



Prevalence of Cardiotoxicity Induced by Chemotherapy Measured by Dobutamine Stress Echocardiogram (DSE) in BSMMU

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Abstract

Background: Cardiotoxicity related to cancer treatment is an alarming source of significant morbidity and mortality, and may differ from subclinical myocardial dysfunction to irreversible heart failure or even death. DSE is a safe, feasible, and accurate modality for finding of myocardial ischemia and prognostication in patients with known or suspected coronary artery disease, particularly when they have limited exercise capacity. **Materials & Methods:** This study is a cross-sectional observational study which was conducted at the department of Cardiology, in BSMMU, Dhaka from June 2019- December 2019. The sample size for this study was 50. **Results:** The mean age was 56±12 where 17(34%) of the respondents were <65 years and 33(66%) were >65 years. The male respondent was 35(70%) where female was 15(30%). Diabetes was found in 3(6%) cases and followed by Acute ischemia, Hypertension 6(12%), Coronary Artery Disease (CAD) 4(8%), ACE-inhibitors 5(10%), Beta-blockers 3(6%), Nitrates 3(6%). Acute leukemia was found in 13(26%). in M12-18 was 45±2 and followed by mean of LVESD (mm) was 27±4, 29±4, 29±4, 30±2, 30±3, 31±2. Mean of IVSd (mm) was 9±1, 9±1, 9±1, 9±2, 8±2, 8±3. Mean of Peak E (cm/s) was 80±10, 76±11, 74±16, 73±12, 66±9, 63±15 and the p-value was seen <0.001 which denotes a significant improvement in treatment (p<0.005). **Conclusions:** The early discovery of cardiotoxicity may ensure the improved chemotherapeutic process and timely management of the treatment of cardiomyopathy, such as beta-blockers and ACE inhibitors.

Keywords:- Cardiotoxicity, Chemotherapy, Dobutamine Stress Echocardiogram (DSE).

INTRODUCTION

Cardiotoxicity related to cancer treatment is an alarming source of significant morbidity and mortality, and may differ from subclinical myocardial dysfunction to irreversible heart failure or even death.^[1] There are two

treatment options such as: conventional therapies (i.e., chemotherapy and radiotherapy) which is characterized to have a significant effect on cancer cells without directed to them and newer molecular targeted therapies (i.e., trastuzumab), to recognize the specific cancer cell in order to save the normal

cells.^[2] Generally, chemotherapy is more likely given to those patients who are less than 75 years and have no history of heart failure or pulmonary disease.^[3] But, sometimes normal cells and tissues also get affected by the chemotherapy which leads to several mild and severe adverse effects, like nausea and vomiting, bone marrow suppression, and cardiovascular side effects, hypotension, tachycardia, arrhythmias, and heart failure.^[4] Besides, the risk of cardiotoxicity is more frequent in patients with hypertension, diabetes mellitus, liver disease, and those having previous cardiac diseases.^[5] Moreover, a combination of potential cardiotoxic agents, paclitaxel or trastuzumab with anthracyclines, may severely increase the risk of cardiotoxicity that can lead to disastrous congestive heart failure.^[6,7,8,9] Cardiovascular vulnerability may increase due to cumulative doses and concomitant use of adjuvant therapies, thorax radiation therapy along with other risk factors, like preexisting cardiovascular disease, age, obesity, smoking, hypertension, diabetes and physical inactivity.^[10] The main manifestations of acute cardiotoxicity are cardiac rhythm disturbances and the pericarditis/myocarditis syndrome.^[11,12] Stress echocardiography is a useful tool for assessing risk in coronary artery disease and is used when exercise testing is difficult or the findings are difficult to interpret.^[13,14,15,16,17] Dobutamine stress echocardiography (DSE) is a safe, feasible, and accurate modality for finding of myocardial ischemia and prognostication in patients with known or suspected coronary artery disease, particularly when they have limited exercise capacity.^[18,19,20,21,22,23] Dobutamine is a synthetic catecholamine having a comparatively short plasma half-life of 2 minutes for rapid

metabolization in the liver to inactive metabolites.^[24,25] Several studies demonstrated, the usefulness of DSE, for monitoring the cardiac function of patients receiving chemotherapy.^[26,27] Hence, this study aims to measure the dobutamine stress Echocardiogram (DSE) and to investigate the prevalence of Cardiotoxicity in patients receiving chemotherapy.

Objective of the Study

The objective of this study was to measure the dobutamine stress Echocardiogram (DSE) and to investigate the prevalence of Cardiotoxicity in relation with chemotherapy.

