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Subclinical left ventricular dysfunction in children after hematopoietic stem cell transplantation for severe aplastic anemia: a case control study using speckle tracking echocardiography

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Purpose: Severe aplastic anemia (SAA), a fatal disease, requires multiple transfusion, immunosuppressive therapy, and finally, hematopoietic stem cell transplantation (HSCT) as the definitive treatment. We hypothesized that iron overloading associated with multiple transfusions and HSCT-related complications may adversely affect cardiac function. Left ventricular (LV) function was assessed in children after HSCT for SAA.
Methods: Forty-six consecutive patients with a median age of 9.8 years (range, 1.5–18 years), who received HSCT for SAA and who underwent comprehensive echocardiography before and after HSCT, were included in this study. The data of LV functional parameters obtained using conventional echocardiography, tissue Doppler imaging (TDI), and speckle-tracking echocardiography (STE) were collected from pre- and post-HSCT echocardiography. These data were compared to those of 40 age-matched normal controls.
Results: In patients, the LV ejection fraction, shortening fraction, end-diastolic dimension, mitral early diastolic E velocity, TDI mitral septal E' velocity, and STE LV longitudinal systolic strain rate (SSR) decreased significantly after HSCT. Compared to normal controls, patients had significantly lower post-HSCT early diastolic E velocity and E/A ratio. On STE, patients had significantly decreased LV deformational parameters including LV longitudinal systolic strain (SS), SSR, and diastolic SR (DSR), and circumferential SS and DSR. Serum ferritin levels showed weak but significant correlations ($P<0.05$) with LV longitudinal SS and SSR and circumferential SS and DSR.
Conclusion: Subclinical LV dysfunction is evident in patients after HSCT for SAA, and was associated with increased iron load. Serial monitoring of cardiac function is mandatory in this population.

Key words: Aplastic anemia, Stem cell transplantation, Ventricular function, Speckle tracking echocardiography, Strain rate

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Introduction

Severe aplastic anemia (SAA) is a potentially fatal disease characterized by peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. If untreated, most patients die within 1–2 years after diagnosis[1]. The principal therapeutic interventions for SAA include repeated red blood cell transfusion, immunosuppressive therapy, and

hematopoietic stem cell transplantation (HSCT) as the definitive treatment. In children and young adults, HSCT is the initial treatment of choice if a matched sibling donor is available. A recent large retrospective study showed that the 5-year survival rate after HSCT in patients under 20 years old was around 80%[2].

There have been few reports regarding the late effects that are associated with systemic organ dysfunction after HSCT in SAA survivors[3,4]. Late cardiovascular complications are supposed to be uncommon in this population because SAA patients are rarely exposed to well-known cardiotoxic agents such as anthracyclines, which are widely used in pediatric cancer patients. However, SAA patients require multiple transfusions as a pre-HSCT supportive care, which may inevitably lead to systemic organ iron overload[5,6]. Iron overloading in the cardiac tissues can progress to iron overload cardiomyopathy and heart failure, which are the major causes of late death in patients with transfusion-dependent hematologic disease[7]. In addition, HSCT conditioning-related toxicity and HSCT-related complications might adversely affect cardiac function[4]. Long-term HSCT survivors are likely to have an increased risk of premature cardiovascular accidents[8,9]. A recent study in children who underwent HSCT showed that subclinical changes in systolic and diastolic function are evident at one year after HSCT, and suggested that serial cardiac function assessment is necessary in all HSCT patients[10].

Left ventricular ejection fraction (LVEF) or fractional shortening (FS) measured by 2-dimensional (2D) echocardiography have been generally used to monitor left ventricular (LV) function and included in long-term follow-up protocols of pediatric cancer survivors. Recently, studies using tissue Doppler imaging (TDI) and 2D speckle-tracking echocardiography (STE) have shown that subclinical LV dysfunctions were not uncommon in this population with normal EF[11-14]. However, there have been no reports on the use of TDI or 2D STE for the LV functional assessments of children who underwent HSCT for SAA.

The purpose of this study was to assess the LV functions in patients who had undergone HSCT for SAA using TDI and STE, and compare them to those of age-matched normal controls. In addition, we evaluated the changes in LV functional parameters from pre- to post-HSCT echocardiographic findings in order to examine the influence of HSCT on cardiac function. We hypothesized that iron overloading associated with multiple transfusion and HSCT-related complications may adversely affect cardiac function.

