

# Cardio-protective effect of regular transfusion in children with non-transfusion dependent thalassemia (NTDT): A cohort study

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**Abstract.** *Background and aim of the work:* Cardiac complications occur in patients with non-transfusion dependent thalassemia (NTDT). The study aimed to evaluate transfusion effect on systolic and diastolic cardiac function in young NTDT patients. *Methods:* Study design: Cohort study. Seventeen regularly-transfused patients with NTDT (12.5±5.3 years; group 1) and 15 none/minimally transfused patients (13.2±4.8 years; group 2) were followed up for 5 years and compared as regards their clinical parameters, echocardiographic and Tissue-Doppler-Imaging. *Results:* Group 2 patients had significantly higher peak late-diastolic velocity of the left-ventricular-inflow Doppler (Am). Mitral-valve A-wave duration/pulmonary-veins, A-wave duration-ratio and pulmonary-vein S/D velocities-ratio were larger in group 2 as well ( $p = \leq 0.01$ ). The diameters of right and left outflow-tract were larger with a higher cardiac-index in patients of group 2. Systolic-function was similar in the 2 studied groups. *Conclusion:* Diastolic function assessment revealed indicators of an abnormal relaxation of left-ventricle in non-transfused patients, which suggests a diastolic dysfunction. An increase in the diameter of the outflow-tract is likely attributed to high cardiac-output status in non-transfused NTDT patients as they have a higher cardiac index. Early start of regular transfusion for NTDT patients might prevent serious long-term cardiac complications. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Non-transfusion dependent thalassemia (NTDT), regular blood transfusion, echocardiography

## Introduction

Non-transfusion dependent thalassemia (NTDT) is a term used to label thalassaemic patients who do not require such lifelong regular transfusions for survival. This group of patients have significant genetic and clinical heterogeneity. They may require occasional or even frequent transfusions in certain clinical settings and for defined periods of time (1). Patients with NTDT have increased absorption of dietary iron and mild chronic hemolysis which may result in signs

and symptoms of iron overload (2). NTDT patients are very likely to develop serious complications including marked thalassaemic facies, which is usually irreversible, growth retardation with short stature, splenomegaly, hypersplenism, hypercoagulable state, pulmonary hypertension (PHTN) and congestive heart failure (CHF) (3). The heart is primarily affected by PHTN, which is the leading cause of CHF. High cardiac output resulting from chronic tissue hypoxia and increased pulmonary vascular resistance (PVR) are the main contributing factors (4).

Hb Dhofar is a variant haemoglobin (beta (29 (GGC-GGT) gly-gly), beta (58 (CCT-CGT) pro-arg) associated with a moderate to severe NTDT phenotype that is unique to the Sultanate of Oman and represent almost one third of our thalassemia cohort (5). Patients with Hb Dhofar develop early thalassaemic facies and many severe complications, and therefore, we offer them regular transfusion-chelation therapy quite early in life (at the age of 3 years), however, transfusions were not accepted by all families and many patients continued without transfusion.

Currently there are no evidence based guidelines for transfusion therapy of moderately severe NTDT (6). Regular transfusion/iron chelation therapy seems to have a cardio-protective role (4, 7). Several studies revealed that cardiac dysfunction and PHTN are the main causes of early deaths among the NTDT adult patients however, pediatric data are limited (8).

Echocardiographic techniques such as Tissue Doppler Imaging (TDI) offers a unique method of quantitative assessment of longitudinal systolic and diastolic ventricular performance by measuring velocities directly from myocardium (9-11).

### **Aim of the work**

The current study aims at evaluating the cardiac abnormalities in a cohort of young patients with moderately severe NTDT on regular transfusion-chelation therapy and compare them to never transfused or minimally transfused patients.

### **Study population**

This prospective cohort study was conducted at Sultan Qaboos University Hospital (SQUH), Muscat, Oman during the period 1/12/2014-31/12/2019. It was approved by the Ethics Committee of the College of Medicine and Health Science, SQU and informed written assents/consents were obtained from the patients or their guardians.

All patients followed-up in day care unit of SQUH diagnosed with NTDT were offered to start regular monthly transfusion program to keep their minimal hemoglobin level around 10 g/dl with a maximum of

14 g/dl. They were divided into 2 groups. Group 1 accepted the regular transfusion-chelation program and group 2 included patients who refused the transfusion program and remained on no transfusion or minimally transfused ( $\leq 3$  packed red blood cell transfusion/year). Patients with history of cardiac disease were excluded from the study.

