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To cite this version:

Athanasios Aessopos, Dimitrios Farmakis, Christos Trompoukis, Maria Tsironi, Ioannis Moyssakis, et al.. Cardiac involvement in sickle β-thalassemia. Annals of Hematology, 2008, 88 (6), pp.557-564. 10.1007/s00277-008-0661-y . hal-00535013

HAL Id: hal-00535013

https://hal.science/hal-00535013v1

Submitted on 11 Nov 2010

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Ann Hematol (2009) 88:557–564
DOI 10.1007/s00277-008-0661-y

ORIGINAL ARTICLE

Cardiac involvement in sickle β-thalassemia

Athanasios Aessopos · Dimitrios Farmakis · Christos Trompoukis · Maria Tsironi · Ioannis Moyssakis · Panagiotis Tsaftarides · Markisia Karagiorga

Received: 20 March 2008 / Accepted: 2 December 2008 / Published online: 24 December 2008
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Abstract Cardiovascular involvement is a leading cause of mortality and morbidity in patients with inherited hemoglobinopathies, but it has not been adequately assessed in sickle β-thalassemia. We evaluated 115 sickle β-thalassemia patients, aged 34±14 years, along with 50 healthy controls, by resting echocardiography. Patients with systolic left ventricular (LV) dysfunction or severe pulmonary hypertension (PHT) also underwent left and right cardiac catheterization and cardiac magnetic resonance imaging (CMR). Left and right chamber dimensions, LV mass, and cardiac index were significantly higher in patients compared to controls ($p<0.001$ in most cases). Three patients (2.9%) had reduced LV ejection fraction (<55%); mean LV ejection fraction was significantly lower in patients ($p<0.001$). Left and right ventricular systolic tissue Doppler indices and LV diastolic tissue Doppler indices were also impaired in patients. All three patients with systolic LV dysfunction had normal coronary arteries and mild myocardial iron load (CMR T2* values, 18–25 ms). Systolic pulmonary artery pressure was significantly higher in patients compared to controls ($p=0.002$); PHT was present in 28 patients (27%), while severe PHT in three (2.9%). In three patients with severe PHT, only one had impaired LV ejection fraction and increased pulmonary wedge pressure. Overall, three patients (2.9%) had a history of heart failure, two with systolic LV dysfunction, and one with severe PHT. Cardiac involvement in sickle β-thalassemia concerns biventricular dilatation and dysfunction along with PHT, leading to congestive heart failure.

Keywords Sickle cell disease · Thalassemia · Sickle β-thalassemia · Pulmonary hypertension · Heart failure

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Introduction

Sickle β-thalassemia (S-Thal) is a hereditary hemoglobinopathy that results from the compound heterozygosity of sickle (β^s) and β-thalassemia (β^0 or β^+) traits [1]. The clinical phenotype is a chronic hemolytic anemia that resembles mainly that of homozygous sickle cell disease (SCD), especially when the interacting β-thalassemia allele is β^0, which does not produce any β-chains. The form β^s/β^+ is generally milder, depending on the residual β-globin chain synthesis. In Greece, S-Thal is the most prevalent form of sickling syndromes due to high frequency of the β-thalassemia trait [2]; the most frequent genotype in Greek S-Thal populations is the β^s/β^0, which leads to a clinical phenotype very similar to that of SCD patients [2].

Cardiovascular involvement represents a leading cause of mortality and morbidity both in SCD and in β-thalassemia and has extensively been described in these two conditions [3, 4]. Studies addressing cardiac status in patients with SCD have applied a wide range of diagnostic modalities, including electrocardiography, Doppler echocardiography, scintigraphic techniques, cardiac catheterization and angiography, and more recently cardiac magnetic resonance imaging (CMR) [3]. In some of those studies,

patient populations have included a number of S-Thal cases; most of them have focused on specific cardiovascular aspects, such as left ventricular (LV) function, valvular involvement, coronary artery involvement, endothelial function, or right heart function [4–7]. In the present study, motivated by some preliminary data showing that pulmonary hypertension (PHT), although an important determinant of prognosis in sickle cell anemia, was rather mild in S-Thal patients [5], we sought to perform a global evaluation of cardiac function in a large cohort of Greek S-Thal patients and discuss our findings in comparison with the existing data in sickling syndromes.

