

## Bone marrow transplantation may augment cardiac systolic function in patients with a reduced left ventricular ejection fraction

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### ABSTRACT

**Introduction:** Cardiac function is influenced by bone marrow transplantation (BMT). Studies have shown the various cardiotoxic effects of high-dose chemotherapy. In this study, we aimed to determine the effects of BMT on cardiac systolic function using echocardiographic indices. **Materials and Methods:** Patients with lymphoma (Hodgkin's and non-Hodgkin's), multiple myeloma, and solid tumors which were candidates for autologous BMT were selected. The tissue Doppler S wave velocity in left ventricular echocardiographic segments and the Swave velocity in right ventricle, the left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and ejection fraction (EF) were measured before and after BMT. **Results:** Nineteen patients studied. The mean systolic function variable measures were calculated before and after BMT. The tissue Doppler S mean decreased in the septal, lateral and anterior walls by 8%, 7.9%, and 4.9% ( $P = 0.017$ ), respectively. The tissue Doppler S mean increased in the inferior, anteroseptal and posterior walls by 1%, 0.6%, and 6.1%, respectively (not significant). The right ventricle Doppler S mean decreased by 7.5% after BMT ( $P = 0.03$ ). The LVEDD and LVESD decreased significantly by 4.8% ( $P = 0.003$ ) and 3.3% ( $P = 0.015$ ), respectively, following BMT. The ejection fraction increased by about 7% after BMT ( $P = 0.05$ ). **Conclusion:** The tissue Doppler S increased in all LV walls in patients with an EF less than 47%; surprisingly, tissue Doppler S decreased in all patients with an EF greater than 47%; and the ejection fraction increased by 13.6% and 3.1% in patients with a pre-BMT EF less than 47% and above 47%, respectively.

**Key words:** Bone marrow transplantation, echocardiography, systolic function, tissue Doppler

### INTRODUCTION

High-dose chemotherapy and bone marrow transplantation result in direct and indirect changes in cardiac function. A number of chemotherapy agents are known for their adverse effects on cardiac contractility. Cardiac function

can be influenced acutely, subacutely, or chronically after chemotherapy. Despite the growing number of patients undergoing bone marrow transplantation, a lack of data regarding the effect of this procedure on cardiac function remains.

The cardiotoxic effects of cyclophosphamide on cardiac function are well known and consist of acute, dose-dependent cardiac damage, which is morphologically characterized by necrosis, hemorrhage, and a later development of fibrosis.<sup>[1-5]</sup>

High-dose cyclophosphamide is widely employed in transplant conditioning regimens and sequential,

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high-dose chemotherapy protocols for solid and hematologic malignancies. The dose-limiting toxicity of cyclophosphamide lies in its unique capability of causing an acute cardiomyopathy within 48 h of administration, which presents with tachycardia and refractory hypotension that is often unresponsive to treatment. Although a fulminant syndrome is rare, a significant proportion of patients receiving high-dose chemotherapy were shown to have paraclinical signs of cardiotoxicity (ECG and ECHO) even without clinical findings.<sup>[6-8]</sup>

Morandi *et al.* showed that fractional shortening (FS) and ejection fraction (EF) never fell below 30% and 50%, respectively, in any patient after high-dose cyclophosphamide treatment. The Doppler E/A mitral ratio significantly changed in two patients and was not related to fluid loading, pharmacological intervention, or heart rate variation, suggesting a decreased left ventricular diastolic compliance.<sup>[9]</sup>

Allogeneic or autologous hematopoietic stem cell transplantation (HSCT) offers the possibility of a cure or long-term remission in a number of malignancies. Acute cardiac toxicity after transplantation has been well described in previous research. As compared with other complications of HSCT, the cardiac side effects are less worrisome. The most commonly encountered cardiac adverse effects include electrocardiographic changes and transient arrhythmias. Pericarditis, heart failure, pulmonary edema, and cardiac death are less common.<sup>[10,11]</sup>

Gupta and colleagues found various cardiotoxic effects with the use of high-dose chemotherapy for conditioning before autologous bone marrow transplant (ABMT), including arrhythmias, but only a small, transient decrease in left ventricular EF.<sup>[12]</sup>

Bone marrow transplantation and total body irradiation in children has been associated with a decreased myocardial contractility. Both acute and late cardiotoxicity may occur after BMT.<sup>[13]</sup>

