Pulmonary hypertension in patients with sickle cell/β thalassemia: incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations

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ABSTRACT

Background and Objectives

Pulmonary hypertension (PH) is increasingly observed in sickle cell disease (SCD) and β-thalassemia (β-thal), but there is no information on its prevalence in patients with HbS/β-thal. The amino-terminal fragment of B-type natriuretic peptide (NT-proBNP) is considered as an independent prognostic factor in PH. The aim of this study was to evaluate the incidence of PH and its correlation with clinical and laboratory findings, including NT-proBNP, in patients with HbS/β-thal.

Design and Methods

We studied 84 HbS/β-thal patients; 51% had been receiving hydroxyurea for a median time of 9 years. The presence of PH was evaluated using Doppler echocardiography and NT-proBNP serum levels were determined by an electrochemiluminescence immunoassay.

Results

The incidence of PH in our cohort of HbS/β-thal patients was 33%. PH patients had elevated values of NT-proBNP, reticulocyte counts and serum ferritin compared with patients without PH. However, even patients without PH had elevated concentrations of NT-proBNP compared with controls. An NT-proBNP level of 153.6 pg/mL had the highest sensitivity (85.7%) and specificity (94.6%) for detecting PH in our patients. NT-proBNP levels correlated with measures of pulmonary artery systolic pressure (tricuspid regurgitant jet velocity and right ventricular systolic pressure), left atrial area and diastolic dysfunction. The administration of hydroxyurea did not affect the presence of PH.

Interpretation and Conclusions

The incidence of PH in patients with HbS/β-thal is similar to that observed in patients with SCD. Serum NT-proBNP is a strong indicator of PH in HbS/β-thal. The correlation between PH and reticulocyte counts and ferritin suggests that the degree of hemolysis and iron overload is implicated in the pathogenesis of PH in HbS/β-thal.

Key words: pulmonary hypertension, sickle cell disease, β-thalassemia, HbS/β-thalassemia, amino-terminal B-type natriuretic peptide, NT-proBNP.

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Pulmonary hypertension (PH) is characterized by the obstruction of small pulmonary arteries leading to progressive right ventricular failure. PH is recognized as a severe complication of hemolytic anemia, including hemoglobinopathies, such as β-thalassemia major, thalassemia intermedia, and sickle cell disease (SCD).[1-4] Several studies have revealed that the prevalence of PH is approximately 20-40 % in SCD patients and that the presence of PH is associated with an increased risk of death, regardless of its severity.[5-8] Hemodynamic measurements and biochemical tests, such as the 6-minute walk test and detectable troponin T levels, are well recognized as prognostic markers in PH, since they reflect the progressive obstruction of blood flow.[9,10] Echocardiography remains the cornerstone screening test for the diagnosis of PH. Pro B-type natriuretic peptide (proBNP) is a hormone released in response to cardiomyocyte stretching. The prognostic significance of proBNP has been demonstrated in several cardiovascular disorders. ProBNP is involved in the activation of the cyclic guanylate cyclase system as a counter-regulatory mechanism in heart failure and its levels correlate with the severity of pulmonary artery pressure elevation and right ventricular dysfunction.[11-16] ProBNP is cleaved into an inactive part, N-terminal proBNP (NT-proBNP) and the biologically active hormone BNP.[15] The high stability of NT-pro BNP in the serum and the convenience of assaying the levels of this protein under routine laboratory conditions have made the measurement of NT-proBNP a useful tool for patient stratification in PH.[17] In SCD, patients with PH often have lower pulmonary pressures than do patients with primary PH.[5,6,18] In this cohort of patients the measurement of NT-proBNP is of particular value.

Although the prevalence of PH in thalassemia major and SCD has been reported, there is no information on the incidence of PH in patients with double heterozygous HbS trait and β-thalassemia (HbS/β-thal). The aim of this study was to evaluate the incidence of PH in a cohort of patients with HbS/β-thal and reveal possible correlations between the presence of PH and clinical characteristics, hemolytic findings and NT-proBNP levels.