Patients and methods

Patient population

The study population was recruited from the group of patients followed regularly in the Cardiac Outpatient Clinic for Hemoglobinopathies of our Unit. Inclusion criterion was the diagnosis of S-Thal, made by solubility screening test for sickling, hemoglobin electrophoresis, and a/β chain synthesis. Exclusion criteria were (a) a history of painful crises or infection throughout the 2-month period prior to the study; (b) a history of regular or frequent blood transfusion therapy; (c) a history of severe hepatic dysfunction with ascites of non-cardiac origin. According to the above criteria, 115 consecutive S-Thal patients, aged 34±14 years (range, 15–72 years), were finally enrolled out of a total of 124 patients initially screened; nine patients were excluded in total: five due to painful crises, three due to regular or frequent blood transfusions and one due to hepatic cirrhosis. A group of 50 age-matched healthy subjects served as controls.

Assessment included review of patients' medical records, history taking, echocardiography, and determination of total blood count, including reticulocyte count and serum, lactate dehydrogenase (LDH), and ferritin concentrations. Patients with impaired systolic LV function, defined as an echocardiographically determined ejection fraction <55%, were further investigated by right and left cardiac catheterization, including coronary angiography, as well as CMR for myocardial iron load estimation. Moreover, patients with severe pulmonary hypertension (PHT), defined as a continuous Doppler-determined peak systolic tricuspid pressure gradient >50 mmHg, underwent right cardiac catheterization. Patients were asked to discontinue temporarily any cardioactive medication 5 days prior to the examination. All patients enrolled gave an informed written consent. Moreover, the study conformed to the Declaration of Helsinki and was approved by the institutional ethics committee.

Echocardiography

A complete M-mode, two-dimensional, and Doppler (pulsed wave, continuous wave, and color) echocardiography examination was performed in all patients and controls at rest, using an Aloca ProSound SSD 5500 ultrasound system (Aloca Co, LTD, Tokyo, Japan). All echo-Doppler studies were carried out by the same observer. The intraobserver variability regarding echocardiographic and Doppler measurements in this clinic has previously been reported to be less than 4% [8]. All measurements represent the average values of at least three cardiac cycles.

Cardiac chamber dimensions were measured according to the recommendations of the American Society of Echocardiography (ASE) by M-mode echocardiography, while two-dimensional echo was used wherever M-mode measurements were considered unreliable [9–11]. Left ventricular mass was calculated using the ASE-cube formula as corrected by Devereux et al. [12]. Stroke volume, ejection fraction, and cardiac output estimation were based on the calculation of LV volumes by the method of discs, following the ASE recommendations and using apical two- and four-chamber views [10]. Left ventricular diastolic function was assessed by the pulsed-Doppler recording of mitral inflow. Standard diastolic Doppler indexes were recorded, including early (E) and late (A) transmitral peak flow velocities, E deceleration time (DT), and LV isovolumic relaxation time (IVRT) [13]. Additionally, using tissue Doppler imaging from the four-chamber apical view, with the sample volume placed at the lateral border of mitral annulus and the lateral border of tricuspid annulus, three velocities were recorded, one during systole (s), a second during early diastole (e), and a third at late diastole (a). Systolic pulmonary artery pressure was evaluated by the peak systolic right ventricular to right atrial (tricuspid) pressure gradient, derived by the continuous-Doppler tracing of the tricuspid valve flow in the presence of tricuspid regurgitation [14]; the apical four-chamber, the parasternal short-axis, and the parasternal long-axis views were used while the subject suspended breathing at the end of a normal expiration. According to the recent literature, increased systolic pulmonary artery pressure was defined by a tricuspid gradient >30 mmHg [15, 16].