Subacute cardiac toxicity is common after autologous hematopoietic stem cell transplantation, even in patients with an apparently normal left ventricular function. Anticipating the period of greatest risk and recognizing patients with subclinical myocardial dysfunction may prevent clinical heart failure.<sup>[14]</sup>

According to the above-mentioned studies, BMT may alter cardiac function. The acute effects of chemotherapy on cardiac systolic function have been researched, but

the effects of BMT, not chemotherapy *per se*, on cardiac systolic function are studied less frequently. In this study, we aimed to evaluate the changes in cardiac systolic function in patients undergoing BMT before and after the procedure.

## MATERIALS AND METHODS

To evaluate the effects of bone marrow transplantation on systolic cardiac function, we designed a before-after study. Patients with lymphoma (Hodgkin's and non-Hodgkin's), multiple myeloma, and solid tumors who were candidates for autologous bone marrow transplantation were selected for the study. These patients underwent a cardiac consultation and echocardiography before their admission for BMT. The same specialized echocardiographer conducted the echocardiographies with a ViVid 3 unit with the same probe and settings for all patients. For each case, the following echocardiographic indices were measured and recorded: the left ventricular end diastolic diameter (LVEDD); the left ventricular end systolic diameter (LVESD); the tissue Doppler Swave velocity measurement in septal, lateral, anterior, inferior, anteroseptal, and posterior walls; the Swave velocity of the right ventricle; and the ejection fraction (EF).

After the patient's admission to the BMT ward, mobilization with a granulocyte colony stimulating factor (GCSF) at a dose of 5 mg/kg BID was given over a one hour infusion for five days. On the sixth day, cell harvesting from the peripheral blood (apheresis) with a cell separator unit (COB brand) was performed. If the mononuclear cell count was below  $4 \times 10^8/\text{kg}$ , apheresis was repeated the following day. When the stem cell collection was completed, the cells were maintained at 4 °C, and induction chemotherapy was initiated. Lymphoma patients were treated using the CEAM regimen, which included CCNU 200 mg/m<sup>2</sup>, etoposide 300 mg/m<sup>2</sup> for 2 days, Cytosar 300 mg/  $\frac{\text{m}^2}{\text{BID}}$  for 2 days, and melphalan 140 mg/m<sup>2</sup>. Multiple myeloma patients were treated with melphalan 200 mg/m<sup>2</sup>, and solid tumor patients were treated with ifosfamide 9 g/m<sup>2</sup>, carboplatin 1200 mg/m<sup>2</sup> and etoposide 1500 mg/m<sup>2</sup>. Depending on the half-life of the prescribed chemotherapeutic agents, the harvested cells were infused 12--36 hours after the completion of the chemotherapy. The infusion was performed via arrow catheters placed in jugular or subclavian vein. One day later, GCSF 5 mg/kg was initiated. After the engraftment of the white blood cells (absolute neutrophil count  $\geq 500$ ), which usually occurs 10--20 days later, the patients underwent a post-BMT echocardiography. Again, the aforementioned variables assessed with the pre-BMT echocardiography were recorded.

After data collection, the variables were entered into the SPSS data sheet and analyzed by an expert statistician. All data analysis was performed using SPSS software (PASW statistics 18 version). For the before-after analysis we used paired samples *T*-test. The study protocol was in accordance with the Helsinki protocol and was approved by the medical ethics committee of Shaheed Beheshti Medical University. The study protocol imposed no harm to the participants, all patients were clearly informed about the study design, and written consent was obtained from each patient.

## RESULTS

Nineteen patients fulfilled our inclusion criteria and entered the study. Fifteen patients (78.9%) were male and 21.1% were female. The mean age of the patients was 41.9 years. Average courses of chemotherapy before transplantation were 5.7. The mean systolic function variable measures were calculated before and after the BMT. The mean tissue Doppler S measurements decreased in the septal, lateral, and anterior walls by 8%, 7.9%, and 4.9% ( $P = 0.017$ ), respectively. The tissue Doppler S mean increased in the inferior, anteroseptal and posterior walls by 1%, 0.6%, and 6.1%, respectively (not significant) [Table 1]. The right ventricle S mean decreased by 7.5% after BMT ( $P = 0.03$ ). Pre-BMT LVEDD mean was 4.74 cm and post-BMT LVEDD was 4.51 cm. Pre-BMT LVESD was 2.98 cm and post-BMT LVESD was 2.88 cm. The LVEDD and LVESD decreased by 4.8% ( $P = 0.003$ ) and 3.3% ( $P = 0.015$ ), respectively, following BMT. The ejection fraction increased by about 7% after BMT ( $P = 0.05$ ).

