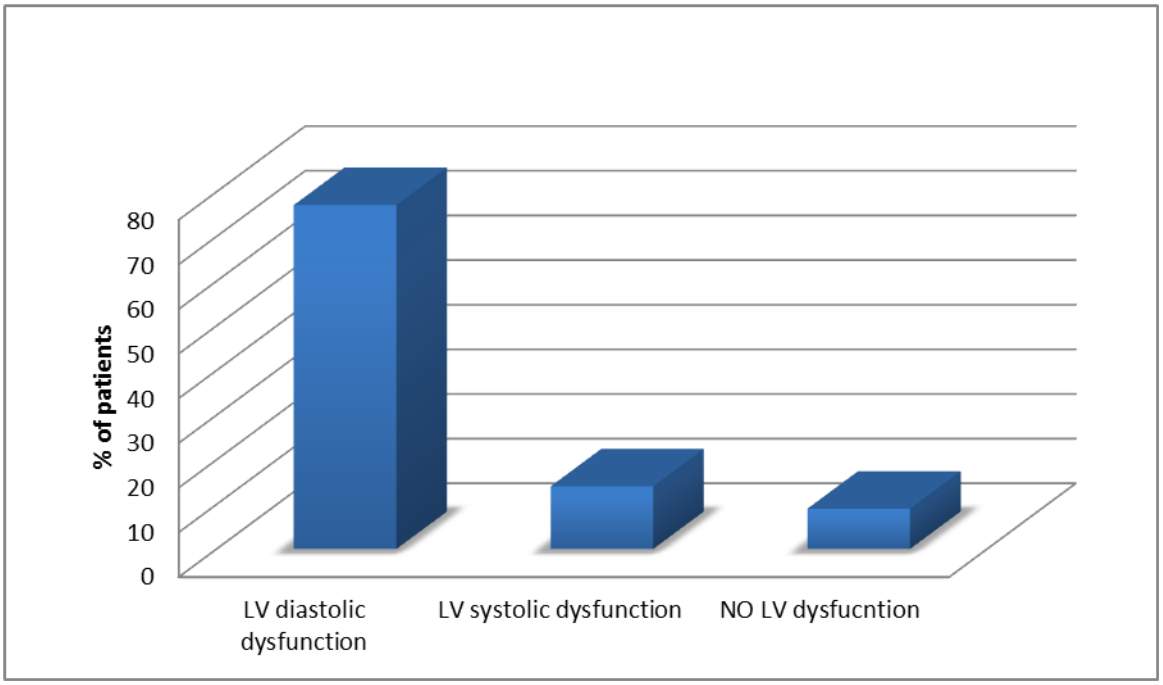

Figure 2. Distribution of Echocardiographic Left ventricular (LV) dysfunction in Study population
LV diastolic dysfunction on echocardiography was highly prevalent (77%) in patients following anthracycline chemotherapy.