Materials and methods

1. Study design

We had previously described the study design and methods in a study involving children with acute leukemia who underwent HSCT at the Seoul St. Mary's Hospital[14]. This study was a retrospective study on 46 children (<19 years) who had received the first HSCT for SAA at the Seoul St. Mary's Hospital between January 1, 2009 and December 31, 2013. According to HSCT protocol at our institution, all patients had comprehensive echocardiography including LV TDI and STE measurements before (within 3 months) and after HSCT during a follow-up study. The study included patients who performed a pre- and post-HSCT echocardiography within 3 months before and at least 6 months after HSCT, respectively. Patients with congenital heart disease, risk factors for cardiovascular complications such as hypertension, diabetes, or hyperlipidemia, or who died within 6 months after HSCT, were excluded from the study. The echocardiographic LV functional parameters were compared between patients and 40 age-matched normal controls. The control subjects included children who had heart murmurs, nonspecific chest pain, palpitations, or syncope, and had definitively normal cardiac structure and functions as seen on echocardiography. Patients' demographic and HSCT characteristics were collected from the HSCT database at our institute.

2. Transplant procedure

All patients received the same conditioning regimen including cyclophosphamide (25 mg/kg), antithymocyte globulin (2.5 mg/kg), and fludarabine (30 mg/m^2 body surface area). For the prophylaxis of graft-versus-host disease (GVHD), cyclosporine (3 mg/kg/day, from day 1 after HSCT) and methotrexate (5 mg/m^2/day, at days 1, 3, 6, and 11) were administered. Stem cell sources were bone marrow (n=9) and peripheral blood stem cells (n=37).

3. Echocardiography

According to our institutional HSCT protocol, comprehensive echocardiography using the Vivid 7 ultrasound machine (GE Medical Systems, Horten, Norway) was performed in all patients in order to assess their systolic and diastolic functions before and after HSCT, during the follow-up study[14]. Echocardiographic data were collected from two studies, a pre-HSCT study performed closest to the time that HSCT was performed and the latest study performed at least 6 months following HSCT. Measurements were performed on ultrasound machines and/or customized EchoPAC software (GE Medical Systems) as described in our previous study[14]. The average value of the echocardiographic indices from three cardiac cycles was recorded.

For conventional echocardiographic assessment, the LV end-systolic and end-diastolic dimensions, as well as the LVEF and FS were derived from M-mode assessment of the mid-LV parasternal long axis view. Mitral inflow Doppler velocities at early (E) and late (A) diastole, E/A ratio, and early diastolic E deceleration time, were recorded. From the TDI, the mitral septal annular velocities, including peak early diastolic (E'), late diastolic (A'), peak systolic

myocardial tissue velocity (S'), and E'/A' ratio, were recorded. For STE, the apical four-chamber plane was used to assess the LV global longitudinal strain, longitudinal systolic strain rate (SR), and longitudinal diastolic SR[14]. The parasternal short-axis plane at the level of papillary muscle was used to assess the LV global circumferential strain, circumferential systolic SR, and circumferential diastolic SR. Echocardiographic variables measured after HSCT in patients were compared to those of normal controls and pre-HSCT echocardiography.

4. Statistical analysis

Data were analyzed using the commercially available software PASW Statistics ver. 18 (IBM, Armonk, NY, USA) and were expressed as mean±standard deviation. Demographic and echocardiographic variables were compared between patients and controls using two-tailed independent-sample *t* tests for normally distributed data and the two-tailed Mann-Whitney *U* test for nonnormally distributed data, or Fisher exact test, when appropriate. Pre- and post-HSCT changes in echocardiographic parameters were compared using the paired-sample *t* test. The potential effects of age, sex, serum ferritin levels, and acute GVHD after transplant on cardiac functions (TDI and STE parameters) were assessed using the independent-samples *t* test for dichotomous variables and Pearson correlation analysis for continuous variables. Statistical significance was considered when the *P* value was less than 0.05.