To evaluate the effect of BMT on systolic function according to the patients' baseline EF, we divided the patients into two groups. The first group included patients with a pre-BMT reduced EF, and the second group included patients with a normal or preserved pre-BMT EF. We defined the normal and preserved EF to be above 47%. Among 19 participants, nine patients had pre BMT EF less than 47%. The data presented here were obtained after reanalyzing and grouping the patients according to a normal or reduced EF. The tissue Doppler S increased significantly in all LV walls in patients with an EF less than 47%. The most striking increase was in the anteroseptal wall (20%), and the least increase in tissue Doppler S was in the septal wall (7.6%) [Table 2]. Surprisingly tissue Doppler S decreased in all patients with an EF greater than 47%. The most remarkable decrease in tissue Doppler S in this group was in the lateral wall (24.5%), and the smallest decrease was in the posterior wall (3.1%) [Table 3]. The LVEDD and

LVESD in patients with an EF less than 47% decreased by 4.9% and 6.1%, respectively, after BMT ( $P = 0.014$ ). The LVEDD in patients with an EF greater than 47% increased by 6.9% ( $P = 0.04$ ), and the LVESD decreased by 1% after BMT ( $P = 0.07$ ). The ejection fraction increased by 13.6% ( $P < 0.001$ ) and 3.1% ( $P = 0.05$ ) in patients with a pre-BMT ejection fraction of less than 47% and above 47%, respectively.

## DISCUSSION

Patients undergoing HSCT are exposed to several cardiotoxins, including high-dose cyclophosphamide, radiation, and infections. Previous studies have focused on the acute cardiotoxic effects, but there are great differences in the reported incidence of cardiotoxicity in these studies. Kupari *et al.*<sup>[15]</sup> found severe arrhythmias and heart failure in 5-10% of the patients, which is similar to Hertenstein *et al.*<sup>[11]</sup> who found an overall cardiac toxicity of 4.5% and a life-threatening toxicity of 1.8%.

Kupari *et al.* also performed echocardiographic examinations at 1 month and 1 year after HSCT. An increase in the mass index and the pre-ejection period/ejection time as well as a decrease in the fractional shortening and a peak normalized diameter-lengthening rate was found after 1 month; however, 1 year after the transplantation, the measurements were no longer significantly different from the pre-transplant values.

Carlsson *et al.* followed 111 patients with radionuclide ventriculography examinations up to 5 years after the autologous HSCT and found a significant decrease in the LV EF in lymphoma patients at 6 and 36 months after HSCT. In non-lymphoma patients, there were no changes in cardiac function after transplantation. The authors found no increase in cardiac complications in patients with a low pre-transplant LVEF (below 50%).

The baseline LVEF significantly differed between patients with CML and those with acute leukemia or multiple myeloma. This difference may be because only five of the CML patients had a history of previous anthracycline treatment whereas this treatment was considerably more common in patients with the other diagnoses. No significant changes in the mean ejection fraction were seen in comparing the pre- and post-transplant examinations. This finding was true for all diagnostic subgroups as well as autologous and allogeneic recipients. However, a slight but nonsignificant increase in the mean LV EF was observed in some groups. Only 8% of patients had a significant decrease in ejection fraction. The majority of these patients

**Table 1: Tissue Doppler S measurements in different LV walls before and after BMT**

LV wall	Tissue Doppler S pre-BMT (cm/s)	Tissue Doppler S (post-BMT)	Change (%)	Standard deviation	P value
Septal	8	7.36	-8	2.31	0.017
Lateral	9.89	9.10	-7.9	2.78	0.017
Anterior	9.26	8.80	-4.9	1.66	0.016
Inferior	8.57	8.66	+1	1.62	0.08
Posterior	9.05	9.61	+6.1	2.13	0.06
Anteroseptal	7.26	7.31	+0.6	1.80	0.1