MATERIAL AND METHODS

This study is a cross-sectional observational study which was conducted at the Department of Cardiology, in BSMMU, Dhaka from June 2019- December 2019. The sample size for this study was 50.

Inclusion criteria:

The patients who had a normal baseline ejection fraction (EF) and had not received anthracyclines before the study period were included in this study.

Adult patients in between ≤ 65 years and > 65 years who had undergone chemotherapy were included in this study.

The patients who were willing to give consent after knowing the study purpose were included.

Exclusion criteria:

Patients who had received antihypertensive or cardiologic therapy, cardioprotective agents (dexrazoxane), and antidiabetic drugs before were excluded.

Those patients with poor cardiac echogenicity were excluded.

The patients with the history of ischemic, valvular and hypertensive heart disease, left ventricular ejection fraction (LVEF) < 50%, acute and chronic renal insufficiency (serum creatinine > 1.5 mg/dl), and liver disease (aspartate aminotransferase more than twice the upper normal limit) were also excluded from the study.

All the patients were treated as per the oncological protocol practice by international standard. All drugs were administered accordingly, basically at intervals of three times for four weeks. No patient had received chemotherapy before. The primary clinical examination include electrocardiogram, and chest X-ray. Patients underwent rest echocardiography and DSE before the 1st chemotherapy cycle (C1), before the 2nd chemotherapy cycle (C2) and before the 3rd chemotherapy cycle (C3), and at 1st month after chemotherapy (M1), and 6 months after chemotherapy (M6) and A final evaluation of rest LVEF was performed within eighteen months after HDC (f-LVEF). Each cycle was completed by an infusion of autologous peripheral blood progenitors' cells and granulocyte colony-stimulating factor. At the end of the follow-up patients were categorized according to the international guidelines for cardiac toxicity definition. A 12-lead

electrocardiogram was routinely recorded during dobutamine infusion and also the blood pressure was measured in every 3 min, even at the end of each dobutamine phase. Echocardiographic images were recorded at rest and at the end of each dobutamine phase which also helped in this study. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients who were willing to take participate in this study. For statistical analysis SPSS version was used.

RESULTS

[Table 1] shows the age distribution of the respondents. The mean age was 56 ± 12 where 17(34%) of the respondents were <65 years and 33(66%) were >65 years.

[Figure 1] shows the sex distribution of the respondents. The male respondent was 35(70%) where female was 15(30%).

[Table 2] shows the clinical History of the respondents. Among the associated diseases, diabetes was found in 3(6%) cases and followed by Hypertension in 6(12%), Coronary Artery Disease (CAD) in 4(8%), ACE-inhibitors in 5(10%), Beta-blockers in 3(6%), Nitrates in 3(6%). In assessing the hematological disorders, acute leukemia was found in 13(26%), Hodgkin's disease in 8(16%), Non-Hodgkin lymphoma in 22(44%), Multiple myeloma in 5(10%) and Myelodysplastic syndrome in 2(4%).

[Table 3] Echocardiographic Findings at Baseline and During the Study Period. The mean LVEDD (mm) in C1 was 43 ± 4 , in C2 was 43 ± 2 , in C3 was 44 ± 2 , in M1 was 45 ± 2 , in M6

was 44 ± 3 and in M12-18 was 45 ± 2 and followed by mean of LVESD (mm) was 27 ± 4 , 29 ± 4 , 29 ± 4 , 30 ± 2 , 30 ± 3 , 31 ± 2 . Mean of IVSd (mm) was 9 ± 1 , 9 ± 1 , 9 ± 1 , 9 ± 2 , 8 ± 2 , 8 ± 3 . Mean of IVSs (mm) was 13 ± 1 , 12 ± 2 , 12 ± 2 , 11 ± 3 , 11 ± 2 , 10 ± 2 . Mean of PWTd (mm) was 8 ± 1 , 8 ± 2 , 8 ± 3 , 8 ± 1 , 8 ± 1 , 8 ± 1 . Mean of PWTs (mm) was 15 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 1 , 12 ± 2 . Mean of LVEDV (ml) was 88 ± 19 , 90 ± 6 , 92 ± 11 , 96 ± 19 , 96 ± 18 , 100 ± 16 . Mean of LVESV (ml) was 31 ± 8 , 35 ± 5 , 37 ± 8 , 38 ± 9 , 42 ± 9 , 50 ± 7 . Mean of Peak E (cm/s)