Statistical analysis

Statistical analysis was performed using the SPSS 13.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean±standard deviation. Mean values were compared between groups using Student's *t* test or Mann–Whitney *U* test, according to whether the corresponding variables were normally distrib-

uted or not, as tested by the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-squared test. Bivariate correlation and multivariate regression analyses were performed to investigate for potential relationships between variables. A $p<0.05$ was considered statistically significant.

Results

Clinical and hematological variables in the patient group are shown in Table 1. Body surface area did not differ between patients and controls (1.66±0.17 vs 1.69±0.16 m^2, respectively). A history of symptoms and/or signs of heart failure was present in three patients (2.6%). Moreover, nine (7.8%) patients had a history of arterial hypertension. None of the patients studied herein had a known connective tissue disease or HIV infection. One female patient had a history of pulmonary embolism 3 years before, but she had a normal pulmonary artery pressure both 6 months after that episode and during the evaluation in the context of this study.

Echocardiographic parameters in patients and controls are shown in Table 2. Left and right cardiac chamber dimensions, LV mass, and cardiac index were significantly higher in patients compared to controls ($p<0.001$ in most of the cases).

A detectable tricuspid regurgitation was present in 110 of 115 patients (95.7%). Other valvular abnormalities included mitral valve prolapse, observed in 17 patients (14.8%) versus two controls (4.0%, $p=0.028$), as well as mild aortic regurgitation in eight patients (7.0%) and mitral regurgitation—mild in 22 patients (19.3%) and moderate in three patients (2.6%). Fifteen patients (13.0%) had mitral annulus and aortic valve calcification, while mild aortic stenosis was present in two patients (1.7%).

Three patients (2.6%) had reduced LV ejection fraction (<55%); both mean ejection fraction and tissue Doppler s velocity at lateral mitral annulus were significantly lower in patients compared to controls ($p<0.001$). Left ventricular ejection fraction and s velocity at lateral mitral annulus were inversely correlated with age ($r=-0.543$, $p=0.045$ and $r=-0.672$, $p=0.01$) but not with hemoglobin, serum ferritin, or cardiac output levels.

Regarding LV diastolic function indices, S-Thal patients had significantly higher E and A wave velocities ($p\leq0.001$), while E/A ratio, DT, and IVRT did not differ significantly between the two groups. In contrast, tissue Doppler e wave velocity at lateral mitral annulus and e/a ratio were significantly lower in S-Thal patients compared to controls ($p<0.01$), while a wave did not differ between the two groups. Transmitral flow pattern was consistent with impaired LV relaxation in 12 patients (10.4%), all with a history of arterial hypertension. Finally, e wave velocity at lateral mitral annulus was inversely correlated with age ($r=-0.602$, $p=0.027$).

Table 1 Clinical and hematological data in the patient group

	$n=115$
Gender: men/women	50 (43.5%)/65 (56.5%)
Age, years	34±14
Body surface area, m^2	1.66±0.17
β-thalassemia gene: β^0/β^+	82 (71.3%)/33 (28.7%)
Hemoglobin, g/dl[a]	9.1±1.2
Serum ferritin, ng/ml[b]	1,896±1,994
Mean reticulocyte count, %	9.8±3.8
Lactate dehydrogenase, mg/dl[c]	720±287
Serum creatinine, mg/dl	0.8±0.3
Cystatin-C, mg/l	1.1±0.4
Splenectomy	4 (3.5%)
Previous hydroxyurea therapy	43 (37.4%)

[a] Range, 7.0–12.0 g/dl
[b] Range, 10–7,500 ng/ml
[c] Normal values, 200–460 mg/dl

