Carvedilol improves left ventricular diastolic dysfunction in patients with transfusion-dependent thalassemia

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ABSTRACT

Background	:	Iron overload cardiomyopathy is the most common cause of death in patients with transfusion-dependent thalassemia.
Aim	:	The aim of this study was to determine the efficacy of carvedilol treatment in patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction.
Methods	:	Eighteen patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction were enrolled. All patients had normal left ventricular systolic function and were given carvedilol with the target dose of 0.8 mg/kg/day. Ventricular function and the level of cardiac iron were assessed by echocardiography and magnetic resonance imaging at 0, 3, and 6 months.
Results	:	The median age of the patients was 19 years (range 13–25 years). Four patients had severe left ventricular Grade III diastolic dysfunction and fourteen patients had Grade II diastolic dysfunction. The grade of left ventricular diastolic dysfunction was improved at 3 months after the carvedilol treatment. The Doppler parameters, including pulmonary vein atrial reversal velocity, pulmonary vein atrial reversal duration, and the difference of pulmonary vein atrial reversal and the mitral valve atrial contraction wave duration at 3 months after the carvedilol treatment, were significantly lower than these parameters before the treatment.
Conclusions	:	Among patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction without systolic dysfunction, treatment with carvedilol for 3 months was associated with improvement in Doppler parameters of left ventricular diastolic function. However, this finding and its clinical significance need to be confirmed in further double-blind controlled studies.
Keywords	:	CARDIAC T2*, carvedilol, tissue Doppler echocardiography, transfusion-dependent thalassemia

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INTRODUCTION

Patients with severe forms of homozygous beta-thalassemia and beta-thalassemia/hemoglobin E disease often display symptoms related to hemolysis and ineffective erythropoiesis, including anemia, jaundice, hepatosplenomegaly, skeleton change, and delayed growth. The mainstay of treatment in these patients is regular blood transfusion with an aim to inhibit the synthesis of abnormal red blood cells and iron chelation to reduce iron deposition in the vital organs. Consequences of transfusional iron overload are ventricular dysfunction, arrhythmia, hepatitis, diabetes mellitus, failure of sexual maturation, and growth retardation.[1,2] Iron overload cardiomyopathy is the most common cause of death in patients with transfusion-dependent thalassemia.[1-5] To reduce the risk of both mortality and morbidity, these patients need to receive iron chelation therapy to reduce iron in the body.[6-10] Although iron chelation is widely used in patients with transfusion-dependent thalassemia, iron overload cardiomyopathy remains one of the major causes of death.[11,12] The factors affecting mortality are the presence of a left ventricular restrictive filling pattern and a low left ventricular ejection fraction.[13,14] The pathophysiology of iron overload cardiomyopathy is the formation of highly reactive oxygen free radicals that cause oxidative damage-associated ischemia–reperfusion injury.[15,16] An angiotensin-converting enzyme inhibitor used in adult patients with thalassemia has been shown to be capable of improving both systolic and diastolic left ventricular impairments.[17] Amlodipine used in conjunction with standard chelation therapy shows a potential for reducing cardiac iron overload as voltage-gated calcium channel blockade might prevent iron uptake into the cardiomyocytes.[18,19] However, there has been no study of whether the effect of the amlodipine therapy improves ventricular function.

Carvedilol is a nonselective adrenergic blocker combining an antioxidant effect.[20] Several studies show that carvedilol can improve both systolic and diastolic ventricular function, reduce free radical release and apoptosis, and reduce mortality in children and adults with congestive heart failure.[21-24] The hypothesis for this study was that carvedilol can attenuate left ventricular diastolic dysfunction due to iron overload in patients with transfusion-dependent thalassemia who had ventricular dysfunction.

METHODS

Sixty-one patients with transfusion-dependent thalassemia were evaluated in this study between January 2014 and December 2016. All consecutive patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction were enrolled in this study. All patients or their parents provided written informed consent for research participation. All patients were initially given carvedilol in doses of 0.1 mg/kg/day, with the medication being divided into two separate doses. The dosage was doubled every 2 weeks until the target dose of 0.8 mg/kg/day was reached and was continued for 6 months. The maximum dose was 50 mg/day. All patients had normal left ventricular systolic function and no symptom of congestive heart failure. The patients who received other medications for congestive heart failure were excluded. All patients had their cardiac function assessed by echocardiography as the primary outcome at 0, 3, and 6 months, and the level of iron in the heart was also evaluated at 0, 3, and 6 months using cardiac magnetic resonance imaging (MRI). Side effects of the drug were monitored through the study.

