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PULMONARY HYPERTENSION IN β-THALASSEMIA MAJOR AND THE ROLE OF L-CARNITINE THERAPY

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□ *Cardiac complications, such as pulmonary hypertension (PHT), are the leading cause of death in β-thalassemia patients. L-Carnitine, due to its role in fatty acid oxidation, might help control the elevation in pulmonary artery systolic pressure (PASP). The objectives of this study were to assess the prevalence of PHT in β-thalassemia major patients, identify clinical predictors for its development, and determine the potential effects of L-carnitine. In total, 32 patients with β-thalassemia major were recruited; 16 age- and sex-matched children constituted the control group. Cardiac evaluation was performed by using echocardiography. The patients with PHT received 50 mg/kg/day L-carnitine orally for 3 months and were then reevaluated. Based on PASP, the patients were divided into group A without PHT and group B with PHT. The prevalence of PHT was 37.5%. The other echocardiographic measurements were not significantly different between groups A and B. PASP did not have any significant correlation with the following variables: age, total number of blood units received, splenic status, serum ferritin level, and ejection fraction. Following the administration of L-carnitine, there was a significant decrease in the mean PASP from 33.96 ± 7.85 to 24.11 ± 7.61. All cardiac dimensions decreased following L-carnitine, but the changes were not statistically significant. Even though β-thalassemia major resulted in an elevation in the PASP in only a fraction of the patients, it seems to have an impact on the heart dimensions and function of all patients. No clinical predictors were identified. Oral administration of L-carnitine appears to significantly improve PASP.*

Keywords L-carnitine, echocardiography, pulmonary hypertension, β-thalassemia

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After the introduction of regular transfusion therapy with iron chelation, the prognosis of patients with β-thalassemia major has markedly improved. However, they remain prone to develop cardiac complications, which are the leading cause of death in these patients. One of these complications is right ventricular failure, which is frequently attributed hemosiderosis-induced myocardial injury [1]. Another possible cause of right-sided heart failure is the development of pulmonary hypertension (PHT), which is a chronic process attributed to many factors. First, the chronic anemia leads to increased cardiac output and pulmonary blood flow, resulting in pulmonary vasoconstriction. Second, the hypoxemia, the chronic pulmonary hemosiderosis, and the hypersensitivity reaction to deferoxamine therapy can cause arterial fibrosis and increased pulmonary vascular resistance. Third, the hypercoagulable state secondary to increased platelet counts following splenectomy may restrict the pulmonary vascular bed [2, 3].

L-Carnitine (3-hydroxy-4-*N*-trimethylaminobutyric acid), a butyrate analogue, is a cheap, orally administered, and well-tolerated physiological compound. It plays an essential role in fatty acid oxidation, glucose metabolism, and energy production in the cardiac muscle [4]. Supplementing patients with cardiac diseases or complications with L-carnitine has been shown to be beneficial [5, 6]. Moreover, studies have demonstrated that L-carnitine might be helpful in the management of chronic anemia since it can improve the hemoglobin level [7].

This study aims at assessing the prevalence of PHT in β-thalassemia major patients, identifying possible clinical predictors for the development of this complication, and determining the potential effects of L-carnitine therapy on elevated pulmonary artery pressure.

MATERIALS AND METHODS

Study Population

A total of 32 patients, diagnosed to have β-thalassemia major and regularly followed up at the hematology clinic in the New Cairo University Children Hospital, were recruited for this study. Sixteen age- and sex-matched children, not known to have any chronic medical problems, constituted the control group. All patients were started on regular blood transfusion therapy before the age of 1 year. They did not have any signs or symptoms suggestive of cardiac or pulmonary abnormalities. This study was approved by the Institutional Review Board and written informed consents were obtained from all the participating subjects. Patient recruitment started in January 2006 and the study was completed 6 months later.

Echocardiography

All echocardiograms were performed by the same cardiologist, who was not aware of the subject's group assignment. M-mode, 2-dimensional, and Doppler (pulsed-wave, continuous-wave, and color) echocardiography were performed at rest, using HP Sonos 5000 echocardiogram with a 3- to 8-MHz transducer and simultaneous EKG recording.