**Table 2: Tissue Doppler S measurements in patients with a pre-BMT EF below 47% in different LV walls before and after BMT**

LV wall	Tissue Doppler S pre-BMT (cm/s)	Tissue Doppler S post-BMT (cm/s)	Change (%)	Standard deviation	P value
Septal	7.22	7.77	+7.6	1.70	0.02
Lateral	9.11	10.33	+13.3	1.64	0.005
Anterior	8.11	8.82	+8.75	1.58	0.01
Inferior	8.33	9.3	+11.6	1.66	<0.001
Posterior	8.55	10.07	+17.8	1.78	<0.001
Anteroseptal	6.66	8	+20	1.84	<0.001

**Table 3: Tissue Doppler S measurements in patients with a pre-BMT EF above 47% in different LV walls before and after BMT**

LV wall	Tissue Doppler S pre-BMT (cm/s)	Tissue Doppler S post-BMT (cm/s)	Change (%)	P value
Septal	8.7	7	-19.5	<0.001
Lateral	10.6	8	-24.5	<0.001
Anterior	10	8.8	-12	<0.001
Inferior	8.9	8.1	-8.9	0.005
Posterior	9.5	9.2	-3.1	0.04
Anteroseptal	7.8	6.7	-14.1	<0.001

had a decrease of more than 10 percentage points, and only two patients dropped below 50%. In conclusion, it seems that the cardiotoxic factors of the HSCT procedure are insufficient to exert an effect on cardiac systolic function in most patients, measured as a change in the ejection fraction 1–7 months after the transplantation. Patients with a low LV EF before HSCT and patients with a significant decline in LVEF after HSCT were not at a greater risk of developing clinical signs of heart failure.<sup>[16]</sup> Age, previous anthracycline exposure, and prior abnormal cardiac function are established risk factors.<sup>[17,18]</sup>

Our findings confirm the effects of BMT on the EF found in previous studies. We report no harmful effect of BMT on the EF. As mentioned before, BMT surprisingly increased the EF in our patients, and the increase was more pronounced in patients with a lower pre-BMT EF.

In our study, in addition to evaluating cardiac systolic function using EF and LV diameters, we incorporated tissue Doppler measurements. After a comprehensive tissue Doppler evaluation of different LV walls, variables indicating systolic function were analyzed before and

after BMT. When patients were divided into two groups according to their pre-BMT EF, we unexpectedly found that the tissue Doppler S increased in patients with a lower pre-BMT EF and decreased in patients with a normal and preserved EF. An increase in tissue Doppler S denotes an improvement in cardiac systolic function. We conclude that BMT does not worsen systolic function but rather augments the systolic function, especially in patients with a lower pre-BMT ejection fraction. This finding contradicts the previous concern of deteriorating cardiac function after BMT in patients with a reduced EF.

Previous research has investigated the effects of high-dose chemotherapy on cardiac systolic function; however, our study focused on the effects of BMT on cardiac systolic function. BMT includes more factors than simple chemotherapy. High-dose chemotherapy is one part of BMT, but other interventions, including the introduction of stem cells, are more important components. The results of our study may be due to the effect of stem cells on heart. As mentioned before, when the systolic function is within normal range, the tissue Doppler indices indicate that the systolic function is slightly worse, which the effects

of high-dose chemotherapy can explain. When the cardiac systolic function was lower before BMT, the EF and tissue Doppler indices increased significantly after BMT, possibly because of the effects of stem cells on the failing heart.

We propose that stem cells with an ability to transform into specialized cardiomyocytes may improve the systolic function of patients with a pre-BMT reduced EF.

According to our findings, BMT is a safe procedure for patients with a reduced EF and may improve cardiac systolic functioning.

A limitation of our study was lack of the control group. We must state that finding a matched control group for our patient samples is very difficult. We studied on group of patients who were candidate of BMT, in order to have a control group we must find similar cancer patients with identical candidacy for BMT, depriving this control group from BMT is not ethical. For example patients with lymphoma who had multiple relapses are candidate of BMT; we ethically cannot deprive these patients from BMT because BMT may be a cure for them. But preparing a clinical setting with the availability of control group certainly adds value to the findings. Future research with more participants is required to delineate the exact effect of BMT on cardiac systolic functioning.

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