Echocardiography

Echocardiographic data were obtained using the Philips iE33 system (Philips Healthcare, Bothell, WA, USA). Echocardiography was performed in nonfasting state after the blood transfusion. Complete two-dimensional, M-mode, Doppler (pulsed wave, continuous wave, and color) echocardiography was performed according to the American Society of Echocardiography recommendations.[25,26] The quality of Doppler echocardiographic imaging was satisfactory enough for measurement. Echocardiographic parameters included left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and left ventricular fractional shortening. Echocardiographic data included pulse wave Doppler assessment of mitral and pulmonary venous flows (ventricular diastolic filling analysis) and tissue Doppler imaging. Pulse wave Doppler of mitral valve flow included peak early ventricular filling velocity, peak atrial contraction velocity, and atrial contraction wave duration and deceleration time. Pulse wave Doppler of pulmonary venous flow included systolic forward flow velocity, diastolic forward flow velocity, atrial reversal flow velocity, and atrial reversal flow duration. Tissue Doppler imaging signals were obtained from an apical four-chamber view at the septal mitral annulus. Tissue Doppler imaging variables included systolic myocardial velocity, early diastolic myocardial velocity, and late diastolic myocardial velocity. Doppler characteristics of left ventricular diastolic dysfunction with increased ventricular end-diastolic and left atrial pressure included increased atrial reversal flow velocity and atrial reversal flow duration, pulmonary vein atrial reversal duration exceeding the A wave duration, decreased early diastolic myocardial velocity, and increased mitral early ventricular filling velocity-to-early diastolic myocardial velocity ratio. Myocardial performance

Table 1: Clinical and laboratory characteristics at baseline and after 3 and 6 months of treatment with carvedilol

	Before treatment	3-month treatment	6-month treatment	*P*
Hemoglobin (g/dL)	8.0 (7.3-8.6)	8.3 (5.9-9.7)	7.4 (6.1-9.0)	0.05
Serum ferritin (ng/mL)	1679 (430-9277)	1925 (161-6622)	1574 (426-8867)	0.98
Heart rate (bpm)	88 (74-114)	93 (64-116)	89 (72-112)	0.63
Systolic BP (mmHg)	111 (98-129)	101 (90-123)	101 (85-109)*	0.01
Diastolic BP (mmHg)	59 (50-76)	56 (49-76)	55 (42-68)	0.46
Cardiac T2* (ms)	36.1 (3.9-40.9)	37.5 (3.7-45.8)	38.3 (4.1-46.8)	0.58

*$P<0.05$ versus before the treatment; #$P<0.05$ versus after 3 months of treatment. BP: Blood pressure

Table 2: Comparison of the pulse wave Doppler parameters at baseline and after 3 and 6 months of treatment

	Before treatment	3-month treatment	6-month treatment	*P*
Heart rate (bpm)	88 (74-114)	93 (64-116)	89 (72-112)	0.63
E (cm/s)	122 (83-147)	117 (95-150)	121 (88-145)	0.85
A (cm/s)	54 (30-109)	73 (45-103)	65 (44-124)	0.23
E/A	2.0 (1.3-3.7)	1.7 (0.9-2.6)	1.9 (0.9-2.8)	0.31
DT (ms)	159 (127-236)	180 (130-250)	180 (130-257)	0.33
PVS (cm/s)	69 (53-91)	74 (55-87)	72 (39-88)	0.77
PVD (cm/s)	66 (43-83)	60 (38-80)	62 (44-82)	0.60
PVAR (cm/s)	34 (26-45)	31 (22-38)*	28 (20-37)*	0.004
PVAR duration (ms)	143 (109-180)	116 (67-144)*	113 (88-128)*	<0.0001
PVAR-MVA duration (ms)	16 (−25-60)	−3 (−49-14)*	−10 (−56-17)*	0.004
TR gradient (mmHg)	22 (18-33)	24 (18-33)	27 (15-38)	0.19
MAPSE (mm)	17 (14-24)	18 (12-25)	18 (11-23)	0.74
FS (%)	38 (33-42)	40 (30-45)	38 (31-46)	0.54
CI (L/min/m²)	4 (3-6)	5 (2-5)	4 (3-9)	0.43