Parasternal long-axis and parasternal short-axis views at the midventricular level were used to measure cardiac dimensions by M-mode according to the recommendation of the American Society of Echocardiography (ASE) [8]. Left ventricular (LV) percentage of fractional shortening and subsequently LV ejection fraction, stroke volume (SV), and cardiac output (CO) were estimated according to the recommendation ASE and using apical 2- and 4-chamber views [9]. The lowest wall filter settings were used to record flow velocities. Doppler signal and lead II ECG were recorded simultaneously. Diastolic LV function was evaluated by Doppler parameters, including early (E) and late (A) diastolic peak flow velocities, E/A ratio, deceleration time of E wave (DT) [10], and LV isovolumic relaxation time (IVRT) [11]. Assessment of pulmonary artery flow was performed using Doppler recording of the systolic pulmonary flow, pulmonary acceleration time (PAT), right ventricular ejection time (RVET), and the ratio of PAT-to-RVET [12]. Pulmonary artery systolic pressure (PASP) was measured using tricuspid regurgitation, which was carefully assessed by color and continuous-wave Doppler tracing to measure peak systolic right ventricular to right atrial pressure gradient [13]. A tricuspid regurgitation of 2.5 m/s was taken as the cutoff level for diagnosis of pulmonary hypertension [14, 15]. The maximal transtricuspid gradient was calculated according to the simplified Bernoulli equation [11] using an apical 4-chamber and parasternal short-axis and long-axis views. If a holosystolic flow was still not observed, the regurgitation was considered not to be measurable. PASP was computed as the sum of the transtricuspid gradient and the right atrial pressure. In children not in heart failure, the right atrial pressure is less than 10 mm Hg with a mean less than 5 mm Hg; accordingly, it can be ignored. Thus, PASP in clinically normal patients approximately equals the tricuspid regurgitation [13, 15].

Drug Regimen and Follow-up

Only thalassemia patients with PHT (group B) received L-carnitine therapy. The medication was administered orally at a dose of 50 mg/kg/day for a period of 3 months. After completion of the treatment, the patients were reevaluated. All of the recruited patients completed the study and none of them showed any side effects that could be attributed to L-carnitine.

Statistical Analysis

Continuous variables were expressed as means ± standard deviation. $p < .05$ was considered statistically significant. ANOVA test followed by post hoc Bonferroni test was used to compare variables between the different groups. Multivariate regression analyses were performed to investigate for potential relations between variables [16].

RESULTS

Echocardiographic Studies

Based on their PASP, the recruited patients were divided into 2 groups: group A ($n = 20$ patients) did not have PHT (PASP $\leq$ 25 mm Hg) and group B ($n = 12$ patients) had PHT (PASP >25 mm Hg). Thus, the prevalence of PHT in β-thalassemia major patients was calculated to be 37.5%. The subjects' medical charts were reviewed and a complete physical examination and laboratory investigation were done. No statistically significant differences were observed when comparing the clinical and laboratory data of the different groups (Table 1). Moreover, the studied echocardiographic measurements assessing for pulmonary flow, cardiac dimensions, and systolic and diastolic function were not significantly different between group A and group B patients ($p > .05$) (Table 2).

Regarding the pulmonary flow parameters, the ratio of PAT/RVET was significantly higher in thalassemia patients compared to the control group ($p = .0007$). Concerning the cardiac dimensions, the mean LA diameter,

TABLE 1 Clinical and Laboratory Data

	Group A ($n = 20$)	Group B ($n = 12$)	Control ($n = 16$)
Age (years)	8.76 ± 5.71	8.15 ± 3.32	6.28 ± 3.64
Gender	11 males (55%) 9 females (45%)	8 males (66.7%) 4 females (33.3%)	11 males (68.8%) 5 females (31.2%)
Height	116.00 ± 22.00	110.83 ± 15.52	121.91 ± 18.76
Weight	25.41 ± 11.71	21.18 ± 7.02	24.39 ± 9.36
Heart rate	106.92 ± 13.11	105.26 ± 9.64	89.92 ± 14.61
Systolic BP (mm Hg)	98.46 ± 6.61	98.42 ± 5.00	95.94 ± 6.62
Diastolic BP (mm Hg)	58.38 ± 6.62	59.95 ± 6.65	55.94 ± 6.65
Duration of disease (years)	6.52 ± 3.13	7.01 ± 5.73	—
Units of blood transfusion	195.25 ± 37.23	192.7 ± 26.41	—
Interval between blood transfusion (weeks)	3.8 ± 1.8	3.96 ± 1.55	—
Splenectomy	11 patients (55%)	7 patients (58.3%)	—
Pretransfusion Hb (g/dL)	7.26 ± 0.83	7.19 ± 0.76	—
Serum ferritin (ng/dL)	2325.52 ± 1285.93	2188.12 ± 1332.23	—
Patients on deferoxamine	9 patients (45%)	5 patients (41.7%)	—

Note. BP, blood pressure; Hb, hemoglobin.