Results

The demographic and HSCT characteristics of the study cohort are summarized in Table 1. Forty-six patients (28 male patients) who had their first HSCT for SAA at the age of 9.9±3.0 years (range, 1.5–18 years) were included in this study. All patients had the same treatment for pretransplant conditioning. Echocardiography was performed within a median of 23 days (range, 1–61 days) before and 11 months (range, 6–20 months) after HSCT, respectively. No patients had symptomatic LV dysfunction needing medication. After HSCT, acute GVHD developed in 20 patients (43%), and were treated with systemic corticosteroids. The serum hemoglobin level increased significantly after HSCT (8.1±1.5 g/dL before vs. 13.0±1.9 g/dL after, $P<0.001$). The serum ferritin levels did not change significantly after HSCT (2,068±3,875 before vs. 1,595±2,165 after, $P=0.30$), and were >1,000 μg/L in 21 patients (46%). No patients had other systemic organ dysfunction needing a special treatment associated with iron overload. Patients with acute GVHD after HSCT had significantly higher serum ferritin levels at the time of echocardiography compared to patients without acute GVHD (2,693±2,898 μg/L vs. 751±585 μg/L, $P<0.05$).

For the 40 control subjects, the mean (±SD) age and weight at study were 9.6±3.0 years and 36.1±15.8 kg, respectively, and did not differ significantly from the patient group (Table 1).

1. Conventional echocardiography parameters

The echocardiographic characteristics of patients and controls are summarized in Table 2. In patients, LVEF ($P<0.001$), LVFS ($P<0.001$), LV end-diastolic dimension ($P<0.001$), and early diastolic E velocity ($P<0.001$) decreased significantly after HSCT compared to the pre-HSCT assessment. However, all patients had LVEF (>55%) and LVFS (>0.28) within normal limits. Compared to normal controls, patients had significantly higher heart rates ($P<0.05$), and decreased early diastolic E velocity ($P<0.001$) and E/A ratio ($P<0.05$) after HSCT. There were no differences in LVEF, LVFS, and LV dimensions between patients and controls.

2. TDI and 2D STE parameters

In patients, post-HSCT mitral septal annular E' ($P<0.01$) and E'/A' ratio ($P<0.05$) were significantly lower compared to those at the pre-HSCT assessment (Table 2). Compared to normal controls, however, there were no significant differences in all post-HSCT LV TDI parameters. On the 2D STE, LV global longitudinal systolic SR decreased significantly after HSCT in the patient group ($P<0.01$). Compared to normal controls, patients had significantly decreased LV myocardial deformation parameters after HSCT in terms of global longitudinal systolic strain, global longitudinal systolic SR, global longitudinal diastolic SR, global circumferential systolic strain, and global circumferential diastolic SR (Table 2). Serum ferritin levels checked at the time of post-HSCT echocardiography showed weak but significant correlations with the global longitudinal systolic strain ($P<0.05$), global longitudinal systolic SR ($P<0.05$), global circumferential systolic strain ($P<0.05$), and global circumferential diastolic SR ($P<0.001$) (Table 3). Sex and age at the time of the study did not show any significant cor-

Table 1. Baseline demographic characteristics of the study cohorts

Variable	Patients (n=46)	Controls (n=40)	*P* value
Female sex	18 (39)	14 (35)	NS
Age at HSCT (yr)	9.9±3.0	-	
Age at study (yr)	10.9±4.7	9.6±3.0	NS
Body weight (kg)	37.3±19.2	36.1±15.8	NS
BSA (m^2)	1.17±0.42	1.12±0.34	NS
Acute GVHD	20 (43)	-	
Hemoglobin (g/dL)			
Before HSCT	8.1±1.5	-	
After HSCT	13.1±1.9*	-	

Values are presented as number (%) or mean±standard deviation.
HSCT, hematopoietic stem cell transplantation; BSA, body surface area; GVHD, graft-versus-host disease; NS, not significant.
*$P<0.001$ compared to the value before HSCT.

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Table 2. Echocardiographic characteristics of the patients and controls