At baseline, anthropometric and physical examination were performed including measurement of heart rate, blood pressure, presence or absence of thalassaemic facies, and liver and spleen size in centimeters below the costal margin.

Blood samples for complete blood count (CBC) and serum ferritin level were collected. Molecular studies were done at diagnosis and confirmed Hb Dhofar genotype in all the study patients. The  $\alpha$ -globin gene status was analyzed by our stepwise diagnostic strategy as described previously (12). The entire alpha hemoglobin stabilizing protein (AHSP) genes were sequenced to detect the AHSP gene single-nucleotide polymorphisms (SNPs) (13). To avoid confounding results, patients with  $\alpha$ -thalassemia trait and/or functional alpha hemoglobin stabilizing protein (AHSP) polymorphisms were excluded.

Twelve-leads electrocardiogram (ECG), two dimensional echocardiogram (2D Echo) and TDI were then performed at baseline before the initiation of any transfusion therapy. The patients had routine clinic visits for follow-up assessment or regular transfusion. After 5 years of follow-up, full clinical assessment, routine blood tests, ECG, 2D Echo and TDI assessments were repeated.

### *Echocardiographic and Tissue Doppler Imaging parameters*

Two dimensional echocardiography was performed using Vivid E9 Echo machine (GE Vingmed Ultrasound, Horten, Norway) at rest. All the M-Mode, two dimensional, Doppler and TDI echocardiographic measures were done by one qualified echocardiographer with the patients fully awake according to the recommendation of the American Society of Echocardiography (ASE) (14). All the measurements represent the average value of at least three cardiac cycles. Our focus as per ASE recommendation, was to assess the systolic function using the standard M-Mode of the left ventricle. Assessment of

diastolic function was mainly via taking Doppler measurement of the mitral valve inflow and the right upper pulmonary vein from four chamber view. Isovolumic relaxation time (IVRT) was measured from placing the continuous Doppler sample volume in the left ventricular outflow tract in 3 chamber view. Also we utilized the TDI to assess the myocardial velocities and their ratios of the lateral mitral valve, upper part of the septum and lateral tricuspid valve. In addition, we measured the diameters of the left and right proximal great arteries for the various groups. During the study, blood pressure and heart rate were measured. Cardiac index assessment was performed as per the standard method of assessment of stroke volume and heart rate previously described (15). Assessment of diastolic function in adults is well established but no consensus yet for the optimal nomograms for assessment of diastolic function in pediatric age groups. Studies were limited by many factors including small sample size, inconsistent methodologies, different age groups and different ethnicities (16).

#### Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago IL, USA). All results

are expressed as mean  $\pm$  SD. The statistical analysis was carried out using student's T-test and Mann-Whitney U-test. Differences were considered statistically significant at  $p \leq 0.05$ .

#### Results

Group 1 included seventeen NTDT patients. Their mean age at starting regular transfusion was  $7.4 \pm 2.1$  years, and the mean duration of regular transfusion was  $5 \pm 0.6$  years. Their mean duration of iron chelation therapy was  $2.1 \pm 0.9$  years. Group 2 included 15 NTDT patients. There was no significant difference in their age, sex body surface area, clinical and hematological characteristics. There was no significant difference in their systolic blood pressure, heart rate and corrected QTc interval (Table 1). The results at the end of study (demographic, blood pressure and ECG data) are shown in table 2. Clinical and hematological characteristics for all the study participants are shown in table 3. Group 2 patients have statistically significant lower hemoglobin and hematocrit level compared to Group 1 ( $p \leq 0.001$ ). In group 2, all patients but one had classic thalassemic facies. Serum ferritin level was

**Table 1.** Baseline demographic, clinical, laboratory and and electrocardiographic (ECG) data of all studied patients at study initiation (N=32)