Table 2 Echocardiographic parameters in patients and controls

	Patients	Controls	*P*
Left atrial, mm	39±6	34±3	<0.001
LV end diastolic diameter, mm	54±5	49±3	<0.001
LV end systolic diameter, mm	32±4	27±2	<0.001
Interventricular septum, mm	9.5±1.2	8.5±0.9	<0.001
Posterior wall, mm	9.0±1.3	8.4±0.8	0.003
LV mass, g	199±59	145±26	<0.001
LV ejection fraction, %	62±6	68±3	<0.001
Cardiac index, L/min per square meter	4.9±1.5	3.8±0.8	<0.001
Transmitral E, cm/s	89±18	80±14	0.001
Transmitral A, cm/s	68±18	58±11	<0.001
Transmitral E/A	1.4±0.4	1.4±0.3	NS
Transmitral E deceleration time, ms	170±38	165±34	NS
TDI mitral annulus s, cm/s	9±3	12±3	<0.001
TDI mitral annulus e, cm/s	11±4	15±4	<0.01
TDI mitral annulus a, cm/s	8±3	9±2	NS
TDI mitral annulus e/a, cm/s	1.3±0.6	1.7±0.4	<0.01
LV isovolumic relaxation time, ms	76±15	70±14	NS
Right ventricular diameter, mm	22±5	18±3	0.002
Peak systolic tricuspid gradient, mmHg	27±13	21±4	0.002
TDI tricuspid annulus s, cm/s	10±6	15±3	<0.001
TDI tricuspid annulus e, cm/s	12±5	14±4	NS
TDI tricuspid annulus a, cm/s	9±4	10±3	NS
TDI tricuspid annulus e/a, cm/s	1.3±0.05	1.4±0.4	NS

LV left ventricular, *NS* not significant, *E* peak early transmitral flow velocity, *A* peak late transmitral flow velocity, *s* peak systolic tissue Doppler velocity at lateral mitral annulus, *e* peak early diastolic tissue Doppler velocity at lateral mitral or tricuspid annulus, *a*: *e* peak late diastolic tissue Doppler velocity at lateral mitral or tricuspid annulus

In what concerns right ventricular function, tissue Doppler s velocity at tricuspid annulus was significantly lower in patients than in controls ($p<0.001$), while e and a velocities and e/a ratio did not differ significantly between the two groups.

Peak systolic tricuspid pressure gradient was significantly higher in patients compared to controls ($p=0.002$) and PHT (tricuspid pressure gradient >30 mmHg) was present in 31 patients (27.0%). Severe PHT (tricuspid pressure gradient >50 mmHg) was encountered in three patients (2.6%, gradient values of 98, 57, and 52 mmHg, respectively), while the mean tricuspid pressure gradient in the remaining 25 patients with pulmonary hypertension was 32±4 mmHg. Systolic pulmonary artery pressure, as estimated by peak systolic tricuspid pressure gradient, was associated with tissue Doppler s velocity ($r=-0.579$; $p=0.014$.) and transmitral E/A ratio ($r=-0.599$; $p<0.001$) but not with hemoglobin level, reticulocyte count, serum concentrations of ferritin, LDH, creatinine, or cystatin-C, former hydroxyurea therapy, and β-thalassemia genotype (β^0 vs β^+).

Table 3 summarizes laboratory findings in patients with systolic LV dysfunction and/or severe PHT. All three patients with systolic LV dysfunction (Fig. 1) had normal coronary arteries; the youngest of them (aged 47 years) reported a positive scintigraphic stress test 5 years prior to the study. Myocardial iron evaluation by CMR revealed T2* values of 18, 20, and 25 ms, respectively (normal range, >25 ms). Two of those three patients also had a history of heart failure. Regarding patients with severe PHT, one had a history of heart failure, an impaired LV ejection fraction, and increased pulmonary wedge pressure, while the remaining two patients had wedge pressure within the normal limits.

Discussion

In the present study, we identified a global cardiac functional impairment in a large cohort of Greek S-Thal patients.