Characteristic	Patients (n=46)			Controls (n=40)	*P* value†
	Pre-HSCT	Post-HSCT	*P* value*		
Heart rate (beats/min)	94±20	88±15	NS	82±13	<0.05
LVEF (%)	68.0±5.5	63.5±5.2	<0.001	65.3±5.7	NS
LVFS (%)	0.38±0.04	0.34±0.04	<0.001	0.35±0.04	NS
LVDD (mm)	43.5±7.0	41.0±6.2	<0.001	40.6±5.2	NS
LVSD (mm)	26.8±4.9	26.9±4.4	NS	26.2±3.7	NS
Mitral inflow Doppler measurements					
Early diastolic E velocity (m/sec)	1.10±0.17	0.88±0.19	<0.001	1.05±0.14	<0.001
Late diastolic A velocity (m/sec)	0.62±0.19	0.54±0.14	NS	0.54±0.11	NS
E/A ratio	1.92±0.59	1.76±0.67	NS	2.06±0.44	<0.05
Early diastolic E DT (ms)	164±34	152±43	NS	154 ±57	NS
Tissue Doppler imaging					
Mitral septal E' velocity (m/sec)	0.14±0.02	0.13±0.02	<0.001	0.14±0.02	NS
Mitral septal A' (m/sec)	0.07±0.02	0.07±0.01	NS	0.06±0.02	NS
E'/A' ratio	2.29±0.73	2.04±0.61	<0.05	2.27±1.17	NS
Mitral septal S' velocity (m/sec)	0.09±0.02	0.08±0.02	NS	0.08±0.05	NS
2D speckle tracking echocardiography					
Global longitudinal systolic strain (%)	–19.8 ±4.7	–18.4±3.8	NS	–20.7±3.0	<0.05
Global longitudinal systolic SR (1/sec)	–1.31±0.25	–1.12±0.28	<0.05	–1.27±0.21	<0.05
Global longitudinal diastolic SR (1/sec)	1.82±0.73	1.64±0.59	NS	2.41±0.67	<0.001
Global circumferential systolic strain (%)	–16.2±5.8	–16.6±5.3	NS	–19.6±3.2	<0.05
Global circumferential systolic SR (1/sec)	–1.24±0.32	–1.18±0.41	NS	–1.30±0.25	NS
Global circumferential diastolic SR (1/sec)	1.59±0.62	1.57±0.62	NS	2.28±0.55	<0.001

Values are presented as mean±standard deviation.
HSCT, hematopoietic stem cell transplantation; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVDD, left ventricular end-diastolic dimension; LVSD, left ventricular end-systolic dimension; DT, deceleration time; 2D, 2-dimensional; SR, strain rate; NS, not significant.
*Comparison between pre-HSCT and post-HSCT parameters in patients. †Compared with post-HSCT parameters in patients.

Table 3. Correlation between the post-transplant 2D STE parameters and the serum ferritin levels

2D STE parameter	Post-HSCT serum ferritin level	
	Pearson correlation	*P* value
Global longitudinal systolic strain	0.42	<0.05
Global longitudinal systolic SR	0.40	<0.05
Global longitudinal diastolic SR	-	NS
Global circumferential systolic strain	0.40	<0.05
Global circumferential systolic SR	-	NS
Global circumferential diastolic SR	–0.40	<0.05

2D STE, 2-dimensional speckle-tracking echocardiography; HSCT, hematopoietic stem cell transplantation; SR, strain rate; NS, not significant.

relations with the LV 2D STE parameters.

Discussion

In this study, we firstly report the LV functional changes measured by STE in patients who underwent HSCT for SAA. Our results showed that LV systolic and diastolic functions based on the STE-derived LV deformation parameters were decreased in children who received HSCT, even with the normal range of LVEF or FS, compared to the control group. Early markers of diastolic dysfunction, the mitral inflow Doppler E velocity, and the E/A ratio also decreased in the patient group. In addition, decreased LV deformation parameters were associated with increased iron load in this population. In the patient group, some LV systolic and diastolic function parameters decreased after HSCT when compared with the pretransplantation assessments.

Patients with SAA suffer from chronic anemia, which can chronically cause a decreased systemic organ oxygen supply. In order to compensate for this, the cardiovascular system increases the myocardial workload and circulatory volume, resulting in LV remodeling including LV dilatation and hypertrophy[15]. In this study, patients had larger LV end-diastolic dimensions but the same LV end-systolic dimensions before compared to post-HSCT. After the HSCT, correction of chronic anemia mignt cause reverse remodeling of the LV, resulting in a decrease in the LV end-diastolic dimensions along with a decrease in LVEF[16]. Therefore,

in terms of LV volumetric functional indices such as LVEF and FS, decreases in the values after HSCT do not necessarily indicate a true decline in the LV function. This might be supported by the fact that LVEF and LVFS were within normal range in all patents after HSCT and were similar to those of normal controls.