*$P<0.05$ versus before treatment, #$P<0.05$ versus after 3 months of treatment. A: Atrial filling velocity, CI: Cardiac index, DT: Deceleration time, E: Early ventricular filling velocity, FS: Fractional shortening, MAPSE: Mitral annular plane systolic excursion, MVA: Mitral valve atrial filling velocity, PVAR: Pulmonary vein atrial reversal filling velocity, PVD: Pulmonary vein diastolic filling velocity, PVS: Pulmonary vein systolic filling velocity, TR: Tricuspid regurgitation

index derived from tissue Doppler imaging was calculated by adding the isovolumic contraction and isovolumic relaxation times together and then dividing this value by the ejection time. Mitral annular plane systolic excursion was assessed with the M-mode in an apical four-chamber view, placing the cursor on the lateral mitral annulus. Diastolic left ventricular dysfunction was graded according to pulse wave Doppler of mitral and pulmonary venous flows and tissue Doppler imaging.[27,28]

Cardiac T2* magnetic resonance

All patients had a cardiac T2* MRI, with the imaging carried out using a 1.5 Tesla MRI scanner (Philips Achieva, the Netherlands) with a sense cardiac phase array of a five-element coil, or SENSE XL Torso 16-element coil, as was used in previous studies.[29] Cardiac T2* was measured from a single short-axis view at the mid-left ventricle with 10 echo times (1.70–26.10 ms with an increment of 2.70 ms). The cardiac T2* protocol included a double inversion recovery black blood gradient echo. A multiecho sequence was applied with a flip angle of 25°, matrix 164 × 154, field of view 36 cm, TR 28 ms, slice thickness 10 mm, and number of signal averages = 1. Data analysis was performed on the workstation with the validated in-house software developed on the MATLAB R2014b (Mathworks, Natick, MA, USA).

Statistical analysis

All statistical calculations were assessed using commercially available software (SPSS version 23, SPSS Inc., Chicago, IL, USA). Continuous data were expressed as median and range or mean and standard deviation. Categorical data were summarized as number and percentage. The differences in the Doppler parameters of ventricular function were assessed using a nonparametric test. $P < 0.05$ was considered statistically significant.

RESULTS

Eighteen patients with transfusion-dependent thalassemia and left ventricular diastolic dysfunction with the median age of 19 years (range 13–25 years) were enrolled in this study. Ten (56%) patients were male. Four patients had severe left ventricular Grade III diastolic dysfunction, and fourteen patients had grade II diastolic dysfunction. All patients tolerated carvedilol with the target dose of 0.8 mg/kg/day with good compliance. No side effects were reported. The clinical characteristics and the results of the cardiac T2* MRI data are summarized in Table 1. Systolic blood pressure 6 months after treatment was lower than that before the carvedilol treatment. At the end of the study, heart rate and diastolic blood pressure were not significantly different from before the treatment.

In addition, levels of serum ferritin and cardiac T2* before and after the treatment were not different.

Conventional echocardiography

Conventional Doppler parameters, including mitral valve inflow, pulmonary vein inflow, fractional shortening, and mitral annular plane systolic excursion, were compared before treatment and then at 3 and 6 months after treatment [Table 2]. Pulmonary vein atrial reversal flow velocity, pulmonary vein atrial reversal flow duration, and the difference of pulmonary vein atrial reversal duration and the mitral valve atrial contraction wave duration in patients 3 and 6 months after the carvedilol treatment were significantly lower than those before the treatment [Figure 1]. Mitral annular plane systolic excursion, left ventricular fractional shortening, and cardiac index were not different after the treatment.

Tissue Doppler echocardiography

Tissue Doppler imaging and the grade of left ventricular diastolic dysfunction are summarized in Table 3. The grade of left ventricular diastolic dysfunction significantly improved after 3 and 6 months of carvedilol treatment [Figure 2]. Systolic myocardial velocity readings 3 and 6 months after the carvedilol treatment was started were higher than those before the treatment.

Early diastolic myocardial velocity, early ventricular filling velocity-to-early diastolic myocardial velocity ratio, and tissue Doppler imaging-derived myocardial performance index were not different after the treatment.