TABLE 2 Echocardiographic Measurements

	Group A ($n = 20$)	Group B ($n = 12$)	Control ($n = 16$)	p value
Pulmonary flow				
PASP (mm Hg)	19.73 ± 4.26(a)	33.96 ± 7.85(b)	20.92 ± 2.86(a)	<.0001*
PAT/RVET (ms/ms)	0.55 ± 0.92(a)	0.41 ± 0.11(a)	0.30 ± 0.07(b)	.0007*
Pul flow velocity (cm/s)	100.61 ± 23.44	105.53 ± 20.61	96.31 ± 8.56	.2
PAT (ms)	106.05 ± 11.96	95.38 ± 19.36	103.75 ± 20.88	.08
Pul deceleration (ms)	182.83 ± 26.56	160.30 ± 29.80	187.25 ± 18.07	.1
Cardiac dimensions				
LA diameter (mm)	27.20 ± 4.21(a)	27.57 ± 4.52(a)	18.21 ± 13.43(b)	<.0001*
RV diameter (mm)	16.96 ± 3.45(a)	17.9 ± 3.43(a)	13.43 ± 1.70(b)	.003*
LVEDD (mm)	44.70 ± 8.33(a)	40.10 ± 8.27(a)	35.81 ± 4.57(b)	.03*
PA (mm)	17.01 ± 3.12	18.38 ± 3.01	16.98 ± 2.55	.1
IVSD (mm)	5.83 ± 1.44	6.77 ± 2.22	5.51 ± 0.91	.3
LVPW (mm)	0.64 ± 0.10	0.65 ± 0.09	0.60 ± 0.05	.1
LVESD (mm)	28.44 ± 6.81	29.53 ± 6.18	21.33 ± 3.75	.07
Systolic function				
Aortic flow velocity (cm/s)	111.26 ± 10.81(a)	105.69 ± 13.73(a)	97.18 ± 12.98(b)	.006*
SV (mL)	62.89 ± 24.55(a)	56.80 ± 20.10(a)	49.67 ± 11.55(b)	.039*
Aortic deceleration (ms)	175.78 ± 49.69(a)	168.50 ± 39.31(a)	204.75 ± 13.16(b)	.03*
EF%	69.94 ± 6.45	68.91 ± 5.99	71.67 ± 5.12	.06
FS%	38.47 ± 4.38	37.76 ± 3.32	39.43 ± 4.77	.1
Diastolic function				
A wave (cm/s)	56.47 ± 9.26(a)	55.07 ± 14.89(a)	47.87 ± 6.56(b)	.04*
Acceleration time (msec)	79.89 ± 15.29(a)	73.84 ± 18.60(a)	113.25 ± 27.80(b)	.0007*
E wave (cm/s)	99.26 ± 21.00	97.30 ± 21.50	94.06 ± 9.12	.08
E/A ratio	1.76 ± 0.54	1.86 ± 0.55	1.70 ± 0.49	.2
DT (ms)	92.89 ± 26.17	94.15 ± 35.26	118.00 ± 27.26	.07
IVRT (ms)	63.75 ± 13.18	66.23 ± 12.01	63.33 ± 9.02	.2

Note. PASP, pulmonary artery systolic pressure; PAT, pulmonary acceleration time; RVET, right ventricle ejection time; pul, pulmonary; LA, left atrium; RV, right ventricle; LVEDD, left ventricular end diastolic diameter; PA, pulmonary artery; IVSD, Interventricular septum diameter; LVPW, left ventricular posterior wall; LVESD, left ventricular end systolic diameter; SV, stroke volume; EF, ejection fraction; FS, fraction shortening; A, late diastole; E, early diastole; DT, deceleration time; IVRT, isovolumic relaxation time.

*Significant.

the mean RV diameter, and the mean LVEDD were significantly higher in both groups A and B compared to the controls ($p < .0001$, $p = .003$ and $p = .03$, respectively) (Table 2).

While the mean aortic flow velocity and the mean stroke volume (SV), as indicators of systolic function, were significantly higher in the patient groups ($p = .006$, and $p = .039$, respectively), the mean aortic deceleration was significantly higher in the controls ($p = .03$). As for the diastolic indices, the patients had a significantly higher A wave and a significantly lower acceleration time in comparison to the healthy subjects ($p = .04$ and $p = .0007$, respectively). Concerning all the other variables no statistically significant differences were noted when comparing the different study groups (Table 2).