Characteristic	Group 1 (n=17)	Group 2 (n=15)
Gender (M:F)	8:9	8:7
Age, years	7.4 $\pm$ 2.1	7.6 $\pm$ 3.2
Height, cm	109.3 $\pm$ 19.2	111.1 $\pm$ 17.2
Weight, kg	17.8 $\pm$ 4.9	18.1 $\pm$ 5.2
BSA, m <sup>2</sup>	0.71 $\pm$ 0.22	0.73 $\pm$ 0.19
Systolic BP, mm/Hg	93 $\pm$ 8	101 $\pm$ 9
Diastolic BP, mm/Hg	61 $\pm$ 7.7	65 $\pm$ 7
Heart Rate, beats/minute	95 $\pm$ 9.6	93 $\pm$ 11
QTc, ms	419 $\pm$ 17	421 $\pm$ 19
Hemoglobin, g/dl	7.9 $\pm$ 1.2	8.2 $\pm$ 1.1
Hematocrit	26 $\pm$ 5	25 $\pm$ 4
Serum ferritin at study initiation before regular blood transfusion, ng/ml	156 $\pm$ 77	161 $\pm$ 83
Splenomegaly (cm below left costal margin in mid-clavicular line)	3.1 $\pm$ 1.05	3 $\pm$ 1.1
Thalassemic facies	2/17 (11.8%)	2/15 (13.3%)

N=number, M=Male, F= Female, kg=Kilogram, cm=Centimeter, BSA=Body surface area, BP=Blood pressure, QTc (corrected QT interval), g/dl=gram/deciliter, ng/ml= Nanogram/milliliter.

significantly higher in group 1 compared to patients of group 2 ( $p \leq 0.041$ ).

At baseline, the standard and tissue Doppler echocardiographic measurements were comparable between the regularly transfused (group 1) and non-transfused patients (group 2). The p-values measuring the difference between mean individual parameters were ranging between 0.6 and 0.9.

Table 4 displays the standard two dimensional echocardiographic measurements at baseline and in both groups after follow-up. The two studied groups had similar left ventricular size measurements. Patients of group 2 had a significant increase in the diameters of the aortic sinus of valsalva, sinotubular junction, main pulmonary artery, right, left pulmonary artery and left atrium to aortic ratio.

**Table 2.** Demographic, blood pressure and electrocardiographic (ECG) data of the 2 studied groups at the end of the study

Characteristic	Group 1 (N= 17)	Group 2 (N = 15)
Gender (M:F)	8/9	8/7
Age (years)	12.5±5.3	13.2±4.8
Height (cm)	139 ± 17.5	128.7 ±31.6
Weight (kg)	32.4 ± 13.7	27.6 ± 16.9
BSA (m <sup>2</sup> )	1.1 ± 0.3	1.0 ± 0.4
Systolic BP (mmHg)	104 ± 5	103 ± 9
Diastolic BP (mmHg)	57 ± 7	53 ± 5
Heart rate	81 ± 13	86 ± 14
QTc, ms	419 ± 19	430 ± 14

BSA, body surface area, Bp, blood pressure, ECG, electrocardiogram, QTc, corrected QT interval for heart rate.

**Table 3.** Clinical and hematological data of the 2 studied groups

	Group 1 (n=17)	Group 2 (n=15)	P-value
Last pre-transfusion Hemoglobin level (g/dl)	10.6. ± .8	8.15 ± 1.6	0.001*
Last hematocrit level	0.30±0.01	0.23±0.04	0.001*
Age of initiation of transfusion (years)	7.4 ±2.1	N/A	
Duration of transfusion (years)	5.06 ± 0.6	N/A	
Duration of chelation therapy (years)	4.8 ± 2.3	2.1 ± 0.9	0.0002*
Current ferritin (post transfusion period) (ng/ml)	1696 ± 1251	374 ± 335	0.041*
Splenomegaly (cm below left costal margin)	(1 patient 2 cm)	5 ± 3	
Thalassemic facies, number	2	13	

\* Statistically significant ( $P \leq 0.05$ )

None of the study patients had evidence of PHTN assessed by the TV max gradient, group 1:  $18.4 \pm 2.1$  and group 2:  $18 \pm 2.9$ .

Standard and tissue Doppler assessment data are summarized in table 5. Patients of group 2 showed a significantly larger peak late diastolic velocity of the left ventricular inflow Doppler (Am) compared to the transfused group ( $p \leq 0.03$ ). Moreover, they had a significantly lower Em/Am ratio of the mitral valve inflow compared to transfused group ( $p \leq 0.03$ ). The right upper pulmonary vein peak velocities were comparable between the groups except the mitral valve A wave duration over the pulmonary vein A wave duration ratio and the pulmonary vein S/D velocities ratio which were larger in the non-transfused group.