DISCUSSION

The results of this study supported the hypothesis in that the carvedilol treatment led to improved left ventricular diastolic function in patients with iron overload cardiomyopathy. Diastolic echocardiographic parameters, including atrial reversal flow velocity, atrial reversal flow duration, and the difference of pulmonary vein atrial reversal duration and the mitral valve atrial contraction wave duration, were significantly improved at 3 months after the treatment. In addition, the grade of left ventricular diastolic dysfunction was significantly improved at 3 months after the carvedilol treatment.

Tissue Doppler echocardiography has been the noninvasive method used in the assessment of early ventricular dysfunction. Left ventricular diastolic dysfunction demonstrated in patients with thalassemia preceded the onset of systolic impairment. Complete assessment of left ventricular diastolic function should be interpreted by both mitral valve and pulmonary venous Doppler inflow. Tissue Doppler imaging has been the additional assessment for grading left

Table 3: Comparison of the tissue Doppler data before and after 3 and 6 months of treatment

	Before treatment	3-month treatment	6-month treatment	P
Sm (cm/s)	7.8 (6.1-9.1)	8.4 (7.4-9.4)*	8.2 (7.5-10.2)*	0.05
Em (cm/s)	12.3 (9.7-14.3)	12.7 (11.4-15.5)	12.3 (11.0-15.3)	0.20
Am (cm/s)	5.7 (3.6-8.3)	7.1 (4.5-9.5)	6.1 (5.1-9.1)	0.20
E/Em	11 (9-15)	9 (6-12)	9 (8-13)	0.20
TDI-derived MPI	0.5 (0.4-0.8)	0.6 (0.4-0.7)	0.6 (0.4-0.7)	0.10
Diastolic dysfunction				
Normal	-	6*	12*	<0.0001
Grade I	-	1	1	
Grade II	14	11	5	
Grade III	4	-	-	

*$P<0.05$ versus before treatment, #$P<0.05$ versus after 3 months of treatment. Am: Late diastolic myocardial velocity, E: Early ventricular filling velocity, Em: Early diastolic myocardial velocity, MPI: Myocardial performance index, Sm: Systolic myocardial velocity, TDI: Tissue Doppler imaging
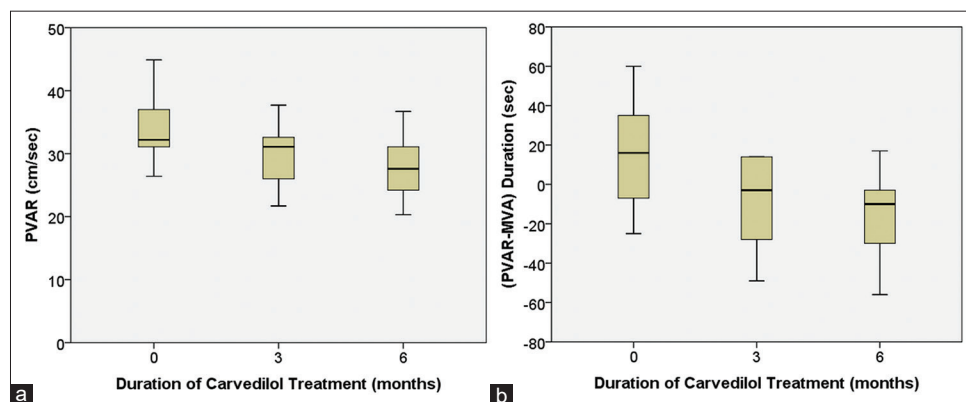
Figure 1: Graph comparing the pulse wave Doppler of mitral valve and pulmonary venous flow after 3 and 6 months of carvedilol treatment. (a) Pulmonary venous atrial reversal flow velocity; (b): The difference in the pulmonary vein atrial reversal duration and the mitral valve A wave (Pulmonary venous atrial reversal-mitral valve atrial filling velocity) duration
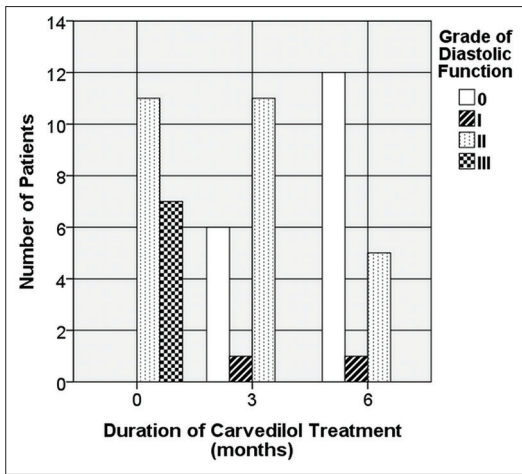
Figure 2: Graph comparing the grade of left ventricular diastolic dysfunction after 3 and 6 months of carvedilol treatment