was 80 ± 10 , 76 ± 11 , 74 ± 16 , 73 ± 12 , 66 ± 9 , 63 ± 15 and the p-value was seen < 0.001 which denotes a significant improvement in treatment ($p < 0.005$). Mean of peak A (cm/s) was 60 ± 7 , 58 ± 9 , 61 ± 20 , 56 ± 18 , 55 ± 7 , 55 ± 7 . Mean of E/ A ratio was 1.35 ± 0.24 , 1.34 ± 0.19 , 1.28 ± 0.31 , 1.29 ± 0.24 , 1.19 ± 0.14 , 1.05 ± 0.27 . Mean of DT (ms) was 157 ± 53 , 183 ± 40 , 187 ± 43 , 157 ± 33 , 169 ± 25 , 184 ± 38 . Mean of IVRT (ms) was 105 ± 15 , 94 ± 36 , 104 ± 13 , 100 ± 19 , 93 ± 14 , 109 ± 25 .

Table 1: Age Distribution of the Respondents

Age Distribution of the Respondents		N=50	Percentage (%)
Age	(Mean \pm SD)	56 ± 12	
	<65 years	17	34
	>65 years	33	66

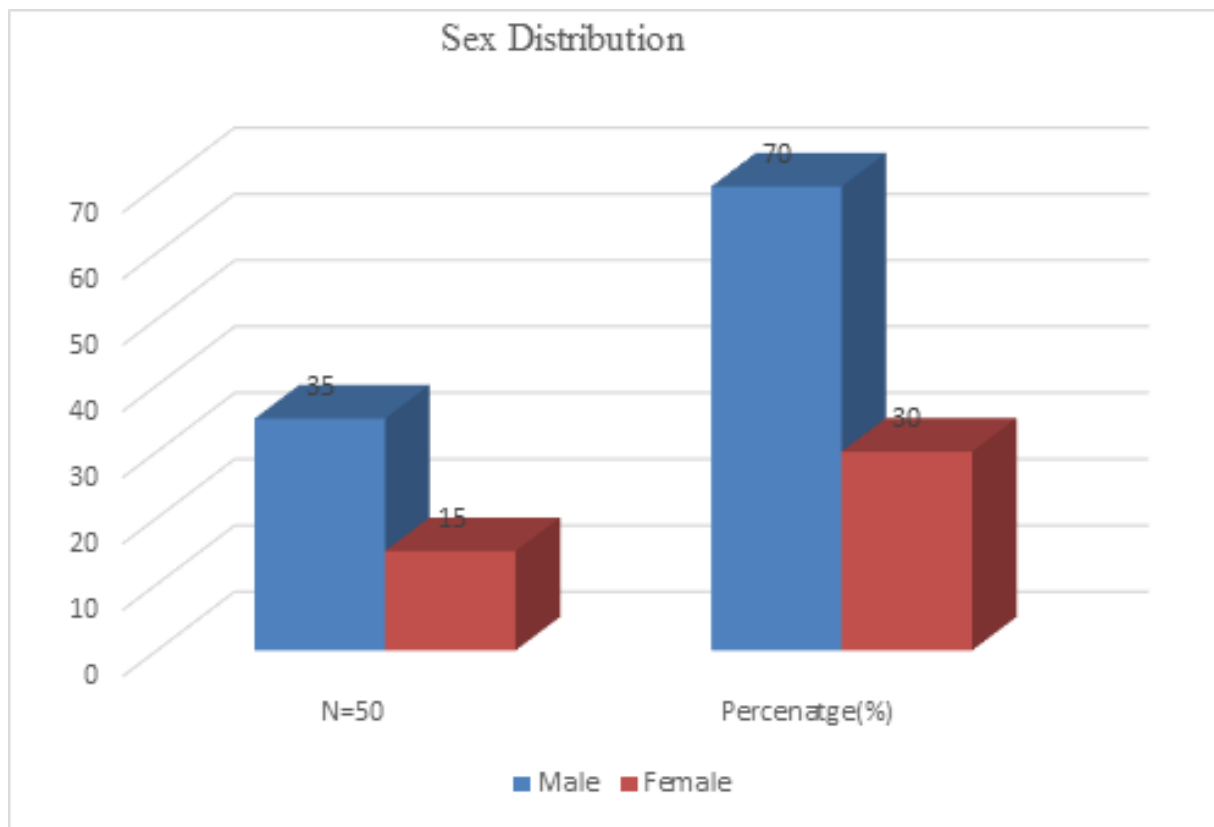


Figure 1: Distribution of the study according to sex

Table 2: Clinical History of the Respondents.