The mitral valve A wave duration over the pulmonary vein A wave duration ratio was significantly larger in non-transfused group compared to the transfused group ( $p \leq 0.001$ ). No significant difference noted between the DTm, TDI of the mitral valve and septum and tricuspid valve between the 2 groups.

## Discussion

We studied clinical parameters, echocardiographic and Tissue-Doppler-Imaging in young patients with Hb Dhofar, which is the main cause of NTDT in our region (5). Although predicting phenotype from genotype in NTDT is difficult, due to the interaction of genetic and environmental factors, it was noted that Hb Dhofar in its homozygous or

**Table 4.** Standard two dimensional echocardiographic measurements and Z scores at baseline and at the end of the study

Characteristic	MeanBaseline (B)	Group 1 (N: 17) (1)	Group 2 (N: 15) (2)	P-value 1,2	1,B	2,B
LVIDd (mm)	40.4 ± 4.6	40.9± 12.3	43.8 ± 7.8	1.00	1.00	0.37
LVIDd/BSA	40.2 ± 8.4	38.6 ± 8.2	46.2±16.6	0.35	0.56	1.00
LVIDd (Z score)	- 0.03 ± 0.9	0.46 ± 0.9	0.91 ± 1.4	1.00	1.00	0.62
LVISd (mm)	25.1 ± 4.8	27.2 ± 4.8	28 ± 7.0	1.00	0.71	0.55
LVISd/BSA	25.0 ± 6.1	23.9 ± 5.6	28.9±10.5	0.37	0.61	1.00
LVISd(Z score)	0.04 ± 0.9	0.2 ± 1.0	0.91 ± 1.4	0.21	0.21	1.00
IVSd (mm)	5.6 ± 1.3	7.0 ± 1.5	6.1± 2.5	0.77	1.00	0.07
IVSd/BSA	5.5 ± 1.6	6.2 ± 1.9	5.9 ± 1.8	1.00	1.00	0.78
IVSd (Z score)	-0.5 ± 1.1	0.4 ± 0.9	0.0026±1.3	1.00	1.00	0.07
LVPWd (mm)	5.0 ± 0.9	5.9 ± 1.3	5.4 ± 2.2	1.00	1.00	0.24
LVPWd/BSA	4.9 ± 0.9	5.2 ± 1.2	5.4 ± 2.2	1.00	1.00	1.00
LVPWd(Zscore)	-0.6 ± 0.6	0.01 ± 1.0	0.1 ± 1.6	1.00	0.36	0.34
EF (%)	68.0 ± 7.3	68.0 ± 7.5	69 ± 8.3	1.00	1.00	1.00
SF (%)	37.9 ± 6.1	38.0 ± 5.8	38 ± 7	1.00	1.00	1.00
AoAn(mm)	16.3 ± 2.1	17.6 ± 1.9	17 ± 3.1	1.00	1.00	0.34