Left ventricular geometry and function

S-Thal patients studied were characterized by LV dilatation and hypertrophy, confirming previous echocardiographic studies in SCD and S-Thal patients [3, 5]; in addition, systolic and diastolic LV dysfunction and increased cardiac output were also encountered.

Regarding LV systolic function, although ejection fraction was within normal limits, it was significantly lower compared to controls. This finding is indicative of a subtle systolic LV dysfunction, since LV ejection fraction should be increased in the presence of a high-output state. Similar results were encountered in SCD and S-Thal patients by CMR imaging, although not pointed out by those authors [17, 18]. Furthermore, tissue Doppler imaging showed lower systolic wave velocity at the lateral mitral annulus, another finding consistent with systolic LV dysfunction. In the individual patient analysis (Table 3), on the other hand, three patients (2.6%), all with normal coronary arteries and without history of hypertension, had evident LV systolic dysfunction (ejection fraction <55%). In a recent study referred on LV function in SCD, an even higher occurrence (9%) of ejection fraction impairment was noticed [19].

Diastolic LV dysfunction was also present. According to tissue Doppler measurements, in particular, which are less affected by loading conditions, early diastolic wave velocity at lateral mitral annulus was significantly reduced in S-Thal patient (11±4 vs 15±4, $p<0.01$). Furthermore, according to transmitral flow pattern, abnormal diastolic function was encountered in 10% of patients studied herein. In a formerly studied group of S-Thal patients, Tei index, which is considered to express both systolic and diastolic LV function, was found to be impaired [5]. In SCD, diastolic dysfunction has recently been noticed in 18% of cases in a large cohort, being at the same time an independent predictor of mortality [19]. Systolic and diastolic LV dysfunctions in the present study were found to be age-related. Two of three patients with impaired LV

Table 3 Clinical and laboratory findings in patients with impaired left ventricular systolic function (cases 1, 2, and 3) and in those with severe pulmonary hypertension (cases 4 and 5)

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years	47	60	62	51	34
History of congestive heart failure	No	Yes	Yes	No	Yes
Echocardiographic LV ejection fraction, %	50	40	31	74	72
Doppler peak systolic tricuspid gradient, mmHg	18	52	37	57	98
Coronary angiography	Normal	Normal	Normal	NP	NP
CMR T2*, ms	25	18	20	NP	NP
PAP, mmHg (systolic/diastolic/mean)	25/17/20	60/38/45	40/25/30	58/29/39	100/48/65
PCWP, mmHg (mean)	12	20	17	10	12

LV left ventricular, *CMR* cardiac magnetic resonance imaging, *PAP* invasive pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *NP* not performed