Multivariate Regression Analysis

In an attempt to identify clinical and laboratory predictors for the development of PHT in β-thalassemia major patients, a multivariate regression analysis was performed. However, the PASP did not have any significant correlation with any of the following variables: age, total number of blood units received, splenic status, serum ferritin level, and ejection fraction.

Effect of L-Carnitine Therapy

Following the administration of L-carnitine to the thalassemic patients with PHT (group B), there was a significant decrease in the mean PASP from 33.96 ± 7.85 to 24.11 ± 7.61. Simultaneously, significant changes were noted in most pulmonary flow indices, including PAT/RVET, pulmonary flow velocity, and pulmonary deceleration ($p = .003$, $p = .009$, and $p = .025$, respectively) (Table 3).

All cardiac dimensions decreased following treatment with L-carnitine, but the changes were not statistically significant. Moreover, the deceleration time increased from 94.15 ± 35.26 to 123.38 ± 26.52 ($p = .033$). The observed changes in the other systolic and diastolic parameters were not statistically significant (Table 3).

DISCUSSION

The prevalence of PHT, defined as a PASP more than 25 mm Hg or tricuspid regurgitation velocity higher than 2.5 m/s, among patients with β-thalassemia major was found to be 37.5% (12/32). Even though the mean PASP was 33.96 ± 7.85 mm Hg, none of these patients had clinical signs or symptoms of cardiac disease. Other studies have reported a prevalence ranging between 10 and 66%, with a mean PASP of 35 ± 3 and 47 ± 15 mm Hg [3]. The wide range of prevalence rates could be attributed to the different characteristics of the studied populations, the treatment modalities they were receiving, in addition to discrepancies in the methods used to calculate the PASP. However, the high prevalence of this cardiac complication among asymptomatic thalassemic patients emphasizes the importance of screening all those patients for PHT and intensifying the treatment in an attempt to limit the development of right heart failure.

Moreover, this study was not able to identify any clinical or laboratory predictors for the development of PHT since the PASP did not have any significant correlation with age, total number of blood units received, splenic status, serum ferritin level, and ejection fraction. These findings were not in concordance with previously published reports demonstrating a correlation between PASP on one hand and FS, EF, age, and total number of blood units received on the other hand [3]. However, both studies were

TABLE 3 Echocardiographic Measurements of Group B Patients Before and After L-Carnitine Therapy

	Before L-carnitine	After L-carnitine	*p*-value
Pulmonary flow			
PASP (mm Hg)	33.96 ± 7.85	24.11 ± 7.61	.004*
PAT/RVET (ms/ms)	0.41 ± 0.11	0.19 ± 0.11	.003*
Pul flow velocity (cm/s)	105.53 ± 20.61	100.23 ± 19.77	.2
PAT (ms)	95.38 ± 19.36	123.69 ± 30.77	.009*
Pul deceleration (ms)	160.30 ± 29.80	190.15 ± 34.04	.025*
Cardiac dimensions			
LA diameter (mm)	27.57 ± 4.52	27.17 ± 5.60	.3
RV diameter (mm)	17.9 ± 3.43	16.96 ± 3.45	.09
LVEDD (mm)	40.10 ± 8.27	39.30 ± 16.35	.3
PA (mm)	18.38 ± 3.01	16.77 ± 5.85	.1
IVSD (mm)	6.77 ± 2.22	5.83 ± 1.44	.3
LVPW (mm)	0.65 ± 0.09	0.62 ± 0.11	.1
LVESD (mm)	29.53 ± 6.18	28.44 ± 6.81	.07
Systolic function			
Aortic flow velocity (cm/s)	105.69 ± 13.73	101.15 ± 16.30	.06
SV (mL)	56.80 ± 20.10	63.80 ± 27.10	.07
Aortic deceleration (ms)	168.50 ± 39.31	200.61 ± 20.45	.07
EF%	68.91 ± 5.99	68.46 ± 9.98	.09
FS%	37.76 ± 3.32	38.47 ± 4.38	.1
Diastolic function			
A wave (cm/s)	55.07 ± 14.89	53.07 ± 8.33	.09
Acceleration time (ms)	73.84 ± 18.60	79.69 ± 15.87	.1
E wave (cm/s)	97.30 ± 21.50	95.15 ± 14.6	.06
E/A ratio	1.86 ± 0.55	1.82 ± 0.38	.2
DT (ms)	94.15 ± 35.26	123.38 ± 26.52	.033*
IVRT (ms)	66.23 ± 12.01	63.75 ± 13.18	.2

Note. PASP, pulmonary artery systolic pressure; PAT, pulmonary acceleration time; RVET, right ventricle ejection time; pul, pulmonary; LA, left atrium; RV, right ventricle; LVEDD, left ventricular end diastolic diameter; PA, pulmonary artery; IVSD, Inter-ventricular septum diameter; LVPW, left ventricular posterior wall; LVESD, left ventricular end systolic diameter; SV, stroke volume; EF, ejection fraction; FS, fraction shortening; A, late diastole; E, early diastole; DT, deceleration time; IVRT, isovolumic relaxation time.