AoAn/BSA	16.0 ± 2.7	15.6 ± 3.1	17.7 ± 5.9	0.64	0.86	1.00
AoAn(Z score)	0.5 ± 0.7	0.8 ± 0.8	1.1 ± 1.2	1.00	0.26	0.82
Sinvals (mm)	20.4 ± 2.9	21.9 ± 2.7	22.8 ± 5.2	1.00	0.34	0.68
Sinvals/BSA	20.0 ± 3.1	19.3 ± 3.5	23.4 ± 7.2	0.13	0.22	1.00
Sinvals(Zscore)	-0.4 ± 0.7	-0.2 ± 0.7	0.73 ± 1.2	<b>0.04</b>	0.06	1.00
Sintubj (mm)	17.9 ± 2.3	19.8 ± 2.6	19.6 ± 3.9	1.00	0.44	0.21
Sintubj/BSA	17.6 ± 3.0	17.4 ± 3.2	20.5 ± 7.6	0.35	0.36	1.00
Sintubj(Z score)	0.4 ± 0.6	0.8 ± 0.7	1.2 ± 1.1	0.94	0.07	0.32
AscAo (mm)	18.1 ± 2.1	21.0 ± 3.1	20.3 ± 4.8	1.00	0.31	0.04
AscAo/BSA	17.8 ± 3.1	18.4 ± 3.4	21.1 ± 7.7	0.57	0.27	1.00
AscAo(Z score)	- 0.2 ± 0.8	1.2 ± 1.7	0.89 ± 1.9	1.00	0.18	0.02
PVAn (mm)	17.2 ± 3.2	19.5 ± 3.4	18.8 ± 4.3	1.00	0.94	0.27
PVAn/BSA	16.9 ± 3.4	17.1 ± 3.7	19.9 ± 8.8	0.70	0.53	1.00
PVAn (Z score)	-0.7 ± 0.9	- 0.3 ± 1.0	0.02 ± 1.5	0.79	1.00	0.38
MPA (mm)	16.3 ± 2.1	17.8 ± 3.2	19.5 ± 4.2	0.63	0.04	0.51
MPA/BSA	16.3 ± 3.8	15.7 ± 3.7	21.86±11.2	0.08	0.10	1.00
MPA(Z score)	-1.1 ± 0.8	- 0.8 ± 1.0	0.01 ± 0.95	0.15	0.07	1.00
LPA (mm)	11.3 ± 1.5	13.3 ± 1.5	16.9 ± 4.7	<b>0.01</b>	0.08	0.09
LPA/BSA	11.6 ± 3.7	12.0 ± 3.5	17.7 ± 7	<b>0.02</b>	0.06	1.00
LPA(Z score)	0.4 ± 1.2	1.3 ± 0.9	2.9 ± 1.3	<b>0.01</b>	0.1	0.15
RPA (mm)	11.1 ± 1.4	14.0 ± 1.8	15.4 ± 2.1	0.20	0.09	0.01
RPA/BSA	11.2 ± 3.4	12.5 ± 3.4	16.5 ± 6.9	0.12	0.08	1.00
RPA (Z score)	- 0.4 ± 1.0	0.5 ± 0.9	1.7 ± 1.1	0.06	0.2	<b>0.02</b>
TVmax	17.7±3.0 (16)	18.4±2.1 (10)	18 ± 2.9	1.00	1.00	1.00
LA/AO	1.5 ± 0.2	1.6 ± 0.2	1.8 ± 0.26	0.29	0.23	0.38
IVRT, ms	66.9±9.6 (17)	70.5±13.0 (13)	77.1 ± 20.4	0.84	0.26	1.00
IVRT, corrected	80.7±11.7 (11)	80.7±17.5 (9)	91.9 ± 23.4	0.45	0.17	1.00
CI	4.1±0.60 (9)	4.6 ± 1.0	4.8±1.2 (7)	1.00	0.98	0.71