ventricular diastolic function. The grading system using a semiquantitative method can classify the severity of left ventricular diastolic ventricular function.[27] In the present study, pulse wave Doppler of mitral valve and pulmonary venous Doppler inflow, including tissue Doppler imaging, were assessed for grading the left ventricular diastolic function. Doppler parameters indicating left ventricular diastolic function, including atrial reversal flow velocity, atrial reversal flow duration, and pulmonary vein atrial reversal duration exceeding the mitral valve atrial contraction wave duration improved during carvedilol treatment. The E/e' ratio was somewhat lower at 3 months after the treatment. We believe that the pulse Doppler of pulmonary venous and mitral valve inflow parameters had more sensitivity for the detection of LV diastolic dysfunction. Conversely, cardiac T2* MRI which is used as a gold standard for early detection of iron overload cardiomyopathy did not change during the treatment. Therefore, the Doppler parameter of left ventricular diastolic function improved as a result of the carvedilol treatment.

Several studies in pediatric patients have shown that carvedilol improved ventricular function, both in cases of dilated cardiomyopathy and in those of congenital heart disease with heart failure.[21-23] Bajcetic *et al.* reported that a 1-year treatment of carvedilol in pediatric patients with dilated cardiomyopathy improved left ventricular function and increased antioxidant enzyme activity.[24] Only one study, involving a randomized controlled trial with 14 adolescent patients with beta-thalassemia major who had left ventricular ejection fraction <55%, revealed that a pulsed Doppler E/A ratio of mitral valve flow in a group undergoing carvedilol treatment and a control group changed from 1.1 ± 0.37 m/s to 1.8 ± 0.40 m/s and from 1.34 ± 0.30 m/s to 2.6 ± 0.23 m/s, respectively. However, this study did not demonstrate that carvedilol therapy led to improvements in both left ventricular

systolic and diastolic functions in these patients.[30] In our study, 18 pediatric and adolescent patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction showed improvement in left ventricular diastolic function after 3 months of carvedilol treatment. These improvements were demonstrated by pulse wave Doppler of the pulmonary vein and mitral valve flow parameters. Carvedilol can improve left ventricular diastolic function by acting as a nonselective adrenergic blocker and through its antioxidant effects that include reducing free radical release and apoptosis.[20-24]

Use of an angiotensin-converting enzyme inhibitor in a study including 14 adult patients with beta-thalassemia major who had asymptomatic or minimally symptomatic left ventricular dysfunction showed increased left ventricular fractional shortening and deceleration time and decreased E/A ratio of mitral valve Doppler flow in the patients.[17] Recently, amlodipine used in combination with standard chelation therapy in patients with thalassemia major who had myocardial T2* <35 ms led to a more effective reduction in cardiac iron overload than chelation therapy alone.[18,19] However, there has been no study into the effect of the amlodipine therapy on the improvement of left ventricular function.

The limitation of this study was that a double-blinded randomized controlled trial could not be conducted because of the small number of patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction. However, the improvement in left ventricular diastolic function in the medium-term follow-up was effectively measured and documented using complete conventional pulse wave Doppler of both the pulmonary vein and mitral valve inflow and tissue Doppler imaging. The encouraging results from the study show that a double-blinded randomized controlled trial of a large number of patients with transfusion-dependent thalassemia is warranted.

CONCLUSIONS

For patients with transfusion-dependent thalassemia who had left ventricular diastolic dysfunction without systolic dysfunction, treatment with carvedilol for 3 months was associated with improvement in Doppler parameters of diastolic function. Doppler parameters, indicating left ventricular diastolic dysfunction including pulmonary vein atrial reversal flow velocity, pulmonary vein atrial reversal flow duration, and the difference of pulmonary vein atrial reversal duration and mitral valve atrial contraction wave duration, were significantly decreased after 3 months of carvedilol treatment. However, this finding and its clinical significance need to be confirmed in further double-blind controlled studies.

Conflicts of interest

There are no conflicts of interest.

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