Clinical History of the Respondents		N=50	Percentage (%)
Associated Diseases drugs	Diabetes	3	6
	Hypertension	6	12
	Coronary Artery Disease (CAD)	4	8
	ACE-inhibitors	5	10
	Beta-blockers	3	6
	Nitrates	3	6
Hematological disorders	Acute leukemia	13	26
	Hodgkin's disease	8	16
	Non-Hodgkin lymphoma	22	44
	Multiple myeloma	5	10
	Myelodysplastic syndrome	2	4

Table 3: Echocardiographic Findings at Baseline and During the Study Period

Echocardiographic Parameters	C1	C2	C3	M1	M6	M12-18	P- value (p<0.005)
LVEDD (mm)	43±4	43±2	44±2	45±2	44±3	45±2	
LVESD (mm)	27±4	29±4	29±4	30±2	30±3	31±2	
IVSd (mm)	9±1	9±1	9±1	9±2	8±2	8±3	
IVSs (mm)	13±1	12±2	12±2	11±3	11±2	10±2	
PWTd (mm)	8±1	8±2	8±3	8±1	8±1	8±1	
PWTs (mm)	15±2	14±2	14±2	14±2	14±1	12±2	0.001
LVEDV (ml)	88±19	90±6	92±11	96±19	96±18	100±16	
LVESV (ml)	31±8	35±5	37±8	38±9	42±9	50±7	0.002
Peak E (cm/s)	80±10	76±11	74±16	73±12	66±9	63±15	<0.001
Peak A (cm/s)	60±7	58±9	61±20	56±18	55±7	55±7	
E/ A ratio	1.35±0.24	1.34±0.19	1.28±0.31	1.29±0.24	1.19±0.14	1.05±0.27	0.001
DT (ms)	157±53	183±40	187±43	157±33	169±25	184±38	
IVRT (ms)	105±15	94±36	104±13	100±19	93±14	109±25	

DISCUSSION

The mean age was 56±12 where 34% of the respondents were <65 years and 66% were >65 years. [Table 1] A related study in this field found the mean age was 57±13.[28] Another study related to this present study was conducted among the patients who were older than 65 years.[29] The male respondent was 70% where female was 30%. [Figure 1] The study of

J. Gavila, et. Al,[29] was conducted only on the female participants where M. Bountiukos, et. al. conducted their study on 71% male and 29% female.[28] Among the associated diseases, diabetes was found in 6% cases and followed by Hypertension in 12%, Coronary Artery Disease (CAD) in 8%, ACE-inhibitors in 10%, Beta-blockers in 6%, Nitrates in 6% patients. In assessing the hematological disorders, acute leukemia was found in 26%, Hodgkin's disease

in 16%, Non-Hodgkin lymphoma in 44%, Multiple myeloma in 10% and Myelodysplastic syndrome in 4%. [Table 2] In the study of M. Bountiukos, et. al., diabetes was found in 6.5% cases and followed by Hypertension in 12.9%, Coronary Artery Disease (CAD) in 12.9%, ACE-inhibitors in 9.7%, Beta-blockers in 6.5%, Nitrates in 6.5% cases, where acute leukemia was found in 26%, Hodgkin's disease in 16%, Non-Hodgkin lymphoma in 44%, Multiple myeloma in 10% and Myelodysplastic syndrome in 3%.^[28]