LVIDd, left ventricular end diastolic dimension; LVISd, Left ventricular end systolic dimension; IVSd, interventricular septal dimension in diastole; LVPWd, left ventricular posterior wall dimension in diastole; EF, ejection fraction; SF, shortening fraction; AoAn, aortic valve annulus; Sinvals, sinus of valsalva; Sintubj, sinotubular junction; AscAo, ascending aorta; PVAn, pulmonary valve annulus; MPA, main pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery; TVmax, tricuspid valve regurgitation maximum peak velocity; LA/Ao, Left atrium aortic dimension ratio by M-mode; IVRT, Isovolumic relaxation time; CI, Cardiac index.

\* Corrected for heart rate. P value is significant  $\leq 0.05$ ; significant values are highlighted in bold.

**Table 5.** Standard and Tissue Doppler Echocardiographic measurement at baseline and at the end of the study

Characteristic	Group 1 (end of study) N=17	Group 2 (end of study) N=15	Mean Baseline (B) N=32	P-value 1 vs.2	P-value 2,B	P-value 1,B
<b>Mitral Valve</b>						
Em, cm/s	114.2 ± 11.9	110 ± 17.8	103.3 ± 19.0	1.00	0.96	0.25
Am, cm/s	55.3 ± 13.4	72 ± 19.7	52.2 ± 11.4	<b>0.03</b>	<b>0.01</b>	1.00
Em/Am ratio	2.2 ± 0.5	1.6 ± 0.39	2.04 ± 0.5	<b>0.03</b>	0.07	1.00
Amd, ms	122.1 ± 30.6	131.3 ± 37.9	110.2 ± 23.0	1.00	0.29	0.81
DTm, ms	165.8 ± 25.4	146.8 ± 27.8	141.8 ± 22.9	0.29	1.00	0.04
DTm, corrected for heart rate	194.1 ± 37.8	173.2 ± 25.5	159. ± 28.6	0.38	1.00	0.05
S'm, cm/s	10.1 ± 1.6	10.25 ± 2.9	9.7 ± 1.7	1.00	1.00	1.00
E'm, cm/s	20.5 ± 2.8	19.8 ± 2.8	19.8 ± 3.3	1.00	1.00	1.00
A'm, cm/s	6.9 ± 1.6	8.5 ± 2.1	7.0 ± 1.02	0.07	0.07	1.00
E'm/A'm	2.9 ± 0.82	2.5 ± 0.69	2.89 ± 0.69	0.75	0.75	1.00
<b>Septum</b>						
S's, cm/s	8.9 ± 1.4	8.9 ± 1.8	8.4 ± 1.1	1.00	1.00	0.89
E's, cm/s	14.5 ± 1.9	13.4 ± 1.5	15.5 ± 2.6	0.83	0.08	0.59
A's, cm/s	7.2 ± 1.5	7.6 ± 1.8	6.5 ± 1.1	1.00	0.21	0.64
E's/A's	2.1 ± 0.5	1.9 ± 0.71	2.4 ± 0.5	1.00	0.08	0.32
Em/E'm	5.4 ± 1.4	5.9 ± 1.8	5.3 ± 1.1	1.00	0.35	0.48
<b>Tricuspid valve</b>						
S't, cm/s	14.8 ± 2.5(12)	13.25 ± 2.5	13.2 ± 2.1	0.49	1.00	0.25
E't, cm/s	15.8 ± 1.8(12)	16.6 ± 2.8	16.1 ± 1.9	1.00	1.00	1.00
A't cm/s,	11.8 ± 3.2	12 ± 3.6	10.2 ± 2.1	1.00	0.41	0.37
E't/A't	1.4 ± 0.48	1.5 ± 0.52	1.7 ± 0.47	1.00	1.00	0.69
<b>Pulmonary vein</b>						
Spv, cm/s	56.4 ± 7.3	57.7 ± 12.5	48.8 ± 9.0	1.00	0.11	0.09
Dpv, cm/s	64.2 ± 9.3	54.6 ± 6.3	60.2 ± 12.2	0.173	0.69	0.92
Apv, cm/s	22.8 ± 7.9	18.9 ± 5.0	19.6 ± 5.0	0.56	1.00	0.50
Apvd, ms	83.0 ± 17.8	80.7 ± 20.8	85.4 ± 18.2	1.00	1.00	1.00
Spv/Dpv	0.9 ± 0.1	1.1 ± 0.27	0.8 ± 0.2	0.09	0.01	1.00
Amd/Apvd	1.5 ± 0.3	2.2 ± 0.95	1.3 ± 0.4	0.001	0.01	1.00

Em, peak early mitral valve flow velocity; Am, peak late mitral valve flow velocity; Em/Am, Em/Am ratio, Amd, Am duration; DTm, deceleration time of Em wave; S'm, peak systolic velocity of mitral valve; E'm, peak early diastolic velocity of the mitral valve; A'm, peak late diastolic velocity of mitral valve; E'm/A'm, E'm/A'm ratio; S's, peak systolic velocity of the septum; E's, peak early diastolic velocity of the septum; A's, peak late diastolic velocity of the septum; E's/A's, E's/A's ratio; S't, peak systolic velocity of the tricuspid valve; E't, peak early diastolic velocity of the tricuspid valve; A't, peak late diastolic velocity of the tricuspid valve; E't/A't, E't/A't ratio; Spv, peak systolic velocity of the pulmonary vein; Dpv, peak diastolic velocity of the pulmonary vein; Apv, peak A wave reversal in the pulmonary vein; Apvd, peak A wave reversal duration in the pulmonary vein; Amd/ Apvd ratio.

P value is significant  $\leq 0.05$ ; significant values are highlighted in bold.

compound heterozygous state clinically presents with moderate to severe phenotype. Daar et al. (5) reported previously that all those patients had splenomegaly, thalassaemic facies, and stunted growth if not managed with regular transfusion.