However, it is note worthy that patients had decreased STE-derived LV deformation paremeters such as myocardial strain and SR, despite having normal LVEF and SF. The exact mechanism of myocardial dysfunction in this population is quite uncertain. The HSCT involves pre-HSCT conditioning chemotherapy, immunosuppresive therapy, and corticosteroids for the treatment of GVHD, which might adversely affect myocarial function and be potential risk factors for the development of late cardiac complications after HSCT[17]. In addition, SAA patients need multiple transfusions for supportive management, which inevitably leads to iron overload in the systemic organs[5,6]. Since humans have no mechanism for iron excretion, cumulative iron overload leads to iron toxicity with organ dysfunction and damage. Chronic iron overload in the cardiac tissue can cause myocyte apoptosis, interstitial fibrosis, and mitochondrial dysfunction, which are responsible for cardiac failure[18]. Iron overload cardiomyopathy and heart failure is the major cause of late death in patients with transfusion-dependent hematologic disease[7]. In this study, almost half of all patients (46%) had serum ferritin levels of >1,000 μg/L more than 6 months after HSCT. Moreover, serum ferritin levels showed weak but significant correlations with the STE LV myocardial strain and SR. These findings suggest that iron overload in the cardiac tissue is a possible mechanism of myocardial dysfunction in our patients. Therefore, continuous monitoring of cardiac function is necessary in this population.

At our institution, in order to reduce complications associated with iron overload, earlier HSCT is considered in severe cases needing frequent transfusion. After HSCT, a phlebotomy is usually done in patients with iron overload. Otherwise in patients who had not received HSCT, iron-chelating therapy is started if serum ferritin level is higher than 1,000 μg/L. In this study, there were no cardiac complication in need of treatment due to iron overload, but unfortunately we could not accurately check for the other systemic organ involvement.

Echocardiogram is the commonly used imaging tool for assessment of cardiac function. Traditionally, echocardiographic LVEF and/or FS were frequently included in follow-up protocols for monitoring LV function in pediatric cancer survivors, despite limitations such as geometric assumption and load dependency[19-21]. Recently, 2D STE has been introduced in order to quantify complex cardiac motions. It can assess global and regional ventricular myocardial deformations such as strain, SR, displacement, and velocity in longitudinal, radial, and circumferential directions without angle dependency[22]. Additionally, it has been known as clinically useful for evaluating cardiac systolic and diastolic functions, providing new insights for understanding cardiac physiology and mechanics, and identifying early subclinical changes in various pathologies[22]. In a study using STE, Cheung et al.[11] reported that, despite having LVFS values that were within normal limits, children had decreased LV myocardial deformation after anthracycline therapy. They suggested that the new echocardiographic techniques can detect early subclinical LV systolic dysfunction in patients who are considered having normal LV systolic function using conventional M-mode techniques[11]. Our previous study involving HSCT among children with acute leukemia also showed that subclinical cardiac dysfunction is obvious in post-HSCT children with normal LVEF and FS[14]. In this study, all patients had similar LVEF, SF, and TDI derived MV annular velocities after HSCT, but had significantly decreased STE-derived LV deformation parameters (strain and SR) compared to controls. It is not clear if this early subclinical change in LV deformation function detected by STE may have long-term cardiovascular consequences. Further long-term longitudinal studies are needed to elucidate this. Furthermore, it should be considered to use 2D STE as a routine imaging techniques to assess cardiac function and detect early myocardial dysfunction in this population.

The present study has several limitations. First, this is a retrospective observational study with a relatively small number of patients, which may affect the power of the study. However, considering that SAA is a very rare disease, this number is not so small for a single center study. In addition, a case control study design may partly overcome this limitation. Second, we only used the serum ferritin level as a marker of iron overload. In these patients, the cumulative transfusion units and/or the results of liver magnetic resonance imaging may provide accurate information on iron overloading. Third, a single observer performed the off-line STE analyses, and the intra- or interobserver reliability was not assessed. However, our previous study that involved STE showed excellent, intra- and interobserver reliability with high intraclass correlation coefficients[23]. This suggests that STE is a reliable imaging modality for assessing complex LV deformation functions in children.