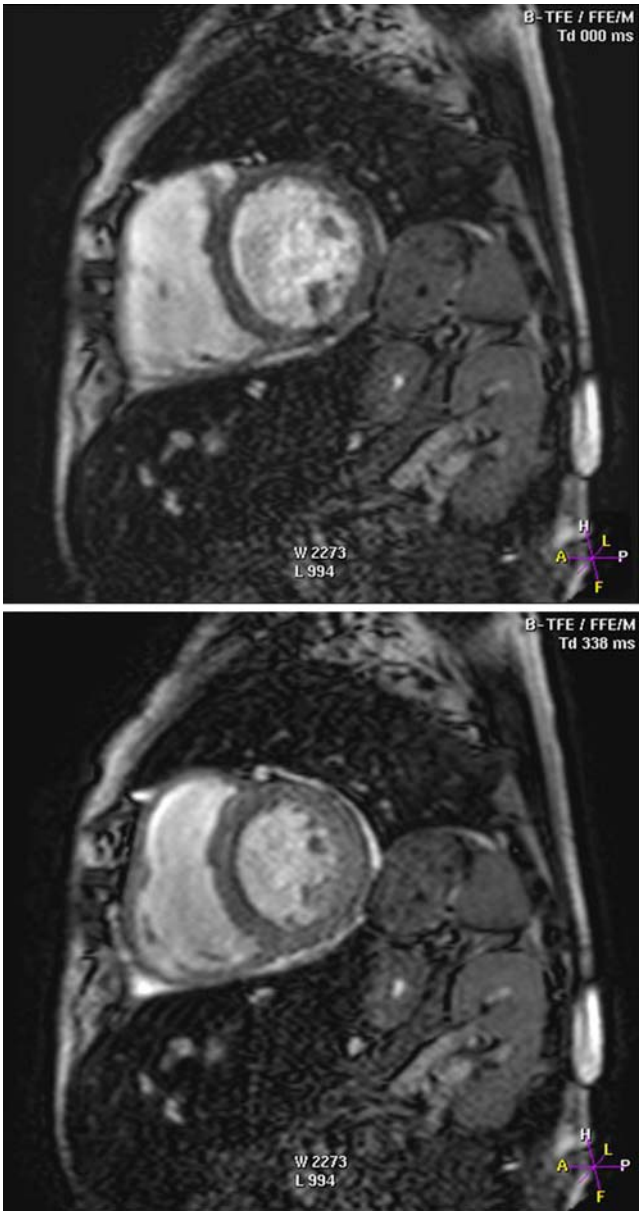

Fig. 1 Cardiac magnetic resonance tomogram in a sickle β-thalassemia patient with biventricular dilatation and systolic dysfunction. *Upper panel*: end diastolic frame; *lower panel*: end systolic frame; the estimated left ventricular ejection fraction is 40% and the T2* value 18 ms (case 2 in Table 3)

contractility were 60 and 62 years old, respectively, and were both on heart failure.

The pathogenesis of LV involvement seems to be multifactorial in S-Thal. High-output state, followed by LV dilatation and hypertrophy, was a constant finding in this cohort. Indeed, the mean cardiac index was nearly 5 l/min per square meter, being significantly higher compared to controls. Besides chronic anemia, the frequently coexistent hepatic involvement [20] as well as the recently described pseudoxanthoma-elasticum-like diffuse elastic tissue [21–25], which probably renders vessels more susceptible to dilatation by pulse pressure increase in the context of a hyperkinetic state, may both play a role [7, 20–25]. However, it has been shown that LV function copes quite well with chronically increased cardiac output [26] whereas there was no correlation between hemoglobin or cardiac output levels with LV ejection fraction or tissue Doppler systolic indices. Thus, high-output state alone is not sufficient to explain the observed LV impairment in these patients and some additional factors probably play a role.

Both endothelial dysfunction and increased arterial stiffness have been encountered in β-thalassemia, SCD, and S-Thal patients [7, 27, 28] while arterial hypertension was encountered in nearly 8% of our patients. Given also the high-output state, it is obvious that the left ventricle is in a continuous state of both volume and pressure overload. Myocardial iron load seems of less importance in sickling syndromes compared to thalassemia major [8, 29, 30]. However, in 50% of S-Thal patients previously studied by CMR, mild iron overload was encountered, despite the absence of regular transfusion therapy [18]. In the present cohort, patients on regular or frequent transfusions were excluded and serum ferritin levels, despite their wide range, were not correlated with LV ejection fraction. Evaluation of myocardial iron by CMR in the three patients with impaired LV ejection fraction revealed absent or borderline iron load (T2* values of 18, 20, and 25 ms, respectively, Table 3). Furthermore, the heart may be directly affected by the main disease as the sickling process may induce myocardial ischemia and heart muscle injury, despite the presence of angiographically normal coronary arteries [6, 31]. Actually, in one of our patients with reduced LV function, a previous myocardial scintigraphic perfusion scan was positive for stress-induced ischemia. Finally, endocardial degenerative lesions, often followed by moderate valvular regurgitation were also observed in our patients. The hyperkinetic state and primarily the aforementioned elastic tissue abnormalities may be responsible, while papillary muscles dysfunction due to ischemia is not a rare finding in the sickling syndromes [32]. The higher occurrence of mitral valve prolapse in SCD, also encountered herein, has previously been discussed in the literature and attributed to elastic fiber degeneration [33]. Although the hemodynamic consequences of the above mild or moderate valvular abnormalities are not usually significant, they may have an additive effect along with the rest of the pathogenetic mechanisms in the development of left ventricular dysfunction.