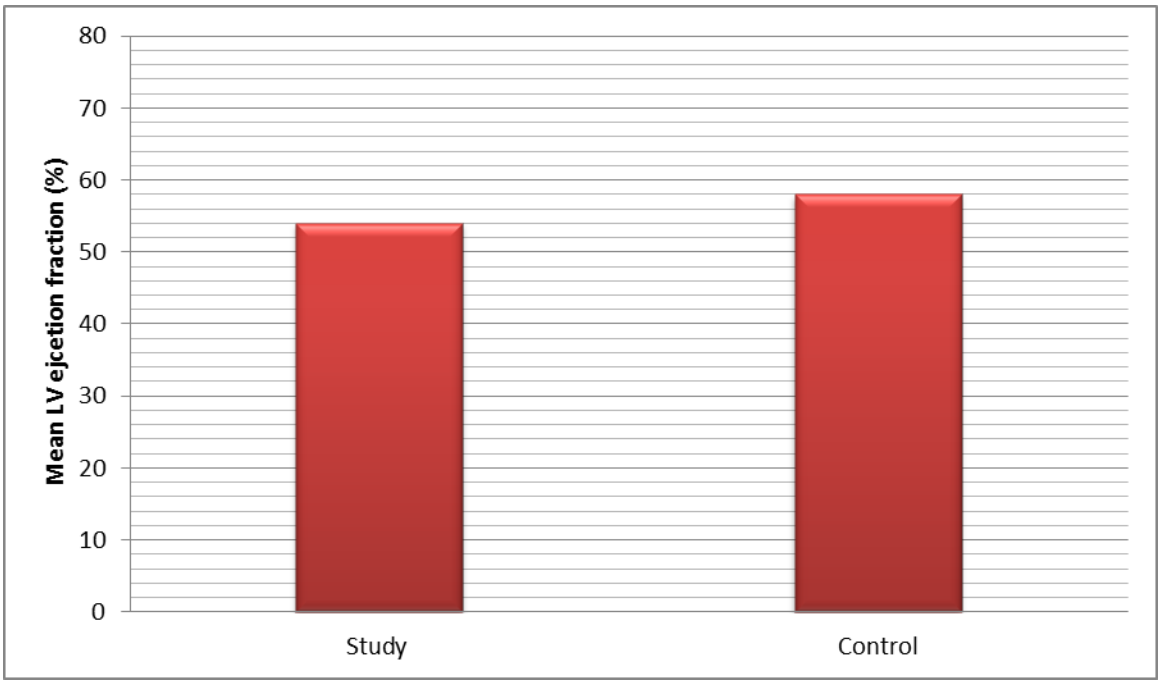

Figure 3. Distribution of Echocardiographic Left ventricular (LV) Ejection fraction between study population & controls
There was a significant fall in mean LV ejection fraction following chemotherapy (53.7 ± 4.2 % vs. 58.2 ± 2.1 % , p= .0003)

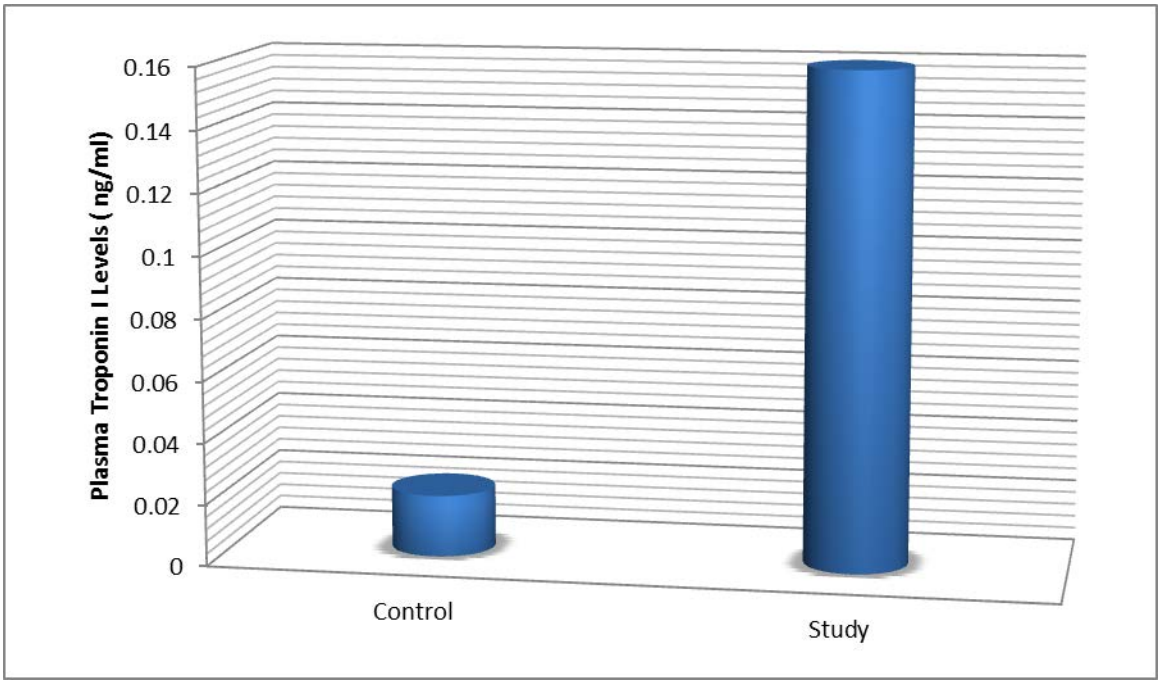

Figure 4. Distribution of Plasma Cardiac troponin I levels between study population & controls. There was a significant rise in plasma troponin I levels following anthracycline chemotherapy. (0.16 ± 0.27 ng/ml vs. 0.02 ± 0.01 ng/ml, p=0.02)