In the current study, never or minimally transfused NTDT patients have abnormal relaxation of the left ventricles that indicates a diastolic dysfunction. The abnormalities are in more than one parameter of the echocardiographic diastolic function assessment tools which may indicate that the changes are clinically significant. Meanwhile, they also have evidence of an increase in the diameters of the left and right outflow tracts secondary to high output status. On the other hand, regularly transfused patients have very mild increase in some parameters with normal systolic and diastolic cardiac function. Moreover, our study showed that tissue Doppler velocities of the lateral mitral annulus, upper part of the septum and the lateral tricuspid valve are comparable between the 2 groups which indicates that the changes in the myocardial velocities are late compared to the pulmonary vein changes and mitral valve inflow indices in the younger age group. Of note, all echocardiographic parameters were comparable at baseline, indicating the initial homogenous nature of our cohort as a whole before starting the interventional transfusion.

Traditionally, management of patients with NTDT was driven by patient symptoms and development of complications. Development of bulky extra-medullary hematopoiesis, splenomegaly, bony deformity, cardiomegaly or worsening anemia would prompt patients and clinician to start regular transfusion. More recently, there are recommendations to start early transfusion in these patients before development of such complications (17, 18).

Knowing the expected course of the disease, families of children affected with Hb Dhofar were counseled regarding optimum management with early regular transfusion/chelation program. However, some parents were reluctant to follow that program, and preferred to continue without transfusion.

Most of the current literature addressed the cardiac abnormalities in older NTDT patients. In several studies reporting on non-transfused adults with NTDT, the heart was primarily affected by PHTN

(4, 19). Actually, PHTN was the main cardiac abnormality detected in older patients with NTDT, both non-transfused and regularly transfused patients (who started transfusion after the age of 5 years) (20). PHTN was reported in 59.1% of NTDT patients (mean age  $32.5 \pm 11.4$  years) in the multicenter study conducted by Aessopos et al. (18) and in 21.5% of a younger group of patients (age  $17.05 \pm 5.8$ ) studied by Amoozgar et al. (21).

Several factors have been implicated in the pathogenesis of increased pulmonary vascular resistance and PHTN in NTDT patients; chronic hypoxia and anemia resulting in high cardiac output status, iron overload, hypercoagulability, splenectomy, chronic hemolysis and consumption of nitric oxide and arginine leading to vasoconstriction, all are implicated. PHTN is the leading cause of congestive heart failure due to the subsequent right heart insufficiency (8). CHF apparently increases with age, as it was reported in 2.7% of 74 patients aged 28.2 years, and in 5.4% of 110 patients aged 32.5 years (22).

Since 2007, Aessopos et al. (18), suggested an early transfusion regimen to patients with severe forms of NTDT however, there are no studies demonstrating the risks of no transfusion or the beneficial effects of regular transfusion/chelation on cardiac functions in the younger age group.

Supporting the early regular transfusion hypothesis, the current cohort prospective study revealed that cardiac abnormalities occur in non-transfused NTDT patients even at younger age ( $13.2 \pm 4.8$  years) than previously described. These changes are avoidable by applying early regular transfusion regimen to those patients, as evidenced by the normal cardiac function in the regularly transfused group. In our series, none of the patients had evidence of PHTN or CHF which are usually late complications in NTDT. Furthermore, non-transfused patients showed evidence of left ventricular diastolic dysfunction. Earlier introduction of blood transfusions would increase the rate of iron accumulation. The benefits of transfusion therapy with an effective iron chelation therapy might outweigh the risks of iron overload (23).

Involvement of the left ventricle have been attributed to volume (high cardiac output) and pressure (rigid vascular bed) overload (8, 24). These changes

are aggravated by age, and therefore are important in older population with NTDT. The current study gives an evidence of the occurrence of those changes also in non-transfused NTDT patients at younger age.

The study was limited by the small sample size and being done in a single center. Long term clinical benefits following such an early intervention in NTDT patients need to be investigated further, preferably in a multi-center study with a larger sample size.

In conclusion, young patients with hemoglobin Dhofar; a specific type of moderately severe NTDT, have normal systolic function. Diastolic function assessment revealed indicators of an abnormal relaxation of the left ventricle in non-transfused group indicating the presence of multiple diastolic function parameters. A statistically significant increase in the diameters of the outflow tracts were likely attributed to high cardiac output status. These findings support the recommendation for an early regular blood transfusion therapy in order to prevent serious cardiac complications in adult life.

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