Design and Methods

Patients and controls

Patients with compound heterozygous HbS/β-thal were studied. The patients had been diagnosed by demonstration of a positive sickling phenomenon and hemoglobin (Hb) electrophoresis at pH 8.6. β-globin gene mutations were detected using standard methodology. All patients were in a stable phase of their disease at the time of evaluation and were transfused sporadically or had not been transfused for at least 3 months prior to the evaluation. They were regularly followed-up at the Thalassemia Center of Laikon Hospital, Athens, Greece. Informed consent was obtained from all patients prior to entering the study. The study was conducted with the approval of the hospital ethical committee and in keeping with the guidelines of the Declaration of Helsinki.

In addition, 15 healthy control subjects, with age and gender distributions similar to those of the patients, were evaluated for race-based comparisons of laboratory and echocardiographic data.

Exclusion criteria

Criteria for exclusion from this study included: 1) evidence of left ventricular failure (defined as fraction shortening below 28% and ejection fraction below 50%) ; 2) a vaso-occlusive crisis during the preceding 15 days; 3) atrial fibrillation or vertricular tachycardia; 4) mitral value regurgitation >2/4+ or mitral value stenosis; and 5) severe pericardial effusion.

Echocardiography measurements

All patients were evaluated for the presence of PH using continuous-wave Doppler echocardiography and then applying the modified Bernoulli equation (pulmonary artery systolic pressure=$4V^2$+right atrial pressure). PH was defined as systolic pulmonary artery pressures of above or equal to 35 mmHg or a tricuspid regurgitant jet velocity (TRV) value of above or equal to 2.5 m/sec. In all patients, we also measured ejection fraction, fraction shortening, left atrial area, right ventricular area and markers of diastolic function, such as peak velocities of the E wave and A wave, the ratio of the E wave to A wave, the end diastolic diameter, deceleration time, and isovolumic relaxation time as the time from aortic-valve closure to the start of mitral inflow. All diastolic parameters were assessed by tissue Doppler imaging.

Laboratory measurements

Hemoglobin levels, leukocyte and platelet counts, reticulocyte counts, lactate dehydrogenase (LDH), aspartate aminotransferase, direct bilirubin, serum creatinine, and Hb F were assessed in all patients, using standard methodologies. Serum ferritin levels were measured by an enzyme immunoassay technique (MEIA; Abbot Diagnostics, IMX System; Ferritin, Illinois, USA; normal range 20-200 mg/L). Serum NT-proBNP levels were evaluated using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in samples that were collected in the morning of the Doppler echocardiograpic examination, and were then centrifuged and stored at -80°C within 4-6 hours after venipuncture. Serum cystatin C was determined by particle enhance immunonephelometry using the Dade-Behring BN Prospec nephelometer (Dade Behring, Liederbach, Germany). Finally, we evaluated the levels of endothelin-1 in the plasma of a subgroup of our HbS/β-thal patients (nine patients with PH and seven without PH) and in all our controls using an ELISA methodology (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

SPSS statistics software version 15.0 (Chicago, IL, USA) was used for the statistical analyses. The Mann-Whitney U test and Student's *t*-test were used to evaluate differences between patients and controls. When a significant association was found, *post-hoc* Bonferroni comparisons were used. A receiver operator characteristic (ROC) curve was constructed to define the level of NT-proBNP with the best sensitivity and specificity for the detection of PH. Spearman's non-parametric correlation test was used to determine possible correlations between the presence of PH and the different clinical and laboratory parameters. Results were considered statistically significant when $p<0.05$.

Results

Patients

We studied 91 patients with compound heterozygote HbS/β-thal of whom 84 (31 males and 53 females) met the criteria for inclusion into this study. Their median age was 35 years (range: 21-62 years). Underlying molecular β^0 gene mutations were found in 51 patients and β^+ gene mutations in 33 patients. The HbA levels of HbS/β-thal$^+$ patients ranged between 5% and 10% (median: 7%). Forty-three patients (51%) had been receiving hydroxyurea for a median time of 9 years. The baseline characteristics of all patients and controls are presented in Table 1.

Table 1. Characteristics of patients with HbS/β-thal and controls. The values are presented as median and range.