In conclusion, this is the first study that evaluated LV function in patients who received HSCT for SAA. This study showed that early subclinical myocardial systolic and diastolic dysfunctions, as assessed by STE LV deformation parameters, were evident in this population, despite the presence of normal LVEF or FS. In addition, LV dysfunction is associated with increased serum ferritin levels, which is a marker of iron overload. The 2D STE is a sensitive and practical imaging modality for detecting early subclinical myocardial dysfunction. In order to examine the effects of this early cardiac dysfunction on long-term outcomes, serial quantitative echocardiography using new imaging techniques should be considered for all post-HSCT patients.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Scheinberg P. Aplastic anemia: therapeutic updates in immunosuppression and transplantation. Hematology Am Soc Hematol Educ Program 2012;2012:292-300.
2. Gupta V, Eapen M, Brazauskas R, Carreras J, Aljurf M, Gale RP, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica 2010;95:2119-25.
3. Sanders JE, Woolfrey AE, Carpenter PA, Storer BE, Hoffmeister PA, Deeg HJ, et al. Late effects among pediatric patients followed for nearly 4 decades after transplantation for severe aplastic anemia. Blood 2011;118:1421-8.
4. Buchbinder D, Nugent DJ, Brazauskas R, Wang Z, Aljurf MD, Cairo MS, et al. Late effects in hematopoietic cell transplant recipients with acquired severe aplastic anemia: a report from the late effects working committee of the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2012;18:1776-84.
5. Berdoukas V, Nord A, Carson S, Puliyel M, Hofstra T, Wood J, et al. Tissue iron evaluation in chronically transfused children shows significant levels of iron loading at a very young age. Am J Hematol 2013;88:E283-5.
6. Pawelec K, Salamonowicz M, Panasiuk A, Leszczynska E, Krawczuk-Rybak M, Demkow U, et al. Influence of iron overload on immunosuppressive therapy in children with severe aplastic anemia. Adv Exp Med Biol 2015;866:83-9.
7. Wongjaikam S, Kumfu S, Chattipakorn SC, Fucharoen S, Chattipakorn N. Current and future treatment strategies for iron overload cardiomyopathy. Eur J Pharmacol 2015;765:86-93.
8. Armenian SH, Bhatia S. Cardiovascular disease after hematopoietic cell transplantation--lessons learned. Haematologica 2008;93:1132-6.
9. Tichelli A, Bhatia S, Socie G. Cardiac and cardiovascular consequences after haematopoietic stem cell transplantation. Br J Haematol 2008;142:11-26.
10. Daly KP, Colan SD, Blume ED, Margossian R, Gauvreau K, Duncan C, et al. Changes in echocardiographic measures of systolic and diastolic function in children 1 year after hematopoietic SCT. Bone Marrow Transplant 2011;46:1532-9.
11. Cheung YF, Hong WJ, Chan GC, Wong SJ, Ha SY. Left ventricular myocardial deformation and mechanical dyssynchrony in children with normal ventricular shortening fraction after anthracycline therapy. Heart 2010;96:1137-41.
12. Alehan D, Sahin M, Varan A, Yildirim I, Kupeli S, Buyukpamukcu M. Tissue Doppler evaluation of systolic and diastolic cardiac functions in long-term survivors of Hodgkin lymphoma. Pediatr Blood Cancer 2012;58:250-5.
13. Baysal T, Koksal Y, Oran B, Sen M, Unal E, Cimen D. Cardiac functions evaluated with tissue Doppler imaging in childhood cancers treated with anthracyclines. Pediatr Hematol Oncol 2010;27:13-23.
14. Yoon JH, Kim HJ, Lee EJ, Moon S, Lee JY, Lee JW, et al. Early left ventricular dysfunction in children after hematopoietic stem cell transplantation for acute leukemia: a case control study using speckle tracking echocardiography. Korean Circ J 2015;45:51-8.
15. Anand IS. Pathophysiology of anemia in heart failure. Heart Fail Clin 2010;6:279-88.
16. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149-54.
17. Tichelli A, Passweg J, Wojcik D, Rovo A, Harousseau JL, Masszi T, et al. Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 2008;93:1203-10.
18. Wijarnpreecha K, Kumfu S, Chattipakorn SC, Chattipakorn N. Cardiomyopathy associated with iron overload: how does iron enter myocytes and what are the implications for pharmacological therapy? Hemoglobin 2015;39:9-17.
19. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers. Version 3.0 [Internet]. Arcadia (CA): Children's Oncology Group; 2008 [cited 2015 Sep 6]. Available from: www.survivorshipguidelines.org.
20. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Reliability of multicenter pediatric echocardiographic measurements of left ventricular structure and function: the prospective P(2)C(2) HIV study. Circulation 2001;104:310-6.
21. Buckberg GD, Weisfeldt ML, Ballester M, Beyar R, Burkhoff D, Coghlan HC, et al. Left ventricular form and function: scientific priorities and strategic planning for development of new views of disease. Circulation 2004;110:e333-6.
22. Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, et al. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. Echocardiography 2013;30:88-105.
23. Kim HJ, Yoon JH, Lee EJ, Oh JH, Lee JY, Lee SJ, et al. Normal left ventricular torsion mechanics in healthy children: age related changes of torsion parameters are closely related to changes in heart rate. Korean Circ J 2015;45:131-40.