Left ventricular dysfunction in such patients, in addition to its role for the development of chronic heart failure, may be a significant determinant of clinical outcome in acute states, such as sickling crises, severe anemia due to aplastic crises, or serious infections. Furthermore, it may also contribute to the development of pulmonary hypertension.

Right-heart involvement

Regarding right-sided cardiac involvement, the presence of rather mild PHT along with signs of right ventricular dysfunction were encountered. Although PHT has long been a well-recognized complication in the sickling syndromes, its importance has been stressed lately since it has been identified as the major determinant of prognosis in SCD [34]. In addition, some new light has recently been shed on the pathogenesis of PHT in the whole spectrum of hemoglobinopathies.

In this study, based on previous reports in normal subjects [15, 16], PHT was defined as a peak systolic tricuspid pressure gradient higher than 30 mmHg, which corresponds to a peak systolic tricuspid velocity of 2.7 m/s. Using this threshold, 27% of our patients presented with age-related PHT. Despite the fact that previous studies have used a slightly lower cutoff (2.5 m/s), the reported frequencies of PHT were similar (33% in S-Thal and 20–35% in SCD) [35, 36]. Severe PHT (gradient values >50 mmHg), followed by normal systolic left ventricular function and low pulmonary capillary wedge pressure was present only in three patients in this cohort, while one of those also had a history of congestive heart failure.

In sickling syndromes, PHT was traditionally thought to be primarily related to the sickling process. Additional factors in sickling syndromes such as thromboembolism, repeated episodes of respiratory track infections, acute chest syndrome, and LV dysfunction may also play a role in lung injury affecting the continuous gradual increase of pulmonary vascular resistance. Moreover, diastolic LV dysfunction was shown to be an independent factor for PHT development in SCD [19]. The recent observation that PHT is a common finding in various forms of chronic hemolytic anemias, both hereditary and acquired ones [37], raised the concept that PHT should somehow be related to hemolysis. Indeed, intravascular hemolysis is now well recognized to reduce NO bioavailability through different mechanisms [38]. Reduced NO availability leads to a continuous process of vascular deregulation, consisting of increased in situ thrombogenicity, vasoconstriction, and, particularly in the case of sickling syndromes, increased erythrocyte adhesion, delayed transient time, and hence increased predisposition to sickling [39]. In parallel, the hemolysis-induced oxidative tissue damage has been related to the aforementioned diffuse elastic tissue defect [21–23], as pulmonary alveoli consist of a high concentration of elastic fibers.

In SCD, hemolysis seems to be a crucial factor for the development of PHT. Various markers of hemolysis, such as plasma LDH concentration, reticulocyte count, plasma arginase activity and hemoglobin, have been correlated with pulmonary hypertension in those patients [40]. A recent study in SCD patients showed that pulmonary artery pressure and pulmonary vascular resistance were increased during vaso-occlusive crises in parallel to hemolysis and hemoglobin level drop [41]. This correlation may represent the functional component of a strong hemolytic effect on the top of chronic lung vascular injury, an injury that may vary according to patients' age.