Characteristic	*Patients (n=84) median values (range)*	*Controls (n=15) median values (range)*	*p value*
Age (years)	35 (21-62)	35 (20-60)	
Gender (n)	31M/53F	5M/10F	
Interacting β-thalassemia genes (n)	β^0 39 (38), IVS1-1 (11), FSC8 (2), IVS1-110 (24), IVS1-6 (9)	–	
On hydroxyurea (n)	43	–	
Months of follow up	91(50-131)		
Hemoglobin (g/dL)	8.9(6.3-12.9)	13.7 (11.5-16.4)	<0.0001
White cell count ($\times10^3/\mu L$)	11.3 (9.9-16.7)	5.6 (3.8-7.4)	<0.0001
Platelet count ($\times10^3/\mu L$)	350 (227-473)	230 (155-295)	0.133
Reticulocyte count ($\times1000/mm^3$)	246 (90-768)	47 (35-90)	<0.0001
Serum creatinine (mg/dL)	0.7 (0.5-1.7)	0.8 (0.6-1.0)	0.212
Serum cystatin-C (mg/L)	1.0 (0.6-1.4)	0.7 (0.2-0.9)	<0.001
Aspartate aminotransferase (U/L)	46 (23-69)	26 (15-41)	0.022
Alanine aminotransferase (U/L)	35 (20-50)	23 (13-37)	0.062
Total bilirubin (mg/dL)	2.0 (0.6-12.3)	0.7 (0.5-0.8)	<0.0001
Lactate dehydrogenase (U/L)	662 (205-1650)	230 (180-355)	<0.0001
Serum ferritin (μg/L)	302 (12-5260)	65 (21-123)	<0.0001
HbF (%) for all patients	14.3 (2-41)	<2	<0.0001
HbF (%) for HU patients	18 (2.6-41)		
HbF (%) for non-HU patients	10 (2-30)		
NT-ProBNT (pg/mL)	81.9 (7.5-3040)	27.9 (14.9-77.6)	<0.0001
Tricuspid regurgitant jet velocity (m/s)	2.3 (2-3.1)	2.1 (2-2.4)	<0.0001
RVSP (mmHg)	31 (25-48)	27 (25-33)	<0.0001
Ejection fraction (%)	71 (53-82)	68 (60-79)	0.205
Fraction shortening (%)	40.5 (24-52)	38 (30-48)	0.210
Left atrial area (cm^2)	3.4 (2.5-4.5)	3.6 (2.8-3.9)	0.777
Right ventricular area (cm^2)	1.8 (1.2-2.5)	2.0 (1.5-2.1)	0.013
E/A ratio	1.2 (0.7-2.2)	1.6 (1.1-2.1)	<0.01
End-diastolic diameter (cm)	5.3 (4-6.8)	5.2 (4.4-5.4)	0.107
Deceleration time (msec)	190 (145-270)	190 (175-225)	0.945
IVRT (msec)	70 (45-130)	70 (55-80)	0.127
Endothelin-1 (pg/mL)*	0.94 (0.41-1.89)	0.49 (ND-1.0)	0.001

**measured in all controls, but in only 16 patients; IVRT: isovolumetric relaxation time.*

Incidence of pulmonary hypertension

Patients had significantly higher median values of TRV compared with controls. Twenty-eight patients (33.3%) had elevated pulmonary artery systolic pressures as defined by a TRV of at least 2.5 m/sec or an estimated right ventricular systolic pressure (RVSP) of at least 35 mmHg. Patients with PH were older than patients without PH (Table 2); age was also significantly correlated with both TRV (r=0.341, $p=0.001$) and right ventricular systolic pressure (RVSP) (r=0.328, $p=0.002$).

Pulmonary hypertension and cardiac function

TRV values were significantly correlated with end-diastolic diameter and E/A ratio (r=0.34, $p=0.001$ and r=-0.52, $p=0.0001$ respectively), while there was no correlation between TRV and variables of systolic function such as ejection fraction, fraction shortening and left atrial area. Furthermore, neither the deceleration time nor the isovolumetric relaxation time showed significant correlations with TRV.

Pulmonary hypertension and presence of hemolysis

Factors reflecting the presence of hemolysis, such as hemoglobin concentration, reticulocyte counts and bilirubin serum levels were significantly correlated with TRV (r=-0.386, $p<0.001$; r=0.361, $p=0.001$; and r=0.25, $p=0.022$, respectively) and RVSP (r=-0.38, $p<0.001$; r=0.345, $p=0.001$; and r=0.26, $p=0.017$, respectively). However, no correlations were observed between serum LDH and either TRV or RVSP. Patients with PH had lower values of hemoglobin and higher reticulocyte counts and ferritin levels compared to patients who did not have PH, although there were no differences in bilirubin and LDH serum levels between patients who did or did not have PH (Table 2).