*Significant.

limited by the small sample size (32 and 33 patients, respectively). This indicates the need for larger studies attempting to identify early markers that would put some thalassemic patients at a higher risk for PHT, thus requiring more intensive treatment and a closer follow-up.

By comparing the 3 groups, it was noted that even though patients in groups B had a significantly higher PASP compared to group A, both groups seem to have similar cardiac dimensions and functions. However, once compared to control, thalassemic patients appear to have significantly higher cardiac dimensions, mainly LA diameter, RV diameter, and LVEDD. This can be attributed to the state of continuous volume overload [3],

and is in accordance with previously published data [17]. EF and FS, which are commonly used as indices of systolic cardiac function, were not significantly different between the patients and the control subjects. These results are in agreement with previous reports of normal systolic indices in thalassemic patients not suffering from heart failure [17]. On the other hand, the stroke volume and the aortic flow velocity, which are more accurate in defining the systolic function, were significantly elevated in the patients' groups, similarly to what was reported by Aessopos et al. [18]. The Doppler echocardiographic assessment of diastolic function revealed that the patients had a significantly high A wave with a nonsignificant elevation in the E wave. However, the E/A ratio was comparable to that of normal subjects. These results are in accordance with those of Spirito et al. and Kremastinos et al. [17, 19]. In short, even though β-thalassemia major resulted in an elevation in the PASP in only a fraction of the patients, it seems to have an impact on the heart dimensions and the overall cardiac function of all patients.

Following the administration of L-carnitine to thalassemia patients known to have PHT, their PASP significantly decreased from 33.96 ± 7.85 to 24.11 ± 7.61. This was associated with a significant decrease in the ratio of PAT/ RVET. Both of these parameters are considered to be indicators of PHT [3]. Moreover, there was a significant increase in the pulmonary acceleration time, a significant decrease in the pulmonary deceleration, and a nonsignificant decrease in the pulmonary flow velocity. All these changes reflect a tendency toward normalization of the echocardiographic parameters of pulmonary flow. Previous studies reported various results concerning the effect of L-carnitine on the cardiopulmonary system of thalassemic patients. In one study, intravenous administration of L-carnitine resulted in significant reduction of pulmonary artery and pulmonary wedge pressures with no other hemodynamic changes [20]. In another study, the administration of L-carnitine for 1 month increased peak O_2 consumption by 45%, exercise time by 21%, and peak exercise heart rate by 12, thus leading to a decrease in PASP [21].

The other echocardiographic parameters, except DT, did not show any significant changes, which is consistent with published data showing that L-carnitine therapy did not result in significant improvement in the echocardiographic indices of systolic and diastolic function in thalassemic patients [22]. However, by observing their trends following L-carnitine therapy and comparing their values to those of normal subjects, it was observed that most of them were trending toward normalization. In fact, it was previously shown that L-carnitine decreased LVEDD in dilated cardiomyopathy [23] and resulted in a reduction in the left ventricular dimensions of congestive heart failure patients [24].

The observed improvement in the PASP of thalassemic patients with PHT after L-carnitine therapy can be attributed to the effect of this

medication on myocardial energy production [25]. In fact, L-carnitine plays a crucial role in the shuttle mechanism of long-chain fatty acid across the inner mitochondrial membrane to provide substrate for β-oxidation. This process is especially important in organs like the heart that preferentially use fatty acid as a source of energy. Furthermore, L-carnitine stabilizes red blood cell membranes and thus improves the anemic state [26].

This study was limited by the small sample size and the shortness of the follow-up period. Moreover, in an attempt to avoid subjecting the patients to invasive measures, echocardiography was used to estimate the pulmonary artery pressure instead performing a right heart catheterization. However, given the promising results, larger crossover placebo-controlled randomized trials with longer follow-up periods and more accurate measurements of the pulmonary artery pressure might be in order.

In conclusion, β-thalassemia major seems to affect several aspects of the heart structure and function in most of the patients in addition to leading to the development of PHT in more than one-third of them. Oral administration of L-carnitine appears to significantly improve PASP in thalassemic patients. However, further studies are still required because this medication might be beneficial in improving other aspects of the cardiopulmonary system.

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