Data on S-Thal, in which a lower hemolytic rate may be present [42], are different and the correlation between the main hemolytic indices and PHT is obscure. In a previous report, although tricuspid pressure gradient correlated with hemoglobin levels, reticulocyte count and ferritin levels were not related with LDH, direct bilirubin, or percentage of hemoglobin F [35]. In the present study, which included patients with a wide age range, the only correlation observed was between hemoglobin and cardiac output levels; tricuspid pressure gradient did not correlate with reticulocyte count, LDH, ferritin, hydroxyurea administration or percentage of hemoglobin F, or the interacting β-thalassemia gene (β^0 or β^+). It seems that the lower hemoglobin level and the concomitant need for a higher cardiac output, in combination with the chronic vascular injury, determine the presence and severity of PHT in the steady-state condition in S-Thal patients. A contribution of LV function was also present in our patients and a correlation between pulmonary artery pressure and systolic and diastolic left ventricular function indices (decreased tissue Doppler s wave velocity and transmitral E/A ratio) was observed. Two patients with congestive heart failure due to LV dysfunction were found to have PHT and increased capillary wedge pressure during right cardiac catheterization (Table 3).

Furthermore, it seems that PHT is less severe in S-Thal patients compared to SCD and much less severe compared to thalassemia intermedia [3, 43]. According to two previous studies in 58 and 84 S-Thal patients, respectively, only a borderline increase of pulmonary arterial pressure was noted [5]. In the present large cohort, only two cases had severe PHT (gradient >50 mmHg), not related to LV systolic dysfunction, and only one had symptoms directly related to PHT. Moreover, the remaining 25 patients with PHT had a mean tricuspid gradient value just above upper normal limit (32±4 mmHg). Some particular features of S-Thal may play a role. A potentially lower degree of hemolysis may be present in S-Thal [42], while the spleen is rarely removed (four cases in this cohort). In SCD, in contrast, an automatic process of spleen destruction occurs, while in thalassemia intermedia, a therapeutic splenectomy is usually performed. The loss of spleen leads to increased platelet count and hypercoagulability, hence increasing the risk of thromboembolic complications. Finally, the characteristic microcytosis observed in S-Thal, may also have an impact, due to the better flexibility of red cells in the microcirculation [42].

Similarly, in SCD, other conditions have been linked to PHT, including renal and liver involvement, arterial hypertension, and LV dysfunction, suggesting the presence of an underlying diffuse vascular injury, related to chronic hemolysis, which is probably the main factor affecting patients' survival [44]. In the present study, with the exception of LV function, no correlation between PHT and arterial hypertension or renal function, as assessed by serum creatinine and cystatin-C, was observed, confirming the results of a previous report on S-Thal patients [35]. These findings may reflect the milder form of the disease, while the impact of PHT on S-Thal patients' survival should be further investigated.

Findings suggestive of right ventricular impairment were also encountered in this study, including right ventricular dilatation and decreased tissue Doppler systolic wave velocity at lateral tricuspid annulus. Consistently, impaired Tie index and reduced tricuspid annulus plane systolic excursion have previously been reported in S-Thal patients [5]. However, no correlation was found between right ventricular structural or functional indices and PHT. A recent CMR study in SCD also stressed the development of systolic right ventricular dysfunction even in cases without PHT [8]. Thus, in addition to the generally mild PHT, the aforementioned factors that affect left ventricular function and are present in all sickling syndromes may also affect right ventricle in S-Thal patients, rendering it more vulnerable to volume and pressure overload, due to its thinner walls. Such effects may be responsible for the observed lack of a clear relationship between PHT and right ventricular indices.

Limitations

Despite the large number of patients recruited, this study was a retrospective analysis of data and lacks prospective follow-up data. Moreover, the conventional and tissue Doppler echocardiographic parameters used for the assessment of patients in this study may be affected by the volume and pressure loading conditions and therefore do not reflect completely the intrinsic cardiac muscle function. The use of the novel techniques of strain and strain rate imaging may be of help in this regard and may constitute the content of a future study in S-Thal patients.

In conclusion, in this global cardiac evaluation performed in a large cohort of S-Thal patients, heart injury was characterized by both left and right cardiac involvement. Congestive heart failure, although rarely present in the steady state, may be related either to LV dysfunction, followed by PHT, or to pure PHT and right ventricular dysfunction. It seems that although S-Thal shares some common features with the rest of the sickling syndromes, it also bears some particular ones, apparently related to its unique genetical background that combines two different hemoglobin defects.

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