NT-proBNP levels and pulmonary hypertension

The median NT-proBNP level was 81.9 pg/mL in patients with HbS/β-thal and 27.9 pg/mL in healthy controls ($p<0.0001$; Table 1). NT-proBNP levels were higher in patients with PH than in either patients without PH or

Table 2. Characteristics of patients with HbS/β-thal according to TRV. The values are presented as median and range for all parameters.

Characteristics	*Jet velocity <2.5 m/sec N=56*	*Jet velocity >2.5 m/sec N=28*	*p value*
Age (years)	33 (21-57)	41 (25-62)	0.001
Gender (n)	18M/38F	13M/15F	0.776
On hydroxyurea (n-%)	22 (39%)	21 (75%)	0.923
NT-proBNP (pg/mL)	63.8 (7.5-1203)	294.7 (33.7-3040)	<0.0001
Hemoglobin (g/dL)	9.2 (6.3-12.9)	8 (6.7-11.7)	0.001
Reticulocyte count (×1000/mm³)	234 (94-540)	376 (90-768)	0.003
Lactate dehydrogenase (U/L)	712 (205-1650)	709 (333-1576)	0.409
Bilirubin (mg/dL)	1.7 (0.6-5.1)	2.3 (0.8-12.3)	0.162
Creatinine (mg/dL)	0.7 (0.5-1.6)	0.7 (0.5-1.7)	0.295
Cystatin-C (mg/L)	1.0 (0.6-1.4)	1.0 (0.6-1.3)	0.465
Ferritin (µg/L)	218.5 (12-5260)	640 (70-4100)	<0.0001
HbF (%)	14 (2-33)	15.2 (2-41)	0.476
TRV (m/s)	2.2 (2-2.4)	2.6 (2.5-3.1)	<0.0001
RVSP (mmHg)	28.5 (25-33)	37.5 (35-48)	<0.0001
Ejection fraction (%)	70.5 (60-82)	50.5 (53-78)	0.144
Fraction shortening (%)	42 (30-52)	40 (24-47)	0.028
Left atrial area (cm²)	3.4 (2.5-4.3)	3.4 (2.9-4.5)	0.204
Right ventricular area (cm²)	1.8 (1.2-2.5)	1.9 (1.3-2.5)	0.171
E/A ratio	1.3 (0.7-2.2)	0.8 (0.7-1.6)	<0.001
End-diastolic diameter (cm)	5.3 (4-5.9)	5.5 (4.7-6.8)	0.004
Deceleration time (msec)	190 (145-255)	190 (150-270)	0.743
IVRT (msec)	70 (45-100)	70 (45-130)	0.143
Endothelin-1* (pg/mL)	0.67 (0.41-0.88)	1.11 (0.47-1.89)	0.11

**measured in only nine patients with PH and seven patients without PH. IVRT: isovolumetric relaxation time.*

healthy controls (p<0.01; Table 2). A ROC curve showed that a cut-off value of 153.6 pg/mL of NT-proBNP had the highest sensitivity (85.7%) and specificity (94.6%) for detecting the presence of PH in our study population. High NT-proBNP levels were significantly correlated with TRV, RVSP, left atrial area and echocardiographic parameters of diastolic dysfunction, such as end-diastolic diameter and E/A ratio (Table 3; Figure 1). NT-proBNP correlated weakly with ejection fraction and fraction shortening (variables of systolic function) but there was no association with deceleration time or isovolumetric relaxation time (variables of diastolic function). NT-proBNP also showed significant correlations with hemoglobin levels, serum creatinine and advanced age (Table 3).

Effect of hydroxyurea therapy and other factors on pulmonary hypertension

Fetal hemoglobin levels were not significantly correlated with TRV (p=0.476), although almost 75% of patients who had a TRV of ≥2.5 m/sec had received hydroxyurea. Thus, the administration of hydroxyurea did not affect PH presentation. Patients with HbS/β-thal had elevated values of endothelin-1 compared with controls (p=0.001; Table 1), while patients with PH had increased values of endothelin-1 (median: 1.11 pg/mL) compared with patients without PH (median: 0.67 pg/mL). However, the p-value between patients with and without PH was not statistically significant (p=0.11), possibly reflecting the low number of patients studied. Finally, white cell count, platelet count and renal function (assessed by both serum creatinine and cystatin-C levels) had no effect on the presence of PH (Table 2).