The mean LVEDD (mm) in C1 was 43 ± 4 , in C2 was 43 ± 2 , in C3 was 44 ± 2 , in M1 was 45 ± 2 , in M6 was 44 ± 3 and in M12-18 was 45 ± 2 and followed by mean of LVESD (mm) was 27 ± 4 , 29 ± 4 , 29 ± 4 , 30 ± 2 , 30 ± 3 , 31 ± 2 . Mean of IVSd (mm) was 9 ± 1 , 9 ± 1 , 9 ± 1 , 9 ± 2 , 8 ± 2 , 8 ± 3 . Mean of IVSs (mm) was 13 ± 1 , 12 ± 2 , 12 ± 2 , 11 ± 3 , 11 ± 2 , 10 ± 2 . Mean of PWTd (mm) was 8 ± 1 , 8 ± 2 , 8 ± 3 , 8 ± 1 , 8 ± 1 , 8 ± 1 . Mean of PWTs (mm) was 15 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 1 , 12 ± 2 . Mean of LVEDV (ml) was 88 ± 19 , 90 ± 6 , 92 ± 11 , 96 ± 19 , 96 ± 18 , 100 ± 16 . Mean of LVESV (ml) was 31 ± 8 , 35 ± 5 , 37 ± 8 , 38 ± 9 , 42 ± 9 , 50 ± 7 . Mean of Peak E (cm/s) was 80 ± 10 , 76 ± 11 , 74 ± 16 , 73 ± 12 , 66 ± 9 , 63 ± 15 and the p-value was seen <0.001 which denotes a significant improvement in treatment ($p<0.005$). Mean of peak A (cm/s) was 60 ± 7 , 58 ± 9 , 61 ± 20 , 56 ± 18 , 55 ± 7 , 55 ± 7 . Mean of E/ A ratio was 1.35 ± 0.24 , 1.34 ± 0.19 , 1.28 ± 0.31 , 1.29 ± 0.24 , 1.19 ± 0.14 , 1.05 ± 0.27 . Mean of DT (ms) was 157 ± 53 , 183 ± 40 , 187 ± 43 , 157 ± 33 , 169 ± 25 , 184 ± 38 . Mean of IVRT (ms) was 105 ± 15 , 94 ± 36 , 104 ± 13 , 100 ± 19 , 93 ± 14 , 109 ± 25 . [Table 3] The study of Maurizio Civelli et. al. also analyzed the echocardiographic parameters where they found the mean LVEDD (mm) in C1 was 44 ± 4 , in C2 was 44 ± 2 , in C3 was 45 ± 2 ,

in M1 was 44 ± 2 , in M6 was 44 ± 3 and in M12-18 was 45 ± 2 and followed by mean of LVESD (mm) was 27 ± 4 , 29 ± 4 , 29 ± 4 , 31 ± 2 , 31 ± 3 , 32 ± 2 . Mean of IVSd (mm) was 9 ± 1 , 9 ± 1 , 9 ± 1 , 9 ± 2 , 8 ± 2 , 8 ± 3 . Mean of IVSs (mm) was 14 ± 1 , 13 ± 2 , 13 ± 2 , 12 ± 3 , 12 ± 2 , 11 ± 2 . Mean of PWTd (mm) was 8 ± 1 , 8 ± 2 , 8 ± 3 , 8 ± 1 , 8 ± 1 , 8 ± 1 . Mean of PWTs (mm) was 15 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 2 , 14 ± 1 , 12 ± 2 . Mean of LVEDV (ml) was 89 ± 19 , 91 ± 6 , 93 ± 11 , 97 ± 19 , 96 ± 18 , 100 ± 16 . Mean of LVESV (ml) was 32 ± 8 , 36 ± 5 , 38 ± 8 , 39 ± 9 , 43 ± 9 , 51 ± 7 . Mean of Peak E (cm/s) was 80 ± 10 , 77 ± 11 , 75 ± 16 , 74 ± 12 , 66 ± 9 , 64 ± 15 and the p-value was seen <0.001 which denotes a significant improvement in treatment ($p<0.005$). Mean of peak A (cm/s) was 60 ± 7 , 58 ± 9 , 61 ± 20 , 56 ± 18 , 55 ± 7 , 55 ± 7 . Mean of E/ A ratio was 1.36 ± 0.24 , 1.35 ± 0.19 , 1.29 ± 0.31 , 1.30 ± 0.24 , 1.20 ± 0.14 , 1.06 ± 0.27 . Mean of DT (ms) was 157 ± 53 , 183 ± 40 , 187 ± 43 , 157 ± 33 , 169 ± 25 , 184 ± 38 . Mean of IVRT (ms) was 105 ± 15 , 94 ± 36 , 104 ± 13 , 100 ± 19 , 93 ± 14 , 109 ± 25 .^[30]

CONCLUSIONS

Although several guidelines are existing but scientific evidence about how often and how long cardiac function should be monitored during and after cancer treatment are not sufficient. The early discovery of cardiotoxicity may ensure the improved chemotherapeutic process and timely management of the treatment of cardiomyopathy, such as beta-blockers and ACE inhibitors. DSE has become an accepted means for evaluating the perfusion-limiting coronary artery. But coronary artery disease with chest pain is a challenge because this is still the chief cause of death in the western region. Formerly, electrocardiography exercise was done as a first-line noninvasive diagnostic stress test.



But, recently, DSE has become a well-known method for assessing a wide spectrum of challenging clinical conditions, including systolic or diastolic heart failure, non-

ischemic cardiomyopathy, valvular heart disease, pulmonary hypertension (PH), athletes' hearts, congenital heart disease (CHD), and heart transplantation.

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