Table 3. Spearman's correlation between NT-proBNP and laboratory and hemodynamic parameters.

Parameter	*r*	*p value*
TRV (m/s)	0.436	<0.0001
RVSP (mmHg)	0.430	<0.0001
Ejection fraction (%)	-0.219	0.046
Fraction shortening (%)	-0.213	0.052
Left atrial area (cm²)	0.364	0.001
Right ventricular area (cm²)	0.069	0.532
E/A ratio	-0.318	0.003
End-diastolic diameter (cm)	0.322	0.003
Deceleration time (sec)	-0.155	0.158
Isovolumetric relaxation time (msec)	-0.042	0.707
Age (y)	0.20	0.072
Hemoglobin (g/dL)	-0.213	0.052
Reticulocyte count (×1000/mm³)	0.044	0.692
Ferritine (µg/L)	0.016	0.888
Lactate dehydrogenase (U/L)	0.129	0.243
Bilirubin (mg/dL)	0.128	0.245
HbF (%)	-0.029	0.796
Creatinine (mg/dL)	0.2	0.068

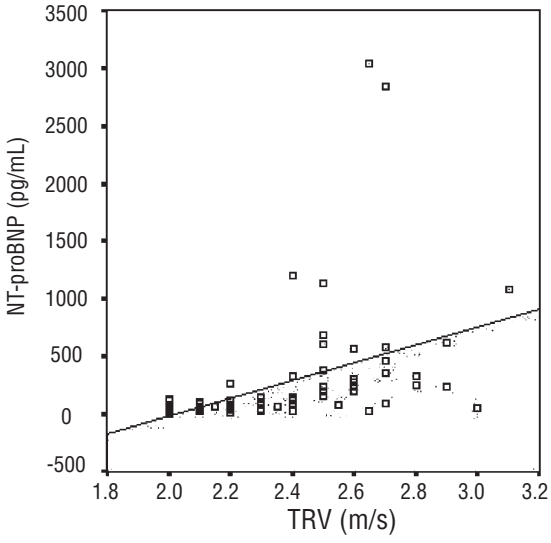

Figure 1. NT-proBNP levels are significantly correlated with PH as assessed by TRV measurement (r=0.436, p<0.0001).

Discussion

SCD is one of the most common genetic blood disorders in the world. Approximately 20-40% of SCD patients have PH, which often leads to heart failure, and is a major risk factor for death in these patients.[4-8] In the present

study, we found that the prevalence of PH among patients with HbS/β-thal was 33.3%, which is similar to that reported in SCD patients.[5,18] Considering the higher mortality rate detected among SCD patients with PH,[4,5,8,18] we assume that our cohort of patients with PH are also at high risk of developing heart failure and dying of cardiac dysfunction. Our study has also confirmed the valuable role of echocardiography and NT-proBNP levels in identifying PH in HbS/β-thal patients. To the best of our knowledge, this is the first study in the literature which gives data for the incidence of PH and its correlations with clinical and laboratory characteristics in patients with HbS/β-thal.

NT-proBNP levels provide diagnostic and mechanistic information concerning the development of PH in patients with SCD and thalassemia major and have been used to identify patients at the highest risk of death.[13-15,17] In our patients, an elevated NT-proBNP level largely reflected the severity of PH (Figures 1A,1B). The NT-proBNP serum level of 153.6 pg/mL had the highest sensitivity and specificity (85% and 94%, respectively) for the detection of PH in our population. These data are in accordance with those of Machado *et al.*, who found that NT-proBNP levels directly correlated with PH in SCD patients, while a level of 160 pg/mL or greater of NT-proBNP had a 78% positive predictive value for the diagnosis of PH.[18] In that study PH seemed to be associated with pulmonary dysfunction rather than left ventricular dysfunction.[18] We found that NT-proBNP levels correlated with parameters of diastolic (end-diastolic diameter, E/A ratio) rather than systolic dysfunction. Deceleration time and isovolumetric relaxation time are also indicators of diastolic dysfunction. The lack of association between these parameters and PH in our study population may be due to volume loading caused by chronic anemia, which possibly leads to pseudo-normalization of the deceleration time and isovolumetric relaxation time. Thus, diastolic dysfunction may have played a role in the development of PH in our population. However, we must mention that diastolic dysfunction is common in the SCD population, but only contributes directly to elevated pulmonary pressures in a small fraction of patients with a high TRV. In a recent study by Sachdev *et al.*, it was found that diastolic dysfunction and PH can develop independently in SCD, each contributing to increased mortality alone, and patients with both risk factors have a poor prognosis.[19]

Our results also suggest that NT-proBNP levels, in combination with TRV and RVSP data, provide a useful tool for recognizing HbS/β-thal patients with hemodynamically significant PH. With regards to this point, we should mention that NT-proBNP is cleared by kidneys and renal impairment, which is observed in sickle-cell syndromes, may alter NT-proBNP levels in such patients. However, our patients with and without PH had similar creatinine and cystatin-C values. Cystatin-C is a cysteine proteinase inhibitor, which participates in intracellular protein catabolism and is considered as a perfect endogenous marker of glomerular filtration rate. Our group has shown that cystatin-C concentration is an early indicator of renal impairment in patients with HbS/β-thal.[20]

The pathogenesis of PH is multifactorial. The observation that markers of hemolysis, such as hemoglobin concentration, reticulocyte counts, and bilirubin, and iron overload are associated with PH and correlated with both TRV and NT-proBNP in our patients, provides a link between HbS/β-thal or other chronic hemolytic disorders with PH and suggests that there is a distinct syndrome of hemolysis-associated PH. Thalassemia major is another chronic hemolytic disease that is associated with secondary PH, which has a different pathophysiology from that of SCD. Several factors that contribute to PH in SCD, such as the sickle phenomenon, vaso-occlusive crises or acute chest syndrome, do not occur in thalassemia major.[2,3,21] Nevertheless, patients with thalassemia and SCD have intravascular hemolysis, which results in the release of hemoglobin into the plasma. Plasma hemoglobin can scavenge nitric oxide and catalyse the formation of reactive oxygen and nitrogen species, processes that can lead to acute and chronic pulmonary vasoconstriction.[22] Hemoglobin-induced scavenging of nitric oxide results in transcriptional up-regulation of adhesion molecules and induces the expression of endothelin-1, a potent vasoconstrictor.[23,24] Indeed, endothelin-1 levels are elevated in the plasma of patients with primary PH and patients with SCD.[25] In our study, patients with HbS/β-thal had higher values of endothelin-1 compared with controls, while patients with PH had increased values of endothelin-1 compared with patients without PH (this difference was of borderline statistical significance mainly due to the low number of patients studied).

We found no correlation between the presence of PH and serum levels of LDH (another marker of hemolysis). This may be explained by the lower rate of hemolysis in this cohort of patients than in patients with thalassemia major or intermedia. On the other hand, the relatively modest degree of PH seen in our study (TRV ≤3.1 m/s) compared with that occurring in HbS patients may also explain the lack of this association. Gladwin *et al.* described three groups of HbS patients with TRV levels <2.5, 2.5-2.9 and >3.0 m/s and LDH levels of 320±129, 357±125 and 491±196 U/L, respectively. Most of our PH patients had a TRV of between 2.5-2.9 m/s (only two patients had a TRV of 3.0 and 3.1 m/s) and their LDH levels were not different from those of patients with a normal TRV (<2.5 m/s).[23]

Additional insults that might lead to end-organ dysfunction and PH in patients with thalassemia major and SCD include iron deposition,[26,27] anemia with a high cardiac-output state, and asplenism. The correlation of ferritin with PH in our study supports the notion that iron overload is also implicated in the pathogenesis of PH in HbS/β-thal.

Hydroxyurea therapy and fetal hemoglobin levels were not associated with lower TRV in our study. These findings are in agreement with those of other recent studies in

which the use of hydroxyurea did not appear to protect against the development of PH or death related to PH in SCD.[5,17] A possible explanation is that although hydroxyurea decreases the rate of hemolysis and increases red blood cell survival, the magnitude of this response may not be sufficient to prevent the development of hemolysis-associated endothelial dysfunction.[2]

In conclusion this study has shown that the frequency of PH in our cohort of HbS/β-thal patients is similar to that observed in patients with SCD.

Hemolysis and iron overload seem to be implicated in the pathogenesis of PH in HbS/β-thal. Serum NT-proBNP level is a strong indicator of PH in these patients and may be used, in combination with echocardiographic measurements, in the screening of patients with HbS/β-thal for the diagnosis of PH.

Authors' Contributions

EV: contribution of patients with HbS/b-thal, conception of the study, acquisition, analysis and interpretation of data, drafting of the manuscript, management of patients, final approval; ET: conception, acquisition, analysis and interpretation of data, measurement of laboratory parameters, critical revision of the manuscript, final approval; GT: echocardiographic evaluation of all patients, final approval; AT: measurement of NT-proBNP in all patients, analysis and interpretation of data, final approval; DC: statistical analysis, final approval; ES: analysis and interpratation of data, management of patients, final approval.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

1. Aessopos A, Farmakis D, Karagiorga M, Voskaridou E, Loutradi A, Hatziliami A, et al. Cardiac involvement in thalassemia intermedia: a multicenter study. Blood 2001; 97: 3411-6.
2. Du ZD, Roguin N, Milgram E, Saab K, Koren A. Pulmonary hypertension in patients with thalassemia major. Am Heart J 1997;134:532-9.
3. Derchi G, Fonti A, Forni GL, Galliera EO, Cappellini MD, Turati F, et al. Pulmonary hypertension in patients with thalassemia major. Am Heart J 1999;138:384.
4. Sutton LL, Castro O, Cross DJ, Spencer JE, Lewis JF. Pulmonary hypertension in sickle cell disease. Am J Cardiol 1994;74:626-8.
5. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004; 350:886-95.
6. Ataga KI, Sood N, De Gent G, Kelly E, Henderson AG, Jones S, et al. Pulmonary hypertension in sickle cell disease. Am J Med 2004; 117: 665-9.
7. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood 2003; 101:1257-61.
8. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol 2006;134:109-15.
9. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:40S-7S.
10. Torbicki A, Kurzyna M, Kuca P, Fijalkowska A, Sikora J, Florczyk M, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation 2003;108:844-8.
11. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997;96:509-16.
12. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med 2005;352:666-75.
13. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004; 350: 655-63.
14. Leuchte HH, Holzapfel M, Baumgartner RA, Ding I, Neurohr C, Vogeser M, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. J Am Coll Cardiol 2004;43:764-70.
15. Yap LB, Ashrafian H, Mukerjee D, Coghlan JG, Timms PM. The natriuretic peptides and their role in disorders of right heart dysfunction and pulmonary hypertension. Clin Biochem 2004;37:847-56.
16. Arad M, Elazar E, Shotan A, Klein R, Rabinowitz B. Brain and atrial natriuretic peptides in patients with ischemic heart disease with and without heart failure. Cardiology 1996;87:12-7.
17. Souza R, Jardim C, Julio Cesar Fernandes C, Silveira Lapa M, Rabelo R, Humbert M. NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension. Respir Med 2007;101:69-75.
18. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA 2006; 296: 310-8.
19. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 2007;49:472-9.
20. Voskaridou E, Terpos E, Michail S, Hantzi E, Anagnostopoulos A, Margeli A, et al. Early markers of renal dysfunction in patients with sickle cell/β-thalassemia. Kidney Int 2006;69:2037-42.
21. Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafair JS, Okon E, et al. Cardiopulmonary assessment in β-thalassemia major. Chest 1990; 98:1138-42.
22. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO 3rd, Schechter AN, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle cell disease. Nat Med 2002; 8: 1383-9.
23. Gladwin MT, Schechter AN, Ognibene FP, Coles WA, Reiter CD, Schenke WH, et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. Circulation 2003;107:271-8.
24. Lin G, Macdonald RL, Marton LS, Kowalczuk A, Solenski NJ, Weir BK. Hemoglobin increases endothelin-1 in endothelial cells by decreasing nitric oxide. Biochem Biophys Res Commun 2001;280:824-30.
25. Rybicki AC, Benjamin LJ. Increased levels of endothelin-1 in plasma of sickle cell anemia patients. Blood 1998;92:2594-6.
26. Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in β-thalassemia major. Circulation 1993; 88:1127-35.
27. Kremastinos DT, Tsetsos GA, Tsiapras DP, Karavolias GK, Ladis VA, Kattamis CA. Heart failure in β thalassemia: a 5-year follow-up study. Am J Med 2001;111:349-54.